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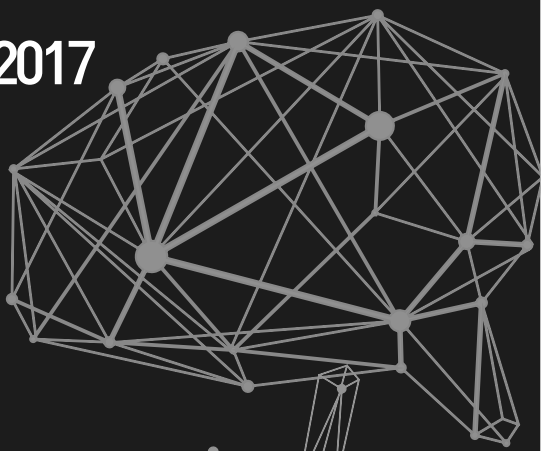

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Physiology &
Pharmacology

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Aims and Scope

The Korean Journal of Physiology & Pharmacology (Korean J. Physiol. Pharmacol., KJPP) is the official journal of both the Korean Physiological Society (KPS) and the Korean Society of Pharmacology (KSP). The journal launched in 1997 and is published bi-monthly in English. KJPP publishes original, peer-reviewed, scientific research-based articles that report successful advances in physiology and pharmacology. KJPP welcomes the submission of all original research articles in the field of physiology and pharmacology, especially the new and innovative findings. The scope of researches includes the action mechanism, pharmacological effect, utilization, and interaction of chemicals with biological system as well as the development of new drug targets. Theoretical articles that use computational models for further understanding of the physiological or pharmacological processes are also welcomed. Investigative translational research articles on human disease with an emphasis on physiology or pharmacology are also invited. KJPP does not publish work on the actions of crude biological extracts of either unknown chemical composition (e.g. unpurified and unvalidated) or unknown concentration. Reviews are normally commissioned, but consideration will be given to unsolicited contributions. All papers accepted for publication in KJPP will appear simultaneously in the printed Journal and online.

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The Korean Journal of
Physiology & Pharmacology

Editorial Board

2017 대한생리학회 임원명단

고 문 강두희 강복순 김광진 김기순 김기환 김명석 김용근 김우겸 김 전
김종규 김종환 김중수 남숙현 남택상 민병일 박양생 박재식 박춘식
박형진 배선호 문창현 서창국 신홍기 양일석 엄대용 엄융의 윤평진
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오석배 우선희 이은희 진영호
차승규 염재범

이 사 강다원 강동묵 강봉균 강 엽 강창원 공인덕 곽지연 구용숙 권성춘
권혁일 김경년 김나리 김동욱 김명준 김민선 김보경 김상정 김선희
김성주 김성준 김세훈 김양인 김영미 김용운 김원재 김의용 김재호
김정훈 김종연 김진혁 김창주 김형찬 나승열 나창수 나흥식 류판동
박경표 박규상 박명규 박병림 박사훈 박소라 박우현 박원균 박종성
박중진 박지호 박진봉 방효원 배영민 배재훈 배혜란 백은주 서덕준
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정승준 정진섭 정창섭 정한성 조성일 조양혁 조영욱 천상우 최장규
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감 사 박원선 차승규

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Exhibited by

싸이텍코리아
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Welcome Message

대한생리학회 회원 여러분,
유난히도 길고 무더운 여름을 지내시면서도 모두 건강하시고 연구에 매진하고 계시리라 기대합니다.

지난 6월 30일 개최된 제25회 기초의학학술대회에서 박규상교수 주관 하에 미토콘드리아의 모든 것을 공부하고 풍성한 초록발표에 참여해 주신 회원님들께 감사의 말씀을 드립니다. 또한 함께 축하할 일은 대한생리학회의 공식학술지인 Korean Journal of Physiology & Pharmacology (KJPP)의 2016 JCR impact factor가 2.062로 발표된 것 입니다. 이는 회원님들께서 우수한 논문 투고와 공평한 심사를 해주신 덕분이라고 생각하며 지속적인 발전을 위해 관심과 노력을 부탁드립니다.

오는 11월 2일~4일에는 서울대학교에서 제69회 대한생리학회 학술대회가 "Biomedical Sciences Converging to Physiology"라는 슬로건으로 개최될 예정입니다. 기조강연, 13개의 심포지엄 그리고 포스터 세션 등으로 구성되고 올해는 특히 국제적으로 저명한 학자 12분을 초청하게 되어 풍성한 학회가 될 것입니다.
올해는 그간의 학술대회에서는 하나의 세션으로만 진행되어 왔던 운동생리학 관련 분야가 한국운동생리학회와 IMPACT가 참여함으로써 운동생리학 관련 저명한 외국학자들이 초청되어 학술대회 수준이 보다 향상되었고 또한 다양한 운동생리학 관련 분야를 다루게 되었습니다.
이번 학술대회를 통해 그 동안의 연구성과를 공유하고 새로운 정보를 교환함은 물론 회원님들의 학문적 성장과 친목의 장이 될 수 있도록 많은 참석을 부탁드립니다.

그간 학회준비를 위해 정성을 다하신 이사님들과 서울의대 관계자 여러분을 비롯하여 도움을 주신 많은 분들께 감사 드립니다.

끝으로 회원님들의 건강과 눈부신 도약을 기원합니다.

대한생리학회 회 장 **김 선 희**
대한생리학회 이사장 **방 효 원**

주관교 환영사

학문과 예술 그리고 젊음이 조화를 이루는 서울 대학로에 위치한 서울대학교 의과대학 연건 캠퍼스에서 2017년 대한생리학회 정기 학술대회를 주관하게 된 것을 기쁘게 생각합니다. 지난해 빛고을 광주 조선대학교에서 받은 환대의 여운이 아직 가시지 않습니다. 다행히도 우리 연건 캠퍼스에 융합의생명연구관이 새로이 완공되어 여러 회원분들이 그 어느 때보다도 풍성하게 구성된 생리학 학술의 향연을 만끽할 수 있는 공간이 준비가 되었습니다. 한 건물의 같은 층에서 3세션을 동시에 운영할 수 있어 모두 13개의 심포지엄 등을 보다 편리하게 개최할 수 있을 것으로 기대합니다. 학회 장소가 메인 캠퍼스가 아니라서 주차 공간 등 부족한 면이 있을 것 같아 염려도 되지만, 여러 회원분들이 한해 동안 이룬 학술적인 활동을 공유하고 발전시키는데 부족함이 없도록 우리 생리학교실의 11명 교수들과 함께 성심껏 학회 준비를 돕도록 하겠습니다.

올 가을 대학로 마로니에 공원을 마주보는 서울대학교 의과대학 연건캠퍼스에서 생리학을 통해 의생명과학이 융합되는 현장을 여러 회원분들과 함께 할 수 있기를 고대합니다. 학술의 장을 마련하시는 생리학회 회장, 이사장, 그리고 학술이사를 포함한 실행이사 등 학회 관계자 여러분께 감사의 말씀을 드립니다.

서울대학교 의과대학 생리학교실 주임교수 **김 상 정**

Schedule (일정표)

▶ 11월 2일 목요일

Time	Contents			
	박희택홀 (Hall A)	양윤선홀 (Hall B)	GDR-1 (Hall C)	GDR3-6
14:00-18:00	**Symposium 1:** TRP Channel (Invited Speakers, Markus Delling, Kido Mizuho, Sponsored by Seoul National University and Prof. So I)			Po-1 (GDR3-4, 오후 1시부터 게시)
18:00-20:00			Poster Presentation and Welcome Reception (Sponsored by Korea Ion Channel Research Group)	

▶ 11월 3일 금요일

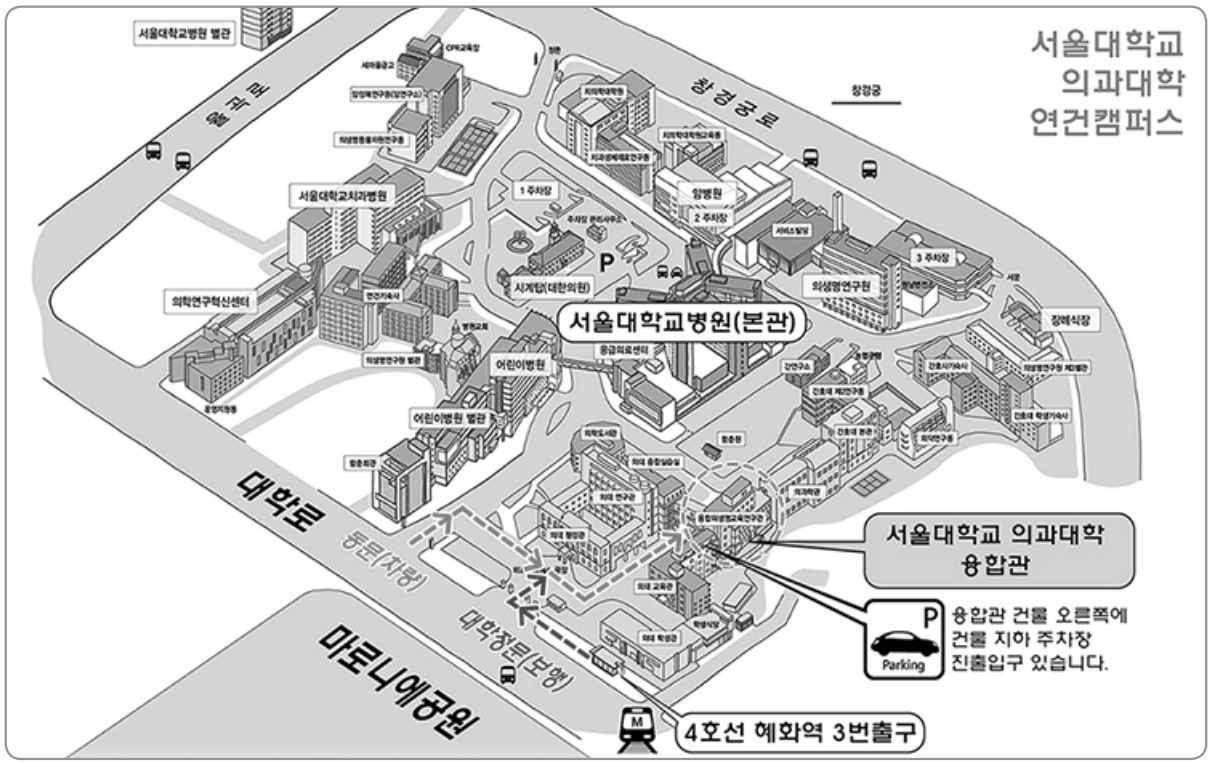
Time	Contents			
	박희택홀 (Hall A)	양윤선홀 (Hall B)	GDR-1 (Hall C)	GDR3-6
09:00-09:15	Opening Ceremony			
09:15-11:30	**Symposium 2:** Physiology of Neuropsychiatric Disease	**Symposium 3:** Inflammation and Pathophysiological Signaling (Sponsored by MRC in Ehwa Womans University)	**Symposium 4:** Cardiac Physiology and Arrhythmia	
11:30-12:00	Coffee Break & Poster Presentation (지정번호 발표자 대기)			
12:00-12:45	Nikon Luncheon Seminar (Lunch, 100 Boxes, 12:00-12:40)	Steering Committee Meeting (Lunch)		
12:45-14:00	**Poster-Oral (A)** (12:45-14:00)		**Poster-Oral (B)** (12:45-14:00)	
14:00-14:30	Coffee Break & Poster Presentation (지정번호 발표자 대기)			
14:30-15:30	**Plenary Lecture** - Prof. Paul Worley			Po-2 (GDR 4-5)
15:30-18:00	**Symposium 5:** Learning & Memory	**Symposium 6:** Mitochondria Physiology (Invited Speaker Prof. Wollheim, Sponsored by MRC in Yonsei Wonju University)	**Symposium 7:** Vascular Physiology (Invited Speaker - Prof. Michael Hill, Sponsored by Ischemic/ Hypoxic Disease Institute, Seoul National University)	
18:00-20:00			Group Photo (사진촬영) Official Buffet-Dinner (간친회)	

▶ 11월 4일 토요일

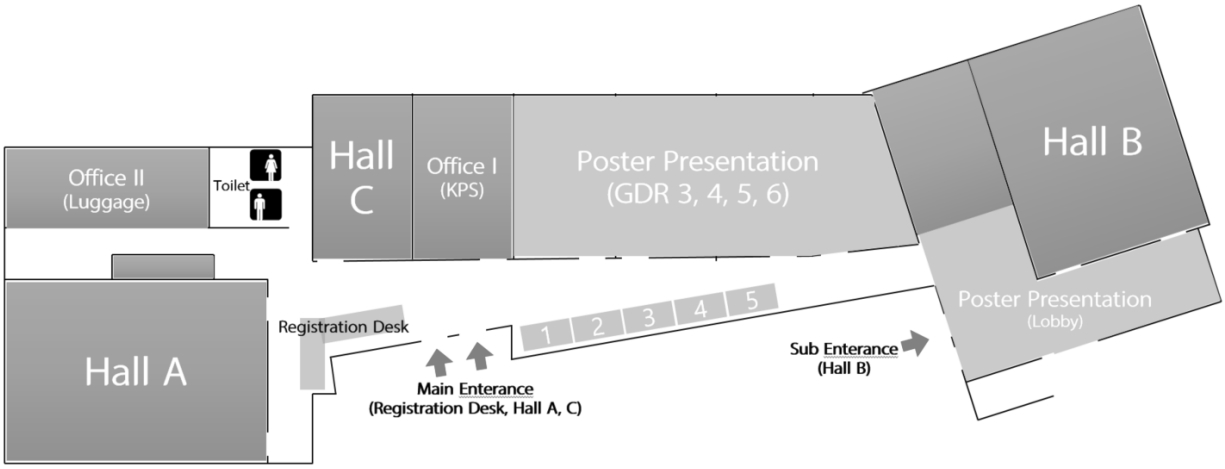
Time	Contents			
	박희택홀 (Hall A)	양윤선홀 (Hall B)	GDR-1 (Hall C)	GDR3-6
09:00-11:15	**Symposium 8:** KSEP/IMPACT Symposium (Invited Speakers; David A. Hood, P. Darrell Neufer)	**Symposium 9:** Chemical Senses (Sponsored by MRC in Yonsei University College of Dentistry)	**Symposium 10:** Recent Biomedical Approaches in the Outside	Po-3 (GDR 5-6)
11:15-12:15	Coffee Break & Poster Presentation (지정번호 발표자 대기)			
12:15-13:30	IMPACT-Lunch for KSEP Members and Speakers	Yudang Awards Ceremony (유당학술상 시상식) KPS Members Annual Ceremoy with Lunch (대한생리학회총회)		
13:30-17:00	**Symposium 11:** KSEP/IMPACT Symposium (Invited Speaker; Jacob M. Haus)	**Symposium 12:** Functional Food	**Symposium 13:** Current Status of Research on Novel Tissue, Primo Vascular System (Invited Speakers, B.S. Kwon, K.A. Kang)	

Venue Guide (학술대회장 안내)

캠퍼스 맵



서울대학교 의과대학 융합관



이사회: Hall B (양윤선홀) – 11.3(금) 12:00
전시 부스: 1–싸이텍코리아, 2–매직트리, 3–에드사이언, 4–라이프텍, 5–KISTI

Scientific Program (학술프로그램)

▶ Symposium (11월 2일 목요일)

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Symposium 1: TRP Channel	**Chair: *서인석 (서울대)***
Dual action of the $G\alpha_q$–PLCβ–PI(4,5)P_2 pathway on TRPC1/4 and TRPC1/5 heterotetramers	*Jongyun Myeong (Seoul National University College of Medicine)*
Functional role of coiled coil domain in the gating of TRPC3/6	*Kyu Pil Lee (Chungnam National University, College of Veterinary Medicine)*
Renoprotection of Klotho through TRPC6 downregulation	*Seung–Kuy Cha (Yonsei University Wonju College of Medicine)*
Role of Trp channels in the control of feeding behavior and metabolism	*Jong–Woo Sohn (Department of Biological Sciences, Korea Advanced Institute of Science and Technology)*
Ca^{2+} signaling in primary cilia during development and disease	*Markus Delling (UCSF, USA)*
Oral barrier formation via temperature–sensitive TRP channels	*Kido Mizuho (Saga University, Japan)*
The hypothalamic TRPV1 channels in regulation of food intake	*Dong Kun Lee (Gyeongsang National University School of Medicine)*
Acceleration of skin barrier restoration by topical botanical products via transient receptor potential V3	*Joo Hyun Nam (Dongguk University College of Medicine)*
The intracellular Ca^{2+} channel TRPML3 is a PtdIns3P effector that regulates early autophagosome biogenesis	*Hyun Jin Kim (Sungkyunkwan University School of Medicine)*
The ER/PM microdomain, PI(4,5)P_2 and the regulation of STIM1–Orai1 channel function	*Seok Choi (Chosun University School of Medicine)*

▶ Poster Oral Presentation (11월 3일 금요일)

Time	Contents
12:45–12:55	PO–A–01 (P1–02): Novel KCNQ4 mutations in Korean patients with nonsyndromic hearing loss *Hyun Been Choi (Sungkyunkwan University)*
12:55–13:05	PO–A–02 (P1–04): PRMT7 regulates neuronal excitability via modulation of NALCN activity *Xianlan Wen (Sungkyunkwan University)*
13:05–13:15	PO–A–03 (P3–02): Peripheral $GABA_A$ receptor–mediated signals facilitate chronic inflammatory pain *Pa Reum Lee (Seoul National University)*
13:15–13:25	PO–A–04 (P3–03): SHP2 mutation mediated cell type specific dysregulation of Ras–Erk signaling pathway *Hyun–Hee Ryu (Seoul National University, Chung–Ang University)*
13:25–13:35	PO–A–05 (P3–04): Climbing fiber burst–mediated sensory coding is directly represented in post–synaptic Purkinje cell *Seung–Eon Roh (Seoul National University, Kyung Hee University)*
13:35–13:45	PO–A–06 (P3–05): Channel–mediated GABA release from reactive astrocytes in epileptic hippocampus *Chiranjivi Neupane (Chungnam National University)*
13:45–13:55	PO–A–07 (P4–02): The E3 ligase c–Cbl inhibits cancer cell migration by neddylating the proto–oncogene c–Src *Jun Bum Park (Seoul National University)*

12:45–12:55	PO–B–01 (P2–03): STIM2 and STIM1 have similarities and differences, but both regulate Ca^{2+} movement in skeletal muscle *Mi Ri Oh (The Catholic University of Korea)*
12:55–13:05	PO–B–02 (P1–01): Calcium–sensing receptor is a critical mediator of chemotaxis and chemokinesis in immune cells *Fengjiao Chang (Seoul National University)*
13:05–13:15	PO–B–03 (P1–03): Molecular mechanism of voltage–gated Ca^{2+} channel regulation by membrane PIP_2 *Cheon–Gyu Park (DGIST)*
13:15–13:25	PO–B–04 (P4–01): WNK1–mediated Ca^{2+} signaling is a novel culprit for hepatic stellate cell activation and fibrosis *Kyu–Hee Hwang (Yonsei University Wonju College of Medicine)*
13:25–13:35	PO–B–05 (P2–01): Higher vulnerability of catecholamine–induced arrhythmia in isolated right atrial myocytes *Ami Kim (Sungkyunkwan University)*
13:35–13:45	PO–B–06 (P3–06): Singular mechanisms of the thermal sweating to central sudomotor in tropical Africans *Jeong–Beom Lee (Soonchunhyang University)*
13:45–13:55	PO–B–07 (P7–01): Mesothelial cells demarcate the subunits of organ surface primo vascular tissue *Chae Jeong Lim (Seoul National University)*

▶ Symposium (11월 3일 금요일)

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Synapse organization by autism-associated synaptic adhesion molecules	*Jaewon Ko (Department of Brain and Cognitive Sciences, DGIST)*
Excessive dopamine receptor activation in the dorsal striatum promotes autistic-like behaviors	*Pyung-Lim Han (Department of Brain and Cognitive Sciences, Ewha Womans University)*
Critical role of NMDA receptor function on the modulation of behavioral deficits in animal models of autism spectrum disorder	*Chan Young Shin (Konkuk University School of Medicine)*
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Jae-Hong Ko (Department of Physiology, College of Medicine, Chung-Ang University)

Impact of mitochondrial stress in POMC neurons on systemic metabolism
Min-Seon Kim (Division of Endocrinology and Metabolism, Asan Medical Center and University of Ulsan College of Medicine)

Regulation of insulin secretion by glucose and its blunting in diabetes through glucotoxicity
Claes B. Wolheim (University Medical Center, Geneva)

Calcineurin as a modulator of mitophagy in pancreatic beta cells
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Department of Neuroscience, Johns Hopkins University School of Medicine, USA

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[1]Department of Physiology, Seoul National University College of Medicine, [2]Department of Physiology, Chosun University School of Medicine, [3]Department of Physiology, College of Medicine, Gachon University, [4]Department of Physiology, Sungkyunkwan University School of Medicine, Korea

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Departments of Physiology and Global Medical Science, Institute of Lifestyle Medicine and Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Korea

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Physiology, UCSF School of Medicine

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Mizuho A. Kido
Department of Anatomy and Physiology, Faculty of Medicine, Saga University

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Dong Kun Lee
Department of Physiology, Institute of Health Sciences, Gyeongsang National University School of Medicine, Korea

S 33 S-I-8 Acceleration of skin barrier restoration by topical botanical products via transient receptor potential V3
Joo Hyun Nam
Department of Physiology, Dongguk University College of Medicine

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[1]Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, [2]Wide River Institute of Immunology, Seoul National University College of Medicine, Gangwon-do, Korea

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Seok Choi
Department of Physiology, College of Medicine, Chosun University

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Sungkun Chun
Department of Physiology, Chonbuk National University Medical School

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Jaewon Ko
Department of Cognitive and Brain Sciences, Daegu Gyeonbuk Institute of Science and Technology (DGIST), Daegu, Korea

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School of Medicine, Konkuk University, Seoul, Korea

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Department of Physiology, Ewha Womans University School of Medicine, Seoul, Korea

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Division of Cardiology, Yonsei University College of Medicine, Seoul, Korea

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Department of Bio-Informational Pharmacology, School of Pharmaceutical Sciences, University of Shizuoka

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State Key Laboratory of Membrane Biology, College of Life Sciences, Peking University, Beijing, China

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Division of Endocrinology and Metabolism, Asan Medical Center and University of Ulsan College of Medicine, Seoul, Korea

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Claes B. Wollheim
Department Cell Physiology and Metabolism, University Medical Center, Switzerland and Lund University Diabetes Center, Malmö, Sweden

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Kihyoun Park[1,2], Heyjin Lim[1,2], Myung-shik Lee[2]
[1]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, [2]Severance Biomedical Science Institute and the Department of internal Medicine Yonsei University College of Medicine, Seoul, Korea

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[1]Department of Life Sciences, [2]School of Interdisciplinary Bioscience and Bioengineering, and [3]Information Technology Convergence Engineering, Pohang University of Science and Technology, Pohang, Gyeongbuk, [4]Research Division, Korea Brain Research Institute, Daegu, Korea

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[1]Department of Integrated Biomedical Science, [2]Department of Physiology, Cardiovascular and Metabolic Disease Center, College of Medicine, Inje University

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Dalton Cardiovascular Research Center and Department of Medical Pharmacology and Physiology, University of Missouri-Columbia, MO 65211, USA

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[1]Division of Sport Science & Sport Science Institute, Incheon National University, Incheon, Korea, [2]Dalton Cardiovascular Research Center and Department of Medical Pharmacology & Physiology, University of Missouri-Columbia, MO, USA

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Moo-Yeol Lee
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Department of Physiology, College of Medicine, Brain Korea 21 Plus Project for Medical Sciences, Yonsei University, Seoul, Korea

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[1]Department of Physiology, [2]Hypoxic/Ischemic Disease Institute, Seoul National University College of Medicine

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Muscle Health Research Centre, School of Kinesiology and Health Science, York University, Toronto, Canada

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[1]East Carolina Diabetes and Obesity Research Institute, [2]Department of Kinesiology, [3]Department of Chemistry, [4]Department of Physiology, [5]Department of Biochemistry & Molecular Biology, East Carolina University, Greenville, NC 27834, USA, [6]Department of Rehabilitation Medicine, Medical School, University of Minnesota, Minneapolis, MN 55455, USA

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[1]Department of Pharmacology, College of Medicine, [2]Hypoxia-related Disease Research Center, [3]Department of Kinesiology, Inha University

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GNU Exe-Physio Lab., Department of Physical Education, College of Education, Gyeongsang National University, Jinju, Korea

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Department of Oral Biology, Yonsei University College of Dentistry

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Kinesiology and Nutrition, University of Illinois at Chicago

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[1]Center for Medical Metrology KRISS, [2]Korean Medicine Fundamental Research Division, KIOM, [3]Department of Biomedical Engineering, Konyang University

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[1]Department of Biomedical Engineering, College of Medicine, Kyung Hee University, [2]Department of Chemistry, College of Natural Science, Kwangwoon University, [3]Department of National Cosmetics Science, Sunchon National University

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Department of Physics and Astronomy, Seoul National University

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[1]Department of Biomedical Laboratory Science, [2]Department of Oriental Biomedical Engineering, [3]Department of Oriental-Western Biomedical Engineering and Goodpl Inc., Sangji University

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[1]Department of Physiology, Single Cell Network Research Center, Sungkyunkwan University School of Medicine, Suwon, [2]Department of Otorhinolaryngology, Brain Korea 21 PLUS Project for Medical Sciences, Yonsei University College of Medicine, Seoul, [3]Department of Pharmacology, Brain Korea 21 PLUS Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea

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Xianlan Wen[1], Tuan Anh Vuong[2], Hyunsu Kang[1], Jong-Sun Kang[2], Hana Cho[1]
[1]Department of Physiology, and [2]Molecular and Cellular Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, Korea

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Pa Reum Lee[1], Seo-Yeon Yoon[1,2], Yong Ho Kim[3], Seog Bae Oh[1,2]
[1]Department of Brain and Cognitive Sci., Col. of Natural Sci., Seoul Natl. Univ., Seoul, [2]Dent. Res. Inst. and Department of Neurobio. & Physiology, School of Dentistry, Seoul Natl. Univ., Seoul, [3]Department of Physiology, Col. of Medicine, Gachon Univ., Incheon, Korea

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[1]Department of Physiology, Seoul National University College of Medicine, [2]Department of Life Science, Chung-Ang University, [3]School of Biological Sciences, College of Natural Sciences, Seoul National University, [4]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [5]Department of Neurobiology, Integrative Center for Learning and Memory, Brain Research Institute, University of California Los Angeles, California, USA, [6]Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, Korea

PO-A-05 (P3-04) Climbing fiber burst-mediated sensory coding is directly represented in post-synaptic Purkinje cell
Seung-Eon Roh[1,3]*, Seung Ha Kim[1,2], Yong-Gyu Kim[1], Chang-Hyun Ryu[1], Chang-Eop Kim[1], Sun Kwang Kim[3], Sang Jeong Kim[1,2]
[1]Department of Physiology and [2]Department of Biomedical Science, College of Medicine, Seoul National University, [3]Department of Physiology, College of Korean Medicine, Kyung Hee University, Seoul, Korea

PO-A-06 (P3-05) Channel-mediated GABA release from reactive astrocytes in epileptic hippocampus
Chiranjivi Neupane[1], Sudip Pandit[1], Ramesh Sarma[1], Junsung Woo[2], C Justin Lee[2], Jin Bong Park[1]
[1]Department of Physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, [2]Center for Neural Science, Korea Institute of Science and Technology (KIST), Seoul, Korea

PO-A-07 (P4-02) The E3 ligase c-Cbl inhibits cancer cell migration by neddylating the proto-oncogene c-Src
Gun-Woo Lee[1], Jun Bum Park[1], Sung Yeon Park[2,3], Seo Jieun[1], Seung-Hyun Shin[1], Jong-Wan Park[1,2], Sang Jung Kim[1,2,3], Masatoshi Watanabe[4], Yang-Sook Chun[1,2,3]*
[1]Department of Biomedical Science, [2]Ischemic/Hypoxic Disease Institute, [3]Department of Physiology, Seoul National University College of Medicine, Seoul, [4]Laboratory for Medical Engineering, Graduate School of Engineering, Yokohama National University

PO-B-01 (P2-03) STIM2 and STIM1 have similarities and differences, but both regulate Ca^{2+} movement in skeletal muscle
Mi Ri Oh[1], Keon Jin Lee[1], Mei Huang[1], Jin Ock Kim[2], Do Han Kim[2], Chung-Hyun Cho[3], Eun Hui Lee[1]
[1]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, [2]School of Life Sciences, GIST, Gwangju, [3]Department of Pharmacology, College of Medicine, Seoul National University, Seoul, Korea

PO-B-02 (P1-01) Calcium-sensing receptor is a critical mediator of chemotaxis and chemokinesis in immune cells
Fengjiao Chang, Jin Man Kim, Kyungpyo Park
Department of Physiology, School of Dentistry, Seoul National University and Dental Research Institute, Seoul, Korea

PO-B-03 (P1-03) Molecular mechanism of voltage-gated Ca^{2+} channel regulation by membrane PIP_2
Cheon-Gyu Park, Byung-Chang Suh*
Department of Brain & Cognitive Sciences, DGIST, Daegu, Korea

PO-B-04 (P4-01) WNK1-mediated Ca^{2+} signaling is a novel culprit for hepatic stellate cell activation and fibrosis
Kyu-Hee Hwang[1-4], Ji-Hee Kim[1,3,4], Soo-Jin Kim[1-4], Hung Minh Tran[1-4], In Deok Kong[1-3], Kyu-Sang Park[1-4], Seung-Kuy Cha[1-4¶]
Departments of [1]Physiology and [2]Global Medical Science, [3]Institute of Lifestyle Medicine, and [4]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Korea

PO-B-05 (P2-01) Higher vulnerability of catecholamine-induced arrhythmia in isolated right atrial myocytes
Ami Kim, Jieun An, Hyun Bin Choi, Tong Mook Kang
Department of Physiology, Single Cell Network Research Center, Sungkyunkwan University School of Medicine, Suwon, Korea

PO-B-06 (P3-06) Singular mechanisms of the thermal sweating to central sudomotor in tropical Africans
Jeong-Beom Lee[1]*, Young-Ki Min[1], Jeong-Ho Kim[2], Yun Su Eun[2], Jin Wook Kim[2], Seo Yun Jung[2], Suk Min Han[2], Jae Yeong Bae[2], Hee-Jin Lee[3], Mi-Young Lee[3]
[1]Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, [2]A Student at the College of Medicine, Soonchunhyang University, Cheonan, [3]Global Graduate School of Healthcare, Soonchunhyang University, Asan, Korea

PO-B-07 (P7-01) Mesothelial cells demarcate the subunits of organ surface primo vascular tissue
Chae Jeong Lim[1], Yeo Sung Yoon[2], So Yeong Lee[1], Pan Dong Ryu[1]
Departments of [1]Veterinary Pharmacology and [2]Anatomy & Cell Biology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

Poster Presentation

P1: Ion Channels

S 53 P1-01 (PO-B-02) Calcium-sensing receptor is a critical mediator of chemotaxis and chemokinesis in immune cells
Fengjiao Chang, Jin Man Kim, Kyungpyo Park
Department of Physiology, School of Dentistry, Seoul National University and Dental Research Institute, Seoul, Korea

S 53 P1-02 (PO-A-01) Novel KCNQ4 mutations in Korean patients with nonsyndromic hearing loss
Hyun Been Choi[1]*, Jinsei Jung[2]*, Young Ik Koh[3]*, Joon Suk Lee[3], Seyoung Yu[3], Sung Huhn Kim[2], Jae Hyun Jae[2], Jieun An[1], Ami Kim[1], Heon Yung Gee[3], Jae Young Choi[2], Tong Mook Kang[1]
[1]Department of Physiology, Single Cell Network Research Center, Sungkyunkwan University School of Medicine, Suwon, [2]Department of Otorhinolaryngology, Brain Korea 21 PLUS Project for Medical Sciences, Yonsei University College of Medicine, Seoul, [3]Department of Pharmacology, Brain Korea 21 PLUS Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea

S 54 P1-03 (PO-B-03) Molecular mechanism of voltage-gated Ca^{2+} channel regulation by membrane PIP_2
Cheon-Gyu Park, Byung-Chang Suh*
Department of Brain & Cognitive Sciences, DGIST, Daegu, Korea

S 54 P1-04 (PO-A-02) PRMT7 regulates neuronal excitability via modulation of NALCN activity
Xianlan Wen[1], Tuan Anh Vuong[2], Hyunsu Kang[1], Jong-Sun Kang[2], Hana Cho[1]
[1]Department of Physiology, and [2]Molecular and Cellular Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, Korea

S 54 P1-05 Regulation of spontaneous glutamate release by presynaptic M-type K^+ channels in the hippocampal pyramidal neurons
Byoung Ju Lee, Jae-Han Kwon, Suk-Ho Lee, Won-Kyung Ho
Cell Physiology Laboratory Department of Physiology, bioMembrane Plasticity Research Center, Seoul National University College of Medicine

S 54 P1-06 Altered Na^+ and Cl^- transporting activity and dysregulated pH homeostasis in hyperkalemic db/db cardiac arrest
Minjeong Ji, Wanhee Suk, Kuk Hui Son, Jeong Hee Hong*
Department of Physiology, College of Medicine, Gachon University

S 55 P1-07 Modulation of mesenchymal stem cell tropism through the recruitment and enhanced activity of SLC4A7
Dongun Lee[1,2], Junyoung Park[3], Dongwoo Khang[3], Jeong Hee Hong[1]
[1]Gachon University, [2]Lee Gil Ya Cancer and Diabetes Institute, [3]Department of Physiology, College of Medicine, Gachon University

S 55 P1-08 Gαi-mediated TRPC4 activation by polycystin-1 contributes to the endothelial function via STAT1 activation
Misun Kwak[1,2], Chansik Hong[3], Jongyun Myeong[1,2], Ju-Hong Jeon[1,2], Insuk So[1,2]
[1]Department of Physiology and Institute of Dermatological Science, [2]Department of Biomedicines, Seoul National University College of Medicine, Seoul, [3]Department of Physiology, School of Medicine, Chosun University, Gwangju, Korea

S 55 P1-09 Regulation of TRPC4, TRPC5 homotetrameric and TRPC1/4, C1/5 heterotetrameric channel activity by $PI(4,5)P_2$ hydrolysis
Juyeon Ko, Jongyun Myeong, Insuk So
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 55 P1-10 Restored activity of HCO_3^- transporters by knockdown of spinophilin enhance invasive function of lung cancer cells
Soyoung Hwang, Kuk Hui Son, Jeong Hee Hong
Department of Physiology, Gachon University College of Medicine, Incheon

S 56 P1-11 Dapoxetine, a selective serotonin reuptake inhibitor inhibits voltage-gated K^+ channels in coronary arterial smooth muscle cells from rabbit
Jin Ryeol An[1], Won Sun Park[1], Sung Hun Na[2]
[1]Department of Physiology, Kangwon National University School of Medicine, Chuncheon, [2]Department of Obstetrics and Gynecology, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P1-12 Anti-diabetic drug nateglinide induces vasodilation via activation of voltage-dependent K^+ channels in aortic smooth muscle
Hongliang Li[1], Sung Hun Na[2], Won Sun Park[1]
[1]Department of Physiology, Kangwon National University School of Medicine, Chuncheon, [2]Department of Obstetrics and Gynecology, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P1-13 A tricyclic antidepressant, nortriptyline inhibits the voltage-dependent K^+ channels in coronary arterial smooth muscle cells from rabbit
Sung Eun Shin[1], Won Sun Park[1], Sung Hun Na[2]
[1]Department of Physiology, Kangwon National University School of Medicine, Chuncheon, [2]Department of Obstetrics and Gynecology, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P1-14 Salivary spinophilin tunes chloride/bicarbonate exchangers for the Cl^- secretion in salivary glands
Sang Ah Lee[1], Dongun Lee[1], Dong Min Shin[3], Jeong Hee Hong[1], Kuk Hui Son[2]
[1]Department of Physiology, College of Medicine, Gachon University, [2]Department of Thoracic and Cardiovascular Surgery, Gachon University Gil Medical Center, Gachon University, [3]Yonsei University School of Dentistry

S 57 P1-15 GNB5 regulates TRPC3 and store-operated Ca^{2+} entry mediated bone remodeling
Namju Kang, Yu-Mi Yang, Dong Min Shin, Soonhong Park
Department of Oral Biology, BK21 PLUS project, Yonsei University College of Dentistry, Seoul, Korea

S 57 P1-16 Real-time assessment of shear-induced ATP release from a rat atrial myocyte using sniffer-patch clamp
Min-Jeong Son, Joon-Chul Kim, Qui Anh Le, Kyoung Hee Kim, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 57 P1-17 Temperature-dependent increase of the calcium sensitivity and activation kinetics of ANO6 Cl^- channel variants
Haiyue Lin[1], Joo Hyun Nam[2], Sung Joon Kim[1]
[1]Department of Physiology, Seoul National University College of Medicine, Seoul, [2]Department of Physiology, Dongguk University College of Medicine, Gyeongju, Korea

S 58 P1-18 Identification of critical amino acids in the C-terminal of TREK-2 K^+ channel for ATP- and pH_i-sensitive regulation
Joohan Woo[1], Young Keul Jeon[1], Yin-Hua Zhang[1], Joo Hyun Nam[2], Dong Hoon Shin[3], Sung Joon Kim[1]
[1]Department of physiology, College of Medicine, Seoul National University, Seoul, [2]Department of physiology & Ion Channel Disease Research Center, College of Medicine, Dongguk University, Kyungju, [3]Department of Pharmacology, College of Medicine, Yonsei University, Seoul, Korea

S 58 P1-19 Anoctamin1 does not function as ion channel in head and neck squamous cell carcinoma due to lack of surface expression
Young Keul Jeon, Joo Han Woo, Ji Hyun Jang, Seong Woo Choi, Hai Yue Lin, Yin Ming Zhe, Sung Joon Kim
Department of Physiology, Seoul National University, College of Medicine

S 58 P1-20 Carbonic anhydrase 12 E/K mutation modulates the function of AQP5 in submandibular glands
Min Jae Kim†, Jung Yun Kang, Jeong Hee Hong, Dong Min Shin*
Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul, Korea

S 58 P1-21

Augmentation of Ca^{2+}-induced Ca^{2+} release by chrysosplenol C via sensitization of Ca^{2+} release sites in ventricular myocytes
Joon-Chul Kim[1], Jun Wang[1], Bojjibabu Chidipi[1], Min-Jeong Son[1], Young Ho Kim[1], Nguyen Manh Cuong[2,3], Sun-Hee Woo[1]
[1]College of Pharmacy, IDRD, Chungnam National University, Daejeon, Korea, [2]Institute of Chemistry, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam, [3]Institute of Natural Products Chemistry, VAST, Hanoi, Vietnam

S 59 P1-22

De-energized mitochondrial function in permeabilized rat ventricle myocytes
Quynh Mai Ho, Jeong Hoon Lee, Duong Duc Pham, Ki Hwan Hong, Kim Sung Jin, Yeon Joo Jung, Ho Sun Lee, Chae Hun Leem
Department of Physiology, College of Medicine, Ulsan University, Seoul, Korea

S 59 P1-23

The critical role of three charged residues in TRPC5 pore region in interaction with englerin A
SeungJoo Jeong[1], Minji Kim[2], Eunice Yon June Park[1], Jinhong Wie[3], Ju-hong Jeon[1], Insuk So[1]
[1]Department of Physiology, Seoul National University College of Medicine, Seoul, [2]Chungnam National University, College of Veterinary Medicine, Daejeon, Korea, [3]Department of Biology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

S 59 P1-24

Identification of clustered phosphorylation sites in PKD2L1: how PKD2L1 channel activation is regulated by cAMP signaling pathway
Eunice Yon June Park[1], Misun Kwak[1], Kotdaji Ha[2], Insuk So[1]*
[1]Department of Physiology, Seoul National University, College of Medicine, Seoul, Korea, [2]Department of Physiology, University of California, San Francisco, California, USA

S 60 P1-25

TRPM7 mediates mechanosensitivity in adult rat odontoblasts
Jonghwa Won[1], Hue Vang[2], Ji Hyun Kim[1], Youngnam Kang[2], Seog Bae Oh[1,2]*
[1]Department of Brain and Cognitive Sciences, College of Natural Sciences, Seoul National University, Seoul, [2]Dental Research Institute and Department of Neurobiology & Physiology, School of Dentistry, Seoul National University, Seoul, Korea

S 60 P1-26

Menadione generates reactive oxygen species and accumulates intracellular calcium in mouse pancreatic acinar cells
Kyung Jin Choi, Shin Hye Kim, Dong Kwan Kim, Se Hoon Kim, Hyung Seo Park
Department of Physiology, College of Medicine, Konyang University, Daejeon, Korea

S 60 P1-27

Function of carboxyl coiled coil of TRPC3 in the gating mechanism
Tharaka Darshana Wijerathne, Ji Hyun Kim, Min Ji Kim, Kyu Pil Lee
Department of Physiology, College of Veterinary Medicine, Chungnam National University, Daejeon, Korea

S 60 P1-28

Quercetin inhabits hSlo3 in a pH and calcium dependent manner through possible inhibition of Phosphatidylinositol kinases
Tharaka Darshana Wijerathne, Ji Hyun Kim, Min Ji Kim, Kyu Pil Lee
Department of Physiology, College of Veterinary Medicine, Chungnam National University, Daejeon, Korea

S 61 P1-29

Electrophysiological characterization of trpc6 mutants associated with kidney diseases
Tharaka Darshana Wijerathne, Ji Hyun Kim, Min Ji Kim, Kyu Pil Lee
Department of Physiology, College of Veterinary Medicine, Chungnam National University, Daejeon, Korea

S 61 P1-30

The N-terminus of β-subunits regulates the PIP_2 sensitivity of voltage-gated calcium channels
Seong-Hyeon Byeon, Byung-Chang Suh
Department of Brain and Cognitive Sciences, DGIST

S 61 P1-31

Hydroxyphenyl octanediamide-induced antinociception via transient receptor potential vanilloid subtype 4 modulation
Geunyeol Choi, Sungjae Yoo, Seung-In Choi, Ji Yeon Lim, Minseok Kim, Hong Hua Piao, Pyung Sun Cho, Sun Wook Hwang
Department of Biomedical Sciences and Department of Physiology, Korea University College of Medicine, Seoul, Korea

S 61 P1-32

Diphenyleneiodonium (DPI) attenuates Ca^{2+} transient and contraction via desensitization of cardiac Ca^{2+} release sites independently of NADPH oxidase
Jun Wang, Joon-Chul Kim, Min-Jeong-Son, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 62 P1-33

Effects of nitric oxide on voltage-dependent K^+ currents in human cardiac fibroblasts by PKC pathway
Hyemi Bae, Jeongyoon Choi, Youngwon Kim, Donghee Lee, Jaehong Ko, Hyoweon Bang, Inja Lim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

S 62 P1-34

Effects of nitric oxide on voltage-gated K^+ currents in human cardiac fibroblasts
Hyemi Bae, Jeongyoon Choi, Youngwon Kim, Donghee Lee, Jaehong Ko, Hyoweon Bang, Inja Lim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

S 62 P1-35

Determine proarrhythmic risk of 4-oxononenal (4-ONE) by the comprehensive *in vitro* proarrhythmia assay (CiPA)
Seong Woo Choi, Yin-Hua Zhang, Sung Joon Kim
Department of Physiology, Seoul National University College of Medicine

S 62 P1-36 Hydrolyzable ATP modulates PIP_2 sensitivity of Anoctamin1/TMEM16A
Woori Ko[1], Joo Hyun Nam[2], Byung-Chang Suh[1]*
[1]Department of Brain & Cognitive Sciences, DGIST, Daegu, [2]Department of Physiology and Ion channel Disease Research Center, College of Medicine, Dongguk University, Korea

S 63 P1-37 Kv3.1 and Kv3.4 are involved in cancer cell migration and invasion
Min Seok Song, Su Min Park, Jeong Seok Park, Jin Ho Byun, Hee Jung Jin, Seung Hyun Seo, Pan Dong Ryu, So Yeong Lee
Laboratory of Veterinary Pharmacology, College of Veterinary Medicine, Seoul National University

S 63 P1-38 Lipopolysaccharide reduces THIK-1 in Macrophages through AMPK activation
Marie Merci Nyiramana[1,2], Eun-Jin Kim[2], Ji Hyeon Ryu[2], Dong-Kun Lee[1,2], Seong-Geun Hong[1,2], Jaehee Han[2], Dawon Kang[1,2]*
[1]Department of Convergence Medical Science, Gyeongsang National University, Jinju, [2]Department of Physiology, College of Medicine Institute of Health Sciences, Gyeongsang National University, Jinju, Korea

S 63 P1-39 The involvement of two-pore domain potassium channels on epithelial-mesenchymal transition in cancer cells
Yangmi Kim
Department of Physiology, College of Medicine, Chungbuk National University, Cheongju, Korea

S 64 P1-40 A novel SCN5A mutation results in ventricular arrhythmia with distinct molecular pharmacology and therapeutic response
Hyun-jeong Pyo[1], Hyun-Ji Kim[1], Bok-Geon Kim[2], June Huh[3], Chang-Seok Ki[4], Jae Boum Youm[5], Jong-Sun Kang[2], Hana Cho[1]
[1]Department of Physiology, and [2]Molecular and Cellular Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, [3]Division of Pediatric Cardiology, Department of Pediatrics, and [4]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [5]Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 64 P1-41 PRMT1-dependent regulation of ventricular myocyte late Na^+ current and excitability
Hyun-ji Kim[1], Jung-hoon Pyun[2], Myong-ho Jeong[2], Jong-Sun Kang[2], Hana Cho[1]
[1]Department of Physiology, and [2]Molecular and Cellular Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, Korea

S 64 P1-42 Nitric oxide stimulation of L-type voltage-dependent Ca^{2+} currents in human cardiac fibroblasts through protein kinase G pathways but not *S*-nitrosylation
Hyemi Bae, Jeongyoon Choi, Youngwon Kim, Donghee Lee, Jaehong Ko, Hyoweon Bang, Inja Lim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

P2: Muscle Physiology

S 64 P2-01 (PO-B-05) Higher vulnerability of catecholamine-induced arrhythmia in isolated right atrial myocytes
Ami Kim, Jieun An, Hyun Bin Choi, Tong Mook Kang
Department of Physiology, Single Cell Network Research Center, Sungkyunkwan University School of Medicine, Suwon, Korea

S 65 P2-02 The vasodilatory mechanisms of repaglinide, a member of meglitinide anti-diabetic drugs by activating protein kinase A and protein kinase G in aortic smooth muscle
Hongliang Li[1], Sung Eun Shin[1], Mi Seon Seo[1], Jin Ryeol An[1], Sung Hun Na[2], Won Sun Park[1]
[1]Department of Physiology, [2]Department of Obstetrics and Gynecology, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea

S 65 P2-03 (PO-B-01) STIM2 and STIM1 have similarities and differences, but both regulate Ca^{2+} movement in skeletal muscle
Mi Ri Oh[1], Keon Jin Lee[1], Mei Huang[1], Jin Ock Kim[2], Do Han Kim[2], Chung-Hyun Cho[3], Eun Hui Lee[1]
[1]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, [2]School of Life Sciences, GIST, Gwangju, [3]Department of Pharmacology, College of Medicine, Seoul National University, Seoul, Korea

S 65 P2-04 Isocitrate dehydrogenase 2 inhibition stimulate vascular inflammation in response to oxidative stress
Su-Jeong Choi[1,2,3], Harsha Nagar[1,2,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Ikjun Lee[1,3], Sung-min Kim[1,3], Saet-byel Jung[1,4], Jeen-Woo Park[5], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,6], Cuk-Seong Kim[1,2,3]*
[1]Department of Medical Science, School of Medicine, Chungnam National University, Daejeon, [2]Department of BK21Plus CNU Integrative Biomedical Education Initiative, [3]Department of Physiology, School of Medicine, Chungnam National University, Daejeon, [4]Department of Endocrinology, [5]Department of Thoracic and Cardiovascular Surgery, School of Life Sciences, College of Natural Science, Kyungbook National University, Taegu, [6]Department of Neurology, School of Medicine, Chungnam National University Hospital, Daejeon, Korea

S 65 P2-05 Altered redox state modulates endothelial $K_{Ca}2.3$ and $K_{Ca}3.1$ levels in normal pregnancy and preeclampsia
Shinkyu Choi, Seung-Eun Cho, Ji Aee Kim, Hai-yan Li, Suk Hyo Suh
Department of Physiology, Medical School, Ewha Womans University, Seoul, Korea

S 66 P2-06 Attenuation of NaHS-induced stimulation of ANP secretion from hypertrophied atria
Lamei Yu, Byung Mun Park, Thi Ai Phuong Hoang, Suhn Hee Kim
Department of Physiology, Research Institute for Endocrine Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 66 P2-07 Cardiprotective effects of alamandine via MrgD receptor by anti-apoptosis and ANP system in rats
Byung Mun Park, Thi Ai Phuong Hoang, Lamei Yu, Suhn Hee Kim
Department of Physiology, Research Institute for Endocrine Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 66 P2-08 CR6-interacting factor 1 deficiency impairs vascular function by inhibiting the Sirt1-endothelial nitric oxide synthase pathway
Harsha Nagar[1,2,3], Su-Jeong Choi[1,2], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Ikjun Lee[1,3], Sung-min Kim[1,3], Saet-byel Jung[1,4], Jeen-Woo Park[5], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,6], Cuk-Seong Kim[1,2,3]*
[1]Department of Medical Science, [2]Department of BK21Plus CNU Integrative Biomedical Education Initiative, [3]Department of Physiology, School of Medicine, Chungnam National University, Daejeon, [4]Department of Endocrinology, [5]Department of Thoracic and Cardiovascular Surgery, School of Life Sciences, College of Natural Science, Kyungbook National University, Taegu, [6]Department of Neurology, School of Medicine, Chungnam National University Hospital, Daejeon, Korea

S 67 P2-09 Neuronal nitric oxide synthase β is attached to myofilament and maintains sarcomere structure in cardiomyocyte
Ji Hyun Jang, Sung Joon Kim, Yin Hua Zhang
Department of Physiology, Seoul National University, College of Medicine, Seoul, Korea

S 67 P2-10 *Salicornia europaea* extract suppresses vascular neointima formation through inhibiting MAPK pathway-mediated responses in vascular smooth muscle cells
Long Cui[1], Kang Pa Lee[1], Seung Hyo Jung[1], Mee-Hyang Kweon[2], Yunkyoung Ryu[1], Kyung Jong Won[1], Bokyung Kim[1]
[1]Department of Physiology, School of Medicine, Konkuk University, Chungju, [2]Research Center, Phyto Corporation, Seoul, Korea

S 67 P2-11 The APE1/Ref-1 inhibits inorganic phosphate-induced vascular calcification in vascular smooth muscle cells and ex vivo aorta
Eun Ok Lee[1], Ki Mo Lee[1], Yu Ran Lee[1], Hee Kyoung Joo[1], Myoung Soo Park[1], Cuk-Seong Kim[1], Sunga Choi[1], Jin Ok Jeong[2], Byeong Hwa Jeon[1]*
[1]Research Institute of Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, Daejeon, [2]Division of Cardiology, Department of Internal Medicine, Chungnam National University, Daejeon, Korea

S 68 P2-12 Fast, transient relaxation of rat pulmonary artery by angiotensin II via AT1-eNOS signaling pathways
Hae Jin Kim, Ji Hyun Jang, Yin-Hua Zhang, Sung Joon Kim
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 68 P2-13 Attenuation of vascular contractility in metastatic breast cancer mice
Rany Vorn[1,2], Hae Young Yoo[1]
[1]Chung-Ang University College of Nursing, Seoul, [2]Chung-Ang University Graduate School, Seoul, Korea

P3: Neurophysiology

S 68 P3-01 Development of autaptic sympathetic neuronal culture for studying the functional communication between autonomic neurons and satellite glial cells
Seong Jun Kang, Choong-Ku Lee, So Hyun Kim, Seong-Woo Jeong
Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea

S 69 P3-02 (PO-A-03) Peripheral $GABA_A$ receptor-mediated signals facilitate chronic inflammatory pain
Pa Reum Lee[1], Seo-Yeon Yoon[1,2], Yong Ho Kim[3], Seog Bae Oh[1,2]
[1]Department of Brain and Cognitive Sci., Col. of Natural Sci., Seoul Natl. Univ., Seoul, [2]Dent. Res. Inst. and Department of Neurobio. & Physiology, School of Dentistry, Seoul Natl. Univ., Seoul, [3]Department of Physiology, Col. of Medicine, Gachon Univ., Incheon, Korea

S 69 P3-03 (PO-A-04) SHP2 mutation mediated cell type specific dysregulation of Ras-Erk signaling pathway
Hyun-Hee Ryu[1,2†], Tae-Hyun Kim[3†], Minkyung Kang[1,4], DaeHee Han[3], Yong Gyu Kim[1,4], Jiyeon Ha[1], Chae-Seok Lim[3], Chul-Hong Kim[2], Sang Jeong Kim[1,4,6], Alcino J. Silva[5], Jung-Woong Kim[2]*, Bong-Kiun Kaang[3]*, Yong-Seok Lee[1,4,6]*
[1]Department of Physiology, Seoul National University College of Medicine, [2]Department of Life Science, Chung-Ang University, [3]School of Biological Sciences, College of Natural Sciences, Seoul National University, [4]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [5]Department of Neurobiology, Integrative Center for Learning and Memory, Brain Research Institute, University of California Los Angeles, California, USA, [6]Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, Korea

S 69 P3-04 (PO-A-05) Climbing fiber burst-mediated sensory coding is directly represented in post-synaptic Purkinje cell
Seung-Eon Roh[1,3]*, Seung Ha Kim[1,2], Yong-Gyu Kim[1], Chang-Hyun Ryu[1], Chang-Eop Kim[1], Sun Kwang Kim[3], Sang Jeong Kim[1,2]
[1]Department of Physiology and [2]Department of Biomedical Science, College of Medicine, Seoul National University, [3]Department of Physiology, College of Korean Medicine, Kyung Hee University, Seoul, Korea

S 69 P3-05 (PO-A-06) Channel-mediated GABA release from reactive astrocytes in epileptic hippocampus
Chiranjivi Neupane[1], Sudip Pandit[1], Ramesh Sarma[1], Junsung Woo[2], C Justin Lee[2], Jin Bong Park[1]
[1]Department of Physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, [2]Center for Neural Science, Korea Institute of Science and Technology (KIST), Seoul, Korea

S 70 P3-06 (PO-B-06) Singular mechanisms of the thermal sweating to central sudomotor in tropical Africans
Jeong-Beom Lee[1]*, Young-Ki Min[1], Jeong-Ho Kim[2], Yun Su Eun[2], Jin Wook Kim[2], Seo Yun Jung[2], Suk Min Han[2], Jae Yeong Bae[2], Hee-Jin Lee[3], Mi-Young Lee[3]
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S 70 P3-07

Selective expression of Kv4.1 in mature granule cells contributes to sparse firing of hippocampal dentate gyrus
Kyung-Ran Kim[1,2,3], Sooyun Kim[1,2,3], Young Ho Suh[4], Jong-Sun Kang[5], Suk-Ho Lee[1,2,3], Hana Cho[6,7*], Won-Kyung Ho[1,2,3*]
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S 70 P3-08

Spinal D-serine modulates neuronal nitric oxide synthase phosphorylation leading to the development of mechanical allodynia in a mouse model of neuropathic pain
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S 70 P3-09

Serotonin increases inhibitory but not excitatory synaptic transmission in the substantia gelatinosa neurons of trigeminal subnucleus caudalis
Seon Hui Jang, Thi Huyen Phuong Tran, Seong Kyu Han, Soo Joung Park
Department of Oral Physiology and Institute of Oral Bioscience, School of Dentistry, Chonbuk National University, Jeonju, Jeonbuk, Korea

S 71 P3-10

The potential role of TLR2 on alcohol-induced behaviors
Yujin Jang, Min hee Lee, Dong Kwan Kim
Department of Physiology, Konyang University College of Medicine, Daejeon, Korea

S 71 P3-11

Regulation of NMDAR receptiveness through calpain inhibition in midbrain dopamine neurons
Shin Hye Kim, Sun Hee Jeon, Hoo Shin Lee, Dong Kwan Kim, Hyung Seo Park, Se Hoon Kim
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S 71 P3-12

Pharmacological inhibition of eIF2α phosphorylation can rescue synaptic plasticity and memory deficits in Alzheimer's disease mouse models
Kyoung-Doo Hwang[1], Myeong Seong Bak[2], Sang Jeong Kim[2], Sangmyung Rhee[1], Yong-Seok Lee[2]
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S 72 P3-13

Branch specific input wiring on distal tuft dendrites of L5 pyramidal neurons in primary somatosensory cortex
Young-Eun Han, Jun-Ho Choi, Jong-Cheol Rah
Department of Structure & Function of Neural Network, Korea Brain Research Institute, Daegu, Korea

S 72 P3-14

The role of spinal cord D-serine in the development of mirror-image pain: different modulation of astrocyte sigma-1 receptors and gap junctions on D-serine production
Hoon-Seong Choi, Sheu-Ran Choi, Ho-Jae Han, Jang-Hern Lee*
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S 72 P3-15

Correlation between hippocampal ensemble dynamics and memory specificity
Myeong Seong Bak, Yong-Seok Lee
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S 72 P3-16

Repurposed drugs for acute ischemic stroke
Dong Hyeon Lee[1,2], Kang Ahn[1], Jongman Yoo[2,3]
[1]Department of Physiology, [2]Institute of Basic Medical Sciences, [3]Department of Microbiology, School of Medicine, CHA University

S 73 P3-17

Adrenergic modulation of cerebellar glial activity during nociception
Seung Ha Kim[1,2], Seung-Eon Roh[1,3], Sun Kwang Kim[3], Sang Jeong Kim[1,2]
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S 73 P3-18

Sex-specific behavioral abnormalities in Tert transgenic mice
Ki Chan Kim[1], Kyu Suk Cho[1], Edson Luck Gonzales[1], Schley Valencia[1], Soo Yeon Kim[2], Kyoung Ja Kwon[1], Chan Young Shin[1]
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S 73 P3-19

Construction of time-evolving pain-related brain network by literature-mining
Jihong Oh, Chang-Eop Kim
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S 73 P3-20

Metabotropic glutamate receptor 5 in the brain governs sensory pain and negative mood symptoms in the spinal nerve injured rats: [11C] ABP688 PET study
Geehoon Chung[1,2], Chae Young Kim[1,3], Sang Jeong Kim[1,2,3,4]
[1]Department of Physiology, Seoul National University College of Medicine, [2]Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, [3]Department of Biomedical Sciences, Seoul National University College of Medicine, [4]Neuroscience Research Institute, Seoul National University College of Medicine

S 74 P3-21

In adolescence, elevation of GABA activity in the ventral hippocampus is related with anxiety- and aggressive- like behavior induced by neonatal maternal separation
Sang Yep Shin, Sun Seek Min
Department of Physiology and Biophysics Eulji University of Medicine, Eulji University, Daejeon, Korea

S 74 P3-22 Pacemaking of midbrain dopamine neurons: role of TRPC3 and NALCN channels
Ki Bum Um[1], Lutz Birnbaumer[2], Hyun Jin Kim[1], Myoung Kyu Park[1]
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S 74 P3-23 Metabotropic glutamate receptor 5 is involved in 0.1 mM $[Mg^{2+}]_o$-induced $[Ca^{2+}]_i$ spikes in cultured rat hippocampal neurons
Su Jeong Jeon, Ji Seon Yang, Yi Jae Hong, Shin Hee Yoon
Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 75 P3-24 Syringaresinol reduces excitatory synaptic transmission and picrotoxin-induced epileptic activity through the presynaptic modulation at the hippocampal CA3-CA1 synapses
Young Seon Cho, Woo Seok Song, Sang Ho Yoon, Kyeong-Yeol Park, Myoung-Hwan Kim
Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine

S 75 P3-25 Purkinje cell specific STAT3 regulates emotional memory formation at excitatory synapses
Jeong-Kyu Han, Sun-Ho Kwon, Yong-Gyu Kim, Seung-Eon Roh, Sang-Kyu Ye, Sang Jeong Kim
Seoul National University College of Medicine

S 75 P3-26 Effect of cell type-specific expression of a RASopathy-associated mutations on learning and memory
Minkyung Kang[1,2], Benjamin G. Neel[3], Yong-Seok Lee[1,2]
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S 75 P3-27 Neuroprotective effects of 3,3'-diindolylmethane on hippocampal neuropathology following pilocarpine-induced status epilepticus
Mi-Hye Kim[1,2], Yeong Ran Hwang[3], Hee Jung Kim[1]
[1]Department of Physiology, College of Medicine, [2]Department of Medical Laser, Graduate School, [3]Department of Biological Sciences, College of Natural Sciences, Dankook University, Cheonan, Korea

S 76 P3-28 Long-term depression of intrinsic excitability accompanied by the synaptic depression in the cerebellar purkinje cells
Hyun Geun Shim[1,2]*, Dong Cheol Jang[1,3]*, Sang Jeong Kim[1,2]
[1]Department of Physiology, [2]Department of Biomedical Science, College of Medicine, [3]Department of Brain and Cognitive Science, College of Natural Science, Seoul National University

S 76 P3-29 Encoding rules for multiple stimulus features of touch and pain in the S1 cortex
Yoorim Kim[1], Chang-Eop Kim[2], Heera Yoon[3], Sun Kwang Kim[3,4], Sang Jeong Kim[1]
[1]Department of Physiology, School of Medicine, Seoul National University, Seoul, [2]Department of Physiology, College of Korean Medicine, Gacheon University, Kyunggi-do, [3]Department of Science in Korean Medicine, Graduate School, Kyung Hee University, Seoul, [4]Department of Physiology, College of Korean Medicine, Kyung Hee University, Seoul, Korea

S 76 P3-30 Effects of resveratrol on the substantia gelatinosa neurons of the subnucleus caudalis in immature mice
Seon Hui Jang, Soo Joung Park, Seong Kyu Han*
Department of Oral Physiology and Institute of Oral Bioscience, School of Dentistry, Chonbuk National University, Jeonju, Jeonbuk, Korea

S 77 P3-31 Activation of pathway-specific synaptic inputs onto layer 5 pyramidal neurons in visual cortex revealed by FM1-43 dye unloading
Kwang-Hyun Cho[1], Kayoung Joo[1], Mina Yoon[1], Hyun-Jong Jang[1,2], Duck-Joo Rhie[1,2]
[1]Department of Physiology, College of Medicine, [2]Catholic Neuroscience Institute, The Catholic University of Korea, Seoul, Korea

S 77 P3-32 Analgesic effects of low frequency stimulator on docetaxel-induced neuropathic pain in mice
Suk-Yun Kang, Yeonhee Ryu, O Sang Kwon, Kwang-Ho Choi, Jun Bum Kim
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S 77 P3-33 Direct experimental evidences for modulation of cortical neural excitability of transcranial direct current stimulation in the intact somatosensory cortex of rats
Min Sun Kim, Ho Koo, Byung Rim Park
Department of Physiology, Wonkwang University School of Medicine

S 78 P3-34 Inhibition of spinal PPAR-gamma affects negative influence to motor function recovery after spinal contusive injury in rats
Youngkyung Kim[1,2], Kyu-Won Park[1], Jeonghwa Oh[1], Junesun Kim[2], Young Wook Yoon[1]
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S 78 P3-35 Layer- and cell type- specific cholinergic regulation of synaptic transmission in pyramidal neurons in the rat visual cortex
Kayoung Joo[1], Mina Yoon[1], Kwang-Hyun Cho[1], Hyun-Jong Jang[1,2], Duck-Joo Rhie[1,2]
[1]Department of Physiology, [2]Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 78 P3-36 Mossy fibre synaptic inputs are privileged to induce long-term potentiation of intrinsic excitability in CA3 pyramidal cells
Kisang Eom[1], Jung Ho Hyun[2], Jaeyoung Yoon[1], Sooyun Kim[1], Won-Kyung Ho[1], Suk-Ho Lee[1]
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S 79 P3-37 Density and output of sweat glands contribute to sudomotor activity in tropical Africans and temperate Koreans
Jeong-Beom Lee[1]*, Young-Ki Min[1], Jeong-Ho Kim[2], Yun Su Eun[2], Jin Wook Kim[2], Seo Yun Jung[2], Suk Min Han[2], Jae Yeong Bae[2], Hee-Jin Lee[3], Mi-Young Lee[3]
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S 79 P3-38 *Cinnamomi Cortex* and its major phytochemicals alleviate oxaliplatin-induced cold and mechanical allodynia in rodents
Ji Hwan Lee[1], Woojin Kim[2], Sun Kwang Kim[1,2]
[1]Department of Science in Korean Medicine, Graduate School, Kyung Hee University, Seoul, [2]Department of Physiology, College of Korean Medicine, Seoul, Korea

S 79 P3-39 Anti-despair-like behavior in RalBP1-mutant mice presumably caused by reduced synaptic inhibition in the hippocampus
Sang Ho Yoon, Kyeong-Yeol Park, Woo Seok Song, Young Seon Cho, Myoung-Hwan Kim
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 79 P3-40 Effects of transcranial direct current stimulation on saturated long-term potentiation in visual cortex of rats
Ho Koo, Byung Rim Park, Min Sun Kim
Department of Physiology, Wonkwang University School of Medicine, Iksan, Korea

S 80 P3-41 Zone-dependency of Purkinje cell Ca^{2+} dynamics originate from zone-dependent heterogeneity of CF input
Seung-Eon Roh[1,3], Seung Ha Kim[1,2], Yong-Gyu Kim[1], Chang-Eop Kim[1], Sun Kwang Kim[3], Sang Jeong Kim[1,2]
[1]Department of Physiology and [2]Department of Biomedical Science, College of Medicine, Seoul National University, [3]Department of Physiology, College of Korean Medicine, Kyung Hee University, Seoul, Korea

S 80 P3-42 Presynaptic mitochondrial calcium release enhances short-term facilitation during brief high-frequency stimulation
Che Ho Yang, Won-Kyung Ho, Suk-Ho Lee
Department of Physiology, Seoul National University College of Medicine

S 80 P3-43 The role of cerebellar Purkinje cell's intrinsic excitability in fear conditioning
Jaegeon Lee, Dong Cheol Jang, Hyun Geun Shim, Myeong-seong Bak, Sang Jeong Kim
Department of Physiology Seoul National University College of Medicine

S 80 P3-44 Phenylalanine facilitates long-term depression in the hippocampus
Woo Seok Song, Sang Ho Yoon, Young Seon Cho, Kyeong-Yeol Park, Myoung-Hwan Kim
Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 81 P3-45 Distinctive firing properties of pyramidal neurons in infralimbic and prelimbic areas of medial prefrontal cortex
Jaehan Kwon, Weonjin Yu, Suk Ho Lee, Won-Kyung Ho
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

P4: Molecular Physiology

S 81 P4-01 (PO-B-04) WNK1-mediated Ca^{2+} signaling is a novel culprit for hepatic stellate cell activation and fibrosis
Kyu-Hee Hwang[1-4], Ji-Hee Kim[1,3,4], Soo-Jin Kim[1-4], Hung Minh Tran[1-4], In Deok Kong[1-3], Kyu-Sang Park[1-4], Seung-Kuy Cha[1-4¶]
Departments of [1]Physiology and [2]Global Medical Science, [3]Institute of Lifestyle Medicine, and [4]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Korea

S 81 P4-02 (PO-A-07) The E3 ligase c-Cbl inhibits cancer cell migration by neddylating the proto-oncogene c-Src
Gun-Woo Lee[1], Jun Bum Park[1], Sung Yeon Park[2,3], Seo Jieun[1], Seung-Hyun Shin[1], Jong-Wan Park[1,2], Sang Jung Kim[1,2,3], Masatoshi Watanabe[4], Yang-Sook Chun[1,2,3]*
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S 81 P4-03 TRPC6 regulate NFATc1 and TLR signaling in osteoclastogenesis
Yu-Mi Yang, Dong Min Shin
Department of Oral Biology, Yonsei University College of Dentistry, Seoul, Korea

S 82 P4-04 Activation of transient receptor potential melastatin 7 (TRPM7) channel increases basal autophagy and reduces amyloid β-peptide
Hyun Geun Oh, Sungkwon Chung
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 82 P4-05 Gas6 inhibit epithelial-mesenchymal transition in lung alveolar epithelial cells
Ji-Hae Jung, Young-So Yoon, Ye-Ji Lee, Jihee Lee Kang
Department of Phsysiology, Tissue Injury Defense Research Center, School of Medicine, Ewha Womans University, Seoul, Korea

S 82 P4-06

Simvastatin treatment boosts benefits of apoptotic cell infusion in murine lung fibrosis
Ye-Ji Lee, Meung-Joo Kim, Ji-Hye Jung, Young-So Yoon, Youn-Hee Choi, Jihee Lee Kang
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S 82 P4-07

Exposure of macrophages to apoptotic cells inhibits lung fibroblast invasion
Yong-Bae Kim[1], Jihee Lee[1,2]
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S 83 P4-08

Downregulation of mitochondrial PDP1 is required for the early stage differentiation of embryonic stem cell to cardiac myocytes
Hyoung Kyu Kim, Hye Jin Heo, Jin Han
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S 83 P4-09

Cardiac mitochondrial metabolism and function
Jin Han
National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 83 P4-10

Low-intensity ultrasound decreases high glucose- and sodium nitroprusside-induced nitric oxide generation in the human retinal pigment epithelial cells
Mrigendra Bir Karmacharya[1], Binika Hada[2], Byung Hyune Choi[2], So Ra Park[1]*
[1]Department of Physiology and Biophysics, [2]Department of Biomedical Sciences, Inha University College of Medicine, Incheon, Korea

S 84 P4-11

Novel function of Jumonji C (JmjC) domain-containing protein in osteoclastogenesis
Seon-Young Kim[1], Hye-Jin Kim[1], Do Won Jung[1], Jong-Wan Park[2], Yang-Sook Chun[1,2]
[1]Department of Physiology, [2]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

S 84 P4-12

Leptin suppresses glutamate-induced apoptosis through regulation of ERK1/2 signaling pathways in rat primary astrocytes
Hyunju Park, So-Hee Ahn, Yieun Jung, Joo Chun Yoon, Youn-Hee Choi*
Departments of Physiology, Tissue Injury Defense Research Center, Ewha Womans University School of Medicine

S 84 P4-13

Minor ginsenosides inhibits growth, migration and invasion of neuroblastoma cells via caspase activation and suppressing epithelial mesenchymal transition
Jung Mi Oh[1], Hye Lan Kim[1], Jung-woo Lee[2], Sungkun Chun[1]
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S 84 P4-14

CRIF-1 deficiency increases senescence through SIRT3 pathway in endothelial cells
Seonhee Kim[1,2,3], Shuyu Piao[1,2,3], Harsha Nagar[1,2,3], Su-jeong Choi[1,2,3], Ik jun Lee[1,3], Sungmin Kim[1,3], Saet-byel Jung[1,4], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,5], Cuk-seong Kim[1,2,3]*
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S 85 P4-15

Minor Rh3 induces apoptotic cell death in SK-N-BE (2) human neuroblastoma cells through a caspase-dependent pathway
Jung Mi Oh[1], Hye Lan Kim[1], Jung-woo Lee[2], Sungkun Chun[1]
[1]Department of Physiology, [2]Department of Anesthesiology and Pain Medicine, Chonbuk National University Medical School, Jeonju, Korea

S 85 P4-16

Glucocorticoid receptor positively regulates transcription of FNDC5 in the liver
Hyoung Kyu Kim, Min Kim, Jin Han*
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S 85 P4-17

Mitochondrial molecular targets of nobiletin in the neuroprotective mechanism in primary cortical neurons and isolated brain mitochondria
Khulan Amarsanaa, Ji Hyung Lee, Sung-Cherl Jung, Su-Yong Eun
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S 85 P4-18

Functional roles of P2X7 receptor and NALP3 inflammasome in head and neck cancer
Sangwoo Lee, JuYoung Bae, Kyungpyo Park*
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S 86 P4-19

Role of NEDDylation pathway in non alcoholic fatty liver disease
Uk-Il Ju[1], Do-Won Jeong[1], Jong-Wan Park[1,2], Yang-Sook Chun[1,2,3]
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S 86 P4-20

Valproic acid promotes caspase-dependent apoptosis and autophagy in human lung cancer cells
Bo Ram Han, Hyun Kyung Park, Woo Hyun Park*
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S 86 P4-21

Crif1 deficiency inhibits keloid fibroblasts migration, proliferation and extracellular matrix synthesis
Sungmin Kim[1,2,3,4], Su-jeong Choi[1,2,3], Harsha Nagar[1,2,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Ikjun Lee[1,2,3], Byeong Hwa Jeon[1,3], Sang-Ha Oh[4], Cuk-Seong Kim[1,2,3]*
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S 87 P4-22

CR6 interacting factor-1 linked with tetrahydrobiopterin deficiency and endothelial nitric oxide synthase uncoupling
Ikjun Lee[1,2,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Harsha Nagar[1,2,3], Su-Jeong Choi[1,2,3], Sung-min Kim[1,2,3], Saet-byel Jung[1,4], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,5], Cuk-Seong Kim[1,2,3]*
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S 87 P4-23

Treatment of valproic acid enhances arsenic trioxide-induced cell death in human large cell lung cancer cells
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Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Korea

S 87 P4-24

Regulation of lipocalin-2 expression by nitric oxide under inflammatory condition in RINm5F islet beta-cells
Seo-Yoon Chang, Hyun-Jong Jang, Yang-Hyeok Jo, Myung-Jun Kim
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S 87 P4-25

Role of PHF2 in the development of non-alcoholic fatty liver disease
Do-Won Jeong[1], Kyoung-Hwa Lee[2], Yang-Sook Chun[1,2]
[1]Department of Physiology, [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 88 P4-26

Inhibitory effect of corylifol C on RANKL-induced osteoclast differentiation and bone resorption
Jung Yun Kang, Inik Chang, Dong Min Shin
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S 88 P4-27

Negative regulation of Wnt/β-catenin signaling pathway by SIRT 6 inhibits the growth and metastasis in hepatocellular carcinoma
Hua Jin, Soo Mi Kim*
Department of Physiology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Korea

S 88 P4-28

Identification of cytokines that induce cisplatin resistance and migration secreted from macrophage
Taehee Kim, Sang Do Lee
Department of Physiology, Department of thoracic surgery, Chungnam National University School of Medicine, Daejeon, Korea

S 89 P4-29

Inactivation of YAP by rhBMP-2 suppresses the proliferation of human colorectal cancer cell
Yu Chuan Liu, Soo Mi Kim*
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 89 P4-30

The effect of macrophage-secreted IL-1β on migration in lung cancer A549 cells
Han Na Choi, Taehee Kim, Sang Do Lee
Department of Physiology, Department of thoracic surgery, Chungnam National University School of Medicine, Daejeon, Korea

S 89 P4-31

Activation of TTP by resveratrol suppresses the growth and invasion of colorectal cancer cells
Hua Jin, Soo Mi Kim*
Department of Physiology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Korea

S 89 P4-32

Protein kinase C beta II induces endothelial dysfunction via mitochondrial ROS generation in HUVECs
Hee Kyoung Joo[1], Yu Ran Lee[1], Eun Ok Lee[1], Myoung Soo Park[2], Sunga Choi[1], Cuk-Seong Kim[1], Byeong Hwa Jeon[1]
[1]Research Institute for Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, Daejeon, [2]Preclinical Research Center, Chungnam National University Hospital, Daejeon, Korea

S 90 P4-33

Activation of SREBP signaling by HN1 promotes the growth and metastasis in hepatocellular carcinoma
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S 90 P4-34

Role of collagen triple helix repeat containing-1 in esophageal adenocarcinoma cells
Soo Mi Kim*
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S 90 P4-35

Inactivation of Akt by UA induced apoptosis in esophageal cancer cells
Ruo Yu Meng, Soo Mi Kim*
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S 90 P4-36

SOX12 is involved in sphingosylphosphorylcholine-induced smooth muscle-like cell differentiation of human mesenchymal stem cells via reactive oxygen species
Suji Baek[1], Kang Pa Lee[1], Seung Hyo Jung[1], Yunkyoung Ryu[1], Hwan Myung Lee[2], Kyung Jong Won[1], Bokyung Kim[1]
[1]Department of Physiology, School of Medicine, Konkuk University, Seoul, [2]Department of Cosmetic Science, College of Life and Health, Hoseo University, Asan, Korea

S 91 P4-37 αKlotho ameliorates diabetic nephropathy via stabilizing podocyte Ca^{2+} signaling
Ji-Hee Kim[1,3,4], Kyu-Hee Hwang[1-4], Hung Minh Tran[1-4], In Deok Kong[1-3], Kyu-Sang Park[1-4], Seung-Kuy Cha[1-4¶]
Departments of [1]Physiology and [2]Global Medical Science, [3]Institute of Lifestyle Medicine, and [4]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Korea

S 91 P4-38 Tau-mediated circadian rhythm disruption and cognitive dysfunction in Alzheimer's disease mouse model
Ahbin Kim[1], Ji Hyun Park[2], Haeng Jun Kim[1], Hyundong Song[1], Sehyung Cho[2], Inhee Mook-Jung[1#]
[1]Department of Biochemistry & Biomedical Science, College of Medicine, Seoul National University, Seoul, [2]College of Medicine, Kyunghee University, Seoul, Korea

S 91 P4-39 In vitro trans-differentiation of primary mouse hepatic stellate cells via TGF-β-ERK-mTOR axis
Soo-Jin Kim, Ranjan Das, Luong Dai Ly, Nhung Thi Nguyen, Kyu-Hee Hwang, Ji-Hee Kim, Seung-Kuy Cha, Kyu-Sang Park
Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea

S 91 P4-40 Role of mitochondrial phosphate transporters in vascular calcification
Nhung Thi Nguyen, Tuyet Thi Nguyen, Soo-Jin Kim, Luong Dai Ly, Seung-Kuy Cha, Kyu-Sang Park
Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea

S 92 P4-41 Association of mGluR-dependent LTD at excitatory synapses with endocannabinoid-dependent LTD of inhibitory synapses leads to EPSP to spike potentiation at Schaffer collateral-CA1 synapses
Hye-Hyun Kim[1,2,3], Joo Min Park[4], Suk-Ho Lee[1,2,3], Won-Kyung Ho[1,2,3*]
[1]Department of Physiology, [2]Biomembrane Plasticity Research Center, [3]Neuroscience Research Center, Seoul National University College of Medicine, Seoul, [4]Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Korea

S 92 P4-42 Investigation of physiological function of the murine bitter taste receptor Tas2r108
Su-Young Ki, Ki-Myung Chung, Young-Kyung Cho, Kyung-Nyun Kim
Department of Physiology and Neuroscience, College of Dentistry and Research Institute of Oral Sciences, Gangneung-Wonju National University, Gangneung, Korea

S 92 P4-43 Hepatoprotective effects of oyster-derived Tyr-Ala peptide on fulminant hepatitis
Adrian S. Siregar[1,2], Soo Buem Cho[3], Eun-Jin Kim[1], Chengliang Xie[4], Marie Merci Nyiramana[1,2], Si-Hyang Park[5], Dae Hyun Song[6], Nam-Gil Kim[7], Yeung Joon Choi[8], Sang Soo Kang[4], Dawon Kang[1,2]
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S 93 P4-44 The intracellular Ca^{2+} channel TRPML3 is a PtdIns3P effector that regulates early autophagosome biogenesis
So Woon Kim[1], Mi Kyung Kim[1], Kyoung Sun Park[2], Hyun Jin Kim[1]
[1]Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, [2]Wide River Institute of Immunology, Seoul National University College of Medicine, Gangwon-do, Korea

S 93 P4-45 Palmitoylation controls trafficking of the intracellular Ca^{2+} channel TRPML3 to regulate autophagy
Dong Hyun Kim, Yun Min Park, Mi Kyung Kim, So Woon Kim, Hyun Jin Kim
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 93 P4-46 Role of endothelin-2 in renal cell carcinoma
SeulKi Kim, InIk Chang, Dong Min Shin
Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul, Korea

S 93 P4-47 Role of physiological ET-1 in bone remodeling
Ji su Sun, Dong Min Shin, Inik Chang
Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul, Korea

S 94 P4-48 Inhibition of neddylation facilitates cell migration through enhanced phosphorylation of caveolin-1 in PC3 and U373 cells
Sung Yeon Park, Yang-Sook Chun
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 94 P4-49 Familial Alzheimer's presenilin 1 mutation elevate cellular cholesterol levels and facilitates lipid raft localization of β-amyloid precursor protein
Yoon Young Cho, Oh-Hoon Kwon, Hyun Geun Oh, Sungkwon Chung
Department of Physiology, Sungkyunkwan University School of Medicine

S 94 P4-50 Insulin increases O-GlcNAcylation of amyloid precursor protein promoting its non-amyloidogenic processing
Oh Hoon Kwon, Sungkwon Chung
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 94 P4-51 Characterization of molecular mechanisms underlying voltage-gated Ca^{2+} channel modulation by DREADD
Yong-Seuk Kim, Byung-Chang Suh
Department of Brain & Cognitive Sciences, DGIST, Daegu, Korea

P5: Exercise & Endocrine Physiology

S 95 P5-01

The effect of fibroblast growth factor receptor signaling inhibition during resistance training on muscle and bone quality in mice

Suhan Cho[1], Hansol Song[1], Byoung Hun So[1], Min-ji Kang[1], Hoyoun Kim[1], Didi Zhang[1], Youn Ju Kim[2,4], Ho-Young Lee[3], Je Kyung Seong[2,4], Wook Song[1,5]

[1]Health and Exercise Science Laboratory, Institute of Sport Science, Seoul National University, Seoul, [2]Laboratory of Developmental Biology and Genomics, Institute of Veterinary Science, and BK21 Program for Veterinary Science, College of Veterinary Medicine, Seoul National University, Seoul, [3]Department of Nuclear Medicine, Seoul National University Bundang Hospital, Seung-Nam, [4]Korea Mouse Phenotyping Center (KMPC), Seoul National University, Seoul, [5]Institute on Aging, Seoul National University, Seoul, Korea

S 95 P5-02

VEGF-A expressing adipose tissue shows rapid beiging, enhanced survival after transplantation and confers IL4-independent metabolic improvements

Min Kim[1], Jiyoung Park[2], Philipp Scherer[3], Jin Han[1]

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S 95 P5-03

Toxicological evaluation of dithiocarbamate fungicide mancozeb in vivo

Hye Yeon Park[1], Seung Hee Choi[1], Nara Kim[1], Hwa-Kyoung Chung[1], Seong-Chun Kwon[1], Daeho Kwon[2], Jae Seok Song[3], Byong-Gon Park[1]

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S 96 P5-04

Effects of exercise training on muscle damage, muscle fatigue, and mitochondrial function in atorvastatin-treated rat skeletal muscles

Jun-Won Heo[1,2], Mi-Hyun No[1,2], Su-Sie Yoo[1,2], Jae-Ho Yang[1,2], Dong-Ho Park[1,2], Ju-Hee Kang[2,3], Dae-Yun Seo[4], Jin Han[4], Chang-Ju Kim[5], Hyo-Bum Kwak[1,2]*

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S 96 P5-05

The effects of neuroimmune cytokines and neurotrophins by exercise in aging rats

Nayoung Ahn[1], Kijin Kim[1], Changhyun Lim[2], Changkeun Kim[2]

[1]Keimyung University, [2]Korea National Sport University

S 96 P5-06

Effects of exercise on cardiac contractility in mouse heart

Tae Hee Koh, Jubert Marquez, Hyoung Kyu Kim, Ji Min Park, Young Deok Seo, Su-Bin Song, Ja Eun Ahn, Hyun Jin Ahn, Chanbo Eun, Jin Han, Jae Boum Youm

Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University

S 97 P5-07

The body weight difference between dual energy X-ray absorptiometry and multi-frequency bioelectrical impedance analysis attenuates the equivalence of the body composition assessment

Duong Duc Pham[1], Seung Ku Lee[3], Chol Shin[2,3]*, Nan Hee Kim[4], Chae Hun Leem[1]*

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S 97 P5-08

Effects of combined treatment of chiropractic and isometric exercise on static balance and dynamic balance in subject of cervical alignment

Il-Yong Park, Jae-Ho Khil

Department of Sports Medicine, Kyung Hee University College of Physical Education

S 97 P5-09

Exercise training improves erectile function in aged rat

Dae Yun Seo[1], Sung Ryul Lee[1], Hyo Bum Kwak[2], Hyuntea Park[3], Hyun Seok Bang[4], Kyo Won Seo[1], Yeon Hee Noh[1], Kang-Moon Song[5], Ji-Kan Ryu[5], Kyung Soo Ko[1], Byoung Doo Rhee[1], Jin Han[1]*

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S 98 P5-10

Effects of exercise training on serum level of sclerostin in breast cancer survivors

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S 98 P5-11

High electrical stimulation of WB-EMS improves adipocytokines, body composition, and isokinetic strength in collegiate male students

Yong-Seok Jee[1], Chan-Bok Lee[1,2], Jae-Wan Park[1], Kang-Ho Kim[1], Jeong-Hoon Jang[1], Eui-Han Pak[1], Jung-Min Park[1,2], Il-Gyu Ko[1,2], Denny Eun[1]

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P6: Diet, Phytochemicals

S 99 P6-01

Spirodela polyrhiza and its chemical constituents vitexin exert anti-allergic effects *via* ORAI1 channel inhibition
Yu-Ran Nam[1,2], Hyun Jong Kim[1,2], Joo Hyun Nam[1,2]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Gyeonggi-do, Korea

S 99 P6-02

Spirodela polyrrhiza extract and its flavonoid luteolin inhibit Cl^- secretion in human airway epithelial cells *via* the calcium-dependent Cl^- channel anoctamin-1
Hyun Jong Kim[1,2], Yu-Ran Nam[1,2], Joo Hyun Nam[1,2]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Gyeonggi-do, Korea

S 99 P6-03

Acceleration of skin barrier restoration by Korean herbs via transient receptor potential V3
Yu-Ran Nam[1,2], Woo Kyung Kim[2,3], Joo Hyun Nam[1,2]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Gyeonggi-do, [3]Department of Internal Medicine, Graduate School of Medicine, Dongguk University, Goyang, Gyeonggi-do, Korea

S 99 P6-04

Systems-level mechanisms of action of *Panax ginseng*: a network pharmacological approach
Sa-Yoon Park[1], Ji-Hun Park[1], Hyo-Su Kim[1], Choong-Yeol Lee[1], Hae-Jeung Lee[2], Ki Sung Kang[3]*, Chang-Eop Kim[1]*
[1]Department of Physiology, College of Korean Medicine, Gachon University, [2]Department of Food and Neutrition, Colledge of BioNano Technology, Gachon University, [3]Department of Preventive Medicine, College of Korean Medicine, Gachon University

S 100 P6-05

Sargacromenol D from Sargassum siliquastrum as a novel selective L-type Ca^{2+} channel blocker
Won-Chul Cho[1], Hwa-Kyoung Chung[2], Nara Kim[2], Seong-Chun Kwon[2], Woon-Seob Shin[3], Seokjoon Lee[4], Byong-Gon Park[2]
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S 100 P6-06

Novel synthetic antihypertensive agents from the marine naturo-mimetics
Nara Kim[1], Hwa-Kyoung Chung[1], Seong-Chun Kwon[1], Woon-Seob Shin[2], Seokjoon Lee[3], Byong-Gon Park[1]
[1]Department of Physiology, [2]Microbiology, [3]Pharmacology, College of Medicine, Catholic Kwandong University, Korea

S 100 P6-07

Symptom regulating effects of *Quisqualis indica linn* in benign prostatic hyperplasia rat model
Dae-geon Kim[1], Joo-heon Kim[1,2], Kyu-pil Lee[3]
[1]Department of Veterinary Physiology, College of Veterinary Medicine, Gyeongsang National University, Jinju, [2]Institute of Animal Medicine, College of Veterinary Medicine, Gyeongsang National University, jinju, [3]Department of Veterinary Physiology, College of Veterinary Medicine, Chungnam National University, Daejeon, Korea

S 101 P6-08

Echinochrome A increase the mass and function of the mitochondria by upregulation of mitochondria biogenesis genes
Joon Yong Noh, Seung Hun Jeong, Hyoung Kyu Kim, Yeon Hee Noh, Jubert Marquez, Kyung Soo Ko, Byoung Doo Rhee, Nari Kim, Jin Han
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S 101 P6-09

HS1793 compound activates PGC-1α via AKT/mTOR signaling and improves mitochondrial biogenesis and function in mouse skeletal muscle cell model
Jubert Marquez, Jin Han#
Department of Physiology, BK21 Plus Project Team, Cardiovascular and Metabolic Disease Center, College of Medicine, Inje University, Busan, Korea

S 101 P6-10

Polygoni avicularis (*polygonum aviculare* L.) improves diabetic nephropathy in db/db mice
Ji Hun Park[1,2], Hye Yoom Kim[1,2], So Young Eun[1,2], Byung Hyuk Han[1,2], Eun Sik Choi[1,2], Yun Jung Lee[1,2], Ho Sub Lee[1,2], Dae Gill Kang[1,2]*
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S 101 P6-11

Ojeoksan suppressed TNF-α-induced vascular inflammation in human umbilical vein endothelial cells
Byung Hyuk Han[1,2], You Mee Ahn[1,2], So Young Eun[1,2], Ji Hun Park[1,2], Chan Ok Son[1,2], Yun Jung Lee[1,2], Dae Gill Kang[1,2], Ho Sub Lee[1,2]*
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S 102 P6-12

Dianthus superbus attenuates angiotensin II-induced glomerular fibrosis in human renal mesangial cells
Jung Joo Yoon[1,2], Byung Hyuk Han[1,2], Ji Hun Park[1,2], Da Hye Jeong[1,2], Chan Ok Son[1,2], Yun Jung Lee[1,2], Ho Sub Lee[1,2], Dae Gill Kang[1,2]*
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S 102 P6-13 Korean red ginseng ameliorates high fat/high cholesterol diet-induced hypertriglyceridemia and endothelial dysfunction
Hye Yoom Kim[1,2], Xian Jun Jin[1,2], Mi Hyeon Hong[2,3], Seon Mi Ko[4], Seung Mi Hwang[4], Dong joong Im[4], You Mee Ahn[1,2], Hyun Ju Kim[1], Ho Sub Lee[1,2], Dae Gill Kang[1,2], Yun Jung Lee[1,2]*
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S 102 P6-14 *Chrysanthemum boreale* makino essential oil and its single compound sabinene alleviates starvation-induced atrophy in L6 cells
Yunkyoung Ryu[1], Long Cui[1], Seung Hyo Jung[1], Suji Baek[1], Kang Pa Lee[1], Junghwan Kim[2], Kyung Jong Won[1], Bokyung Kim[1]
[1]Department of Physiology, School of Medicine, Konkuk University, Chungju, [2]Department of Physical Therapy, College of Public Health & Welfare, Yongin University, Yongin, Korea

S 103 P6-15 *Flos Magnoliae* and its chemical constituents modulates Cl^- secretion *via* ANO1 Cl^- channel inhibition in human airway epithelial cells
Hyun Jong Kim[1,2], Yu-Ran Nam[1,2], Yung Kyu Kim[1], Joo Hyun Nam[1,2]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Gyeonggi-do, Korea

P7: Other Areas

S 103 P7-01 (PO-B-07) Mesothelial cells demarcate the subunits of organ surface primo vascular tissue
Chae Jeong Lim[1], Yeo Sung Yoon[2], So Yeong Lee[1], Pan Dong Ryu[1]
Departments of [1]Veterinary Pharmacology and [2]Anatomy & Cell Biology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

S 103 P7-02 Sex difference of feeding behavior and gastrointestinal function in response to stress in rat
Min Seob Kim, Yong Sung Kim, Han-Seung Ryu, Suck Chei Choi, Mi-sung Park, Seong Hoon Park, Joong Goo Kwon, Moon Young Lee
Wonkwang University, Korea, Iksan, Catholic University of Daegu

S 103 P7-03 The effects of aerobic circulation on the body composition of obese men consuming LCHF
Uichol Kwon
Kongju Nationnal University

S 104 P7-04 Necrox-5 exerts anti-inflammation and regulates mitochondrial biogenesis in hypoxia-reoxygenation (HR) treated rat hearts
Nguyen Thi Tuyet Anh[1], H. K. Kim[1], T. T. Vu[1,2], S. R. Lee[1], J. Marquez[1], N. Kim[1], K. S. Ko[1], B. D. Rhee[1], J. Han[1]
[1]National Research Laboratory for Mitochondrial Signaling, Cardiovascular and Metabolic Disease Center, Department of Medicine, BK21 Project Team, Department of Physiology, Inje University, Busan, Korea, [2]VNU University of Science, Hanoi, Vietnam

S 104 P7-05 ^{1}H-NMR-based metabolomic studies of bisphenol A in zebrafish (Danio rerio)
Changshin Yoon[1,2], Dahye Yoon[1], Junghee Cho[1], Siwon Kim[1], Heonho Lee[1], Hyeonsoo Choi[1], Suhkmann Kim[1]
[1]Department of Chemistry, Center for Proteome Biophysics and Chemistry Institute for Functional Materials, Pusan National University, Busan, [2]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Korea

S 104 P7-06 Morphological changes in organ surface primo vascular tissue in the rats with anemia
Yiming Shen, Chae Jeong Lim, So Yeong Lee, Pan Dong Ryu
Department of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

S 105 P7-07 Histological features of the hyaluronic acid-rich tissue in subcutaneous layer of rat abdomen
Chae Jeong Lim, So Yeong Lee, Pan Dong Ryu
Department of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

S 105 P7-08 Sea hare hydrolysates induce M1 macrophage polarization
In-Seok Jang[1], Marie Merci Nyiramana[2,3], Ji Hyeon Ryu[3], Eun-Jin Kim[3], Adrian S. Siregar[2,3], Hyun Jae Nam[4], Chang Hyun Lee[4], Jae Seok Lee[3], James Hong[5], Si-Hyang Park[6], Yeung Joon Choi[7], Min-Kyoung Shin[8], Jaehee Han[2,3], Dawon Kang[2,3]
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S 105 P7-09 The monosodium iodoacetate (MIA) injection into intervertebral disc of rat accelerate disc degeneration
Hye Rim Suh, Eui Ho Park, Sun Wook Moon, Hee Chul Han
Department of Physiology, College of Medicine and Neuroscience Research Institute, Korea University, Seoul, Korea

S 106 P7-10 Typing individual breast cancer patients using genomic modules activated in normal breast tissue
Hye Young Kim[1,2], Jin Hyuk Kim[1]
[1]Department of Physiology, [2]Institute of Medical Science, Hanyang University, Seoul, Korea

S 106 P7-11 Adipose-derived stem cells enhance phagocytic activity of peripheral blood mononuclear cells in a rat model of atopic dermatitis
Jaehee Lee[1], Leejin Park[2], Hyeyoung Kim[1], Bong-il Rho[2], Rafael Taeho Han[1], Seung Keun Back[3], Heung Sik Na[1]
[1]Neuroscience Research Institute and Department of Physiology, Korea University College of Medicine, Seoul, [2]Glovi Plastic Surgery Clinic, [3]Department of Pharmaceutics & Biotechnology, College of Medicine Engineering, Konyang University, Chungnam, Korea

S 106 P7-12 Expression of interleukin-33 induced by inflammatory cytokines in mouse macrophages
Jeongyoon Choi, Hyoweon Bang
Department of Physiology, College of Medicine, Chung-Ang University

S 107 P7-13 Brain function (effects of physical exercise and calorie restriction)
Yi Sub Kwak
Department of Physical Education, Dong-Eui University, Busan, Korea

Plenary Lecture

Memory, circuits, and cognitive failure in Alzheimer's disease

Paul Worley

Department of Neuroscience, Johns Hopkins University School of Medicine, USA

Memory loss in Alzheimer's disease (AD) is attributed to pervasive weakening and loss of synapses. I will present our recent work that indicates a special role for excitatory synapses connecting pyramidal neurons of the hippocampus and cortex with fast-spiking parvalbumin (PV) interneurons. These synapses mediate feed forward inhibition and control network excitability and brain rhythmicity important for memory. Excitatory synapses on PV interneurons are dependent on the AMPA receptor subunit GluA4, which is regulated by presynaptic expression of the synaptogenic immediate early gene NPTX2 by pyramidal neurons. In a mouse model of AD amyloidosis, *Nptx2*$^{-/-}$ results in reduced GluA4 expression, disrupted rhythmicity, and increased pyramidal neuron excitability. Postmortem human AD cortex shows profound reductions of NPTX2 and coordinate reductions of GluA4. NPTX2 in human CSF is reduced in subjects with AD and shows robust correlations with cognitive performance and hippocampal volume. These findings implicate failure of adaptive control of pyramidal neuron-PV circuits as a pathophysiological mechanism contributing to cognitive failure in AD.

CURRICULUM VITAE

Name: Paul Worley

Position Title: Professor

Education/Training

1976	B.A. & M.A., Chemistry, Johns Hopkins University, Baltimore, MD
1980	M.D., Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

Personal Statement

Paul Worley's laboratory examines the molecular basis of learning and memory, with special focus on mechanisms that are dependent on rapid, de novo mRNA and protein synthesis. The Worley laboratory identified a set of immediate early genes (IEGs) that are rapidly transcribed in neurons involved in information processing, and that are essential for long-term memory. Studies define how IEG proteins can directly modify synapses, and provide insight into cellular mechanisms that support synapse-specific plasticity. Examples of these IEGs include Homer, which plays a role in coupling of multi-protein machines involved in dopamine receptor and glutamate receptor signaling; Arc, which associates with endosomes that function in trafficking of glutamate receptors, amyloid precursor protein (APP), BACE1 and γ-secretase; Narp, which is a secreted glycoprotein and lectin that induces excitatory synapse formation and mediates homeostatic control of inhibitory networks; Rheb, which associates with mTor (target of rapamycin) and is essential in activation of the mTORC1 complex; and LanCL1, which is a glutathione binding protein that promotes glutathione transferase activity and is essential for postnatal neuronal survival. Ideas that have emerged from this work include the notion that the IEG response modulates neuronal function by altering signaling outputs of group 1 metabotropic glutamate receptors (mGluR1/5), that IEGs mediate homeostatic scaling and neuromodulator-dependent plasticity. Current studies indicate that IEGs play an important role in drug addiction and the pathogenesis of diseases of cognition, especially Alzheimer's disease (AD) and autism. A hypothetical model that integrates IEG synaptic functions and distinctive time courses of action proposes that IEGs mediate sequential "check points" in a cellular process of information storage that progressively reduces "noise" by weakening relatively inactive synapses and circuits, while conditionally strengthening active circuits.

Dr. Worley has served the Neuroscience community as a past regular member of NIH study section and currently as a regular member of Molecular and Cellular Substrates of Complex Brain Disorders ZRG1 MDCN-P(57) and ad hoc member of the Board of Scientific Councilors for NINDS. Dr. Worley has helped train several students and postdoctoral fellows who are now productive scientists in academic or NIH positions including Constance Smith-Hicks (URM) Assistant Prof Johns Hopkins Hospital, Katrin Andreasson Prof Stanford, Paul Brakeman Medical Director Pediatric Dialysis UC San Francisco, John Guzowski, Associate Prof UC Irvine, Jason Shepherd Assistant Prof Univ Utah, Guo Huang Assistant Prof UC San Francisco, Sungjin Park Assistant Prof Univ Utah, Sang Jeong Kim Prof Seoul National Univ, Shin Kang Assistant Prof Temple Univ, Joseph Yuan Assistant Prof Univ N. Texas, Jia Hua Hu Staff Scientist NINDS, Jing Wu Staff Scientist NHLBI.

Positions and Honors

1980–1981	Internal Medicine Osler Intern, Johns Hopkins Hospital
1981–1984	Neurology Resident, and Chief Resident, Johns Hopkins Hospital
1984–1988	Instructor, Department of Neurology, Johns Hopkins Hospital
1988–1991	Assistant Professor, Department of Neurology, Johns Hopkins Hospital
1991–1994	Assistant Professor, Department of Neuroscience, Johns Hopkins School of Medicine
1994–1999	Associate Professor, Department of Neuroscience, Johns Hopkins School of Medicine
1999–Present	Professor, Department of Neuroscience, Johns Hopkins School of Medicine

S-I-1

Dual action of the $G\alpha_q$-PLCβ-PI(4,5)P_2 pathway on TRPC1/4 and TRPC1/5 heterotetramers

Jongyun Myeong[1], Juyeon Ko[1], Misun Kwak[1], Kodaji Ha[1], Chansik Hong[2], Dongki Yang[3], Hyun Jin Kim[4]*, Ju-Hong Jeon[1], Insuk So[1]*

[1]Department of Physiology, Seoul National University College of Medicine, [2]Department of Physiology, Chosun University School of Medicine, [3]Department of Physiology, College of Medicine, Gachon University, [4]Department of Physiology, Sungkyunkwan University School of Medicine, Korea

The transient receptor potential canonical (TRPC) 1 channel is widely distributed in mammalian cells and is involved in many physiological processes. TRPC1 is primarily considered a regulatory subunit that forms heterotetrameric channels with either TRPC4 or TRPC5 subunits. Here, we suggest that the self-limiting regulation of TRPC1/4 and TRPC1/5 heterotetrameric channels by the $G\alpha_q$-PLCβ pathway is dynamically mediated by PI(4,5)P_2. We provide evidence indicating that $G\alpha_q$ protein directly interacts with either of the heteromeric channels to permit activation. Simultaneously, $G\alpha_q$-coupled PLCβ activation leads to the breakdown of PI(4,5)P_2, which inhibits activated TRPC1/4 and 1/5 channels. The subsequent increase in cytoplasmic Ca^{2+} due to Ca^{2+} release from the endoplasmic reticulum (ER) and activation of PKC resulted in a second phase of channel inhibition.

Key Words: TRPC1/4, TRPC1/5, G alpha q, PIP_2, Calcium, PKC

S-I-2

Functional role of coiled coil domain in the gating of TRPC3/6

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Gating mechanisms of TRPC (transient receptor potential channel, canonical) cation channel family is suggested to be influenced by several factors including PLC downstream second messengers, STIM1, Calmodulin, redox signals, physiological Ca^{2+}concentration and store depletion of Ca^{2+}. However, the mechanisms by which those factors involve in gating of the TRPC channels still remains enigmatic.TRPC3 possess a N terminus (NT) and a C terminus CCD (CT) were predicted. We presented a Ca^{2+}dependent allosteric gating mechanism of TRPC3 by the CT putative coiled coil domain (CCD). The CT CCD displayed electrophysiological changes in the regulation by STIM1 in addition to changes in the current-voltage relationship (IV curve) which is independent to STIM1. CT CCD mutant not only changed the IV curve, even increased Ca^{2+} permeability and had lower response to calmodulin. The phenotype of mutation was limited within the CCD of the predicted sequence of C-terminus from 804 till 816. These findings support a model in which the TRPC3 CT CCD confer the mechanism of Ca^{2+} dependent inactivation and Ca^{2+} selectivity of TRPC3.
Mutations in TRPC6 have been identified to cause focal segmental glomerulosclerosis (FSGS) in human patients. A total of 18 substitution mutants and a one deletion mutant have been reported from human patients with FSGS. These mutations are distributed from amino-terminus (NT) to Carboxyl terminus (CT) and located in key function sites such as Ankyrin repeats (AKR), NT coiled coil domain (NT CCD), Transmembrane regions (TM), putative calmodulin- and IP3R-binding domain (CIRB) and CT coiled coil domain (CT CCD). However, majority of these mutants are localized in AKR and CT CCD. Interestingly, these mutants display a gain of function as well as CT CCD mutants in TRPC3.
These studies provide evidence that the TRPC channel CCDs participate in channel gating.

Key Words: TRPC channel, Calcium, Coiled coil, Gating

S-I-3

Renoprotection of Klotho through TRPC6 downregulation

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An anti-aging protein Klotho exerts organ protection that is predominantly expressed in the kidney. Perturbation of Ca^{2+} signaling leads to disruption of glomerular filter integrity causing proteinuria and to tumor progression. Whether and how Klotho directly protects the glomerular filter and cancer progression is unknown. Here we report that secreted Klotho suppresses Ca^{2+} influx via inhibiting multiple TRPC channels including TRPC3, TRPC5 and TRPC6. Cytoprotection by Klotho is supported by the reduction of actin remodeling and transepithelial albumin leakage in podocytes and by inhibition of tumor progression in renal cell carcinoma. Notably, transgenic overexpression of TRPC6 in mice causes foot process fusion and albuminuria which are ameliorated by exogenous administration of Klotho. Our results reveal a potential novel function of Klotho in renoprotection and offer a potential new therapeutic strategy for treatment of proteinuric diseases and kidney cancers.

Acknowledgement: This study was supported by NRF-2015R1D1A1A01060454 & 2017R1D1A3B03031760.

Key Words: Klotho, TRPC6, Diabetic nephropathy, Renal cell carcinoma, Ion channel

S-I-4

Role of Trp channels in the control of feeding behavior and metabolism

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It is now well established that brain controls food intake, energy homeostasis and glucose metabolism. In particular, the pro-opiomelanocortin (POMC) neurons within the arcuate nucleus of hypothalamus (ARH) are key to decrease food intake, reduce body weight and maintain glucose homeostasis. The anorexigenic (appetite-suppressing) effects of serotonin and leptin are mediated at least in part by the serotonin 2C receptors (*Htr2cs*) and leptin receptors (LepRs) expressed by POMC neurons. However, cellular and molecular mechanisms of *Htr2c* and LepR action on POMC neurons are not completely understood. Here, I will discuss recent experimental evidence suggesting the involvement of transient receptor potential cation 5 (TRPC5) channel in the effects of *Htr2c* and LepR stimulation on POMC neurons and whole body metabolism.

Key Words: TRPC5, Serotonin 2c receptor, Leptin receptor, Pomc neuron, Hypothalamus

S-I-5

Ca^{2+} signaling in primary cilia during development and disease

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Primary cilia are solitary, generally non-motile, hair-like protrusions that extend from the surface of cells between cell divisions. Only ~200-300 nm in diameter and a few microns long, they are separated from the cytoplasm by the ciliary neck and basal body. Often called sensory cilia, they are hypothesized to receive chemical and mechanical stimuli and initiate specific cellular

signal transduction pathways. Here I will discuss the function of TRP channels in primary cilia. We have shown that primary cilia are a compartmentalized Ca^{2+} signaling organelle. Changes in ciliary calcium concentration ([Ca^{2+}]cilia) occur without substantially altering global cytoplasmic calcium ([Ca^{2+}]cyto). A prominent hypothesis for the mechanism by which primary cilia sense their local environmental postulates the detection of mechanical forces through calcium-permeable ion channels within the cilium. This hypothesis has been invoked to explain the function of primary cilia in a large range of biological responses, from control of left-right axis determination during development to adult progression of polycystic kidney disease, and some cancers. I will further discuss our results demonstrating a complete lack of mechanically induced calcium increases in primary cilia, in tissues upon which this hypothesis has been based.

S-I-6

Oral barrier formation via temperature-sensitive TRP channels

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Skin and mucosa cover the whole body and provide a protective barrier against infection, chemical irritants, mechanical force, or thermal assault. The oral mucosa is continuously exposed to a broad range of temperatures and mechanical or chemical stimuli, therefore is susceptible to injury. The oral epithelium senses environmental changes in the oral cavity and must adapt accordingly with these changes. Consequently, the oral epithelium is considered to have a higher turnover rate and faster wound healing potential. We hypothesized that thermosensitive transient receptor potential (TRP) vanilloid 3 (TRPV3) or 4 (TRPV4) channels are activated by temperature changes in the oral cavity and play a role in the oral mucosal barrier. TRPV3 and TRPV4 were found to be extensively expressed in murine and human oral epithelia. Using calcium imaging and electrophysiological techniques, warm temperatures were found to activate oral epithelial cells via TRPV3 and TRPV4. Interestingly, TRPV3 gene-knockout (V3KO) mice showed a suppressed proliferation rate whereas TRPV4 gene-knockout (V4KO) mice showed an elevated proliferation rate compared with wild type mice. After wounding, healing time was prolonged in V3KO mice compared with wild type mice. We also explored the role of TRPV3 and TRPV4 in epithelial sealing and found that activation of these channels contributed to formation of the epithelial barrier in the oral cavity.

S-I-7

The hypothalamic TRPV1 channels in regulation of food intake

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Despite accumulating evidence for the TRPV1 channels in the regulation of energy balance, the expression and role of TRPV1 channels in the hypothalamus are controversial. Hypothalamic POMC neurons are known to be critical for anorexigenic feeding behaviors related in elevation of energy expenditure. Therefore, here we show that TRPV1 channels expressed in POMC neurons play a critical role in regulating feeding. Single-cell RT PCR and Immunohistochemical experiments show expression of TRPV1 channels in subset of POMC neurons. To investigate the role of TRPV1 in POMC neurons activity, we use capsaicin as an agonist of TRPV1. Electrophysiological experiment shows activation of POMC neurons by capsaicin and selective agonist of TRPV1. Also, capsaicin-induced depolarization is completely abolished by selective inhibition of TRPV1. Moreover, feeding behavior is significantly reduced by i.c.v. injection of capsaicin and this reduction is abolished by selective inhibition of POMC neurons. Therefore, TRPV1 in the melanocortinergic system contribute to the feeding behavior via regulation of POMC neurons.

Key Words: Hypothalamus, TRPV1, POMC, Energy balance

S-I-8

Acceleration of skin barrier restoration by topical botanical products via transient receptor potential V3

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Intracellular Ca^{2+} signaling via various calcium channels such as Orai1 and transient receptor potential (TRP) channels has been shown to directly modulate epidermal proliferation, differentiation, and barrier homeostasis. Ca^{2+} influx through these channels eventually generates intracellular Ca^{2+} signals that result in different outcomes that are dependent on the individual Ca^{2+} channel type.

Among them, TRP cation channel subfamily vanilloid (V) member 3 (TRPV3) was initially proposed as a thermosensor in the human body. However, it was recently reported that TRPV3 is functionally expressed in human keratinocytes. TRPV3 activation increased intracellular Ca^{2+} signaling, which in turn increased the activities of transglutaminase (TGase) 1 and 3, as well as the subsequent formation of cornified cell envelopes in the epidermis. It was also reported that the activation of TRPV3 promotes epithelial cell proliferation and wound healing in the oral epithelium. Therefore, these results suggest that TRPV3 activation could be a potential therapeutic target for skin barrier recovery in various dermatological diseases.

To identify botanically derived extracts and its chemicals for use in topical agents for dermatological diseases, we prepared extracts of 26 medicinal herbs, performed bioassay-guided fractionation of the active extracts, and then isolated and identified the bioactive constituents.

By performing whole-cell patch-clamp studies, we found 11 medicinal herb fractions that showed significant TRPV3 activation at 100 μg/mL. We analyzed the chemical constituents that showed agonistic effects on TRPV3 and identified γ-schisandrin as a potential agonist. We also confirmed that topical application of active extracts and chemicals improved the recovery of skin barrier disruption induced by tape stripping of murine dorsal skin.

Since most regional plants have not been investigated chemically or pharmaceutically, they remain as untapped potential sources of topical agents for drugs. Therefore, our study provides the concept and tools for the potential clinical application of botanically derived extracts for abnormal skin barrier functions, such as atopic dermatitis, elastosis, and contact dermatitis.

Key Words: TRPV3, Keratonocyte, Transglutaminase, Skin barrier, Natural product

S-I-9

The intracellular Ca^{2+} channel TRPML3 is a PtdIns3P effector that regulates early autophagosome biogenesis

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Autophagy is an intracellular degradation pathway that delivers cytoplasmic contents to the lysosome, involving many fusion and fission events which require Ca^{2+}. Although TRPML3 is suggested to regulate autophagy as an autophagosomal Ca^{2+} channel, it is still not clear whether TRPML3 directly provides Ca^{2+} for the process. To image a TRPML3-mediated Ca^{2+} release in specific subcellular compartments, we used a GCaMP6-fusion protein, a genetically encoded calcium indicator attached to C-terminus of TRPML3. TRPML3-GCaMP6 hardly overlapped with LC3 but was mainly localized in ATG5-positive phagophores, indicating that TRPML3 supplies Ca^{2+}

for the early autophagosome biogenesis. Moreover, nutrient starvation activated TRPML3 to release more Ca^{2+}, suggesting that TRPML3 are regulated in the context of autophagy. Indeed, lipid binding assay revealed that both N-terminus and 1st extracytosolic loop of TRPML3 interact with phosphatidylinositol-3-phosphate (PI3P), a key determinant of autophagosome formation. Confocal imaging and electrophysiological experiments showed that TRPML3 is directly activated by PI3P, resulting in increased autophagy. Inhibition of TRPML3 suppressed autophagy even in the presence of excess PI3P, whereas activation of TRPML3 rescued autophagy suppression. Part of the N-terminal and 1st extracytosolic loop sequences of TRPML3 was predicted as phox homology (PX) domain and RxL motif, respectively, which bind primarily to PI3P. Charge removal mutations in the regions disrupted binding to PI3P and abolished TRPML3 activation by PI3P and subsequent increase of autophagy. Taken together, these results suggest that TRPML3 is a key regulator of the autophagy process as a downstream effector of PI3P, providing Ca^{2+} that mediates early steps of autophagosome formation.

Key Words: Autophagy, Ca^{2+} channel, GCaMP6, PI3P, TRPML3

S-I-10

The ER/PM microdomain, PI(4,5)P_2 and the regulation of STIM1-Orai1 channel function

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The Orai1-STIM1 current undergoes slow Ca^{2+}-dependent inactivation (SCDI) mediated by the binding of SARAF to STIM1. Here we report the use of SCDI by SARAF as a probe of the conformation and microdomain localization of the Orai1-STIM1 complex. We find that the interaction of STIM1 with Orai1 carboxyl terminus (C terminus) and the STIM1 K-domain are required for the interaction of SARAF with STIM1 and SCDI. STIM1-Orai1 must be in a PM/ER microdomain tethered by E-Syt1, stabilized by septin4 and enriched in PI(4,5)P2 for STIM1-SARAF interaction. Targeting STIM1 to PI(4,5)P2-rich and -poor microdomains reveals that SARAF-dependent SCDI is observed only when STIM1-Orai1 are within the PI(4,5)P2-rich microdomain. Notably, store depletion results in transient localization of STIM1-Orai1 in the PI(4,5)P_2-poor microdomain, which then translocates to the PI(4,5)P_2- rich domain. These findings reveal the role of PM/ER tethers in the regulation of Orai1 function and a mode of regulation by PI(4,5)P_2 involving translocation between PI(4,5)P_2 microdomains.

Key Words: Orai channels, STIM1, PIP_2, Microdomains

S-II-1

Reduction of microRNA targeting Drd2 leads to thalamocortical dysfunction in schizophrenia mouse models

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A specific disruption of synaptic transmission at thalamocortical (TC) glutamatergic projections in the auditory cortex is caused by an aberrant elevation of Drd2 in the auditory thalamus. This disruption renders 22q11DS TC projections sensitive to antipsychotics and causes a deficient acoustic startle response similar to that observed in schizophrenia patients. Through these findings, auditory TC projections recently emerged as a neural circuit that is specifically disrupted in mouse models of 22q11DS. Haploinsufficiency of the microRNA (miRNA)-processing-factor gene Dgcr8 is responsible for the elevation of the dopamine receptor Drd2 in the auditory thalamus (MGv) and hypersensitivity of auditory TC projections to antipsychotics. It also causes an abnormal acoustic-startle response.
Here we show that these auditory TC phenotypes have a delayed onset in 22q11DS mice and are associated with an age-dependent reduction of miR-338-3p, a miRNA that targets Drd2 and is enriched in the thalamus of both humans and mice. Replenishing depleted miR-338-3p in mature 22q11DS mice rescued the TC abnormalities, and deletion of Mir338 (which encodes miR-338-3p) or reduction of miR-338-3p expression mimicked the TC and behavioral deficits and eliminated the age dependence of these deficits. Therefore, miR-338-3p depletion is necessary and sufficient to disrupt auditory TC signaling in 22q11DS mice, and it may mediate the pathogenic mechanism of 22q11DS-related psychosis and control its late onset.

Key Words: microRNA, Drd2, Thalamocortical dysfunction, 22q11DS, Schizophrenia

S-II-2

Synapse organization by autism-associated synaptic adhesion molecules

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Recent advances in the human genetics of neurodevelopmental disorders (particularly, autism spectrum disorders) have identified recurrent mutations in genes encoding a variety of synaptic genes, including synaptic adhesion molecules. *Trans*-synaptic adhesion molecules and their ligands instruct and specify the properties of synapses and neural circuit, emerging as key synapse organizers. Neurexins and neuroligins are arguably most extensively studied pair of synapse organizers. Neurexins bind to multiple postsynaptic ligands, including LRRTMs and neuroligins. Neuroligins also bind to MDGA family of GPI-anchored proteins for negatively regulating synapse development. My talk is based on two hypotheses: first, that multiple *trans*-synaptic adhesion molecules and their associated proteins (i.e. synapse organizers) are central to synapse formation and function, and second that defective *trans*-synaptic adhesion signaling manifests in the forms of various brain diseases. I will describe some of our recent studies on how LRRTMs, neuroligins, and MDGAs are involved in shaping synapse properties, and discuss how these mechanisms may contribute to our understanding pathophysiology against neurodevelopmental disorders, such as autism spectrum disorders.

Key Words: Synapse, Synaptic adhesion molecule, Autism, LRRTM, MDGA

S-II-3

Excessive dopamine receptor activation in the dorsal striatum promotes autistic-like behaviors

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Autism spectrum disorder (ASD) is a group of neuropsychiatric disabilities characterized by difficulties in social interaction and repetitive stereotyped behaviors. Recent studies have identified several hundred ASD-related genes which encode synapse proteins, transcription factors, epigenetic regulators, and signaling molecules. The diversity of those identified genes and their wide expression patterns in the brain have hampered attempts to determine whether ASD core symptoms are produced by dysfunction of neural network(s) distributed widely in the brain or in specific brain region(s).
Recently we reported that mice lacking adenylyl cyclase 5 (AC5) display autistic-like behavior including sociability deficits and repetitive behaviors. Optogenetic stimulation of the cortico-striatal glutamatergic input induced sociability deficits (Mol Neurobiol 2016 Nov. [Epub]). Regarding these results and that the dorsal striatum is the converging point for glutamatergic and dopamine inputs, it is important to determine whether ASD core symptoms are regulated by dopamine functions in the dorsal striatum. The dopamine system has been characterized in motor function, goal-directed behaviors and rewards. However, focused studies on the striatal dopamine system in ASD pathology have not been conducted yet.
We found that mice with increased dopamine functions in the dorsal striatum via the suppression of dopamine transporter expression in substantia nigra neurons or the optogenetic stimulation of the nigro-striatal circuitry exhibited sociability deficits and repetitive behaviors relevant to ASD pathology in animal models, while these behavioral changes were blocked by a D1 receptor antagonist. Pharmacological activation of D1 dopamine receptors in normal mice or the genetic knockout (KO) of D2 dopamine receptors also produced typical autistic-like behaviors. Moreover, the siRNA-mediated inhibition of D2 dopamine receptors in the dorsal striatum was sufficient to replicate autistic-like phenotype in D2 KO mice. Intervention of D1 dopamine receptor functions or the signaling pathways related D1 receptors in D2 KO mice produced anti-autistic effects. Together, our results indicate that increased dopamine function in the dorsal striatum promotes autistic-like behaviors, and that the dorsal striatum is the neural correlate of ASD core symptoms.

Key Words: ASD, Dopamine, Striatum, Optogenetics

S-II-4

Critical role of NMDA receptor function on the modulation of behavioral deficits in animal models of autism spectrum disorder

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Autism spectrum disorder (ASD) is characterized by two core domains of symptoms such as social communication deficits and restricted repetitive behavior. Multiplex of risk factors and a myriad array of complex symptoms make obtaining the appropriate therapeutic targets against the devastating disorder a formidable challenge. Based on excitatory-inhibitory neuronal imbalance (E/I imbalance) theory of ASD, we tested the possibility of blocking NMDA-type glutamate receptors, as a potential therapeutic target for ASD. In valproic acid animal model of ASD, NMDA blockers such as memantine and MK801 successfully ameliorated behavioral deficits. Treatment of agmatine, an endogenous neuromodulator with antagonistic effects against NMDA receptors also effectively suppressed behavioral deficits. Agmatine also normalized hyperactivity, repetitive behavior and seizure susceptibility of VPA animal model. Administration of agmatine increased the level of agmatine in brain and modulation of agmatine break down also improved the social impairments and repetitive behaviors. As a molecular signaling signature, VPA animal model showed dysregulated phosphorylation of Erk1/2, which is normalized by agmatine administration. These results suggest that modulating glutamatergic neural activity might provide plausible target of ASD therapeutics, at least in a subset of ASD patients.

Key Words: NMDA, MK801, Memantine, Agmatine, VPA

S-III-1

Identification of Sirtuin 6 as a novel target in macrophage switch and inflammation

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Current paradigms suggest that two macrophage subsets, termed M1 and M2, are involved in inflammation and host defense. While the distinct functions of M1 and M2 macrophages have been intensively studied - the former are considered proinflammatory and the latter antiinflammatory - the determinants of their speciation are incompletely understood. Here we evaluated the influence of Sirtuin 6 (Sirt6) on macrophage polarization and function. Macrophages obtained from LysMCre-Sirt6$^{fl/fl}$ mice, which lack Sirt6 in myeloid lineage cells, expressed high levels of M1 markers and lower levels of M2 markers. To determine whether the myeloid Sirt6 deletion similarly affected inflammation *in vivo*, wild type and myeloid Sirt6 KO mice were either fed a high fat diet or were subjected to a full-thickness excisional wound. High fat diet-induced inflammation and insulin resistance were exacerbated in KO mice and was associated with increased plasma levels of M1 cytokines/chemokines. Similarly, compared with wild type mice, wound closure was delayed in KO mice with less collagen deposition, suppressed angiogenesis and reduced expression of wound healing related genes. Altogether, these results identify Sirt6 as what we believe to be a novel regulator of macrophage polarization. Therefore, approaches aimed at modulating myeloid Sirt6 activity may represent a possible therapeutic approach for diseases linked to excessive inflammation.

Key Words: Sirtuin, Macrophage, Insulin resistance

S-III-2

SREBP-1 links lipogenesis to macrophage phagocytosis via mTOR signaling

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Macrophages are highly specialized cells with major functions in the innate immune system. They are critical accessory cells that are important in the defense against invading pathogens and are also strongly implicated in the development of atherosclerotic lesions. In a recent report, it was hypothesized that phagocytes replenish membranes expended during particle engulfment in a rapid phase of lipid synthesis. Sterol response element binding protein (SREBP) is a key transcriptional regulator of lipogenesis and cell growth and its' properly regulated activity plays a role in the cellular lipid homeostasis. Phagocytosis triggered the proteolytic activation of two lipogenic transcription factors, SREBP-1a and SREBP-2. However, a functional role for SREBP-1a in macrophages has not been addressed. In this study, we established a line of mouse that resulted in a greater than 95% knockdown in SREBP-1a mRNA in every tissue examined using a β-geo "gene trap" system. And phagocytosis assay was performed using opsonized targets of sheep red blood cells. We show that macrophages from these SREBP-1a deficient (1aDF) mice exhibit a significant decrease in phagocytosis of sheep red blood cells as compared to macrophages isolated from wild type control mice. Rapamycin, an mTOR inhibitor, reduced phagocytosis through decrease of SREBP-1 in macrophages. These observations indicate that SREBP-1a may play a pivotal role in phagocytosis as an innate immune defense mechanism of macrophages through mTOR signaling.

S-III-3 Young Physiologist Award

Effect of necrotic cell microenvironment on glioma progression

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Glioblastoma multiforme (GBM) is the most common primary intracranial tumor in adults with a poor prognosis. The defining characteristics of GBM are diffused infiltration of tumor cells into normal brain parenchyma, rapid growth, high degree of microglial and macrophage infiltration, and the presence of necrosis. However, the effect of necrotic cells (NCs) on microglial infiltration and the growth and metastasis of GBM is poorly understood at present. In this study, we examined the biological significance of necrotic tissues by exploring the molecular mechanisms underlying the signaling network between necrotic tissues and GBM cells. The migration and invasion of the GBM cell line, CRT-MG, was significantly enhanced after treatment with NCs, as shown by assays for scratch wound healing and spheroid invasion. Using CRT-MG and the microglial cell line, HMO6, we found that the presence of NCs promoted the migration/infiltration of microglia, and that CRT-MG cells exposed to NCs further enhanced the migration and infiltration of HMO6 cells. Moreover, incubation with NCs induced IL-8, MCP-1, and MIP-3α secretion in CRT-MG cells in a dose-dependent manner. In human GBM tissues, IL-8 positive cells were mainly distributed in the perinecrotic region, as seen in the immunohistochemistry and immunofluorescence analyses. NCs induced NF-κB and AP-1 activation and their binding to the IL-8, MCP-1, and MIP-3α promoters, leading to enhanced chemokine production and secretion in GBM cells. Our data demonstrated that NC exposure and stimulation resulted in enhanced GBM cell migration and invasion via the NF-κB/AP-1-mediated IL-8 upregulation, while also facilitating HMO6 cell migration and infiltration by upregulating the MCP-1 and MIP-3α expression in glioblastoma cells. To the best of our knowledge, this study is the first to report the effect of necrosis on chemokine production, cancer cell migration, and microglial infiltration mediated by GBM cells.

Key Words: Glioblastoma multiforme, Necrosis, Microglia, Tumor microenvironment

S-III-4 Yudang Academic Award

Programming of macrophages by apoptotic cancer cells inhibits cancer progression and metastasis

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Apoptotic cell clearance by phagocytes is essential in tissue homeostasis. We demonstrated that conditioned medium (CM) from macrophages exposed to apoptotic cancer cells inhibits TGFβ1-induced epithelial-mesenchymal transition (EMT), migration, and invasion of cancer cells with the acquisition of cancer-stem-like traits. Apoptotic 344SQ (ApoSQ) cell-induced PPARγ activity in macrophages caused increased PTEN levels, secreted in exosomes. PTEN entering into recipient 344SQ cells prevented the disruption of cell polarity and cancer progression. 15-HETE, lipoxin A4, and 15d-PGJ2 also mediated the anti-EMT effects of ApoSQ-exposed CM through PPARγ/PTEN signaling. Moreover, injection of ApoSQ cells inhibited lung metastasis in syngeneic mice with enhanced PPARγ/PTEN signaling. Thus, the early injection of apoptotic cancer cells may offer a new strategy for the prevention of metastasis.

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Key Words: Apoptotic cancer cells, Macrophages, EMT, Metastasis, PPARγ, PTEN, Exosome

S-IV-1

Modulation of autonomic nerve system and cardiac arrhythmia

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The autonomic nervous system plays an important role in the genesis of atrial fibrillation and is one of the candidate targets for atrial fibrillation therapy. The heart is innervated by the extrinsic and intrinsic autonomic nervous systems. The intrinsic autonomic nervous system consists of multiple ganglionatedplexi and axons, which innervate the neighboring atrial myocardium and control their electrophysiological properties. Abnormal autonomic innervation has been observed in an animal model of atrial fibrillation and in humans. Direct recordings of autonomic nerve activity in canine models showed that atrial tachyarrhythmia episodes were invariably preceded by intrinsic cardiac autonomic nerve activity, thus supporting the importance of intrinsic cardiac autonomic nerve activity as the triggers for atrial tachyarrhythmia. Targeting ganglionatedplexi with catheter ablation improves the outcomes of paroxysmal atrial fibrillation ablation in addition to pulmonary vein antrum isolation. Ablation of ganglionatedplexi alone without pulmonary vein isolation is also useful in controlling paroxysmal atrial fibrillation in some patients. However, surgical ganglionatedplexi ablation in patients with a large left atrium, persistent atrial fibrillation and/or a history of prior catheter ablation does not result in additional benefits. These different outcomes suggest that ganglionatedplexi ablation is effective in managing patients with paroxysmal atrial fibrillation, but its effects in patients with persistent atrial fibrillation and advanced atrial diseases might be limited.

Key Words: Atrial fibrillation, Ganglionatedplexi, Autonomic nervous system, Catheter ablation, Surgical ablation

S-IV-2

Sympathetic nerve blocks promote anti-inflammatory response by activating JAK2-STAT3-mediated signaling cascade in rat myocarditis model: a novel mechanism with clinical implications

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Background: The antiarrhythmic mechanism of left stellectomy is not well known. Cholinergic anti-inflammatory pathway (CAIP) is a complex immune mechanism that regulates peripheral inflammatory responses.
Methods and Results: Rat experimental autoimmune myocarditis (EAM) was produced by injecting 2 mg of porcine cardiac myosin into the footpads of rats. Left stellectomy was performed before EAM induction. Left stellectomy prevented arrhythmia and improved survival in EAM rats. Left stellectomy decreased TNF-α, IL-6, and HMGB1 levels ($P<0.05$ versus EAM). In heart rate variability analysis, high-frequency peaks of the power spectrum densities, reflecting parasympathetic cardiovagal tone, was significantly decreased in EAM, but increased after left stellectomy. The ratios of phosphorylated-STAT3/STAT3 and phosphorylated-JAK2/JAK2 decreased in cell lysates of spleen, liver and heart in EAM rats. However, the same ratios significantly increased after left stellectomy.
Conclusion: In EAM models, left stellectomy increased survival of the rats while showing antiarrhythmic effects with reduced inflammation via activation of JAK2-STAT3-mediated signaling cascade. Our findings suggest an exciting opportunity to develop new and novel therapeutics to attenuate cardiac inflammation.

Key Words: Cardiac inflammation, Stellectomy, JAK2-STAT3

S-IV-3

Localized signaling regulation of cardiac ion channels through progesterone receptor

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Sex hormonal regulation in cardiac ion channels accounts for functional responses to sympathetic nervous system stimulation, which show sex differences in susceptibility of arrhythmias associated with QT prolongation (TdP: torsade de pointes). Although it has been known that women have a greater TdP risk than men in both congenital and acquired long QT syndrome, the sex difference becomes evident only when compared with adult men and adult women at the follicular phase,implying androgen and progesterone have protective effects on TdP. Accumulating clinical evidence suggests a protective role for progesterone (P_4). We have demonstrated that a nitric oxide (NO) production induced by stimulation of cardiac progesterone receptors through a non-genomic pathway suppresses L-type Ca^{2+} currents ($I_{Ca,L}$) under cAMP-stimulated condition, suggesting a cross-talk between NO and cAMP/PKA signaling. In this study, our pharmacological analysis revealed that the cross-talk is established by phosphodiesterase 2 (PDE2). Sucrose density gradient fractionation of membrane and proximity ligation assay showed that PDE2 interacts with $I_{Ca,L}$ channel at lipid raft of T-tubules of cardiac myocytes. In order to visualize cAMP/PKA activities in living cell, FRET-based cAMP/PKA biosensors, which are anchored to membrane rafts (Lyn-AKAR4) or non-raft regions (AKAR4-Kras), respectively, were employed. Applications of a beta-adrenergic receptor agonist, isoproterenol, increased FRET as shown by an emission ratio changes for both sensors. With the cAMP-stimulation, additional applications of P_4 suppressed FRET signals of Lyn-AKAR4 only, indicating a subcellular localization of the cross-talk. The response to PRs stimulation was inhibited by PDE2 or progesterone receptor inhibitors. These results suggest that a compartmentalized PKA activity may involve a cross-talk between the non-genomic PRs pathway and beta-ARs pathway to regulate $I_{Ca,L}$.

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Key Words: Progesterone, Cardiac calcium channel, NO, PKA, FRET

S-IV-4

The molecular nature of a calcium spark

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Ca^{2+} sparks as the elementary intracellular Ca^{2+} signaling events has been found for a quarter of century. However, the molecular mechanisms underlying the generation of Ca^{2+} sparks remains elusive. Although it is well known since the inception that a Ca^{2+} spark represents the local Ca^{2+} release events of ryanodine receptors (RyRs) in the sarcoplasmic reticulum, it is still uncertain how many (whether a few or a large number of) RyRs are involved in the Ca^{2+} release during a Ca^{2+} spark, and how RyR Ca^{2+} release is terminated to end a Ca^{2+} spark. One of the reasonskeeping these important issues from clarification is that RyRs are intracellular channels inaccessible to direct electrophysiological measurements, while in situ study of RyRs by Ca^{2+} sparkquantification is tangled with problems such as out-of-focus events. To solve these problems, we designed the loose-patch imaging technique to quantify in-focus Ca^{2+} sparks triggered by their native Ca^{2+} activators from aL-type Ca^{2+} channel in intact cardiomyocytes. We found that Ca^{2+} sparks from individual Ca^{2+} release units exhibited quantized Ca^{2+} releaseflux, whichwas absent in FKBP12.6-knockout cardiomyocytes, suggesting that Ca^{2+} sparks involved coupled gating of multiple RyRs mediated by FKBP12.6. Electron tomographic imaging showed that that the RyRs in a Ca^{2+} release unit were randomly organized in subgroups, with a typical subgroup containing an average of 1.8 RyRs

in mice or 3.5 RyRs in rats. This structural data agreed well with the number of quanta in spark Ca^{2+} release flux, both indicating that a typical Ca^{2+} spark represents the synchronizedCa^{2+} release of 2-4 RyRs in rat or only one RyR in mouse cardiomyocytes.

S-V-1

Neural firing patterns in the hippocampal formation in visual contextual environment

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Animals including humans make numerous choices when facing visual context in the background. Naturally, the first step toward successful decision making should involve recognizing the cueing stimulus (scene) correctly so that its associated behavioral response could be made properly. Years of experiments using neurophysiological and behavioral paradigms have taught us that the currently dominant theoretical framework requires a signification modification and I will provide an overview of our research outcome and progress in this talk. I will focus mostly on the hippocampal formation, the hippocampus and subiculum, to show how the neural networks in this region respond physiologically to use visual contextual information in the environment for decision making. Specifically, discharge rates of place cells in the hippocampus are modulated by changes in the environment. Such *rate remapping* may underlie the neural code responsible for remembering different events that take place in the same location, but it is unknown if rate remapping also occurs in the subiculum, the immediate downstream structure of the hippocampus. Recordings from neurons in the rat subiculum and CA1 during a visual scene-memory task showed that scene-dependent rate remapping occurred more strongly in the subiculum than the CA1 during recognition of a familiar scene. However, increases in scene ambiguity led to a decrease in both performance and scene-specific firing in the CA1; by contrast, no such ambiguity-related neural correlate was found in the subiculum. Our findings suggest that rate remapping occurs globally in the brain, but recognizing an altered environment may be a unique function of the hippocampus.

S-V-2

Neuron-specific nucleosome remodeling factor critical for emotional memory consolidation

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Recent works in the rodent brain begin to link nucleosome remodeling-dependent epigenetic mechanism to memory consolidation. Here we show that *BAF53b*, an epigenetic factor involved in nucleosome remodeling, is induced in the lateral amygdala neurons at the late phase of consolidation after fear conditioning. Using specific gene knockdown or overexpression approaches, we identify the critical role of *BAF53b* in the LA neurons for memory consolidation during long-term memory formation. Knockdown of *Baf53b* before training disrupted long-term memory formation with no effect on short-term memory, basal synaptic transmission and spine structures. We observed in our qPCR analysis that *Baf53b* was induced in the LA neurons at the late consolidation phase after fear conditioning. Moreover, transient *BAF53b* overexpression led to persistently enhanced memory formation, which was accompanied by increase in thin-type spine density. Our results thus provide an idea about how nucleosome remodeling can be regulated during long-term memory formation and contributes to the permanent storage of associative fear memory in the lateral amygdala, which is relevant to fear and anxiety-related mental disorders.

S-V-3

Layer-specific neuromodulation of long-term synaptic plasticity in the visual cortex

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Cortical pyramidal neurons (PyNs) extend their dendrites into apical and basal dendrites, where integration properties differ dependent on their differential geometry and expression of ion channels. Sensory inputs from periphery and associative inputs from higher brain areas terminate preferentially onto perisomatic area including basal dendrites and distal apical dendrites, respectively. Thus, layer-specific signaling properties of the dendrite in pyramidal neurons (PyNs) are important in the integration of cortical information. In addition, neuromodulators, such as acetylcholine and serotonin, regulate synaptic transmission properties in a layer-specific manner, which may be critical in the cortical information processing balance dependent on the brain state. We studied the differential modulation of long-term synaptic plasticity exerted by acetylcholine and serotonin between distal apical dendrites in layer 1 and perisomatic basal dendrites in layer 2/3 in layer 2/3 PyNs of the primary visual cortex of the rat. Under the muscarinic activation or intracellular application of IP_3-3F, synaptic stimulation evoked calcium release from IP_3-sensitive stores and induced long-term potentiation in basal dendrites, but not in distal apical dendrites. We found no expression of type 1 IP_3 receptors in distal apical dendrites in layer 1. Serotonin inhibited the induction of long-term depression in basal dendrites via the increase in inhibitory transmission, which is also dependent on the Ca^{2+} release from the IP_3-sensitive stores only in basal dendrites. Expression of IP_3 receptors is also area and age dependent. These results reveal a novel mechanism for dendritic compartment-specific modulation of long-term plasticity in the neocortex, with implications for the brain state-dependent changes in information-processing balance.

S-V-4

Metaplasticity in the lateral habenula of depressed brains

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Stress exposure is known to cause depression in human patients and animal models, although the responsible cellular mechanisms remain to be elaborated. The lateral habenula (LHb) is a small part of the epithalamus that projects to monoamine centers in the brain. Previously, neurotransmission onto the LHb was shown to be abnormally potentiated in animal models of depression. However, synaptic plasticity in this brain area and the effect of stressor exposure on synaptic plasticity of the LHb have not been investigated. We explored whether the LHb undergoes dynamic changes in synaptic efficacy or not. First, we observed that both long-term potentiation (LTP) and long-term depression (LTD) occurs in LHb neurons obtained from naïve animals. Surprisingly, exposure to acute stressors completely masked the induction of a certain type of LTD, while greatly facilitating LTP induction in the LHb. Stress exposure selectively increased the number of neurons expressing pCREB in the LHb, suggesting that the threshold for LTP induction has lowered in animal models of depression. Pharmacological activation of cannabinoid receptor 1 (CB1R) or blockade of αCaMKII successfully restored LTD in the LHb in an animal model of depression. I will discuss our observations revealing previously unknown forms of synaptic plasticity in the epithalamus and stress-induced shift of the bi- directional synaptic plasticity, i.e. metaplasticity in the LHb in animal models of depression.

S-VI-1

Improvement of mitochondrial function induced by bio-active fabrics and alternative motor effects

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This study surveys the improvement characteristics in old-aged muscular mitochondria by bio-active materials coated fabric (BMCF). To observe the effects, the fabric (10 and 30%) was worn to old-aged rat then the oxygen consumption efficiency and copy numbers of mitochondria, and mRNA expression of apoptosis- and mitophagy-related genes were verified. By wearing the BMCF, the oxidative respiration significantly increased when using the 30% materials coated fabric. The mitochondrial DNA copy number significantly decreased and subsequently recovered in a dose-dependent manner. The respiratory control ratio to mitochondrial DNA copy number showed a dose-dependent increment. As times passed, Bax, caspase 9, PGC-1α and β-actin increased, and Bcl-2 decreased in a dose-dependent manner. However, the BMCF can be seen to have had no effect on Fas receptor. PINK1 expression did not change considerably and was inclined to decrease in control group, but the expression was down-regulated then subsequently increased with the use of the BMCF in a dose-dependent manner. Caspase 3 increased and subsequently decreased in a dose-dependent manner. These results suggest that the BMCF invigorates mitophagy and improves mitochondrial oxidative respiration in skeletal muscle, and in early stage of apoptosis induced by the BMCF is not related to extrinsic death-receptor mediated but mitochondria-mediated signaling pathway. This study will 1) improve mitochondria-related treatment, 2) propose the assist therapeutics of various metabolic disease, 3) help to the popularization of far infrared radiation fabric, and 4) verify for the possibility disease prevention by wearing functional clothing: enhancement of mitochondrial function of functional fiber and alternative exercise effect.

Key Words: Functional fabric, Alternative exercise effect, Mitochondria, Far-infrared radiation

S-VI-2

Impact of mitochondrial stress in POMC neurons on systemic metabolism

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Hypothalamic regulation of food intake and energy expenditure is critical for maintaining whole body energy homeostasis. Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus play an important role in the maintenance of energy balance. Normal mitochondrial dynamics and functions in hypothalamic neurons are pivotal in the maintenance of systemic energy homeostasis. Accumulated evidence suggests that mitochondrial dysfunction is closely linked to aging-related metabolic disorders. In contrast, recent evidences in lower organisms indicate that mitochondrial stress increases life span by induction of mitochondrial unfolded protein responses (UPR^{mt}). CRIF1 has been identified as a mito-ribosomal protein which critically mediates incorporation of mitochondrial DNA (mtDNA)-encoded oxidative phosphorylation (OXPHOS) polypeptides into the inner mitochondrial membrane. Complete loss of CRIF1 in Camk2-expressing neurons causes severe OXPHOS dysfunction and leads to a neuronal death, locomotor disability and short life span. To study the impact of mitochondrial stress in hypothalamic POMC neurons, we generated a mice model lacking CRIF1 expression specifically in the POMC neurons using cre-lox system. I will also present the data of mice with mitochondrial stress in hypothalamic POMC neurons, which demonstrates cell-non-autonomous UPRmt in remote organs.

Key Words: Mitochondrial stress, Oxidative phosphorylation, Mitochondrial unfolded protein response

S-VI-3

Regulation of insulin secretion by glucose and its blunting in diabetes through glucotoxicity

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Type 2 diabetes (T2D) is a world wide health problem with at least 380 million cases and approximately 320 million prediabetic subjects. T2D develops in the wake of the obesity epidemic, when The pancreatic beta cells fail to adequately adapt insulin secretion to the increased needs of obese individuals with insulin resistance. This defective adaptation is genetically determined. Exposure of beta cells to unphysiologically high glucose concentrations (glucotoxicity) attenuates glucose-stimulated insulin secretion (GSIS) both in vivo and in vitro. We hypothesize that beta cell dysfunction develops by exposure to harmful peaks of blood glucose during the years of prediabetes that precede the onset of overt T2D. Glucose stimulates ATP generation in the beta cell mitochondria, which couples metabolism to insulin secretion. Beta cells in T2D organ donor islets fail to raise ATP levels and secrete insulin in response to glucose. We show that exposure to glucotoxic conditions induces the transcription factors carbohydrate response element binding protein (ChREBP) and thioredoxin-interacting protein (TXNIP). This upregulation is also seen in islets from T2D donors. The transcription factors induce a "diabetes executer gene" (to be disclosed in the oral presentation). There is a highly significant correlation between the transcript levels of the executer gene and the average blood glucose (glycated hemoglobin, HbA1c) in organ donor islets. The induction of the executer gene in turn impairs stimulus-secretion coupling, in particular affecting mitochondrial respiration and ATP generation in the beta cells. Suppression of ChREBP or TXNIP prevents upregulation of the executer gene. The overexpression of the executer gene leads to its mistargeting to the beta cell plasma membrane. Inhibiting its function restores ATP generation and GSIS in T2D islet preparations and prevents the outbreak of hyperglycemia in a mouse model of T2D. It is concluded that the conversion of prediabetes to overt hyperglycemia can be prevented in a mouse model of T2D, which, if applicable to the human situation, could be of great importance in the quest of the prevention of T2D.

Key Words: Pancreatic islets, Type 2 diabetes, Mitochondria, ATP, Metabolism-secretion coupling

S-VI-4

Calcineurin as a modulator of mitophagy in pancreatic beta cells

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Autophagy or mitophagy is critical in the maintenance of pancreatic beta cell function. Recently, calcineurin has been reported to play a regulatory role in the lysosomal function and autophagy. We studied whether calcineurin inhibitors can affect mitophagy of pancreatic beta cells and thereby pancreatic beta cell function. FK506, a classical calcineurin inhibitor, suppressed rotenone- or oligomycin/antimycin A-induced mitophagy measured by mito-Keima localization in acidic compartment or RFP-LC3 puncta colocalized with Tom20 in INS-1 cells. FK506 also suppressed spontaneous mitophagy measured in the same way. FK506 reduced nuclear translocation of TFEB, TFE3 or MITF after treatment with rotenone or oligomycin/antimycin A, suggesting the role of decreased nuclear translocation of TFEB family member in FK506-induced reduction of mitophagy. TFEB nuclear translocation by mitochondrial stressors was inhibited by ROS quencher or Ca^{2+} chelation, suggesting the role of ROS-induced Ca^{2+} release. Probably due to reduced mitophagy, recovery of mitochondrial potential after treatment with rotenone or oligomycin/antimycin A was delayed by FK506. Mitochondrial oxygen consumption was also reduced by FK506, supporting reduced mitochondrial function by FK506. Mitochondrial COX activity in pancreatic islets was reduced by prolonged FK506 administration. At least partly due to impaired mitochondrial function, insulin release from INS-1 cells was reduced by FK506 in vitro. FK506 also reduced insulin release and impaired glucose tolerance in vivo. These results suggest that mitophagy is crucial in the maintenance of pancreatic beta cell function and insulin release, and the adverse effect of FK506 could be attributable to the reduced mitophagy of pancreatic beta cells.

Key Words: Mitophagy, Beta cell, Mitochondria, Lysosome, Calcium

S-VI-5

Mitochondrial chaperone HSP-60 enhances anti-bacterial immunity through up-regulating p38 MAP kinase signaling

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Emerging evidence shows that mitochondria play important roles in innate immunity. How specific mitochondrial components modulate host immunity against pathogens is largely unknown. Here, we showed that HSP-60/HSPD1, a major mitochondrial chaperone, boosts anti-bacterial immunity via PMK-1/p38 MAP kinase signaling in *C. elegans*. We first identified 16 evolutionarily conserved mitochondrial components that affected the survival of *C. elegans* under pathogenic *Pseudomonas aeruginosa* (PA14)-infected conditions. Among them, the mitochondrial chaperone HSP-60 was necessary and sufficient for resistance against PA14. We found that PMK-1 signaling, an evolutionarily conserved anti-bacterial immune pathway, was down-regulated by genetic inhibition of *hsp-60*, while being up-regulated by transgenic expression of *hsp-60*. Overexpression of *HSPD1*, the mammalian ortholog of *hsp-60*, increased p38 MAP kinase activity in human cells, indicating an evolutionarily conserved mechanism. Furthermore, we showed that a fraction of HSP-60 was localized in the cytosol and stabilized SEK-1/MAP kinase kinase 3 via physical interaction. This in turn led to up-regulation of PMK-1 and enhanced immunity. Our study suggests that molecular chaperones generated from bacteria-originated mitochondria protect host eukaryotes from pathogenic bacteria.

Key Words: Mitochondria, HSP-60, Immunity Pseudomonas, *C. elegans*

S-VI-6

The critical roles of zinc in the regulation of mitochondrial oxidative stress

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Zinc is an essential heavy metal required in the proper structure and function of about 2800 macromolecules and over 300 enzymes. Whole body and cellular zinc levels are largely regulated by metallothioneins (MTs), zinc importers (ZIPs), and zinc transporters (ZnTs). Excessive production of reactive oxygen species (ROS) is one of the important etiological factors in pathological transitions. Free zinc has not been proven to interact directly with reactive oxygen species or with carbon-centered free radicals. Zinc may function as an antioxidant involved in: 1) the prevention of OH- and

O2- production by transition metals, such as copper and iron, in a defined chemical system; 2) the protection of sulfhydryl groups against oxidation, as observed in δ~aminolevulinate dehydratase, the cytoskeletal protein tubulin, and DNA-binding proteins containing zinc-fingers; 3) reduction in the oxidative/peroxidative damage of biological membranes; and 4) the hydroxyl radical scavenging through the action of MT. Mitochondrial activities can be largely influenced by status of free zinc due to its role as a cofactor for mitochondrial proteins involved in mitochondrial maturation and respiratory chain activity. Dysfunction of mitochondria is connected to aberrant ROS production. In this presentation, our current understating of the involvement of free zinc in the regulation of mitochondrial ROS production is briefly summarized and discussed.

Key Words: Antioxidant, Heavy metal, Mitochondria, Reactive oxygen species, Zinc

S-VII-1

Contribution of AT1R mechanoactivation to the arterial myogenic response and its regulation by RGS5 protein in skeletal muscle arterioles

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The arteriolar myogenic response, or pressure-induced vasoconstriction, is a major factor in the local regulation of hemodynamics. Although intracellular mechanisms underlying the arteriolar myogenic response have been well defined, the mechanotransduction events transducing the mechanical stimulus remain unclear. Recently, ligand-independent activation of G protein-coupled receptors (in particular, the angiotensin II type 1 receptor; AT1R) has been suggested to play a major role in vascular smooth muscle mechanotransduction, thereby contributing to myogenic constriction. However, the downstream pathways following ligand-independent activation of the AT1R have not been clearly elucidated. Using isolated and pressurized small artery preparations our studies provide pharmacological evidence that the mechanically activated AT1R generates diacylglycerol, which in turn activates PKC that subsequently induces actin cytoskeleton reorganization for myogenic constriction. Actin polymerization was confirmed using Western blotting. Further, using atomic force microscopy on single smooth muscle cells we showed thickening of cortical actin fibers in response to hypotonic buffer (a mechanical stimulus) and that this was attenuated by the AT1R blocker, candesartan. In terms of physiological roles, the arterial myogenic response acts to generate vascular tone, prevent capillaries from being damaged, and reduce edema due to high capillary hydrostatic pressure. Thus, an exaggerated AT1R-mediated myogenic constriction could conceivably contribute to vascular disorders. As a result, small arteries likely exhibit negative feedback regulatory mechanisms to prevent such an exaggerated myogenic response. In regard to this, we discovered that ligand-dependent or -independent activation of the AT1R causes trafficking of an important regulatory molecule, RGS5 (Regulators of G protein Signaling) protein, which may modulate Ang II or myogenic-mediated constriction by terminating Gq/11 protein-dependent signaling. Collectively, these data provide further evidence supporting the mechanosensitivity of the AT1R and that its actions occur in concert with appropriate regulatory mechanisms.

S-VII-2

Role of Kv7 channel in vasoreactivity of various blood vessels

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Study1: Heterogeneity in Kv7 channel function in the cerebral and coronary circulation

Recent studies have implicated Kv7 channels as important in the regulation of smooth muscle contractility in the vasculature including in aorta, renal, coronary and cerebral arteries. The present studies examined the hypotheses that 1. Kv7 channels are present in mouse cerebral and coronary arteries and regulate vascular reactivity, and that 2. differences in local requirements result in a heterogeneous role for these channels. End-point and quantitative PCR was performed on male WT mouse basilar, Circle of Willis and left anterior descending (LAD) arteries. Vascular function of the basilar and LAD arteries from WT male mice was assessed (in paired studies) by myography. Basilar, Circle of Willis and LAD expressed predominantly Kv7.1 and 7.4. Relaxation induced by the Kv7 channel activator, retigabine (1-50 μM) was significantly less in the LAD compared to basilar artery. In addition, application of the Kv7 channel blocker, linopirdine (10 μM) resulted in greater contractile responses in basilar artery compared to LAD. An additional Kv7 channel

blocker, XE991 (10 μM) also showed increased contractility in the basilar arteries. Furthermore, pre-incubation with linopirdine (10 μM) reduced forskolin (cAMP activator)-induced vasorelaxation (0.001-1 μM) in the basilar but did not alter forskolin-induced vasorelaxation in the LAD arteries, suggesting that Kv7 channels may play a more prominent role in the cerebral than coronary circulation. Consistent with the pharmacological data, at the single cerebral vascular smooth muscle cell (VSMC) level whole cell Kv7 currents were potentiated by retigabine and inhibited by linopirdine, while these responses were comparatively blunted in coronary VSMCs. This study provides evidence that Kv7 channels may play different roles in the regulation of cerebral and coronary blood flow. The finding of such heterogeneity has important implications in the development of novel therapeutics for cardiovascular diseases including stroke and coronary dysfunction.

Key Words: K^+ channels, Voltage-gated K^+ channels, Cerebral and coronary arteries, Regional heterogeneity, Electrophysiology, Pharmacological manipulation

Study 2: Impaired Kv7 function in the cerebral circulation of type 2 diabetic (db/db mice) mice

Type 2 diabetes (T2D) is associated with a higher risk for development of cardiovascular disease, particularly affecting the cerebral and coronary vasculatures. Recent studies in a variety of vascular beds have implicated Kv7 ion channels as playing a key role in regulating vascular smooth muscle cell (VSMC) function. However, the effect of T2D on Kv7 channel function in the cerebral and coronary vasculature is yet to be thoroughly examined. To test the hypothesis that T2D impairs Kv7 channels function, we studied vascular function of cerebral and coronary arteries from wild-type (WT) and T2D (db/db) male mice using myography and patch clamp. Relaxation induced by the Kv7 channel activator, retigabine (1 μM-50 μM) was significantly reduced in pre-constricted basilar arteries from the db/db compared to WT mice. Retigabine-induced vasorelaxation was minimal, however, in the LAD of both WT and db/db mice. In contrast, relaxation to the BK_{Ca} activator, NS1619 was impaired in both LAD and basilar arteries from db/db compared to WT. The Kv7 inhibitor, linopirdine evoked constriction in both WT and db/db basilar arteries although the contraction was significantly reduced in db/db compared to WT. Consistent with the pharmacological data, cerebral VSMC Kv7 currents were inhibited by linopirdine (10 μM) and increased by retigabine (20 μM) in WT, while these responses were blunted in cerebral VSMCs from db/db. Collectively, the studies indicate that T2D impairs Kv7 function in the cerebrovasculature, suggesting a possible link between dysfunction of this ion channel and vascular disease.

Key Words: Type 2 diabetes, Vascular dysfunction, Voltage-gated K^+ channels, Cerebrovasculature, Coronary vasculature, Myography, Patch clamp

S-VII-3

Ancient signaling revisited: Crosstalk between reactive oxygen species and calcium in vascular smooth muscle angiotensin II signaling

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Angiotensin II (Ang II) exerts its diverse effects through signaling pathways mediated by calcium (Ca^{2+}) and reactive oxygen species (ROS). Although the accumulated evidence suggests the presence of complicate crosstalk between Ca^{2+} and ROS, their reciprocity in Ang II signaling has not been characterized clearly. Hence, the potential interplay between Ca^{2+} and ROS signals was investigated in vascular smooth muscle cells (VSMCs). Intracellular Ca^{2+} and ROS were measured by digital imaging employing a fluorescent Ca^{2+} indicator fura-2 and a genetically-encoded fluorescent H_2O_2 sensor HyPer-Red, allowing real time monitoring of ROS and Ca^{2+} in live VSMCs. Ang II elicited both Ca^{2+} increase and ROS production in VSMCs. Intracellular Ca^{2+} peaked immediately after Ang II application. ROS production was biphasic; a rapid and transient production followed by a delayed and sustained generation. Simultaneous measurement of Ca^{2+} and ROS revealed that initial ROS production preceded Ca^{2+} elevation. NADPH oxidase (NOX) inhibitor diphenyleneiodonium (DPI) and VAS2870 prevented ROS production and reduced the amplitude of Ca^{2+} elevation by Ang II. Removal of extracellular Ca^{2+} and thereby preventing Ca^{2+} influx diminished ROS generation as well as Ca^{2+} elevation, whereas additional depletion of intracellular Ca^{2+} store using sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitor cyclopiazonic acid failed to exhibit further effect on ROS production. Silencing NOX1, but not NOX4, by shRNA reduced Ca^{2+} increase. In addition, NOX1 knockdown delayed first phase of ROS generation and decreased overall ROS formation. Taken together, NOX1-generated ROS is essential for intracellular Ca^{2+} signaling by Ang II and the influx of extracellular Ca^{2+} is required for NOX-mediated ROS production. Ca^{2+} and ROS signals are interdependent and their interplay is essential for full function of Ang II.

Key Words: NADPH oxidase, Angiotensin II, Vascular smooth muscle cells, Calcium, Reactive oxygen species

S-VII-4

Stimulation of autophagy improves vascular function in the mesenteric arteries of type 2 diabetic mice

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Vascular dysfunction is a major complication in type 2 diabetes. It has been suggested that dysregulation of autophagy is associated with various cardiovascular diseases. However, the relationship between autophagy and type 2 diabetic vascular dysfunction remains unclear. Thus, in this study, we examined whether impaired autophagy is involved in vascular dysfunction and stimulation of autophagy improves vascular function in type 2 diabetic mice. Ten to 12-week old male type 2 diabetic (db^-/db^-) mice and their control (db^-/db^+) mice were treated with autophagy inducer (rapamycin, 4 mg/kg/every other day by I.P. injection or trehalose, 3% *ad libitum* in drinking water) for two weeks. In type 2 diabetic mice, blood glucose and body weight were elevated compared with control mice. The myogenic response was increased and endothelium-dependent relaxation was impaired in mesenteric arteries from the type 2 diabetic mice. Interestingly, treatment with rapamycin or trehalose normalized the myogenic responses and endothelium-dependent relaxation. These data were associated with changes in the expressions of autophagy markers (LC3II, beclin-1, and p62). In the present study, we provide evidence that microvascular function is impaired in type 2 diabetic mice which is associated with dysregulation of autophagy markers and stimulation of autophagy improves vascular function in type 2 diabetic mice. Therefore, autophagy could be a potential target for cardiovascular diseases in type 2 diabetes.

Key Words: Autophagy, Type 2 diabetes, Mesenteric artery, Myogenic response, Endothelium-dependent relaxation

S-VII-5

Physiological roles of ion channels and eNOS expressed in pulmonary artery smooth muscle

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Pulmonary arteries (PAs) show unique properties such as hypoxic pulmonary vasoconstriction (HPV) where hypoxic inhibition of K^+ channels in PA smooth muscle cells (PASMCs) is a key mechanism. In addition, we have suggested that the depolarization via nonselective cation channels (NSC) activated by intrinsic thromboxane A2 (TXA2) is a prerequisite condition. PASMCs also show stretch-activated NSC (NSC-SA) that are responsible for the myogenic contractile responses (MT) of small systemic arteries. However, PAs do not show MT, and our myography studies suggest that the NSC-SA in PASMCs are functionally coupled to the activation of eNOS expressed

in PASMCs. The muscular eNOS appear to be activated by mechanical stretch-associated ROS signal combined with TXA2 and NSC-SA. TXA2 and H_2O_2 induced Akt-dependent eNOS Ser^{1177} phosphorylation.
Although angiotensin II (Ang II) is a well-known PA agonist, actual studies *in vitro* or *in vivo* showed only a transient contraction with persistent desensitization, in the endothelium-denuded PA. The transient PA contraction by Ang II became largely augmented and sustained when treated by L-NAME. Ang II-induced In human PASMCs, eNOS expression and Ser^{1177} phosphorylation by Ang-II were observed. Collectively, we proposed that the auto-inhibitory role of the muscle eNOS in PAs play physiological roles of active relaxation under various vasoconstrictive conditions, preventing excessive contractile response of the low-pressure pulmonary circulation.

Key Words: Pulmonary artery, Smooth muscle, Ion channel, eNOS, Thromboxane A2

S-VIII-1

Molecular evidence for "exercise as mitochondrial medicine"

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Skeletal muscle comprises 40% of body mass and is a major determinant of whole body metabolic rate. In particular, mitochondrial health is critically important for the maintenance of muscle metabolism as organelle dysfunction can contribute to muscle atrophy, metabolic inflexibility and insulin resistance. In contrast, exercise can up-regulate mitochondrial content and function, and can reverse disease and aging phenotypes. However, the molecular basis for this is incompletely understood. Our research has revealed several defective pathways reversed by exercise which can improve mitochondrial and whole muscle health. Mitochondrial biogenesis requires the expression of nuclear and mitochondrial-encoded proteins that are regulated by the transcriptional coactivator PGC-1α. PGC-1α is controlled by various upstream kinases as well as the NAD+–dependent deacetylase, SirT1, such that mice deficient in either PGC-1α or SirT1 exhibit defects in mitochondrial function. Likewise, mTORC1 is a regulator of mitochondrial functions since inhibition of mTORC1 in muscle produces a reduction in state 3 respiration. Notably, treatment of PGC-1α or SirT1 KO mice, or mTORC1-deficient skeletal muscle cells with exercise or contractile activity reverses the mitochondrial deficiency typical of each condition (1, 2, 5). Mitochondrial biogenesis is also heavily dependent on the import of nuclear-encoded mitochondrial proteins into the appropriate sub-compartment through the protein import machinery. We have observed that in animals with impaired protein import, exercise training is capable of rescuing this defect to restore the incorporation of nuclear-encoded proteins within the mitochondria (6). Moreover, exercise also improves the protein handling ability of muscle by activating the UPR, thus equipping the cell with the capacity to withstand additional proteotoxic stress associated with enhanced protein synthesis (4). In addition, the removal of dysfunctional organelles by the lysosome through mitophagy is also important in regulating muscle health. Once again, we have observed that exercise is capable of regulating mitophagy through the upregulation of the master regulator of lysosomal biogenesis, TFEB, which increases the capacity of the cell to clear out dysfunctional organelles from the mitochondrial pool (3). Thus, our results provide a better molecular understanding of how exercise serves as "mitochondrial medicine" to improve mitochondrial content and function in the context of various dysfunctional phenotypes.

References

1. Adhihetty PJ, et al. Am J Physiol Cell Physiol 2009;297:C217-25.
2. Carter HN & Hood DA. AJP Cell Physiol 2012;303:C540-C547.
3. Kim Y & Hood DA. Physiol Rep 2017;5:e13307.
4. Memme JM, et al. Am J Physiol - Cell Physiol 2016;310.
5. Menzies KJ, et al. J Biol Chem 2013;288:6968-6979.
6. Zhang Y, et al. AJP Cell Physiol 2013;305:C502-C511.

S-VIII-2

17β-estradiol directly lowers mitochondrial membrane microviscosity and improves bioenergetic function in skeletal muscle

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Menopause results in a progressive decline in 17β-estradiol (E2) levels, increased adiposity, decreased insulin sensitivity, and a higher risk for type-2 diabetes. Estrogen therapies can help reverse these effects, but the mechanism(s) by which E2 modulates susceptibility to metabolic disease is not well understood. In young C57BL/6N mice, short-term ovariectomy decreased, whereas E2 therapy restored, mitochondrial respiratory function, cellular redox state (GSH/GSSG) and insulin sensitivity in skeletal muscle. E2 was detected by LC/MS in mitochondrial membranes and varied according to whole body E2 status independent of ERα. Loss of E2 increased mitochondrial membrane microviscosity and H_2O_2 emitting potential, whereas E2 administration *in vivo* and *in vitro* restored membrane E2 content, microviscosity, complex I and I+III activities, H_2O_2 emitting potential and submaximal OXPHOS responsiveness. These findings demonstrate that E2 directly modulates membrane biophysical properties and bioenergetic function in mitochondria, offering a novel mechanism by which E2 status broadly influences energy homeostasis.

Acknowledgement: Supported by NIH R01 DK096907.

Key Words: Menopause, Mitochondria, Estrogen, Membrane viscosity, Insulin resistance, Hydrogen peroxide

S-VIII-3

Effects of inflammation on myogenic differentiation: Role of myokines and secretory vesicles

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Skeletal muscle is the largest organ in the body of non-obese human, and plays key roles in whole-body metabolism. Therefore, inflammation in skeletal muscle is important in the development of insulin resistance, aging, and chronic diseases including cancer cachexia and congestive heart failure. Furthermore, these pathologic conditions with acute or chronic muscle inflammation lead to physical inactivity and aggravate loss of skeletal muscle oxidative capacity, and *vice versa*.

Recently, skeletal muscle is also a secretory organ, which by secretion of muscle cell-derived effector molecules, 'myokines' may regulate skeletal muscle metabolism and differentiation through intercellular communication. Given that a number of myokines was found in secretory intercellular communicating vesicle, the regulation of myogenesis by inflammation through the secretory vesicles has not been elucidated. Therefore, we hypothesized that inflammation alters myokine expression in skeletal muscle cells, and exosome released from inflammatory muscle cells may be responsible for suppressing muscle differentiation.

In this study, we demonstrated that inflammation induced by treatment of cytokine mixture significantly inhibited myogenic signal and induced proteins responsible for muscle atrophy in a cellular model. The inflammation-induced inhibition of myogenic signals may be associated with alteration in the levels of myokines and AMPK-, Akt- and MAPKs-mediated pathways. Furthermore, our results suggested that exosome-like vesicles (ELVs) released from myotubes can contribute to regulation of muscle differentiation. In conclusion, our results, at least in part, provided an evidence that inflammatory ELVs contributes to the inhibition of myoblast differentiation by inflammation via multiple myogenic signaling pathways which are partly associated with myokine expression. We are currently further characterizing the molecular contents in ELVs, and that will warrant for the mechanisms of inflammation-induced muscle atrophy.

Acknowledgement: This study was supported by the Mid-Career Researcher Program (2016R1A2B4008399) through the NRF funded by the Ministry of Science, ICT and Future Planning.

Key Words: Inflammation, Myokine, Myogenesis, Skeletal muscle, Secretory vesicles

S-VIII-4

Exercise, SIRT1, and mitochondrial biogenesis in vascular homeostasis

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Endothelial activation and senescence, a pro-inflammatory state of vascular endothelial cells (EC), are known characteristics of early-stage vascular disease of aging, such as atherosclerosis and vascular dysfunction. SIRT1, a first known mammalian sirtuin, is known to suppress the development of atherosclerosis by suppressing EC activation and senescence.

Purpose: To test a hypothesis that the prolonged exposure of exercise-induced laminar shear stress (LSS) prevents endothelial activation and premature senescence.

Methods: In *in vivo* study, 21 prehypertensives underwent a 6-month supervised aerobic exercise training (AEXT) in 65% HRmax for 40 min/day and 3 days/week. In *in vitro* study, cultured HUVECs were exposed to LSS using a cone-and-plate shear apparatus. Antimycin A, SIRT1 siRNA, Sirtinol, and PGC-1α siRNA were used for the disruption of mitochondrial functional/structural integrity. Protein expressions were analyzed by western-blotting. EMP productions were measured by flow cytometry. Premature cell senescence was induced by the treatment of 100 μM H_2O_2 for 1 h. EC senescence was microscopically examined by determining the percentage of senescence-associated β-galactosidase positive staining (SA-β-gal).

Results: Circulating levels of microparticles released from activated ECs were significantly decreased ($p<.01$) after 6-month AEXT in prehypertensives. In human ECs, LSS attenuated EC activation, which was accompanied by an increase in mitochondrial content. SIRT1 knockdown completely abolished the protective effect of LSS. Disruption of mitochondrial integrity by either antimycin A or PGC-1α siRNA treatment provoked the activated- and apoptotic- statuses and LSS normalized these impairments. The % SA-β-gal positive EC was significantly increased 3 days after H_2O_2 incubation, while LSS pre-treatment alleviated senescence (Control, 3.8%; H_2O_2, 53.4%; LSS/H_2O_2, 18.4%). This result was confirmed by the level of p21 expressions (H_2O_2, 3.8-fold; LSS/H_2O_2, 1.6-fold increase compared to Control). However, this protective effect of LSS pre-treatment was disappeared in the inhibition of SIRT1. Level of SIRT1 expression was decreased in H_2O_2-induced senescent cells, while it was sustained in LSS pre-treated endothelial cells (H_2O_2, 0.5-fold; LSS/H_2O_2, 0.89-fold increase).

Conclusion: The present study suggests that exercise attenuates EC activation and oxidative stress-induced premature senescence in part by enhancing SIRT1 expression and mitochondrial biogenesis.

Key Words: Exercise, SIRT1, Mitochondrial biogenesis, Vascular homeostasis

S-IX-1

Molecular mechanism of *Drosophila* taste receptors

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Animals should defend themselves from environmental toxic chemicals by using chemosensation such as bitter taste. Thus, the number and the chemical coverage of bitter taste receptors should be more diverse than those of sweet taste receptors. *Drosophila* gustatory receptors (GRs) had been suggested as G-protein coupled receptors because they were proposed to possess seven transmembrane domain. However, their molecular identity has been challenged due to the atypical membrane topology. Despite of many efforts for solving this issue, recapitulation of the function of the bitter GRs in heterologous system has been unsuccessful so far for several reasons. First, detection of an aversive tastant requires multiple *Gr* genes. In other words, they may act as heteromultimer. Second, there are too many bitter *Grs* in fly genome. Among 68 GR proteins, only nine of them belong to sweet clade. The remainders are believed to be bitter *Grs* based on loss-of-function and expression data. Here, using fly genetics which enable a small scale of screening based on RNA interference for *Grs*, simultaneous overexpression of bitter *Grs*, as well as multiple *Gr* mutants generation, behavior, and electrophysiologic approaches *in vivo* and *in vitro*, we demonstrate that *Drosophila* bitter GRs function as heteromultimer which consists of three independent GRs, and their functional receptor complex acts as the ligand-gated cation channel. Our results would provide attractive platform for the development of insect chemosensation-specific repellent to prevent insect disease vectors.

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Key Words: *Drosophila*, Taste, Gustatory receptor (GR), Ion channels

S-IX-2

The chemosensory GPCR SRI-14 are required for concentration-dependent odor preference in *C. elegans*

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Animals must recognize and discriminate thousands of chemicals in order to generate the correct behavioral responses. Understanding basic scheme of a sensory system in simple animals gives the opportunity to elucidate detailed molecular and neural mechanisms underlying sensory responses in higher animals. *C. elegans* detects a large number of odorants via three neuron pairs including AWA, AWB, and AWC, which elicit a multitude of olfactory behaviors (Bargmann et al., 1993). Previous genetic and behavioral experiments have identified set of signaling genes including olfactory receptors, but the knowledge is still limited. Specifically, the mechanisms of how the same odorants can elicit either attractive or aversive responses depending on the chemical concentration have not been known yet.
We first aim to construct a comprehensive map of odorants and their receptors in *C. elegans*. We screened 29 volatile chemicals that have not been tested previously, and found that animals respond to 13 volatiles. We then performed candidate gene searches and found that the chemosensory GPCR *sri-14* is required for both attraction to low concentration of DMTS (Dimethyl trisulfide) and aversion to high concentration of DMTS. The defects of DMTS attraction in *sri-14* mutants were restored when we expressed the wild-type *sri-14* gene to the AWC neurons. For DMTS avoidance, expression *sri-14* gene in the nociceptive ASH neurons fully rescued the defects in *sri-14* mutants, suggesting that SRI-14 is required for both attraction and avoidance to DMTS and acts in AWC and ASH, respectively. We next found that Ca^{2+} responses of AWC to acute exposure of low concentration of DMTS was decreased in *sri-14* mutants. We also observed Ca^{2+} responses of ASH to High concentration of DMTS was decreased in *sri-14* mutants. We are currently investigating the circuit mechanisms how the SRI-14 regulates both chemotactic and aversive behavior to the same chemical.

S-IX-3

Mood, memory and oral sensory input

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Sensory information plays an important role to determine psycho-emotional behaviors of individuals. Taste sensory is mainly in charge of evaluating the nutritious content of food and preventing the ingestion of toxic substances, and importantly also has the additional value of contributing to the overall pleasure and enjoyment of a meal. Eating, especially sweet palatable foods, has been viewed as a strategy to improve negative mood and to mask stress. Partial deprivation of oral sensory relay to brain increased depression- and anxiety-related behaviors in rats. Chronic taste sensory overload such as long-term access to sweet palatable food or oral administration of capsaicin also increased anxiety- and/or depression-like behaviors in rats. However, oral sensory overloads with sweet palatable or hot spicy taste improved the psycho-emotional adversities in animal models of affective disorders. Studies have demonstrated that oral sensory and motor stimulations are necessary to maintain normal function of hippocampus. Psycho-emotional symptoms either by oral sensory overload or by deprivation seemed to be associated with dysfunctions in the hippocampus, possibly in relation with the hypothalamic-pituitary-adrenal (HPA) axis activity. Mastication is of great importance for oral sensory input to the hippocampus for preserving and promoting the cognitive function. Impaired mastication; i.e. impaired oral motor stimulation, causes morphological and functional alterations of the hippocampus inducing impairments in hippocampus-dependent learning and memory. Tongue movements are essential for an effective mastication and deglutition. Tongue motor loss with bilateral transection of hypoglossal nerves induced psycho-emotional adversities and impaired hippocampus-dependent cognitive function in rats, in relation with a HPA axis dysfunction.

Key Words: Anxiety, Depression, Taste

S-IX-4

Microfluidics-on-a-tongue imaging chamber for functional screening of taste cells in vivo

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The current understanding on taste encoding process on the tongue has relied on studies using *ex vivo* model systems, which cannot fully recapitulate the native cellular microenvironment. To resolve this methodological limitation, we invented a new imaging window with integrated microfluidics enabling simultaneous chemical and optical access to the intact mouse tongue in real-time. Using the imaging chamber, we recorded calcium activity of taste cells under various taste stimuli in live mice, and obtained a comprehensive cellular-level functional taste map. We observed that taste encoding is more complex than previous understanding, exhibiting several prominent crosstalk between different taste qualities. We further revealed existence of novel populations of tastes cells by *in situ* hybridization, which are responsible for the crosstalk among different taste qualities.

Key Words: Taste, Imaging, Microfluidics, Screening, In vivo

S-X-1

A regulatory mechanism for tumor malignancy through a Zinc-finger protein 143

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Cancer is caused by dysregulation of tissue growth, which has led many scientists to study cell cycle, mitosis, cell death and so on resulting in identification of oncogene and tumor suppressors. Recent advances in biotechnology, especially sequencing and bioinformatics, get us more insights about cancer. However, there are still many genes and drugs to be investigated and validated before getting in to the platform. Thus we are focusing on genes important for tumor malignancy and investigating the function of genes and validating their clinical application. Malignancy in cancer means almost metastasis which covers so many aspects of cancer biology. The most important part of the processes is enhanced motility within tissue which is obtained by many ways such as alteration of genes involved in motility, cell-cell interaction or differentiation after transformation. We are focusing on the process after transformation in terms of motility. Another condition to choose genes is that the genes and its relatives could be regulated by drugs approved already. The type I insulin-like growth factor receptor (IGF-1R) has been emerged as a therapeutic target for cancer because of its increased expression in a wide range of tumors and its crucial role for cell transformation. We investigated and identified the altered genes in response to IGF-1 treatment in HCT116 colon cancer cells by microarray to identify effective downstream mediators involved in IGF-1/IGF-1R signaling to cell survival and anti-apoptotic pathway and to study the detail mechanism. We have identified zinc-finger protein 143 (ZNF143) which is a human homolog of xenopus transcriptional activator staf, as an IGF-1-inducible gene in colon cancer cells. To investigate the role of ZNF 143 in cancer cells, we stably introduced ZNF143 expression knockdown by infecting colon cancer cells with short hairpin (sh) RNA-lentiviral particles against ZNF143 (HCT116 sh-ZNF143), Compared to sh-control cells, HCT116 sh-ZNF143 cells showed faster wound healing, increased migration through Transwell chambers, and increased invasion through Matrigel in Transwell chambers. ZNF143 knockdown increased transcriptional expression of ZEB1. These data suggest that ZNF143 is involved in cellular motility through a ZEB1-E-cadherin-linked pathway in cancer cells. These data suggest that modulation of IGF-1 signaling through its receptor binding partner or downstream targets contributes to tumor malignancy.

Key Words: Tumor, Malignancy, Motility, ZNF143

S-X-2

Development of stem cell therapy

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Umbilical cord blood is the blood found in the umbilical cord of a newborn and is the source of the purest stem cells. The human Umbilical Cord Blood-derived Mesenchymal Stem Cells (hUCB-MSCs) retain the highest vitality and regenerative capacity among all types of adult stem cells and deliver highly efficacious and safe clinical results.

Through investigation on the characteristics of human cord blood-derived stem cell, MEDIPOST is currently proceeding further researches on verification of the effect of cell therapeutic drugs; exploration on the therapeutic mechanisms and administration path; and improvement of culture technique and productivity.

The previous stem cell drugs have limit on their high cost due to difficulties for mass production. Our team is developing manufacturing process for the next generation cell therapy drugs. We focus on mass-production from upstream and downstream process, which will improve the productivity and therapeutic effects.

Through innovations in treating incurable diseases with stem cell technologies, MEDIPOST will improve the quality of human lives.

S-X-3

Protein shelled nanoparticle (PSNP) synthesis and its applications

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Fluorescent semiconductor nanocrystals (also known as quantum dots, QDs) have shown great potential in cellular imaging, bio-labeling, and deep tissue structure mapping for their high quantum efficiency, long-term photo stability, narrow emission, and continuous absorption spectra. However, electrical properties are still unrevealed. It is well know that carbon nanostructures, including carbon nanotubes (CNTs) and graphene, are composed almost entirely of surface atoms and have greater modulation of electrical properties (e.g., capacitance, resistance) upon exposure to analytes. In this work, we describe the procedure to encapsulate CdSe QDs in the ClpP cage via an EDTA-mediated approach, where the protein coat was put on the QDs by forming CdSe particles *in situ* in the ClpP cavity. The ClpP-coated CdSe QDs were characterized by UV-vis spectroscopy, transmission electron microscopy (TEM), and energy dispersive X-ray spectroscopy (EDX). These coated QDs are aqueous soluble and biocompatible. Further, for the first time we evaluated the electrical transport properties with and without graphene field effect transistor (FET) device. The enhancement in the conduction with graphene indicates that the protein molecules has adsorbed onto the graphene surface. The outcome of this research shows that graphene FET can act as very fast, sensitive and inexpensive detectors for bio-molecules.

S-X-4

Novel effects of extrinsic factors on skin homeostasis

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Lipolysis in the adipocytes provide free fatty acids for other tissues in response to the energy demand. With the rapid increase in obesity-related diseases, finding novel stimuli or mechanisms that regulate lipid metabolism becomes important. We examined the effects of visible light (410, 457, 505, 530, 590, and 660 nm) irradiation on lipolysis regulation in adipocytes differentiated from human adipose-derived stem cells (ADSCs). Interestingly, specific light irradiation significantly reduced the concentration of lipid droplets (LDs). We further investigated the lipolytic signaling pathways that are involved in specific light irradiation-induced breakdown of LDs. Immunoblot analysis revealed that specific light irradiation-induced phosphorylation of hormone-sensitive lipase (HSL) was insufficient to promote reduction of LDs. We observed that specific light irradiation decreased the expression of perilipin 1. We found that specific light irradiation induced conversion of LC3 I to LC3 II, a representative autophagic marker. We further demonstrated that the lysosomal inhibitors leupeptin/NH4Cl inhibited specific light irradiation-induced reduction of LDs in differentiated adipocytes. Our data suggest that specific light irradiation-induced LD breakdown is partially mediated by autophagy-related lysosomal degradation, and can be applied in clinical settings to reduce obesity.

References

1. Kim HJ, Choi MS, Bae IH, Jung JY, Son ED, Lee TR*, Shin DW*. Short wavelength visible light suppresses innate immunity-related responses by modulating protein S-nitrosylation in keratinocytes. J. Invest. Dermatol. 2016 Mar;136(3):727-31
2. Choi MS, Jung JY, Kim HJ, Ham MR, Lee TR*, Shin DW*. S-nitrosylation of fatty acid synthase regulates its activity through dimerization. J Lipid Res. 2016 Apr;57(4):607-15.
3. Choi MS, Kim HJ, Ham M, Choi DH, Lee TR*, Shin DW*. Amber Light (590nm) Induces the Breakdown of Lipid Droplets through Autophagy-Related Lysosomal Degradation in Differentiated Adipocytes. Sci Rep. 2016 Jun 27;6:28476.

Key Words: Extrinsic factors, Skin homesostasis

S-XI-1-1

Resolution of RAGE-mediated inflammation via aerobic exercise: acute and chronic effects

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Activation of RAGE (receptor of advanced glycation endproducts (AGEs)), via binding of AGEs and other ligands, modulates the development and progression of diabetic complications through persistent and cyclic activation of nuclear factor-KB. Targeting RAGE directly as a therapeutic strategy has largely been unsuccessful. However, RAGE signaling can be interrupted, *in vivo*, by ADAM10 (a disintegrin and metalloproteinase 10) directed proteolytic cleavage of the RAGE ectodomain, and thus creating a soluble isoform of RAGE (sRAGE) that is released from the cell and appears into the circulation. Maintaining high levels of circulating sRAGE is advantageous as sRAGE will sequester RAGE ligands and prevent RAGE cell signaling. *Our long-term goal* is to identify strategies for the prevention and treatment of diabetic complications. Using lifestyle intervention, we have elucidated a mechanism for ADAM10 upregulation to increase RAGE shedding. At the completion of our studies, it is our expectation that we will have identified a novel mechanism of ADAM10 activation and an important tissue source of sRAGE production. Ultimately, such an insight has the potential to improve the prevention and therapeutic management of diabetes and its complications, thus reducing the financial and social burden that affects the ~347 million people worldwide with diabetes.

S-XI-1-2

Physical activity differences in different symptoms among Korean population

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Objective: Being physically active is an important element that people of all ages can take to improve their health and the well-being. Recent researches demonstrate that virtually all individuals can benefit from regular physical activity, whether they participate in a vigorous or moderate exercise. Particularly low physically activity is known to be associated with obesity and metabolic syndromes. In Korean medicine, researchers have shown that the Sasang constitution or some pattern identification is highly related to certain diseases such as obesity and metabolic syndromes. Then, considering physical activity and pattern identification coupled with sasang constitution in Korean medicine, we may be able to better understand the association with metabolic diseases. However, until now there has been no such study. From this point of view, we first try to confirm the association between the Korean medical constitution (Sasang constitution) and the amount of physical activity.
Method: A total of 1,101 adults are engaged in this study, and the subjects were surveyed by Gallup Korea and Korea Institute of Oriental Medicine in 2015 Korean medical constitution (Sasang constitution) was diagnosed using the constitution questionnaire KS-15, and the physical activity was assessed by IPAQ (International and Global Physical Activity Questionnaires) and Baecke Physical Activity questionnaire. The quality of life used the SF-12 questionnaire. The quality of life used the SF-12 questionnaire. ANCOVA analysis and logistic regression analysis were used for statistical analysis by adjusting gender, age, and BMI.
Result: The distribution of body composition according to the amount of physical activity was different. Physical activity was divided into light exercise, moderate exercise, and intense exercise for analyzing the association with PCS of SF-12. In light exercise, there was a significant correlation between physical activity and PCS in all constitutions. In moderate exercise, TE and SY only showed a significant correlation. In intense exercise, it was irrelevant in all constitutions.

Key Words: Physical activity, Sasang constitution, Quality of life, Korean medicine

S-XI-1-3

Effect of muscle fatigue by neuromuscluar electrical stimulation on ankle dorsiflexion, leaning backward and leaning forward

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Brain motor control assessment (BMCA) is an sEMG-based technique to overcome the limitation of inter-individual difference for clinical use. Despite the benefits of the method, very limited previous research regarding BMCA application for muscle fatigue and peripheral minor damage. In this study, the authors evaluated how SI values are changed by the neuromuscular electrical stimulation (NMES) on an agonist muscle using a healthy subject.
Twenty-one young, healthy male subjects (average age=21.85±1.49 years) participated in the study. Ankle dorsiflexor was fatigued for 15 minutes using the self-selected electrical intensity. Surface electromyography (sEMG) was recorded from 15 muscles pre- and post- NMES during ankle dorsiflexion on supine position and forward and backward voluntary body lean task. Similarity index (SI) and total EMG magnitude were used for the quantitative sEMG evaluation, as well as maximum muscle strength.
The results found a significant decrement in the muscle strength of the ankle dorsiflexor (15.3% decrement, $p<0.01$), the total sEMG magnitude of sEMG (40.1 %, $p<0.001$) and SI (3%, $p<0.05$) post NMES during dorsiflexion. Thirteen out of 21 patients (=62%) showed significantly decreased SI for forward voluntary body lean. Our findings indicate total sEMG magnitude and similarity index on supine, under no weight bearing condition, would be more appropriate to evaluate the slight change of the motor control.

Key Words: Motor control recovery, Quantitative evaluation, Electromyography, Multi-electrodes

S-XI-1-4

Can neuroimaging be a plausible technique for qigong rehabilitation research?

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Purpose: Qigong has been known to help in Bell's palsy (BP) rehabilitation and also it contains a technique very similar to motor imagery for enhanced body awareness. According to previous studies, facial movement may lead to increased activity in attention and sensory-motor areas in order to improve the facial motor performance in BP. So we tested the effect of motor imagery for BP rehabilitation and investigated brain areas that correlates to facial motor imagery.
Methods: fMRI was applied to two groups (34 normal, and 14 BP subjects). The paradigm consisted of mouth and forehead motor imagery with 2 seconds animation movie and inter-stimulus interval of 9.81±1.6 seconds. General linear model and unpaired T-test were done and for the BP group we flipped the individual maps for those who had right side BP, so that the right hemisphere represents paretic side. Also correlation analysis was used to correlate brain activity with a facial motor imagery index.
Results: Interestingly, mouth motor imagery in both normal and BP subjects showed activation in MI, SI, superior temporal sulcus, superior temporal gyrus, and supplementary motor area which are main sensory-motor areas shown in motor tasks. Additionally, mouth motor imagery in BP induced greater activity in contralateral sensory-motor areas (MI, SI, premotor cortex, and SII) compared to normal subjects. Also facial motor imagery index was positively correlated with contralateral posterior insula in BP.
Conclusion: Facial motor imagery shares similar activation in sensory-motor areas with facial motor tasks, and BP facial motor imagery has greater activity in contralateral sensory-motor areas than normal subjects. Additionally, higher facial motor imagery performance induces more activation

in interoceptive sensory processing areas. So it could be speculated that facial motor imagery could be helpful in BP rehabilitation in same way with motor task.

Key Words: Neuroimaging, Qigong, Motor respiratory coordination

S-XI-2-1

Functional changes in the skeletal muscle fibers with aging and exercise

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Aging is associated with loss of muscle mass and strength, which is a primary cause of sarcopenia, resulting in impaired posture and locomotion as well as reduced daily activity and quality of life. The prevention of muscle atrophy and muscle dysfunction is critical for solving these major problems encountered as people age. Exercise has been suggested to in part adverse the degenerative effects in muscles with aging. However, it's controversial if muscle wasting observed with aging and its mitigation by exercise is the result of alterations in individual muscle fibers. To comprehend the overall changes in contractile function according to aging and exercise, it is important to understand the muscle function at cellular and molecular levels. Single fiber physiology technique using a permeabilized muscle fiber preparation has been used to determine various biochemical and molecular mechanisms by measuring contractile properties in muscle fibers. The purpose of this study is to introduce current knowledge regarding the effect of aging and exercise on skeletal muscle fiber function in animals and humans.

Acknowledgement: Supported by NRF-2016R1D1A1B03933286.

Key Words: Sarcopenia, Frailty, Muscle wasting, Physical performance

S-XI-2-2

Neuro-muscular junction and exercise

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Age-associated muscle strength decline is a major contributing factor for increased late life morbidity and mortality. While numerous observations have been made for the phenotypical changes in the aging neuromuscular system, it is still not clear what the driving event of age-associated muscle weakness is. Most recently, it is proposed that dying-back axonal degeneration of motor neuron is causally related to age-associated muscle weakness, with the degeneration of the most distal part of motor nerve, neuromuscular junction (NMJ), being the earliest event. This idea is primarily based on morphological changes in the NMJ structure in aging skeletal muscle, but to prove dying-back process, the comparison between the distal and proximal parts of motor nerve – NMJ (distal) and ventral roots (proximal) – is necessary in different age groups. Herein, we present histological evidences of dying-back axonal degeneration in aging neuromuscular system by comparing the denervation in NMJ and ventral roots, and correlate them with physical strength and electrophysiological properties in young and old wild type B6 mice. Careful quantification of NMJ and ventral roots shows the greater extent of denervation at the NMJ than at ventral roots of old mice, whereas there is no significant denervation in both NMJ and ventral root axons in young mice. Our findings suggest that the dying-back axonal degeneration is responsible for the electrophysiological and strength changes with aging.

Key Words: Neuromuscular junction (NMJ), Exercise, Aging, Muscle weakness

S-XI-2-3

Muscle over mind

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Exercise has many health benefits for body and mind. Accumulating re-

search in rodents and humans indicates that exercise benefits brain function and may prevent or delay onset of neurodegenerative conditions. Research into underlying mechanisms has focused on central changes in neurotransmission, neurogenesis, growth factors, and blood flow. Less attention has been given to peripheral factors that may affect brain function during exercise. In particular, activation of skeletal muscle may play an important role. This has become particularly relevant with the identification of muscle fiber contractile and metabolic genes, which can be activated by exercise, pharmacological agents, and the overexpression of selected transcription factors. Here, we show that a muscle secretory factor, cathepsin B (CTSB) protein, is important for the cognitive and neurogenic benefits of running. Proteomic analysis revealed elevated levels of CTSB in conditioned medium derived from skeletal muscle cell cultures treated with AMP-kinase agonist AICAR. Consistently, running increased CTSB levels in mouse gastrocnemius muscle and plasma. Furthermore, recombinant CTSB application enhanced expression of brain-derived neurotrophic factor (BDNF) and doublecortin (DCX) in adult hippocampal progenitor cells through a mechanism dependent on the multifunctional protein P11. In vivo, in CTSB knockout (KO) mice, running did not enhance adult hippocampal neurogenesis and spatial memory function. Interestingly, in Rhesus monkeys and humans, treadmill exercise elevated CTSB in plasma. In humans, changes in CTSB levels correlated with fitness and hippocampus-dependent memory function. Our findings suggest CTSB as a mediator of effects of exercise on cognition.

Key Words: Cathepsins, Neurogenesis, Exercise

S-XI-2-4

Is ursolic acid an exercise mimetics?

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Introduction: Endurance and strength are reduced in elderly people. There are many difficulties in performing the exercise more than moderate-intensity for improving the health effectively. Ursolic acid (UA) intake can achieve the effects of endurance (Chu et al., 2015; Kunkel et al., 2012) and strength (Kunkel et al., 2011; Jeong et al., 2015) training. We would like to confirm the possibility of UA as an exercise mimetics for health promotion of elderly people.
Methods: Approximately 250 g of Sprague-Dawley (SD) male rats were divided into Sed (sedentary), Ex (treadmill exercise), UA (ursolic acid supplementation) and UEx (UA+Ex) groups. The left hindlimb was casting-induced hindlimb immobilization to induce muscle atrophy and the contralateral, non-immobilized right leg being used as an internal control. UA (5mg / kg body weight) or placebo alone (corn oil) was administrated once a day for 8 weeks. The exercise group performed running (12-15 m/min) on a treadmill for 60 minutes once a day and 3 times a week for 8 weeks.
Results: The skeletal muscle weights were reduced by immobilized for 10 days in the tibialis anterior (29.2%) and gastrocnemius muscles (39.2%). The UEx group effectively reduced body weight and fat mass by immobilization for 10 days. Muscle mass did not improve after 8-weeks of UA supplementation and exercise training. However, UEx group was significantly improved muscle mass after 8-weeks of treatment. Also UEx group were effectively reduce fat mass and body weight. Endurance capacity was increased only by exercise training and UA supplementation had no effect.
Discussion: UA improves the insulin/IGF-1 signaling pathway to increase muscle mass and reduces the expression of Muscle RING-finger protein-1 (MuRF1) and Muscle atrophy F-box (MAFbx) to prevent muscle atrophy (Kunkel et al., 2011). UA also increases energy expenditure by enhancing beta oxidation through mechnisms dependent on UCP3 and AMPK (Chu et al., 2015). Therefore, additional analysis of the relevant signaling pathway is required to verify the effects of the UA alone or the concurrent treatment of UA and exercise training.

References

1. Chu X, He X, Shi Z, Li C, Guo F, Li S, et al. (2015). Mol Nutr Food Res. 59*8):1491-503.
2. Jeong JW, Shim JJ, Choi ID, Kim SH, Ra J, Ku HK et al. (2015). J Med Food. 18(12):1380-6.
3. Kunkel SD, Elmore CJ, Bongers KS, Ebert SM, Fox DK, Dyle MC et al. (2012). PLoS One. 7(6):e39332.
4. Kunkel SD, Suneja M, Ebert SM, Bongers KS, Fox DK, Malmberg SE, et al. (2011). Cell Metab. 13(6):627-38.

S-XII-1

Development of functional food for improving sperm motility

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The purpose of this study is to develop herbal medicinal product improving sperm motility for male infertility and to accomplish clinical trial for functional food development. The evaluation of efficacy on natural products improving sperm motility for male infertility was performed in a rat varicocele model with the standardized products (MOTILIPERM: CINThera 1, 2 and 3). The investigation of active components from Motiliperm was also conducted. Sperm motility and counts, Johnsen's score, spermatogenic cell density and testosterone level were significantly improved in Motiliperm-treated varicocele model groups compared with the varicocele model group. Monotropein, kaemferol-3-O-glucoside and spiraeoside were revealed as active components in Motiliperm. The clinical protocol for a human clinical study using *in vivo* study data with Motiliperm was developed. The double-blind randomized controlled crossover trial will be conducted on 92 subjects. This study will be contributed to national policy about recovery of birth rate and development of response system to aging society with treatment for infertile couples. The development of herbal medicinal product or functional food will induce the creation of economic profit, vitalizations of industry and enlargement of national interests.

Acknowledgements: This study was supported by grants from the Korean Healthcare Technology R&D Project, Ministry for Health, Welfare, & Family Affairs, Republic of Korea (HI14C0018).

Key Words: Herbal medicinal product, Functional food, Infertility, Sperm motility

S-XII-2

Nitrate-nitrite-nitric oxide pathway: the missing link in the management of blood pressure

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In the human body, nitric oxide (NO) synthesized from NO synthase (NOS) is a key signaling molecule capable of many important functions, acting primarily by stimulating intra-cellular receptors within the target cell. In the vascular system, the primary role for the action of NO is for the regulation of vascular function and blood pressure. However, when the bioavailability of NO is compromised, the beneficial effects of NO are lost. Because NO is rapidly oxidized to nitrite and nitrate, plasma nitrite and nitrate were considered to be biologically inactive end-products of NO production in the human body. However, it is now clear that under specific conditions, nitrate and nitrite can be recycled *in vivo* back to NO. This process is widely known as the nitrate-nitrite-NO pathway, and is thought to be one of the body's major sources of NO generation, especially in situations when NO bioavailability *via* the conventional L-arginine-NOS pathway is compromised. In this lecture, it will be suggested that the nitrate-nitrite-NO pathway may play a significant role in maintaining levels of bioactive NO and may be critical for maintaining vascular homeostasis in the body. Especially, it will be emphasized that the activation of the nitrate-nitrite-NO pathway by functional foods is an alternate pathway that may generate NO from both anions and exert antihypertensive effects.

Key Words: Nitric oxide, Nitrite, Nitric oxide synthase, Blood pressure

S-XII-3

In vivo nitric oxide measurements using an electrochemical microelectrode in a rat model

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Nitric oxide (NO) is a diatomic free radical endogenously synthesized in the human body when L-arginine is converted to L-citrulline by a class of enzymes known as nitric oxide synthases (NOS's). Designing appropriate strategies for measuring NO in physiological milieu is challenging due to sampling constraints associated with measurement in tissue and cells, NO's low concentration (nM-μM), interference from various endogenous components (e.g., nitrite, ascorbic acid, and uric acid), and short half-life (typically <10 s). Miniaturized electrochemical sensors represent the most promising means for determining the spatial and temporal distributions of NO in physiology. The use of such sensors, however, has been limited by low sensitivity, slow response times relative to the rate of physiological changes in NO levels, lack of sensor specificity, and difficulties in sensor miniaturization. Herein, we report the preparation of "Teflon-like" perfluorinated xerogel-modified NO microsensors, exhibiting high sensitivity (detection limit down to sub-nanomolar levels) and high specificity over various interfering species (e.g., nitrite, peroxynitrite, hydroxyl radical, and superoxide). Furthermore, using such an amperometric NO microsensor, we monitor the changes in NO levels in the myocardium during myocardial ischemia/reperfusion (IR) injury in a rat heart model.

Key Words: Nitric oxide, Electrochemical microsensor, Ischemia/reperfusion injury

S-XII-4

Potential protective effects of fermented garlic extract against myocardial ischemia-reperfusion injury

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Myocardial infarction is caused by a sudden interruption of blood supply to the heart that give rise to tissue necrosis. Though reperfusion disturbs the process of ischemic cell death, reperfusion per se may augment tissue injury in excess of that produced by ischemia alone. A variety of pharmacological protection strategies, including reactive oxygen species scavengers and agents capable of inducing antioxidants and of supplementing antioxidants, have been developed to protect organs from ischemia-reperfusion (IR) injury. Nitrite, an inert oxidation product of nitric oxide (NO), is a storage reservoir of NO that is readily reduced to NO under pathological conditions like hypoxic and acidic conditions. Dietary nitrite as an alternative source of NO may be helpful as a prevention strategy for protecting the myocardium from IR injury. The oxygen levels of the myocardium can be utilized as a reliable index for the analysis of myocardial viability. Therefore, the accurate measurement of myocardial oxygen levels would be helpful to the evaluation of myocardial viability after IR injury. In this work, we evaluate the cardioprotective effects of FGE against IR injury in H9c2 cells (in vitro model) and myocardium at isolated hearts perfusion system (ex-vivo model) using sol-gel-derived oxygen sensor. Our results suggest that supplementing with FGE before ischemia induction might be helpful as a therapeutic strategy for protecting myocardium from IR injury.

Key Words: Fermented garlic extract, Myocardial ischemia-reperfusion, Nitrite, Amperometric oxygen sensor, Reoxygenation

S-XII-5

Rice bran promotes non-rapid eye movement sleep through histamine type 1 receptors

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Rice is one of the most important cereal crops in Asian countries and mostly consumed as a type of white rice. Thus, rice bran (which comprises approximately 10% of the weight of whole-grain brown rice) is produced as a by-product during the milling process. Rice bran contain multiple phytochemicals that include gamma-oryzanol, phytosterols, tocopherols, tocotrienols, fatty acids, and phenolic compounds. The health benefits of rice bran and its constituent phytochemicals include antioxidant, anti-inflammatory, antibiotic, and immune-enhancing effects. In addition, there are a few articles described involvement of rice bran components in neurological activity but its effect on sleep is not known yet. Increasing incidence of sleep deprivation and insomnia are common health care problem in developed countries and often treated with various type of sleeping pills. Most of the pre-existing sleep promoting drugs have diverse adverse effects. Thus, attempts have been made to develop sleep-promoting agents with low side-effects from natural constituents of edible plants. In this study, we investigated whether rice bran has sleep-promoting effects using a standardized rice bran supplement (RBS). The effects of RBS on sleep were evaluated through the analysis of electroencephalograms and electromyograms obtained from mice. We sought to identify the possible mechanism for the hypnotic effect of RBS using tuberomammillary nucleus neurons and knockout mice.

Acknowledgement: This study was supported by a grant from the Korea Food Research Institute.

Key Words: Electroencephalograms, Electrophysiology, Tuberomammillary nucleus

S-XIII-1

Historical review on the primo vascular system

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This review on the historical development of the primo vascular system (PVS) consists of four parts. The first part is a brief summary of Bong-Han Kim's life and his discoveries of the PVS. His work is five reports published by the Kyungrak Institute in the period between 1961 and 1965. They are, in turn, divided into two parts: The first three reports presented the network of the PVS while the second parts dealt with Sanal or the primo micro-cell which might be called a seed of embryonic-like stem cells. The second part covers the research progress in the period between 2002 and 2010. In this period confirmation of Kim's work on the PVS in the blood vessels, the lymph vessels and on the surfaces of various visceral organs was performed. This revival of Kim's work was done in the Biomedical Physics Laboratory, the Physics Department of Seoul National University. In the year 2010 the first International Symposium on PVS was held where the term PVS was announced to replace the old term 'Bonghan System' for the purpose of global acceptance of the theory. The third part deals with the work done in the period from 2010 to the present time 2017. In this current period new discoveries beyond the Kim's work were made. First of all, the findings of the PVS around cancer opened up transformative approaches to the metastasis of cancer cells through the PVS among others. Another important finding was more abundance of mast cells and innate immune cells in the PVS compared to other tissues such as lymph nodes. Still more significant discovery was the presence of hematopoietic stem cells and embryonic-like stem cells in the primo nodes. The last part presents future prospective of medical applications of the PVS. Among various applications the treatment of spinal and brain injury by injecting stem cells into the primo node at acupuncture points was proposed where the PVS is considered as the homing path of stem cells.

Key Words: Bonghan Kim, Primo vascular system, Cancer, Stem cell, Innate immune cells

S-XIII-2

HAR-NDS (hyaluronic acid-rich node and duct system): stem cells and innate immunity

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HAR-NDS appeared to form a network throughout the body, on the surface of internal organs, inside blood and lymph vessels and along nervous system. The HAR-NDS was covered by a layer of EMP-3-positive spindle-shaped epithelium with, below, a layer of vWF-positive but CD31-negative endothelium. The HAR-NDS on the surface of intestine contained a variety of immune cells, usually enriched with mast cells, eosinophils, neutrophils and histiocytes as well as chromaffin cells. Secretory granules from mast cells in the node appeared to pass along the ductules, two or more of which made up a duct. We consistently found that ~2% of the cells in the node were immature type, and hypothesized that the system might contain pluripotent and committed stem cells. HAR-NDS contained hematopoietic progenitor cells (HPC), such as granulocytes-macrophage, erythroid, multipotential and mast cell progenitors (MCP). MCPs were the most abundant among the HPCs in the HAR-NDS. Their frequency was fivefold higher than that of the MCPs in bone marrow. The system also contained pluripotent stem cells (PSCs) capable of producing hemangioblast-like cells, which subsequently generated various types of HPCs and differentiated blood cells. We further demonstrated potential PSCs by isolating sca-1$^+$ lin- CD45- small (3.0-5.0 μm in diameter) cells. The PSCs were named as "Node and Duct Stem Cells (NDSC)". NDSCs formed colonies on C_2C_{12} feeders, were positive for fetal alkaline phosphatase, and could the subcultured on the feeders. They were differentiated into neuronal cell in in vitro. Injection of NDSC into mice partially repaired ischemic brain damage. Taken together, we report the discovery of potential adult stem cells that may be involved in an alternative

means of blood cell production and tissue regeneration. The HAR-NDS may serve as a route that delivers the stem cells to their target tissues.

Key Words: Hematopoietic progenitor cells, Pluripotent stem cells, Node and duct stem cells, Ischemic brain damage, Tissue regeneration

S-XIII-3

A review on primo vascular system research in the U.S.

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PVS research in the U.S. started approximately 10 years ago, and it became possible with Dr. Kwang-Sup Soh's generous support. The first International Symposium of Primo Vascular System held in Jaechon Korea in 2010, organized by Dr. Soh, was also very important for educating U.S. scientists on the PVS. In 2010, the International Society of Primo Vascular System (ISPVS) was founded by Soh and Kang, with 13 scientists from 9 countries as founding members. In 2012, the website for the ISPVS (www.ispvs.org) was established in English. Bonghan Kim's five reports in English are now available. Since then, numerous scientific presentations on the PVS have appeared in the U.S. and international conferences.

U.S. Research teams. The first PVS researcher in the U.S. is Vodyanoy (veterinary medicine) at the Auburn Univ. The next was Kang (bioengineer) at the Univ. of Louisville (UofL). She introduced the PVS to Achilefu (optical imaging) at the Washington Univ. and the Miller (Director of the Brown Cancer Center, UofL). Upon their requests, Dr. Soh sent his team members to train all four teams. Their PVS research topics were in their respective research areas: Vodyanoy has been studying the micro-structures of the PVS and characterizing Sanals. Kang focused on identifying the PVS on the tumor; and developing techniques for detecting the PVS using nanoparticles; and Achilefu and Miller have studied the PVS roles in cancer.

Research Supports. Most PVS research in the U.S. has been done using their discretionary funds because it is still very new to U.S. scientists. They have submitted many grant proposals to the funding agencies, e.g., U.S. NSF; NIH; DOD Medical Command; and private foundations, without much success, due to the reviewers' unfamiliarity with it and the agencies' unwillingness to fund for a highly unusual topic. Vodyanoy may be the only one that currently holds research fund, which is from a private foundation.

Concluding Remarks. The PVS research progress in the U.S. has been painfully slow, mainly due to the lack of research funds. Most U.S. scientists are not only unaware of the PVS but refused to accept this radically new science. Nevertheless there has been important progress, particularly on how Sanals are associated with the stem cell. Although the PVS is now found to be fundamental for maintaining mammalian lives there is still so much to learn about it before it is fully understood and its knowledge is utilized for the human healthcare. A focused, multi-disciplinary research approach is thus highly desired.

Key Words: Primo vascular system, PVS research in the U.S., Cancer, Regeneration, Stem cell

S-XIII-4

Plasticity of organ surface primo vascular system tissue in heart failure

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The primo-vascular system (PVS), composed of primo-nodes (PNs) and primo-vessels (PVs), has been identified in various animal models. However, little is known about its function. In this study, we investigated the changes in gross morphology and cellular composition of the organ-surface PVS (osPVS) in the rats with heart failure (HF), which was induced by ligating the left descending coronary artery. At 8 weeks post the ligation, the osPVS tissues were sampled from the surface of the abdominal organs. The size of PNs in the rats with HF was larger than in sham rats (1.94 vs. 0.91 mm; $P<0.001$) and the number of osPVS tissue per rat was greater for the HF rats (21 from 9 rats vs. 31 from 6 rats; $P<0.001$). In addition, the number of osPVS tissues containing red chromophore was more numerous in HF rats ($P<0.01$). The chromophore was identified as hemoglobin. Transmission electron microscopy and H&E staining revealed that the osPVS of HF rats ($P<0.001$) possessed more red blood cells (RBCs) than that of the sham rats. In particular, immature RBC number increased in the HF rats (83.7 vs. 42.3%; $P<0.001$). The results indicates possible erythropoiesis inside the PN and PV of osPVS. In considering the HF is frequently accompanied by anemia, we further examined the morphological changes of the osPVS in rats with anemia, which was induced by intraperitoneal injection of phenylhydrazine (PHZ, 40 mg/kg/day) for 2 days. At the 3rd day after the injection, the signs of anemia was fully expressed. The RBC, hematocrit, and hemoglobin were decreased, whereas the reticulocytes, WBC, and MCH were increased. The size of the PNs in the rats with anemia was larger than in the control rats ($P<0.001$) and the number of osPVS per rat was greater for the anemia rats (11 from 4 control rats vs. 23 from 4 anemia rats; $P<0.01$). In addition, the osPVS number containing red chromophore was greater in anemia rats ($P<0.001$). Taken together, the results newly reveal that the osPVS tissues are greater in its size, frequency, and immature RBC number in HF rats than in sham rats, and also in the rat with anemia than in the normal rats. The findings in this study indicate that the erythropoiesis takes place inside the PN and PV of osPVS, and that the HF-induced plasticity in the osPVS is likely due to the anemia accompanying the HF. Collectively, the results suggest that the PVS can function as an extra-marrow hematopoietic organ.

Key Words: Primo-node, Primo-vessel, Phenylhydrazine, Red blood cells, Anemia, Reticulocytes, Hematopoiesis

S-XIII-5

Expression of genes in primo vasculature floating lymphatic endothelium under lipopolysaccharide

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Purpose: Since primo vascular system (PVS) is discovered by Kim at 1962, many papers have been published for PVS, also known as bonghan circulatory system containing corpuscle and ducts. Although existence of primo vasculature is revealed in many species including mouse, rat and rabbits as well as human, biologic role of primo vasculature including expression of genes and proteins has not yet been investigated. Especially, transcriptional action by mRNA, which is required to accomplish biological action, is urgently to be studied in PVS biology. Emerging data also suggested that pathophysiologic condition such as inflammation and tumor can progress into inflamed lymphatic endothelial cells (LECs), leads to expand primo vasculature in lymphatic endothelium. Thus, we examined gene expression in both isolated primo vasculature and lymphatic vessels containing primo vessels under lipopolysaccharides (LPS).

Materials and Methods: The New Zealand female rabbits were purchased from The Dae Han Biolink Company and all animal protocol was approved by the Institutional Animal Care and Use Committees of the Sangji University. All experiments were performed as previously described (PMID. 23040099). Real-time RT-PCR following RNA extraction was performed using tiny primo vessels and lymphatic vessels. Primer efficiency and RNA purity were confirmed prior to carry out real time PCR. In total, ten samples (the six lymphatic vessels containing primo vessels and four pure primo vessels) were used in present study.

Results: We investigated whether marker gene for LECs, Flt4 was enriched in primo vessels and several genes including Hif1a, Atgr1, Atgr2, Hsph1, Mtf2, Pdarg, Pdgfd, and Hspa4, were highly expressed in primo vessels,

compared to lymphatic vessels. Our data showed that almost genes except Hspa4 were increased or sustained in isolated primo vessels compared with lymphatic vessels (by RQ-PCR, Flt4, 2.58 fold; Hif1a, 1.95 fold; Agtr1, 2.03 fold; Mtf2, 1.44 fold; Hsph1, 1.83 fold; Agtr2, 1.52 fold; Pparg, 1.05 fold; Pdgfd, 1.02 fold; Hspa4, decreased 0.50 fold), suggesting primo vessels as a central regulator in diverse physiology. Also, relative expression of all genes revealed that expression of Agtr1, Mtf2, Hsph1, Agtr2 and Hspa4 were remarkably increased in primo vessels, compared to other genes such as Flt4, Hif1a, Pparg, Pdgfd (In RE value with *gene/Gapdh*×10^4, Agtr1, 132.1; Mtf2, 109.1; Hsph1, 94.4; Agtr2, 71.4; Hspa4, 105.7; Flt4, 15.7; Hif1a, 2.5; Pparg, 7.8; Pdgfd, 11.0). It implied that Mtf2, Hsf1, Hsp 4, Agtr1 and Agtr2 with high amounts may involve in functional activity of primo vessels.

Conclusion: Our results are the first data that several genes are highly enriched in primo vessels. Additionally, these genes also could be expected to function specific role in primo vessels under patho/physiologic condition. Based on this result, we will further investigate the functional role of PVS in biology.

Acknowledgment: This work was supported by the National Research Foundation of Korea (NRF) funded by the Korea government (Ministry of Science and ICT) under Grant No. 2016R1E1A2A01953467.

Key Words: Primo vasculature, Lymphatic vessels, Gene expression, Flt4, Agtr1, Hif1a

P1-01 (PO-B-02)

Calcium-sensing receptor is a critical mediator of chemotaxis and chemokinesis in immune cells

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Calcium-sensing receptor (CaSR) has a universal function in the maintenance of biological balance. CaSR senses the extracellular change of various ions such as Ca^{2+} and OH-, and transfers the environmental changes into intracellular signaling pathways. To date, diverse cellular functions have been extensively discussed within different CaSR-expressing cell types. However, limited insight into the link between CaSR and immune cell migration has been explored. Here we report that CaSR is a critical mediator on enhancing both chemotactic and chemokinetic immune cell migration. By using versatile live imaging techniques, we demonstrated that CaSR activation induces diverse downstream pathways that govern the migratory capacity. In this context, Cdc42 generates cytoskeleton-driven cellular protrusions to steer directional cell migration (chemotaxis) through the phosphatidylinositol 3-kinase pathway. Whereas, Ca^{2+}-calmodulin dependent myosin light chain kinase (MLCK) induces cell contractility that plays an important role in speeding up the average migration speed (chemokinesis). Moreover, perturbation of MLCK induced myosin light chain phosphorylation process completely turned off the cell motility, and also chemotactic response, indicating that MLCK-induced cell contractility plays a fundamental role-giving a starting signal-in immune cell migration. Our findings illuminate an unrecognized role of CaSR signaling network in immune cell migration, providing potential evidences for developing novel approaches for immunological therapies.

Key Words: Calcium sensing receptor, Immune cell, Chemotaxis, Chemokinesis

P1-02 (PO-A-01)

Novel KCNQ4 mutations in Korean patients with nonsyndromic hearing loss

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KCNQ4 encodes a voltage-gated K^+ channel (Kv7.4), and is highly expressed in the hair cells of the cochlea and plays a pivotal role in maintaining cochlear K^+ homoeostasis. It has been known that many mutations in the *KCNQ4* gene induce autosomal dominant non-syndromic hearing loss (ADNSHL) prominent in the high frequencies and associate with deafness mapping the DFNA2 locus. In the current study, we utilized WES to identify the causative mutation of NSHL in two Korean families. The WES analysis revealed a missense mutation (c.796G>T; p.Asp266Tyr) and an in-frame deletion mutation (c.259_267del; p.Val87_Asn89del) in *KCNQ4*. While p.Asp266Tyr showed early onset feature and moderate hearing loss, p.Val87_Asn89del showed late onset and high frequency specific hearing loss. In the heterologous expression of the mutants in *KCNQ4* in HEK293T cells, it revealed that both mutations did not have any problem in protein trafficking to plasma membrane. In addition, both mutant *KCNQ4* proteins interacted with wild type *KCNQ4*, which indicate that mutant proteins hinder the function of wild type *KCNQ4* and had dominant negative effects. p.Asp266Tyr was located in channel pore region, whereas p.Val87_Asn89del was located in 1st transmembrane domain. Both mutants showed no appreciable amounts of linoperdine-sensitive *KCNQ4* current and was not further activated by KCNQ channel openers (retigabine and zinc pyrithione), confirming their patho-

genic potential. Each mutant was co-expressed with WT-KCNQ4 at the various ratios, and was exhibited dominant negative effects. Patch-clamp experiments using tandem concatemers demonstrated that WT-D266Y exhibited comparable K^+ currents to that of WT-WT, and was activated by KCNQ openers. On the contrary, WT-V87_N89del failed to exhibit K^+ currents and was not further activated by openers. These results suggest that mutations in KCNQ4 should be examined in individuals with progressive NSHL and the main pathomechanism is related with decreased potassium channel activity instead of the problem in protein synthesis and trafficking.

Key Words: DFNA2, KCNQ4, Nonsyndromic hearing loss, Whole exome sequencing

P1-03 (PO-B-03)

Molecular mechanism of voltage-gated Ca^{2+} channel regulation by membrane PIP_2

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Voltage-gated calcium (Ca_V) channels play essential roles in adjusting calcium influx upon membrane depolarization. Ca_V2 (N-, P/Q- and R-type) channels are concentrated in the presynaptic nerve terminals and important for the neurotransmitter release. Adjusting the presynaptic calcium channel gating exerts potent influence on synaptic plasticity. Ca_V channels need auxiliary subunits for proper trafficking to the plasma membrane and the channel gating. Especially β subunit plays crucial roles in the surface expression of Ca_V channel and the fine-tuning of gating. It has been known that Ca_V channels are modulated by membrane phosphatidylinositol 4,5-bisphosphate (PIP_2). The binding affinity between ion channel and PIP_2 is important for the channel gating normally, but molecular mechanism of PIP_2 regulation remains unclear. It was recently reported that subcellular localization of β subunit is a key factor for the control of PIP_2 sensitivity of the Ca_V channels. Here we found that PIP_2 sensitivity of Ca_V channels is determined by the bending of I-II linker of Ca_V channels. When the I-II linker bends to the plasma membrane, current inhibition by PIP_2 depletion significantly decreased. We also found that inserting a flexible linker between Lyn and GK domain of β subunit increased the PIP_2 sensitivity of Ca_V channels. Together, our results suggest that the extent of bending of I-II linker to the plasma membrane is the regulatory mechanism of PIP_2 sensitivity on Ca_V channels and this is mainly regulated by Ca_V β subunit.

Key Words: Voltage-gated calcium channel, PIP_2, Channel gating, Ca_V β subunit

P1-04 (PO-A-02)

PRMT7 regulates neuronal excitability via modulation of NALCN activity

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NALCN is a Na^+ leak channel that is predominantly expressed in neurons where it regulates the resting membrane potential and neuronal excitability. NALCN is activated by decreases in extracellular calcium and mediated the vast majority of calcium-dependent excitability. However, the regulatory mechanisms of NALCN in neurons are still unclear. Here we show that protein arginine methyltransferase PRMT7 controls NALCN activity, thereby regulating neuronal excitability. We found that hippocampal dentate gyrus granule cells (DG-GCs) from Prmt7-/- mice exhibit increased excitability compared to WT DG-GCs. The elevated neuronal excitability in Prmt7-/- mice appears to be a direct result of increased NALCN activities. PRMT7 depletion activates NALCN and occludes the effects of extracellular calcium in 293T cells. An arginine residue in NALCN's intracellular tail is critical for this effect. Taken together, these data suggest that PRMT7 inhibits NALCN activity through arginine methylation, thereby preventing neuronal hyperexcitability. This work describes a novel pathway of NALCN regulation.

Key Words: PRMT7, NALCN, Neuronal excitability

P1-05

Regulation of spontaneous glutamate release by presynaptic M-type K^+ channels in the hippocampal pyramidal neurons

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Spontaneous neurotransmitter release has important functions, including regulation of dendritic protein synthesis and stability of synaptic networks. Stochastic opening of presynaptic Ca^{2+} channels is suggested to cause vesicle fusion, but the mechanism of how it is regulated is poorly understood. In the present study, we investigated the effect of presynaptic M-type K^+ currents (I_M) and presynaptic membrane potentials on spontaneous glutamate release. Blockade of I_M using linopirdine or XE-991 increased frequency of miniature excitatory postsynaptic currents (mEPSCs) by 2.1 fold in pyramidal cells of CA1 hippocampus (CA1-PCs). Linopirdine or XE-991 induced depolarization of pyramidal cells of CA3 hippocampus, which are presynaptic cells for CA1-PCs, by 2.8 mV. We examined effects of membrane potential changes on mEPSCs frequency in hippocampal autaptic cultured neurons under voltage clamp conditions, and found that depolarization from -70 to -60 mV increased mEPSCs frequency by 1.4 fold. Interestingly, I_M blockade increased mEPSCs frequency by 1.7 fold, even though membrane potential was held at -70 mV. These results suggest that the effect of I_M blockade on stochastic opening of Ca^{2+} channels its more powerful than its effect on membrane potentials. Possible mechanisms underlying this disparity are discussed. Furthermore, we suggested that the main Ca^{2+} fluxes via M-channel blockade should be arranged by L-type Ca^{2+} channels, so that M-channels could be coupled with L-type Ca^{2+} channels.

Key Words: M-type K^+ channels, mEPSCs

P1-06

Altered Na^+ and Cl^- transporting activity and dysregulated pH homeostasis in hyperkalemic db/db cardiac arrest

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During the cardiac surgery, hyperkalemic cardioplegic solutions such as Gustodiol prevent cardiac depolarization and sustain the arrest. The ionic properties and function of ion transporters have been well established in isolated cardiac myocytes. However, whether the transporting activities of ion channels are maintained during the cardioplegic arrest and any difference between normal and diabetic heart remain unknown. In this study, we found that mis-localized Na-K-Cl cotransporter NKCC1 was observed in db/db diabetic heart. Cardiac arrest by Gustodiol solution preserved acidification property mediated by NH_4^+ pulse in wild type. Although no difference of the expression of NKCC1 and phosphorylated NKCC1 protein was revealed between wild type and db/db cardiac tissues, enhanced NKCC1 activity was observed in LV of db/db during the cardiac arrest. To evaluate the dependency of Cl^-, changes of intracellular Cl^- concentration in WT and db/db during Reg and HTK arrest were examined the MQAE fluorescence quenching technique. Analysis of Cl^- transporting activity in LV cardiac tissues of WT and db/db mice addressed that the Cl^- transporting activity of db/db LV was dramatically increased compared to that of wild type LV. The pH changes by chloride/bicarbonate exchange activities of LV were not statistically different between WT and db/db mice. To evaluate the expres-

sion of SLC26A6, a dominant Cl^-/HCO_3^- exchanger, between WT and db/db mice, we performed the western blot analysis in WT and db/db cardiac tissues. Interestingly, SLC26A6 expression and also SLC26A6 activating component carbonic anhydrase II and IV were increased. The Na^+ and Cl^- transporting activity were mainly mediated by NKCC. We examined the effect of NKCC inhibitor Bumetanide with Gustodiol solution during cardioplegic arrest. The acidification rate was decreased by Bumetanide with dose-dependent manner in wild type. However, the inhibitory effect of Bumetanide on acidification rate was abolished in db/db, although no difference in resting pH level between wild type and db/db. As such, this study address that the regulation of Cl^- transporting activity in db/db cardiac tissue will provide an effective strategy for preventing cardiac damage in diabetic patients.

Key Words: Cardioplegia, NKCC1, SLC26A6, Chloride, Diabetes

P1-07

Modulation of mesenchymal stem cell tropism through the recruitment and enhanced activity of SLC4A7

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Cell migration of mesenchymal stem cells (MSCs) is a central process for using therapeutic method. Recent studies show that ion channels are involved in cell migration by recruiting ion channels to leading edge of migrating cells. However, whether sodium/bicarbonate cotransporter (NBC) is associated with migration toward cancer cells in human MSCs is poorly understood. In this study, we investigated the migration of MSCs through the effect of human lung cancer cells A549 and the involvement of SLC4A7, NBCn1-A. A549 cells enhanced the migration of MSCs and inhibition of SLC4A7 by NBC inhibitor DIDS and anti-SLC4A7 antibody decreased the migration. The cancer provides more acidic circumstances. The alkalization of extracellular pH level of A549 decelerated the MSC migration. The treatment of alkalized agents NH4Cl and acetazolamide had no effect on secreted interleukins and chemokines, MCP-1, CXCL12 and IL-8 of A549. The activity of SLC4A7 was increased in the enhanced migration-showed MSC, however mRNA level of SLC4A7 was not changed. The expression of SLC4A7 condensed on plasma membrane and expression of cytoskeletal proteins, F-actin and vinculin, also increased in the enhanced migration-showed MSC with using 3D-reconstructive imaging. Above all, our results show that cancer cells and its circumstances increase MSC migration through the involvement of SLC4A7, suggesting that MSCs could be considered as cancer trackers and a useful tool for cancer cell therapy.

Key Words: MSC, Migration, SLC4A7

P1-08

Gαi-mediated TRPC4 activation by polycystin-1 contributes to the endothelial function via STAT1 activation

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Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder caused by polycystin-1 and polycystin-2 mutations. Hypertension and aneurysm are frequently associated with polycystic kidney disease, which is closely related to endothelial dysfunction. Polycystin-1 is an atypical G protein-coupled receptor that activates G protein by self-cleavage, induces intracellular signaling via activated G protein, and cell response by ion channel activation has been reported. TRPC4 is a calcium-permeable cation channel and is activated by a specific subtype of G protein ($G\alpha_i$). In this study, we hypothesized that polycystin-1 acts as a G protein-coupled receptor and activates G protein, resulting in TRPC4 activity. The C-terminus of polycystin-1 contains a G protein binding domain and selectively bound to $G\alpha_{i3}$ among the inhibitory G protein subtypes. The increase of TRPC4 activity by polycystin-1 was mediated by $G\alpha_{i3}$ and its mechanism was found to be the dissociation of the $G\alpha_{i3}$ from cleavage of PC1 C-terminus. Calcium influx through TRPC4 activated signal transducer and activator of transcription (STAT) 1 to regulate cell proliferation and death. In endothelial cells, endogenous expression and calcium influx of polycystin-1 and TRPC4 were observed. Inhibition of their expression or antagonist inhibited endothelial cell migration and weakened endothelial junctions. These results suggest that TRPC4 activity by polycystin-1 is important for endothelial cell monolayer formation and permeability through endothelial cells, and that TRPC4 is a target in the mechanism and treatment of aneurysms associated with ADPKD.

Key Words: Polycystin, TRPC, $G\alpha_i$, STAT1, Endothelial cells

P1-09

Regulation of TRPC4, TRPC5 homotetrameric and TRPC1/4, C1/5 heterotetrameric channel activity by $PI(4,5)P_2$ hydrolysis

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Transient receptor potential canonical (TRPC) 4 and TRPC5 are known to be modulated by Gq-PLC pathway. Since phosphatidylinositide 4,5-biphosphate ($PI(4,5)P_2$) maintains TRPC4 and TRPC5 channels, Gq-PLC pathway inhibits channel activities through the hydrolysis of $PI(4,5)P_2$. However, not only the effects of $PI(4,5)P_2$ on TRPC4, C5 homotetrameric channels, but also on heterotetrameric channels with TRPC1 were not known. Thus, we investigated the difference in $PI(4,5)P_2$ sensitivity not only between the channel types but also between homo- and heteromers. First, by using a voltage-sensing phosphatase (DrVSP), we show that $PI(4,5)P_2$ dephosphorylation robustly inhibited not only TRPC4α, C4β, C5 homotetramer currents but also TRPC1/C4α, C1/C4β, C1/C5 heterotetramer currents. Secondly, the sensitivity to $PI(4,5)P_2$ dephosphorylation of homotetramer followed by TRPC5 > TRPC4α > TRPC4β. Interestingly, when forming heterotetramers with TRPC1, the sensitivity curve converged and showed only mimic difference between the channels. Thirdly, neutralization of basic residues, we determined the $PI(4,5)P_2$ binding sites which showed low FRET with $PI(4,5)P_2$ sensor. Furthermore, these sites show two kinetically distinct effect independently; regulate voltage sensitivity that affects $PI(4,5)P_2$ affinity to channel and change in current amplitude. In conclusion, our results indicate a fundamental role for $PI(4,5)P_2$ in regulating TRPC1/4 and C1/5 heterotetramer activity as well as TRPC4, C5 homotetramer.

Key Words: TRPC, Gq-PLC pathway, $PI(4,5)P_2$, DrVSP

P1-10

Restored activity of HCO_3^- transporters by knockdown of spinophilin enhance invasive function of lung cancer cells

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The spinophilin (SPL) involves in the cell migration and invasion with arrangement of cytoskeletal protein. Polarized variety of ion transporters also systematically involves in cell migration. Here, we showed that SPL was essential for the lung cancer cell migration with regulated HCO_3^- transporter activity. Although there was no interaction between SPL and Na^+/HCO_3^- cotransporter NBCn1, knockdown of SPL modulated the expression of NBCn1, addressed a migration-associated protein at leading edge. Dis-

ruption of actin cytoskeleton by Latrunculin A attenuated the surface expression and NBC activity of NBCn1. We examined the chemotactic agarose assay to evaluate the invasive role of SPL. The siRNA-SPL enhances the lung cancer cell invasion. To evaluate the involvement of HCO_3^- transporter, the chloride/bicarbonate exchange (CBE) and NBC activities were measured in response to pH-dependent chemotactic agarose assay. The NBC and CBE activities were restored during the knockdown of SPL. The inhibition of cancer suppressive role by siRNA-SPL enhanced cell invasion through the restored activity of HCO_3^- transporters. Collectively, these results reveal important functions for SPL in regulating cancer cell–invasive growth via modulation of HCO_3^- transporting activity.

Key Words: SPL, Migration, Ion transporter, A549 cells, Lung cancer

P1-11

Dapoxetine, a selective serotonin reuptake inhibitor inhibits voltage-gated K^+ channels in coronary arterial smooth muscle cells from rabbit

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We investigated the inhibitory effect of dapoxetine, a selective serotonin reuptake inhibitor (SSRI), on voltage-dependent K^+ (Kv) channels using native smooth muscle cells from rabbit coronary arteries. Dapoxetine inhibited Kv channel currents in a concentration-dependent manner, with an IC_{50} value of 2.68±0.94 μM and a slope value (Hill coefficient) of 0.63±0.11. Application of 10 μM dapoxetine accelerated the rate of inactivation of Kv currents. Although dapoxetine did not modify current activation kinetics, it caused a significant negative shift in the inactivation curves. Application of train step (1 or 2 Hz) progressively increased the inhibitory effect of dapoxetine on Kv channels. In addition, the recovery time constant was extended in its presence, suggesting that the longer recovery time constant from inactivation underlies a use-dependent inhibition of the channel. From these results, we conclude that dapoxetine inhibits Kv channels in a dose-, time-, use-, and state (open)-dependent manner, independent of serotonin reuptake inhibition.

Key Words: Dapoxetine, Voltage-dependent K^+ channel, Coronary artery, Smooth muscle, Serotonin reuptake inhibitor

P1-12

Anti-diabetic drug nateglinide induces vasodilation via activation of voltage-dependent K^+ channels in aortic smooth muscle

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We investigated the vasorelaxant effect of nateglinide using phenylephrine-induced pre-contracted aortic rings. The application of nateglinide induced vasorelaxation in a concentration-dependent manner. Pretreatment with the BK_{Ca} channel inhibitor paxilline, Kir channel inhibitor Ba^{2+}, and K_{ATP} channel inhibitor glibenclamide, did not affect the vasorelaxant effect of nateglinide. However, pretreatment with the Kv channel inhibitor 4-AP, effectively reduced the vasorelaxant effect of nateglinide. Pretreatment with the Ca^{2+} inhibitor nifedipine and the SERCA inhibitor thapsigargin did not change the vasorelaxant effect of nateglinide. Additionally, the vasorelaxant effect of nateglinide was not altered in the presence of an adenylyl cyclase, a protein kinase A, a guanylyl cyclase, or a protein kinase G inhibitor. The vasorelaxant effect of nateglinide was not affected by the elimination of the endothelium. In addition, pretreatment with a nitric oxide synthase inhibitor, L-NAME, and a SK_{Ca} channel inhibitor, apamin did not change the vasorelaxant effect of nateglinide. From these results, we concluded that nateglinide induced vasorelaxation via the activation of the Kv channel independent of other K^+ channels, Ca^{2+} channels, intracellular Ca^{2+} ($[Ca^{2+}]_i$), and the endothelium.

Key Words: Nateglinide, Aortic smooth muscle, Voltage-dependent K^+ channel

P1-13

A tricyclic antidepressant, nortriptyline inhibits the voltage-dependent K^+ channels in coronary arterial smooth muscle cells from rabbit

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We demonstrated the effect of nortriptyline, a tricyclic antidepressant drug and serotonin reuptake inhibitor, on voltage-dependent K^+ (Kv) channels in freshly isolated rabbit coronary arterial smooth muscle cells using a whole-cell patch clamp technique. Nortriptyline inhibited Kv currents in a concentration-dependent manner, with an apparent IC_{50} value of 2.86±0.52 μM and a Hill coefficient of 0.77±0.1. Although application of nortriptyline did not change the activation curve, nortriptyline shifted the inactivation current toward a more negative potential. Application of train pulses (1 or 2 Hz) did not change the nortriptyline-induced Kv channel inhibition, suggesting that the effects of nortiprtyline were not use-dependent. Preincubation with the Kv1.5 and Kv2.1/2.2 inhibitors, DPO-1 and guangxitoxin did not affect nortriptyline inhibition of Kv channels. From these results, we concluded that nortriptyline inhibited Kv channels in a concentration-dependent and state-independent manner by changing the steady-state inactivation curves independently of serotonin reuptake.

Key Words: Nortriptyline, Voltage-dependent K^+ channel, Coronary artery

P1-14

Salivary spinophilin tunes chloride/bicarbonate exchangers for the Cl^- secretion in salivary glands

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The chloride/bicarbonate exchangers are implicated in the regulation of intracellular pH and fluid secretion in salivary glands. Previous studies have reported that the scaffolding protein spinophilin is associated with anion exchanger AE2 and enhances the chloride/bicarbonate exchange activity. However, the role of spinophilin on the regulation of transporters and the balance of chloride/bicarbonate exchange in exocrine glands still remain unknown. In this study, SPL was upregulated upon stimulation of the salivary glands with agonist of β-adrenergic receptors isoproterenol. Interestingly, the spinophilin enhanced the chloride/bicarbonate exchanger activity of basolateral anion exchanger AE2, whereas, attenuated that of solute carrier family SLC26A6. Furthermore, the spinophilin associated with a STE20/SPS1-related kinase SPAK and showed an additive effect on the modulation of the activity of AE2, not SLC26A6. In the presence of protein phosphatase 1, the spinophilin had no effect on AE2 activity. The intracellular Ca^{2+} depletion by Ca^{2+} chelator BAPTA-AM inhibited the interaction with AE2 and spinophilin and abrogated the enhanced effect of spinophilin on AE2 activity; however, it increased the interaction between SLC26A6 and spinophilin but had no effect on SLC26A6 activity. We evaluated the physiological effect of sympathetic nervous system activation on salivary

glands and found that the acute stimulation of submandibular acinar and ductal cells with isoproterenol increased the intracellular Ca^{2+} level but had no effect on chloride/bicarbonate exchange activity. Ductal chloride/bicarbonate exchange activity was increased following pretreatment with isoproterenol. Pretreatment with calmodulin-dependent protein kinase II inhibitor KN-93 suppressed the chloride/bicarbonate exchange activity of isolated ducts but had no effect on that of acinar cells. Thus, the calmodulin-dependent protein kinase II and spinophilin are required for AE2 activity in the duct. Considering the actin polymerization-dependent regulatory role of spinophilin on chloride/bicarbonate exchange activity, the treatment of (Sarrouilhe et al., 2006)actin depolymerization agent cytocalasin D induced the mis-localized AE2 in the membrane and isolated salivary cells were reduced chloride/bicarbonate exchange activities. The basolateral Cl^- uptake by AE2, not luminal uptake SLC26A6, was mediated by the association of actin-dependent spinophilin. Therefore, spinophilin may act as a regulatory protein to preserve the concentration and path of Cl^- trans-epithelial flux from basolateral to luminal direction in salivary glands.

Key Words: Spinophilin, AE2, SLC26A6, Secretion, Salivary glands

P1-15

GNB5 regulates TRPC3 and store-operated Ca^{2+} entry mediated bone remodeling

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Store-operated Ca^{2+} entry (SOCE), play a critical role in bone homeostasis. We hypothesized that SOCE mediated by TRPC3, also regulates bone remodelling via osteoblast or osteoclast activation. We measured μCT analysis, and alizarine red staining for bone phenotype in TRPC3 KO mice. Next, we tried to find the regulators of TRPC3 in heterologous expression system. We expressed guanine nucleotide-binding protein subunit beta-5 (GNB5) in HEK293T and measured a substantial cytosol Ca^{2+} by fluorescence imaging system using a Fura2-AM. Bone phenotype of *TRPC3*$^{-/-}$ mice, increased bone mass was found in μCT analysis, and alizarine red staining was also increased. From these results we infer TRPC3 is important in regulates osteoblast's function. Cells that co-expressed STIM1, TRPC3, and GNB5 represent higher store-operated Ca^{2+} influx than that of only, STIM1 and TRPC3 co-expression. From these results indicate that GNB5 over-expression induces increase of STIM1-TRPC3 dependent store-operated Ca^{2+} entry. It may relate with the interaction of GNB5 and component of the store-operated Ca^{2+} channel. From this preliminary result, regulation of bone remodelling via GNB5 and TRPC3 would be possible.

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Key Words: Store-operated Ca^{2+} entry (SOCE), Guanine nucleotide-binding protein subunit beta-5 (GNB5), TRPC3, Bone remodeling

P1-16

Real-time assessment of shear-induced ATP release from a rat atrial myocyte using sniffer-patch clamp

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Atrial myocytes are subjected to shear stress during the cardiac cycle and haemodynamic disturbance. We have previously shown evidence that shear stress (~16 dyn/cm^2)-induced atrial global Ca^{2+} waves are abolished by the blockades of ATP release, gap junction hemichannel or P2 purinergic signaling. In this study, we directly examined ATP release from single atrial myocytes under shear stress using the sniffer patch clamp technique. We first made HEK293 cells expressing the $P2X_7$ purinoceptors together with green fluorescence proteins and used the cell to report ATP released from nearby atrial cell as $P2X_7$ current. Overexpression of $P2X_7$ in these HEK293 cells was confirmed by RT-PCR, western blotting, and a green fluorescence. To functionally confirm the overexpression of $P2X_7$ receptors, we measured ATP-induced inward current using CsCl-rich internal solutions (in mM: 137 CsCl, 10 HEPES, 1 MgCl2, 5 EGTA). ATP generated transient inward currents at –70 mV in HEK293 cells expressing GFP-tagged $P2X_7$ in a concentration-dependent manner (EC_{50}=31.2 μM; 14.2±1.76 pA/pF at 3 mM ATP, n=10). This current was almost completely suppressed by the application of suramin (30 μM), the P2 purinergic antagonist (0.17±0.13 pA/pF at –70 mV, n=10, P<0.0001), and was negligible in the HEK293 cells expressing GFP only (0.28±0.07 pA/pF at –70 mV). Simultaneous measurement of ATP release and Ca^{2+} images using a sniffer patch clamp and two-dimensional confocal microscopy, respectively, revealed that ATP-sensitive current (peak: 1.34±0.30 pA/pF, n=19) was developed at 200-300-ms prior to the onset of the global Ca^{2+} waves after shear (~16 dyn/cm^2) application. Note that there was no shear-induced current in the HEK293 cells without neighboring atrial myocytes. The magnitude of $P2X_7$ current in sniffer cells under shear stress was comparable to that induced by external application of 0.1 μM ATP with no shear stress. Our results suggest that shear stress induces ATP release from atrial myocytes, thereby initiating P2 purinoceptor-dependent proarrhythmic Ca^{2+} waves.

Key Words: Shear stress, $P2X_7$, ATP, Sniffer-patch clamp, Ca^{2+} wave, Inward current, HEK293 cell, Atrial myocyte

P1-17

Temperature-dependent increase of the calcium sensitivity and activation kinetics of ANO6 Cl^- channel variants

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Anoctamin-6 (ANO6) belongs to a family of Ca^{2+}-activated Cl^- channels (CaCCs) and four types of splicing variants have been identified. Unlike other CaCCs, ANO6 activation requires high intracellular free Ca^{2+} concentrations ($[Ca^{2+}]_i$>1 μM) and shows delayed activation, requiring several minutes to reach full activation. These findings have raised doubts about the physiological role of ANO6 as an ion channel. Since previous experiments have been conducted under non-physiological conditions (room temperature), we hypothesized that temperature might modulate the activity of ANO6 variants. We identified that the physiological temperature condition (37°C) increased the calcium sensitivity and activation kinetics of ANO6. Under 37°C, V1, V2 and V5 were activated with 1 μM $[Ca^{2+}]_i$, and V2 and V5 were activated with a sub-micromolar concentration of 300 nM $[Ca^{2+}]_i$. Moreover, the physiological temperature significantly accelerated the activation kinetics of the three variants. Although surface biotinylation immunoblot showed higher membrane expression of V1, V2 and V5 showed larger whole-cell currents with faster activation than V1 at 37°C. Interestingly, however, the temperature-dependent Ca^{2+}-sensitization of ANO6 became insignificant in the inside-out path clamp conditions, suggesting critical roles of cytosolic factors yet identified. Different from the anion channel activity, the physiological temperature did not induce the scramblase function of ANO6 with submicromolar $[Ca^{2+}]_i$ (ca. 300 nM), irrespective of the variant types. Our present results suggest the physiologically meaningful anion conducting property of ANO6, especially V2 and V5, under the body temperature, which might precede the scramblase activity.

Key Words: ANO6 variants, Temperature regulation, Calcium sensitivity, Delayed activation, Chloride channel

P1-18

Identification of critical amino acids in the C-terminal of TREK-2 K^+ channel for ATP- and pH_i-sensitive regulation

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TWIK-Related two-pore domain K^+ channels (TREKs) are regulated by intracellular pH (pH_i) and $PI(4,5)P_2$. Previously, Glu306 in proximal c-terminal (pCt) of mouse TREK-1 was identified as the sensing residue for the acidic pH_i-dependent activation. However, the direction of $PI(4,5)P_2$ sensitivity is controversial between research groups. We have suggested that TREKs are inhibited by intracellular ATP via endogenous $PI(4,5)P_2$ formation. Here we investigate the anionic and cationic residues of Ct for the pH_i and ATP-sensitivity in human TREK-2 (hTREK-2). In inside-out patch clamp recordings ($I_{TREK\text{-}2,i\text{-}o}$), acidic pH_i-induced activation was absent in E332A, and was partly attenuated in E335A. Neutralization of cationic Lys (K330A) also eliminated the acidic pH_i-sensitivity of $I_{TREK\text{-}2,i\text{-}o}$. Unlike the inhibition of wild type (WT) $I_{TREK\text{-}2,i\text{-}o}$ by intracellular ATP, neither E332A nor K330A were sensitive to ATP. Opposite to E332A or K330A, neutralization of triple Arg (R355-7A) suppressed the basal activity of $I_{TREK\text{-}2,i\text{-}o}$ even without ATP. Nevertheless, R355-7A could be still activated by acidic pH_i. In whole-cell recordings of TREK-2 ($I_{TREK\text{-}2,w\text{-}c}$), K330A and E332A showed nearly saturated high activity, showing attenuated or insignificant activation by chemical activating conditions such as arachidonic acid. $I_{TREK\text{-}2,w\text{-}c}$ of R355-7A was markedly lower than wild type, while showing prominent activation by arachidonic acid. The results suggest concerted roles of the charged residues Lys^{330} and Glu^{332} for the inhibition by physiological $PI(4,5)P_2$ and activation by acidic pH_i. The more distal triple $Arg^{355\text{-}7}$ might play as a pivotal role for the spontaneous activation of TREK-2 under the ATP-free condition, i.e. disinhibition from the intrinsic $PI(4,5)P_2$.

Key Words: K2P, TREK channel, PIP_2, pH, C-terminal

P1-19

Anoctamin1 does not function as ion channel in head and neck squamous cell carcinoma due to lack of surface expression

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Anoctamin1 (ANO1) gene (*TMEM16A*) encodes a calcium-activated chloride channel (CaCC) in various epithelial cells, and its role has also attracted attention in cancer research. In several tumors including head and neck squamous cell carcinoma (HNSCC), the expression of ANO1 is significantly amplified, and the ANO1 knock-down reduces cell migration and/or proliferation. However, the electrophysiological role of ANO1 in the tumor biology is still unclear. Here, we detected a highly over-expressed ANO1 in HNSCC patients and significant correlation between the expression level of ANO1 and prognosis by analyzing TCGA database. We further measure the current of ANO1 (I_{ANO1}) in three type of HNSCC, breast cancer (BCa), and prostate cancer (PCa) cell lines using whole-cell patch clamp. I_{ANO1} was detected in BCa and PCa, while not in any HNSCC cell line. Confocal imaging and immunoblot analysis of HNSCCs revealed no significant expression of ANO1 in the plasma membrane despite the high cytosol expression. In contrast, BCa and PCa cells show unequivocal membrane expression, consistent with the I_{ANO1} recordings. Moreover, in the present of ANO1-specific inhibitors, the migration and proliferation of cancer cell was reduced only in BCa and PCa cell lines with the surface expresses ANO1. Taken together, our results suggest that ANO1 does not function as ion channel in HNSCC due to the lack of surface expression. The surface expression of ANO1 is a prerequisite for the modulation of cancer cell proliferation and migration by the ANO1 channel inhibitor.

Key Words: ANO1, TMEM16A, Head and neck squamous cell carcinoma, Surface expression

P1-20

Carbonic anhydrase 12 E/K mutation modulates the function of AQP5 in submandibular glands

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Aquaporin 5 is a major water channel in submandibular gland. Recently, the carbonic anhydrase CA12 E143K mutation decreased the activities of transporters and subsequent ductal fluid secretion. The patients who have CA12 E143K mutation revealed dry mouth phenotype. But how basolateral CA12 modulates luminal aquaporin5 expression and function in salivary glands remains unknown. In this study, we found the mis-localized aquaporin5 in CA12 E143K mutated salivary glands. The CA12 and CA12 E143K co-localized with aquaporin5 *in vitro*. The CA12 E143K mutation lost membrane localization and also affected the localization of aquaporin5 in the cytosol not in the plasma membrane. Surface biotinylation assay also showed the reduced surface expression of aquaporin5 in the presence of CA12 E143K. The basal pH of CA12 E143K was lower than that of CA12. To mimic the intracellular acidosis, cells were treated the $0Na^+$ and DIDS, an anion exchanger inhibitor, followed by NH4Cl stimulation. The surface expression of aquaporin5 was diminished by acidosis. To evaluate the role of CA12 on the volume regulation of aquaporin5, overexpressed cells were applied by hypertonic and hypotonic stimuli and measured regulation of volume. The volume of CA12-enriched cells was sensitive to hypertonic stimulation, whereas, the volume regulation of aquaporin5 was resistant to stimulation in the presence of CA12. Interestingly, CA12 E143K mutation induced dramatic cell swelling or shrinkage in hyper/hypotonic solution, suggesting dysfunction of cytosolic aquaporin5 induced by CA12 E143K mutation in response to hyper/hypotonic stimuli. Our findings suggest that the aquaporin5 expression was modulated by intracellular pH and its volume regulation was modulated by CA12 in salivary glands, indicative of impaired fluid secretion associated with inhibition of CA12.

Key Words: Carbonic anhydrase 12, Aquaporin5, Submandibular gland

P1-21

Augmentation of Ca^{2+}-induced Ca^{2+} release by chrysosplenol C via sensitization of Ca^{2+} release sites in ventricular myocytes

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We investigated cellular mechanisms for the positive inotropic effects of chrysosplenol C (4',5,6-trihydroxy-3,3',7-trimethoxyflavone), isolated from *Miliusa balansae*, in rat ventricular myocytes. The effects of chrysosplenol C on intracellular Ca^{2+} signal and L-type Ca^{2+} current were assessed using two dimensional rapid confocal Ca^{2+} imaging and whole-cell patch clamp technique, respectively, in freshly isolated adult rat ventricular myocytes. The systolic Ca^{2+} concentrations and the magnitudes Ca^{2+} transients, measured at 1 Hz, were significantly increased (by about 40%) by chrysosplenol C (50 μM). This chemical enhanced the frequency of Ca^{2+} sparks representing in situ behavior of ryanodine receptor clusters (Ca^{2+} release units). The amplitude, size (width and area), and duration of Ca^{2+} sparks were not altered by

chrysosplenol C. The Ca^{2+} loading in the sarcoplasmic reticulum (SR), estimated as caffeine (10 mM)-induced Ca^{2+} releases, was reduced, which is consistent with no change in the unitary properties of Ca^{2+} sparks. Interestingly, chrysosplenol C significantly augmented fractional releases from the SR on depolarizations, further supporting that it enhances the sensitivity of Ca^{2+} release units. Patch clamp study showed that this augmentation in Ca^{2+} releases did not appear to be caused by Ca^{2+} current change. These results suggest that chrysosplenol C increases contractility via sensitizing Ca^{2+} release sites in ventricular myocytes.

Key Words: Chrysosplenol C, Ryanodine receptor, Ca^{2+} sparks, Ca^{2+} current, Ventricular myocytes

P1-22

De-energized mitochondrial function in permeabilized rat ventricle myocytes

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Mitochondria are organelles which play a critical role in the generation of metabolic energy in cells. The supply of mitochondrial substrates is crucial for the mitochondrial functions. In previous study, we showed de-energized mitochondria in absence of mitochondrial substrates have also a membrane potential. To understand mitochondrial bioenergetics, the effects of Pi and ATP on the de-energized mitochondria were investigated. In this study, NADH, FAD and mitochondrial membrane potential (Ψ_m) were monitored using permeabilized ventricular myocytes of the rat. The Ψ_m of de-energized mitochondria was about -42 mV. The addition of Pi could hyperpolarize further about -2 mV. Surprisingly, when we add both Pi and ATP, $\Delta\Psi_m$ was dramatically hyperpolarized to about 51 mV. In addition, FAD signal was greatly increase which reflected FADH consumption. NADH signal was also increased, however, very small compared to FAD change. Interestingly, the addition of diazoxide (mitochondrial K_{ATP} channel opener) could inhibit Pi/ATP-induced hyperpolarization and FAD increase, but not completely. The cytosolic K^+ replacement with N-methyl-d-glucamine(NMDG) also attenuated Pi/ATP-induced effects, however, the states of the de-energized mitochondria was not changed by NMDG, that is, the FAD signal and the Ψ_m were not changed. A K_{ATP} channel blocker, 100 μM 5-HD, did not show any effect. Therefore K^+ flux via K_{ATP} channel may not participated in Pi/ATP-induced effects. The treatment of oligomycin A (F_1,F_0-ATPase blocker) like diazoxide could block the Pi/ATP-induced changes. From the above results, we postulated cytosolic K^+ is essential to generate Pi/ATP-induced changes. Mitochondrial K_{ATP} channel may not be related to those changes. Somehow, F_1,F_0-ATPase may control the FADH/FAD conversion with K^+ ion.

Acknowledgement: This research was supported by a fund (#R0005739) from KIAT.

Key Words: Mitochondria, NADH, FAD, Diazoxide, 5-HD

P1-23

The critical role of three charged residues in TRPC5 pore region in interaction with englerin A

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The classical transient receptor potential channel 5 (TRPC5), a nonselective cation channel (NSCC), has a crucial role in calcium influx. TRPC5 has been reported to be activated by muscarinic receptor activation, extracellular pH change, and inhibited by protein kinase C (PKC) pathway. Recent studies have also suggested that TRPC5 is extracellularly activated by englerin A (EA), but the mechanism is remained unclear. The purpose of this study is to investigate on the interaction site between TRPC5 and EA and thereby clarify the mechanism of TRPC5 activation through further studies. Human embryonic kidney (HEK293) cells were maintained according to the supplier's recommendations. The cells were seeded in 12-well plates prior to transient transfection. The following day, 0.5 μg/well of pcDNA3 vector containing the cDNA was mixed and transfected using the transfection reagent FuGENE 6 (Roche Molecular Biochemicals) according to manufacturer's protocol. Within 24 to 48 hours, the cells were trypsinized and collected for patch clamp recordings. Point mutations in TRPC5 were introduced using the QuickChange site-directed mutagenesis kit and appropriate primer sets. Sequences of the mutants were confirmed by DNA sequencing. In order to identify the interaction site between TRPC5 and EA, we first generated pore mutants. When screening the mutants with EA, we observed the EA-induced current increases of TRPC5 abolished in K554N, H594N, and E598Q mutants. The current increases of other mutants were reduced in different levels. We also tested the functional intactness of the mutants that showed no response to EA by using GTPγS and inferred that the three sites were responsible for the interaction between TRPC5 and EA. Our results suggest that the three residues, Lys-554, His-594, and Glu-598, in TRPC5 are responsible for direct interaction with EA inducing the channel activation. We also suggest that though other pore residues are not critical, they can partly contribute to the channel activation by EA.

Key Words: TRPC5, Englerin A, Pore mutant, Ion channel

P1-24

Identification of clustered phosphorylation sites in PKD2L1: how PKD2L1 channel activation is regulated by cAMP signaling pathway

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Polycystic kidney disease 2-like-1 (PKD2L1), or polycystin-L or TRPP2, formerly TRPP3, is a transient receptor potential (TRP) superfamily member. It is a calcium-permeable non-selective cation channel that regulates intracellular calcium concentration and thereby calcium signaling. PKD2L1 has been reported to take part in hedgehog signaling in renal primary cilia and sour tasting coupling with PKD1L3. In addition to the previous reports, PKD2L1 is recently found to play a crucial role in localization with β2-adrenergic receptor (β2AR) on the neuronal primary cilia. The disruption of PKD2L1 leads to the loss of β2AR on the primary cilia and reduction in intracellular concentration of cyclic AMP (cAMP). Since the role of cAMP and PKA is frequently mentioned in the studies of PKD diseases, we investigated on the mechanism of cAMP regulation in relation to the function of PKD2L1 channel. In this study, we observed the activity of PKD2L1 channel increased by the downstream cascades of β2AR and found the clustered phosphorylation sites, S682, S685, and S686 that are significant in the channel regulation by phosphorylation.

Acknowledgement: We thank Dr. Markus Delling (UCSF) for kindly donating human PKD2L1 construct.

Key Words: PKD2L1, TRPP3, Ion channel, Calcium, Phosphorylation, cAMP

P1-25

TRPM7 mediates mechanosensitivity in adult rat odontoblasts

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Odontoblasts, with their strategic arrangement along the outermost compartment of the dentin-pulp complex, have been suggested to have sensory function. In addition to their primary role in dentin formation, growing evidence shows that odontoblasts can act as mechanical transducer. Previously, we found that the majority of odontoblasts express TRPM7, the non-selective mechanosensitive ion channel reported to be critical in Mg^{2+} homeostasis and dentin mineralization. In line with this finding, we sought to elucidate the functional expression of TRPM7 in odontoblasts by pharmacological approaches and mechanical stimulation. Naltriben, a TRPM7-specific agonist, induced calcium transient in the majority of odontoblasts which was blocked by TRPM7 blockers such as high extracellular Mg^{2+} and FTY720. Mechanical stretch of odontoblastic membrane with hypotonic solution also induced calcium transient which was blocked by Gd^{3+}, a non-selective mechanosensitive channel blocker, and also by high extracellular Mg^{2+} or FTY720. When TRPM7-mediated calcium transients in odontoblasts were analyzed on subcellular level, remarkably larger transients were detected in the distal odontoblastic process compared to the cell bodies, which was further verified with comparable immunocytochemical analysis. Our results demonstrate that TRPM7 in odontoblasts can serve as a mechanical sensor, with its distribution to facilitate intracellular Ca^{2+} signaling in the odontoblastic process. These findings suggest TRPM7 as a mechanical transducer in odontoblasts to mediate intracellular calcium dynamics under diverse pathophysiological conditions of the dentin.

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Key Words: Odontoblast, Dental biology, Mechanotransduction, Electrophysiology

P1-26

Menadione generates reactive oxygen species and accumulates intracellular calcium in mouse pancreatic acinar cells

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Menadione belongs to the Vitamin K class of compounds, but can induce apoptosis of cultured cells via elevation of peroxide and superoxide radical levels. Reactive oxygen species (ROS) are known to be related to a variety of oxidative stress-induced pancreatic disorders including pancreatitis. We have previously reported that exogenous hydrogen peroxide accumulates intracellular calcium by attenuating refilling of intracellular calcium stores in mouse pancreatic acinar cells. In this study, we confirmed the effects of menadione on ROS generation and intracellular calcium accumulation in mouse parotid acinar cells. The intracellular calcium concentrations were measured in 2 μM of Fura-2/AM loaded cells, and the ROS generations were monitored in 10 μM of CM-H2DCFDA loaded cells. The oscillatory calcium signals were induced by perfusion of 500 nM carbamylcholine (CCh). The perfusion of 10 μM menadione resulted in additional elevation of intracellular calcium levels and termination of oscillatory calcium signals induced by physiological concentration of CCh. Antioxidants, N-acetyl-L-cysteine (NAC) or catalase, completely prevented menadione-induced intracellular calcium accumulation. The perfusion of menadione effectively enhanced cellular ROS generations, and that was completely blocked by pretreatment of NAC. These results provide evidence that endogenously generated ROS could accumulate intracellular calcium in mouse pancreatic acinar cells.

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Key Words: Reactive oxygen species, Menadione, Intracellular calcium, Antioxidants, Pancreatic acinar cells

P1-27

Function of carboxyl coiled coil of TRPC3 in the gating mechanism

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Canonical transient receptor potential 3 (TRPC3) amino acid sequence follows a coiled coil pattern (heptad repeat sequence) at both N and C terminus. Coiled coil domains of some voltage gated ion channels have been shown to modulate the channel gating. Therefore the objective of this project was to investigate the structure and function relationship of carboxyl terminus (CT) coiled coil domain (CCD) of TRPC3 channel. Following the identification of key hydrophobic residues of the heptad repeat, coiled coil breaking mutations were introduced to the coiled coil sequences of both amino terminus (NT) and CT-CCDs. CT-CCD breaking mutants but not the NT-CCD breaking mutants resulted a gain of function phenotype in TRPC3. The putative CT-CCD commences from M779 and continues up to end of CT. The calcium dependent inactivation is lost in the CT-CCD mutants and they show a calcium dependent gain of function. Furthermore, this gain of function phenotype of each amino acid mutation corresponds to the predicted CCD probability of each amino acid and the hydrophobicity of the amino acids. The peak of this phenotype is shown at I807 site. The coiled coil mutants show an increased permeability to calcium while permeability of magnesium, monovalent permeability and pore size remains intact. This gain of function is independent from STIM1 regulation. However, the gain of function can be partially related to lack of sensitivity for Calmodulin dependent regulation. Together, these findings points towards an allosteric calcium dependent regulation of TRPC3 by TRPC3 CT-CCD.

Key Words: TRPC3, CT, NT, CCD, Calcium dependent regulation

P1-28

Quercetin inhabits hSlo3 in a pH and calcium dependent manner through possible inhibition of Phosphatidylinositol kinases

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Slo3 is one of the most potent contributor to KSper. Dietary chemical compounds that can modulate hSlo3 poses possible modulatory effects on human fertility. Quercetin is a common dietary flavonoid known to modulate ion channels mainly by inhibition of protein kinase, inhibition of phospholipase and allosteric binding. The aim of this study is to find the effect of quercetin on KSper ion channels and mechanism by which quercetin affect the channel function. We used HEK293 co-transfected with hSlo3 and hLRRC52 in the patch clamp experiments. The results indicate that quercetin and its analogues dose-dependently inhibited hSlo3 current. Furthermore, external and internal acidic environment enhanced the quercetin effect on hSlo3. Increasing the internal free-calcium concentration diminished the effect of quercetin on hSlo3. PI3Kinase inhibitors and inhibitors of Phospha-

tidylinositol (3,4,5)-trisphosphate (PIP3) downstream signaling had strong inhibitory effects on hSlo3. Pre-treatment of PI3 kinase inhibitor LY 294002 rapidly inhibited the hSlo3 current and diminished the effect of quercetin. Inhibition of PIP3 downstream pathways, mTOR and guanylyl cyclase by rapamycin and ODQ respectively, could rapidly inhibit the hSlo3 current, however those treatments failed to hinder the effect of quercetin. Therefore the results indicate that the calcium and pH defendant inhibitory effect of quercetin on Slo3 is mainly though the inhibition of phosphatidylinositol kinases.

Key Words: Slo3, LRRC52, PIP2, PI3K, Ksper, Quercetin, Voltage gated Potassium channels

P1-29

Electrophysiological characterization of trpc6 mutants associated with kidney diseases

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Mutations in transient receptor potential cation channel, subfamily C, member 6 (TRPC6) have been identified to cause focal segmental glomerulosclerosis (FSGS) in human patients. A total of 18 substitution mutants and a one deletion mutant have been recorded in TRPC6 isolated from the kidneys of human patients with FSGS. Majority of these mutants are localized in AKR and CT-CCD. Interestingly, these mutants localized in AKR and CT-CCD, when over expressed in HEK 293 cells and tested using whole cell patch clamp experiments display a gain of function in the presence of free calcium containing electrophysiological solutions. Therefore, we selected an AKR mutant, N109H, and CT-CCD mutant, R894C, which displayed the greatest gain of function from the tested mutants for further experiments.
AKR mutant, N109H, displayed a slight gain of function compared to wild type (wt) TRPC6. N109H displayed delayed and slow inactivation due to external 2mM calcium while wt displayed a rapid inactivation of both inward and outward current in the presence of external 2 mM calcium. CT-CCD mutant, R894C however displayed a clear gain of function compared to wt and N109H. R894C displayed increased the inward currents while outward currents remained unchanged after the introduction of external 2mM calcium. Furthermore, increasing the internal calcium buffering capacity enhanced the gain of function phenotype of the AKR mutant to a level similar to that of CT-CCD mutant while wt currents did not change much with the increased internal calcium buffering conditions. Increasing the internal free calcium concentration resulted in an increase in function of all TRPC6 constructs up to a certain threshold level after which the function of TRPC6 activity went down with the increasing free calcium concentration. This threshold concentration however, changed with the AKR and CT-CCD mutants. CT-CCD mutant had the highest threshold concentration while AKR mutant had the second highest threshold concentration and wt TRPC6 had the lowest threshold concentration.
These results indicate the inhibition of wt TRPC6 by calcium carrying currents is lowered by both NT-AKR and CT-CCD mutations. Any drugs or treatments that can restore the response of these FSGS mutants to intercellular and extracellular calcium to a level comparative to wt TRPC6 can act as useful therapeutics to patients suffering with FSGS.

Key Words: TRPC6, AKR, NT, CT, CCD, CIRB

P1-30

The N-terminus of β-subunits regulates the PIP_2 sensitivity of voltage-gated calcium channels

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Plasma membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) controls the voltage-gated Ca^{2+} channels (CaV). Especially, Cav β subunits regulate PIP_2 sensitivities of Ca^{2+} channels. PIP_2 depletion by a voltage-sensing 5-phsphatase from zebra fish (Dr-VSP) inhibits CaV2.2 channel currents. However, when the CaV2.2 channels are co-expressed with different types of cytosolic β-subunits, currents inhibition by PIP_2 depletion using activation of Dr-VSP are respectively different depending on types of β subunits. CaV2.2 currents inhibition by PIP_2 depletion with β3 subunits are approximately ~60%, but CaV2.2 currents inhibition with β2b or β2c subunits are approximately ~40%. We found that the N-terminus of β subunits induced different PIP_2 sensitivities through activation of Dr-VSP at each type of β subunits. For example, β3 subunits are composed of negative charged amino acids in the N-terminus. If the N-terminus of β3 subunits are deleted or mutated negative to neutral or positive amino acids, the currents inhibition by PIP_2 depletion are changed because of the negative charged PIP_2. Thus, we suppose that electrostatic interaction exists between PIP_2 and the charged N-terminus of β subunits. Therefore, each CaV current has different percentages of inhibition depending on types of β subunits. Finally, we suggest that PIP_2 sensitivities of CaV are determined by the charged amino acids in the N-terminus of β subunits.

Key Words: PIP_2, CaV, β subunits, Dr-VSP

P1-31

Hydroxyphenyl octanediamide-induced antinociception via transient receptor potential vanilloid subtype 4 modulation

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Biological effects of hydroxyphenyl octanediamide have mainly been tested in the context of tumor suppression via its inhibitory effect on histone deacetylases, but other potential outcomes from its use have also been proposed in different fields such as pain modulation. Although the mechanisms are still blurred, non-epigenetic and non-histone off-target actions of the compound have been raised. We hypothesized and examined whether the compound may modulate pain by a mechanism not limited to the epigenetic mechanisms. Its localized treatment acutely attenuated inflammatory pain and chemical-induced pain in a modality-specific manner in animal models. It is likely that its inhibition of sensory neuronal transient receptor potential vanilloid subtype 4 (TRPV4), despite being unstable, can explain the non-epigenetic mechanism. Thus this study provides evidence for a novel off-target action of hydroxyphenyl octanediamide in modality-specific anti-nociception and suggests a TRPV4-related mechanism, and raises the utility of this compound for pharmacological modulation of pain.

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Key Words: Pain, Hydroxyphenyl octanediamide, TRPV4, Inhibitor

P1-32

Diphenyleneiodonium (DPI) attenuates Ca^{2+} transient and contraction via desensitization of cardiac Ca^{2+} release sites independently of NADPH oxidase

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Diphenyleneiodonium (DPI) is a well-known inhibitor for the NADPH oxidase (Nox) that is one of the major enzymes producing reactive oxygen

species (ROS) in mammalian cells. DPI is widely used to determine the functional role of this enzyme in cellular signaling pathway. In the present study, we examined whether this enzyme inhibitor has effects on intracellular Ca^{2+} and contractility in cardiac myocytes. We measured local and global Ca^{2+} concentrations, and cell shortenings in isolated rat ventricular myocytes using two-dimensional confocal Ca^{2+} imaging and video edge detection, respectively. Ventricular cell shortenings, measured at 1-Hz field stimulation, were suppressed by DPI in a concentration-dependent manner with an IC_{50} of approximately 200 nM. Maximum negative inotropic effect (70%-inhibition) by DPI was observed at about 10 μM. DPI (3 μM) reduced the magnitude of Ca^{2+} transients (by about 40%) as well as diastolic and systolic Ca^{2+} levels. Sarcoplasmic reticulum Ca^{2+} loading, measured as the magnitude of caffeine (10 mM)-induced Ca^{2+} release, was significantly decreased (by 30%) by DPI (3 μM). Fractional Ca^{2+} release was also significantly attenuated by this compound. Consistently, Ca^{2+} spark frequency at resting conditions was significantly reduced by the DPI exposure. A reducing agent DL-dithiothreitol, mitochondrial ROS scavenger Mito-TEMPO, or Nox2 inhibitor gp91dstat did not alter the frequency of Ca^{2+} sparks. Our data suggest that DPI, at the concentrations generally used to block Nox proteins, may decrease cardiac Ca^{2+} transient and contraction via desensitization of Ca^{2+} release sites independently of Nox and ROS.

Key Words: Diphenyleneiodonium, Ca^{2+} transient, Ca^{2+} spark, Ventricular myocytes, Contraction

P1-33

Effects of nitric oxide on voltage-dependent K^+ currents in human cardiac fibroblasts by PKC pathway

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We investigated the effect of nitric oxide (NO) on voltage-dependent K+ channels and the mechanism in human cardiac fibroblasts. Two subtypes of voltage-dependent K^+ currents were detected in HCFs: large-conductance Ca^{2+}-activated K^+ (K_{Ca}) currents and delayed rectifier K^+ (K_{DR}) currents. S-nitroso-N-acetylpenicillamine (SNAP; a NO donor) significantly increased the amplitude of K_{Ca} currents. The SNAP-stimulating effect on K_{Ca} currents was blocked by pretreatment with three types of protein kinase C blockers; bisindolylmaleimide, chelerythrine, and staurosporine. K_{DR} currents was also activated by SNAP and the stimulating effect of SNAP was also blocked by pretreatment with bisindolylmaleimide, chelerythrine, or staurosporine. These data suggest that NO activates voltage-dependent K^+ currents through the protein kinase C pathway in human cardiac fibroblasts

Key Words: Human cardiac fibroblast, Nitric oxide, Protein kinase C pathway, Voltage-dependent K^+ currents

P1-34

Effects of nitric oxide on voltage-gated K^+ currents in human cardiac fibroblasts

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We investigated the effect of nitric oxide (NO) on voltage-gated K^+ (Kv) channels and the mechanism in human cardiac fibroblasts (HCFs). Two subtypes of Kv channels were detected in HCFs: delayed rectifier K^+ (K_{DR}) channels and transient outward K^+ (K_{TO}) channels. In RT-PCR, the strong mRNA expression of Kv1.2, Kv1.5, and Kv3.1 was responsible for the K_{DR} channels, while Kv3.3 and Kv3.4 for the K_{TO} channels were found in HCFs. In whole-cell mode patch clamping, the K_{DR} currents (IK_{DR}) exhibited fast activation and slow or partial inactivation, while the K_{TO} currents (IK_{TO}) exhibited fast activating and inactivating kinetics. S-nitroso-N-acetylpenicillamine (SNAP; a NO donor) increased the amplitude of IK_{DR} in a concentration-dependent manner, but did not affect IK_{TO}. The SNAP-stimulating effect on IK_{DR} was blocked by pretreatment with ODQ (a soluble guanylate cyclase inhibitor) or KT5823 (a PKG inhibitor). Additionally, 8-bromo-cyclic GMP (a membrane-permeable cGMP analogue) stimulated the K_{DR} currents. Conversely, the SNAP-stimulating effect on IK_{DR} was not blocked by *N*-ethylmaleimide (NEM; a thiol-alkylating reagent) pretreatment. In addition, DL-dithiothreitol (DTT; a reducing agent) could not inhibit the SNAP effect on IK_{DR}. Our data suggests that NO enhanced IK_{DR} in human cardiac fibroblasts through the PKG pathway and not through *S*-nitrosylation. KT5720 (a PKA blocker) and SQ22536 (an adenylyl cyclase inhibitor) also inhibited the SNAP stimulating effect on K_{DR} currents. 8-Br-cAMP also activated the K_{DR} currents. These data suggest that NO activates K_{DR} currents through the PKG and PKA pathways but not *S*-nitrosylation in human cardiac fibroblasts.

Key Words: Human cardiac fibroblast, Nitric oxide, PKA pathway, PKG pathway, Voltage-gated K^+ currents

P1-35

Determine proarrhythmic risk of 4-oxononenal (4-ONE) by the comprehensive *in vitro* proarrhythmia assay (CiPA)

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CiPA is a proposal for progressive research paradigm designed to apply *in vitro* and *in silico* assays for determining electrophysiological mechanisms conferring proarrhythmic risk to candidate drugs. The first CiPA assay determines effects on cloned human cardiac ion channels. The second investigates whether the measured effects provoke proarrhythmic markers on a computationally reconstructed human ventricular action potential. The third evaluates conclusions by measuring field potential from human stem cell-derived cardiomyocytes (hSC-CMs).
In this study, we evaluate the proarrhythmic risk of 4-oxononenal (4-ONE), highly reactive endogenic lipid peroxidant. 4-ONE (10 μM) decreased the currents of KCNH2 (I_{KCNH2}), KCNQ1/KCNE1 ($I_{KCNQ1/E1}$) and L-type Ca^{2+} current ($I_{Ca,L}$). The inactivation time constant of $I_{Ca,L}$ was significantly slowed by 4-ONE. The action potential duration (APD) of guinea-pig ventricular myocytes (GPVMs) was prolonged by 10 μM 4-ONE. The data from *in vitro* measurement were then applied to computational human ventricular myocyte model. 4-ONE prolonged the simulated APD. We then finally evaluated the proarrhythmic ability of 4-ONE by using multi-electrodes array (MEA) system from human embryonic stem cell-derived cardiomyocytes (hESC-CMs). 4-ONE (10 μM) prolonged field potential duration and slowed spontaneous beating rate of hESC-CMs. In conclusion, we demonstrated the proarrhythmic potential of 4-ONE by using CiPA assay, suggesting that 4-ONE may participate in proarrhythmic process of oxidative stress conditions in heart.

Key Words: Comprehensive *in vitro* proarrhythmia assay, CiPA, 4-oxononenal, Lipid peroxidation product

P1-36

Hydrolyzable ATP modulates PIP_2 sensitivity of Anoctamin1/TMEM16A

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Anoctamin1/TMEM16A (ANO1), a Ca^{2+}-activated Cl- channel, plays a number of physiological roles such as contraction of smooth muscle, secretion, gastrointestinal motility, nociception, neuronal excitability, and cell volume regulation. Activity of ANO1 is affected by various regulatory factors and

it is important to understand these mechanisms. A recent study showed that ANO1 activity is regulated by membrane Phosphatidylinositol 4,5-bisphosphate (PIP_2), a necessary cofactor for ion channels and receptors. Here, we demonstrate that PIP_2 sensitivity on ANO1 is modulated by hydrolyzable ATP. When depleted PIP_2 by voltage-sensing 5-phosphatase (VSP) or chemical translocation of PIP_2 5-phosphatase, ANO1 current is decreased by ~20%. Removal of ATP in the pipette solution decreases more strongly current by activation of Dr-VSP than in the presence of ATP. Similarly, by using translocatable PI-metabolite enzymes that recruit to the membrane, we also identified that ANO1 current is decrease much better in the absence of ATP in the pipette solution. We thought that the increase of inhibition may be due to dephosphorylation of ANO1 in the ATP-free condition. Further, we confirmed that KN-62 to suppress CaMKII enhances Dr-VSP-induced inhibition on ANO1 current. These results suggest that hydrolyzable ATP plays important role in PIP_2 sensitivity on ANO1 channel activity.

Key Words: Ca^{2+}-activated Cl^- channel, TMEM16A, Anoctamin1, PIP_2, Intracellular ATP

P1-37

Kv3.1 and Kv3.4 are involved in cancer cell migration and invasion

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Hypoxia is one of the representative characteristics of cancer tissue that differs from normal tissue. Our data demonstrate a close relationship between several oxygen-sensitive voltage-gated K^+ (Kv) channel subunits and tumor hypoxia, as well as an importance of these channels in cancer progression. Kv3.1, Kv3.3, and Kv3.4, which belong to the Kv3 subfamily, were examined as tumor hypoxia-related Kv channels in A549, MDA-MB-231, and HT-29 cells. All three cells lines highly expressed these channels. We found a cell-density dependent increment of HIF-1α, a tumor hypoxia marker, in A549 and MDA-MB-231 cells, whereas HIF-1α showed no similar increment in HT-29 cells, which grow in an aggregate form. Interestingly, expression of Kv3.1 and Kv3.4 showed the same pattern with HIF-1α in all three cell lines, and we determined that Kv3.1 and Kv3.4 are tumor hypoxia-related Kv channels. Furthermore, blood depressing substance (BDS) toxin, a Kv3 subfamily specific blocker, inhibited cancer cell migration and invasion. Our results demonstrate that tumor hypoxia related oxygen-sensitive Kv channels, including Kv3.1 and Kv3.4, appear to be new therapeutic targets for tumor metastasis.

Key Words: Tumor hypoxia-related Kv channels, Cell density, Cell migration and invasion, BDS, Tumor metastasis

P1-38

Lipopolysaccharide reduces THIK-1 in Macrophages through AMPK activation

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Our previous study has been demonstrated that the expression of tandem-pore domain halothane inhibited potassium (THIK)-1 channel is reduced under inflammatory condition, such as secretion of inflammatory mediators. However, the mechanism by which LPS reduces THIK-1 expression is still unknown. In the present study, we investigated the connection of AMP-activated protein kinase (AMPK) signaling in the THIK-1 expression downregulated by inflammatory mediators. The AMPK phosphorylation site is identified at the carboxyl terminal of THIK-1. RT-PCR data showed LPS reduced the expression of THIK-1 mRNA in RAW264.7 and BV2 macrophage cell lines. In addition to LPS, AICAR, an AMPK activator, also reduced THIK-1 expression levels in a dose- and time-dependent manner in THIK-1 overexpressed HEK293 cells and macrophage cell. AMPK was activated by LPS treatment in RAW264.7 cells, like by AICAR. However, LPS treatment did not affect THIK-1 protein expression level in the presence of compound C, an AMPK inhibitor, which was pretreated to RAW264.7 cells. In cells transfected with C-terminal deletion THIK-1 variant, LPS had no effect on THIK-1 expression level. The secretion of IL-1β and IL-6 by LPS or AICAR was reduced in THIK-1 overexpressed cells compared to vector transfected cells. AMPK was phosphorylated and THIK-1 mRNA expression level was reduced in the liver obtained from LPS/D-Gal-induced liver injury model. These results show that AMPK activation is involved in the down-regulation of THIK-1 channel by inflammatory mediators. We suggest that THIK-1 could be a target for treatment of inflammatory diseases.

Key Words: Potassium channel, Inflammation, Macrophage, AMPK, THIK-1

P1-39

The involvement of two-pore domain potassium channels on epithelial-mesenchymal transition in cancer cells

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The two-pore domain potassium channels (K2P channels) play an important role in stabilizing the membrane potential and are not restrained by the classical potassium channel blocker. Of the K2P channels, the mechanosensitive K2P channel is located near the focal adhesion molecule, possibly related to the stress fibers of cells, cytoskeleton, and adhesion molecules. The epithelial-mesenchymal transition (EMT) induction may affect those channel proteins, which can disturb cell homeostasis by changing cell membrane voltage. The phenomenon of EMT is involved in invasion, metastasis, relapse, and anticancer drug resistance as well as cancer development. Among the EMT markers, E-cadherin and N-cadherin are involved in cell membrane structure are likely to be associated with ion channel proteins in the cell membrane. In this study, we investigated whether K2P channel contributes to the regulation of EMT to using K2P channel small interfering RNA (siRNA). The knockdown of K2P channel using K2P siRNA transfection system was induced the changes of EMT markers such as vimentin, E-cadherin and N-cadherin. The mRNA quantities were observed in K2P siRNA treated cells and negative siRNA treated cells by real-time RT-PCR. Cells treated with K2P siRNA for 4 days showed increase in the mRNA of vimentin compared to the negative control, whereas K2P channel overexpression leads to decrease in mesechymal marker vimentin compared to the non-transfected control cells. Epithelial marker E-cadherin also slightly decreased in cells treated with K2P siRNA. In analysis of immunocytochemistry, compared with negative control siRNA, zinc finger E-box binding homeobox transcription factor 1 (Zeb1) was upregulated by K2P siRNA. These results suggest that K2P channel may involve in EMT process of cancer cells.

Key Words: Epithelial-mesenchymal transition, Two-pore domain potassium channels, Small interfering RNA E-cadherin, Vimentin

P1-40

A novel SCN5A mutation results in ventricular arrhythmia with distinct molecular pharmacology and therapeutic response

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Long QT syndrome (LQTS) is a rare congenital and inherited or acquired heart condition in which delayed repolarization of the heart following a heartbeat increases the risk of episodes of torsades de pointes. In genetic analysis of R/O LQTS patient with arrhythmias during fetus period, we identified a novel SCN5A variant (A1656D) in a highly conserved region of the S4-S5 Intracellular Loop in Domain IV. We investigated whether this SCN5A missense mutation could form the genetic basis for LQTS in this patient. Patch clamp analysis of HEK 293 cells transiently transfected with wild-type or mutant Na^+ channels revealed a defective inactivation in A1656D channel, consistent with LQT phenotype. In addition, we found that the subtle differences of Na^+ channel blockers, ranolazine and mexiletine in correcting A1656D mutant channel activity. Incorporation of the A1656D mutation-induced biophysical changes in channel gating described above into a model of an adult human ventricular myocyte yielded simulated action potentials with markedly delayed repolarization that are qualitatively similar to the patient's phenotype. Simulations suggest mexilentine as beneficial in recovering channel function consistent with the successful arrhythmia management obtained by mexiletine. The A1656D SCN5A mutation confers gain-of-function effects on Na^+ channel activity. Reduction of a mutation-induced current by mexiletine suggests a therapeutic mechanism.

Key Words: Ventricular arrhythmia, Molecular pharmacology

P1-41

PRMT1-dependent regulation of ventricular myocyte late Na^+ current and excitability

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Arginine methylation is one of the most important post-translational modifications (PTMs). It is mediated by protein arginine methyltransferases (PRMTs). In mammals, nine PRMTs have been characterized and PRMT1, originally identified as a histone H4 methyltransferase, methylate many non-histone proteins and implicated in diverse cellular processes. However, there is little information on the effects of PRMT1 on cardiovascular function. In this study, we demonstrate that PRMT1 regulates action potential duration via modulation of late Na^+ currents. The loss of cardiac PRMT1 in mice resulted in sinus bradycardia and increased QT intervals. Consistently, PRMT1 depletion in isolated cardiomyocytes induces prolonged action potential duration with higher incidence of early afterdepolarizations (EADs). In addition, PRMT1 inhibition with furamidine (20 μM) increases late Na^+ currents in 293T cells. We found that KN93 (1μM) can suppress PRMT1 depletion-associated afterdepolarizations. Taken together, these data suggest that PRMT1 might be an important target for prevention of late Na^+ currents in pathological conditions.

Key Words: PRMT1, Na^+ channel, EAD

P1-42

Nitric oxide stimulation of L-type voltage-dependent Ca^{2+} currents in human cardiac fibroblasts through protein kinase G pathways but not *S*-nitrosylation

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Human cardiac fibroblasts (HCFs) represent the most numerous cell type in heart and play an important role in cardiac function and diseases, including arrhythmogenesis. Nitric oxide (NO) has emerged as an important signaling molecule in the regulation of physiological and pathophysiological processes in heart. The purpose of the present study is to know the effects of NO on voltage-dependent Ca^{2+} channels (VDCCs) and underlying signaling pathways in HCFs. Various subtypes of VDCCs; L-type, N-type, R-type and T-type in the cells by RT-PCR. In whole cell mode patch-clamp recordings, nifedipine sensitive L-type Ca^{2+} currents ($I_{Ca,L}$) and pimozide sensitive T-type Ca^{2+} currents ($I_{Ca,T}$) were recorded. S-nitroso-N-acetylpenicillamine (SNAP; a NO donor) inhibited the $I_{Ca,L}$ but not $I_{Ca,T}$. Pretreatment of 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, a soluble guanylate cyclase blocker) or KT5823 (a PKG blocker) blocked the inhibitory effect of SNAP on $I_{Ca,L}$. 8-bromo-cGMP also decreased these currents. However, pretreatment of *N*-ethylmaleimide (NEM; a thiol-alkylating reagent) could not block the SNAP effect on $I_{Ca,L}$. In addition, DL-dithiothreitol (DTT; a reducing agent) could not reverse the SNAP inhibition on $I_{Ca,L}$. Our data suggest that NO inhibited $I_{Ca,L}$ in HCFs through the PKG but not *S*-nitrosylation.

Key Words: Human cardiac fibroblast, L-type voltage-dependent Ca^{2+} currents, Nitric oxide, PKG pathway, *S*-nitrosylation

P2-01 (PO-B-05)

Higher vulnerability of catecholamine-induced arrhythmia in isolated right atrial myocytes

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Spatiotemporal organization of atrial fibrillation (AF) shows chamber-specific patterns, and AF frequency is known to have left-to-right gradient between left (LA) and right atrium (RA). High-frequency AF sources near the pulmonary veins and enhanced sympathovagal discharges are well-known arrhythmogenic factors. However, it is underrated whether different electrophysiological properties found in LA and RA myocytes give intrinsic substrate for spatiotemporal AF organization and LA-RA gradient. From this point of view, we aimed to better understand structural and electrophysiological differences between LA and RA myocytes. Rat atrial myocytes were isolated from each chamber and compared their structure, electrophysiological properties, E-C coupling, and arrhythmic fragility in response to sympathetic stimulation. RA myocytes are smaller (lower C_m values) than LA, and have poorly developed intracellular T-tubule network. Under current-clamp configuration, RA myocytes have much shorter action potential duration (APD) but higher L-type Ca^{2+} channel (LTCC) densities compare to LA. In response to β-adrenergic stimulation (isoproterenol with caffeine), RA myocytes showed much higher frequency of arrhythmias, which is evaluated by occurrence of delayed after depolarization (DAD), triggered activities (TA), and triggered contractions (TC). Higher arrhythmic incidence of RA myocytes accorded well with higher LTCC increase in response to isoproterenol stimulation, suggesting that β-adrenergic stimulation-induced $[Ca^{2+}]_i$ overload occurs more severely in smaller and poorly T-tubulated RA myocytes. As expected, catecholaminergic arrhythmia was further enhanced by a LTCC opener (Bay-K 8644) and attenuated by moderate concentration of a LTCC blocker (nifedipine). Both in LA and RA myocytes, acute removal of T-tubules resulted in a decrease of T-tubule density, cell capacitance, APD, LTCC density, and frequency of catecholaminergic arrhythmia. In spite of detubulation, isoproterenol-in-

duced LTCC increase and arrhythmic frequency was maintained higher in RA over LA myocytes. Our study suggests that RA myocytes are more vulnerable than LA in response to catecholaminergic $[Ca^{2+}]_i$ overload, and weaker Ca^{2+} handling power of RA leads higher incidence of triggered arrhythmias upon β-adrenergic stimulation.

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Key Words: Arrhythmia, Atrium, Calcium channel, Catecholamine

P2-02

The vasodilatory mechanisms of repaglinide, a member of meglitinide anti-diabetic drugs by activating protein kinase A and protein kinase G in aortic smooth muscle

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We investigated the vasorelaxant effect of repaglinide and its related signaling pathways using phenylephrine (Phe)-induced pre-contracted aortic rings. Repaglinide induced vasorelaxation in a concentration-dependent manner. The repaglinide-induced vasorelaxation was not affected by removal of endothelium. Pre-treatment with adenylyl cyclase inhibitor or the PKA inhibitor effectively reduced repaglinide-induced vasorelaxation. Also, pretreatment with guanylyl cyclase inhibitor or the PKG inhibitor effectively inhibited repaglinide-induced vasorelaxation. However, pretreatment with voltage-dependent K^+ channel inhibitor (4-AP), ATP-sensitive K^+ channel inhibitor (glibenclamide), big-conductance Ca^{2+}-activated K^+) channel inhibitor (paxilline), and the inwardly rectifying K^+ channel inhibitor (Ba^{2+}) did not affect the vasorelaxant effect of repaglinide. Furthermore, pretreatment with Ca^{2+} inhibitor (nifedipine) and SERCA inhibitor (thapsigargin) also did not affect the vasorelaxant effect of repaglinide. From these results, we concluded that repaglinide induced vasorelaxation by activation of adenylyl cyclase/PKA and guanylyl cyclase/PKG signaling pathway independently of endothelium, K^+ channels, Ca^{2+} channel and intracellular Ca^{2+} ($[Ca^{2+}]_i$).

Key Words: Repaglinide, Diabetes, Protein kinase A, Protein kinase G

P2-03 (PO-B-01)

STIM2 and STIM1 have similarities and differences, but both regulate Ca^{2+} movement in skeletal muscle

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Stromal interaction molecule 1 (STIM1) along with Orai1 mediates extracellular Ca^{2+} entry into the cytosol through a store-operated Ca^{2+} entry (SOCE) mechanism in various tissues including skeletal muscle. However, the role(s) of STIM2, a homolog of STIM1, in skeletal muscle has not been well addressed. The present study, first, was focused on searching for STIM2-binding proteins from among proteins mediating skeletal muscle functions. This study used a binding assay, quadrupole time-of-flight mass spectrometry, and co-immunoprecipitation assay with *bona-fide* STIM2- and SERCA1a-expressing rabbit skeletal muscle. The region for amino acids from 453 to 729 of STIM2 binds to sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 1a (SERCA1a). Next, oxalate-supported $^{45}Ca^{2+}$-uptake experiments and various single-myotube Ca^{2+} imaging experiments using STIM2-knockdown mouse primary skeletal myotubes have suggested that STIM2 attenuates SERCA1a activity during skeletal muscle contraction, which contributes to the intracellular Ca^{2+} distribution between the cytosol and the SR at rest. In addition, STIM2 regulates Ca^{2+} movement through RyR1 during skeletal muscle contraction as well as SOCE. Therefore, via regulation of SERCA1a activity, STIM2 regulates both intracellular Ca^{2+} distribution and Ca^{2+} movement in skeletal muscle, which makes it both similar to, yet different from, STIM1.

Key Words: STIM (stromal interaction molecule), SERCA1a (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 1a), Cytosolic Ca^{2+} level, SR (sarcoplasmic reticulum), SOCE (store-operated Ca^{2+} entry), RyR1 (ryanodine receptor 1)

P2-04

Isocitrate dehydrogenase 2 inhibition stimulate vascular inflammation in response to oxidative stress

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In pathophysiological condition, vascular inflammatory responses, oxidative stress and ROS are increased due to mitochondrial dysfunction. Isocitrate dehydrogenase 2 (IDH2) is an $NADP^+$-dependent mitochondrial enzyme. It is deacetylated by SIRT3 and then used as antioxidant protein by producing NADPH in the antioxidant system. In this study, we investigated whether IDH2 knockdown causes mitochondrial dysfunction and vascular inflammation *in vitro* HUVECs and *in vivo* IDH2 knockout mice. We showed that knockdown of IDH2 expression decreased mitochondrial oxidative phosphorylation (OXPHOS) activities, increased mitochondrial ROS (mtROS) and depolarization of the mitochondrial membrane potential (MMP). Mitochondrial dynamics is mitochondrial fusion and fission. Knockdown of IDH2 increased Drp1 (fission protein) and mfn1 (fusion protein) compared with COX4 (control). Knockdown of IDH2 also stimulated p66shc phosphorylation, increased cytosolic ROS in endothelial cells. Moreover, expression of vascular cell adhesion molecule-1 (VCAM1) and intercellular adhesion molecule-1 (ICAM1) were increased after knockdown of IDH2 in endothelial cells. The expression of adhesion molecules such as VCAM-1 in endothelial cells leads to the recruitment of inflammatory leukocytes. P66shc knockdown decreased the IDH2 deficiency-induced increases in adhesion between monocytes and endothelial cells. In addition, IDH2 deficiency increased production of pro-inflammatory cytokines (IL-6 (a), TNF-α (b), IL-1β) in the plasma in IDH2 knockout models *in vivo*. Our data show that IDH2 deficiency induces mitochondrial dysfunction as well as endothelial dysfunction and inflammation via increased p66shc phosphorylation and oxidative stress. These findings provide novel strategy for the development of therapeutic agents for restoring mitochondrial and endothelial function.

Key Words: IDH2, Mitochondria, Endothelial cells, ROS, Inflammation

P2-05

Altered redox state modulates endothelial $K_{Ca}2.3$ and $K_{Ca}3.1$ levels in normal pregnancy and preeclampsia

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Altered redox state has been related to the development of normal preg-

nancy (NP) and preeclampsia (PE). Endothelial K_{Ca}2.3 and K_{Ca}3.1 (K_{Ca}s) play an important role in vasodilation, and K_{Ca}s expression levels are affected by oxidative stress. We thus investigated the mechanisms of oxidative stress-mediated K_{Ca}s expression modulation during NP and PE.
Human uterine microvascular endothelial cells were incubated in serum from normal non-pregnant women (n=13) and women with NP (n=24) or PE (n=15), or in VEGF, oxidized low-density lipoprotein (ox-LDL), progesterone, or estradiol-17β-containing medium for 24 hours. NP serum elevated H_2O_2 levels via reducing catalase and glutathione peroxidase 1 levels, thereby enhancing K_{Ca}s levels via a H_2O_2/fyn/ERK-mediated pathway. VEGF enhanced H_2O_2 and K_{Ca}s levels and K_{Ca}3.1 currents. K_{Ca}s were upregulated and K_{Ca}s activation-induced endothelium-dependent relaxation was augmented in vessels from pregnant mice and rats. Whereas, PE serum, ox-LDL, and progesterone elevated superoxide levels via elevating NADPH oxidase 4 levels and reducing SOD1 levels, thereby downregulating K_{Ca}s. Soluble fms-like tyrosine kinase-1 generated superoxide, thereby inhibiting endothelium-dependent relaxation. PE serum- or progesterone-induced alterations in levels of K_{Ca}s were reversed by polyethylene glycol-SOD, NADPH oxidase 4 inhibition, or estradiol-17β.
These results suggest that endothelial K_{Ca}s were modulated by altered redox state in NP and PE, which may contribute to hemodynamic adaptations in NP or to the development of PE.

Key Words: Ca^{2+}-activated K^+ channels, Endothelial cells, Redox state, Normal pregnancy, Preeclampsia

P2-06

Attenuation of NaHS-induced stimulation of ANP secretion from hypertrophied atria

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Hydrogen sulfide (H_2S), the third gasotransmitter, is normally produced from L-cysteine in mammalian tissues and related to the pathogenesis of cardiovascular diseases. However, the relation between H_2S and cardiac hormone, atrial natriuretic peptide (ANP), is not clear. The aim of this study is to investigate the effects of H_2S donor on ANP secretion and define its mechanism using normal and isoproterenol (ISP)-treated hypertrophied rat atria. Different doses of H_2S donors (NaHS, Na_2S, GYY4137, and sodium thiosulfate) were perfused into isolated beating rat atria, and atrial pressure and ANP secretion were measured. NaHS (1, 10, 50, 100 μM) augmented high stretch-induced ANP secretion and decreased systolic atrial pressure (SAP) in a dose-dependent manner. These effects were blocked by the pretreatment with nitric oxide synthase inhibitor, soluble guanylyl cyclase inhibitor, and K_{ATP} channel antagonist. The high stretch-induced ANP secretion was stimulated by Na_2S but was not changed by GYY4137 and sodium thiosulfate. H_2S synthesis enzyme inhibitor (DL-propargylglycine) did not show any significant changes in atrial parameters. However, the response of ANP secretion to NaHS markedly attenuated and DL-propargylglycine suppressed ANP secretion in ISP-treated rat atria. The expression of eNOS protein was decreased but the expression of cardiomyocyte-specific H_2S producing enzyme, cystathione γ-lyase, was not changed in ISP-treated rat ventricles. These findings clarify that NaHS stimulates ANP secretion through NO-cGMP and K_{ATP} channel pathway. The modification of ANP secretion by NaHS and H_2S synthesis enzyme inhibitor suggests the possible role of endogenous H_2S in the pathogenesis of cardiac hypertrophy.

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Key Words: H_2S, Atrial natriuretic peptide, NaHS, Na_2S, GYY4137, Cardiac hypertrophy, NOS

P2-07

Cardiprotective effects of alamandine via MrgD receptor by anti-apoptosis and ANP system in rats

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Alamandine is a heptameric peptide hormone of renin-angiotensin system that differs from angiotensin-(1-7) [Ang-(1-7)] in a single N-terminal alanine residue. The aim of this study is to investigate whether alamandine protects the heart against ischemia-reperfusion (I/R) injury. After sacrificing Sprague-Dawley rats, the hearts were perfused with Krebs-Henseleit buffer for a 20 min pre-ischemic period with and without alamandine followed by 20 min global ischemia and 50 min reperfusion. Pretreatment with alamandine (0.1 mg/kg) for 2hr before ischemia improved an increased post-ischemic left ventricular end-diastolic pressure (LVEDP) and a decreased post-ischemic left ventricular developed pressure (LVDP) induced by reperfusion compared to untreated hearts. Alamandine markedly decreased infarct size and lactate dehydrogenase levels in effluent during reperfusion. Alamandine also increased coronary flow and the concentrations of atrial natriuretic peptide (ANP) in coronary effluent during reperfusion. Pretreatment with MrgD receptor blocker and Ang II type 2 receptor (AT2R) antagonist but not with Ang II type 1 receptor (AT_1R) antagonist for 2.5hr before ischemia attenuated the improvement of LVEDP, LVDP, and ±dP/dt induced by alamandine. Alamandine treatment increased Mn-superoxide dismutase, catalase, and heme oxygenase-1 protein levels, which was attenuated by pretreatment with MrgD receptor blocker and AT2R antagonist. Alamandine treatment also decreased Bax, caspase-3 and caspase-9 protein levels, and increased Bcl-2 protein level, which were attenuated by pretreatment with MrgD receptor blocker and AT2R antagonist. Alamandine also caused increases in ANP secretion from isolated perfused beating atria, which was completely blocked by the pretreatment with MrgD receptor blocker and partially blocked by AT2R antagonist but not by AT1R antagonist or Mas receptor blocker. These results suggest that the cardioprotective effects of alamandine against I/R injury may be partly related to activating anti-oxidant and anti-apoptotic enzymes via MrgD receptor and ANP system.

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Key Words: Alamandine, Ischemia, Reperfusion, Heart, Atrial natriuretic peptide, Apoptosis, MrgD receptor

P2-08

CR6-interacting factor 1 deficiency impairs vascular function by inhibiting the Sirt1-endothelial nitric oxide synthase pathway

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Aims: One of the major contributing factors to endothelial dysfunction and vascular disease is mitochondrial dysfunction, but the key mechanisms underlying the relationship between mitochondrial dysfunction-induced endothelial dysfunction remain to be elucidated. In this study, we aim at determining whether mitochondrial dysfunction in endothelial cells plays a key role in vascular disease, by examining the phenotype of endothelial-specific CR6-interacting factor 1 (CRIF1) knockout mice. We also used siRNA-mediat-

ed downregulation of CRIF1 gene in the endothelial cells (HUVECs) to study about the *in vitro* pathophysiological mechanisms.
Results: Downregulation of CRIF1 in endothelial cells caused disturbances of mitochondrial oxidative phosphorylation complexes and membrane potential, leading to enhanced mitochondrial reactive oxygen species production. Gene silencing of CRIF1 results in decreased SIRT1 expression along with increased endothelial nitric oxide synthase (eNOS) acetylation, leading to reduced nitric oxide production bothin vitro andin vivo. Endothelium-dependent vasorelaxation of aortic rings from CRIF1 knockout (KO) mice was considerably less than in wild-type mice, and it was partially recovered by Sirt1 overexpression in CRIF1 KO mice.
Conclusion: Our results show for the first time a relationship between mitochondrial dysfunction and impaired vascular function induced in CRIF1 deficiency conditions and also the possible underlying pathway involved. These findings indicate that CRIF1 plays an important role in maintaining mitochondrial and endothelial function through its effects on the SIRT1-eNOS pathway.

Key Words: OXPHOS complex, CRIF1, SIRT1, eNOS, Nitric oxide

P2-09

Neuronal nitric oxide synthase β is attached to myofilament and maintains sarcomere structure in cardiomyocyte

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nNOSα, μ and β are the splice variants of neuronal nitric oxide synthase (nNOS or NOS1) established to be functionally expressed in discrete compartments at the cellular level. Basically, nNOSα has been acknowledged to be a key regulatory factor of excitation-contraction coupling in the myocardium. On the other hand, convincing evidences have shown that nNOS plays an important role part in the preservation of myofilament structure and the integrity of striated muscle. So far, involvement of nNOS splicing variants in maintaining the structure of cardiomyocyte is unclear. Accordingly, we investigated the splice variants of nNOS in the myofilament of left ventricular (LV) myocytes and its functional relevance in sarcomere structure.
Both mRNA sequences of nNOSβ and nNOSα were identified in rat LV myocytes. Immunoblotting of individual proteins showed that unlike nNOSα (M.W. ~ 155 kDa), which is expressed in the cytosolic/plasma membrane fraction, a lower molecular weight nNOSβ (M.W. ~ 138 kDa) was detected in the myofilament fraction of LV myocytes. Chronic inhibition of nNOS (SMTC: S-methyl-L-thiocitrulline) for 4 weeks increased the protein expression of nNOSβ in vivo (but not nNOSα). In addition, transmission electron microscopic images revealed that both sarcomere and I-band lengths were significantly elongated in SMTC without changing the length of thick filament (sarcomere length in μm: 1.87±0.017 in Sham *vs*. 2.12±0.038 in SMTC; $p<0.001$; I band length in μm: 0.156±0.007 in Sham *vs*. 0.214±0.005 in SMTC; $p<0.001$). These structural changes occurred without altering the protein expressions of thin, thick filaments and Z-disc before and after nNOS inhibition (detected proteins were: myosin light chain, cardiac myosin binding protein C, tropomyosin, troponin C and troponin I, actinin and desmin). nNOSα$^{-/-}$ (nNOSα null mice) did not affect sarcomere length (sarcomere length in μm: 1.67±0.03 in nNOSα$^{+/+}$ *vs*. 1.66±0.02 in nNOSα$^{-/-}$), suggesting that inhibition of nNOSβ increases sarcomere length and changes the structure of myofilament. Furthermore, unlike nNOSα, nNOSβ did not affect intracellular Ca^{2+} transient (F360/380 of Fura 2AM) and myofilament Ca^{2+} sensitivity in LV myocytes of nNOSα$^{-/-}$. In addition, under the chronic inhibition of nNOSα and β, additional angiotensin II-infusion of rat showed that LV chambers were thickened with excessive interstitial fibrosis and reduced chamber sizes (concentric hypertrophy).
Our results suggest that nNOSβ in the myofilament plays an essential role in the maintenance of myocardial structure under normal conditions. Importantly, distinguishing nNOSβ-regulation of myofilament structure and nNOSα-regulation of intracellular Ca^{2+} handling shed light on a new conceptual framework for better understanding of the physiology and pathology of the heart.

Key Words: nNOSβ, Myofilament, Cardiomyocyte

P2-10

Salicornia europaea extract suppresses vascular neointima formation through inhibiting MAPK pathway-mediated responses in vascular smooth muscle cells

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Salicornia europaea L. (SE) has been used as folk medicine for the treatment of various diseases such as obesity, diabetes, and cancer. However, its effects on atherosclerotic events in vascular smooth muscle cells (VSMCs) have not yet been investigated. The present study aimed to explore the effects of the ethyl acetate fraction of SE hot water extract (SEWEAF) on atherosclerotic responses in VSMCs and vascular neointima formation. The anti-atherosclerotic activity was evaluated by estimating the levels of platelet-derived growth factor (PDGF)-BB (10 ng/ml)-induced proliferation and migration of VSMCs and the phosphorylation of their intracellular kinases and analyzing the vascular neointima formation via an *in vivo* assay. Treatment of VSMCs with the SEWEAF significantly suppressed the PDGF-BB-induced VSMC migration and proliferation as well as the phosphorylation of mitogen-activated protein kinases (MAPKs) such as the p38 MAPK and extracellular signal-regulated kinase (ERK) 1/2. Moreover, oral administration of the SEWEAF resulted in the attenuation of neointima formation in balloon-injured carotid arteries of rats. Additionally, HPLC analysis showed that the major components in the two subfractions of the SEWEAF were five phenolic acids and four flavonols (isorhamnetin-3-β-D-glucoside, isorhamnetin, quercetin-3-β-D-glucoside, quercetin). These results suggest that the SEWEAF may suppress PDGF-BB-induced VSMC migration by downregulating the phosphorylation of p38 MAPK and ERK1/2, thus leading to the reduction of neointimal hyperplasia during vascular remodeling. Therefore, the SEWEAF may be a potential ingredient for use in functional foods or nutraceuticals that are formulated for preventing/treating vascular remodeling-related disorders.

Key Words: *Salicornia europaea*, Vascular smooth muscle cells, Migration, Proliferation, Anti-atherosclerotic effect, Vascular remodeling

P2-11

The APE1/Ref-1 inhibits inorganic phosphate-induced vascular calcification in vascular smooth muscle cells and ex vivo aorta

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Vascular calcification is an important marker in atherosclerosis and chronic inflammation, which is strongly associated with cardiovascular mortality in chronic kidney diseases. In the present study, we studied a novel role of apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) in Pi-induced vascular calcification and vascular smooth muscle cell (VSMC) phenotype changes and showed that the redox function of APE1/Ref-1 was involved in the inhibition of inorganic phosphate (Pi)-induced oxidative stress and vascular calcification in VSMCs. To determine the role of APE1/Ref-1 in the Pi-induced VSMC calcification, we studied the effect of adenoviral over-

expression of APE1/Ref-1 (200 MOI) on the Pi-induced VSMC calcification. Adenoviral-transfected cells were exposed to Pi (5 mM) in the presence of 10% FBS for 6 days. The overexpression of APE1/Ref-1 inhibited Pi-induced loss of the alpha-smooth muscle actin and smooth muscle protein 22-alpha, and VSMC calcification, which was examined by alizarin red staining and a calcium content assay. In the ex vivo system overexpression of APE1/Ref-1 suppressed the Pi-induced aortic calcification (alizarin red staining) and phosphate precipitation (von Kossa staining). We demonstrated that Pi-induced VSMC calcification is associated with decreased APE1/Ref-1 expression. APE1/Ref-1 overexpression suppressed the Pi-induced VSMC calcification and prevented a loss of the smooth muscle phenotype.

Key Words: APE1/Ref-1, Vascular calcification, Vascular smooth muscle cells, Inorganic phosphate

P2-12

Fast, transient relaxation of rat pulmonary artery by angiotensin II via AT1-eNOS signaling pathways

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Angiotensin II (AngII) is conventionally known as a vasoconstrictive agonist in the large conduit arteries. However, our preliminary study showed that the application of Ang II induces only a transient, weak contraction in pulmonary arteries (PAs) followed by persistent desensitization. We have previously reported eNOS expression in pulmonary smooth muscle cells (PASMC). Here we hypothesized that the concomitant activation of the myogenic eNOS by Ang II might limit the contractile responses of PA. Myograph study (isometric contraction of vessel rings) of the rat PAs showed biphasic dose-response to Ang II with peak response at 0.1 μM When pre-treated with L-NAME (NOS inhibitor) or ODQ (guanylate cyclase inhibitor), the transient AngII-contraction became augmented and sustained. The AngII-contraction was abolished by losartan, (AT1 receptor antagonist), while neither PD123319 (AT2 receptor antagonist) nor A779 (Mas receptor antagonist) affected the AngII-contraction. In human PASMCs, eNOS expression was confirmed, and the pro-activating phosphorylation of Ser1177 in eNOS by AngII treatment was consistently observed by immunoblot. Also, the membrane expression of AT1 was sensitively shifted to the cytosol by AngII. Consistent with the AT1 internalization, the second Ang II hardly induced any contractile response in PAs. Interestingly, the desensitization was also significantly removed by the treatment of L-NAME, immediately after the washout of first AngII application, suggesting the involvement of eNOS signaling pathway in the control of AT1 recycling. Taken together, we proposed that the auto-inhibitory role of the muscular eNOS in PAs play physiological roles of active relaxation under various vasoconstrictive conditions, preventing excessive contractile response of the low-pressure pulmonary circulation.

Key Words: eNOS, Angiotensin II, Desensitization, Pulmonary artery, Smooth muscle

P2-13

Attenuation of vascular contractility in metastatic breast cancer mice

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Breast cancer (BC) is the one of crucial health burden among women worldwide. Even though the alteration of vascular function were observed by few researchers in metastatic BC, the changes in vascular reactivity and its underlying mechanism were not fully understood. Here, we investigate the physiological changes of vascular function from isolated mesenteric arteries in metastatic breast cancer mice model. In this study, 105 of 4T1 murine BC cells were injected into the subcutaneous or tail vein of female Balb-c mice aged 8 weeks old. Mice were randomly divided into the following group: 1) control; n=10, 2) non-metastatic model (4T1; n=10), 3) tumor-bearing model (4T1M; n=10), and 4) tail vein injection model (4T1ML; n=10). Mesenteric arteries were removed after 4 weeks of tail vein injection group and 5 weeks of tumor-bearing groups. Isometric tension was investigated in response to various vasoconstrictors such as phenylephrine (PhE), Serotonin (5-HT), Angiotensin II (ANG II) and high potassium chloride (HK). Our results showed that PhE-induced vasoconstriction was no significant differences in the non-metastatic group compared to control. However, the attenuated vasoconstriction in response to PhE, 5-HT, and High K was found in metastatic cancer groups. Application of L-type voltage-gated calcium channel inhibitor (Nifedipine) induced vascular relaxation with PhE-induced contraction in each group, but there were no significant differences among groups. Interestingly, PhE-induced contraction in metastatic groups was not inhibited by Rho kinase inhibitor (Y-27632), but not in control. From above reslts, it is suggested that decreased Rho kinase activity might be attributable to attenuated vasoconstriction in mesenteric artery from metastatic breast cancer mice.

Acknowledgement: This study was supported by National Research Foundation of Korea grant funded by Ministry of Science, ICT, & Future Planning (2015R1C1A1A01054038).

Key Words: Vascular reactivity, Breast cancer metastasis, Mesenteric artery, Rho kinase, L-type voltage-gated calcium channel

P3-01

Development of autaptic sympathetic neuronal culture for studying the functional communication between autonomic neurons and satellite glial cells

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Satellite glial cells (SGCs) were classically considered as simple supportive cells for autonomic neurons. Until now, the roles of the SGCs in regulation of autonomic functions have not been explored. Thus, we hypothesized that the SGCs play significant roles in processing of information through autonomic ganglia. As an initial attempt for studying the effects of the SGCs on autonomic synaptic events, we developed autaptic sympathetic neuronal culture. The sympathetic neurons were enzymatically dissociated from the superior cervical ganglia or stellate ganglia of neonatal rats (P0-P2), and plated onto agarose-coated culture dishes with microdots of growth-permissive substrate. We tested different culture media containing different types of serum for optimizing culture conditions. Nerve growth factor and ciliary neurotrophic factor were supplemented to the culture media for a long-term culture and induction of cholinergic phenotype, respectively. The neurite growth and formation of autaptic synapse (autapse) were promoted only in the L15 and DMEM/F12 containing rat serum. Electrical measurements were performed under the gramicidin-perforated configuration of the patch-clamp recording techniques. To evoke synaptic currents, a single neuronal soma was stimulated by a 2 ms depolarizing step from a holding potential of -60 mV to 0 mV. Hexamethonium-sensitive excitatory postsynaptic currents (EPSCs) were observed from four days in culture, which indicates the formation of cholinergic autapse. Interestingly, however, the EPSCs were not completely abolished in the presence of the hexamethonium, suggesting non-cholinergic neurotransmitter release at the autapses. The EPSCs and the readily releasable pool of vesicles increased time-dependently and reached the maximum size around 12-14 days in culture. The spontaneous miniature EPSCs were observed in the presence of tetrodotoxin. The autaptic neuronal cultures also exhibited short-term plasticity as demonstrated with a paired pulse stimulation. Taken together, we successfully developed the autaptic sympathetic neuronal culture which exhibit the previously reported characteristics of cholinergic synaptic transmission.

Acknowledgement: This research was supported by Basic Science Research Program through the National Research Foundation funded by the Ministry of Education, Science and Technology (NRF-2016R1D1A1B01015042).

Key Words: Autonomic neuron, Autaptic synapse, Synaptic transmission, Satellite glial cell, Cholinergic

P3-02 (PO-A-03)

Peripheral $GABA_A$ receptor-mediated signals facilitate chronic inflammatory pain

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It is well known that peripheral GABA, unlike in CNS, produces excitatory effects. Indeed, exogenous GABA and muscimol, $GABA_A$ receptor ($GABA_AR$) agonists, induce pain hypersensitivity in rodents under acute inflammation. However, it still remains unclear whether peripheral $GABA_AR$ and the endogenous GABA play an important role in chronic inflammatory pain. In this study, we investigated how peripheral $GABA_AR$ affected pain hypersensitivity by using complete Freund's adjuvant (CFA)-induced chronic inflammatory pain model in adult mice. We found that intraplantar (i.pl.) administration of $GABA_AR$ antagonists, picrotoxin (3 mM, 10 μL) and 1(S),9(R)-(-)-bicuculline methiodide (3 mM, 10 μL) significantly inhibited both spontaneous nociceptive (paw licking and paw flinching) behavior and mechanical hypersensitivity in CFA-injected mice at 3 d, but not in naïve mice. CFA-induced mechanical hypersensitivity was also significantly reversed by GABA specific antibodies (anti-GABA, 10 μL, i.pl.). Besides, RT-qPCR and immunohistochemistry revealed up-regulation of glutamate decarboxylase (GAD) 65 and GAD 67, two isoforms which produce GABA, in the ipsilateral hind paw of CFA-injected mice at 3 d. Finally, 5α-pregnan-3α-ol-20-one (3α,5α-THP; 100 μM, 20 μL), a selectively positive allosteric modulator of $GABA_AR$, produced mechanical hypersensitivity in naïve mice in a dose-dependent manner. Taken together, our results indicate that peripheral $GABA_A$ receptor and the endogenous GABA, possibly produced by inflamed tissue, can potentiate CFA-induced chronic inflammatory pain, suggesting that peripheral $GABA_AR$ can be a therapeutic target for alleviating chronic inflammatory pain.

Key Words: $GABA_AR$, Endogenous GABA, Chronic inflammatory pain, Picrotoxin, Bicuculline, 3α,5α-THP

P3-03 (PO-A-04)

SHP2 mutation mediated cell type specific dysregulation of Ras-Erk signaling pathway

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RAS-MAPK signaling network plays critical roles in learning and memory. Mutations of genes in RAS signaling are associated with neurodevelopmental disorders such as Noonan syndrome (NS) and neurofibromatosis type 1 (NF1), collectively called RASopathy. Interestingly, previous studies have suggested that each RASopathy affects distinct cell types in the nervous system and subsequently alters synaptic functions and behaviors. However, molecular mechanisms underlying the cell type-specific pathophysiology in RASopathies are unclear. Mutations in *PTPN11*, which encodes SHP2, are major cause of NS. Expression of $PTPN11^{D61G}$, which is a gain-of-function mutation, leads to deficits in hippocampal memory and long-term potentiation (LTP). Here, we show that activity of Ras-Erk signaling, LTP and spatial memory are differentially affected in αCaMKII and vGAT-positive neurons-specific expression of $PTPN11^{D61G}$. In addition, using cell type-specific transcriptome analyses, we found that gene expression profiles of Ras-Erk signaling networks are significantly different between αCaMKII-positive and vGAT-positive neurons. These data demonstrate that each neuronal type has distinct Ras-Erk signaling network, which may have distinct roles in neurodevelopmental disorders.

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Key Words: Neurodevelopmental disorder, RAS-ERK signaling, Learning and memory, Hippocampus

P3-04 (PO-A-05)

Climbing fiber burst-mediated sensory coding is directly represented in post-synaptic Purkinje cell

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During cerebellar learning, CF fires in response to unexpected sensory event providing instructive signals to PC, turning on the Ca^{2+}mediated plasticity mechanisms. According to Marr-Albus-Ito theory of learning, CF-induced PC Complex spike (CpS) response is "all-or-none". Although this notion has been prevailing until recently, the previously-unknown complexity of the error signal has been paid attention as the CF axon burst properties were described. Also, the longer CS duration, presumably resulted from longer burst, was associated with enhanced cerebellum-dependent motor learning. However, whether CFs encode the magnitude of sensory stimuli has not been established in awake behaving animals due to difficulties in CF recording *in vivo*. Using GCaMP intravital Ca^{2+} imaging in awake mice, we show CF Ca^{2+} activity directly encodes CF burst and exhibits great variability in strength at rest. Employing unexpected sensory stimuli, we reveal CF bursts encode sensory stimulus intensity. Surprisingly, PC Ca^{2+}-mediated sensory coding appears similar with CF-mediated sensory coding. Finally, dual color simultaneous Ca^{2+} imaging of CF and PC strongly indicates the linear correlation between CF and PC responses. Taken together, the results indicate powerful influence of the intensity-dependent presynaptic CF inputs on post-synaptic PC modulation during sensory coding.

Key Words: Climbing fiber, Purkinje cell, Sensory coding, Ca^{2+}, 2-photon microscopy

P3-05 (PO-A-06)

Channel-mediated GABA release from reactive astrocytes in epileptic hippocampus

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Bestrophin1 (Best1), a Ca^{2+}-activated anion channel, can release GABA from astrocytes in the brain. However, the functional significance of Best1-mediated astrocytic GABA release is still in debate. Here, we show that Best1 mediating GABA release from reactive astrocytes generated tonic inhibition, thus, stabilized the neural circuit in epileptic hippocampi. Kainic acid (KA)-induced seizure generated tonic GABAA inhibition (I_{tonic}) in CA1 neurons, which was blocked by a Cl- channel antagonist (5-nitro-2-(3-phenyl-

propylamino) benzoic acid, NPPB). KA failed to generate the NPPB-sensitive I_{tonic} in Best-1 knock out (KO) mice. GABA transporter (GAT) blockers potentiated I_{tonic} in normal hippocampi, which was facilitated by KA-injected epileptic hippocampi of wild type (WT) mice. KA-injection failed to affect I_{tonic} facilitation by GAT blockers, while it increase GABA in reactive astrocytes in both WT and KO mice. In an agreement, while seizure sensitivity were not different in normal WT and Best-1 KO mice, KA significantly increased seizure activity and sensitivity to electrical stimuli in Best-1 KO mice. Finally, astrocyte specific Best-1 rescue efficiently restored KA-enhanced seizure susceptibility in Best1 KO mice. Taken together, our results showed that Best-1 channel-mediated astrocytic GABA release damps epileptic insults in the normal brain.

Key Words: Bestrophin1, Reactive astrocytes, Tonic $GABA_A$ inhibition, Epilepsy

P3-06 (PO-B-06)

Singular mechanisms of the thermal sweating to central sudomotor in tropical Africans

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During heat stress, tropical natives are reported to economize body fluid by exhibiting suppressed sweating compared to temperate natives. However the mechanisms involved in this suppressed sweating has not been not fully understood. In this study, we examined the sudomotor responses of tropical natives (Africans) and temperate native subjects (Republic of Korea) when exposed hot water (43°C) both leg immersions (central sudomotor responses). All experiments were performed in an automated climate chamber. Local skin temperatures and basal metabolic rate were measured, and mean body temperature was calculated. Central sudomotor activity, including evaporative water loss, local sweat onset time, local sweat rate, local sweat volume, and whole body water loss volume, was tested. Africans maintained lower mean body temperature and local skin temperatures compared to republic of Koreans before and after heat load test. Basal metabolic rate decreased significantly in Africans compared to republic of Koreans. The local sweat onset time was delayed in Africans compared to Koreans. The local evaporative loss volume, sweat volume, sweat rate, and whole body sweat loss volume decreased in Africans compared to those in republic of Koreans. In conclusion, results of present study demonstrate the singular mechanisms of the thermal sweating in tropical Africans compared to republic of Koreans due to lower resting mean body (skin) temperature and resting BMR than those of temperate native subjects.

Key Words: Thermal sweating, Heat acclimatization, Tropical, Temperate

P3-07

Selective expression of Kv4.1 in mature granule cells contributes to sparse firing of hippocampal dentate gyrus

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Sparse firing of dentate granule cells (GCs) serves as key cellular correlate of pattern separation, the unique ability of dentate gyrus. However underlying mechanisms for sparse firing during maturation of adult-born GCs remain elusive. Here we show that Kv4.1 channel is critical for intrinsic excitability determining sparse coding. Unlike the broad expression of Kv4.2 in hippocampus and its steady activity during maturation, Kv4.1 is more specifically expressed in mature GCs. Kv4.1 inhibition increases intrinsic excitability in mature GCs, while not activating young GCs. Consistently, it alters signal input-output properties only in mature GCs with larger EPSP amplitudes, increased spiking in response to perforant path stimulation, and unchanged EPSCs. Kv4.1 exhibits slowly inactivating K^+ currents in native neurons accounting for its role as frequency regulator. These data indicate that Kv4.1 regulates sparse coding particularly through intrinsic excitability, independently of synaptic current regulation, suggesting a gating function for Kv4.1 in cognitive abilities.

Key Words: Hippocampus, Dentate gyrus, Sparse firing, Kv4.1, Hyperexcitability

P3-08

Spinal D-serine modulates neuronal nitric oxide synthase phosphorylation leading to the development of mechanical allodynia in a mouse model of neuropathic pain

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We have recently demonstrated that D-serine plays an important role in spinal nociceptive signaling transmission via an increase in phosphorylation of N-methyl-D-aspartate receptor (NMDAR) GluN1 subunit (pGluN1). However, the cellular mechanisms underlying the action of D-serine in this process have not been investigated. Here we examine the possible role of neuronal nitric oxide synthase (nNOS) in the D-serine-induced potentiation of NMDAR function using animal models of NMDA-induced nociception and neuropathic pain following chronic constriction injury (CCI) of the sciatic nerve. Exogenous D-serine increases spinal nitrate concentration, and this increase was attenuated by pretreatment with the nNOS inhibitor, 7-nitroindazole. Intrathecal administration of D-serine facilitates NMDA-induced nociception and increases in PKC-dependent (Ser896) pGluN1 expression, which were attenuated by pretreatment with 7-nitroindazole or the calcineurin inhibitor, cyclosporine A. In CCI mice, intrathecal administration of the serine racemase inhibitor, LSOS or the D-serine degrading enzyme, DAAO suppressed the increase in nitrate concentration and the decrease in ratio of phosphorylated nNOS (Ser847) to nNOS. NADPH-diaphorase-positive cells also decreased by the injection of LSOS or DAAO in CCI mice. Intrathecal administration of 7-nitroindazole, the soluble guanylyl cyclase (sGC) inhibitor, ODQ or the PKC inhibitor, chelerythrine attenuated CCI-induced mechanical allodynia and pGluN1. Collectively D-serine modulates spinal nNOS activation leading to the increase in PKC-dependent pGluN1 expression, and ultimately contributes to the development of mechanical allodynia following peripheral nerve injury.

Key Words: D-serine, Phosphorylation, Mechanical allodynia, Neuropathic pain

P3-09

Serotonin increases inhibitory but not excitatory synaptic transmission in the substantia gelatinosa neurons of trigeminal subnucleus caudalis

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The substantia gelatinosa (SG, lamina II) of the trigeminal subnucleus caudlias (Vc; also called medullary dorsal horn) is an important brainstem relay site for nociceptive input from the orofacial region. Serotonin (5-hydroxytryptamine, 5-HT) is involved in the descending modulation of nociceptive transmission in the spinal and medullary dorsal horn. According to immunohistochemical studies, 5-HT-containing axons are numerous in the superficial laminae, especially SG, and the 5-HT receptors are found at pre- or postsynaptic locus of SG neurons in the medullary or spinal dorsal horn. In the present study, we investigated the role of 5-HT on synaptic transmission in SG neurons of the Vc using whole-cell patch clamp technique in immature mice. Bath application of 5-HT (3 or 10 μM) significantly increased the frequency of spontaneous postsynaptic currents (sPSCs), although amplitudes of sPSCs were not significantly changed. 5-HT-induced frequency increase of sPSCs was abolished by pretreatment of strychnine and picrotoxin, but not by pretreatment of CNQX and AP5. These results indicate that application of 5-HT significantly increased the frequency of inhibitory sPSCs, but not excitatory sPCS, through GABA and/or glycine release and suggest that inhibitory control by 5-HT might contribute to the modulation of orofacial nociceptive neurotransmission in SG neurons of the Vc.

Acknowledgement: This research was supported by the Basic Science Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2015R1D1A3A01018700).

Key Words: Serotonin, Inhibitory spontaneous postsynaptic current, Whole-cell patch clamp, Substantia gelatinosa

P3-10

The potential role of TLR2 on alcohol-induced behaviors

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Alcohol abuse and alcoholism cause brain damages. In some cases, alcohol consumption leads to neurodegeneration and behavior impairment. Recent studies demonstrate that the inflammatory response is associated with the activation of Toll-like receptors (TLRs) during brain infections, neurodegeneration and neural damage. This study was designed to evaluate the role of TLRs in behavioral consequence induced by alcohol consumption using TLR knockout (KO) mice. The behavior test was performed at 15 days of 10% alcohol consumption followed by 24 h withdrawal. In two bottle test, the alcohol consumption and preference were increased in TLR2 KO mice. In dark and light box test, withdrawal anxiety was reduced in TLR2 KO mice. The locomotor activity was increased in TLR2 KO mice. In CPP, reward property was also increased in TLR2 KO mice. These results suggest that the role of TLR2 could be related to the alcohol-induced behaviors and TLRs might be a potential drug target for alcohol-induced disorders in the future.

Key Words: Toll-like receptor2, Alcohol consumption, Alcohol preference, Withdrawal anxiety

P3-11

Regulation of NMDAR receptiveness through calpain inhibition in midbrain dopamine neurons

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Midbrain dopamine neurons exhibit spontaneous firings whose activities and patterns are tightly regulated by calcium signals. The NMDA receptor (NMDAR) is a cation channel highly permeable to calcium and plays essential roles in modulation of firing patterns and dopamine release in dopamine neurons. Cytosolic Ca^{2+} influx through NMDAR can lead to the activation of the Ca^{2+}-dependent protease, calpain. Calpain activation regulates numerous downstream targets such as ROS and is highly involved in the pathogenesis of several diseases such as brain injury, Alzheimer disease and Parkinson's disease. However it remains largely unclear how calpain inhibition affect firing activities in the dopamine neurons. Therefore in the acutely dissociated midbrain dopamine neurons, we studied the involvement of calpain in regulation of NMDA-induced calcium increases and firing patterns.

In the dopamine neurons, when we increased spontaneous firing rate with doses of NMDA, the rise in global $[Ca^{2+}]_c$ levels was correlated with the spontaneous firing rate. However, when we blocked calpain activation with membrane permeable calpain inhibitor, MDL 28170 (30 uM), the NMDA (50-100 uM)-induced Ca^{2+} rises were significantly exaggerated by contrast with those of control condition. In patch clamp recording, MDL 28170 increased the amplitude and duration of afterhyperpolarized potentials in tie dopamine neuron. After pretreatment with MDL 28170, NMDAR-mediated firing increases regular patterns were significantly changed burst-phase patterns. Another membrane permeable calpain inhibitor, calpeptin, also turned regular firing patterns into burst-pause firing patterns.

All these data indicate that calpain inhibition activated NMDA receptiveness in evoked burst changes and Ca^{2+} rises, which mechanisms of burst generation in dopamine neuron may be important to understand pathophysiology of Parkinson's disease.

Key Words: Dopamine neuron, NMDAR, Calpain inhibition, Calcium, Firing patterns

P3-12

Pharmacological inhibition of eIF2α phosphorylation can rescue synaptic plasticity and memory deficits in Alzheimer's disease mouse models

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Eukaryotic translation initiation factor 2α (eIF2α) is reported to have roles in regulating long-term synaptic plasticity and memory by their phosphorylation at Ser 51. Its persistent, hyperactive phosphorylation occurs in neurodegenerative diseases such as Alzheimer's disease (AD). Therefore, balancing its phosphorylation can be critical in a number of neural functions. It is also known that the inhibition of eIF2α phosphorylation enhances learning and memory in naïve mice. However, the effect of pharmacological inhibition of eIF2α phosphorylation on synaptic plasticity and memory in AD mouse models remains elusive. In this study, we tested whether pharmacological inhibition of eIF2α phosphorylation can restore LTP and memory deficits in two AD mouse models: 5XFAD transgenic mice and mice acutely infused with Aβ. We found that pharmacological inhibition of eIF2α phosphorylation can acutely rescue the deficits in synaptic plasticity and memory in both AD mouse models. Our findings raise the possibility of treatment of AD by manipulating the eIF2α-mediated signaling pathway.

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Key Words: Alzheimer's disease, Long-term potentiation (LTP), Object recognition memory, Contextual fear conditioning

P3-13

Branch specific input wiring on distal tuft dendrites of L5 pyramidal neurons in primary somatosensory cortex

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Functions of the central nervous system depends on connectivity between neurons and brain regions. However, wiring specificity of cortical circuit is still far not complete understanding. We analyzed spatial distribution pattern of paralemniscal inputs from posterior medial thalamic nucleus (POm) and motor inputs from primary motor cortex (M1) onto distal tuft dendrites of layer 5 (L5) pyramidal neurons in the barrel cortex (S1BF).
Axons both from POm and M1 ramify in layer 1 and make synaptic contacts on distal dendrites of layer 5 of S1BF. Because of long length of apical dendrites with intracellular resistivity, synaptic voltage on these synapses will be transformed smaller and broader signal when it arrives at axon hillock. We hypothesized synapses from POm and M1 are wired to support effective regenerative dendritic activity to overcome the passive attenuation. More specifically, we are tackling the question whether tuft dendritic branches of L5 pyramidal neuron have distinctive response specificity, depending on origin of synaptic inputs. Corroborating with this idea, frequent Ca^{2+} spikes were observed in tuft dendrite of L5 pyramidal neurons and some of which were strongly dependent on active whisker touch as well as M1 activity. In order to examine this possibility, we use two-photon Ca^{2+} imaging combined with optogenetic stimulation of POm or M1. We have successfully adopted experimental setup to identify input specific functional synapses in vitro and in vivo. Now, we are making effort to identify the specificity of synaptic input and the correlate between stimulation-evoked Ca^{2+} responses and whisker behavior-evoked dendritic activity so as to decipher the input-specific, thus function-specific, synaptic wiring in neocortex.

Key Words: Barrel cortex, Layer 5 pyramidal neurons, Posterior medial thalamic nucleus, Primary motor cortex, Synaptic wiring

P3-14

The role of spinal cord D-serine in the development of mirror-image pain: different modulation of astrocyte sigma-1 receptors and gap junctions on D-serine production

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Mirror-image pain (MIP) is mysterious symptom which damage on one side of the body can also result in pain from the contralateral unaffected side. In the present study, we demonstrated the role of spinal D-serine in the development of MIP and the involvement of astrocyte sigma-1 receptors and gap junctions on ipsilateral versus contralateral D-serine production, respectively. Following intraplantar injection of carrageenan, mechanical allodynia (MA) was tested at various time points to examine the effect of individual drugs. Expression levels of spinal D-serine, serine racemase (SeRa), sigma-1 receptor, and Cx43 was evaluated by immunohistochemical or Western blot assay. The expression of ipsilateral D-serine was upregulated during the early phase of inflammation, while contralateral D-serine increased during the later phase of inflammation. The pharmacological inhibition of D-serine during the early phase blocked the development of both ipsilateral and contralateral MA. However, the inhibition of D-serine during the late phase of inflammation only blocked contralateral MA. Interestingly, the inhibition of sigma-1 receptors during the early phase of inflammation inhibited the increase in ipsilateral D-serine, while the blockade of astrocyte gap junctions during the late phase of inflammation suppressed the upregulation of contralateral D-serine. These results implying that spinal astrocyte D-serine plays an important role in the development of mirror-image pain. Furthermore, astrocyte sigma-1 receptors and astrocyte gap junction signaling mediate ipsilateral and contralateral D-serine production, respectively.

Key Words: Mirror-image pain, D-serine, Sigma-1 receptor, Gap junction

P3-15

Correlation between hippocampal ensemble dynamics and memory specificity

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Memory generalization and discrimination are critical survival strategies for animals to adapt to the constantly changing environment. However, the excess memory generalization compromises the accuracy of a memory, which may cause inappropriate responses. In contrast, the excessive memory specificity may hinder an animal to display adjusted responses to environmental changes. The balance between memory generalization and discrimination has been studied extensively. According to previous studies, hippocampus has been known to be important for the memory discrimination. The hippocampus has a specific neural ensemble pattern for each context, which stores an individual memory called the memory engram. A specific neural ensemble for each contexts is considered to be crucial for the ability to discriminate between each context. Although, several regulation factors for memory generalization and discrimination have been reported, the cellular mechanism is still elusive. As the first step toward understanding the mechanism for memory generalization and discrimination, we analyzed ensemble dynamics under the experimental condition that the memory discrimination is gradually increasing through repeated learning by using in vivo calcium imaging in mice hippocampus. In addition, we also aim to investigate relationship between hippocampal ensemble dynamics and mPFC-mediated circuit. We found that overlap between neuronal ensembles is significantly higher when the animal was tested in two similar contexts than in two completely different contexts. Therefore, we can speculate that overlapped ensemble neurons will also be decreased as memory becomes more specific through repetitive learning. Our study may contribute to reveal a cellular mechanism of memory specificity and generalization.

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Key Words: Memory engram, Contextual fear conditioning, Context discrimination, Hippocampus, Medial prefrontal cortex

P3-16

Repurposed drugs for acute ischemic stroke

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Stroke leads 6.5 million deaths world-wide, which is the second most common global cause of death. The reperfusion therapy with tissue plasminogen activator and endovascular embolectomy is effective within 4-8 hours after ischemic accident. Other approaches for ischemic stroke treatment such as neuroprotective therapies and cell-based therapies have been tried to reduce damaged brain and promote neural recovery, however, clinical efficacy has not been proved. In this study, based on drug repositioning methodology which oppose gene expression pattern of immune cells in ischemic stroke using GEO and L1000CDS[2], new therapeutic candidates for ischemic stroke were found. Most of top ranked candidates pharmacologically work as cellular signal inhibitors. We choose three core signal in-

hibitor, A, Z, and G to validate therapeutic effect in a rat model of ischemic stroke. The Z-treated and A-treated groups showed significant differences in neurological recovery as indicated by the mNSS compared with the control group as early as 4 days or 10 days after middle cerebral artery occlusion(MCAO) surgery, respectively ($p<0.05$). The A-treated and Z-treated group showed better performance in the stepping test compared with the control group from the first day or 14 days after MCAO surgery, respectively ($p<0.01$). Taken together, these behavioral analyses suggest that A and Z attenuated behavioral impairments after MCAO. The administration of A and Z also exerted therapeutic effects on structural recovery in a model of ischemic stroke. It provides valuable insights into the development of therapeutic strategy for ischemic stroke patients who are less benefit from thrombolytic therapy.

Key Words: Ischemic stroke, Therapeutic strategy, Drug repositioning

P3-17

Adrenergic modulation of cerebellar glial activity during nociception

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The alteration of the cerebellar metabolic level in pain state has been observed in previous human brain imaging studies. However, it is unknown whether and how the cerebellar Bergmann glia (BG) is involved in pain processing. To address this question, we monitored the calcium activity of BG in intact cerebellar cortex lobule IV/V by using *in vivo* two-photon calcium imaging in anesthetized mice. Various noxious electrical stimuli were delivered to the mouse hind-paw during calcium imaging with pharmacological manipulation. Capsaicin was also injected to the hind paw to identify BG calcium responses under an acute spontaneous pain condition. We found that strong calcium activation in BG network was evoked by noxious electrical stimuli. This calcium activation was blocked by an infusion of alpha1-adrenergic receptor (α1-AR) antagonist into the cerebellar cortex, but not by glutamatergic or purinergic receptor antagonists. The capsaicin injection also induces strong BG calcium responses, which were blocked by a cerebellar infusion of the α1-AR antagonist. Moreover, the capsaicin-induced pain behavior (i.e. licking duration) was robustly reduced by an α1-AR antagonist infusion. Taken together, we suggest that noradrenergic signaling mediates the activation of the glial network during noxious information processing in the cerebellum.

Key Words: Cerebellum, Pain, Noxious information processing, Norepinephrine, Bergmann glia

P3-18

Sex-specific behavioral abnormalities in Tert transgenic mice

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Telomerase reverse transcriptase (TERT) is an enzyme regulating the length of telomeres, which shortens during cell division. Besides this critical role during cell proliferation, recent evidences suggest that TERT behaves like a transcription factor during development and overexpression of TERT induces developmental factors such as Pax6, the aberration of which expression has been implicated in manifestation of autism spectrum disorder (ASD)-like behavioral deficits in experimental animals. We behaviorally characterized tert transgenic (tg) mice and found abnormal sociability, social novelty preference, anxiety and electroseizure threshold in males but not in female mice. We observed male-specific increased expression of NMDA receptors in the prefrontal cortex of tert tg mice. These results suggest that tert tg mice mimics one of the key clinical observation of ASD, i.e. male predominance in prevalence as well as the major pathophysiological hypothesis of ASD, excitatory/inhibitory imbalance. Additional studies should be followed to investigate the mechanism regulating sex-specific aberrant excitatory neuronal differentiation, which might provide valuable information regarding neural abnormalities underlying ASD-like behaviors.

Key Words: Tert Tg, Sex, Excitatory neuron, NMDA, Social interaction

P3-19

Construction of time-evolving pain-related brain network by literature-mining

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Pain is a multidimensional phenomenon emerging from the integrated activity of the brain. Therefore, it is necessary to understand pain in terms of a complex brain network. There have been many successful studies investigating the molecular networks using text mining approaches based on the accumulated biomedical data. Likewise, there are hundreds of thousands of accumulated papers about pain so far, and each of the papers contains information about the related brain areas.
Here, we constructed time-evolving pain-related brain networks using the information from the biomedical literature of PubMed database, considering the advances and changes in pain research over the last few decades. We retrieved 141,552 abstracts and publication dates of pain-related articles using Biopython Entrez API (Pubmed query: 'Pain[majr]', 2017.05.28.) In order to define nodes for the network construction, we got 594 brain regions as candidates after curating the brain area lists downloaded from Brede database. The occurrence frequency of each brain region in the retrieved abstracts were counted and areas with more than 100 were selected for the network construction. Edges were defined as the co-occurrence between two brain areas in abstracts. The established time-evolving pain-related brain networks showed remarkable changes in our understanding of the pain-related network over the few decades and provided the insights for the future research direction about the brain mechanism of pain.

Key Words: Pain, Text mining, Brain network

P3-20

Metabotropic glutamate receptor 5 in the brain governs sensory pain and negative mood symptoms in the spinal nerve injured rats: [11C] ABP688 PET study

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Patients with chronic neuropathic pain easily accompany the negative mood symptoms such as depression and anxiety, and these disturbances in turn affect the aversive sensory perception. However, the underlying mechanisms are largely unknown. Recent neuroimaging studies of neuropathic pain model animals and human chronic pain patients emphasize the critical role of corticolimbic structures of the brain. In this study, we demonstrate that metabotropic glutamate receptor 5 (mGluR5) in the brain regions mediate such a comorbidity of aversive states. We scanned the brain of chronic neuropathic pain model rats using positron emission tomography (PET) technique with an mGluR5-selective radiotracer [11C] ABP688 and found

various brain regions of which the mGluR5 level is related to the pathological behaviors of neuropathic pain model animals. Among the brain areas, a prominent upregulation of mGluR5 was shown in the prelimbic region (PrL) of the medial prefrontal cortex (mPFC) of chronic neuropathic pain animals. A pharmacological blockade of upregulated mGluR5 in the PrL ameliorated the negative symptoms including tactile hypersensitivity and depressive-like behavior, which relieved the subjects from the unpleasant state of chronic neuropathic pain condition. Conversely, lentiviral overexpression of the mGluR5 in the PrL of naïve rats successfully induced comorbid pain and negative moods. Our data provide deeper insight into the shared mechanism of pain perception and negative emotions, identifying a therapeutic target for the treatment of chronic pain and mood disorders.

Key Words: Neuropathic pain, Depression, mGluR5, PET, Neuroimage

P3-21

In adolescence, elevation of GABA activity in the ventral hippocampus is related with anxiety- and aggressive- like behavior induced by neonatal maternal separation

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Neonatal maternal separation (MS) is one of the animal models for emotional disorder such as anxiety and depression. Thus far, MS study has been done by many researchers on many different kinds of species from rats to apes and produced a lot of behavioral results. However, the effects of MS on the synaptic plasticity of the hippocampus remain imperfect understanding. This study investigated the effects on the behavioral changes and mechanisms of the synapse plasticity in the hippocampus in MS mice. Following a periodic neonatal MS (4-hour a day, during 19 days), adolescent mice were employed for behavioral experiments for depression, learning, memory, anxious and aggressive behavior using the forced swimming test (FST), Y-maze, Morris water maze (MWM), elevated plus maze (EPM), three consecutive days of the open field test, the social interaction test, the tube-dominance test and the resident-intruder test. The results showed that there was no difference in FST, Y-maze, and MWM performance. However, MS mice showed more anxiety-like behavior in the EPM test and aggressive-like behavior in the tube-dominance and resident-intruder tests. In addition, the magnitude of long-term potentiation (LTP) and release probability in the dentate gyrus (DG)-CA3 synapses were significantly reduced in the MS group but not in the CA3-CA1 synapse. Thereafter, the excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSC) were measured in the hippocampal dentate granule cells by using patch clamp recording. MS mice showed elevated gamma-aminobutyric acidA ($GABA_A$) receptor-mediated IPSCs in the ventral hippocampal dentate granule cell. These results indicate that early life stress based on MS may induce anxiety- and aggressive-like behavior during adolescence, and these behavioral alterations are associated with reduced synaptic plasticity and release probability at the DG-CA3 synapses. In addition, these changes can be associated with the elevation of the $GABA_A$ receptor-mediated IPSCs in the ventral hippocampal dentate gyrus, although the precise mechanism between the alterations of behavior and the synaptic plasticity remains to be elucidated.

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Key Words: GABA, Adolescence, Anxiety, Aggression, Hippocampus

P3-22

Pacemaking of midbrain dopamine neurons: role of TRPC3 and NALCN channels

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Dopamine neurons in the midbrain are slow pacemakers that generate spontaneous action potentials at 2-6 Hz, regularly. Although this pacemaking activity is essential for maintenance of background dopamine levels and proper functioning of basal ganglia, it is not known what channels are responsible for pacemaking in the midbrain dopamine neurons. Here we report that two ion channels, TRPC3 and NALCN channels, are essential for robust pacemaking in the midbrain dopamine neurons. In dissociated dopamine neurons and midbrain slices, when pyr10, a specific TRPC3 channel blocker, was applied, spontaneous firing and Ca^{2+} oscillations were completely abolished, together with a substantial hyperpolarization of membrane potential. Somatic current injection regenerated pacemaker activity again, suggesting that TRPC3 channels act as a part of leak channels, known as major inward currents in dopamine neurons. However, not only spontaneous firing survived in dopamine neurons of TRPC3 knockout (KO) mice but also spontaneous firing rates in the TRPC3 KO did not differ from those of wild type mice. Nevertheless, in the TRPC3 KO mice, application of pyr10 did not affect spontaneous firing, Ca^{2+} oscillations, and membrane potentials, at all, indicating that pyr10, in wild type mice, blocked spontaneous firing by specifically blocking only TRPC3 channels. In TRPC3 KO mice, blockade of NALCN channels with Gd2+, but not SKF-96365, hyperpolarized membrane potentials, indicating that NALCN channels completely compensate pacemaking in TRPC3 KO mice in SNc dopamine neurons. In wild type mice, although pyr10 hyperpolarized membrane potential, additional higher concentration of Gd2+(20 um), amenable to block NALCN channels, further moved membrane potential into K+ equilibrium potential. Taken together, we conclude that TRPC3 and NALCN channels are essential components for pacemaking in midbrain dopamine neurons.

Key Words: TRPC3, NALCN, Dopamine neuron, Pacemaking

P3-23

Metabotropic glutamate receptor 5 is involved in 0.1 mM $[Mg^{2+}]_o$-induced $[Ca^{2+}]_i$ spikes in cultured rat hippocampal neurons

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Reducing $[Mg^{2+}]_o$ to 0.1 mM has elicited repetitive $[Ca^{2+}]_i$ spikes in cultured rat hippocampal neurons, driven by glutamatergic synaptic transmission. Group 1 metabotropic glutamate receptors (mGluRs), positively affect postsynaptic neuronal excitability. Present study was investigated to determine whether group 1 mGluRs are involved in the synaptically-inducced $[Ca^{2+}]_i$ spikes induced by HEPES-buffered Hank's salt solution containing 0.1 mM MgCl2 and 10 μM glycine in cultured rat hippocampal neurons from embryonic day 17 fetal Sprague-Dawley rats using digital imaging methods for Ca^{2+}. Reduction of $[Mg^{2+}]_o$ to 0.1 mM induced synchronized and repetitive $[Ca^{2+}]_i$ spikes within 30 s at day 11.5. The group 1 mGluR agonist, DHPG (1 μM), significantly increased the frequency and the area under the curve of the 0.1 mM $[Mg^{2+}]_o$-induced $[Ca^{2+}]_i$ spikes. The mGluR5 antagonist MPEP (25 μM) significantly inhibited the frequency and the area under the curve of the $[Ca^{2+}]_i$ spikes, but the mGluR1 antagonist LY367385 (100 μM) did not affect the $[Ca^{2+}]_i$ spikes. The IP3 receptor antagonist 2-APB (30 μM) or the ryanodine receptor antagonist TMB-8 (10 μM) also inhibited the $[Ca^{2+}]_i$ spikes. Ryanodine receptor antagonist caffeine (20 mM) increased the frequency and decreased the area under the curve of the $[Ca^{2+}]_i$ spikes. The protein kinase C (PKC) activator OAG (30 μM) increased the frequency and

the area under the curve of the $[Ca^{2+}]_i$ spikes. All these results suggest that mGluR 5 is involved in the 0.1 mM $[Mg^{2+}]_o$-induced $[Ca^{2+}]_i$ spikes in cultured rat hippocampal neurons through release of Ca^{2+} from intracellular stores and activation of PKC.

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Key Words: $[Ca^{2+}]_i$ spike, IP3 receptor, Low Mg^{2+}, Metabotropic glutamate receptor 5, Protein kinase C, Ryanodine receptor

P3-24

Syringaresinol reduces excitatory synaptic transmission and picrotoxin-induced epileptic activity through the presynaptic modulation at the hippocampal CA3-CA1 synapses

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Many conventional drugs acting on the nervous system are originated from botanical sources. These substances affect the nervous system by mimicking actions of endogenous neuromodulators or neurotransmitters. Here we present that a plant lignan Syringaresinol (SYR) suppresses excitatory but not inhibitory synaptic transmission onto hippocampal CA1 neurons through presynaptic modulation. Bath application SYR rapidly suppressed both fEPSPs and evoked EPSCs at the Schaffer collateral (SC)-CA1 synapses. However, SYR had no effect on the conductance and desensitization of AMPA receptors. SYR-induced synaptic depression was accompanied by the increase of paired-pulse ratios and reduction of readily releasable pool size. These presynaptic modulations are presumably mediated by inhibitory G-protein mediated signaling in that SYR reduced Ca^{2+} currents and hyperpolarized membrane potentials of hippocampal neurons. In addition, SYR exhibits anti-epileptic activity that bath application of SYR suppressed picrotoxin-induced epileptiform activities in hippocampal slices. Overall, our study identifies SYR as a new neuromodulating agent that suppresses excitatory synaptic transmission by modulating presynaptic transmitter release.

Key Words: Synaptic transmission

P3-25

Purkinje cell specific STAT3 regulates emotional memory formation at excitatory synapses

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It is increasingly recognized that there is a critical relationship between cerebellum and emotion, particularly in fear responses and fear memory consolidation. However, underlying mechanism for molecular regulation of memory formation remains unclear. To address this issue, we targeted signal transducer and activator of transcription (STAT) family, which is known as a strong etiological factor for posttraumatic stress disorders (PTSD), characterized by a hypermnesia of the trauma. Herein, we hypothesize that cerebellar STAT3 contributes to PTSDlike memory formation. Using Purkinje cell-specific STAT3 knockout (KO) mice model in fear conditioning paradigm, we found that long-term fear memory was increased in STAT3- deficient group, and avoidance memories were significantly increased in STAT3 KO group after 24 hours. When learned fear, STAT3 KO group showed more exaggerated responses (fearpotentiated responses) than wildtype group. After fear conditioning, long-term potentiation (LTP) was reframed to long-term depression (LTD) at parallel fiber-Purkinje cell synapses of STAT3 KO mice. Reframing LTP/LTD was also confirmed in in vitro slice physiology. However, long-term potentiation of inhibitory synapses at molecular layer interneuronPurkinje cell synapses of STAT3 KO mice were not involved in the consolidation of fear memory. To investigate how Purkinje cell-specific STAT3 modulates bidirectional plasticity in memory formation, we considered the transcriptional regulations mediated by STAT3. Expression level of AMPA receptor gluA1/2 subunits was increased in STAT3 KO mice. All things considered, these results demonstrated that Purkinje cell STAT3 regulates PTSD-like memory formation revealing the novel mechanisms of traumatic memories.

Key Words: Purkinje cell, STAT3, PTSD-like memory, Reframing LTP/LTD, AMPA receptors

P3-26

Effect of cell type-specific expression of a RASopathy-associated mutations on learning and memory

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Ras pathway is the signaling cascade which regulates large numbers of biological processes. As this signaling pathway plays various roles in a wide range of physiological processes, germline mutations in Ras pathway are associated with neurodevelopmental disorders, collectively called RASopathies. Most of RASopathies show common phenotypes such as short stature, heart defect, facial abnormalities, and especially, cognitive deficits. Although recent studies have shown that Ras signaling plays a different role in each cell type in the brain, how Ras signaling affects cognition in each cell type remains unclear. Here, we investigated the effects of cell type-specific regulation of Ras signaling on learning and memory by using RASopathy-associated conditional BRAF knock-in (cKI) mouse models. BRAF is a direct downstream effector of Ras and mutations of BRAF are associated with RASopathies such as Cardio-facio- cutaneous (CFC) syndrome and Noonan syndrome which of patients show cognitive deficits such as mental retardation and learning disabilities. We crossed floxed mutant BRAF mice with cell-type-specific Cre transgenic lines for cell type-specific expression of RASopathy-associated BRAF mutation. To reveal the effect of BRAF mutation in which cell type, we screened the behavioral, histological and electrophysiological phenotypes of cKI mice. Our study will contribute to identify cell types as well as underlying cellular mechanism accounting for the cognitive deficits in RASopathies.

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Key Words: Ras signaling, Neurodevelopmental disorder, Cognitive deficit, Cell type-specificity

P3-27

Neuroprotective effects of 3,3′-diindolylmethane on hippocampal neuropathology following pilocarpine-induced status epilepticus

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Status epilepticus triggers neuronal cell death, reactive gliosis, thus leading to unusual behavioral changes such as deterioration of neurological function. Status epilepticus causes destructive damage to the brain leading to cognitive impairment and increased risk of epilepsy. Pilocarpine-induced status epilepticus model has been widely used because its characteristics

are consistent with those of temporal lobe epilepsy model. Regular intake of 3,3'-diindolylmethane (DIM) and Indole-3-carbinol (I3C), dietary components found in *cruciferous* vegetables, has been reported to prevent cancer and promote good health. DIM and I3C have also been examined for their use in reversing the progression of cancer as a chemopreventive agent. However, their actions in cellular damages occurs in neurodegenerative diseases are not very well understood. In this study, we investigated the effect of DIM on synapse loss evoked by NMDA using an imaging-based assay that detected an intensity of green fluorescence expressing postsynaptic density 95 (PSD95). DIM protected against NMDA-induced synapse loss and subsequent neuronal death. In addition, we investigated the effect of DIM on hippocampal neuropathology evoked by pilocarpine-induced status epilepticus. DIM prevented the neuronal death induced by status epilepticus *in vivo*. Furthermore, DIM suppressed status epilepticus-induced brain inflammation in mouse hippocampus. Collectively, these results indicate that DIM has neuroprotective effects on status epilepticus-induced synapse loss followed by neuronal death and glial activation and, thus, would contribute to develop an effective drug to treat various neurodegenerative diseases, especially status epilepticus.

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Key Words: 3,3'-diindolylmethane, Status epilepticus, Synapse loss, Neuronal death, Glial activation

P3-28

Long-term depression of intrinsic excitability accompanied by the synaptic depression in the cerebellar purkinje cells

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Long-term depression (LTD) at parallel fibres (PF) to cerebellar Purkinje cells (PC) synapse is implicated in the output of PC, the sole output of the cerebellar cortex. Besides the synaptic plasticity, intrinsic excitability is also one of the components which determines the PC output. Although long-term potentiation of intrinsic excitability (LTP-IE) has been suggested, it has yet to be investigated how PF-PC LTD modifies intrinsic excitability of PC. Here, we show that pairing of the PF and climbing fibre (CF) for PF-PC LTD induction evokes long-term depression of intrinsic excitability (LTD-IE) in the cerebellar PCs from C57BL/6 mice. Interestingly, this intrinsic plasticity showed different kinetics from synaptic plasticity, but both forms of plasticity share Ca^{2+} signalling and protein kinase C (PKC) pathway as their underlying mechanism. While small-conductance Ca^{2+}-activated K^+ channels (SK channels) play important roles in LTP-IE, no direct implication was found in LTD-IE. After PF-PC LTD induction, neither the temporal summation of dendritic EPSP nor the power of spike frequency adaptation is changed, indicating that cerebellar LTD executes the information processing in a quantitative way without quality changes of synaptic integration and generation of output signals. Our results suggest that LTD-IE may have a synergistic effect with synaptic depression on the total net output of neurons by amplifying the modification of PF synaptic transmission.

Key Words: Long-term depression, Cerebellar purkinje cell, Intrinsic excitability, Plasticity

P3-29

Encoding rules for multiple stimulus features of touch and pain in the S1 cortex

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Innocuous and noxious peripheral stimuli are transformed into touch and pain sensations in the cortex, respectively, via the spinal cord and thalamus. The primary somatosensory (S1) cortex plays an important role in the perception and discrimination of these mechanosensation. Traditionally, the CNS somatosensory neurons have been classified into low/high threshold (non-nociceptive/nociceptive) and wide dynamic range (WDR, convergent) neurons by their electrophysiological responses to innocuous and noxious stimuli, such as brush-stroke, forceps-press and forceps-pinch. Besides this modality (M, innocuous/noxious) or intensity (I, weak/strong) feature, each stimuli also includes other stimulus features: texture (T, brush hairs/forceps steel arms) and dynamics (D, dynamic/static), and little is known about how S1 neurons encode such diverse features of sensory stimuli. Using *in vivo* two-photon Ca^{2+} imaging in lightly anesthetized mice expressing GCaMP6s in the layer 2/3 neurons of S1 cortex, we identified clearly separated response patterns of S1 neural population with distinct tuning properties of individual cells to texture, dynamics and modality features of cutaneous stimuli in descending order by selectivity. Our findings suggest a mixed specificity and pattern encoding strategy for multiple stimulus features of touch and pain by S1 neurons.

Key Words: Touch and pain, In vivo two-photon imaging, Primary somatosensory cortex

P3-30

Effects of resveratrol on the substantia gelatinosa neurons of the subnucleus caudalis in immature mice

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Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenol compound in grapes, red wines, and various plant species, which has been reported to have various biological actions. The substantia gelatinosa (SG) neurons of trigeminal subnucleus caudalis (Vc) receive orofacial nociceptive information from the primary afferents and transmit the information to higher brain center. Although a number of studies reported that resveratrol has analgesic effects, the direct effect of resveratrol on the SG neurons of Vc involved in nociceptive information transmission has not been clearly examined. In this study, the effects of resveratrol were examined on the SG neurons of Vc in immature mice using whole-cell patch clamp technique. In high Cl^- pipette solution, resveratrol (500 μM) induced repeatable inward currents without desensitization and the resveratrol-induced inward currents were shown in a concentration-dependent manner. The resveratrol-induced responses were remained to sustain in the presence of tetrodotoxin, a voltage gated Na+ channel blocker, CNQX, a non-NMDA glutamate receptor antagonist and AP5, an NMDA receptor antagonist. However, the resveratrol-inward currents were suppressed in the presence of strychnine, a glycine receptor antagonist and picrotoxin, a $GABA_A$ receptor antagonist. These results indicate that resveratrol directly acts on the SG neurons of Vc and may have inhibitory effects on the SG neurons through activation of glycine receptor and/or $GABA_A$ receptor and suggest that resveratrol might be a potential target molecule as complementary and alternative medicine for pain modulation.

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Key Words: Resveratrol, Substantia gelatinosa, Whole-cell patch clamp, Orofacial pain

P3-31

Activation of pathway-specific synaptic inputs onto layer 5 pyramidal neurons in visual cortex revealed by FM1-43 dye unloading

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Layer 5 pyramidal neurons (L5 PyNs) of the neocortex uniquely possess dendrites spanning almost all cortical layers. In L5 PyNs of the primary sensory cortex, perisomatic dendritic area including basal dendrites receives sensory feedforward inputs from the thalamus and layer 4 and 5 whereas the distal apical dendrite in layer 1 receives feedback associative inputs from higher brain areas. Thus L5 PyNs is well suited for the integration of feedback and feedforward synaptic inputs like L2/3 PyNs. Although the properties of the information flow in these two pathways are critical for understanding of cortical information processing, almost nothing is known yet due to the structural complexity of the neocortex. Because simple extracellular electrical stimulation is widely used to activate synaptic inputs, it is a prerequisite to know whether local electrical stimulation activates specific inputs. Here, we investigated the layer-specific synaptic activation with local extracellular stimulation using FM1-43 dye unloading in the primary visual cortex. To load FM1-43 dye into synaptic vesicles, visual cortical slices were exposed to high KCl (40 mM) with FM1-43 dye and washed with ADVASEP-7 (chelator of FM dye). For the unloading of FM1-43 dye, electric stimulation (5 Hz) was delivered to either layer 1 or layer 5 with extracellular stimulus electrodes. Unloading of FM1-43 in layer 1 was occurred only by electrical stimulation of layer 1 but not by layer 5. Likewise, unloading of FM1-43 at the layer 5 was detected by electric stimulation of layer 5 but not of layer 1. Thus, these results indicate that stimulation of layer 1 and layer 5 specifically activates inputs in distal apical dendritic and perisomatic basal dendritic areas, respectively. Moreover, FM1-43 dye unloading experiments revealed segregation of sensory and associative inputs in L5 PyN of the primary visual cortex.

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Key Words: Primary visual cortex, Layer 5 pyramidal neuron, FM1-43, Pathway-specific, Dendrites

P3-32

Analgesic effects of low frequency stimulator on docetaxel-induced neuropathic pain in mice

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Docetaxel, a chemotherapeutic agent used to treat breast cancer, produces a robust painful neuropathy signs that are aggravated by mechanical and thermal stimuli. The aims of this study were to investigate the analgesic effects of low frequency stimulator on docetaxel-induced neuropathic pain in mouse and to identify a role of median nerve. Peripheral neuropathy was induced with intraperitoneally injected docetaxel (5 mg/kg) on 5 consecutive days in male ICR mouse. Low frequency stimulation (Care band, 30 Hz) was administered on top of the median nerve of the bilateral wrist. The pain behavior signs were evaluated by von Frey filaments and thermal stimulator on the hind paw, respectively. Also, we measured "50 kHz" and "22 kHz" ultrasonic vocalizations using ultrasound microphones (frequency range: 10-200 kHz, Avisoft Bioacoustics) before and after low frequency stimulation. After the mouse developed neuropathic pain behavior, a single administration of low frequency stimulator significantly attenuated docetaxel-induced mechanical allodynia and thermal hyperalgesia. In addition, treatment with docetaxel for five consecutive days selectively increased the 22 kHz ultrasonic vocalization while administration with low frequency stimulator showed a meaningful decrease. Interestingly, the amputation of bilateral median nerve completely reversed analgesic effect of low frequency stimulator. Although this study might be performed in the animal model by well-designed manner, clinical study will be needed to confirm the analgesic effect of low frequency stimulator. We showed that low frequency stimulator significantly alleviated docetaxel-induced mechanical allodynia and thermal hyperalgesia in neuropathic mouse via a bilateral median nerve. Collectively, results of this study suggest that median nerve stimulation using low frequency can be a potential strategy for the management of chemotherapy induced neuropathy.

Key Words: Chemotherapy, Docetaxel, Analgesic, Low frequency, Ultrasound

P3-33

Direct experimental evidences for modulation of cortical neural excitability of transcranial direct current stimulation in the intact somatosensory cortex of rats

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Transcranial direct current stimulation (tDCS) has been known as a non-invasive brain stimulation technique to modulate cortical excitability. In most animal experiments, craniotomy and durotomy over the cortex were an inevitable step to record single unit activity in the cortex. These procedures hamper a study to evaluate the effect of tDCS on cortical activities. To overcome this problem we introduced the new recording method that directly measure single unit activity in the cortex during tDCS without the craniotomy. Under urethane anesthesia, a small-sized craniotomy over the ventral surface of the brainstem was made in adult rats. Tetrode wire electrodes were introduced into the brainstem and then reached to the somatosensory cortex after fixing a tDCS electrode on the skull. Single unit in each electrode were isolated extracellularly and their activities were measured before and after anodal or cathodal tDCS with different current intensity of 50-200 μA. Cathodal tDCS decreased neural firing rates in the somatosensory cortex with dose-dependent manner. Oppositely, we found significant current intensity-dependent increase in single unit activity for about 30 min following anodal tDCS. This upregulation of single unit firing by anodal tDCS was block by pretreatment of glutamate receptor blocker.

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Key Words: tDCS, Cortex, Somatosensory, Neural excitability, Brainstem

P3-34

Inhibition of spinal PPAR-gamma affects negative influence to motor function recovery after spinal contusive injury in rats

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Mechanical force to the spinal cord disrupts the vascular and nervous systems. This events lead to cell death in the injured area causing mitochondrial dysfunction and energy deprivation. The debris prolong the enhancement of phospholipid-derived inflammatory mediators, which are the ligands of Peroxisome proliferator-activated receptors (PPARs). PPARs are the nuclear receptors, and three isotypes of PPARs have been identified in humans and rodents: alpha, beta/delta and gamma. In particular, the spinal cord is a lipid rich tissue, and PPAR-gamma is expressed abundantly in the fatty tissues. Therefore, we investigated the role of spinal PPAR-gamma after spinal cord injury (SCI).
All animal procedures were approved by KU-IACUC. Sprague-Dawley rats (Male, 220-250 g) were used in this study. Under isoflurane inhalation, a 10 gram load was dropped from 12.5 mm above the surface after exposure of T10 vertebra using NYU impactor. We performed western blotting to analyze protein expression of spinal PPAR-gamma. PPAR-gamma protein levels increased at the beginning and then gradually returned to basal level depending on the injury severity in all the spinal regions after SCI, particularly the caudal region. We administrated antagonist or agonist of PPAR-gamma into the subarachnoid space through PE10 catheter in SCI rats. The exogenously administrated PPAR-gamma agonist did not change locomotor behavior in SCI rats. Intrathecally administrated PPAR-gamma antagonist aggravated locomotor behavior and increased mRNA expression of inflammatory mediators in the late phase rather than the early phase after SCI.
These results suggest that exogenously increasing PPAR-gamma after SCI is not effective for motor function recovery, but it may have a negative effect when it is reduced.

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Key Words: PPAR-gamma, Spinal cord injury, Motor function recovery, Neuroprotection, Neuro-inflammation

P3-35

Layer- and cell type- specific cholinergic regulation of synaptic transmission in pyramidal neurons in the rat visual cortex

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Each cortical layer has distinct roles in information processing in the neocortex. In all layers, cholinergic modulation of synaptic transmission is crucial for cognition, learning, memory and sensory processing. Cholinergic receptors are differentially distributed across visual cortical layers and modulate the activity and plasticity of the visual cortex. In this study, we studied layer-specific cholinergic modulation on short-term plasticity in the visual cortex, because modulation of synaptic transmission in different layers is important in the pathway-specific control of cortical information flow. We recorded excitatory postsynaptic potentials with whole-cell patch-clamp technique by alternating stimulation applied to layers 1 and 4 (20-s intervals each) in layer 2/3 pyramidal neurons or layers 1 and 5 in layer 5 pyramidal neurons of the rat primary visual cortex. Bath application of acetylcholine (10 μM, 10 min) and the nicotinic receptor agonist nicotine (10 μM, 10 min) did not change the paired-pulse ratio (PPR) and the amplitudes of EPSP in layer 2/3 pyramidal neurons. However, the muscarinic receptor agonist muscarine (10 μM, 10 min) increased the PPR at 20-and 40-ms interstimulus interval (ISI) in layer 1 inputs of layer 2/3 pyramidal neurons and decreased PPR at 40-ms ISI in layer 4 inputs of layer 2/3 pyramidal neurons. Layer 5 pyramidal neurons were divided into two types according to the electrophysiological and morphological characteristics as regular-spiking (RS) and burst-spiking (BS) pyramidal neurons. Application of acetylcholine decreased PPR at 40-ms ISI in layer 5 inputs of RS pyramidal neurons, but not in layer 1. Moreover, EPSP amplitudes in layer 5 inputs of BS pyramidal neurons decreased only. Therefore, these results indicate that cholinergic modulation of synaptic transmission differs cell type and layer specifically, which might be important for the cortical information processing dependent on the brain state.

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Key Words: Acetylcholine, Nicotine, Muscarine, Short-term synaptic plasticity, Visual cortex

P3-36

Mossy fibre synaptic inputs are privileged to induce long-term potentiation of intrinsic excitability in CA3 pyramidal cells

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Dendritic excitability is implicated in metaplastic regulation of synapses. Previously, we reported that Kv1.2 on distal apical dendrites of CA3 pyramidal cells is down-regulated by back-propagating action potential-induced activation of protein tyrosine kinase, resulting in long-term potentiation of intrinsic excitability (LTP-IE). LTP-IE could be induced by 20 Hz stimulation of mossy fibres (MFs) or somatic train stimulation at 10 Hz, but not by somatic stimulation at 50 Hz, stimulation of afferent fibres other than MFs or a long depolarising current injection to the soma. We categorised these stimulations into two groups based on the induction of LTP-IE: adequate or inadequate stimulations. Adequate stimulations evoked a plateau-like cytosolic $[Ca^{2+}]$ elevation at distal dendrites with little cell-to-cell variance, whereas calcium signalling caused by inadequate stimulations was more transient with a higher peak level, suggesting that LTP-IE can be induced by a narrow window of calcium signalling. Interestingly, LTP-IE could be induced by MF inputs at frequencies higher than 20 Hz, which evoked distal Ca^{2+} signalling with peaks out of the aforementioned calcium window. Such prerogative of MF inputs for induction of LTP-IE was abrogated by chelation of extracellular Zn^{2+}. Moreover, the incompetence of inadequate stimulations was rescued by intracellular protein tyrosine phosphatase (PTP) inhibitors or bath-application of $ZnCl_2$, implying that MF input-induced Zn^{2+} signalling inhibits PTP, and thus enables MF inputs to induce LTP-IE at a wide range of frequencies. These results indicate that high frequency MF inputs are endowed with privileged induction of LTP-IE because of Zn^{2+} signalling.

Key Words: Mossy fibre, CA3 pyramidal cells, Dendritic excitability

P3-37

Density and output of sweat glands contribute to sudomotor activity in tropical Africans and temperate Koreans

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Modification of sweating could be due to changes in activated sweat gland density (ASGD) and/or activated sweat gland output (ASGO). However, how the two factors are changed in tropical natives remains unknown. In addition, the distributions of ASGD and ASGO over the body in tropical natives are unclear. The present study determined regional and inter-ethnic differences in ASGD and ASGO during passive heating between tropical natives (Africans, n=22) and temperate natives (Republic of Korean, n=25). Heat load was carried out by immersing the half body into a hot water bath (42±0.5°C) for 30 min. All experiments were performed in an automated climate chamber. Tympanic temperature (Tty) and skin temperature (Ts) were measured. Mean body temperature (Tb) was calculated. Sudomotor activities including sweat onset time, sweat rate, ASGD, and ASGO were examined in eight regions of the skin. Africans had smaller increase in Tb during passive heating than Koreans. The onset time of sweating was much more delayed in Africans compared to Koreans. In response to thermal load, ASGD and ASGO differed between body regions in Africans and Koreans. In most skin regions, ASGD and ASGO were decreased in tropical Africans compared to those in temperate Koreans. Trunk portion including chest, upper back, lower back, abdomen had greater swear rate, ASGD, and ASGO compared to peripheral segments including upper arm, forearm, leg, and thigh in both ethnic groups. Distribution patterns of ASGD over the body appeared to be similar in both Africans and Koreans at the peak of thermal loading. In conclusion, the present study demonstrates that sudomotor activity in tropical Africans is suppressed with decreased ASGD and ASGO over the body surface compared to temperate Koreans.

Key Words: Thermal sweating, Heat acclimatization, Sweat glands density, Sweat gland output, Tropical, Temperate

P3-38

Cinnamomi Cortex and its major phytochemicals alleviate oxaliplatin-induced cold and mechanical allodynia in rodents

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Oxaliplatin, a widely used anti-cancer drug against metastatic colorectal cancer, can trigger peripheral neuropathy as a side-effect. Activation of spinal glial cells, such as astrocytes and microglia, and increase of pro-inflammatory cytokines levels in the spinal cord play a crucial role in the pathogenesis of neuropathic pain. *Cinnamomi Cortex* has been used as a medicinal herb in East Asia to treat inflammation and cold. Analgesic effects of Coumarin and Cinnamic acid, major phytochemicals of *Cinnamomi Cortex*, on different kinds of pain were reported. This study investigated whether and how *Cinnamomi Cortex*, Coumarin and Cinnamic acid alleviate oxaliplatin-induced cold and mechanical allodynia in Sprague Dawley rats and c57/bl6 mice. To access cold allodynia, tail immersion test in cold water (4°C) and plantar acetone test were performed. von Frey hair tests were used to evaluate mechanical allodynia. Significant pain behaviors were observed three days after an oxaliplatin injection. *Cinnamomi Cortex* (200 mg/kg) and Coumarin (10 mg/kg) were orally administered and Cinnamic acid (40 mg/kg) was intraperitoneally injected for five consecutive days after oxaliplatin injection. Behavioral studies reveal that *Cinnamomi Cortex* and Cinnmic acid increased the tail withdrawal latency to cold stimuli and decreased the plantar response to both cold and mechanical stimuli, whereas Coumarin only lowered the tail withdrawal latency to cold stimuli. Immunohistochemistry results showed that *Cinnamomi Cortex* and Coumarin suppress activation of spinal astrocytes and microglia. Increased pro-inflammatory cytokines, interleukin-1β and tumor necrosis factor, after oxaliplatin injection were decreased by orally treated *Cinnamomi Cortex*. In summary, *Cinnamomi Cortex* and its phytochemical Coumarin have potent anti-allodynic effect on oxaliplatin-induced neuropathic pain via attenuating activation of spinal glia and release of pro-inflammatory cytokines. This study suggests that *Cinnamomi Cortex* could be an alternative therapeutic agent on oxaliplatin-induced cold and mechanical allodynia, and Coumarin and Cinnamic acid may play a major role in this efficacy of *Cinnamomi Cortex*.

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Key Words: Pain, Glia, *Cinnamomi cortex*, Oxaliplatin, Chemotherapy

P3-39

Anti-despair-like behavior in RalBP1-mutant mice presumably caused by reduced synaptic inhibition in the hippocampus

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Balanced synaptic excitation and inhibition are important for brain functions including cognition and emotion. Mice deficient of RalBP1, a multifunctional protein that interacts with the small GTPase RalA and RalB, display defective inhibitory synaptic transmission in the hippocampus. However, behavioral consequences of imbalanced hippocampal synaptic transmission in RalBP1-mutant mice (RalBP1$^{-/-}$) are unclear. In the present study, we show that RalBP1 deficiency induces anti-despair-like behaviors in mice and reduction of interneurons in the hippocampus. RalBP1$^{-/-}$ mice display reduced density of GABAergic interneurons in the hippocampus. Behaviorally, RalBP1$^{-/-}$ mice were less immobile during both the tail-suspension and forced swim tests. However, cognitive function and anxiety-related behaviors in RalBP1$^{-/-}$ mice were not changed. Administration of the $GABA_A$ agonist muscimol reverted anti-despair-like behaviors in RalBP1$^{-/-}$ mice. Conversely, virus-mediated knockdown of Gabrg2 in CA1 neurons of WT mice suppressed GABAergic transmission and recapitulated anti-despair-like behaviors of RalBP1$^{-/-}$ mice. Similarly, suppression of inhibitory neurotransmission rescued despair-like behaviors in the chronic restraint stress model of depression. These results suggest that hippocampal interneurons play critical role in the regulation of behavioral despair.

Key Words: RalBP1, Hippocampus, GABAergic interneuron, Inhibitory synaptic transmission, Depression

P3-40

Effects of transcranial direct current stimulation on saturated long-term potentiation in visual cortex of rats

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Transcranial direct current stimulation (tDCS) has been known as a tool to modulate neural plasticity. However, it has been unknown how tDCS has an effect on saturated plasticity. Here, we investigated changes of field potentials in visual cortex, evoked by stimulating dorsal lateral geniculate nucleus (dLGN), on the visual cortex of rats before and after anodal or cathodal tDCS

under urethane anaesthesia. Both anodal and cathodal tDCS tends to return saturated long-term potentiation (LTP) to normal state before inducing LTP. Field potentials in the visual cortex after anodal tDCS decreased faster than cthodal tDCS. In addition, the sufficient duration of stimulation (more 20 minutes) with 200 μA intensity was required to return to normal state. We propose that tDCS may be used to regulate saturated neural plasticity to normal state regardless of tDCS polarities.

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Key Words: tDCS, Visual cortex, LTP, Plasticity, Regulation

P3-41

Zone-dependency of Purkinje cell Ca^{2+} dynamics originate from zone-dependent heterogeneity of CF input

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Climbing fiber (CF) input produces a complex spike in a Purkinje cell (PC), inducing strong depolarization with substantial Ca^{2+} influx in dendrites. Although the cerebellar circuitry was postulated to be uniform, it has recently been revealed that cerebellar cortical circuit differs between compartmental zones separated by PC marker expressions such as Zebrin II. Hence, we set out to characterize the CF-evoked dendritic Ca^{2+} spike dynamics of PC between compartments in awake mice during resting and sensory processing. Also, we investigated the mechanism of differential PC responses between zones by directly observing CF Ca^{2+} activity. Surprisingly, GCaMP6f intensities appear greater in Zebrin II positive PC that this property enabled us to distinguish between different zones. CF-evoked PC Ca^{2+} spike frequency was lower and the amplitude/synchrony were higher in ZebrinII-positive (Z(+)) zones than Zebrin II–negative (Z(-)) zones during resting state. Sensory response of PC Ca^{2+} was distinct between zones: response probability and the amplitude/synchrony were prominent in Z(+) and slight in Z(-) zone. Interestingly, CFs projecting to Z(+) zones display enhanced amplitude/synchrony than CFs of Z(-) zones. Also, Z(+) CFs respond to sensory stimuli with high probability; Z(-) PC almost not responding. The region difference in CF-PC activity is presumed to arise from differential expression of gap junctions between subnucleus in inferior olive. Taken together, the results suggest that presynaptic CF Ca^{2+} shapes zone-distinctive PC Ca^{2+} activity, sophisticating the sensory processing.

Key Words: Cerebellar output, Purkinje cell, Sensory processing, Zebrin compartment, 2-photon microscopy

P3-42

Presynaptic mitochondrial calcium release enhances short-term facilitation during brief high-frequency stimulation

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Mitochondria are known to play important roles in generating ATP and calcium sequestration. However, little is known about the role of mitochondrial calcium dynamics in synaptic transmission induced by a brief high frequency stimulation (HFS). We have previously shown that 2 μM tetraphenylphosphonium (TPP^+) specifically blocks mitochondrial Na^+/Ca^{2+} exchanger (mNCX) without affecting the peaks and fast decaying phase of calcium transients (CaTs) at the calyx of Held. Nevertheless, we found that TPP^+ reduces paired pulse facilitation at mature calyx of Held but not at immature one. We further investigated this issue and found that when HFS, a train of 30 pulses at 100 Hz, was applied under 0.1 mM EGTA that mimics the physiological calcium buffer concentration of immature calyx of Held, TPP^+ had no effect on short-term plasticity (STP) of EPSCs. Under the conditions of 0.5 mM EGTA, however, TPP^+ reduced short-term facilitation (STF) of EPSCs evoked by the HFS, suggesting that high calcium buffering may be required for mitochondrial Ca^{2+} release via mNCX during HFS to modulate STP. We studied effects of TPP^+ on mitochondrial ($[Ca^{2+}]m$) and cytoplasmic global Ca^{2+} ($[Ca^{2+}]_i$) during HFS using 10 μM rhodFF-AM and 100 μM Fura-4F, respectively. TPP^+ enhanced the peak $[Ca^{2+}]m$ level caused by HFS under 0.5 mM EGTA, but not under 0.1 mM EGTA conditions. In contrast, 2 μM TPP^+ had no effect on global $[Ca^{2+}]_i$, under the 0.5 mM EGTA conditions, indicating that mitochondrial calcium release regulates microdomain calcium during HFS, and thus enhances STF in the presence of high calcium buffers. In addition, not only STF but steady-state EPSC (EPSCss) was also decreased by 2 μM TPP^+. Since EPSCss is known to be related to calcium-dependent recovery (CDR) of fast-releasing vesicles (Hosoi et al., JNS 2007), we investigated effects of TPP^+ on CDR. To this end, we studied EPSCs evoked by a 3 ms depolarizing pulse (DP3) which depletes a FRP (fast-releasing vesicle pool) at various intervals after the HFS. We found that the recovery of DP3-induced EPSCs was retarded by TPP^+. Moreover, this effect of TPP^+ was occluded by CaM-binding domain peptide in the patch pipette, suggesting that mitochondrial calcium contributes the CDR. These results suggest that the mitochondrial calcium buffering can regulate STP under high calcium buffering conditions.

Key Words: Calyx of held, Mitochondria, Short-term plasticity, Calcium-dependent recovery, Fast-releasing vesicle pool

P3-43

The role of cerebellar Purkinje cell's intrinsic excitability in fear conditioning

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In recent studies, it has been found that the cerebellum is related to non-motor function, such as fear conditioning. Long-term potentiation of synapse between Parallel fibers (PFs) and Purkinje cell (PC) occurs in the cerebellar lobule V-VI of a fear conditioned juvenile rat. However, recent *in vitro* studies found that synaptic plasticity of PF-PC synapse accompanies plasticity of intrinsic excitability of PC. Therefore, we hypothesized that synaptic LTP induced by fear conditioning is also followed by plasticity of intrinsic excitability. We studied *ex vivo* using fear conditioned adult mice with patch clamp technique, whole-cell recording and cell-attached recording, to prove the plasticity of intrinsic excitability present in mature PC. We found no changes with whole-cell recordings, but, there was the depression of spontaneous firing in conditioned mice cerebellar PCs with cell-attached recordings. It means that intrinsic properties of cerebellar PCs are affected by fear conditioning and play a role in fear memory processing.

Key Words: Cerebellum, Fear conditioning, Plasticity, Excitability

P3-44

Phenylalanine facilitates long-term depression in the hippocampus

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Phenylketonuria (PKU) is an inborn error of metabolism that caused by mutations in the gene encoding phenylalanine hydroxylase. Defective

phenylalanine hydroxylase activity leads to accumulation (up to 1 mM) of phenylalanine in the blood and cerebrospinal fluid, which leads to brain dysfunction such as intellectual disability. Previous studies have shown that L-phenylalnine (L-phe) attenuates NMDAR-mediated current in cultured hippocampal neurons. However, precise role for L-phe in the hippocampal synaptic function is unclear. Here we show that L-phe facilitates long-term depression (LTD) in the hippocampus. Bath application L-phe (1 mM) had no effect on NMDAR-mediated synaptic transmission onto CA1 neurons. However, in the presence of L-phe, paired-pulse low-frequency stimulation (PP-LFS) elicited significantly facilitated synaptic depression at the SC-CA1 synapse. This abnormally enhanced PP-LFS-induced LTD was insensitive to the NMDAR blocker AP-5. Mice deficient in phenylalanine hydroxylase activity (Pah^{enu2}) also exhibited exaggerated PP-LFS-induced LTD in the absence of L-phe in the bathing solution, while long-term potentiation (LTP) was comparable to WT mice. These results suggest that accumulation of phenylalanine in the cerebrospinal fluid rapidly induces permanent changes in neurons, and exaggerated LTD may contribute to intellectual disability in phenylketonuria.

Key Words: Hippocampus, Phenylalanine, Long-term depression, LTD, NMDAR

P3-45

Distinctive firing properties of pyramidal neurons in infralimbic and prelimbic areas of medial prefrontal cortex

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The prefrontal cortex (PFC) is a critical compartment of motivational network, working memory and mediating executive function and this region receives dopaminergic input from ventral tegmental area (VTA) and projects glutamatergic output to the nucleus accumbens (NAc). The PFC is divided to two area—Prelimbic (PL) which has afferent to NAc core and Infralimbic (IL) which has afferents to NAc shell. Despite PFC has distinct 2 region, most studies have focused on PFC's neuronal properties without classification. Using electrophysiological recording, we investigated that layer 5 pyramidal neuron (PN) in PL and IL of medial PFC have different neuronal intrinsic property. When square current is injected to PN for making action potential (AP) firing, we found that PL-PN is more sensitive to persistent sodium channel blocker, riluzole, than IL-PN and we also discovered that DHPG, group1 metabotropic receptor agonist, enhances PL-PN's AP firing while IL-PN is not affected. In addition to these results, we found that DHPG amplifies persistent firing of PL-PN while there is any change in IL-PN when we evoked burst firing. These results mean that identical input leads to distinct neuronal activities in medial PFC PN, and these differences in neuronal property can make distinct role between PL and IL.

Key Words: Medial prefrontal cortex, Prelmibic, Infralimbic, Persistent sodium current, Metabotropic glutamate receptor

P4-01 (PO-B-04)

WNK1-mediated Ca^{2+} signaling is a novel culprit for hepatic stellate cell activation and fibrosis

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Hepatic stellate cells (HSCs) activation is a primary event of hepatic fibrosis. WNK1 is downstream target kinase of multiple hormones and growth factors, which are mediators of HSCs activation and hepatic fibrosis. WNK1 is known to regulator of renal ion transport whose perturbation by WNK1 mutation has been implicated in hypertension and hyperkalemia. However, if and/or how WNK1 signaling contributes to hepatic fibrosis has not been elucidated. Hereby, we report that WNK1 aggravates Ca^{2+} influx in HSCs leading to hepatic fibrosis. WNK1 and Ca^{2+}-permeable channel TRPC6 are highly expressed in the *in vivo* liver fibrosis animal models (bile duct ligation and thioacetamide administration) and *in vitro* primary HSCs activation model. Functionally, fibrotic changes and WNK1-stimulated Ca^{2+} entry are ameliorated by suppressing WNK1 and its downstream targets in *in vitro* cultured HSCs. Together, WNK1-mediated Ca^{2+} influx involves in HSCs activation leading to hepatic fibrosis, indicating *de novo* role of WNK1 in the liver. These results offer new perspective on the pathogenesis of hepatic fibrosis and may provide clues for treatment of liver cirrhosis.

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Key Words: WNK1, Ca^{2+} signaling, Hepatic fibrosis, Hepatic stellate cells

P4-02 (PO-A-07)

The E3 ligase c-Cbl inhibits cancer cell migration by neddylating the proto-oncogene c-Src

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Neddylation is a cellular process that covalently conjugates substrate proteins with the small ubiquitin-like molecule NEDD8. As neddylation is required for fast turnover of proteins in proliferating cancer cells, the neddylation process is currently regarded as a potential target for cancer therapy. However, little is known about the role of neddylation in cancer invasion and metastasis. Unexpectedly, we here found that the neddylation blockade stimulates migration of lung cancer and glioblastoma cells. Mechanistically, c-Cbl acts as the E3 ligase for neddylation of the proto-oncogene c-Src. After neddylation, c-Src is poly-ubiquitinated and degraded through the proteasome, which inhibits the PI3K-AKT pathway responsible for cell migration. In human lung cancer tissues, the down-regulation of c-Cbl was associated with phosphorylation of c-Src/AKT, cancer metastasis, and poor survival in patients. Therefore, c-Cbl is likely to play a tumor suppressive role by antagonizing a robust oncogenic signaling driven by c-Src. This study provides new insight about the role of neddylation in cancer metastasis. It is also implied that the metastasis risk should be carefully evaluated before the clinical application of neddylation inhibitors as anticancer regimens.

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Key Words: Neddylation, c-Src, c-Cbl, Cell migration, Metastasis

P4-03

TRPC6 regulate NFATc1 and TLR signaling in osteoclastogenesis

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Bone remodeling and maintenance require a fine balance between bone formation of osteoblasts and resorption of osteoclasts. RANKL induces Ca^{2+} oscillations and activates NFATc1 during osteoclast differentiation. Although intracellular Ca^{2+} play a key role for osteoclast differentiation and inflammatory response, the molecular mechanism of Ca^{2+} signaling via mechanosensitive calcium channels located on the plasma membrane is poorly understood. In this study, we investigated the role of TRPC6 in Ca^{2+} signaling during the osteoclast differentiation and inflammatory responses

by LPS using *TRPC6* knockout (KO) mice. Deletion of *TRPC6* markedly decreased the bone density of the femur, resulting in bone erosion. *TRPC6* KO bone marrow-derived monocytes/macrophages (BMMs) facilitated greatly osteoclast differentiation through increased NFATc1 expression after RANKL treatment. RANKL treatment of *TRPC6* KO BMMs significantly increased induction of multinucleated cells formation. Finally, LPS treatment of *TRPC6* KO BMMs affected the expression of TLR receptors and NF-kB signaling. These findings suggest that TRPC6 modulate the NFATc1 pathway and RANKL-induced osteoclast differentiation during bone metabolism in a normal healthy and the inflammatory response.

Acknowledgement: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2015R1A2A1A15054157) and (MOE) (2015R1D1A1A01057277).

Key Words: TRPC channel, Calcium signaling, Osteoclast differentiation

P4-04

Activation of transient receptor potential melastatin 7 (TRPM7) channel increases basal autophagy and reduces amyloid β-peptide

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Cerebral accumulation of amyloid β-peptide (Aβ), which is produced from amyloid precursor protein (APP), is the primary cause of Alzheimer's disease (AD). Autophagy digests intracellular components, and recycles cellular components including Aβ. The Ca^{2+}- and Mg^{2+}-permeable transient receptor potential melastatin 7 (TRPM7) channel underlies the constitutive Ca^{2+} influx in some cells. Since we already reported that TRPM7 channel-mediated Ca^{2+} entry regulates basal autophagy, we hypothesize that the activation of TRPM7 channel could increase basal autophagy and consequently decrease Aβ. In this study, we showed that naltriben (NTB), a novel TRPM7 channel activator, induced Ca^{2+} influx and increased autophagic signaling. NTB also promoted co-localization of LC-3 and APP, and reduced Aβ. Furthermore, we found that an early-onset familial AD-associated presenilin1 ΔE9 (PS1 ΔE9) mutant cells had attenuated basal autophagy. NTB was able to restore autophagy and decrease Aβ from PS1 ΔE9 cells. Our results show that the up-regulation of TRPM7 channel may prevent AD-related Aβ neuropathology via modulating basal autophagy.

Key Words: TRPM7, Autophagy, Amyloid β-peptide, Alzheimer's disease

P4-05

Gas6 inhibit epithelial-mesenchymal transition in lung alveolar epithelial cells

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We investigated a role of growth arrest-specific protein 6 (Gas6) and its underlying mechanisms in prevention of epithelial-to- mesenchymal transition (EMT) process in alveolar type II epithelial cells. Pretreatment with Gas6 20 h before TGF-β1 stimulation inhibited EMT process in LA-4 cells, based on morphologic cellular alteration, changes in EMT marker expression profiles, including loss of E-cadherin, synthesis of N-cadherin and α-smooth muscle actin, and induction of EMT-activating transcription factor, such as Snail1/2, Zeb1/2, and Twist1. Exposure of LA-4 cells to cyclooxygenase (COX-2) inhibitors or RhoA/Rho kinase inhibitors before Gas6 treatment and to antagonists of prostaglandin E_2 (PGE_2) receptors (EP2, EP4), PGD_2 receptors (DP1 and DP2), or the hepatocyte growth factor (HGF) receptor c-Met 1h before TGF-β1 stimulation, reversed EMT inhibition by Gas6 treatment. Additionally, we found that Gas6-induced COX-2-dependent PGE_2 and PGD_2 production and RhoA/Rho kinase-dependent HGF production, and consequently blocked anti-EMT effect of Gas6 in LA-4 cells. Our data suggest Gas6 plays a potential role in resistance to induction of EMT via the production of potent autocrine EMT inhibitors.

Key Words: Gas6, EMT

P4-06

Simvastatin treatment boosts benefits of apoptotic cell infusion in murine lung fibrosis

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A single early-phase infusion of apoptotic cells can inhibit bleomycin-induced lung inflammation and fibrosis; however, it is unknown whether these effects can be enhanced with additional infusions and/or statin treatment. Here, we investigated whether an increased frequency of apoptotic cell injection, with or without efferocytosis enhancer simvastatin, facilitates therapeutic efficacy. An additional injection of apoptotic cells during the intermediate phase or simvastatin administration alone on days 7-13 post-treatment did not promote anti-fibrotic responses beyond those induced by a single early apoptotic cell infusion alone. Additional administration of apoptotic cells with simvastatin further enhanced the efferocytic ability of alveolar macrophages and PPARγ activity, and induced hepatocyte growth factor and interleukin-10 expression, in alveolar macrophages and lung tissue. Additional administration of apoptotic cells with simvastatin also reduced mRNA expression of bleomycin-induced epithelial-mesenchymal transition (EMT) markers in isolated alveolar type II epithelial cells, fibrotic markers in fibroblasts, and hydroxyproline in lung tissue. Enhanced anti-EMT and anti-fibrotic efficacy was confirmed by immunofluores-cence and trichrome staining of lung tissue. This suggests that additional administration of apoptotic cells with simvastatin during the intermediate phase of bleomycin-induced lung fibrosis may boost the anti-fibrotic properties of early apoptotic cell infusion.

Key Words: Simvastatin, Lung fibrosis

P4-07

Exposure of macrophages to apoptotic cells inhibits lung fibroblast invasion

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Apoptotic cell clearance is important in maintaining tissue homeostasis. The invasion of activated fibroblasts is a key mechanism of tissue fibrosis pathology. Here, we investigated the effects of conditioned medium from macrophages exposed to apoptotic cells on invasiveness of lung fibroblasts. TGF-β1 or EGF-induced Matrigel invasive capacity of MLg fibroblasts was blocked by conditioned medium derived from apoptotic Jurkat T lymphocyte cell-stimulated RAW 264.7 cells (ApoJ CM) only, but not non- (CM) or necrotic cell-stimulated (NecJ CM). The ApoJ CM from RAW cells with the specific siRNA, such as COX-2 or RhoA, suppressed MLg cell invasion. Consistent with these results, MLg cells with pharmacological inhibitors of prostaglandin E_2 (PGE_2) receptor (EP4 [AH-23848]), PGD_2 receptors (DP1 [BW-A868C] and DP2 [BAY-u3405]), or the hepatocyte growth factor (HGF) receptor c-Met (PHA-665752), reversed reduction of TGF-β1-induced fibroblast invasion by ApoJ CM. In addition, the invasive capacity and mRNA expression of invasive fibroblast phenotype markers, such as hyaluronan, CD44, and matrix metalloproteinases (MMPs), in lung fibroblasts isolated from bleomycin (BLM)-treated murine lungs were suppressed by apoptotic cell administration. A targeted qPCR array showed that genes involved in cell adhesion and ECM remodeling are also significantly down-regulated

in primary lung fibroblasts from the BLM+ApoJ group, compared to those in the BLM+ViaJ group. Taken together, these findings suggest that macrophages exposed to apoptotic cells can prevent lung myofibroblast invasion.

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Key Words: Apoptotic cells, Macrophages, Lung fibroblasts, Invasion, Lung fibrosis

P4-08

Downregulation of mitochondrial PDP1 is required for the early stage differentiation of embryonic stem cell to cardiac myocytes

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Mitochondria are crucial for maintaining the properties of embryonic stem cells (ESCs) and for regulating their subsequent differentiation into diverse cell lineages, including cardiomyocytes. However, mitochondrial regulators that manage the rate of differentiation or cell fate have been rarely identified. This study aimed to determine the potential mitochondrial factor that controls the differentiation of ESCs into cardiac myocytes. We induced cardiomyocyte differentiation from mouse ESCs (mESCs) and performed microarray assays to assess mRNA expression changes at differentiation day 8 (D8) compared with undifferentiated mESCs (D0). Among the differentially expressed genes, Pdp1 expression was significantly decreased (27-fold) on D8 compared to D0, which was accompanied by suppressed mitochondrial indices, including adenosine triphosphate (ATP) levels, membrane potential, ROS, and mitochondrial Ca^{2+}. Notably, Pdp1 overexpression significantly enhanced the mitochondrial indices and pyruvate dehydrogenase activity and reduced the expression of cardiac differentiation marker mRNA and the cardiac differentiation rate compared to a mock control. In confirmation of this, a knockdown of the Pdp1 gene promoted the expression of cardiac differentiation marker mRNA and the cardiac differentiation rate. In conclusion, our results suggest that mitochondrial PDP1 is a potential regulator that controls cardiac differentiation at an early differentiation stage in ESCs.

Key Words: Stem cells, Cardiomyocytes, Differentiation, Energy metabolism, PDP1

P4-09

Cardiac mitochondrial metabolism and function

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Mitochondria are complex organelles essential for the production of energy. These dynamic, complex organelles found in every cell and tissues of the body have been well-studied in various physiological models, stressing that mitochondrial dysfunction is characteristic of pathological states, especially in cardiovascular diseases and heart failure. Cardiomyocytes that differentiate from pluripotent stem cells (PSCs) provide a crucial cellular resource for cardiac regeneration. The mitochondrial metabolic and redox regulation is essential for cardiomyocyte differentiation and pathophysiology. The inhibition of the mitochondrial permeability transition pore (mPTP) by Cyclosporin A (CsA) promoted cardiomyocyte differentiation from PSCs. We induced cardiomyocyte differentiation from mouse and human PSCs and examined the effect of CsA on the differentiation process. The cardiomyogenic effect of CsA mainly resulted from mPTP inhibition. CsA treated cells showed an increase in mitochondrial calcium, mitochondrial membrane potential, oxygen consumption rate, ATP level, and expression of genes related to mitochondrial function. Furthermore, inhibition of mitochondrial oxidative metabolism reduced the cardiomyogenic effect of CsA while antioxidant treatment augmented the cardiomyogenic effect of CsA. Our data show that mPTP inhibition by CsA alters mitochondrial oxidative metabolism and redox signaling, which leads to differentiation of functional cardiomyocytes from PSCs.

Key Words: Mitochondria, Cardiac differentiation, Cyclosporin A, Mitochondrial permeability transition pore

P4-10

Low-intensity ultrasound decreases high glucose- and sodium nitroprusside-induced nitric oxide generation in the human retinal pigment epithelial cells

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Nitric oxide (NO) is a small hydrophobic molecule with chemical properties that make it uniquely suited as both intra- and extracellular messenger. While NO is well-known to play important roles in a wide range of physiological processes including neurotransmission and vasodilation; excessive production of NO has been implicated in a number of inflammation-related pathological conditions such as diabetic retinopathy and others. High glucose (HG) and sodium nitroprusside (SNP) are two well-known NO generators in cells leading to various inflammatory diseases. We have been studying low-intensity ultrasound (LIUS), a type of mechanical stimulation, as a potential therapeutic alternative in a number of *in vitro* and *in vivo* disease models. Particularly, we have shown earlier that LIUS stimulation reduces generation of reactive oxygen species (ROS) in cellular models of Parkinson's disease and glaucoma *in vitro*. In this study, we demonstrate that LIUS stimulation reduces the HG- or SNP-induced NO generation in human retinal pigmented epithelial (ARPE-19) cells in an intensity-dependent manner. It should be importantly noticed here that the mode of NO production in ARPE-19 cells induced by HG and SNP treatment are different. While the HG-evoked NO generation is mediated via oxidative stress caused by an excessive ROS production; the SNP-induced NO generation involves an electron transfer mechanism mediated by sulfhydryl-containing compounds like glutathione and cysteine. Notwithstanding the distinct mechanisms and kinetics of NO production by HG and SNP in ARPE-19 cells, LIUS stimulation acted well against NO generated by both HG and SNP treatments. Furthermore, the effects of LIUS-induced inhibition of NO generation is also seen on the subsequent decrease in the expression of few key inflammatory proteins downstream, namely, cyclooxygenase-2 (COX2) and vascular endothelial growth factor (VEGF). Here, we suggest that LIUS stimulation decreases the NO production irrespective of the initial NO generation process, namely, be it by an ROS-mediated process or by a direct electron transfer process. Nonetheless, the precise mechanism of the LIUS action on reducing the HG- or SNP-induced NO generation is yet to be well-understood. With these data, we think that LIUS stimulation can be studied further for its latent healing capacity for the treatment of the NO-induced inflammatory pathways.

Key Words: Low-intensity ultrasound (LIUS), Nitric oxide (NO), High glucose (HG), Sodium nitroprusside (SNP), Vascular endothelial growth factor (VEGF), Cyclooxygenase-2 (COX2)

P4-11

Novel function of Jumonji C (JmjC) domain-containing protein in osteoclastogenesis

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The regulation of osteoclastogenesis is critical to maintain physiological bone homeostasis and prevent bone-destructive diseases. The nuclear factor of activated T-cells calcineurin-dependent 1 (NFATc1) plays an essential role in osteoclastogenesis, and its expression is induced during early osteoclastogenesis. On the other hand, the Jumonji C (JmjC) domain-containing protein (JHDM), a histone demethylase, catalyzes histone 3 lysine 9 and is involved in osteoblastic bone formation. However, the mechanism for regulation of the enzymatic activity of JHDM in osteoclastogenesis is not yet well known. Here, we show that JHDM is a key negative regulator during receptor activator of nuclear factor-kB ligand (RANKL)-induced osteoclastogenesis. The expression level of JHDM gradually decreased during osteoclastogenesis in bone marrow macrophages (BMMs) treated with RANKL. Down-regulated expression of JHDM strongly facilitated osteoclast formation together with induction of several osteoclast-specific genes such as TRAP, Oscar and CathepsinK. NFATc1 proteins are ubiquitinated and rapidly degraded during late stage osteoclastogenesis. Interestingly, overexpression of JHDM induces NFATc1 degradation during late stage osteoclastogenesis. Taken together, the present study demonstrated that JHDM is a post-translational co-repressor for NFATc1 that attenuates osteoclastogenesis.

Key Words: Jumonji C (JmjC) domain-containing protein (JHDM), NFATc1, Osteoclastogenesis, Ubiquitination

P4-12

Leptin suppresses glutamate-induced apoptosis through regulation of ERK1/2 signaling pathways in rat primary astrocytes

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Background: Leptin is a hormone expressed by adipose tissue that regulates body energy homeostasis and weight loss by activating leptin receptors in the hypothalamus. Leptin receptors are also expressed in astrocytes. An anti-apoptosis effect of leptin in brain has recently been reported. However, the anti-apoptosis mechanism of leptin in the brain is unknown.
Methods: To investigate whether leptin exerts protective effects against glutamate-induced apoptosis in astrocytes, we performed cell viability assays and apoptosis assays using rat primary astrocytes. Intracellular signaling pathways involved in anti-apoptosis effects of leptin were analyzed by immunoblotting together with a leptin mutant (S120A/T121A) with antagonist function and pharmacological inhibitors.
Results: We found that glutamate-induced apoptosis in rat primary astrocytes was significantly decreased by treatment with leptin. Leptin inhibited glutamate-induced phosphorylation of ERK1/2 in astrocytes. The leptin S120A/T121A mutant did not inhibit glutamate-induced ERK1/2 phosphorylation and ERK1/2-mediated apoptosis.
Conclusions: Collectively, our results provide initial evidence that leptin exerts an anti-apoptotic effect against glutamate toxicity through activation of intracellular signaling pathways which reverse glutamate-induced ERK1/2 phosphorylation in primary astrocytes. Therefore, our findings suggest that leptin might be considered a candidate for potential therapeutic applications in glutamate-induced brain excitotoxicity.

Key Words: Leptin, Glutamate, ERK1/2, Astrocytes

P4-13

Minor ginsenosides inhibits growth, migration and invasion of neuroblastoma cells via caspase activation and suppressing epithelial mesenchymal transition

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Ginseng has already been proved to exert potential benefits on antitumor activity via its antioxidant properties from other cancer cell lines. In this study, we investigated the potential pharmacological activity of several minor ginsenosides in neuroblastoma cell lines. Among all tested ginsenoside compounds, four minor ginsenosides had strong cytotoxicity and became more effective agents to display the protective effects. As a result, these compounds were significantly increased the apoptosis rate in dose dependent manner which was accompanied by mitochondrial membrane potential (MMP, $\Delta\Psi m$) loss. We found that the expression levels of cleaved caspase 3, cleaved PARP, PUMA, Noxa, and E-cadherin were upregulated, whereas the expression levels of survivin, Bcl-2, Bcl-xL, MMP-2, MMP-9, vimentin and snail protein were down-regulated by treatment of minor ginsenosides. These results suggest that four minor ginsenosides might be promising compounds to have therapeutic effect on neuroblastoma cell lines.

Key Words: Neuroblastoma, Ginsenosides, Apoptosis, Cell proliferation, MMP ($\Delta\Psi m$)

P4-14

CRIF-1 deficiency increases senescence through SIRT3 pathway in endothelial cells

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CR6-interacting factor 1 (CRIF-1) is a protein that exists in mitochondria and interacts with large ribosomal subunits, the deficiency of CRIF-1 induces mitochondrial dysfunction and mitochondrial reactive oxygen species (mtROS). Oxidative stress, which can be defined as disturbance between mtROS and anti-oxidant molecules, is one of the most critical factors contributing to endothelial dysfunction. Consequence of mitochondrial dysfunction is cellular apoptosis and senescence. SIRT3, a mitochondrial deacetylase, plays a major role in mitochondrial biogenesis and is related with oxidative stress. Furthermore, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), which is a downstream protein of SIRT3, plays a major role in apoptosis, inflammation, and proliferation in endothelial cells. Our data confirmed that CRIF-1 downregulation destroyed anti-oxidant system in mitochondria by decreasing SIRT3 expression. SIRT3 downstream gene, SOD2 mRNA and protein were level dramatically decreased in CRIF-1 deleted endothelial cells. SOD2 is an important antioxidant against oxidative stress. Thus, CRIF-1-mediated SOD2 reduction may accumulate mtROS production in mitochondria. CRIF-1 deficiency induced apoptosis and senescence progression in HUVECs by alterating their morphology, β-galactosidase activity, expression of molecular senescence marker (P-p53 (S15), p21) and apoptosis marker (bcl-2, bax, caspase-3). In addition, we proved that SIRT3 overexpression could attenuate CRIF-1 deficiency induced senescence in endothelial cells. We also demonstrated the same results in CRIF-1 knockout mice. Our data identify a distinct senescence response and provide a mechanism by which mitochondrial dysfunction can drive ageing. The final purpose of study is to delay the de-

velopment of senescence already in vascular damage.

Key Words: CRIF-1, mtROS, SIRT3, Senescence

P4-15

Minor Rh3 induces apoptotic cell death in SK-N-BE (2) human neuroblastoma cells through a caspase-dependent pathway

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Minor Rh3, which contain an aglycone with dammarane sapogenins isolated from Korean Red Ginseng (KRG), has been shown to exhibit anticancer properties in various cancer cell lines. However, the anticancer activity of Rh3 on human neuroblastoma cells (NB) has not been understood. In this study, we investigated the effects of Rh3 on cell viability and apoptosis in SK-N-BE (2) human NB. Rh3 dose-dependently inhibited growth of SK-N-BE (2) cells. The typical hallmarks of apoptosis, such as chromatin condensation, a sub-G1 peak and phosphatidylserine externalization were detected by Hoechst 33342 staining, flow cytometry and Annexin V staining following treatment with Rh3. Western blot analysis revealed that Rh3 induced increase in the levels of cleaved caspase 3 and the cleavage of poly (ADP-ribose) polymerase (PARP). The apoptotic cell death induced by Rh3 was completely abrogated by the pan-caspase inhibitor, z-VAD-FMK. Furthermore, Rh3 upregulated the levels of pro-apoptotic proteins, such as Bax, and Bak while downregulated the levels of anti-apoptotic proteins, such as Bcl-2, Bcl-xL and survivin, which was accompanied by mitochondrial membrane potential (MMP, $\Delta\Psi m$) loss in SK-N-BE (2) cells. Also, this compounds inhibit of NB cell migration and invasion. Collectly, our data provide insight into the molecular mechanisms of Rh3-induced apoptosis in NB cells, rendering this compound a potential anticancer agent for the treatment of NB.

Key Words: Neuroblastoma, Minor Rh3, Apoptosis, Cell proliferation, MMP ($\Delta\Psi m$)

P4-16

Glucocorticoid receptor positively regulates transcription of FNDC5 in the liver

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Irisin is secreted by skeletal muscle during exercise and influences energy and metabolic homeostasis. This hormone is a cleaved and secreted fragment of fibronectin type III domain-containing 5 (FNDC5). Elucidation of the *FNDC5* gene regulation mechanism is necessary to clarify the function of irisin as a potential therapeutic target in human metabolic diseases. Thus, we investigated the genetic and epigenetic mechanisms that regulate expression of the *FNDC5* gene. *FNDC5* mRNA was strong expressed in major energy-dependent human tissues, including heart, brain, liver, and skeletal muscle. Promoter analysis of the *FNDC5* gene revealed that the core promoter region of the *FNDC5* gene contained one CpG island that was located just upstream of the transcriptional start site for variants 2 and 3. Treatment with the histone deacetylase inhibitor sodium butyrate and the demethylating agent 5-azacytidine increased mRNA expression of *FNDC5* in Huh7 cells. Prediction of transcription factor binding sites suggested that the glucocorticoid receptor was involved in the regulation of *FNDC5* expression, and indeed, cortisol treatment increased mRNA expression of *FNDC5* in Huh7 cells. Collectively, these findings offer insight into the genetic and epigenetic regulation of *FNDC5*, providing the initial steps required for understanding the role of irisin in the metabolic homeostasis.

Key Words: *FNDC5*, Epigenetics, Methylation, Genetics, Irisin

P4-17

Mitochondrial molecular targets of nobiletin in the neuroprotective mechanism in primary cortical neurons and isolated brain mitochondria

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Mitochondrial calcium overload is a crucial event in determining the fate of neuronal cell survival and death. Therefore, the regulation of mitochondrial calcium overload is considered to be an important strategy to prevent neuronal cell death. We investigated here the mechanism of nobiletin prevent neurotoxic mitochondrial calcium overload and neuronal cell death during glutamate toxicity through mitochondrial membrane potential. Primary cortical neurons were obtained from the cerebral cortices of postnatal 1 day Sprague-Dawley rats. Real-time optic measurements were performed using fluorescent indicators such as TMRE for $\Delta\Psi$m, Fura-2 AM for cytosolic calcium, Rhod-2 AM for mitochondrial calcium and mitoSox/DCF-DA for mitochondrial reactive oxygen species (ROS) in primary cortical neurons and the isolated mitochondria. The results demonstrated that neuronal viability was significantly increased by nobiletin (100 μM) treatment in glutamate (100 μM, 20 min)-exposed primary cortical neurons. Nobiletin is able to evoke mild mitochondrial depolarization in both primary cortical neurons and isolated mitochondria, which is able to suppress neurotoxic mitochondrial calcium overload. Nobiletin-induced mild mitochondrial membrane depolarization was significantly abolished in K^+-free condition using CsCl in the isolated mitochondria. Furthermore, The alteration of $\Delta\Psi$m by nobiletin was significantly abolished by iberiotoxin (10 nM), a selective blocker of large-conductance Ca^{2+}-activated K+ channels (BKCa) in primary cortical neurons. Recently, the regulation of complex I in electron transport system (ETC) by nobiletin is being studied in the neuroprotective mechanism. We propose that nobiletin may be a promising neuroprotective agent to prevent neuronal cell death through the regulation of mitochondrial K channels and ETC complex I.

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Key Words: Mitochondria, Nobiletin, Mitochondrial calcium, Mitochondrial membrane potential, Complex I, Neuronal cell death

P4-18

Functional roles of P2X7 receptor and NALP3 inflammasome in head and neck cancer

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In this study, we investigated P2X7 receptor and NLRP3 inflammasome expressions, and their role in head and neck cancer. We found that P2X7R and all NLRP3 inflammasome components were significantly upregulated in oral squamous cell carcinoma tissues biopsied from patients. Similarly, the expression of P2X7R, ASC, and pro-form caspase 1 in A253, one of the epidermoid carcinoma cell lines, were highly upregulated in comparison to Human Salivary Gland cell lines, considered to be not cancerous. Active caspase-1 and its final product, active interleukin-1β, were both increased in primed A253 cells stimulated with P2X7R agonists, while this elevated NLRP3 inflammasome activity was suppressed by P2X7R antagonists. However, we observed none of these effects in normal cells. Inhibition of both NLRP3 inflammasome and P2X7R led to the significant cell death of primed A253 cells, but had no effect on the viability of primed normal cells. Furthermore, inhibition of either P2X7R or NLRP3 inflammasome decreased invasiveness of A253, and this effect became more significant when both P2X7R and NLRP3 inflammasome were simultaneously blocked. Therefore, it is concluded that the increased P2X7R and the activation of NLRP3 inflammasome in head and neck cancer play important roles in the survival and

invasion.

Key Words: Purinergic receptor P2X 7, NLRP3 inflammasome, Oral squamous cell carcinoma, A253 cells

P4-19

Role of NEDDylation pathway in non alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is increasingly diagnosed worldwide and is the most common cause of abnormal liver function tests and chronic liver disease in both developed and developing countries. NAFLD includes all liver-related diseases such as fatty liver in which hepatocyte accumulates more than 5% of triglycerides, fatty liver hepatitis in which inflammation occurs, and liver cirrhosis caused by the scars in the absence of excessive alcohol consumption. NAFLD is also associated with an increased risk for developing cardiovascular disease, insulin resistance (IR), type 2 diabetes (T2D), obesity, chronic kidney disease, post-operative complications after major liver surgery and colorectal cancer. NAFLD is processed through multistep gene regulations that are mainly driven by sterol regulatory element binding proteins.(SREBPs) SREBPs are transcription factors that activate the synthesis of fatty acids (FAs), triglycerides (TGs), and cholesterol in liver. The ubiquitin-like peptide, Neuronal precursor cell expressed, developmentally downregulated 8 (NEDD8) is a protein that in humans is encoded by the *NEDD8* gene. This ubiquitin-like protein (ULP) becomes covalently conjugated to a limited number of cellular proteins in a manner analogous to ubiquitination. Ubiquitination mainly degrades proteins while Neddylation mainly increases protein stabilization or increases activity. Interestingly, in *ob/ob* mice, a DNA microarray study has demonstrated that NEDD8 was upregulated in white adipose tissues whereas ubiquitin was downregulated. Also, inhibition of neddylation in hepatic stellate cells decreased hepatocyte cell death and inflammation. Recently, we have reported that the Neddylatin of PPARγ is important in adipogenesis. So, we checked the possibility that the neddylation of lipogenesis transcription factors is essential for NAFLD.

References

1. Angulo P. GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2007;25:883-9.
2. Law K, Brunt EM. Nonalcoholic fatty liver disease. Clin Liver Dis 2010;14: 591-604.
3. Oh MK, Winn J, Poordad F. Review article: diagnosis and treatment of nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2008;28:503-22.
4. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387-1395.
5. Horton, J.D., Goldstein, J.L., and Brown, M.S. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J. Clin. Invest. 2002;109:1125-1131.
6. Osaka F, Kawasaki H, Aida N, Saeki M, Chiba T, Kawashima S et al. A new NEDD8-ligating system for cullin-4A. Genes Dev 1998;12: 2263-2268.

Key Words: Neddylation, Obesity, NAFLD, Transcription factor, SREBP1c

P4-20

Valproic acid promotes caspase-dependent apoptosis and autophagy in human lung cancer cells

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Valproic acid (VPA), a histone deacetylase (HDAC) inhibitor, has an anti-cancer effect on various cancer cells. However, little is known about the apoptosis and autophagy effects of VPA in lung cancer cells. In the present study, the effects of VPA on apoptosis and autophagy were evaluated in lung cancer cell lines (A549, Calu-6, SK-LU-1, NCI-H460 and NCI-H1299) and human pulmonary fibroblast (HPF) normal lung cells. VPA inhibited the growth of A549, Calu-6 and NCI-H460 cells. However, SK-LU-1, NCI-H1299 and HPF normal cells were resistant to VPA. This drug also triggered a G2/M phase of cell cycle arrest in A549 and Calu-6 cells whereas it led to a G1 phase arrest in NCI-H1299 cells. VPA induced apoptosis, which was accompanied by the loss of mitochondrial membrane potential (MMP; ΔΨm), PARP-1 cleavage and caspase-3 activation in A549, Calu-6 and NCI-H460 cells. Z-VAD, a pan-caspase inhibitor, prevented the death of those cells caused by VPA. Furthermore, this agent induced autophagy, as evidenced by LC3B increase and p62 decrease in A549, Calu-6 and NCI-H460 cells. Interestingly, the basal levels of LC3B increased in VPA-untreated SK-LU-1 and HPF cells. In conclusion, VPA induced caspase-dependent apoptosis and autophagy in lung cancer cells.

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Key Words: Histone deacetylase inhibitor, Lung cancer, Apoptosis, Autophagy

P4-21

Crif1 deficiency inhibits keloid fibroblasts migration, proliferation and extracellular matrix synthesis

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A keloid is an abnormal proliferation tissue in excessive response to wound that damages normal skin tissue. This disorder appears in the wound healing process. Keloid fibroblasts (KF) are the main cells that induce keloid disease. The migration of KF may play an important role in infiltrating abnormal tissue and forming keloid scar, but the mechanism has not been elucidated. In this study, we investigated whether CR6-interacting factor 1(CRIF1) deficiency-induced mitochondrial dysfunction reduced cell migration in human primary KF. Our results show that cell migration in crif1 knockdown group was significantly reduced in KF as measured by using scratch assay, compared with control siRNA group. Also, cell proliferation and extracellular matrix synthesis was decreased. TGF/SMAD pathway proteins is key proteins in extracellular matrix synthesis. Western blot data showed that CRIF1 deficiency activated SMAD proteins (SMAD2, 3) and activated AMPK protein. Although SMAD pathway proteins were activated, extracellular matrix synthesis was decreased, because AMPK block the extracellular matrix synthesis in SMAD pathway. Our results proved that crif1 knockdown-induced mitochondrial dysfunction decreased cell migration, cell proliferation, extracellular matrix synthesis by activating AMPK, which further suggest that Crif1 may be used as a therapeutic target protein in the treatment of keloid disease.

Key Words: Keloid, Keloid fibroblast, Crif1, AMPK

P4-22

CR6 interacting factor-1 linked with tetrahydrobiopterin deficiency and endothelial nitric oxide synthase uncoupling

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CR6 interacting factor 1 (CRIF-1) is essential for the translation and integration of mitochondrial oxidative phosphorylation complex, CRIF-1 deficiency induces mitochondrial dysfunction and mitochondrial reactive oxygen species. Endothelial nitric oxide synthase (eNOS) is a primary protein responsible for nitric oxide (NO) generation in the vascular endothelium, which plays a major role in regulating cardiovascular tone and inflammation. eNOS needs tetrahydrobiopterin (BH_4) for eNOS dimerization and it must exist in dimer containing two identical monomers to generate NO. In the absence of BH_4, eNOS shifts from dimer to uncoupled form which promotes producing ROS instead of synthesizing NO. Our previous studies showed that vascular tone and NO synthesis were decreased in CRIF-1 deficiency. In this study, we investigated whether CRIF-1 deletion had an effect on eNOS uncoupling. We examined that the concentration of BH_4 in CRIF-1 deleted cells was significantly diminished compare with control cells by using high pressure liquid chromatography (HPLC). BH_4 biosynthesis is consist of de novo pathway and recycling pathway. De novo pathway has four enzymes including GTP cyclohydrolase I (GCH-1), sepiapterin reductase (SPR), pyruvoyl tetrahydropterin synthetase (PTS) and GCH-1 Feedback reguratory protein (GCHFR). These enzymes were significantly decrease in CRIF-1 deficiency endothelial cells. Recycling pathway has two enzymes including dihydrofolate reductase (DHFR) and pterin-4α-carbinolamine dehydrogenase (PCD), which were are also decreased in CRIF-1 deficiency endothelial cells. To confirm our result, we incubate CRIF-1 knockout HUVEC with BH_4. And then uncoupled eNOS was recovered to dimer. Also, we incubate control HUVEC with BH_2, an oxidative form of BH_4, eNOS exists in uncoupled form. In conclusion, CRIF-1 is essential for synthesize BH_4 and eNOS dimerization in endothelial cells

Key Words: CRIF-1, ROS, BH_4, eNOS uncoupling

P4-23

Treatment of valproic acid enhances arsenic trioxide-induced cell death in human large cell lung cancer cells

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Valproic acid (VPA) is known for histone deacetylase inhibitor (HDACi). VPA shows anti-cancer effects on various cancer cells. Arsenic trioxide (ATO; As2O3) is a therapeutic drug clinically being used for relapsed or refractory acute promyelocytic leukemia (APL) patients. Recently, combinations of ATO and other anti-cancer drugs have been explored in various cancer types. However, little is known about the combined cellular effects of ATO and valproic acid (VPA) in lung cancer cells. Herein, we investigated the synergistic cell death effects of ATO and VPA in large cell lung cancer (LCLC) cell lines (NCI-H460 and NCI-H1299). ATO dose-dependently inhibited the growth of NCI-H460 and NCI-H1299 cells with an IC_{50} of 9-10 μM and 3-4 μM at 72 h, respectively. Based on MTT assays, combined treatment of ATO and VPA showed a synergistic effect on cell growth inhibition in NCI-H460 and NCI-H1299 cells at 72 h. VPA increased the percentages of sub-G1 cells and annexin V-FITC positive cells in ATO-treated NCI-H1299 cells, which were accompanied by the loss of mitochondrial membrane potential (MMP; ΔΨm). The increase of intracellular ROS levels was detected when NCI-H460 cells were treated with ATO and VPA. In the nude mouse xenograft model, the combined treatment of ATO and VPA significantly reduced the tumor size of NCI-H460 xenograft mouse. In conclusion, co-treatment with ATO and VPA has a synergistic cell death effect in NCI-H460 and NCI-H1299 cells.

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Key Words: Arsenic trioxide, Valproic acid, Large cell lung cancer, Cell death

P4-24

Regulation of lipocalin-2 expression by nitric oxide under inflammatory condition in RINm5F islet beta-cells

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We previously reported that proinflammatory cytokines (interleukin-1β and interferon-γ) induced the expression of lipocalin-2 (LCN-2) together with inducible nitric oxide synthase (iNOS) in RINm5F beta-cells. Therefore, we examined the effect of nitric oxide (NO) on LCN-2 expression in cytokines-treated RINm5F beta-cells. Additionally, we observed the effect of LCN-2 on cell viability. First, we found the existence of LCN-2 receptor and the internalization of exogenous recombinant LCN-2 peptide in RINm5F and INS-1 beta-cells. Next, the effects of NO on LCN-2 expression were evaluated. Aminoguanidine, an iNOS inhibitor and iNOS gene silencing significantly inhibited cytokines-induced LCN-2 expression while sodium nitroprusside (SNP), an NO donor potentiated it. Luciferase reporter assay showed that transcription factor NF-κB was not involved in LCN-2 expression. Both LCN-2 mRNA and protein stability assays were conducted. SNP did not affect LCN-2 mRNA stability, however, it significantly reduced LCN-2 protein degradation. The LCN-2 protein degradation was significantly attenuated by MG132, a proteasome inhibitor. Finally, the effect of LCN-2 on cell viability was evaluated. LCN-2 peptide treatment and LCN-2 overexpression significantly reduced cell viability. FACS analysis showed that LCN-2 induced the apoptosis of the cells. Collectively, NO level affects LCN-2 expression via regulation of LCN-2 protein stability under inflammatory condition and LCN-2 may reduce beta-cell viability by promoting apoptosis.

Key Words: Lipocalin-2, Nitric oxide, Interleukin-1β, Interferon-γ, RINm5F cells

P4-25

Role of PHF2 in the development of non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is caused by excessive fat accumulation in the hepatocytes. Mild steatosis may develop into aggressive forms of Hepatic fibrosis, cirrhosis and carcinoma. Plant homeodomain finger 2 (PHF2), a JmjC histone demethylase, is known as the demethylase of the Histone H3K9 while it binds to H3K4me3 with the PHD domain. PHF2 is known to have associated with metabolism-related transcription factors. In this study, we identified the role of PHF2 in the progression of hepatic steatosis. For in vivo study, WT and PHF2 overexpressed TG mice were fed normal diet or high fat diet for 8 weeks. And then, Liver steatosis and blood chemistry were analyzed. The expression level of protein and genes involved in liver lipid metabolism were measured. For in-vitro study, PHF2 was stably silenced in HepG2, human liver cell line. Overexpression of PHF2

attenuated lipid accumulation in liver and insulin tolerance in mice fed with high fat diet. The expression of lipogenic genes was decreased in TG mice liver. In in vitro study, increased levels of lipogenic genes were confirmed in PHF2 knock-down stable cell. In addition, we found that PHF2 directly interacts with SREBP1c through protein-protein interaction. These results suggest that PHF2 plays a role as a repressor in the progression of hepatic steatosis through the association with SREBP1.

References

1. Baba A, Ohtake F, Okuno Y, Yokota K, Okada M, Imai Y, Ni M. PKA-dependent regulation of the histone lysine demethylase complex PHF2-ARID5B. Nat Cell Biol 2011;13:668-675.
2. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 2005;115:1343-1351.
3. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-873.
4. Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 2013;28 Suppl 1:11-17.
5. Foretz M, Pacot C, Ugail I, Lemarchand P, Guichard C, Lie`ovre XL, Bertheier-lubrano C. ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose. MCB 1999;19:3760-3768.

Key Words: PHF2, SREBP1c, NAFLD

P4-26

Inhibitory effect of corylifol C on RANKL-induced osteoclast differentiation and bone resorption

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An excessive increase in osteoclast differentiation and bone resorption gives rise to various bone-resorptive diseases. Lately, the study of anti-resorptive agents from natural compounds has become a topic of interest. Corylifol C is a compound isolated from the seeds of *Psoralea corylifolia* that has been used as a traditional medicine in Asia. Corylifol C has previously been shown to have weak antioxidative effects; however, its effect on osteoclast differentiation and bone resorption remains unclear. In this study, we investigated the effects of corylifol C on osteoclast differentiation and bone resorption. Corylifol C dose-dependently inhibited RANKL-induced osteoclast differentiation from 5 uM. It is evaluated on bone marrow-derived monocytes (BMMs) by a tartrate-resistant acid phosphatase (TRAP) staining and TRAP activity assay. Expression of RANKL-induced osteoclastogenesis-related marker genes including acid phosphatase 5 (ACP5), nuclear factor of activated T-cells 1 (NFATc1), cathepsin K (Ctsk), d2 isoform of vacuolar (H+) ATPase V0 domain (Atp6v0d2), chloride channel 7 (CLCN7), dendritic cell-specific transmembrane protein (DC-STAMP) and matrix metalloproteinase-9 (MMP-9) was inhibited by corylifol C treatment. Moreover, corylifol C inhibits RANKL-induced bone resorption demonstrated by a bone resorption assay. In addition, corylifol C decreased the generation of RANKL-mediated reactive oxygen species (ROS) in BMMs. Our results revealed that corylifol C could be a potential therapeutic agent of the treatment of bone-resorptive diseases. Further investigations are required to evaluate the molecular mechanism of action of corylifol C on osteoclast differentiation and bone resorption.

Key Words: Corylifol C, Osteoclast differentiation, Bone resorption, ROS

P4-27

Negative regulation of Wnt/β-catenin signaling pathway by SIRT 6 inhibits the growth and metastasis in hepatocellular carcinoma

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Sirtuin6 (SIRT6) which is implicated in the control of aging and metabolism, has been shown to have anti-cancer function in liver. However, the precise biological role of SIRT6 in human hepatocellular cancers (HCC) has not been fully elucidated. To investigate the biological mechanism of SIRT6 in HCC, we have studied the importance of SIRT6 function in HCC cell lines, HepG2 and SNU449. SIRT6 was highly expressed in human HCC cells. Overexpression of SIRT6 significantly diminished the viability of HCC cells whereas silencing of SIRT6 stimulated the viability of HCC cells. Overexpression of SIRT6 increased expression of cleaved-caspase-9 and cleaved-PARP and decreased the numbers of colonies. In addition, overexpression of SIRT6 significantly inhibited the invasion and metastasis of HCC cells whereas silencing of SIRT6 increased the invasion and metastasis abilities of HCC cells with time dependent manner. Moreover, overexpression of SIRT6 inhibited vimentin, β-catenin, and UPA protein levels while silencing of SIRT6 in HCC cells induced increase the protein levels of UPA, vimentin, and twist. P-β-catenin levels was increased by overexpression of SIRT6 and was decreased by silencing of SIRT6. In conclusion, SIRT6 inhibited the proliferation and invasion of HCC cells and may plays as a tumor suppressor in HCC cells.

Key Words: SIRT6, Hepatocellular carcinoma cells, Metastasis, Cell proliferation, β-catenin

P4-28

Identification of cytokines that induce cisplatin resistance and migration secreted from macrophage

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Macrophages promote the angiogenesis, metastasis, and drug resistance of several cancers, including non-small-cell lung cancer (NSCLC). In this study, we investigate whether migration of cancer cells according to the various types of macrophages. And we analyze the differences of secreted cytokines between macrophage and macrophages cultured with cancer cells. A549 cells were cultured alone, cultured with monocyte conditioned medium (CM), macrophage CM, and co-cultured with macrophage and A549 (co-macrophage) CM for 24 hours. After induction, cisplatin was treated for 24 hours. As a result of the experiment, it was observed that macrophage and co-macrophage induced cisplatin resistance but did not induce monocyte CM. Macrophages also induced a change in morphology of A549 Cells. However, macrophage and monocyte-induced changes in cell shape were different. Macrophages induce the shape of cells to be rounded, while, co-macrophage transformed cells into long shapes like fibroblast. The effect of macrophage CM on cell migration was investigated. Similar to cisplatin resistance, cell migration was increased in macrophage CM and co-macrophage CM. Next, we searched cytokines secreted from macrophages through Cytokine Profiling Antibody Array. Although CCL3L1 is the most abundant cytokine, it has been widely known as an HIV inhibitor, but only a small number of studies have been published that association with cancer cells. CCL3L1 promote cell growth in glioblastoma. CCL3, CCL4, and CCL21 are closely associated with metastasis, and it was demonstrated through various studies. In particular, CCL3 promotes migration and invasion in lung cancer. CCL21 has been shown to induce not only metastasis of cancer cells but also resistance to anticancer drugs. CXCL1 and CXCL3 were increased in co-macrophages compared to macrophage. CXCL1 and CXCL3 promote the growth and metastasis of cancer cells as well as the angiogenesis of cancer cells. Cytokines that promote angiogenesis of cancer cells show a signifi-

cantly increased in co-macrophages compared to macrophage. From these results, we can conclude that macrophages and co-macrophage enhance migration and induce cisplatin resistance. Secretion of CCL3L1, CCL3, CCL4, and CCL21 were increased in macrophage and co-macrophage. And Secretion of CXCL1, CXCL2, and CXCL3 were more increased in co-macrophage than macrophage.

Key Words: Cytokines, Macrophage, A549, Migration

P4-29

Inactivation of YAP by rhBMP-2 suppresses the proliferation of human colorectal cancer cell

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Despite that the use of recombinant human bone morphogenetic protein (rhBMP)-2 in bone surgery for cancer risk has been debated for a decade, the biological functions of rhBMP-2 in human colorectal cancer cells remain poorly understood. Here, we investigated the effect of rhBMP-2 and its signaling pathways involved in colorectal cancer cell (CRC) proliferation using HT-29 and HT-116 cell lines. MTT assay analysis revealed that rhBMP-2 significantly inhibited proliferation of CRC cells in a dose-dependent manner. RhBMP-2 treatment resulted in reduced protein expression levels of poly (ADP-ribose) polymerase (PARP) whereas those of cleaved PARP and cleaved caspase-9 were significantly increased in CRC cells. In addition, rhBMP-2 increased MST1, MST2, Sav1, and p-YAP protein levels. Our results indicate that rhBMP-2 suppresses CRC cell proliferation which is mediated via the hippo signaling pathway. Taken together, targeting BMP-2 may constitute a potential therapeutic strategy for CRC.

Key Words: CRC, rhBMP-2, Apoptosis, Hippo signaling pathway

P4-30

The effect of macrophage-secreted IL-1β on migration in lung cancer A549 cells

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It is well known that tumor-associated macrophages (TAMs) secrete cytokines and growth factors which are strongly correlated with migration. Therefore we investigated the signaling pathways that are activated by macrophage-secreted interleukin-1β (IL-1β). Only the macrophage, not monocyte, expressed IL-1β. IL-1β induced cancer cells to enhance migration, which was similar to that caused by macrophages. IL-1β receptor antagonist reduced the effect of IL-1β and macrophage on migration. IL-1β knockdown also showed similar effect on migration. Signaling of extracellular signal-regulated kinase (ERK), p38, c-Jun NH2-terminal kinase (JNK), and nuclear factor kappa B (NF-κB) by IL-1β has been reported to be associated with migration in lung, tongue, and breast cancers. ERK, JNK, p38 and NF-κB were activated by macrophages and IL-1β. IL-1β receptor antagonist reduced IL-1β effect on activation of ERK and p38, but had no effect in macrophage-induced A549 cells. Inhibitors of ERK and p38 also decreased migration effect in IL-1β induced cells. JNK and NF-κB activated by macrophage and IL-1β were reduced by IL-1β receptor antagonist. NF-κB inhibitor reduced migration effect of IL-1β, but JNK inhibitor had no effect. In conclusion, IL-1β secreted from macrophage can change the lung cancer A549 cells resulting in the increase of migration via NF-κB activation in A549 cells.

Key Words: Macrophage, Migration, A549, IL-1β, NF-κB

P4-31

Activation of TTP by resveratrol suppresses the growth and invasion of colorectal cancer cells

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Colorectal cancer is one of the most common cancers in the world and the second most lethal cancer in the USA. Tristetraprolin (TTP) is an AU-rich elements-binding protein that regulates mRNA stability. Resveratrol is a polyphenolic compound naturally found in grapes, peanuts, and berries. Considerable research has been performed to determine the benefits of RSV against various human cancers. In this study, we investigated the biological effect of RSV in colorectal cancer cells. RSV inhibited the proliferation of colorectal cancer cells. RSV induced the expression of TTP in a dose-dependent manner in HCT116 and SNU81 cells. Silencing of TTP inhibited TTP mRNA expression but after treatment of RSV recovered the expression of the TTP mRNA. HTC116 and SNU81 cells were transfected with pGL3/TTPp-1411 containing the TTP promotor for 24 hours and then treated with RSV in a dose-dependent manner for 24 hours. RSV induced the mRNA decaying activity of TTP. RSV inhibited the relative luciferase activity of cIAMP2, LATS2, Lin 28, and MDM2 in HCT116 and SNU81 cells. In addition, RSV significantly inhibited the rate of invasive and migratory effect of colorectal cancer cells. In conclusion, RSV suppressed the proliferation of colorectal cancer cells by induced the expression of TTP.

Key Words: Resveratrol, Colorectal cancer cells, TTP, Metastasis, Invasion, Cell proliferation

P4-32

Protein kinase C beta II induces endothelial dysfunction via mitochondrial ROS generation in HUVECs

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Protein kinase C (PKC) induces endothelial dysfunction, which is an important pathological factor in cardiovascular diseases. However, the effect of PKCβII on the endothelial dysfunction has not been characterized in cultured endothelial cells. Here, using adenoviral PKCβII gene transfer and pharmacological inhibitors, the role of PKCβII on the endothelial dysfucntion were investigated in cultured endothelial cells. Phorbol 12-myristate 13-acetate (PMA) increased reactive oxygen species (ROS), p66shc phosphorylation, intracellular adhesion molecule-1 and monocyte adhesion which were inhibited by PKCβi (10 nM), a selective inhibitor of PKCβII. PMA increased the phosphorylation of CREB and manganese superoxide dismutase (MnSOD) which were also inhibited by PKCβi. Gene silencing of CREB inhibited PMA-induced MnSOD expression, suggesting CREB plays a key role of MnSOD expression. Gene silencing of PKCβII inhibited PMA-induced mitochondrial ROS, MnSOD, and ICAM-1 expression. On contrast, overexpression of PKCβII using AdPKCβII increased mitochondrial ROS, MnSOD, ICAM-1 and p66shc phosphorylation in cultured endothelial cells. Finally, PKCβII-induced ICAM-1 expression is inhibited by Mito-TEMPO, mitochondrial ROS scavenger, suggesting involvement of mitochondrial ROS in PKC-induced vascular inflammation. Taken together, it is suggested that PKCβII plays an important role of PMA-induced endothelial dysfunction, and the inhibition of PKCβII-dependent p66shc signaling acts as a therapeutic target for vascular inflammatory diseases.

Key Words: Protein kinase C beta II, ICAM-1, Mitochondria, Reactive oxygen species, Endothelial cells

P4-33

Activation of SREBP signaling by HN1 promotes the growth and metastasis in hepatocellular carcinoma

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Despite that hematological and neurological expressed 1 (HN1) was found to be overexpressed in various cancers, the important functional role of HN1 in human hepatocellular carcinoma (HCC) cells still remains unclear. Thus, we investigated the biological role of HN1 in HCC using two HepG2 and SNU449 cells. HN1 was significantly overexpressed in HCC tumors compared to normal liver tissues. Silencing of HN1 significantly diminished the viability of HCC cells whereas overexpression of HN1 stimulated the viability of HCC cells. Silencing of HN1 inhibited the invasion and metastasis of HCC cells whereas overexpression of HN1 promoted the invasion and metastasis of HCC cells. In addition, silencing of HN1 significantly inhibited the expression levels of SREBP1 and SREBP2 of HCC cells whereas overexpression of HN1 increased the expression levels of SREBP1 and SREBP2 of HCC cells. Silencing of SREBP1 also diminished the expression levels of HN1 and suppressed the survival and metastasis of HCC cells. In cholesterol assay, silencing of HN1 inhibited the lipid formation of HCC cells whereas overexpression of HN1 promoted the lipid formation of HCC cells. In conclusion, HN1 encourages the proliferation and metastasis of HCC cells in part through the activation of SREBP signaling pathway. Taken together, our results suggest that targeting HN1 may constitute a potential therapeutic strategy for HCC.

Key Words: HN1, Hepatocellular carcinoma cells, Cell proliferation, Lipogenesis, Microarray

P4-34

Role of collagen triple helix repeat containing-1 in esophageal adenocarcinoma cells

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Collagen triple-helix repeat-containing 1 (CTHRC1) has been identified via genome-wide multiplatform approaches as risk factors associated with esophageal adenocarcinoma (EAC). The incidence of EAC has risen dramatically worldwide without clear etiology recently. Thus, the aim of the current study was to examine the molecular mechanisms by which CTHRC1 regulates growth and metastasis in EAC cells. We use BE3 and OE-33cell lines. Knockdown of CTHRC1 expression significantly decreased the cell viability and the colony numbers and size in EAC cells. To identify important gene expression patterns related to CTHRC1 in EAC, we utilized genome-wide transcriptome analyses. A total of 739 genes were significantly associated with CTHRC1 knockdown in EAC cell lines (567 genes from BE-3 and 194 genes from OE-33). Among 22 common genes shared by both cell lines, CTHRC1 knockdown resulted in the suppression of several oncogenes (TGFß1, JUN and FOS). Knockdown of CTHRC1 in EAC cells significantly reduced levels of β-catenin and c-Myc, but increased p-β-catenin level. The mRNA and protein levels of vimentin, twist, MMP9, and uPA were also decreased in CTHRC1 knockdown EAC cells. In addition, knockdown of CTHRC1 led to increased apoptotic protein levels. Taken together, CTHRC1 promotes the growth and invasion/metastasis of EAC cells through activation of the TGFß/ERK pathway and targeting TGFß/ERK pathway via CTHRC1 may constitute a potential strategy for the prevention and treatment of EAC.

Key Words: Esophageal adenocarcinoma cells, CTHRC1, Genome-wide transcriptome analyses, Metastasis, TGFβ/ERK pathway

P4-35

Inactivation of Akt by UA induced apoptosis in esophageal cancer cells

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Ursolic acid (UA) was found to be induced apoptosis in various cancers. However, the precise mechanism of UA in esophageal squamous cell carcinoma (ESCC) has not been fully understood. In this study, we investigated the effects of UA as well as its combination treatment with paclitaxel in ESCC cells by using TE-12 and TE-8 cell lines. UA plus paclitaxel treatment inhibited the proliferation of TE-12 cells and TE-8 cells in a dose-dependent manner when compared to treatment with UA or paclitaxel alone. In colony formation assay, UA potentiated the inhibition of colony formation by paclitaxel when compared to treatment with a single agent. Combination treatment substantially induced apoptosis as indicated by increased levels of cleaved polyADP-ribose polymerase (PARP) and cleaved caspase-9 protein. In addition, combination treatment increased the protein levels of p-Akt in ESCC cells. These results suggest that UA effectively potentiates the efficacy of chemotherapeutic agents such as paclitaxel via inhibition of proliferation and increased apoptosis by inactivation of Akt in ESCC cells. Taken together, UA enhances the therapeutic efficacy of paclitaxel in esophageal cancer and is a potential clinical anticancer agent for the prevention and/or treatment of esophageal cancer.

Key Words: Ursolic acid, Esophageal squamous cell carcinoma, Apoptosis, Akt

P4-36

SOX12 is involved in sphingosylphosphorylcholine-induced smooth muscle-like cell differentiation of human mesenchymal stem cells via reactive oxygen species

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Differentiation of human MSCs (hMSCs) into various cell types is stimulated by oxygen species (ROS) and is controlled by a complex transcriptional program. Differentiation of hMSC into smooth muscle cell (SMC)-like cells was induced by sphingosylphosphorylcholine (SPC). However, whether interaction of ROS and transcription factor is linked to SPC-stimulated differentiation of hMSC into SMC-like cell has not been elucidated. In the present study, we identified altered transcription factors in SPC-stimulated hMSCs using microarray technique and explored correlation between ROS, transcription factors and SPC-induced differentiation of hMSC into SMC-like cell. Treatment with SPC resulted in increased ROS generation and upregulated expressions of SMC markers (α-smooth muscle actin [SMA] and calponin) in hMSCs. Microarray analysis of SPC-stimulated hMSCs showed that the distinctive expression alterations of SOX12 and SOX18 transcription factors. SPC increased SOX12 protein and mRNA level but decreased SOX18 mRNA expression in hMSCs. SPC also enhanced α-SMA expression in hMSCs. Exogenous H_2O_2 increased SOX12 mRNA expression. Moreover, overexpression of SOX12 enhanced expression of α-SMA in hMSCs. These results demonstrate that SOX12 may participate in differentiation of hMSCs into SMC-like cells via ROS in response to SPC.

Key Words: Differentiation, Human mesenchymal stem cell, Reactive oxygen species, Smooth muscle cell, Sphingosylphosphorylcholine, SOX12

P4-37

αKlotho ameliorates diabetic nephropathy via stabilizing podocyte Ca^{2+} signaling

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αKlotho is an anti-aging protein predominantly produced in the kidney, which stabilizes renal ion homeostasis and protects glomerular filter. Deregulation of podocyte Ca^{2+} signaling is postulated as an early event in proteinuria and diabetic nephropathy. However, it has been yet unknown how and/or if αKlotho protects glomerular filter integrity in diabetic nephropathy. Here, we demonstrate that αKlotho ameliorates Ca^{2+}-induced podocyte actin remodeling via downregulating multiple Ca^{2+}-permeable channels including TRPCs and Orai1. We show that TRPC5 and Orai1 channels are overexpressed in early phase of diabetic *db/db* mice, while TRPC6 channel is upregulated in the late phase (~19 weeks). Exogenous administration of purified αKlotho protein or pharmacological blockade of TRPC6 and Orai1 attenuate proteinuria and foot process effacement in *db/db* mice demonstrating a linkage between αKlotho and Ca^{2+}-permeable channels. αKlotho suppresses Orai1- and TRPC6-induced Ca^{2+} influx via inhibiting phosphoinositide-3-kinase-dependent exocytosis of the channels in mouse podocyte. Activation of Orai1 or TRPC6 disturbs the Ca^{2+}-calcineurin pathway and subsequent actin remodeling, leading to transepithelial albumin leakage. Ca^{2+}-induced podocytopathy and slit-diaphragm disruption are rescued by administration of αKlotho. Taken together, αKlotho protects glomerular filter and podocyte actin remodeling by stabilizing Orai1 and TRPC channels in diabetic nephropathy. These results provide a novel function of αKlotho in protecting the kidney filter and open a new avenue for potential therapeutic strategy for proteinuria.

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Key Words: Klotho, TRPC6, Orai1, Proteinuria, Podocyte, Diabetic nephropathy

P4-38

Tau-mediated circadian rhythm disruption and cognitive dysfunction in Alzheimer's disease mouse model

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Two pathological characteristics of Alzheimer's Disease (AD), the most common type of dementia, are Aβ senile plaques and Neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau aggregation. Circadian rhythm disruption is commonly reported by patients with AD and Mild cognitive impairment (MCI). Clock genes, such as PER2, BMAL1, and CLOCK, show oscillating expression patterns in Suprachiasmatic Nucleus (SCN), the master pacemaker generating circadian rhythm. This rhythmic expression influences several physiological function including metabolism and memory formation. Moreover, some of hippocampal gene expressions are also modulated by circadian rhythm generated by SCN and show similar oscillation pattern. Thus, disruption in circadian rhythm can attributes to cognitive dysfunction in AD patients. Here, we showed that the oscillating patterns of clock genes are altered in SCN and hippocampus of AD mouse model with human tau P301L mutation. Moreover, Tau P301L mutant mice have different oscillation cycle in synaptic molecules compared to littermate. Tau P301L mutant mice has strikingly different behavior pattern measured by in vivo circadian rhythm behavior tests. In addition, we showed that MEF, mouse embryonic fibroblast, cell lines transfected with human tau P301L mutation have different clock genes promotor activity. These results clearly provide the evidence that Tau P301L mutation cause circadian rhythm disruption which ultimately affects synaptic dysfunction in hippocampus. Therefore, the mechanism of tau-mediated circadian dysfunction will provide a probable solution for AD patients to treat their difficulties caused by circadian rhythm disruption and cognitive dysfunction.

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Key Words: Alzheimer's disease, Circadian rhythm, Synaptic molecule, Clock genes, Tau P301L mutation

P4-39

In vitro trans-differentiation of primary mouse hepatic stellate cells via TGF-β-ERK-mTOR axis

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Hepatic stellate cells (HSCs) in the space of Dissé represent 5-8% of the total number of liver cells and remain a quiescent state with vitamin A storage in a healthy condition. However, noxious stimuli trans-differentiate HSCs into myofibroblasts, which plays an essential role in the pathogenesis of liver cirrhosis. We sought to investigate molecular mechanisms responsible for this trans-differentiation process. HSCs isolated from Balb/C mice (20 weeks) were cultured on uncoated dishes, which closely mimics the hallmark of hepatic fibrosis. Filaments of α-smooth muscle actin (α-SMA) and vimentin became prominent in HSCs from 3 days after isolation. Intriguingly, expression of TGF-β in HSCs strongly increased with phosphorylation of Smad-2 and -3, which were followed by activation of extracellular signal-regulated kinase (ERK) and ribosomal protein S6 kinase (S6K) during trans-differentiation. Silencing of either ERK or S6K decreased expressions of α-SMA and plasminogen activator inhibitor 1 (PAI-1) in activated HSCs. Consistent with NADPH oxidase 4 (NOX4) upregulation, cytosolic ROS was elevated during HSC trans-differentiation. Blocking the activation of TGF-β receptor (SB431542), ERK (PD184352) or mTOR (rapamycin) abolished fibrotic changes as well as ROS production during trans-differentiation. We suggest that oxidative stress-related myofibroblast differentiation is mediated by autocrine TGF-β action and its downstream, ERK-mTOR signaling, inhibition of which could be therapeutic strategies against the progression of liver cirrhosis.

Key Words: Hepatic stellate cell, Trans-differentiation, Transforming growth factor-β, Oxidative stress

P4-40

Role of mitochondrial phosphate transporters in vascular calcification

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Inorganic phosphate (P_i) plays an essential role in cell signaling and energy metabolism. However, elevated serum P_i results in a variety of serious disorders including cardiovascular complications. Until now, the underlying molecular mechanisms of how P_i induces vascular calcification have not been clearly elucidated. Here we investigated whether mitochondrial P_i uptake followed by reactive oxygen species (ROS) generation acts a critical role in high P_i-induced vascular calcification in rat aortic smooth muscle cells. Type III Na^+-P_i cotransporters (PiT-1/2) which are the predominant plasmalemmal P_i transporters expressed in vascular smooth muscle, were upregulated by high P_i incubation. Cellular P_i uptake elicited cytosolic alkalinization that

further facilitated P_i transport into mitochondrial matrix. Increased mitochondrial P_i uptake accelerated superoxide generation (ROS), upregulation of osteogenic genes and calcific changes in aortic smooth muscle cells. Vascular calcification by high P_i was effectively prevented by mitochondrial ROS scavengers or pharmacologic blocking of mitochondrial P_i transporter. We propose that P_i transport across mitochondrial inner membrane could be a novel therapeutic target for vascular calcification and cardiovascular morbidities.

Key Words: Vascular smooth muscle, Calcification, Phosphate, Mitochondrial phosphate transporters, Superoxide

P4-41

Association of mGluR-dependent LTD at excitatory synapses with endocannabinoid-dependent LTD of inhibitory synapses leads to EPSP to spike potentiation at Schaffer collateral-CA1 synapses

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Input-output relationship of neural network is determined not only by synaptic efficacy but also by neuronal excitability. Alterations of synaptic efficacy by various forms of synaptic stimulations have been extensively investigated, but relatively less is known about how input-output relationship of neuronal network is modulated when changes in synaptic efficacy is associated with changes in neuronal excitability. Here, we demonstrate that paired pulses of low frequency stimulation (PP-LFS) induced metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD) at Schaffer collateral (SC)-CA1 synapses and this LTD was associated with long-term potentiation of intrinsic excitability (LTP-IE) and action potential outputs (LTP-AP) in SD rats (either sex). The LTP-IE and LTP-AP were accompanied by hyperpolarized AP threshold (V_{th}) without significant changes in resting membrane potential (RMP) or voltage sag. Further studies revealed that LTP-IE and LTP-AP after PP-LFS were abolished by blockade of GABA receptors (GABARs), suggesting the involvement of disinhibition of GABAergic pathway. Indeed, PP-LFS at SC induced LTD of inhibitory synapse (i-LTD) and inhibition of type I cannabinoid receptors (CB1Rs) prevented LTP-IE and LTP-AP. By contrast, group I mGluR agonist, 3, 5-dihydroxyphenylglycine (DHPG), also induced LTD, but failed to elicit endocannabinoids (eCBs)-dependent i-LTD. Together, we propose that co-expression of mGluR-LTD at the excitatory and inhibitory synapses regulates excitation-inhibition balance to increase neuronal output in CA1 pyramidal neurons.

Key Words: mGluR-LTD, LTP-IE, i-LTD, Endocannabinoid, E-I balance

P4-42

Investigation of physiological function of the murine bitter taste receptor Tas2r108

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The sense of taste plays a critical role in the life and nutritional status of human and other organisms. Bitter taste among 5 basic tastes is associated with survival and avoids mammals from poisonous substances. Murine type 2 taste receptors (Tas2rs) mediating bitter taste consist of a family of 35. We found that Tas2r108, out of murine 35 Tas2rs, was expressed at highest levels in tongue papillae and exocrine glands. However, physiological functions of T2Rs remain poorly understood. Expression locations of messenger RNAs (mRNAs) and specific agonist screening of Tas2r108 help to determine those function.

In situ hybridization (ISH) was performed to identify mRNAs expression location of Tas2r108 in the submandibular glands. After generating the digoxigenin (DIG) labeled-cRNA probes, dot blot hybridization was performed to estimate integrity and optimal diluting concentration of these probes. Then, we carried out ISH to detect Tas2r108 mRNA in the submandibular glands. ISH results showed that the anti-sense probes labeled acinar and ductal cells. These results suggest that Tas2r108 may be associated with primary saliva secretion and ductal modification of saliva composition.

We drew up calcium imaging for agonist screen of Tas2r108 receptor, with the specific purpose of identifying novel activating agonists for the Tas2r108. The plasmids harbor the Tas2r108 coding sequences preceded by the first 45 amino acids of rat somatostatin receptor 3 for cell surface localization. CHO-K1 cells stably expressing the chimeric G protein subunit Gα16gust44 were activated Tas2r108 to phospholipase C activity, inositol trisphosphate, and mobilization of intracellular calcium. We will proceed with present study using bitter compounds. The bitter taste compounds to be used are quinine and denatonium benzoate of agonists of T2R4 that has genetically similar structure and chloramphenicol and saccharin, known as Tas2r108 agonists of the murine heart.

Future experiments will demonstrate the exact physiological function of Tas2r108 expressed in various tissues using in vivo analysis of Tas2r108 knockout.

Key Words: Tas2r108, Bitter taste calcium imaging, Bitter taste in situ hybridization

P4-43

Hepatoprotective effects of oyster-derived Tyr-Ala peptide on fulminant hepatitis

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Our previous study reported that oyster hydrolysate (OH) had hepatoprotective effect on lipopolysaccharide (LPS)/D-galactosamine (D-GalN)-induced fulminant hepatitis via inhibition of oxidative stress and inflammation. Here we ask whether which molecule in OH is responsible for protection from LPS/D-GalN-induced acute liver injury. High-performance liquid chromatography (HPLC) was used to determine the major component in OH. Tyrosine-Alanine (YA) was highly and easily detected in the OH. The experimental acute liver injury model was induced with LPS (1 μg/kg) and D-GalN (400 mg/kg). Animal experimental groups were divided into 6 groups as follows: control (saline), LPS/D-GalN, LPS/D-GalN+OH (200 mg/kg), LPS/D-GalN+YA (10 mg/kg), LPS/D-GalN+YA (50 mg/kg) and LPS/D-GalN+silymarin (25 mg/kg, positive control). YA peptide was analyzed to measure the antioxidant and anti-inflammatory activities. YA peptide showed high DPPH and ABTS radical scavenging activities in a dose-dependent manner. In addition, YA reduced production of nitric oxide in LPS-activated RAW264.7 cells in a dose-dependent manner. Both 10 mg/kg and 50 mg/kg of YA significantly reduced LPS/D-GalN-induced increases in the concentrations of alanine transaminase and aspartate aminotransferase in serum. In the LPS/D-GalN group, liver tissues exhibited apoptosis of hepatocytes with hemorrhages. These pathological alterations were ameliorated by YA treatment. YA markedly reduced the LPS/D-GalN-induced increase in the expression of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 mRNA in liver tissue. Furthermore, YA also reduced the protein level of AMPK, which is known as a detrimental factor in fulminant hepatitis, phosphorylated by LPS/D-GalN. Taken together, these results show that YA has hepatoprotective effects on LPS/D-GalN-induced fulminant hepatitis via inhibition of oxidative stress

and inflammation, suggesting that YA could be used as a functional peptide for treatment of acute liver injury.

Key Words: YA peptide, Acute liver injury, Antioxidant, Anti-inflammatory

P4-44

The intracellular Ca^{2+} channel TRPML3 is a PtdIns3P effector that regulates early autophagosome biogenesis

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Autophagy is an intracellular degradation pathway that delivers cytoplasmic contents to the lysosome, involving many fusion and fission events which require Ca^{2+}. Although TRPML3 is suggested to regulate autophagy as an autophagosomal Ca^{2+} channel, it is still not clear whether TRPML3 directly provides Ca^{2+} for the process. To image a TRPML3-mediated Ca^{2+} release in specific subcellular compartments, we used a GCaMP6-fusion protein, a genetically encoded calcium indicator attached to C-terminus of TRPML3. TRPML3-GCaMP6 hardly overlapped with LC3 but was mainly localized in ATG5-positive phagophores, indicating that TRPML3 supplies Ca^{2+} for the early autophagosome biogenesis. Moreover, nutrient starvation activated TRPML3 to release more Ca^{2+}, suggesting that TRPML3 are regulated in the context of autophagy. Indeed, lipid binding assay revealed that both N-terminus and 1st extracytosolic loop of TRPML3 interact with phosphatidylinositol-3-phosphate (PI3P), a key determinant of autophagosome formation. Confocal imaging and electrophysiological experiments showed that TRPML3 is directly activated by PI3P, resulting in increased autophagy. Inhibition of TRPML3 suppressed autophagy even in the presence of excess PI3P, whereas activation of TRPML3 rescued autophagy suppression. Part of the N-terminal and 1st extracytosolic loop sequences of TRPML3 was predicted as phox homology (PX) domain and RxL motif, respectively, which bind primarily to PI3P. Charge removal mutations in the regions disrupted binding to PI3P and abolished TRPML3 activation by PI3P and subsequent increase of autophagy. Taken together, these results suggest that TRPML3 is a key regulator of the autophagy process as a downstream effector of PI3P, providing Ca^{2+} that mediates early steps of autophagosome formation.

Key Words: Autophagy, Ca^{2+} channel, GCaMP6, PI3P, TRPML3

P4-45

Palmitoylation controls trafficking of the intracellular Ca^{2+} channel TRPML3 to regulate autophagy

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TRPML3 is a Ca^{2+}-permeable cation channel that is expressed in multiple subcellular compartments with dynamic localization. Our previous studies suggest that upon autophagy induction TRPML3 is recruited and provides Ca^{2+} for the fusion process in autophagosome biogenesis. However, intracellular trafficking and Ca^{2+} channel function of TRPML3 related to autophagy are not known. Here we report that TRPML3 undergoes palmitoylation at its C-terminal region, which is required for dynamic trafficking and cellular function of TRPML3 in autophagy. Palmitoylation regulated TRPML3 surface expression and trafficking, but not channel properties nor localization and function of intracellular TRPML3. Activation of intracellular TRPML3 by agonist stimulation induced robust Ca^{2+} release, which solely increased autophagy in Ca^{2+} and palmitoylation-dependent manners. Palmitoylation regulated not only intracellular TRPML3 trafficking to autophagosomes but also autophagic flux in induced autophagy. Importantly, nutrient starvation activated TRPML3 to release Ca^{2+} and increased the level of TRPML3 palmitoylation. Disruption of TRPML3 palmitoylation, however, abolished the starvation-induced TRPML3 activation without affecting channel activity. These results suggest that trafficking and channel function of TRPML3 are regulated in the context of autophagy and palmitoylation is a prerequisite for the function of TRPML3 as a Ca^{2+} channel in autophagosome formation by controlling its trafficking between subcellular compartments.

Key Words: Autophagy, Ca^{2+} channel, Membrane trafficking, Palmitoylation, TRPML3

P4-46

Role of endothelin-2 in renal cell carcinoma

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Endothelins (ETs) are 21-amino acid vasoactive peptides that bind to G-protein-linked receptor ET-A receptors and ET-B receptors. These peptides are important regulator in several cell types and affect angiogenesis, migration and inflammation. In cancer, they have roles in the control of numerous factors in cancer growth and progression, inducing proliferation, survival, angiogenesis, migration and metastases. Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, responsible for approximately 90-95% of cases. When RCC metastasises, it most commonly spreads to the lymph nodes, lungs, liver, adrenal glands, brain or bones. But the role of ET-2 in renal cell carcinoma has not been investigated comprehensively. We investigated ET-2 expression in renal cell carcinoma and the relationship between ET-2 and migration. Of six human renal cell carcinoma cell lines tested, Caki-1 cells expressed mRNAs for ET-A, ET-B and ET-2. Experiments with endothelin receptor antagonists showed that migration to ET-2 is mediated via the ET-A, ET-B receptor. We suggest that expression of ETs and their receptors by human renal cell carcinoma, may have a role in the progression of renal cell carcinoma and migration of cancer cells.

References

1. A role for endothelin-2 and its receptors in breast tumor cell invasion. Grimshaw MJ. Cancer Res. 2004 Apr 1;64(7):2461-8.
2. The endothelin axis: emerging role in cancer. Nelson J. Nat Rev Cancer. 2003 Feb;3(2):110-6.

Key Words: Endothelin, Renal cell carcinoma

P4-47

Role of physiological ET-1 in bone remodeling

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Endothelin (ET) system comprises three 21-amino acid peptides, ET-1, -2, and -3 that activate two G-protein coupled receptors, ET receptor A (ET_A) and B (ET_B). Endothelial cell products may affect bone cell function, since trabecular and cortical bone are in close proximity to vascular endothelial cells. The abundance of endothelial cells in bone marrow and the proximity of these cells to osteoclasts and osteoblasts suggest a role for endothelin-1 (ET-1) on bone metabolism. The role of ET-1 via ET_A activation in the regulation of osteoblastic function has been widely discussed. However, the information about ET-1 function in osteoclasts is limited and ambiguous despite the elevation of its plasma levels in patients of osteoporosis and Paget's disease of bone. But in animal studies, mice completely lacking endothelin-1 have severe anomalies in the heart and aorta with craniofacial abnormalities and die at age 10-12 d post coitum. To gain a better understanding of the physiological role of endothelin-1 in mammals, we used transgenic mice that high expressed ET-1 and low expressed ET-1 targeted to the osteoclast that develop an osteoporosis bone phenotype. We confirmed that our transgenic mice have distinguishable levels of ET-1 from

low to high expression in plasma endothelin-1. ET-1 high expression mice showed a decreased trabecular thickness and bone volume than ET-1 low expression mice in micro CT analysis. Together, our findings reveal a critical role of endothelin in the regulation of osteoclast differentiation and bone mass. ET-1 in our transgenic could perhaps represent a new useful marker of oeteoporosis.

References

1. R. Tarquini, F. Perfetto, B. Tarquini, Endothelin-1 and Paget's Bone Disease: Is There a Link?/Received: 29 April 1997 / Accepted: 20 February 1998.
2. Catherine K. Hathawaya Endothelin-1 critically influences cardiac function via superoxide-MMP9 cascade. PNAS April 21, 2015;112(16):5141-5146.

Key Words: Endothelin-1, Bone, Osteoclast, Transgenic mice, Osteoporosis

P4-48

Inhibition of neddylation facilitates cell migration through enhanced phosphorylation of caveolin-1 in PC3 and U373 cells

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Protein neddylation is a post-translational modification by a covalent conjugation with the neural precursor cell expressed, developmentally down-regulated 8 (NEDD8). Although this process has been reported to participate in diverse cellular signaling, little is known about its role in cancer cell migration.Given a recent proteomics report showing that NEDD8 is down-regulated in prostate cancer tissues versus normal prostate tissues, we tested the possibility that neddylation plays a role in cancer evolution, and then tried to identify target proteins of the neddylation. Caveolin-1, which plays a critical role in cell migration, was identified to be conjugated with NEDD8. When the neddylation was inhibited by transfecting cancer cells with NEDD8-targeting siRNAs or by treating the cells with a NAE1 inhibitor MLN4924, the phosphorylation of caveolin-1 at Tyr14 was augmented in PC3 and U373MG cells, thereby leading to increased cell migration. Such consequences by neddylation inhibition were abolished in the presence of a Src family kinase inhibitor PP2. Although the neddylation process is currently regarded as an emerging target for cancer therapy, our results suggest the possibility that the inhibition of neddylation could facilitate cancer invasion or metastasis at least in some types of cancers.

Key Words: MLN4924, Caveolin-1, Src, Cell migration

P4-49

Familial Alzheimer's presenilin 1 mutation elevate cellular cholesterol levels and facilitates lipid raft localization of β-amyloid precursor protein

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Cerebral deposition of amyloid β-peptide (Aβ) is crucial in the pathogenesis of Alzheimer's disease (AD). The highly amyloidogenic 42-residue Aβ (Aβ42) is the first species to be deposited in both sporadic and familial AD (FAD). Mutations in FAD-associated presenilin1 (PS1) and 2 (PS2) increase the ratio of Aβ42 over 40-residue (Aβ40). A PS mutant reportedly elevates the level of cholesterol due to the increased expression of CYP51, which is critical for cholesterol biosynthesis. Since the elevated cholesterol is a well-known risk factor for AD, it may contribute to the increased Aβ production in PS1 mutant cells. However, this possibility has never been directly examined. In this study, we confirmed that the expression of CYP51 and cholesterol level were elevated in CHO cells transfected with PS1 ΔE9 mutant, compared to cells transfected with PS1 wild type (WT). The elevated cholesterol level in PS1 ΔE9 cells was decreased to a level comparable to that in PS1 WT cells by incubating cells with CYP51 specific inhibitor, tebuconazole. In PS1 ΔE9 cells, tebuconazole significantly decreased secreted level of Aβ42, but not that of Aβ40, confirming that the increase cholesterol level contributes to the increased Aβ42 from PS1 ΔE9 cells. We also showed that the elevated cholesterol level in PS1 °ΔE9 cells increased APP localization in lipid raft, which underlies increased Aβ42 levels. These results suggest that the impaired cholesterol homeostasis in FAD PS mutants directly linked to the altered APP processing and increased Aβ42 production.

Key Words: Alzheimer's disease, APP, Cholesterol, Lipid raft

P4-50

Insulin increases O-GlcNAcylation of amyloid precursor protein promoting its non-amyloidogenic processing

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Alzheimer's disease (AD) is a neurodegenerative disorder affecting elderly people. Amyloid-beta (Aβ) plays a central role in the development of AD. Aβ is amino acid peptide that is derived from amyloid precursor protein (APP). APP has two metabolic pathways, namely non-amyloidogeinic pathway and amyloidogenic pathway. In non-amyloidogenic pathway, APP can be cleaved by α-secretase and γ-secretase at the plasma membrane excluding Aβ production. Alternatively, APP in the plasma membrane is internalized through clathrin-dependent endocytosis, and delivered to early endosomes and lysosomes, where it is cleaved by α-secretase and γ-secretase. Decreased insulin signaling and insulin resistance in brain has been found recently in AD. Intranasal insulin administration improves memory impairments and cognition. Although, growing evidence suggests that insulin has important effects on AD, the underlying mechanism is still unknown. To investigate the effects of insulin on APP processing, we tested whether insulin affected APP processing and Aβ production from neuroblastoma cell line (SH-SY5Y) overexpressing hemagglutinin-tagged wild-type APP and BACE1 (BGWT8). We found that insulin changed APP processing, increasing the level of cell surface APP, decreasing the endocytosis rate of APP, and reducing Aβ generation. We also found that insulin treatment changed the translocation of APP from lipid-raft to non-raft area, and all of these effects of insulin were mediated via Akt insulin signaling. Our present data suggest that insulin may affect Aβ production by regulating APP processing and APP translocation, providing a mechanistic insight into the beneficial effects of insulin and possible link between insulin deficient diabetes and cerebral amyloidosis in the pathogenesis of AD.

Key Words: Insulin, O-GlcNAcylation, Alzhimer's disease, APP

P4-51

Characterization of molecular mechanisms underlying voltage-gated Ca^{2+} channel modulation by DREADD

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Voltage-gated calcium (Ca_V) channels play essential roles in adjusting Ca^{2+} influx upon membrane depolarization. These channels are important for various physiological responses, such as gene expression and neurotransmitter release. Therefore, if the gating of Ca_V channel is not able to be regulated normally, some serious diseases like epilepsy and autism could occur. In synapse, an electrical signal of presynaptic neuron is converted to and released as neurotransmitter. Specifically, the presynaptic Ca_V channels opened by depolarized membrane potential take Ca^{2+} intracellularly, and then the depolarization of membrane potential is accelerated. These series of process potentiate neurotransmitter release from the presynaptic nerve

terminals. The Ca_V channels which control neural signal transduction are tightly modulated by transmembrane proteins called GPCRs. Gating of Ca_V channels can be inhibited by activating muscarinic acetylcholine receptor (mAchR). According to the subtypes of mAchR, the major signaling pathways to inhibit Ca_V channels are different depending on the receptors; one is G_qPCR-mediated voltage-independent inhibition (VI) and the other is $G_{i/o}$PCR-mediated voltage-dependent inhibition (VD). In neurotransmission release, VD pathway mainly regulates the activity of Ca_V channels which are localized in the presynaptic terminals. However, it was impossible so far to evaluate detailed contribution of VD pathways to the regulation of synaptic transmission, because, in synapse, Oxo-M, a ligand of mAchR, cannot selectively discriminate those two separate GPCRs. To solve this problem, we are applying a chemogenetic system called DREADD, which can activate those signaling pathways selectively and artificially. At the present stage, we are going to characterize the differences between DREADD- and normal mAchR-induced signaling pathways to the modulation of ion channels. DREADD has been used in vivo experiments under the indefinite assumption that there would be no difference in signaling kinetics between DREADD and mAchRs. However, in our FRET experiments for confirming the kinetic specificity seen in PIP_2 depletion process caused by DREADD and G_qPCR activation, we found that the activation of hM3Dq (human M3 DREADD) needs more time than that of hM3Rq (human M3 receptor). It was also detected that hM3Dq scarcely ever stop their activation once they have been activated. However, there was no big difference in the amount of PIP_2 depletion between hM3Dq and hM3Rq. Those kinetic specificities of DREADD will be also tested in the modulation of ion-channels.

Key Words: DREADD, PIP_2, Voltage gated Ca^{2+} channel

P5-01

The effect of fibroblast growth factor receptor signaling inhibition during resistance training on muscle and bone quality in mice

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Purpose: Maintaining the quality and strength of muscle and bone is important for quality of human life. Aging decreased many signaling activities, result in loss of function. FGFR signaling known to involve with both muscle regeneration and bone mineralization. Here, we examine the relationship linking fibroblast growth factor receptor signaling to bone and muscle quality during resistance exercise. To elucidate the relationship and potential role of FGFR signaling, FGFR inhibitor was used while 8 weeks of resistance training was conducted.
Method: The animals were randomly assigned to each of the following groups: inhibition control group (Inh-C), Sham control group (Sham-C), Resistance Training with Sham administration group (RT-Sham) and Resistance Training with inhibitor administration group (RT-Inh). At least 6-7 mice were conducted with experiment for each group. FGFR inhibitor NVP-BGJ398 (50 mg/kg body weight; Novartis, Switzerland) or sham (PEG-300 [AppliChem]/ Glucose 5%, 2:1 mix) were administered by oral gavage. Administration was initiated at 9 weeks old mice over 8 weeks with three treatments per week.
Result: Administration of FGFR inhibitor decreased grip strength, reduced muscular endurance, and running capacity. These effects were consistent during 8 weeks of resistance training. However, resistance training managed to reduce atrophic and osteoclastogenic gene responses in gastrocnemius muscle and tibia bone.
Conclusion: Although resistance training is effective regime to increase muscle and bone quality, 8 weeks of training failed to increase attenuated muscle and bone quality. However, resistance training managed to reduce atrophic and osteoclastogenic gene responses in gastrocnemius muscle and tibia bone. Collectively, our results suggest that loss of FGFR signaling resulted in both muscle and bone quality modulation and resistance exercise attenuated adverse effect on muscle and bone gene expression which may suggested that exercise can be a therapeutic method to target systemic loss function during altered physiology.

Key Words: FGFR signaling, Resistance training, Ladder climbing exercise, Muscle and bone quality

P5-02

VEGF-A expressing adipose tissue shows rapid beiging, enhanced survival after transplantation and confers IL4-independent metabolic improvements

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Adipocyte-derived VEGF-A plays a crucial role in angiogenesis and contributes to adipocyte function and systemic metabolism, such as insulin resistance, chronic inflammation and beigeing of subcutaneous adipose tissue. Utilizing a doxycycline (Dox)-inducible adipocyte-specific VEGF-A overexpressing mouse model, we investigated the dynamics of local VEGF-A effects on tissue beiging of adipose tissue transplants. VEGF-A overexpression in adipocytes triggers angiogenesis. We also observe a rapid appearance of beige fat cells in subcutaneous white adipose tissue (sWATs) within as early as 2 days post induction of VEGF-A. In contrast to conventional cold-induced beiging, VEGF-A - induced beiging is independent of IL-4. We subjected metabolically healthy VEGF-A overexpressing adipose tissue to autologous transplantation. Transfer of subcutaneous adipose tissues taken from VEGF-A overexpressing mice into diet-induced obese mice resulted in systemic metabolic benefits, associated with improved survival of adipocytes and a concomitant reduced inflammatory response. These effects of VEGF-A are tissue autonomous, inducing WAT beigeing and angiogenesis within the transplanted tissue. Our findings indicate that manipulation of adipocyte functions with a *bona fide* angiogenic factor, such as VEGF-A, significantly improves the survival and volume retention of fat grafts and can convey metabolically favorable properties on the recipient on the basis of beiging.

Key Words: VEGF-A, Adipose tissue, Interleukin-4

P5-03

Toxicological evaluation of dithiocarbamate fungicide mancozeb in vivo

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Mancozeb, a polymeric complex of zinc and manganese salts of ethylene bisthiocarbamate (EDBC), is used widely in agriculture as fungicides. In mice, mancozeb induces embryo apoptosis, affects oocyte meiotic spindle morphology and impairs fertilization rate even when used at very low concentrations. In the present study, we evaluated the mancozeb-induced toxicity on the thyroid and testis of male rats. When the chronic administrated mancozeb at 800 mg/kg body weight per day for 30 days, body weight slightly decreased, however, liver, thyroid, and testis weight per 100 g body weight were not changed. Histologic studies of the testis of the male rat

treated with mancozeb revealed spermatogenesis inhibition reflected by significant decrease in the number of spermatogoniums, primary spermatocytes, spermatids, and sperms, when compared with that of controls. Chronic exposure of mancozeb induced gonadal hormone disturbance. Estradiol, progesterone, and testosterone levels in serum were significantly decreased in mancozeb-treated rats. Also, the volume and histopathology of thyroid gland were distinctly altered, whereas thyroid weight per 100 g body weight was not changed. Disruption of thyroid follicles reflected in nucleus-to-cytoplasm ratio (N/C) in epithelial and stromal cells, epithelial cell hypertrophy and altered colloid volume. To functional correlation, we tested the T3 and T4 levels in serum that were significantly decreased in mancozeb treated rats compared with control. Also, based on the epigenetic analysis, chronic exposure of mancozeb evoked up-regulation of miRNA profiles represent to oncogene and liver toxicity.

Key Words: Mancozeb, Epigenetic toxicity, Endocrine disruptor, Fungicide

P5-04

Effects of exercise training on muscle damage, muscle fatigue, and mitochondrial function in atorvastatin-treated rat skeletal muscles

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Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are cholesterol-lowering drugs widely used in the treatment of cardiovascular disease. However, statins also cause adverse side effects in skeletal muscle ranging from fatigue to severe rhabdomyolysis. Recently, we found that long-term (48 hour) treatment of simvastatin induced cell death due to impaired mitochondrial respiration, Ca^{2+} retention capacity, and oxidative stress leading to mitochondrial apoptotic signaling in primary human skeletal muscle cells (Kwak et al., 2012). However, the effects of exercise training on muscle damage, muscle fatigue, and mitochondrial function in statin-treated skeletal muscle have not been clearly elucidated. Therefore, the purpose of this study was (1) to determine the impacts of in vivo atorvastatin treatment on muscle damage, muscle fatigue/strength, and mitochondrial function (e.g., mitochondrial O_2 respiration, H_2O_2 emission, Ca^{2+} retention capacity) in rat skeletal muscles and (2) to determine the effects of exercise training on muscle damage, muscle fatigue/strength, and mitochondrial function in atorvastatin-treated rat skeletal muscles.
Male Wistar rats were randomly divided into three groups: control (CON), 5 mg/kg atorvastatin treated group (ATOR), and 5 mg/kg atorvastatin plus aerobic exercise training group (ATOR+EX). Animals were administered through oral gavage with a vehicle or 5 mg/kg/day atorvastatin dissolved in 0.25% w/v hydroxypropyl methylcellulose for 12 weeks. Forelimb muscle strength and serum creatine kinase (CK) concentration (i.e., muscle damage marker) were measured. The skeletal muscles such as soleus (SOL, Type I) and white gastrocnemius (WG, Type IIb) were permeabilized by saponin for measurement of mitochondrial respiratory capacity, mitochondrial H_2O_2 emission, and mitochondrial Ca^{2+} retention capacity.
Maximal forelimb strength and forelimb fatigue index were significantly decreased after 6 weeks and 8 weeks, respectively in ATOR. In contrast, serum CK concentration was significantly increased in ATOR compared with CON. However, exercise training attenuated atorvastatin-induced impairment in maximal forelimb strength and fatigue index, as well as reduced serum CK concentration ($p<0.05$). The mitochondrial O_2 respiratory capacity and Ca^{2+} retention capacity were significantly reduced by 12 weeks of ATOR in both SOL and WG ($p<0.05$). In addition, mitochondrial H_2O_2 emission was significantly increased in ATOR compared with CON in both SOL and WG ($p<0.05$). However, exercise training attenuated mitochondrial O_2 respiratory capacity, Ca^{2+} retention capacity, and mitochondrial H_2O_2 emission in atorvastatin-treated skeletal muscles.
These data demonstrate that long-term treatment of atorvastatin results in muscle damage, reduced muscle strength, and impaired mitochondrial function in skeletal muscles. However, aerobic exercise training for 12 weeks attenuates muscle damage, maintains muscle strength, and ameliorates mitochondrial dysfunction induced by atorvastatin, suggesting that aerobic exercise training plays a therapeutic role in atorvastatin-induced myopathy (NRF-2016R1A2B4014240).

Reference

1. Kwak HB, Thalacker-Mercer A, Anderson EJ, Lin CT, Kane DA, Lee NS, Cortright RN, Bamman MM, Neufer PD. Simvastatin impairs ADP-stimulated respiration and increases mitochondrial oxidative stress in primary human skeletal myotubes, Free Radic Biol Med, 52: 198-207, 2012.

Key Words: Atorvastatin, Exercise training, Muscle damage, Muscle fatigue, Mitochondrial function

P5-05

The effects of neuroimmune cytokines and neurotrophins by exercise in aging rats

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Purpose: Many patients with neuroimmune disorders, including depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke, endure pathological levels of fatigue. Exercise can stimulate the neuroimmune cytokines and neurotrophins secretion and induce activation in brain tissues. So, we tested whether exercise modulates neuroimmune cytokines and neurotrophins in aging rats.
Methods: 50 weeks old male Wistar rats were randomly assigned to four groups: the sedentary (Con, n=10), resistance exercise (ladder-climbing exercise, n=10), aerobic exercise (treadmill exercise, n=10) and dynamic resistance exercise group (ladder-climbing + treadmill, n=10). Exercise performed 3 days per week, for 12 weeks.
Results: Results showed that 12 weeks exercise, neuroimmune function and neurotrophins showed increased compared to control group. Interleukin 6, Interleukin 4, Interleukin 15 and brain-derived neurotrophic factor were significantly ($p<0.05$) increased in hippocampus. Also, fibronectin type III domain-containing 5 protein was significantly ($p<0.05$) increased in resistance exercise group.
Conclusion: Therefore, exercise in aged rats was increased neuroimmune cytokines and neurotrophins in hippocampus.

Key Words: Exercise, Aging, Neuroimmune cytokines, Neurotrophins, Hippocampus

P5-06

Effects of exercise on cardiac contractility in mouse heart

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Exercise is well known as an alternative therapy for cardiovascular diseases. However, effects of exercise on cardiac function and Ca^{2+} homeostasis are still controversial. The aim of this study is to investigate whether exercise alters cardiac function and Ca^{2+}-handling. C57BL/6 mice (7-week-old) were divided into two groups; control (Con) and exercise (Ex) groups. Ex groups were trained on treadmill for 8 weeks (15m/min for 45 minutes a day). After 8 weeks of exercise, the effects of exercise on cardiac function and Ca^{2+}-handling were investigated by echocardiography, edge detection, Ca^{2+}

transient, patch clamp, and western blot. After exercise, Ex groups showed lower body weight and white adipose tissue compared to Con groups. In vivo, Ex groups significantly enhanced cardiac contraction (EF and FS) and performance (SV) compared to Con groups. Improved cardiac contraction was related to increased time constants of Ca^{2+} transient and longer action potential durations (APD). Expression of Ca^{2+}-handling proteins such as FKBP12.6, p-PLB (Thr-17), troponin was significantly increased by exercise, while L-type Ca^{2+} current density was decreased in Ex compared to Con groups. Our data shows that exercise enhances cardiac contractility via higher expression of Ca^{2+}-handling proteins despite lower L-type Ca^{2+} current density. Therefore, the changes in cardiac contraction by exercise may be associated with other Ca^{2+} influx-related channels rather than L-type Ca^{2+} channel.

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Key Words: Exercise, Cardiomyocyte, Cardiac contraction, Ca^{2+}-handling, L-type Ca^{2+} channel

P5-07

The body weight difference between dual energy X-ray absorptiometry and multi-frequency bioelectrical impedance analysis attenuates the equivalence of the body composition assessment

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Background/Objectives: Low agreement of body composition analysis (BCA) between dual-energy X-ray absorptiometry (DXA) and multi-frequency bioelectrical impedance analysis (MF-BIA) has been reported. We examine whether this discrepancy is influenced by the precision of DXA in body weight (BW) measurement.
Subjective/Methods: This cross-sectional study enrolled 1353 participants aged 53-83. Whole body scan of DXA and eight-polar tactile-electrodes impedance-meter using four electronic frequencies of 5, 50, 250, and 500 kHz were employed for BCA. Agreement level between BW estimated by DXA and actual BW (WgtA) was calculated. Agreement of BCA by DXA versus MF-BIA across WgtA groups was assessed.
Results: DXA substantially wrongly estimated BW, especially in men. 13.5%, 5.1%, and 5.6% participants accompanied with BW bias levels as 2%, 3%, and 4% and higher, respectively. Correlation of BCA by DXA versus by MF-BIA in body fat mass, percent body fat, and lean body mass (LBM) was gradually reduced, whereas root mean squared error was increased in concordance with the reduction of WgtA. DXA provided a lower LBM amount compared to that of MF-BIA and this difference increased significantly across groups of poor WgtA.
Conclusions: Lower WgtA contributed remarkably to the difference in BCA measured by DXA and MF-BIA.

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Key Words: Dual-energy X-ray absorptiometry, Lean body mass, Body weight

P5-08

Effects of combined treatment of chiropractic and isometric exercise on static balance and dynamic balance in subject of cervical alignment

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This study was designed to investigate the effects of combined chiropractic and isometric exercise on the static balance and dynamic balance of cervical alignment subjects for 8 weeks. X-rays were measured on Eighteen subjects who had cervical alignment. And cervical straight group (n=9) and inverse curve group (n=9) based on cervical curvature. Both groups treated chiropractic once a week for 20 minutes and isometric exercise for 30 minutes three times a week. Statistical analysis was performed using SPSS (Ver.23.0). The mean and standard deviation of each variable were calculated and two-way ANOVA was performed. Independent t-test and paired t-test were performed when there was interaction between groups. The significance level was set to .05. Static balance ability of the cervical straight group and the inverse curve group showed a significant effect on both the left and right sides. The dynamic balance ability of both groups showed a significant change in the left side and no significant change in the right side. Static balance ability of the cervical straight group and the inverse curve group showed a significant effect on both the left and right sides. The dynamic balance ability of both groups showed a significant change in the left side and no significant change in the right side. The two groups divided on the basis of cervical alignment showed improvement in balance ability after 8 weeks of the same treatment but there was a difference between the two groups. The effect of difference of cervical alignment on balance ability Supplementary studies are needed.

Key Words: Cervical inverse curve, Cervical straight, Chiropractic, Static balance ability, Dynamic balance ability

P5-09

Exercise training improves erectile function in aged rat

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Purpose: Aging changes the balance of sex hormones and causes endothelial dysfunction in the penis, and these are important determinants of erectile dysfunction (ED). The objective of this study was to determine whether exercise training could alter the aging-related molecular mechanisms that underlie parameters related to sex hormone balance and endothelial, and erectile function in aged rats.
Methods: A total of 14 young (2-month-old) and 14 aged (18-month-old) Sprague Dawley rats were randomly assigned to either untrained control (young control, [YC], old control, [OC]) or endurance exercise-trained (young exercise, [YE], old exercise, [OE]) groups with seven rats per group. The exercise groups trained with treadmill running for 6 weeks. Body composition parameters (body weight, heart mass, liver mass, and testicular mass), serum sex hormone levels (testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin), endothelial function-related parameters in the penis (endothelial nitric oxide synthase [eNOS], CD31, alpha smooth muscle actin [α-SMA]), and penile erection function were analyzed in aged rats.

Results: The old groups showed increased body weight compared with the young groups, but exercise training attenuated aging-induced increase in body weight. The old groups had lower testicular mass compared with the young groups, but exercise training attenuated aging-induced decreases in testicular mass. Exercise training increased serum testosterone levels in both the young and old groups. However, there were no changes in the levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin among the groups. The old control group showed less positive staining for eNOS and decreased in the protein levels of p-eNOS compared with the young control group. However, exercise training protected against aging-induced decrease in eNOS and p-eNOS protein levels in penis. Interestingly, exercise training increased protein levels of α-SMA and improved erectile function in the old group.
Conclusions: Exercise training has beneficial effects on erectile function in aging rats via activation of eNOS as well as increased levels of testosterone, suggesting that exercise training may be a therapeutic modality for improving the erectile dysfunction associated with aging.

Key Words: Exercise, Aging, Testosterone, eNOS, Erectile function

P5-10

Effects of exercise training on serum level of sclerostin in breast cancer survivors

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Wingless and integration site growth factor (Wnt) signaling is one of the major carcinogenesis-related signaling pathway. Sclerostin, which is expressed in osteocytes and chondrocytes, antagonizes canonical Wnt/β-catenin signaling through binding to LRP5/6 receptors. Numerous studies suggested that an increased level of serum sclerostin is associated with poor prognosis of breast cancer patients. Yet, the relationship between sclerostin and exercise is still unclear. We, hereby, investigated whether an exercise training causes changes in the level of serum sclerostin in the survivors of breast cancer. Thirty-nine survivors of breast cancer who completed anticancer therapy and forty healthy women volunteers were enrolled in this study. Breast cancer subjects were randomly allocated to either an exercise group or a control group for 12 weeks. All participants completed health-related fitness tests. Subsequently, their anthropometric and serological biomarker variables were measured both at baseline and at the 12-week follow-up. Wilcoxon signed-rank test and Independent t-test were analyzed for the changes of variables between- and within-groups. Breast cancer survivors showed higher levels of serum sclerostin compared to the age-matched healthy women at baseline (mean±SD; 115.6±58.8 vs. 86.5±53.2 pg/ml, p=0.016). Exercise training for 12 weeks significantly improved the physical fitness including muscle strength, endurance, and flexibility while it reduced the body fat percentage, waist circumference, and visceral fat area in breast cancer survivors (all $p<0.05$). In addition, the exercise training also decreased the serum levels of insulin, leptin, interleukin-8 and -11, and increasedinterlukin-10 (all $p<0.05$). The serum level of sclerostin was also notably reduced in the exercised breast cancer survivors (124.4±17.0 vs. 106.3±42.6 pg/ml, p=0.021). Meanwhile, there was no change of serum sclerostin in the control group during this clinical trial period. Our study showed that the exercise training ameliorated the risk factors associated with poor prognosis of breast cancer. The level of serum sclerostin may be a potential serological biomarker reflecting the beneficial effects of exercise in breast cancer survivors.

Key Words: Breast cancer survivors, Exercise training, Sclerostin, Health-related physical fitness

P5-11

High electrical stimulation of WB-EMS improves adipocytokines, body composition, and isokinetic strength in collegiate male students

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Aim: Exercise training tends to increase fat oxidation and lead to positive changes in the expression of genes essential for fat metabolism. In addition to exercise and diet, sports scientists have developed a new technology called whole-body electromyostimulation (WB-EMS), that can potentially replace exercising at a conventional gym. Even though there is some evidence that WB-EMS favorably improves body condition, the issues have not been confirmed that a dose-response relationship exists between different stimulations and how WB-EMS affects body composition, muscular strength, and inflammation-related conditions. Therefore, this study was designed to investigate the stimulation parameter-effect of WB-EMS exercise on adipocytokines, body composition, and isokinetic strength in healthy men.
Materials and Methods: The subjects were aged between 20 and 31 who were students of Hanseo University. The goal of this study was to recruit healthy male college students who did not exercise regularly for a duration of six months. Participants were randomly assigned to one of four groups: the control group (CG, n=3), low stimulation group (LSG, n=3), mid stimulation group (MSG, n=4), or high stimulation group (HSG, n=4). Participants were given a WB-EMS suit made by the Miracle® (Seoul, Korea) that fit their individual size. They wore their wet innerwear during the stimulation session. WB-EMS equipment used in this study enables the simultaneous activation of 8-12 muscle groups. The stimulation-frequency was selected at 85 Hz, the impulse-width at 350 microseconds and the impulse-rise as direct application. Impulse duration was 6 seconds with a 4 second break between impulses. Three groups underwent 20-minute WB-EMS-sessions 3 times a week for 6 weeks. Measurement variables included adipocytockines taken from blood samples, body composition measured by bioelectrical impedance analysis (BIA) and computer tomography (CT), and muscular functions measured by an isokinetic machine.
Results: First, although there were no significant differences in all of the variables among groups and testing intervals during 6 weeks, the visfatin and resistin of MSG and HSG showed decreasing tendencies whereas adiponectin of all electrically stimulated groups represented increasing tendencies. Second, the body weight and body mass index of HSG decreased significantly from Week 0 to Week 6 as measured by BIA. Although there were no significant differences among groups and intervals in the abdominal CT, the abdominal visceral fat, subcutaneous fat, and total fat of HSG showed continuously decreasing tendencies from Week 0 to Week 6. Specifically, the thigh subcutaneous and total fat masses of HSG were significantly decreased throughout the 6 weeks. Third, right flexor peak torque at Week 6 was significantly higher in HSG compared with those of the other three groups. All work per repetition (WRs) of HSG showed higher tendencies and WRs of the right and left flexors at Week 6 were significantly higher in HSG than those of the other three groups. The total work (TW) of the right flexor at Week 6 and TW of the left flexor at Week 2 were significantly higher in HSG compared with those of the other three groups.
Conclusion: This study confirmed that the high electrical stimulation of WB-EMS can improve adipocytokines, body composition, and isokinetic strength in collegiate male students.

Acknowledgement: This study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A1B03034766).

Key Words: Whole-body electromyostimulation, Body composition, Computed tomograph, Adipocytokine, Isokinetic muscle function

P6-01

Spirodela polyrhiza and its chemical constituents vitexin exert anti-allergic effects *via* ORAI1 channel inhibition

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Intracellular calcium signaling cascades are integral to early and late allergic responses involving mast cell degranulation and type 2 helper T cell activation, respectively. Both responses are accompanied by calcium movement through the calcium release-activated calcium (CRAC) channel, encoded by the *ORAI1* gene. *Spirodela polyrhiza* (L.) Schleid (SP) has anti-inflammatory and anti-allergic effects, but its effects on calcium signaling have not been reported. This study investigated whether a 30% ethanolic SP extract (SP_{EtOH}) and its constituents could reduce CRAC currents (I_{CRAC}), and thus inhibit mast cell degranulation and T cell activation. In Jurkat T lymphocytes, we found that 3 mg/mL SPEtOH inhibited ICRAC by 81.0±11.1%, while one of its constituents (vitexin; 100 μM) inhibited ICRAC by 48.9±8.71%. Investigation of human primary T cell proliferation induced by co-stimulation with antibodies to cluster of differentiation 3 and 28, and of RBL-2H3 mast cell degranulation following IgE-antigen complex stimulation, revealed that 100 μM vitexin inhibited both T cell proliferation (by 34.8±6.08%) and mast cell degranulation (by 36.7±0.07%); these effects were concentration-dependent and no cytotoxicity was observed. Our findings suggest that vitexin represents a promising candidate compound for the development of therapeutic agents for the prevention and treatment of allergic diseases.

Key Words: *Spirodela polyrhiza*, Vitexin, Apigenin 7-O-glucoside, Calcium release-activated calcium channel, ORAI1, Anti-allergic effect

P6-02

Spirodela polyrrhiza extract and its flavonoid luteolin inhibit Cl^- secretion in human airway epithelial cells *via* the calcium-dependent Cl^- channel anoctamin-1

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Spirodela polyrhiza (SP) is used for the treatment of urticarial, allergic, and non-allergic inflammation in traditional Korean medicine. Previous studies have shown that SP can suppress pro-inflammatory cytokine secretion, histamine release, and associated ion channel inhibition in atopic dermatitis. However, the effects of SP in other allergic diseases such as allergic rhinitis have not been studied. In the present study, we investigated whether SP can regulate the activity of anoctamin-1 (ANO1), which is an ion channel associated with nasal hypersecretion in allergic rhinitis. A 30% ethanolic extract of SP (SP_{EtOH}) and its five major flavonoids constituents in SP_{EtOH} were prepared. To elucidate whether human ANO1 activity is modulated by SP_{EtOH} and its chemical constituents, a conventional whole-cell patch clamp was performed in hANO1-overexpressing HEK293T cells. We also investigated whether calcium-activated chloride channel current (I_{CaCC}) and cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride current (I_{CFTR}) in human airway epithelial cells (Calu-3) are modulated by SP_{EtOH} and its chemical constituents. SP_{EtOH} (30, 100 and 300 μg/ml) and luteolin, one of the major chemical constituents in SP_{EtOH}, significantly inhibited hANO1 activity in the HEK293T cells. In addition, SP_{EtOH} and luteolin specifically modulated I_{CaCC} but not I_{CFTR} in the Calu-3 cells. The half-maximal inhibitory concentration (IC_{50}) of luteolin against I_{CaCC} was found to be 27.91±1.61 μM. SP_{EtOH} and luteolin suppress ANO1 activity; therefore, they may be suitable candidates for development as potent agents for the prevention and treatment of allergic rhinitis.

Key Words: *Spirodela polyrhiza*, Luteolin, Anoctamin-1, Calcium activated Cl^- channel, Allergic rhinitis, Airway hypersecretion

P6-03

Acceleration of skin barrier restoration by Korean herbs via transient receptor potential V3

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Intracellular Ca^{2+} signaling via various calcium channels such as Orai1 and transient receptor potential (TRP) channels has been shown to directly modulate epidermal proliferation, differentiation, and barrier homeostasis. Ca^{2+} influx through these channels eventually generates intracellular Ca^{2+} signals that result in different outcomes that are dependent on the individual Ca^{2+} channel type. Among them, TRP cation channel subfamily vanilloid (V) member 3 (TRPV3) was initially proposed as a thermosensor in the human body. However, it was recently reported that TRPV3 is functionally expressed in human keratinocytes. TRPV3 activation increased intracellular Ca^{2+}signaling, which in turn increased the activities of transglutaminase (TGase) 1 and 3, as well as the subsequent formation of cornified cell envelopes in the epidermis. It was also reported that the activation of TRPV3 promotes epithelial cell proliferation and wound healing in the oral epithelium. Therefore, these results suggest that TRPV3 activation could be a potential therapeutic target for skin barrier recovery in various dermatological diseases. To identify botanically derived extracts and its chemicals for use in topical agents for dermatological diseases, we prepared extracts of 26 medicinal herbs, performed bioassay-guided fractionation of the active extracts, and then isolated and identified the bioactive constituents. By performing whole-cell patch-clamp studies, we found 11 medicinal herb fractions that showed significant TRPV3 activation at 100 μg/mL. We analyzed the chemical constituents that showed agonistic effects on TRPV3 and identified γ-schisandrin as a potential agonist. We also confirmed that topical application of active extracts and chemicals improved the recovery of skin barrier disruption induced by tape stripping of murine dorsal skin. Since most regional plants have not been investigated chemically or pharmaceutically, they remain as untapped potential sources of topical agents for drugs. Therefore, our study provides the concept and tools for the potential clinical application of botanically derived extracts for abnormal skin barrier functions, such as atopic dermatitis, elastosis, and contact dermatitis.

Key Words: Skin barrier, TRPV3, Transglutaminase, Agrimonia pilosa, Schisandra chinensis, γ-schisandrin, Tape stripping test

P6-04

Systems-level mechanisms of action of *Panax ginseng*: a network pharmacological approach

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Panax ginseng has long been used since ancient times based on Traditional Asian Medicine theory and clinical experiences, and currently, is one of the most popular herbs in the world. To date, most of the studies with *P. ginseng* have focused on specific mechanism of actions of individual constituents. However, in spite of many studies on the molecular mechanisms of *P. ginseng*, it still remains unclear how multiple active ingredients of *P. ginseng* interact with multiple targets simultaneously, giving the multidi-

mensional effects on various conditions and diseases. In order to decipher the systems-level mechanism of multiple ingredients of *P. ginseng*, a new approach is needed beyond conventional reductive analysis. The aim of this paper is to review the systems-level mechanism of *P. ginseng* by adopting a novel analytical framework-network pharmacology. Here, we constructed a compound-target network of *P. ginseng* using experimentally validated and machine leaning-based prediction results. The targets of the network were analyzed in terms of related biological process, pathways, and diseases. It turned out that majority of targets were related with primary metabolic process, signal transduction, nitrogen compound metabolic process, blood circulation, immune system process, cell-cell signaling, biosynthetic process, and neurological system process. In pathway enrichment analysis of targets, mainly the terms related with neural activity showed significant enrichment and formed a cluster. Finally, relative degrees analysis for target-disease association of *P. ginseng* revealed several categories of related diseases including respiratory, psychiatric, and cardiovascular diseases.

Key Words: *Panax ginseng*, Network pharmacology, Polypharmacology, Traditional Asian medicine

P6-05

Sargacromenol D from Sargassum siliquastrum as a novel selective L-type Ca^{2+} channel blocker

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A specific blocker of L-type Ca^{2+} channels may be useful in decreasing arterial tone by reducing the open-state probability of L-type Ca^{2+} channels. The aim of the present study was to evaluate the sargacromenol D, which are major active constituents of Sargassum siliquastrum, regarding their vasodilatation efficacies, selectivities toward L-type Ca^{2+} channels, and in vivo antihypertensive activities. The application of sargacromenol D induced concentration-dependent vasodilatation effects on the basilar artery that was pre-contracted with depolarization and showed ignorable the potential role of endothelial-derived nitric oxide. We also tested sargacromenol D to determine their pharmacological profiles for the blockade of native L-type Ca^{2+} channels in cloned L- (α1C/β2a/α2δ), N- (α1B/β1b/α2δ), and T-type Ca^{2+} channels (α1G, α1H, and α1I). Sargacromenol D showed greater selectivity toward the L-type Ca^{2+} channels among the tested voltage-gated Ca^{2+} channels. Based on a comparative analysis of the pharmacological data, the ranked order of the potency of sargacromenol D was cloned L-type (α1C) > cloned N-type (α1B) > cloned T-type (α1H) > cloned T-type (α1I) > cloned T-type (α1G) Ca^{2+} channels. However, sargacromenol D was not sensitive to hERG channels. The oral administration of the sargacromenol D (80 mg/kg) conferred potent, long-lasting antihypertensive activity in spontaneous hypertensive rats, but it did not alter the heart rate.

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Key Words: Sargacromenol D, L-type Ca^{2+} channel, Vasodilatation, Hypertension

P6-06

Novel synthetic antihypertensive agents from the marine naturo-mimetics

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Curcumin isolated from the root of Curcuma longa L. has versatile and useful biological properties. It shows anti-inflammatory, antioxidant, antiviral, chemopreventive, anti-infective, and wound-healing properties. In this study, we synthesized a library of curcumin mimics with diverse alkylsulfonyl and substituted benzenesulfonyl modifications through a simple addition reaction of important intermediate, 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone, with various sulfonyl chloride reactants and then tested their vasodilatation effect on depolarization (50 mM K+)- and endothelin-1 (ET-1)-induced basilar artery contraction. Generally, curcumin mimics with aromatic sulfonyl groups showed stronger vasodilation effect than alkyl sulfonylated curcumin mimics. Among the tested compounds, six curcumin mimics (11g, 11h, 11i, 11j, 11l, and 11s) in a depolarization-induced vasoconstriction and seven compounds (11g, 11h, 11i, 11j, 11l, 11p, and 11s) in an ET-1-induced vasoconstriction showed strong vasodilation effect. Based on their biological properties, synthetic curcumin mimics can act as dual antagonist scaffold of L-type Ca^{2+} channel and endothelin A/B2 receptor in vascular smooth muscle cells. In particular, compounds 11g and 11s are promising novel drug candidates to treat hypertension related to the overexpression of L-type Ca^{2+} channels and ET peptides/receptors-mediated cardiovascular diseases.

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Key Words: Naturo-mimetics, L-type Ca^{2+} channel, Endothelin, Vasodilatation, Hypertension

P6-07

Symptom regulating effects of *Quisqualis indica linn* in benign prostatic hyperplasia rat model

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Benign Prostate Hyperplasia (BPH) is a common disease in old-age-male, has about 77% of morbidity from 40s to 70s. It is shown that morbidity would be increased with social graying. Meanwhile, *Quisqualis indica linn* (QI) has been used for treating inflammation, stomach pain and digestion problem. Our study was aimed to evaluate the symptom regulating effects of QI extract on testosterone induced BPH rat model. After induce BPH rat model, we assessed basal intraurethral pressure (IUP) and increments of IUP elicited by electrical-field stimulation (5V, 5, 10, 20 Hz) or Phenylephrine (Phe) (0.01, 0.03, 0.1 mg/kg IV). After measured IUP, Low urinary track (LUT), Ventral prostate (VP), Testicle and corpus spongiosum were weighting by autopsy. For inducing BPH, 8 weeks rats were subjected to a Testosterone propionate (TP) (3 mg/kg) subcutaneous injection daily for 4 weeks. The rats in treatment groups were QI (150 mg/kg. PO) and Finasteride (Fina) (10 mg/kg PO) as standard drug together with the TP injection respectively. In results, basal IUP of Fina group was 87.6% of BPH group, and QI group was almost same 86.8%. Either in electrical stimulation or Phe induced IUP increase, QI group was significantly decreased compared to BPH and Fina group. However in LUT and VP organs weighting QI group was tend to less decreased compared to Fina group, Testicle and corpus spongiosum were show no tendency. In conclusions, these results suggest that QI can be beneficial on BPH symptom regulating and it also a little effect on decreasing

LUT and VP organ size.

Key Words: BPH, *Quisqualis indica linn*, Intraurethral pressure, Lower urinary tract symptoms

P6-08

Echinochrome A increase the mass and function of the mitochondria by upregulation of mitochondria biogenesis genes

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Echinochrome A (Ech A) is a substance extracted from sea urchin, and is known to have antioxidant and cardioprotective effects against ischemia reperfusion injury. In this study, we investigated whether mitochondrial biogenesis and oxidative phosphorylation in cardiomyoblast H9C2 cells are due to Ech A. To study the effects of Ech A on mitochondrial biogenesis, we measured mitochondrial mass, level of oxidative phosphorylation, and mitochondrial biogenesis regulatory gene expressions. As a result, it has been shown that Ech A does not cause cytotoxicity. However, it enhanced oxygen consumption rate and mitochondrial ATP level. Likewise, treatment with Ech A increased mitochondrial content in h9c2 cells. Furthermore, treatment with Ech A upregulated biogenesis of regulatory transcription genes, including proliferator-activated receptor gamma co-activator (PGC)-1α, estrogen-related receptor (ERR)-α, peroxisome proliferator-activator receptor (PPAR)-γ, and nuclear respiratory factor (NRF)-1 and such mitochondrial transcription regulatory genes as mitochondrial transcriptional factor A (TFAM), single strand binding protein (SSBP). In conclusion, these data suggest that Ech A is a potentiate marine drug which enhances mitochondrial biogenesis.

Key Words: Echinochrome A, Mitochondria biogenesis, Oxygen consumption rate

P6-09

HS1793 compound activates PGC-1α via AKT/mTOR signaling and improves mitochondrial biogenesis and function in mouse skeletal muscle cell model

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In this study, we focused on targeting the mitochondria to regulate energy homeostasis through HS1793, a novel and potent analogue of resveratrol. We first determined the most effective dosage at which HS1793 takes effect in mouse myoblast C2C12 cells. Dosage screening was performed by evaluating for cytotoxicity and cell proliferation, which showed that higher than 10 μM are were anti-proliferative and detrimental to the cells. The succeeding experiments used dosages lower than 10 μM. Mitochondrial mass, mitochondrial membrane potential, reactive oxygen species (ROS) level, and mitochondria biogenesis-regulated genes were analyzed to determine the effects on mitochondrial biogenesis. HS1793 reduced ROS generation, but treatment did not interfere with cellular viability at low dosages. HS1793 also enhanced mitochondrial biogenesis function by increasing cellular and mitochondrial ATP synthesis function, but induced multinucleation in cells as an adaptive response. HS1793 also upregulated vital mitochondrial biogenesis-related genes such as PGC1-α, activated by AKT and mTOR, which are considered as important regulators of skeletal muscle function. When taken altogether, it shows the viability of HS1793 as a compound that can restore mitochondrial function and promote myogenesis and hypertrophy, especially in cancer wasting.

References
1. Hong et al. J Biol Chem. 2014 Jul 18;289(29):20012-25.
2. Jeong et al. Mar Drugs. May 2014;12(5): 2922-2936.
3. Jeong et al. Int J Oncol. 2009 Dec;35(6):1353-60.
4. Kim et al. International journal of oncology 43.6 (2013): 1915-1924.
5. Kitada et al. Diabetes. 2011 Feb;60(2):634-43. doi: 10.2337/db10-0386.
6. Song et al. Bioorg Med Chem Lett. 2007;17:461-464.

Key Words: Mitochondria, Skeletal cell, HS1793, PGC-1α, AKT

P6-10

Polygoni avicularis (*polygonum aviculare* L.) improves diabetic nephropathy in db/db mice

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Progressive diabetic nephropathy (DN) in diabetes leads to major morbidity and mortality. The glomerulus damaged by renal inflammation and fibrosis increase diabetic nephropathy. Polygonum avicularis L. (PA), is used in traditional oriental medicine and has traditionally been used as a diuretic, astringent, insecticide, and antihypertensive. However, improving effects of PA on diabetic nephropathy have not been assessed until now. This study aimed to identify the effect of PA on diabetic nephropathy and investigate its action mechanisms in type 2 diabetic mice model. PA were administrated to db/db mice (n=8) to 10 or 50 mg/kg/day concentrations. The experiment was measured for 8 weeks following PA treatment respectively. As a result, PA group significantly ameliorated oral glucose tolerance test (OGTT), blood glucose, insulin, HOMA-IR and HbA1c of diabetic index. PA significantly improved volume, albumin excretion, urea, electrolyte and osmolality in urine. PA dramatically reduced creatinine clearance (Ccr) and kidney injury molecules-1 (KIM-1) of kidney function index and C-reactive protein (CRP) of inflammation marker. In addition, PA significantly suppresses intercellular adhesion molecule-1 (ICAM-1) and Monocyte chemoattractant protein-1 (MCP-1) of inflammation cytokines. In histopathologic study, PA attenuated glomerular expansion and tubular fibrosis. TGF-β and smad signal associated with kidney fibrosis mechanism significantly suppressed by PA treatment. Moreover, PA significantly improved nephrin and podocin expression in glomerulus of cortex. These findings suggest that PA improves diabetics and kidney injury including kidney inflammation and fibrosis in diabetic nephropathy.

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Key Words: *Polygonum avicularis* L. (PA), Diabetic nephropathy (DN), db/db mice, Type 2 diabetic, Kidney injury, Inflammation

P6-11

Ojeoksan suppressed TNF-α-induced vascular inflammation in human umbilical vein endothelial cells

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Vascular inflammation is regarded as an important role in endothelial dysfunction of atherosclerosis. Ojeoksan (OJS), originally recorded in an ancient Korean medicinal book named "Donguibogam", is a well-known blended traditional herbal formula. This study was carried out to investigate the ef-

fect of OJS on tumor necrosis factor-alpha (TNF-α)-induced vascular inflammation in human umbilical vein endothelial cells (HUVECs).
Pretreatment of OJS suppressed TNF-α-induced expression of cell adhesion molecules, such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial selectin in TNF-α-stimulated HUVECs. OJS also decreased the adhesion of HL-60 cells to HUVECs. Moreover, OJS inhibited TNF-α-induced matrix metalloproteinase-2/-9 (MMP-2/-9) expression; significantly decreased TNF-α-induced production of intracellular reactive oxygen species (ROS); and inhibited the phosphorylation of IκB-α in the cytoplasm. Pretreatment with OJS also inhibited the translocation of NF-κB p65 to the nucleus. TNF-α significantly increased protein expression while the pretreatment of cells with OJS inhibited the protein expression of TLR-2/-4, and MyD88. OJS increased the phosphorylation of endothelial nitric oxide synthase (eNOS) and Akt (protein kinase B) which are related with NO production. In addition, OJS increased the protein expression of Nrf2 and HO-1 in TNF-α-stimulated HUVECs, suggesting its protective effect against vascular inflammation. OJS also inhibited phosphorylation of MAPKs.
Taken together, Ojeoksan has a protective effect on vascular inflammation, and might be a potential therapeutic agent for early atherosclerosis.

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Key Words: Ojeoksan, HUVECs, TNF-α, Vascular inflammation, Adhesion molecules, NF-κB, TLR, NO, HO-1, MAPKs

P6-12

Dianthus superbus attenuates angiotensin II-induced glomerular fibrosis in human renal mesangial cells

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Glomerular fibrosis is caused by accumulation of extracellular matrix (ECM) proteins in the mesangial interstitial space resulting in fibrosis manifested by either diffuse or nodular changes. *Dianthus superbus* belongs to the Caryophyllaceae family and has been used in traditional medicine as a diuretic, a contraceptive, and an anti-inflammatory agent. The aim of this study was to investigate the effects of *Dianthus superbus* on angiotensin II (Ang II)-stimulated glomerular fibrosis in human renal mesangial cells.
Dianthus superbus pretreatment attenuated inflammatory factors such as intracellular cell adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1). Additionally, *Dianthus superbus* suppressed transforming growth factor β (TGF-β)/Smad signaling pathway. Collagen type IV, glomerular fibrosis biomarker, was significantly decreased by *Dianthus superbus*. Moreover, *Dianthus superbus* inhibited translocation of nuclear factor kappa B (NF-κB) in Ang II-stimulated mesangial cell. This study further revealed that *Dianthus superbus* significantly improved Ang II-induced reactive oxygen species (ROS) in a dose dependent manner.
These findings suggest that *Dianthus superbus* have protective effect against renal inflammation, fibrosis and oxidative stress. Therefore, *Dianthus superbus* may be potential therapies targeting glomerulonephritis and glomerulosclerosis leading to diabetic nephropathy.

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Key Words: *Dianthus superbus*, Angiotensin II, Mesangial cell, Fibrosis

P6-13

Korean red ginseng ameliorates high fat/high cholesterol diet-induced hypertriglyceridemia and endothelial dysfunction

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Korean Red Ginseng (RG) are used as a traditional treatment for improve blood circulation. This experimental study was designed to investigate the inhibitory effects of JinAn Red Ginseng on lipid metabolism in high fat/cholesterol diet (HFCD)-induced hypertriglyceridemia. Sprague Dawley rats were fed the HFCD diet with/without fluvastatin (Flu, positive control) 3 mg/kg/day, and RG 125 or 250 mg/kg/day, respectively. All groups received regular diet or HF diet, respectively, for 13 weeks. The last three groups treatment of Flu and RG125, and RG250 orally for a period of 9 weeks. Treatment with low or high doses of RG markedly attenuated plasma levels of triglycerides and augmented plasma levels of high-density lipoprotein (HDL) in HFCD-fed rats. RG and Flu also led to an increase in lipoprotein lipase activity in the HFCD group. On the other hand, RG and Flu led to a decrease in fatty acid synthase and free fatty acid activity in the HFCD group. Treatment with RG suppressed increased expressions of PPAR-α and AMPK in HFCD rat liver or muscle. In addition, the RG attenuated triglyceridemia by inhibition of PPAR-γ and FABP protein expression levels and LXR and SREBP-1 gene expression in liver or muscle. The RG significantly prevented the development of the metabolic disturbances such as hypertriglyceridemia and hyperlipidemia. Taken together, the administration of RG improves hypertriglyceridemia through the alteration in suppression of triglyceride synthesis and accentuated of triglyceride decomposition. These results suggested that Korean Red Ginseng is useful in the prevention or treatment of hypertriglyceridemia-related disorders such as triglyceride metabolism.

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Key Words: Korean red ginseng, Triglyceride, Hypertriglyceridemia, Triglyceride synthesis, Metabolism

P6-14

Chrysanthemum boreale makino essential oil and its single compound sabinene alleviates starvation-induced atrophy in L6 cells

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Essential oil of *Chrysanthemum boreale* Makino (CBM) has diverse biological activities including skin regeneration and antibacterial action. However, no investigation on its muscle atrophy has been reported. In the present study, we explored the effects of CBM essential oil and its single compounds on L6 cell atrophy. L6 cell line, rat skeletal muscle cell line (myoblast), was cultivated in unnourished condition of serum-free and low glucose for *in vitro* experimental model of atrophy and was tested by cell toxicity and size, and atrophy marker protein expression alteration. *In vivo* test was performed by rat skeletal muscle atrophy model. Essential oil of CBM recovered decreased

size of cells cultivated in unnourished condition. Among fifteen compounds of essential oil of CBM, 12 compounds did not affect cell viability. Of the twelve compounds, two compounds, eugenol and sabinene induced predominant increase of decreased size of cells cultivated in unnourished condition. Sabinene, which is known to be nontoxic to human, was confirmed to increase the expression of an E3 ubiquitin ligase MuRF-1, an excellent marker of muscle atrophy, in cells cultivated in unnourished condition. In addition, atrophied muscle in starved rat, an *in vivo* animal model of atrophy, was recovered by treatment of sabinene. These results demonstrated that CBM essential oil and its single compound sabinene may promote recovery of starvation-induced atrophy in L6 cells. Therefore, CBM essential oil and sabinene may be promise candidate agents for alleviation of the starvation-induced skeletal muscle atrophy.

Key Words: *Chrysanthemum boreale* makino essential oil, Skeletal muscle, Atrophy, Sabinene, L6 cell

P6-15

Flos Magnoliae and its chemical constituents modulates Cl^- secretion *via* ANO1 Cl^- channel inhibition in human airway epithelial cells

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Flos Magnoliae (FM, Chinese name: Xin-yi) is an oriental medicinal herb commonly used for symptomatic relief from allergic rhinitis, sinusitis, and headache. FM has also been used in traditional Chinese and Korean medicine formulations. It has been reported to inhibit histamine release from mast cells and cytokine secretion from T cells. However, the mechanism of action of FM on anoctamin-1 (ANO1) ion channel, which is responsible for nasal hypersecretion in allergic rhinitis, has not been elucidated. Therefore, we investigated whether FM and its chemical constituents can regulate the activity of ANO1. A 30% ethanolic extract of FM (FM_{EtOH}) was prepared and five major constituents of the extract were identified. By using a conventional whole-cell patch clamp, we revealed that FM_{EtOH} (30, 100, and 300 μg/mL) and its chemical constituent tiliroside inhibited ANO1 activity in ANO1-overexpressing HEK293T cells. In addition, we showed that the treatment of the airway epithelial cell line Calu-3 with 100 ng/ml IL-4 significantly increased ANO1 current (IANO1), but not cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride current (I_{CFTR}). IANO1 was specifically modulated by FM_{EtOH} and tiliroside. In this study, we identified a novel mechanism underlying the alleviation of allergic rhinitis by FM_{EtOH}. FM_{EtOH} and its chemical constituent tiliroside can be potent agents for the prevention and treatment of allergic rhinitis.

Key Words: *Flos Magnoliae*, Tiliroside, Allergic rhinitis, Hypersecretion, ANO1, Calcium-activated chloride channel, Anti-allergic effect

P7-01 (PO-B-07)

Mesothelial cells demarcate the subunits of organ surface primo vascular tissue

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Primo-vascular system (PVS) composed of primo nodes (PN) and primo vessels (PV) has been identified in various animal tissues. Previously, the outer layer of organ surface PN (osPN) was densely stained with Hemacolor in slice (200 μm in thickness). In this study, we examined the morphological features of the outer layer of osPVS tissue of rats. For the sampling of the tissue, milky colored and semi-transparent osPVS tissue was collected on the surface of internal organs in the peritoneal cavity of rats under a stereomicroscope with 10-20x. For the identification of the cellular morphology of osPVS, samples were sectioned at 4 and 20 μm in thickness and then stained with hematoxylin and eosin (H&E, Harris hematoxylin solution; Eosin Y solution, Sigma) and 4′,6-Diamidino-2-Phenylindole (DAPI, Immuno-BioScience, AR-6501-01). In the section (20 μm) of the osPN stained with DAPI and H&E, the cell density is 1.3-folds higher in the outer layer than that in the inner layer ($P<0.001$). In the thin section (4 μm) of the osPN and osPV, we found flattened cells and the basement membrane, which were linearly aligned along the boundary surface of the osPN and osPV. Based on the morphology, the flattened cells were considered as visceral mesothelium. An osPVS tissue is consisted of multiple subunits demarcated by mesothelial cells. In conclusion, this study shows that there is a single layer of the visceral mesothelium located on the surface of osPVS. The results also suggest that one osPVS is composed of multiple independent subunits demarcated by these mesothelial cells and basement membranes. Our findings will help to further elucidate the inner structure and function of the PVS as a circulatory channel.

Key Words: Organ-surface PVS, Primo-node, Primo-vessel, Outer layer, Basement membrane

P7-02

Sex difference of feeding behavior and gastrointestinal function in response to stress in rat

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Background/Aims: Stress could affect appetite and bowel function. The aim of this study is to investigate the difference of eating behavior and gastric motility according to the type of stressor, sex in rat and type of food.
Methods: Both sex of Spargue-Dawely rats were used. All rats underwent foot shock stress (FSS) for 5 minutes one day before experiment. We used two type of stressor physical stress "FSS" as physical stress and "watching other rat exposed to FSS" as psychological stress. In each type of stress, rats were randomly divided into three groups as (1) regular food supply before stress, (2) regular food supply after stress, and (3) concomitant regular and sweet food supply after stress in male and female, respectively. After stress session, food consumption, gastric emptying (GE), and sweet food preference, serum ACTH/corticostereone were measured in all rats.
Results: In male rats, both psychological and physical stress decreased the food consumption. In female rats, however, only physical stress decreased the food consumption. When food was supplied before stress, both psychological and physical stress delayed GE during stress in male rat. In female rats, however, only physical stress delayed GE during stress. When food was supplied after stress, physical stress increased GE in both male and female, however psychological stress showed no effect on GE. Restoration of stress-induced eating inhibition by concomitant sweet food was observed only in males rats exposed to physical stress.
Conclusions: These results indicate that sex as well as type of stressor is a crucial factor affecting on feeding behavior and gastric motility in stress response in rat.

Key Words: Sex difference, Foot shock stress, Psychological stress, Gastric emptying

P7-03

The effects of aerobic circulation on the body composition of obese men consuming LCHF

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This study aims to investigate the effect of aerobic circulation on the body

composition of obese men consuming LCHF. The subjects were participated as male with a BMI of 25 kg/m^{2}or more and were assigned to exercise and control groups. Paired T-test from SPSS was used to analysis the differences between groups.
The experimental results are as follows for 8 weeks. Body composition, BMI, body fat, body fat and visceral fat were significantly decreased in both groups and there was no change in muscle mass. Also there was no difference between the exercise group and control group. The intake LCHF in body composition was more affected than aerobic exercise. Obesity is important for men to diet. Also it is important to reduce carbohydrates and to consume protein and fat. During the LCHF diet, the muscle mass was reduced to a small extent.
For obese men, the LCHF diet is effective in reducing body fat, but it will be necessary to find efficient ways to diet and exercise according to the degree of obesity.

Key Words: LCHF, Aerobic, Body fat, Muscle mass

P7-04

Necrox-5 exerts anti-inflammation and regulates mitochondrial biogenesis in hypoxia-reoxygenation (HR) treated rat hearts

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NecroX compounds have been shown to protect the liver and heart from ischemia-reperfusion injury. In this study, we verified whether the Necrox-5 modulates cardiac proteomic alteration and mitochondrial biogenesis, inflammation and fibrosis responses in a hypoxia-reoxygenation (HR) treated rat heart. Necrox-5 treatment (10 μM) and non-treatment were employed on isolated rat hearts during hypoxia/reoxygenation treatment using an ex vivo Langendorff system. Level of mitochondrial biogenesis related proteins has dramatically decreased and level of pro-inflammatory proteins was increased in HR treatment heart. However, treated with NecroX-5 significantly attenuated those HR-induced proteomic alterations, practically which are involved in oxidative phosphorylation and metabolic function. NecroX-5 treatment improved mitochondrial complex activities, markedly higher peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) expression levels were observed in NecroX-5-treated group. In addition, HR- or LPS-induced TNF-α and TGF-β1 and phosphorylation of Smad2 productions were reduced with NecroX-5 supplement. The findings suggested the cardio-protective effect of NecroX-5 against cardiac HR injuries by modulating mitochondrial biogenesis and exerting anti-inflammation actions.

References

1. Thu, V. T., et al. (2012). "NecroX-5 prevents hypoxia/reoxygenation injury by inhibiting the mitochondrial calcium uniporter." Cardiovasc Res 94(2): 342-350.
2. Thu, V. T., et al. (2016). "NecroX-5 protects mitochondrial oxidative phosphorylation capacity and preserves PGC1alpha expression levels during hypoxia/reoxygenation injury." Korean J Physiol Pharmacol 20(2): 201-211.
3. Thu, V. T., et al. (2016). "NecroX-5 exerts anti-inflammatory and anti-fibrotic effects via modulation of the TNFalpha/Dcn/TGFbeta1/Smad2 pathway in hypoxia/reoxygenation-treated rat hearts." Korean J Physiol Pharmacol 20(3): 305-314.

Key Words: NecroX-5, Hypoxia/reoxygenation, Inflammation, Mitochondria

P7-05

^{1}H-NMR-based metabolomic studies of bisphenol A in zebrafish (Danio rerio)

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Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy was used to study the response of zebrafish (Danio rerio) to increasing concentrations of bisphenol A (4,4′-(propane-2,2-diyl)diphenol, BPA). Orthogonal partial least squares discriminant analysis (OPLS-DA) was applied to detect aberrant metabolomic profiles after 72 h of BPA exposure at all levels tested (0.01, 0.1, and 1.0 mg/L). The OPLS-DA score plots showed that BPA exposure caused significant alterations in the metabolome. The metabolomic changes in response to BPA exposure generally exhibited non-linear patterns, with the exception of reduced levels of several metabolites, including glutamine, inosine, lactate, and succinate. As the level of BPA exposure increased, individual metabolite patterns indicated that the zebrafish metabolome was subjected to severe oxidative stress. Interestingly, ATP levels increased significantly at all levels of BPA exposure. In the present study, we demonstrated the applicability of ^{1}H-NMR-based metabolomics to identify the discrete nature of metabolic changes.

References

1. Staples CA, Dorn PB, Klecka GM, O'Block ST, Harris LR (1998) A review of the environmental fate, effects, and exposures of bisphenol A. Chemosphere 36: 2149. doi:10.1016/S0045-6535(97)10133-3
2. Baluka SA, Rumbeiha WK (2016) Bisphenol A and food safety: Lessons from developed to developing countries. Food Chem Toxicol. 92:58. doi: 10.1016/j.fct.2016.03.025.
3. Demierre AL, Peter R, Oberli A, Bourqui-Pittet M (2012) Dermal penetration of bisphenol A in human skin contributes marginally to total exposure. Toxicol Lett. 213(3): 305. doi 10.1016/j.toxlet.2012.07.001
4. Mikolajewska K, Stragierowicz J, Gromadzinska J (2015) Bisphenol A - Application, sources of exposure and potential risks in infants, children and pregnant women. Int J Occup Med Environ Health. 28(2): 209. doi 10.13075/ijomeh.1896.00343
5. Rochester JR (2013) Bisphenol A and human health: a review of the literature. Reprod Toxicol. 42:132. doi 10.1016/j.reprotox.2013.08.008

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Key Words: Bisphenol A, ^{1}H-NMR spectroscopy, Metabolites, Zebrafish (Danio rerio)

P7-06

Morphological changes in organ surface primo vascular tissue in the rats with anemia

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The primo-vascular system (PVS) is a newly identified vascular structure composed of primo-vessels (PV) that connect primo-nodes (PN) and has been observed in various animal tissues. Previously, we suggested that the organ surface PVS (osPVS) may have hematopoietic activity in heart failure rats. However, it is not yet identified which accompanying symptoms of heart failure affected the osPVS tissue. In this study, we investigated the morphological feature of osPVS tissue in anemia, which is known to be associated with heart failure. Anemia was induced by injection of phenylhydrazine (PHZ, 40 mg/kg/day, i.p) for 2 days. Blood samples collected from the orbital blood in a microtainer with EDTA. RBC (red blood cell), WBC

(white blood cell), Hb (hemoglobin), hematocrit, MCH (pg), MCV (fl), and reticulocytes (%) were determined by high-volume hematology analyzer (ADVIA 2120) on day 0, 3, 6, 10. For the sampling of the tissue, milky colored osPVS tissue was collected on the surface of abdominal organs of rats under a stereomicroscope with 10-20x. The RBC, hematocrit, and hemoglobin were decreased at 3rd day after two days PHZ injection. The reticulocytes, WBC, and MCH were increased at 3rd day. While, the MCV increased at 6th day. All the parameters were trend to be normal level at 10th day. Collectively, these blood tests indicated that the hematic parameters were largest variation at 3rd day following the two days continuous PHZ injection. At the 3rd day after PHZ administration, the size of the PNs in rats with anemia was larger than in control rats ($P<0.01$) and the number of osPVS per rat was greater for the anemia rats (11 of 4 control rats vs. 23 of 4 rats; $P<0.01$). In addition, the osPVS number containing red chromophore was greater in anemia rats ($P<0.001$). In conclusion, the results showed the PHZ-induced anemia increased the size and the number of osPVS tissue, which suggest that there may be hematopoiesis in the PVS in diseases accompanied by anemia.

Key Words: Primo-node, Phenylhydrazine, Red blood cells, Reticulocytes, Hematopoiesis

P7-07

Histological features of the hyaluronic acid-rich tissue in subcutaneous layer of rat abdomen

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The primo-vascular system (PVS) is a newly identified vascular tissue that was first reported in the 1960s by BH Kim, who claimed that the PVS is a reality of classical acupuncture meridians. The PVS is composed of nodes and vessels, and has been observed in various sites in the mammalian body. Previous study showed the PVS tissue is present in the subcutaneous layer of rat abdomen and its distribution pattern is similar to the acupuncture meridian. However, its histological feature is largely unknown. In this study, we examined the histology of the tissue using H&E staining. To identify the PVS containing hyaluronic acid contents, the skin slice was stained with 0.1% alcian blue solution. To stain resident cells in the PVS, Hemacolor staining, a system of three solutions (solution 1: methanol fixative; solution 2: eosin stain; solution 3: methylene blue stain) was conducted. To confirm mast cells in the PVS, the skin slice was stained with 1% toluidine blue solution. The PVS tissue was stained light blue with alcian blue dye, which indicated that the tissue was rich in hyaluronic acid. The hyaluronic acid-rich (HAR)-tissue consists of a HAR-node and HAR-vessel and is distributed linearly, along the midline of the abdominal skin. HAR-nodes were at the midpoint (conception vessel acupoint), and both points were about 4 mm (kidney acupoint) or 14-15 mm (stomach acupoint) away from the midpoint in the subcutaneous layer, which indicated that the HAR-nodes were located at the various acupoints. In addition, it was identified that HAR-tissue contains mast cells, arteries, veins, and nerves and is surrounded by fibroblasts and collagen fibers. In conclusion, the present study indicated the HAR tissue in subcutaneous layer is different from the organ surface PVS in terms of its resident cells and structures. Further studies are needed to confirm whether the HAR tissue is belong to the PVS or not.

Key Words: Primo vascular system, Alcian blue, Fibroblasts, Mast cells, Acupoints

P7-08

Sea hare hydrolysates induce M1 macrophage polarization

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Our previous studies have demonstrated that sea hare-derived glycosaminoglycans induce macrophage activation and sea hare hydrolysates (SHH) reduce asthmatic parameters in a mouse model of allergic asthma. These results led us to study the effect of SHH on macrophage polarization. Here, we identified the effects of SHH on macrophage polarization and on phagocytosis of A549 lung cancer cell by macrophage. M1 or M2 macrophage polarization was induced by exposure to lipopolysaccharide (LPS, 1 μg/mL)/interferon (IFN)-γ (20 ng/mL) or IL-4 (10 ng/mL)/IL-13 (10 ng/mL), respectively, in RAW264.7, mouse peritoneal macrophage, and PMA-treated THP-1 cells. The effect of SHH was compared to that of LPS/IFN-γ or IL-4/IL-13 treatments. In RAW264.7 cells, SHH induced macrophage activation showing vacuolization and spreading, like LPS did. In addition, SHH treatment increased TNF-α, IL-1, and IL-6 production and iNOS and TNF-α mRNA expression. However, arginase (Arg)-1, a representative marker for M2 polarization, was not detected in RAW264.7 cells. The Arg-1 transcript was detected in mouse peritoneal macrophage treated with IL-4/IL-13, but not with SHH. In addition, IL-4/IL-13-treated peritoneal macrophage did not express iNOS and TNF-α. Furthermore, SHH promoted phagocytic ability of macrophage. Taken together, these results show that SHH induces M1 polarization and promotes phagocytic ability of macrophage. SHH could be a potential therapeutic agent for cancer immune therapy.

Key Words: Cancer, Macrophage, Sea hare hydrolysates

P7-09

The monosodium iodoacetate (MIA) injection into intervertebral disc of rat accelerate disc degeneration

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Degenerative disc is related to the increased cytokine expression, neo-vasculation and nociceptive nerve innervation. However, there have not been useful animal models to study pathological state of human degenerative disc. In this study, I examined whether MIA injection into the IVD of rat could induce disc degeneration and painful disc. SD rats weighing 250-300 g were used to develop this disc model and divided into 2 groups (sham and MIA 4 mg). Pain behaviors were examined by measuring weight load shift of hind paw to fore paw, rearing number, and mechanical withdrawal in hindpaw. For a single nerve recording of lumbar IVDs, afferents firings evoked by intradiscal pressure were calculated with maximum spikes per second. In addition, to examine the change of inflammatory cytokines expression, IVDs (normal, sham, and MIA 4 mg) were harvested and measured the protein expression level of cyclooxygenase-2 (COX-2) and Interleukin-6 (IL-6) using western blotting. Bone alterations were assessed by microfocal computed tomography (micro-CT).
The 4 mg MIA-injected rats showed the body weight load shift to fore paw

at 7D, 14D, and 21D and the number of rearing is decreased at 14D and 21D after surgery. However, mechanical sensitivity of hind paw did not change in all experimental time. Also, the changes of firing rate of afferents of the IVD in MIA-injected rats induced by intradiscal pressure stimulation were greater than those in control rats. The expression of COX-2 and IL-6 increased in sham and MIA 4mg injected-IVD. Especially, the inflammatory cytokines is more expressed in the MIA injected-IVD. Micro-CT analyses suggested progressive bone deformation in MIA 4mg-injected rat.
These results suggest that MIA injection provides a useful model for studying degenerative changes in the IVD and this IVD degeneration can cause chronic low back pain.

Key Words: Intervertebral disc, Monosodium iodoacetate, Degenerative disc

P7-10

Typing individual breast cancer patients using genomic modules activated in normal breast tissue

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Genome activates as modules composed of genes. The proper regulation of networks among the genomic modules makes a variety of cell phenotypes in normal tissue. When we examined genome activities in normal breast tissue with gene expression data of 28 samples, we found 85 genomic modules, 7 domains of the modules, and the intermodular network. In the study of breast cancer with gene expression data of 248 samples, we found that the genome modules having activated in normal tissue were partly disintegrated or inactivated in cancer. In addition, when modular sample probabilities of the breast cancer samples were measured with the genomic modules of the normal breast, they showed a clear pattern depending on the module domains. The breast cancer samples were classified into 8 sample groups with reference to the modular sample probability. The sample groups showed a pattern of module disintegration in specific domains and transitions of the malignancy. The most benign sample group showed high modular sample probabilities for all genomic modules, while the most malignant sample group showed significantly low probabilities in *ccdr* (for cell cycle regulation and DNA repair), *epi* (for epithelial cells), and *adipo* (for adipocytes) domains. Among the 7 module domains, *epi* domain represented the difference in the breast cancer samples at the most. The sample group having high probabilities at modules in *epi* domain showed significantly longer survival rates, higher percentage of normal cells, and lower percentages of necrosis, tumor cells, and tumor nuclei than the other group ($p<0.01$). This group also included higher rates of ER-positive, PR-positive and/or Her2-positive samples. This indicates that the maintenance of epithelial cells in the breast cancer samples is sample-dependent and can be an indicator of the malignancy of breast cancer. The modular sample probabilities represent the malignancy of individual breast cancer samples. These results hint that cancer has various characteristics depending on the patients and the modular sample probability can be a guideline of the cancer treatment of individual patients.

Key Words: Breast cancer, Genomic module, Module domain, Modular sample probability, Cancer typing

P7-11

Adipose-derived stem cells enhance phagocytic activity of peripheral blood mononuclear cells in a rat model of atopic dermatitis

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Cutaneous infection of *Staphylococcus aureus* (*S. aureus*) is generally observed in the patients with atopic dermatitis (AD). *S. aureus* induces cell apoptosis that is common during bacterial infection and is now considered to be a pivot in the pathogenesis of AD. Apoptosis of immune cells may facilitate *S. aureus* infection and improper clearance of apoptotic cells can aggravate the inflammatory skin disease. Accumulating research data have showed that adipose-derived stem cells (ASCs) improved AD. In the present study, therefore, we examined whether ASCs affected apoptotic cell death and phagocytic clearance of peripheral blood mononuclear cells (PBMCs) using a rat model of AD (Back et al., 2012). AD rats were subjected to intravenous injection of ASCs (1×10^6 cells/30 ul) or culture medium (30 ul without cells) once a week for a month, and then PBMCs were collected one week after the last treatment. Apoptosis and phagocytosis were assayed by flow cytometry using annexin V/7-AAD and CD163 fluorescent staining, respectively. ASCs treatment ameliorated skin diseases and reduced skin colonization with *S. aureus*. In the AD rats treated with ASCs, annexin V/7-AAD double stained cells were significantly reduced compared to the control AD rats. On the other hand, the number of CD163-positive cells and fluorescence of bioparticles in these individual cells were markedly increased in the AD rats treated with ASCs, suggesting the increase of phagocytic activity. Our results indicates that ASCs enhance the phagocytic activity of PBMCs, and therefore, are available for the control of *S. aureus* pathogenesis.

Key Words: Adipose-derived stem cells, Atopic dermatitis, Apoptosis, Phagocytosis, *Staphylococcus aureus*

P7-12

Expression of interleukin-33 induced by inflammatory cytokines in mouse macrophages

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Interleukin (IL) 33, a member of the IL-1 cytokine family, is mainly expressed when cells are stimulated by various types of stress. IL-33 has been reported to be involved in the development of atopic dermatitis through T helper 2 (Th2) and Th1 activation. However, different mechanisms are involved in the expression of IL-33 depending on the cell type, which has not been fully understood. Mouse macrophage cell line, RAW264.7 were treated with pro-inflammatory cytokine lipopolysaccharide (LPS), interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α) IL-33 mRNA expression patterns measured by reverse transcriptase polymerase chain reaction (RT-PCR) were different depending on the inflammatory sources and anti-inflammatory chemicals such as hirsutenone (HIR) or corticosteroid dexamethasone (DEX) or mithramycin A (MMA). With LPS treatment, IL-33 expression was up-regulated, which was not inhibited by anti-inflammatory chemicals. Upon treatment with IFN-γ, IL-33 expression was also up-regulated, which was reduced by HIR or DEX. IL-33 was not expressed by TNF-α. The expression of IL-33 was different in macrophages depending on the type of pro-inflammatory cytokines and anti-inflammatory chemicals. This suggests that IL-33 expression is regulated by a wide variety of factors, and the mechanisms controlling Th2 and Th1 immune responses are also variable. Therefore, elucidation of the mechanism of IL-33 expression is through to be crucial for the understanding of inflammatory pathways involved in certain allergic diseases, and for the development of drugs that block these pathways.

Key Words: Atopic dermatitis (AD), Interleukin 33, Interferon-γ, Macrophage, Th2-immunity

P7-13

Brain function (effects of physical exercise and calorie restriction)

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Brain development is a complex process, and stimuli during this devel-opment period may modulate the functional maturation of the brain.
It has been shown that environmental stimuli, such as physical activity habits, have a beneficial effect on brain development.
Endurance exercise and prolonged fasting state are known to improve brain function including cognition. The exact mechanisms of exercise improving brain function are still unknown. However, it can be considered that energy restriction and stressful challenge induced by long-lasting physical exercise might cause direct effect on brain function.
Up regulation of brain-derived neurotrophic factor and ketone body caused by exercise might be considered as the mechanism of exercise on brain function.
In the present study, we discussed on two main topics: "exercise and BDNF" and "exercise and energy restriction.

Key Words: Physical activity, Energy restriction, Brain-derived neuro-trophic factor, Ketone body

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