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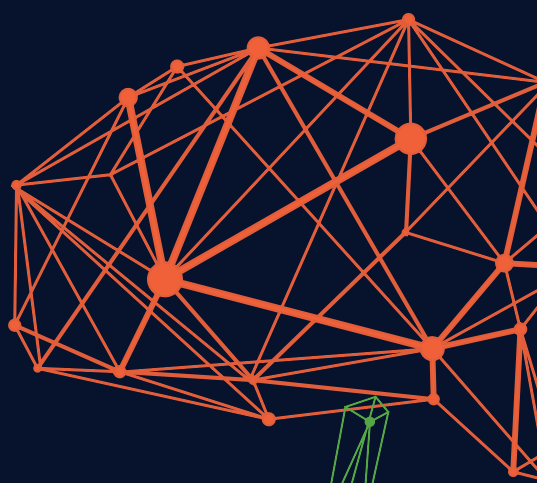

The Korean Journal of Physiology & Pharmacology

October 31 (Thu) - November 2 (Sat), 2019

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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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김정훈 김종연 김진혁 김창주 김형찬 나창수 나흥식 류판동 박경표
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송대규 신동민 신형철 심은보 안덕선 안도환 안동국 안승철 양훈모
연동수 염재범 오석배 오우택 우선희 우재석 윤신희 윤영욱 이 광
이덕주 이무열 이문영 이상진 이석호 이성중 이수환 이영만 이영호
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감 사 양동기 이규필

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Welcome Message

대한생리학회 회원 여러분, 안녕하십니까?

풍요로운 가을이 익어가고 있습니다.

그간 교육과 연구에 몰두하신 여러분의 열정과 기쁨이 드디어 한자리에 모이게 되었습니다. 지난 6월 '실험동물의 생리학적 이해'라는 주제로 기초학술대회부터 시작된 공식적인 행사에 이어 이번에는 여기 대구 영남대학교 의과대학에서 그간의 결실을 알리고 서로 발전할 수 있는 대한생리학회가 벌써 71회 째에 들어섰습니다.

이번에는 "Leading the Future"라는 슬로건에 걸맞게 주로 사카이, 마틴 모라드 등 두 교수님의 Plenary lecture를 비롯해 워크샵, Satellite meeting, 젊은 과학자 세션, 다양하고 9개의 심포지움이 마련되어 있습니다. 올해 심포지움에서는 대사, 줄기세포 및 피부와 이온통로와 운동생리 세션 등 다양하고 흥미로우면서도 중요한 연구주제와 연자로 구성되어 있어 우리 대한생리학회 회원 여러분을 즐겁게 할 것으로 기대하고 있습니다. 이번 프로그램을 마련한 회원 여러분과 이사님들 노고에 진심으로 감사드립니다

오랜만에 다시 만나는 가족의 정으로 가득한 제71회 대한생리학회에서 기쁘고 즐겁게 그간의 결실을 알리고 토론하면서 깊어가는 가을의 풍요로움을 만끽하시기 바랍니다. 끝으로 이 자리를 마련해 주신 영남대학교 의과대학 김종연 학장님과 관계자 여러분께 깊은 감사를 학회를 대표하여 우리 회원님의 고마움을 전하고자 합니다.

회원 여러분 또 다시 만날 때까지 행복하시기를 기원합니다.

대한생리학회 회 장 **홍 성 근**
대한생리학회 이사장 **서 인 석**

주관교 환영사

회원 여러분 안녕하십니까?

제71회 대한생리학회 학술대회를 영남대학교 의과대학에서 개최하게 된 것을 영광으로 생각합니다. 영남의대는 제40회 학술대회를 경주에서 주관하였으며, 올해는 개교 40주년이 되는 해에 학회를 의대 캠퍼스에서 개최하게 되어 더욱 뜻깊습니다. 그동안 우리 학회는 영남대학교의 창학 역사와 같은 1947년에 결성된 이후로 괄목할 만한 양적 및 질적 성장을 이루었습니다. 이러한 성장에는 경제발전과 국력의 신장이 큰 역할을 하였으며, 지금은 선진국 수준의 의학 연구와 의료 서비스로 인류 건강 향상에 이바지하고 있습니다. 우리나라의 의학 발달에는 생명의 본질을 연구하는 생리학의 기여를 결코 간과할 수가 없을 것입니다.

이번 학술대회에서는 미래 생명과학을 선도하는 학문적 성과의 공유와 더불어 회원 여러분의 친목도 돈독히 하시기를 바랍니다. 마지막으로 학회의 성공적인 개최를 위하여 애쓰신 홍성근 대한생리학회장님과 서인석 이사장님 이하 모든 임원과 관계자 여러분께 감사드리고, 또한 영남의대 생리학교실 교직원과 대구.경북 생리학연구회 교수님들께도 깊은 감사 말씀 드립니다.

영남대학교 의과대학 생리학교실 **김 종 연**

Schedule (일정표)

▶ 10월 31일 목요일

Time	Contents
12:00–12:30	Registration
12:30–13:20	**Laboratory Workshop with Lunch Box**
13:20–13:30	Opening Remarks
13:30–15:00	**Special Academic Session: Systems biology for physiologists**
15:00–15:20	Coffee Break
15:20–16:10	**Poster–Oral Session**
16:20–18:40	**Young Physiologists' Session**
18:40–20:00	Welcome Reception with Poster Session

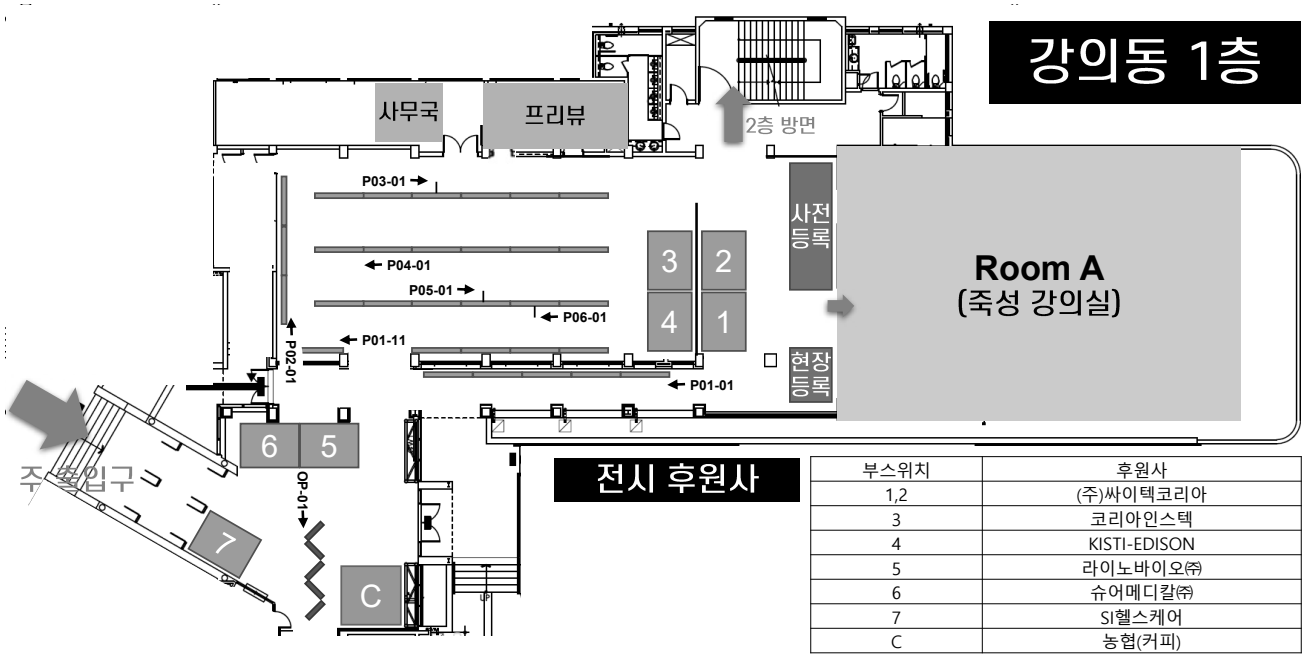
▶ 11월 1일 금요일

Time	Contents		
	Room A	Room B	Room C
09:00–10:40	**Symposium 1**: Modeling pathologic pain	**Symposium 2**: Pathophysiology of metabolic diseases	**Symposium 3**: Multifaceted functions of ion channels
10:40–11:00	Coffee Break		
11:00–11:45	**Plenary Lecture 1**: Juro Sakai (Univ. Tokyo, Japan)		
11:45–12:30	**Plenary Lecture 2**: Martin Morad (Medical Univ. South Carolina, USA)		
12:30–13:40	Lunch / Committee Meeting		
13:40–14:40	**Poster Session – 2**		
14:40–15:00	Coffee Break		
15:00–16:40	**Symposium 4**: Physiology of higher nervous functions	**Symposium 5**: Cardiac physiology and pathophysiology	**Symposium 6**: Stem cell physiology; beyond the limits
16:40–18:00	Move & Relax		
18:00–20:00	Official Buffet		

▶ 11월 2일 토요일

Time	Contents		
	Room A	Room B	Room C
09:00–09:40	**Yudang Lecture**		
09:40–10:00	Coffee Break		
10:00–11:40	**Symposium 7:** Exercise physiology	**Symposium 8:** Skin pathophysiology and ion channels	**Symposium 9:** Altered shape and work of mitochondria
11:40–12:10	**General Assembly**		
12:10–12:20	Closing Remarks		

Venue Guide (학술대회장 안내)



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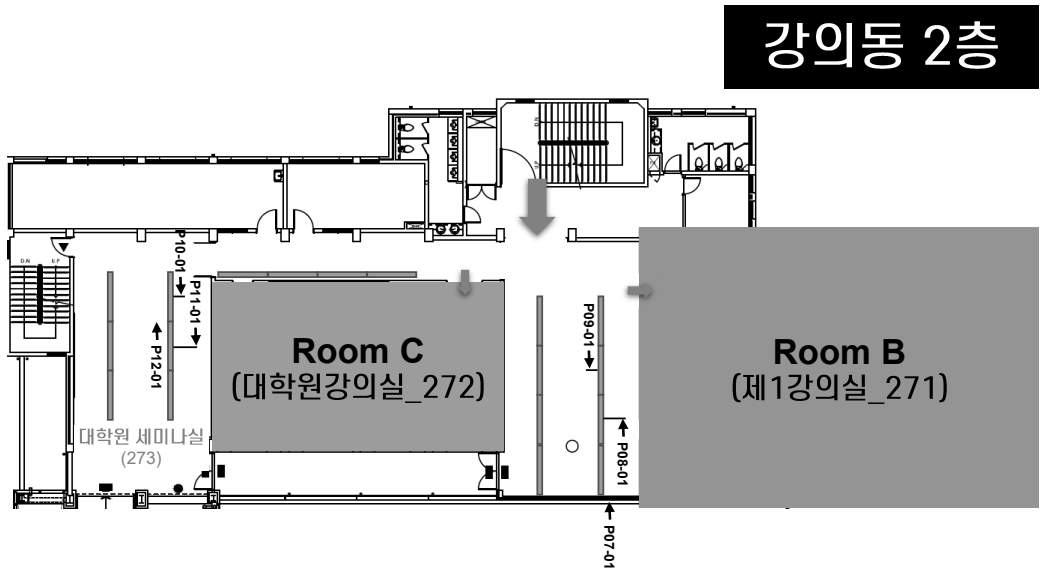

▶ Special Academic Session (10월 31일 목요일)

Contents		
Systems biology for physiologists (13:30–15:00)		**Chair: *우현구, 박웅양***
13:30–14:00	1. Re-wiring intercellular interaction in colon cancer	*박웅양 (성균관대)*
14:00–14:30	2. Highly efficient base-editing in mice	*김경미 (고려대)*
14:30–15:00	3. Pharmacogenomic landscape of patient-derived tumor cells for precision oncology	*이진구 (아주대)*

▶ Poster-Oral Session (10월 31일 목요일)

Contents		
Room A		**Chair: *진영호 (경희의대)***
15:20–15:30	PO-01	Early administration of progesterone activates spinal astrocytes and enhances the development of neuropathic mechanical allodynia *Sheu-Ran Choi (Seoul National University)*
15:30 – 15:40	PO-02	NALCN channel is essential for pacemaking and burst activities in substantia nigra dopamine neurons *Suyun Hahn (Sungkyunkwan University)*
15:40–15:50	PO-03	Three-dimensional heart model-based screening of proarrhythmic potential by in silico simulation of action potential and electrocardiograms: verapamil and ranolazine vs. dofetilide *Eun Bo Shim (Kangwon National University)*
15:50–16:00	PO-04	Feature selection models for the survival of human pancreatic cancer patients using deep learning algorithms *Han-Jun Cho (CHA University)*
16:00–16:10	PO-05	HCN channel regulates somatodendritic membrane trafficking of voltage-gated potassium channel *Sol Hee Park (Kyung Hee University)*

Room B		**Chair : 김성준 *(서울의대)***
15:20–15:30	PO-06	TRPML1/3 heteromer regulates autophagosome-lysosome fusion as a PI4P downstream effector *So Woon Kim (Sungkyunkwan University)*
15:30–15:40	PO-07	Orai1-Mediated Store-Operated Ca^{2+} Entry in Podocyte is Critical for Kidney Filter Integrity *Bao Thi Ngoc Dang (Yonsei University Wonju College of Medicine)*
15:40–15:50	PO-08	Neddylation blockade induces HIF-1α driven cancer cell migration via upregulation of ZEB1 *Jun Bum Park (Seoul National University)*
15:50–16:00	PO-09	Sympathetic stimulation-mediated mitochondrial regulation in mouse beige and brown adipocytes *Dat Da Ly (Yonsei University Wonju College of Medicine)*
16:00–16:10	PO-10	Reduction of human non-small cell lung cancer cell growth by sea hare hydrolysates through regulation of macrophage polarization and pyroptosis and necroptosis *Marie Merci Nyiramana (Gyeongsang National University)*

▶ Young Physiologists' Session (10월 31일 목요일)

Contents		
16:20–16:40	YP-01	Neutrophil-derived extracellular vesicles: proinflammatory trails and anti-inflammatory microvesicles *Chang-Won Hong (Kyungpook National University)*
16:40–17:00	YP-02	Effect of proton pump inhibitor on gastric smooth muscle in functional dyspepsia *Heeman Kim (Yonsei University Wonju College of Medicine)*
17:00–17:20	YP-03	Effects of lipid peroxidants on ion channels and proarrhythmia potential *Seong Woo Choi (Seoul National University)*
17:20–17:40	YP-04	Distress, behavioral coping, and correlation patterns of mGluR5 in neuropathic pain brain *Geehoon Chung (Kyung Hee University)*

17:40–18:00	YP–05	Disruption of $Ca^{2+}i$ Homeostasis and Connexin 43 Hemichannel Function in the Right Ventricle Precedes Overt Arrhythmogenic Cardiomyopathy in Plakophilin–2–Deficient Mice *Joon–Chul Kim (New York University)*
18:00–18:20	YP–06	An Autaptic Culture System for Standardized Analyses of iPSC–Derived Human Neurons *ChoongKu Lee (Max Planck Institute)*
18:20–18:40	YP–07	Induction of AP–1 by YAP/TAZ contributes to cell proliferation and organ growth *Ja Hyun Koo (The Catholic University of Korea)*

▶ Plenary Lecture (11월 1일 금요일)

Contents		
Plenary Lecture 1 (11:00–11:45)		**Chair: *박소영 (영남의대)***
11:00–11:45	Histone demethylase–mediated adaptive thermogenesis *Juro Sakai (Univ. Tokyo, Tohoku University Graduate school of Medicine, Japan)*	
Plenary Lecture 2 (11:45–12:30)		**Chair: *홍성근 (경상의대)***
11:45–12:30	Cardiac calcium signaling: Calcium Imaging, Genetically–engineered Mice, and RyR2–Gene editing *Martin Morad (Medical Univ. South Carolina, USA)*	

▶ Symposium (11월 1일 금요일)

Contents		
Symposium 1: Modeling pathologic pain		**Chair: *황선욱 (고려의대), 김선광 (경희대)***
09:00–09:25	1. Development of depression–related pain animal model	*김현우 (충남의대)*
09:25–09:50	2. Decoding of spontaneous pain information from cortical two–photon calcium imaging in awake mice with machine learning	*김선광 (경희한의대)*
09:50–10:15	3. Novel Strategies for Inhibiting TRPV1 Activation using Human DRG Neuron Platform	*김용호 (가천의대)*
10:15–10:40	4. In vitro Spine–on–a–chip for application of biological microenvironment	*최 혁 (고려의대)*
Symposium 2: Pathophysiology of metabolic diseases		**Chair: *임승순 (계명의대), 전태일 (전남대)***
09:00–09:25	1. Obesity–induced inflammation in the development of insulin resistance	*이종순 (순천향대)*
09:25–09:50	2. The role of cytosolic calcium in insulin resistance	*오병철 (가천의대)*
09:50–10:15	3. The role of ER stress on the development of obesity and type 2 diabetes	*이재민 (DGIST)*
10:15–10:40	4. Fat depot selective inflammation and insulin resistance in obesity	*김재범 (서울대)*
Symposium 3: Multifaceted functions of ion channels		**Chair: *서인석 (서울의대), 김성준 (서울의대)***
09:00–09:25	1. Lipid transports by TMEM16 channel/ scramblases	*이병철 (한국뇌연구원)*
09:25–09:50	2. Allosteric modulation of TMEM16A channels by PI(4,5)P2 and CaMKII	*서병창 (DGIST)*
09:50–10:15	3. Bicarbonate permeation through anion channels	*이민구 (연세의대)*
10:15–10:40	4. Biophysical and physiological functions of Tentonin 3	*오우택 (KIST)*
Symposium 4: Physiology of higher nervous functions		**Chair: *이덕주 (가톨릭의대)***
15:00–15:25	1. Sensory encoding in the cerebellar climbing fiber	*김상정 (서울의대)*
15:25–15:50	2. The origin and function of cerebellar tonic inhibition	*윤보은 (단국의대)*
15:50–16:15	3. Serotonin–induced excitation of deep cerebellar nuclei mediates muscle tension abnormalities	*김대수 (KAIST)*
16:15–16:40	4. Cerebellar modulation of emotional learning and memory	*이용석 (서울의대)*

Symposium 5: Cardiac physiology and pathophysiology		Chair: *김성준 (서울의대), 우선희 (충남대)*
15:00–15:20	1. Ryanodine receptor type 2 as a potential target for novel antiarrhytmic drugs	*Nagomi Kurebayashi (Juntendo Univ., Japan)*
15:20–15:40	2. Mechanism of atrial fibrillation	*최종일(고려의대)*
15:40–16:00	3. A multidisciplinary approach for pharmacological assessment using human iPS-derived cardiomyocytes	*Junko Kurokawa (Univ. Shizuoka, Japan)*
16:00–16:20	4. NOS signaling in cardiac E-C coupling and metabolism	*Yin Hua Zhang (서울의대)*
16:20–16:40	5. Role of extracellular matrix in cardiac tissue regeneration	*김민석 (이화의대)*

Symposium 6: Stem cell physiology; beyond the limits		Chair: *정진섭 (부산의대), 권상모 (부산의대)*
15:00–15:20	1. Plant callus reprograms human dermal fibroblasts into multipotent skin-derived neural precursor cells	*권유욱 (서울의대)*
15:20–15:40	2. Blood cell production using human hematopoietic stem cells	*백은정 (한양의대)*
15:40–16:00	3. Expression profiles of MSCs in FBS-based and chemically defined media	*박상규 (아주약대)*
16:00–16:20	4. Salivary gland organoid-based development of exosome therapeutics for menopause-induced xerostomia	*김형식 (부산치대)*
16:20–16:40	5. Dissecting cellular heterogeneity using singl-cell RNA sequencing	*김종경 (DGIST)*

Symposium 7: Exercise physiology		Chair: *한 진 (인제의대), 곽효범 (인하대)*
10:00–10:20	1. The role of arginine methylation in the maintenance of skeletal muscle function	*강종순(성균관대)*
10:20–10:40	2. Effect of exercise on p66shc and vascular function in cardiovascular diseases	*이상기 (충남대)*
10:40–11:00	3. Smooth muscle cell mineralocorticoid receptor contributes to pathogenesis of heart failure	*김승겸(서울과기대)*
11:00–11:20	4. Can exercise intervention improve endothelial TRPV4 channel-dependent cell-cell communication?	*홍광석 (중앙대)*
11:20–11:40	5. Cerebral and peripheral microvascular function in individuals with elevated cardiovascular disease risk	*허찬솔 (전북대)*

Symposium 8: Skin pathophysiology and ion channels		Chair: *남주현 (동국의대), 고재홍 (중앙의대)*
10:00–10:30	1. Skin aging and ion channels	*정진호(서울의대)*
10:30–10:55	2. The involvement of TRPV1 in the effects of external stressors on the skin	*이종성(성균관대)*
10:55–11:20	3. Understanding molecular mechanisms of histamine-independent itch pathways	*심원식(가천약대)*
11:20–11:40	4. Transcriptomic analysis of gene expressions in two different murine models: prediction of itching diagnostic markers on early stage of scratching behavior	*김영원(중앙의대)*

Symposium 9: Altered shape and work of mitochondria		Chair: *임채헌 (울산의대), 박규상 (원주의대)*
10:00–10:30	1. Defective D-lactate metabolism induces methylglyoxal accumulation and causes cardiomyopathy	*박찬배 (아주의대)*
10:30–10:55	2. The coordinated regulation of mitochondrial structure and function for mitochondrial quality surveillance	*선 웅 (고려의대)*
10:55–11:20	3. Function of mitochondrial chaperone TRAP1 during progression of metabolic diseases	*강병헌 (UNIST)*
11:20–11:40	4. Anovel post-transcriptional regulation of L-type calcium channel in mice heart	*김형규 (인제의대)*

▶ Yudang Academic Award (11월 2일 토요일)

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09:00–09:40	Central sensitization: chronic pain and chronic itch	*나흥식 (고려의대)*

Special Academic Session

New applications in systems biology and physiology

S 24 SS-1 Altered tumor microenvironment in colorectal cancer
Woong-Yang Park
Samsung Genome Institute, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea

S 24 SS-2 Highly efficient base-editing in mice
Kyoungmi Kim
Department of Physiology, Korea University College of Medicine, Seoul, Korea

S 24 SS-3 Pharmacogenomic landscape of patient-derived tumor cells for precision oncology
Jin-Ku Lee
Department of Biochemistry, Ajou University, School of Medicine, Suwon, Korea

Oral Poster

S 25 PO-01 Early administration of progesterone activates spinal astrocytes and enhances the development of neuropathic mechanical allodynia
Sheu-Ran Choi, Ho-Jae Han, Jang-Hern Lee
Department of Veterinary Physiology, BK21 PLUS Program for Creative Veterinary Science Research, Research Institute for Veterinary Science and College of Veterinary Medicine, Seoul National University, Seoul, Korea

S 25 PO-02 NALCN channel is essential for pacemaking and burst activities in substantia nigra dopamine neurons
Suyun Hahn, So Woon Kim, Ki Bum Um, Hyun Jin Kim, Myoung Kyu Park
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 25 PO-03 Three-dimensional heart model–based screening of proarrhythmic potential by in silico simulation of action potential and electrocardiograms: verapamil and ranolazine vs. dofetilide
Minki Hwang[1], Chae Hun Leem[2], Dong-Seok Yim[3], Eun Bo Shim[1,4]
[1]SiliconSapiens Inc., [2]Department of Physiology, College of Medicine, University of Ulsan and Seoul Asan Medical Center, [3]Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary's Hospital, Seoul, [4]Department of Mechanical and Biomedical Engineering, Kangwon National University, Chuncheon, Korea

S 25 PO-04 Feature selection models for the survival of human pancreatic cancer patients using deep learning algorithms
Han-Jun Cho, Sangcheol Lee, Dong Hyeon Lee
Department of Physiology, CHA University School of Medicine, Korea

S 26 PO-05 HCN channel regulates somatodendritic membrane trafficking of voltage-gated potassium channel
Sol Hee Park[1], Ji-Yeon Hwang[1], Kang-Sik Park[1,2]
[1]Department of Physiology, School of Medicine, and [2]KHU-KIST Department of Converging Science and Technology, Kyung Hee University, Seoul, Korea

S 26 PO-06 TRPML1/3 heteromer regulates autophagosome-lysosome fusion as a PI4P downstream effector
So Woon Kim, Hyun Jin Kim
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 26 PO-07 Orai1-mediated store-operated Ca^{2+} entry in podocyte is critical for kidney filter integrity
Bao Thi Ngoc Dang[1-5], Ji-Hee Kim[1-5], Kyu-Hee Hwang[1-5], Phan Anh Nguyen[1-5], Dat Da Ly[1-5], Kyu-Sang Park[1-5], Seung-Kuy Cha[1-5]
[1]Department of Physiology, [2]Department of Global Medical Science, [3]Mitohormesis Research Center, [4]Institute of Mitochondrial Medicine, and [5]Institute of Lifestyle Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

S 27 PO-08 Neddylation blockade induces HIF-1α driven cancer cell migration via upregulation of ZEB1
Jun Bum Park[1,2], Jieun Seo[1,2], Sung Yeon Park[1,2], 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, Korea

S 27 PO-09 Sympathetic stimulation-mediated mitochondrial regulation in mouse beige and brown adipocytes
Dat Da Ly[1,2], Hanh Minh T. Nguyen[1,2], Nuoc Non Tran[3], Luong Dai Ly[1,2], Nhung Thi Nguyen[1,2], Soo-Jin Kim[1,2], Ha Thu Nguyen[1,2], Seung-Kuy Cha[1,2], Byung-Hoon Lee[3], Kyu-Sang Park[1,2]
[1]Department of Physiology, [2]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, [3]Department of New Biology, Daegu Gyeongbuk Institute of Science and Technology, Daegu, Korea

S 27 PO-10 Reduction of human non-small cell lung cancer cell growth by sea hare hydrolysates through regulation of macrophage polarization and pyroptosis and necroptosis

Marie Merci Nyiramana[1,2†], Soo Buem Cho[3†], Eun-Jin Kim[1], Min Jun Kim[4], Ji Hyeon Ryu[1,2], Hyun Jae Nam[5], Chang Hyeun Lee[5], Nam-Gil Kim[6], Si-Hyang Park[7], Yeung Joon Choi[8], Sang Soo Kang[4], Myunghwan Jung[9], Min-Kyoung Shin[9], Jaehee Han[1,2], In-Seok Jang[10], Dawon Kang[1,2,3]

[1]Department of Physiology and Institute of Health Sciences, [2]Department of Convergence Medical Science, Gyeongsang National University, Jinju, [3]Department of Radiology, Ewha Womans University Medical Center, Seoul, [4]Department of Anatomy, [5]Department of Medicine, College of Medicine, Gyeongsang National University, Jinju, [6]Department of Marine Biology and Aquaculture and Institute of Marine Industry, Gyeongsang National University, [7]Sunmarin Biotech, [8]Department of Seafood Science and Technology and Institute of Marine Industry, Gyeongsang National University, Tongyeong, [9]Department of Microbiology, College of Medicine, Gyeongsang National University, [10]Department of Thoracic and Cardiovascular Surgery, Gyeongsang National University Hospital, Jinju, Korea

Young Physiologists' Session

S 28 YP-01 Neutrophil-derived extracellular vesicles: proinflammatory trails and anti-inflammatory microvesicles

Young-Jin Youn[1,†], Sanjeeb Shrestha[1,†], Jun-Kyu Kim[1], Yu-Bin Lee[1], Jee Hyun Lee[2], Keun Hur[2], Nanda Maya Mali[3], Sung-Wook Nam[4], Sun-Hwa Kim[1], Dong-Keun Song[5], Hee Kyung Jin[6,7], Jae-sung Bae[1,7], Chang-Won Hong[1]

Department of [1]Physiology, [2]Department of Biochemistry and Cell Biology,[3]Anatomy, and [4]Molecular Medicine School of Medicine, Kyungpook National University, Daegu, [5]Department of Pharmacology, College of Medicine, Hallym University, Chuncheon, [6]Department of Laboratory Animal Medicine, College of Veterinary Medicine, [7]Stem Cell Neuroplasticity Research Group, Kyungpook National University, Daegu, Korea

S 28 YP-02 Effect of proton pump inhibitor on gastric smooth muscle in functional dyspepsia

Heeman Kim[1], Seung-Bum Ryoo[2], Tae Sik Sung[3], Jiyeon Lee[3], Sang Don Koh[3]

[1]Department of Gastroenterology, Yonsei University Wonju College of Medicine, Wonju, [2]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Physiology & Cell Biology, University of Nevada Reno, Reno, Nevada

S 28 YP-03 Effects of lipid peroxidants on ion channels and proarrhythmia potential

Seong Woo Choi[2], Sung Joon Kim[1,2]

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

S 28 YP-04 Distress, behavioral coping, and correlation patterns of mGluR5 in neuropathic pain brain

Geehoon Chung[1], Sang Jeong Kim[2], Sun Kwang Kim[1]

[1]Department of Physiology, College of Korean Medicine, Kyung Hee University, [2]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 29 YP-05 Disruption of Ca^{2+}_i homeostasis and connexin 43 hemichannel function in the right ventricle precedes overt arrhythmogenic cardiomyopathy in Plakophilin-2–deficient mice

Joon-Chul Kim[1], Marta Pérez-Hernández[1], Francisco J. Alvarado[2], Svetlana R. Maurya[3], Jerome Montnach[4], Yandong Yin[5], Mingliang Zhang[1], Xianming Lin[1], Carolina Vasquez[1], Adriana Heguy[6], Feng-Xia Liang[7], Sun-Hee Woo[8], Gregory E. Morley[1], Eli Rothenberg[5], Alicia Lundby[3,9], Hector H. Valdivia[2], Marina Cerrone, Mario Delmar

[1]The Leon H Charney Division of Cardiology, New York University School of Medicine, New York NY, [2]Department of Medicine and Cardiovascular Research Center, University of Wisconsin-Madison School of Medicine and Public Health, Madison WI, [3]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, [4]Institut du Thorax, Nouvelle Universite a Nantes. INSERM. Nantes Cedex [1], France,[5]Department of Pharmacology and Biochemistry, [6]Department of Pathology and Genome Technology Center, [7]Microscopy laboratory, Division of Advanced Research Technologies. New York University School of Medicine. New York NY, [8]Laboratory of Physiology, College of Pharmacy, Chungam National University, Daejeon, Korea, [9]NNF Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen

S 29 YP-06 An autaptic culture system for standardized analyses of iPSC-derived human neurons

ChoongKu Lee[1], Hong Jun Rhee[1], Ali H. Shaib[1], Kristina Rehbach[2,3,6], Anja Guenther[1], Tamara Krutenko[2], Matthias Hebisch[2], Michael Peitz[2,4], Nils Brose[1], Oliver Brustle[2], Jeong Seop Rhee[1]

[1]Max Planck Institute of Experimental Medicine, Department of Molecular Neurobiology, Göttingen, [2]Institute of Reconstructive Neurobiology, University of Bonn School of Medicine & University Hospital Bonn, [3]LIFE & BRAIN GmbH, Cellomics Unit, [4]Cell Programming Core Facility, University of Bonn School of Medicine, Bonn, Germany

S 29 YP-07 Induction of AP-1 by YAP/TAZ contributes to cell proliferation and organ growth

Ja Hyun Koo

Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

Plenary Lecture

S 30 Plenary Lecture 1 Acute response and chronic adaptation to cold stress *via* a single epigenetic enzyme but through distinct mechanisms

Juro Sakai

Division of Metabolic Medicine, RCAST, The University of Tokyo, Tokyo, Japan, Division of Molecular Physiology, Tohoku University Graduate School of Medicine, Sendai, Japan

S 31 Plenary Lecture 2 Cardiac calcium signaling: calcium imaging, genetically-engineered mice, and RyR2-gene editing

Martin Morad

Cardiac Signaling Center of USC, MUSC and Clemson University, Charleston, USA

Symposium

Symposium 1: Modeling pathologic pain

S 33 S-1-1 Development of depression-related pain animal model
Hyun-Woo Kim
Departments of Physiology and Medical Science, College of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

S 33 S-1-2 Decoding of spontaneous pain information from cortical two-photon calcium imaging in awake mice with machine learning
Sun Kwang Kim
Department of Physiology, College of Korean Medicine, Kyung Hee University, Seoul, Korea

S 33 S-1-3 Novel strategies for inhibiting TRPV1 activation using human DRG neuron platform
Yong Ho Kim
Gachon Pain Center and Department of Physiology, College of Medicine, Gachon University, Incheon, Korea

S 33 S-1-4 In vitro spine-on-a-chip for application of biological microenvironment
Min Ho Hwang[1], Hyuk Choi
Department of Medical Sciences, Graduate School of Medicine, Korea University, Seoul, Korea

Symposium 2: Pathophysiology of metabolic diseases

S 34 S-2-1 Obesity-induced inflammation in the development of insulin resistance
Jongsoon Lee
Soonchunhyang Institute of Medi-bio Science (SIMS), Soonchunhyang University, Cheonan, Korea

S 34 S-2-2 Molecular mechanism of insulin resistance and Akt inactivation by intracellular calcium
Byung-Chul Oh
Department of Physiology, Lee Gil Ya Cancer and Diabetes Institute, Gachon University College of Medicine, Incheon, Korea

S 34 S-2-3 The role of the endoplasmic reticulum stress on the development of leptin resistance and obesity
Jaemin Lee
Departments of New Biology, DGIST, Daegu, Korea

S 35 S-2-4 Different fat depots with different adipogenic progenitor cells in metabolic regulation
In Jae Hwang, Kyung Cheul Shin, Jeu Park, Jong In Kim, Sung Sik Choe, Jae Bum Kim
Center for Adipose Tissue Remodeling, Department of Biological Sciences, Institute of Molecular Biology and Genetics, Seoul National University, Seoul, Korea

Symposium 3: Multifaceted functions of ion channels

S 35 S-3-1 Lipid transports via TMEM16 channel/scramblases
Byoung-Cheol Lee
Department of Structure and Function on Neural Network, Korea Brain Research Institute, Daegu, Korea

S 35 S-3-2 Allosteric modulation of TMEM16A channels by PI(4,5)P2 and CaMKII
Byung-Chang Suh
Department of Brain & Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu, Korea

S 35 S-3-3 Bicarbonate permeation through anion channels
Min Goo Lee
Department of Pharmacology and Brain Korea 21 Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea

S 35 S-3-4 Biophysical and physiological functions of Tentonin 3
Uhtaek Oh
Brain Science Institute, KIST, Seoul, Korea

Symposium 4: Physiology of higher nervous functions

S 36 S-4-1 Sensory encoding in the cerebellar climbing fiber
Sang Jeong Kim
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 36 S-4-2 The origin and function of cerebellar tonic inhibition
Bo-Eun Yoon
Department of Molecular biology, Dankook University, Cheonan, Korea

S 36 S-4-3 Cerebellar 5HT-2A receptor agonism mediates stress-induced dystonia
Jungeun Kim, Sujin Chae, Sungsoo Kim, Myounggoo Kang, Wondo Heo, Daesoo Kim
Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Korea

S 36 S-4-4 Cerebellar modulation of emotional learning and memory
Yong-Seok Lee
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

Symposium 5: Cardiac physiology and pathophysiology

S 37 S-5-1 Ryanodine receptor type 2 as a potential target for novel anti-arrhythmic drugs
Nagomi Kurebayashi
Cellular and Molecular Pharmacology, Juntendo University Graduate School of Medicine, Tokyo, Japan

S 37 S-5-2 Mechanism of atrial fibrillation
Jong-Il Choi
Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine and Korea University Anam Hospital, Seoul, Korea

S 37 S-5-3 A multidisciplinary approach for pharmacological assessment using human iPS-derived cardiomyocytes
Junko Kurokawa
Departments of Bio-Informational Pharmacology, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan

S 37 S-5-4 NO signaling in cardiac E-C coupling and metabolism
Yin Hua Zhang
Department of Physiology & Biomedical Sciences, Seoul National University, College of Medicine, Seoul, Korea

S 38 S-5-5 Extracellular matrix-derived vesicles affect cardiac atria
Minsuk Kim
Department of Pharmacology, College of Medicine, Ewha Womans University, Seoul, Korea

Symposium 6: Stem cell physiology; beyond the limits

S 38 S-6-1 Plant callus reprograms human dermal fibroblasts into multipotent skin-derived neural precursor cells
Yoo-Wook Kwon
Institute for Cell Therapy, Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea

S 38 S-6-2 Blood cell production using human hematopoietic stem cells
So Yeon Han[1], Eun Mi Lee[1], Eun Jung Baek[1,2]
[1]Department Translational Medicine, Graduate School of Biomedical Science and Engineering, Hanyang University; [2]Department of Laboratory Medicine, Hanyang University College of Medicine, Hanyang University, Seoul, Korea

S 38 S-6-3 Differential gene expression in mesenchymal stem cells
Sang Gyu Park
Department of Pharmacy, Ajou University, Suwon, Korea

S 39 S-6-4 Organoid-based study of epithelial homeostasis and regeneration
Hyung-Sik Kim[1,2]
[1]Department of Life Science in Dentistry, School of Dentistry, Pusan National University, [2]Dental and Life Science Institute, Pusan National University, Yangsan, Korea

S 39 S-6-5 Dissecting cellular heterogeneity using single-cell RNA-seq
Jong Kyoung Kim
Department of New Biology, DGIST, Daegu, Korea

Symposium 7: Exercise physiology

S 39 S-7-1 Protein arginine methylation in muscle aging
Jong-Sun Kang
Departments of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 39 S-7-2 Effect of exercise on p66shc and vascular function in cardiovascular diseases
Sang Ki Lee
Departments of Sport Science, Chungnam National University College of Natural Science, Daejeon, Korea

S 39 S-7-3 Smooth muscle cell mineralocorticoid receptor contributes to pathogenesis of heart failure
Seung Kyum Kim
Departments of Sports Science, Seoul National University of Science and Technology, Seoul, Korea

S 40 S-7-4 Can exercise intervention improve endothelial TRPV4 channel-dependent cell-to-cell communication?
Kwangseok Hong
Department of Physical Education, College of Education, Chung-Ang University, Seoul, Korea

S 40 S-7-5 Cutaneous microvascular function in individuals with elevated cardiovascular disease risk
Chansol Hurr
Departments of Physical Education, Chonbuk National University, Jeonju, Korea

Symposium 8: Skin pathophysiology and ion channels

S 40 S-8-1 Skin aging and ion channels
Jin Ho Chung
Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea

S 41 S-8-2 Effects of blue-light irradiation on human keratinocytes are mediated via transient receptor potential vanilloid (TRPV)-1-mediated signaling
Jongsung Lee
Molecular Dermatology Laboratory, Department of Integrative Biotechnology, College of Biotechnology and Bioengineering, Sungkyunkwan University, Suwon, Korea

S 41 S-8-3 Understanding molecular mechanisms of histamine-independent itch pathways
Won-Sik Shim
College of Pharmacy, Gachon University, Incheon, Korea

S 41 S-8-4 Transcriptomic analysis of gene expressions in two different murine models: prediction of diagnostic markers on early stage of scratching behavior
Young-Won Kim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

Symposium 9: Altered shape and work of mitochondria

S 41 S-9-1 Defective D-lactate metabolism induce methylglyoxal accumulation and cause cardiomyopathy
Chan Bae Park
Department of Physiology, Ajou University School of Medicine, Suwon, Korea

S 42 S-9-2 Drp1-dependent mitochondrial fission for the quality surveillance
Woong Sun
Department of Anatomy, Korea University College of Medicine, Seoul, Korea

S 42 S-9-3 Function of mitochondrial chaperone TRAP1 during progression of metabolic diseases
Byoung Heon Kang
Department of Biological Sciences, Ulsan National Institutes of Science and Technology (UNIST), Ulsan, Korea

S 42 S-9-4 A novel post-transcriptional regulation of L-type calcium channel in mice heart
Hyoung Kyu Kim, Nammi Park, Jubert Marquez, Tae Hee Ko, Pham Trong Kha, Sung Hak Choi, Jiyoung Moon, Jae Boum Youm, Jin Han
Cardiovascular and Metabolic Disease Center, Department of Physiology, Department of Health Sciences and Technology, BK21 plus Project Team, College of Medicine, Inje University, Busan, Korea

Yudang Academic Award

S 43 Central sensitization: chronic pain and chronic itch
Heungsik Na
Neuroscience Research Institute and Department of Physiology, Korea University College of Medicine, Seoul, Korea

Poster Presentation

P01: Basic neurophysiology and Pain

S 43 P01-01 Examination of tetraspan contribution to sensory TRP-mediated pain
Ji Yeon Lim, Pyung Sun Cho, Minseok Kim, Haiyan Zheng, Sun Wook Hwang
Departments of Biomedical Sciences and Department of Physiology, Korea University College of Medicine, Seoul, Korea

S 43 P01-02 Differential induction of long-term synaptic plasticity in interneurons of layer 2/3 in rat primary visual cortex
Kayoung Joo[1], Kwang-Hyun Cho[1], Jin Hwa Jang[1], Dongchul Shin[1], Duck-Joo Rhie[1,2]
[1]Department of Physiology, [2]Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 44 P01-03 Inhibitory effects of aripiprazole on $K_v1.4$ potassium channels
Jeaneun Park[1], Kwang-Hyun Cho[1], Hong Joon Lee[1], Sang June Hahn[1], Duck-Joo Rhie[1,2]
[1]Department of Physiology, [2]Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 44 P01-04 Cholinergic and serotonergic modulation of long-term synaptic plasticity in lateral prefrontal cortex of rats
Dongchul Shin[1], Kayoung Joo[1], Kwang-Hyun Cho[1], Duck-Joo Rhie[1,2]
[1]Department of Physiology, [2]Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 44 P01-05 Central VEGF-A pathway plays a key role in the development of trigeminal neuropathic pain in rats
Jo-Young Son[1], Jin-Sook Ju[1], Geun-Woo Lee[1], Min-Kyoung Park[2], Min-Kyung Lee[3], Dong-Kuk Ahn[1]
[1]Department of Oral Physiology, School of Dentistry, Kyungpook National University, Daegu, [2] Department of Dental Hygiene, Kyung-Woon University, Gumi, [3] Department of Dental Hygiene, Dong-Eui University, Busan, Korea

S 45 P01-06 Methylene Blue is involved in anti-inflammation by lowering the expression level of pro-inflammatory cytokines in knee arthritis rats
Seung-Won Lee[1], Jin-Sung Park[1],Sun-Wook Moon[1], Eui-ho Park[1], Hye-Rim Suh[1], Yu-Jin Kim[1], Hee-Chul Han[1]
[1]Department of Physiology, Korea University College of Medicine, Seoul, Korea

S 45 P01-07 Endogenous spinal PPAR-gamma is necessary to motor function recovery after spinal cord injury in rats
Youngkyung Kim, Kyu-Won Park, Jeonghwa Oh, Young Wook Yoon
Department of Physiology and Neuroscience Research Institute, Korea University, Seoul, Korea

S 45 P01-08 The migration of GABAergic interneurons is modulated by JAK3 signaling during developing brain.
A Young Kim, Jee Min Chung, Eun Joo Baik
Department of Physiology, Ajou University School of Medicine, Suwon, Korea

S 46 P01-09 Understanding the neural and genetic basis of odor discrimination in C. elegans
Hee Kyung Lee[1], Saebom Kwon[1], Jessica Antonio[1], Jin il Lee[2], Kyoung-Hye Yoon[1]
[1]Department of Physiology, Mitohormesis Research Center, Wonju College of Medicine and [2]Division of Basic Science and Technology, Yonsei University, Wonju, Korea

S 46 P01-10 Pituitary adenylate cyclase-activating peptide enhances cholinergic transmission at the autonomic synapses via presynaptic mechanisms
Seong Jun Kang, Seong-Woo Jeong
Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea

S 46 P01-11 Assessment of visceral pain using telemetry recording of blood pressure in conscious rat
Tae Wan Kim[1], Dong-ho Youn[2]
[1]Department of Physiology, College of Veterinary Medicine, [2]Department of Oral Physiology, School of Dentistry, Kyungpook National University, Daegu, Korea

S 46 P01-12 Anatomical analysis of branch specific origin-wise synaptic distribution on tuft dendrites in the neocortex using array tomography
Nari Kim, Sang-kyu Bahn, Joon Ho Choi, Jinseop Kim, Jong-Cheol Rah
Korea Brain Research Institute, Daegu, Korea

P02: Neuronal pathophysiology

S 47 P02-01 The RNAi line of *kdm4a* ameliorates tau-engendered defects in *Drosophila melanogaster*
Sung Yeon Park[1,3], Jieun Seo[2], Uk Il Ju[2], Yang-Sook Chun[1,2,3]
[1]Ischemic/Hypoxic Disease Institute, [2]Department of Biomedical Sciences and [3]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea.

S 47 P02-02 Membrane targeting of the astrocytic membrane protein, MLC1 regulates cellular morphology and motility
Junmo Hwang[1], Hyun-Ho Lim[1,2]
[1]Neurovascular Unit Research Group, Korea Brain Research Institute and [2]Department of Brain & Cognitive Sciences, Daegu Gyeongbuk Institute of Science & Technology, Daegu, Korea

S 47 P02-03 Role of group I metabotropic glutamate receptor in low Mg^{2+}-induced interictal-like epileptiform activity in rat hippocampal slice
Ji Seon Yang, Hyun-Jong Jang, Duck-Joo Rhie, Shin Hee Yoon
Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 47 P02-04 SCAMP5-dependent localization of NHE6 to synaptic vesicles is critical for regulating quantal size at glutamatergic synapses
Unghwi Lee[1], Daehun Park[1], Soohyun Kim[1], Sang-Eun Lee[1], Yujin Kim[1, 2], Sunghoe Chang[1, 2]
[1]Department of Physiology and Biomedical Sciences, [2]Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, Korea

S 48 P02-05 Hypothalamic peptide hormone A controls appetite via leptin signaling and induction of α- melanocyte-stimulating hormone
Yunseon Jang[1,2,3], Soo Jeong Kim[1,3], Xianshu Ju[1,2,3], Min Joung Lee[1,2,3], Jianchen Cui[1,2,3], Jiebo Zhu[1,2,3], Yu Lim Lee[1,2,3], Min Jeong Ryu[1,4], Gi Ryang Kweon[1,2,4], Jun Young Heo[1,2,3]
[1] Department of Biochemistry, [2] Department of Medical Science, [3] Infection Control Convergence Research Center, [4] Research Institute for Medical Science, Chungnam National University School of Medicine, Daejeon, Korea

S 48 P02-06 Crif1 deletion in endothelial cells affects blood-brain barrier maintenance by the alteration of actin cytoskeleton
Min Joung Lee[1,2], Yunseon Jang[1,2], Soo Jeong Kim[1,2], Xianshu Ju[1], Yu Lim Lee[1,2], Jeong Hwan Son[2], Jianchen Cui[1], Min Jeong Ryu[2,3], Song-Yi Choi[6], Woosuk Chung[7], Chaejeong Heo[8], Yang Hoon Huh[9], Gi Ryang Kweon[1,2,3], Jun Young Heo[1,2,4,5]
[1]Department of Medical Science, [2]Department of Biochemistry, [3]Research Institute for Medical Science, [4]Brain research institute Chungnam National University School of Medicine, [5]Infection Control Convergence Research Center, College of Medicine, Chungnam National University. [6]Department of Pathology, Chungnam National University School of Medicine, [7]Department of anesthesiology and pain medicine, Chungnam National University Hospital, Daejeon, [8]Center for Neuroscience Imaging Research (CNIR), Institute for Basic Science (IBS), Suwon, [9]Electron Microscopy Research center, Korea Basic Science Institute, Cheongju, Korea

S 48 P02-07 Experimental evidences for functional changes in cortical blood flow by transcranial direct current stimulation
Ho Koo, Se Jin, Moon, Xiao Yong Zhang, Myoung Ae Choi, Min Sun Kim
Department of Physiology, Wonkwang University School of Medicine & Brain Science Institute at Wonkwang University, Iksan, Korea

S 49 P02-08 Obstructive sleep apnea-induced pathological changes in the rabbit brain
Hyeyun Kim[1], Seungeun Lee[2], Minchae Kim[2], Yein Choi[2], Jiyeon Moon[2], Byong-Gon Park[2]
Departments of [1]Neurology and [2]Physiology, College of Medicine, Catholic Kwandong University, Gangneung, Korea

S 49 P02-09 The epigenetic changes in rabbit brain of chronic obstructive sleep apnea model
Hyeyun Kim[1], Minchae Kim[2], Yein Choi[2], Jiyeon Moon[2], Seungeun Lee[2], Byong-Gon Park[2]
Departments of [1]Neurology and [2]Physiology, College of Medicine, Catholic Kwandong University, Gangneung, Korea

S 49 P02-10 Decreased expression of miR-200a-3p and 200b-3p of rat brain in obstructive sleep apnea associated with Alzheimer's disease
Hyeyun Kim[1], Yein Choi[2], Jiyeon Moon[2], Seungeun Lee[2], Minchae kim[2], Byong-Gon Park[2]
Departments of [1]Neurology and [2]Physiology, College of Medicine, Catholic Kwandong University, Gangneung, Korea

S 49 P02-11 Optogenetic stimulation of cortico-subthalamic projections ameliorate the motor symptoms in the 6-hydroxydopamine model of Parkinson's disease
In sun Choi, Joon Ho Choi, Jong Cheol Rah
Korea Brain Research Institute, Laboratory of Neurophysiology, Daegu, Korea

P03: Electrophysiology and Ca^{2+} signaling

S 50 P03-01 Tricyclic antidepressant doxepin inhibits voltage-dependent K^+ channels in rabbit coronary arterial smooth muscle cells
Jin Ryeol An, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 50 P03-02 The inhibitory effect of anticholinergic drug oxybutynin on voltage-dependent K^+ channels in coronary arterial smooth muscle cells
Jin Ryeol An, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 50 P03-03 Functional role of the C-terminal domain of Bestrophin-1, a calcium-activated chloride channel
Dong-Hyun Kim, Junmo Hwang, Hyun-Ho Lim
Lab. of Molecular Physiology and Biophysics, Neurovascular Unit Research Group, Korea Brain Research Institute, Daegu, Korea

S 50 P03-04 Carbon monoxide stimulates large conductance Ca^{2+}-activated K^+ currents of human cardiac fibroblasts through diverse mechanisms
Hyemi Bae, Jeongyoon Choi, Young-Won Kim, Donghee Lee, Yelim Seo, Seong-Tae Kim, Jae-Hong Ko, Hyoweon Bang, Inja Lim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

S 51 P03-05 Effect of carbon monoxide on delayed rectifier K^+ currents of human cardiac fibroblasts by diverse signaling pathways
Hyemi Bae, Jeongyoon Choi, Young-Won Kim, Donghee Lee, Yelim Seo, Seong-Tae Kim, Jae-Hong Ko, Hyoweon Bang, Inja Lim
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

S 51 P03-06 Different context for shear signaling in left versus right atrial myocytes: differential roles of $P2Y_1$- and $P2X_4$-purinoceptors
Joon-Chul Kim, Qui Anh Le, Kyeong-Hee Kim, Vu Thi Van Anh, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 51 P03-07 Chronic hemodynamic overload of the atria is an important factor for shear signaling remodeling in rat hearts
Qui Anh Le, Joon-Chul Kim, Vu Thi Van Anh, Berihun Dires Mihiretu, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 51 P03-08 Adaptive voltage control ensures the precise half inactivation application of voltage gated sodium channels on Qube, 384-well automated patch clamp system
Hironori Ohshiro[1], Kazuya Tsurudome[1], Anders Lindqvist[2]
[1]Sophion Bioscience KK, [2]Sophion Bioscience A/S, Japan

S 52 P03-09 Regulation of transient receptor potential canonical 4 activity by phospholipase C δ1
Juyeon Ko[1], Jongyun Myeong[2], Misun Kwak[1], Insuk So[1]
[1]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, USA

S 52 P03-10 Different effects of PCBs on steady-state current of human $K_v1.3$ channel
Jong-hui Kim[1], Su-Hyun Jo[1,2]
[1]Interdisciplinary Graduate Program for BIT Medical Convergence, [2]Department of Physiology, School of Medicine, Kangwon National University, Chuncheon, Korea

S 52 P03-11 Frequency-dependent Block of K_v1.5 Channel by Ifenprodil
Soobeen Hwang[1], Su-Hyun Jo[1,2]
[1]Interdisciplinary Graduate Program for BIT Medical Convergence [2]Department of Physiology, School of Medicine, Kangwon National University, Chuncheon, Korea

S 53 P03-12 Voltage-independent inhibition of human K_v1.5 currents by cinnarizine
Soobeen Hwang[1], Su-Hyun Jo[1,2]
[1]Interdisciplinary Graduate Program for BIT Medical Convergence, [2]Department of Physiology, School of Medicine, Kangwon National University, Chuncheon, Korea

S 53 P03-13 Potentiation of the glycine response by bisphenol A, an endocrine disrupter, on the substantia gelatinosa neurons of the trigeminal subnucleus caudalis in mice
Hoang Thi Thanh Nguyen[1], Soo Joung Park[1], Dong Hyu Cho[2], Seong Kyu Han[1]
[1]Department of Oral Physiology, School of Dentistry and Institute of Oral Bioscience, Chonbuk National University, [2]Department of Obstetrics and Gynecology, Chonbuk National University Hospital and School of Medicine, Jeonju, Korea

S 53 P03-14 Naringenin suppresses the miniature inhibitory transmission on the terminal of substantia gelatinosa neurons in immature mice
Thao Thi Phuong Nguyen[1], Soo Joung Park[1], Dong Hyu Cho[2], Seong Kyu Han[1]
[1]Department of Oral Physiology, School of Dentistry and Institute of Oral Bioscience, Chonbuk National University, [2]Department of Obstetrics and Gynecology, Chonbuk National University Hospital and School of Medicine, Jeonju, Korea

S 53 P03-15 Novel marine compound Echinochrome A is a negative regulator of cardiac contractility
Ji Young Moon, Hyoung Kyu Kim, Jae Boum Youm, In Sung Song, Seung Hun Jeong, Sung Ryul Lee, Nari Kim, Kyung Soo Ko, Byoung Doo Rhee, Jin Han
National Research Laboratory for Mitochondrial Signaling, Cardiovascular and Metabolic Disease Center, Department of Physiology, Inje University, Busan, Korea

S 54 P03-16 Verapamil improves glucose homeostasis and insulin sensitivity in a mouse model of diet-induced obesity by modulating calcium channels
Ye Rim Kang[1,2], Jin-Wook Lee[1,2], Gun-woo Won[2], Ok-Hee Kim[2], Byung-Chul Oh[1,2]
[1]Department of Health Sciences and Technology (GAIHST), Gachon University, [2]Department of Physiology, Lee Gil Ya Cancer and Diabetes Institute, Gachon University College of Medicine, Incheon, Korea

S 54 P03-17 Plakophilin-2, a negative regulator for fluid shear-induced Cx43 hemichannel activation in cardiac myocytes
Vu Thi Van Anh, Qui Anh Le, Berihun Dires Mihiretu, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 54 P03-18 Blockade of heterotetrameric hERG 1A/3.1 channels by iloperidone
Hong Joon Lee, Sang June Hahn
Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 55 P03-19 Onion peel extract and its constituent, quercetin inhibits human Slo3 in a pH and calcium dependent manner
Tharaka Darshana Wijerathne[1], Ji Hyun Kim[1], Min Ji Kim[1], Chul Young Kim[2], Mee Ree Chae[3], Sung Won Lee[3], Kyu Pil Lee[1]
[1]Department of Physiology, College of Veterinary Medicine, Chungnam National University, Daejeon, [2]College of Pharmacy, Hanyang University, Ansan, [3]The Department of Urology, Samsung Medical Center, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Seoul, Korea

S 55 P03-20 Group 1 metabotropic glutamate receptors increases Ca^{2+} levels and tonic firing rate via TRPC3 channels in SNc dopamine neurons
Ki Bum Um, Myoung Kyu Park
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

S 55 P03-21 The biphasic effect of TRPC4 and TRPC5 activity by the tricyclic antidepressant depending on modulation of μ-opioid receptor
Byeongseok Jeong, Chansik Hong
Department of Physiology, Chosun University School of Medical, Gwangju, Korea

S 55 P03-22 TRPC5 channel instability induced by depalmitoylation protects striatal neurons against oxidative stress in Huntington's disease
Chansik Hong[1], Insuk So[2]
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S 56 P03-23 Inhibition of K_v3.1 currents by citalopram
Hyang Mi Lee[1], Seong Han Yoon[1], Sang June Hahn[2], Bok Hee Choi[1]
[1]Department of Pharmacology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, [2]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 56 P03-24 Ca^{2+}-CaM binding anchor residue for PKD2L1 channel activity regulation
Hana Kang, Julia Young Baik, Eunice Yon June Park, Insuk So
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 56 P03-25

Effects of various fibrosis patterns on ventricular arrhythmogenesis and pumping efficacy
Abrha Abebe Tekle, Ki Moo Lim
Departments of IT Convergence Engineering, Kumoh National Institute of Technology, Gumi, Korea

S 57 P03-26

Computational analysis of cardiac electromechanical delay under normal and irregular heartbeat by using 3D ventricular model
Aulia Khamas Heikhmakhtiar, Ki Moo Lim
Departments of IT Convergence Engineering, Kumoh National Institute of Technology, Gumi, Korea

S 57 P03-27

Computational analysis of proarrhythmic estimation under the influence of dofetilide, quinidine, and cisapride
Aulia Khamas Heikhmakhtiar, Ki Moo Lim
Departments of IT Convergence Engineering, Kumoh National Institute of Technology, Gumi, Korea

S 57 P03-28

Kinetic analysis of activation process of $K_v7.4$ channel with novel pharmacological activators targeted for erectile dysfunction
Hana Kang, Jung Eun Lee, Insuk So
Department of Physiology, College of Medicine, Seoul National University, Seoul, Korea

S 58 P03-29

Mutual interaction of high-order thalamic and top-down inputs on apical tuft dendrites of layer 5 pyramidal neurons
Young-Eun Han, Joon Ho Choi, Jong-Cheol Rah
Korea Brain Research Institute, Deagu, Korea

S 58 P03-30

STING-GABA transporters pathway and memory deficits
Chiranjivi Neupane[1,2,3], Ramesh Sharma[1,2,3], Hyun Jin Shin[1,2,3], Su Eun Park[1,2,3], Jin Bong Park[1,2,3]
[1]Department of Medical Sciences, [2]Department of BK21plus CNU Integrative Biomedical Education Initiative, [3]Department of physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

S 58 P03-31

Sustained activity by cholinergic modulation in anterior cingulate and posterior parietal cortices
Yoon-Sil Yang, Joon Ho Choi, Jong-Cheol Rah
Korea Brain Research Institute, Research Division, Deagu, Korea

S 58 P03-32

Involvement of GluN2D subunits containing NMDA receptors in experimental models of Parkinson's disease
Ramesh Sharma[1,2,3], Chiranjivi Neupane[1,2,3], Hyun Jin Shin[1,2,3], Su Eun Park[1,2,3], Miae Lee[1], Jin Bong Park[1,2,3]
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S 59 P03-33

Ethanol elevates excitability of superior cervical ganglion neurons by inhibiting K_v7 channels in a cell type-specific and $PI(4,5)P_2$-dependent manner
Kwon-Woo Kim[1], Keetae Kim[2], Hyosang Lee[1], Byung-Chang Suh[1]
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S 59 P03-34

Mitochondrial Ca^{2+} uptake relieves palmitate-induced cytosolic Ca^{2+} overload and lipotoxicity in MIN-6 cells
Luong Dai Ly[1,2], Dat Da Ly[1,2], Nhung Thi Nguyen[1,2], Ji-Hee Kim[2], Heesuk Yu[3], Jongkyeong Chung[3], Myung-Shik Lee[4], Seung-Kuy Cha[1,2], Kyu-Sang Park[1,2]
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S 59 P03-35

Characterization of molecular mechanisms underlying voltage-gated Ca^{2+} channel modulation by DREADD
Yong-Seok Kim[1], Woori Ko[1], Yong-Seok Oh[1], Jong-Cheol Rah[2], Byung-Chang Suh[1]
[1]Department of Brain & Cognitive Sciences, DGIST, [2]Laboratory of Cortical Neurophysiology, Korea Brain Research Institute, Daegu, Korea

S 60 P03-36

Analysis of blocking mechanism and binding sites of intracellular spermine to TRPC4 ion channel
Jinsung Kim[1], Sang-Hui Moon[2,3], Tae-Wook Kim[1], Juyeon Ko[1], Young Keul Jeon[1], Young-cheul Shin[4], Ju-Hong Jeon[1], Insuk So[1]
[1]Department of Physiology, [2]Office of Medical Education, [3]Department of Surgery, College of Medicine, Seoul National University, Seoul, Korea, [4]Department of Cell Biology, Harvard Medical School, Boston, USA

S 60 P03-37

Temperature-dependent increase in the calcium sensitivity and acceleration of activation of TMEM16F variants
Haiyue Lin[1], Sung Joon Kim[2], Joo Hyun Nam[3,4]
[1]Department of Otorhinolaryngology, Yonsei University College of Medicine, [2]Department of Physiology, Seoul National University College of Medicine, [3]Department of Physiology, Dongguk University College of Medicine, [4]Channelopathy Research Center (CRC), Korea

S 60 P03-38

Post-translational palmitoylation of voltage-gated calcium channels regulates their $PI(4,5)P_2$ sensitivity and inactivation
Jun-Hee Yeon, Byeol-I Kim, Byung-Chang Suh
Department of Brain and Cognitive Sciences, DGIST, Daegu, Korea

S 60 P03-39

Gain of function mutation in the TM2 inner pore helices of TREK/TRAAK channels exhibits strong inward rectification
Eun-Jin Kim[1], Dong Kun Lee[1], Seong-Geun Hong[1], Jaehee Han[1], Delphine Bichet[2], Dawon Kang[1]
[1]Department of Physiology, College of Medicine and Institute of Health Sciences, Gyeongsang National University, Jinju, Korea, [2]Institut de Pharmacologie Moléculaire et Cellulaire, LabEx ICST, CNRS UMR, Université de Nice Sophia Antipolis, Valbonne, France

S 61 P03-40 Nortriptyline lowers basal calcium level of dopamine neurons through ion channels inhibition
Sun Hee Jeon, Hyung Seo Park, Se Hoon Kim, Shin Hye Kim
Department of Physiology, College of Medicine, Konyang University, Daejeon, Korea

S 61 P03-41 Na_v beta3 promotes polarized trafficking of voltage-dependent potassium channel in neurons
Ji Seon Shim[1], Dong-Hyun Kim[3], Young Wook Choi[1], Min-Young Song[1], Seok Kyo Shin[1], Jin-Sung Choi[4], Kang-Sik Park[1,2]
[1]Department of Physiology, School of Medicine, and [2]KHU-KIST Department of Converging Science and Technology, Kyung Hee University, Seoul, [3]College of Pharmacy, Catholic University of Korea, Bucheon, Korea

P04: Muscle physiology

S 61 P04-01 Decreased inward-rectifier K^+ current of the septal coronary artery smooth muscle cells in pulmonary arterial hypertensive rats
Sung Eun Kim, Ming Zhe Yin, Hae Jin Kim, Rany Vorn, Hae Young Yoo, Sung Joon Kim
Department of Physiology, Department of Biomedical Sciences, Ischemic/Hypoxic Disease Institute[3], Seoul National University College of Medicine, Seoul, Korea

S 62 P04-02 PPARδ protects muscle from EtOH induced insulin resistance by enhanced AMPK activation and mitochondrial function
Jin-Ho Koh, Sol-Yi Park, Jong-Yeon Kim
[1]Department of Physiology, College of Medicine, Yeungnam University, Daegu, Korea

S 62 P04-03 Cardioprotective effects of angiotensin-(1-5) by anti-apoptosis and anti-oxidant via MasR-PI3K-Akt-eNOS pathway in rats
Byung Mun Park, Weijian Li, Suhn Hee Kim
Department of Physiology, Research Institute for Endocrine Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 62 P04-04 Mitochondrial biogenesis is increased by cyclic stretch in a mouse cardiac cell line
Hyoung KyuKim[1,2,†], Yun Gyeong Kang[3,†], Seung Hun Jeong[1], Nammi Park[1], Jubert Marquez[1], Sunwoo Kim[1], Kyung Soo Ko[1], Byoung Doo Rhee[1], Jung-Woog Shin[3], Jin Han[1]
[1]Cardiovascular and Metabolic Disease Center, Department of Physiology, Department of Health Sciences and Technology, BK21 Plus Project Team, College of Medicine, [2]Department of Integrated Biomedical Science, College of Medicine, Inje University, Busan, [3]Department of Biomedical Engineering, Inje University, Gimhae, Korea

S 63 P04-05 STIM1 affects intracellular Ca^{2+} movement as well as extracellular Ca^{2+} entry in skeletal muscle
Jun Hee Choi[1,2,†], Mei Huang[1,2,†], Changdo Hyun[1,2], Mi Ri Oh[1,2], Keon Jin Lee[1,2], Eun Hui Lee[1,2]
[1]Department of Physiology, College of Medicine, [2]Department of Biomedicine & Health Sciences, Graduate School, The Catholic University of Korea, Seoul, Korea

S 63 P04-06 Involvement of TRPC4 channel in regulation of spontaneous myometrial contraction in pregnant myometrium
Young Hwan Kim[1,3], Young Han Kim[2], Duck-Sun Ahn[1], Seungsoo Chung[1]
[1]Department of Physiology, Brain Korea 21 Plus Project for Medical Science, Yonsei University College of Medicine, [2]Department of Obstetrics and Gynecology, Yonsei University College of Medicine, [3]Division of Research and Development, BnH Research co., Ltd

S 63 P04-07 Involvement of autophagy in mesenteric artery dysfunction of angiotensin II-induced hypertensive mice
Youngin Kwon, Soo-Kyoung Choi, Seonhee Byeon, Young-Ho Lee
Department of Physiology, College of Medicine, Brain Korea 21 PLUS Project for Medical Science, Yonsei University, Seoul, Korea

S 64 P04-08 Role of the 5-HT on pacemaker potentials in colonic interstitial cells of Cajal of mouse
Wenhao Wu, Seok Choi
Department of Physiology, College of Medicine, Chosun University, Gawngju, Korea

S 64 P04-09 Action of fluoxetine on pacemaker activity in interstitial cells of Cajal from mouse large intestine
Xingyou Huang, Seok Choi
Department of Physiology, College of Medicine, Chosun University, Gwangju, Korea

P05: Organ physiology

S 64 P05-01 Role of Rho-associated protein kinase in the vasorelaxation induced by linagliptin
Mi Seon Seo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 64 P05-02 Vasorelaxant effect of dipeptidyl peptidase-4 inhibitor sitagliptin via the activation of K_v channels and PKA on aortic smooth muscle
Mi Seon Seo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 65 P05-03 Role of SERCA pump and K_v channels on vildagliptin-induced vasorelaxation
Hee Seok Jung, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 65 P05-04 Roles of nNOS and eNOS in rat heart; comparison between the left and right ventricle myocytes
Jae Won Kwon[1], Young Keul Jeon[1], Sung Joon Kim[1,2]
Departments of [1]Physiology and [2]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

S 65 P05-05 Interventricular difference in calcium sensitivity with lower expression of calcium binding proteins
Young Keul Jeon[1,2,3], Ji Hyun Jang[1,2,3], Juhan Woo[1,2,3], Ming Zhe Yin[1,2,3], Jae Won Kwon[1,2,3], Yin Hua Zhang[1,2,3], Sung Joon Kim[1,2,3]
[1]Department of Physiology, [2]Department of Biomedical Sciences, [3]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

S 66 P05-06 Dipeptidyl peptidase-4 inhibition with evogliptin improves cardiac functions and fibrosis in type 2 diabetic *db/db* mice
Pham Trong Kha[1], Hyoung Kyu Kim[1], Ji Young Moon[1], Joon Young Noh[1], Jin Han[1]
[1]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, Department of Health Sciences and Technology, BK21 Plus Project Team, and Cardiovascular and Metabolic Disease Center, Inje University College of Medicine, Busan, Korea

S 66 P05-07 Mitochondrial ROS and TRPC6-mediated Ca^{2+} signaling nexus contributes to hepatic stellate cell activation and fibrosis
Kyu-Hee Hwang[1-5], Phan Anh Nguyen[1-5], Ji-Hee Kim[1-5], Soo-Jim Kim[1-5], Bao Thi Ngoc Dang[1-5], Kyu-Sang Park[1-5], Seung-Kuy Cha[1-5]
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S 66 P05-08 αKlotho as a negative regulator of store-operated Ca^{2+} entry
Ji-Hee Kim[1-5], Kyu-Hee Hwang[1-5], Bao Thi Ngoc Dang[1-5], Phan Anh Nguyen[1-5], Kyu-Sang Park[1-5], Seung-Kuy Cha[1-5]
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P06: Endocrine and Energy Metabolism

S 66 P06-01 Pine needle extract activates POMC neurons in the hypothalamus
Eun A Kim[1], Eun Hye Byeon[1], Dawon Kang[1,2], Sung-Geun Hong[1,2], Jae Hee Han[1,2], Dong Kun Lee[1,2]
[1]Department of Physiology and Convergence Medical Sciences, School of Medicine, [2]Institute of Health Sciences, School of Medicine, Gyeongsang National University, Jinju, Korea

S 67 P06-02 Effects of octanoic acid on glucose-stimulated insulin secretion and expression of glucokinase through the olfactory receptor in pancreatic beta-cells
Jung-A Jung[1], Hye-Jeong Kim[1], Jae-Hyung Park[1]
[1]Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

S 67 P06-03 Effect of endoplasmic reticulum stress on expression of adipsin in adipocytes
Hye-Jeong Kim[1], Jung-A Jung[1], Jae-Hyung Park[1]
[1]Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

S 67 P06-04 The role of MsrB3 on high-fat diet induced insulin resistance
Hye-Na Cha[1], Soyoung Park[1], Hwa-Young Kim[2], So-Young Park[1]
[1]Department of Physiology and Smart-Aging Convergence Research Center, [2]Department of Biochemistry and Molecular Biology, College of Medicine, Yeungnam University, Daegu, Korea

S 68 P06-05 Lactate shifts mitochondrial bioenergetics in skeletal muscle and adipose tissue mitochondria and increases metabolic rate
Jin-Ho Koh, Jong-Yeon Kim, Kyung-Oh Doh
Department of Physiology, College of Medicine, Yeungnam University, Daegu, Korea

S 68 P06-06 The effect of CORM-2 on ANP secretion
Weijian Li, Byung Mun Park, Suhn Hee Kim
Department of Physiology, Research Institute for Endocrine Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 68 P06-07 Tetrahydrobiopterin enhanced mitochondria biogenesis and cardiac contractility via stimulation of PGC-1α signaling pathway
Hyoung Kyu Kim, Sung Ryul Lee, Nari Kim, Jin Han
Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 68 P06-08 Melatonin regulates gonadotropin releasing hormone neurons excitability via kainate receptors and kisspeptin signaling in immature mice
Santosh Rijal[1], Seon Hui Jang[1], Dong Hyu Cho[2], Seong Kyu Han[1]
[1]Department of Oral Physiology, School of Dentistry & Institute of Oral Bioscience, Chonbuk National University, [2]Department of Obstetrics and Gynecology, Chonbuk National University Hospital and School of Medicine, Jeonju, Korea

S 69 P06-09 N-terminal pro-B-type natriuretic peptide as an index in patients with obesity and acute coronary syndrome
Lan Hong[1], Larry F Lemanski[2], Zhengshan Zhao[2], Xiaoxuan Cao[3], Honghua Chi[3], Honghua Jin[3]
[1]Department of Physiology and Pathophysiology, College of Medicine, Yanbian University, Yanji, China, [2]Biomedical institute for Regenerative Research, Texas A&M University-Commerce, Texas, USA, [3]Department of Pharmacy, Yanbian University Hospital, Yanji, China

S 69 P06-10 Non-cell autonomous modulation of tyrosine hydroxylase by HMGB1 released from astrocytes in an acute MPTP toxin-induced mouse model
Soo Jeong Kim[1,2,8], Min Jeong Ryu[1,4,8], Jeongsu Han[1,2], Yunseon Jang[1,2,3], Min Joung Lee[1,2,3], Xianshu Ju[1,2,3], Ilhwan Ryu[1,2,3], Yu Lim Lee[1,2,3], Eungseok Oh[5], Woosuk Chung[6,7], Jun Young Heo[1,2,3,7], Gi Ryang Kweon[1,3,4]
[1]Department of Biochemistry, [2]Infection Control Convergence Research Center, [3]Department of Medical science, [4]Research Institute for Medical Science, Chungnam National University School of Medicine, [5]Department of Neurology, [6]Department of Anesthesiology and Pain Medicine, Chungnam National University Hospital, [7]Brain research Institute, Chungnam National University School of Medicine, Daejeon, Korea [8]Co-first author

S 69 P06-11 Effects of thermotherapy on irisin and orexin levels metabolic of glucose regulating factors in middle-aged obese women
Hye-Jin Lee[1], Tae-Wook Kim[1], Young-Ki Min[1], Won-Jun Lee[2], Yun Su Eun[2], Tae-Hwan Pak[2], Seon Ah Jeon[1], Hee-Kyoung Kim[1], Mi-Young Lee[3], Jeong-Beom Lee[1]
[1]Department of Physiology, College of Medicine, [2]A student at the College of Medicine, Soonchunhyang University, Cheonan, [3]Global Graduate School of Healthcare, Soonchunhyang University, Asan, Korea

S 70 P06-12 Effects of acute ingestion of caffeine on dopamine release and serotonin in a human with thermotherapy
Seon Ah-Jeon[1], Hye-Jin Lee[1], Young-Ki Min[1], Won-Jun Lee[2], Yun Su Eun[2], Tae-Hwan Pak[2], Hee-Kyoung Kim[1], Mi-Young Lee[3], Jeong-Beom Lee[1]
[1]Department of Physiology, College of Medicine, [2]A student at the College of Medicine, Soonchunhyang University, Cheonan, [3]Global Graduate School of Healthcare, Soonchunhyang University, Asan, Korea

S 70 P06-13 Seasonal acclimation in sudomotor function evaluated by acetylcholine in healthy humans
Hee-Kyoung Kim[1], Hye-Jin Lee[1], Young-Ki Min[1], Won-Jun Lee[2], Yun Su Eun[2], Tae-Hwan Pak[2], Mi-Young Lee[3], Seon Ah Jeon[1], Jeong-Beom Lee[1]
[1] Department of Physiology, College of Medicine, [2] A student at the College of Medicine, Soonchunhyang University, Cheonan, [3]Global Graduate School of Healthcare, Soonchunhyang University, Asan, Korea

S 70 P06-14 Investigating the mechanism of the cell-nonautonomous roles of the nuclear hormone receptor NHR-49 in the nervous system of *Caenorhabditis elegans*
Saebom Kwon, Jessica Antonio, Kyoung-Hye Yoon
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 70 P06-15 Role of mitochondrial phosphate transporters in vascular calcification
Nhung Thi Nguyen, Tuyet Thi Nguyen, Soo-Jin Kim, Luong Dai Ly, Dat Da Ly, Ha Thu Nguyen, Hanh Minh Nguyen, Seung-Kuy Cha, Kyu-Sang Park
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 71 P06-16 High phosphate diet upregulates antioxidant enzymes and FGF21 leading to metabolic stress resistance in mouse models
Nhung Thi Nguyen, Ha Thu Nguyen, Tuyet Thi Nguyen, Soo-Jin Kim, Luong Dai Ly, Dat Da Ly, Hanh Minh Nguyen, Seung-Kuy Cha, Kyu-Sang Park
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 71 P06-17 Interaction between cardiac nNOS and mitochondrial complex I and its regulation of mitochondrial activity in sham and hypertensive hearts
Yu Na Wu[1], Ying Li[2], Yin Hua Zhang
Department of Physiology & Biomedical Sciences, Seoul National University, College of Medicine, Seoul, Korea

P07: Epithelium and Exocrine Physiology

S 71 P07-01 Prediction of itching diagnostic marker through RNA sequencing of contact hypersensitivity and skin scratching stimulation mice models
Seongtae Kim[1], Young-Won Kim[1], Donghee Lee[1], Yelim Seo[1], Jeongyoon Choi[1], Hyemi Bae[1], Inja Lim[1], Hyoweon Bang[1], Jung-Ha Kim[2], Jae-Hong Ko[1]
[1]Department of Physiology, Chung-Ang university, College of Medicine, [2]Department of Family Medicine, College of Medicine, Chung-Ang University Hospital, Seoul, Korea

S 72 P07-02 Role of ERK1/2-mTORC1-NOX4 axis on epithelial-mesenchymal transition of retinal pigment epithelial cells
Soo-Jin Kim[1,2], Yoon-Sang Kim[1], Nhung Thi Nguyen[1,2], Luong Dai Ly[1,2], Seung-Kuy Cha[1,2], Ranjan Das[3], Kyu-Sang Park[1,2]
[1]Department of Physiology, [2]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea, [3]Department of Internal Medicine, Rush University Medical Center, Chicago, USA

S 72 P07-03 Expression of organic cation and anion transporters in 3D-cultured human kidney proximal tubular epithelial cell line
Chae Young Lee, Seo Min Jun, Hae-Rahn Bae
Department of Physiology, College of Medicine, Dong-A University, Busan, Korea

P08: Inflammation and Immune Physiology

S 72 P08-01 Novel function of Jumonji C(JmjC) domain – containing protein in osteoclastogenesis
Seon-Young Kim, Hye-Jin Kim, Joo Seung Lee, Do Won Jung, Jong-Wan Park, Yang-Sook Chun
Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 72 P08-02 CRIF1 deficiency mediated tetrahydrobiopterin biosynthesis regulation induced eNOS uncoupling
Ikjun Lee[1,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Harsha Nagar[1,2,3], Su-Jeong Choi[1,2,3], Sung-min Kim[1,3], 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 73 P08-03 *Alnus Sibirica* extracts suppress the inflammatory response in vitro and skin inflammation in vivo
Jeongyoon Choi, Sunghee Moon, Hyemi Bae, Young-Won Kim, Seongtae Kim, Yelim Seo, Jae-Hong Ko, Inja Lim, Hyoweon Bang
Department of Physiology, College of Medicine, Chung-Ang University, Seoul, Korea

S 73 P08-04 IL-10 suppresses caspase-1-dependent IL-1β secretion via production of apoptosis inhibitor of macrophage protein (AIM)
KyungwonYang[1,2], Taehyun Kim[1,2], Jihee Lee[1,2]
[1]Department of Physiology, [2]Tissue Injury Defense Research Center, College of Medicine, Ewha Womans University, Seoul, Korea

S 73 P08-05 Secretory Ref-1 exhibited protective effects against inflammatory responses in lipopolysaccharide-induced septic mice
Hee Kyoung Joo, Yu Ran Lee, Eun-Ok Lee, Sung Min Kim, Hao Jin, Byeong Hwa Jeon
Research Institute for Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, Daejeon, Korea

S 74 P08-06 The reducing APE1/Ref-1 inhibits an inflammatory reaction by inducing a reduction of inflammation mediated receptor
Sungmin Kim[1,2,3], Hao Jin[1,2,3], Yu Ran Lee[2], Eun Ok Lee[2], Hee Kyoung Joo[2], Byeong Hwa Jeon[1,2,3]
[1]Department of Medical Science, [2]Research Institute of Medical Science, Department of Physiology, [3]Department of BK21Plus CNU Integrative Biomedical Education Initiative, College of Medicine, Chungnam National University, Daejeon, Korea

S 74 P08-07 Analysis of systemic inflammation on organ dysfunction in pre-eclampsia patients
Hui Xing Cui, Chun Yu Dong, Yin Hua Zhang
Department of Physiology & Biomedical Sciences, Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea; Department of Obstetrics, Yanbian University Hospital, Yanji, China

S 74 P08-08 Macrophage-specific deletion of SCAP induces inflammation by promoting M1 macrophage polarization
Sun Hee Lee, Dae-Kyu Song, Jae-Hoon Bae, Seung-Soon Im
Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

P09: Cellular Physiology and Cancer

S 74 P09-01 Nitric oxide level regulates lipocalin-2 expression and the viability of RINm5F insulinoma cells in response to cytokines
Seo-Yoon Chang, Myung-Jun Kim
Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

S 75 P09-02 Upregulation of thioredoxin and its reductase attenuates arsenic trioxide-induced growth suppression in human pulmonary artery smooth muscle cells by reducing oxidative stress
Woo Hyun Park, Sun Hyang Park
Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Korea

S 75 P09-03 Role of Jumonji-C histone demethylase in the development of hepatocellular carcinoma
Do-Won Jeong[1], Yang-Sook Chun[1]
[1]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 75 P09-04 Auranofin induces cell death in lung cancer cells via oxidative stress
Xia Ying Cui, Woo Hyun Park
Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Korea

S 76 P09-05 Ginsenosides enhanced the Irinotecan- induced cell death against colon cancer HCT116 and SW620 cells.
Arulkumar Nagappan, Sungkun Chun
Department of Physiology, Chonbuk National University Medical School, Jeonju, Korea

S 76 P09-06 Ginsenoside compound K increases adult hippocampal neurogenesis in aged-mice
Jae Hoon Jeong, Sun Young Park, Sungkun Chun
Department of Physiology, Chonbuk National University Medical School, Jeonju, Korea

S 76 P09-07 Exosomal PTEN from macrophages exposed to apoptotic cancer cells inhibits EMT and invasion of cancer cells
Yong-Bae Kim[1,2], Ye-Ji Lee[1,2], Young-Ho Ahn[2,3], Jihae Jung[1], Jihee Lee[1,2]
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S 77 P09-08

IDH2 mediates mitophagy through changes in mtUPR in endothelial cells
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], Jeen-Woo Park[4], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,5], Cuk-Seong Kim[1,2,3]
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S 77 P09-09

The effect of neddylation blockade on cancer metastasis depends on p53 status
Ye Lee Kim, Jun Bum Park, Yang-Sook Chun
Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 77 P09-10

Overcoming drug resistance in multiple myeloma by targeting cereblon
Jubert Marquez[1], Nam-Mi Park[1], Bayalagmaa Nyamaa[1], Hyoung Kyu Kim[1], Jin Han[1]
[1]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 77 P09-11

Induction of FABP by fatty acid is crucial for switching on HIF-driven lipid accumulation and cell growth in hepatocellular carcinoma
Jieun Seo[1], Do-Won Jeong[1], Yang-Sook Chun[1]
[1]Department of Physiology and Biomedical Science, Seoul National University College of Medicine, Seoul, Korea

S 78 P09-12

The role of K_v3 channels in regulating epithelial mesenchymal transition
Hun Ju Sim, So Yeong Lee
Laboratory of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

S 78 P09-13

Evaluation of functional integrity of human dopaminergic organoid iPSC neurons with electro physiological methods
Eunhee Yang[1], YunSu Bang[2], Juhyun Choi[2], Zewon Park[2], Jong Gu Lee[2], Young-Ho Jin[1]
[1]Department of Physiology, School of Medicine, Kyung Hee University, Seoul, [2]Clinical Research Division, National Institute of Food and Drug Safety Evaluation, Osong, Korea

S 78 P09-14

CR6-interacting factor 1 deficiency induces vascular senescence through SIRT3 inhibition in endothelial cells
Seonhee Kim[1,2,3], Shuyu Piao[1,2,3], Ikjun Lee[1,2,3], Harsha Nagar[1,2,3], Su-jeong Choi[1,2,3], Byeong Hwa Jeon[1,2,3], Cuk-seong Kim[1,2,3]
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S 78 P09-15

Dopamine D2 blockade inhibits cell growth of neuroblastoma cell lines in vitro and in vivo.
Seo-Hyun Yu[1,2], Sungkun Chun[1,2]
Department of [1]Physiology,[2] Brain Korea 21 Plus Program, Chonbuk National University Medical School, Jeonju, Korea

S 79 P09-16

Internalization and transportation of endothelial cell surface $K_{Ca}2.3$ and $K_{Ca}3.1$ in normal pregnancy and preeclampsia
Shinkyu Choi, Ji Aee Kim, Hai-yan Li, Suk Hyo Suh
Department of Physiology, Medical School, Ewha Womans University, Seoul, Korea

S 79 P09-17

Differential effect of PML on OSM-induced STAT-3 activity depending on p53 status
Jiwoo Lim, Seulgi Lee, Youn-Hee Choi
Department of Physiology, Tissue Injury Defense Research Center, College of Medicine, Ewha Womans University, Seoul, Korea

S 79 P09-18

Ursolic acid plus paclitaxel induced anti-cancer efficacy through Akt/FOXM1 signaling cascade in esophageal cancer cells
Ruo Yu Meng, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 79 P09-19

UA plus 3,3-diindolyl-methane enhanced anti-tumor activity in esophageal cancer cells
Ruo Yu Meng, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 80 P09-20

Combined treatment of 3,3-diindolylmethane and 5-fluorouracil leads to apoptosis of gastric cancer cells
Li CongShan, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 80 P09-21

Panobinostat inhibit gastric cancer cells through cell cycle arrest
Da-Yeah Kim, Soo Mi Kim
Department of Physiology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Korea

S 80 P09-22

Anti-cancer effect of SIRT6 in hepatocellular carcinoma
Da-Yeah Kim, Soo Mi Kim
Department of Physiology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Korea

S 81 P09-23 Recombinant human BMP-2 suppresses the proliferation of Human colorectal cancer cells by activation of Hippo signaling
Yu Chuan Liu, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 81 P09-24 Knockdown of hematopoietic- and neurologic-expressed 1 induces autophagy in colorectal cancer
Yu Chuan Liu, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Korea

S 81 P09-25 Effects of ursodeoxycholic acid on lipopolysaccharide-stimulated signals in biliary epithelial cells (BECs)
Yangmi Kim
Department of Physiology, Chungbuk National University College of Medicine, Cheongju, Korea

S 81 P09-26 ATP binding cassette transporter A1 is involved in extracellular secretion of acetylated APE1/Ref-1
Yu Ran Lee[2], Hee Kyoung Joo[2], Eun Ok Lee[2], Sung Min Kim[1,2], Hao Jin[1,2], Byeong Hwa Jeon[1,2]
[1]Research Institute of Medical Sciences, Department of Physiology, [2]Department of BK21Plus CNU Integrative Biomedical Education Initiative, College of Medicine, Chungnam National University, Daejeon, Korea.

S 82 P09-27 Recombinant Ac-APE1/Ref-1 induces apoptotic cell death in hyperacetylated TNBC cells
Hao Jin[1,2,3], Yu Ran Lee[3], Hee Kyoung Joo[3], Eun Ok Lee[3], Sung Min Kim[1,2,3], Byeong Hwa Jeon[1,2,3]
[1]Department of Medical Science, [2]Research Institute of Medical Sciences, Department of Physiology, [3]Department of BK21Plus CNU Integrative Biomedical Education Initiative, College of Medicine, Chungnam National University, Daejeon, Korea.

S 82 P09-28 Effect of histone deacetylase inhibitors on differentiation of human bone marrow-derived stem cells into neuron-like cells
Sujeong Jang[1], Han-Seong Jeong[1], Hyong-Ho Cho[2], Seokho Park[1], Ung Yang[3], Maru Kang[4], Jong-Seong Park[1], Sah-Hoon Park[1]
[1]Department of Physiology, [2]Department of Otolaryngology-Head and Neck Surgery, Chonnam National University Medical School, [3]Department of Horticulture, Asian Pear Research Institute, College of Agriculture and Life Sciences, Chonnam National University, [4]Department of Defense Science & Technology, Gwangju University, Gwangju, Korea

S 82 P09-29 The APE1/Ref-1 inhibits vascular calcification and loss of the smooth muscle phenotype in vascular smooth muscle cells
Eun Ok Lee[1], Ki Mo Lee[1], Yu Ran Lee[1], Hee Kyoung Joo[1], Sung Min Kim[1], Hao Jin[1], Cuk-Seong Kim[1], Jin Ok Jeong[2], Byeong Hwa Jeon[1]
[1]Research Institute of Medical Sciences, Department of Physiology, School of Medicine, [2]Division of Cardiology, Department of Internal Medicine, Chungnam National University, Daejeon, Korea

S 82 P09-30 HB-EGF mediates A549 cell migration
Hee Ju Song, Taehee Kim, YHST wickramasinghe, Sang Do Lee
Department of Physiology, Chungnam National University School of Medicine, Daejeon, Korea

P10: Exercise and Integrative physiology

S 83 P10-01 Resistance exercise in the heart of diabetic rats improves cardiac function and mitochondrial efficiency
Hamin Choi[1], Tae Hee Ko[1], Jubert C. Marquez[1], Hyoung Kyu Kim[1,2], Seung Hun Jeong[1], SungRyul Lee[1,2], Jae Boum Youm[1], In Sung Song[1], Dae Yun Seo[1], Hye Jin Kim[3], Du Nam Won[3], Kyoung Im Cho[4], Mun Gi Choi[5], Byoung Doo Rhee[6], Kyung Soo Ko[6], Nari Kim[1], Jong Chul Won[6], Jin Han[1]
Department of [1]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, Department of Health Sciences and Technology, BK21 plus Project Team, College of Medicine, Cardiovascular and Metabolic Disease Center, [2] Department of Integrated Biomedical Science, College of Medicine, Inje University, [3] GE Healthcare Ultrasound Applications, [4] Division of Cardiology, Department of Internal Medicine, College of Medicine, Kosin University, Busan, [5] Departments of Sports and Leisure Study, Inje University, Gimhae,[6] Department of Internal Medicine, College of Medicine, Sanggye Paik Hospital, Cardiovascular and Metabolic Disease Center, Inje University, Seoul, Korea

S 83 P10-02 Aerobic exercise training decreases hepatic asprosin in diabetic rats
JeongRim Ko[1], DaeYun Seo[1], HyunSeok Bang[2], Jin Han[1]
[1]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, BK21 Plus Project Team, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, [2]Department of Physical Education, College of Health, Social Welfare and Education, Tong Myong University, Busan, Korea

P11: Physiomes and Systems Biology

S 83 P11-01 Effects of virtual inhibition of Na^+/Ca^{2+} exchanger on the pacemaker mechanisms in the computational model of human sinoatrial cell; a case of pre-med students' research program in SNU
Seong Won Jo[1], Seung June Yoo[1], Chang Hyun Lee[2], Young-Keul Jeon[3], Sung Joon Kim[3]
[1]Premedicine Course (Gr 2) and [2]Medicine Course (Gr 1), [3]Department of Physiology and Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 84 P11-02 A computational study on the interatrial difference of rat in the arrhythmogenicity on sympathetic stimulation
Jieun An[1], Ami Kim[1], Sun Hwa Park[1], Hyun Bin Choi[1], Tong Mook Kang[1], Jae Boum Youm[2]
[1]Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, [2]Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 84 P11-03 Investigation of hemodynamic behavior using computational fluid dynamics in the human coronary arteries
Jung Joo Kim, John Mark Matulac, Nazatul Nurzazlin Zakariah, Nari Kim
NLRL for Innovative Cardiovascular Engineering, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 84 P11-04 Teaching cardiac excitation-contraction coupling using a mathematical computer simulation model of human ventricular myocytes
Young Keul Jeon[1], Jae Boum Youm[2], Chae Hun Leem[3], Sung Joon Kim[1,4]
[1]Department of Physiology, [4]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, [2]Cardiovascular and Metabolic Disease Center, Department of Physiology, College of Medicine, Inje University, Busan, [3]Department of Physiology, University of Ulsan College of Medicine, Seoul, Korea

S 85 P11-05 Lessons from artificial neural network for studying coding principles of biological neural network
Hyojin Bae, Chang-Eop Kim
Department of Physiology, Gachon University College of Korean Medicine, Korea

S 85 P11-06 Long-range projectome from and to the mouse posterior parietal cortex with bioinformatic analysis
Sook Jin Son[1+], Seung Wook Oh[2+], John A. Morris[2], Changkyu Lee[3], Jong-Cheol Rah[1, 4]
[1]Korea Brain Research Institute, Daegu, Korea,[2]Grace Medical Institute, Lynnwood, Washington, [3]Allen Institute for Brain Science, Seattle, [4]Daegu Gyeongbuk Institute of Science & Technology, Daegu, Korea

S 85 P11-07 Feature selection models for the survival of human pancreatic cancer patients using deep learning algorithms
Han-Jun Cho, Sangcheol Lee, Dong Hyeon Lee
Department of Physiology, CHA University School of Medicine, Gyeonggi, Korea

P12: Others: Drugs, Phytochemicals, Miscellaneous

S 85 P12-01 Melatonin attenuates cisplatin-induced acute kidney injury through dual suppression of apoptosis and necroptosis
Jung-A Jung, Hye-Jeong Kim, Jae-Hyung Park
Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

S 86 P12-02 CRIF1 deficiency induced p66shc-regulated mitophagy in endothelial cells
Shuyu Piao[1,3], Harsha Nagar[1,2,3], Seonhee Kim[1,2,3], Su-Jeong Choi[1,2,3], Ikjun Lee[1,3], Byeong Hwa Jeon[1,3], 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, Korea

S 86 P12-03 Profiling of remote skeletal muscle gene changes resulting from stimulation of atopic dermatitis disease in NC/Nga mouse model
Yelim Seo[1], Young-Won Kim[1], Seongtae Kim[1], Jeongyoon Choi[1], Hyemi Bae[1], Inja Lim[1], Hyoweon Bang[1], Jung-Ha Kim[2], Jae-Hong Ko[1]
Departments of [1]Physiology, Chung-Ang University College of Medicine, [2]Department of Family Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea

S 86 P12-04 Functional characterization of the 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 87 P12-05 Varying blood glucose level affects atherosclerosis progression in streptozotocin-induced diabetic ApoE knockout mice
John Mark Matulac, Nazatul Nurzazlin, Jungjoo Kim, Nari Kim
NLRL for Innovative Cardiovascular Engineering, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University

S 87 P12-06 Osteopontin expression of streptozotocin-induced diabetic ApoE knockout mice model
Nazatul Nurzazlin Zakariah, John Mark Matulac, Jung Joo Kim, Nari Kim
NLRL for Innovative Cardiovascular Engineering, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 87 P12-07 Sympathetic activity mediates hypertrophic morphological changes in the primo vascular system of heart failure rats
Yiming Shen, Pan-Dong Ryu
Departments of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

S 87 P12-08 Cationic oligopeptide-functionalized mitochondria targeting sequence show mitochondria targeting and anticancer activity
Jessa Flores[1], Yoonhee Bae[2], Kyung Soo Ko[3], Jin Han[1], Joon Sig Choi[2]
[1]Department of Physiology, College of Medicine, Cardiovascular and Metabolic Diseases Center, Inje University, Busan, [2]Department of Biochemistry, College of Natural Sciences, Chungnam National University, Daejeon, [3]Department of Internal Medicine, Sanggye Paik Hospital, Cardiovascular and Metabolic Diseases Center, Inje University, Seoul, Korea

S 88 P12-09

Functional nanosome for enhanced mitochondria-targeted gene delivery and expression

Amy H. Kim[2], Yoonhee Bae[2], Min Kyo Jung[6], Su Jeong Song, [1]Eric S. Green[7], Seulgi Lee[1], Hyun-Sook Park[8], Seung Hun Jeong[2], Jin Han[2], Ji Young Mun[4,5], Kyung Soo Ko[3], Joon Sig Choi[1]

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S 88 P12-10

Effects of energy metabolism of astrocytes on neural activities in the medial vestibular nucleus of rats

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S 88 P12-11

Chronic exposure of ethylenethiourea induces nephrotoxicity and poly-cysts in mice

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S 89 P12-12

Fluorescence size-exclusion chromatography (FSEC) for studying mammalian membrane proteins

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S 89 P12-13

Flos Magnoliae and its constituent linoleic acid suppress T lymphocyte activation via store-operated calcium entry

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S 89 P12-14

Cytotoxicity of hair dye ingredients on human conjunctival epithelial cells and fibroblasts

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SS-1

Altered tumor microenvironment in colorectal cancer

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Despite recent advancement in anti-cancer therapies, long-term survival of metastatic colorectal cancer (CRC) remains low. Immunotherapy is effective in microsatellite unstable CRC tumors. However, PD-L1 expression and tumor mutational burden (TMB) are not prognostic marker for immune check point inhibitor therapy in CRC, which might require stronger neoantigen stimulation or immune suppression than other cancer types. Comprehensive landscape of immune cell status and the cellular interactions between cancer cells and the immune microenvironment could facilitate our understanding of the unique characteristics of CRC. In this study, we analyzed transcriptome of unsorted CRC single cells from 29 patients. We will discuss about cellular landscape and intercellular interactions in CRC, which can provide mechanistic grounds of efficient immuno-oncology treatment.

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Keywords: single cell RNA-seq, colorectal cancer, tumor microenvironment

SS-2

Highly efficient base-editing in mice

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Point mutations caused by nucleobase deamination are a major source of human genetic disorders and diversity. Unlike mutagens causing random nucleobase deamination, RNA-programmable deaminase systems, composed of a catalytically impaired CRISPR–Cas9 variant (D10A Cas9 nickase (nCas9) or catalytically deficient D10A/H840A Cas9 (dCas9) from S. pyogenes) and a deaminase protein from various sources, enable single-nucleotide conversions or base editing in cells and organisms in a guide RNA-dependent manner. These base editing systems can be divided into two categories: cytosine base editors (CBEs) that convert a C:G base pair to a T:A pair and Adenine base editors (ABEs) that convert a A:T pair to a G:C pair. Here we demonstrated the application of this technology in mouse embryos and adult mice.

Keywords: CRISPR–Cas9, cytosine base editors (CBE), Adenine base editors (ABE)

SS-3

Pharmacogenomic landscape of patient-derived tumor cells for precision oncology

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Outcomes of anticancer therapy vary dramatically among patients, which may be caused by the specific molecular alterations in each patient's tumor. Precision oncology aims to apply optimal therapies for each tumor based on its molecular characteristics. We have established a resource reporting the genomic and transcriptomic profiles of 462 patient tumor-derived cells (PDCs) across 14 cancer types, together with responses to 60 targeted agents. Compared with long-term cultured cancer cell lines, PDCs better recapitulate the molecular profiles of the original tumors. Among other unreported associations, we identified molecular factors, including NRG1 to induce resistance to EGFR inhibitors, and suggested repurposing ibrutinib (currently used in hematological malignancies) for EGFR-specific therapy in gliomas. In addition, we discovered lineage-specific drug sensitivities based on subcategorization of gynecologic tumors and identified TP53 mutation as a molecular determinant that elicits therapeutic response to a poly (ADP-Ribose) polymerase (PARP) inhibition therapy. We further identified transcriptome expression of inhibitor of DNA biding 2 (ID2) as a potential predictive biomarker for treatment response to olaparib. Lastly, using a retrospective clinical study, we find that PDC-derived sensitivities can be used to predict patient responses.

Keywords: Precision oncology, Patient tumor-derived cells, Pharmacogenomics, Drug screening

OP-01

Early administration of progesterone activates spinal astrocytes and enhances the development of neuropathic mechanical allodynia

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Progesterone exerts neuroprotective effects after nervous system injuries, however, there is a growing list of negative clinical trials that have failed to show a beneficial effect of progesterone treatment. Here we examined whether spinal progesterone has an effect on neuropathic pain, and whether progesterone-metabolizing enzyme cytochrome P450c17 is associated with the actions of progesterone. Neuropathic pain was produced by chronic constriction injury (CCI) of the right sciatic nerve in mice. Mechanical allodynia was evaluated using a von-Frey filament (0.16 g). Western blotting, co-immunoprecipitation, and immunohistochemistry were performed to assess the changes in cytochrome P450c17 activation and glial fibrillary acidic protein (GFAP) expression in spinal cord. Intrathecal administration of progesterone on post-operative days 0 to 3 enhanced the development of mechanical allodynia and spinal GFAP expression on day 1 post-surgery, while administration of progesterone on post-operative days 14 to 17 inhibited the developed pain and increased GFAP expression on day 17 post-surgery. Phospho-serine levels of spinal P450c17 were increased on day 1 post-surgery, but not on day 17 post-surgery. Co-administration of the P450c17 inhibitor, ketoconazole with progesterone on post-operative days 0 to 3 attenuated the progesterone-induced enhancement of mechanical allodynia and spinal GFAP expression in CCI mice. By contrast, co-administration of ketoconazole with progesterone on post-operative days 14 to 17 had no effect on the progesterone-induced inhibition of mechanical allodynia and GFAP expression. Collectively these results demonstrate that late administration of progesterone has an analgesic effect on the mechanical allodynia following peripheral neuropathy, whereas early administration of progesterone activates astrocytes and enhances the development of neuropathic mechanical allodynia via the activation of progesterone-metabolizing enzyme P450c17.

Keywords: Progesterone, Cytochrome P450c17, Astrocytes, Mechanical Allodynia, Neuropathic pain

OP-02

NALCN channel is essential for pacemaking and burst activities in substantia nigra dopamine neurons

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Midbrain dopamine neurons exhibit two major firing patterns: slow tonic firing and high-frequency phasic (burst) firing. Tonic pacemaking occurs spontaneously and regularly to maintain basal dopamine level, whereas phasic burst firing is evoked by glutamatergic afferents to increase dopamine transients in target brain areas. Sodium leak channel (NALCN), a major Na^+-permeable nonselective cation channel, generates background Na^+ leak conductance, resulting in regulation of resting membrane potential (RMP) and neuronal excitability. Despite the importance of background Na^+ leak conductance in several pacemaker neurons, it has been not investigated whether NALCN channel contributes to these firing patterns in nigral dopamine neurons. Moreover, lack of specific inhibitors has hindered detailed investigation on physiological roles of NALCN. Recently, we found that NBQN compounds inhibit NALCN without affecting transient receptor potential (TRPC) cation channels. Using this pharmacological tool, we observed that inhibition of NALCN channels suppresses background Na^+ leak current and hyperpolarizes membrane potential in the dopamine neurons that express NALCN endogenously. In addition, when NALCN was blocked, pacemaking was completely abolished and it can be reinstated by injecting similar linear-shape currents. NALCN channels blockers also attenuated the glutamate-evoked burst firing. From these results, we conclude that NALCN could play an important role not only in generation of pacemaker activity, but also in regulation of evoked burst discharges in nigral dopamine neurons.

Keywords: NALCN channel, Dopamine neuron, Pacemaking, Burst firing

OP-03

Three-dimensional heart model–based screening of proarrhythmic potential by in silico simulation of action potential and electrocardiograms: verapamil and ranolazine vs. dofetilide

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The proarrhythmic risk is a major concern in drug development. The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative has proposed the JTpeak interval on electrocardiograms (ECGs) and qNet, an in silico metric, as new biomarkers that may overcome the limitations of the hERG assay and QT interval. In this study, we simulated body-surface ECGs from patch-clamp data using realistic models of the ventricles and torso to explore their suitability as new in silico biomarkers for cardiac safety. We tested three drugs in this study: dofetilide (high proarrhythmic risk), ranolazine, and verapamil (QT increasing, but safe). Human ventricular geometry was reconstructed from computed tomography (CT) images, and a Purkinje fiber network was mapped onto the endocardial surface. The electrical wave propagation in the ventricles was obtained by solving a reaction-diffusion equation using finite-element methods. The body-surface ECG data were calculated using a torso model that included the ventricles. The effects of the drugs were incorporated in the model by partly blocking the appropriate ion channels. The effects of the drugs on single-cell action potential were examined first, and three-dimensional (3D) body-surface ECG simulations were performed at free Cmax values of 1x, 5x, and 10x. In the single-cell and ECG simulations at 5x Cmax, dofetilide, but not verapamil or ranolazine, caused arrhythmia. However, the non-increasing JTpeak caused by verapamil and ranolazine that has been observed in humans was not reproduced in our simulation. Our results demonstrate the potential of 3D body-surface ECG simulation as a biomarker for evaluation of the proarrhythmic risk of candidate drugs.

Keywords: 3D heart model, ECG simulation, hERG, QT, Torsade de pointes

OP-04

Feature selection models for the survival of human pancreatic cancer patients using deep learning algorithms

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Pancreatic duct carcinoma (PDAC) is a cancer that is highly chemo-resistant and is easily spread from pancreas to other organs. New biomarkers for diagnosis and prognosis prediction are needed because of the heterogeneous molecular profile and low survival rate of PDAC. In this study, based on the gene expression profile, the goal is to develop a classification model that distinguishes survival and death of patients of PDAC. We employed supervised learning algorithms deep learning with enriched model learning by 6 feature selection(information gain, Chi-squared test, MRMR, Gini index,

Relief, Fast Correlation based filter) to develop classification models trained on sequencing based gene expression data of RNA expression, obtained from GEO data set. A total of 88 genes were selected and the 15 genes were overlapped. Other models developed in this study were evaluated based on attribute verification and independent data set testing. Information gain and genie index-deep learning-based forecasting models performed best among the models developed in the study, with a precision, recall, specificity and accuracy of 100% and a auROC 100%. It is expected that the prioritized subset of 88 genes and forecasting models found in this study will be able to quickly understand the molecular mechanism of experimental survival progression and will help to identify the mechanism of predictive factors for PDAC tumors.

Keywords: Pancreas ductal adenocarcinoma, GEO data, RNA expression, Deep learning

OP-05

HCN channel regulates somatodendritic membrane trafficking of voltage-gated potassium channel

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The voltage-gated potassium channel $K_v2.1$ has a critical role in regulating neuronal membrane excitability and is localized to plasma membrane clusters on the soma, proximal dendrites, and axon initial segment (AIS). Hyperpolarization activated cyclic nucleotide-gated channel 2 (HCN2) is localized to the soma, dendrites, and axon terminals in neurons, and these localizations show differences among neuronal cell types. HCN2 channel is implicated in neuropathic pain, febrile seizure, and depression and contributes spontaneous rhythmic activity in brain. Here, we show that $K_v2.1$ channels affinity-purified from rat brain are associated with HCN2 channels using mass spectrometry. HCN2 and $K_v2.1$ channel expressions reveal a different distribution among the distinct regions of the brain. Co-expression of HCN2-WT and $K_v2.1$ in heterologous cells results in plasma membrane localization, while HCN2-N380Q, a trafficking-defective mutant, retains $K_v2.1$ in the endoplasmic reticulum. In hippocampal neurons, HCN2-WT dramatically reconstitutes the large somatodendritic and axonal clusters of $K_v2.1$ in plasma membrane, whereas HCN2-N380Q significantly leads to disruption of the clustering and AIS specific localization of $K_v2.1$. Thus, these results suggest that HCN2 channel regulates the surface localization and axonal trafficking of $K_v2.1$ in neurons.

Keywords: Hyperpolarization activated cyclic nucleotide-gated channel 2, Voltage-gated potassium channel, membrane trafficking

OP-06

TRPML1/3 heteromer regulates autophagosome-lysosome fusion as a PI4P downstream effector

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TRPML subfamily consists of TRPML1, TRPML2 and TRPML3, all of which are intracellular Ca^{2+}-permeable cation channels. Among them, both TRPML1 and TRPML3 are implicated in autophagy, but their roles are distinctly different. We have previously shown that TRPML3 acts as a downstream effector of PI3P, providing Ca^{2+} in autophagosome biogenesis. Because TRP channels often form heteromers between subfamily members, we hypothesized that TRPML1/3 heteromeric channels may play a different role in autophagy from homomeric channels. TRPML1 and TRPML3 co-immunoprecipitated each other both in the native and heterologous expression systems and TRPML1-mediated Ca^{2+} efflux was nearly completely inhibited by the dominant-negative TRPML3(D458K), suggesting that TRPML3 forms a functional heteromeric channel with TRPML1. To experimentally produce a heteromeric channel, we generated TRPML1/3 concatemers with various tags including GCaMP6, a genetically encoded Ca^{2+} indicator, for visualization of TRPML1/3 activity in the subcellular compartments. Similarly to TRPML3 homomer, TRPML1/3 heteromer was also expressed at the plasma membrane and endocytic and autophagic pathways and functions as a Ca^{2+}-permeable cation channel. Unlike TRPML3 homomer, however, TRPML1/3 heteromer was active in the acidic organelles such as lysosomes and mature autophagosomes, indicating that the heteromer provides Ca^{2+} at the later stage of autophagy. TRPML1/3 dramatically accelerated autophagosome degradation processes rather than autophagosome formation, leading to increased autophagic flux. Importantly, TRPML1/3 was activated by PI4P that is essential for autophagosome-lysosome fusion. Overexpression of TRPML1/3 similarly increased autophagosome-lysosome fusion events to PI4P application, implying that TRPML1/3 heteromer functions downstream of PI4P in autophagy. Taken together, these results suggest that TRPML3 regulates autophagy by homo- and heteromerization and heteromeric TRPML1/3 contributes more to later stage of autophagy by supplying Ca^{2+} for the autophagosome-lysosome fusion step.

Keywords: TRPML1/3, Heteromer, Autophagy, GCaMP6, PI4P

OP-07

Orai1-mediated store-operated Ca^{2+} entry in podocyte is critical for kidney filter integrity

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Podocyte, the gatekeeper of kidney filter, is a primary target for Ca^{2+} signaling whose perturbation causes actin remodeling leading to slit diaphragm disruption and proteinuria. Gain-of-function mutations of *TRPC6* and/or hyperactivation of TRPC5 and TRPC6 are associated with podocyte dysfunction and albuminuria. Store-operated Ca^{2+} entry (SOCE) is a ubiquitous Ca^{2+} influx mechanism mediated by ER Ca^{2+} sensors (STIM1 and 2) and Ca^{2+}-selective channels (Orai1-3). However, it is currently unknown whether SOCE-mediated Ca^{2+} signaling in podocyte directly regulates actin dynamics and filter function. Here we find that Orai1/STIM1 couple is the primary molecular machinery of SOCE and is critical for regulating actin cytoskeleton architecture of podocyte. To explore whether Orai1-mediated SOCE in podocytes is functional Ca^{2+} entry mechanism regulating filter integrity *in vivo*, we generate mice with podocyte-specific *Orai1* deletion. These mice show impaired SOCE in isolated glomeruli together with decreased Orai1 expression. Moreover, transgenic overexpression of *Orai1* in mice causes foot process fusion and albuminuria supporting that Orai1 is a novel culprit for slit diaphragm dysfunction and proteinuria. Notably, SOCE is preserved in isolated glomeruli from *Trpc6* knockout mice, proving that TRPC6 barely influences SOCE. Our results demonstrate that Orai1-medicated SOCE is vital for maintaining filter integrity providing a novel perspective on the pathogenesis of podocyte injury and clues for treatment of the proteinuric diseases.

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Keywords: SOCE, STIM1, TRPC6, Ca^{2+} signaling, Actin cytoskeleton, Proteinuria

OP-08

Neddylation blockade induces HIF-1α driven cancer cell migration via upregulation of ZEB1

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Neddylation is a process by which NEDD8 is covalently conjugated to target proteins by sequential enzymatic reaction. Its role in cancer cell migration has only been recently acknowledged. Previously in cancer cell migration, the epithelial to mesenchymal transition (EMT) process has been well-known to play an important role in both invasion and metastasis by promoting mesenchymal phenotype in epithelial cells. However, the role of neddylation in the EMT process and its mechanistic details are yet to be elucidated. We recently reported that neddylation plays a crucial role in cancer cell migration through the PI3K-Akt pathway. Here, we report that inhibiting neddylation activates the hypoxia-inducible factor 1α (HIF-1α) through the PI3K-Akt pathway, which eventually regulates the EMT-activator ZEB1 (zinc finger E-box binding homeobox 1) in various cancer cell lines. As induction of HIF-1α is known to deteriorate the state of cancer and EMT process is one of the hallmarks of metastasis in cancer, our findings uncover the novel association of HIF-1α and ZEB1 through the process of neddylation.

Keywords: EMT, Neddylation, HIF-1α, ZEB1, Metastasis

OP-09

Sympathetic stimulation-mediated mitochondrial regulation in mouse beige and brown adipocytes

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Brown fat mass declines particularly in obese adults as well as diabetes mellitus patients, while thermogenic induction in brown adipose tissue (BAT) is accompanied by the improvement of insulin resistance, hyperlipidemia and adiposity. In this study, we focused on the acute regulation of adipocyte thermogenesis stimulated by exogenous (β_3-adrenergic) and endogenous (mitochondrial Ca^{2+}) mechanism. We used immortalized brown adipocytes or differentiated cells from mouse brown adipose tissues. Beige adipocytes were isolated from white adipose tissue and induced browning with rosiglitazone and triiodo-L-thyronine. In either brown or beige adipocytes, norepinephrine (NE) enhanced mitochondrial respiration and mitochondrial proteins including uncoupling protein 1 (UCP1) and mitochondrial calcium uniporter (MCU) within 1 hour. The transcriptional level of mitochondrial proteins remained unchanged by NE, implying that this early mitochondrial activation might be caused by the alteration of proteins' stability. In the presence of MG132, a proteasome inhibitor, mitochondrial proteins such as UCP1 and MCU maintained higher protein levels without further increase by NE, revealing that NE-mediated acute upregulation of mitochondrial proteins resulted from the inhibition of proteasomal degradation. While the thermogenic consequence of UCP1 abundance has been well-known, there is still controversy about the role of mitochondrial Ca^{2+} uptake via MCU on thermogenesis. Suppressing MCU expression using siRNA strategy diminished mitochondrial respiration as well as mitochondrial proteins including UCP1. NE-mediated elevation in mitochondrial activities and protein abundance were also attenuated by MCU knockdown. Furthermore, mitochondria became more fragmented with depolarized membrane potential in MCU-silenced cells. Taken together, we propose a novel acute regulatory mechanism in sympathetic-stimulated thermogenesis of brown and beige adipocytes, which provides significant implications for therapeutic applications on obesity and various metabolic diseases.

Keywords: Brown adipose tissue, Browning, Thermogenesis, Mitochondria, Uncoupling protein 1, Sympathetic stimulation, Norepinephrine, Mitochondrial calcium uniporter

OP-10

Reduction of human non-small cell lung cancer cell growth by sea hare hydrolysates through regulation of macrophage polarization and pyroptosis and necroptosis

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Sea hare-derived glycosaminoglycans and sea hare hydrolysates (SHH) induce macrophage activation and reduction of asthmatic parameters in a mouse model of allergic asthma, respectively. These findings led us to study the function of SHH on cancer pathophysiology. The effects of SHH on macrophage polarization were identified in mouse RAW264.7 cells and peritoneal macrophages and human THP-1 cells. SHH treatment induced macrophage activation in RAW264.7 cells, peritoneal macrophages, and THP-1 cells, like lipopolysaccharide (LPS) (+ INF-γ) did. However, SHH reduced interleukin (IL)-4 (+IL-13)-induced M2 macrophage polarization. In addition, SHH treatment inhibited the actions of M1 and M2 macrophage, which have anti-cancer and pro-cancer effect, respectively, in A549 and TAM. Furthermore, SHH induced cell death and inhibition of cell growth in A549 cells. The SHH-induced G2/M phase arrest and inhibition of M2 macrophage polarization were mediated through down-regulation of STAT3 activation. The inhibition was recovered by colivelin, a STAT3 activator. Pyroptosis and necroptosis were involved in SHH-induced cell death and growth inhibition. Caspase-1 and necroptosis inhibitors were reduced the cell death, G2/M arrest, and growth inhibition by SHH treatment. Taken together, our results showed that SHH modulated macrophage polarization and induced cell death and growth inhibition. These results suggest that SHH may be offered as a potential remedy for cancer immunotherapy.

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Keywords: Lung cancer, Macrophage polarization, Necroptosis, Pyroptosis, Sea hare hydrolysates

YP-01

Neutrophil-derived extracellular vesicles: proinflammatory trails and anti-inflammatory microvesicles

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Extracellular vesicles (EVs) are membrane-derived vesicles that mediate intercellular communications. Neutrophils produce different subtypes of EVs during inflammatory responses. Neutrophil-derived trails (NDTRs) are generated by neutrophils migrating toward inflammatory foci, whereas neutrophil-derived microvesicles (NDMVs) are thought to be generated by neutrophils that have arrived at the inflammatory foci. However, the physical and functional characteristics of neutrophil-derived EVs are incompletely understood. In this study, we investigated the similarities and differences between neutrophil-derived EV subtypes. Neutrophil-derived EVs shared similar characteristics regarding stimulators, generation mechanisms, and surface marker expression. Both neutrophil-derived EV subtypes exhibited similar functions, such as direct bactericidal activity and induction of monocyte chemotaxis via MCP-1. However, NDTR generation was dependent on the integrin signaling, while NDMV generation was dependent on the PI3K pathway. The CD16 expression level differentiated the neutrophil-derived EV subtypes. Interestingly, both subtypes showed different patterns of miRNA expression and were easily phagocytosed by monocytes. NDTRs induced M1 macrophage polarization, whereas NDMVs induced M2 macrophage polarization. Moreover, NDTRs but not NDMVs exerted protective effects against sepsis-induced lethality in a murine sepsis model and pathological changes in a murine chronic colitis model. These results suggest a new insight into neutrophil-derived EV subtypes: proinflammatory NDTRs and anti-inflammatory NDMVs.

Keywords: EV, Extracellular vesicle, NDMV, Neutrophil-derived microvesicle, NDTR, Neutrophil-derived trail

YP-02

Effect of proton pump inhibitor on gastric smooth muscle in functional dyspepsia

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Functional dyspepsia (FD) is a common disorder of gastrointestinal tract. Proton pump inhibitor (PPI) is empirically used for management of FD, but PPI develops delayed gastric emptying, one of caused of FD, in 30 % of healthy people. To explain this paradoxical effects of PPI, we investigated the direct effect of PPI on human gastric smooth muscle (SM). Human gastric SM strips were prepared in organ bath, and isometric contraction was measured after pantoprazole treatment. Calcium imaging of SM and ICC-IM of mouse was performed. Whole-cell patch-clamp recordings were performed to measure ANO1 currents of HEK293 cells. Using ex-vivo mouse stomach, intra-gastric pressure was measured. Pantoprazole (200 uM) inhibited amplitude (1 vs. 0.665 ± 0.084), frequency (1 vs. 0.649 ± 0.154) and AUC (1 vs. 0.874 ± 0.053) significantly in human gastric SM strips (n=5). Frequency of calcium transient decreased in SMC GCAmP3 (n=3) and kit GCaMP3 (n=3) after pantoprazole. Pantoprazole (200 μM) reduced Ano1 current significantly. Intra-gastric pressure decreased significantly after pantoprazole treatment. pT853 and pT696 of MYPT1 decreased significantly after pantoprazole treatment. PPI inhibited contraction of human gastric smooth muscle, also decreased intra-gastric pressure in ex-vivo mouse stomach. These findings suggest that PPI develop delayed gastric emptying, and gastric accommodation, which may relieve symptoms of FD.

Keywords: Proton pump inhibitor, Functional dyspepsia, Smooth muscle, Stomach, Contraction

YP-03

Effects of lipid peroxidants on ion channels and proarrhythmia potential

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Oxidative stress under pathological conditions, such as ischemia/reperfusion and inflammation, results in the production of various reactive chemicals. Of these chemicals, 4-hydroxy-nonenal (4-HNE) and 4-oxo-nonenal (4-ONE), end products of ω6-polyunsaturated fatty acids peroxidation, have garnered significant attention. Our previous study revealed that 4-HNE suppresses both cardiac hERG channel activity and membrane expression resulting an action potential prolongation. However, the cardiotoxic effects of 4-ONE has not yet been reported. In the present study, we assessed the proarrhythmic potential of 4-ONE using the comprehensive in vitro proarrhythmia assessment (CiPA), which has been proposed from FDA. CiPA designed to apply in vitro and in silico assays for determining electrophysiological mechanisms conferring proarrhythmic risk to testing compounds. CiPA analyzes human cardiac ion channels including hERG, L-type Ca^{2+} current ($I_{Ca,L}$) and late $Na_v1.5$ current. We evaluated the effects of 4-ONE on the ion channels. Interestingly, the inactivation time constant of $I_{Ca,L}$ was significantly slowed by 4-ONE. In addition, late Nav1.5 current was evoked by 4-ONE application. The results from ionic currents are used for in silico simulations to calculate the proarrhythmic risk marker (qNet) by computational cardiomyocyte model (O'hara & Rudy model). In conclusion, we demonstrated the proarrhythmic risk of 4-ONE by using CiPA protocol, suggesting that 4-ONE may participate in proarrhythmic process of oxidative stress conditions in heart.

Keywords: Lipid peroxidation, 4-oxo-nonenal, Comprehensive in vitro Proarrhythmia assay

YP-04

Distress, behavioral coping, and correlation patterns of mGluR5 in neuropathic pain brain

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Helplessness and passive coping are common in chronic pain patients. Prolonged exposure to stressor alters individual's coping strategy to the persistent distress of aversive states. We investigated the relationship between metabotropic glutamate receptor 5 (mGluR5) levels in the brain regions and maladaptive behavioral responses in chronic neuropathic pain model animals. Regression analyses using [11C] ABP688 PET data from the previous study revealed distinct patterns of mGluR5 correlation between brain regions in pain animals. Investigation on the mGluR5 patterns showed that the mGluR5 levels in the pain-related brain areas were tightly connected to a common factor. In this study, we focused on the dysgranular zone of primary somatosensory cortex (S1DZ) and the prelimbic subregion of medial prefrontal cortex (PrL). Unexpectedly, mGluR5 levels in these regions were positively correlated in normal state, implying functional connection. This correlation between S1DZ and PrL disappeared in chronic neuropathic pain state, with significantly increased mGluR5 levels in both brain regions. Local treatment of mGluR5 antagonist reversed the behavioral alteration such as sensitized paw withdrawal response to von Frey filaments and impaired es-

cape response in the forced swimming test. These data reveal the previously unknown patterns of mGluR5 levels among brain regions and provide deeper insight into the mechanisms underlying altered coping strategy in subjects with persistent distress.

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Keywords: Neuropathic pain, Metabotropic glutamate receptor 5, Depression, PET

YP-05

Disruption of Ca^{2+}_i homeostasis and connexin 43 hemichannel function in the right ventricle precedes overt arrhythmogenic cardiomyopathy in Plakophilin-2–deficient mice

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Plakophilin-2 (PKP2) is classically defined as a desmosomal protein. Mutations in PKP2 associate with most cases of gene-positive arrhythmogenic right ventricular cardiomyopathy (ARVC). A better understanding of PKP2 cardiac biology can help elucidate the mechanisms underlying arrhythmic and cardiomyopathic events consequent to PKP2 deficiency. Here, we sought to capture early molecular/cellular events that can act as nascent arrhythmic/cardiomyopathic substrates. We used multiple imaging, biochemical and high-resolution mass spectrometry methods to study functional/structural properties of cells/tissues derived from cardiomyocyte-specific, tamoxifen-activated, PKP2 knockout mice ("PKP2cKO") 14 days post-tamoxifen (post-TAM) injection, a time point preceding overt electrical or structural phenotypes. Myocytes from right or left ventricular free wall were studied separately. Most properties of PKP2cKO left ventricular (PKP2cKO-LV) myocytes were not different from control; in contrast, PKP2cKO right ventricular (PKP2cKO-RV) myocytes showed increased amplitude and duration of Ca^{2+} transients, increased $[Ca^{2+}]$ in the cytoplasm and sarcoplasmic reticulum (SR), increased frequency of spontaneous Ca^{2+} release events (sparks) even at comparable SR load, and dynamic Ca^{2+} accumulation in mitochondria. We also observed early- and delayed-after transients in RV myocytes and heightened susceptibility to arrhythmias in Langendorff-perfused hearts. In addition, RyR2 in PKP2cKO-RV cells presented enhanced Ca^{2+} sensitivity and preferential phosphorylation in a domain known to modulate Ca^{2+} gating. RNAseq at 14 days post-TAM showed no relevant difference in transcript abundance between RV and LV, neither in control nor in PKP2cKO cells. Instead, we found an RV-predominant increase in membrane permeability that can permit Ca^{2+} entry into the cell. Cx43 ablation mitigated the membrane permeability increase, accumulation of cytoplasmic Ca^{2+}, increased frequency of sparks and early stages of RV dysfunction. Cx43 hemichannel block with GAP19 normalized $[Ca^{2+}]_i$ homeostasis. Similarly, PKC inhibition normalized spark frequency at comparable SR load levels. Loss of PKP2 creates an RV-predominant arrhythmogenic substrate (Ca^{2+} dysregulation) that precedes the cardiomyopathy; this is, at least in part, mediated by a Cx43-dependent membrane conduit and repressed by PKC inhibitors. Given that asymmetric Ca^{2+} dysregulation precedes the cardiomyopathic stage, we speculate that abnormal Ca^{2+} handling in RV myocytes can be a trigger for gross structural changes observed at a later stage.

Keywords: Arrhythmogenic right ventricular cardiomyopathy, Right ventricle, Plakophilin-2, Ca^{2+} homeostasis, connexin43 hemichannel

YP-06

An autaptic culture system for standardized analyses of iPSC-derived human neurons

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Recently the innovatively developed technology to differentiate human neurons has directly enabled to study the human brain disease models instead of rodent or fish. The molecular biological and morphological approaches have gone a step further in identifying the more specific causes of brain diseases. However, without any functional analysis, we could not achieve to progress furthermore because each neuron has unique properties. Thus, to understand and standardize this heterogeneity of neuronal actions, we developed an autaptic neuronal culture system that single neuron grows on astrocyte island and consequently form the synapses by themselves. This system allows simultaneously to analyze the functional and morphological aspect of each neruons. Using this system, we studied single neuronal level induced from 22q11 deletion syndrome patients, one of the neuropsychiatric disorders. The mutant neurons showed rapid growth, early synapse formation and increase in densities of voltage-dependent potassium and sodium channels. We propose our optimized autaptic culture system as a tool to study functional features of human neurons, particularly in the context of disease phenotypes and experimental therapy.

Keywords: Human iPSCs, Autaptic culture, 22q11 deletion syndrome

YP-07

Induction of AP-1 by YAP/TAZ contributes to cell proliferation and organ growth

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Yes-associated protein (YAP) and its homolog transcriptional coactivator with PDZ-binding motif (TAZ) are key effectors of the Hippo pathway to control cell growth and organ size, of which dysregulation yields to tumorigenesis or hypertrophy. Upon activation, YAP/TAZ translocate into the nucleus and bind to TEAD transcription factors to promote transcriptional programs for proliferation or cell specification. Immediate early genes, represented by AP-1 complex, are rapidly induced and control later-phase transcriptional program to play key roles in tumorigenesis and organ maintenance. Here, we report that YAP/TAZ directly promote *FOS* transcription that in turn contributes to the biological function of YAP/TAZ. YAP/TAZ bind to the promoter region of *FOS* to stimulate its transcription. Deletion of YAP/TAZ blocks the induction of immediate early genes in response to mitogenic stimuli. *FOS* induction contributes to expression of YAP/TAZ downstream target genes. Genetic deletion or chemical inhibition of AP-1 suppresses growth of YAP-driven cancer cells, such as *Lats1/2*-deficient cancer cells as well as $G\alpha_{q/11}$-mutated uveal melanoma. Furthermore, AP-1 inhibition almost completely abrogates the hepatomegaly induced by YAP overexpression. These reveal a feedforward interplay between immediate early transcription of AP-1 and Hippo pathway function.

Keywords: YAP/TAZ, Hippo pathway, Hepatomegaly, Uveal melanoma

Plenary Lecture 1

Acute response and chronic adaptation to cold stress *via* a single epigenetic enzyme but through distinct mechanisms

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Recent studies suggest that mammals have thermogenic adipocytes referred to as beige/brite adipocyte. Under chronic cold stress, beige adipocytes emerge in WAT depots, especially in subcutaneous WAT (scWAT) to augment whole body thermogenesis in an adaptive process referred to as "browning" or "beige-ing" of scWAT which is thought to be associated with epigenetic modifications.

The epigenome is a "memory system" at cellular level and is pivotal for long-term adaptation to a given environment. Histone 3 lysine 9 (H3K9) methylation causes transcriptionally inactive condensed chromatin. JMJD1A demethylates di- and mono- lysine 9 methylated histone H3 (H3K9me1 and me2) and activates transcription by inducing the de-condensation of chromatin. Due to its demethylation activity, JMJD1A has a wide array of metabolic functions. It affects glucose and lipid metabolism, normal body weight control, thermogenesis, etc. JMJD1A-null mice exhibit obesity due to reduced energy expenditure. Through multi-omics analyses, we revealed that, when sympathetic nerve is activated (e.g. exposure to cold), subsequent β-adrenergic activation leads to JMJD1A phosphorylation at specific serine residues. This, in turn, triggers protein complex formation with SWI/SNF chromatin remodeler, which regulates nucleosome ejection and repositioning. It also regulates nuclear receptor PPARγ, and triggers changes to distal enhancers and promoter proximity via 3D chromatin structure changes. This leads to rapid gene transcription. Using this integrated "-omics" technology, we further demonstrated that under chronic cold stress, JMJD1A promotes browning of white adipose tissue via H3K9 demethylation. These studies proposed the concept of epigenetic regulation comprising a two-step process, acute response and chronic adaptation, for adaptation to cold environment.

Keywords: epigenome, adipocyte, adaptive thermogenesis, environmental cue, cold

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Jan 2003 - Jun 2009	Project Professor (The University of Tokyo)
July 2009 - present	Professor (The University of Tokyo)
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Research History and current focus

Professor Juro Sakai, when he was a graduate student, discovered very low-density lipoprotein receptor, which was the 2nd lipoprotein receptor, the 1st one is the low-density lipoprotein receptor discovered by Drs. Goldstein and Brown who were awarded Nobel Laurence in 1985. Juro Sakai spent his postdoctoral fellowship in their laboratory and studied the transcription factor called Sterol Regulatory Element binding protein. He revealed how SREBP senses cholesterol and is activated (Sakai J et al Cell 1996). He eventually discovered the protease that cleaves SREBP to activate it (Sakai J et al Mol Cell 1998). After coming back to Japan, he started his research related to energy expenditure and obesity. Using genome science, he showed important role of orphan nuclear receptor PPAR-delta in energy expenditure and preventive effect on obesity (PNAS 2003). He also found the important role of acetate as a fuel under fasting/ketogenic condition (Cell met 2009). He also started epigenetics and metabolism especially in adipocyte biology and endocrinology (Mol Cell 2015, Nature Commun 2015, 2016, 2018, Nature reviews molecular and cellular biology 2016). He is currently focusing on the environmental cue and development of health and diseases.

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Plenary Lecture 2

Cardiac calcium signaling: calcium imaging, genetically-engineered mice, and RyR2-gene editing

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Over the last 60 years, the field of EC-coupling (Ca^{2+} signaling) has had immense progression from measurements of action potential and contraction in intact heart, to voltage clamping intact ventricular trabeculae, to introducing calcium sensitive dyes into intact tissue, to dialyzing fluorescent Ca^{2+} sensing dyes into patch clamped single cardiomyocytes, to imaging and quantifying ryanodine receptor (RyR2) Ca^{2+} sparks, to genetically overexpressing or deleting the proteins of calcium signaling pathway in mice hearts, to isolating, cloning, and determining the crystal structure of Ca^{2+} signaling proteins, and finally to editing the genes of calcium signaling cascade using CRISPR/Cas9 and examining their functional E-C coupling consequences. My lab has been fortunate to have had the technology and the talents of younger scientists from around the world to have contributed to many aspects of this scientific progression.

CRISPR/Cas9 mediated gene editing of human induced pluripotent stem cells (hiPSCs) provides a novel platform to study precisely the functional consequences of point mutations in RyR2, especially those associated with the CPVT1 arrhythmia. We have already reported that CRISPR/Cas9 engineered CPVT1 associated RyR2 mutations, R420Q, Q4201R and F2483I, introduced in hiPSC-CMs reproduce reliably the CPVT1 electrophysiological phenotype of patient derived cardiomyocytes, by showing increased diastolic Ca^{2+} leaks, smaller SR Ca^{2+} stores, long lasting Ca^{2+} sparks that wander and reignite, producing often EADs and DADs and aberrant action potential rhythm. We have extended these studies by creating cardiomyocytes with other CPVT1-associated mutations not only in 3-different domains of RyR2 (central, carboxyl- and N-terminal), but also in Ca^{2+} (Q3925E), caffeine (W4645R), and FKBP binding sites (N771D) of RyR2, based on near-atomic (2.8 Å) structure of RyR. Ca^{2+} imaging of patch-clamped hiPSC-CMs expressing Q3925E although revealed somewhat suppressed ICa triggered Ca^{2+}-transients, unexpectedly showed suppressed caffeine-induced Ca^{2+}-release, similar to mutation of caffeine binding site W4645R, which had an enhanced CICR, suggesting possible interaction of the caffeine and Ca^{2+} sites. Interestingly, the N771D mutation had lower diastolic leak compared to WT, not predicted from the proposed stabilizing effects of FKBP on RyR2. Surprisingly, in <50% of intact mutant cardiomyocytes, 20 mM caffeine triggered either aberrant Ca^{2+} "puffs" or smaller and slower, and 2APB–sensitive Ca^{2+} releases in Q3925E, but not in W4645R mutants suggestive of possible IP3 mediated Ca^{2+} releases. It is likely that Q3925E-RyR2 mutation suppression of caffeine-triggered release maybe mediated by decreased caffeine-induced sensitization of RyR2 to Ca^{2+} as reflected in the inhibition of Ica-gated release in Q3925E mutant. We posit that the molecular proximity of the two sites may mediate the molecular interaction of the two sites. Our data suggests that hiPSC-CMs are an appropriate human cellular model to study the Ca^{2+} signaling related CPVT1 pathology and provide novel insights into structure/function of RyR2, and provides evidence that CPVT1-associated mutations are causative and their pharmacotherapy related, in part, to RyR2 mutation-domains.

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S-1-1

Development of depression-related pain animal model

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According to the social development, health problem related with functional somatic syndrome is increasing. Functional somatic syndrome can be characterized by multiple somatic symptoms caused by unknown reason and tension headache, temporomandibular dysfunction and fibromyalgia are included. In most case of this syndrome, pain is the primary somatic symptom in the functional somatic syndrome and depression is the dominant symptom of mental disorder. Because of this, pain and depression are believed to be closed related each other. However, pathophysiology and related neuronal mechanism of pain and depression disorder remain unrevealed due to lack of proper animal model. For this reason, I want to introduce recent scientific results for the study of "Pain-Depression Dyad".

Keywords: Pain, Depression, Animal Model

S-1-2

Decoding of spontaneous pain information from cortical two-photon calcium imaging in awake mice with machine learning

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Various animal models of pain have been developed for studying its basic mechanisms and evaluating the analgesic efficacies of drugs. Generally, behavioral responses (e.g. licking and withdrawal) have been measured as the quantitative endpoint of pain in those animal models. In such conventional behavioral response paradigms, however, an objective measurement of spontaneous ongoing pain during chronic neuropathic pain, headache, motor impairment or other CNS diseases is not possible. The primary somatosensory (S1) cortex plays an important role in the perception and discrimination of pain sensation. In the present study, we hypothesized that neuronal activity patterns in the mouse S1 cortex are distinct between pain and non-pain conditions, and that this discrepancy can be used for measuring spontaneous pain and then evaluating the analgesic efficacies of pain killers. To explore this hypothesis, we performed in vivo two-photon calcium imaging in the S1 cortex of awake, head-fixed mice with or without formalin-induced spontaneous pain. We also applied a machine learning to decode spontaneous pain information from the recorded neuronal calcium activity patterns. In this talk, I will explain and discuss in detail what the issues of conventional analyses were and how to achieve the goal of this study.

Acknowledgement: This study was supported by National Research Foundation of Korea grants funded by the Korea government (NRF-2017M3C7A1025604) and by a grant (HI17C0309) from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Korea.

Keywords: Spontaneous pain, In vivo two-photon calcium imaging, S1 cortex, Machine learning

S-1-3

Novel strategies for inhibiting TRPV1 activation using human DRG neuron platform

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Transient Receptor Potential Vanilloid 1 (TRPV1) is a non-selective Ca^{2+}-permeable cation channel that can be activated in peripheral terminals of nociceptive fibers by diverse stimuli including noxious heat, protons, and chemicals such as capsaicin or resiniferatoxin (RTX). It is a key molecule involved in the development of peripheral and central sensitization contributes to chronic pain. Recently, several studies reported that TRPV1 antagonists are potential drugs for pain treatment. However, it has an obstacle for drug development due to side effects such as hyperthermia and the increase in heat pain threshold. Here, we suggest novel strategies for inhibiting TRPV1 activation without side effects using human DRG neuron platform. First, we can develop activation modality-specific TRPV1 antagonists since the hyperthermic effect has the highest sensitivity to the extent of TRPV1 blockade in the proton mode. Second, we can also modulate TRPV1 indirectly using receptor-mediated inhibition mechanisms such as ChemR23/GPR37-dependent inhibition of TRPV1 in nociceptive neurons. Third, we could control TRPV1 functional expression by modulating TRPV1 membrane trafficking in primary nociceptive neurons. Finally, inhibition of spinal TRPV1 can alleviate mechanical pain while avoiding the hyperthermic side effect of systemic treatment. In conclusion, novel strategies and approaches to develop the next generation of mode-specific TRPV1 antagonists are required since the full adoption of TRPV1 antagonists into clinical practice would depend on the development of effective measures to counter drug-induced hyperthermia.

Acknowledgement: This work was supported by the National Research Foundation of Korea (NRF) grant (NRF-2017M3C7A1025602 and NRF-2019R1C1C1010822) funded by the Korean government.

Keywords: TRPV1, Human DRG, Pain, Hyperthermia, Drug Development

S-1-4

In vitro spine-on-a-chip for application of biological microenvironment

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Intervertebral disc (IVD) degeneration is one of the main causes of chronic low back pain (LBP). Under normal conditions, the IVD is an avascular and aneural organ except for the outer third of the annulus fibrous (AF) region. However, several clinical studies have observed an ingrowth of blood vessels and nerve fibers within the inner IVD region in patients experiencing LBP. This phenomenon requires multiple series of processes including inflammatory reactions, angiogenesis, and nerve innervations that occur during normal tissue healing. However, in the hostile microenvironment of the IVD, these processes augment the catabolic reactions and immoderate expressions of inflammatory mediators. During this pathological process, interactions occur between the human IVD cells and adjacent non-IVD cells including immune cells, endothelial cells (ECs), and nerve fibers that originate from the dorsal root ganglion (DRG).

In the first phase of IVD degeneration, immune cells infiltrate into the area of the lesion through the vascular structure and secrete proinflammatory cytokines including IL-1β. In this inflammatory environment, AF cells stimulated by proinflammatory cytokines also express several catabolic enzymes including MMPs, inflammatory mediators, and angiogenic factors such as IL-6, IL-8, and VEGF. In the second phase of the disease, these mediators promote the continuous breakdown of the ECM components. The resulting chemoattractive response allows for the invasion of EC tubules, which are primarily responsible for angiogenesis, from the outer third of the AF region

into deeper IVD regions. ECs also produce several MMPs and inflammatory mediators necessary for matrix degradation and invasion. Clinically, the invasion of blood vessels has been observed within deeper IVD tissues. As a result, invasive EC can interact with NP cells located in inner IVD tissues. Variations in this microenvironment by invasive ECs or cytokine-mediated inflammatory response influence IVD cell behavior such as cellular mobility and migration. This is important for the progression of IVD disorders. Additionally, ECs may also produce a neurogenic factor including a β-nerve growth factor (β-NGF) and brain-derived neurotrophic factor (BDNF). These exhibit the potential to induce an expression of neuronal pain-associated cation channels related to pain development.
Together, these results indicate that the progression of IVD degeneration is defined by major interdependent and overlapping phases that result in pain. Thus, an enhanced understanding of the contributors, including the major molecules and types of cells, in the stepwise phase of IVD degeneration could enable the identification of novel therapeutic targets and the effective treatment of symptomatic IVD disease. In addition, the microfluidic platform can be extended to study the migration of other cells relevant to the progression of disc diseases. This can also aid in quantifying the potency of various cytokines and chemokines that have been detected in the IVD tissues alone and in combination, in modulating the recruitment and ingrowth mechanisms of non-IVD cells including immune, endothelial, and neuronal cells.

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 (2017R1D1A1A09000962 and 2019R1A6A3A01091920).

Keywords: Intervertebral disc degeneration, Annulus fibrosus, Nucleus pulposus, Inflammation, Microfludics, Lab-on-a-chip

S-2-1

Obesity-induced inflammation in the development of insulin resistance

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Obesity is the major cause of the development of insulin resistance and Type 2 Diabetes. Recently, the notion that obesity-induced inflammation mediates the development of insulin resistance in animal models and humans has been gaining strong support. Furthermore, numerous studies have also shown that immune cells in local tissues, in particular in visceral adipose tissue, play a major role in the regulation of obesity-induced inflammation. It has been shown that obesity disrupts the immune balance by suppressing anti-inflammatory cells (e.g., regulatory T cells [Tregs]) while simultaneously activating pro-inflammatory cells (e.g., adipose tissue macrophages [ATMs]). Many studies from the classical immunology field show that complex cross-regulating interactions between different immune cell types control inflammation. However, the roles these interactions play have not been studied extensively in the metabolism field. We have recently shown that natural killer (NK) cells play a critical role in the development of obesity-induced inflammation and insulin resistance, in part by controlling ATM activation and adipose tissue inflammation. Hence, our studies may provide important preclinical evidence for the notion that obesity-induced inflammation regulated by adipose NK cells could be a therapeutic target for the treatment of insulin resistance and Type 2 Diabetes.

S-2-2

Molecular mechanism of insulin resistance and Akt inactivation by intracellular calcium

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Insulin resistance, a key etiological factor in metabolic syndrome, is closely linked to ectopic lipid accumulation and increased intracellular Ca^{2+} concentrations in muscle and liver. However, the mechanism by which dysregulated intracellular Ca^{2+} homeostasis causes insulin resistance remains elusive. Here, we show that increased intracellular Ca^{2+} acts as a negative regulator of insulin signaling. Chronic intracellular Ca^{2+} overload in hepatocytes during obesity and hyperlipidemia attenuates the phosphorylation of protein kinase B (Akt) and its key downstream signaling molecules by inhibiting membrane localization of pleckstrin homology (PH) domains. Pharmacological approaches showed that elevated intracellular Ca^{2+} inhibits insulin-stimulated Akt phosphorylation and abrogates membrane localization of various PH domain proteins such as phospholipase Cδ and insulin receptor substrate 1, suggesting a common mechanism inhibiting the membrane targeting of PH domains. PH domain-lipid overlay assays confirmed that Ca^{2+} abolishes the binding of various PH domains to phosphoinositides (PIPs) with two adjacent phosphate groups, such as $PI(3,4)P_2$, $PI(4,5)P_2$, and $PI(3,4,5)P_3$. Finally, thermodynamic analysis of the binding interaction showed that Ca^{2+}-mediated inhibition of targeting PH domains to the membrane resulted from the tight binding of Ca^{2+} rather than PH domains to PIPs forming Ca^{2+}-PIPs. Thus, Ca^{2+}-PIPs prevent the recognition of PIPs by PH domains, potentially due to electrostatic repulsion between positively charged side chains in PH domains and the Ca^{2+}-PIPs. Our findings provide a mechanistic link between intracellular Ca^{2+} dysregulation and Akt inactivation in insulin resistance.

S-2-3

The role of the endoplasmic reticulum stress on the development of leptin resistance and obesity

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The obesity becomes serious health issue by creating significant risks for a variety of diseases including type 2 diabetes, cardiovascular diseases and cancers. Obesity is characterized by central leptin resistance. Unfortunately, there is no effective option to treat obesity by reversing leptin resistance. The endoplasmic reticulum (ER) is a central organelle for protein biosynthesis, folding, and traffic. Perturbations in ER homeostasis (ER stress) and associated signaling cascades (the unfolded protein response, UPR) have been implicated in a variety of metabolic disorders, such as obesity and type 2 diabetes. In an attempt to identify compounds that could reverse leptin resistance and ER stress, two natural compounds, celastrol and withaferin A, have been discovered to suppress food intake and lead to healthy body weight loss in leptin-resistant obese mice by reducing hypothalamic ER stress and increasing leptin sensitivity. From recent efforts to decipher the molecular mechanism of celastrol in leptin action, we have identified interleukin-1 receptor 1 (IL1R1) as a mediator of celastrol's action on food intake and body weight control. Our works suggest that intervening in ER stress and modulating signaling components of the UPR would provide promising therapeutics for the treatment of human metabolic diseases such as obesity.

Keywords: ER stress, Leptin resistance, Obesity, Leptin sensitizer

S-2-4

Different fat depots with different adipogenic progenitor cells in metabolic regulation

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Adipose tissues are actively engaged in the regulation of energy homeostasis to respond to dynamic changes in obesity and cold acclimation. In mammals, adipose tissues have been traditionally classified into white adipose tissue (WAT) and brown adipose tissue (BAT). These two types of adipose tissues differ in various aspects, including anatomical locations, cellular morphologies, and metabolic characteristics. In response to changes in nutritional status, adipose tissue undergoes dynamic remodeling, accompanied with quantitative and qualitative alterations of adipose tissue resident cells. Notably, there is a growing body of evidence that adipose tissue remodeling in obesity is closely associated with changes of adipose tissue functions. Obese adipose tissue is characterized by chronic and low grade inflammation accompanied with macrophage accumulation, eventually leading to metabolic disorders including insulin resistance and type 2 diabetes. Adipose tissue macrophages (ATMs) are key players to affect adipose tissue inflammatory responses in obesity. In lean animals, the large number of ATMs is composed of alternatively activated (M2-like) macrophages which express high levels of interleukin (IL)-10 and arginase (ARG) 1 to maintain insulin sensitivity. On the contrary, in obese animals, the population of classically activated (M1-like) macrophages is rapidly increased in adipose tissue. M1-like ATMs secret numerous pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα), IL-6, and IL-1β, which aggravates adipose tissue inflammation and insulin resistance in obesity. In obese adipose tissue, pro-inflammatory cytokines secreted from M1-like ATMs induce adipokine dysregulation and impair insulin action to confer systemic insulin resistance. Therefor, the imbalance between M1- and M2-like ATMs appears to be crucial to provoke proinflammatory responses in obese adipose tissue. Despite of recent findings, it has not yet been clearly elucidated why and how subcutaneous WAT is less prone to adipose tissue inflammation than visceral WAT in obesity. In this presentation, I will also present and discuss novel findings for different immune responses in different fat depots and mechanistic understandings of adipose tissue remodeling process in obesity.

S-3-1

Lipid transports via TMEM16 channel/scramblases

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Members of the TMEM16/ANO family of membrane proteins are Ca^{2+}-activated phospholipid scramblases and/or Cl- channels. A membrane-exposed hydrophilic groove in these proteins serves as a shared translocation pathway for ions and lipids. However, the mechanism by which lipids gain access to and permeate through the groove remains poorly understood. Here, in order to find out key residues for the lipid translocation, we introduced tryptophan (W) residue into the hydrophilic groove and investigated the effects of mutation on nhTMEM16, channel/scramblase. Also, we combined quantitative scrambling assays and molecular dynamic simulations to identify the key steps regulating lipid movement through the groove. Lipid scrambling is limited by two constrictions defined by evolutionarily conserved charged and polar residues, one extracellular and the other near the membrane mid-point. The region between these constrictions is inaccessible to lipids and water molecules, suggesting that the groove is in a non-conductive conformation. A sequence of lipid-triggered reorganizations of interactions between these residues and the permeating lipids propagates from the extracellular entryway to the central constriction, allowing the groove to open and coordinate the headgroups of transiting lipids.

Keywords: TMEM16, Scramblase, Lipid transport

S-3-2

Allosteric modulation of TMEM16A channels by PI(4,5)P2 and CaMKII

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Transmembrane 16A (TMEM16A, anoctamin1), one of ten TMEM16 family proteins, is a Cl- channel activated by intracellular Ca^{2+} and membrane voltage. This channel is regulated by intracellular lipids including phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2), fatty acids, and cholesterol. We studied the PI(4,5)P2 sensitivity, finding that intracellular ATP modulates the PI(4,5)P2 sensitivity through phosphorylation of the channel protein. We identified arginine 486 in the first intracellular loop as a putative binding site for PI(4,5)P2, and serine 673 in the third intracellular loop as a site for regulatory channel phosphorylation that modulates the actions of PI(4,5)P2. In-silico simulation explains how phosphorylation of S673 changes the structure of the distant PI(4,5)P2-binding site in channel splice variants with and without the c-segment exon. Our study reveals differential regulation between alternatively spliced TMEM16A(ac) and (a) by plasma membrane PI(4,5)P2, modification of these effects by channel phosphorylation, identification of the molecular sites, and mechanistic explanation by in-silico simulation.

Keywords: TMEM16A, PI(4,5)P2, CaMKII, Phosphorylation

S-3-3

Bicarbonate permeation through anion channels

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Anion channels are an essential component of the cells for keeping them alive and mediating their diverse functions. Although many anions can permeate anion channels, chloride and bicarbonate are the two most abundant anions that can be the charge carrier of anion channels in animal cells. Increasing evidence indicates that bicarbonate permeation though anion channel is involved in many basic biologic processes ranging from epithelial fluid secretion to neuronal excitation. However, the principle of ion selection and permeation by the anion channels, in particular that of bicarbonate, is largely unknown. By employing an integrated study of combined molecular, physiological, structural, and mathematical approaches, we provide evidence that electric permittivity and channel pore diameter are cardinal features, which determine the ion selectivity of anion channels. Importantly, many cellular stimuli dynamically modulate anion channel ion selectivity by changing pore size. Pore size change affects the bicarbonate permeability of anion channels by altering energy barriers of size-exclusion and ion dehydration of bicarbonate permeation. These findings provide key insights into the mechanism of how the ion permeation and selectivity of anion channels are determined.

Keywords: Bicarbonate, Anion channel, Permeability

S-3-4

Biophysical and physiological functions of Tentonin 3

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Mechanosensation is essential for the survival of animals. Numerous phys-

iological functions such as tactile sensation, proprioception, hearing, baroreceptor reflex, and pain require mechanotransduction process. Mechanosensation begins with mechanotransduction channels in nerve terminals or receptor cells. With bioinformatics, we identified that TMEM150C/Tentonin 3 confers mechanosensitive currents in DRG neurons with slowly-adapting inactivation kinetics. Tentonin 3 (TTN3) is expressed highly in DRG neurons and activated by mechanical stimuli with distinctly slow inactivation kinetics. Baroreceptors present in carotid sinus and aorta are stretch receptors detecting blood pressure changes. As TTN3 is a mechanosensitive channel, therefore, it is likely that TTN3 acts as a mechanosensitive channel responsible for baroreceptor function. Indeed, TTN3 is expressed in nodose ganglion neurons that innervate in baroreceptors. Neural activity of aortic depressor nerves in response to intra-aortic is markedly reduced in TTN3-/- mice. Ambient blood pressures and heart rates of freely moving TTN3-/- mice were higher. The sensitivity of baroreceptor reflex was markedly reduced in TTN3-/- mice. We also found a clear rescue of blood pressure, heart rate, and baroreceptor reflex sensitivity to the levels of those of wild-type mice when Ttn3 is overexpressed in nodose ganglion in TTN3-/- mice. These results suggest that TTN3 is a mechanosensitive channel responsible for detecting dynamic change in arterial pressures in baroreceptors.

Keywords: Tentonin 3, Mechanosensation, Baroreceptor, DRG neuron

S-4-1

Sensory encoding in the cerebellar climbing fiber

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Climbing fibers (CFs) generate complex spikes (CS) and Ca^{2+} transients in cerebellar Purkinje cells (PCs), serving as instructive signals. The so-called "all-or-none" character of CSs has been questioned since the CF burst was described. Although recent studies have indicated a sensory-driven enhancement of PC Ca^{2+} signals, how CF responds to sensory events and contributes to PC dendritic Ca^{2+} and CS remains unexplored. Here, single or simultaneous Ca^{2+} imaging of CFs and PCs in awake mice revealed the presynaptic CF Ca^{2+} amplitude encoded the sensory input's strength and directly influenced post-synaptic PC dendritic Ca^{2+} amplitude. The sensory-driven variability in CF Ca^{2+} amplitude depended on the number of spikes in the CF burst. Finally, the spike number of the CF burst determined the PC Ca^{2+} influx and CS properties. These results reveal the direct translation of sensory information-coding CF inputs into PC Ca^{2+}, suggesting the sophisticated role of CFs as instructive signals.

Keywords: Climbing fiber, complex spike, Purkinje cell, sensory encoding, two-photon microscope, calcium imaging

S-4-2

The origin and function of cerebellar tonic inhibition

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Cerebellar tonic inhibition is mediated through an activation of extrasynaptic $GABA_A$ receptors, resulting in a persistent GABAergic inhibitory action. It is key regulators for neuronal excitability, exerting a powerful action on excitation/inhibition balance. Maintaining the balance is important for essential brain function and if that control won't work, neuronal excitability is altered and can lead to disease.

We have investigated mechanism, sources and function of cerebellar tonic inhibition and our recent findings indicate that cerebellar tonic inhibition is a key player in motor coordination by modulating neuronal excitability and could be a good therapeutic target for various movement and psychiatric disorders, which show a disturbed excitation/inhibition balance. Also, in our developmental disorder research on cerebellum of attention deficits / hyperactivity disorder (ADHD) model, GIT1 (G protein-coupled receptor kinase-interacting protein-1) deficient mice, we observed decreased glial GABA and tonic inhibition current in cerebellar cortex suggesting possible mechanism of their hyperactivity.

Keywords: Cerebellum, Tonic inhibition, Glia, Astrocyte, ADHD

S-4-3

Cerebellar 5HT-2A receptor agonism mediates stress-induced dystonia

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Stress increases muscle tension and worsens abnormal muscle contractions in patients with dystonia. Here, we reveal that the serotonin (5HT) system is involved in stress-induced dystonia through specific deep cerebellar nuclei (fDCN). Photostimulation of 5HT-fDCN inputs increases the excitability of fDCN neurons to induce dystonia in wildtype mice. Cerebellar 5HT input activity increases during stress-induced dystonia in a genetic model of generalized dystonia, *cacna1a*$^{tg/tg}$ mice. Photoinhibition of 5HT-fDCN inputs, administration of 5HT-2A receptor inverse agonist (1 mg/kg, i. p.) or knockdown by shRNA dramatically prevents the onset of stress-induced dystonia in *cacna1a*$^{tg/tg}$ mice under stressed condition. These results suggest that cerebellar 5HT-2A receptor signaling mediates stress-induced dystonia, shedding light on the relief of patients from the onset of dystonia.

S-4-4

Cerebellar modulation of emotional learning and memory

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The cerebellum is well known for its roles in motor coordination and motor learning. Recently, the cerebellum has also been reported to be involved in regulating non-motor functions such as social behaviors and goal-directed behaviors via its functional projections to other brain regions. Although the cerebellum has also been shown to be involved in several affective behaviors including the consolidation of fear memory, how its output from deep cerebellar nuclei (DCN) regulates the fear learning and memory is unclear. In this talk, I will show that a subpopulation of DCN neurons project to parabrachial nucleus (PBN), which is known for a locus for detecting danger signals. Optogentic inhibition of PBN-projecting DCN neurons impaired the expression of cued fear memory without affecting either contextual fear memory or innate fear response. In addition, we also found that PBN-projecting DCN neurons do not overlap with VTA-projecting DCN neurons which has recently been shown to be involved in social reward. Taken together, we found that the cerebellum is involved in modulating fear memory through its output to PBN. Furthermore, our results also suggest that DCN neurons have distinct outputs modulating distinct emotional valences.

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Keywords: cerebellum, fear, parabrachial nucleus, optogenetics

S-5-1

Ryanodine receptor type 2 as a potential target for novel anti-arrhythmic drugs

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Type 2 ryanodine receptor (RyR2) is the Ca^{2+} release channel on the sarcoplasmic reticulum (SR) and plays a central role in EC-coupling in the heart. Abnormal activation of RyR2 has been linked to arrhythmogenesis, where spontaneous Ca^{2+} release from SR is thought to trigger arrhythmia. For example, chronic phosphorylation of RyR2 in heart failure (HF) may lead to ventricular arrhythmia due to enhanced Ca^{2+} leak from ER, and mutations in RyR2 have been implicated in various types of arrhythmias including catecholaminergic polymorphic ventricular tachycardia (CPVT). Therefore, drugs that modify activity of RyR2 are expected to have anti-arrhythmic effects, but specific inhibitors and activators of RyR2 have not been reported yet. We have recently developed an efficient and quantitative approach for functional evaluation of disease-linked mutant RyR2s using HEK293 expression system (Ref 1&2), and furthermore, established a high-throughput screening procedure for detection of RyR1 and RyR2 inhibitors with the RyR-expressing HEK293 cells (Ref 3). In this presentation, I will introduce our screening procedure for RyR modifiers and show the effects of the recently identified RyR2 inhibitors on Ca^{2+} homeostasis in cultured cardiac cells and cardiomyocytes from HF and arrhythmogenic model mice.

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Keywords: Ryanodine receptor type 2, arrhythmia, calcium

S-5-2

Mechanism of atrial fibrillation

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Atrial fibrillation (AF) is most common cardiac arrhythmia, and atrial fibrosis has been implicated in the development, maintenance, and progression of AF. However, little is known about fibrosis as a electrophysiologic and cellular mechanisms of AF. Mean plasma levels of both TGF-β1 and TIMP-1 were higher in patients with AF than in the control. Plasma levels of TIMP-1 were higher in patients with recurrence compared with those without recurrence. Late gadolinium enhancement (LGE)–MRI scar burden in patients with clinical recurrence (CR) after catheter ablation were higher than those without CR. Angiotensin-II receptor blockers (ARBs) are known to reduce the development of AF through reverse-remodeling. The grades of endocardial fibrosis after 12 weeks but not those of myocardial fibrosis were slightly reduced in the candesartan group compared to the control group. Future studies using a larger number of subjects are warranted to determine the therapeutic effect of renin-angiotensin-aldosterone system blockade on fibrosis in AF. Atrial fibrosis is led by profibrotic process through TGF-β/Smad 3-mediated signaling transduction. Activation of Akt is known to play a role in cardioprotection in cardiac diseases. In the paced atrial HL-1 cells, p-Smad3 and p-Akt were highly increased compared to non-paced cells. In ranolazine-applied cells, p-Akt were significantly increased compared to paced cells, however, phosphorylation of Smad3 was attenuated.
Voltage-gated sodium channel ($Na_v1.5$)-related channelopathy is associate with cardiac arrhythmia. However, the underlying molecular mechanism of these contributions in AF remains unclear. We found that 6-hour paced cells showed significantly decreased peak sodium current density than in normal HL-1 cells. In contrast, late sodium current density was significantly increased in 6-h paced condition compared with normal HL-1 cells. However, there was no significant change in $Na_v1.5$ protein expressions between 6-hour paced cells and normal HL-1cells. Further studies are needed to investigate the mechanism of how $Na_v1.5$ activations is mediated under AF condition

Keywords: atrial fibrillation, fibrosis, cellular mechanism, ion channel

S-5-3

A multidisciplinary approach for pharmacological assessment using human iPS-derived cardiomyocytes

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Human iPS cell-derived cardiomyocyte (hiPSC-CM) is conceptually promising as an unlimited source of human cardiomyocytes for cardiac pharmacological assessment including pre-clinical safety testing. However, intra- and interline variation in functional properties of hiPSC-CM remain to be solved completely.
In order to improve the accuracy of pharmacological assessment, we conducted a multidisciplinary approach for developing new methods to evaluate effects of drugs on contractile functions. We aimed to increase throughput of pharmacological assessment for contractile functions of hiPSC-CMs using a motion field imaging (MFI) which is a noninvasive assay system using high speed video image of hiPSC-CMs. The technique enabled us to obtain precise and stable quantitative values for contractile functions of hiPSC-CMs from single cells, and revealed a relationship between contractile function and molecular expression in hiPSC-CMs. The relationship was consistent with what we investigated in murine cardiac cells. We would like to discuss how the multidisciplinary approach can improve predictability of pharmacological/toxicological assessment for physiological functions of hiPSC-CMs. (JSPS KAKENHI JP17K19499, JP19H03380, ExCELLS from NIPS Japan)

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Keywords: iPS cells, contractility, cardiomyocytes

S-5-4

NO signaling in cardiac E-C coupling and metabolism

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Nitric oxide signaling plays critical parts in cardiovascular physiology and pathology. It is established that neuronal nitric oxide synthase (nNOS) is essential in regulating plasmalemmal Ca^{2+} channels, ryanodine receptors, Ca^{2+}-ATPase in sarcoplasmic reticulum and various second messengers those mediate cardiac contraction and relaxation in healthy and diseased hearts. Recently, we have identified that nNOS maintains myofilament Ca^{2+} sensitivity in normal rat cardiomyocytes but attenuates myofilament Ca^{2+} sensitivity in hypertension. Concomitantly, intracellular Ca^{2+} transient is decreased and increased, respectively, secondary to nNOS regulation of the myofilament. Further research from our group has shown that fatty acid supplementation and enhancement of metabolism attenuates myofilament Ca^{2+} sensitivity through the acidification in cardiomyocytes from normal rats. In hypertension, where myofilament Ca^{2+} sensitivity was down-regulated by nNOS, fatty acid failed to affect intracellular Ca^{2+} transient and myofilament Ca^{2+} sensitivity. Base on the evidences, I would like to discuss novel insights into nNOS in cardiac E-C coupling and intracellular Ca^{2+} homeostasis in normal and hypertensive hearts.

S-5-5

Extracellular matrix-derived vesicles affect cardiac atria

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Extracellular matrix (ECM) plays a critical role in the provision of the necessary microenvironment for the proper regeneration of the cardiac tissue. However, specific mechanisms that lead to ECM-mediated cardiac regeneration are not well understood. To elucidate the potential mechanisms, we investigated ultra-structures of the cardiac ECM using electron microscopy. Intriguingly, we observed large quantities of micro-vesicles from decellularized right atria. RNA and protein analyses revealed that these contained exosomal proteins and microRNAs (miRNAs), which we referred to herein as ECM-derived extracellular vesicles (ECM-EVs). One particular miRNA from ECM-EVs, miR-199a-3p, promoted cell growth of isolated neonatal cardiomyocytes and sinus nodal cells by repressing homeodomain-only protein (HOPX) expression and increasing GATA-binding 4 (Gata4) acetylation. To determine the mechanisms, we knocked down Gata4 and showed that miR-199a-3p actions required Gata4 for cell proliferation in isolated neonatal cardiomyocytes and sinus nodal cells. To further explore the role of this miRNA, we isolated neonatal cardiac cells and recellularized into atrial ECM, referred here has engineered atria. Remarkably, miR-199a-3p mediated the enrichment of cardiomyocyte and sinus nodal cell population, and enhanced electrocardiographic signal activity of sinus nodal cells in the engineered atria. In conclusion, these results provide clear evidence of the critical role of ECM, in not only providing a scaffold for cardiac tissue growth, but also in promoting atrial electrical function through ECM-derived miR-199a-3p

Keywords: Extracellular matrix, microRNAs, atria, Gata4

S-6-1

Plant callus reprograms human dermal fibroblasts into multipotent skin-derived neural precursor cells

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Our previously established method for producing induced pluripotent stem cells by treating adult mouse fibroblasts with human embryonic or induced pluripotent stem cell extract requires a large amount of human stem cell extract. To overcome this drawback, we hypothesized that plant stem cell-derived proteins could reprogram human fibroblasts. Herein, we demonstrated that somatic human dermal fibroblasts were reprogrammed into multipotent skin-derived neural precursor cells by treatment with shikimic acid, a major component of Sequoiadendron giganteum callus extract. The reprogrammed cells expressed nestin (a neural precursor-specific protein), fibronectin, and vimentin, and could differentiate into the ectodermal and mesodermal lineage. Nestin expression was induced by shikimic acid binding to the mannose receptor and subsequent MYD88 activation, leading to P38 phosphorylation and then CREB binding to the nestin gene promoter. Finally, we confirmed that shikimic acid facilitated healing of cut-injury and enhanced dermal reconstruction in a human artificial skin model. Moreover, in clinical study with healthy volunteers, plant callus extracts increased the expression of stem cell markers in basal layer of epidermis and collagen deposit in dermis. These results indicate that shikimic acid is an effective agent for direct conversion of fibroblast to multipotent skin-derived neural precursor cell and for tissue regeneration.

Keywords: Shikimic acid, cell reprogramming, neural precursor, skin-derived precursor, single chemical derived trans-differentiation

S-6-2

Blood cell production using human hematopoietic stem cells

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In vitro production of stem cell-derived erythrocytes is a promising alternative to donor blood as the blood donor pool markedly decreases especially in Korea. Evolving from the conventional 2D plate culture, large scale manufacturing at a GMP grade using bioreactors is an essential process for better productivity and efficiency in making RBCs. Bioreactors are the only equipment that can manage the tremendous number of cells necessary and meet the requirements for clinical trials. Also, development of serum-free media is necessary for safe clinical trials and large scale production. This study aims to develop robust automated production systems and continuous process assessments using bioreactors and supporting culture media for successful culture of the RBC products in clinical settings. **Methods:** Cord blood CD34+ cells were isolated and differentiated to erythroid progenitor cells in 2-dimensional plates. Then, the cells were transferred and cultured in differentiation media with various additives using a bioreactor. To develop the best parameters, several culture conditions and media were compared. **Results:** We successfully developed a RBC production process in a chemically defined serum-free media using a bioreactor that showed very effective maturation and enucleation with high viability. The produced RBCs showed similar functions compared to donor fresh RBCs and could be stored for one month. Summary / **Conclusions:** The optimized culture process using bioreactors would make possible to produce transfusable RBC products in a large scale.

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Keywords: erythropoiesis, red blood cells, in vitro culture, transfusion

S-6-3

Differential gene expression in mesenchymal stem cells

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The multipotency and anti-inflammatory effects of mesenchymal stem cells (MSCs) are attractive for cell therapy in regenerative medicine. However, the animal factors and unknown viruses included in classical culture media limit clinical application. Currently, a variety of serum free media or chemically-defined media are being developed. In this lecture, I will talk about the differential gene expression of mesenchymal stem cells that cultured in DMEM/FBS and chemically-defined media, respectively. These results can inform the reason why mesenchymal stem cells for clinical application should be cultured in chemically-defined media.

Keywords: Mesenchymal stem cells, regenerative medicine, cell therapy

S-6-4

Organoid-based study of epithelial homeostasis and regeneration

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Accurate and tractable disease models are essential for elucidating disease pathogenesis and for developing new therapeutics by discovering targets. As stem cells are capable of self-renewal and differentiation, they are ideally suited both for generating these models and for obtaining the large quantities of cells required for drug screening. Beginning from the single stem cells, tools for disease modeling have been rapidly advanced. Recent advances in 3D culture technology allow pluripotent and multipotent stem cells to exhibit their remarkable self-organizing properties, and the resulting organoids reflect key structural and functional properties of organs such as kidney, lung, gut, brain and retina. Organoid technology can therefore be used to model human organ development and various human pathologies 'in a dish' with the properties that closely resemble the real organs in its structure and function. Additionally, patient-derived organoids hold promise to predict drug response in a personalized fashion. Organoids open up new avenues for regenerative medicine and, in combination with editing technology, for gene therapy. Various applications of this technology are only beginning to be explored. Taken together, organoids can be utilized as a modeling system for the investigation of stem cell biology, organ development and disease progression, as well as for drug discovery. In this lecture, we will show some of our studies using small intestinal organoids and salivary gland organoids to investigate their generation and epithelial physiology.

Keywords: intestinal organoid, salivary gland organoid, epithelial physiology, xerostomia

S-6-5

Dissecting cellular heterogeneity using single-cell RNA-seq

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Cell-to-cell variability in gene expression exists even in a homogeneous population of cells. Dissecting such cellular heterogeneity within a biological system is a prerequisite for understanding how a biological system is developed, homeostatically regulated, and responds to external perturbations. Single-cell RNA sequencing (scRNA-seq) allows the quantitative and unbiased characterization of cellular heterogeneity by providing genome-wide molecular profiles from tens of thousands of individual cells. In this talk, I present an overview of scRNA-seq protocols and apply this approach to dissect cellular heterogeneity in stomach and adipose tissues.

Keywords: Single-cell RNA-seq, cellular heterogeneity, cellular plasticity, adult stem cells

S-7-1

Protein arginine methylation in muscle aging

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Skeletal muscle aging, known as sarcopenia, is characterized by the progressive loss of muscle mass and strength, leading to reduced functionality and the increased risk of developing chronic diseases. Dysregulation of mitochondrial function and muscle regeneration are closely associated with muscle loss and weakness related to sarcopenia or other muscle diseases. To treat muscle atrophy, one needs to develop the strategy that boosts the anabolic response and mitochondrial function. Protein arginine methyltransferases (PRMTs) have emerged as important regulators of diverse biological processes including muscle regeneration. However, the direct roles of the various PRMTs in muscle homeostasis remain unclear. Using genetic ablation mouse models, we attempted to elucidate the function of PRMTs 1 and 7 in muscle homeostasis. Our published and unpublished data suggest that PRMTs are key regulators for maintenance of stem cell function, skeletal muscle metabolism and motor neuron function. Thus, PRMTs are attractive molecular targets for the development of therapeutics to intervene muscle atrophy and weakness related to aging or muscle diseases.

Keywords: Protein Arginine methyltransferases, Muscle aging, Neuromuscular interaction, Anabolic pathway, Mitochondria

S-7-2

Effect of exercise on p66shc and vascular function in cardiovascular diseases

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Exercise plays a pivotal role in prevention and treatment of cardiovascular disease. Phosphorylation of p66shc is known to be mediated oxidative stress in many cell types and tissues. In the vasculature, p66shc plays a pivotal role in endothelial dysfunction associated with pathophysiological conditions such as atherosclerosis and hypertension. We investigated the role of endurance exercise training on p66shc activation and endothelial function in aorta of hypertensive rats and balloon-induced atherosclerosis rat models. In conclusion, our date suggest that regular endurance exercise training blood pressure and neointimal formation via reduction of p66shc phosphorylation in hypertension and atherosclerosis.

Keywords: exercise, p66shc, endothelial function, hypertension, atherosclerosis

S-7-3

Smooth muscle cell mineralocorticoid receptor contributes to pathogenesis of heart failure

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The renin-angiotensin-aldosterone system is a hormonal cascade that culminates in activation of mineralocorticoid receptors (MR) by aldosterone and contributes to cardiovascular diseases. In addition to regulating blood pressure by modulating sodium retention in kidney, MR is also expressed in vascular smooth muscle cells (SMC). We previously found that MR antagonist (MRA) treatment in aged mice or SMC-specific MR-deletion in mice (SMC-MR-KO) mitigates aging-associated cardiac dysfunction and remodeling, which are also prominent features of heart failure (HF). Thus, to explore our hypothesis that SMC-MR plays a significant role in the pathogenesis of HF, male MR-intact or SMC-MR-KO mice were received a surgery, called transverse aortic constriction (TAC), to trigger pressure overload-induced HF. After 4 weeks of TAC, morphological, functional and molecular changes in left ventricles (LV) were assessed by state-of-the-art techniques. We found that deletion of SMC-MR mitigates TAC-induced increases in LV hypertrophy and fibrosis. Also, TAC-induced HF phonotypes, such as increased lung edema, LV dysfunction and decreased exercise capacity, were attenuated in SMC-MR-KO mice, indicating that SMC-MR contributes to developing HF when exposed to increased pressure. To address the mechanism(s), leukocyte infiltration in response to TAC was further assessed by histology and flow cytometry, and we observed a small contribution of SMC-MR to in-

flammatory responses to TAC. Rather, decreased coronary artery blood flow and LV capillary density by TAC were significantly mitigated in SMC-MR-KO, suggesting that the beneficial effects of SMC-MR deletion on HF phenotypes are mechanically driven by enhanced coronary blood supply. These findings suggest therapeutic potential for antagonism of MR as targets for HF and the associated adverse outcomes.

Acknowledgement: Majority of this study was executed during the presenter's postdoctoral training period at Molecular Cardiology Research Institute in Tufts Medical Center, Boston, MA, USA.

Keywords: Heart failure, smooth muscle cell mineralocorticoid receptor, leukocyte recruitment, coronary artery blood flow

S-7-4

Can exercise intervention improve endothelial TRPV4 channel-dependent cell-to-cell communication?

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Ca^{2+} signalling in endothelial cells (ECs) plays an essential role in preventing excessive vasoconstriction caused by sympathetic nerve stimulation of α1-adrenergic receptors (α_1ARs) on smooth muscle cells (SMCs). It has been reported that α1AR activation produces inositol triphosphate (IP_3) and induces Ca^{2+} release/influx in the SMCs. In addition, these 2nd messengers, IP_3 and Ca^{2+}, can be transported to the ECs via myoendothelial gap junctions. However, exact mechanisms underlying SMC-EC communication-mediated prevention of exaggerated vasoconstriction have not been fully delineated. Recently, it has been demonstrated that elementary Ca^{2+} entry via EC TRPV4 (transient receptor potential vanilloid 4) channels, termed TRPV4 Ca^{2+} sparklets, evokes endothelium-dependent vasodilation in small resistance arteries. Although TRPV4 channel was found to be activated by both IP_3 and Ca^{2+}, whether SMC-derived second messengers potentiate EC TRPV4 Ca^{2+} sparklets for negative feedback regulation remains unknown. Thus, we sought to test the hypothesis that SMC α1AR activation triggers EC TRPV4 Ca^{2+} sparklets to oppose α_1AR-induced vasoconstrictions in resistance arteries. Local Ca^{2+} influx in the ECs was assessed in the *en face* 3rd order mesenteric arteries (MAs) treated with fluo-4 synthetic Ca^{2+} indicator or obtained from the mice expressing Ca^{2+} biosensor (GCaMP2) using high-speed spinning disk confocal microscopy. Phenylephrine (PE, 10 μM, α_1AR agonist) strikingly stimulated TRPV4 Ca^{2+} sparklets in the presence of cyclopiazonic acid (CPA, 20 μM, an inhibitor of sarco/endoplasmic reticulum Ca^{2+} ATPase was used to remove IP3R-mediated Ca^{2+} release). However, this fascinating evidence was completely abrogated in the presence of a specific TRPV4 inhibitor GSK2193874(GSK219, 100 nM). Further, PE-induced EC TRPV4 channel activation was abolished in the pre-treatment of phospholipase C inhibitor U73122 (3 μM) or gap junction uncoupling agent 18β-glycyrrhetinic acid (30 μM). Furthermore, BayK8644 (1 uM), a direct activator of SMC L-type Ca^{2+} channels, did not alter EC TRPV4 sparklet activity, implying that SMC Ca^{2+} signalling following α1AR activation does not contribute to the stimulation of EC TRPV4 sparklets. Collectively, the major findings in this study suggest that SMC-derived IP_3 following the activation of α_1ARs may provoke the activation of EC TRPV4 sparklet activity. These results uncover that EC TRPV4 channels are notably involved in limiting SMC α1AR-induced vasoconstrictions and shed light on the novel paradigm that SMC-derived IP3 can stimulate EC TRPV4 channels. In addition, this study warrants consideration in future studies to elucidate effects of acute or long-term exercise training on SMC-EC negative feedback communication.

Keywords: G protein-coupled receptors, second messengers, negative feedback mechanisms, vascular reactivity

S-7-5

Cutaneous microvascular function in individuals with elevated cardiovascular disease risk

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Cardiovascular disease is the leading cause of morbidity and mortality. The microcirculation is a novel region to detect and predict cardiovascular and metabolic disease risk. Impairments in microvascular endothelial function, including reduced nitric oxide (NO)-dependent vasodilation, vessel structural remodeling, and blunted perfusion due to rarefaction, precede the development of hypertension, atherosclerosis and insulin resistance. Investigation of the cutaneous microvasculature is a suitable model for assessment of mechanisms underlying systemic vascular impairment. Also, with the simultaneous application of intradermal microdialysis this technique could offer the advantage of being able to systematically investigate mechanisms of impairment at the microvascular level without having a systemic effect. Using the microdialysis technique, we previously investigated cutaneous microvascular function in individuals with elevated cardiovascular disease risk such as young healthy obese population and African Americans who did not have overt signs of disease. Both groups showed blunted microvascular function when compared to their control counterparts; however, mechanisms underlying the microvascular dysfunction were different. Investigation in microcirculatory function with intradermal microdialysis technique may have potential to facilitate and broaden research field of exercise physiology.

Keywords: microvascular function, microdialysis, cardiovascular disease

S-8-1

Skin aging and ion channels

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Transient receptor potential vanilloid 1 (TRPV1) channel is a molecular sensor for detecting adverse stimuli during inflammation and can be activated by vanilloids, heat, or protons, and conditions that occur during tissue injury. Although TRPV1 has been localized in the epidermis and dermis, the role of TRPV1 in skin has not been elucidated. We found that UV radiation increases the expression of TRPV1 in human skin in vivo. UV increases the calcium influx, indicating that UV activated TRPV1. UV-induced MMP-1 and -9 expressions were decreased by treatment of TRPV1 inhibitors. We also demonstrated that there is increased expression of TRPV1 in the aged and photoaged human skin. It has been known that TRPV1 is phosphorylated and activated by both protein kinase C (PKC) and Ca^{2+}/calmodulin-dependent protein kinase (CAMK). Based on these information, we designed new TRPV1 inhibitory peptide mimicking the phosphorylated site by both PKC and CAMK in TRPV1 (a.a 701-709 : QRAITILDT), and investigated whether this TRPV1 inhibitory peptide can reduce UV-induced responses. Treatment with this TRPV1 inhibitory peptide prevented UV-induced skin responses in mice and human skin. This TRPV1 inhibitory peptide could be used for photo-protection or anti-skin aging.

Keywords: UV irradiation, Photoaging, Keratinocytes, TRPV1, CAMK

S-8-2

Effects of blue-light irradiation on human keratinocytes are mediated via transient receptor potential vanilloid (TRPV)-1-mediated signaling

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The skin plays an important role as a barrier protecting the human body against external stresses. Calcium ion is an important factor that contributes to the skin barrier function. TRPV1 is a nonselective cation receptor that can be a source of calcium. Although blue light has been reported to affect retinal cells negatively, little is known about its effects on skin cells. In this study, we aimed to investigate the role of TRPV1 in blue light-induced effects on human keratinocytes and its underlying mechanisms. Firstly, blue light (470–480 nm) decreased the viability of HaCaT (a human keratinocyte cell line) cells. In experiments involving its mechanism of action, TRPV1 expression was found to be upregulated by blue-light irradiation, as evidenced by Western blotting for quantifying TRPV1 and the TRPV1-luciferase reporter activity in the HEK293-TRPV1-luciferase stable cell line. Additionally, blue light suppressed the epidermal growth factor receptor (EGFR)-mediated signaling pathway by reducing the protein levels of EGFR. Specifically, blue-light irradiation suppressed the EGFR/PI3K/AKT/GSK3β/FoxO3a signaling pathway. Immunocytochemistry imaging demonstrated that FoxO3a, a downstream signaling molecule of AKT, was activated by blue light. TRPV1 knockdown using small interfering RNA (siRNA) for TRPV1 was found to attenuate the inhibitory effects of blue-light irradiation on cell survival. Secondly, apart from suppressing cell survival, blue-light irradiation increased the production of reactive oxygen species (ROS) and tumor necrosis factor-α (TNF-α). In experiments investigating the mechanisms underlying blue light-induced ROS production, blue-light irradiation was found to increase both the phosphorylation levels of TRPV1 and calcium influx. The blue light-induced increase in calcium influx and ROS production was reversed by capsazepine, a TRPV1-specific antagonist. Additionally, this was confirmed by TRPV1 knockdown experiments using TRPV1 siRNA. In experiments to elucidate the mechanisms underlying blue light-induced TNF-α production, blue-light irradiation was found to increase NF-κB and AP-1 promoter activities, but not CRE promoter activity. Among mitogen-activated protein kinases (MAPKs), blue-light irradiation increased the JNK phosphorylation levels, but suppressed the phosphorylation levels of p38 MAPK and p44/42 MAPK. Furthermore, the increased production of TNF-α was attenuated by capsazepine and TRPV1 knockdown using TRPV1 siRNA. Collectively, for the first time, these findings show that blue-light irradiation regulates cell survival and the production of ROS and TNF-α; its effects are mediated via TRPV1. Specifically, the effects of blue light on cell survival are mediated by TRPV1 upregulation, which regulates EGFR/PI3K/AKT/GSK3β/FoxO3a signaling. Blue light-induced production of ROS and TNF-α is also mediated through increased calcium influx via TRPV1 activation. Furthermore, these data suggest that the blue light-induced suppression of keratinocyte proliferation may serve as a useful therapeutic strategy for treating hyperproliferative human dermatoses.

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Keywords: Blue light, TRPV1, Calcium influx, EGFR, Foxo3a, AKT, ROS, Cell survival

S-8-3

Understanding molecular mechanisms of histamine-independent itch pathways

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Itch is a sensation felt on the skin, which evokes a desire to scratch. The underlying mechanism of itch was thought to be mainly mediated by histamine, an endogenous itch-inducing agent (pruritogen) released from the mast cell. Once histamine is released from the mast cell, it binds to its own histamine receptor, leading to activation of TRPV1 ion channel in the sensory neurons to relay the itch signal. Indeed, most of antipruritic agents are based on this mechanism, which interfere with the binding of histamine to its own receptors. However, it was obvious that a different type of itch which is not alleviated by antihistamine agents also exist. Although the presence of this "histamine-independent" itch has been known for decades, its molecular mechanisms were mostly elusive up until recently. This mystery has been shattered in 2011 by the finding that the itch induced by chloroquine, an antimalarial agent that evokes itch as a side effect, activates its own receptor called MRGPRA3, and histamine is not completely involved in the pathway. Starting from this discovery, plethora of histamine-independent itch mechanisms have been identified. Surprisingly, most of histamine-independent itch are related to MRGPR (MAS-related G protein–coupled receptors), which is a group of GPCR mostly found in sensory neurons. Today, the presentation will summarize the current findings of these histamine-independent itch mechanisms, with special focus on MRGPRs.

Keywords: itch, histamine, MRGPR

S-8-4

Transcriptomic analysis of gene expressions in two different murine models: prediction of diagnostic markers on early stage of scratching behavior

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Pruritus (itching) is classically defined as an unpleasant cutaneous sensation that leads to scratching behavior. Although the scientific criteria of classification for pruritic diseases are not clear, it can be divided as acute or chronic by duration of symptoms. In this study, we investigated whether skin injury caused by chemical (contact hypersensitivity, CHS) or physical (skin-scratching stimulation, SSS) stimuli causes initial pruritus and analyzed gene expression profiles systemically to determine how changes in skin gene expression in the affected area are related to itching. In both CHS and SSS, we ranked the Gene Ontology Biological Process terms that are generally associated with changes. The factors associated with upregulation were keratinization, inflammatory response and neutrophil chemotaxis. The Kyoto Encyclopedia of Genes and Genomes pathway shows the difference of immune system, cell growth and death, signaling molecules and interactions, and signal transduction pathways. Il1a, Il1b and Il22 were upregulated in the CHS, and Tnf, Tnfrsf1b, Il1b, Il1r1 and Il6 were upregulated in the SSS. Trpc1 channel genes were observed in representative itching-related candidate genes. By comparing and analyzing RNA-sequencing data obtained from the skin tissue of each animal model in these characteristic stages, it is possible to find useful diagnostic markers for the treatment of itching, to diagnose itching causes and to apply customized treatment. And by integrating these data with human cohort data, it is expected to provide clues for translational research on initial pruritus.

Keywords: Cytokines, Pruritus, RNA sequence analysis, Transient receptor potential channels, Wound healing

S-9-1

Defective D-lactate metabolism induce methylglyoxal accumulation and cause cardiomyopathy

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Methylglyoxal is a highly reactive a-oxoaldehyde that is formed in cells primarily from the triose phosphate intermediates of glycolysis, dihydroxy-

acetone phosphate and glyceraldehyde 3-phosphate. In diabetic heart, hyperglycemia triggers enhanced production of methylglyoxal, one consequence of which is the rapid modification of proteins and other substrates to generate what are called advanced glycation end products, AGE. One mechanism known to detoxify MG is the glyoxalase system, composed of two enzymes, glyoxalase 1 and glyoxalase 2, which act sequentially to convert MG into D-lactate. We discovered that protein X is responsible for D-lactate metabolism. Here, we describe that deficiency of protein X gene increased the level of D-lactate and induced accumulation methylglyoxal. Mouse strains deficient in protein X gene develop cardiomyopathy at the age of 40 weeks.

Keywords: methylglyoxal, mitochondria, d-lactate

S-9-2

Drp1-dependent mitochondrial fission for the quality surveillance

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Mitochondrial morphology is spontaneously and continuously changing via fusion and fission, but it is unclear what the functional importance of this energy-consuming process. Several data have suggested that mitochondrial fission executed by Drp1 is necessary to select out a damaged spot from the interconnected mitochondrial network, but the precise mechanism for the recognition and isolation of a damaged sub-mitochondrial region during mitochondrial fission is yet unclear. Recently, my research group found that the mitochondrial membrane potential (MMP) is transiently reduced by the physical interaction of Drp1 and mitochondrial Zinc transporter, Zip1, at the fission site prior to the typical mitochondrial division, and we found that this event is essential for a mitochondrial quality surveillance. In this short talk, I will discuss the role of a mitochondrial fission in the mitochondrial quality surveillance system.

Keywords: mitochondria, Zn, Drp1, MMP

S-9-3

Function of mitochondrial chaperone TRAP1 during progression of metabolic diseases

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TRAP1 is an ATP-dependent molecular chaperone found in the mitochondria and overexpressed in various human cancers. TRAP1 maintains mitochondrial integrity to increase cell death threshold upon various cellular stresses and reprograms mitochondrial metabolism to meet metabolic demand during tumorigenesis. Thus, targeting TRAP1 could be an efficient strategy for development of potent anticancer drugs with novel mode of drug action. We have developed various TRAP1 inhibitors targeting not only the ATP binding pocket but also allosteric drug binding site in TRAP1 as cancer therapeutics. Those inhibitors have also been utilized to understand TRAP1 functions during various metabolic diseases. In this talk, I will briefly introduce TRAP1 functions in cancer mitochondria and our inhibitors with or without the mitochondria-targeting drug delivery systems, and discuss about implication of TRAP1 in metabolic diseases.

Keywords: mitochondria, chaperone, TRAP1, metabolic diseases, inhibitors

S-9-4

A novel post-transcriptional regulation of L-type calcium channel in mice heart

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Cereblon (CRBN) is an interacting protein with large-conductance calcium-activated potassium channels. A mutation of CRBN causes a mild type of mental retardation in humans. While, recent study suggested its novel function as AMPK inhibitor via direct interaction with AMPK α1 subunit. Disruption of CRBN gene enhanced hepatic AMPK activity and prevents high-fat diet induced obesity and insulin resistance in mice. The aim of study is to figure out the effect of CRBN KO in heart and its mitochondrial function. Eight weeks of Control (CRBN+/+) and CRBN KO (CRBN-/-) models were examined their body weight, heart rate and heart/body ratio. In vivo cardiac functions of animals were assessed by echocardiography. To evaluate mitochondrial function of those animals, cardiac mitochondria of CRBN+/+ and CRBN-/- were isolated then examined their ATP contents and ATP production rate, ROS production rate, oxygen consumption rate (OCR) and membrane potential ($\Delta\Psi m$). As results, the body weight, heart weight and heart/body ration were not significantly different between CRBN+/+ and CRBN-/- mice. Echocardiography showed enhanced cardiac contractility in CRBN-/- mice based on increased ejection fraction (%) and fractional shortening (%). In their mitochondria, basal ATP contents and substrate/ADP stimulated ATP production rate were significantly higher in CRBN-/- mice than CRBN+/+. In addition, basal H_2O_2 level and rotenone induced ROS production rates were significantly lower in CRBN-/- mice than CRBN+/+. CRBN KO mice showed higher single cell contractility with higher Ca^{2+} transient amplitude in isolated left ventricular cardiac myocytes. Our results suggested that CRBN is an important mitochondrial functional regulator which link cytosol to mitochondrial energy metabolic signaling.

Keywords: Cardiac contractility, mitochondrial energy metabolism

Yudang Academic Award

Central sensitization: chronic pain and chronic itch

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Central sensitization represents an enhancement in the activity of neurons and neural circuits induced by increases in membrane excitability and synaptic efficacy through the activation of NMDA and AMPA receptors, etc. Thus, central sensitization is responsible for the changes in pain sensitivity in chronic pains and exemplifies the contribution of the central nervous system to the generation of chronic pain. Similarly, itch sensitization can also be caused by a continuous activation of peripheral itch neurons. Gabapentin, selective in its binding to the α2δ VDCC (voltage dependent calcium channel) subunit, is effective for not only chronic pain such as neuropathic pain but chronic itch via the attenuation of central sensitization.

Long-term potentiation (LTP) is a persistent strengthening of synapses based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons through the phosphorylation of NMDA and AMPA receptors, etc. As memories are thought to be encoded by modification of synaptic strength, LTP is widely considered one of the major underlying mechanisms of memory.

"Pain memory" hypothesis is one of the mechanisms for chronic pain due to that both of central sensitization and LTP are induced by similar changes. In fact, patients with poor memory have less chance to develop pain memory, thus less possibility to develop chronic pain. Herein, we will discuss the relation between chronic abnormal sensation and memory loss.

Key words: central sensitization, long-term potentiation, chronic pain, chronic itch, memory, pain memory

P01-01

Examination of tetraspan contribution to sensory TRP-mediated pain

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Modulation of the nociceptor activity is an important analgesic strategy. Information on the analgesic target molecules expressed in nociceptors is currently expanding. In this regard, we tried to unveil a previously unknown target among proteins encoded by nociceptor-specific genes and to examine its analgesic utility. We analyzed parametric data from previous studies regarding gene expressions in dorsal root ganglionic (DRG) neurons, of which an important and major subset consist of nociceptors and obtained a number of candidate genes. As a result of further logical selection process, we chose the tetraspan subfamily as the principal object of the present study. This group is shown to be composed of 6 subtypes, but its roles in the somatosensory system such as nociception have not been explored. The contributions to pain by three of these tetraspans were evaluated by using RNA interference in DRG neurons. As result, one subtype exhibited most significant contribution to inflammatory pain. We further examined the role of the tetraspan subtype in modulation of the activity of various pain receptors expressed in the nociceptor and also in its contribution to synaptic transmission of the nociceptors. Our data suggest that the tetraspan may tune the sensitivity of a receptor ion channel, exacerbating pain.

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Keywords: Pain, Tetraspan, Neuron, DRG

P01-02

Differential induction of long-term synaptic plasticity in interneurons of layer 2/3 in rat primary visual cortex

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The neocortex consists of two main categories of neurons, excitatory neurons that convey information to distinct neurons within and outside the cortex and GABAergic inhibitory interneurons that provide local inhibition to modulate excitatory neuron activity through feedforward and feedback manners. In our previous studies, GABAergic interneurons in primary visual cortex of rat classified into four subtypes according to their electrophysiological properties: fast spiking (FS), late-spiking (LS), burst spiking (BS) and regular-spiking non-pyramidal (RSNP) cells. In the neocortex, LS cells receive thalamic and/or local cortical inputs providing feedforward inhibition. In addition, FS cells are the most prevalent type of inhibitory neuron in the cortex. Although the contributions of inhibitory interneurons to cortical activity have been extensively studied, the induction profiles and mechanism of long-term synaptic plasticity among the interneurons in the sensory cortex were not fully understood. Therefore, we investigated induction of long-term synaptic plasticity by layer 4 synaptic input in various layer 2/3 interneurons in rat primary visual cortex and compared induction mechanisms between LS and FS cells. We found that interneurons in layer 2/3 have shown different long-term plasticity by stimulus conditions and LS cells exhibit bidirectional synaptic plasticity which is dependent on intracellular calcium signaling. FS cells have shown long-term potentiation induction by either L-type calcium channel- or IP3-dependent signaling. Therefore, this study show that sensory input from layer 4 causes differential induction of long-term synaptic plasticity via distinct induction mechanism among interneurons in layer 2/3 of visual cortex. This result might be important in controlling visual information processing and cortical excitatory-inhibitory

balance.

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Keywords: Interneurons, Long-term synaptic plasticity, L-type calcium channels, IP3 receptors, Visual cortex, Layer 2/3

P01-03

Inhibitory effects of aripiprazole on K_v1.4 potassium channels

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Aripiprazole is a quinolinone derivative with partial agonist for dopamine D2 receptors. It also has antagonist activity at 5-HT2A receptor. Aripiprazole has been approved as an atypical antipsychotic drug for the treatment of schizophrenia and bipolar disorder. Although aripiprazole appears to have a low propensity for weight gain, a favorable metabolic profile, scores on extrapyramidal syndrome, and no association with hyperprolactinemia, it might has been associated with cardiovascular adverse effect as sudden cardiac death and myocardial infarction. However, electrophysiological study of aripiprazole for voltage gated potassium channel which is critical for the repolarization of the cardiac action potential are sparse. In this study, we studied the effects of aripiprazole on K_v1.4 currents expressed in HEK293 cells using the whole-cell patch-clamp technique. Aripiprazole blocked K_v1.4 in a concentration-dependent manner with an IC_{50} value of 2.7 ± 0.1 μM and a Hill coefficient of 2.0 ± 0.1. Aripiprazole accelerated the inactivation and activation (time-to-peak) kinetics in a concentration-dependent manner. The block of K_v1.4 by aripiprazole was voltage-dependent with a steep increase across the voltage range of channel activation (-20 and +20 mV). In the full activation voltage range, voltage-dependency of inhibition was diminished. These results suggest that aripiprazole blocks K_v1.4 by preferentially interacting with the open state of the channel. The effects of aripiprazole on the closed inactivated state of the K_v1.4 channels are under investigation.

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Keywords: Aripiprazole, Schizophrenia, K_v1.4

P01-04

Cholinergic and serotonergic modulation of long-term synaptic plasticity in lateral prefrontal cortex of rats

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The lateral prefrontal cortex especially, orbitofrontal cortex, is implicated in behavioral flexibility, goal-directed decision-making, reversal learning, odor processing, and reward. In previous study, we have shown that local electrical stimulation of layer 1 (L1) and layer 2/3 (L2/3) activates inputs in distal apical dendritic and perisomatic basal dendritic compartments, respectively. However, basic properties of these synaptic inputs, synaptic plasticity, and their modulations remain unclear. Therefore, we investigated the properties of synaptic transmission and cholinergic and serotonergic modulation of long-term synaptic plasticity in L2/3 pyramidal neurons (L2/3 PyNs) of lateral prefrontal cortex in rats using whole-cell recording. We positioned bipolar tungsten (100 μm diameter) and glass (10-20 μm diameter) electrodes at L2/3 and L1, respectively, to stimulate the different set of synaptic inputs. Homosynaptic long-term depression (LTD) was induced by low frequency stimulation (LFS, 900 pulses at 1 Hz) at both synaptic inputs in L2/3 and L1. There was no modulation of serotonin (5-HT) on these homosynaptic LTD. The bath application of non-specific cholinergic agonist, carbachol, for 10 min induced postsynaptic LTD. The extent of LTD was similar between L1 and L2/3. Next, we examined the effect of serotonin on the basal synaptic transmission. The amplitude of EPSP was inhibited by bath application of 5-HT (10 μM) for 10 min, which resulted in LTD. There was no layer-specific serotonergic modulation in synaptic transmission of L2/3 PyNs. Among the specific agonists of 5-HT receptors, 5-carboxamidotryptamine, a specific agonist of 5-HT5R, mimicked the inhibitory effect of 5-HT. The effects of specific antagonists of 5-HT receptors are under investigation. These results provide basic properties and cholinergic and serotonergic modulation of synaptic transmission in L2/3 PyNs of the lateral prefrontal cortex, which might be important to understanding for neocortical circuit and the role of neuromodulator.

Acknowledgement: Supported by Basic Science Research Program through the NRF funded by the Ministry of Education, Science and Technology (2016R1A2B2016533).

Keywords: Lateral prefrontal cortex, Orbitofrontal cortex, Layer-specific, cholinergic, Serotonergic, Long-term synaptic plasticity, Layer 2/3 pyramidal neuron

P01-05

Central VEGF-A pathway plays a key role in the development of trigeminal neuropathic pain in rats

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The study reported here investigated the role of the central vascular endothelial growth factor-A (VEGF-A) pathway in the development of trigeminal neuropathic pain following nerve injury. **Methods:** A male Sprague-Dawley rat model of trigeminal neuropathic pain was produced using malpositioned dental implants. The left mandibular second molar was extracted under anesthesia and replaced with a miniature dental implant to induce injury to the inferior alveolar nerve. VEGF-A164 antibody was infused intracisternally on POD1 for 7 days via an Alzet osmotic mini pump. ZM306416, VEGF-A receptor 1 inhibitor, or Vandetanib, a VEGF-A receptor 2 inhibitor was administered intracisternally on POD5. The expression of VEGF-A and its receptor were detected in the medullary dorsal horn. The inferior alveolar nerve injury produced a significant upregulation of astrocytic VEGF-A expression in the medullary dorsal horn. The nerve injury-induced mechanical allodynia was inhibited by an intracisternal infusion of VEGF-A164 antibody. Although both VEGF-A Receptor 1 (VEGF-A R1; colocalized with the blood–brain barrier) and VEGF-A Receptor 2 (VEGF-A R2; colocalized with astrocytes) participated in the development of trigeminal neuropathic pain following nerve injury, only the intracisternal infusion of a VEGF-A R1 antibody, and not that of a VEGF-A R2 antibody, inhibited the increased blood–brain barrier permeability produced by nerve injury. Finally, we confirmed the participation of the central VEGF-A pathway in the development of trigeminal neuropathic pain by reducing VEGF-A expression using VEGF-A164 siRNA. This suppression of VEGF-A produced significant prolonged anti-allodynic effects. These results suggest that the central VEGF-A pathway plays a key role in the development of trigeminal neuropathic pain following nerve injury through two separate pathways: VEGF-A R1 and VEGF-A R2. Hence, a blockade of the central VEGF-A pathway provides a new therapeutic avenue for the treatment of trigeminal neuropathic pain.

Acknowledgement: This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2017R1A5A2015391 and NRF-2018R1D1A1B07049025).

Keywords: VEGF-A, Antinociception, Blood–brain barrier, Trigeminal neuropathic pain

P01-06

Methylene Blue is involved in anti-inflammation by lowering the expression level of pro-inflammatory cytokines in knee arthritis rats

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Methylene blue (MB) is a cationic thiazine dye, commonly used as a biological stain and vasoconstrictor. It is well established that MB directly inhibits nitric oxide (NO) formation by suppressing inducible NO synthase (iNOS) activity and blocks also conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) by suppressing soluble guanylate cyclase (sGC) in vascular smooth muscles, which in turn leads to vasoconstriction (2). In this regard, MB may be also deeply engaged in anti-inflammation since NO is believed to play a crucial role in modulating inflammation (1, 4). In addition, it is well known that pro-inflammatory cytokines are one of the most vital factors for causing inflammation (3). However, much less is known about whether MB can regulate cytokine expression and finally mitigate inflammation. Accordingly, in the present study, we explored the expression level of the most representative pro-inflammatory cytokines focusing on the NF-κB pathway in knee arthritis rats before and after MB administration for elucidating how MB contributes to anti-inflammation. The expression levels of TNF-α, IL-β, IL-6 and COX-2 were measured by quantitative PCP (qPCR) in the synovial membranes of the rats three days after intra-articular complete Freund's Adjuvant (CFA) administration, as well as in the macrophage cell line inflamed by LPS (2μg/ml). Subsequently, it was compared to that of the control (saline, instead of CFA and MB, administration) and MB (MB administration after CFA injection) group, respectively. As a result, it was found that, post-MB application (0.1 and 0.2mg/ml), the expression levels of the cytokines were dramatically reduced in a dose-dependent manner compared to those of the inflammation groups (CFA or LPS application without MB treatment) in the tissue and, moreover, cell line, and that there were no significant differences between the MB and control group in terms of cytokine expression. Thus, these results imply that MB has enough capability to control the pro-inflammatory mediators and may be a therapeutically compelling agent in inflammatory diseases. Concerning further studies, we have a plan to conduct in vivo single nerve recordings and weight distribution experiments aiming to this model to figure out whether MB is indeed able to improve knee arthritis animals.

Keywords: Methylene blue, Anti-inflammation, Nitric oxide, Pro-inflammatory cytokine, Knee arthritis, Macrophage

P01-07

Endogenous spinal PPAR-gamma is necessary to motor function recovery after spinal cord injury in rats

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Traumatic spinal cord injury occurs motor function deficit below the injured level immediately after accident. 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, 220-250g) 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 there has no further beneficial effects of exogenously increased PPAR-gamma on motor function recovery, but it may have negative effects when it is reduced.

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

P01-08

The migration of GABAergic interneurons is modulated by JAK3 signaling during developing brain.

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The proper function of cerebral cortex requires a balanced and coordinated network with the excitatory glutamatergic projection neurons and the inhibitory GABAergic interneurons. During development, these different types of neurons are originated from spatially and molecularly segregated progenitors and are moved along the distinct migratory pathways. Among several types of neurons, interneurons navigate along multiple tangential migration routes to settle into appropriate developing cortical layers. Disturbed neuronal migration gives rise to neurological or neuropsychiatric disorders, such as congenital epilepsy, autism spectrum disorder, and schizophrenia. Here, we identified JAK3 as a modulator of migration and differentiation of interneurons during developmental stage. More than 70% of interneurons are produced in medial ganglionic eminence (MGE) and move to the developing cortex in mouse embryonic day 13.5 to 15.5. In the present study, we found the JAK3 expression of the lateral migrating stream of interneurons in the E13.5 and E15.5 embryonic brain was prominent. In *ex vivo* slice culture also, interneurons from MGE moved to the dorsal cortex, however, inhibition of JAK3 delayed the tangential migration of interneurons toward the developing cortex. In *in vitro* neuroprecursor cell cultures from MGE in E13.5 mice, MGE-derived interneurons could cross the scratched space in wound-healing, and pharmacological or genetic inhibition of JAK3 significantly decreased the migration of interneurons. These effects may be shown that nestin-positive neuroprecursor cells from MGE guide the interneuronal tangential migration and JAK3 signaling control the movement of nestin-positive precursor cells. These results suggest the possibility that JAK3 is a proper modulator of migration of GABAergic interneurons from MGE to cortex during corticogenesis.

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Keywords: Interneuron, Migration, JAK3, Corticogenesis

P01-09

Understanding the neural and genetic basis of odor discrimination in C. elegans

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Accurate assessment of the surrounding environment is crucial for the survival of any animal. C. elegans dedicate a large part of the genome to chemosensory GPCRs, even compared to their closest evolutionary cousins. Unlike other animals that express only one receptor per neuron to ensure odor discrimination, C. elegans and related nematodes express many chemosensory GPCRs in only 4 pairs of odor-sensing neurons. The extent of odor discrimination and how it may occur with such limited number of neurons is not known. Previously, we identified additional attractive odors sensed by the AWC neuron. Using this larger pool of odorants, we are currently conducting a detailed characterization of odor discrimination in C. elegans. For this, we use the paradigm of cross-adaptation, where worms are previously exposed to one odor, then tested for chemotaxis to a second odor sensed by the same neurons. We aim to divide odors into different categories based on whether they cross-adapt to one another. Then, we will investigate whether odors in the different categories signal through distinct cellular signaling pathways or neuronal circuitry.

Keywords: Odor, Memory, Behavior, Sensory, Neuron, Adaptation

P01-10

Pituitary adenylate cyclase-activating peptide enhances cholinergic transmission at the autonomic synapses via presynaptic mechanisms

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Pituitary adenylate cyclase activating peptide (PACAP) is an excitatory peptide transmitter which is co-localized with acetylcholine (ACh) in presynaptic nerve terminals of sympathetic and parasympathetic ganglia. Some studies have shown that PACAP is capable of modulating cholinergic transmission at autonomic synapses. To date, however, the cellular mechanisms underlying the PACAP-induced synaptic plasticity remain unclear. In the present study, thus, we investigated the potential mechanisms underlying the PACAP-induced synaptic modulation at the autonomic synapses. In this regard, 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 substrates or glial feeder layers to induce formation of cholinergic autaptic synapses in the presence of NGF and CNTF. Between DIV 10-14 in culture, electrical measurements were performed under whole-cell ruptured configuration of the patch-clamp recording techniques. To evoke excitatory postsynaptic currents (EPSCs), a single neuronal soma was stimulated by a 2 ms depolarizing step from a holding potential of -60 mV to 0 mV. Pretreatment of PACAP (100 nM) for 48 hr enhanced axonal and dendritic growth of the autonomic neurons. Importantly, PACAP significantly increased the evoked EPSCs, but not ACh-evoked nicotinic currents in the autaptic neurons. We further found that PACAP increased the readily reliable pool, release probability, and the number of transmitter release sites. All these effects of PACAP on the autonomic synapses were mediated via PACAP1 receptor activation. Taken together, our results suggest that PACAP presynaptically modulates cholinergic transmission in the autonomic ganglia.

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Keywords: Autonomic neuron, Autaptic synapse, Cholinergic, PACAP, Synaptic transmission

P01-11

Assessment of visceral pain using telemetry recording of blood pressure in conscious rat

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Telemery sensor for blood pressure (TRM54P, Millar, Australia) was inserted into abdominal artery in kyoto rats wheighing 180~220g. Five days after the insertion, the blood pressure was recorded. Signal from telemetry sensor was detected by antena TR180 Smartpad (Telemetry researchMillar, Australia) then connected by data acquision system Powerlab 8/35 and recored by software Labchart 8.0 (ADinstruments, Australia). Foley catheter (fr 6) was inserted into anus upto 4cm depth under anethesia using 2% isoflorane. After awakening, Colorectal distension, CRD) was performed in a 0.05 - 0.7 mL ranges. Without any treatment, systolic, diastolic and mean blood pressure were increased by CRD in a volume-dependent fashion. However, pulse pressure was not significantly changed by CRD. Vehicle 3% HPMC did not affect on the changes of blood pressure induced by CRD. DA-9701 showed the tendency of decreasing th changes in systolic, diastolic and mean blood pressure induced by CRD. Taken together, We suggest that using telemetry recording of blood pressure is a useful method for evaluation of visceral pain.

Keywords: Visceral pain, Telemetry, Blooc pressure, Colorectal distension

P01-12

Anatomical analysis of branch specific origin-wise synaptic distribution on tuft dendrites in the neocortex using array tomography

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Synaptic inputs on tuft dendrites of layer 5 (L5) pyramidal neurons are of interest because without non-linear dendritic integration, synaptic inputs will be severely degraded through the long dendritic filtering. Anatomically, on the other hand, pararlemniscal thalamocortical inputs from POm (Posterior medial nucleus) and primary motor cortex (M1) form rich synaptic connections on tuft dendrites of L5 pyramidal neurons. Recent studies with in vivo Ca^{2+} imaging showed that spikes on a subset of dendritic branch strongly correlated with voluntary whisker-object touch and diminished by selective inactivation of primary motor cortex (M1) form rich synaptic connections on tuft dendrites of L5 pyramidal neurons. Based on these findings, we hypothesized that synapses on tuft dendrites of L5 neurons are segregated in a branch specific manner, according to their origins and/or information conveyed. To test this hypothesis, subcellular synaptic input patterns on tuft dendrites were examined using array tomography. The Barrel Cortex area, where input from M1 and POm, is collected and cut consecutively at 90 nm thickness after embedding in resin. A total of 330 consecutive slices were obtained, and the total thickness of the tissue was approximately 30 μm. 330 consecutive slice were imaging after Immunostaining. Distal tuft dendrites of layer V pyramidal neurons were reconstructed using a set of custom-modified software. We traced dendritic structure and annotated locations of synapses from POm and M1 on 18 dendritic branches in layer I. Currently, only the process of synapse detection is left in the dendritic branch we find. Therefore, after finding all of the synapses by origin, we will analyze the branch specific input wires in the turf dendrites.

Keywords: Primary motor cortex, Posterior medial nucleus

P02-01

The RNAi line of *kdm4a* ameliorates tau-engendered defects in *Drosophila melanogaster*

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Tauopathies including Alzheimer's disease (AD), are characterized by the deposition of neurofibrillary tangles composed of the hyper-phosphorylated tau protein. Given that the abnormal alteration of histone acetylation and methylation have been documented in AD patients with cause and effect relationship, we extended our investigation to the role of several *JHDM* (Jumonji histone demethylase) genes, which have never been studied in AD etiology. According to bioinformatics analysis, the expressions of *JHDM1A*, *JHDM2A/2B*, *JHDM3A/3B* were slightly but significantly increased in postmortem brain tissue with Alzheimer's disease than non-demented control, whereas *JHDM1B* mRNA level was downregulated in brain of Alzheimer's disease patients. To directly identify the possible relationship between alterations in expression profile of *JHDM* genes and AD etiology in vivo, we examined whether tissue specific downregulation of *JHDM Drosophila* homologues (*kdm*) can affect *tau*-induced defects using transgenic flies. We discovered that *tau*-engendered defects in the eye was ameliorated toward less severe phenotypes, when crossed with any one of RNAi lines of *kdm2*, *kdm3*, *kdm4a*, and *kdm4b* genes. But, when expressed in their CNS, uniquely, the RNAi lines of *kdm4a* ameliorated *tau* induced locomotion deficits and extended the life span by restoring the heterochromatin loss and the altered histone methylation (H3K9me2 and H3K27me3) patterns.

Keywords: *Drosophila melanogaster*, Alzheimer, *JHDM* (Jumonji Histone demethylase), Tau

P02-02

Membrane targeting of the astrocytic membrane protein, MLC1 regulates cellular morphology and motility

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Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a very rare form of infantile-onset leukodystrophy. The disorder is caused primarily by mutation of *MLC1*, which leads to vacuolation of myelin and astrocytes, subcortical cysts, brain edema, and macrocephaly. However, the physiological role of MLC1 in cellular communication remains poorly understood. In this study, we aimed to investigate the molecular function of MLC1 and its effects on cell–cell interactions. Regulating the level of MLC1 expression drastically altered cellular morphology and motility via actin remodeling: Overexpression induced filopodia formation and suppressed motility. Interestingly, expression of patient-derived *MLC1* mutants, which were mainly trapped in the endoplasmic reticulum (ER), failed to exhibit the morphological changes and alter motility changes. These data suggest that the expression of MLC1 at the plasma membrane is critical for changes in actin dynamics, cell shape, and cell motility. Moreover, knockdown of *Mlc1* induced lamellipodia formation and showed unstable membrane fluctuation of the primary astrocytes. Thus, our results suggest that disturbed homeostasis of interactions among neurons, glia, and the vasculature in patients with MLC could be associated with the misallocation of mutant MLC1, which induces unstable cell–cell communication.

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Keywords: MLC disease, MLC1, Actin remodeling, Cell motility, Cell communication

P02-03

Role of group I metabotropic glutamate receptor in low Mg^{2+}-induced interictal-like epileptiform activity in rat hippocampal slice

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Group I glutamate metabotropic receptor (mGluR) has been shown to be involved in postsynaptic neuronal excitability, which may induce long lasting synaptic and cellular plasticity. In addition, activation of group I mGluR may initiate epileptogenesis. In this study, we investigated roles of group I mGluR on low Mg^{2+}-induced epileptiform activity in isolated rat hippocampal slices without the entorhinal cortex using extracellular recordings. Exposure to Mg^{2+}-free artificial cerebrospinal fluid can induce interictal-like epileptiform activity in rat hippocampal slices. While antagonists of group I mGluR, either mGluR5 (MPEP, 50 μM) or mGluR1 (LY367385, 100 μM) significantly inhibited the frequency of the low Mg^{2+}-induced interictal-like epileptiform activity, the group 1 mGluR agonist DHPG (10 μM) significantly increased the frequency of the interictal-like epileptiform activity. The phospholipase C inhibitor U 73122 (10 μM) inhibited the frequency of the interictal-like epileptiform activity. Thapsigargin (10 μM), which blocks ER Ca^{2+}-ATPase resulting in depletion of ER Ca^{2+} stores, significantly inhibited the frequency of the interictal-like epileptiform activity, but ryanodine receptor antagonist dantrolene (30 μM) did not affect the epileptiform activity. The protein kinase C (PKC) activator phorbol 12,13-dibutyrate (PdBu, 1 μM) significantly increased the frequency of the epileptiform activity, but chelerythrine (10 μM), protein kinase C inhibitor, did not affect the epileptiform activity. While the transient receptor potential-canonical (TRPC) channel blocker flufenamic acid (100 μM) significantly inhibited frequency of epileptiform activity, SKF367385 (10 μM) and 2-APB (30 μM) did not affect the epileptiform activity. All these results suggest that group I glutamate metabotropic receptor is involved in the low Mg^{2+}-induced interictal-like epileptiform activity in rat hippocampal slices through phospholipase C, release of Ca^{2+} from intracellular stores, activation of PKC and TRPC channels.

Acknowledgement: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2016R1D1A1B03934176)

Keywords: Ca^{2+} store, Interictal epileptiform activity, Metabotropic glutamate receptors, Phospholipase C, Rat hippocampal slice, TRPC channel

P02-04

SCAMP5-dependent localization of NHE6 to synaptic vesicles is critical for regulating quantal size at glutamatergic synapses

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Quantal size of synaptic vesicle (SV) is regulated by a chemical gradient (ΔpH) and membrane potential (Δψ) generated by the vacuolar H^+-ATPase. The relative roles of ΔpH and Δψ vary with the type of neurotransmitters, and glutamate uptake more depends on the electrical component of Δψ than ΔpH. Monovalent cation/H^+ exchanger plays an important role in establishing Δψ, thus the proper localization of this protein to SV is critical for regulating glutamate quantal size, but the underlying mechanism remains poorly understood. In this study, we demonstrated that trafficking of (Na^+/

K^+)/H^+ exchanger 6 (NHE6) to SV is regulated by its interaction with secretory carrier membrane protein 5 (SCAMP5). We showed that 2/3 loop of SCAMP5 interacts with C-terminus of NHE6 and SCAMP5 knockdown (KD) hinders localization of NHE6 to SV in hippocampal neurons. Using fluorescent glutamate sensor iGluSnFR, we found that the amount of glutamate release at presynaptic bouton decreased with SCAMP5 KD. This result was further corroborated by electrophysiological recording. Together, our results suggest that SCAMP5 has a critical role in proper localization of NHE6 to SVs and quantal size at glutamatergic synapses. Since both NHE6 and SCAMP5 are autism candidate genes, the reduced quantal size by perturbing their interaction may underscore synaptic dysfunction observed in autism.

Keywords: NHE6, SCAMP5, Synaptic vesicle, Quantal size, Autism

P02-05

Hypothalamic peptide hormone A controls appetite via leptin signaling and induction of α- melanocyte-stimulating hormone

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Hypothalamic regulation of appetite governs whole body energy balance. Satiety is regulated by endocrine factors including leptin and impairment of its induction causes obesity. Peptide hormone A (PHA), is induced by high fat diet in liver of mice and promotes lipolysis in periphery. However, its role in hypothalamus to control food intake is unknown. We demonstrated that PHA is expressed in proopiomelanocortin (POMC) expressing neurons located in arcuate nucleus (ARC) of hypothalamus which is a target of leptin and has an anorectic effect. PHA expression was promoted by leptin- induced STAT3 phosphorylation. Intracerebroventricular injection of PHA significantly reduced food intake via increasing α-melanocyte-stimulating hormone (α-MSH) content in hypothalamus. We also found that hypothalamic injection of PHA significantly decreased body weight of high fat diet-induced obese mice which showing leptin insensitivity. We suggest that hypothalamic PHA provokes anorectic melanocortin pathway activation and mediates leptin signaling to prevent obesity.

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Keywords: Hypothalamus, Peptide hormone A, Appetite, α-MSH, POMC

P02-06

Crif1 deletion in endothelial cells affects blood-brain barrier maintenance by the alteration of actin cytoskeleton

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Endothelial cells (ECs) in Blood-brain barrier (BBB) have higher volume of mitochondria than endothelial cells of peripheral capillaries. Cerebral endothelial cells have junctional proteins to maintain BBB integrity by restricting toxic substances and peripheral immune cells. Although it is known that mitochondrial inhibitors cause BBB disruption and decrease of tight junctions, the mechanism underlying BBB disruption by defective mitochondrial oxidative phosphorylation (OXPHOS) is unclear in mitochondrial related gene-targeted animal model. To assess the mitochondrial OXPHOS function in endothelial cells for maintaining of BBB, we tried to establish endothelial specific Crif1 deletion mouse. We observed encephalomyelitis-like behavior, myelin damage and leukocyte infiltration through the BBB disruption and decrease of tight junction protein expression. Furthermore, we investigated the alteration of actin cytoskeletons that interacted with junctional proteins to support BBB integrity. Crif1 loss leads to reorganization of actin cytoskeletons and decrease of tight junction-associated protein through the defect of ATP production in vivo and in vitro. We suggest that endothelial specific Crif1 defect mouse is encephalomyelitis genetic animal model and demonstrate that the role of mitochondrial OXPHOS as supply of ATP in cerebral endothelial cells.

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Keywords: Blood-brain barrier, Mitochondria

P02-07

Experimental evidences for functional changes in cortical blood flow by transcranial direct current stimulation

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Several clinical studies have demonstrated that Transcranial direct current stimulation (tDCS) can change cerebral blood flow with a polarity - specific manner. However, there is a little information about possible underlying mechanisms for modulation of cerebral blood flow by tDCS. **Purpose:** The purpose of this study was to evaluate changes in functional or structural changes in cortical blood vessel by tDCS. **Method and Materials:** tDCS was applied bilaterally on the skull with intensity of 150uA and duration of 20min from Sprague – Dawley rats. Structural changes in cortical blood vessel were evaluated by imaging cortical blood vessel stained with Evans-blue dye or by direct visualization of cortical vessels stained with fluorescent dye with a confocal microscope. Functional changes were monitored by direct measurement of cortical blood flow with a Laser-Doppler and by direct recording of oxygen and nitric oxide concentration from the cortex using a voltammetric technique. **Results:** Anodal tDCS resulted in increase in diameter of blood vessels in the cortex and also upregulation of oxygen and nitric oxide concentrations in the cortex. In contrast to, cathodal tDCS cause the reduction of size of cortical blood vessels and of oxygen concentration. But there is a little change in concentration of nitric oxide in the cortex under cathodal tDCS. Therefore, this results suggest that tDCS may modulate functional changes in blood flow by changes in release of nitric oxide in the cortex.

Acknowledgement: This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (2017R1D1A1B03032034).

Keywords: Transcranial direct current stimulation, Cortical blood vessel, Polarity-specific, Nitric oxide, Oxygen

P02-08

Obstructive sleep apnea-induced pathological changes in the rabbit brain

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Obstructive sleep apnea(OSA) is well known risk factor for dementia and cerebrovascular disorder. However, the affective mechanisms of OSA on dementia or cerebrovascular disorder have not been well reported. In this study, we have tried to make proper animal model which is similar anatomical and physiological dysfunction to human OSA. After establishing OSA animal model, we studied the brain pathological change of OSA model. We used New Zealand white rabbits (n=6) for establishing OSA model. Six rabbits had been underwent tongue base collagen filler injections to make tongue hypertrophy which is main pathology of OSA. Three months after, brain tissue of control and OSA rabbits were subsequently fixed in 10% neutral buffered formalin for 24 hr, were paraffin embedded, cut into 5 μm sections, and were processed for hematoxylin and eosin(H&E) staining. The stained sections were analyzed and captured the images of the representative fields. Among 6 rabbits, 5 rabbits showed sleep apnea proved by polysomnography. The H&E staining in OSA rabbit brains showed degenerative changes and increased inflammatory changes with eosinophilic neutrophil infiltrations and cortical dys-organizations in frontal and temporal cortex examinations. In this study, we have successfully established the OSA rabbit model with tongue base filler injection. The chronic OSA rabbit showed degenerative pathologic changes of brain.

Keywords: Obstructive sleep apnea, Polysomnography, Neurodegeneration, Dementia

P02-09

The epigenetic changes in rabbit brain of chronic obstructive sleep apnea model

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Obstructive sleep apnea(OSA) is a common sleep disorder which showed clinical symptoms such as difficulty in breathing control during sleep, blockage of the airways, might make results in sleep fragmentation, leading to daytime symptoms of drowsiness and decreased attention ability, cognitive decline. Recent studies have been showed that OSA is the independent risk factor of dementia such as Alzheimer's disease(AD). In this study, we studied the epigenetics with OSA rabbit model to investigate the relationships between AD and OSA. We used New Zealand white rabbits(n=6) for establishing OSA model. Six rabbits had been underwent tongue base collagen filler injections to make tongue hypertrophy which is main pathology of OSA. After 3 months, we studied the mRNA array to investigate the difference of epigenetic factors in OSA rabbit model. Among 6 rabbits, 5 rabbits showed sleep apnea proved by polysomnography that is gold standard to diagnose the sleep disorders. The results of mRNA gene arrays showed high fold increasing mRNA of olfactory receptors(Olfr194; 13.77 folds, 591; 2.71 folds, 4c11; 2.47 folds and 648; 2.06 folds) associated with AD pathogenesis. In addition, muscarinic type 2 acetylcholine receptor of cholinergic system showed 2.3 fold decreased in OSA rabbit brain compared with control brain. A number of gene expression changes associated with Alzheimer's disease have also been identified. These results suggested that the association of AD and OSA.

Keywords: Obstructive sleep apnea, Alzheimer's disease, Polysomnography, Olfactory receptor, Muscarinic receptor

P02-10

Decreased expression of miR-200a-3p and 200b-3p of rat brain in obstructive sleep apnea associated with Alzheimer's disease

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The association of OSA and Alzheimer's disease (AD) was known with several studies. However, the pathological mechanism of those relations have not been clearly reported. In this study, we investigate the miRNA array to study the relation between AD and OSA. Four rats had been underwent tongue base collagen filler injections to make tongue hypertrophy which is main anatomical changes of OSA. After 3 months, we studied the miRNA arrays with brain tissues to investigate the difference of epigenetic factors in OSA rat model compared to the control. Three rats showed sleep apnea proved by polysomnographic study. There are 61 microRNAs 2.0 fold changes with 29 up-regulations and 34 down-regulations. Among those changed miRNAs, decreased expression of miR-200a-3p and 200b-3p was already known as promoting β-Amyloid-induced neuronal apoptosis and hyper-phosphorylation of tau in AD. In our results, miR-200a-3p and 200b-3p was down regulated in OSA(10.6 and 31.2 fold, respectively) compared to the control. In addition, it also identified a number of miRNA changes associated with pathology of Alzheimer's disease.

Keywords: Obstructive sleep apnea, Alzheimer's disease, miR-200a-3p, miR-200b-3p, Microarray

P02-11

Optogenetic stimulation of cortico-subthalamic projections ameliorate the motor symptoms in the 6-hydroxydopamine model of Parkinson's disease

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The subthalamic nucleus (STN) is one of the primary input areas of basal ganglia circuitry and often serves as a target of deep brain stimulation(DBS) for Parkinson's disease (PD) therapy. Although the exact mechanism of DBS remains unclear, optogenetic stimulation of motor cortical neurons projecting to STN, the hyper-direct pathway, has been reported to ameliorate the PD-like symptoms in the model mouse. In the present study, we analyze the circuit mechanism of this phenomenon. First we explored the electrophysiological features that can be used for the sign of the symptom from PD model mouse by unilateral nigrostriatal 6-hydroxydopamine (6-OHDA) lesioning. We found that the power of local field potentials (LFP) in both motor cortex (M1) and STN in the beta frequency (12-30 Hz) range and frequency of burst-like firing were significantly enhanced in the dopamine-depleted hemispheres, compared with non-lesioned hemispheres. The exaggerated oscillatory synchronization in the beta (12-30Hz) frequency band has been reported to be associated with the motor symptoms of PD patients. We then tested if high-frequency activity of STN-projecting neurons reduces the beta activity. We used a retrograde adeno associate virus to selectively express channelrhodopsin-2 in the STN-projecting neurons in mice made parkinsonian. We then applied 140 Hz consecutive optogenetic stimulation on the STN projecting neurons. We observed a significant reduction in the beta-band oscillation and the frequency of burst-like firing. Our findings suggest that elucidation of synaptic properties during M1-STN stimulation could lead to better understanding of DBS mechanism modulating pathological patterns of synchronized oscillations, such as reduction of pathological beta activity in PD.

Acknowledgement: This research was supported by Brain Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science and ICT(2017M3C7A1048086)

Keywords: 6-OHDA, Parkinson's disease, M1, STN

P03-01

Tricyclic antidepressant doxepin inhibits voltage-dependent K^+ channels in rabbit coronary arterial smooth muscle cells

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Doxepin, tricyclic antidepressant (TCA), is widely used for the treatment of depressive disorders. Our present study determined the inhibitory effect of doxepin on voltage-dependent K^+ (K_v) channels in freshly isolated rabbit coronary arterial smooth muscle cells by using a whole-cell patch clamp technique. Vascular K_v currents were inhibited by doxepin in a concentration-dependent manner, with a half-maximal inhibitory concentration (IC_{50}) value of 6.52 ± 1.35 μM and a Hill coefficient of 0.72 ± 0.03. Doxepin did not change the steady-state activation curve or inactivation curve, suggesting that doxepin does not alter the gating properties of K_v channels. Application of train pulses (1 or 2 Hz) slightly reduced the amplitude of K_v currents. However, the inhibition of K_v channels by train pulses were not changed in the presence of doxepin. Pretreatment with K_v1.5 inhibitor, DPO-1, effectively reduced the doxepin-induced inhibition of the K_v current. However, pretreatment with K_v2.1 inhibitor (guangxitoxin) or K_v7 inhibitor (linopirdine) did not change the inhibitory effect of doxepin on K_v currents. Inhibition of K_v channels by doxepin caused vasoconstriction and membrane depolarization. Therefore, our present study suggests that doxepin inhibits K_v channels in a concentration-dependent, but not use-, and state-dependent manner, irrespective of its own function.

Keywords: Doxepin, Voltage-dependent K^+ channels, Coronary artery, Smooth muscle

P03-02

The inhibitory effect of anticholinergic drug oxybutynin on voltage-dependent K^+ channels in coronary arterial smooth muscle cells

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This study demonstrates the inhibitory effect of anticholinergic drug oxybutynin on voltage-dependent K^+ (K_v) channels in rabbit coronary arterial smooth muscle cells. Oxybutynin inhibited vascular K_v channels in a concentration-dependent manner, with an IC_{50} value of 11.51 0.38 μM and a Hill coefficient (n) of 2.25 ± 0.12. Application of oxybutynin shifted the activation curve to the right and the inactivation curve to the left. Pretreatment with the K_v1.5 subtype inhibitor DPO-1 and the K_v2.1 subtype inhibitor guangxitoxin suppressed the oxybutynin-induced inhibition of the K_v current. However, application of the K_v7 subtype inhibitor linopirdine did not affect the inhibition by oxybutynin of the K_v current. The anticholinergic drug atropine did not inhibit the K_v current nor influence oxybutynin-induced inhibition of the K_v current. From these results, we concluded that oxybutynin inhibited the vascular K_v current in a concentration-dependent manner by influencing the steady-state activation and inactivation curves independent of its anticholinergic effect.

Keywords: Oxybutynin, Voltage-dependent K^+ channels, Coronary artery

P03-03

Functional role of the C-terminal domain of Bestrophin-1, a calcium-activated chloride channel

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The Bestrophin-1 (BEST1), calcium-activated chloride channels, are widely expressed in a variety of tissues including the brain. Functional calcium-activated chloride channels are consist of homo-pentamer of BEST1 protein symmetrically arranged around a central axis, which forms a Cl^--conduction pathway. The N-terminal region (amino acids 1-390) of BEST1 shows highly conserved amino acids among vertebrate orthologues, but the C-terminal region (amino acids 391-585) is rather distantly related. The highly conserved N-terminal region contains membrane spanning transmembrane domains as well as a calcium-binding domain, Ca^{2+}-clasp. Structural studies suggested that direct binding of Ca^{2+} to Ca^{2+}-clasp induce the conformational changes and open the BEST1 channel. However, the structural and functional roles of weakly conserved and structurally disordered C-terminal region of BEST1 channel remain poorly understood. Here, we present a clue for understanding the functional role of C-terminal region with the result of electrophysiological studies on wild-type and mutant BEST1 channels from human and mouse. Interestingly, the results suggest that the C-terminal region could functionally confer calcium sensitivity on BEST1 channels without bearing any known calcium-binding motifs. Currently, we are trying to identify the molecular mechanism of C-terminus-dependent gating of BEST1 channels.

Acknowledgement: This research was supported by KBRI Basic Research Program funded by Ministry of Science and ICT (19-BR-01-02).

Keywords: Calcium-activated chloride channels, Bestrophin-1, C-terminal domain, Calcium sensitivity

P03-04

Carbon monoxide stimulates large conductance Ca^{2+}-activated K^+ currents of human cardiac fibroblasts through diverse mechanisms

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Cardiac fibroblasts have been proposed to be important determinants of both structure and function of the myocardium. Ca^{2+}-activated K^+ (K_{Ca}) channels play a role in cardiac remodeling and carbon monoxide (CO) is an important, physiological signaling molecule and is now known to regulate a growing number of different ion channel types. We used the whole-cell patch-clamp technique to examine the role of CO in regulating K_{Ca} channels and the mechanisms in human cardiac fibroblasts (HCFs). Application of CO delivery by CORMs (carbon monoxide releasing molecule: CORM2 or CORM3) increased the amplitude of K_{Ca} currents and the currents were large conductance Ca^{2+}-activated K^+ currents ($I_{BK_{Ca}}$) because paxilline (a specific BK_{Ca} blocker) inhibited the current. CO-induced $I_{BK_{Ca}}$ stimulation was inhibited by pre-treatment with L-N^G-monomethyl Arginine citrate (L-NMMA) or L-N^G-Nitroarginine Methyl Ester (L-NAME), nitric oxide synthase (NOS) blockers. 8-bromo-cyclic GMP (a membrane permeable cGMP analog) also increased $I_{BK_{Ca}}$. The CO-stimulating effect on $I_{BK_{Ca}}$ was blocked by pre-treatment with KT5823 (a PKG inhibitor) or 1 H-[1,-2, -4] oxadiazolo-[4,-3-a] quinoxalin-1-one (ODQ; a soluble guanylate cyclase inhibitor). Additionally, 8-bromo-cyclic AMP increased the $I_{BK_{Ca}}$ and pre-treatments with KT5720 (a PKA inhibitor) or SQ22536 (an adenylyl cyclase inhibitor) blocked the CO-stimulating effect on $I_{BK_{Ca}}$. In addition, pre-treatment of N-ethylmaleimide (a thiol-alkylating reagent) blocked CO effect on $I_{BK_{Ca}}$ and DL-dithiothreitol (a reducing agent) reversed the effect. Pre-treatment with SB239063 (a p38 MAPK inhibitor) or PD98059 (a MEK inhibitor) also blocked the CO-effect on $I_{BK_{Ca}}$. These data suggest that CO enhances $I_{BK_{Ca}}$ through NO, PKG,

PKA, and *S*-nitrosylation, MAPK pathways in HCFs.

Keywords: Ca^{2+}-activated K^+ currents, Carbon monoxide, Human cardiac fibroblast, Nitric oxide synthase

P03-05

Effect of carbon monoxide on delayed rectifier K^+ currents of human cardiac fibroblasts by diverse signaling pathways

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Human cardiac fibroblasts (HCFs) are the highest cell population in the myocardium, accounting for approximately two-thirds of the cells and play a role in cardiac development, myocardial structuring, cell signaling, and electro-mechanical function in healthy and diseased myocardium. We investigated the effect of carbon monoxide (CO) on delayed rectifier K^+ (K_{DR}) channels and the mechanism in human cardiac fibroblasts. Carbon monoxide releasing molecule 3 (CORM3; a CO producing molecule) significantly increased the amplitude of K_{DR} currents. The CORM3 stimulating effect on K_{DR} currents were blocked by pretreatment with KT5823 (a PKG inhibitor) or 1 H-[1,-2, -4] oxadiazolo-[4,-3-a] quinoxalin-1-one (ODQ; a soluble guanylate cyclase inhibitor). Additionally, pretreatment with KT5720 (a PKA inhibitor) and SQ22536 (an adenylyl cyclase inhibitor) blocked the CORM-3 stimulating effect on the currents. 8-bromo-cyclic GMP (a membrane permeable cGMP analog) or 8-bromo-cyclic AMP increased the currents. In addition, pre-treatment of N-ethylmaleimide (a thiol-alkylating reagent) before CORM-3, the CO could not stimulate K_{DR} and DL-dithiothreitol (a reducing agent) reversed the effect. Pre-treatment with SB239063 (a p38 MAPK inhibitor) or PD98059 (a MEK inhibitor) also blocked the CO-stimulating effects. These data suggest that CO enhances the K_{DR} currents through PKG, PKA, *S*-nitrosylation, and MAPK pathways in HCFs.

Keywords: Human cardiac fibroblast, Delayed rectifier K^+ currents, Carbon monoxide, PKG pathway, PKA pathway, S-nitrosylation, MAPK pathway

P03-06

Different context for shear signaling in left versus right atrial myocytes: differential roles of $P2Y_1$- and $P2X_4$-purinoceptors

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Shear stress induces slow longitudinal Ca^{2+} wave (L-wave) and action potential (AP)-triggered transverse Ca^{2+} wave (T-wave) in atrial myocytes. Although both waves are caused by autocrine action of ATP, released via connexin-43 hemichannels, $P2Y_1$ receptor signaling and ionotropic P2X receptors mediate L-wave and T-wave, respectively. Here, we present a basis for the observations of different types of shear-induced Ca^{2+} waves. Shear stress (~16 dyn/cm^2) was applied onto single myocytes using micro-flow apparatus. We compared propensities of the Ca^{2+} waves and AP, and purinoceptor protein levels between left and right atrial myocytes. Most of left atrial myocytes (≅69.8%) showed L-waves under shear stress, while right atrial myocytes (≅77.4%) mainly produced T-waves under shear stress. Consistently, shear-induced AP was more frequent in right atrial cells. The amount of shear-induced ATP release was bigger in left atrial cells than in right atrial cells. The level of $P2Y_1$ receptor proteins is higher in left atrial cells than in right atrial cells. $P2X_4$ and $P2X_5$ receptors were significantly expressed in rat atrial cells. The $P2X_4$ protein level was two-fold higher in right atrial myocytes than in left atrial myocytes. That of $P2X_5$ receptor was similar between left and right atrial cells. $P2X_4$ or $P2Y_1$ receptors, but not $P2X_5$ receptors, were significantly co-localized with connexin-43 in the lateral membrane as well as in the intercalated discs. Dialysis of $P2X_4$ antibodies into atrial cells suppressed P2X component of shear-induced cation currents, while that of $P2X_5$ did not alter the current. Our data suggest that left and right atrial myocytes have different context for shear signaling in terms of P2 receptor subtypes, thereby generating $P2Y_1$ receptor-specific slow Ca^{2+} wave mainly in left atrial myocytes and $P2X_4$-depedent T-wave/AP in right atrial cells during shear stimulation.

Keywords: Shear stress, Ca^{2+} waves, Right and left atrial myocytes, P2X4 receptor, P2Y1 receptor

P03-07

Chronic hemodynamic overload of the atria is an important factor for shear signaling remodeling in rat hearts

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Hemodynamic disturbances induced by hypertension, heart failure, and valve diseases lead to atrial fibrillation. We have previously shown that shear stress induces proarrhythmic Ca^{2+} waves via connexin43 (Cx43) hemichannel opening, and that ATP release through the Cx43, in turn, activates P2Y1 receptors (P2Y1Rs) and P2X4 receptors (P2X4Rs) in rat atrial myocytes. To understand cellular mechanism for mechanically-induced atrial arrhythmia and role of shear signaling in this pathogenesis, we compared atrial shear signaling between sham-operated rats and the rats subjected to prolonged transverse aortic constriction (TAC). Atrial cell hypertrophy with higher fractional shortening and dilation of atrial chamber were observed at 5 weeks (wk) after TAC surgery. On 4-month (mon) after TAC surgery, more severe dilation in atrium with lower fractional shortening was detected. Whole-cell patch clamp studies revealed that shear-induced nonselective cation currents that are mediated by P2X4Rs (about 50%) and Cx43 (about 20%), were enhanced with hypertrophy, but they were no longer enhanced during atrial failure. Total Cx43 proteins and phosphorylated Cx43 at its ser-368 residue were gradually increased by TAC, which was consistent with larger shear-induced NMDG+ currents in TAC rat atrial myocytes. P2X4R expression increased in 5-wk-TAC atrial cells, but decreased in 4-mon-TAC atrial cells. On the other hand, P2Y1R-dependent longitudinal Ca^{2+} waves and P2Y1R expression were significantly increased by 4-mon-TAC. Our data suggest that Cx43-P2 receptor-mediated shear signaling is significantly altered by the progress of atrial dilation and volume overload, and that biphasic changes in P2X4R function and expression versus TAC duration may play a role in the progression from hypertrophy to failure in atrium subjected to aortic stenosis and increased afterload.

Keywords: Transverse aortic constriction, Shear stress signaling, Atrial hypertrophy and failure, Cx43, P2 receptors

P03-08

Adaptive voltage control ensures the precise half inactivation application of voltage gated sodium channels on Qube, 384-well automated patch clamp system

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Voltage-gated sodium channels have been being studied extensively due to their potential as targets for several indications, such as pain, epilepsy, cardiac and muscle paralysis syndromes. Several compounds bind preferentially to the inactivated state of the channel and the potency are vary depending on the % inactivation of the channels. Sophion has newly released the adaptive protocol block for the Qube, 384-well automated patch

clamp system. Using this new protocol, it is possible to separately define a voltage applied to each individual recording well both for activation and for inactivation of the channels, enabling the generation of more precise data from voltage-gated ion channels. In order to validate this adaptive protocol, we recorded voltage-dependent inactivation of the sodium channels and compared the half-inactivation potential (V½) values between the online analysis from the adaptive protocol and the offline analysis from the standard protocol in the same experiment. As expected, the V½ values obtained from these two protocols agreed well each other. Thereafter we determined IC_{50} values of a set of compounds both at closed and at inactivated states and the results suggested that the use of an individual V½ value in a corresponding recording well contributed to reduce data variability. Those results indicate that new adaptive voltage protocol improves control of the voltage-gated channel state during an experiment, reduces data variability, and increases the reliability of compound test results, on a 384-well high throughput automated patch clamp platform.

Keywords: Automated patch clamp, Sodium channel, Safety pharmacology, Cardiac ion channels, Pain

P03-09

Regulation of transient receptor potential canonical 4 activity by phospholipase C δ1

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Transient receptor potential canonical (TRPC)4 and TRPC5 channels are non-selective calcium-permeable cation channels that maintained by phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) and inactivated due to its depletion. Phospholipase C (PLC) is an enzyme that cleaves phospholipids and the PLCδ is the most calcium-sensitive form among the isozymes that stimulated by physiological concentration of Ca^{2+}. Here, we investigated the regulation mechanism of TRPC4 by the Ca^{2+}-PLCδ-$PI(4,5)P_2$ signaling cascade. In order to identify the interaction between ion channel and PLCδ protein, we implied co-immunoprecipitation and fluorescence imaging including Föster Resonance Energy Transfer. We evaluated the activity of channels with electrophysiological recording in HEK293 cells expressing TRPC channels. Here, we demonstrate that TRPC4 directly interacts with PLCδ1. We also found that PLCδ isozymes are activated by the calcium through opened channels but not by the cytosolic calcium increase. Our study established the PLCδ1 inhibits overall TRPC4's currents activity, but mainly regulates the basal TRPC4 currents to have a characteristic low basal activity. These regulation of PLCδ1 on TRPC4 activity occurs depend on $PI(4,5)P_2$ hydrolysis. Resultantly, PLCδ1 is considered to be a negative regulator of TRPC4.

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Keywords: Transient receptor potential channels (TRP channels), Phospholipase C, Calcium, Phosphoinositide, Fluorescence resonance energy transfer (FRET)

P03-10

Different effects of PCBs on steady-state current of human $K_v1.3$ channel

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Polychlorinated biphenyls (PCBs) are a family of bicyclic chlorinated aromatic hydrocarbons. PCBs' unique chemical properties and the low cost of producing PCBs have contributed to their extensive industrial use. PCBs are detected in air, water, sediments, fish, and wild life and human adipose tissue, milk, and serum. Acute and long-term exposure to the compounds has been known to causes diseases such as developmental delays and motor dysfunction. The toxic effects of PCBs on cardiovascular system have been mainly explored in long-term effects. PCB 77 reduced thyroid function, increases uterine and breast cell tumors, inhibits humoral and cellular immunity through activation of Ah receptor, and impairs immune function. One immune-modulating mechanism is achieved by the $K_v1.3$ voltage-dependent potassium channel, which is expressed highly in lymphocytes including effector memory T lymphocytes. Here we studied the effect Polychlorinated biphenyls (PCB77 and PCB126) on human $K_v1.3$ channels expressed in Xenopus oocytes. When we exposed the oocytes with PCB77 and PCB126 for 8 min and 15min, the peak current of K_v 1.3 channel did not change significantly by PCB77 and PCB126. However, PCB77 increased $K_v1.3$ channel steady-state currents and did right shift the steady-state activation curves. These results suggest that PCBs could affect the heart in a way that did not block, a voltage-dependent potassium channel, $K_v1.3$ channel directly.

Keywords: Polychlorinated biphenyls, PCBs, PCB77, $K_v1.3$

P03-11

Frequency-dependent Block of $K_v1.5$ Channel by Ifenprodil

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Ifenprodil (2-(4-benzyl-piperidino)-1-(4-hydroxyphenyl)-1-pro-panol), an alpha1 (a1)-adrenergic receptor antagonist, is initially developed as a vasodilating and anti-ischemic agent and then has been clinically used in the treatment of peripheral arterial obliterative disease and cerebrovascular diseases. The $K_v1.5$ channel is a shaker-type, voltage-gated potassium channel encoded by the KCNA5 gene involved in phase 2 of action potential in cardiac myocytes. It contributes to the maintenance of cell membrane potential in a wide variety of tissues, including myocytes, pancreatic β-cells, neurons, and smooth muscle cells in the pulmonary vasculature. We examined the effect of ifenprodil on the human $K_v1.5$ channel using a Xenopus oocyte expression system and a two-microelectrode voltage clamp technique. Ifenprodil reduced the amplitude of the $K_v1.5$ channel current in a concentration-dependent manner. Ifenprodil rapidly inhibited $K_v1.5$ currents, eliminating the possibility of genomic regulation. Inhibition rate was concentration-dependent however it was not voltage-dependent. Inhibition rates for peak and steady state currents were not significantly different at all voltage we examined. These results suggested that ifenprodil inhibit $K_v1.5$ currents via a non-genomic mechanism, providing a mechanism for the possible arrhythmogenic effects of ifenprodil.

Keywords: Ifenprodil · $K_v1.5$ channel

P03-12

Voltage-independent inhibition of human $K_v1.5$ currents by cinnarizine

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Cinnarizine is an antagonist of several vasoactive drugs including adrenaline, angiotensin and 5-hydroxytryptamine. Cinnarizine used in the treatment of vestibular dysfunction, migraine, cerebral, or peripheral vascular insufficiency with rare major adverse effect**.** The $K_v1.5$ channel is a shaker-type, voltage-gated potassium channel encoded by the KCNA5 gene. It contributes to the maintenance of cell membrane potential in a wide variety of tissues, including myocytes, pancreatic β-cells, neurons, and smooth muscle cells in the pulmonary vasculature. We examined the effect of cinnarizine on the human $K_v1.5$ channel using a *Xenopus* oocyte expression system and a two-microelectrode voltage clamp technique. Cinnarizine reduced the amplitude of the $K_v1.5$ channel current in a concentration-dependent manner. Cinnarizine rapidly inhibited $K_v1.5$ currents in 6 min, eliminating the possibility of genomic regulation. Inhibition rate for cinnarizine on $K_v1.5$ channel was dependent on the degree of concentration. Inhibition rates for peak and steady state currents were not significantly different at all voltage we examined. These results suggested that cinnarizine inhibited $K_v1.5$ currents via a non-genomic mechanism, providing a mechanism for the arrhythmogenic effects of cinnarizine.

Keywords: Cinnarizine · $K_v1.5$ channel

P03-13

Potentiation of the glycine response by bisphenol A, an endocrine disrupter, on the substantia gelatinosa neurons of the trigeminal subnucleus caudalis in mice

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The lamina II, also called the substantia gelatinosa (SG), of the medullary dorsal horn (the trigeminal subnucleus caudalis (Vc), is thought to play an essential role in the control of orofacial nociceptive because it receives the nociceptive events from primary afferents, including thin myelinated Aδ- and unmyelinated C- fibers. Glycine, the main inhibitory neurotransmitter in the central nervous system has been recognized to contribute an essential function in the transference of nociceptive signals from the periphery to the higher brain regions. Bisphenol A (BPA), one of the dangerous endocrine disrupter, is reported to alter the morphological and functional characteristics of neuronal cells in the central nervous system. However, the electrophysiological effects of BPA on the glycine receptors on SG neurons of the Vc have not been well studied yet. Therefore, in this study, we used the whole-cell patch-clamp technique to explore the effect of BPA on the response of glycine on SG neurons of the V_C in mice. We have demonstrated that in the neonatal mice (0-3 postnatal day), BPA did not show any effect on the glycine-induced inward current. However, at the juvenile and adult groups, BPA enhanced the glycine-mediated responses. This modulation by BPA was proved to be involved in the heteromeric glycine receptors. The interaction between BPA and glycine appears to have a significant role in regulating the transmission of the nociceptive pathway.

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Keywords: Subtantia gelatinosa, Bisphenol A, Glycine, Patch-clamp technique, Orofacial pain

P03-14

Naringenin suppresses the miniature inhibitory transmission on the terminal of substantia gelatinosa neurons in immature mice

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The substantia gelatinosa (SG) of the trigeminal subnucleus caudalis (Vc; medullary dorsal horn) is admitted as a pivotal site of integrating and modulating afferent fibers which carry the orofacial nociceptive information. Although naringenin (4′,5,7- thrihydroxyflavanone), a natural bioflavonoid is proved to possess various biological effects in central nervous system, up to now, there has been no report about activity of naringenin on the orofacial nociceptive site yet. In this study, whole-cell patch-clamp technique was applied to examine the direct membrane action of naringenin and how naringenin activates responses on the SG neurons of the Vc in immature mice. Under the high chloride pipette solution, naringenin 2mM suppressed both spontaneous postsynaptic currents, without any noxious stimuli and miniature postsynaptic currents which were isolated by tetrodotoxin (TTX), a voltage gated Na^+ channel blocker. Further, in the presence TTX, CNQX, a non-NMDA glutamate receptor antagonist and AP5, an NMDA receptor antagonist, naringenin almost completely blocked the miniature inhibitory postsynaptic currents. These results suggest that naringenin acts on the SG neurons endings of the Vc by suppressing the miniature excitatory postsynaptic currents. Taken together, naringenin contributes toward at least a part of orofacial nociceptive modulation and should be a promising target to develop therapeutic agents for orofacial pain treatment.

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Keywords: Substantia gelatinosa, Naringenin, Patch-clamp technique, Orofacial pain, Inhibitory Neurotransmission

P03-15

Novel marine compound Echinochrome A is a negative regulator of cardiac contractility

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Echinochrome A (Ech A), a marine bio-product isolated from sea urchin eggs, is known to have cardioprotective effects through its strong antioxidant and ATP-sparing capabilities. However, the effects of Ech A on cardiac excitation–contraction (E-C) are not known. In this study, we investigated the effects of Ech A on cardiac contractility and Ca^{2+} handling in the rat heart. In ex vivo Langendorff hearts, Ech A (3 μM) decreased left ventricular developing pressure to 77.7±6.5 % of basal level. In isolated ventricular myocytes, Ech A reduced the fractional cell shortening from 3.4 % at baseline to 2.1 %. Ech A increased both diastolic and peak systolic intracellular Ca^{2+} ($[Ca^{2+}]_i$). However, the ratio of peak $[Ca^{2+}]_i$ to resting $[Ca^{2+}]_i$ was significantly decreased. Ech A did not affect the L-type Ca^{2+} current. Inhibiting the Na^+/Ca^{2+} exchanger with either NiCl2 or SEA400 did not affect the Ech A-dependent changes in Ca^{2+} handling. Our data demonstrate that treatment with Ech A results in a significant reduction in the phosphorylation of phosphol-

amban at both serine 16 and threonine 17 leading to a significant inhibition of SR Ca^{2+}- ATPase 2A (SERCA2A) and subsequent reduced Ca^{2+} uptake into the intracellular Ca^{2+} store. Taken together, our data show that Ech A negatively regulates cardiac contractility by inhibiting SERCA2A activity, which leads to a reduction in internal Ca^{2+} stores.

Keywords: Echinochrome A, Negative inotropic effect, SERCA2A inhibition, Phospholamban phosphorylation

P03-16

Verapamil improves glucose homeostasis and insulin sensitivity in a mouse model of diet-induced obesity by modulating calcium channels

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Insulin resistance is closely associated with elevated intracellular Ca^{2+} concentration under ectopic lipid accumulation and hyperglycemia-induced intracellular stress conditions. We recently identified that obesity impairs intracellular Ca^{2+} homeostasis, which prevents membrane localization of PH domain containing proteins such as AKT, PLCδ, and IRS through the formation of Ca^{2+}-phosphoinositides, resulting in dysregulation of glucose homeostasis and insulin resistance. However, the mechanism by which Ca^{2+} channels cause intracellular Ca^{2+} overloading is largely unknown. Here, we aim to investigate the expression levels of various Ca^{2+} channels in mouse models of obesity and therapeutic potential of verapamil, a Ca^{2+} channel inhibitor, in a mouse model of diet-induced obesity (DIO) and palmitate-treated HepG2 hepatocytes. We find that the expression levels of ATP2B2 and ATP2A2 were significantly decreased while the expression levels of ORAI2 were markedly increased in mouse models of obesity. Administration of 100 mg/kg verapamil to DIO mice significantly reduced body weight and fasting blood glucose levels without food intake. Furthermore, intraperitoneal glucose tolerance test and insulin tolerance test showed significantly improved glucose tolerance and insulin sensitivity, respectively. Verapamil also normalized the expression levels of ATP2B2, ATP2A2, and ORAI2 in DIO mice, enhanced membrane targeting of AKT PH domain, and sensitized insulin signaling by decreasing intracellular Ca^{2+} concentration. Taken together, our data suggest that verapamil could be a potential therapy for obesity or diabetes through targeting intracellular Ca^{2+} signaling.

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Keywords: Verapamil, Insulin resistance, Intracellular calcium, Calcium channel, ATP2A2

P03-17

Plakophilin-2, a negative regulator for fluid shear-induced Cx43 hemichannel activation in cardiac myocytes

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Plakophilin-2 (PKP2) is the major component of desmosomal protein, which connects to adherence junctions. Mutations in PKP2 are the most common cause of familial arrhythmogenic right ventricular cardiomyopathy (ARVC), a disease characterized by ventricular arrhythmias and sudden death. ATP release through connexin43 (Cx43) has a correlation with loss of PKP2 function. In addition, alteration in Ca^{2+} homeostasis due to Cx43 hemichannel upregulation is thought to be a major trigger for arrhythmia in PKP2-deficient right heart. Since Cx43 hemichannel-mediated ATP release is a major event to regulate intracellular Ca^{2+} in cardiac myocytes under shear stress, we hypothesized that PKP2 may play a role in the regulation of Cx43 hemichannel function under shear stress. Pressurized flow (~16 dyn/cm2) was applied to both HL-1 control cells and PKP2-deficient (by ~50%) HL-1 cells. ATP release and membrane currents were measured by luciferin-luciferase chemiluminescence assay and whole-cell patch clamp, respectively. The ATP release of *PKP2-knockdown* HL-1 cells under shear stress increased by ~70% and ~50% in Ca^{2+}-free and 2 mM Ca^{2+}-containing external solutions, respectively, compared to wild-type cells. Consistently, shear stress-induced currents carried by Cs^+ and $NMDG^+$ were enhanced by ~80% and ~100%, respectively, in PKP2 knockdown HL-1 cells, suggesting increase in Cx43 activity by a loss of PKP2. The data suggest that PKP2 may be a negative regulator for Cx43 hemichannel opening by shear stress in cardiac myocytes.

Keywords: Plakophilin-2, Cx43 hemichannels, Cardiac myocytes, ATP release, Shear-induced currents

P03-18

Blockade of heterotetrameric hERG 1A/3.1 channels by iloperidone

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Iloperidone is a novel antipsychotic that is mixed dopamine D_2/serotonin 5-HT_{2A} receptor antagonist for the treatment of schizophrenia. hERG 3.1 potassium channels is a brain-specific alternative isoform of hERG 1A, and is significantly associated with a potential therapeutic target for antipsychotic drugs. Since hERG 3.1 shows poor expression, trafficking deficits and low current densities, we generated hERG 1A/3.1 heterotetramers, which have intermediate phenotype between hERG 1A and hERG 3.1. In this study, we investigated the pharmacological effects of iloperidone on these currents elicited from cell model expressing hERG 1A/3.1 heterotetramers amenable to an efficient electrophysiological recording. We used the whole-cell patch-clamp technique to investigate the effects of iloperidone on heterotetrameric hERG 1A/3.1 potassium channels expressed in HEK293 cells. Western blot analysis was used to study the effects of iloperidone on hERG 1A/3.1 channel trafficking. Iloperidone inhibited the hERG 1A/3.1 tail currents at -50 mV in a concentration-dependent manner with an IC_{50} value of 0.42 μM. The block of hERG 1A/3.1 currents by iloperidone was voltage-dependent, and increased over a range of voltage for channel activation. A fast application of iloperidone inhibited the hERG 1A/3.1 currents elicited by a 5 s depolarizing pulse to +60 mV to fully inactivate the hERG 1A/3.1 currents. During a repolarizing pulse at -40 mV for 10 s, iloperidone rapidly and reversibly blocked the open state of the hERG 1A/3.1 current. However, iloperidone did not affect hERG 1A/3.1 channel trafficking to the cell membrane. Our results indicated that iloperidone concentration-dependently inhibited hERG 1A/3.1 currents by preferentially interacting with the open states of the hERG 1A/3.1 channel, but not by the disruption of hERG 1A/3.1 channel protein trafficking. Our study examined iloperidone's mechanism of action provides a biophysical profile that is necessary to assess the potential therapeutic effects of this drug.

Keywords: Iloperidone, hERG 1A/3.1, Activated state block

P03-19

Onion peel extract and its constituent, quercetin inhibits human Slo3 in a pH and calcium dependent manner

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Sperm function and male fertility are closely related to pH dependent K^+ current (Ksper) in human sperm, which is most likely composed of *Slo3* and its auxiliary subunit *LRRC52*. Onion peel extract (OPE) and its major active ingredient quercetin are widely used as fertility enhancers; however, the effect of OPE and quercetin on Slo3 has not been elucidated. The purpose of this study is to investigate the effect of quercetin on human Slo3 channels. Human Slo3 and LRRC52 were co-transfected into HEK293 cells and pharmacological properties were studied with the whole cell patch clamp technique. We successfully expressed and measured pH sensitive and calcium insensitive Slo3 currents in HEK293 cells. We found that OPE and the key ingredient quercetin inhibit Slo3 currents. Inhibition by quercetin is dose dependent and decreases with elevating internal alkalization and internal free calcium concentrations. Functional groups in the quercetin polyphenolic ring govern the degree of inhibition of Slo3 by quercetin, and the composition of such functional groups are sensitive to the pH of the medium. These results suggest that quercetin inhibits Slo3 in a pH and calcium dependent manner. Therefore, we surmise that quercetin induced depolarization in spermatozoa may enhance a voltage gated proton channel (Hv1), and thus activate non-selective cation channels of sperm (Catsper) dependent calcium influx to trigger a capacitation and acrosomic reaction.

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Keywords: Ksper, LRRC52, Phosphoinositides, Quercetin, Slo3

P03-20

Group 1 metabotropic glutamate receptors increases Ca^{2+} levels and tonic firing rate via TRPC3 channels in SNc dopamine neurons

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Pacemaker dopamine neurons in the substantia nigra pars compacta (SNc) exhibit low-frequency spontaneous firing without any input stimuli. Since the tonic firing of dopamine neurons determines ambient dopamine levels, regulation of tonic firing rate is very important. Although activation of mGluR1 is reported to increase cell excitability via activation of some type of TRP channels, it is still unclear how mGluR1 regulates tonic firing activities in SNc dopamine neurons. In this study, we present that mGluR1 increases Ca^{2+} levels and tonic firing rate via TRPC3 channels in SNc dopamine neurons. In SNc dopamine neurons, activation of mGluR1 inhibited spontaneous firing transiently but subsequently led to a slow increase in tonic firing rate. DHPG, a mGluR1 agonist, evoked two clear phases of Ca^{2+} elevations: the fast Ca^{2+} surge released from the endoplasmic reticulum (ER) Ca^{2+} store and then the following sustained Ca^{2+} influxes. When the intracellular Ca^{2+} store was emptied by caffeine or thapsigargin, we could not observe any Ca^{2+} influxes but DHPG induced a sustained Ca^{2+} influx, suggesting that DHPG induces Ca^{2+} influx regardless of store operated Ca^{2+} channels in dopamine neurons. Using the several TRP channel blockers, we found that DHPG-induced Ca^{2+} influx was dramatically reduced by pre-treatment of TRPC3 channel blockers. In addition, we observed that DHPG-induced Ca^{2+} influx was inhibited by L-type Ca^{2+} channel blockers, but not by P/Q- or T- type channel blockers. Taken together, these data suggest that mGluR1 activate TRPC3 channels which induces Ca^{2+} influx by increased tonic firing rate and consequential activation of L-type Ca^{2+} channels. Therefore, we conclude that TRPC3 channels are a key player in mGluR1-induced cytosolic Ca^{2+} and tonic firing changes in SNc dopamine neurons.

Keywords : Dopamine neuron, mGluR1, TRPC3

P03-21

The biphasic effect of TRPC4 and TRPC5 activity by the tricyclic antidepressant depending on modulation of μ-opioid receptor

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Tricyclic antidepressants (TCAs) require medical attention in the treatment of patients with depression due to adverse effects such as drowsiness, arrhythmia, constipation and sex performance disruption in various tissues. Transient receptor potential channel canonical subfamily (TRPC) members 4 and 5, which are non-selective cation channel, are highly expressed in regions including central nervous system, heart, gastrointestinal and testis. TRPC4 and TRPC5 have been reported to be involved in fear-like behavior, anxious response and depression. However the functional roles of TRPC channel on action of TCAs remain poorly understood. Here, we report that TCAs regulate TRPC4/C5 channel activity using whole cell patch clamp. In HEK293 cells overexpressed with TRPC4 or TRPC5, all of TCAs (desipramine, amitriptyline, and imipramine) inhibited the activity of TRPC4/C5 channel. We observed that TCAs decreased inward current of TRPC4/C5 channel in a few minutes. The TCAs inhibited the basal activity of TRPC5 in a dose-dependent manner with IC50 (values of 10.31 μM DES, 2.88 μM AMI, and 10.96 μM IMI). The short (5 min) or long-term (16 h) incubation with TCAs did not show any change in the expression of TRPC4/C5 on surface membrane. Interestingly, when coexpressed with μ-opioid receptor (OPRM), TCAs significantly increased the inward current of TRPC4/C5 channels and intracellular calcium concentration through the channels. We identified using ELISA that TCAs stimulated OPRM, resulting in decreased levels of cAMP. The TRPC4 or TRPC5 activation with OPRM by TCAs was completely inhibited by coexpression with dominant-negative mutant (G203T) of Gαi2 and pretreatment with pertussis toxin (PTX). Taken together, the action of TCAs on TRPC4/C5 channel activity was biphasic in absence or presence of OPRM. Our data provides evidence that adverse symptoms of TCAs are correlated with dysfunction of TRPC4/C5 and OPRM. Depending on the expression level of OPRM, the activity of TRPC4/C5 channel could be altered in a certain cell or tissue type. These findings may help to understand the complexity of adverse side-effects of TCAs

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Keywords: TRPC, Tricyclic antidepressants, Depression μ-opioid receptor

P03-22

TRPC5 channel instability induced by depalmitoylation protects striatal neurons against oxidative stress in Huntington's disease

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Protein S-palmitoylation, the covalent lipid modification of the side chain

of Cys residues with the 16-carbon fatty acid palmitate, is the most common acylation, and it enhances the membrane stability of ion channels. This post-translational modification (PTM) determines a functional mechanism of ion channel life cycle from maturation and membrane trafficking to localization. Especially, neurodevelopment is regulated by balancing the level of synaptic protein palmitoylation/depalmitoylation. Recently, we revealed the pathological role of the transient receptor potential canonical type 5 (TRPC5) channel in striatal neuronal loss during Huntington's disease (HD), which is abnormally activated by oxidative stress. Here, we report a mechanism of TRPC5 palmitoylation at a conserved cysteine residue, that is critical for intrinsic channel activity. Furthermore, we identified the therapeutic effect of TRPC5 depalmitoylation by enhancing the TRPC5 membrane instability on HD striatal cells in order to lower TRPC5 toxicity. Collectively, these findings suggest that controlling S-palmitoylation of the TRPC5 channel as a potential risk factor can modulate TRPC5 channel expression and activity, providing new insights into a therapeutic strategy for neurodegenerative diseases.

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Keywords: TRPC, Palmitoylation, Depalmitoylation, Huntington's disease, Trafficking

P03-23

Inhibition of $K_v3.1$ currents by citalopram

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This study examined whether citalopram interacts with $K_v3.1$, one of K_v channels. Using the whole-cell patch-clamp technique, interaction between citalopram and $K_v3.1$ expressed in Chinese hamster ovary cells was studied. Citalopram reduced $K_v3.1$ whole-cell currents in a reversible concentration-dependent manner, with an IC_{50} value and a Hill coefficient of 27.9 μM and 1.0, respectively. Citalopram-induced inhibition of $K_v3.1$ is associated with time-dependent development of block without modifying the kinetics of current activation. The inhibition increased steeply between −20 and +30 mV, which corresponded with the voltage range for channel opening. In the voltage range positive to +30 mV, inhibition displayed an additional voltage dependence, consistent with an electrical distance δ of 0.37. Citalopram did not affect the ion selectivity of $K_v3.1$. Citalopram slowed the deactivation time course, resulting in a tail crossover phenomenon when the tail currents, recorded in the presence and absence of citalopram, were superimposed. The present results suggest that citalopram acts on $K_v3.1$ currents as an open-channel blocker.

Keywords: Citalopram, Serotonin reuptake inhibitor, $K_v3.1$, Open channel block

P03-24

Ca^{2+}-CaM binding anchor residue for PKD2L1 channel activity regulation

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Polycystic kidney disease 2-like-1 (PKD2L1) is a non-selective cation channel that regulates intracellular calcium concentration, also known as polycystin-L or TRPP3. Calmodulin (CaM) is a calcium binding protein, two lobes are composed of N-lobe and C-lobe, and calcium binds to four EF-hands, resulting in conformational changes. CaM is known to bind to various targets, including binding to the CaM-binding domain (CaMBD) in the channel, but the CaM binding region of PKD2L1 has not yet been identified. In our previous studies, we confirmed that CaM is involved in PKD2L1 desensitization, especially N-lobe is important for its regulation and predicted an putative CaM binding site (K590-E600). To investigate this putative CaM-binding site, we generated single mutants of this domain with or without ΔEF at the same time and current changes were recorded using Calmidazolium (CMZ) at different intracellular calcium concentrations with whole-cell patch-clamp. CMZ is also known as an antagonist of CaM and an activator of PKD2L1, and its activating mechanism still needs to be explained. If the CaM binding site mutant is indeed CaM binding site, CaM cannot bind and CMZ will not change the current. In this study, we propose the possibility of Leu593 as an anchoring residue to bind to CaM N-lobe based on the change of channel current depending on intracellular calcium concentration and the presence or absence of EF hand. Taken together, our results provide a predictive model for the mechanism by which CaM binds to PKD2L1 and modulates its channel activity.

Keywords: Calmodulin, PKD2L1, Calcium sensitivity, CaM binding site

P03-25

Effects of various fibrosis patterns on ventricular arrhythmogenesis and pumping efficacy

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Cardiac fibrosis is an integral component of nearly all forms of cardiac arrhythmias [1]. It alters the architecture of the myocardium [2] and disrupts the coordination of myocardial excitation-contraction coupling in both systole and diastole and may result in profound systolic and diastolic dysfunction [3]. It has been reported that ventricular arrhythmogenesis increased in linear fashion as the fibrosis amount increased [1]. Moreover, clinical studies furthermore suggest that both fibrosis pattern and spatial distribution of fibrosis also exacerbates the arrhythmogenecity effect [4, 5]. For instance, Kazbanov et al. [6] in their computational study showed that the onset of arrhythmias depends on spatial size of diffuse fibrotic region and degree of fibrosis heterogeneity. In this study, we extended the study made by Kazbanov et al. [6] and compare the arrhythmogenesis of diffuse, compact, interstitial and patchy fibrosis patterns in different amounts of fibrosis, ranging from 10 to 50 percent. In addition, we study how the different fibrosis patterns and fibrosis densities compromise the pumping efficacy of the ventricles. For that, we employed Ten Tussher [7] model to simulate the ventricular cardiomyocyte behavior. The regional electrophysiological changes due to fibrosis is represented by 50% reduction in inward rectifier potassium current (IKs); 50% reduction in L-type calcium current (ICaL); and 40% reduction in sodium current (INa). Furthermore, conductivity values in fibrotic regions were reduced by 30% to mimic the conduction delay due to fibrosis[8, 9].To assess the effect of fibrosis density and spatial distribution, we conducted 3D electrophysiological simulation under reentry condition with BCL of 600 ms and then we extracted the transient Ca^{2+} information. The extracted Ca^{2+} information was used to the mechanical simulation to mimic the cardiac excitation contraction coupling. As a result, for each fibrosis density case the arrhythmogenesis effect of diffuse fibrosis pattern was higher than the other fibrosis patterns. In diffuse fibrosis pattern, the conduction velocity required to sustain the reentry was relatively higher. In both patchy/interstitial and compact fibrosis patterns, the arrhythmogenesis was highly dependent on the fibrosis structure than on the fibrosis amount. The pumping capacity of the ventricles was reduced as the diffuse fibrosis amount increased. However, this result was not persistently shown in compact fibrosis pattern. In conclusion, in addition to the fibrosis amount and the fibrosis structure plays a major role in the inducibility of ventricular arrhythmias.

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Keywords: Fibrosis, arrhythmogenesis, Pumping capacity, Conduction ve-

locity, Fibrosis pattern

P03-26

Computational analysis of cardiac electromechanical delay under normal and irregular heartbeat by using 3D ventricular model

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A subset of heart failure (HF) includes dyssynchronous HF, which is an impaired activation of the electrical propagation sequence with the cardiac pumping activation. The time interval between the local electrical activation time (EAT) to the onset myofilament shortening or mechanical activation time (MAT) is defined as electromechanical delay (EMD). One experimental study showed that the EMD is non-uniform, depending on the electrical activations pattern and mechanical loading conditions [1]. Measuring the EMD distribution in three-dimensional heart is currently not available due to the limitation of measuring instruments. Hence, a realistic computational modeling of human heart is such a powerful tools to measure EMD in the heart. Constantino et al. performed a computational simulation analyzing the EMD on normal and HF conditions [2]. The goal of this computational study is to enhance the analysis on cardiac EMD under reentry and fibrillation conditions. We used a realistic electromechanical model of human ventricle that combine the electrophysiological model with the myofilament dynamic model following Gurev et al. [3]. To involve the fibrillation condition, we set the slope of APD restitution as 1.8 (exceeded 1). We simulated sinus rhythm and ventricular tachyarrhythmia conditions by implementing Purkinje fiber activation and standard S1-S2 protocol, respectively. We compared each conditions between the normal and VF-prone condition. Our results shows that the EMD is prolonged under sinus rhythm compared to that under fibrillation condition. The broader understanding on the EMD phenomenon in the intact ventricle is a great importance in order to open possibilities for a novel treatment.

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Keywords: Cardiac electromechanical delay, Arrhythmia, Cardiac simulation

P03-27

Computational analysis of proarrhythmic estimation under the influence of dofetilide, quinidine, and cisapride

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In the past few years, researchers have been pursuing a novel proarrhythmic assessment on the characteristic of drugs effect on the myocytes by using in-silico methods [1-3]. The purpose of the in-silico method is to advance the current regulation which filter the drug by observing the effect on the hERG channel and QT interval of the ECG before entering the market. The advancement of the in-silico method is to observe the drug effect on other ionic current as well which presumably contribute in arrhythmia. The aim of this study is to observe the effect of dofetilide, quinidine, and cisapride on the cardiac cell in silico by using human ventricular electrophysiological model. The ventricular model used in this study is the model of O'hara Rudy model (2011). In order to incorporate the drug effect, we follow the methods of Mirams et al. [1] which modified the maximum conductance block involving the value of IC50 (the concentration amount of the drug needed for the current to reach half of the activation in nmol) and the concentration of the drugs (denoted by D). The equation is shown as follows:

$$g_i = g_{control,j}\left[1+\left(\frac{[D]}{[IC_{50}]_j}\right)^h\right]^{-1} \quad (1)$$

Where *h* is hill coefficient, and *j* is the maximum conductance of *j* current. Our results showed that the dofetilide, quinidine, and the cisapride expand the APD90 in agreements with the experimental data and the previous studies. In conclusion, in silico model exhibits a great performance to assess the drugs characteristics and the effect on the proarrhythmogenic.

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Keywords: In silico drug assessment, Cardiac arrhythmia, Torsade de pointes

P03-28

Kinetic analysis of activation process of K_v7.4 channel with novel pharmacological activators targeted for erectile dysfunction

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Among several types of K_v7 (*KCNQ*) voltage gated potassium channel family, K_v7.4 (*KCNQ4*) channel shows prominent expression in smooth muscle, cardiac tissues and vasculature. In general, activation of the channel would mediate strong efflux of potassium and lead membrane potential to hyperpolarization, though the extent may depend on established potassium concentration gradient and membrane potential. Once membrane potential is hyperpolarized, it would decrease the excitability of excitable cells. Decreased excitability may reduce calcium spikes and Ca-CaM mediated activation of myosin light chain kinase (MLCK) in smooth muscle cells. Recently, it was reported that K_v7.4 channels are highly expressed in *corpus cavernosum* smooth muscle cells. Since smooth muscle relaxation of *corpus cavernosum* is essential in physiological penile erection, we examined the effect of novel K_v7.4 activators to the channel activation kinetics. In HEK293 cells stably expressing human K_v7.4 channel, we performed whole-cell patch clamp technique with two different voltage protocols in order to measure specific activity of the channel. For kinetic analysis of the activation process, voltage steps from –100mV to +100mV with 10mV of step interval was applied. For each step, pulse duration was 3 seconds for activation process of K_v7.4 channels is rather slow. Intersweep duration was 10 seconds and holding potential was –80mV. For measurement of time-dependent action of the drug, 5 seconds single step with +50mV was applied in every 20s with holding potential of –80mV. The composition of internal solution is as following; 120 KCl, 5.37 $CaCl_2$, 1.75 $MgCl_2$, 10 EGTA, 10 HEPES, 4 ATP, 0.2 GTP. pH was adjusted to 7.3 using NaOH and $[Ca^{2+}]_{free}$ = 100nM. Normal tyrode solution was used for external solution and drugs stocked with DMSO was diluted to 1uM with the Normal tyrode solution. We have found that drug A increases not only maximum conductance of the channel but also time constant of activation gate. In comparison to positive control, ML-213, a specific K_v7.4 channel activator, drug A showed significant supremacy. All drugs tested for the activation of the channel showed consistent result; increase of maximum conductance and time constant of activation gate. Similar analysis with different concentration of the drugs is in need for complete pharmacological assay of the drugs, *i.e.*, both potency and efficacy of the drugs would be addressed soon.

P03-29

Mutual interaction of high-order thalamic and top-down inputs on apical tuft dendrites of layer 5 pyramidal neurons

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Dendritic integration of motor and sensory inputs formulates a mixed response selectivity in the distal dendrites. However, wiring specificity to produce such feature selectivity is still far from complete understanding. We analyzed relative spatial distribution of representative sensory and motor inputs on distal tuft dendrites of layer 5 (L5) pyramidal neurons in the whisker field of somatosensory cortex (S1BF); paralemniscal inputs from posterior medial thalamic nucleus (POm) and motor inputs from primary motor cortex (M1). Axons both from POm and M1 ramify in layer 1 and make extensive synaptic contacts on distal dendrites of L5 neurons in S1BF. Without regenerative dendritic events, voltage changes occurred in these synapses are significantly diminished along the long dendritic path and subsequently contribute little to the generation of action potential. We hypothesized that synapses on the distal dendrites are wired so as to evoke an effective regenerative dendritic activity to overcome the passive attenuation. Using in vivo two-photon Ca^{2+} imaging, we observed that indeed dendritic activity can be efficiently induced by electrical stimulation of POm or M1 in the overlapping set of dendritic branches. This result rejects the idea that exclusive origin selective dendritic tropism might account for the efficient dendritic spike generation. Furthermore, we found in the majority of cases that coincident activation of POm inputs is suppressive on the M1-driven activity. Currently, we are examining the circuit mechanisms by which high-order thalamic input and top-down input from M1 modulate apical tuft dendritic activity in L5 pyramidal neuron of S1BF and plan to investigate the physiological effect of such negative modulation on the perception of whisker-dependent object recognition.

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Keywords: Posterior medial thalamic nucleus (POm), Primary motor cortex (M1), Barrel cortex, Dendritic integration, in vivo two-photon Ca^{2+} imaging, high-order thalamic input, Top-down input

P03-30

STING-GABA transporters pathway and memory deficits

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Stimulator of Interferon Genes (STING) is a transmembrane protein. STING plays important role in innate immunity by production of type I interferons and proinflammatory cytokines. Role of sting and sting activated pathways have been studied in systemic inflammation, infection and cancer but its role in the CNS remains unclear. Here we showed genetically deletion of STING decreased GABA transporters which cause increase tonic GABAA inhibition in dentate gyrus granules (DGG) cells of hippocampus but the total GABAA receptors are unchanged compared to wild type. We further confirm GABA transporter subtypes GAT1 and GAT3 expression, sting knockout mice has decreased GATs expression. Evidences suggest that STING stimulates IRF3 phosphorylation by TBK1 in cytosolic DNA signaling pathway. In an agreement, in our experiment downregulation of STING decreased pTBK1 and pIRF3 expression causing decrease in GATs expression in hippocampus tissue sample. In addition, Y-maze task was performed to access the spatial working memory, STING knockout mice shown less spontaneous alteration compared to wild type. Systemic injection (for 7days) of L-655,708, a selective inverse agonist of α-5 subunit containing GABAA receptor, reverse the spontaneous alteration in knockout mice. Our study for the first time uncover that STING-TBK1-IRF3 signaling pathway regulates GABAergic signaling to be responsible for memory deficits.

Keywords: STING, TBK1, IRF3, GATs, tonic $GABA_A$ inhibition, Memory

P03-31

Sustained activity by cholinergic modulation in anterior cingulate and posterior parietal cortices

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The activation of cholinergic receptors in the prefrontal cortex (PFC) induces intrinsic mechanisms for sustained neuronal firing, a cellular mechanism for working memory. In the posterior parietal cortex (PPC) functionally connected with the PFC, changes of sustained neural activity have been found and suggested to play important roles in evidence accumulation and decision making. However, it is still unclear whether the cholinergic modulation can evoke the sustained activity in the PPC. To further understand the effects of cholinergic innervation in both medial PFC (mPFC) and PPC, we investigated the firing property changes of regular spiking (RS) and fast spiking (FS) neurons by application of acetylcholine receptor (AChR) agonist. We report in present study that, in layers II/III neurons of anterior cingulate cortex (ACC), activation of AChR induces sustained firing in half of RS neurons (50%) and increases intrinsic excitabilities. Whereas in the RS neurons of PPC, intrinsic excitabilities are increased but sustained firing was scarcely detected (10%). We observed significant differences in resting membrane potentials (RMPs), threshold of action potentials (APs) and input resistance (Rin) between RS neurons in PPC and mPFC. Also, sustained activities by AChR activation were observed when membrane potentials of RS neurons in PPC were held at potentials close to the level of mPFC. These results suggest that sustained activity by cholinergic modulation are appears at different ratio because RS neurons of mPFC have greater intrinsic excitabilities than in PPC.

Keywords: Sustained activity, Intrinsic excitability, Cholinergic modulation, Membrane potentials, Posterior parietal cortex

P03-32

Involvement of GluN2D subunits containing NMDA receptors in experimental models of Parkinson's disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by degeneration of dopaminergic (DA) neurons in substantia nigra pars compacta (SNpc) causing various motor and non-motor dysfunctions. Although, N-Methyl-D-Aspartate receptors (NMDARs), ion channels composed of tetrameric assemblies of GluN1 and GluN2 (GluN2A-2D) have been suggested to involve in degeneration of DA neurons in SNPc, role of GluN2D subunit containing NMDARs in DA neurons in experimental PD models and its functional role were not disclosed. Our experiment explore that Mg^{++} resistant tonic NMDA current, sensitive to PPDA (a GluN2C/2D antagonist) is generated in SNPc-DA neurons in MPTP-injected wild type mice but not in GluN2D-KO mice, suggesting GluN2D mediates Mg^{++} resistant tonic NMDA current in SNpc-DA neurons in MPTP insult. In addition, GluN2D expression was increased in in-vitro model of PD (MPP^{++} treated SN4741 cell line). Interestingly, PPDA protects SN4741 cell against MPP^{++} induced cell damage. Furthermore, in our automated gait analysis

(CatWalk system), MPTP injected wild type mice show decreased in stride length and increased in stance duration that causes increased in run duration and decreased in cadence. In addition, MPTP induced gait impairment and dopaminergic neuronal loss in substantia nigra pars compacta (SNPc) was reduced in GluN2D-KO mice. Our results demonstrated that the GluN2D mediated Mg^{++} resistant tonic NMDA current is generated in mid brain dopaminergic neurons in MPTP intoxication and GluN2D selective antagonist protects dopaminergic neurons and ameliorates gaits deficits in MPTP induced PD.

Keywords: MPTP, NMDARs, GluN2D, Parkinson's disease, Gait analysis

P03-33

Ethanol elevates excitability of superior cervical ganglion neurons by inhibiting K_v7 channels in a cell type-specific and PI(4,5) P_2-dependent manner

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Alcohol causes diverse acute and chronic symptoms that often lead to critical health problems. Exposure to ethanol alters the activities of sympathetic neurons that control the muscles, eyes, and blood vessels in the brain. Although recent studies have revealed the cellular targets of ethanol, such as ion channels, the molecular mechanism by which alcohol modulates the excitability of sympathetic neurons has not been determined. Here, we demonstrated that ethanol increased the discharge of membrane potentials in sympathetic neurons by inhibiting the M-type or K_v7 channel consisting of the $K_v7.2/7.3$ subunits, which were involved in determining the membrane potential and excitability of neurons. Three types of sympathetic neurons, classified by their threshold of activation and firing patterns, displayed distinct sensitivities to ethanol, which were negatively correlated with the size of the K_v7 current that differs depending on the type of neuron. Using a heterologous expression system, we further revealed that the inhibitory effects of ethanol on $K_v7.2/7.3$ currents were facilitated or diminished by adjusting the amount of plasma membrane phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$). These results suggested that ethanol and $PI(4,5)P_2$ modulated gating of the K_v7 channel in superior cervical ganglion neurons in an antagonistic manner, leading to regulation of the membrane potential and neuronal excitability, as well as the physiological functions mediated by sympathetic neurons.

Keywords: K_v7 channel, $K_v7.2/7.3$ current, ethanol, SCG neuron, $PI(4,5)P_2$

P03-34

Mitochondrial Ca^{2+} uptake relieves palmitate-induced cytosolic Ca^{2+} overload and lipotoxicity in MIN-6 cells

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Saturated fatty acids contribute to β-cell dysfunction involved in the onset of type 2 diabetes mellitus. Many deleterious aspects of lipotoxicity have been reported including oxidative stress, ER stress, and blockage of autophagy. We demonstrated that palmitate induced ER Ca^{2+} depletion ranging from partial to complete loss, followed by notable store-operated Ca^{2+} entry in a mouse clonal β-cell, MIN-6. Subsequent cytosolic Ca^{2+} elevation can activate undesirable signaling pathways culminating in cell death. Mitochondrial Ca^{2+} uniporter (MCU) is the major route for Ca^{2+} uptake into the matrix and couples metabolism with insulin secretion. However, it has been unclear whether mitochondrial Ca^{2+} uptake plays a protective role or participates in the lipotoxicity due to permeability transition pore opening and cytochrome c release. Here, we observed that palmitate upregulated MCU protein expression in normal glucose but not in high glucose culture medium. Palmitate elevated baseline cytosolic Ca^{2+} concentration ($[Ca^{2+}]i$) and reduced depolarization-triggered Ca^{2+} influx maybe due to inactivation of voltage-gated Ca^{2+} channels (VGCCs). Suppression of MCU expression using RNA interference abolished mitochondrial superoxide production, but it exacerbated palmitate-induced $[Ca^{2+}]i$ overload. Consequently, blockage of autophagic degradation, ER stress as well as cell death were aggravated by MCU knockdown. Contrarily, co-treatment with verapamil, a VGCC inhibitor, prevented palmitate-induced basal $[Ca^{2+}]i$ elevation and defective $[Ca^{2+}]i$ transients. Extracellular Ca^{2+} chelation as well as VGCC inhibitors effectively rescued autophagy defects and cytotoxicity. Taken together, we suggest that enhanced mitochondrial Ca^{2+} uptake via MCU upregulation is an essential compensation to alleviate cytosolic Ca^{2+} overload and lipotoxicity in pancreatic β-cells.

Keywords: Mitochondrial Ca^{2+} uniporter, Palmitate, Oxidative stress, Pancreatic β-cell, Autophagy

P03-35

Characterization of molecular mechanisms underlying voltage-gated Ca^{2+} channel modulation by DREADD

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In synapse, the voltage-gated calcium (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 is supposed to 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 hM3D (human M3 DREADD) needs more time than that of hM3R (human M3 receptor). It was also detected that hM3D scarcely ever stop their activation once they have been activated. However, there was no big difference in the amount of PIP_2 depletion between hM3D and hM3R. Those kinetic specificities of DREADD was also tested in the modulation of ion-channels.

Keywords: DREADD, FRET

P03-36

Analysis of blocking mechanism and binding sites of intracellular spermine to TRPC4 ion channel

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Transient receptor potential canonical 4 (TRPC4) channel is a nonselective calcium-permeable cation channels. In intestinal smooth muscle cells, TRPC4 currents contribute more than 80% to muscarinic cationic current (mIcat). With its inward-rectifying current-voltage relationship and high calcium permeability, TRPC4 channels permit calcium influx once the channel is opened by muscarinic receptor stimulation. Polyamines are known to inhibit nonselective cation channels that mediate the generation of mIcat, moreover, it is reported that TRPC4 channels are blocked by the intracellular spermine through electrostatic interaction with glutamate residues (E728, E729). Here, we investigated the correlation between channel inactivation by spermine and channel conductance, and additional putative spermine binding residues in TRPC4 channel. We evaluated channel activity with electrophysiological recordings and revalidated structural significance based on Cryo-EM structure, which was resolved recently. We found that there is no correlation between magnitude of inhibitory action of spermine and magnitude of maximum current of the channel. In intracellular region, TRPC4 attracts spermine at channel periphery by reducing access resistance, and acidic residues contribute to blocking action of intracellular spermine; channel periphery, E649; cytosolic space, D629, D649 and E687.

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Keywords: Transient receptor potential channels (TRP channels), Polyamine, Spermine

P03-37

Temperature-dependent increase in the calcium sensitivity and acceleration of activation of TMEM16F variants

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TMEM16F (Anoctamin-6, ANO6) belongs to a family of calcium (Ca^{2+})-activated chloride channels (CaCCs), and has three splicing variants (V1, V2, and V5), which are expressed on the plasma membrane. Unlike other CaCCs, TMEM16F requires a non-physiological intracellular free calcium concentration ([Ca^{2+}]i > 1 μM) and several minutes for full activation under a whole-cell patch clamp. Therefore, its physiological role as an ion channel is uncertain and it is more commonly considered as a Ca^{2+}-dependent phospholipid scramblase. Here, we demonstrated that physiological temperature (37°C) increased the Ca^{2+} sensitivity of TMEM16F under a whole-cell patch clamp; V1 was activated by 1 μM [Ca^{2+}]i, whereas V2 and V5 were activated by 300 nM [Ca^{2+}]i. All TMEM16F variants were activated by 100 nM [Ca^{2+}]I when the temperature was increased to 42°C. The delay in the activation of the three variants decreased significantly at 37°C. Notably, the temperature-dependent Ca^{2+}-sensitisation of TMEM16F was not significant under inside-out patch clamp, suggesting a critical role of unknown cytosolic factors. Conversely, unlike channel activity, room temperature (27°C), but not physiological temperature (37°C), induced the scramblase activity of TMEM16F with submicromolar [Ca^{2+}]i (300 nM), irrespective of the variant type. Our results highlight the physiologically meaningful ion conducting property of TMEM16F at 37°C and indicate that the channel function and scramblase activity of TMEM16F may be functionally separated.

Keywords: TMEM16F, Calcium sensitivity, Latency time, Variants

P03-38

Post-translational palmitoylation of voltage-gated calcium channels regulates their PI(4,5)P_2 sensitivity and inactivation

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Voltage-gated calcium (Ca_V) channels mediate Ca^{2+} entry in to the cells in response to membrane depolarization. Ca^{2+} influx controls a diverse essential physiological function. Although it is well known that plasma membrane trafficking and gating mechanism of Ca_V channels, the post-translational modification of Ca_V channels and their functional role remains unclear. Palmitoylation, the reversible post-translational modification of cysteine residues with the 16-carbon lipid palmitate, is the most important mechanism for regulating the diverse physiological functions of intracellular proteins. Recent studies show that many types of transmembrane ligand- and voltage-gated ion channels are also palmitoylated in resting cell condition. Here, we investigated the functional role of palmitoylation in $Ca_V2.2$ channels. As is well known, palmitoylation of Ca_V β2a controls $Ca_V2.2$ channels slow inactivation and is not affected by PI(4,5)P_2. When Ca_V β2a is depalmitoylated by 2BP, palmitoylation inhibitor, leading to accelerated inactivation and enhanced PI(4,5)P_2 sensitivity of $Ca_V2.2$ channels. We found that 2BP regulates not only Ca_V β2a but also Ca_V α1B palmitoylation. Depalmitoylation of Ca_V α1B increases inactivation velocity and PI(4,5)P_2 sensitivity, suggesting that Ca_V α1B may subject to be palmitoylation. We predicted three cysteine residues, C1, C2, and C3 as possible palmitoylation sites in Ca_V 2.2 channels via CSS Palm 4.0, a prediction program of putative palmitoylation site in protein. We found that ACC, CAC, and AAC mutant $Ca_V2.2$ channels show the high PI(4,5)P_2 sensitivity and fast inactivation than wild type $Ca_V2.2$ channels, but not CCA mutant channels. These data suggesting that the C1 and C2 cysteine residues as possible $Ca_V2.2$ channels palmitoylation site. Thus, our data indicate the palmitoylation of $Ca_V2.2$ control their PI(4,5)P_2 sensitivity and inactivation.

Keywords: Voltage-gated calcium (Ca_V) channel, PI(4,5)P_2, Palmitoylation, Depalmitoylation, Post-translational modification

P03-39

Gain of function mutation in the TM2 inner pore helices of TREK/TRAAK channels exhibits strong inward rectification

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TREK/TRAAK channels, which are members of two-pore domain K^+ (K2P) channels, are strongly involved in the pathophysiology of pain and mood disorders. A better understanding of the gating and activity properties of TREK/TRAAK channels is important in finding more powerful and selective modulators for these channels. Recent studies have demonstrated that mutation of TM2.6 glycine residue of TREK-1 channel increases or decreases its activity depending on the substitute amino acid. In our previous study, gain of function mutants of the TREK-1 and TRAAK in which TM2.6 glycine residue was mutated with aspartate (G171D for TREK-1 and G133D for TRAAK), showed slight inward rectification. This study was performed to compare the single-channel properties of TREK-2 TM2.6 gain of function mutant

(G196D) to those of TREK-1G171D and TRAAKG133D. TREK/TRAAK TM2.6 GxxxD mutants showed significantly increased channel activity compared to each wild-type ($p < 0.05$). TREK-1G171D forms two channel phenotypes: TREK-1L and TREK-1S. The conductance of TREK-1L at positive membrane potentials was similar to TREK-1 wild-type, but TREK-1-S showed very small conductance with 22.5±10.4 pS. TREK-2 mutant also displayed more inward rectification properties compared to wild-type. The single-channel properties of TRAAKG133D was dramatically changed with inward rectification. Channel activity and mean open time were markedly increased in TRAAKG133D. Our results show that TREK/TRAAK TM2.6GxxxD mutants exhibit inward rectifying profile. In addition, our findings will be helpful in the studying TREK/TRAAK channelopathies and in the finding more powerful and selective modulators for these channels.

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Keywords: Two-Pore Domain K^+ Channel, TREK-1, TREK-2, TRAAK, Rectification

P03-40

Nortriptyline lowers basal calcium level of dopamine neurons through ion channels inhibition

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Midbrain dopamine neurons exhibit spontaneous firings whose activities and patterns are tightly regulated by various ion channels including Na^+ channels. Although tricyclic antidepressant (TCA) blockade, Nortriptyline of cardiac Na^+ channels are appreciated, actions for dopaminergic neuronal ion channels are less clear. Using the antidepressant Nortriptyline, which is expected to help alleviate many symptoms of Parkinson's disease, it is observed the effect of the firing pattern and calcium signal changes in cells at the single dopamine cell level. Therefore, the effects of nortriptyline on various ion channels including voltage-gated Na^+ channels were examined in single dissociated dopamine neurons of substantia nigra pars compacta using the nystatin perforated patch-clamp method and Ca^{2+} measurements. In the dopamine neurons, nortriptyline was produced concentration-dependent suppression of firing frequency and cytosolic calcium level as like as tetrodotoxin (TTX) responses. However, it can be assumed that there will be a calcium signal change of the other path except for the calcium signal reduction by the TTX- sensitive voltage-gated Na^+ channels block because the calcium signal reduction by nortriptyline appeared stronger. Due to the effects of nortriptyline (10μM) and TTX (500nM), but the firing of cells disappears, when treated with NMDA (50uM) calcium basal oscillation potential increases, calcium increases by NMDA in cells pre-treated with nortriptyline and TTX appears at the same size regardless of pretreatment. Calcium increase in dopamine cells by neurotensin is significantly suppressed by nortriptyline, this phenomenon appears like the inhibitory phenomenon caused by TTX. When the K_v7(KCNQ) channel blocker, XE991 (10μM) is processed in the cells nortriptyline pre-treated does not appear calcium signal reduction by the K_v7 channels blocker, however K_v7 channels opener retigabine (10μM) when processing, calcium signal reduction by nortriptyline is more strongly observed. Therefore, nortriptyline not only block the voltage-gated Na^+ channels, but also block the K_v7 channels, so it can have an excellent effect of lowering the basal calcium concentration of cells will be able to play a role in inhibiting apoptosis due to increased calcium concentration.

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Keywords: Nortriptyline, Dopamine neuron, Calcium, Firing, Voltage-gated sodium channel, K_v7 channel

P03-41

Na_v beta3 promotes polarized trafficking of voltage-dependent potassium channel in neurons

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Voltage-gated K^+ channel $K_v3.1b$ play a crucial role in regulating fast-spiking properties of neurons and is wildly expressed in the dendrites, the somatodendritic region, and the axonal nodes of Ranvier in neurons. It has been reported that balance activity of K_v3 and Na_v channels is important for inducting and maintaining fast-spiking. Here, we show that $Na_v\beta3$, an auxiliary subunit of Na_v channels, is a part of the $K_v3.1b$ channel complex in rat brain using mass spectrometry. Co-expression of $Na_v\beta3$ results in changes in the steady-state expression levels and stability of $K_v3.1b$ channels. Interestingly, $K_v3.1b$ and $Na_v\beta3$ are differentially expressed between distinct regions of the brain and have a different expression pattern during brain development. $Na_v\beta3$ regulates $K_v3.1b$ channel trafficking to the cell surface and reduces the localization and expression of $K_v3.1b$ in dendrites in hippocampal neurons. In addition, $Na_v\beta3$ dramatically decrease the current densities of $K_v3.1b$ channel in a voltage-dependent manner and induces a hyperpolarizing shift in the voltage dependence of steady-state inactivation. Therefore, these data suggest an unexpected role for $Na_v\beta3$ in regulating the biophysical characteristics and localization of $K_v3.1b$ channel.

P04-01

Decreased inward-rectifier K^+ current of the septal coronary artery smooth muscle cells in pulmonary arterial hypertensive rats

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In vascular smooth muscle, K^+ channels such as voltage-gated K^+ channels (K_v), inward rectifier K^+ channels (Kir), and big-conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) set the hyperpolarized membrane potential and counterbalance the depolarizing vasoactive stimlui. Also, Kir mediate the endothelium dependent hyperpolarization and active hyperemia response in various vessels including coronary artery. Pulmonary arterial hypertension (PAH) induces right ventricle hypertrophy (RVH), elevating the risk of ischemia and right heart failure. Here, using whole-cell patch clamp technique, we compared K_v and K_{ir} current densities (I_{Kv} and I_{Kir}) in the left (LCSMC), right (RCSMC) and septal branches of coronary smooth muscle cell (SCSMC) from control and monocrotaline-induced PAH rats showing right ventricular hypertrophy. In the control rats, (1) I_{Kv} was larger in RCSMC than SCSMC and LCSMC, (2) I_{Kv} inactivation of SCSMC occur at the more negative voltages than those of RCSMC and LCSMC. (3) I_{Kir} was smaller in SCSMC than RCSMC and LCSMC, (4) I_{BKCa} was not different between the branches. In the PAH rats showing right ventricular hypertrophy at 3 weeks after the monocrotaline injection, (1) I_{Kir} and I_{Kv} were decreased in SCSMC while not in RCSMC and LCSMC, (2) I_{BKCa} did not change in the three branches. The present study shows SCSMC-specific decrease of K_v and K_{ir} function in monocrotaline-induced RVH model, which might underlie pathophysiological implication of the coronary blood flow regulation in PAH. Even in the control rats, Kir of SCSMC was smaller than the other branches, suggesting less effective vasodilatory response of the septal branch to the moderate increase in extracellular K^+ concentration under increased activity of myocardium.

Keywords: Coronary artery, Smooth muscle, Pulmonary artery hypertension, Potassium channel, Inward rectifier Kir channel

P04-02

PPARδ protects muscle from EtOH induced insulin resistance by enhanced AMPK activation and mitochondrial function

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Alcohol consumption leads to dysregulation of metabolism in multiple organs including the liver, heart and skeletal muscle. Alcohol effects on insulin resistance in the liver are well evidence, whereas the effects in skeletal muscle still controversial. Emerging evidence indicates that alcohol promotes adipose tissue dysfunction, which may induce the dysregulation in other organs. To date, there is not fully understand the mechanisms of how alcohol-induced adipose tissue dysfunction can influence insulin resistance in skeletal muscle. Hence, we sought to identify how fatty acid metabolism in both adipose tissue and skeletal muscle were regulated by alcohol, and to find these effects by alcohol influence insulin resistance in muscle. We also sought to demonstrate whether peroxisome proliferate-activated receptor beta/delta (PPARδ) can attenuate alcohol-induced insulin resistance in myotube. Rats were subjected to 2 weeks of either tap water or 5% ethanol (EtOH) ingestion. Adipocyte size of the epididymal fat tissue and triglyceride concentrations in the skeletal muscles were measured. The free fatty acids level in plasma and hormone-sensitive lipase (HSL) activity in the epididymal fat tissue in rats were measured at before and 1, 3, 6hr after a single oral administration of 25% EtOH. Cell line studies identified mechanisms of PPARβ and EtOH regulates fatty acid metabolism and mitochondrial oxygen consumption. EtOH consumption decreases adipose tissue and cell size and increases free fatty acid in blood by HSL, these effects promote the accumulation of fatty acid in muscle tissue. EtOH increases fatty acid synthase (FAS) and decreases mitochondrial fatty acid uptake enzyme (carnitine palmitoyltransferase 1, CPT1) in myotubes. We found that mitochondrial oxygen consumption with fatty acid fuel is lower in EtOH treated myotubes. These all effects by EtOH promote insulin resistance in myotube as evidenced by AKT signaling and glucose uptake in myotubes. We also found PPARδ can reverses back EtOH-induced insulin resistance by reduced FAS and enhanced expression of GLUT4, CPT1, and activation of AMPK, and EtOH decreases palmitate-fueled mitochondrial respiration, however, PPARδ prevents or reverses EtOH-induced dysregulation of mitochondrial respiration. Taken together, EtOH induces a release free fatty acid from adipose tissue leads to promote accumulation of fatty acid in muscle tissue and reduces fatty acid oxidation and mitochondrial respiration. These all effects by EtOH induces insulin resistance in the muscle cell. However, PPARδ protects muscle cell form EtOH-induced insulin resistance by enhanced AMPK activation, and fatty acid-fueled mitochondrial respiration.

Keywords: Alcohol, PPARδ, Insulin resistance, Mitochondria, AMPK, GLUT4

P04-03

Cardioprotective effects of angiotensin-(1-5) by anti-apoptosis and anti-oxidant via MasR-PI3K-Akt-eNOS pathway in rats

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Angiotensin-(1-5) [Ang-(1-5)], which is a metabolite of Angiotensin-(1-7) catalyzed by angiotensin-converting enzyme, is a novel vasoactive pentapeptide of the renin-angiotensin system. Our lab has reported that Ang III and Ang IV have a cardioprotective effect via Ang II type 2 receptor (AT2R) and AT4R, respectively. However, it is not clear whether Ang-(1-5) has cardioprotective effects. The aim of this study is to investigate whether Ang-(1-5) 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 Ang-(1-5) followed by 20 min global ischemia and 50 min reperfusion. Pretreatment with Ang-(1-5) (1μM) for 10min 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. Ang-(1-5) markedly decreased infarct size and lactate dehydrogenase levels in effluent during reperfusion. Ang-(1-5) also increased coronary flow and the concentrations of atrial natriuretic peptide (ANP) in coronary effluent during reperfusion. Pretreatment with Mas receptor antagonist (A779) but not with AT1R antagonist (Losartan) or AT2R (PD123319) for 15min before ischemia attenuated the improvement of LVEDP, LVDP, and ±dp/dt induced by Ang-(1-5). Ang-(1-5) treatment increased Mn-superoxide dismutase, catalase, and heme oxygenase-1 protein levels, which was attenuated by pretreatment with A779. Ang-(1-5) treatment also decreased Bax, caspase-3 and caspase-9 protein levels, and increased Bcl-2 protein level, which were attenuated by pretreatment with A779. Ang-(1-5) also caused increases in ANP secretion from isolated perfused beating atria, which was blocked by the pretreatment with A779 but not by Losartan or PD123319. Co-treatment with inhibitors of downstream signaling pathway including phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and endothelial nitric oxide synthase (eNOS) attenuated ANP secretion. These results suggest that the cardioprotective effects of Ang-(1-5) against I/R injury may be related to activating anti-oxidant and anti-apoptotic enzymes via MasR- PI3K-Akt-eNOS pathway.

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P04-04

Mitochondrial biogenesis is increased by cyclic stretch in a mouse cardiac cell line

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In this study, we assessed the effect of mimetic cyclic stretch on mitochondria in a cardiac cell line, as mitochondria play an essential role in maintaining heart function by producing biological energy molecules. To mimic the geometric and biomechanical conditions surrounding cells in vivo, cyclic stretching was performed on HL-1 murine cardiomyocytes seeded onto an elastic micropatterned substrate (10% elongation, 0.5 Hz, 4 h/day). The expression of mitochondria biogenesis-related genes and mitochondria oxidative phosphorylation-related genes and respective protein levels were increased in the cyclic stretch stimulated cell lines as opposed to the non-stimulated controls. Consequently, cyclic stretch increased mitochondrial mass and ATP production in treated cells. Our results suggest that cyclic stretch transcriptionally enhanced mitochondria biogenesis and oxidative phosphorylation without detrimental effects in the cultured cardiac cell line.

Acknowledgement: †These authors contributed equally to this work.

Keywords: Cyclic stretch, Mouse cardiac cell line, Mitochondria biogenesis

P04-05

STIM1 affects intracellular Ca^{2+} movement as well as extracellular Ca^{2+} entry in skeletal muscle

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Stromal interaction molecule 1 (STIM1) mediates extracellular Ca^{2+} entry into the cytosol through a store-operated Ca^{2+} entry (SOCE) mechanism, which is involved in the physiological functions of various tissues, including skeletal muscle. STIM1 is also associated with skeletal muscle diseases, but its pathological mechanisms have not been well addressed. The present study focused on examining the pathological mechanism(s) of a mutant STIM1 (R429C) that causes human muscular hypotonia. R429C was expressed in mouse primary skeletal myotubes, and the properties of the skeletal myotubes were examined using single-cell Ca^{2+} imaging of myotubes and transmission electron microscopy (TEM) along with biochemical approaches. R429C abolished SOCE. In contrast, R429C increased intracellular Ca^{2+} movement in response to membrane depolarization by eliminating the attenuation on dihydropyridine receptor-ryanodine receptor (DHPR-RyR1) coupling by STIM1. The cytosolic Ca^{2+} level was also increased due to the reduction in SR Ca^{2+} level. In addition, R429C-expressing myotubes showed abnormalities in mitochondrial shape and a significant decrease in ATP levels. Therefore, serial defects in SOCE, intracellular Ca^{2+} movement, and cytosolic Ca^{2+} level along with mitochondrial abnormalities in shape and ATP level could be a pathological mechanism of R429C for human skeletal muscular hypotonia.

Acknowledgement: These authors contributed equally to this work.

Keywords: Skeletal muscle, STIM1, SOCE, DHPR, RyR1, Intracellular Ca^{2+} movement, Muscular hypotonia

P04-06

Involvement of TRPC4 channel in regulation of spontaneous myometrial contraction in pregnant myometrium

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Contractions of uterine myocytes are generally instigated by depolarization of the membrane potential. The depolarization opens voltage-gated Ca^{2+} channels and initiates action potential (AP) discharges, which results in increase of intracellular Ca^{2+} concentrations. Therefore, any stimulus which triggers membrane depolarization enough to cause AP discharges can contract myometrium. As a result, it is possible that the occurrence of spontaneous myometrial contraction (SMC) during late gestational age is mediated by the depolarization of membrane potential, which should be caused by a mechanical stretch. Recently, transient receptor potential (TRP) channels have been strongly suggested as a strong candidate to mediate the mechanical stretch-induced depolarization of uterine myocytes. For examples, mechanical stretch induced by hypoosmotic cell swelling activates TRPC4/5 like channel in pregnant rat myometrium, which strongly suggests involvement of TRPC4/5 to SMC in pregnant rat. But, decisive discrimination between TRPC4 and 5 for the contributions to SMC has not been elucidated yet. Therefore, to determine a major contribution between TRPC4 and 5 to the mechanical stretch-induced uterine contraction, we here investigated in detail electrophysiological and pharmacological characteristics of the mechanical stretch-induced ion channel to elucidate a molecular identity between TRPC4 and 5 using single-channel patch clamp technique. We also confirmed a physiological contribution of TRPC4 and 5 to SMC using isometric tension measurement technique. Our results demonstrate for the first time that mechanical stretch evoked by negative pressure application mainly activates TRPC4 channels in pregnant rat myometrium. In addition, The TRPC4 other than 5 may mainly contribute to membrane depolarization to instigate spontaneous uterine contraction of pregnant rat. In the present results, hypoosmotic cell swelling activated a potent outward rectifying current in G protein-dependent manner in rat pregnant myocyte. To elucidate the molecular identity of the SAC_{np} (stretch-activated ion channel negative pressure) in pregnant rat uterine myocytes more clearly, we examine the effects of micromolar Gd3+, a potent TRPC4/5 and 2-APB, a potent TRPC4/5 blocker on SAC activity in pregnant rat myocytes. The SAC_{np} activity in the side-out patch clamp mode, was significantly augmented by 1 μM Gd3+. In addition, SAC_{np} activities were nearly completely prevented by application of 10 μM 2-APB, a potent TRPC in the uterine myocytes. Single-channel activities of the SAC were significantly attenuated by ML-204 (3 μM), a selective blocker for TRPC4 over TRPC5 but, not affected by application of clemizole (1 μM), a selective TRPC5 inhibitor over TRPC4 in both cells. Similarly, hypoosmotic swelling-evoked currents were significantly suppressed by application of 3 μM ML-204, but clemizole (1 μM) had little effect on the I_{hypo} in both cells. the frequencies of the stretch-induced SMCs were significantly attenuated by 3 μM ML-204 without effect on SMC amplitudes, but clemzole (1 μM) failed to affect the mechanical stretch-evoked SMC in pregnant rat myometrium. In summary, we have demonstrated hypoosmotic- and pressure-induced membrane stretch activate TRPC4 channels using electrophysiological and pharmacological tools. We also have suggested TRPC4 as a dominant contributor to SAC evoked by mechanical stretch in pregnant rat myometrium, which encompasses regulating SMC during pregnancy.

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Keywords: Osmotic stress, Spontaneous uterine contraction, Stretch, Transient receptor potential C4/5

P04-07

Involvement of autophagy in mesenteric artery dysfunction of angiotensin II-induced hypertensive mice

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Autophagy is an intracellular degradation system that disassembles cytoplasmic components through autophagosomes with lysosomes. Recently, there are increasing interests about involvement of autophagy in cardiovascular disease including hypertension, pulmonary hypertension and atherosclerosis. However, the functional role of autophagy in hypertension is not well understood. In this study, we hypothesized that autophagy is involved in dysfunction of mesenteric arteries in angiotensin II-induced hypertensive mice. We observed expression levels of autophagic markers, beclin1 and LC3 I/II, in aorta from Ang II-induced hypertensive mice and primary cultured aortic vascular smooth muscle cells (AVSMCs). Expression levels of beclin1 and LC3 II were significantly increased in Ang II-induced hypertensive mice. We assumed that alterations in autophagic flux may change function of mesenteric arteries from Ang II-induced hypertensive mice. We used chloroquine (CQ) and 3-methylademnine (3-MA), autophagy inhibitors, to identify direct effect of autophagy in vasoconstriction induced by U-46619 (100 nM). The CQ and 3-MA dose-dependently increased the diameter of mesenteric arteries. To determine *in-vivo* role of autophagy in hypertension, we treated Ang II-induced hypertensive mice with autophagy inhibitors (CQ, 50 mg/kg/day or 3-MA 30 mg/kg/day). Endothelium-dependent relaxation (EDR) was significantly reduced in Ang II-treated mice. Treatment of 3-MA improved EDR in mesenteric arteries from Ang II-treated mice. Our results may provide that inhibition of autophagy exert beneficial effects in dysfunction of mesenteric artery. This study will provide the role of autoph-

agy in vascular dysfunction in hypertension.

Keywords: Autophagy, Hypertension, Mesenteric arteries, Endothelium-dependent relaxation

P04-08

Role of the 5-HT on pacemaker potentials in colonic interstitial cells of Cajal of mouse

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5-hydroxytryptamine (5-HT) causes tonic inward currents on pacemaker currents in interstitial cells of Cajal (ICC)in small intestine. 5-HT regulates pacemaker currents through 5-HT3/4/7 receptors via $[Ca^{2+}]i$ mobilization and MAPKS regulation. This study aims to investigate physiological role of 5-HT for pacemaker potentials on colonic ICC. Treatment of 5-HT depolarized membrane potential and increased frequency of pacemaker potential in a dose dependent manner. While 5-HT-stimulated pacemaker potential was not affected by 5-HT receptor blockers including SB-204741 (5-HT2B receptor antagonist), tropanylindole-3-carboxylate methiodide (3-TCM, a 5-HT3 receptor antagonist), SDZ 2055571 (5-HT4 receptor antagonist) and SB 269970 (5-HT7 receptor antagonist), calcium-activated Cl- channel inhibitors, T16Ainh-Ao1 and CaCCinh-Ao1, attenuated depolarization and increased pacemaker potential by 5-HT on colonic ICC. In addition, T-type calcium channel blockers (NiCl2 and ML-218) inhibited 5-HT-induced pacemaker potentials. Moreover, small spikes among the pacemaker potentials were emerged by all Ano-1 blockers but the frequency was unaltered. 5-HT-stimulation was also downregulated by inhibitors of hyperpolarization-activated cyclic nucleotide-gated cation channel such as ZD7288 and CsCl. In Ca^{2+} imaging, spontaneous $[Ca^{2+}]i$ oscillations were increased by 5-HT. These data suggest that Ano-1 and T-type Ca^{2+} channel may be involved in the generation of small spike and pacemaker potentials. Beyond that, it is likely that HCN channels are involved either. Taken together, these results demonstrate that 5-HT regulates pacemaker potentials through modulating calcium-activated Cl- channel-mediated $[Ca^{2+}]i$ mobilization.

Keywords: 5-hydroxytryptamine, interstitial cells of Cajal, Calcium channel

P04-09

Action of fluoxetine on pacemaker activity in interstitial cells of Cajal from mouse large intestine

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Fluoxetine is antidepressant of the selective serotonin reuptake inhibitor (SSRI) that has been widely used for the treatment of depression, obsessive compulsive disorder (OCD) and other diseases. In gastrointestinal (GI) tract, antidepressants such as SSRIs and tricyclic antidepressants (TCAs) are considered as therapeutic options for patients with irritable bowel syndrome (IBS). However, interstitial cells of Cajal (ICCs) are spontaneously active pacemaker cells in the gastrointestinal tract. Therefore, we investigate the effects of fluoxetine on pacemaker activity in colonic ICCs using whole-cell patch clamp and live-cell intracellular Ca^{2+} ($[Ca^{2+}]i$) imaging techniques. Imipramine, desipramine and amitriptyline depolarized the membrane potentials and increased the generation of pacemaker potential. However, fluoxetine depolarized the membrane potentials with decreased pacemaker potential frequency. Moreover, fluoxetine decreased the frequency of spontaneous $[Ca^{2+}]i$ oscillations. In addition, pacemaker potential frequency was decreased by pretreatment of multiple 5-HT receptor blockers including ritanserin (a 5-HT2a receptor blocker), SB204741 (a 5-HT2b receptor blocker), SDZ20557 (a 5-HT4 receptor blocker), SB269970 (a 5-HT7 receptor block), and 3TCM (a 5-HT_3 receptor blocker), but not by ketanserin (a 5-HT2 receptor blocker). Ketanserin depolarized the membrane potential and increased pacemaker potential frequency. Of note, the 5-HT reuptake blocker, escitalopram, had no effects on pacemaker potentials.

This result suggests that the effects of fluoxetine on pacemaker activity in colonic ICCs may be relevant with several 5-HT receptors and could not take an action through 5-HT reuptake transporter.

Keywords: Obsessive compulsive disorder, interstitial cells of Cajal, fluoxetine

P05-01

Role of Rho-associated protein kinase in the vasorelaxation induced by linagliptin

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In this study, we used the phenylephrine-precontracted aortic ring preparation to investigate the mechanisms underlying the vasorelaxant effect of linagliptin. We found that linagliptin induced vasorelaxation in a dose-dependent manner. The vasorelaxant effect of linagliptin was not changed by the removal of the endothelium, or by pre-treatment with a NO synthase inhibitor (L-NAME) or a small-conductance Ca^{2+}-dependent K^+ channel inhibitor (apamin). Moreover, administration of the adenylyl cyclase inhibitor SQ22536, protein kinase A (PKA) inhibitor KT5720, guanylyl cyclase inhibitor ODQ, or protein kinase G (PKG) inhibitor KT5823 did not change the vasorelaxant effect of linagliptin. However, blocking of Rho-associated protein kinase by Y-27632 significantly reduced linagliptin-induced vasorelaxation. Involvement of vascular ion channel in the vasorelaxant effect of linagliptin was also investigated. Pre-treatment with the vascular K^+ channel inhibitors Ba^{2+}, 4-AP, paxilline, and glibenclamide did not affect linagliptin-induced vasorelaxation. Furthermore, the *L*-type Ca^{2+} channel inhibitor, nicardipine, and the SERCA pump inhibitor, cyclic piazonic acid, were not related with the vasorelaxant effect of linagliptin. From these findings, we concluded that linagliptin-induced vasorelaxation was mediated by the inhibition of Rho-associated kinase, but not with the endothelium, PKA or PKG-dependent signaling cascades, vascular K^+ channels, Ca^{2+} channels, or intracellular Ca^{2+}.

Keywords: Linagliptin, Rho kinase, Vasodilation, Aortic smooth muscle

P05-02

Vasorelaxant effect of dipeptidyl peptidase-4 inhibitor sitagliptin via the activation of K_v channels and PKA on aortic smooth muscle

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The present study investigated the vasorelaxant effects of sitagliptin, which is a dipeptidyl peptidase-4 (DPP-4) inhibitor in aortic rings pre-contracted with phenylephrine (Phe). Sitagliptin induced vasorelaxation in a concentration-dependent manner but the inhibition of voltage-dependent K^+ (K_v) channels by pretreatment with 4-aminopyridine (4-AP) effectively reduced this effect. By contrast, the inhibition of inward rectifier K^+ (Kir) channels by pretreatment with barium (Ba^{2+}), large-conductance calcium (Ca^{2+})-activated K^+ (BK_{Ca}) channels with paxilline, and adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels with glibenclamide did not change this effect. Although the application of SQ 22536, which is an adenylyl cyclase inhibitor, also did not change this effect, treatment with KT 5720, a protein kinase A (PKA) inhibitor, effectively reduced the vasorelaxant effects of sitagliptin. ODQ, which is a guanylyl cyclase inhibitor, and KT 5823, a protein kinase G (PKG) inhibitor, did not impact the effect. Similarly, the effects of sitagliptin were not altered by eliminating the endothelium, by pretreatment with a nitric oxide (NO) synthase inhibitor (L-NAME), or by inhibition of small-conductance Ca^{2+}-activated K^+ channels (SK_{Ca}) using apamin. Furthermore,

neither the inhibition of Ca^{2+} channels by pretreatment with nifedipine nor the inhibition of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps by pretreatment with thapsigargin changed the effect. Taken together, these results suggest that sitagliptin induces vasorelaxation by activating PKA and K_v channels independent of PKG signaling pathways, other K^+ channels, Ca^{2+} channels, SERCA pumps, and the endothelium.

Keywords: Sitagliptin, Voltage-dependent K^+ channels, Protein kinase A, Aorta

P05-03

Role of SERCA pump and K_v channels on vildagliptin-induced vasorelaxation

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In this study, we explored vildagliptin-induced vasorelaxation and its related signaling mechanisms using phenylephrine induced pre-contracted rabbit aortic rings. Vildagliptin induced vasorelaxation in a dose-dependent fashion. Pre-treatment with the large-conductance Ca^{2+}-dependent K^+ channel inhibitor paxilline, ATP-dependent K^+ channel inhibitor glibenclamide and inward rectifier K^+ channel inhibitor Ba^{2+} did not change the vasorelaxant effects of vildagliptin. However, administration of the voltage-gated K^+ (K_v) channel inhibitor 4-aminopyridine significantly decreased the vasorelaxant effects of vildagliptin. In addition, application of two SERCA inhibitors, cyclopiazonic acid or thapsigargin, effectively reduced the vasorelaxant effects of vildagliptin. These vasorelaxant effects were not changed by pretreatment with adenylyl cyclase, guanylyl cyclase, protein kinase A (PKA), or protein kinase G (PKG) inhibitors, or by elimination of the endothelium. Based on these results, we suggested that vildagliptin induced vasorelaxation via activation of the SERCA pump and K_v channels. However, PKA/PKG-related signaling pathways associated with vascular relaxation, other K^+ channels, and the endothelium was not related in vildagliptin-induced vasorelaxation.

Keywords: Vlldagliptin, Voltage-dependent K^+ channel, SERCA pump, Aortic smooth muscle

P05-04

Roles of nNOS and eNOS in rat heart; comparison between the left and right ventricle myocytes

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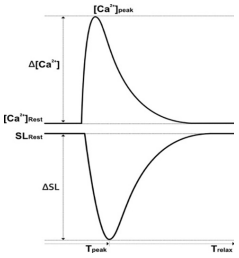
Right ventricle (RV) has physiological as well as anatomical differences compared with left ventricle (LV). There are constitutive NO synthase isoforms, neuronal NOS (nNOS) and endothelial NOS (eNOS) in myocardium, regulating the calcium dynamics and contractility (see the figure). Here we compared the roles of nNOS and eNOS in the RV and LV myocytes from Sprague Dawley rats. After isolating the myocytes using Langendorff perfusion system, their sarcomere shortening and $[Ca^{2+}]_i$ were simultaneously measured using the Ionoptix system while paced by 2 Hz field stimulation. nNOS-specific inhibitor, S-methyl-L-thiocitrulline (SMTC) and the non-specific NOS inhibitor, L-NG-Nitroarginine methyl ester (L-NAME) were used to pharmacologically dissect the roles of NOS isoforms. According to the immunoblot assay, the protein amounts of nNOS and its phosphorylated form were not different between RV and LV. Although the amount of eNOS was lower in RV than LV, its phosphorylated form was similar. RV myocytes showed slower contraction (longer T_{Peak}) and slower relaxation (longer T_{relax}) than LV myocytes. The treatment with SMTC or L-NAME shortened T_{Peak} and T_{relax} of RV myocytes, abolishing the kinetic differences of ΔSL. It was notable that the T_{relax} of LV myocytes became slightly longer by SMTC. Paradoxically, the length of sarcomere shortening (ΔSL) was increased while the amplitude of calcium transient ($\Delta[Ca^{2+}]$) was decreased by SMTC in RV myocytes. However, SMTC did not affect the ΔSL and $\Delta[Ca^{2+}]$ of LV myocytes. Our study suggest that the slower contraction and relaxation of RV myocytes might be partly due to differential responses to the nNOS-dependent intracellular signaling. The opposite direction of changes in the amplitudes of ΔSL and $\Delta[Ca^{2+}]$ by SMTC suggest that the nNOS in RV myocytes is responsible for negative inotropy despite the positive effects on the calcium transient, which is not evident in LV myocytes.

Keywords: Right ventricle, Cardiomyocyte, Contraction, Intracellular Ca^{2+}, Nitric oxide synthase



P05-05

Interventricular difference in calcium sensitivity with lower expression of calcium binding proteins

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Left ventricle (LV) and right ventricle (RV) have distinctive structural and functional characteristics as well as heterogeneous physiological properties. Consistent with the less mechanical afterload, the RV has a thinner free wall than the LV, and the movement of its contraction is geometrically different. Despite these definite differences, the studies of basic excitation-contraction coupling and calcium homeostasis of RV has been less studied than in LV. To establish the interventricular difference, we evaluated the basic electrophysiological and calcium-contractile properties of myocyte with or without β-adrenergic stimulation. Analyses of contraction and Ca^{2+} signaling and action potential duration (APD) in isolated RV myocytes showed more prominent APD prolongation with less significant changes in sarcomere shortening and calcium transient, implying less efficient E-C coupling RV myocytes. Comparing with LV, RV myocytes showed round peak, slower early relaxation, and faster late relaxation, suggesting the difference of calcium sensitivity between two ventricles. To investigate the difference, we examined the expression level of calcium-binding proteins that regulate myofilament activities. Results showed that the calcium binding proteins such as troponin I were lower in RV. Taken together, our results suggest that calcium binding proteins of RV was differ from that of LV, which is a clue to explain the different physiological properties of the RV.

Keywords: Interventricular difference, Right ventricle, Transient outward, Excitation-contraction coupling

P05-06

Dipeptidyl peptidase-4 inhibition with evogliptin improves cardiac functions and fibrosis in type 2 diabetic *db/db* mice

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Dipeptidyl peptidase-4 (DPP-4) inhibitors are popularly used antihyperglycemic drugs for the treatment of type 2 diabetes mellitus (T2D). Currently, the pleiotropic effects of DPP-4 inhibitors have drawn much attention. Our investigation aimed to examine whether evogliptin, a recently developed DPP-4 inhibitor, could protect against T2D-induced cardiomyopathy. Eight-week-old diabetic and obese *db/db* mice received one of two doses of evogliptin – incorporated chow diet (100mg/kg and 300mg/kg body weight), *db/db* control mice and *db*/m control mice received chow diet daily for 12 weeks. Body weight and feeding weight was measured one time and three times per week respectively. Cardiac function was assessed using echocardiography at before and after feeding 12 weeks. Histological and molecular markers of cardiac fibrosis were assessed in the left ventricle (LV) at 20 weeks old. The results showed that evogliptin improved T2D-induced cardiac dysfunction, as shown by analysis of 2D and doppler echocardiography (LV ejection fraction, fractional shortening was higher, E/A and e'/a' ratios increased, E/e' ratio and deceleration time decreased in evogliptin - treated groups compared to *db/db* control group). Evogliptin also attenuated interstitial fibrosis and reduced mitochondrial damage. Our data suggest that evogliptin might be of benefit in cardio-dysfunction patients with type 2 diabetes.

Keywords: Dipeptidyl peptidase-4, Type 2 diabetes mellitus, Cardiac fibrosis, Diabetic cardiomyopathy

P05-07

Mitochondrial ROS and TRPC6-mediated Ca^{2+} signaling nexus contributes to hepatic stellate cell activation and fibrosis

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Activation of hepatic stellate cell (HSC) is primary event of liver fibrosis. Disturbances in Ca^{2+} and reactive oxygen species (ROS) signaling have been postulated as an early event in HSCs activation leading to fibrosis. Hepatic fibrosis mediators including TGFβ and Angiotensin II are not only linked to Ca^{2+} signaling but also the potent oxidative stress mediators. It is yet unknown how ROS initiates HSC activation by Ca^{2+}-permeable channels. Here, we examined whether ROS activates HSCs to initiate the fibrosis, and how Ca^{2+} signaling links to mitochondrial ROS production to HSC activation. We find that TRPC6 channel is predominant Ca^{2+} influx mechanism in HSC activation and hepatic fibrosis. TRPC6 deletion (*Trpc6*$^{-/-}$) ameliorates fibrosis induced by thioacetamide (TAA) administration or bile duct ligations (BDL), *in vivo*. ROS production and TRPC6 and TGFβ expressions are increased during HSC activation. Accordingly, H_2O_2 directly upregulates TRPC6 currents density and TRPC6-induced Ca^{2+} influx. Moreover, TRPC6 activation by OAG and/or endothlelin-1 causes depolarization of mitochondrial membrane potential followed by mitochondrial ROS production. ROS are significantly elevated in both fibrosis animal models and it is reduced by *Trpc6* knockout. Fibrosis is ameliorated by suppressing TRPC6 or mitochondrial ROS production in *in vitro* primary and cultured HSCs. Taken together, our findings demonstrate that the deleterious action of oxidative stress on HSCs and its pathophysiological role in liver fibrosis involve exaggerated TRPC6 activation via signaling nexus of plasma membrane TRPC6 and mitochondrial ROS. These results provide new perspective on the pathogenesis of hepatic fibrosis and clues for therapeutic approach for the cirrhosis.

Keywords: Oxidative stress, Liver fibrosis, TGFβ, Mitochondria

P05-08

αKlotho as a negative regulator of store-operated Ca^{2+} entry

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αKlotho is type 1 transmembrane antiaging protein. Aging is the primary risk factor for chronic human pathologies such as diabetes and cancers. The extracellular domain of αKlotho is cleaved off into blood and urine and function as a humoral factor. αKlotho-deficient mice have premature aging and imbalance of ion homeostasis including Ca^{2+} signaling. αKlotho is known to regulate multiple ion channels and transporters. Store-operated Ca^{2+} entry (SOCE) is a ubiquitous Ca^{2+} influx mechanism and has been implicated in diseases, directly or indirectly. However, it is currently unknown whether αKlotho stabilizes SOCE-mediated Ca^{2+} signaling. SOCE is mediated by ER Ca^{2+} sensor STIM1 and plasma membrane (PM) Ca^{2+}-selective channel, Orai1. Here we show that serum and growth factors activate not only Orai1-mediated SOCE but also its currents density. Furthermore, the cell surface abundance of Orai1 channel is upregulated by the serum and growth factors without affecting gating and activation kinetics of Orai1 channel. Both SOCE and plasma membrane (PM) expression of Orai1are blunted by preincubation of inhibitors of phosphoinositide-3-kinase (PI3K)/Akt and Erk1/2 kinase. Moreover, those SOCE and cell surface Orai1 are reduced by pretreatment of brefeldin A, tetanus toxin and/or by siRNA knockdown of VAMP2. Interestingly, we find that Orai1 physically interacts with VAMP2. Indeed, soluble αKlotho inhibits serum growth factors-stimulated Akt and Erk1/2 pathway and downregulates SOCE as well as cell surface abundance of Orai1 by blocking PI3K-dependent exocytosis of the channel. αKlotho further ameliorates SOCE-mediated cancer behaviors and actin remodeling of podocyte causing proteinuria. These findings reveal that αKlotho protects pathogenesis by aggravated SOCE signaling pathway through downregulation of Orai1 PM expression. Our data provide evidence for an important mechanism of SOCE and αKlotho protection on Ca^{2+} signaling in disease.

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Keywords: Orai1, VAMP2, SOCE, Aging

P06-01

Pine needle extract activates POMC neurons in the hypothalamus

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Prolonged excessive energy intake over the energy consumption leads to obesity which is a major cause of metabolic disease such as type 2 diabetes. The arcuate nucleus (ARC) of the hypothalamus is the most important brain area to regulate energy balance. The ARC is a major component of the melanocortin system, a regulation center of energy balance in the hypothalamus. Two distinct neuronal types of ARC are anorexigenic POMC (Pro-opi-

omelanocortin) and orexigenic NPY (Neuropeptide Y)/AgRP (Agouti related peptide) neurons. Also, the POMC neurons in the ARC are known as an energy expenditure enhancing neurons. In addition, the pine needle contains strong antioxidant polyphenols and has capability of lipolysis and improve elevated blood glucose levels by obesity. However, the role of pine needle extract (PNE) onto the hypothalamic POMC neurons remain unclear. In this study, we use hot water extracted PNE to investigate the role of PNE in regulation of energy balance via hypothalamic POMC neurons. Orally injected PNE (200mg/kg) increases c-fos expression in the ARC and the paraventricular nucleus of the hypothalamus. Also, PNE increased 20% of c-fos expression in the hypothalamic POMC neurons as compared to control group. And, direct application of PNE (200μM) on the brain slice with patch clamp showed that 78% of POMC were depolarized by PNE (200μM). Moreover, body weight and food intake were decreased by 2 weeks consecutive oral injection of PNE after 12 weeks high fat fed. Simultaneously, PNE improved blood glucose levels after high fat fed as compared to control. Overall, these findings strongly suggest that PNE plays pivotal to regulate energy balance via melanocortin system.

Keywords: Hypothalamus, POMC, Pine needle extract, Energy balance, Obesity

P06-02

Effects of octanoic acid on glucose-stimulated insulin secretion and expression of glucokinase through the olfactory receptor in pancreatic beta-cells

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Olfactory receptors (ORs) are G protein-coupled receptors that mediate olfactory chemosensation, leading to the perception of smell. ORs are expressed in many tissues, but their functions are largely unknown. Here, we show that the olfactory receptor Olfr15 is highly and selectively expressed in both mouse pancreatic beta-cells and MIN6 cells. In addition, octanoic acid (OA), a medium-chain fatty acid, potentiates glucose-stimulated insulin secretion (GSIS). The OA-induced enhancement of GSIS was inhibited by Olfr15 knockdown. Treatment with a PLC inhibitor or an Ins(1,4,5)P_3 receptor (IP_3R) antagonist also blocked the OA-induced enhancement of GSIS. These results suggest that OA potentiates GSIS via Olfr15 though the PLC-IP_3 pathway. Furthermore, long-term treatment with OA increased cellular glucose uptake in MIN6 cells by upregulating the expression of glucokinase (GK). Moreover, this process was blocked by an IP_3R antagonist and a Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) inhibitor. Similarly, OA stimulated GK promoter activity, while either Olfr15 or CaMKIV knockdown blocked the stimulatory effect of OA on GK promoter activity. These results suggest that long-term treatment of OA induces GK promoter activity via Olfr15 through the IP_3-CaMKK/CaMKIV pathway. In islets from type 2 diabetic mice, the expression level of Olfr15 and the OA-induced enhancement of GSIS were strongly reduced. Collectively, our results highlight the crucial role of the olfactory receptor Olfr15 in potentiating GSIS in pancreatic beta-cells, suggesting that Olfr15 may be an important therapeutic target in type 2 diabetes.

Keywords: Octanoic acid, Olfactory receptor, Insulin secretion, Pancreatic beta-cells

P06-03

Effect of endoplasmic reticulum stress on expression of adipsin in adipocytes

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Adipsin is one of the adipokines secreted by adipocytes. In pancreatic beta-cells, adipsin play a pivotal role in insulin secretion. Adipsin secreted from adipocytes is involved in the complement mediator pathway and activates the final product, complement component 3, to enhance intracellular ATP synthesis, Ca^{2+} uptake and insulin secretion in pancreatic beta-cells. Furthermore, knockdown of adipsin expression results in impairment of insulin secretion. Thus, adipsin might be an important regulator of beta-cell function and may be a new therapeutic target for pancreatic dysfunction in type 2 diabetes (T2D). However, the changes of adipsin expression in obesity and T2D have not been elucidated yet. The aim of this study was to investigate the changes of adipsin expression in obese and T2D animal models and identify the factors that affect expression level of adipsin in adipocytes. In white adipose tissue of db/db mice, adipsin level was decreased compared to wild-type mice, while expression levels of endoplasmic reticulum (ER) stress markers were increased. High fat diet-fed mice demonstrated similar results. In thapsigargin or tunicamycin-treated 3T3-L1 adipocytes, the expression level of adipsin was decreased, while the expression levels of ER stress markers were increased. The reduced expression of C/EBPα and PPARγ induced the decrease of adipsin expression in thapsigargin-treated cells. Pretreatment of chemical chaperone restored the ER stress-induced downregulation of adipsin both *in vivo* and *in vitro*. Taken together, these data demonstrated that increased ER stress during obesity or T2D reduces synthesis and secretion of adipsin in adipocytes. Thus, restoring adipsin expression may provide a promising new therapeutic strategy for beta-cell dysfunction in T2D.

Keywords: Adipsin, Adipokine, Endoplasmic reticulum stress, Type 2 diabetes

P06-04

The role of MsrB3 on high-fat diet induced insulin resistance

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Insulin resistance links obesity and type 2 diabetes and is also associated with metabolic diseases. Oxidative stress is one of the important mechanisms underlying insulin resistance. Methionine Sulfoxide reductase B3 (MsrB3) is an important protein repair enzyme that also act as antioxidant and protect cells from oxidative stress. In this study, we examined the role of MsrB3 deficiency on high-fat diet induced insulin resistance in wild-type (WT) and MsrB3 knockout(KO) mice using hypeinsulinemic-euglycemic clamp technique. Mice were fed on the control and high-fat diet for 16 weeks. Body weight was significantly increased by high-fat diet in both WT and KO mice, but it was not different between WT and KO mice in both control and high-fat diet. Plasma glucose and insulin levels were similar between WT and MsrB3 KO mice in control diet, but it was significantly elevated only in wild-type mice. Plasma free fatty acid (FFA) level was increased only in WT mice by high-fat diet, and it was significantly lower in MsrB3 KO mice than WT mice in high-fat diet group. Glucose infusion rate was decreased in WT mice by high-fat diet, but it was not significantly changed by high-fat diet in MsrB3 KO mice. Whole-body and skeletal muscle glucose uptake were significantly reduced by high-fat diet in WT mice, but not in MsrB3 KO mice. These results suggest that MsrB3 deficiency paradoxically attenuates high-fat diet induced insulin resistance.

Keywords: Insulin resistance, MsrB3, High-fat diet, Hypeinsulinemic-euglycemic clamp

P06-05

Lactate shifts mitochondrial bioenergetics in skeletal muscle and adipose tissue mitochondria and increases metabolic rate

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Lactate that is the last metabolite of glycolysis is induced by muscle contraction was recognized as a signal molecule for various tissue including adipose tissue and brain. Lactate can be resynthesized to energy substrate for muscle during exercise, and also be molecule to signals for the muscle cell and adipocyte to regulate energy metabolism via autocrine and paracrine, respectively. However, how this role is regulated has not been defined. To identify how the lactate regulates energy metabolism in muscle and adipose tissue, lactate was daily administered (i.p.) in chow and high fat diet (HFD) mouse, respectively, for 8 weeks. We found that glucose disposal rate and metabolic rate were higher in lactate group, whereas RER was lower in lactate group when compared with saline group regardless of chow and high-fat diet. We observed that the running endurance was lower in lactate mice group than saline group, thus, we studied the bioenergetic characteristics of mitochondria in muscle and adipose tissue to understand the potential link to increased metabolic rate and attenuated running endurance. We could not find any difference of mitochondrial respiration when using glucose and malate as substrate in muscle mitochondria, whereas state III respiration in lactate muscle mitochondria were significantly lower than saline. We also found lactate with high fat diet had significantly lower respiratory control ratio (RCR) when using palmitate and malate as substrate. Different phenomena were observed in adipose tissue, lactate with HFD had higher state III respiration and RCR when using glucose and malate as substrate, whereas RCR was lower in lactate with HFD when using palmitate and malate as substrate. Overall, these results indicate that lactate mice exhibit marked shifts in skeletal muscle and adipose tissue mitochondrial bioenergetics and this shift might induce higher metabolic rate and glucose disposal rate as well as lower running endurance capacity in lactate with HFD mice.

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Keywords: Lactate, Metabolic rate, Mitochondria respiration, Running endurance

P06-06

The effect of CORM-2 on ANP secretion

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Along with hydrogen sulfide (H_2S) and nitric oxide (NO), carbon monoxide (CO) has been characterized as a gaseous bioactive substance in numerous body systems. However, the application of CO in humans is full of challenging because of its toxicity characterized by inhibition of oxygen delivery at high concentrations. Abundant evidence has demonstrated that CO treatment exerts anti-inflammatory, anti-apoptotic and vasodilatory effects in many experimental models. There are different ways to deliver CO as potential therapeutic interventions, one of which is administration of carbon monoxide-releasing molecules (CORMs) and is reported to have cardioprotection in both ex vivo and in vivo models. However, whether CORMs affects ANP secretion remains unacquainted. The purpose of the present study is to explore the effect of CORMs on ANP secretion and to detect its signaling pathway. The atria were perfused for 80 min to stabilize secretion of ANP. The atrial perfusate was collected at 2-min intervals at 4 °C for 10 min while paced at 1.2 Hz. To induce atrial stretch, the height of the outflow catheter was increased from 5.0 to 7.5 cmH_2O by a connecting 2.5-cm-long catheter after a 10-min collection period and the atrial perfusate was collected for 50 min. CORM-2 (50μM) but not CORM-3 decreased high stretch induced-ANP secretion significantly in normoxic condition. Moreover, the decreasing CORM-2 induced-ANP secretion did not be reversed by the pretreatment of PD98059 (MAPK inhibitor) and LY294002 (PI3K inhibitor). More studies are ongoing to define the signaling pathway.

Acknowledgement: Supported by the NRF grant

Keywords: CORM-2, High stretch, ANP, MAPK pathway and PI3K pathway

P06-07

Tetrahydrobiopterin enhanced mitochondria biogenesis and cardiac contractility via stimulation of PGC-1α signaling pathway

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Tetrahydrobiopterin (BH4) shows therapeutic potential as an endogenous target in the cardiovascular diseases. It has been involved in cardiovascular metabolism and mitochondria biology without clear underlying mechanism. The purpose of this study is to investigate the novel mechanism of BH4 regulating cardiovascular metabolism through unbiased multiple proteomics approach using a sepiapterin reductase knockout (*Spr*$^{-/-}$) mouse, a model of BH4 deficiency. *Spr*$^{-/-}$ mice had a significantly shortened life span, cardiac contractile dysfunction, and morphological changes. Multiple proteomics and systems-based data integrative analysis identified that BH4 deficiency mainly changes mitochondrial oxidative phosphorylation (OXPHOS) in the heart. Due to decreased transcription of major mitochondrial biogenesis regulating genes including *Ppargc1a, Ppara, Esrra,* and *Tfam, Spr*$^{-/-}$ mice had lower mitochondria mass and severe defects in OXPHOS system. Exogenous BH4 supplementation successfully rescued cardiac and mitochondrial defects. However, nitric oxide supplementation and nitric oxide inhibition failed to rescue mitochondrial or cardiac function of *Spr*$^{-/-}$ mice. BH4 supplement recovered mRNA and protein level of PGC1α and its target proteins involved in mitochondria biogenesis (mtTFA and ERRα), antioxidant (Prx3 and SOD2) and fatty acid utilization (CD36 and CPTI-M) in the *Spr*$^{-/-}$ mice hearts. These results provide a novel NO-independent molecular mechanism of BH4 activating transcription of PGC1α in the regulation of cardiac energy metabolism and suggest that BH4 has therapeutic potential for cardiovascular diseases characterized by mitochondrial dysfunction.

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Keywords: Tetrahydrobiopterin, Proteomics, Mitochondria biogenesis, PGC-1α, Cardiovascular metabolism

P06-08

Melatonin regulates gonadotropin releasing hormone neurons excitability via kainate receptors and kisspeptin signaling in immature mice

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Gonadotropin releasing hormone (GnRH) neurons distributed in the hypothalamic preoptic area are the central regulator of reproductive physiology in vertebrates. Excitability of the GnRH neurons is regulated by various neurotransmitter systems, neuropeptides, and neuro-hormones. Melatonin, a pineal secretion is a fat-soluble neuro-hormone involved in biological and physiologic regulation of body functions. Numerous *in vivo* studies

have shown the effect of melatonin on the release of gonadotropins and its action at one or several levels of the hypothalamic pituitary gonadal (HPG) axis. However, its control of GnRH neurons at the hypothalamic level remains unclear. Therefore, we investigated the role of melatonin in GnRH neuronal excitability using patch-clamp techniques. Whole-cell, perforated, and cell-attached recording were made from GFP-tagged GnRH neurons of immature mice. In this study, we found that melatonin administration in vitro in bath solution elicited no change in resting membrane potential or current and did not alter the electrical firing in GFP-tagged GnRH neurons. Therefore melatonin effect on neurotransmitter activity of GnRH neurons was assessed. Inhibitory neurotransmitters like GABA, dopamine and serotonin receptors-mediated responses remained unaffected in presence of melatonin. However, when melatonin was co-applied with glutamate receptor agonists such as α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-Methyl-D-aspartic acid (NMDA), and kainate, it suppressed kainate receptor-mediated responses without affecting the AMPA and NMDA receptor-mediated responses. The suppression of kainate receptors by melatonin remained persisted in the presence of tetrodotoxin, a voltage sensitive Na^+ channel blocker, indicating melatonin action on postsynaptic kainate receptors. Furthermore, melatonin suppressed the kisspeptin-induced increased neuronal firing in a majority of neurons tested. These results suggest that melatonin regulates the GnRH neuronal activities by suppressing the excitatory neurotransmission via kainate receptors and kisspeptin signaling, and modulates the HPG axis.

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Keywords: Gonadotropin releasing hormone neuron, Melatonin, Kainate, Kisspeptin, Patch-clamp technique

P06-09

N-terminal pro-B-type natriuretic peptide as an index in patients with obesity and acute coronary syndrome

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Patients with obesity have low N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. However, the cut-off levels of NT-proBNP in obese patients with acute coronary syndrome (ACS) is unclear. This study aimed to assess the predictive value of NT-proBNP in patients with obesity and ACS. A total of 1246 patients with ACS were enrolled in this study. Patients were divided into three groups (unstable angina, ST-segment elevation myocardial infarction[STEMI], non-STEMI [NSTEMI]) according to clinical characteristics and biochemical parameters. Medical indicators and NT-proBNP levels were compared between patients with obesity (body mass index [BMI]≥25kg/m^2) and those with normal weight (BMI<25 kg/m^2). ROC curves were used to evaluate the predictive value of NT-proBNP levels in patients with obesity and UA, STEMI, or NSTEMI. A total of 553 patients were overweight or obese. Among them, 238 (42.5%) patients had UA, 208 had STEMI (45.9%), and 107 (45.9%) had NSTEMI. Patients with obesity showed significantly lower NT-proBNP levels compared with normal weight patients in the three types of ACS. NT-proBNP levels in patients with overweight or obesity showed areas under the curve of 0.7560 for STEMI and 0.7664 for NSTMI, but it was less than 0.7 for UA. This suggested that NT-proBNP had predictive value for patients with obesity and STEMI or STEMI. Additionally, age was an independent positive correlate of NT-proBNP in every type of ACS. Patients with obesity and STEMI or NSTEMI have lower (25% and 75%, respectively) cut-off levels of NT-proBNP vs normal weight patients.

Acknowledgments: This work was supported by a National Natural Science Foundation of China (NSFC) grant (81860077) and a National Natural Science Foundation of China (NSFC) grant (81760047).

Keywords: Acute coronary syndrome, N-terminal pro-B-type natriuretic peptide, Obesity, ST-segment elevation myocardial infarction, Non-STEMI, Index

P06-10

Non-cell autonomous modulation of tyrosine hydroxylase by HMGB1 released from astrocytes in an acute MPTP toxin-induced mouse model

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High-mobility group box 1 (HMGB1) is actively secreted from inflammatory cells and acts via a non-cell autonomous mechanism to play an important role in mediating cell proliferation and migration. The HMGB1-RAGE (receptor for advanced glycation end products) axis upregulates tyrosine hydroxylase (TH) expression in response to extracellular insults in dopaminergic neurons *in vitro*, but little is known about HMGB1 in modulation of dopaminergic neurons *in vivo*. Here, using immunohistochemistry, we show that HMGB1 and RAGE expression are higher in the nigral area of MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated mice, a toxin-induced Parkinsonian mouse model, compared with saline-treated controls. HMGB1 was predominantly localized to astrocytes and may affect neighboring dopaminergic neurons in the MPTP mouse model owing to co-localization of RAGE in these TH-positive cells. In addition**,** MPTP induced a decrease in TH expression, an effect that was potentiated by inhibition of c-Jun N-terminal kinase (JNK) or RAGE. Moreover, stereotaxic injection of recombinant HMGB1 attenuated the MPTP-induced reduction of TH in Parkinsonian mouse model. Collectively, our results suggest that increased and released HMGB1 from astrocytes upregulates TH expression in an acute MPTP-induced Parkinsonian mouse model, thereby maintaining dopaminergic neuronal functions.

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Keywords: Parkinson's disease, Dopaminergic neurons, High-mobility group box 1, Tyrosine hydroxylase, JNK

P06-11

Effects of thermotherapy on irisin and orexin levels metabolic of glucose regulating factors in middle-aged obese women

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Many women gaining weight as they transition as they approach menopause. Weight gain during menopause is predominantly due to a reduction in physical activity. For women who are obesity menopause women, appropriate therapy about controlling weight and increasing lipid metabolism is

required to prevent metabolic syndrome. The main aim of this study was to analyze the how thermotherapy (half bath in hot water, 42±0.5°C, 3-4 times/week, 30 min/time, 15 times for 4 weeks) affects the orexin A (OxA), adiponectin and c-reactive protein (CRP) expression in menopausal overweight-obese women (n=15, age, 55.12±3.27 yrs; height, 157.92±4.87 cm; weight, 62.19±7.52 kg). Significant increased of OxA ($p<0.01$), adiponectin ($p<0.05$) and CRP ($p<0.01$) after thermotherapy. We found that the increased lipid metabolism with thermotherapy was associated with the OxA and adiponectin. Also, the role of OxA on lifestyle and eating behavior in menopausal overweight-obese women can be further explored to identify obesity and lifestyle-related diseases.

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

P06-12

Effects of acute ingestion of caffeine on dopamine release and serotonin in a human with thermotherapy

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It is widely known that caffeine is closely associated with neuroendocrine system such as dopamine (DA), serotonin (5-hydroxytryptamine; 5-HT) and β-endorphin from previous studies. However, to our knowledge, there is no study to compare the change in serum hormone levels during thermotherapy with caffeine ingestion in human. Therefore, this study's aim is to investigate the effect of caffeine on blood levels of DA, 5-HT and β-endorphin during thermotherapy in human. Based on our experimental results, we studied how caffeine ingestion with thermotherapy affected sympathetic activation. Also, we confirmed whether caffeine ingestion with thermotherapy would be useful of preventing cold. Blood levels of DA, 5-HT and β-endorphin before and after thermotherapy were measured. Thermotherapy was carried out by immersing the half body into a hot water bath (exposure, 42±0.5°C) for 30 min. Mean body temperature (mTb) and mean skin temperature (mTs) were calculated. Active sweat gland density (ASGD) of the eight regions of the skin areas was determined with iodine impregnated paper method. After thermotherapy, the mTb and mTs were increased significantly ($p < 0.001$) in caffeine (CAFF) group as compared to control (CON) group. In ASGD measurements, CAFF group showed more activation in sweat gland as compared to CON group. Changes in circulating DA, 5-HT and β-endorphin levels increase more in CAFF group as compared to CON group. In conclusion, caffeine ingestion with thermotherapy would be useful of treatment for autonomic dysregulation and preventing cold.

Keywords: Caffeine, Dopamine, Serotonin, Prolactin, β-endorphin

P06-13

Seasonal acclimation in sudomotor function evaluated by acetylcholine in healthy humans

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The quantitative sudomotor axon reflex testing (QSART) is a classic test of routine postganglionic sudomotor function. We investigated sudomotor function by QSART after summer (July 2017) and winter (January 2018) seasonal acclimation in the Republic of Korea. QSART with acetylcholine (ACh) iontophoresis were performed to determine directly activated (DIR) and axon reflex-mediated (AXR1, 2) sweating rate. Onset time of axon reflex, activated sweat gland density (ASGD), activated sweat gland output (ASGO), tympanic and skin temperatures (Tty, Tsk), basal metabolic rate (BMR), and evaporative loss volume changes were measured. Tympanic and mean body temperature (Tb; calculated from Tty, Tsk) were significantly lower after summer-SA than that of winter-SA. Sweat onset time was delayed during winter-SA compared to that after summer-SA. BMR, AXR(1), AXR(2), and DIR sweat rates, ASGD and ASGO, and evaporative loss volume were significantly diminished after winter-SA relative to after summer-SA. In conclusion, changes in sweating activity measured by QSART confirmed the involvement of the peripheral nervous system in variation of sudomotor activity in seasonal acclimation

Keywords: Acetylcholine (ACh), QSART (quantitative sudomotor axon reflex testing), Seasonal acclimation, Sweat

P06-14

Investigating the mechanism of the cell-nonautonomous roles of the nuclear hormone receptor NHR-49 in the nervous system of *Caenorhabditis elegans*

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The central nervous system plays a key role in regulating whole-body metabolism. Examples of neuronal regulation of fat metabolism and lifespan have also been reported for C. elegans. NHR-49 is one of the 284 nuclear hormone receptors expressed in C. elegans and is an important regulator of fat metabolism and lifespan. Recently, it was found that NHR-49 expression in the neurons is sufficient to restore some of the key nhr-49-dependent functions in the worm (Burkewitz et al., 2015). In order to elucidate how the nuclear receptor signals from the neurons, we characterized which of the known NHR-49 functions are carried out by the neurons. In addition to near-wild type lifespan that was previously reported, we found that neuronal rescue of NHR-49 restored the expression of select nhr-49-dependent genes in a cell non-autonomous fashion. On the other hand, loss of fat stores in adult worms and sensitivity to oxidative stress of nhr-49 mutants was not ameliorated by the neuronal rescue. We are currently conducting genetic and biochemical analyses to understand how neuronal NHR-49 signals to the periphery to affect gene expression and lifespan.

Keywords: Metabolism, Cell-nonautonomous, Caenorhabditis elegans, Nuclear hormone receptor, neuron

P06-15

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 Pi 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 Pi-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 Pi incubation. Cellular P_i uptake elicited cytosolic alkalinization that further facilitated Pi transport into mitochondrial matrix. Increased mitochondrial P_i uptake accelerated superoxide generation (ROS), upregulation of osteogenic genes and calcific changes in primary rat aortic smooth muscle cells. Vascular calcification by high Pi was effectively prevented by mitoTEMPO, a mitochondrial ROS scavenger. Genetic suppression or pharmacologic blocking of mitochondrial P_i transporters also inhibit ROS generation as well as calcific changes induced by high Pi. We propose that P_i transport across mitochondrial inner membrane could be a novel therapeutic target for vascular calcification and cardiovascular morbidities.

Keywords: Hyperphosphatemia, Vascular calcification, Oxidative stress, Phosphate transporters, Mitochondria

P06-16

High phosphate diet upregulates antioxidant enzymes and FGF21 leading to metabolic stress resistance in mouse models

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Defective phosphate (Pi) excretion such as chronic kidney disease induces hyperphosphatemia and its serious complications such as vascular calcification. Notably, it has been suggested that higher Pi dietary intake by fast food consumption in a modern society also contributes to a higher serum Pi level. A wide range of studies has demonstrated that high extracellular Pi causes detrimental consequences related with oxidative stress in different type of tissues. Until now, however, systemic effect of high Pi particularly on energy metabolism in vivo has not been clearly elucidated. We established animal models using 8-week old C57BL mice fed with normal chow diet including 0.45% Pi (NCD), high-fat diet (HFD), high Pi diet (HPiD; 1.1% Pi), or high-fat with high Pi diet (HFD + HPiD) for 10 weeks. Interestingly, mice with HPiD was reluctant to body weight gain by HFD and prone to metabolic amelioration such as improved insulin sensitivity and increased browning of white adipose tissue. Accessing liver tissue showed the upregulation of various antioxidant enzymes with NRF-2, PPARγ and FGF21. Consistently, serum levels of FGF21 in HPiD mice were significantly higher than those in NCD mice. Contrary to its beneficial actions on metabolism, renal fibrosis and pathologic albuminuria were elicited in HPiD group which were more severe in HFD+HPiD group. Taken together, we suggest that HPiD animal could be a useful model to investigate endogenous defense mechanisms triggered by noxious stress, which could provide novel therapeutic targets against metabolic diseases.

Keywords: Hyperphosphatemia, High phosphate diet, Antioxidant genes, FGF21, Metabolism

P06-17

Interaction between cardiac nNOS and mitochondrial complex I and its regulation of mitochondrial activity in sham and hypertensive hearts

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Recently, neuronal nitric oxide synthase (nNOS) has been shown to be co-localized with complex I, whose activity may function as an electron donor to activate nNOS in the mitochondria. Here, we aimed to investigate the interaction between nNOS and mitochondrial complex I and its regulation of mitochondrial activity in sham and angiotension II-induced hypertensive rat left ventricular myocytes. Sprague-Dawley rats (10-12 weeks old, male) were used in the study. Left ventricle (LV) myocytes were isolated enzymatically. Oxygen consumption rate (OCR, Instech), NO production (Griess Reagent Nitrite assay), intracellular ATP level, mitochondrial complex I activity (NADH assay) were detected in LV myocytes with fatty acid (palmitic acid, PA) supplemented and in isolated mitochondria with palmitocarnitine and compared between sham and hypertensive (HTN) groups. Our results showed that rotenone, an inhibitor that prevents electron transfer from complex I to ubiquinone, significantly increased nNOS-derived NO in both isolated LV myocytes and in cardiac mitochondrial fraction from sham rats. Conversely, complex I activity was significantly increased by a nNOS inhibitor, SMTC, in cardiac mitochondria. These results indicate an interaction between nNOS and complex I activity in the mitochondria of LV myocytes from sham. We went on and analyzed the effect of nNOS on OCR in LV myocytes. Results showed that OCR was not affected by SMTC. However, SMTC significantly increased OCR in the presence of malonate, such an effect was not observed with rotenone. In HTN, rotenone did not affect nNOS-derived NO in LV myocytes or in mitochondria. Nevertheless, SMTC reduced OCR with or without malonate. The present study confirmed the interaction between nNOS and complex I in sham LV mitochondria. The roles of nNOS in cardiac mitochondrial activity of hypertension warrants further investigation.

Keywords: nNOS, Mitochondria, Complex I, Hypertension

P07-01

Prediction of itching diagnostic marker through RNA sequencing of contact hypersensitivity and skin scratching stimulation mice models

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Pruritus is an offensive cutaneous sensation that leads to scratching behavior. Excessive pruritus results in skin barrier dysfunction. In this study, we investigated whether skin injury caused by chemical (contact hypersensitivity; CHS) or physical (skin-scratching stimulation; SSS) stimuli causes initial pruritus, and analyzed gene expression profiles systemically to determined how changes in skin gene expression in the itching area are related to itching. We compared RNA-seq data obtained from the skin tissue of each animal model. In both CHS and SSS, we ranked the Gene ontology biological process (GOBP) terms that are generally associated with changes. The factors associated with upregulation were keratinization, inflammatory response and neutrophil chemotaxis. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway shows the difference of immune system, cell growth and death, signaling molecules and interactions, and signal transduction pathways. The highlights of results are listed below. 1) SSS quickly reached an inflammation reaction leading to the wound treatment phase instead of the itching step, which causes the scratching action due to the duplication of pain signals (Tnf and SP), resulting in the normal wound treatment result; 2) Results of the CHS model suggests that the initial inflammatory signal is reduced, the sequential wound healing process is delayed, and if this condition persists, it eventually progresses to the itching stage; 3) By comparing and analyzing the RNA-seq data obtained from the skin tissue of each animal model in these makers for the treatment of itching, to diagnose causes of itching, to apply customized treatment. We expect this data to be used ad useful in the future of itching treatment.

P07-02

Role of ERK1/2-mTORC1-NOX4 axis on epithelial-mesenchymal transition of retinal pigment epithelial cells

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Epithelial-mesenchymal transition (EMT) of retinal pigment epithelial (RPE) cell induced by TGF-β plays a pivotal role in the pathogenesis of serious diseases including proliferative vitreoretinopathy (PVR). TGF-β, a pleiotropic cytokine, accumulates in injured tissue and elicits pathologic consequences in various tissues. Recently, we reported that activation of ERK1/2-mTORC1-NOX4 participates in fibrosis and destruction of the glomerular filtration barrier. Here, we investigated whether this axis critically mediates TGF-β1-induced EMT in a human RPE cell line, ARPE-19. TGF-β1 treatment markedly increased phosphorylations of ERK1/2 and mTORC1. This activation led to NOX4 upregulation and reactive oxygen species (ROS) generation in TGF-β1 treated cells. TGF-β1 markedly increased expressions of α-smooth muscle actin (α-SMA), plasminogen activator inhibitor-1 (PAI-1) and collagen 4α3 (Col4α3) and their secretions into the extracellular compartment. All these signaling and fibrogenic upregulations were abolished by SB431542, UO126 and rapamycin, which are blockers of TGF-β receptor-I, ERK1/2 and mTORC1, respectively. Interestingly, either scavenging ROS by N-acetylcystein or NOX inhibition by DPI prevented TGF-β1-induced ERK1/2-mTORC1 activation. This finding implies that NOX4-mediated oxidative stress activates the upstream of TGF-β signaling as a positive feedback mechanism. Moreover, we have found that MEK/ERK inhibitor trametinib/GSK1120212 ameliorated most of the TGF-β1-mediated pathologic changes. Taken together, we suggest that TGF-β-ERK1/2-mTORC1-NOX4 axis plays an essential role in EMT of retinal pigment epithelium, which provides novel therapeutic targets for PVR as well as other retinal fibrotic diseases.

Keywords: Retinal pigment epithelium, TGF-β, Epithelial-mesenchymal transition (EMT), Trametinib

P07-03

Expression of organic cation and anion transporters in 3D-cultured human kidney proximal tubular epithelial cell line

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Drug excretion through the kidney is mediated by organic cation and anion transporters in renal proximal tubules (RPT). Thus it is useful to develop the tissue model of human RPT for studying of drug excretion and toxicity in kidney. Although development of tissue model for in vitro human RPT is absolutely required for evaluations of efficacy and safety of new drug candidates, the corresponding tissue models or related commercial products are not readily available at present. In this study, to recapitulate the tissues for human RPT, three-dimensional (3D) cellular model for human RPT was established by co-cultures of human fibroblasts and RPT cells, and expression of the organic cation and anion transporters in this tissue model was investigated. Human fibroblasts were obtained from primary culture of human conjunctival tissues and HK-2 cells were employed as human RPT cells. The 3D culture of human fibroblasts in the poly-ε-caprolactone(PCL) nanofiber scaffold exhibited various shapes and sizes along with distribution pattern of F-actin, vimentin and focal adhesions depending on their attachment in the scaffold. The secretions of collagen I, fibronectin and CTGF were significantly increased in 3D cultured fibroblasts, but TGF-β secretion was rather decreased. Expression of organic cation and anion transporters in 3D cultured HK-2 cells on the nanofiber scaffolds was monitored by reverse transcription polymerase chain reaction and immunofluorescence techniques. Both OCT2 and MATE2-K (organic cation transporters), and OAT2 and MRP2 (organic anion transporters) were confirmed to express in 3D-cultured HK-2 cells. Taken together, it is suggested that fibroblasts cultured in nanofiber scaffolds provide a favorable environment for epithelial cell growth and that 3D-cultured HK-2 cells and fibroblasts in this scaffold could be a useful 3D RPT model for studying drugs that are excreting through these transporters.

Keywords: Organic cation transporters (OCT), Organic anion transporters (OAT), Human kidney proximal tubular epithelial cell line (HK-2 cell). Human primary conjunctival fibroblasts, 3D culture, Poly(ε-caprolactone) nanofibrous scaffold

P08-01

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 bond-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-κB 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.

Keywords: Osteoclastogenesis, JHDM, NFATc1, Post-translational modification

P08-02

CRIF1 deficiency mediated tetrahydrobiopterin biosynthesis regulation induced eNOS 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). BH4 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.

Keywords: CRIF-1, BH4, eNOS uncoupling

P08-03

Alnus Sibirica extracts suppress the inflammatory response in vitro and skin inflammation in vivo

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Introduction: Extracts of Alnus sibirica (A. sibirica) have been used in oriental medicine to treat fever, bleeding, diarrhea, gastrointestinal disorders, lymphatic diseases and cancer. Recently, the anti-inflammatory effect of AS has been reported by few researchers. We conducted the study to confirm the anti-inflammatory effects of AS extracts (AS) on in vitro cell and in vivo mice models. **Methods:** The experiment investigated the anti-inflammatory effects of AS in human dermal fibroblasts (HDFs) in which inflammatory response induced by inflammatory stimulants (lipopolysaccharide; LPS, tumor necrosis factor-alpha; TNF-α, interferon gamma; IFN-γ), and in two types of mice model in which skin inflammation was induced by allergens (1-chloro-2,4-dinitrobenzen; DNCB, house dust mite; HDM). The MTT-assay and reverse-transcription polymerase chain reaction (RT-PCR) techniques were used to observe the effects of AS on cell viability and expression of inflammation-associated cytokines in HDFs. In vivo mice models were made with DNCB treatment in the back of BALB/c mice and HDM treatment in the ears/back of NC/Nga mice. To induce the skin inflammation in mice model, we repeatedly treated allergens for 8weeks. After 4 weeks induction, skin lesions were treated with hydrocortisone (Hc) and AS for 4 weeks. To verify the effects of AS in mice model, we measured the skin modalities, eosinophil/mast cell infiltration, serum IgE and serum cytokines levels. **Results:** In HDFs, increased expression of acute-phase inflammatory cytokines were inhibited by AS. In mice models, 4 weeks treatment of allergens increased skin severity, eosinophils/mast cells infiltration, and serum IgE levels. After 4 weeks treatment of AS, the clinical skin severity, the level of inflammation (eosinophils/mast cell infiltration) in the skin and total serum IgE were significantly inhibited. **Conclusion:** AS showed the excellent anti-inflammatory effects on the inflammatory response-induced in-vitro cell model and dermatitis-induced in-vivo mice model. These suggest that AS could be developed as an excellent alternative anti-inflammatory drug.

Keywords: Human dermal fibroblasts (HDFs), Inflammatory stimulants, BALB/c mice, NC/Nga mice, 1-Chloro-2,4-dinitrobenzen (DNCB), House dust mite (HDM), Alnus sibirica (AS), anti-inflammation

P08-04

IL-10 suppresses caspase-1-dependent IL-1β secretion via production of apoptosis inhibitor of macrophage protein (AIM)

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Interleukin-10 (IL-10) is a key anti-inflammatory cytokine well-known as 'turn-off' signal produced by activated immune cells. Recent studies have shown that the IL-10 is a main target cytokine in inhibition of inflammasome activation. Inflammasome activation triggers activation of caspase-1, resulting in the induction of pyroptosis and the secretion of pro-inflammatory cytokines, such as IL-1β and IL-18. Previously, we found that IL-10 upregulates apoptosis inhibitor of macrophage (AIM) at the mRNA and protein levels in murine bone marrow-derived macrophages (BMDMs). Thus, we investigated whether AIM is involved in IL-10-induced inhibition of the inflammasome activation and caspase-1-dependent IL-1β secretion in BMDMs. Treatment of with IL-10 inhibited the secretion of IL-β and tumor necrosis factor-alpha (TNF-α) after lipopolysaccharide (LPS) or LPS+adenosine 5'-triphosphate (ATP) stimulation. However, IL-10-induced reduction of IL-1β was not observed in BMDMs from $AIM^{-/-}$ mice after LPS or LPS+ATP stimulation, whereas the secretion of TNF-α was reduced by IL-10. Moreover, treatment with recombinant AIM protein (rAIM) resulted in reduction of secretion of IL-1β and IL-18 as well as caspase-1 activity. Furthermore, rAIM inhibited the ASC speck formation, a hallmark of inflammasome activation by treatment with LPS+ATP in BMDMs. Our data suggest that both of endogenous AIM and rAIM protein inhibit the inflammasome activation, leading to blocking the secretion of active form of IL-1β.

Keywords: IL-10, AIM, Inflammasome, IL-1β, BMDM

P08-05

Secretory Ref-1 exhibited protective effects against inflammatory responses in lipopolysaccharide-induced septic mice

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Apurinic/apyrimidinic endonuclease/redox factor-1 (Ref-1) is a multifunctional protein identified as a DNA base excision repair enzyme and redox modulator for several transcriptional factors. Despite recent reports on the role of Ref-1 in inflammation, the biological function of secreted Ref-1 remains unknown, especially in vivo. This study aimed to evaluate the possible roles of secreted Ref-1 in lipopolysaccharide-induced systemic inflammation in vivo. To investigate the role of extracellular Ref-1 in circulation system, we developed the designated secretory Ref-1, PPT-LS-Ref-1, which is an adenoviral vector system targeting to secrete Ref-1 in systemic circulation. Expression of tumor necrosis factor-α (TNF-α)-induced vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells and lipopolysaccharide (LPS)-induced cyclooxygenase-2 in Raw264.7 cells was inhibited by secretory Ref-1, and this inhibitory effect was abrogated following neutralization of Ref-1 with anti-Ref-1 antibody. Plasma Ref-1 levels following administration of AdPPT-LS-Ref-1 were substantially higher than those recorded following administration of Adβgal. Treatment with LPS markedly increased VCAM-1 expression, cathepsin or myeloperoxidase activity, which were significantly suppressed by treatment with AdPPT-LS-Ref-1. Furthermore, LPS-induced cytokines, such as TNF-α, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein 1, were significantly inhibited in AdPPT-LS-Ref-1-treated mice. However, LPS-induced myeloperoxidase activities were not suppressed by treatment with the redox mutant of secretory Ref-1, AdPPT-LS-Ref-1(C65A/C93A), or wild-type AdRef-1. Collectively, these results suggest that secreted Ref-1 has anti-inflammatory properties and that its redox

cysteine residue is associated with the anti-inflammatory activity in vivo. Furthermore, our findings indicate that secretory Ref-1 may be useful as a therapeutic biomolecule against systemic inflammation.

Keywords: Secretory Ref-1, Inflammation, Septic mice, Cytokines, Lipopolysaccharide

P08-06

The reducing APE1/Ref-1 inhibits an inflammatory reaction by inducing a reduction of inflammation mediated receptor

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We determined the redox activity of recombinant human APE1/Ref-1 (rh APE1/Ref-1) by measuring luminescent intensity, which was generated by luciferin formation after substrate reduction and reacted with luciferase, in a mixture containing the reductase substrate proluciferin and reductase rh APE1/Ref-1. rh APE1/Ref-1, which maintained its reduced form in the presence of 1 mM dithiothreitol (DTT), affected the reduction of TNFR1 as evidenced by S-biotinylation and binding to streptavidin-conjugated beads. Both rh APE1/Ref-1 and DTT caused a reduction in TNFR1 and the reducing activity of rh APE1/Ref-1 was higher than that of the reducing agent DTT. To evaluate the function of the reducing APE1/Ref-1, the effect of rh APE1/Ref-1 on TNF-α -induced VCAM-1 expression was determined. Pretreatment with the reducing APE1/Ref-1 (0.5–2 μg/ml) suppressed TNF-α -induced VCAM-1 expression in a concentration-dependent manner, suggesting that extracellular secreted APE1/Ref-1 has an anti-inflammatory function. Based on our studies, inflammatory reactions stimulated by cytokines through the IL-1 receptor or the Toll-like receptor (each has 5 disulfide bonds in the extracellular domain) were effectively attenuated by exposure to APE1/Ref-1. In accordance with TNF-α /TNFR regulation, the IL-1 or LPS-stimulated inflammatory signal was also inhibited by reduction of disulfide bonds, implying a broad-spectrum reducing effect of APE1/Ref-1. These results strongly indicate that anti-inflammatory effects in TNF-α-stimulated endothelial cells by the reducing APE1/Ref-1, which inhibits TNF-α binding to TNFR1 by reductive conformational change, with suggestion as an endogenous inhibitor of vascular inflammation.

Keywords: Ref-1, inflammation, Redox activity

P08-07

Analysis of systemic inflammation on organ dysfunction in pre-eclampsia patients

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Preeclampsia (PE) is an abnormal condition during late pregnancy, characterized by high blood pressure, kidney or liver dysfunction and thrombosis. Here, we aimed to analyze the effects of hypertension and inflammation indexes on organ function in control groups and in patients with PE. Clinical examination data from normal pregnancy women (Ctr, 188), mild PE (mPE, 73) and severe PE (sPE,170) patients who delivered babies in the Department of Obstetrics, Yanbian University Hospital during 2016 to 2019 were enrolled. Results showed that mPE and sPE patients were hypertensive (P<0.0001 for mPE and P< 0.0001 for sPE). The liver and renal functional parameters and coagulation indexes were significantly different between normal and PE patients (P<0.0001, P<0.0001, and P=0.03). Systolic blood pressure showed no correlation with renal, liver or coagulation functions in normal or PE patients (Pearson's analysis). In addition, we analyzed inflammatory indexes in normal, mPE and sPE groups. Lymphocyte (Lym) and basophil counts were significantly increased in sPE patients (P<0.001, P<0.0001). Although neutrophil (Neu) and monocyte (Mon) counts were not changed in PE (P=0.2 and P=0.3), further analysis showed that Neu, Mon and Neu to Lym ratio (NLR) were positively correlated with liver and coagulation parameters in sPE patients. (r=0.124,p<0.0001 r=0.135, P<0.0001;r=0.169, P<0.0001 r= 0.183, P<0.0001;r=0.0167, P<0.0001 r=0.143, P<0.0001) However, no correlation was observed between inflammatory indexes and kidney function in normal and PE groups. Liver dysfunctional indexes, AST and ALT were correlated with PT and PTINR in sPE (r= 0.175, P<0.0001 r=0.166, P<0.0001; r=0.161, P<0.0001 r=0.155, P<0.0001). These findings suggest that systemic inflammation function as a critical factor for liver dysfunction or impaired coagulation in PE patients and the two are linked in the pathogenesis of PE.

P08-08

Macrophage-specific deletion of SCAP induces inflammation by promoting M1 macrophage polarization

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Macrophages play a crucial role in development, metabolism and maintenance of homeostasis, as well as mediating inflammation. Regulation of the macrophage polarization has been reported to be effective therapeutic approaches for inflammatory diseases. Depending on the different microenvironment stimulations, macrophages may be polarized into pro-inflammatory M1 phenotype and anti-inflammatory M2 phenotype. Sterol regulatory element binding proteins (SREBPs) cleavage-activating protein (SCAP) plays an important role in regulating cholesterol balance. SCAP, a cholesterol sensor on proteolytic cleavage activates SREBPs in endoplasmic reticulum membrane to produce mature SREBPs. The present study aims to investigate the roles of macrophage SCAP in macrophage polarization and inflammation. In this study, macrophage-specific deficiency of SCAP mice was generated using the Lys2-Cre model. To address the hypothesis that SCAP regulates macrophage phenotypic polarization, we isolated bone marrow-derived macrophage (BMDMs) from SCAP $^{fl/fl}$ (SCAP WT) or SCAP $^{fl/fl}$ Lys2-Cre (SCAP mko) mice. In the absence of SCAP, macrophages polarized with LPS expressed significantly higher levels of M1-marker genes, such as iNOS, IL-12β, CD80, IL-6 and IL-1β. Unlike, IL-4 treated BMDMs showed reduced expression M2-marker genes Arg1, CD206, IL-10, CLEC10A and Fizz1. In flow cytometry analysis, SCAP mko BMDMs treated with LPS showed a significant increase in F4/80$^+$CD80$^+$ cells, whereas a significant decrease was reported in F4/80$^+$CD206$^+$ cells with IL-4 treatment. Indeed, lack of SCAP uplift the biosynthesis of the pro-inflammatory cytokine IL-1β upon LPS treatment. SCAP dysfunction stimulated inflammatory responses via activating the NF-κB and STAT1 signaling pathway. These findings identify SCAP as a regulator of macrophage polarization with possible roles in inflammatory diseases.

Keywords: Macrophage, SCAP, M1 polarization, Inflammation, BMDM

P09-01

Nitric oxide level regulates lipocalin-2 expression and the viability of RINm5F insulinoma cells in response to cytokines

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We recently reported LCN-2 expression in RINm5F beta-cells under inflammatory condition, which means that LCN-2 may be involved in beta-cell inflammation as a positive or negative molecule. Also, our previous study

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 aimed to explore the relevance of nitric oxide (NO), the product of iNOS, in LCN-2 expression under the exposure to cytokines in RINm5F beta-cells as well as the effect of LCN-2 on the 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. Both LCN-2 peptide treatment and LCN-2 overexpression significantly reduced cell viability. FACS analysis showed that LCN-2 induced the apoptosis of the cells. Taken together, NO level modulates LCN-2 expression via regulation of LCN-2 protein stability under inflammatory condition and LCN-2 may reduce beta-cell viability by promoting apoptosis.

Keywords: Lipocalin-2, Nitric Oxide, Interleukin-1β, Interferon-γ, RINm5F cells

P09-02

Upregulation of thioredoxin and its reductase attenuates arsenic trioxide-induced growth suppression in human pulmonary artery smooth muscle cells by reducing oxidative stress

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Thioredoxin (Trx) system is an important enzymatic complex involved in cellular redox homeostasis. Arsenic trioxide (ATO; As2O3) is known to trigger cell death in vascular smooth muscle cells (VSMCs) via oxidative stress. In the present study, the effects of changes in Trx1 and Trx reductase1 (TrxR1) on cell growth, death, reactive oxygen species (ROS), and glutathione (GSH) levels were evaluated in ATO-treated human pulmonary artery SMCs (HPASMCs). ATO inhibited growth and induced cell death in HPASMCs at 24 h. Overexpression of Trx1 and TrxR1 using adenoviruses attenuated cell growth inhibition caused by ATO and partially prevented cell death. ATO increased ROS levels including the mitochondrial superoxide anion (O^{2-}) at 5 min. Administration of adTrx1 or adTrxR1 reduced the increased mitochondrial O^{2-} level in these cells. HPASMCs treated with Trx1 or TrxR1 siRNA showed increases in ROS levels with or without treatment of ATO at 5 min. Although ATO transiently increased GSH levels at 5 min, Trx1 and TrxR1 siRNAs reduced the increased GSH levels in these cells. In addition, PX-12 (a Trx1 inhibitor) and Auranofin (a TrxR1 inhibitor) diminished the cellular metabolism in HPASMCs at 4 h, accompanied by an increase in ROS level and a decrease in GSH level. In conclusion, upregulation of Trx1 and TrxR1 somewhat decreased cell growth inhibition and death in ATO-treated HPASMCs, which was accompanied by reduced oxidative stress.

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Keywords: Vascular smooth muscle cells, Arsenic trioxide, Cell death, Thioredoxin, Reactive oxygen species, Glutathione

P09-03

Role of Jumonji-C histone demethylase in the development of hepatocellular carcinoma

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Reprogramming in lipid metabolism has received increasing recognition as a hallmark of cancer cells. In cancer cells, large demands of lipids were required to meet excessive synthesis of membranes, energy production and activation of intracellular signaling pathways during cell proliferation and division. To meet these demands, cancer cells express increased levels of lipogenic enzymes responsible for FAs synthesis, which is a target of crucial transcriptional regulator, sterol regulatory element binding protein 1c (SREBP1c). SREBP1c is a well-known master transcription factor for de novo lipogenesis and is found frequently increased in many human cancers. However, the molecular mechanisms involved in the regulation of SREBP1c remain incompletely understood. In this study, we uncover the role of jumonji-C histone demethylase (JHDM) as a repressor of SREBP1c, thereby preventing lipogenesis and proliferation of hepatocellular carcinoma (HCC) cells. JHDM directly interacts with SREBP1c at basic helix-loop-helix domain of SREBP1c and plant homeodomain of JHDM. In addition, knockdown of JHDM stimulates mRNA levels of lipogenic enzymes and induces lipogenesis in HCC cells. However, JHDM-loss-induced lipogenesis is recovered by SREBP1c knockdown, implying that SREBP1c is crucial for the effects of JHDM toward lipogenesis. We also found that JHDM knockdown using siRNAs promotes mRNA expressions of cell cycle regulators, accompanied with enhanced cell growth, colony formation and spheroid formation. Overall, our findings suggest that JHDM serves as a molecular bridge between lipid metabolism and cancer development through regulation of SREBP1c and thus JHDM could be a therapeutic target in defense against HCC.

Keywords: JHDM, SREBP1c, Proliferation

P09-04

Auranofin induces cell death in lung cancer cells via oxidative stress

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Auaranofin (AU), an inhibitor of thioredoxin reductase, has an anti-cancer effect. In the present study, the anti-growth effects of AU on A549 and Calu-6 lung cancer cells were examined in association with levels of reactive oxygen species (ROS) and glutathione (GSH). AU inhibited the growths of A459 and Calu-6 cells with IC50 values of approximately 5 μM and 3 μM at 24 h, respectively. Both cancer cells treated with AU had no effect on cell cycle change. This agent induced apoptosis and necrosis, accompanied by the cleavage of poly (ADP –ribose) polymerase and loss of mitochondrial membrane potential (MMP; ΔΨ). The caspase inhibitors (Z-VAD-FMK, Z-DE-VD-FMK, Z-IETD-FMK and Z-LEHD-FMK) reduced apoptosis, necrosis and lose of MMP (ΔΨ) in AU-treated Calu-6 cells but not A549 cells. AU increased intracellular ROS and GSH depletion levels in A549 and Calu-6 cells. The antioxidant, N-acetyl cysteine not only attenuated apoptosis and necrosis in AU-treated A549 and Calu-6 cells, but also decreased the levels of O_2^- and GSH depletion in these cells. By contrast, L-buthionine sulfoximine, a GSH synthesis inhibitor intensified cell death, O_2^- level and GSH depletion in the AU-treated A549 and Calu-6 cells. In conclusion, AU induced apoptosis and necrosis in A549 and Calu-6 cells via the induction of oxidative stress and the depletion of GSH.

Acknowledgement: The present study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2019R1I1A2A01041209)

Keywords: Auranofin, Lung cancer, Apoptosis, Necrosis, Reactive oxygen

species, Glutathione

P09-05

Ginsenosides enhanced the Irinotecan- induced cell death against colon cancer HCT116 and SW620 cells.

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Irinotecan (CPT11) and Oxaliplatin have been used in combination with 5-fluorouracil and leucovorin for treatment of colorectal cancer. CPT-11 is a compound belonging to the class of topoisomerase I inhibitors, used as second-line treatment, and induces adverse effects with serious life-threatening toxicities. Ginseng (*Panax ginseng* C.A. Meyer) has been used as a traditional herb in many Asian countries including China, Korea and Japan for stimulating immune function, enhancing cardiovascular health and learning and memory, and anti-stress activities. The ginsenosides such as Rg3, Rg5, Rk1, CK and Rh2 are the main bioactive compounds present in the root of Ginseng that exhibits various biological activates such as anti-cancer, anti-inflammatory, anti-oxidative, anti-diabetic etc. However, no studies reported the combination effects of ginsenosides with CPT-11, and their molecular mechanisms remain to be determined. Hence, we aimed to investigate whether ginsenosides Rk1 and CK have synergic effects with CPT-11 against colon cancer cells HCT116 and SW620 cells and explored the possible signaling pathways. We found that Rk1 and CK combination with CPT-11 significantly inhibited the cell proliferation of HCT116 and S620 cells. We also found that Rk1 or CK combination treatment with CPT-11 induced morphological changes such as cell shrinkage and density and decreased cell numbers in HCT116 and S620 cells. These findings suggest that ginsenosides Rk1 and CK enhanced CPT-11-indeuced cell death and, it may helpful to improve the efficacy of Irinotecan and reduce the toxicity of chemotherapy.

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Keywords: Irinotecan (CPT11), Ginsenoside RK1, Ginsenoside CK, Colon cancer, Synergism, Cell death

P09-06

Ginsenoside compound K increases adult hippocampal neurogenesis in aged-mice

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The cognitive impairment is associated with reduced adult hippocampal neurogenesis by aging, which may contribute to age-associated neurodegenerative disease such as Alzheimer's disease (AD). Compound K (CK) is produced from PPD-type ginsenosides Rb1, Rb2, and Rc by microbial conversion in intestine. Although CK has been reported to have neuroprotective and cognition inducing effects, the role of CK on adult neurogenesis has not been explored yet. Here we investigated the effect of CK on hippocampal neurogenesis in both young (2 month) and old aged (24 month) mice. We found that CK enhanced the proliferation rate of new born cells in the dentate gyrus of both young and old-aged mice, resulting in increased number of 5-ethynyl-2'-deoxyuridine (EdU) and proliferating cell nuclear antigen (PCNA) co-labelled cells. Moreover, CK increased the number of $EdU^+/NeuN^+$ cells in the dentate gyrus, suggesting that newly generated cells by CK differentiated into mature neurons (NeuN marker) in both ages. These findings demonstrate that compound K increases adult hippocampal neurogenesis, which may have beneficial effect in neurodegenerative disorders such as AD.

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Keywords: Ginsenoside CK, Neurogenesis, Cell proliferation, EdU, Neuroprotection

P09-07

Exosomal PTEN from macrophages exposed to apoptotic cancer cells inhibits EMT and invasion of cancer cells

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It has been demonstrated that PTEN (phosphatase and tensin homolog on chromosome ten) secreted via exosome formation, or PTEN-Long can be internalized by recipient cells. Previously, we demonstrated that interaction of macrophages and apoptotic cancer cells resulted in inhibition of epithelial-mesenchymal transition (EMT), migration, and invasion of cancer cells. In the present study, apoptotic 344SQ (ApoSQ) cell-induced PPARγ activity in macrophages caused increased PTEN levels. PTEN was recovered in the insoluble fraction with the exosomal markers, such as CD63, CD81, and CD9, confirming the presence of PTEN in ApoSQ-exposed CM, whereas treatment with GW9662, an antagonist of PPARγ, reduced PTEN abundance. Transmission electron microscopy revealed the isolates contained nano-sized vesicles and the number of vesicles in a unit area appeared to be decreased by treatment with GW4869, an inhibitor of exosome biogenesis/release. Nanoparticle tracking analysis (NTA) using NanoSight demonstrated that the size distribution of exosomes from macrophages treated with ApoSQ in the absence or presence of GW4869, did not change, but the concentration of exosomes present was decreased upon GW4869 treatment. PTEN-bearing exosomes secreted from macrophages was uptaken by the recipient cancer cells. Purified exosomes from macrophages exposed to ApoSQ downregulated EMT, Akt/p38 signal cascades, and cancer cell invasion. In conclusion, this study suggests that PTEN secretion in exosomes from macrophages exposed to apoptotic lung cancer cells can be internalized into recipient cancer cells, inhibiting cell polarity disruption, EMT and invasion.

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Keywords: Apoptotic cancer cells, Exosomal PTEN, Epithelial-mesenchymal transition, Macrophages

P09-08

IDH2 mediates mitophagy through changes in mtUPR in endothelial cells

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In this study, we investigated whether IDH2 knockdown causes mitochondrial dysfunction, mitophagy and mtUPR *in vitro* in HUVECs and *in vivo* in IDH2 knock out mice. We showed that knockdown of IDH2 expression induced depolarization of mitochondrial membrane potential (MMP). Mitochondrial dynamics is mitochondrial fusion and fission. Knockdown of IDH2 increased Drp1 (fission protein) and mfn1 (fusion protein) compared with Tom20 (control). IDH2 deficiency increase Mitophagy related protein PINK-1 and Parkin expression and mRNA level (PINK-1, Parkin, BNIP3, NIX, FUNDC-1). Moreover, knockdown of IDH2 induced mtUPR mRNA level (USP30, Clpp) *in vitro*. In addition, IDH2 deficiency increases mtUPR mRNA level and decreases PINK-1 and Parkin protein expression *in vivo*. Our data show that IDH2 deficiency induces mitochondrial dysfunction and then Mitophagy and mtUPR expression in endothelial cells. These findings provide novel strategy for the development of therapeutic agents for restoring mitochondrial and endothelial function.

Keywords: IDH2, Mitophagy, mtUPR, Mitochondria, Endothelial cells

P09-09

The effect of neddylation blockade on cancer metastasis depends on p53 status

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The tumor suppressor p53 gene is lost or mutated in more than 50 percent of human cancers. It plays important role in preventing cancer cell migration, indirectly targeting various EMT markers such as E-Cadherin, ZEB1, Snail, and Slug. Neddylation, well known pathway which ubiquitin-like protein NEDD8 (Neural precursor cell-expressed developmentally downregulated-8) is conjugated to target protein, has been demonstrated to inhibit transcriptional activity of p53. Thus blockade of neddylation increases function of p53 as a transcription factor. However, little is known about how neddylation inhibition affects cancer migration dependent on p53 status. Here, we compared the effect of neddylation blockade on cancer cell migration between p53-wild type (MCF7, SW480, A549) and p53-mutant/null (SKOV3, PC3, H1299) cell lines and figured out only p53-mutant/null cells migrate when neddylation was inhibited. In addition, we further found that this phenomenon results from different slug protein level, which is increased only in p53-mutant/null cells. Critical in progressing cancer migration, slug acts as important target in this mechanism. Finally, we suggest that the effect of neddylation blockade on cancer metastasis exhibit different consequences by p53 status.

Keywords: Neddylation, p53, slug, Cancer migration, Post-translational modification

P09-10

Overcoming drug resistance in multiple myeloma by targeting cereblon

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Cereblon (CRBN) is a thalidomide binding protein which plays an essential role in anti-myeloma effects associated with the teratogenicity of immunomodulatory drugs (IMiDs). CRBN expression level may serve as a potential biomarker to predict patients' response to IMiDs. However, CRBN-related mitochondrial biomarkers in multiple myeloma have not been reported. This study aimed to identify the correlation between CRBN and mitochondrial function modification in multiple myeloma. Multiple myeloma patients displayed higher CRBN levels than normal patients, and its expression depends on drug resistance and susceptibility. Intriguingly, CRBN negatively regulates mitochondrial function. Mitochondrial proteins (PGC-1α, NRF1, TFAM, ERRα), mitochondrial membrane potential (ΔΨm), mitochondrial ATP levels and mitochondrial mass were higher in drug-resistant multiple myeloma cells and lower in drug-sensitive multiple myeloma cells. After silencing CRBN, expression of mitochondrial proteins, ΔΨm, mitochondrial ATP level, and mitochondrial mass were significantly increased in drug-sensitive multiple myeloma cells. Conversely, adenovirus-infected CRBN leads to decreased mitochondrial function. Using a xenograft model, tumor growth was decreased and survivals were extended significantly in KMS26 tumor-bearing mice by thalidomide treatment. Furthermore, CRBN expression in KMS20 tumor by adenovirus successfully increased susceptibility to thalidomide. These findings suggest that CRBN is a novel therapeutic target for overcoming drug resistance in multiple myeloma via the mediation of mitochondrial dysfunction. Furthermore, combined CRBN and mitochondria marker evaluation is more effective in patients suited for thalidomide therapy.

Keywords: CRBN, Multiple myeloma, Thalidomide, Mitochondria

P09-11

Induction of FABP by fatty acid is crucial for switching on HIF-driven lipid accumulation and cell growth in hepatocellular carcinoma

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As a hallmark of cancer malignancy, reprogramming of lipid metabolism is currently rising since lipid metabolic abnormalities in cancer are distinguished from normal cells. Increasing demands for rapid growth even under harsh cancer microenvironment, cancer cell alters increasing uptake of exogenous fatty acid and accumulation of lipid droplets, and decreasing beta-oxidation. Previous researches focused on metabolic changes mediated by Hypoxia Inducible Factor-1 (HIF-1) have been discussed intensively, however, its precise mechanism in reprogramming of lipid metabolism is to be fully clarified. Here, we report that a novel HIF-1 binding partner, Fatty acid binding protein (FABP), is required for switching on reprogramming of lipid metabolism through reinforcing HIF-1 function. Mechanistically, we demonstrate that FABP binds to N-terminal of HIF-1 and enhances HIF-1 activity. Furthermore, treatment of fatty acid triggers FABP gene expression and sequentially activates HIF-1 function in hepatocellular carcinoma (HCC) cell. Up-regulated FABP under fatty acid enriched condition results in HIF-1-mediated shift toward lipid storage and accelerates HCC cell growth. We utilize bioinformatics analysis and clinical data to confirm FABP and HIF-1 expression in the liver of HCC tissues, and both expressions are up-regulated in HCC patients and positively correlated. Finally, we demonstrate that Fatty acid/FABP/HIF-1 axis facilitates HCC proliferation using colony forma-

tion and three-dimensional culture. Our findings suggest important roles of fatty acid induced FABP/HIF-1 signaling pathway on lipid accumulation and proliferation in HCC, and this axis might be a potential therapeutic target for metabolism related development of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, Lipid metabolism, Cancer progression, Hypoxia inducible Factor-1

P09-12

The role of K_v3 channels in regulating epithelial mesenchymal transition

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Epithelial mesenchymal transition (EMT) is closely related to cancer progression, which is demonstrated to alter cell adhesion and cell motility. Recently, it has been suggested that ion channels, including voltage-gated potassium (K_v) channels are also involved in a consequence of EMT. In the present study, we used HeLa and canine breast cancer cells, CHMp, to investigate the involvement of K_v3 channels in the EMT processes. We found that treatment with blood depressing substance II (BDS), which is a specific K_v3 subfamily blocker, decreased the protein expressions of vimentin and N-cadherin, mesenchymal cell markers. In addition, BDS inhibited cancer cell migration. Blocking K_v3 subfamily by BDS down-regulated of phospho-Akt S473 and up-regulated of PTEN. These results suggest that blockade of K_v3 using BDS induced reversed EMT through Akt pathway in HeLa and CHMp cells. Future research is needed to elucidate the specific mechanisms governing the relationship between K_v3 and EMT.

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Keywords: K_v3 channels, EMT, BDS, Akt pathway

P09-13

Evaluation of functional integrity of human dopaminergic organoid iPSC neurons with electro physiological methods

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Despite significant advance in medical science and treatment still some *diseases* remain incurable. Especially, neurological diseases are not curable with conventional medical treatment. Therefore, it is necessary to develop new ways to treat those diseases. Recent progress in human stem cell research present new vison for treatment incurable neurological diseases especially for Parkinson's disease (PD). PD is a long-term degenerative disorder of the central nervous system and mainly affects the motor system. PD is caused by a loss of neurons in the substantia nigra that produce a neurotransmitter dopamine. Hence it is expected that therapeutic transplants of the human induced *pluripotent stem cells (*iPSC) to PD patient may improve PD symptoms. Recent reports show that transplant of dopaminergic iPSC cell improved movement in the PD model animals. Despite inspiring animal trial, human iPSC cell transplantation requires more solid basic research to obtain necessary safety and assure efficacy. To do that many research groups cultivate human iPSC cells and test it's potently to make functioning dopaminergic neurons. In this presentation we present recent our work on two different types of dopaminergic iPSC cells (from PD neurons and normal cells). We tested whether those neurons have basic properties of neurons. In this experiments we measured resting membrane potential and evaluated whether these neurons have basic property of functioning neurons by estimate presence of spontaneous synaptic responses, action potentials.

Acknowledgement: This research was supported by a grant form National Institute of Food and Drug Safety Evaluation

Keywords: Stem cell, Parkinson's disease, Induced *pluripotent stem cells (*iPSC), Electro physiology

P09-14

CR6-interacting factor 1 deficiency induces vascular senescence through SIRT3 inhibition in endothelial cells

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Vascular endothelial cell senescence is an important cause of cardiac-related diseases. Mitochondrial reactive oxygen species (mtROS) has been implicated in cellular senescence and multiple cardiovascular disorders. CR6 interacting factor (CRIF1) deficiency increased mtROS via impairing mitochondrial oxidative phosphorylation; however, the mechanisms by which mtROS regulate vascular endothelial cell senescence has not been thoroughly explored. The aim of this study is to investigate whether CRIF1 deficiency could accelerate endothelial cell senescence and attempt to elucidate the underlying mechanism. We observed that CRIF1 deficiency increased the activity of senescence-associated β-galactosidase (SA-β-gal) and the protein expression of p53 phosphorylation, p21 and p16. CRIF1 deficiency exerted the senescence effect by reducing the expression of Sirtuin 3 (SIRT3) through the degradation of transcription factor PGC1α and NRF2 expression by ubiquitination. CRIF1 downregulation also destroyed the function of mitochondrial antioxidant enzymes (manganese superoxide dismutase (MnSOD), Foxo3a, nicotinamide-adenine dinucleotide phosphate, glutathione) by decreased SIRT3 expression. Interestingly, overexpression of SIRT3 in CRIF1 deficient endothelial cells not only reduced mtROS levels by elevating antioxidant enzyme MnSOD, but lessened the expression of cell senescence markers. In conclusion, these results suggest that CRIF1 deficiency induces vascular endothelial cell senescence through suppressing SIRT3 generation, which was destroyed by inhibiting transcription coactivators PGC1α and NRF2 expression.

Keywords: CRIF1, mtROS, SIRT3, MnSOD, Senescence, PGC1α, NRF2

P09-15

Dopamine D2 blockade inhibits cell growth of neuroblastoma cell lines in vitro and in vivo.

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Neuroblastoma (NB) is the most common extra-cranial pediatric solid tumor in early childhood, develops from immature nerve cells found in several areas of the body. High risk of NB is difficult to treat due to the lack of response to current therapies and aggressive disease progression. Haloperidol is a typical antipsychotic medicine that is widely used in the treatment of schizophrenia. It exhibits high affinity dopamine D2 receptor (DRD2) antagonism. Some of neuroblastoma cell lines have dopamine D2 receptor expression, but not in all of them also. However, the relationship between D2R expression and cell death mechanisms remains to be unrevealed yet. This study focuses on investigating effect of haloperidol in NB, how to induce neuronal toxicity through the dopaminergic pathway. We performed RT-PCR to analyze DRD2 gene expression levels in SK-N-BE(2), SK-N-SH,

and SH-SY5Y cell lines. We checked that SK-N-BE(2) cells have more high expression of DRD2 gene than other cells. With different concentrations of haloperidol, apoptotic cell death was measured using MTT assay in three cell lines. Treatment with L741,626, a selective D2R antagonist, caused more increased cell death in three cell lines. In conclusion, we found that DRD2 blockade with haloperidol or L741,626 induced apoptosis but also autophagic flux inhibition. These findings suggest that DRD2 blockade can induce cell death of dopamine D2 upregulated neuroblastoma and it may be good alternatives for treatment of neuroblastoma.

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Keywords: Neuroblastoma, Haloperidol, Dopamine receptor D2, Apoptosis, Autophagy

P09-16

Internalization and transportation of endothelial cell surface K_{Ca}2.3 and K_{Ca}3.1 in normal pregnancy and preeclampsia

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Altered redox state modulates the expression levels of endothelial K_{Ca}2.3 and K_{Ca}3.1 (K_{Ca}s) in normal pregnancy (NP) and preeclampsia (PE), thereby regulating vascular contractility. The mechanisms underlying K_{Ca}s endocytosis and transportation remain unknown. We investigated the regulation of K_{Ca}s expression in plasma membrane (PM) during NP and PE. Cultured human uterine artery endothelial cells were incubated in serum from normal non-pregnant women and women with NP or PE, or in oxidized LDL-, or lysophosphatidylcholine (LPC)-containing medium for 24 h. NP serum elevated PM levels of K_{Ca}s and reduced caveolin-1 and clathrin levels. PE serum, oxidized LDL, or LPC reduced PM levels of K_{Ca}s, and elevated caveolin-1, clathrin, Rab5c and early endosome antigen-1 (EEA1) levels. Reduced K_{Ca}s levels by PE serum or LPC were reversed by siRNA-mediated inhibition of caveolin-1, clathrin or EEA1. Catalase and glutathione peroxidase 1 (GPX1) knock-down elevated PM-localized K_{Ca}s levels, and reduced caveolin-1 and clathrin levels. Elevated K_{Ca}2.3 levels upon catalase and GPX1 knock-down were reversed by PEG-catalase treatment. An H_2O_2 donor reduced clathrin and Rab5c. In contrast, elevated clathrin, caveolin-1, or co-localization of caveolin-1 with K_{Ca}3.1 by PE serum or LPC was reversed by NADPH oxidase inhibitors or antioxidants. A superoxide donor xanthine+xanthine oxidase elevated caveolin-1 or Rab5c levels. We concluded that K_{Ca}s are endocytosed in a caveolae- or a clathrin-dependent manner and transported in a Rab5c- and EEA1-dependent manner during pregnancy. The endocytosis and transportation processes may slow down via H_2O_2-mediated pathways in NP and may be accelerated via superoxide-mediated pathways in PE.

Keywords: Ca^{2+}-activated K^+ channel, internalization and transportation, redox state, normal pregnancy and preeclampsia

P09-17

Differential effect of PML on OSM-induced STAT-3 activity depending on p53 status

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A single promyelocytic leukemia (*PML*) gene, through alternative splicing of exons 4-9 in its C-terminal regions, generates several PML isoforms that can interact with specific partners and perform distinct functions. The PML protein is a tumor suppressor that plays important roles in the apoptosis, cytokine signaling, and senescence by interacting with various proteins. Herein, we investigated the effect of the PML on oncostatin M (OSM)-mediated STAT-3 transcriptional activity. Interestingly, PML influenced OSM-induced STAT-3 activity in a cell type-specific manner, which was dependent on p53 status of the cells but regardless of PML isoforms. Overexpression of PML exerted opposite effects on OSM-induced STAT-3 activity in p53 wild-type and mutant cells. Specifically, overexpression of PML decreased OSM-induced STAT-3 transcriptional activity in the cell lines bearing wild-type p53 (NIH3T3 and U87-MG cells), whereas overexpression of PML in mutant p53-bearing cell lines (HEK293T and U251-MG cells) increased OSM-induced STAT-3 transcriptional activity. When cells bearing wild-type p53 were co-transfected with PML-IV and R273H-p53 mutant, OSM-induced STAT-3 transcriptional activity was significantly enhanced, compared to that of cells which were transfected with PML-IV alone; however, when mutant p53 cells were co-transfected with PML-IV and wild-type p53, OSM-induced STAT-3 transcriptional activity was significantly decreased, compared to that of transfected cells with PML-IV alone. In conclusion, PML acts together with wild-type or mutant p53 and influences OSM-mediated STAT-3 activity in a negative or positive manner, resulting in the aberrant activation of STAT-3 in cancer cells bearing mutant p53 probably might occur through the interaction of mutant p53 with PML.

Keywords: PML, p53, STAT-3, Transcriptional activity

P09-18

Ursolic acid plus paclitaxel induced anti-cancer efficacy through Akt/FOXM1 signaling cascade in esophageal cancer cells

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The present study is performed to detect the combined anticancer ability of UA and paclitaxel in esophageal cancer. 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. UA plus paclitaxel treatment significantly inhibited the invasion and metastasis of TE-12 and TE-8 cells. In addition, combination treatment increased the protein levels of p-Akt and decreased FOXM1 in ESCC cells. These results suggest that UA effectively potentiates the efficacy of chemotherapeutic agents such as paclitaxel via inhibition of proliferation and metastasis by inactivation of FOXM1 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.

Keywords: Ursolic acid, Esophageal squamous cell carcinoma, Apoptosis, FOXM1

P09-19

UA plus 3,3-diindolyl-methane enhanced anti-tumor activity in esophageal cancer cells

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To determine whether UA induced the anticancer efficacy of DIM in esophageal squamous cancer cells (ESCC) ,the present study was performed by using TE-12 and TE-8 cell lines . Treatment with UA plus DIM

suppressed the cell viability and cell proliferation more markedly compared to single reagent treatment. Treatment with UA plus DIM considerably induced apoptosis as indicated by increased levels of cleaved PARP with cleaved caspase-9 protein and subG1 phase. UA plus DIM treatment inhibited the metastasis. FACS analysis showed that the percentage of cells in the G1/S phase was dramatically increased in combination treatment. Decreased CDK4, CDK6 and cyclin D1 were observed, while Akt activation was suppressed by combination treatment with UA and DIM. In addition, combination treatment regulated the Hippo pathway by enhancing the dephosphorylation of MST1 and MST1, resulting in induced phosphorylation of Mob1 but reduced Yes-associated protein (YAP). Moreover, combination treatment markedly increased the protein level of Rassf1 compare to single agent treatment. These results suggest that combination treatment effectively potentiates the anti-tumor effect via inhibition of proliferation and induced apoptosis by activation of hippo signaling pathway in ESCC cells. Taken together, UA plus DIM enhances the therapeutic efficacy in esophageal cancer cell compare with treatment with UA or DIM alone.

Keywords: Ursolic acid, 3,3-diindolylmethane, Esophageal squamous cell carcinoma, Apoptosis, Hippo signaling pathway,

P09-20

Combined treatment of 3,3-diindolylmethane and 5-fluorouracil leads to apoptosis of gastric cancer cells

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Gastric cancer is the fifth most common cancer and the third leading cause of cancer deaths worldwide. Current treatments for gastric cancer have many limitations, and therefore development of new therapy is needed. Thus, our study was aimed to explore whether DIM potentiates chemotherapeutic agents induced apoptosis of gastric cancer cells and investigate the possible mechanisms of this process. 3'-Diindolylmethane (DIM), a component of cruciferous vegetables, have been shown to protect against various types of cancer. However, very rarely have non-traditional agents been used with more traditional chemotherapies to study their effect.5-Fluorouracil (5-Fu) has been one of the most frequently used first-line treatment for patients with advanced GC. Combination treatment with DIM and 5-FU significantly and dose-dependently inhibited the proliferation of SNU638 and SNU484 cells when compared to treatment with DIM or 5-FU alone. The results of colony formation assay show that the number of colonies were significantly decreased by combined treatment.Annexin V results also revealed that DIM combined with 5-FU significantly induces dose-dependent apoptosis in both the cells. In addition, DIM combined with 5-FU significantly induce apoptosis in vitro through enhancing cleavage of caspase-9 and cleaved polyADP-ribose polymerase (PARP). Caspase-9 and PARP were downregulated in gastric cancer cells by combination treatment with DIM and 5-FU. Therefore, the combined treatment of DIM and 5-FU suggests that it is much more effective in treating gastric cancer cells than administration alone.

Keywords: 3'-Diindolylmethane, 5-Fluorouracil, gastric carcinoma, Apoptosis

P09-21

Panobinostat inhibit gastric cancer cells through cell cycle arrest

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Panobinostat (LBH-589, Novartis) is a pan-HDAC inhibitor approved by FDA for multiple myeloma. The clinical and pre-clinical tries of Panobinostat on various cancer have been attempted. Gastric cancer is the second leading cause of cancer-related deaths worldwide. Despite the significant progress made in gastric cancer chemotherapy, the advanced disease remains incurable and novel chemotherapies are needed. The purpose of this experiment was to investigate the functional role of panobinostat in gastric cancer cells. panobinostat significantly inhibited cell viability and proliferation of SNU484 and SNU638 cells in a dose-dependent manner. panobinostat induced apoptosis as indicated by increased protein levels of cleaved-poly ADP-ribose polymerase (PARP), cleaved-caspase 3 and cleaved-caspase9 in SNU484 and SNU638 cells. Statistical analyses of gene expression data from panobinostat treated cells revealed that 2814 genes were significantly up-regulated, while 1788 genes were down-regulated in SNU484 cells. Putative canonical pathways showed that ATM signaling and G2/M DNA damage checkpoint genes were significantly altered by panobinostat treatment. panobinostat inhibited the protein levels of MMP9 and uPA, and increased the protein levels of E-cadherin in SNU484 and SNU638 cells, suggesting suppressed the metastasis of gastric cancer cells. In addition, panobinostat diminished the gastric tumor size in a xenograft animal mouse models. Therefore, our present study suggests that panobinostat inhibits proliferation and metastasis of gastric cancer cells by induce cell apoptosis through G2/M cell cycle DNA damage regulation.

Keywords: Panobinostat, Gastric cancer cells, Apoptosis, Gene expression profiling, Cell cycle

P09-22

Anti-cancer effect of SIRT6 in hepatocellular carcinoma

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Liver cancer is the leading cause of cancer-related deaths worldwide and its incidence is increasing. SIRT6 (sirtuin 6) is a member of sirtuin family of NAD+-dependent enzymes and plays a key role in DNA repair, telomere maintenance, aging, tumor suppression and cellular metabolic processes. Several recent studies reported that SIRT6 functions as a tumor suppressor. In this study, we investigated the role of SIRT6 in hepatocellular carcinoma cell line, HepG2 and SNU449. SIRT6 was highly expressed in human HCC cells. Overexpression of SIRT6 significantly suppressed the viability of HCC cells whereas silencing of SIRT6 stimulated the viability of HCC cells. Overexpression of SIRT6 increased expression of cleaved-PARP and cleaved-caspase9 and decreased the PARP, caspase9, and caspase3. Knockdown of SIRT6 increased the number and size 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 in a time dependent manner. Moreover, overexpression of SIRT6 inhibited vimentin, UPA, and MMP9 protein levels while silencing of SIRT6 in HCC cells increased the protein levels of vimentin, UPA, and MMP9. P-β-catenin levels was increased by overexpression of SIRT6 and was decreased by silencing of SIRT6. In vitro, knockdown of SIRT6 significantly promoted the tumor growth. Therefore, SIRT6 suppresses the proliferation, invasion and metastasis of HCC cells and may play as a tumor suppressor in HCC cells.

Keywords: SIRT6, Hepatocellular carcinoma cells, Metastasis, Cell proliferation, β-catenin

P09-23

Recombinant human BMP-2 suppresses the proliferation of Human colorectal cancer cells by activation of Hippo signaling

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In spite of that the use of recombinant human bone morphogenetic protein (rhBMP)-2 has been debated during the past decade due to its oncogenic characteristics. However, the safety issues of rhBMP-2 usage and its underlying molecular mechanism remain poorly understood. In this study, we investigated the effect of rhBMP-2 and its signaling pathways involved in colorectal cancer cell using HT-29 and HCT116 cells. RhBMP-2 significantly inhibited proliferation of CRC cells in dose-dependent way by MTT assay. Cell cycle arrest in G1 phase was induced at 24h after rhBMP-2 treatment. RhBMP-2 also stimulated Smad4, p53 and p21 levels, and reduced cyclin D1, cyclin-dependent kinase (CDK) 4 and CDK6 activities. On the other hand, rhBMP-2 treatment resulted in reduced protein expression levels of poly (ADP-ribose) polymerase (PARP) and caspase-9 whereas those of cleaved PARP and cleaved caspase-9 were significantly increased in CRC cells. In addition, rhBMP-2 increased MST1, MST2, Mob1, p-Mob1, Sav1, and p-YAP protein levels. Therefore, our results indicate that rhBMP-2 suppresses colorectal cell proliferation which is mediated via inactivation of hippo signaling pathway. Therefore, targeting BMP-2 may constitute a potential therapeutic strategy for human colorectal cancer.

Keywords: Colorectal cancer, rhBMP-2, Hippo signaling pathway, Apoptosis, Cell cycle

P09-24

Knockdown of hematopoietic- and neurologic-expressed 1 induces autophagy in colorectal cancer

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Colorectal cancer is one of the most common leading causes of cancer death worldwide and the incidence of colorectal cancer is increasing dramatically in Asian countries including South Korea. Previous studies demonstrated that the hematopoietic- and neurologic-expressed sequence 1 (HN1) is strongly associated with survival of cancer patients and its depletion leads to cell cycle arrest in several cancer cells. Although it has been reported that HN1 is overexpressed in various cancers, the specific functional significance of HN1 in colorectal cancer cells remains largely unknown. In our present study, we investigated the underlying molecular mechanisms by which HN1 regulates proliferation, metastasis, apoptosis and autophagy in colorectal cancer cells. Knockdown of HN1 significantly decreased the viability of colorectal cancer cells, inducing G1 cell cycle arrest and apoptosis. In addition, knockdown of HN1 inhibited the invasion and metastasis of colorectal cancer cells. Moreover, downregulation of HN1 induced autophagy. On the other hand, overexpression of HN1 promoted CRC cell proliferation, metastasis and inhibited autophagy. Furthermore, EGF treatment to CRC cells induced HN1 expression. Knockdown of HN1 on EGF treated cells counteracted the effects of EGF induction. Therefore, our results suggest that HN1 regulates growth, metastasis, apoptosis and autophagy of colorectal cancer cells and targeting HN1 may constitute a therapeutic strategy for colorectal cancer.

Keywords: Colorectal cancer, HN1, Proliferation, Metastasis, Autophagy

P09-25

Effects of ursodeoxycholic acid on lipopolysaccharide-stimulated signals in biliary epithelial cells (BECs)

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Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid extracted from bile and has a wide range of biological functions. Lipid polysaccharides (LPS) promote epithelial-mesenchymal metastasis (EMT) in biliary epithelial cells (BEC). EMT is known to play an important role in biliary fibrosis. Currently, UDCA has been approved as a primary biliary cirrhosis (PBC) drug to have a beneficial effect on hepatocytes and liver damage, and has been proposed as a treatment for biliary identity liver disease. This study examined the effect of UDCA on LPS stimulus signals in BEC. At the protein level, changes in LPS stimulated Toll-like receptor-4 (TLR4) were reduced by applying UDCA. LPS induced phosphorylation of JNK and p38, which was further potetiated by UDCA application. In cell cycle analysis, LPS-induced BEC was arrested at G0/G1 phase by UDCA. Depolarization of the mitochondrial membrane potential was suppressed compared to the control when five passages were performed at low UDCA concentrations. Taken together, UDCA was found to be involved in the inhibition of LPS-induced TLR4, potentiation of LPS-induced JNK phosphorylation, cell cycle arrest and mitochondrial depolarization inhibition. These results suggest that UDCA may be a potential drug that modulates LPS-simulated signals and prevents biliary fibrosis in BEC.

Keywords: Ursodeoxycholic acid, Lipopolysaccharide, JNK, Biliary epithelial cells

P09-26

ATP binding cassette transporter A1 is involved in extracellular secretion of acetylated APE1/Ref-1

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Acetylation of nuclear apurinic/apyrimidinic endonuclease-1/redox factor-1 (APE1/Ref-1) is associated with its extracellular secretion, despite the lack of an N-terminal protein secretion signal. In this study, we investigated plasma membrane targeting and translocation of APE1/Ref-1 in HEK293T cells with enhanced acetylation. While APE1/Ref-1 targeting was not affected by inhibition of the endoplasmic reticulum/Golgi-dependent secretion, its secretion was reduced by inhibitors of ATP-binding cassette (ABC) transporters, and siRNA-mediated down- regulation of ABC transporter A1. The association between APE1/Ref-1 and ABCA1 transporter was confirmed by proximal ligation assay and immunoprecipitation experiments. An APE1/Ref-1 construct with mutated acetylation sites (K6/K7R) showed reduced co-localization with ABC transporter A1. Exposure of trichostatin A (TSA) induced the acetylation of APE1/Ref-1, which translocated into membrane fraction. Taken together, acetylation of APE1/Ref-1 is considered to be necessary for its extracellular targeting via non-classical secretory pathway using the ABCA1 transporter.

Keywords: APE1/Ref-1, Acetylation, Secretion, Non-classical pathway, ABCA1 transporter

P09-27

Recombinant Ac-APE1/Ref-1 induces apoptotic cell death in hyperacetylated TNBC cells

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Triple-negative breast cancer (TNBC) represents a relatively small proportion of all BCs but a relatively large proportion of BC-related death. Thus, more effective therapeutic strategies are needed for the management of TNBC. APE1/Ref-1 is a multifunctional protein involved in DNA repair that controls transcription factor activity based on its redox status. The expression status of this protein is altered in numerous cancers, including prostate, lung, colon, and ovarian tumors, and elevated APE1/Ref-1 level in cancer cells have been targeted to increase susceptibility to both radiation and chemotherapy in vivo and in vitro. previously study, we demonstrated that the stimulation of apoptosis by the binding of secreted acetylated-Ac-APE1/Ref-1(Ac-APE1/Ref-1) to RAGE was essential for TNBC cell death in response to hyperacetylation. The aim of the present study was to assess the potential therapeutic efficacy of recombinant Ac-APE1/Ref-1 proteins in TNBC. The treatment of MDA-MB-231 cells with recombinant human Ac-APE1/Ref-1 (rh Ac-APE1/Ref-1) markedly decreased cell viability compared to rh Ac-APE1/Ref-1-treated cells even in hyperacetylation. Consistent with the cell viability results, the cytoplasmic histone-associated DNA fragmentation induced by exposure to rh Ac-APE1/Ref-1 was significantly increased. Similar to findings in MDA-MB-231 cells, the treatment with rh Ac-APE1/Ref-1 also caused decreased viability and increased apoptosis in other hyperacetylated MDA-MB-468 and BT-549 cells with up-regulated RAGE. We found that clearly demonstrate that rh Ac-APE1/Ref-1 possesses potent chemotherapeutic efficacy against hyperacetylated TNBCs based on stimulation of cell death by RAGE dependent triggering of Ac-APE1/Ref-1.

Keywords: Triple-negative breast cancer, APE1/Ref-1, Acetylation, Apoptosis

P09-28

Effect of histone deacetylase inhibitors on differentiation of human bone marrow-derived stem cells into neuron-like cells

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Mesenchymal stem cells (MSCs) are known to differentiate into multiple lineages, making neurogenic differentiation an important target in the clinical field. In the present study, we induced the neurogenic differentiation of the cells using histone deacetylase (HDAC) inhibitors and studied their mechanisms for further differentiation *in vitro*. We treated cells with the HDAC inhibitors, MS-275 and NaB; and found that the cells had neuron-like features such as distinct bipolar or multipolar morphologies with branched processes. The mRNA expressions encoding for *NEFL*, *MAP2*, *TUJ1*, and *OLIG2* was significantly increased following HDAC inhibitors treatment compared to without HDAC inhibitors; high protein levels of MAP2 and Tuj1 were detected by immunofluorescence staining. The expression of ion channel-related genes, such *as NE-Na* and *KCNA4 w*as highly increased with MS-275 or NaB treatment; *SCN5A, KCNH2,* and *CACNA1G* expressions were increased only MS-275. The expression of others was either decreased or unchanged. We examined the mechanisms of differentiation and found that the Wnt signaling pathway and downstream mitogen-activate protein kinase were involved in neurogenic differentiation of MSCs. Importantly, Wnt4, Wnt5a/b, and Wnt11 protein levels were highly increased after treatment with NaB; signals were activated through the regulation of Dvl2 and Dvl3. Interestingly, NaB treatment increased the levels of JNK and upregulated JNK phosphorylation. After MS-275 treatment, Wnt protein levels were decreased and GSK-3β was phosphorylated. In this cell, HDAC inhibitors controlled the non-canonical Wnt expression by activating JNK phosphorylation and the canonical Wnt signaling by targeting GSK-3β.

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Keywords: Glycogen synthase kinase 3, Histone deacetylase inhibitors, Mesenchymal stem cells, Wnt signaling pathway, Cell differentiation

P09-29

The APE1/Ref-1 inhibits vascular calcification and loss of the smooth muscle phenotype in vascular smooth muscle cells

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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. We observed that Pi decreased endogenous APE1/Ref-1 expression and promoter activity in VSMCs, and that adenoviral overexpression of APE1/Ref-1 inhibited Pi-induced calcification in VSMCs and in an ex vivo organ culture of a rat aorta. However, a redox mutant of APE1/Ref-1(C65A/C93A) did not reduce Pi-induced calcification in VSMCs, suggesting APE1/Ref-1-mediated redox function against vascular calcification. Additionally, APE1/Ref-1 overexpression inhibited Pi-induced intracellular and mitochondrial reactive oxygen species production, and APE1/Ref-1 overexpression resulted in decreased Pi-induced lactate dehydrogenase activity, pro-apoptotic Bax levels, and increased anti-apoptotic Bcl-2 protein levels. Furthermore, APE1/Ref-1 inhibited Pi-induced osteoblastic differentiation associated with alkaline phosphatase activity and inhibited Pi-exposure-induced loss of the smooth muscle phenotype. Our findings provided valuable insights into the redox function of APE1/Ref-1 in preventing Pi-induced VSMC calcification by inhibiting oxidative stress and osteoblastic differentiation, resulting in prevention of altered osteoblastic phenotypes in VSMCs.

Keywords: APE1/Ref-1, Vascular calcification, Smooth Muscle Phenotype, Vascular smooth muscle cells

P09-30

HB-EGF mediates A549 cell migration

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Macrophage is known to be involved in cancer progression, migration and invasion. In this study, we found that macrophage-induced HB-EGF increased migration in A549 cells. HB-EGF is known to function by ectodomain shedding by metalloprotease. We observed on increase in HB-EGF at the mRNA level by macrophage conditioned media. However, the protein expression of HB-EGF was reduced because of the increased cleavage of HB-EGF. We confirmed that the secretion of HB-EGF was increased by ELISA, and the protein expression was increased by treatment with TAPI-1, a

metalloprotease blocker. We used siRNA for gene knockdown of HB-EGF to investigate whether HB-EGF is associated with cell migration. We also used miR-17, known to be upstream of HB-EGF. Transfection of miR-17 mimic resulted in a decrease in HB-EGF protein. In addition, migration was observed after transfection of miR-17 mimic to investigate the correlation between miR-17 and cell migration. After transfection of miR-17 mimic, migration was reduced in A549 cells. In this study, we found that HB-EGF is related to the increase in migration by macrophage in A549 cells.

P10-01

Resistance exercise in the heart of diabetic rats improves cardiac function and mitochondrial efficiency

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Metabolic disturbance and mitochondrial dysfunction are a hallmark of diabetic cardiomyopathy (DC). Resistance exercise (RE) not only enhances the condition of healthy individuals but could also improve the status of those with disease. However, the beneficial effects of RE in the prevention of DC and mitochondrial dysfunction are uncertain. Therefore, this study investigated whether RE attenuates DC by improving mitochondrial function using an in vivo rat model of diabetes. Fourteen Otsuka Long-Evans Tokushima Fatty rats were assigned to sedentary control (SC, n = 7) and RE (n = 7) groups at 28 weeks of age. Long-Evans Tokushima Otsuka rats were used as the non-diabetic control. The RE rats were trained by 20 repetitions of climbing a ladder 5 days per week. RE rats exhibited higher glucose uptake and lower lipid profiles, indicating changes in energy metabolism. RE rats significantly increased the ejection fraction and fractional shortening compared with the SC rats. Isolated mitochondria in RE rats showed increase in mitochondrial numbers, which were accompanied by higher expression of mitochondrial biogenesis proteins such as proliferator-activated receptor-γ coactivator-1α and TFAM. Moreover, RE rats reduced proton leakage and reactive oxygen species production, with higher membrane potential. These results were accompanied by higher superoxide dismutase 2 and lower uncoupling protein 2 (UCP2) and UCP3 levels in RE rats. These data suggest that RE is effective at ameliorating DC by improving mitochondrial function, which may contribute to the maintenance of diabetic cardiac contractility.

Keywords: Diabetic cardiomyopathy, Resistance exercise, Cardiac function, Mitochondrial function

P10-02

Aerobic exercise training decreases hepatic asprosin in diabetic rats

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Asprosin, a novel hormone released from white adipose tissue, regulates hepatic glucose metabolism and is pathologically elevated in the presence of insulin resistance. It is unknown whether aerobic exercise training affects asprosin levels in type 1 diabetes mellitus (T1DM). The aim of this study was to determine whether (1) aerobic exercise training could decrease asprosin levels in the liver of streptozotocin (STZ)-induced diabetic rats and (2) the reduction in asprosin levels could induce asprosin-dependent downstream pathways. Five-week-old male Sprague-Dawley rats were randomly divided into control, STZ-induced diabetes (STZ), and STZ with aerobic exercise training groups (n = 6/group). T1DM was induced by a single dose of STZ (65 mg/kg intraperitoneally (i.p.)). The exercise group was made to run on a treadmill for 60 min at a speed of 20 m/min, 4 days per week for 8 weeks. Aerobic exercise training reduced the protein levels of asprosin, PKA, and TGF-β but increased those of AMPK, Akt, PGC-1β, and MnSOD. These results suggest that aerobic exercise training affects hepatic asprosin-dependent PKA/TGF-β and AMPK downstream pathways in T1DM.

Keywords: AMPK, PKA, TGF-β, Aerobic exercise, Asprosin, Liver, Type 1 diabetes

P11-01

Effects of virtual inhibition of Na^+/Ca^{2+} exchanger on the pacemaker mechanisms in the computational model of human sinoatrial cell; a case of pre-med students' research program in SNU

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Sinoatrial nodal cells (SANCs) initiate the heartbeat, and their pacemaker mechanism have been intensively studied. A widely accepted model ascribe the pacemaker potential to the interaction of various voltage-dependent channels includinge the funny current (I_f), called 'membrane clock theory'. In addition, periodic oscillations of $[Ca^{2+}]_i$ and associated changes of the electrogenic Na^+/Ca^{2+} exchanger (NCX) has been proposed, namely 'Ca^{2+} clock theory'. The bidirectional activity of NCX could functionally couple the two models via dynamic fluctuation of the subsarcolemmal Ca^{2+} ($[Ca^{2+}]_{sl}$). Here, by using a computational model of human SANC (Fabri et al., 2015), we examined the effects of virtual changes of NCX activity, i.e. functional expression, on the pacemaker properties and the secondary changes of relevant ionic currents. Decrease of NCX by 80% initially lowered the rate of diastolic depolarization (DD), especially at the late period of DD, which was consistent with the suggested role of NCX in the Ca^{2+} clock theory. Unexpectedly, the amplitude of action potential (AP) was also decreased. Further investigation of L-type Ca^{2+} channel ($VOCC_L$) activity suggested that the augmented Ca^{2+}-dependent inactivation of the $VOCC_L$ was induced by the increased $[Ca^{2+}]_{sl}$ due to the NCX inhibition. The virtual experiments of using computational physiological model was very helpful for the deep understanding of cardiac electrophysiology, even at the period of premedicine course.

Keywords: Sinoatrial nodal cells, Na^+/Ca^{2+} exchanger, Premedicine course, Medical education

P11-02

A computational study on the interatrial difference of rat in the arrhythmogenicity on sympathetic stimulation

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The incidence of arrhythmias and vulnerability to sympathetic stimulation is different between the left and right atrium. The incidence of arrhythmias including delayed afterdepolarization (DAD) and triggered activity (TA) on β-adrenergic stimulation is higher in right atrial myocytes. As the arrhythmogenicity depends on both the membrane excitation and intracellular Ca^{2+}-dynamics, the ion channel profile, and development of t-tubule and sarcoplasmic reticulum (SR) may be the key determinants for the interatrial difference. In order to explain the interatrial difference, computational models of left and right rat atrial myocytes were developed. Models of L-type Ca^{2+} channels (LTCCs) and outward K^+ currents of left and right atrial myocytes were constructed based on patch-clamp recordings and were incorporated into the computational models of rat atrial myocytes. The relative density of LTCCs on the junctional SR was assumed to be lower in the right atrial myocytes. The reconstructed computational models of rat atrial myocytes successfully reproduced the interatrial difference in the shape of the action potential in unstimulated condition. Action potential duration was shorter in right atrial myocytes. β-adrenergic stimulation was assumed to increase the intracellular protein kinase A (PKA) and shift the voltage-dependence of activation in LTCCs. The incidence of DAD and TA on β-adrenergic stimulation was higher in the computational model of right atrial myocytes than that of left atrial myocytes. As the t-tubule is essential for the excitation-contraction coupling, the detubulation procedure may reduce the incidence of arrhythmias on adrenergic stimulation. Indeed, both the detubulation procedure of rat atrial myocytes and simulation of detubulation in computational models inhibited the incidence of DAD and TA. These results indicate that the different profile of ion channels and Ca^{2+}-release machinery could explain the interatrial difference in arrhythmogenicity on β-adrenergic stimulation as well as the shape of the action potential in unstimulated rat heart.

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Keywords: Atrial arrhythmias, Delayed afterdepolarization, Computational model, Rat atrial myocytes, Adrenergic stimulation

P11-03

Investigation of hemodynamic behavior using computational fluid dynamics in the human coronary arteries

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Coronary artery disease (CAD) is caused by a blockage or narrowing of the artery that supplies blood to the cardiac muscle and is a major cause of heart attack or myocardial infarction. However, since CAD is mostly asymptomatic even if half of the vessels are clogged, early detection or prediction of the stenosis can be essential to help clinicians to make a better diagnostic or therapeutic decision. The prediction of CAD has been doing recently with diverse approaches, and a computer simulation technique using computational fluid dynamics (CFD) is popularly employed. As it is not possible to acquire CT images before the stenotic lesions exist to predict CAD, we developed a 3D structural models for predictive simulation using a retrospective approach in this study. 3D structures of healthy and stenotic models based on CT images were generated, and the stenosis-free model was also reconstructed based on a stenotic model, then the CFD analysis was applied to the structural models. The fundamental parameters (pressure and velocity) and wall shear stress-related parameter were obtained from the analysis. In the results, it is a significant difference in velocity near the stenosis lesions between the healthy and the stenosis-free models with an only geometric difference under the same other conditions. However, the pressure made little difference in all groups. Another significant finding is the difference in the patterns of velocity streamlines between systolic and diastolic phases during the cardiac cycle among the groups. Larger differences in flow patterns may have been caused by disturbed flows that are well known to be associated with the stenosis. These novel findings would be used to predict the initiation and progression of atherosclerotic stenosis in the coronary artery and are also to develop a prediction system for cardiovascular disease in the near future.

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Keywords: Coronary artery, Atherosclerosis, Computational fluid dynamics, Wall shear stress, prediction

P11-04

Teaching cardiac excitation-contraction coupling using a mathematical computer simulation model of human ventricular myocytes

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Understanding excitation-contraction (E-C) coupling of cardiomyocytes and the electrophysiological mechanisms of their characteristic long action potential duration (APD) are the major learning goals in medical physiology. However, the integrative interpretation of the responses simultaneously occurring during the contraction-relaxation cycle is challenging due to the dynamic interaction of underlying factors. Since 2017, we adopted the mathematical computer simulation model of human ventricular myocyte (Cardiac E-C_Sim) hypothesizing that this educational technology may improve students' learning of the cardiac physiology. Here, we describe the overall process for the educational application of 'Cardiac E-C_Sim' in the human physiology practicum of Seoul National University College of Medicine. We also report on the results from questionnaires covering the detailed assessment about practicum class. The analysis of results and feedback opinion enabled us to understand how the students had approached the problem-solving process. As a whole, the students could better accomplish the teaching goals through the practicum using Cardiac E-C_Sim followed by constructive discussions on the complex and dynamic mechanisms of the cardiac E-C coupling. We suggest that the combined approach of lecture-based education and the manual-guided computer simulations with clinical context could be broadly applicable in physiology education.

Keywords: Excitation-contraction coupling, medical education, computer simulation, cardiac physiology

P11-05

Lessons from artificial neural network for studying coding principles of biological neural network

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An individual neuron or neuronal population is conventionally said to be "selective" to a feature of stimulus if they differentially respond to the feature. Also, they are considered to encode certain information if decoding algorithms successfully predict a given stimulus or behavior from the neuronal activity. However, an erroneous assumption about the feature space could mislead the researcher about a neural coding principle. In this study, by simulating several likely scenarios through artificial neural networks (ANNs) and showing corresponding cases of biological neural networks (BNNs), we point out potential biases evoked by unrecognized features i.e., confounding variable. We modeled an ANN classifier with the open-source neural network library Keras, running Tensorflow as backend. The model is composed of five hidden layers, dense connections and rectified linear activation. We added a dropout layer and l2-regularizer on each layer to apply penalties on layer activity during optimization. The model was trained with CIFAR-10 dataset and showed a saturated test set accuracy at about 53%. (the chance level accuracy = 10%) For a stochastic sampling of individual neuron's activity from each deterministic unit, we generated the Gaussian distribution through modeling within-population variability according to each assumption. Using this model, we showed 4 possible misinterpretation cases induced by a missing feature. (1). The researcher can choose the second-best feature which has similarity to ground truth feature. (2). An irrelative feature which correlated with ground truth feature can be chosen. (3). Evaluating decoder in incomplete feature space could result in the overestimation of the performance of the decoder. (4). Misconception about the receptive field of the unit could make a signal to be incorporated in noise. In conclusion, we suggest that the comparative study of ANN and BNN from the perspective of machine learning can be a great strategy for deciphering the neural coding principle.

Keywords: Feature space, Neural coding, Artificial neural network, Deep learning, Biological neural network

P11-06

Long-range projectome from and to the mouse posterior parietal cortex with bioinformatic analysis

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The posterior parietal cortex (PPC) is a major multimodal association cortex implicated in a variety of higher-order cognitive functions, such as visuospatial perception, spatial attention, categorization, and decision-making. In corroboration with this notion, inactivation of the PPC both in human and in non-human primate lead to trouble in sensory integration and movement planning without significant deficits in sensory perception per se. As the evidence-related preparatory neural activity was reported in mouse PPC became an attractive model system to study how the neural correlates of evidence were brought about. However, in spite that many recent works have been performed with the mouse as a model system, systematic analysis of long-range connectivity of mouse PPC is still limited and prevents integrative interpretation of the rapidly accumulating functional data. In the present study, we provide quantitative long-range connectivity from- and to PPC by reanalyzing Allen brain connectivity map and consequently confirmed by neuro-tracers of both directions. Specifically, we conducted a detailed bioinformatic analysis to segregate input/output signal by cortical layers, sub-regions of the PPC, functional/anatomical modalities, or cell-types and experimentally confirmed the major connectivity so as to summarize the organizational principle of the mouse PPC. A comprehensive survey of the reciprocity, topography and bilateral connectivity between the PPC and cortical/subcortical brain areas will provide an important future reference to comprehend the function of the PPC and allow effective paths forward to various studies using mice as a model system. This work will provide a ground truth knowledge on the PPC based on the mouse connectivity data sets, leading to the identification of key input/output regions and organizing principles of the PPC.

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Keywords: Posterior parietal cortex, Long-range connectivity, Decision making center, Bioinformatic analysis

P11-07

Feature selection models for the survival of human pancreatic cancer patients using deep learning algorithms

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Pancreatic duct carcinoma (PDAC) is highly chemo-resistant cancer and is easily invade and spread to other organs. New biomarkers for diagnosis and prognosis prediction are needed because of the heterogeneous molecular profile and low survival rate of PDAC. In this study we developed a prediction model for survival and survival time of PDAC patients based on the gene expression profile. Deep learning algorithms were employed with enriched learning by 6 feature selection (information gain, Chi-squared test, MRMR, Gini index, Relief, Fast Correlation based filter) to develop classification model trained using gene expression data of GEO data set (GSE2OOOO, n=90). A total of 82 genes such as DLEU and NCCRP were selected by feature selections and the 15 genes were duplicated. The models developed were evaluated by attribute verification and independent data set testing. Information gain / deep learning and genie index / deep learning models performed best among the models, with precision, recall, specificity, accuracy, and area under the receiver operating characteristic (auROC) of 100%. The biomarkers and prediction model help to predict the survival of PDAC patients and to understand the molecular mechanism of PDAC progression.

Keywords: Pancreas ductal adenocarcinoma, GEO data, RNA expression, Deep learning

P12-01

Melatonin attenuates cisplatin-induced acute kidney injury through dual suppression of apoptosis and necroptosis

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Melatonin is well known to modulate the sleep–wake cycle. Accumulating evidence suggests that melatonin also has favorable effects such as antioxidant and anti-inflammatory properties in numerous disease models. It has been reported that melatonin has therapeutic effects against cisplatin-induced acute kidney injury (AKI). However, mechanisms underlying the therapeutic action of melatonin on the renal side-effects of cisplatin therapy remain poorly understood. In this study, we showed that melatonin treatment significantly ameliorates cisplatin-induced acute renal failure and histopathological alterations. Increased expression of tubular injury markers was largely reduced by melatonin. Melatonin treatment inhibited caspase-3 activation and apoptotic cell death. Moreover, protein levels of key components of the molecular machinery for necroptosis were decreased by melatonin. Melatonin also attenuated nuclear factor-κB activa-

tion and suppressed expression of pro-inflammatory cytokines. Consistent with *in vivo* findings, melatonin dose-dependently decreased apoptosis and necroptosis in cisplatin-treated mouse renal tubular epithelial cells. Collectively, our findings suggest that melatonin ameliorates cisplatin-induced acute renal failure and structural damages through dual suppression of apoptosis and necroptosis. These results reveal a novel mechanism underlying the therapeutic effect of melatonin against cisplatin-induced AKI and strengthen the idea that melatonin might be a promising therapeutic agent for the renal side-effects of cisplatin therapy.

Keywords: Melatonin, Cisplatin, Acute kidney injury, Apoptosis, Necroptosis

P12-02

CRIF1 deficiency induced p66shc-regulated mitophagy in endothelial cells

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Inhibition of mitochondrial protein CR6 interacting factor 1 (CRIF1) disturbs mitochondrial function, depolarizes membrane potential, and increases reactive oxygen stress (ROS) levels in endothelial cells. Impaired mitochondrial function with oxidative damage is a major contributor to initiate the mitophagy process. We hypothesized that CRIF1 deficiency-induced harmful effect may promote mitophagy and attempted to explore the mechanism in human umbilical vein endothelial cells (HUVECs). Our results showed that CRIF1 downregulation not only increased mitophagy-related markers LC3 (LC3-II/I), PINK1, Parkin but stimulated redox enzyme p66shc expression. Scavenging mitochondrial ROS markedly blunted CRIF1 deficiency-induced increase in p66shc expression. In addition, knockdown of p66shc inhibited the CRIF1 deletion-triggered mitochondrial ROS increase, membrane potential depolarization, and mitochondrial fusion. Since the decreased p66shc alleviates mitochondrial dysfunction, the CRIF1 deficiency-induced mitophagy proteins (LC3 (LC3-II/I), PINK1, Parkin) were also inhibited by p66shc downregulation. These findings suggest that CRIF1 deficiency induced mitophagy process via p66shc-regulated ROS in endothelial cells.

Keywords: CR6 interacting factor 1, Mitochondrial dysfunction, Mitophagy, p66shc, ROS

P12-03

Profiling of remote skeletal muscle gene changes resulting from stimulation of atopic dermatitis disease in NC/Nga mouse model

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Although atopic dermatitis (AD) is known to be a representative skin disorder, it also affects the systemic immune response. In a recent study, myoblasts were shown to be involved in the immune regulation, but the roles of muscle cells in AD are poorly understood. We aimed to identify the relationship between mitochondria and atopy by genome-wide analysis of skeletal muscles in mice. We induced AD-like symptoms using house dust mite (HDM) extract in NC/Nga mice. The transcriptional profiles of the untreated group and HDM-induced AD-like group were analyzed and compared using microarray, differentially expressed gene and functional pathway analyses, and protein interaction network construction. Our microarray analysis demonstrated that immune response-, calcium handling-, and mitochondrial metabolism-related genes were differentially expressed. In the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology pathway analyses, immune response pathways involved in cytokine interaction, nuclear factor-kappa B, and T-cell receptor signaling, calcium handling pathways, and mitochondria metabolism pathways involved in the citrate cycle were significantly upregulated. In protein interaction network analysis, chemokine family-, muscle contraction process-, and immune response-related genes were identified as hub genes with many interactions. In addition, mitochondrial pathways involved in calcium signaling, cardiac muscle contraction, tricarboxylic acid cycle, oxidation-reduction process, and calcium-mediated signaling were significantly stimulated in KEGG and Gene Ontology analyses. Our results provide a comprehensive understanding of the genome-wide transcriptional changes of HDM-induced AD-like symptoms and the indicated genes that could be used as AD clinical biomarkers.

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Keywords: Microarray, Mitochondria, Atopic dermatitis, Skeletal muscle

P12-04

Functional characterization of the bitter taste receptor *Tas2r108*

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The sense of taste provides animals with valuable information about the natural quality and nutritional value of food. The bitter taste of the five basic tastes plays an important role since it may indicate whether a particular food is corrupted and potentially harmful for intake. The bitter taste is sensed by type 2 taste receptors(T2Rs) in the vertebrates. It has been shown that T2Rs are found on extra-oral tissues, including the gut, respiratory system, genitourinary system, brain, and immune cells. Depending on their location expressed, they play different physiological roles and have been shown to be associated with different diseases. For example, T2Rs are expressed on the smooth muscle cells in the airways and agonists of T2Rs relaxed pre-contracted airway smooth muscle and reduced airway resistance in mice. The specific agonists of T2Rs could be used as a medication for asthma symptoms by relaxing the airway and inhibiting airway constriction. These results show that T2Rs are meaningful as new pharmacological targets. We have found that *Tas2r108* of 35 T2rs in mice was the most highly expressed in various exocrine tissues such as salivary glands, lacrimal glands, and pancreas as well as in tongue. *Tas2r108* mRNA expression was demonstrated in submandibular glands through *in situ* hybridization(ISH). ISH results showed that expression levels of *Tas2r108* mRNA in submandibular glands were higher in acinar cells than in ductal cells. The results suggest that *Tas2r108* may play a role in causing saliva secretion to dilute harmful substances rather than altering saliva constituents. To determine whether *Tas2r108* expressed in submandibular glands respond to bitter taste compounds, *Tas2r108* specific agonist should be identified. But *Tas2r108* specific agonist has not yet been identified. We performed calcium imaging using Chinese hamster ovary (CHO) cells. The CHO cells expressing *Tas2r108* and Gα16gust44 were activated by cycloheximide, resulting in the mobilization of intracellular calcium ions. The important study to identify the physiological role of *Tas2r108* is to produce mice lacking *Tas2r108* gene and perform *in vivo* experiments. It is necessary that oral experts should pay attention to taste in order to diagnose and treat the salivary gland diseases closely related to oral diseases.

Keywords: Bitter taste, Submandibular gland, Tas2r108

P12-05

Varying blood glucose level affects atherosclerosis progression in streptozotocin-induced diabetic ApoE knockout mice

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There is a close pathogenic link between diabetes and cardiovascular disease where hyperglycemia plays a major role in the development of diabetic macrovascular complications such as atherosclerosis and restenosis. It has been established that hyperglycemia affects the progression of atherosclerosis. This study aimed to determine the difference in aortic plaque formation when exposed to varying hyperglycemic conditions (200-400mg/dl, 400-600mg/dl and >600mg/dl). Male ApoE knockout mice were fed high fat diet (HFD) for two weeks. Diabetes was induced by daily intraperitoneal injection of 40 mg/kg streptozotocin (STZ) for 5 consecutive days. For the control group, citrate buffer (vehicle) was used. Blood glucose was monitored weekly and mice were grouped based on their corresponding blood glucose level. Mouse were sacrificed five weeks after STZ treatment and whole aorta and aortic root was extracted. *En face* Oil Red O staining and aortic root haematoxylin and eosin staining showed increased plaque progression with increasing glucose concentration. Immunohistochemistry of the aortic root showed increased expression of markers for vascular phenotypic switching such as KLF4 and osteopontin. In conclusion, the degree by which diabetic condition aggravates atherosclerotic plaque progression is highly affected by the glucose concentration and this should be taken into account when using diabetic STZ mice model.

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Keywords: Atherosclerosis, Diabetes, ApoE, Glucose, High fat diet

P12-06

Osteopontin expression of streptozotocin-induced diabetic ApoE knockout mice model

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Osteopontin (OPN) is a matricellular protein that acts as a mediator for multiple biological functions. It is involved in normal physiological processes and implicated in the pathogenesis of several diseases, including atherosclerosis. Osteopontin can interact with many cell types including smooth muscle cells, endothelial cells, and inflammatory cells. Atherosclerosis is a systemic inflammatory disease that causes plaque build-up inside the artery. The aim of this study was to establish a streptozotocin (STZ)-induced diabetic ApoE knockout (ApoE $^{-/-}$) mice model and observe their osteopontin expression for the study of diabetes complications in atherosclerosis. ApoE $^{-/-}$ mice were divided into three groups. Diabetic group (HFD+STZ) were fed with high fat diet (Envigo TD.88137) starting at 5 weeks old and injected with STZ (Sigma S0130) dissolved in 100 mM citrate buffer (pH 4.5) at 40 mg/kg through intra-peritoneal injection for five consecutive days. Nondiabetic group (HFD) was fed with high fat diet and injected with citrate buffer only. Control group (ND) was fed with normal diet without treatment. Mice were tested for blood glucose level, intra-peritoneal glucose tolerance test (IPGTT), osteopontin expression in aortic root and plaque formation through Oil Red O *en face* aorta staining. Blood glucose of HFD+STZ mice shows a significant increase from 8 weeks until 12 weeks old compared to HFD and ND groups ($p<0.05$). IPGTT results further validate that HFD+STZ mice have the highest insulin resistance compared to other groups. HFD+STZ mice show a higher expression of osteopontin compared to HFD and ND groups. The phenotypic changes in HFD+STZ mice can be observed through higher plaque formation in the aorta compared to HFD and ND groups. In conclusion, HFD+STZ mice show a promising quality as a research animal model for the study of diabetes complications and osteopontin relations in atherosclerosis.

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Keywords: Atherosclerosis, Diabetes, Osteopontin

P12-07

Sympathetic activity mediates hypertrophic morphological changes in the primo vascular system of heart failure rats

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The primo-vascular system (PVS) is a newly identified vascular tissue composed of primo-nodes (PN) and primo-vessels. Recently we reported that in the heart failure (HF), or hemolytic anemia rats there are similar morphological changes of organ surface (os) PVS associated with extra-medullary erythropoiesis. Exercise training (ExT) is known to induce beneficial effects on HF patients by normalizing the elevated sympathetic tone. However, little is known about whether ExT could also inhibit such HF-induced-morphological changes in the PVS. In this study, we examined 1) the effects of ExT on the morphology of the PVS in the HF rats, 2) the effects of 6-hydroxydopamine (6-OHDA), a chemical sympathectomy agent on the morphological changes in the PVS of rats with phenylhydrazine-induced hemolytic anemia. 3) the effects of the norepinephrine (NE) on the morphological changes in the PVS from normal rats. HF rats were prepared by ligating the left descending coronary artery. In HF rats, we observed an increase in the size of the PNs ($p<0.01$), the number of the osPVS tissue samples per rat ($p<0.05$), the proportion of osPVS tissue samples with red chromophore ($p<0.001$), and the number of RBCs ($p<0.001$) in PN. ExT ameliorated these HF-induced changes in osPVS except the number of samples per rat. Blocking sympathetic activity with 6-OHDA dramatically reduced the number of samples per rat in normal rats. The treatment of 6-OHDA normalized the enlarged PN size ($p<0.05$) and the elevated proportion of the tissues with red chromophore ($p<0.001$) in the rats with hemolytic anemia. The PN size ($P<0.05$) and sampling frequency ($P<0.05$) were enlarged with continuous infusion of NE. Taken together, the results show that the inhibition by ExT or removal by 6-OHDA of sympathetic tone blocks the erythropoietic morphological changes of the osPVS tissue in the HF and anemia rats, and activation of sympathetic tone by NE enlarged the osPVS tissue in the normal rats, respectively. The results indicate that HF-induced morphological changes are mediated by sympathetic activity.

Keywords: Excise training, Complete blood count, 6-hydroxydopamine, Norepinephrine

P12-08

Cationic oligopeptide-functionalized mitochondria targeting sequence show mitochondria targeting and anticancer activity

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Mitochondrial drug delivery systems require development of highly selective mitochondria-targeting carriers. In this study, we report that MTS-hybrid

cationic oligopeptide, MTS-H3R9, shows the dual role of mitochondria targeting vector along with anticancer effect for cancer therapy. In cytotoxicity assays, MTS-H3R9 was shown to be more effective than MTS. MTS-H3R9 showed significant cell penetration and internalization activity compared to that of MTS along with the more efficient escape from the lysosome to the cytosol. We showed efficient targeting of MTS-H3R9 to mitochondria in the HeLa cell line. Furthermore, we exhibited anticancer agent properties that mitochondrial-accumulated MTS-H3R9 caused cell death by reactive oxygen species (ROS) generation and loss of mitochondrial membrane potential. MTS-H3R9 exhibited dramatically increased anticancer activity in 3D spheroids as well as in a 2D culture model. We demonstrated that MTS-H3R9 provides dual potentials both as a vehicle for targeted delivery and as a cancer treatment agent for therapeutic applications.

Keywords: Mitochondria targeting, MTS-H3R9, 3D spheroids, Anticancer activity

P12-09

Functional nanosome for enhanced mitochondria-targeted gene delivery and expression

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Mitochondria dysfunction plays a role in many human diseases. Therapeutic techniques for these disorders require novel delivery systems that can specifically target and penetrate mitochondria. In this study, we report a novel nanosome composed of dequalinium-DOTAP-DOPE (1,2 dioleoyl-3-trimethylammonium-propane-1,2-dioleoyl-sn-glycerol-3-phosphoethanolamine) (DQA80s) as a potential mitochondria-targeting delivery vector. The functional DQAsome, DQA80s, showed enhanced transfection efficiency compared to a vector DQAsomes in HeLa cells and dermal fibroblasts. In addition, DQA80s/pDNA complexes exhibited rapid escape from the endosome into the cytosol. We observed the delivery of pDNA to mitochondria in living cells using flow cytometry, confocal microscopy, and TME imaging. More specifically, we confirmed our results by co-localization of hmtZsGreen constructs to mitochondria when delivered via DQAsomes and DQA80s in living cells. The mitochondria-targeting DQAsomes and DQA80s induced mitochondrial dysfunction through depolarization of mitochondrial membrane potential. Our data demonstrate that DQA80s show promise for use as a mitochondria-targeted carrier system for the treatment of mitochondria diseases *in vivo*.

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Keywords: Mitochondria, Dequalinium, Mitochondria-targeting, hmtZsGreen, Gene delivery

P12-10

Effects of energy metabolism of astrocytes on neural activities in the medial vestibular nucleus of rats

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Abnormal energy metabolism of astrocytes in the central vestibular system may be the main reason for vertigo pathogenesis caused by impaired saccharometabolism or blood flow. To demonstrate this hypothesis, we confirmed whether controlling the metabolism of astrocyte in the central vestibular system of rats can regulate the excitability of metabolism and neural plasticity in the central vestibular system. The astrocyte provides L-lactate to neurons through monocarboxylate transporter (MCT). In addition, L-lactate has been known as a main fuel for neuronal activities. In *in vitro* and *in vivo* animal experiments, we blocked MCT by the injection of α-cyano-4-hydroxy-cinnamate (4-CIN) to verify the role of astrocytes to control neuronal activities in the medial vestibular nucleus (MVN). EPSPs recorded through Multi-Electrode Array (MEA) on the MVN in a brainstem slice were suppressed after injecting 500 μM 4-CIN into the MVN. Moreover, spontaneous firing rates recorded from type I and II neurons in the MVN of anesthetized rats decreased for roughly 30 minutes after the injection of 4-CIN (25μg/ml) into the MVN. In conclusion, we suggest that lactate provided from astrocytes to neurons plays an important role as a vital energy source and the regulator of the vestibular system. Furthermore, abnormal energy metabolism of astrocytes may be a cause of vertigo as well as stabilizing metabolism in the vestibular system may also be a possible approach for alternative therapy of vertigo.

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Keywords: Vestibular, Astrocyte, Vertigo, Metabolism

P12-11

Chronic exposure of ethylenethiourea induces nephrotoxicity and poly-cysts in mice

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Ethylenethiourea(ETU) was mainly used as a vulcanizing catalyst for polychlorophrene and polyacrylate rubbers and used in dyes, synthetic resins, pharmaceuticals, and intermediate in antioxidant production. ETU is also one of the main metabolites of ethylenebisdithiocarbamate(EDBC) fungicides including maneb, zineb, and mancozeb. Therefore, potential occupational exposure to ETU is greatest for workers involved in machine and metal manufacturing, rubber production, and manufacture of EDBC fungicides. The pathways of potential human exposure to ETU are dermal contact, ingestion, and inhalation. The toxicological studies of ETU were extensively investigated to the endocrine disruption, teratogenesis, goiter, and carcinogenicity. An extensive study on the carcinogenicity demonstrates that ETU increases adenocarcinomas and thyroid follicular adenomas in rodents. ETU has also demonstrated developmental toxicity including the central nervous system and skeletal structure. Recently, it has been reported that a high dose of ETU(300 mg/L) resulted in ultrastructure alteration in proximal tubular epithelial cells. In the present study, we evaluated that the changes in visceral organ weight, cholesterol levels in serum, renal and liver function index, and epigenetic miRNA expression levels in C57BL/6 mouse with chronic exposure of ETU for 58 weeks. Chronic exposure of low dose ETU(250 ppm) induced toxicological effects which as followed; 1) lowered body weight, 2) increased triglyceride and cholesterol in serum, 3) increased blood urea nitrogen(BUN) and creatine levels, 4) induced extreme malfunc-

tion of the kidney including decreased number and size of the glomerulus, 5) and induced severe hydronephrosis or poly-cystogenesis compared to the control. Also, ETU diet increased expression levels of miR-1971, miR-155, miR-135, miR-125, and miR-21, as known to a biomarker for renal injury and fibrosis, in the kidney. In the cause of polycystic kidney disease, ETU diet increased expression levels of miR-17~92 cluster, known as an oncogenic miRNA cluster and renal cyst growth, and miR-182, a novel regulator of the actin cytoskeleton and cyst progression. Taken together, these data suggest that chronic exposure to ETU, at low concentration without causing acute toxicity, evoked renal dysfunction such as glomerular dysfunction and renal cyst development.

Keywords: Ethylenethiourea, Polycystic kidney disease, Nephrotoxicity, miR-17~92 cluster, Hydronephrosis

P12-12

Fluorescence size-exclusion chromatography (FSEC) for studying mammalian membrane proteins

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For studying eukaryotic membrane proteins at the biochemical and biophysical levels, it is necessary to isolate membrane proteins with preservation of their conformational integrities. However, it is a labor-intensive and time-consuming process to optimize conditions for over-expression, purification, and reconstitution of a membrane protein with high enough amount for the subsequent studies. In order to accelerate this process, we have applied the fluorescence size-exclusion chromatography (FSEC) (1) to screen optimal condition for stabilizing a GFP-tagged membrane protein without purification, which can be evaluated by the monodispersity of a detergent-solubilized membrane protein in the size-exclusion chromatography. We have been successfully using this strategy for expression and purification of human membrane proteins: TRPML1-3 hetero-oligomeric channel, an astrocytic membrane protein MLC1, and a microglial membrane receptor TREM2 for structural and biochemical studies. The FSEC-based membrane protein screening led us to screen optimal conditions for large-scale expression of eukaryotic membrane proteins within two weeks.

Keywords: Membrane protein, Structural study, Florescence size-exclusion chromatography

P12-13

Flos Magnoliae and its constituent linoleic acid suppress T lymphocyte activation via store-operated calcium entry

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Intracellular calcium signaling is crucial for type 2 helper T cell and mast cell activation, which is essential for allergic inflammation. It is initiated by antigen-mediated receptor stimulation that triggers store-operated calcium entry (SOCE) via ORAI1 calcium channel. *Flos Magnoliae* (FM) is widely used to treat allergic diseases such as allergic rhinitis and asthma. Although many studies have reported that FM regulates intracellular calcium signaling, research on the exact type of calcium channel modulated by FM is scarce. Therefore, we hypothesized that the anti-allergic effects of FM might result from ORAI1 inhibition in T cells. We investigated whether a 70% ethanolic extract of FM (FM_{EtOH}) and its constituents inhibit ORAI1 channel activity and subsequent T cell activation. We performed conventional whole-cell patch clamp studies in hSTIM1 and hORAI1-overexpressing HEK293T cells (HEK_{ORAI1}). Intracellular calcium concentration was determined using Fura-2 dye and cytokine production measurement in Jurkat T lymphocytes. FM_{EtOH} (0.03 mg/mL) and its fractions, especially hexane fraction (FM_{Hex}, 0.01 mg/mL), significantly inhibited SOCE and IL-2 cytokine production in Jurkat T lymphocytes. GC/MS analysis showed linoleic acid (LA) as the major component of FM_{Hex}. FM_{Hex} at 0.01 mg/mL (equivalent to 10 μM LA) inhibited not only SOCE but also IL-2 production, as well as CD3/CD28 receptor co-stimulation induced calcium signaling in Jurkat T lymphocytes. FM_{EtOH} and LA suppressed CD4+ T lymphocyte activation, at least in part, by inhibiting I_{SOCE}. Thus, I_{SOCE} inhibition may be a potential strategy to inhibit immune responses in inflammation.

Keywords: *Flos Magnoliae*, Linoleic acid, store-operated calcium entry, Interleukin-2, T lymphocytes, ORAI1

P12-14

Cytotoxicity of hair dye ingredients on human conjunctival epithelial cells and fibroblasts

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Along with the increased use of hair dyes, there has been a growing concern about the potential health problems associated with chronic exposure to the hair dye ingredients. Although eye, especially cornea and conjunctiva, is one of the most frequently exposed sites to the hair dyes, ophthalmological studies on the hazards of hair dye ingredients are limited. This study was aimed to analyze the toxic effects of representative hair dye ingredients on the conjunctiva using primary cultured human conjunctival epithelial cells and fibroblasts. We also compared the toxicity of hair dye ingredients between three-dimensional (3D) and conventional 2D cell cultures to develop a more physiologically relevant tissue model of human conjunctiva for studying ocular drug toxicity. As a result of investigating 10 commercially available hair dyes on the market, we have found that the most common ingredients are para-phenylenediamine (PPD), toluene-2,5-diamine, resorcinol, m-aminophenol, and p-aminophenol. The cytotoxicity assay revealed that all hair dye ingredients tested were toxic to conjunctival epithelial cells and fibroblasts in a dose-dependent manner. Epithelial cells were more susceptible to hair dye ingredients tested than fibroblasts. Toluene-2,5-diamine exhibited the strongest cytotoxicity on epithelial cells, whereas P-aminophenol did on fibroblasts. The concentrations causing 50% cell death (IC_{50}) were 0.1~0.4 ug/ml for epithelial cells and 0.4~1.0 ug/ml for fibroblasts. 3D culture model for human conjunctiva established by co-cultures of human conjunctival epithelial cells and fibroblasts in the poly-ε-caprolactone (PCL) nanofiber scaffold revealed that 3D cultured cells were less susceptible to the hair dye ingredients than 2D cultured cells. Taken together, although PPD is widely known to be harmful among hair dye ingredients in the skin, toluene-2,5-diamine and p-aminophenol exhibited stronger toxicity than PPD on conjunctival epithelial cells and fibroblasts, respectively. 3D co-culture of human conjunctival epithelial cells and fibroblasts in the nanofiber scaffold provides a more physiologically relevant tissue model of human conjunctiva for studying ocular drug toxicity.

Keywords: Human conjunctival epithelial cells, Human conjunctival fibroblasts, Hair dye, Toluene-2,5-diamine, p-aminophenol, Cytotoxicity, 3D culture

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