pISSN 1226-4512
eISSN 2093-3827

# KJPP

Volume 25, Supplement 1, October 2021

The Korean Journal of
Physiology &
Pharmacology

October 27 (Wed) - October 28 (Thu), 2021
온라인 학술대회

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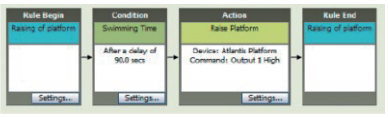


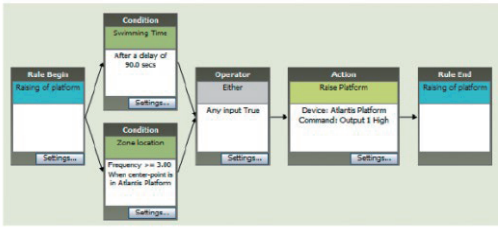


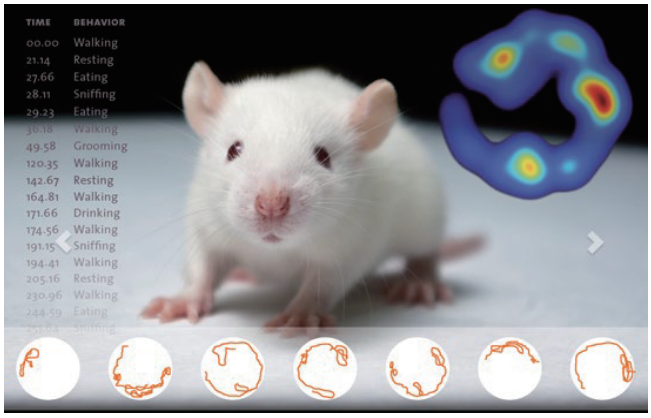


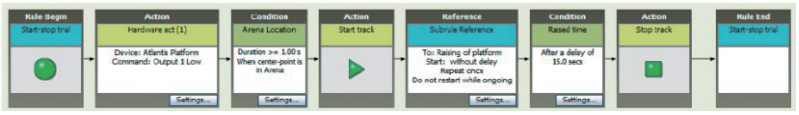


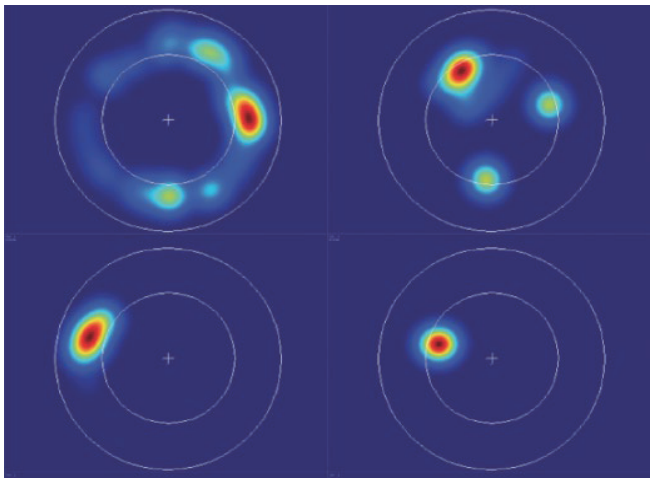

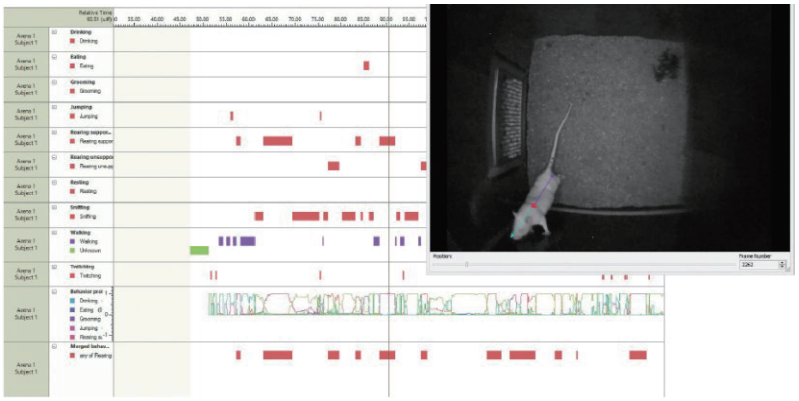

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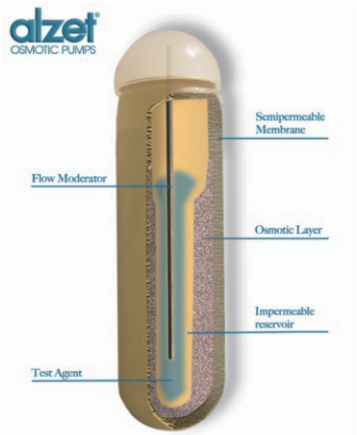


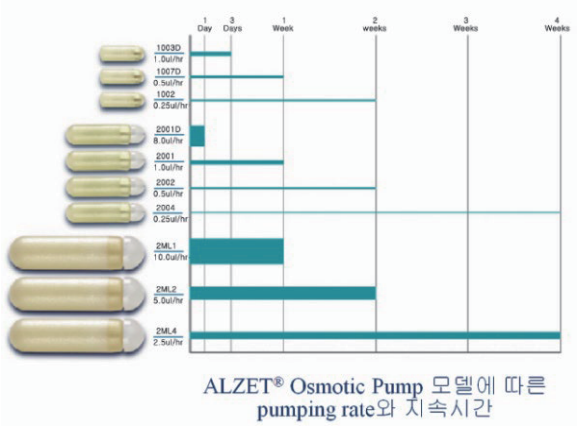


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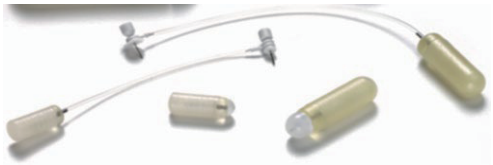

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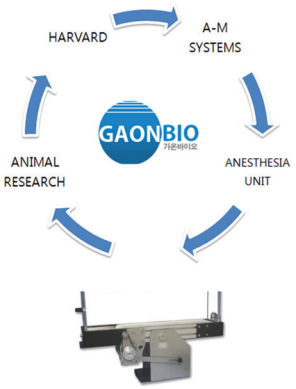




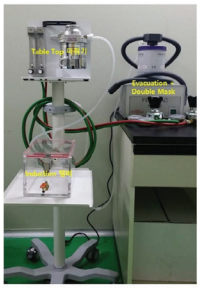

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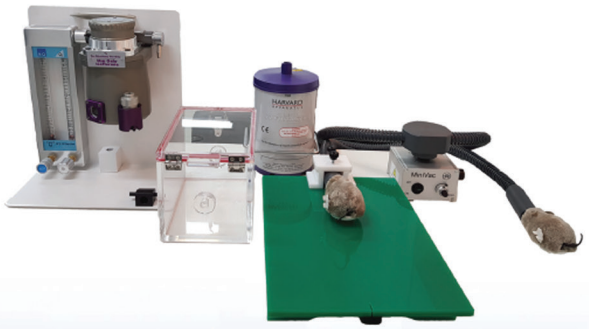

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- ▷ Whole Brain
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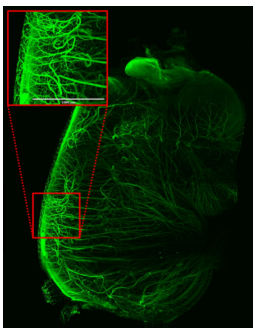
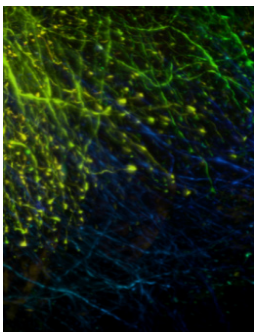
- ▷ Neurobiology





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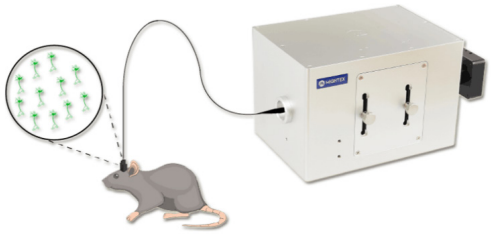

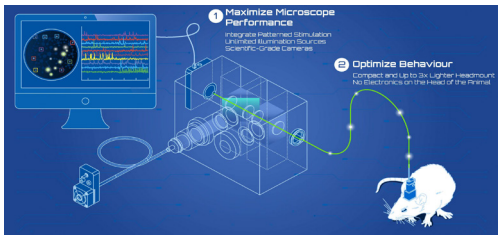


### Application

- ▷ In Vivo Optogenetics & Calcium Imaging
  - ⦿ Freely-Behaving
  - ⦿ Multi-Region
  - ⦿ Cortical Circuit Mapping
- ▷ Photostimulation
  - ⦿ In vitro Neuroscience Optogenetics
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KJPP
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pISSN 1226-4512, eISSN 2093-3827

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**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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### Subscription

Annual Institutional Subscription Rate: U.S. $80.00. Personal Subscription Rate: U.S. $50.00. Prices include postage and insurance and are subject to change without notice. Circulation number of print copies is 350 per issue.



Printed on acid-free paper effective with Volume 25, No. 5, 2021.
Printed by MEDrang Inc. (Tel. 82-2-325-2093, Fax. 82-2-325-2095, E-mail. info@medrang.co.kr)
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This journal was supported by the Korean Federation of Science and Technology Societies (KOFST) Grant funded by the Korean Government.

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# Acknowledgement


## Supported by

This work was supported by the Korean Federation of Science and Technology Societies (KOFST) Grant funded by the Korean Government

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# Contents

# Welcome Message

대한생리학회 회원여러분,

안녕하십니까?

COVID-19로 인한 "거리두기" 강제가 여러 분야에서 우리의 일상을 바꾸어 놓았습니다. 저희 대한생리학회 역시 지난해에 이어 올해도 대면 학술대회를 갖지 못하고 비대면으로 개최하게 되었습니다.

이렇게 비대면 학술대회로 바뀌면서 우리가 기존의 대면 학술대회에서 기대했던 많은 일들 예를 들어, 연구자들 간의 소통, 관계 구축, 친목 도모 등에서 많은 어려움이 있음을 잘 알고 있습니다. 그러나 동시에 비대면 학술대회가 갖고 있는 효용성에 대해서도 새롭게 인식하는 기회가 되었습니다. 이는 COVID-19가 우리에게 제공한 새로운 기회라고 생각합니다.

COVID-19로 인해 비대면으로 거의 모든 일이 이루어지고 있는 상황을 "New normal"이라고 부르고 있습니다. 이러한 "New normal"의 명칭에는 COVID-19 사태가 해결되고 난 이후에도 현재의 비대면 위주의 상황이 원래대로 돌아가지는 못하리라는 일말의 우려를 담고 있다고 생각합니다.

이번 학술대회의 슬로건으로 "Return to normal"을 정한 것은 이런 우려를 창조적으로 극복하고자 하는 의미를 담고 있습니다. COVID-19 사태가 일단락되더라도 COVID-19 사태 전으로 단순하게 돌아가는 것이 아니라, 창조적 변화를 동반한 정상화라는 의미를 담고 있습니다. 어쩌면 지금의 "New normal"이 끝나는 시점에서는 우리의 시야가 한결 멀리 닿아있을지도 모르겠습니다.

마지막으로 이번 학술대회를 주최하여 주신 연세의대 생리학교실 교수님들과 학술대회 프로그램 준비에 수고와 협조를 아끼지 않으신 모든 임원과 회원님들께 감사 말씀드립니다.

대한생리학회 회 장 **김 종 연**
대한생리학회 이사장 **안 덕 선**

# Schedule (일정표)

## ▶ 10월 27일 수요일

| Time | Contents | | |
|---|---|---|---|
| | Room A | Room B | Room C |
| 09:20~09:30 | 개회사 | | |
| 09:30~12:00 | **Symposium 1:** Discovery and function of appetite-related neuropeptides beyond appetite | **Symposium 2:** Metabolic regulation of Cardiovascular diseases | **Symposium 3:** Environmental Physiology |
| 12:00~13:20 | 점심식사 및 포스터 질의응답(댓글) / 이사회 | | |
| 13:20~15:50 | **Symposium 4:** Unconventional ion channels; New Kids on the Channel Block | **Symposium 5:** 염증-암 미세환경 'Inflammation-Cancer Microenvironment Research Center (MRC) Joint Symposium' | **Symposium 6:** Open Session |
| 15:50~16:00 | 휴식 | | |
| 16:00~18:30 | **Symposium 7:** Neuro AI & Neural data science in physiology research | **Symposium 8:** Hearing loss | **Symposium 9:** Exercise Physiology |

## ▶ 10월 28일 목요일

| Time | Contents | | |
|---|---|---|---|
| | Room A | Room B | Room C |
| 9:00~10:00 | **PL:** Prof. JoelElmquist | | |
| 10:00~12:30 | **Symposium 10:** Recent update in taste research | **Symposium 11:** Pathophysiology of hepatic fibrosis | **Symposium 12:** 피부질환 중개연구 |
| 12:30~13:30 | 점심식사 및 포스터 질의응답(댓글) | | |
| 13:30~15:30 | 포스터 세션(소규모 Zoom 회의) | | |
| 15:30~18:00 | **Symposium 13:** Brain processing of pain | **Symposium 14:** Vital signaling platform, mitochondria | **Symposium 15:** 교육세션 |
| 18:00~18:20 | 총회 | | |
| 18:20~18:30 | 폐회사 | | |

## ▶ Plenary Lecture (10월 28일 목요일)

| Contents | |
|---|---|
| **Plenary Lecture (09:00~10:00)** | |
| SF-1 Neurons in the Hypothalamus: A Link between Exercise Training and Metabolic Adaptations | *Joel Elmquist (Univ. Texas Southwestern Medical Center)* |

## ▶ Symposium (10월 27일 수요일)

| Contents | |
|---|---|
| **Symposium 1: Discovery and function of appetite-related neuropeptides beyond appetite (09:30~12:00)** | **Organizer: *연세의대 김정훈*** |
| 1. Discovery of neuropeptides in human serum samples associated with addiction | *이지은(KIST)* |
| 2. Ghrelin in Alzheimer's disease: pathologic roles and therapeutic implications | *문민호(건양대)* |
| 3. Food restriction, ghrelin, and amphetamine | *김정훈(연세의대)* |

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|---|---|
| **Symposium 2: Metabolic regulation of Cardiovascular diseases (09:30~12:00)** | **Organizer: 서울의대 장은화** |
| 1. Metabolic perturbations in cardiovascular disease | *Derek J. Hausenloy (Singapore)* |
| 2. Immunometabolism and Vascular Injury-Role of Hyperhomocysteinemia | *Xian Wang (China)* |
| 3. Molecular imaging for evaluating metabolic characteristics of cardiovascular system | *팽진철(서울의대)* |
| 4. GSK-3$\beta$ signaling pathway induced cardioprotection | *한 진(인제의대)* |
| 5. Fatty acid metabolism in hypertension | *장은화(서울의대)* |

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| **Symposium 3: Environmental Physiology (09:30~12:00)** | **Organizer: *순천향의대 이정범*** |
| 1. Differences of residential environment in the physiological adaptations to heat acclimatization: Perspiration Research | *이정범(순천향의대)* |
| 2. Multi sensor fabrication and precise calibration for the measurement of thermo-physiological responses | *송국섭(테크녹스연구소)* |
| 3. Particulate matter exposure aggravates IL-17 inflammation in the eye and nose of OVA/Poly(I:C) mouse | *배준상(단국의대)* |
| 4. Thermal comfort and skin temperature with radiant cooling panels as a proximity cooling device | *전정윤(연세대)* |
| 5. Cutaneous warmth thresholds to conductive and radiant heat exposure: body regional differences | *이주영(서울대)* |

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|---|---|
| **Symposium 4: Unconventional ion channels; New Kids on the Channel Block (13:20~15:50)** | **Organizer: *서울의대 김성준*** |
| 1. CALHM1/3 channels mediate chemosensory neurotransmission | *Akiyuki Taruno (Kyoto Prefectual Univ)* |
| 2. Biophysical regulation of CALHM channel and its structural understanding | *김성준(서울의대)* |
| 3. Shear stress mechanotransduction in atrial myocytes and its pathological implication | *우선희(충남대)* |
| 4. Physiological roles of ANO9 channel | *오우택(KIST)* |

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| **Symposium 5: 염증-암 미세환경 'Inflammation-Cancer Microenvironment Research Center (MRC) Joint Symposium' (13:20~15:50)** | **Organizer: *이화의대 이지희*** |
| 1. Rewiring tumor microenvironment to establish premetastatic niche | *석승혁(서울의대)* |
| 2. Rolling the Cancer Immunity Cycle | *김인산(KIST)* |
| 3. MicroRNA-196a activates lung cancer-associated fibroblasts | *안영호(이화의대)* |
| 4. Reprogramming of CAFs by apoptotic cancer cells | *이지희(이화의대)* |
| 5. New strategy for immunotherapeutics based on engineered T cell-derived immune-exosomes | *백문창(경북의대)* |

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|---|---|
| **Symposium 6: Open Session (13:20~15:50)** | **Organizer: *연세 원주의대 박규상*** |
| 1. Targeted downregulation of Hipp1 ameliorates tau-engendered deficits in *Drosophila melanogaster* | *박성연 (서울의대)* |
| 2. Evaluation of novel cellular arrhythmia models in patient-specific iPSC-derived cardiomyocytes | *최성우 (동국의대)* |
| 3. Regulation of smooth muscle contraction by channel modulators | *김영철 (충북의대)* |
| 4. PTEN-induced kinase 1 (PINK1) ameliorates lupus nephritis via regulation of Stimulator of interferon genes (STING) signaling pathway | *우진석 (가톨릭의대)* |

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|---|---|
| **Symposium 7: Neuro AI & Neural data science in physiology research (16:00~18:30)** | **Organizer: *가천한의대 김창업*** |
| 1. Emergence of cognitive functions in the brain | *백세범(KAIST)* |
| 2. Neural mechanisms of individual recognition in the hippocampus | *이도윤(IBS)* |
| 3. Cracking the neural population code of complex cognitive behavior | *현정호(DGIST)* |
| 4. Revisiting the cerebellar memory consolidation mechanism from AI perspective: The cerebellum as a dual learning machine | *김상정(서울의대)* |
| 5. Characterizing neural selectivity using a data-driven interpretable feature finding method in multidimensional stimulus space | *김창업(가천한의대)* |

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|---|---|
| **Symposium 8: Hearing loss (16:00~18:30)** | **Organizer: *성균관의대 강동묵*** |
| 1. Elucidate novel genetics and pathobiology of hearing loss | *지헌영(연세의대)* |
| 2. TMEM43, a novel cation channel in cochlear glia is critical for maintenance of speech perception | *이창준(Justin Lee)(IBS)* |
| 3. Cholesterol metabolites mediate Hearing Loss in Pex5 cKO mice | *박래길(GIST)* |
| 4. Gene therapy of sensorineural hearing loss using adeno-associated virus in mouse model | *김언경(경북대학교)* |
| 5. *In vivo* gene editing prevents progressive hearing loss in KCNQ4 dominant murine model | *정진세(연세의대)* |

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| **Symposium 9: Exercise Physiology (16:00~18:30)** | **Organizer: *인하대 곽효범*** |
| 1. Tracing Metabolic Flux In Vivo in Exercise | *김일영(가천의대)* |
| 2. Enhancement of Anaerobic Glycolysis – a Novel Role of PGC-1α4 in Resistance Exercise | *고진호(영남의대)* |
| 3. Mild exercise intervention improves human cognitive function with increased neural efficiency of prefrontal cortex in the older adults | *변경호(인천대)* |
| 4. Treadmill exercise alleviates behavioral deficits by regulating dopamine metabolism and mitochondrial homeostasis in the mouse model of Parkinson's disease | *구정훈(한국체대)* |

## ▶ Symposium (10월 28일 목요일)

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| **Symposium 10: Recent update in taste research (10:00~12:30)** | **Organizer: *연세치대 문석준*** |
| 1. Making sense of flavor | *문석준(연세치대)* |
| 2. Cellular and molecular mechanisms underlying attractive sodium taste in taste buds | *Kengo Nomura (Kyoto PrefecturalUniversity of Medicine)* |
| 3. Single cell transcriptomic atlas of mouse taste bud organoids | *정용택(고려의대)* |
| 4. Live imaging of taste cells in action | *최명환(서울대)* |

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| **Symposium 11: Pathophysiology of hepatic fibrosis (10:00~12:30)** | **Organizer: *계명의대 임승순*** |
| 1. Pathophysiology of TM4SF5-mediated steatohepatitis associated with fibrosis | *이정원(서울대)* |
| 2. Deficiency of formyl peptide receptor 2 exacerbates liver inflammation and fibrosis in mice with nonalcoholic fatty liver disease/steatohepatitis | *정영미(부산대)* |
| 3. Function of SREBP-1c in the development of hepatic fibrosis | *임승순(계명대)* |
| 4. Kctd17, a novel regulator in progression of NAFLD/NASH | *김경진(인하대)* |
| 5. Hepatic stellate cell-derived hyaluronan in nonalcoholic hepatitis | *양윤미(강원대)* |

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| **Symposium 12: 피부질환 중개연구 (10:00~12:30)** | **Organizer: *동국의대 남주현*** |
| 1. Naturally occurring compounds with autophagy-inducing property and their application for skin health | *조재열(성균관대)* |
| 2. Punicalagin ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis-like lesions via PAR2 inhibition | *남궁완(연세대)* |
| 3. Drug discovery of natural products targeting ion channels in non-excitable cells | *남주현(동국의대)* |
| 4. Clinical immunology of psoriasis and its application to the treatment | *김태균(연세의대)* |
| 5. Methods to probe the efficacy of GPCR modulator through measuring activity of ion channels | *이한미(비보존)* |

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| **Symposium 13: Brain processing of pain (15:30~18:00)** | **Organizer: *경희한의대 김선광*** |
| 1. Parallel Ascending Spinal Pathways for Affective Touch and Pain | *최승원(Harvard Med. School)* |
| 2. Decoding of spontaneous pain from two-photon microscopy images of brain cellular calcium using deep learning | *김선광(경희한의대)* |
| 3. Involvement of the insular cortex in central modulation of neuropathic pain | *이배환(연세의대)* |
| 4. Top-down components of acupuncture treatment in pain control | *채윤병(경희한의대)* |

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| **Symposium 14: Vital signaling platform, mitochondria (15:30~18:00)** | **Organizer: *KAIST 이승재, 인제의대 김형규*** |
| 1. Mitochondria:Powerhouse, Slaughterhouse, and Speaker of the House | *이장한(USC, USA)* |
| 2. Lysosomal SLC46A3 modulates hepatic cytosolic copper homeostasis, mitochondrial function and triglyceride accumulation | *김정환(경상대)* |
| 3. Suppressive effects of stress-induced glucocorticoid on mitochondrial clearance and trafficking trigger synapse defects | *한호재(서울대)* |
| 4. Mitohormesis in hypothalamic POMC neurons mediates regular exercise induced high turn metabolism | *김민선(울산대)* |

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| **Symposium 15: 교육세션 (15:30~18:00)** | **Organizer: *인제의대 염재범*** |
| 1. How to teach and learn in an online environment? | *최효선(조선의대)* |
| 2. Changes in students' physiological learning attitudes due to flipped learning | *임채헌(울산의대)* |
| 3. Teaching well is how to learn well | *한재희(경상의대)* |

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| **Yudang Academic Award** | **Organizer:** |
| Rewiring lipid metabolism by hypoxia-inducible factor-1 in tumor microenvironment: New targets for cancer therapy? | *전양숙(서울의대)* |

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| **Young Scientist Session** | **Organizer:** |
| Role of Brainstem Serotonin Receptors in the Regulation of Sodium Appetite | *손종우(KAIST)* |

## Plenary Lecture

**S 21** PL-1 SF-1 Neurons in the Hypothalamus: A Link between Exercise Training and Metabolic Adaptations
Joel Elmquist
University of Texas Southwestern Medical Center

## Symposium

### Symposium 1: Discovery and function of appetite-related neuropeptides beyond appetite

**S 21** S-1-1 Discovery of neuropeptides in human serum samples associated with addiction
Ji Eun Lee
Center for Theragnosis, Korea Institute of Science and Technology, Seoul, Korea

**S 21** S-1-2 Ghrelin in Alzheimer's disease: pathologic roles and therapeutic implications
Minho Moon
Department of Biochemistry, Konyang University College of Medicine, Daejeon, Korea

**S 21** S-1-3 Food restriction, ghrelin, and amphetamine
Jeong-Hoon Kim
Department of Physiology, Yonsei University College of Medicine, Seoul, Korea

### Symposium 2: Metabolic regulation of Cardiovascular diseases

**S 22** S-2-1 Metabolic perturbations in cardiovascular disease
Derek Hausenloy
Duke-NUS Medical School, Singapore

**S 22** S-2-2 Immunometabolism and Vascular Injury-Role of Hyperhomocysteinemia
Xian Wang
Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing, P. R. China

**S 22** S-2-3 Molecular imaging for evaluating metabolic characteristics of cardiovascular system
Jin Chul Paeng
Department of Nuclear Medicine, Seoul National University Hospital, Seoul, Korea

**S 22** S-2-4 GSK-3β signaling pathway induced cardioprotection
Jin Han
Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutic Center, Inje University, Busan, Korea

**S 23** S-2-5 Fatty acid metabolism in hypertension
Yin Hua Zhang
Department of Physiology & Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

### Symposium 3: Environmental Physiology

**S 23** S-3-1 Differences of residential environment in the physiological adaptations to heat acclimatization: Perspiration Research
JeongBeom Lee, Hye-Jin Lee, Tae-Hwan Park
Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, Korea

**S 23** S-3-2 Multi sensor fabrication and precise calibration for the measurement of thermo-physiological responses
Gook-Sup Song
Head of Research Center, Technox Inc.

**S 23** S-3-3 Particulate matter exposure aggravates IL-17 inflammation in the eye and nose of OVA/Poly(I:C) mouse
Jun-Sang Bae[1,2,3], Kyong Jin Cho[4], Ji-Hun Mo[1,2,3]
[1]Department of Otorhinolaryngology, College of Medicine, Dankook University, Cheonan, Korea, [2]Beckman Laser Institute Korea and [3]Medical Laser Research Center, Dankook University, Cheonan, Korea, [4]Department of Ophthalmology, College of Medicine, Dankook University, Cheonan, Korea

**S 24** S-3-4 Thermal comfort and skin temperature with radiant cooling panels as a proximity cooling device
Chungyoon Chun, Jiwon Yoo
Department of Interior Architecture and built environment, Yonsei UniversitySeoul, Korea

**S 24** S-3-5 Cutaneous warmth thresholds to conductive and radiant heat exposure: body regional differences
Joo-Young Lee
Department of Textiles, Merchandising and Fashion Design, Seoul National University, Seoul, Korea

## Symposium 4: Unconventional ion channels; New Kids on the Channel Block

**S 24** S-4-1

CALHM1/3 channels mediate chemosensory neurotransmission
Akiyuki Taruno
Department of Molecular Cell Physiology, Kyoto Prefectural University of Medicine, Kyoto, Japan, Japan Science and Technology Agency, CREST and PRESTO, Saitama, Japan

**S 25** S-4-2

Biophysical regulation of CALHM channel and its structural understanding
Sung Joon Kim
Department of Physiology, Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

**S 25** S-4-3

Shear stress mechanotransduction in atrial myocytes and its pathological implication
Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

**S 25** S-4-4

Physiological roles of ANO9 channel
Uhtaek Oh
Brain Science Institute, KIST, Seoul, Korea

## Symposium 5: 염증-암 미세환경 'Inflammation-Cancer Microenvironment Research Center (MRC) Joint Symposium'

**S 26** S-5-1

Rewiring tumor microenvironment to establish premetastatic niche
Seung Hyeok Seok[1,2]
[1]Macrophage Lab, Department of Microbiology and Immunology, and Institute of Endemic Disease, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

**S 26** S-5-2

Rolling the Cancer Immunity Cycle
In-San Kim[1,2]
[1]Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, Korea, [2]KU-KIST Graduate School of Converging Science and Technology, Korea University, Seoul, Korea

**S 26** S-5-3

MicroRNA-196a activates lung cancer-associated fibroblasts
Young-Ho Ahn
Department of Molecular Medicine and inflammation-Cancer Microenvironment Research Center, Ewha Womans University College of Medicine, Seoul, Korea

**S 26** S-5-4

Reprogramming of CAFs by apoptotic cancer cells
Jihee Lee[1,2]
[1]Department of Physiology, College of Medicine, Ewha Womans University, Seoul, Korea, [2]Inflammation-Cancer Microenvironment Research Center, College of Medicine, Ewha Womans University, Seoul, Korea

**S 27** S-5-5

New strategy for immunotherapeutics based on engineered T cell-derived immune-exosomes
Moon-Chang Baek
Exosome Convergence Research Center (ECRC), Department of Molecular Medicine, School of Medicine, Kyungpook National University, Daegu, Korea

## Symposium 6: Open Session

**S 27** S-6-1

Targeted downregulation of ***Hipp1*** ameliorates tau-engendered deficits in ***Drosophila melanogaster***
Sung Yeon Park[1,3], Jieun Seo[2], Seulbee Lee[2], Sang Jeong Kim[1,2,3], Yang-Sook Chun[1,2,3]
[1]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

**S 27** S-6-2

Evaluation of novel cellular arrhythmia models in patient-specific iPSC-derived cardiomyocytes
Seong Woo Choi
Department of Physiology, College of Medicine, Dongguk University, Kyungju, Korea

**S 28** S-6-3

Regulation of smooth muscle contraction by channel modulators
Young Chul Kim[1], Dae Hoon Kim[2], Seung Myeung Son[3], Jin Young Choi[4], Su Mi Kim[4], Seung Hwa Hong[4], Bang Yeon Hwang[5], Chul Lee[5], Ra Young You[1], Chan Hyung Kim[6], Woong Choi[6], Hun Sik Kim[6], Song-Yi Choi[7], Wen-Xie Xu[8], Sang Jin Lee[1], Hyo-Yung Yun[2]
[1]Department of Physiology, [2]Department of Surgery, [3]Department of Pathology, [4]Department of Obstetrics and Gynecology, [5]Department of Pharmacy, [6]Department of Pharmacology, College of Medicine, CBNU, Cheongju, [7]Department of Pathology, School of Medicine, Chungnam National University, Daejeon, Korea; [8]Department of Physiology, College of Medcine, Shanghai Jiaotong University, Shanghai, P.R. China

**S 28** S-6-4

PTEN-induced kinase 1 (PINK1) ameliorates lupus nephritis via regulation of Stimulator of interferon genes (STING) signaling pathway
Jin Seok Woo[1,2], Yeon Su Lee[1,2,3], Kun Hee Lee[1,2,3] and Mi-La Cho[1,2,4]
[1]Rheumatism Research Center, Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, Korea, [2]Lab of Translational ImmunoMedicine, Catholic Research Institute of Medical Science, College of Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, [3]Department of Biomedicine & Health Sciences, College of Medicine, The Catholic UniverWsity of Korea, Seoul, Korea, [4]Department of Medical Lifescience, College of Medicine, The Catholic University of Korea, Seoul, Korea

## Symposium 7: Neuro AI & Neural data science in physiology research

**S 28** S-7-1 Emergence of cognitive functions in the brain
Se-Bum Paik
Department of Bio and Brain Engineering, Program of Brain and Cognitive Engineering, College of Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea

**S 29** S-7-2 Neural mechanisms of individual recognition in the hippocampus
Doyun Lee
Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Korea

**S 29** S-7-3 Cracking the neural population code of complex cognitive behavior
Jung Ho Hyun
Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu, Korea

**S 29** S-7-4 Revisiting the cerebellar memory consolidation mechanism from AI perspective: The cerebellum as a dual learning machine
Sang Jeong Kim
Laboratory of Neurophysiology, Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

**S 30** S-7-5 Characterizing neural selectivity using a data-driven interpretable feature finding method in multidimensional stimulus space
Chang-Eop Kim
Department of Physiology, College of Korean Medicine, Gachon University, Seongnam, Korea

## Symposium 8: Hearing loss

**S 30** S-8-1 Elucidate novel genetics and pathobiology of hearing loss
Heon Yung Gee[1], Jinsei Jung[2], Jae Young Choi[2]
[1]Department of Pharmacology, Graduate School of Medical Science, Brain Korea [2]Department of Otorhinolaryngology, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, Korea

**S 30** S-8-2 TMEM43, a novel cation channel in cochlear glia is critical for maintenance of speech perception
C. Justin Lee
IBS Center or Cognition and Sociality, Daejeon, Korea

**S 30** S-8-3 Cholesterol metabolites mediate Hearing Loss in Pex5 cKO mice
Raekil Park
Department of biomedical Science and Engineering, Gwangju Institute of Science & Technology (GIST), Gwangju, Korea

**S 31** S-8-4 Gene therapy of sensorineural hearing loss using adeno-associated virus in mouse model
Un-Kyung Kim
Department of Biology, Kyungpook National University, Daegu, Korea

**S 31** S-8-5 ***In vivo*** gene editing prevents progressive hearing loss in KCNQ4 dominant murine model
Jinsei Jung
Department of Otorhinolaryngology, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, Korea

## Symposium 9: Exercise Physiology

**S 31** S-9-1 Tracing Metabolic Flux In Vivo in Exercise
Il-Young Kim
Department of Molecular Medicine, Lee Gil Ya Cancer and Diabetes Institute, College of Medicine, Gachon University, Seongnam, Korea

**S 31** S-9-2 Enhancement of Anaerobic Glycolysis – a Novel Role of PGC-1α4 in Resistance Exercise
Jin-Ho Koh[1,2], Mark W. Pataky[1], Surendra Dasari[3], Katherine A. Klaus[1], Ivan Vuckovic[4], Gregory N. Ruegsegger[1], Arathi Prabha Kumar[1], Matthew M. Robinson[5], & K. Sreekumaran Nair[1]
[1]Division of Endocrinology and Metabolism, Mayo Clinic, Rochester, MN, [2]Department of Physiology, College of Medicine, Yeungnam University, Daegu, Korea, [3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Mayo Clinic Regional Comprehensive Metabolomics Core, Mayo Clinic, Rochester, MN, [5]School of Biological and Population Health Sciences, College of Public Health and Human Sciences, Oregon State University, Corvallis, OR, USA

**S 32** S-9-3 Mild exercise intervention improves human cognitive function with increased neural efficiency of prefrontal cortex in the older adults
Kyeongho Byun
Division of Sport Science, College of Arts & Physical Education, Incheon National University, Incheon, Korea

**S 32** S-9-4 Treadmill exercise alleviates behavioral deficits by regulating dopamine metabolism and mitochondrial homeostasis in the mouse model of Parkinson's disease
Woong-Bae Lee[1], Yong-Chul Jang[2], Tae-Kyung Kim[2], Joon-Yong Cho[2], Jung-Hoon Koo[2]
[1]Department of Beauty Health Science, Shin Han University, Gyeonggi, Korea, [2]Department of Exercise Biochemistry, Korea National Sport University, Seoul, Korea

## Symposium 10: Recent update intaste research

S 32 S-10-1 Making sense of flavor
Seok Jun Moon
Department of Oral Biology, Yonsei University College of Dentistry, Seoul, Korea

S 32 S-10-2 Cellular and molecular mechanisms underlying attractive sodium taste in taste buds
Kengo Nomura[1], Akiyuki Taruno[1,2]
[1]Department of Molecular Cell Physiology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Japan Science and Technology Agency, PRESTO, Kawaguchi, Saitama, Japan

S 33 S-10-3 Single cell transcriptomic atlas of mouse taste bud organoids
Yong Taek Jeong
Department of Pharmacology, College of Medicine, Korea University, Seoul, Korea

S 33 S-10-4 Live imaging of taste cells in action
Myunghwan Choi
School of Biological Sciences, Seoul National University, Seoul, Korea

## Symposium 11: Pathophysiologyof hepatic fibrosis

S 33 S-11-1 Pathophysiology of TM4SF5-mediated steatohepatitis associated with fibrosis
Jung Weon Lee
Department of Pharmacy, Seoul National University College of Pharmacy, Seoul, Korea

S 33 S-11-2 Deficiency of formyl peptide receptor 2 exacerbates liver inflammation and fibrosis in mice with nonalcoholic fatty liver disease/steatohepatitis
Chanbin Lee[1], Youngmi Jung[1,2]
[1]Department of Integrated Biological Science, [2]Department of Biological Sciences, Pusan National University, Pusan, Korea

S 34 S-11-3 Function of SREBP-1c in the development of hepatic fibrosis
Seung-Soon Im
Department of Physiology, Keimyung University College of Medicine, Daegu, Korea

S 34 S-11-4 Kctd17, a novel regulator in progression of NAFLD/NASH
KyeongJin Kim
Department of Biomedical Sciences, College of Medicine, Inha University, Incheon, Korea

S 34 S-11-5 Hepatic stellate cell-derived hyaluronan in nonalcoholic hepatitis
Yoon Mee Yang
Department of Pharmacy, Kangwon National University, Chuncheon, Korea

## Symposium 12: 피부질환 중개연구

S 34 S-12-1 Naturally occurring compounds with autophagy-inducing property and their application for skin health
Jae Youl Cho
Department of Integrative Biotechnology, Sungkyunkwan University, Suwon, Korea

S 35 S-12-2 Punicalagin ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis-like lesions via PAR2 inhibition
Wan Namkung
College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Korea

S 35 S-12-3 Drug discovery of natural products targeting ion channels in non-excitable cells
Joo Hyun Nam[1,2]
[1]Department of Physiology, Dongguk University College of Medicine, Kyungju, Korea, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Korea

S 35 S-12-4 Clinical immunology of psoriasis and its application to the treatment
Tae-Gyun Kim
Department of Dermatology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

S 36 S-12-5 Methods to probe the efficacy of GPCR modulator through measuring activity of ion channels
Hanmi Lee
R&D Center in VIVOZON Inc.

## Symposium 13: Brain processingof pain

S 36 S-13-1 Parallel Ascending Spinal Pathways for Affective Touch and Pain
Seungwon Choi[1], Junichi Hachisuka[2], Matthew Brett[1], Alexandra Magee[1], H. Richard Koerber[2], Sarah Ross[2], and David Ginty[1]
[1]Department of Neurobiology, Howard Hughes Medical Institute, Harvard Medical School, Longwood Avenue, Boston, MA, USA, [2]Department of Neurobiology and the Pittsburgh Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, USA

## Symposium 14: Vital signalingplatform, mitochondria



## Symposium 15: 교육세션



## Yudang Academic Award



## Young Scientist Session



# Poster Presentation

## P01: Basic neurophysiology and Pain

S 41 P21-01-02

Involvement of Brain-derived neurotrophic factor and redox factor-1 in formalin-induced pain mouse model
Dong-Wook Kang, Jae-Gyun Choi, Jaehyuk Kim, Miae Lee, Cuk-Seong Kim, Sang Do Lee, Jin Bong Park, Byeong Hwa Jeon, Hyun-Woo Kim
Department of Physiology and Medical Science, College of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

S 41 P21-01-03

Postsynaptic mitochondrial dysfunction in striatum determines the development of Levodopa-induced dyskinesia mouse model
Sung Kyung Yoon, Min Joung Lee, Jiebo Zhu, Da Hyun Go, Jun Young Heo
Department of Biochemistry, Department of Medical Science, Infection
Control Convergence Research Center, School of Medicine, Chungnam National University, Daejeon, Korea

S 41 P21-01-04

KDS2010, a novel MAO-B inhibitor, alleviates spinal nerve ligation-induced neuropathic pain in rats through BDNF-TrkB signaling
Thuy Linh Pham[1,2], Chiranjivi Neupane[1,2], Ramesh Sharma[1,2], Hyun Jin Shin[1,2], Ki Duk Park[3], C. Justin Lee[4], Jin Bong Park[1,2]
[1]Department of Medical Science, College of Medicine and Brain Research Institute, Chungnam National University, [2]Department of Physiology, College of Medicine and Brain Research Institute, Chungnam National University, [3]Convergence Research Center for Diagnosis, Treatment and Care System of Dementia Korea Institute of Science and Technology, [4]Center for Cognition and Sociality Institute for Basic Science

S 42 P21-01-05

Intermittent fasting reduces formalin-induced pain without elevation of corticosterone in mice
Jaehyuk Kim, Jae-Gyun Choi, Dong-Wook Kang, Miae Lee, Cuk-Seong Kim, Sang Do Lee, Jin Bong Park, Byeong Hwa Jeon, Hyun-Woo Kim
Department of Physiology and Medical Science, College of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

S 42 P21-01-06

SCAMP5 mediates activity-dependent enhancement of NHE6 recruitment to synaptic vesicles during synaptic plasticity
Unghwi Lee[1], Seung Hyun Ryu[1], Sunghoe Chang[1,2]
[1]Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, [2]Neuroscience Research Institute Seoul National University College of Medicine, Seoul, Korea

S 42 P21-01-07

Multiplexed processing of vibrotactile information in the mouse primary somatosensory cortex
Yoo Rim Kim[1], Chang-Eop Kim[2], Heera Yoon[3], Sun Kwang Kim[4], Sang Jeong Kim[5]
[1]Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, [2]Department of Physiology, College of Korean Medicine, Gachon University, Seongnam, [3]Department of Physiology, College of Korean Medicine, Kyung Hee University, [4]Department of Physiology, College of Korean Medicine, Kyung Hee University, [5]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 43 P21-01-08

Pathway-specific cholinergic modulation of long-term synaptic plasticity in rat primary visual cortex in vivo
Kayoung Joo[1], Kwang-Hyun Cho[1], Duck-Joo Rhie[1,2]
[1]Department of Physiology, College of Medicine The Catholic University of Korea, [2]Catholic Neuroscience Institute The Catholic University of Korea, Seoul, Korea

S 43 P21-01-09

Common bacterial metabolite indole activates nociceptive sensory neurons and induces nocifensive behavior through TRPA1
Hayun Kim[1], Sena Chung[2], Doyun Kim[3], Jung Moo Lee[4,5], Changjoon Justin Lee[4,5], Seog Bae Oh[1,2,3]
[1]Interdisciplinary Program in Neuroscience, [2]Department of Brain and Cognitive Sciences, [3]Department of Neurobiology and Physiology, School of Dentistry and Dental Research Institute, Seoul National University, [4]KU-KIST Graduate School of Converging Science and Technology, Korea University, Seoul, [5]Center for Cognition and Sociality Institute for Basic Science, Daejeon, Korea

S 43 P21-01-10

Ethanol-induced ceramide production causes neuronal cell death through ER-mitochondria contacts increased by MCL1S-mediated INF2 activation
Jae Ryong Lim, Ho Jae Han
Veterinary Physiology, College of Veterinary Medicine, Research Institute for Veterinary Science, Seoul National University BK21 FOUR Future Veterinary Medicine Leading Education & Research Center, Seoul, Korea

S 44 P21-01-11

Somatic ATP release triggers neuron-satellite glial cell communication in sympathetic ganglia
Sohyun Kim, Huu Son Nguyen, Seong Jun Kang, Seong-Woo Jeong
Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea

S 44 P21-01-12

The role of mitochondria calcium uniporter in C. elegans odor learning
Hee Kyung Lee, Saebom Kwon, Jessica Antonio, Kyoung-hye Yoon
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 44 P21-01-13

Characterizing neural selectivity using a data-driven interpretable feature finding method in multidimensional stimulus space
Sa-Yoon Park[1], Yoo Rim Kim[2], Sang Jeong Kim[2], Chang-Eop Kim[1]
[1]Department of Physiology, College of Korean Medicine, Gachon University, Seongnam, [2]Department of Physiology, College of Medicine, Seoul National University, Seoul, Korea

S 45 P21-01-14

Electrical stimulation of insular cortex modulates synaptic plasticity to attenuate neuropathic pain in rats
Kyeongmin Kim[1,2], Myeounghoon Cha[1], Leejeong Kim[1,2], Guanghai Nan[1,2], Bae Hwan Lee[1,2]
[1]Department of Physiology, Yonsei University College of Medicine, Seoul, Korea, [2]Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

S 45 P21-01-15 NACA leads to neuroprotection against oxidative injury in long-term cultured OHSCs
Un Jeng Kim[1], Bae Hwan Lee[1], Kyung Hee Lee[2]
[1]Department of Physiology, Yonsei University College of Medicine, Seoul, Korea, [2]Department of Dental Hygiene Division of Health Science, Dongseo University, Busan, Korea

S 45 P21-01-16 Neural circuit from deep cerebellar nuclei to lateral parabrachial nuclei regulates cued fear learning and memory
Kyoung-Doo Hwang[1,2], Jaegeon Lee[1,2], Hyun-Hee Ryu[1,3], Hyun Geun Shim[1,2], Sang Jeong Kim[1,2,3], Yong-Seok Lee[1,2,3]
[1]Department of Physiology, Seoul National University, College of Medicine, [2]Department of Biomedical Science, Seoul National University, College of Medicine, [3]Neuroscience Research Institute, Seoul National University, College of Medicine, Seoul, Korea

S 46 P21-01-17 Protective effect of TRESK on hydrogen peroxide- and lipopolysaccharide-induced cellular stress
Marie Merci Nyiramana[1,2], Eun-Jin Kim[1], Min Seok Woo[1], Dong Kun Lee[1,2], Seong-Geun Hong[1,2], Jaehee Han[1], Dawon Kang[1,2]
[1]Department of Physiology, College of Medicine, Gyeongsang National University, [2]Department of Convergence Medical Science, Gyeongsang National University, Jinju, Korea

S 46 P21-01-18 Revisiting the cerebellar memory consolidation mechanism from AI perspective: The cerebellum as a dual learning machine
Hyojin Bae[1], Jewoo Seo[2], Chang-Eop Kim[1], Sang Jeong Kim[2]
[1]Department of Physiology, Gachon University College of Korean Medicine, Seongnam, Korea, [2]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

## P02: Neuronal pathophysiology

S 47 P21-02-01 Neural circuit and molecular mechanisms of social competition and hierarchy behavior
Tae-Yong Choi[1], Hyoungseok Jeon[2], Sejin Jeong[1], Eum Ji Kim[1], Jeong Seop Kim[1,3], Yun Ha Jeong[4], Byungsoo Kang[5], Murim Choi[2], Ja Wook Koo[1,3]
[1]Emotion, Cognition and Behavior Research Group, Korea Brain Research Institute (KBRI), Daegu, [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, [3]Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST), [4]Neurodegenerative Diseases Behavior Research Group Korea Brain Research Institute (KBRI), [5]R&D Center SYSOFT, Daegu, Korea

S 47 P21-02-02 Stem cell restores thalamocortical plasticity to rescue cognitive deficit in neonatal intraventricular hemorrhage
Hyesoo Jie[1], So Yoon Ahn[2], Won-Beom Jung[3], Ji-Hyun Jeong[1], Sukjin Ko[1], Geun Ho Im[4], Won Soon Park[2], Jung Hee Lee[3], Yun Sil Chang[2], Seungsoo Chung[1]
[1]Department of Physiology, Yonsei University College of Medicine, [2]Department of Pediatrics Samsung Medical Center, [3]Department of Global Biomedical Engineering Sungkyunkwan University, [4]Center for Neuroscience Imaging Research Institute for Basic Science (IBS), Seoul, Korea

S 47 P21-02-03 Reactive microglia and mitochondrial unfolded protein response are following ventriculomegaly and behavior defects in kaolin-induced hydrocephalus
Jiebo Zhu[1,2,3], Min Joung Lee[1,2,3], Hee Jin Chang[1,4], Xianshu Ju[1,3], Jianchen Cui[1,3], Yu Lim Lee[1,3], Dahyun Go[1,2,3], Woosuk Chung[1,5,6], Eungseok Oh[1,4], Jun Young Heo[1,2,3]
[1]Department of Medical Science Chungnam National University School of Medicine, Daejeon, Korea, [2]Department of Biochemistry Chungnam National University School of Medicine, Daejeon, Korea, [3]Infection Control Convergence Research Center Chungnam National University School of Medicine, Daejeon, Korea, [4]Department of Neurology Chungnam National University Hospital, Daejeon, Korea, [5]Department of Anesthesiology and Pain Medicine Chungnam National University School of Medicine, Daejeon, Korea, [6]Department of Anesthesiology and Pain Medicine Chungnam National University Hospital, Daejeon, Korea

S 47 P21-02-04 Prenatal Stress Impairs Neuroligin 1-dependent Neurogenesis through Suppressing Astrocytic FGF2-Neuronal FGFR1 interaction
Gee Euhn Choi, Ho Jae Han
Veterinary Physiology Department of Veterinary Physiology, College of Veterinary Medicine, Research Institute for Veterinary Science, and BK21 Four Future Veterinary Medicine Leading Education & Research Center, Seoul National University, Seoul, Korea

S 48 P21-02-05 Sleep promotion and quality improvement of poria cocos extracts on animal models with sleep disturbance
Hyeyun Kim[2], Kyunyong Park[1], Seohyun Park[1], Jiyeon Moon[1], Seungeun Lee[1], Yein Choi[1], Minchae Kim[1], Byong-Gon Park[1]
[1]Department of Physiology, College of Medicine, Catholic Kwandong University, Gangneung, Korea, [2]Department of Neurology, St. Mary's Hospital, Catholic Kwandong University, Incheon, Korea

S 48 P21-02-06 Pathological findings and epigenetic biomarkers for cognitive impairment in rats with chronic obstructive sleep apnea
Seungeun Lee[1], Jiyeon Moon[1], Minchae Kim[1], Yein Choi[1], Kyunyong Park[1], Seohyun Park[1], Hyeyun Kim[2], Byong-Gon Park[1]
[1]Department of Physiology, College of Medicine, Catholic Kwandong University, Gangneung, Korea, [2]Department of Neurology, St. Mary's Hospital, Catholic Kwandong University, Incheon, Korea

S 49 P21-02-07 Role of mTOR, AMPK, and LC3B signaling in rotenone-induced SH-SY5Y cells treated neural induced-human adipose stem cells conditioned medium
Mahesh Ramalingam[1], Jinsu Hwang[1], Hyong-Ho Cho[2], Byeong C Kim[3], Sujeong Jang[1], Han-Seong Jeong[1]
[1]Department of Physiology, Chonnam National University Medical School, [2]Department of Otolaryngology-Head and Neck Surgery, Chonnam National University Medical School, [3]Department of Neurology, Chonnam National University Medical School, Gwangju, Korea

## P03: Electrophysiology and $Ca^{2+}$ signaling

**S 49** P21-03-01
Cell type dependent post-critical-period intrinsic plasticity in layer 4 of mouse barrel cortex
Minhee Jeong, Chae lim Park, Seungsoo Chung
Department of Physiology, Graduate School of Medical Science Yonsei University College of Medicine

**S 49** P21-03-02
Characterization of KCNQ1 expression and IKs of a novel 845T>G-KCNQ1 mutation in LQT1 patient using hiPSC-derived cardiomyocytes and HEK293 heterologous expression
Seung Beom Oh[1], Sung Joon Kim[1], Seong Woo Choi[2]
[1]Department of Physiology, Department of Biomedical Sciences, Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Physiology, College of Medicine, Dongguk University, Kyungju, Korea

**S 49** P21-03-03
Functional analysis of novel SCN5A mutations related to Brugada syndrome
Hyun Namgoong[1], SungJoon Kim[1], Seong Woo Choi[2]
[1]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Physiology, College of Medicine, Dongguk University, Kyungju, Korea

**S 50** P21-03-04
Bi-directional pH-dependent regulation of calcium homeostasis modulator 1 (CALHM1) ion channel
Jae Won Kwon[1], Young Keul Jeon[1], Sung Joon Kim[1,2]
[1]Department of Physiology, Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [2]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

**S 50** P21-03-05
Multiple effects of α-mangostin on the ion channels in small DRG neurons consistent with the known analgesic effect
Sung Eun Kim[1], Sung Joon Kim[1], Joo Hyun Nam[2]
[1]Department of physiology, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Physiology, College of Medicine, Dongguk University, Kyungju, Korea

**S 50** P21-03-06
Enhanced tonic NMDA current in SON MNCs in DOCA-salt hypertensive rats
Hyun Jin Shin[1,2,3], Chiran jivi Neupane[1,2,3], Ramesh Sharma[1,2,3], Thuy Linh Pham[1,2,3], Jin Bong Park[1,2,3]
[1]Department of Medical Sciences, Chungnam National University, Daejeon, Korea, [2]Department of BK21plus CNU Integrative Biomedical Education Initiative, Chungnam National University, Daejeon, Korea, [3]Department of physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

**S 51** P21-03-07
Deep Learning based the hERG model fitting
Jaekyung Song, Duong Duc Pham, Yunwan Jeon, Hajar Ibrahimi, Chae Hun Leem
Department of Physiology, University of Ulsan College of Medicine, Seoul, Korea

**S 51** P21-03-08
Tonic activation of GluN2D containing NMDA receptors in hippocampal GABAergic interneurons modulates status epilepticus
Ramesh Sharma[1,2,3], Chiranjivi Neupane[1,2,3], Hyun Jin Shin[1,2,3], Thuy Linh Pham[1,2,3], Jin Bong Park[1,2,3]
[1]Department of Medical Sciences, School of Medicine, Chungnam National University, Daejeon, Korea, [2]Department of BK21plus CNU Integrative Biomedical Education Initiative, Chungnam National University, Daejeon, Korea, [3]Department of Physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

**S 52** P21-03-09
cGAMP improves learning and memory via STING-IRF3-GATs pathway in Alzheimer's disease mouse model
Chiranjivi Neupane[1,2,3], Ramesh Sharma[1,2,3], Hyun Jin Shin[1,2,3], Thuy Linh Pham[1,2,3], Jin Bong Park[1,2,3]
[1]Department of Medical Sciences, Chungnam National University, Deajeon, Korea, [2]Department of BK21plus CNU Integrative Biomedical Education Initiative, Chungnam National University, Daejeon, Korea, [3]Department of Physiology, School of Medicine and Brain Research Institute, Chungnam National University, Daejeon, Korea

**S 52** P21-03-10
Chrysosplenol-C increases contraction by augmentation of sarcoplasmic reticulum $Ca^{2+}$ loading and release via protein kinase C in rat ventricular myocytes
Tran. N. Trinh[1], Jun Wang[1], Anh T. V. Vu[1], Joon-Chul Kim[1,4], A.T.N. Hoang[2], Celine J. Ohk[3], Yin Hua Zhang[3], Cuong Manh. Nguyen[2], Sun-Hee Woo[1]
[1]College of Pharmacy, Chungnam National University, Daejeon, Korea, [2]Institute of Natural Products Chemistry VAST, Hanoi, Vietnam, [3]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea, [4]NEXEL Co., Ltd., Seoul, Korea

**S 52** P21-03-11
Inhibition of TRPC4 channel activity in colonic myocytes by tricyclic antidepressants disrupts colonic motility causing constipation
Byeongseok Jeong, Chansik Hong
Department of Physiology, Chosun University School of Medicine, Gwangju, Korea

**S 53** P21-03-12
GABA- and glycine-mimetic responses of isopulegol on substantia gelatinosa neurons of trigeminal subnucleus caudalis in mice
Seon-Hui Jang, Soo-Joung Park, Seong-Kyu Han
Department of Oral Physiology & Institute of Oral Bioscience, School of Dentistry, Jeonbuk National University, Jeonju, Korea

**S 53** P21-03-13
Hydrogen peroxide affects the gonadotropin-releasing hormone neuronal activities in mice
Santosh Rijal[1], Dong-Hyu Cho[2], Seong-Kyu Han[1]
[1]Department of Oral Physiology & Institute of Oral Bioscience, School of Dentistry, Jeonbuk National University, Jeonju, Jeonbuk, Korea, [2]Department of Obstetrics and Gynecology, Jeonbuk National University Medical School, Research Institute of Clinical Medicine of Jeonbuk National University & Biomedical Research Institute of Jeonbuk National University, Korea

S 53 P21-03-14
Group I metabotropic glutamate receptor is involved in low $Mg^{2+}$-induced interictal-like epileptiform activity and cell death 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 54 P21-03-15
TRPC1/4 heteromeric channel's current characteristic is unaffected by mutations in TRPC1 residues lining the pore region
Christine Haewon Park, Insuk So
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 54 P21-03-16
Characteristic analysis of mutation in TRPC4 residue
Jung Lee, Insuk So
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 54 P21-03-17
S2-S3 WW site mediates direct calcium binding and gating of TRPC4 channel
Jinhyeong Kim, Insuk So
Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 55 P21-03-18
Non-selective cation currents mediated by Cx43 hemichannel-P2X4 receptor signaling pathway in rat atrial myocytes under shear stress
Tran Trinh, Long N.H. Do, Nipa Eslenur, Joon-Chul Kim, Sun-Hee Woo
Department of Physiology, College of Pharmacy, Chungnam National University, Korea

## P04: Muscle physiology

S 55 P21-04-01
The vasorelaxant effect of alogliptin, a member of the DPP-4 inhibitor class of anti-diabetic drugs, in rabbit aortic smooth muscle
Ryeon Heo, Minji Kang, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 55 P21-04-02
The inhibitory effect of darifenacin, an anticholinergic agent, on voltage-dependent $K^+$ channels in rabbit coronary arterial smooth muscle cells
Minji Kang, Ryeon Heo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 55 P21-04-03
Inhibition of voltage-dependent $K^+$ channels by atypical antipsychotic olanzapine in coronary arterial smooth muscle cells
Minji Kang, Ryeon Heo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P21-04-04
The suppression of voltage-dependent $K^+$ channels by an antipsychotic drug pimozide in rabbit coronary arterial smooth muscle cells
Minji Kang, Ryeon Heo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P21-04-05
Vasorelaxation of aortic smooth muscle by sitagliptin via the activation of PKA and voltage-gated $K^+$ channels
Ryeon Heo, Minji Kang, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P21-04-06
Tegaserod, a gastrokinetic agent, inhibits voltage-dependent $K^+$ channels in coronary arterial smooth muscle cells from rabbits
Ryeon Heo, Minji Kang, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 56 P21-04-07
The vasodilatory effect of trelagliptin via activation of Kv channels and SERCA pumps in aortic smooth muscle
Ryeon Heo, Minji Kang, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 57 P21-04-08
The state-dependent inhibition of voltage-dependent $K^+$ channels by ziprasidone in coronary arterial smooth muscle cells
Minji Kang, Ryeon Heo, Won Sun Park
Department of Physiology, Kangwon National University School of Medicine, Chuncheon, Korea

S 57 P21-04-09
Pathological mechanism of a constitutively active form of stromal interaction molecule 1 in skeletal muscle
Ji Hee Park[1,2], Seung Yeon Jeong[1,2], Jun Hee Choi[1,2], Eun Hui Lee[1,2]
[1]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, [2]Department of Biomedicine & Health Sciences Graduate School, The Catholic University of Korea, Seoul, Korea

S 57 P21-04-10
Roles of calsequestrin 1 in skeletal muscle
Seung Yeon Jeong[1,2], Mi Ri Oh[1,2], Jun Hee Choi[1,2], Jin Seok Woo[3], Eun Hui Lee[1,2]
[1]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, [2]Department of Biomedicine & Health Sciences Graduate School, The Catholic University of Korea, Seoul, [3]Department of Physiology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

S 57 P21-04-11 Mechanism of vasomotion in human left gastroepiploic artery and human uterine artery
Dae Hoon Kim[1], Jin Young Kim[2], Su Mi Choi[2], Young Chul Kim[3], Seung Myeung Son[4], Ra Young You[3], Chan Hyung Kim[5], Woong Choi[5], Hun Sik Kim[5], Wen-Xie Xu[6], Sang Jin Lee[3], Hyo-Yung Yun[1]
[1]Department of Surgery, [2]Department of Obstetrics and Gynecology, [3]Department of Physiology, [4]Department of Pathology, Department of Pharmacology, College of Medicine, CBNU, Cheongju, Chungbuk, Korea, [5]Department of Physiology, [6]Department of Physiology, College of Medcine, Shanghai Jiaotong University, Shanghai, P.R. China

S 58 P21-04-12 Activation of cardiac connexin 43 hemichannels by shear stress and subsequent contribution of pannexins in left-side cardiac muscle cells
Long Nguyen Hoang Do, Nipa Eslenur, Tran N. Trinh, Sun-Hee Woo
College of Pharmacy, Chungnam National University, Daejeon, Korea

S 58 P21-04-13 Interventricular differences explained by the lower troponin expression in the right ventricle of rats
Young Keul Jeon[1], Jae Won Kwon[1], Ji Hyun Jang[1], Jae Boum Youm[2], Yin Hua Zhang[1,3,4], Sung Joon Kim[1,3,4]
[1]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea, [2]Cardiovascular and Metabolic Disease Center, Department of Physiology, College of Medicine, Inje University, Busan, Korea, [3]Biomedical Sciences Seoul National University College of Medicine, Seoul, Korea, [4]Ischemic/Hypoxic Disease Institute Seoul National University College of Medicine, Seoul, Korea

## P05: Organ physiology

S 58 P21-05-01 MLCP downregulation in the monocrotaline-induced pulmonary hypertensive rats impaired the relaxation of pulmonary arteries via T18/S19 diphosphorylation of myosin regulatory light chain (MLC2)
Suhan Cho[1], Sung Joon Kim[1,2]
[1]Department of Physiology, Seoul National University College of Medicine, [2]Ischemic/Hypoxic Disease Institute Seoul National University College of Medicine, Seoul, Korea

S 59 P21-05-02 APE1/Ref-1 Inhibits Phosphate-Induced Loss of Vascular Smooth Muscle Cells Phenotype and vascular calcification
Eun ok Lee, Yu Ran Lee, Hee Kyoung Joo, Sung Min Kim, Hao Jin, Yeon Hee Choi, Byeong Hwa Jeon
Research Institute of Medical Sciences, Department of Physiology, School of Medicine Chungnam National University, Daejeon, Korea

S 59 P21-05-03 NOS and angiotensin II receptor subtype profiling in uterine and placental tissues in angiotensin II-induced novel preeclampsia rat model
Hui Xing Cui, Li Yuan Jin, Jun Xian Liu, Yin Hua Zhang
Department of Medicine, Seoul National University College of Medicine, Seoul, Korea

S 60 P21-05-04 Mitochondrial Phosphate Carrier Participates in Superoxide Generation and Vascular Calcification
Nhung Thi Nguyen[1,2,3], Tuyet Thi Nguyen[1,4], Thu Ha Nguyen[1,2], Seung-Kuy Cha[1,2], Kyu-Sang Park[1,2]
[1]Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea, [2]Mitohormesis Research Center Yonsei University Wonju College of Medicine, Wonju, Korea, [3]Physiology College of Health Sciences, VinUniversity, Hanoi, Vietnam, [4]Internal Medicine Residency Program College of Health Sciences, VinUniversity, Hanoi, Vietnam

S 60 P21-05-05 The Effects of Capsanthin in a Mouse model of Nonalcoholic Fatty Liver Disease
Sungmin Kim[1,2,3], Hao Jin[1,2,3], Yeon Hee Choi[1,2,3], Hee Kyoung Joo[2], Yu Ran Lee[2], Eun Ok Lee[2], Byeong Hwa Jeon[1,2,3]
[1]Department of Physiology, College of Medicine, Chungnam National University, Daejeon, Korea, [2]Department of BK21Plus CNU Integrative Biomedical Education Initiative College of Medicine, Chungnam National University, Daejeon, Korea, [3]Research Institute for Medical Science College of Medicine, Chungnam National University, Daejeon, Korea

## P06: Endocrine and Energy Metabolism

S 60 P21-06-01 Cell-nonautonomous roles of the nuclear hormone receptor NHR-49 in the nervous system of Caenorhabditis elegans
Saebom Kwon, Hee Kyung Lee, Jessica Antonio, Kyoung-hye Yoon
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 61 P21-06-02 Effect of heat stimulation on circulating irisin in humans
Tae-Hwan Park[1], Jeong-Beom Lee[2], Hye-Jin Lee[2]
[1]Department of Physiology, A student at the College of Medicine, Soonchunhyang University, Cheonan, Korea, [2]Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, Korea

S 61 P21-06-03 Carbon Monoxide Attenuates Monocrotaline-induced Right Ventricle Hypertrophy in Rats
Weijian Li[1], Sun Hwa Lee[2], Suhn Hee Kim[1]
[1]Department of Physiology, Jeonbuk National University Medical School, Jeonju, Korea, [2]Internal Medicine, Jeonbuk National University Hospital, Jeonju, Korea

S 61 P21-06-04 Particulate matter exposure aggravates IL-17 inflammation in the eye and nose of OVA/Poly(I:C) mouse
Jun-Sang Bae[1,2,3]
[1]Department of Otorhinolaryngology, College of Medicine, Dankook University, Cheonan, Korea, [2]Beckman Laser Institute Korea, Dankook University, Cheonan, Korea, [3]Medical Laser Research Center, Dankook University, Cheonan, Korea

S 62 P21-06-05 Skeletal muscle-specific FoxO1 deletion improves high-fat diet-induced insulin resistance and increased endurance exercise capacity via enhanced mitochondrial function in mice
Soyoung Park[1,2], Hye-Na Cha[1,2], Min-Gyeong Shin[1,2], Han-Byul Jung[1,2], Jin-Ho Koh[1], So-Young Park[1,2]
[1]Department of Physiology, Yeungnam University College of Medicine, Daegu, Korea, [2]Smart-aging Convergence Research Center, Yeungnam University College of Medicine, Daegu, Korea

S 62 P21-06-06
Peri-lysosomal Calcium overload by Palmitate in Pancreatic β-cells
Thu Ha Nguyen[1,2], Luong Dai Ly[1,2], Ji-Hyun Lee[2], Soo-Jin Kim[1,2], Nhung Thi Nguyen[1,2], Minh-Hanh Thi Nguyen[1,2], Seung-Kuy Cha[1,2], Kyu-Sang Park[1,2]
[1]Department of Physiology, Yonsei University, Wonju College of Medicine, Wonju, Korea, [2]Mitohormesis Research Center, Yonsei University, Wonju College of Medicine, Wonju, Korea

S 62 P21-06-07
Enhancing β-cells function by Sarco/Endoplasmic Reticulum Calcium ATPase (SERCA) activator
Thu Ha Nguyen[1,2], Ji-Hyun Lee[2], Soo-Jin Kim[1,2], Nhung Thi Nguyen[1,2], Minh-Hanh Thi Nguyen[1,2], Kyu-Sang Park[1,2]
[1]Department of Physiology, Wonju College of Medicine, Yonsei University, Wonju, Korea, [2]Mitohormesis Research Center, Wonju College of Medicine, Yonsei University, Wonju, Korea

S 62 P21-06-08
Relationships between exposed surface area and cutaneous thermal sensitivity to radiant heat exposure
Sang Hyun Roh[1], Ju Hyun Moon[1], Chan Hyeok Kang[2], Joo Young Lee[1,3,4]
[1]Department of Textiles, Merchandising and Fashion Design, [2]Department of Physical Education, [3]Research Institute for Human Ecology, [4]Graphene Research Center for Convergence Technology Advanced Institute of Convergence Technology, Seoul National University, Seoul, Korea

S 63 P21-06-09
Body Regional Differences in Cutaneous Warm and Hot Thresholds using a Radiant Heater
JuYoun Kwon
Research Institute of Human Ecology, Seoul National University, Seoul, Korea

S 63 P21-06-10
The role of FGF signaling in C. elegans' aging
Jessica Antonio, Kyoung-hye Yoon
Department of Physiology, Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 64 P21-06-11
Cutaneous warmth thresholds to conductive and radiant heat exposure: body regional differences
Joo-Young Lee
Department of Textiles, Merchandising and Fashion Design, College of Human Ecology, Seoul National University, Seoul, Korea

S 64 P21-06-12
Effects of intake of caffeine with thermotherapy on active sweat gland density in humans
Hye-Jin Lee[1], Bahda Yun[2], Ryeo-Won Kwon[1], Jin-Sun Park[1], Ha-Gyoung Lee[1], Da-Jeong Bae[1], Jeong-Beom Lee[1]
[1]Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, Korea, [2]College of Arts and Sciences, Case Western Reserve University, Ohio, USA

S 64 P21-06-13
Sweat gland density and output during passive heat load might be lower in tropical natives than in temperate natives
Ryeo-Won Kwon, Jin-Sun Park, Da-Jeong Bae, Ha-Gyoung Lee, Jeong-Beom Lee
Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, Korea

S 65 P21-06-14
Effects of detention living on the immune index in female youths in the youth detention center
Eon-Ah Choo, Ryeo-Won Kwon, Ha-Gyoung Lee, Jeong-Beom Lee
Department of Physiology, College of Medicine, Soonchunhyang University, Cheonan, Korea

## P07: Epithelium and Exocrine Physiology

S 65 P21-07-01
Tas2r108 knock-out induced change in growth and metabolism
Ji-Young Heo[1], Ki-Myung Chung[1,2], Young-Kyung Cho[1,2], Kyung-Nyun Kim[1,2]
[1]Department of Physiology & Neuroscience, College of Dentistry, Gangneung-Wonju National University, Gangneung, Korea, [2]Research Institute of Oral Sciences, Gangneung-Wonju National University, Gangneung, Korea

S 65 P21-07-02
Hyperbaric oxygen therapy promotes wound healing in diabetic mice
Kyu-Hee Hwang[1,3], Subo Lee[1,2,3], Taeui Hong[1,3], Ha-Yeong Young[1,2,3], Su-Yeon Choi[1,2,3], Kyu-Sang Park[1,2,3], Seung-Kuy Cha[1,2,3]
[1]Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea, [2]Department of Global Medical Science, Yonsei University Wonju College of Medicine, Wonju, Korea, [3]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 65 P21-07-03
The Effects of Mitochondria-derived Peptides on Skin Wound Healing
Airr Yeuanmany[1,2,3], Kyu-Hee Hwang[1,3], Kyu-Sang Park[1,2,3], Seung-Kuy Cha[1,2,3]
[1]Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea, [2]Department of Global Medical Science, Yonsei University Wonju College of Medicine, Wonju, Korea, [3]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

S 66 P21-07-04
Co-cultures of human conjunctival epithelial cells on PVA scaffolds and conjunctival fibroblasts in PCL scaffolds better mimic tissue architecture and microenvironment in vivo
Ji Woo Im, Hae-Rahn Bae
Department of Physiology, College of Medicine, Dong-A University, Busan, Korea

## P08: Inflammation and Immune Physiology

S 66 P21-08-01
Hepatic stellate cell-specific HAS2 deficiency attenuates CCl4-induced liver fibrosis
Jee Hyung Lee, Sun Myoung Kim, Cheol Bin Eom, Yoon Mee Yang
Department of Pharmacy, KNU Researcher training program for developing Anti-Viral Innovative Drugs, Kangwon National University, Chuncheon, Korea

S 66 P21-08-02 Molecular protective mechanisms of kaempferol in RINm5F islet β-cells under exposure to interleukin-1β
Seo-Yoon Chang[1], Yong-Jun Ko[1], Dong-Bin Kim[2], Myung-Jun Kim[1]
[1]Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul, Korea, [2]Department of Internal Medicine, College of Medicine, The Catholic University, Seoul, Korea

S 67 P21-08-03 Plasma APE1/Ref-1 is upregulated in relation to vascular inflammation in ApoE knockout mice
Hee Kyoung Joo, Yu Ran Lee, Eun-Ok Lee, Sungmin Kim, Hao Jin, Yeon-Hee Choi, Byeong Hwa Jeon
Department of physiology, Chungnam national university, Daejeon, Korea

S 67 P21-08-04 Majonoside-R2 postconditioning protects cardiomyocytes against hypoxia/reoxygenation injury
Hyoung Kyu Kim[1], Vu Thi Thu[2], Jin Han[1]
[1]Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutic Center, Department of Physiology, Inje University, Busan, Korea, [2]Center for Life Science Research, Faculty of Biology, VNU University of Science, Vietnam National University, Vietnam

S 67 P21-08-05 Inhibition of mitochondrial calcium uniporter attenuates mouse bone marrow-derived mast cell degranulation induced by beta-1,3-glucan
Dang Van Cuong[1], Hyoung Kyu Kim[1,2], Jubert Marquez[1], Amy Kim[1], Kyung Soo Ko[1], Byoung Doo Rhee[1], Jin Han[1]
[1]Department of Physiology, Department of Health Sciences and Technology College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea, [2]Department of Integrated Biomedical Science College of Medicine, Inje University, Busan, Korea

## P09: Cellular Physiology and Cancer

S 68 P21-09-01 Palmitic acid remodels lipid metabolism in hepatocellular carcinoma
Do-Won Jeong, Jieun Seo, Yang-Sook Chun
Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 68 P21-09-02 CR6-interacting factor 1 deficiency induces vascular senescence through SIRT3 inhibition in endothelial cells
Seonhee Kim, Shuyu Piao, Ikjun Lee, Harsha Nagar, Su-Jeong Choi, Byeong Hwa Jeon, Cuk-Seong Kim
Department of Physiology, Chungnam National University College of Medicine, Daejeon, Korea

S 68 P21-09-03 CR6-interacting factor 1 deficiency inhibits BH4 production and induces eNOS uncoupling
Ikjun Lee, Shuyu Piao, Seonhee Kim, Su-Jeong Choi, Harsha Nagar, Byeong Hwa Jeon, Cuk-Seong Kim
Department of Physiology & Medical Science, School of Medicine, Chungnam National University, Daejeon, Korea

S 68 P21-09-04 Butylated hydroxyanisole reduces the growth of lung cancer and normal fibroblast cells via apoptosis and cell cycle arrest
Xia Ying Cui, Woo Hyun Park
Department of Physiology, Medical School, Jeonbuk National University, Jeonju, Korea

S 69 P21-09-05 Butylated hydroxyanisole inhibits the growth of lung cancer and normal cells accompanied by increased ROS levels and GSH depletion
Xia Ying Cui, Woo Hyun Park
Department of Physiology, Medical School, Jeonbuk National University, Jeonju, Korea

S 69 P21-09-06 Apoptotic lung cancer cells suppress migration and invasion of cancer-associated fibroblasts via inhibition of TGF-β1 signaling
Hee Ja Kim, Kiyoon Kim, Jihee Lee
Department of Physiology, Inflammation-Cancer Microenvironment Research Center, School of Medicine, Ewha Womans University, Seoul, Korea

S 69 P21-09-07 Butylated hydroxytoluene decreases HeLa, Calu-6, and A549 cell growth via cell death and cell cycle arrest accompanied by increased ROS levels and GSH depletion
Xia Ying Cui, Woo Hyun Park
Department of Physiology, Medical School, Jeonbuk National University, Jeonju, Korea

S 70 P21-09-08 Each inhibitor of mitogen-activated protein kinases influences the growth inhibition of Calu-6 and A549 lung cancer cells induced by Auranofin
Xia Ying Cui, Woo Hyun Park
Department of Physiology, Medical School, Jeonbuk National University, Jeonju, Korea

S 70 P21-09-09 Interaction between cancer-associated fibroblasts and apoptotic lung cancer cells inhibits migration and invasion of cancer cells via downregulation of TGF-β1 signaling
Hee Ja Kim, Ye-JI Lee, Kyungwon Yang, Kiyoon Kim, Jihee Lee
Department of Physiology, Inflammation-Cancer Microenvironment Research Center, School of Medicine, Ewha Womans University, Seoul, Korea

S 70 P21-09-10 CRIF1 knockdown suppresses endothelial cell migration via upregulation of RhoGDI2
Harsha Nagar[1], Seonhee Kim[1], Ikjun Lee[1,2], Su-Jeong Choi[1], Shuyu Piao[1], Byeong Hwa Jeon[1], Minho Shong[3], Cuk-Seong Kim[1]
[1]Department of Physiology and Medical Science, Chungnam National University, [2]Department of BK21 Plus CNU Integrative Biomedical Education Initiative, Chungnam National University, [3]Research Center for Endocrine and Metabolic Diseases, Chungnam National University, Daejeon, Korea

S 71 P21-09-11
Autophagy dysfunction in an in vitro and in vivo model of diabetic peripheral neuropathy
Su-Jeong Choi[1], Harsha Nagar[1], Shuyu Piao[1], Seonhee Kim[1], Ikjun Lee[1,2], Miae Lee[1], Byeong Hwa Jeon[1], Hee Jung Song[3], Sang-Ha Oh[4], Cuk-Seong Kim[1,2]
[1]Department of Physiology, Medical science, School of Medicine Chungnam National University, [2]Department of BK21Plus CNU Integrative Biomedical Education Initiative Chungnam National University, [3]Department of Plastic and Reconstructive Surgery, School of Medicine Chungnam National University Hospital, [4]Department of Neurology Chungnam National University Hospital, Daejeon, Korea

S 71 P21-09-12
Upregulation of metabokine and UPRmt in amygdala by treatment of β-Guanidinopropionic acid induces anxiolytic behavior
Da Hyun Go[1,2,3], Min Joung Lee[1,2,3], Jiebo Zhu[1,2,3], Sung Kyung Yoon[1,2,3], Hyoeun Kang[1,2,3], Jun Young Heo[1,2,3]
[1]Department of Medical Science, [2]Department of Biochemistry, [3]Infection Control Convergence Research Center, Chungnam National University School of Medicine,Daejeon, Korea

S 71 P21-09-13
Mitochondrial creatine kinase phosphorylation in novel tyrosine residues confers cardioprotection against hypoxia/reoxygenation injury
Jubert Marquez, Nammi Park, Hyoung Kyu Kim, Jin Han
Department of Physiology, Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutics Center, Inje University, Busan, Korea

S 72 P21-09-14
The protective effect of HS 1793 via mitochondrial function regulation from oxidative stress in C2C12 cells
Jubert Marquez[1,2], Nammi Park[2], Maria Victoria Faith Garcia[1,2], Hyoung Kyu Kim[1,2], Jin Han[1,2]
[1]Department of Health Science and Technology, BK21 Plus Project Team, Graduate School of Inje University, College of Medicine, [2]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, BK21 Plus Project Team, College of Medicine Smart Marine Therapeutics Center, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 72 P21-09-15
17β-estradiol increases APE1/Ref-1 secretion via calcium-dependent exosome pathway
Yu Ran Lee[1,2], Hee Kyoung Joo[1,2], Eun-Ok Lee[1,2], Sungmin Kim[1,2], Hao Jin[1,2], Yeon Hee Choi[1,2], Byeong Hwa Jeon[1,2]
[1]Department of Physiology, and [2]Research Institute for Medical Sciences, College of Medicine, Chungnam National University, Daejeon, Korea

S 72 P21-09-16
Knockdown of hematopoietic- and neurologic-expressed sequence 1 stimulated autophagy in colorectal cancer
Ruo Yu Meng, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Jeonbuk National University Medical School, Jeonju, Korea

S 73 P21-09-17
Hematopoietic- and eurologic-expressed sequence 1 regulates autophagy and ERstress in hepatocellular carcinoma cell
Ruo Yu Meng, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Jeonbuk National University Medical School, Jeonju, Korea

S 73 P21-09-18
Recombinant human BMP-2 induced tumorigenesis in human colorectal cancer cells
Ruo Yu Meng, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Jeonbuk National University Medical School, Jeonju, Korea

S 73 P21-09-19
Ursolic acid and Doxorubicin combination therapy enhance the anti-tumor activity in human colorectal cancer by inactivation of Akt signaling
Soo Mi Kim, Dan Hu
Department of Physiology, Institute for Medical Sciences, Jeonbuk National University Medical School, Jeonju, Korea

S 73 P21-09-20
3,3'-diindolylmethane combination with 5-fluorouracil strength the anti-tumor effect through Akt and Wnt/β-catenin pathway in gastric carcinoma
CongShan LI, Soo Mi Kim
Department of Physiology, Institute for Medical Sciences, Jeonbuk National University Medical School, Jeonju, Korea

S 74 P21-09-21
Sirtuin 6 deacetylation TFEB induces cell autophagy in hepatocellular carcinoma
Congshan Li, Soo Mi Kim
Department of Physiology, Institute for Medical, Jeonbuk National University Medical School, Jeonju, Korea

S 74 P21-09-22
Role of TGF-β-mTORC1-NOX4 signaling in pathogenic alterations in the retinal pigment epithelium
Soo-Jin Kim[1,2], Kyu-Sang Park[1,2], Seok Jae Lee[3], Jeong Hun Kim[3]
[1]Department of Physiology, [2]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea, [3]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

S 74 P21-09-23
Autocrine activation of TGF-β mediates transdifferentiation of hepatic stellate cells and liver fibrosis
Soo-Jin Kim[1,2], Kyu-Hee Hwang[1,2], Ha Thu Nguyen[1,2], Su-Yeon Choi[1,2], Aye Hsu Lae[1,2], Ha Yeong Young[1,2], Seung-Kuy Cha[1,2], Kyu-Sang Park[1,2]
[1]Department of Physiology, Yonsei University Wonju College of Medicine, Wonju, Korea, [2]Mitohormesis Research Center, Yonsei University Wonju College of Medicine,Wonju, Korea

S 74 P21-09-24
Deficiency of SREBP-1c protects against liver fibrosis in a mouse model of nonalcoholic steatohepatitis
Do Young Kim, Dae-Kyu Song, Jae-Hoon Bae, Seung-Soon Im
Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

S 75 P21-09-25
Autophagy regulation in TREK1 and TREK2 overexpressed Chinese hamster ovary cells
Yangmi Kim
Department of Physiology, College of Medicine, Jeonbuk National University, Jeonju, Korea

S 75 P21-09-26 IL-1 beta secreted by macrophages induces migration in A549 cells
Hee Ju Song, Taehee Kim, Sang Do Lee
Department of Physiology, Medical Science, Chungnam National University, Daejeon, Korea

## P10: Exercise and Integrative physiology

S 75 P21-10-01 Amphetamine-induced locomotor sensitization is inhibited by alteration of dendritic thin spines in the nucleus accumbens core
Wen Ting Cai[1], Wha Young Kim[1], Myung Ji Kwak[2], Haeun Rim[2], Jeong-Hoon Kim[1]
[1]Department of Physiology, Yonsei University College of Medicine, Seoul, Korea, [2]Department of Medical Sciences, Yonsei University College of Medicine, Seoul, Korea

S 76 P21-10-02 Genome-wide association study and gene-lifestyle interaction of gout in Korean population
Hye Kyung Jeon[1,2], Hae Young Yoo[1]
[1]Department of Nursing, [2]Graduate School, Chung-Ang University, Seoul, Korea

S 76 P21-10-03 Sex differences in genetic polymorphisms of dyslipidemia in Korean populations
Kyung Hee Lee[1,2], Hae Young Yoo[1]
[1]Department of Nursing, [2]Graduate School, Chung-Ang University, Seoul, Korea

## P11: Physiomes and Systems Biology

S 76 P21-11-01 A simplification of glucose-insulin model
Yun Wan Jeon, Jae Kyung Song, Duong Duc Pham, Hajar Ibrahimi, Chae Hun Leem
Department of Physiology, University of Ulsan College of Medicine, Seoul, Korea

## P12: Others: Drugs, Phytochemicals, Miscellaneous

S 77 P21-12-01 The structure-based designing approach revealed TMEMinh001 as a novel inhibitor of ANO1
JooHan Woo[1,2], Raju Das[1], Yohan Seo[3]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, Korea, [2]Channelopathy Research Center (CRC) Dongguk University College of Medicine, Goyang, Korea, [3]New Drug Development Center Daegu Gyeongbuk Medical Innovation Foundation, Daegu, Korea

S 77 P21-12-02 Auraptene alleviates blood-brain barrier leakage after ischemic stroke by enhancing junction proteins through activation of antioxidant enzymes
Min Joung Lee[1,2,3], Jiebo Zhu[1,2,3], Dahyun Go[1,2,3], Sung Kyung Yoon[1,2,3], Jun Young Heo[1,2,3]
[1]Department of Medical Science, Chungnam National University School of Medicine, Daejeon, Korea, [2]Department of Biochemistry, Chungnam National University School of Medicine, Daejeon, Korea, [3]Infection Control Convergence Research Center, Chungnam National University School of Medicine, Daejeon, Korea

S 77 P21-12-03 Unveiling ligand based structural insights targeting SARS-CoV-2 main protease through molecular dynamics
JooHan Woo[1,2], Raju Das[1]
[1]Department of Physiology, Dongguk University College of Medicine, Gyeongju, Korea, [2]Channelopathy Research Center (CRC), Dongguk University College of Medicine, Goyang, Korea

S 77 P21-12-04 N-terminally truncated hERG channels generated by KCNH2 frameshift mutation (c.453delC) induces LQT phenotype in patient-derived iPSC-CMs
Na kyeong Park[1], Sung Joon Kim[1], Seong woo Choi[2]
[1]Department of physiology, Department of Biomedical Sciences, Seoul National University, Seoul, Korea, [2]Department of physiology, Dongguk University College of Medicine, Kyungju, Korea

S 78 P21-12-05 Regulation of murine myometrial and gastric smooth muscle contraction by ginger extracts
Dae Hoon Kim[1], Young Chul Kim[2], Bang Yeon Hwang[3], Chul Lee[3], Jin Young Choi[4], Su Mi Kim[4], Seung Myeung Son[5], Ra Young You[2], Chan Hyung Kim[6], Hun Sik Kim[6], Woong Choi[6], Wen-Xie Xu[7], Sang Jin Lee[2], Hyo-Yung Yun[1]
[1]Department of Surgry, [2]Department of Physiology, [3]Department of Pharmacy, [4]Department of Obstetrics and Gynecology, [5]Department of Pathology, [6]Department of Pharmacology, College of Medicine, CBNU, Cheongju, Korea, [7]Department of Physiology, College of Medcine, Shanghai Jiaotong University, Shanghai, P.R. China

S 78 P21-12-06 Targeted downregulation of Hipp1 ameliorates tau-engendered deficits in Drosophila melanogaster
Sung Yeon Park[1,3], Jieun Seo[2], Seulbee Lee[2], Sang Jeong Kim[1,2,3], Yang-Sook Chun[1,2,3]
[1]Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Physiology, Seoul National University College of Medicine, Seoul, Korea

S 78 P21-12-07 Evaluation of image processing and reconstruction procedures for diffusion tensor imaging in ex-vivo rat brain
Young-Ji Eum[1], Chaejoon Cheong[1], Jin-Hun Sohn[2], Myeounghoon Cha[2], Bae Hwan Lee[2]
[1]Center for Research Equipment Korea Basic Science Institute, Daejeon, Korea, [2]Department of Physiology, Yonsei University College of Medicine, Seoul, Korea

S 79 P21-12-08 Development of a 3-dimensional culture model of mouse hair follicles using dermal fibroblast-grown hydrogels
Ji Woo Im, Hae-Rahn Bae
Department of Physiology, College of Medicine, Dong-A University, Busan, Korea

S 79 P21-12-09

Vasodilatory effect of Alpinia officinarum Hance extract in rat mesenteric arteries
Chae Eun Haam, Soo Yeon Choi, Seonhee Byeon, Soo-Kyoung Choi, Young-Ho Lee
Department of Physiology, Yonsei University College of Medicine, Seoul, Korea

S 79 P21-12-10

ASK 최신 의대인증평가에 즈음한 충북대학교 의과대학 생리학교실의 교육 및 실습 지도 경험의 예
김영철, 이상진
충북의대 생리학교실

S 80 P21-12-11

Effects of chondroT on monosodium iodoacetate (MIA) induced osteoarthritis rats
Myeong-Hun Kim[1], Ji-Min Choi[2], Sang-Mee Gang[1], Seon-Jong Kim[2], Chang-Su Na[1]
[1]Department of Meridian & Acupoint College of Korean Medicine, Dongshin University, Naju, Korea, [2]Department of Korean rehabilitation Medicine College of Korean Medicine, Dongshin University, Naju, Korea

S 80 P21-12-12

A study on the anti-inflammatory effect of Herbal medicine mix (modified Iksuyongjingo) in LPS-induced inflammatory mice
Myeong-Hun Kim[1], Sang-Mee Gang[1], Yang-Seon Moon[2], Hyeong-Seok Kim[3], Hee-Myeong Park[4], Chang-Su Na[1]
[1]Department of Diagnsis and Meridian & Acupoint College of Korean Medicine, Dongshin University, Naju, Korea, [2]Department of Research & Development Nawoori(Ltd), [3]Department of Research & Development Petobio(Ltd), [4]Department of Veterinary Internal Medicine College of Veterinary Medicine, Konkuk University, Seoul, Korea

S 80 P21-12-13

Daeyeongjeon ameliorates particulate matter 2.5-induced lung and vascular injury via NLRP3 dependent inflammasome pathway
Se Hoon Jang[1,2], Byung Hyuk Han[1,2], Youn Jae Jang[1,2], Yun Jeong Yang[1,2], Jung Joo Yoon[1,2], Hye Yoom Kim[1,2], Yun Jung Lee[1,2], Dae Gill Kang[1,2], Ho Sub Lee [1,2]
[1]Hanbang Cardio-Renal Syndrome Research Center, Wonkwang University, Iksan, Korea, [2]College of Oriental Medicine and Professional Graduate School of Oriental Medicine, Wonkwang University, Iksan, Korea

S 81 P21-12-14

Protective Effect of Gunryeong-tang on Diabetic Cardio-renal Syndrome in db/db Mice
Ailin Tai[1,2], Hyeon Kyoung Lee[1,2], Byung Hyuk Han[1,2], Mi Hyeon Hong[1,2], Se Won Na[1,2], Jung Joo Yoon[1,2], Hye Yoom Kim[1,2], Dae Gill Kang[1,2], Ho Sub Lee [1,2]
[1]Hanbang Cardio-Renal Syndrome Research Center, Wonkwang University, Iksan, Korea, [2]College of Oriental Medicine and Professional Graduate School of Oriental Medicine, Wonkwang University, Iksan, Korea

## PL-1

### SF-1 Neurons in the Hypothalamus: A Link between Exercise Training and Metabolic Adaptations

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Exercise has beneficial effects in nearly all organ systems. This includes the CNS, which regulates all peripheral tissues, including the liver, pancreas, skeletal muscle, the heart and adipose tissue. Relatively little is known about the mechanisms underlying the changes in the CNS following exercise training that contribute to the beneficial effects of exercise. Most of the attention in neuroscience has focused on the ability of exercise to improve several parameters of learning and memory, including synaptic plasticity in the hippocampus, and increased neurogenesis. Much less is known about the changes in hypothalamic neurons and circuits following exercise training. We will discuss recent findings that provide evidence how distinct hypothalamic cell groups including the ventral medial nucleus of the hypothalamus (VMH) link exercise and altered energy balance and glucose homeostasis.

## S-1-1

### Discovery of neuropeptides in human serum samples associated with addiction

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While addiction is a medical condition characterized by compulsive engagement in rewarding stimulation, non-drug addictions such as gambling, shopping, exercising, and sexual behavior addictions, and internet gaming disorder (IGD) have become a social issue. Specifically, more people including adolescents are exposed to a high risk of indulging in internet games, further resulting in IGD characterized by excessive and uncontrolled gaming behavior. While there have been few studies of comparative analyses for finding neuropeptides specific to IGD, we pursued comparative analyses of serum samples from the control and IGD groups using the antibody-based array and mass spectrometric analysis to find the neuropeptides or peptide hormones specific to the IGD. From the comparative analyses, several neuropeptides and neurotransmitters were found to show differential abundance levels between the control and IGD groups and they were also validated enzyme-linked immunosorbent assay.

**Keywords:** Internet gaming disorder, Mass spectrometry, Antibody-based array, Neuropeptide

## S-1-2

### Ghrelin in Alzheimer's disease: pathologic roles and therapeutic implications

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Ghrelin, which has many important physiological roles, such as stimulating food intake, regulating energy homeostasis, and releasing insulin, has recently been studied for its roles in a diverse range of neurological disorders. Despite the several functions of ghrelin in the central nervous system, whether it works as a therapeutic agent for neurological dysfunction has been unclear. Altered levels and various roles of ghrelin have been reported in Alzheimer's disease (AD), which is characterized by the accumulation of misfolded proteins resulting in synaptic loss and cognitive decline. Interestingly, treatment with ghrelin or with the agonist of ghrelin receptor showed attenuation in several cases of AD-related pathology. These findings suggest the potential therapeutic implications of ghrelin in the pathogenesis of AD. We summarize the roles of ghrelin in AD pathogenesis, amyloid beta (Aβ) homeostasis, tau hyperphosphorylation, neuroinflammation, mitochondrial deficit, synaptic dysfunction and cognitive impairment. Additionally, we address the roles of ghrelin in the behavioral/psychological symptoms and metabolic syndrome accompanying AD. The findings from these studies suggest that ghrelin has a novel therapeutic potential for AD treatment. Thus, rigorously designed further studies are needed to establish an effective AD-modifying strategy.

**Keywords:** Ghrelin, Alzheimer's disease, Amyloid beta, Tau, Mitochondrial deficits, Neuroinflammation

## S-1-3

### Food restriction, ghrelin, and amphetamine

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Ghrelin, an orexigenic peptide hormone derived from the stomach, mainly functions to increase appetite. In addition, it also affects various brain functions including reward-seeking and addictive behaviors. We previously demonstrated that microinjection of ghrein into the NAcc core produced

the expression of locomotor sensitization in amphetamine (AMPH) pre-exposed rat, in the presence of dopamine D1 receptor agonist. Here, we further investigated whether actual food restriction replacing microinjection of ghrelin may produce similar effects. Rats were housed as one half with food pellets restricted, while the other half with no restriction. With this procedure, plasma ghrelin concentration was found to be significantly increased in food-restricted rats. After 2 weeks, they were all challenged with AMPH (1 mg/kg, IP) and their locomotor activities were measured. Interestingly, food-restricted rats produced sensitized-locomotor activity compared to normal feeding rats. These results elucidate that food restriction by itself is sufficiently able to produce locomotor sensitization to psychomotor stimulants, possibly by ghrelin functioning in the NAcc as shown in our previous findings. We further examined whether there are any differential molecular changes accompanied in the NAcc with AMPH challenge under the food-restriction, and it will be discussed in the present presentation.

**Keywords:** Food restriction, Ghrelin, Nucleus accumbens, Amphetamine, Locomotor sensitization

## S-2-1

### Metabolic perturbations in cardiovascular disease

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Metabolic perturbations underlie a number of cardiovascular diseases. In this talk, I will present data from 3 recent research studies which highlight different aspects of cardiac metabolism and cardiac disease. Firstly, we investigate changes in mitochondrial morphology as a target for cardioprotection showing that hydralazine targets Drp-1 mediated mitochondrial fission and protects the heart from acute ischaemia/reperfusion injury (IRI). Next, we investigate the role of mitochondrial Sirtuin-3 in modulating cardiac metabolism and mediating susceptibility to acute myocardial IRI following starvation. Finally, we investigate metabolic perturbations underlying hypertrophic cardiomyopathy using human induced pluripotential stem cell-derived cardiomyocytes from patients with HCM. Elucidation of the metabolic pathways underlying cardiac disease should result in the identification of novel treatment targets for improving outcomes in patients with heart disease.

## S-2-2

### Immunometabolism and Vascular Injury-Role of Hyperhomocysteinemia

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Hyperhomocysteinemia (HHcy), which is caused by genetic defects on methionine metabolism or metabolic defects on trans-sulfurization pathways, is an independent risk factor for cardiovascular diseases. Immune cells are highly dependent on oxidative metabolism, and their mitochondrial pathogenic mutation threshold is low, therefore immune cells are more sensitive to multiple stress. Adaptive responses of metabolic remodeling will be induced when immune cells are under stimulation with immunogenic stimuli. While these responses are overwhelming, abnormally metabolic status will be induced and the immune system will be reshaped. This process is called 'immunometabolism'. In recent years, our group has continuously reported that HHcy induces metabolic remodeling of T lymphocytes, B lymphocytes, macrophages, adipocytes and platelets with high metabolic rate by causing cellular hypoxia and metabolic stress. HHcy significantly increases the decomposition of membrane phospholipids into proinflammatory lysophosphatidylcholine and polyunsaturated fatty acids. HHcy also increases the oxidation or glycosylation modification of membrane phospholipids, and ultimately accelerate the chronic inflammatory injury in adipose tissues and blood vessels. On the other hand, these cells can also significantly reduce the above-mentioned pathological changes by increasing mitochondrial β oxidation or thermogenesis. The membrane phospholipid decomposition inhibitors, AMPK kinase agonists or peroxisome proliferator activated receptor alpha (PPARα) agonists can significantly improve immunometabolism and chronic vascular inflammation. Therefore, targeting immunometabolism is an important strategy for early prevention and treatment of metabolic cardiovascular diseases.

## S-2-3

### Molecular imaging for evaluating metabolic characteristics of cardiovascular system

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Molecular imaging is an imaging method that visualizes specific molecules or molecular processes in living body. Among several imaging methods including optical imaging, computed tomography, magnetic resonance imaging, gamma camera and positron emission tomography (PET), nuclear molecular imaging uses tracers labeled with radioisotopes and has advantages of high tissue penetration and quantitation ability. Additionally, nuclear imaging has another advantage of trace versatility. For several decades, many radiotracers have been developed and used for animal and human researches and even for clinical practice. For example, in the evaluation of metabolic characteristics of myocardium, F-18 FDG, F-18 FTHA, C-11 acetate PET have been used for glucose, fatty acid, and oxygen metabolism, respectively. Although some elaborate processes such as dynamic image acquisition and tracer kinetic analyses are required, metabolic characteristics can be assessed non-invasively and quantitatively, by using these PET images. As PET imaging uses tracer amount of radiopharmaceuticals and imposed tolerable radiation dose to human, PET imaging can easily be applied to human studies. Many studies have been conducted using metabolic PET in heart failure or toxic myocardial injuries. Recently, newly developed radiotracers are used for specific metabolism, tissue microenvironment of various cell components, and some specific molecule deposition in myocardium. In this talk, methodological aspect of nuclear molecular imaging is discussed, and some representative examples of application are presented.

## S-2-4

### GSK-3β signaling pathway induced cardioprotection

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GSK-3β is a key kinase involved in several cellular signaling pathways and sensitizes cells for cell death. GSK-3β is a protein kinase that participates in fundamental cellular processes, such as cellular metabolism, transcription, and cytoskeleton dynamics. Likewise, GSK-3β is a key regulator of cardiomyoblast survival and death and is involved in the pathogenesis of hypertrophy, fibrosis, heart failure, and ischemia/reperfusion (I/R) injury. Moreover ischemic preconditioning induces phosphorylation and inhibition of GSK-3β, and its pharmacological inhibition mimics the cardioprotective effects of preconditioning. Pharmacological inhibition of GSK-3β protects against I/R-induced damage in the heart, and as a result, inhibitors of GSK-3β have been investigated both for therapeutic use and to better understand how GSK-3β activity is regulated in the heart. As a cardioprotective mechanism, GSK-3β inhibition prevents opening of the mitochondrial permeability transition pore under oxidative stress condition. Inhibition of GSK-3β also confers cardioprotection through reduction of oxidative stress under I/R condition. In the present study, we proposed that GSK-3β inhibition increases the NAD+/NADH ratio via activation of the Nrf2/ Nqo1 axis. This downstream signaling pathway of GSK-3β could be used for the development of GSK-3β-targeted cardiac therapeutics.

**Acknowledgement:** This work was supported by the Basic Science Research Program [2018R1A2A3074998] and by the International Research & Development Program [2017K1A3A1A49070056] through the National Research Foundation of Korea (NRF), funded by the Ministry of Education and Ministry of Science and ICT.

**Keywords:** Mitochondria, Ischemia/reperfusion injury, GSK-3β inhibition

## S-2-5

### Fatty acid metabolism in hypertension

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Cardiac metabolism is essential in myocardial contraction. In addition to glucose, fatty acids (FA) are essential in producing energy in the myocardium since FA-dependent beta-oxidation accounts for > 70-90% of cellular ATP under resting conditions. However, metabolism shifts from FAs to glucose utilization during disease progression (e.g. hypertrophy and ischemic myocardium), where glucose oxidation and glycolysis become the predominant sources of cellular ATP. At advanced failing stage, both glycolysis and beta-oxidation are dysregulated, result in insufficient supply of intracellular ATP and weakened myocardial contractility.

Undeniably, our understandings of myocyte function in healthy and diseased hearts are based on glucose (10 mM)-dependent metabolism because glucose is the "sole" metabolic substrate in most of the physiological experiments. In view of the importance of FAs in cardiovascular health and diseases, we aimed to elucidate the impacts of FA supplementation on myocyte contractility and evaluate cellular mechanisms those mediate the functions in normal heart and with pathological stress. In particular, we have investigated cardiac excitation-contraction (E-C) coupling in the presence and absence of FAs in normal and hypertensive rat left ventricular (LV) myocytes.

Our results reveal that FAs increase mitochondrial activity, intracellular $[Ca^{2+}]_i$ and LV myocyte contraction in healthy LV myocytes whereas FA-dependent cardiac inotropy is attenuated in hypertension. FA-dependent myofilament $Ca^{2+}$ desensitization could be fundamental in regulating $[Ca^{2+}]_i$.

Collectively, FAs supplementation resets cardiac E-C coupling scheme in healthy and diseased hearts.

## S-3-1

### Differences of residential environment in the physiological adaptations to heat acclimatization: Perspiration Research

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Sudomotor activity is modified by repetitive physical and/or thermal training. Physical activities induce internal thermal loads and then raise the overall body temperature. Environmental heat or passive heating, such as hot water immersion, also increases body temperature and results in sweating. Repetitive physical activity or thermal load induces physiological heat adaptation in parallel with modified sudomotor activity. Sweating sensitivity depends on the extension of the period of environmental acclimation. Tropical natives sweat less and preserve more body fluid than temperate natives, tolerating heat stress. However, the mechanisms involved in such sweating reduction has not been fully elucidated. The sudomotor mechanism, wich contributes to tolerating thermal environments, is affected by not only the body temperature, but also sex, ethnicity, exercise training, region, season, and heat adaptation. Aging attenuates the sudomotor function by the decreased peripheral sensitivity to acetylcholine and demyelination of innervating nerves. Women show less sudomotor activity than men. Heat adaptation with sudomotor modification is induced by repetitive physical and/or thermal training. Short-term heat acclimation increases sweat gland activity. Long-term heat acclimation results in a reduction in the sweating response to stimuli. Residents of tropical areas sweat less and more slowly than residents of temperate areas. Short-term heat acclimation enhances the sweating response. Long-term heat acclimation, from seasonal change or migration, diminishes the sweating response. Also, deacclimation can be induced by migration from a tropical area to a temperate area. Body composition, especially brown adipose tissue, and weight affect thermal responses. Further studies should investigate BAT and endocrinal pyrogens as additional factors.

**Acknowledgement:** The authors wish to thank the subjects whose participation made this study possible. No conflicts of interest, financial or otherwise, are declared by the authors. This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(grant number 2016R1D-1A3B2015394).

**Keywords:** Heat acclimatization, Mean body temperature, Sweat, BMR, Sudomotor Function

## S-3-2

### Multi sensor fabrication and precise calibration for the measurement of thermo-physiological responses

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The multi sensor is fabricated by installing several sensing elements in one housing or on one substrate material. Based on the MEMS technology using in the field of semiconductor manufacturing, it could be performed the desired purpose with a small area and tiny volume. External physical environmental factors such as the air temperature, relative humidity, MRT, contacted surface temperature, solar radiation, ultraviolet rays (UVA, UVB), and illuminance etc., that affect the human thermal responses. Personal factors affecting thermal responses are metabolic rate, clothing value, gender, and genetic characteristics etc. The core temperature, skin temperature, heart rate, sweating, etc. are determined by the environmental and personal factors. Sophisticated corrections are needed to study the thermal regulatory system and the thermal behaviors. Since the analysis of the correlation between body temperature and biomarkers requires extremely accurate sensor calibration technology, it is introduced a technique that improved the ultra precision body thermometer to be the accuracy ±0.02 ºC using trimmer resistance control techniques. It became possible to analyze the relationship between the body temperature and the neurotransmitters (NTs); Cortisol, Growth hormone, Melatonin, COX2, PGE2, Orexin, Serotonin etc.

## S-3-3

### Particulate matter exposure aggravates IL-17 inflammation in the eye and nose of OVA/Poly(I:C) mouse

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Data on the effects of direct particulate matter (PM) exposure on the eyes and nose are limited. Here, the IL-17/neutrophil-dominant Ovalbumin (OVA)/polyinosinic-polycytidylic acid (Poly(I:C)) mouse model was used to evaluate the effect of different-sized titanium dioxide ($TiO_2$) particles on the eye and nose. We also examined whether IL-17-neutralizing antibody treatment could reverse $TiO_2$ effects. The nasal cavity and conjunctival sac of mice were challenged with OVA and Poly(I:C) to induce neutrophil

dominant inflammation and then exposed to Micro- and Nano-$TiO_2$. Subsequently, IL-17-neutralizing antibody was administered to investigate the role of IL-17 and inflammatory parameters were evaluated. Micro- and Nano-$TiO_2$ resulted in a significant decrease in tear break up time and increase in corneal damage. Airborne micro-$TiO_2$ also increased the nasal rubbing and sneezing counts compared with those of the OVA/Poly(I:C) group. Micro-$TiO_2$ exposure increased infiltration of neutrophils and IL-17A+ cells in the conjunctival tissue and the nasal mucosa. In addition, these increased symptoms and inflammation in the eye and nose by Micro-$TiO_2$ exposure were inhibited by the IL-17 neutralizing antibody, suggesting the IL-17 dependency. $TiO_2$ increased IL-17-related inflammation in the eyes and nose of the OVA/Poly(I:C) mice and the IL-17-neutralizing antibody alleviated inflammation. The data might help to develop therapeutic modalities for PM exposure and provide evidence for PM-associated diseases.

## S-3-4

### Thermal comfort and skin temperature with radiant cooling panels as a proximity cooling device

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As the development and research of autonomous vehicles has been actively conducted in recent years, 'completely autonomous driving', which is a stage that does not require a driver is approaching. The advent of the era of fully autonomous vehicles is expected to bring about many changes in people's lifestyles by greatly increasing the degree of freedom in the configuration of space in the vehicle. Accordingly, the automobile will go beyond the concept of a simple means of transportation and become a living space. As the time spent in the vehicle increases, research on the thermal comfort of passengers is becoming more and more important to provide comfortable indoor environment.

In addition, the electric vehicle market is starting to be newly formed to convert the vehicle's energy source from fossil fuels to electric vehicles. Expectations and interest in electric vehicles are increasing due to the government's active support policy, and global companies' interest. However, unlike an internal combustion engine vehicle, an electric vehicle has to operate an air conditioning system using electric energy, and thus a reduction in mileage is a problem. Therefore, in order to minimize the reduction in mileage due to air conditioning, the development of a high-efficiency electric vehicle cooling system is most importantly required.

In this context, interest in proximity cooling and heating devices that can improve or maintain the thermal comfort of passengers while reducing power consumption is increasing. For example, a radiant cooling/heating device or cool/warm seat at a close distance to enable individual heating and cooling for each occupant is an example. If used effectively, it is possible to reduce a lot of power consumption even under the same thermal comfort conditions.

Against this background, this study aims to examine the thermal comfort and skin temperature change of occupants when using a proximity radiant cooling device through experiments. These research results can be used as basic data for the development of comfortable proximity cooling systems in the future.

## S-3-5

### Cutaneous warmth thresholds to conductive and radiant heat exposure: body regional differences

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The purpose of the present study was to explore cutaneous warmth thresholds during conductive and radiant heat exposure on 17 body regions. For the conductive heat exposure trials, seven male subjects participated in this study (25.7 ± 7.1 y in age, 176 ± 7.4 cm in height, 70.0 ± 7.5 in body weight, 22.2 ± 1.2 kg/$m^2$ in BMI). All tests were performed in a climate chamber and subjects were seated in a comfortable recliner posture at an air temperature of 23 ℃ and 50%RH. All measurements were conducted using a thermal stimulator (Intercross-210, Intercross Co., Japan, stimulating probe surface area: 2.5 × 2.5 $cm^2$) and repeated three times at each of the 17 body sites (the forehead, neck, chest, abdomen, upper back, lower back, upper arm, forearm, palm, back of hand, front thigh, shin, back of foot, buttock, back thigh, calf, and sole). The values of three repetitions were averaged. A warmth threshold was measured by a methods of limit, which was that the stimuli of the probe started from baseline skin temperature (33°C) and increased at a constant rate of 0.1°C $s^{-1}$ until the subject reported feeling warmth. Warmth sensation was defined as initially sensed warmth on the skin. Subjects pushed the button of the thermal stimulator as soon as they felt warmth. For the radiant heat exposure trials, the surface temperature of a radiant film heater increased by 0.01 A per 0.7 s (0.9oC/s increase) and the film (10 × 10 cm) was fixed using a wood frame to keep a distance of 10 cm from the skin. Fourteen male subjects participated in this study (age: 25 ± 5.1 y, height: 176.6 ± 5.5 cm, body weight: 70 ± 5.8 kg, body surface area (BSA): 1.89 ± 0.11 $m^2$). Cutaneous warmth thresholds on the identical 17 body regions as the conductive heat exposure experiment. A warmth and hotness thresholds were defined as same as the definition in the conductive heat experiment. All trials were conducted in a climate chamber (23oC and 50%RH) and subjects were in a fowler's or prone position on a recliner. A one-way ANOVA was used to test the body regional differences, and Tukey's post hoc test was conducted for multiple comparisons. Statistical significance was set at $P<0.05$. The results showed that there were significant differences in warmth thresholds among the 17 body regions for both conductive and radiant heat exposure, showing higher thresholds on the forehead, back and palm when compared to the foot and sole ($P<0.05$), which were explained higher initial skin temperatures on the forehead, back and palm. For the most body regions, warmth thresholds were higher for the conductive heat exposure than for the radiant heat exposure. The biggest differences were found on the foot (2.6oC-difference) and sole (3.0oC-difference). The results might suggest that the skin was relatively less sensitive to catch conductive heat than radiant heat, but the surface area of heaters was 16 times greater for the radiant heating film than for the conductive heating element and the radiant heater was placed at a 10-cm distance from the skin, while the conductive heating element was contacted to the skin in direct. Therefore, direct comparison in warmth thresholds between conductive and radiant heating was not feasible, but body regional differences in both conductive and radiant heat exposures can be accepted in terms of biological and statistical significance. To conclude, cutaneous thermal thresholds to radiant heat exposure at a distance of 10 cm had higher on the forehead, lower back and palm than the values on the foot and sole, which were related to the level of initial skin temperatures.

## S-4-1

### CALHM1/3 channels mediate chemosensory neurotransmission

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Among six members of the calcium homeostasis modulator (CALHM) family, we originally identified CALHM1 as a pore-forming subunit of a slowly-activating voltage-gated channel with a wide pore which is permeable to adenosine triphosphate (ATP)[1]. Subsequently, we discovered that CALHM1 and CALHM3 hetero-oligomerize to form a fast-activating voltage-gated channel, CALHM1/3. Both subunits are expressed in taste bud cells (TBCs) and genetic elimination of either subunit abolishes the release of neurotransmitter ATP from TBCs and, consequently, the perception of tastes[2,3]. Remarkably, instead of synaptic vesicles, TBCs employ a noncanonical chemical synapse involving CALHM1/3 as the conduit for neurotransmitter release. As chemical neurotransmission was supposed to be mediated sole-

ly by $Ca^{2+}$-dependent exocytosis, we termed this unique chemical synapse "channel synapse". We further reported the structure of CALHM channels and channel synapse[4]. In the first half, the discovery, function, and structure of the channel synapse will be discussed[5].
Although the CALHM1/3 channel synapse potentially mediates various cell-cell communications throughout the body, it remains unclear where it exists and functions outside the tongue. Here, we generated a reporter mouse model for *Calhm1* and *Calhm3*, screened > 40 organs for reporter protein expression, and revealed tissue distribution of cells expressing CALHM1/3. In one of those CALHM1/3$^+$ tissues, we genetically, anatomically, and functionally identified the presence of channel synapses and its physiological relevance. In the second half, extra-oral distribution and function of the CALHM channel synapse will be discussed.

**Keywords:** CALHM, Synapse, Neurotransmission, ATP, Taste

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## S-4-2

### Biophysical regulation of CALHM channel and its structural understanding

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Calcium homeostasis modulator (CALHM) gene family is composed of six members of membrane protein with four transmembrane helices, among which CALHM1 has been investigated in terms of its electrophysiology and physiological roles. Octameric assembly of CALHM1 forms functional channels, activated by membrane depolarization with unselective permeability to various ions including $Ca^{2+}$ and ATP ($I_{CALHM1}$). There are four conserved Cys residues in the extracellular domain that form two intramolecular disulfide bonds. Site-directed mutagenesis of CALHM1 revealed that the intramolecular disulfide bonds are essential for the multimerization and trafficking to the plasma membrane. Despite their critical structural role, a treatment with the membrane-impermeable reducing agent tris(2-carboxyethyl) phosphine (TCEP, 2 mM, 1-30 min) did not affect $I_{CALHM1}$. Interestingly, incubation with TCEP for 2–6 h reduced both $I_{CALHM1}$ and the surface expression of CALHM1 in a time-dependent manner. We propose that the intramolecular disulfide bonds are essential for proper folding, while dispensable for the voltage-dependent activation in the plasma membrane. The activation of $I_{CALHM1}$ is exceedingly slow, which is facilitated by lowering extracellular [$Ca^{2+}$]. We found that physiological temperature facilitates the activation of the CALHM1.[1]) Both voltage-dependence ($V_{1/2}$) and speed of activation are thermosensitive. A heteromultimeric expression of CALHM1 and CALHM3 (CALHM1/3) shows higher amplitude, faster activation, and left-shifted voltage dependence as like the increased temperature condition. Interestingly, the thermosensitivity of CALHM current was not significant in the cells co-expressing CALHM1/3. Apart from the thermosensitivity, The voltage-dependent activation of $I_{CALHM1}$ was markedly facilitated by increasing either extracellular or intracellular pH, and inhibited by acidic pH. The pH-sensitivity was preserved in the excised membrane patch (i-o configuration). We constructed a homology structure model based on the cryo-EM structure of hCALHM2 by using the SWISS-MODEL workspace, and conducted the site-directed mutagenesis of the water-accessible charged amino acids in hCALHM1. We found four charged residues gathering closely in the intracellular space responsible for the alkali-induced facilitation of $I_{CALHM1}$. Considering the large pore diameter of hCALHM1 (14 Å), we interpret that the sensitivity to pHe could be due to the proton transfer between hydronium ions in the pore. Taken together, we report the remarkable temperature and pH-dependent regulation of CALHM1, which might be responsible for the modulation of neurons, taste receptors or immune cells expressing the CALHM family proteins in the plasma membrane.

**Keywords:** CALHM, Disulfide bond, Temperature, PH, Molecular structure

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## S-4-3

### Shear stress mechanotransduction in atrial myocytes and its pathological implication

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Cardiac myocytes are subjected to fluid shear stress during the cardiac cycle and haemodynamic disturbance. The level of interlaminar shear stress in the normal adult rat atria is thought to be very low, but it significantly increases during regurgitant blood-jet and volume/pressure overload due to conditions such as valvular heart disease, congestive heart failure and hypertension. These pathological conditions are associated with atrial fibrillation and cardiac remodeling. Using fluid micro-jet in single cardiac cells and laminar field shear combined with whole-cell and/or reporter patch clamp, confocal imaging or bioluminescence assay, we have discovered that cardiac myocytes from atrium and ventricle respond to fluid shear stress and alter their $Ca^{2+}$ signaling and membrane conductance. In these responses, ATP is generally released through connexin 43 hemichannels and mediates early activation of P2 purinergic receptors. It turned out that activation of P2Y1 receptor (P2Y1R) induces slow longitudinal $Ca^{2+}$ wave that deteriorates regular $Ca^{2+}$ releases, via phospholipase C-IP3 receptor 2 signaling, and that P2X4 receptor (P2X4R) activation causes cation currents to lead spontaneous action potential with subsequent fast transverse $Ca^{2+}$ wave in atrial myocytes. Interestingly, distribution of the P2Y1R and P2X4R between right atrial (RA) and left atrial (LA) myocytes are distinct, in that RA myocytes with higher P2X4R expression tend to show transverse waves, while LA cells expressing more P2Y1R protein expression mostly present longitudinal waves in response to same shear force. Further investigations with prolonged pressure-overloaded rats using transverse aortic constriction (TAC) method revealed enhanced P2Y1R function and expression, with downregulations of P2X4R and Cx43 function in dilated LA myocytes from failed rat hearts. Shear-specific mechanotransduction and the subsequent $Ca^{2+}$ waves may be one way for atrial myocytes to access mechanical stimuli directly and alter their contractility and rhythm accordingly. The remodeling of shear signaling context under prolonged atrial volume-overload suggests implication of shear mechanotransduction in the atrial pathogenesis under chronic hypertension.

**Keywords:** Shear stress, $Ca^{2+}$ wave, Cx43, P2 receptor, Atrial volume-overload

## S-4-4

### Physiological roles of ANO9 channel

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Anoctamin (ANO)/TMEM16 gene family consists of 10 homologs. Anoctamins are expressed in numerous tissues with diverse functions. Notably, ANO1 and ANO2 are Cl- channels activated by intracellular $Ca^{2+}$. ANO6 is known to be a cation channel as well as a scramblase. However, the biophysical and physiological properties of ANO9 are not known.
We found that ANO9 is activated by the phosphorylation by cAMP-dependent PKA. Intracellular cAMP evoked robust currents in HEK cells transfected with Ano9, which is blocked by PKA inhibitors. Cholera-toxin that stimulates adenylate cyclase also induces ANO9 currents. Unlike ANO1, ANO9 is a cation channel permeable to cations including divalent cations. Interestingly, intracellular $Ca^{2+}$ augments the cAMP-induced ANO9 currents, suggesting a common feature of Anoctamins, the $Ca^{2+}$ dependency.
We also found that ANO9 is highly expressed in the cilia of olfactory sensory

neurons (OSNs) in the olfactory epithelium (OE), where it amplifies olfactory signals in OSNs. ANO9 was activated by odorants via their respective receptors. *Ano9*-deficient mice elicited reductions in olfactory behavioral sensitivity, electro-olfactogram signals, and neural activity in the olfactory bulb. Thus, the signal amplification by ANO9 is essential for olfactory signal transduction.

**Keywords:** Anoctamin 9, Channel, CAMP, PKA, Olfaction

## S-5-1

### Rewiring tumor microenvironment to establish premetastatic niche

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Primary tumor induces recruitment of macrophages within the metastatic sites and generates a hospitable metastatic niche to enhance homing and colonization of circulating tumor cells. However, the molecular mechanism underlying endothelial remodeling that favors macrophages infiltration and subsequent niche formation is not fully understood. Here, we found that tumor-derived factors activated endothelial cells to increase adhesive efficacy of monocytes to the endothelium, leading to macrophage infiltration. In mouse models of pulmonary metastasis, this endothelial activation triggered formation of premetastatic niche via accumulation of macrophages in the lungs. Of note, macrophages primed the metastatic microenvironment through enhancing expression of niche-related genes including S100A8, S100A9, MMP9 and fibronectin within the premetastatic lungs and directly transmitted survival signal to tumor cells in a contact-dependent manner. Furthermore, we demonstrated that depletion of macrophages specifically during premetastatic stages reduced niche formation and also resulted in reduced metastatic burden. Our study reveals a novel mechanism by which tumor establishes premetastatic niche via regulation of endothelial cells and macrophages, and provides a therapeutic target for patients with metastatic cancers.

**Keywords:** Macrophages, Metastatic niche, Endothelium, Premetastatic lung, Metastasis

## S-5-2

### Rolling the Cancer Immunity Cycle

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Immunotherapy is revolutionizing the treatment of cancer. The current immunotherapeutics that work by taking the brakes off T cells have been particularly transformational, dramatically improving outcomes for some cancer patients. But we still need to answer to those patients whose cancers do not respond to these immunotherapeutics, and those whose cancers respond initially but then become resistant to the treatments. The more we study the major issues of tumors, the more we come to realize that they cannot be understood in isolation. Tumors are systemic problems, which mean that they are interconnected and interdependent. Cancer cells are present within a complex adaptive ecosystem consisted of associated cells including immune cells, connective tissue cells, endothelial cells within a scaffold of matrix altogether forming tumor microenvironment. Cancer, perhaps uniquely among human illnesses, is a disease that arises through Darwinian interactions of microenvironmental selection and phenotypic adaptation, which are both causes and consequences of its complexity and heterogeneity. Since a life has begun 3.5 billion years ago, they ensured continuous interaction between the diverse species, both cooperative and fiercely competitive in nature. So they have developed complex and sophisticated immune system to survive. Can we develop better systems to fight against cancer than our own immune system? Even though we do not understand completely our own immune systems, we could try at least to awaken our own immune system to fight against cancer. In an attempt to trigger our own immunity against cancers, we utilized the characteristic of genetic instability to our advantage, as the expression of cancer cell neoantigens triggers immunity against cancer cells, which can be called "intrinsic cancer vaccination". For patients who have nonimmunogenic tumors, we need to transplant xenogenic molecules to roll the cancer immunity cycle. For this purpose, we designed protein nanocages or extracellular vesicles (exosomes), which hold not only ligands or xenogenic molecules for enhancing cancer cell phagocytosis but also drugs for inducing immunogenic cancer cell death. This strategy will allow us to avoid using known tumor specific antigens, ex vivo manipulation and adoptive cell therapy, instead, efficiently present neoantigens of cancer cells to our immune system. This strategy could be combined with other treatment modalities to potentiate the therapeutic efficacy.

**Keywords:** Cancer immunotherapy, Cancer immunity cycle, Exosome, Intrinsic cancer vaccination

## S-5-3

### MicroRNA-196a activates lung cancer-associated fibroblasts

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Cancer-associated fibroblasts (CAFs) in the tumor microenvironment promote the migration, invasion, and metastasis of cancer cells. CAFs are activated through diverse processes, including post-transcriptional regulation by microRNAs (miRNAs). To identify the miRNAs that regulate CAF activation, we tried NanoString assay to profile global miRNA expression within normal mouse lung fibroblasts (LFs) and CAFs. Based on NanoString profiling, miR-196a was selected as a candidate that was up-regulated during CAF activation. miR-196a-overexpressed LFs (LF-196a) promoted the migration and invasion of lung cancer cells in co-culture systems. ANXA1 was confirmed as a direct target of miR-196a, and adding back ANXA1 to LF-196a diminished the cancer cell invasion promoted by miR-196a. miR-196a facilitated CCL2 secretion in fibroblasts, which was suppressed by ANXA1. Furthermore, blocking CCL2 impeded cancer spheroid invasion. In lung adenocarcinoma patients, high miR-196a expression was associated with poor prognosis. On the basis of these results, we suggest that CAF-specific miR-196a promotes lung cancer progression in the tumor microenvironment via ANXA1 and CCL2 and that miR-196a will be a good therapeutic target for lung adenocarcinoma patients.

**Acknowledgement:** This research was supported by National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (NRF-2020R1A5A2019210).

**Keywords:** Cancer-associated fibroblasts, Invasion, Lung adenocarcinomas, Tumor microenvironment, MiR-196a

## S-5-4

### Reprogramming of CAFs by apoptotic cancer cells

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The interplay between apoptotic cancer cells and the tumor microenviron-

ment modulates cancer progression and metastasis. However, whether and how cancer-associated fibroblasts (CAFs)-mediated efferocytosis might influence the tumor progression and metastasis have not been studied. We demonstrate that treatment with conditioned medium derived from CAFs exposed to UV-irradiated apoptotic cancer cells suppresses TGFβ1-induced migration and invasion of cancer cells. Direct exposure of CAFs to apoptotic 344SQ (ApoSQ) cells inhibits also the migration and invasion of CAFs. Preferentially enhanced the Wnt-induced signaling protein 1 (WIPS-1) secretion by CAFs in response to ApoSQ is required for the anti-migration and anti-invasion effects in 344SQ and CAFs. Pharmacologic inhibition of Notch1 activation or siRNA-mediated silencing Notch1 markedly prevents WISP-1 expression and secretion by CAFs, which consequently reverses the anti-migration and anti-invasion effects. Moreover, single injection of ApoSQ cells suppresses mRNA expression of various CAF activation markers, but enhances WISP-1 mRNA and protein expression in isolated $Thy1^+$ CAFs from primary tumors in syngeneic immunocompetent mice. Importantly, administration of ApoSQ-exposed CAF CM suppresses lung metastasis, whereas WISP-1-immunodepleted ApoSQ-exposed CAF CM reverses anti-metastatic effect. Thus, treatment with apoptotic cancer cells or the CM from CAFs exposed to apoptotic lung cancer cells could be an effective therapeutic approach against tumor progression and lung metastasis with suppressing CAF activation.

**Acknowledgement:** This work was supported by the National Research Foundation of Korea grants funded by the Korean government (MSIT) (2020R1A5A2019210).

**Keywords:** Cancer-associated fibroblasts, Apoptotic cancer cells, Notch1, WISP-1, Metastasis

## S-5-5

### New strategy for immunotherapeutics based on engineered T cell-derived immune-exosomes

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Antibody blockade of PD-L1 has shown effectiveness against many cancers, including melanoma and non-small-cell lung cancer. However, only small portion of patients respond to anti-PD-L1/PD-1 therapy. Recently, it has been reported that activated CD8+ T cell-derived extracellular vesicles (EVs) inhibit fibroblastic stroma-mediated tumor progression. Additionally, elevation of exosomal PD-L1 from cancer cells is one of reasons for resistance of anti-PD-L1/PD-1 therapy. It suggests that inhibition of exosomal PD-L1 may overcome the resistance of this immunotherapy.
In this study, we tried to find endogenous cytokines which suppress exosomal PD-L1 from cancer cells and further develop engineered T-cell derived exosomes containing the cytokine. This engineered T cell-derived exosomes would show two characteristics, immune modulation and inhibition of exosomal PD-L1 from cancer cells.
We used a lentivirus-based cytokine library to screen for cytokines that inhibit the secretion of metastatic cancer cell derived exosomes and finally identified a cytokine. Next, we used membrane bound cytokine (MBC) platform. This platform is composed of the transmembrane domain of the cytokine-linker-PDGF receptor. We engineered T cells which express the cytokine on the surface of T cells. The engineered immune exosomes are evaluated using western blot and enzyme linked immunosorbent assay. Immune exosomes reduced the secretion of exosomes from metastatic melanoma cells and suppressed PD-L1 expression on the exosomes. Furthermore, by the immune exosomes, cytotoxic T cell activity was enhanced as shown in increase of interferon gamma, granzyme B and perforin.
In this study, we first identify an endogenous cytokine which could reduce the exosomal PD-L1 in cancer cells, and engineered T cell derived therapeutic exosomes lead the increase of anti-cancer effects on melanoma. This new strategy would become a new technological breakthrough to overcome the limitation of anti-PD L1 immunotherapies.

**Acknowledgement:** This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT.

**Keywords:** Exosomes, PD-L1, T-cell, Cytokine

## S-6-1

### Targeted downregulation of *Hipp1* ameliorates tau-engendered deficits in *Drosophila melanogaster*

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Tauopathies, such as Alzheimer's disease (AD), are neurodegenerative diseases characterized by the deposition of neurofibrillary tangles comprising hyperphosphorylated tau protein in the human brain. Given that abnormal epigenetic alterations in heterochromatin configuration have been documented in AD patients and transgenic animal models of AD, we investigated the roles of novel heterochromatin-associated interactors in tauopathies. We examined whether tissue-specific downregulation or loss-of-function alleles of heterochromatin-associated interactors can affect tau-induced neurotoxicity using transgenic flies via UAS-Gal4 binary system. Here, we found that knockdown of HP1 and insulator partner protein (*Hipp1*) ameliorates tau-engendered eye defects, locomotion defects, reduced lifespan, weight loss, and neurodegeneration by preventing hyperphosphorylation of tau. Nonetheless, RNAi-mediated reduction of *Hipp1* failed to restore tau-induced heterochromatin loosening; it accelerated abnormal overexpression of heterochromatic genes. Instead, knockdown of *Hipp1* restored tau-driven aberrant expression of putative insulator targets and aberrant insulator-mediated epigenetic alterations. HIPP1 may have a role as an insulator binding partner regarding to be implicated in tau-induced neurodegeneration. Moreover, knockdown of *Hipp1* in flies overexpressing tau restored the aberrant expression of AD susceptibility genes, *Amph* and *Sox102F*. These results suggest that downregulation of *Hipp1* expression may be a potential therapeutic target in neurodegenerative diseases; they also provide new insights regarding the roles of insulator proteins in tauopathies.

## S-6-2

### Evaluation of novel cellular arrhythmia models in patient-specific iPSC-derived cardiomyocytes

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Life threatening ventricular arrhythmias leading to sudden cardiac death are a major cause of morbidity and mortality. These arrhythmias are often the result of genetic defects in special membrane proteins called ion channels. Understanding the pathophysiology of inherited arrhythmias can be challenging because of the complexity of the disorder and lack of appropriate cellular and in vivo models. Recent advances in human induced pluripotent stem cell technology have provided remarkable progress in comprehending the underlying mechanisms of ion channel disorders or channelopathies by modeling these complex arrhythmia syndromes in vitro in a dish. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are now promising option for either patient-specific or patient-independent application. In this study, we characterized the hiPSC-CMs obtained in different patients with different types of arrhythmia. The arrhythmia properties of hiPSC-CMs were evaluated with electrophysiological methods using patch clamp and multi-electrode array. The arrhythmic potentials were also evaluated by treating drugs with different risk of arrhythmia.

## S-6-3

### Regulation of smooth muscle contraction by channel modulators

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For last 10 years, our groups have studied about mechanism of spontaneous vascular contraction (vasomotion) and effect of extract from natural substances on human and murine smooth muscles. Vasomotion is the oscillatory rhythmic contraction in tone of blood vessel. It is believed to gives rise in flowmotion of blood into an each organ. However, the mechanism of generation and/or regulation including physiological meaning of human vasomotion need more careful studies. Another focus of our study is regulation of smooth muscle by natural substances and to purify its final medicinal components. From 2007, our research team have studied to find medicinal candidate substances from over 20 natural substances. Among them, now we got some strong biological and physiological substances from physiological studies. One of them is ginger (Zingiber officinae Roscoe) which is a flowering plant in family Zingiberaceae. Its roots is widely used as an ingredient in the world and East Asian traditional medicine. Ginger is traditionally used to treat paralytic ileus, fever, nausea, vomiting, and uterine disorders. In addition, it can also regulate contractility of some smooth muscles.

Firstly, mechanism of vasomotion and its regulatory factors in human stomach and uterus was studied. In circular muscle of human gastric and uterine artery, repetitive application of stepwise stretch with high $K^+$ (50mM) produced nerve-independent vasomotion. It was inhibited by nifedipine and facilitated by Bayk 8644, activator of VDCCL. Blocking of intracellular $Ca^{2+}$ from SR(sarcoplasmic reticulum) also inhibited vasomotion reversibly. Inhibitors of $Ca^{2+}$-activated Cl- channels (DIDS, niflumic acid) and/or opener of ATP-sensitive $K^+$ (KATP) channels inhibited human gastric vasomotion. In the case of human uterine artery, application of stepwise stretch with high $K^+$ (50mM), prostaglandin F2a and oxytocin (OXT) also produced nifedipine- and Bayk 8644-sensitive vasomotion. Vasomotion and OXT-induced vasomotion of human uterine artery was also blocked by DIDS and cromakalim. Under molecular study, we identified $Ca^{2+}$-activated $Cl^-$ channels, subunits of ATP-sensitive $K^+$ ($K_{ATP}$) channels(Kir 6.2 and sulfonylurea receptor 2B (SUR2B)), and c-Kit positive band in Western blot.

Another theme of our research is to find the physiological and/or medicinal component from natural substance in the regulation of function of smooth muscle. Several ginger extract such as methanol extract, oleoresinginer, and subordinate extract from oleoresinginer showed diverse effects on murine gastric and uterine smooth muscle. Low- and high-concentration of ginger showed both increase and decrease of basal, acetylcholine- OXT-, and $PGF_{2\alpha}$-induced contractions. Furthermore, in murine stomach, oleoresinginer and water fraction of it increased of ACh-induced phasic contractions. It means extract from ginger have strong effective physiological and functional components for regulation of gastric and myometrial smooth muscle contractility.

These results might raise the importance of basic-clinical combined research for future treatment of drug development.

**Keywords:** Human artery, Vasomotion, $Ca^{2+}$, $Ca^{2+}$-activated Cl- channels, ATP-sensitive $K^+$ (KATP) channel, Natural Substance, Ginger

## S-6-4

### PTEN-induced kinase 1 (PINK1) ameliorates lupus nephritis via regulation of Stimulator of interferon genes (STING) signaling pathway

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Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. Mitophagy is a type of autophagy for selective removal of dysfunctional or redundant mitochondria and known to be linked to autoimmune diseases, including SLE. However, the mechanism of mitophagy is still contradictory. Stimulator of interferon genes (STING) is an endoplasmic reticulum (ER) signaling adaptor that is essential for the type I interferon response to DNA pathogens. STING signaling pathway is known to be linked to autoimmune disease, too. Here, we investigated the role of PTEN-induced kinase 1 (PINK1), which is a master regulator of mitophagy, and STING in lupus mouse model. In this study, we used female MRL/lpr mice, which are unique among lupus strains that develop a full panel of lupus autoantibodies. Mock and PINK1 plasmids were administered intravenously every 5 days. Blood serum and urine were collected biweekly to assess autoantibody level and renal functions. Splenocytes were analyzed for immune phenotype. The kidney tissues were analyzed histologically. PINK1 administration resulted in significant attenuations in inflammation, renal function activity. The level of albumin and creatinine was assessed to evaluate renal function and was significantly decreased in PINK1 administered group. H&E result showed less glomerulonephritis and vasculitis, which are major histological phenotype of lupus nephritis, by PINK1 administration. Furthermore, infiltration of Th17 and activation of STING in kidney was dramatically decreased in PINK1 administered group. Our findings indicate that PINK1 ameliorates lupus disease through regulating of STING signaling pathway.

**Keywords:** Systemic lupus erythematosus (SLE), Lupus nephritis, Autoimmune disease, PTEN-induced kinase 1 (PINK1), Stimulator of interferon genes (STING)

## S-7-1

### Emergence of cognitive functions in the brain

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Recently, biologically inspired artificial neural networks have provided insight into the underlying mechanisms of brain functions, particularly regarding information processing for visual perception. A number of studies using artificial neural networks revealed that visual functions can emerge from supervised and unsupervised learning, suggesting a possible scenario of how visual object recognition in the brain circuits arise. However, the ability to perform various cognitive functions is often observed in naïve animals, and this raises questions about the origin of early cognitive functions in the brain before visual training. In this talk, I will introduce our recent findings that visual cognitive functions such as number sense or face recognition can emerge spontaneously in hierarchical neural networks in the complete absence of visual training. Using a biologically inspired deep neural network, we found that neurons tuned to face images or stimulus numerosity arise in untrained random feedforward networks. These neurons also showed single- and multi-neuron characteristics of the types

observed in biological brains, such as Weber-Fechner law. The responses of these neurons enable the network to perform a visual comparison task, even under the condition that the information in the stimulus is incongruent with low-level visual cues. These results suggest that cognitive functions can emerge from the statistical properties of bottom-up projections in hierarchical neural networks, and provide new insight into the origin of early cognitive functions in biological brains, as well as in artificial deep neural networks.

**Keywords:** Deep neural network, Innate brain function, Number sense, Face recognition, Random feedforward network

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## S-7-2

### Neural mechanisms of individual recognition in the hippocampus

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Within a close-knit social group, recognizing an individual as a unique identity and associating and retrieving individual-specific information during social interactions are fundamental abilities for living as a member of the group. Although individual recognition has been reported in many species, including rodents, its neural underpinnings remain unclear. Here, we show that dorsal hippocampal activity discriminates between male littermates that are identical in sex, age, and genetic makeup, and similarly familiar to subject mice, and thus are different only in their individually unique characteristics. Using a simplified and precisely controlled Go-NoGo individual discrimination task, we found that mice could discriminate familiar individual conspecifics through a brief face-to-face investigation, and this ability depended on the dorsal hippocampus. Two-photon imaging of the activity of neuronal populations revealed that subsets of hippocampal neurons selectively responded to individual stimulus mice regardless of their reward contingency. Population activity also predicted the identity of stimulus mice with high accuracy. These findings suggest that the individual-specific neuronal activity provides a possible neural substrate for individual recognition.

**Keywords:** Social memory, Individual recognition, Hippocampus, Two-photon calcium imaging

## S-7-3

### Cracking the neural population code of complex cognitive behavior

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Cognitive flexibility is a fundamental feature of high-level brain function. However, neuronal pathways that control flexibility and the mechanisms by which flexibility is encoded are unknown. Previous studies have reported that neurons in the orbitofrontal cortex (OFC) encode the value of an external environment and lesions in the OFC area in human have led to deficits in choice behavior. Depletion of serotonin in the OFC area caused impaired reversal learning (RL). However, we still do not know how flexibility is represented by individual neurons or synapses. Fundamental questions underlying cognitive flexibility would be to understand a specific brain condition where new information can be updated without losing existing memories. In order to understand these brain mechanisms, we examined neuronal changes within a specific time window of behavior and control the exact timing of serotonin and glutamate release. We specifically targeted the DRN-OFC circuits and controlled their functions in a high spatiotemporal resolution. In brief, we identified the direct long-range projection from the DRN to the OFC anatomically and functionally. Optogenetic stimulation of serotonergic inputs to the OFC facilitated the RL and the inhibition of DRN-OFC circuits slowed down the speed of RL. We also found that the membrane potential of pyramidal neurons was increased by serotonin, resulting in the enhanced spiking probability of the OFC network. Imaging through a miniscope in behaving animals revealed *in vivo* functions of serotonin in the OFC. Combined two-photon $Ca^{2+}$ imaging and uncaging showed that serotonin boosted $Ca^{2+}$ transients and promoted the synaptic plasticity at dendritic spines. Thus, we revealed that cognitive flexibility may not be encoded as a form of specific cell types or circuit pathways, but rather be represented via state-dependent synaptic plasticity. We believe that these findings are important early steps which will furnish new insights into general cognitive learning.

**Keywords:** Cognitive flexibility, OFC, Serotonin, Internal brain state, Reversal learning

## S-7-4

### Revisiting the cerebellar memory consolidation mechanism from AI perspective: The cerebellum as a dual learning machine

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The cerebellum is known for the critical site for motor learning, and many studies have been conducted to explore the neural circuits and mechanisms responsible for the memory formation and consolidation. Although they have provided detailed observations in several cerebellum-dependent motor learning paradigms, our knowledge of the underlying processes remains fragmentary. In this study, we employ statistical learning theory in machine learning to propose a novel framework that can explain why and how the cerebellum learns and consolidates memories by transfer mechanism.

We model the cerebellar system as dual learning machine which composed of two systems with different dimensions-cerebellar cortex and vestibular nuclei. Based on modified empirical risk minimization theory, we predicted the preference of each system according to two factors of learning-phase and task difficulty. Predictions were validated with both computer simulation and behavioral experiments. For in vivo validation, optokinetic response and vestibulo-ocular reflex were regarded as easy and hard task, respectively, and parameters to quantify the task difficulty were specified.

The results of the theoretical analysis suggest that adaptive learning occurs first in the cerebellar cortex and simple components are then transferred to the vestibular nuclei, and the extent and timing of the transfer can vary depending on the task difficulty. We also suggested that learning by adjusting the cerebellar cortex is beneficial for stabilizing performance especially when changes in the target function are transient. To compare the specificity of learning, we measured the degree of generalization in untrained conditions in each behavioral task. As a result, it was confirmed that generalization occurred at all frequencies tested in optokinetic response, which is expected to be less dependent on the cerebellar cortex, whereas learning occurred specifically only in trained frequency in vestibular-ocular reflex.

In this study, we tried to model and interpret the cerebellar system from the machine learning perspective. This framework can provide a comprehensive understanding on the cerebellar learning and contribute to further

elucidating the essence of cerebellar computations.

**Keywords:** Cerebellum, Motor learning, Memory transfer, Machine learning theory, Computational modeling

## S-7-5

### Characterizing neural selectivity using a data-driven interpretable feature finding method in multidimensional stimulus space

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Characterizing neural selectivity is a common approach to understand how cortical neurons process information, i.e., the first step to understand the computation mechanism of neurons. Although there have been persistent attempts to investigate neural selectivity, mischaracterization often occurs due to the conventional method using researcher-defined features. Despite the importance of this problem, the reason that causes mischaracterization is not defined well enough and the solution has not been proposed yet. Here, we suggest possible scenarios of mischaracterizing neuronal selectivity and demonstrate that a data-driven interpretable feature finding method for characterizing neural selectivity can solve this problem. We propose the data-driven interpretable feature finding algorithm that can find all feasible features given stimuli by fitting neural response vector in multidimensional sensory feature space. It suggests possible features with a normalized value, which reflects the p-value of linear regression analysis. To validate the usefulness of our algorithm, we applied it to in vivo two-photon $Ca^{2+}$ imaging data of primary somatosensory cortex neurons using peripheral stimulation, such as innocuous brush stroke and noxious forceps pinch. As a result of applying our algorithm on the peripheral stimulation dataset, among known-features, brush texture, forcpes texture, and noxiousness features are in high rank, while other features such as dynamicity, staticity, and pressure have low probability that population of S1 neurons would be tuned to these features. Also, this algorithm suggests some unknown features in high rank, such as brush stroke, forceps press + forceps pinch, forceps stroke + forceps pinch features.
In conclusion, we propose a data-driven method for characterizing neural selectivity. We demonstrate that our method can be used for finding missing features and for verifying whether all possible features are known. These results show that data-driven approach can be the crux when investigating neural selectivity.

**Keywords:** Neural selectivity, Neural computation, Interpretable stimulus feature, Data-driven approach, Primary somatosensory cortex

## S-8-1

### Elucidate novel genetics and pathobiology of hearing loss

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The Global Burden of Disease Study measured years lived with disability and found that hearing loss is the fourth leading cause of disability. Globally, the prevalence of hearing loss doubles with every 10-year increase in age. The main causes of hearing loss are genetic mutations, aging, noise exposure, exposure to therapeutic drugs that have ototoxic side effects, and chronic conditions. More than 126 genes have known mutations that result in hearing loss that is not associated with disorders of other organs (nonsyndromic hearing loss) and explain approximately 50% of childhood-onset hearing loss. Therefore, 50% of childhood-onset hearing loss are still molecularly unsolved. In addition, age-related and noise-induced hearing loss are affected by genetic and environmental factors, but genetics of susceptibility to age-related and noise-induced hearing loss are poorly understood. Here, we hypothesize that comprehensive genetic study will reveal genetic landscape of hearing loss. We aim to identify novel genes and gene-gene interactions that lead to hearing loss and biologically validate genetic findings to reveal new pathobiology of hearing loss, therefore, establish a new paradigm that will ultimately realize precision medicine for hearing loss.

**Acknowledgement:** This study is supported by the Team Science Award of Yonsei University College of Medicine.

**Keywords:** Hearing loss, Genetics, Mutation

## S-8-2

### TMEM43, a novel cation channel in cochlear glia is critical for maintenance of speech perception

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Cochlear glia-like supporting cells (GLSs) have been suggested to play an important role in development and maintenance of auditory system. However, genes that are primarily expressed in GLSs have never been clearly associated with progressive human deafness. Herein, we present a novel deafness locus mapped to chromosome 3p25-26 and a new human auditory neuropathy spectrum disorder (ANSD) gene, *TMEM43* mainly expressed in GLSs. We specify p.R372X of *TMEM43* as a cause of the significant deterioration of speech discrimination in humans. *TMEM43* shown as a novel pH-sensitive channel mediates the passive conductance current in GLSs via interacting with TASK-1. This current is abolished by gene-silencing of either *Tmem43* or *Task-1* and in p.R372X knock-in mouse in a dominant-negative fashion. Given the pathogenic effect limited to GLSs, speech discrimination of the affected ANSD subjects was successfully restored by cochlear implant. Our study elucidates an unprecedented pathological role of cochlear GLSs by identifying a novel deafness gene and its causal relationship with ANSD, paving the way for precision medicine in deafness.

**Keywords:** Cochlear glia, Cation channel, Deafness, Speech perception, TMEM43

## S-8-3

### Cholesterol metabolites mediate Hearing Loss in Pex5 cKO mice

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Peroxisomes are subcellular organelles that are involved in various metabolic reactions, including fatty acid oxidation, bile acid synthesis, plasmalogen biosynthesis, and detoxification of reactive oxygen species. Defects in peroxisomal function are associated with severe inheritable genetic and metabolic disorders. However, many of peroxisomal functions are still remain to be elucidated in the field of hearing research. Herein, we found observed that peroxisomes play pivotal roles on morphology of auditory cells and hearing functions in Pax2-Pex5-/- mice. Stereociliopathy of outer hair cells and mispositioining of kinocilium were observed in Pax2-Pex5-/- mice without any distinctive defect in inner ear development. ABR thresholds, including frequency and click, were significantly increased in Pax2-Pex5-/- mice along with severe impairment of mechanotransduction activity. Also, reduction and demyelination of spiral ganglion neuron were accompanied, which was caused by inflammatory responses of reactive oxygen species and cholesterol metabolites.

## S-8-4

### Gene therapy of sensorineural hearing loss using adeno-associated virus in mouse model

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Mutations of *SLC26A4* that abrogate pendrin, expressed in endolymphatic sac, cochlea and vestibule, are known to cause autosomal recessive sensorineural hearing loss with enlargement of the membranous labyrinth. This is the first study to demonstrate the feasibility of gene therapy for pendrin-related hearing loss. We used a recombinant viral vector to transfect *Slc26a4* cDNA into embryonic day 12.5 otocysts of pendrin-deficient knock-out (*Slc26a4*$^{\Delta/\Delta}$) and pendrin-deficient knock-in (*Slc26a4*$^{tm1Dontuh/tm1Dontuh}$) mice. Local gene-delivery resulted in spatially and temporally limited pendrin expression, prevented enlargement, failed to restore vestibular function, but succeeded in the restoration of hearing. Restored hearing phenotypes included normal hearing as well as sudden, fluctuating, and progressive hearing loss. Our study illustrates the feasibility of gene therapy for pendrin-related hearing loss, suggests differences in the requirement of pendrin between the cochlea and the vestibular labyrinth, and documents that insufficient pendrin expression during late embryonal and early postnatal development of the inner ear can cause sudden, fluctuating and progressive hearing loss without obligatory enlargement of the membranous labyrinth.

**Keywords:** Enlarged vestibular aqueduct, Gene therapy, In-utero, Pendred syndrome, Recombinant adeno-associated virus, Solute carrier family 26 member 4

## S-8-5

### *In vivo* gene editing prevents progressive hearing loss in KCNQ4 dominant murine model

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Hearing loss is the most common sensorial disorder; 50% cases are attributable to genetic variations. Recently, gene editing with Cas9-guide RNA complex packaged in liposome or adeno-associated virus (AAV) was applied to rescue hearing loss caused by the transmembrane channel-like gene family 1 (*Tmc1*) variant in inner hair cells. However, deafness caused by the main pathology in the outer hair cells (OHCs), which is the common reason for progressive hearing loss, has not been treated with genome editing approach. Here, we show that in vivo gene editing in the cochlea can ameliorate hearing deterioration in *Kcnq4*$^{W276S/+}$ knock-in mice, which mimic human genetic deafness caused by a functional defect in the OHCs. Although the optimized efficacy of gene editing by AAV in the genomic DNA level was ~0.6%, the gene-edited mice exhibited significantly improved auditory function and more hyperpolarized steady-state OHCs, implying that KCNQ4 channel activity was sufficiently improved. Our findings suggest that the low efficiency of gene editing in the OHCs does not hinder the therapeutic development for deafness but rather confirms that minimal gene editing at the genotype level can also rectify deafness caused by the OHCs.

**Acknowledgement:** This work was supported by the Basic Science Research Program of the National Research Foundation of Korea (grant number 2018R1A5A2025079, 2019R1A2C108403); the Korean Health Technology R&D Project of the Ministry of Health and Welfare, Republic of Korea (grant number HI17C0676; HI18C0160); and the Team Science Award of Yonsei University College of Medicine (grant number 6-2021-0003, 6-2021-0002).

**Keywords:** Adult-onset hearing loss, Outer hair cell, DFNA2, KCNQ4, Cas9, Gene editing

## S-9-1

### Tracing Metabolic Flux In Vivo in Exercise

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Exercise induces dynamic changes in metabolic architecture in skeletal muscles directly and other tissues such as adipose tissue indirectly, contributing largely to improvements in exercise performance as well as health. Biomolecules in metabolic architecture like glucose, amino acids, and lipids are in a constant state of turnover in living organisms at varying rates. Dysregulation of metabolic turnover leads to pathological conditions such as obesity, insulin resistance, diabetes, whereas regular exercise reverses these unfavorable conditions and/or improve exercise performance through adjustments of these metabolic fluxes. Despite dynamic nature of biomolecules, metabolic research has focused heavily on static, snapshot information such as abundance of mRNA, protein, and metabolites and/or (in) activation of molecular signaling, often leading to erroneous conclusions on the metabolic status. Over the past century, stable, nonradioactive isotope tracers have been used to provide critical information on dynamics of specific biomolecules (metabolites and polymers including lipids, proteins, DNA, etc.), ranging from in vitro cell to in vivo animals to humans. In this talk, I will discuss 1) the importance of obtaining kinetic information for a better understanding of metabolism, 2) basic principles of stable isotope tracer methodology using substrate level tracers (e.g., $^{13}C$ or $^{2}H$ labelled tracers of glucose, amino acids, etc.) in lab settings or deuterium oxide in free-living settings, and then 3) how to assess various aspects of metabolism at systemic and intracellular levels (e.g., glycolysis, PPP, Krebs cycle, etc.).

## S-9-2

### Enhancement of Anaerobic Glycolysis – a Novel Role of PGC-1α4 in Resistance Exercise

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Resistance exercise training (RET) is an effective countermeasure to sarcopenia, related frailty and metabolic disorders. Here, we show that an RET-induced increase in PGC-1α4 (an isoform of the transcriptional co-activator PGC-1α) expression not only promotes muscle hypertrophy but also enhances glycolysis, providing a rapid supply of ATP for muscle contractions. In human skeletal muscle, PGC-1α4 binds to the nuclear receptor PPARβ following RET, resulting in downstream effects on the expressions of key glycolytic genes and proteins. In myotubes, we show that PGC-1α4 overexpression increases anaerobic glycolysis in a PPARβ-dependent manner and promotes muscle glucose uptake and fat oxidation. In contrast, we found that an acute resistance exercise bout activates glycolysis in an AMPK-dependent manner. These results provide a mechanistic link between RET and improved glucose metabolism, offering an important therapeutic target to counteract aging and inactivity-induced metabolic diseases benefitting those who cannot exercise due to many reasons.

## S-9-3

### Mild exercise intervention improves human cognitive function with increased neural efficiency of prefrontal cortex in the older adults

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It has not been revealed how a long-term mild exercise impact on executive function which is localized in the prefrontal cortex. This study used a color word matching Stroop task and a functional near-infrared spectroscopy to examine whether a three-month's mild exercise intervention would be beneficial to prevent an executive decline in the older adults, compared to the older adults who keep their sedentary lifestyle. We further examined its underlying neural mechanism based on the neural efficiency (NE) hypothesis. Mild exercise intervention significantly decreased the Stroop interference (SI)-related reaction time (RT) in the older adults, but there were any significant interaction or main effects on the SI-related oxy-Hb changes or SI-related NE scores in any prefrontal sub-regions. Intriguingly, we found that SI-related NE scores were significantly decreased with aging only in the control group, not in the exercise group. Then we further examined effects of mild exercise on the SI-related NE scores in the older adults divided into two groups (younger-old aged vs. older-old aged) based on the median age (68 yrs. old). Interestingly, it was founded that not only SI-related RT significantly decreased, but also SI-related NE scores in all ROIs of prefrontal cortex significantly increased in the older-old aged adults. Taking these results together, it is revealed that a long-term mild exercise intervention has preventive effects of executive decline especially in the older-old adults by increasing executive relevant neural efficiency of the prefrontal cortex.

**Acknowledgement:** This work was supported by the Ministry of Education of the Republic of Korea and National Research Foundation of Korea (2021S1A5A806936311).

**Keywords:** Mild exercise intervention, Executive function, Neural efficiency, Functional near-infrared spectroscopy, Stroop task, Prefrontal cortex

## S-9-4

### Treadmill exercise alleviates behavioral deficits by regulating dopamine metabolism and mitochondrial homeostasis in the mouse model of Parkinson's disease

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Parkinson's disease (PD) is characterized by progressive dopaminergic neuron loss, which is significantly correlated with the presence of progressive motor deficits. Although exercise intervention improves motor dysfunction, the molecular mechanisms remain to be elucidated. We hypothesized that treadmill exercise (TE) improves motor deficits by regulating dopamine metabolisms and mitochondrial homeostasis in the chronic 1-methyl-1,2,3,6-tetrahydropyridine with probenecid (MPTP/P)-induced mouse model of PD. Our data show that MPTP/p treatment significantly impaired motor function and TE could reverse this effect. TE inhibited dopaminergic neuron loss by activating the expression of dopamine-related proteins such as tyrosine hydroxylase (TH), vesicular monoamine transporter-2 (VMAT-2), dopamine decarboxylase (DDC), and dopamine transporter (DAT). In addition, TE and seemed to reduce α-Syn levels and α-Syn-mediated apoptotic cell death. Additionally, TE activates mitophagy and mitochondrial biogenesis and decreased oxidative stress. Taken together, our results demonstrate that TE may improve dopamine metabolisms and reduce α-Syn levels by improving mitochondrial homeostasis, thereby ameliorating chronic MPTP/P-induced motor dysfunction in PD mice.

**Keywords:** Treadmill exercise, Dopamine metabolism, Mitochondrial biogenesis, Mitophagy, A-Synuclein

## S-10-1

### Making sense of flavor

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Feeding is one of the most critical animal behaviors. Taste is a major player in regulating feeding behavior, which allows animals to discriminate nutritious foods from toxic substances in their natural environment. However, in actual life, a variety of sensory information such as olfaction, texture, and temperature is also involved in identifying and evaluating the food.
Over the last few decades, there has been much progress in understanding how animals can taste single taste modality in peripheral and central levels. However, relatively little is known about how taste perception changes when multiple taste stimuli are present together or when the taste is combined with other sensory modalities.
*Drosophila* tastes a diversity of molecules that mediate stereotypical behaviors by activating taste receptor cells. Combining the molecular, genetic, calcium imaging, and electrophysiological approaches available in *Drosophila* offers an ideal opportunity to study these interactions in taste. I will discuss how these interactions affect animal feeding behavior.

**Acknowledgement:** This work was supported by National Research Foundation of Korea (NRF) Grants funded by the Korean Government (NRF-2016R1A5A2008630).

**Keywords:** *Drosophila*, Feeding, Flavor, Taste, Olfaction, Mechanosensation

## S-10-2

### Cellular and molecular mechanisms underlying attractive sodium taste in taste buds

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Sodium taste, a distinct taste modality that is selectively induced by sodium ions ($Na^+$), mediates attractive behavior to sodium salts, e.g. NaCl, and thereby regulates the amount of salt consumption. The amiloride-sensitive epithelial sodium channel (ENaC) is the $Na^+$ sensor located in the apical membranes of taste cells dedicated to sodium taste, which we can refer to as sodium cells. However, the identity of sodium cells and their intracellular signaling cascade downstream of ENaC, including the involvement of action potentials and $Ca^{2+}$ signals and neurotransmission mechanism remain long-standing enigmas. In this study, we show that a subset of taste cells with ENaC activity fire action potentials in response to ENaC-mediated Na+ influx without changing the intracellular $Ca^{2+}$ concentration, and form an atypical chemical synapse with afferent neurons involving the voltage-gated ion channel CALHM1/3 as the conduit for neurotransmitter release, which we have termed the "channel synapse". Genetic elimination of ENaC in *Calhm1*-expressing cells (ENaC cKO) as well as global *Calhm3* knockout (KO) abolished the amiloride-sensitive component of the gustatory nerve responses and attenuated behavioral attraction to NaCl. Together, cells expressing ENaC and CALHM1/3 constitute sodium cells, where the entry of oral Na+ elicits suprathreshold depolarization for action potentials driving voltage-dependent neurotransmission via the channel synapse. Thus, from the sensor to neurotransmission process, sodium taste signaling bypasses $Ca^{2+}$ signals by involving only $Ca^{2+}$-independent ion channels: ENaC, the Nav channel, and CALHM1/3 channel.

**Acknowledgement:** JST (PRESTO), the JSPS (KAKENHI), the Salt Science Research Foundation, and the Kyoto Prefectural Public University Corporation.

**Keywords:** Sodium taste, Channel synapse

## S-10-3

### Single cell transcriptomic atlas of mouse taste bud organoids

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Human can recognize and distinguish five (or possibly more) dedicated taste modalities: Sweet, bitter, salty, sour and umami tastes. Although each taste modality could affect the intensity and the duration of perception of other taste modalities, the nature of each modality is preserved independently. The ability that we distinguish taste modalities is originated from the heterogeneity of taste cells in the taste buds. According to the morphology, the physiologic responses to tastants, and the molecular expression patterns, the taste buds are composed of four types of intragemmal taste cells: Type I cells similar to glial cells; Type II, the receptor cells; Type III cells, the presynaptic cells; and Type IV cells, the intragemmal progenitor cells. Various genes and proteins have been revealed to be involved in the mechanism for the detection of chemicals in taste cells. However, high-throughput, unbiased screening data has been absent due to the technical limitation. Here, we will present our recent ongoing progress of the large-scale single cell RNAseq experiments and its preliminary analysis of the taste bud organoids derived from mouse circumvallate papillae. This study will not only reveal novel genes expressed in the taste buds, but also broaden our understanding the molecular and cellular heterogeneity of the entire taste bud cells.

**Acknowledgement:** This work was supported by National Research Foundation of Korea (NRF) Grants funded by the Korean Government (NRF-2019R1C1C1006751 and NRF-2020R1A4A3078962).

**Keywords:** Taste, Taste bud, Organoid, Single cell RNAseq

## S-10-4

### Live imaging of taste cells in action

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The initial event in taste sensation is mediated by taste cells on the tongue that translate ingested chemicals into cellular signals. Current understanding on this cellular level taste encoding process has relied on ex vivo model systems that cannot fully recapitulate natural cellular microenvironment in vivo. To resolve this methodological limitation, we invented a microfluidics-on-a-tongue imaging chamber that has integrated multichannel microfluidics for auto-controlled tastant delivery. Using this system, we screened over 100 fungiform taste cells to the five basic taste qualities, and obtained comprehensive functional maps. We revealed that taste cells are composed of 70% of single-tuned and 30% of dual-tuned cells, and also discovered a novel population of dual-tuned taste cells encoding a positive valence. We believe that our novel screening platform will pave a way for the deeper understanding of taste coding logic.

**Keywords:** Taste, Imaging, In vivo

## S-11-1

### Pathophysiology of TM4SF5-mediated steatohepatitis associated with fibrosis

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Diverse functions of normal or cancerous cells including proliferation, migration and invasion critically and greatly depend on extracellular environment during their survival and metastasis. The environment consists of extracellular matrix (ECM) proteins, neighboring cells, and soluble factors, including of cytokines, chemokines, and growth factors. Driving factor(s) mechanistic for the chronic and multiphase liver malignancy remains unclarified. We investigated roles of transmembrane 4 L six family member 5 (TM4SF5) in the aggravation of liver malignancy, using cognately genetic or chemical-induced models of *in vitro* primary cells and *in vivo* animals. TM4SF5 is a transmembrane glycoprotein of the transmembrane 4 L six family, a branch of the tetraspan(in) family, highly expressed in many types of cancers including hepatic cancer and shown to cause epithelial-mesenchymal transition (EMT). TM4SF5 in hepatocytes is induced by cytokines/chemokines including TGFβ1, CCL2, CCL5, and others, which are known to be involved in development of NASH and liver fibrosis. We have recently found that TM4SF5 expression in hepatocytes can cause or promote nonalcoholic fatty liver disease (NAFLD) including steatohepatitis associated with fibrosis presumably following abnormal metabolic-inflammatory dysfunctions. The relevance of TM4SF5 in the bidirectional communications between hepatocytes and macrophages can also be importantly involved in the pathological development. Further anti-TM4SF5 reagents including small compound or antibody appears to inhibit the TM4SF5-mediated NAFLD.

**Keywords:** NAFLD, Inflammation, Metabolism, Tetraspanin, Signal transduction, Therapeutic reagent

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## S-11-2

### Deficiency of formyl peptide receptor 2 exacerbates liver inflammation and fibrosis in mice with nonalcoholic fatty liver disease/steatohepatitis

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Nonalcoholic fatty liver disease (NAFLD) is a worldwide leading cause of chronic liver disease that extends from steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. NASH is a more severe form of NAFLD accompanying with persistent inflammation and increased fibrosis in damaged liver. Inflammation and/or fibrosis plays a pivotal role in progression from steatosis to NASH; however, the pathogenesis of NASH has not been fully elucidated. Formyl peptide receptor 2 (FPR2), a G protein-coupled receptor, modulates inflammatory responses in several organs such as lung, kidney and salivary gland. However, the role of FPR2 in liver remains unknown. Hence, we aimed to investigate the role of FPR2 in liver. 7-week-old male C57BL/6 wild-type (WT) and FPR2-knockout (FPR2KO) mice were fed with either normal chow diet or choline-deficient L-amino acid defined high-fat diet (CDAHFD) for 6 or 12 weeks. Although WT and FPR2KO mice showed a similar increase in the ratio of liver weight to body weight and the serum levels of ALT/AST after CDAHFD feeding, CDAHFD-fed FPR2KO mice had more excessive inflammation and severe hepatocyte death in the livers with the increased levels of triglyceride than CDAHFD-fed WT mice. The number of Kupffer cells also increased in the livers of CDAHFD-fed FPR2KO mice compared with CDAHFD-fed WT mice. The mRNA and protein levels of profibrotic markers, such as collagen1α1 and α-smooth muscle actin, were elevated in the livers of CDAHFD-fed FPR2KO mice compared to CDAHFD-fed WT mice. Sirius red staining and hydroxyproline assay also showed more deposition of collagen fibrils in the livers of CDAHFD-fed FPR2KO mice than CDAHFD-fed WT mice. Our findings demonstrate that FPR2 deficiency exacerbates liver inflammation and fibrosis contributing to rapid progression

of NASH, suggesting that FPR2 plays important role in modulating anti-inflammatory response in the liver.

**Keywords:** Formyl peptide receptor 2, Nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis, Inflammation, Fibrosis

## S-11-3

### Function of SREBP-1c in the development of hepatic fibrosis

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Nonalcoholic steatohepatitis (NASH) is a leading cuase of chronic liver disease worldwide and is characterized by lipid accumulation, inflammation, and fibrosis. Here, we report that high-fat-diet-induced sterol regulatory element-binding protein (SREBP)-1c, a key transcription factor that regulates lipid biosynthesis, impairs autophagic lipid catabolism via altered H2S signaling. SREBP-1c reduced cystathionine gamma-lyase (CSE) via miR-216a, which in turn decreased hepatic H2S levels and sulfhydration-dependent activation of Unc-51-like autophagy-activating kinase 1 (ULK1). Furthermore, Cys951Ser mutation of ULK1 decreased autolysosome formation and promoted hepatic lipid accumulation in mice, suggesting that the loss of ULK1 sulfhydration was directly associated with the pathogenesis of NAFLD. Moreover, silencing of CSE in SREBP-1c knockout (KO) mice increased liver triglycerides, confirming the connection between CSE, autophagy, and SREBP-1c. Overall, our results uncover a 2-fold mechanism for SREBP-1c-driven hepatic lipid accumulation through reciprocal activation and inhibition of hepatic lipid biosynthesis and degradation, respectively. Also, the molecular mechanism by which SREBPs regulate cell signaling pathway in NASH animal model has not been fully addressed. Here, we identify the novel target of SREBP-1c in high-fat/high-sucrose diet-mediated steatohepatitis animal model. We found that hepatic fibrosis was decreased in SREBP-1c KO mice compared with wild type mice. In addition, we characterized the specific target of SREBP-1c in the liver, resulting in stimulating steatohepatitis development. Based on those data, we suggest that SREBP-1c is involved in chronic inflammation and fibrosis by reducing target gene expression in NASH.

**Acknowledgement:** This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2019R1A2C2085302, 2021R1A4A029238).

**Keywords:** SREBP-1c, NASH, Firobosis, Sulfhydration, Autophagy

## S-11-4

### Kctd17, a novel regulator in progression of NAFLD/ NASH

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Obesity-induced fatty liver predisposes to non-alcoholic steatohepatitis (NASH), which has no approved pharmacotherapy, making it the fastest growing indication for liver transplantation. Previously, we identified that hepatic *Kctd17* (Potassium Channel Tetramerization Domain Containing 17) expression was increased in murine obesity, and *Kctd17* was correlated with excess hepatic fat in patients. Knockdown of hepatic *Kctd17* in obese mice allowed to repression of fat accumulation, while hepatocyte-specific *Kctd17* overexpression in heathy mice provoked fatty liver. Furthermore, overexpression of *Kctd17* exacerbated fibrosis in mice fed a NASH-provoking diet, whereas hepatocyte-specific *Kctd17* knockout mice were protected from NASH-induced liver fibrosis. To test therapeutic potential of this biology, we designed a *Kctd17*-directed antisense oligonucleotide (ASO), which reduced high fat diet-induced fatty liver and NASH diet-induced liver fibrosis in mice. These results demonstrate that increased hepatocyte Kctd17 promotes hepatic steatosis and fibrosis and suggest translational potential of Kctd17 inhibitors in patients with NAFLD/NASH.

**Acknowledgement:** This work was supported by the National Research Foundation (NRF) grant funded by the Korea government (MSIT) (No. 2020R1C1C1004015 and 2021R1A5A2031612) and INHA UNIVERSITY Research Grant.

**Keywords:** Kctd17, Fatty liver, Fibrosis

## S-11-5

### Hepatic stellate cell-derived hyaluronan in nonalcoholic hepatitis

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Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver diseases. Approximately 25% of these patients can develop nonalcoholic steatohepatitis (NASH), which is the advanced form of NAFLD with liver inflammation and damage. NAFLD/NASH-cirrhosis is considered to become the leading indication for liver transplantation in the next decade. We found that hepatic stellate cells are the major source of hyaluronan (HA) during liver fibrosis. NASH patients with fibrosis showed increased HA accumulation and HA synthase 2 (HAS2) expression in the liver. During the last 25 years, we and other investigators have proved that HA have distinct physiological and pathophysiological roles depending on their size. We suggested that low-molecular weight-HA (LMW-HA; 100-300 kDa) was the predominant form in the fibrotic liver. In addition, LMW-HA was greatly increased in sera from NAFLD patients with fibrosis as compared to subjects without fibrosis. LMW-HA regulated proinflammatory chemokine production and profibrogenic gene expression. We identified Notch1 as a downstream molecule of HAS2-HA-CD44 signaling, which promotes liver fibrosis. Pharmacological inhibition of HA synthesis reduced Notch1 expression and successfully attenuated NASH. Taken together, we demonstrated that LMW-HA is a potent regulator of liver fibrosis via activation of Notch1 signaling in the liver and proposed HAS2 as a therapeutic target for NASH.

**Acknowledgement:** This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korea Government (MSIT) (Nos. 2021R1A4A3031661 and 2020R1C1C1004185).

**Keywords:** HAS2, CD44, TLR4, Liver fibrosis

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## S-12-1

### Naturally occurring compounds with autophagy-inducing property and their application for skin health

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Human skin acts as a barrier to protect our bodies from UV rays and exter-

nal pathogens and to prevent water loss. Phenotypes of aging, or natural aging due to chronic damage, include wrinkles and the reduction of skin thickness that occur because of a loss of skin cell function. The dysregulation of autophagy, a lysosome-related degradation pathway, can lead to cell senescence, cancer, and various human diseases due to abnormal cellular homeostasis. Here, we discuss the roles and molecular mechanisms of autophagy involved in the anti-aging effects of autophagy and the relationship between autophagy and aging in skin cells. In addition, we will introduce quantitative screening method established under AKT2 and c-Fos coexpression conditions to find autophagy-regulatory compounds. Finally, we will show skin protective activities of screened autophagy-regulatory natural products derived from *Penthorum chinense* and *Patrinia villosa* in terms of photo-aging and melanogenesis.

**Keywords:** Autophagy, AKT2, C-Fos, Natural compound, Skin, Melanogenesis

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## S-12-2

### Punicalagin ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis-like lesions via PAR2 inhibition

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Protease-activated receptor 2 (PAR2) is a G-protein-coupled receptor that is expressed in various cell types and activated by serine proteases such as trypsin and tryptase. PAR2 plays several important roles in many physiological events, including inflammation, pain and itch. Interestingly, PAR2 is significantly increased in primary afferent nerve fibers on skin biopsy of patients with atopic dermatitis, and application of a PAR-2 agonist enhanced and prolonged itching. In this study, we identified a novel and potent PAR2 antagonist, punicalagin, using a cell-based highthroughput screening. Punicalagin potently and selectively blocked PAR2 activation in various cell types endogenously expressing PAR2. Punicalagin strongly reduced PAR2-activating peptide (PAR2-AP)-induced itch in a dose-dependent manner in normal mice. Punicalagin reduced PAR2-AP-induced elevations of IL-2, IL-6, IL-8, and CCL3 in HaCaT human keratinocytes. In addition, punicalagin significanly decreased the dermatitis score, bouts of scratching, epidermal thickness and serum TSLP levels in 2,4-dinitrofluorobenzene (DNFB)-induced atopic dermatitis mouse model. Our results suggest that punicalagin has beneficial effects on atopic dermatitis via inhibition of PAR2, and punicalagin is a potential therapeutic agent for atopic dermatitis.

**Acknowledgement:** The author would like to thank Prof. Won-Sik Shim (College of Pharmacy, Gachon University) for evaluating the efficacy of punicalazine in a model of DNFB-induced atopic dermatitis.

**Keywords:** Protease-activated receptor 2, Itch, Atopic dermatitis, Punicalagin, Antagonist

## S-12-3

### Drug discovery of natural products targeting ion channels in non-excitable cells

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Natural products are complex mixtures of bioactive compounds having potential utility in medical applications. Natural products have been considered for many protein targets but few have been developed for new ion channel targeting drugs. Although ubiquitously present in mammalian cell membranes, ion channels show different expression types and patterns depending on the cell type. Their general physiological role is the regulation of electrical potential across the membrane but they can also control intracellular calcium signal transduction and regulate secretion and contractility. Generation of intracellular $Ca^{2+}$ signaling requires not only calcium channels such as Orai1 but also potassium channels that can maintain electrical driving force. $Ca^{2+}$ influx through channels eventually generates intracellular $Ca^{2+}$ signaling that results in different outcomes depending on the individual $Ca^{2+}$ channel type such as T cell proliferation and differentiation through Orai1, epidermal barrier formation, and keratinocyte differentiation through TRPs. Therefore, a specific agonist/antagonist for each ion channel is required to maintain cell homeostasis and for the treatment of various diseases.
In this presentation, I will discuss our progress in new drug discovery and the development of applicable botanically derived chemicals to modulate the activity of ion channels.

## S-12-4

### Clinical immunology of psoriasis and its application to the treatment

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Psoriasis is a common and chronic inflammatory skin disease characterized by long-lasting thick erythematous scaly plaques. Psoriasis lesions show distinct histologic features such as hyperproliferation of epidermal keratinocytes and dense upper dermal mononuclear cell infiltration. Recent molecular and clinical studies have shown that psoriasis is principally mediated by IL-23/IL-17 cytokine responses. Dendritic cells (DCs) are heterogeneous groups of innate immune cells, which orchestrate immune responses by presenting antigens to cognate T cells and stimulating other types of immune cells. Skin contains a unique DC network mainly composed of epidermal Langerhans cells, bone marrow DC precursor-derived dermal conventional DCs, and monocyte-derived DCs. In the psoriatic skins, DCs are prominent cellular sources for TNF-α and IL-23, and the use of blocking antibodies against TNF-α and IL-23 leads to a significant clinical improvement in psoriatic patients. Recent elegant human and mouse studies have shown that LCs, dermal cDC2, and inflammatory myeloid DCs are pivotal DC subsets in psoriatic microenvironment. In psoriatic lesions, both innate and adaptive IL-17A-producing T cells are involved and blocking upstream cytokines leads to efficient inhibition of IL-17-producing T cell responses. However, as psoriasis easily recurs once after stopping antibody-based treatment, it is urgently needed to understand how IL-17-producing T cell responses would be suppressed by other molecular mechanisms. Thus, elucidating those mechanisms in psoriatic microenvironment would be potential therapeutic targets for alleviating and preventing DC-derived IL-23-dependent psoriatic inflammation in the future.

**Keywords:** Immunology, Interleukin, Pathogenesis, Psoriasis, Treatment

## S-12-5

### Methods to probe the efficacy of GPCR modulator through measuring activity of ion channels

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인체를 이루는 거의 모든 세포들은 다양한 ion channels 과 receptor 를 발현하고 있고, 이들의 활성에 의해서 다양한 기능을 구현함. Ion channel 은 선택적으로 특정 이온을 통화시키면서 막전극을 변화시키고, receptor 는 ion channel과 coupling 되어서 세포 활성을 조절하거나 혹은 2차 시그널링을 조절하면서 세포내의 다양한 변화를 부여함. 수백~수천가지 종류의 G-protein coupled receptors 는 발현부위와 세포 형태에 따라서 세포 활성, hormone release 조절, cell cycle regulation, homeostasis 조절 등의 수많은 기능을 부여하므로 다국적 제약회사들의 drug target 이 되어왔음.
GPCR receptor modulator 는 agonist binding site 와 agonist binding affinity 를 조절하는 modulation site 에 binding 하는지에 따라서 agonist 혹은 modulator 로 구분되고, modulator 는 다시 agonist binding affinity 를 증가시키면 Positive Allosteric Modulator, 감소시키면 Negative Allosteric Modulator 등으로 구분되는데 이들의 efficacy를 확인 하는 다양한 in-vitro & ex-vivo 방법이 있음. 특히 Ex-vivo system 을 이용하여 drug target 의 효능을 규명하는 연구는 drug candidate 의 efficacy를 실제 physiological condition 에서 규명할 수 있는 장점을 지니고 있음. 전기생리기법을 이용하여 GPCR과 효능적으로 상호작용을 하는 이온채널의 활성을 기록함으로써 ex-vivo system 에서 GPCR target drug 의 효능을 규명할 수 있는 방법을 소개하고자 함.

## S-13-1

### Parallel Ascending Spinal Pathways for Affective Touch and Pain

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The anterolateral pathway consists of ascending spinal tracts that convey pain, temperature and touch information from the spinal cord to the brain. Projection neurons of the anterolateral pathway are attractive therapeutic targets for pain treatment because nociceptive signals emanating from the periphery are channeled through these spinal projection neurons en route to the brain. However, the organizational logic of the anterolateral pathway remains poorly understood. Here we show that two populations of projection neurons that express G-protein coupled receptors TACR1 and GPR83 form parallel ascending circuit modules that cooperate to convey thermal, tactile and noxious cutaneous signals from the spinal cord to the lateral parabrachial nucleus of the pons. Within this nucleus, axons of spinoparabrachial (SPB) neurons that express Tacr1 or Gpr83 innervate distinct sets of subnuclei, and strong optogenetic stimulation of the axon terminals induces distinct escape behaviors and autonomic responses. Moreover, SPB neurons that express Gpr83 are highly sensitive to cutaneous mechanical stimuli and receive strong synaptic inputs from mechanosensory neurons. Notably, the valence associated with activation of SPB neurons that express Gpr83 can be either positive or negative, depending on stimulus intensity. These findings reveal anatomically, physiologically and functionally distinct subdivisions of the SPB tract that underlie affective aspects of touch and pain.

**Keywords:** Touch, Pain, Spinal cord circuit

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## S-13-2

### Decoding of spontaneous pain from two-photon microscopy images of brain cellular calcium using deep learning

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Chronic pain remains intractable in millions of patients worldwide. Spontaneous ongoing pain is a major clinical problem of chronic pain and extremely challenging to diagnose and treat compared to stimulus-evoked pain. Here, we developed a deep learning algorithm, named AI-bRNN (Average training, Individual test-bidirectional Recurrent Neural Network), to decipher spontaneous pain information from brain cellular calcium signals recorded by two-photon imaging in awake, head-fixed mice. The AI-bRNN determines the intensity and time point of spontaneous pain even during the chronic pain period and evaluates the efficacy of analgesics. Furthermore, it could be applied to different cell types and brain areas, and it distinguished between itch and pain, proving its versatility.

**Acknowledgement:** This work was supported by grants from the National Research Foundation of Korea funded by the Korean government (NRF-2017M3C7A1025604, NRF-2017M3A9E4057926, and NRF-2019R1A2C2086052).

**Competing interests:** SKK hold the patent applications related to the contents of this work (10-2019-0173382 in Korea and PCT/KR2020/006221).

**Keywords:** Two-photon microscopy images, Brain cellular calcium, Deep learning, Spontaneous pain

## S-13-3

### Involvement of the insular cortex in central modulation of neuropathic pain

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Neuropathic pain has been shown to be developed by nerve injury. It was recently reported that the insular cortex (IC) which conventionally has been regarded as a gustatory cortex may play an important role in pain information processing and pain modulation. Evidence from an optical imaging study showed that augmented optical signals were elicited in the IC by peripheral stimulation. Plastic changes in the IC following nerve injury may be accompanied by long-term potentiation. According to one of our studies, protein kinase Mζ in the IC can lead to nerve injury-induced plasticity which contributes to the maintenance of neuropathic pain states. Similarly, signaling via mammalian target of rapamycin (mTOR), which is known to control mRNA translation, can influence synaptic plasticity in relation to neuropathic pain. In this regard, we found that application of rapamycin, an antagonist of mTOR, into the IC reduced mechanical allodynia, down-regulated the expression of postsynaptic density protein 95, and decreased neural excitability, implying inhibition of neuropathic pain by control of synaptic plasticity in the IC. Furthermore, electrical stimulation of the IC reduced neuropathic pain by changing plasticity in the IC. These findings suggest that neuroplastic changes in the IC may be a critical mechanism involved in the modulation of neuropathic pain.

**Acknowledgement:** This work was supported by Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Korean Government (MSIT) (NRF-2020R1A2C3008481).

**Keywords:** Neuropathic pain, Insular cortex, Neural plasticity, Pain modulation

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## S-13-4

### Top-down components of acupuncture treatment in pain control

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Acupuncture uses needles to stimulate a particular part of the body for the purpose of inducing beneficial clinical effects. It has been applied for a wide variety of disorders, though application to analgesia has attracted the most scientific interest in the past few decades. Humans perceive somatic sensations by integrating afferent signals and higher cognitive processes. Experiences and expectations prior to tactile stimulation can influence the perception of somatic sensations. In this talk I will give a short overview of placebo needle and show how top-down components of acupuncture acts on the acupuncture action. Acupuncture treatment involves touch, insertion, and healing ritual, consisting of multiple components including somatosensory stimulation, treatment context, and attention to needle-based procedures. Even placebo needle also includes the tactile stimulation, an enhanced doctor-patient relationship, bodily sensation, and the expectation of the treatment. These factors can contribute to the effect of placebo analgesia, and ultimately combine to create a medical context. Body ownership, enhanced bodily attention, anticipation of stimulation are a crucial factor that influences physiological responses during acupuncture stimulation. Understanding the top-down components of acupuncture treatment may be important for further scientific investigation of the effects and underlying mechanisms of acupuncture.

**Keywords:** Acupuncture, Analgesia, Expectation, Pain, Placebo

## S-14-1

### Mitochondria:Powerhouse, Slaughterhouse, and Speaker of the House

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Assistant Professor of Gerontology

The mitochondrion, being the single most important metabolic organelle, is strongly implicated in aging and age-related diseases. However, the role of mitochondria in regulating life/healthspan has been largely unclear. Mitochondrial communication with the cell is dominantly viewed as a unidirectional process, in which mitochondria are at the receiving end as 'end-function' organelles. The existence of retrograde signaling, where the mitochondria respond back to the cell, is known, but the currently described signaling molecules are limited to secondary or transient metabolites (e.g. ca2+, ROS) or mitochondria-resident proteins encoded in the nuclear genome (e.g. cytochrome C). This has been recently challenged by the discovery of novel genes encoded in the mitochondrial genome that produce small bioactive peptides. These peptides can act both non-cell autonomously and cell-autonomously, and represent inherent signals originating from mitochondria. The talk focuses on how mitochondria communicate back to the cell and organism to regulate aging and age-related diseases using these innate signals encoded within its genome, especially those in the 12S rRNA locus. We hypothesize that these novel short open reading frames (ORFs) are potential candidate mitochondrial longevity genes and therapeutic/diagnostic targets.

## S-14-2

### Lysosomal SLC46A3 modulates hepatic cytosolic copper homeostasis, mitochondrial function and triglyceride accumulation

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The environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) causes hepatic toxicity associated with prominent lipid accumulation in humans. Here, the authors report that the lysosomal copper transporter SLC46A3 is induced by TCDD and underlies the hepatic lipid accumulation in mice, potentially via effects on mitochondrial function. SLC46A3 was localized to the lysosome where it modulated intracellular copper levels. Forced expression of hepatic SLC46A3 resulted in decreased mitochondrial membrane potential and abnormal mitochondria morphology consistent with lower copper levels. SLC46A3 expression increased hepatic lipid accumulation similar to the known effects of TCDD exposure in mice and humans. The TCDD-induced hepatic triglyceride accumulation was significantly decreased in Slc46a3−/− mice and was more pronounced when these mice were fed a highfat diet, as compared to wild-type mice. These data are consistent with a model where lysosomal SLC46A3 induction by TCDD leads to cytosolic copper deficiency resulting in mitochondrial dysfunction leading to lower lipid catabolism, thus linking copper status to mitochondrial function, lipid metabolism and TCDD-induced liver toxicity.

## S-14-3

### Suppressive effects of stress-induced glucocorticoid on mitochondrial clearance and trafficking trigger synapse defects

Gee Euhn Choi, Ho Jae Han

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Neurons are particularly vulnerable to mitochondrial dysfunction due to high energy demand and an inability to proliferate. When damage occurs in mitochondria, the mitochondrial quality control (MQC) system maintains appropriate morphology, localization, and removal/replacement of mitochondria to sustain brain homeostasis and counter progression of neurological disorders. Glucocorticoid release is an essential response to stressors for adaptation; however, it often culminates in maladaptation if neurons are exposed to chronic and severe stress. Stress-induced glucocorticoids disturb mitochondrial bioenergetics and dynamics; however, instead of being removed via mitophagy, the damaged mitochondria accumulate. Therefore, we investigate the role of glucocorticoids in mitophagy inhibition and subsequent synaptic defects in hippocampal neurons, SH-SY5Y cells, and ICR mice. First, we observe that glucocorticoids decrease both synaptic density and vesicle recycling due to suppressed mitophagy. Screening data reveal that glucocorticoids downregulate BNIP3-like (BNIP3L)/NIX, resulting in the reduced mitochondrial respiration function and synaptic density. Notably, we find that glucocorticoids direct the glucocorticoid receptor to bind directly to the PGC1α promoter, downregulating its expression and nuclear translocation. PGC1α downregulation selectively decreases NIX-dependent mitophagy. Consistent with these results, NIX enhancer pre-treatment of a corticosterone-exposed mouse elevates mitophagy and synaptic density in hippocampus, improving the outcome of a spatial memory task. Despite mitophagy deficiency, homeostasis in neurons can be maintained when newly generated healthy mitochondria migrate back to synapse. However, we confirmed that stress induces disturbance in mitochondrial migration.

Cortisol inhibits mitochondrial division through reduction of Drp1 and decreased activity of adaptor protein Miro1 in human neural stem cell (NSC) undergoing differentiation. It is expected that Miro1 will not be able to detach from the microtubule due to reduction in Ca2+ levels due to decreased in glutamate receptor at postsynaptic compartment, as revealed in the previous study. In conclusion, glucocorticoids inhibit mitophagy and mitochondrial trafficking via downregulating NIX and Miro1 activity, which represent the potential target for restoring synapse function.

## S-14-4

### Mitohormesis in hypothalamic POMC neurons mediates regular exercise induced high turn metabolism

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Low-grade mitochondrial stress can promote health and longevity, a phenomenon termed mitohormesis. Here, we demonstrate the opposing metabolic effects of low-level and high-level mitochondrial ribosomal (mitoribosomal) stress in hypothalamic proopiomelanocortin (POMC) neurons. POMC neuron-specific severe mitoribosomal stress due to *Crif1* homodeficiency causes obesity in mice. By contrast, mild mitoribosomal stress caused by *Crif1* heterodeficiency in POMC neurons leads to high-turnover metabolism and resistance to obesity. These metabolic benefits are mediated by enhanced thermogenesis and mitochondrial unfolded protein responses ($UPR^{mt}$) in distal adipose tissues. In POMC neurons, partial *Crif1* deficiency increases the expression of β-endorphin (β-END) and mitochondrial DNA-encoded peptide MOTS-c. Central administration of MOTS-c or β-END recapitulates the adipose phenotype of *Crif1* heterodeficient mice, suggesting these factors as potential mediators. Consistently, regular running exercise at moderate intensity stimulates hypothalamic MOTS-c/β-END expression and induces adipose tissue UPRmt and thermogenesis. Our findings indicate that POMC neuronal mitohormesis may underlie exercise-induced high-turnover metabolism.

## S-15-1

### How to teach and learn in an online environment?

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In order to suggest how to teach and learn in online learning, it is necessary to review various learning theories. In particular, it is necessary to apply a learning theory that actively considers the learning goals and characteristics in medical education or physiology education. Therefore, in this presentation, learning theories will be explained for effective teaching and learning in medical education and physiology education. We will also briefly discuss the challenges learners face in online learning. Finally, based on a learning theory suitable for the learning goals and characteristics of medical education and physiological education, some teaching and learning strategies will be proposed for effective physiology learning in an online learning environment.

**Keywords:** Online learning, Medical education, Learning theory, Structure, Dialogue

## S-15-2

### Changes in students' physiological learning attitudes due to flipped learning

Chae Hun Leem

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현 의과대학에서 생리학 교육의 가장 큰 어려움은 복잡한 인체시스템의 작동원리를 자연과학 법칙을 기반으로 이해하고 적용하는 내용을 단순 강의를 통해 전달하는 것이다. 이러한 문제는 많은 생리학 교육자가 안고 있는 문제이며 한정된 시간에 생리학의 핵심적 내용을 단순 암기가 아닌 시스템의 이해와 인체 적용까지 이끌어내는 것은 무척 어려운 과제이다. 최근 코로나 사태로 인해 비대면으로 교육을 진행해야 하는 상황에서 거꾸로학습 기반의 생리학 교육을 시도하여 보았으며 무척 만족스러운 결과를 얻었다. 핵심틀은 학생들 스스로 공부하고 강의시간에는 이를 평가한다는 점이다. 기본 과정은 강의를 영상강의로 미리 배포하고 학생들로 하여금 실제 강의시간 이틀전까지 학습하여 강의내용 중 질문을 이메일로 보내도록 하였고 원활한 공지 및 대화통로를 위해 카톡을 운영하였으며 보내온 문의 이메일은 강의시간 전날 학생들에게 일일이 답을 하였다. 시간당 15~30형성평가 문제를 만들어 강의 시작 시 시험을 치루어 학생들이 어느 정도 이해하고 아는 지 스스로 평가하도록 하였고 이메일 문의 내용 중 여러 학생들이 공유해야 하는 부분에 대해 좀 더 자세히 설명하였다. 그리고 남은 시간에 추가질의와 시험문제에 대한 질의응답시간을 가졌으며 이후에도 수시로 언제든지 궁금한 내용이 있는 경우 질의 이메일을 보내도록 하여 바로 답변을 보냈다. 학생들이 보내온 질의응답은 정리하고 다시 배포하여 학생들이 다시 한번 강의 내용을 복습하는 기회로 활용할 수 있도록 하였다. 시험문제의 형식은 O/X기반문제로 3개를 묶음으로 3개 모두 정답 시 1점을 부여하는 방식으로 문제를 만들었다. 이러한 과정으로 교육을 하면서 기존 강의중심의 교육보다 여러가지 점에서 우수한 점들이 확인되었다. 첫 번째로 질의학생들의 참여가 훨씬 활발해졌으며 두 번째로 기존 강의중심 대비 질의내용도 훨씬 깊이 있는 내용이 많았고 세 번째로 질문을 하는 횟수 또한 기존과 비교가 안되게 증가되었다. 가르치는 입장에서도 여러가지로 도움이 되었는데 첫 번째로 질의를 통해 학생들이 강의 내용에서 어느 부분에서 어려워하는 지 파악이 쉽게 되어 향후 강의준비 시 해당 내용에 대해 좀 더 면밀하게 학생들이 이해하기 쉽게 준비를 할 수 있게 되었고 두 번째로 강의내용 중 부실한 부분에 대해 훨씬 쉽게 파악할 수 있었으며 세 번째로 비대면이지만 학생들과 훨씬 많은 소통을 하여 교육과정에 대한 만족도가 크게 증가하였다는 점이다. 처음 진행 시 강의 시간당 소요되는 시간이 8시간 정도였지만 향후 교육 시 영상강의 자료의 재활용, 학생들의 질의응답내용의 보편화, 시험문제에 대한 재활용 등으로 소요되는 시간은 크게 줄어들 것으로 예상되며 언제 어디서든 학생들과 교류하며 교육을 할 수 있다는 점에서 기존 강의실 중심의 교육보다 훨씬 낫다고 생각한다. 이를 진행하면서 생리학 교육내용에서 추가로 가장 절실히 필요로 하는 부분은 병태생리학이며 이를 위해 배운 생리학 지식을 활용하는 기회를 효율적으로 제공할 수 있는 교육 내용을 개발하고 발굴해서 제대로 교육되고 있지 못하는 병태생리분야를 의과대학 과정에 들여와야 한다는 점이다.

**Acknowledgement:** This work was supported by the National Research Foundation of Korea (NRF-2016M3C1A6936605).

**Keywords:** Flipped learning, Physiology education

## S-15-3

### Teaching well is how to learn well

한재희

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의대생들은 입학할 때부터 유능한 의사로 성장한 후의 자신의 모습을 상상하지만, 그 성장 과정에 대해서는 큰 관심이 없는 듯하다. 그들은 아동학습자와 성인학습자의 특징을 동시에 나타내는 것 같다. 그들은 교수나 학교에 의존적이며 경험이 부족하다는 점에서는 아동학습자의 특징을 가지며, 임상 요구에 부합하는 학습에 가치를 부여하고 임상 문제 중심적 접근에 더 흥미를 나타내는 점에서는 성인학습자의 특징을 갖는다.
기초의학 교수들은 주로 교과목 중심의 접근을 통해 장차 학생들에게서 유용할 것으로 확신하는 지식을 교육한다. 지식은 공식적이고 이론적이므로 복잡하고 불확실한 임상 문제를 해결하는 데 유용하지 못한 경우가 많다. 학생들은 실용적이고 현실 문제 해결에 도움이 되는 지식을 추구하는 경향을 보이므로 기초의학은 그들의 학습 동기를 유발하는 데 어려움을 겪을 가능성이 많다.
의대생들은 학습 태도에 있어 일부 성인학습자의 특징을 가지고 있으며, 의학교육학자들은 학습은 의료현장에서 이뤄지며 역량 계발이 목적이라고 주장한다. 이러한

태도나 주장은 수긍할 수 있는 점도 있지만, 기초의학 관점에서 보면 수긍하기 어려운 점도 많다. 그러나 이런 현실적 문제를 무시하고 해결책을 마련하지 않는다면 기초의학은 점점 주류 의학에서 밀려날 가능성이 높다. 그러므로 기초의학 교수들은 강의 주제의 범위를 기초 지식에서 임상 적용까지 넓혀야 하며, 현실 문제 해결에 도움이 되는 실용적인 내용으로 전환해야 할 것으로 보인다. 한 가지 예를 들면, 질병의 병태생리와 발병 알고리즘 등을 설명함으로써 학습에 대한 내적동기를 유발하는 것도 좋은 방법이라 생각된다.

**Keywords:** 동기유발, 필요한 지식, 현실문제중심, 내적동기, 학습, 역량, 병태생리

## Yudang Academic Award

### Rewiring lipid metabolism by hypoxia-inducible factor-1 in tumor microenvironment: New targets for cancer therapy?

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Cancer cells rewire metabolic processes to adapt to the nutrient- and oxygen-deprived tumor microenvironment, Promoting their proliferation and metastasis. Studies of the Warburg effect have shown that glycolytic cancer cells are more invasive and aggressive. Lipid metabolism is important because lipids function as energy sources, In cell membranes, And as signaling molecules. Obesity is also a risk factor for various cancer types; therefore, Targeting lipid metabolism shows promise for cancer therapy. Here we review the lipid metabolic reprogramming in cancer cells mediated by hypoxia-inducible factor-1 (HIF-1). HIF-1 is the master transcription factor for tumor growth and metastasis and transactivates genes related to proliferation, Survival, Angiogenesis, Invasion, And metabolism. The glucose metabolic shift (Warburg effect) is mediated mainly by HIF-1. HIF-1 modifies lipid accumulation, B-oxidation, And lipolysis in cancer, Triggering its progression. We found that the lipid/HIF-1 axis promoted tumor metastasis in a colon cancer xenograft mouse model. In addition, Lipid-enhanced HIF-1α triggers 3D cell growth of hepatocellular cellular carcinoma (HCC) cells. Mechanistically, HIF-1α regulated lipid metabolism in hepatocellular carcinoma through fatty acid binding protein 5 (FABP5) that identified as a driver for HIF-1α synthesis and a disrupter for FIH/HIF-1α interaction at the same time. Our results show an in vitro model of a biomimetic TME and provide new mechanistic insights into the effects of ADSC-released fatty acids on cancer cells as oncometabolites. Therefore, Targeting lipid metabolic alterations by HIF-1 has therapeutic potential for cancer.

## Young Scientist Session

### Role of Brainstem Serotonin Receptors in the Regulation of Sodium Appetite

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The drive for sodium intake, sodium appetite, is a powerful form of motivation that can drive ingestion of high, yet aversive concentrations of sodium in animals and humans depleted of sodium. However, in normal conditions sodium appetite is suppressed to prevent homeostatic deviations. While molecular and neural mechanisms underlying the stimulation of sodium appetite received much attention recently, those that act to inhibit sodium appetite remain largely obscure. Here, I discuss our recent finding that serotonin 2c receptor (Htr2c)-expressing neurons in the lateral parabrachial nucleus (LPBNHtr2c neurons) act to inhibit sodium appetite. Activity of these neurons are regulated by bodily sodium content and their forced activation can rapidly suppress sodium intake. Conversely, inhibition of these neurons specifically drives sodium appetite, even during euvolemic conditions. We further show that the physiological role of Htr2c expressed by LPBN neurons is to disinhibit sodium appetite. Our results suggest that LPBNHtr2c neurons may act as a brake against sodium appetite and that its alleviation is required for the full manifestation of sodium appetite.

## P21-01-01

### Inhibition of angiotensin converting enzyme (ACE) causes increasing substance P expression on cultured astrocyte in mice

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**Purpose:** Angiotensin converting enzyme inhibitor (ACEi) inhibits the enzyme dipeptidyl carboxypeptidase, which is involved in the conversion of angiotensin I to II and degradation of kinins like substance P (SP). However, the role of ACEi (Captopril and Enalapril) has not yet been studied much about the cultured astrocyte. Here we investigated whether administration of the ACEi is that increases the expression of SP and whether this contributes to the protein level of PKC subunits by ACE inhibition on cultured astrocyte.
**Methods:** In light of these observations, we hypothesized that: 1) Involvement of the SP by ACE inhibition on cultured astrocyte. 2) Involvement of the SP by pretreatment of ACEi treated with ACE on cultured astrocyte. 3) Protein level of PKC subunits (PKCa, PKCbI, and PKCe) of treatment of SP receptor (neurokinin-1 receptor; NK-1R) antagonist (L-733,060) on the ACE inhibition (24 h or 48 h) in cultured astrocyte. Astrocyte cultures were prepared from cerebral cortexes of neonatal mice [postnatal day 2 (P2)].
**Results:** Treatment of the ACEi, for 24 h significantly increased the levels of SP on cultured astrocyte. In addition, suppressed the levels of SP that was induced by pretreatment of ACEi treated with ACE on cultured astrocyte. Administration of the NK-1R antagonist, L-733,060 reduced the protein levels of PKC subunits that was induced by pretreatment of ACEi.
**Conclusions:** These findings demonstrate that inhibition of ACE increases the levels of SP on cultured astrocyte. In addition, inhibition of ACE on cultured astrocyte plays an important role in the control of inflammation cell signaling pathway though reducing the levels of SP. Moreover, inhibition of ACE increases the protein levels of PKC subunits on cultured astrocyte, which stimulate NK-1R signaling, ultimately astrocyte may modulate cell signaling pathway via the mediation of PKC protein levels by ACE inhibition.

**Keywords:** Angiotensin converting enzyme, Astrocyte, Neurokinin-1 receptor, PKC, Substance P

## P21-01-02

### Involvement of Brain-derived neurotrophic factor and redox factor-1 in formalin-induced pain mouse model

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**Purpose:** Brain-derived neurotrophic factor (BDNF) is one of the well-known neurotrophins that is widely expressed in the peripheral and central nervous system and plays as a regulator of various pain condition. Apurinic / apyrimidinic endonuclease1 (APE1), also called redox factor-1 (Ref-1), is a multifunctional protein that regulates various cellular responses, including oxidative stress. Moreover, Ref-1 is distributed in the nervous system and is involved in pain regulation as well as results associated with neuroinflammation. based on these findings, the present study hypothesized that BDNF and Ref-1 may play an important role in various pain conditions through the regulation of expression and interaction in formalin-induced pain model.
**Methods:** To produce acute pain, a 30 μl volume of 5% formalin was subcutaneously injected into the right hind paw of the mouse using microsyringes with 30 gauge needles, paw licking time was measured every 5 minutes for 60 minutes. Analysis by western blot was performed using dorsal root ganglion (DRG) to measure the expression of peripheral BDNF and Ref-1. Moreover, spinal cord dorsal horn samples were also analyzed by western blot to confirm the alteration of the BDNF-TrkB signal in the central nervous system.
**Results:** Injection of 5% formalin produced significant biphasic pain responses during the 60 minute observation period. On western blotting at each time point after formalin injection, increased significantly more BDNF and cytoplasmic Ref-1 is also increased and then Ref-1 accumulates in the nuclear over time.
**Conclusions:** The results of the present study suggest that the peripheral BDNF/Ref-1 signal triggers pain sensitization by modulating central sensitization through activation of the NMDA receptor-related TrkB signaling in formalin-induced pain mouse model.

**Keywords:** Formalin, Acute pain, Brain-derived neurotrophic factor (BDNF), Redox Factor-1 (Ref-1)

## P21-01-03

### Postsynaptic mitochondrial dysfunction in striatum determines the development of Levodopa-induced dyskinesia mouse model

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**Purpose:** Levodopa (LID) is the first line therapy for Parkinson's disease (PD), which improves PD behavioral symptoms. However, long terms (over 5 years) treatment of LID could occur dyskinetic movement over 80% of PD patients. Levodopa-induced dyskinesia (LID) can be treated with DBS (deep brain stimulation), but it faced on the risk of bleeding, infection accompany with surgery, so the development of a medicine that alleviates LID symptom is essential.
**Methods:** We first tried to develop the LID animal model based on the causative factor of PD, we administrated levo/carbi dopa until appearance of dyskinetic movement after A53T mutant α-syn viral injection to SN area or MPTP Intraperitoneal injection. Due to the mitochondrial dysfunction correlate levodopa induced neuronal cell death, we assessed OCR(oxygen consumption rate) by XF24 analyzer with isolated mitochondria in striatal area in each groups.
**Results:** Interestingly, we found that combined LID animal model (A53T α-syn + MPTP) showed more severe abnormal involuntary movement scale (AIMS) than only α- synuclein injected or MPTP treated model. Expectedly combined LID animal model had lowest mitochondrial respiration among three groups.
**Conclusions:** Our study provide an important experimental platform that serves for clinical trial as animal models that most closely recapitulate patients with LID symptoms.

**Keywords:** Levodopa-induced dyskinesia, Parkinson's disease, A-synuclein, MPTP

## P21-01-04

### KDS2010, a novel MAO-B inhibitor, alleviates spinal nerve ligation-induced neuropathic pain in rats through BDNF-TrkB signaling

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**Purpose:** Million people all over the world are suffering from neuropath-

ic pain without effective cures. Over time, neuropathic pain tends to get worse, instead of better, and can lead to serious disability and complications, including depression, sleeping problems, anxiety, and more. Inhibiting monoamine oxidase B (MAO-B), a key enzyme in monoamine metabolism, has been proposed to treat neurological diseases, such as Parkinson Disease (PD), or depression. MAO-B inhibitors have also been implicated to reverse neuropathic pain behaviors, however the mechanisms of action are still understudied. In this study, we evaluated the analgesic effect of KDS2010 (KDS), a newly developed reversible MAO-B inhibitor

**Methods:** A well-known neuropathic pain model was established by L5 spinal nerve ligation (SNL) in rats. KDS was then administered orally to the neuropathic rats to test the analgesic effects. The molecular changes were determined by Western Blot and immunohistochemistry.

**Results:** Oral administration of KDS effectively enhanced mechanical thresholds in the SNL induced neuropathic pain in rats. Moreover, we discovered that KDS dramatically increased brain-derived neurotrophic factor (BDNF) levels, and elevated BDNF in turn acted through TrkB receptors to suppress increased p-NR2B-induced hyperexcitability in spinal dorsal horn sensory neurons after nerve injury. In addition, KDS showed its anti-inflammatory effects by reducing microgliosis and astrogliosis and the activation of MAPK and NF-κB inflammatory pathways in these glial cells. The levels of ROS production in the spinal cords after SNL procedure were also decreased with KDS treatment

**Conclusions:** Our results suggest that KDS may represent a promising therapeutic option for treating neuropathic pain

**Keywords:** Neuropathic pain, MAO-B inhibitors, KDS2010, BDNF

## P21-01-05

### Intermittent fasting reduces formalin-induced pain without elevation of corticosterone in mice

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**Purpose:** Expression of orexin A (OXA) can be enhanced by the peripheral nerve stimulation in the lateral hypothalamus (LH) and this leads to the pain inhibition by activating orexin-1 receptor (OX1R) of periaqueductal gray matter. Since LH is known to be a hunger center and fasting can produce antinociception, fasting may produce its effect via the activation of OXA-OX1R pathway. However, previous studies have suggested that the stress-related peripheral corticosterone (CORT) may be a key factor for the antinociception by fasting. In this regard, we designed this study to determine whether the programmed and learned fasting may inhibit pain only through the activation of OXA-OX1R but not affecting the level of CORT as one sign of fasting-related stress.

**Methods:** As a pain mice model, formalin solution (1%, 20 ul) was injected into the plantar surface of the right hind paw and pain behavior was recorded for 40 min and paw licking time (sec) was measured. Acute fasting (AF) mice received 6, 12, or 24 hr of fasting period before the formalin test and intermittent fasting (IF) group mice were given 12 hr/12 hr or 24 hr/24 hr (food/fasting) protocol for one week before test.

**Results:** All group of mice showed antinociception in the formalin test except 6 hr of AF. Co-expression of OXA and fos-B (a marker of neuronal activation) of LH was also enhanced both AF and IF, but not 6 hr of AF. CORT level was elevated in 12 and 24 hr of AF and 24 hr of IF, but not in 6 hr of AF and 12 hr of IF.

**Conclusions:** In conclusion, programmed fasting such as IF may produce antinociception via the activation of OXA-OX1R pathway and 12 hr of IF may produce its effect without affecting the sign of stress.

**Keywords:** Pain, Intermittent fasting, Lateral hypothalamus, Orexin A, Corticosterone

## P21-01-06

### SCAMP5 mediates activity-dependent enhancement of NHE6 recruitment to synaptic vesicles during synaptic plasticity

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**Purpose:** $Na^+(K^+)/H^+$ exchanger 6 (NHE6) on synaptic vesicle (SV) is critical for the presynaptic regulation of quantal size at the glutamatergic synapses by converting the chemical gradient (ΔpH) into membrane potential (Δψ) across the SV membrane. We recently found that NHE6 directly interacts with secretory carrier membrane protein 5 (SCAMP5), and SCAMP5-dependent recruitment of NHE6 to SVs controls the strength of synaptic transmission by modulation of quantal size of glutamate release at rest. It is, however, unknown whether NHE6 recruitment by SCAMP5 plays a role during synaptic plasticity.

**Methods:** Since presynaptic efficacy is enhanced by activity-dependent neuronal modifcation and the proper localization of NHE6 is important for presynaptic regulation of glutamate quantal size, we wondered that an increase in synaptic activity would affect NHE6 recruitment to the presynaptic terminals. To address this possibility, we induced a chemical long-term potentiation (cLTP) in cultured hippocampal neurons by using forskolin, an adenylyl cyclase activator, which is known to induce presynaptic LTP by activating cAMP/PKA signaling pathway.

**Results:** We found that the number of NHE6-positive presynaptic boutons was significantly increased by the cLTP. Since cLTP involves new synapse formation, our results indicated that NHE6 was recruited not only to the existing presynaptic boutons but also to the newly formed presynaptic boutons. Knockdown of SCAMP5 completely abrogated the enhancement of NHE6 recruitment by cLTP. Interestingly, despite an increase in the number of NHE6-positive boutons by cLTP, the quantal size of glutamate release at the presynaptic terminals remained unaltered.

**Conclusions:** Together with our recent results, our findings indicate that SCAMP5-dependent recruitment of NHE6 plays a critical role in manifesting presynaptic efficacy not only at rest but also during synaptic plasticity. Since both are autism candidate genes, reduced presynaptic efficacy by interfering with their interaction may underlie the molecular mechanism of synaptic dysfunction observed in autism.

**Keywords:** SCAMP5, NHE6, Activity-dependent synaptic localization, Autism, Presynaptic quantal size

## P21-01-07

### Multiplexed processing of vibrotactile information in the mouse primary somatosensory cortex

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**Purpose:** The primary somatosensory (S1) cortex plays a key role in distinguishing different sensory stimuli. Vibrotactile touch information is conveyed from the periphery to the S1 cortex through three major classes of mechanoreceptors: slowly adapting type 1 (SA1), rapidly adapting (RA), and Pacinian (PC) afferents. It has been a long-standing question whether specific populations in the S1 cortex preserve the peripheral segregation by the afferent submodalities. Here, we investigated whether S1 neurons exhibit specific responses to two distinct vibrotactile stimuli, which excite different types of mechanoreceptors (e.g., SA1 and PC afferents).

**Methods:** Using in vivo two-photon microscopy and genetically encoded calcium indicator,GCaMP6s, we recorded calcium activities of S1 L2/3 neurons. At the same time, static (<1 Hz) and dynamic (150 Hz) vibrotactile stimuli, which are known to excite SA1 and PC, respectively, were pseudo-randomly applied to the right hind paw in lightly anesthetized mice.
**Results:** We found that most active S1 neurons responded to both static and dynamic stimuli, but more than half of them showed preferred responses to either type of stimulus. Only a small fraction of the active neurons exhibited specific responses to either static or dynamic stimuli. However, the S1 population activity patterns by the two stimuli were markedly distinguished.
**Conclusions:** These results indicate that the vibrotactile inputs driven by excitation of distinct submodalities are converged on the single cells of the S1 cortex, but are well discriminated by population activity patterns composed of neurons that have a weighted preference for each type of stimulus.

**Keywords:** Vibrotactile, Mechanoreceptors, Primary somatosensory cortex, Two-photon imaging

## P21-01-08

### Pathway-specific cholinergic modulation of long-term synaptic plasticity in rat primary visual cortex in vivo

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**Purpose:** Acetylcholine is an important neuromodulator for regulation of visual attention, plasticity, and perceptual learning. Acetylcholine is released in the visual cortex from cholinergic projections of the basal forebrain, where may differentially modulate synaptic transmission between sensory and associative inputs depending on the brain state. Previously, we demonstrated that cholinergic stimulation differentially modulated long-term synaptic plasticity in acute slice preparation, depending on cortical layers in layer 2/3 pyramidal neurons of the primary visual cortex (V1). However, little is known about layer-specific cholinergic modulation of long-term synaptic transmission in vivo. The aim of this study was to know pathway-specific cholinergic modulation of long-term synaptic transmission evoked by the lateral geniculate nucleus (LGN) and contralateral V1 (cV1).
**Methods:** We stimulated the basal forebrain with optical stimulation to increase acetylcholine level in V1 and recorded field potentials (FPs) evoked by electrical stimulation of either LGN or cV1 using a 16-channel multi-electrode array. Channelrhodopsin-2 (ChR2) was delivered by AAV-viral vector to the basal forebrain of rats at age of 3 week. After 2 weeks, optical stimulation (480 nm) was applied to the basal forebrain. Viral expression was monitored by fluorescence imaging of reporter proteins. Tungsten electrodes were positioned in the LGN for activation of sensory inputs and cV1 for activation of associative inputs.
**Results:** Both amplitudes of LGN-FPs and of cVC-FPs were not changed by electrical stimulation only. However, when exist the optical stimulation of ChR2-expressed basal forebrain, the amplitude of FPs evoked by electrical stimulation of the LGN increased in layers 1, 2/3, and 4 of V1, while FPs evoked by electrical stimulation of cV1 were not changed in layers 1 and 2/3. Moreover, muscarinic and nicotinic receptors exhibited differential effects depending on inputs. The amplitude of LGN-FPs decreased by the muscarinic antagonist scopolamine (5 mg/kg, i.p.) and the nicotinic antagonist mecamylamine (5 mg/kg). However, the amplitude of cV1-FP was not changed by scopolamine and mecamylamine.
**Conclusions:** Therefore, these results indicated that cholinergic modulation of synaptic transmission differs depending on inputs to V1, which might be important for the information processing balance depending on the brain state.

**Keywords:** Acetylcholine, Muscarinic receptors, Nicotinic receptors, Basal forebrain, LGN, Visual cortex

## P21-01-09

### Common bacterial metabolite indole activates nociceptive sensory neurons and induces nocifensive behavior through TRPA1

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**Purpose:** Nociceptors are known to directly recognize bacterial cell wall components or secreted toxins, thereby leading to pain induced by bacterial infection. However, direct activation of nociceptors by bacterial metabolites remains unclear, even though bacteria produce numerous metabolites. In the current study, we thus investigated whether and how common bacterial metabolites indole, mainly produced by normal microflora of the gastrointestinal tract (GI tract) and oral cavity, interacts with nociceptive sensory neurons.
**Methods:** We employed Fura-2 based ratiometric calcium imaging and whole-cell patch clamp recordings to examine the response of sensory neurons to bacterial metabolites in adult mice.
**Results:** We found that indole directly activates nociceptive sensory neurons. Indole elicited calcium transients in subsets of primary cultured dorsal root ganglia (DRG) neurons in a dose-dependent manner. Indole (500μmol/L) evoked inward currents in DRG neurons with a current density of 18.67 ± 4.65 pA/pF (n=4). Also, subcutaneous injection of 100μg indole produced nocifensive licking behavior in adult mice (n=5, 59±15.32 second/10min), which was enhanced in complete Freund's adjuvant (CFA)-induced chronic inflammatory condition (n=4, 141.5±10.99 second/10min, student's t-test, p=0.0165). Exposure to indole increased CGRP release about 7-fold in cultured DRG neurons (6.25±4.91 pg/mL in control versus 44.63±13.13 pg/mL in indole-treated, student's t-test, p=0.0023), and subcutaneous injection of indole increased paw thickness (n=4, 2.05±0.068mm in control, n=7, 2.61±0.037mm in indole-treated, student's t-test, p<0.0001), suggesting its role in the generation of neurogenic inflammation. These indole-induced responses were blocked by HC-030031 and abolished in TRPA1 knockout mice, indicating that indole targets TRPA1.
**Conclusions:** These results suggest that indole can induce pain through TRPA1 by activating sensory neurons, likely during bacterial infection. The action of indole on nociceptive sensory neurons provides insight into bacterial-neural interactions and the role of bacterial metabolites in pain signaling.

**Keywords:** Nociceptor, TRPA1, Indole, Bacteria, Metabolites

## P21-01-10

### Ethanol-induced ceramide production causes neuronal cell death through ER-mitochondria contacts increased by MCL1S-mediated INF2 activation

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**Purpose:** Heavy alcohol consumption is the cause of neuronal cell death and cognitive impairment. An increase of sphingolipid metabolites ceramide is one of the suggested pathways of ethanol-induced neuronal cell death. However, the molecular mechanism of neuronal cell death caused by ethanol-induced ceramide production has not been elucidated. Therefore, we investigated the detailed mechanism how ethanol-increased ceramide induces neuronal apoptosis in SH-SY5Y human neuroblastoma cells.

**Methods:** In this study, we used the SH-SY5Y human neuroblastoma cell line. To confirm the expression level of the mRNA and protein, real time quantitative PCR and western blot were performed. Co-immunoprecipitation, Immunofluorescence staining and proximal ligation assay were conducted to confirm the interaction of proteins. Flow cytometry was used to analyze calcium levels, mitochondrial ROS and neuronal apoptosis.
**Results:** Ceramide increased by ethanol activates protein phosphatase 1 (PP1), which inhibits nuclear translocation of serine/arginine-rich splicing factor 1 (SRSF1) leading to myeloid cell leukemia 1 (MCL-1) pre-mRNA missplicing. Missplicing of MCL-1 pre-mRNA upregulates MCL-1S expression. The interaction of MCL-1S with inositol 1, 4, 5-trisphosphate receptor (IP3R) increases calcium release from the endoplasmic reticulum (ER), which is the main reason for mitochondrial calcium overload and activates ER-bound inverted formin 2 (INF2). F-actin polymerization through INF2 activation promotes ER-mitochondria contact and mitochondrial calcium influx. This eventually leads to neuronal apoptosis through mitochondrial ROS (mtROS) accumulation.
**Conclusions:** Suppression of excessive mitochondrial calcium influx from ER through regulation of ceramide-mediated MCL-1S expression is a promising strategy for preventing ethanol-induced apoptosis.

**Keywords:** Ethanol, Ceramide, MCL-1S, INF2, MAM

## P21-01-11

### Somatic ATP release triggers neuron-satellite glial cell communication in sympathetic ganglia

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**Purpose:** Adenosine triphosphate (ATP) is co-released with norepinephrine from postganglionic sympathetic nerve terminals, and mediates fast excitatory synaptic transmission to various visceral tissues. Some studies have suggested that ATP is also extrasynaptically released from the cell body (soma) of autonomic neurons. To date, however, the functional significance of the somatic ATP release remains unsolved. In the current study, we tested whether the somatic ATP release triggers calcium signaling in the satellite glial cells (SGCs) which envelope neurons in the autonomic ganglia.
**Methods:** We isolated the SGC-attached superior cervical ganglion (SCG) neurons by a partial enzymatic digestion. The presence of the SGCs were confirmed by immunostaining of the inwardly rectifying potassium channel (Kir 4.1) and S100β. Then, cytosolic calcium was measured using Fura-2/AM in the neuron-SGC units.
**Results:** Depolarization of the SCG neurons with 80 mM KCl significantly increased the intracellular calcium in the SGCs attached to the SCG neurons, but not in singly isolated glial cells. Apyrase, which hydrolyzes extracellular ATP, and PPADS, the non-selective P2X antagonist, significantly abolished the high potassium-evoked event in the SGCs. RT-PCR analysis and immunohistochemistry revealed that the SGCs primarily express P2X4 and P2X7. In addition, we found that high potassium application significantly faded the quinacrine and FM1-43 stains of ATP-containing vesicles in the soma of the SCG neurons out.
**Conclusions:** Taken together, these data suggest that the vesicular ATP release from the soma of the SCG neurons triggers calcium signaling through activation of P2X receptors (i.e., P2X4 and P2X7) in the SGCs.

**Keywords:** Calcium, Purinergic, Satellite glial cell, Somatic ATP release, Sympathetic neuron

## P21-01-12

### The role of mitochondria calcium uniporter in C. elegans odor learning

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**Purpose:** We sought to find the role of MCU and mitochondrial calcium in neurons using the model organism C. elegans.
**Methods:** To assess learning and memory, we used well-established and simple C. elegans learning paradigms: negative and positive associative odor learning assays. Worms were pre-exposed to innately attractive odors, either with (positive) or without (negative) food for 60-90 min. The change in worms' attractive response was assayed by a standard odor chemotaxis assay, where the worms are given a choice between the same attractive odor and solvent (no odor). For salt chemotaxis assay, worms are given a choice between high and low concentrations of salt. To see the effect of salt pre-exposure, grown worms were temporarily moved to different salt concentration media, where they remained for 6 hrs until the assay.
**Results:** We found that mcu-1 mutants require a longer time for odor learning, whereas 60 min is sufficient for wild type. This defect was specific to odors sensed by the AWCON sensory neuron. Transgenic rescue experiments showed that MCU-1 in the sensory neuron is sufficient to restore odor learning. Expressing MCU-1 under an inducible promoter showed that MCU-1 is needed during early larval stages. Surprisingly, transgenic rescue worms expressing MCU-1 in all neurons or just in the AWC sensory neuron showed longer memory retention. Lastly, we found that mcu-1 mutants are also defective for taste (salt) memory, suggesting that MCU-1 may be involved in other forms of learning and memory.
**Conclusions:** Our results so far show that MCU facilitates at least two forms of learning in C. elegans. We also found that transgenic rescue strains that are expected to overexpress MCU-1 in the neurons take longer to forget the memory. Our results suggest that MCU may be involved in forming and maintaining neuronal plasticity, which supports learning and memory.

**Keywords:** Mitochondrial calcium uniporter, C. elegans, Neuron, Learning, Memory

## P21-01-13

### Characterizing neural selectivity using a data-driven interpretable feature finding method in multidimensional stimulus space

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**Purpose:** Characterizing neural selectivity is a common approach to understand how cortical neurons process information, i.e., the first step to understand the computation mechanism of neurons. Although there have been persistent attempts to investigate neural selectivity, mischaracterization often occurs due to the conventional method using researcher-defined features. Despite the importance of this problem, the reason that causes mischaracterization is not defined well enough and the solution has not been proposed yet. Here, we suggest possible scenarios of mischaracterizing neuronal selectivity and demonstrate that a data-driven interpretable feature finding method for characterizing neural selectivity can solve this problem.
**Methods:** The data-driven interpretable feature finding algorithm can find all feasible features given stimuli by fitting neural response vector in multidimensional sensory feature space. It suggests possible feature with a normalized value, which reflects the p-value of simple linear regression analysis. To validate the usefulness of our algorithm, we applied it to in vivo two-photon $Ca^{2+}$ imaging data of primary somatosensory cortex neurons using peripheral stimulation, such as innocuous brush stroke and noxious

forceps pinch.
**Results:** As a result of applying our algorithm on the peripheral stimulation dataset, among known-features, brush texture, forcpes texture, and noxiousness features are in high rank, while other features such as dynamicity, staticity, and pressure have low probability that population of S1 neurons would be tuned to these features. Also, this algorithm suggests some unknown features in high rank, such as brush stroke, forceps press + forceps pinch, forceps stroke + forceps pinch features.
**Conclusions:** In this study, we identify a data-driven method for characterizing neural selectivity. We demonstrate that our method can be used for finding missing features and for verifying whether all possible features are known. These results show that data-driven approach can be the crux when investigating neural selectivity.

**Keywords:** Neural selectivity, Neural computation, Interpretable stimulus feature, Data-driven approach, Primary somatosensory cortex

## P21-01-14

### Electrical stimulation of insular cortex modulates synaptic plasticity to attenuate neuropathic pain in rats

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**Purpose:** Neuropathic pain is an abnormal phenomenon including allodynia or hyperalgesia that persists for days or years. Several studies have reported that the reinforcement of synaptic plasticity deteriorated the symptoms. One of the brain regions related to pain perception and generation of synaptic plasticity is the insular cortex (IC), and many researches have shown that the IC is a potential target to control pain effectively. Although many treatments have been developed to attenuate the neuropathic pain, the side effects and tolerance remained. For patients who are refractory to medical therapies, many prospective cases of brain stimulation in neuropathic pain have reported the pain-relieving effect. However, the fundamental mechanisms of brain stimulation, especially the insular cortex stimulation (ICS), are still elucidated. The aim of this study was to determine the pain-relieving effect induced by ICS in neuropathic rats and reveal the mechanisms of the synaptic plasticity modulation through ICS.
**Methods:** Behavioral tests were conducted to observe the pain-relieving effects in neuropathic rats. Western blot was performed to identify the changes in the synaptic plasticity-related receptors such as the subunit of N-methyl-D-aspartate receptor (NMDAR), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) after ICS was applied. Proteomics was conducted to detect specific protein expression patterns among groups.
**Results:** Neuropathic pain was attenuated by ICS and the effect was maintained for 4 days after ICS was stopped. The expression level of NR2A which is a subunit of NMDAR was not changed. However, the expression level of NR2B was decreased after ICS. The expression level of AMPAR also decreased after ICS was applied. Bioinformatics analysis of proteomics suggested that the levels of proteins involved in collapsin response mediator protein 2 (CRMP2) were dramatically altered between groups.
**Conclusions:** These results inferred that the ICS reduced the long-term potentiation (LTP) and CRMP2 could attenuate LTP accompanied by neuropathic pain following neural injury.

**Keywords:** Neuropathic pain, Synaptic plasticity, Insular cortex, Insular cortex stimulation, Collapsin response mediator protein 2

## P21-01-15

### NACA leads to neuroprotection against oxidative injury in long-term cultured OHSCs

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**Purpose:** N-acetylcysteine amide (NACA), a modified form of NAC, has been known to more effectively permeate cell membranes and prevent oxidative stress-related disorders. However, there are few studies which have addressed age-related changes and/or the electrophysiological function with NACA in the brain. Thus, aim of this study is to observe whether NACA exerts neuroprotective effects against oxidative stress in long-term cultured organotypic hippocampal slice cultures (OHSCs) and to evaluate the synaptic efficacy of survival neurons using optical imaging.
**Methods:** Postnatal 7 day Sprague-Dawley rats were used. Hippocampal slices were cultured in vitro for 9 weeks in medium. To observe effect of NACA-treatment in aged condition, OHSCs were once treated with dose-dependent NACA in cell medium for 24 h after the kainic acid (KA) treatment. Neuronal cell death was measured by propidium iodide uptake. Western blot and optical imaging with voltage sensitive dye were performed to observe the antioxidant signals and to examine electrophysiological function in the OHSCs respectively.
**Results:** Neuronal death was dose dependently reduced by NACA-treatment. 1 mM NACA-treated group exhibited significantly increased expression of superoxide dismutase (SOD) compared with the KA only group. NACA activated Nrf2-dependent anti-inflammation signaling. According to optical imaging, a typical spatiotemporal changes in the signal transmission were observed in the hippocampus after electrical stimulation. A normal tissue exhibited strong activity accompanied by normal synaptic propagation. In contrast, the KA only group exhibited few activated areas around the stimulation areas, indicating less propagation and significantly delayed latency. The KA group showed delayed latencies and decreased signal activity compared to the vehicle group, but NACA-treated group showed shorter latencies and increased signal activity.
**Conclusions:** This study revealed that the treatment of NACA has neuroprotective effects on KA-induced oxidative stress in the hippocampus. NACA reduced neuronal cell death and also the generation of ROS. Therefore, these results suggest that NACA may protect hippocampal neurons against oxidative stress and the survived neurons may be functional to synaptic plasticity changes.

**Keywords:** NACA, Kainic acid, Organotypic hippocampal slice culture, Antioxidant, Oxidative stress

## P21-01-16

### Neural circuit from deep cerebellar nuclei to lateral parabrachial nuclei regulates cued fear learning and memory

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**Purpose:** The cerebellum is a core brain region that integrates various types of sensory stimuli. Its characteristic makes it possible to contribute to various functions including not only motor coordination but also non-motor roles such as social rewarding, cognition and emotional processing. Although a large amount of evidence indicate that the cerebellum processes non-motor emotional processing, how the cerebellum modulates emotional learning via interacting with other brain regions is not clear. We found a cerebellar projection from deep cerebellar nuclei (DCN) to lateral parabrachial nuclei

(LPBN), which is a center for danger detection. We investigated whether and how the DCN-LPBN circuit modulates fear learning and memory.
**Methods:** We used optogenetic tools for activating or inactivating the DCN-LPBN circuit during behavioral tests in mice. For mouse behavioral tests, laser delivery was targeted to DCN soma for optogenetic manipulation. For electrophysiological recordings of synaptic responses of DCN-LPBN circuit, we expressed channelrhodopsin (ChR2) in the DCN neurons, acquired the mouse brain slices containing LPBN, and stimulated ChR2-expressing cerebellar axons with whole-cell patch recording in LPBN. We also used the fiber photometry system to monitor in-vivo neural activities in the DCN-LPBN circuit using the genetically encoded calcium indicator (GCaMP6s).
**Results:** To examine whether the DCN-LPBN circuit is involved in fear learning and memory, we optogenetically inhibited the LPBN-projecting DCN neurons during fear learning and memory retrieval. Optogenetic inhibition in these neurons disrupted cued fear learning and memory without affecting contextual fear learning and memory. Optogenetic activation of DCN-LPBN circuit alone did not induce freezing behavior, suggesting that the optogenetic stimulation may not substitute footshock. However, optogenetic activation of this circuit induced freezing behavior in mice trained by pairing the optogenetic stimulation and footshock, suggesting that the activity of this circuit may convey conditioned stimulation (CS) information. Furthermore, we found that the DCN-LPBN synapse is potentiated by auditory fear conditioning, but not by contextual fear learning using ex vivo slice recording.
**Conclusions:** Taken together, these results show that the learning-dependent potentiation in DCN-LPBN circuit modulates auditory fear learning and memory via conveying CS information to the frontal fear networks through LPBN.

**Keywords:** Deep cerebellar nuclei (DCN), Brainstem, Fear memory, Optogenetics, Plasticity

## P21-01-17

### Protective effect of TRESK on hydrogen peroxide- and lipopolysaccharide-induced cellular stress

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**Purpose:** The pathological responses of spinal cord injury (SCI) are complicated, including oxidative stress and inflammation. Pro-inflammatory cytokines and reactive oxygen species (ROS) cause secondary damage in the spinal cord. A recent study demonstrated that upregulation of the TRESK channel contributes to motor and sensory recovery after spinal cord injury (SCI) using transgenic mice that overexpress the TRESK gene (TGTRESK). This study was performed to identify the physiological role of high TRESK expression after SCI.
**Methods:** Hydrogen peroxide (H2O2) and lipopolysaccharides (LPS) induced oxidative stress and inflammatory conditions. H2O2-induced cell death was analyzed in HEK-293 stable cell line and dorsal root ganglion (DRG) cell line F11 transfected with either TRESK/pcDNA3.1 or empty pcDNA3.1 vector. LPS-induced production of inflammatory mediators was analyzed in TRESK overexpressed RAW264.7 and F11 cells. The ninth thoracic (T9) spinal cord injury (T9 SCI) animal model was generated using wild-type (WT) and TGTRESK mice. Inflammatory and cell death signals were compared between WT-SCI and TGTRESK SCI mice.
**Results:** An MTT assay showed that the H2O2-induced cell death was significantly reduced by 20% in cells that stably expressed TRESK compared to vector-transfected cells. LPS-induced production of pro-inflammatory mediators such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and nitric oxide (NO) were significantly decreased in TRESK overexpressed RAW264.7 and F11 cells. In the caudal spinal cord and DRG, Bcl-2-associated X protein (Bax) and cleaved poly (ADP-ribose) polymerase (PARP), apoptotic proteins, and a cluster of differentiation 68 (CD68), a marker of inflammation associated with monocytes/macrophage infiltration, were upregulated in WT-SCI mice. However, the apoptotic signals were dramatically reduced in TGTRESK SCI mice compared to WT-SCI mice. In addition, IL-1β secretion and caspase 1 activity were also dramatically decreased in TGTRESK SCI mice compared to WT-SCI mice.
**Conclusions:** These results showed that upregulation of TRESK reduced the secretion of inflammatory mediators and cell death. We suggest that upregulated TRESK expression after SCI may contribute to motor and sensory recovery by inhibiting oxidative and inflammatory processes and cellular excitability.

**Keywords:** Inflammation, Oxidative stress, Spinal cord injuries, Two-pore domain $K^+$ channel

## P21-01-18

### Revisiting the cerebellar memory consolidation mechanism from AI perspective: The cerebellum as a dual learning machine

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**Purpose:** The cerebellum is known as a critical site for motor learning, and many studies have been conducted to explore the neural circuits and mechanisms responsible for memory formation and consolidation. Although they have provided detailed observations in several cerebellum-dependent motor learning paradigms, our knowledge of the underlying processes remains fragmentary. In this study, we employ statistical learning theory in machine learning to propose a novel framework that can explain why and how the cerebellum learns and consolidates memories by the transfer mechanism
**Methods:** We model the cerebellar system as a dual learning machine composed of two systems with different dimensions-cerebellar cortex and vestibular nuclei. The cerebellar cortex represents a "complex" system, which can be characterized as complex representation, fast adaptation, but relatively large overheads. The vestibular nuclei represent a "simple" system, which can be characterized as simple representation, slow adaption, but low overheads. Based on the modified empirical risk minimization theory, we predicted the preference of each system according to two factors of learning-phase and task difficulty. Predictions were validated with both computer simulation and behavioral experiments. For in vivo validation, optokinetic response and vestibulo-ocular reflex were regarded as an easy and hard task, respectively, and parameters to quantify the task difficulty were specified.
**Results:** The results of the theoretical analysis suggest that adaptive learning occurs first in the cerebellar cortex and simple components are then transferred to the vestibular nuclei, and the extent and timing of the transfer can vary depending on the task difficulty. While the complex system is commonly favored in the early phase, system preference is determined by bias-overhead tradeoff in the late phase. We also demonstrated that learning by adjusting the complex system is beneficial for stabilizing performance especially when changes in the target function are transient. These hypotheses can explain previously reported experimental results and were well matched with both the simulation and behavioral results.
**Conclusions:** In this study, we tried to model and interpret the cerebellar system from the machine learning perspective. This framework can provide a comprehensive understanding of cerebellar learning and contribute to further elucidating the essence of cerebellar computations.

**Keywords:** Cerebellum, Motor learning, Memory transfer, Machine learning theory, Computational modeling

## P21-02-01

### Neural circuit and molecular mechanisms of social competition and hierarchy behavior

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**Purpose:** Social animals compete each other and it makes social hierarchy. Although it was recently revealed that the medial prefrontal cortex (mPFC) is a hub brain region of social hierarchy, we still do not know about the relevant neural circuit and molecular mechanisms in detail.
**Methods:** To address this question, we investigated neural circuit activities and gene expression in mPFC subpopulation neurons projecting to other brain regions that has been implicated in social behaviors, especially in social competition - nucleus accumbens (mPFC-NAc) and ventral tegmental area (mPFC-VTA) - from social dominant and subordinate animals.
**Results:** Inhibition of mPFC-NAc circuit using taCasp3-TEVp significantly increased social losing, and optogenetic activation of this projection in subordinate mice increased their social ranks. Oppositely, genetic ablation of mPFC-VTA circuit significantly increased social wining, and activation of this neural circuit in dominant animals decreased their social ranks. We next conducted single-cell RNA sequencing (scRNA-seq) of mPFC regions from social dominant and subordinate mice, and found some differentially expressed genes (DEGs) between social dominant and subordinate mice in these two subpopulations in mPFC. Manipulating the expression of Gene X in mPFC-VTA circuit regulates social dominance.
**Conclusions:** Collectively, these results suggest that specific physiological and molecular changes in distinct projections of mPFC oppositely orchestrate social competition and hierarchy behavior.

**Keywords:** Social hierarchy, Medial prefrontal cortex, Nucleus accumbens, Ventral tegmental area

## P21-02-02

### Stem cell restores thalamocortical plasticity to rescue cognitive deficit in neonatal intraventricular hemorrhage

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**Purpose:** Severe neonatal intraventricular hemorrhage (IVH) patients incur long-term neurologic deficits such as cognitive disabilities. Recently, the intraventricular transplantation of allogeneic human umbilical cord blood-derived mesenchymal stem cells (MSCs) has drawn attention as a therapeutic potential to treat severe IVH. However, its pathological synaptic mechanism is still elusive.
**Methods:** We here demonstrated that the integration of the somatosensory input was significantly distorted by suppressing feed-forward inhibition (FFI) at the thalamocortical (TC) inputs in the barrel cortices of neonatal rats with IVH by using brain slice patch-clamp technique and sensory-guided decision making task.
**Results:** This is induced by the suppression of Hebbian plasticity via an increase in tumor necrosis factor-α expression during the critical period, which can be effectively reversed by the transplantation of MSCs. Furthermore, we showed that MSC transplantation successfully rescued IVH-induced learning deficits in the sensory-guided decision-making in correlation with TC FFI in the layer 4 barrel cortex.
**Conclusions:** The present study unraveled the synaptic and molecular mechanisms underlying cognitive dysfunctions induced by IVH, and further emphasized the therapeutic implications of MSC transplantation to reverse the neurodevelopmental damage caused by neonatal IVH. More specifically, using behavioral study techniques, our study has provided clear evidence on the critical role of the TC FFI in the sensory cortex during the learning dynamics of perceptual decision-making.

**Keywords:** Intraventricular hemorrhage, Mesenchymal stem cell, Thalamocortical input, Barrel cortex, Sensory-guided decision making

## P21-02-03

### Reactive microglia and mitochondrial unfolded protein response are following ventriculomegaly and behavior defects in kaolin-induced hydrocephalus

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**Purpose:** We investigated to assess the role of inflammatory response and UPRmt in the pathogenesis of hydrocephalus.
**Methods:** We established a kaolin-induced hydrocephalus model in 8-week-old male C57BL/6J mice and evaluated it over time.
**Results:** We found that kaolin-injected mice showed prominent ventricular dilation, motor behavior defects at the 3-day, followed by the activation of microglia and UPRmt in the motor cortex at the 5-day. In addition, PARP-1/NF-κB signaling and apoptotic cell death appeared at the 5-day.
**Conclusions:** Taken together, our findings demonstrate that activation of microglia and UPRmt occurs after hydrocephalic ventricular expansion and behavioral abnormalities which could be lead to apoptotic neuronal cell death, providing a new perspective on the pathogenic mechanism of hydrocephalus.

**Keywords:** Hydrocephalus, Microglia, Neuroinflammation, UPRmt

## P21-02-04

### Prenatal Stress Impairs Neuroligin 1-dependent Neurogenesis through Suppressing Astrocytic FGF2-Neuronal FGFR1 interaction

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**Purpose:** Exposure to maternal stress irreversibly and permanently impairs neurogenesis of offsprings through inducing life-long effects on interaction between neurons and glia under raging differentiation process, culminating in cognitive and neuropsychiatric abnormalities in adulthood. Therefore, we identified how prenatal exposure to a major stress-responsive hormone glucocorticoid impairs synapse formation and subsequent neurogenesis

**Methods:** We used human induced neural stem cell (NSC) and ICR mice.
**Results:** First, we observed that maternal corticosterone exposure during embryonic day 14 triggered both depression/anxiety-like behaviors and spatial memory dysfunction in littermates at postnatal day 23. We observed that phenotypes of differentiated astrocytes from NSC were changed as A1-like astrocytes, which lose their neurotrophic functions. Cortisol-treated astrocyte conditioned media (ACM) then specifically downregulated AMPA-mediated glutamatergic synaptic formation and transmission in differentiating neurons, especially via decreasing localization of ionotropic glutamate receptor (GluR) 1/2 in synapse. Data from RNA sequencing, antibody array, and subcellular fraction revealed that downregulated astrocytic fibroblast growth factor 2 (FGF2) and nuclear fibroblast growth factor receptor 1 (FGFR1) of neurons are key factors for reducing glutamatergic synapse formation. We further confirmed that cortisol-treated ACM specifically decreased binding of neuronal FGFR1 to the NLGN1 promoter among the synaptogenic genes, but reversed by FGFR1 restoration in differentiated neurons. Upregulation of neuroligin 1, an important molecule to scaffold GluR1/2 into the postsynaptic compartments, eventually normalized glutamatergic transmission and neurogenesis. Consistent with these results, FGF2 pretreatment of a prenatal corticosterone-exposed mouse elevated neuroligin 1 expression and trafficking of GluR1/2 into postsynaptic compartment, improving the outcome of a spatial memory task and depression/anxiety-like behaviors.
**Conclusions:** In conclusion, our results identified the restoration of astrocytic FGF2 and its downstream neuronal nuclear FGFR1 as critical targets of prenatal stress-induced glutamatergic synapse formation through regulating neuroligin 1 and demonstrated its function in controlling both neurogenesis and hippocampal-related behaviors including spatial memory and mood formation.

**Keywords:** Prenatal stress, Glucocorticoid, Neurogenesis, Astrocyte, Neuroligin 1

## P21-02-05

### Sleep promotion and quality improvement of poria cocos extracts on animal models with sleep disturbance

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**Purpose:** To evaluate whether the sedative properties of Poria cocos extract can improve sleep quality and structure in animal models with sleep disturbance by promoting inhibitory neurotransmission through the GABA type A receptor.
**Methods:** Pentobarbital-induced sleep test was conducted to determine whether Poria cocos extract improves the sleep quality and structure in normal ICR mice. Poria Cocos extract was administered orally 45 min prior to intraperitoneal injection of pentobarbital (42 mg/kg). Sleep latency and duration was checked with the righting reflex. In order to simulate the state of awakening as well as normal sleep state, caffeine (50 mg/kg) was administered orally before the Poria cocos extract diet. We measured the real time EEG by implanting wireless Bluetooth electrodes and transmitters in the skull of SD rats that can measure in real time of the EEG and analyzing the structure of sleep. Adrenocortical stimulating hormone (ACTH) was subcutaneously injected to stimulate a stress-based sleep disturbed model caused by hyperactivity of hypothalamus-pituitary-adrenal axis.
**Results:** After oral administration of Poria cocos extract, sleep latency was decreased concentration-dependently and total sleep duration was also increased. Caffeine administration significantly increased and decreased sleep latency and total sleep duration in ICR mice, respectively. The sleep latency and total sleep duration changes by caffeine were improved by administration of Poria cocos extract. After 10 days of subcutaneous injection for ACTH, the sleep latency and non-REM sleep time were significantly changed in ACTH injection group (73.8±6.3 and 356.4±7.3) compared to the control (35.6±5.7 and 380.7±8.6 min, n=3) . In ACTH-induced sleep disturbed models, administration of Poria cocos extract has significantly reduced sleep latency and increased non-REM sleep duration.
**Conclusions:** The results showed that the Poria cocos extract dose-dependently reduced sleep latency and increased sleep duration in normal, caffeine-induced sleep disturbance ICR mice, and in ACTH-induced sleep disturbance SD rat models.

**Keywords:** Sleep disturbance, GABA A receptor, Poria cocos, Insomnia

## P21-02-06

### Pathological findings and epigenetic biomarkers for cognitive impairment in rats with chronic obstructive sleep apnea

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**Purpose:** Obstructive sleep apnea (OSA) is a common disorder which is associated with increased cardiovascular disease and neurocognitive impairment. Although studies on cardiovascular and cerebrovascular morbidity have been conducted, there are few research on the mechanism related to cognitive decline and dementia especially, Alzheimer's disease (AD). Recent study reinforces OSA-AD link with amyloid deposition in OSA brain and APOE genotype prevalence in OSA. This study was designed to identify early warning biomarkers for the risk of cognitive decline in OSA patients.
**Methods:** A total of 12 rats were used, divided into 6 control group and 6 OSA group. For OSA, collagen fillers were injected into the base of the tongue to create a OSA model. After 12 weeks, chronic OSA was identified with full channel polysomnography (PSG). The Morris water maze (MWM) test was conducted in control and OSA groups, and the changes in brain weight and pathological findings were subsequently confirmed. In addition, we studied the epigenetic changes with mRNA and miRNA to identify the biomarkers for prediction of dementia in OSA.
**Results:** In MWM test, the speed of finding the platform was lower than that of the control group (47.0±13.9 seconds; OSA group/ 12.4±6.1 seconds; control, $p<0.01$). In each group, the brain weight showed no difference (2.14±0.06 mg; control/ 20.8±0.09 mg OSA group). In brain histopathologic changes, disorganized cortex layers in OSA group were prominent compared with control cortex. Hippocampal cortex in OSA also showed a disorganized CA1 region with degenerative neurons and fibrillary changes, compared with control. The mRNA analysis identified a decreased expression of Olfr 110 known to be expressed in dementia models in the apnea group, an up-regulation of MiR-132/137/502, also known as AD, and a down-regulation of MiR-21/182/183/200a/200b.
**Conclusions:** OSA rat model showed neurodegenerative changes in brain and the epigenetic changes of mRNA/miRNA which have been known as AD related genes.

**Keywords:** Sleep apnea, Dementia, Cognitive impairment, MiR-200b, Polysomnography

## P21-02-07

### Role of mTOR, AMPK, and LC3B signaling in rotenone-induced SH-SY5Y cells treated neural induced-human adipose stem cells conditioned medium

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**Purpose:** Mechanistic/mammalian target of rapamycin (mTOR) exists in two distinct multiprotein complexes, mTORC1 and mTORC2. They control several cellular function through nutrient signal transduction with their unique subunit composition. DEPTOR is a negative regulator of mTORC1 and mTORC2. In addition, AMPK driven mTOR downregulation serves as a turn-off switch of the cellular anabolic program that regulates the autophagy-associated kinase ULK1. The present study was designed to determine the effect of neurogenic differentiation of human adipose-derived stem cells (NI-hADSC) conditioned medium (NI-hADSC-CM) in rotenone (ROT)-induced toxicity in SH-SY5Y cells.
**Methods:** SH-SY5Y neuroblastoma cells seeded in 1% fetal bovine serum containing culture media were treated without or with ROT for 48 h and/or NI-hADSC-CM for last 24 h.
**Results:** ROT toxicity increased the reactive oxygen species (ROS), which was inhibited significantly by NI-hADSC-CM treatment. Western blotting results showed that decreased p-/t-mTORC1, p-/t-mTORC2, p-/t-ULK1, and ATG13 while increased DEPTOR and p-/t-AMPK by ROT. Treatment of NI-hADSC-CM for 24 h showed decreased DEPTOR and p-/t-AMPK with increased p-/t-mTORC1, p-/t-mTORC2, p-/t-ULK1, and ATG13 protein levels. In addition, LC3BI at 16 kDa protein level decreased with increased LC3BII at 14 kDa protein level by ROT toxicity was also significantly inhibited by treatment of NI-hADSC-CM.
**Conclusions:** Our study results post-treatment of NI-hADSC-CM significantly decreased the ROT-induced autophagy concludes that NI-hADSC-CM have therapeutic effects on Parkinson's disease.

**Keywords:** Rotenone, MTOR, AMPK, LC3B, Mesenchymal stem cells

## P21-03-01

### Cell type dependent post-critical-period intrinsic plasticity in layer 4 of mouse barrel cortex

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**Purpose:** Recent work has revealed that thalamocortical (TC) synapses can be plastic after the end of the critical period. However, it is still unclear whether the intrinsic properties of postsynaptic neurons receiving TC synapses are changed after the synaptic plasticity. This study is to examine the intrinsic excitabilities of regular spiking (RS) and fast spiking (FS) neurons in the spared barrel cortex layer 4 after unilateral infra-orbital nerve (ION) lesioning.
**Methods:** 4-week-old male mice were used for ION denervation and sham operation. The infra-orbital branch of the trigeminal nerve was exposed and ligated for animals in the ION denervation group. For sham operation group, skin incision was made, but the nerve was not ligated. Whole cell patch clamp recording using TC brain slices was performed at 2~3 weeks after the surgical procedures. 500ms-length current steps were injected to neurons in the spared barrel cortex layer 4 and corresponding voltage responses were obtained in current-clamp mode.
**Results:** Significant decreases in action potential (AP) half-width, decay slope and afterhyperpolarization were observed in RS neurons. FS neurons showed decreasing trend in AP threshold. These results suggest increased neuronal excitabilities in both RS and FS cells. Sharp falling phase with mild overshooting makes RS neurons generate another APs more easily. In addition, decreased AP threshold allows FS neurons to initiate firing at lower membrane voltage.
**Conclusions:** This study demonstrated that intrinsic firing properties of TC recipient neurons are also changeable even after the critical period and this alteration occurred in a cell-type-dependent manner. Increased excitabilities in both RS and FS neurons imply that the intrinsic properties were modulated to maintain a balance between excitation and inhibition in layer 4 feedforward inhibition circuits.

**Keywords:** Post-critical-period plasticity, Intrinsic plasticity, Synaptic plasticity, Barrel cortex, Brain slice patch clamp

## P21-03-02

### Characterization of KCNQ1 expression and IKs of a novel 845T>G-KCNQ1 mutation in LQT1 patient using hiPSC-derived cardiomyocytes and HEK293 heterologous expression

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**Purpose:** Long QT syndrome type 1 (LQT1) is the most common subtype long QT syndrome. LQT1 is associated with loss-of-function mutations of KCNQ1 gene, which encodes the slow component of the delayed rectifier $K^+$ current, IKs. We identified the novel KCNQ1 missense mutated gene (c. 845T>G, p. L282R) in a LQT1 patient. Since the mutation is located in the transmembrane domain 5 end close to pore region, it can lead to dysfunctional property of the channel. However, functional analysis of these mutation was not conducted yet.
**Methods:** Here, we employed LQT1 patient-specific cardiomyocytes from human induced pluripotent stem cells (hiPSC-CM) to investigate electrophysiological properties. Furthermore, we performed whole-cell patch clamp and immunofluorescence HEK293 cells transfected with 845T>G-KCNQ1.
**Results:** The KCNQ1 mutant-specific hiPSC-CM from a heterozygote patient showed significantly prolonged action potential duration (APD) and reduced density of the slow activating delayed rectifier $K^+$ current (IKs). KCNQ1 mutant channels expressed in HEK293 cells failed to conduct any $K^+$ current in the homozygous state. When co-expressed with wild type KCNQ1, the density of IKs in HEK293 cell was reduced to 58.4 % and the voltage activation curve was shifted to the right by 5 mV. Confocal imaging analysis revealed that the mutant KCNQ1 was retained in the endoplasmic reticulum, whereas wild type KCNQ1 was localized in the plasma membrane.
**Conclusions:** These results suggest that the 845T>G-KCNQ1 co-assembles with wild type KCNQ1 and causes a dominant-negative effect due to trafficking defect.

**Keywords:** Human induced pluripotent stem cells-cardiomyocyte, Long QT syndrome type 1, KCNQ1 mutation

## P21-03-03

### Functional analysis of novel SCN5A mutations related to Brugada syndrome

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**Purpose:** Brugada syndrome (BrS) is an arrhythmogenic disorder that has been linked to mutations in SCN5A, the gene encoding for the pore-form-

ing α-subunit of the cardiac $Na^+$ channel. Recently, novel SCN5A missense mutations (A385T and R504T) were identified in a BrS patient. Since the mutations are in the loop connecting transmembrane segments 5 and 6 in domain 1 (S5-S6 in DI) and segments 6 and 1 between domain 1 and 2 (DI-DII linker), it can lead to dysfunctional property of the $Na^+$ channel. Here we aimed to characterize the electrophysiological properties of A385T and R504T.

**Methods:** The wild-type (WT) and mutant SCN5A were transiently transfected in HEK293 cells, and the $Na^+$ channel was analyzed using the whole-cell patch-clamp technique at room temperature.

**Results:** WT, A385T, R504T, and double mutant (A385T/R504T) showed no significant differences in the current density and the voltage-dependent activation. Unexpectedly, a rightward shift of the voltage-dependent inactivation was identified in the three groups of mutation. Besides, the recovery from inactivation of A385T+R504T was faster than that of WT.

**Conclusions:** These results suggest that, contrary to the expected mechanism of BrS, the mutations cause a gain-of-function of NaV1.5 at the room temperature. A previous study reported that a BrS-related SCN5A mutation showed functional inhibition at physiological temperature while not in the room temperature. Therefore, to further understand the phenotypic consequences of SCN5A mutation, further experiments at physiological temperature will be conducted.

**Keywords:** Brugada syndrome, Cardiac $Na^+$ channel, SCN5A mutation

## P21-03-04

### Bi-directional pH-dependent regulation of calcium homeostasis modulator 1 (CALHM1) ion channel

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**Purpose:** Calcium homeostasis modulator (CALHM) membrane proteins are nonselective ion channels drawing attention regarding their roles in modulating neuronal activity and taste sensation. CALHM1-expressing cells show voltage-gated slowly activating ionic currents. The voltage-dependence of CALHM1 is negatively affected by extracellular $Ca^{2+}$ ($[Ca^{2+}]e$), while facilitated by temperature.

**Methods:** Here we investigated the effect of extracellular and intracellular pH (pHe and pHi) on the electrophysiological properties of hCALHM1 (ICALHM1) overexpressed in CHO cells.

**Results:** When normalized to the control at pHe 7.4, the amplitudes of ICALHM1 were suppressed to 20 % at pHe 6.2, while increased to 500 % at pHe 8.6. In the same manner, changing intracellular pH from 7.4 to 6.2 or 8.6 showed the acid-induced inhibition and alkali-induced activation of ICALHM1. The pHi effect was also confirmed in the inside-out configuration of patch clamp. The voltage-dependence of ICALHM1 was shifted to the negative membrane potential at the alkaline pHe and pHi. The open probability (Po) of multiple hCALHM1 channel decreased at pH 6.2, while increased at pH 8.6 compared with pH 7.4. To get a clue to identify the pH sensing amino acid residues, we utilized homology model performed with the SWISS-MODEL workspace, based on the cryo-EM structure of hCALHM2. Then we conducted site-directed mutagenesis of the water-accessible charged amino acids of hCALHM1. Among 23 candidates, mutations at E17, K229, E233, D257 and E259 in the intracellular space reduced the alkali-induced facilitation of ICALHM1. According to the molecular structure model of hCALHM1 with octameric structure, the five residues located at N or C termini gathered closely in the intracellular space. Considering the large pore diameter of hCALHM1 (14 Å), we cautiously propose that the sensitivity to pHe could be due to the proton transfer between hydronium ions in the pore.

**Conclusions:** The study firstly demonstrated the remarkable pH-sensitivity of hCALHM1, which might be responsible for the modulation of neuronal excitability during dynamic changes of the regional pH in brain or sensory organs.

**Keywords:** Calcium homeostasis modulator channel 1 (CALHM1), PH sensitivity, Acid-induced inhibition, Alkali-induced activation, PH sensing residues

## P21-03-05

### Multiple effects of α-mangostin on the ion channels in small DRG neurons consistent with the known analgesic effect

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**Purpose:** The effect of α-mangostin on the function of ion channels involved in pain sensation was determined.

**Methods:** Using patch clamp study, multiple effects of α-mangostin on the ion channels expressed in small DRG neurons were examined.

**Results:** In mouse DRG neurons treated with α-mangostin (1–3 μM) under zero-current clamp condition, the resting membrane potential (RMP) was initially hyperpolarized and slowly depolarized with increased membrane conductance. Interestingly, the generation of action potential (AP) by current injection was inhibited by α-mangostin at 3 μM. Consistent with the initial hyperpolarization, α-mangostin treatment increased the activity of TREK-1 and TREK-2 overexpressed in HEK293 cells, but not the activity of TRESK. Under the voltage-clamp condition, the TTX-sensitive NaV currents in the small DRG neuron and ND7/23 cells was inhibited to ~40 % by α-mangostin at 3 μM. Furthermore, α-mangostin potently inhibited capsaicin-induced TRPV1 currents in human TRPV1 overexpressing HEK293T cells and in the cultured mouse DRG sensory neurons (IC50 = 0.33±1.05 μM).

**Conclusions:** The multiple effects on TRPV1, TREK-2 and NaV commonly explain the analgesic action of α-mangostin. Although the mechanism of the delayed depolarization by higher concentration of α-mangostin was not identified, the inactivation of NaV at sustained partial depolarization along with the direct inhibition by α-mangostin appears to be responsible for the AP failure and analgesic effects.

**Keywords:** Ion channels, Patch clamp, Pain, Phytochemicals, Analgesic effect

## P21-03-06

### Enhanced tonic NMDA current in SON MNCs in DOCA-salt hypertensive rats

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**Purpose:** Activation of NMDA receptors (NMDARs) by increased glutamate tone plays a critical role in modulating glutamate excitatory function in magnocellular neurosecretory cell (MNCs) in the supraoptic nucleus and paraventricular nucleus of hypertensive subjects. Hypertensive patients show elevated circulating vasopressin (VP), which closely associated with enhanced excitability of hypothalamic magnocellular neurosecretory cell (MNCs). However elevated levels of circulating VP have been shown to contribute to hypertension in experimental animal models but roles of NMDARs activity in hypertension remains to be explored. Here, we aimed to determine whether changes in NMDARs activity contributes to exacerbated MNCs activity during hypertension.

**Methods:** All rats were uni-nephrectomised and kept for 7-days of recovery. After 7-days, deoxycorticosterone acetate (DOCA) was implanted sub-dermally, and the DOCA-salt group was provided 0.8% NaCl and 0.2% KCl in tap water. DOCA-H2O group was provided free access of normal tap water. On

the 6th day after DOCA implantation, mice were kept in metabolic cage for 24 hour urine collection to measure the metabolic rate. After 24 hour, water intake, urine output and urine osmolality were measured. Before decapitation of rats for electrophysiology, systolic blood pressure was measured by tail cuff method.

**Results:** In this study we demonstrate that tonic NMDA currents in SON MNCs contribute to neurohumoral activation in DOCA-salt hypertension rats. Blood pressure started to increase at 2-week and reached maximum at 4-week DOCA-salt model. In SON MNCs, tonic NMDA current (INMDA) significantly increased in DOCA-salt rats of 1-week model, decreased at 2-week, and returned to basal level at 4-week groups. While there is no difference in blood pressure and urine osmolality between 1-week DOCA-salt and DOCA-H2O groups, water intake and urine volume were significantly increased in 1-week DOCA-salt rats than DOCA-H2O groups. INMDA of SON MNCs was blocked by an NR2A antagonist (PEAQX) but not by NR2B antagonist (ifenprodil) and NR2C/D antagonist (PPDA) in both 1-week DOCA-salt and DOCA-H2O groups. Interestingly, INMDA difference between the groups was not observed with increased glutamate concentration in extracellular recording solution. The increased glutamate tone was mediated by the reduced glutamate transporter activity in DOCA-salt model.

**Conclusions:** In summary, our studies indicate that an elevated endogenous glutamate tone results in an increased activation of NR2A-containig NMDARs in SON NMCs of 1-week DOCA-salt model.

**Keywords:** Glutamate, Glutamate transporter, NR2A , DOCA, SON MNCs

## P21-03-07

### Deep Learning based the hERG model fitting

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**Purpose:** The parameter identification of the ion channels is important to reconstruct the ion channel activities and to identify its role in physiological function. There are many mathematical methods to infer the parameters, however, there are two main difficulties in fitting parameters. The first is that parametric inference can be highly time-consuming, depending on data and model. The second is that the fitting itself can fail due to local minima problems. The simplest and the most effective way to solve these issues is to provide an appropriate initial value. We propose a method to improve model fitting by providing the appropriate initial values using deep learning.

**Methods:** We propose a method to improve model fitting by providing the appropriate initial values using deep learning. We generated the data set by changing the model parameters and trained the convolutional neural network (CNN). To improve the accuracy, we converted the time-series data to the spectrogram which contains time, frequency, and amplitude. We made 500,000 simulation data for training and used 36 real data for evaluation, and 36 real data for the test. We obtained the real dataset from https://github.com/CardiacModelling/hERGRapidCharacterisation.

**Results:** The mean square error (MSE) of the best neural network for the evaluation dataset was 0.004. MSE for the test dataset was 0.0058. When applying the parameters suggested by our neural network as an initial value, we can significantly improve the fitting speed and never get the fitting failure.

**Conclusions:** This method can be very useful when the model is very well developed and reflects the real data. If the model may not be perfect to reconstruct the real data, this method may not be applicable. Any in silico method will use the identified model to apply to the target purpose such as the new drug development, the toxicity identification, the environmental effect, etc. This method will significantly reduce the time and the effort to analyze the data.

**Keywords:** Parameter inference, Electrophysiology, HERG, Deep learning, CNN

## P21-03-08

### Tonic activation of GluN2D containing NMDA receptors in hippocampal GABAergic interneurons modulates status epilepticus

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**Purpose:** N-Methyl-D-Aspartate receptors (NMDARs) are ion channels, which are involved in most of the excitatory transmissions in the central nervous system. They are typically composed of GluN1 and GluN2 (GluN2A-D) receptors subunits which are expressed differentially in the brain regions throughout the development. GluN2D mRNA is selectively expressed in GABAergic interneurons but not in glutamatergic neurons in developing and mature hippocampus. Very little is known about the role of GluN2D-containing NMDARs in hippocampal GABAergic interneuron in a mature brain. We hypothesized that GluN2D in GABAergic interneurons contributes to maintaining E/I balance during neuronal hyperexcitability conditions such as epilepsy. Here, we evaluate the role of tonic activation of GluN2D subunit-containing NMDA receptors in pilocarpine-induced status epilepticus mice.

**Methods:** Pilocarpine-induced status epilepticus were developed by i.p injection of 180-200 mg/kg pilocarpine in mice. The electrophysiological recording was measured from hippocampal slices obtained from GAD-67-GFP transgenic ICR mice and C57BL/6-WT mice with or without pilocarpine injection. Electroshock-induced seizure activity was recorded after electroconvulsive were produced by a current (5–6 mA, 60 Hz, 0.2 s stimulus duration) delivered via ear-clip electrodes in C57BL/6- WT and GluN2D KO mice. Spontaneous seizures were recorded using continuous video recording and were analyzed manually. Frozen brain sections were immunostained to determine pilocarpine-induced neuronal death.

**Results:** Our experiment explores that $Mg^{2+}$ resistant tonic NMDA current mediated by GluN2D containing NMDA receptors is generated in hippocampal GABAergic interneurons in pilocarpine-induced epileptic mice but not in control mice. In addition, tonic activation of GluN2D containing NMDA receptors in GABAergic interneurons regulates synaptic inhibition in hippocampal CA1 pyramidal neurons. Furthermore, we examined the role of GluN2D in epilepsy progression after pilocarpine injection. Interestingly, transauricular electroshock-induced seizure activity was increased in pilocarpine injected GluN2D knockout (KO) mice compared to wild-type (WT) mice. In addition, KO mice show spontaneous recurrent seizures in chronic stages, starting after the third week of pilocarpine injection. Along with spontaneous seizure, KO mice show progressive death of hippocampal pyramidal neurons. At the same time, pilocarpine effects are minimal in WT mice.

**Conclusions:** Our results demonstrated that the GluN2D mediated $Mg^{2+}$ resistant tonic NMDA current in GABAergic interneurons regulates GABA inhibition in pyramidal neurons in pilocarpine-induced epileptic hippocampi and modulates the epilepsy progression.

**Keywords:** Status epilepticus, NMDARs, GluN2D, GABAergic interneurons

## P21-03-09

### cGAMP improves learning and memory via STING-IRF3-GATs pathway in Alzheimer's disease mouse model

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**Purpose:** Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by cognitive deficits. Recently, immunotherapy emerged as a promising treatment strategy for AD. STING (stimulator of interferon genes) is a protein, plays a crucial role in innate immunity. Role of STING and STING activated pathways have been studied in systemic inflammation, infection and cancer but its role in the central nervous system (CNS) remains to be elucidated. In our previous study, we explore that STING and its downstream signaling molecule interferon regulatory factor 3 (IRF3) regulated the GABA transporters (GATs) expression in CNS. In this study, we evaluate the effects of cGAMP in STING-IRF3-GATs pathway and cognitive functions in AD mouse model.
**Methods:** The littermate control (WT) and APP/PS1 transgenic mice were subjected to systemic administration of either saline or cGAMP (a STING agonist for 14 days, ip) and its effects were analysed using behavioural test, western blot and electrophysiology. The learning and memory was accessed using Y-maze test and Barnes maze test. The open field test and rotarod test were performed to access motor activity. To detect the protein expression hippocampal and cortical tissues were harvested and performed the western blot analysis. Electrophysiological recording were performed in hippocampal DG granules cells to detect GABAA inhibition.
**Results:** Our results show that systemic injection of cGAMP significantly improved the learning and memory with reduced tonic GABAA inhibition in the AD mouse model. cGAMP caused minimal effect in WT mice in terms of learning and memory and tonic GABAA inhibition. The phasic current properties were unchanged in both WT and APP/PS1 mice before and after cGAMP treatment. In addition, we examined the motor activity and motor learning, which were not affected by cGAMP treatment in both WT and APP/PS1 mice. Interestingly, cGAMP increased GATs expression along with TBK1 and IRF3 in both WT and APP/PS1 mice.
**Conclusions:** Our findings demonstrate that cGAMP treatment sufficiently improves the cognitive deficits in AD model mouse via STING-IRF3-GATs pathway.

**Keywords:** Alzheimer's disease, STING, GATs, Learning and memory, Hippocampus, GABAA inhibition

## P21-03-10

### Chrysosplenol-C increases contraction by augmentation of sarcoplasmic reticulum $Ca^{2+}$ loading and release via protein kinase C in rat ventricular myocytes

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**Purpose:** Naturally found chrysosplenol-C (4',5,6-trihydroxy-3,3',7-trimethoxyflavone) increases the contractility of cardiac myocytes independent of beta-adrenergic signaling. We investigated the cellular mechanism for chrysosplenol-C-induced positive inotropy.
**Methods:** We investigated the cellular mechanism for chrysosplenol-C-induced positive inotropy. Global and local $Ca^{2+}$ signals, L-type $Ca^{2+}$ current (ICa), and contraction were measured from adult rat ventricular myocytes using two-dimensional confocal $Ca^{2+}$ imaging, the whole-cell patch clamp technique, and video-edge detection, respectively.
**Results:** Application of chrysosplenol-C reversibly increased $Ca^{2+}$ transient magnitude with a maximal increase of approximately 55% within 2-3-min-exposures (EC50=21 μM). This chemical did not alter ICa and slightly increased diastolic $Ca^{2+}$ level. The frequency and size of resting $Ca^{2+}$ sparks were increased by chrysosplenol-C. Chrysosplenol-C significantly increased sarcoplasmic reticulum (SR) $Ca^{2+}$ content but not fractional release. Pretreatment of protein kinase C (PKC) inhibitor, but not $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) inhibitor, abolished the stimulatory effects of chrysosplenol-C on $Ca^{2+}$ transients and $Ca^{2+}$ sparks. Chrysosplenol-C-induced positive inotropy was removed by the inhibition of PKC, but not CaMKII or phospholipase C. Western blotting assessment revealed that PKC-δ protein level in the membrane fractions significantly increase within 2 min after chrysosplenol-C exposure with a delayed (5 min) increase in PKC-α levels in insoluble membrane.
**Conclusions:** These results suggest that chrysosplenol-C enhances contractility via PKC (most likely PKC-δ)-dependent enhancement of SR $Ca^{2+}$ releases in ventricular myocytes.

**Keywords:** Chrysosplenol-C, PKC-δ, Positive inotropy, Calcium signaling, Ventricular myocytes

## P21-03-11

### Inhibition of TRPC4 channel activity in colonic myocytes by tricyclic antidepressants disrupts colonic motility causing constipation

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**Purpose:** Tricyclic antidepressants (TCAs) have been used to treat depression for ages, and now, TCAs have recently been shown to have clinical efficacy in treating irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). However, molecular mechanism of TCA action in gastrointestinal (GI) tract remains poorly understood. Transient receptor potential channel canonical subtype (TRPC) members 4, which is nonselective cation channels, is important regulators of electrical excitability in both GI smooth muscle. Herein, we investigated whether TCA modulates TRPC4 channel activity, and by what mechanism in colonic myocytes consequently causing constipation.
**Methods:** Mechanical tension recording in human colon was analyzed in three ways: migrating motor complexes (MMC), electric field stimulation (EFS)-induced contraction, and spontaneous contraction. Whole cell current was measured in TRPC4-overexpressed HEK293 cells and colonic myocytes by patch clamp technique. Membrane expression of TRPC4 was measured in TRPC4-overexpressed HEK293 cells by surface biotinylation.
**Results:** In the contraction of human colon segments, TCAs (amitriptyline, desipramine, and imipramine) reduced the amplitude of colonic MMC at least 60-70%. Then, we attempted to distinguish mechanisms by neurogenic and muscular contractions in the inhibitory effects of TCA. In EFS-induced contraction, TCAs significantly reduced the amplitude. And, regardless of the inhibition of neural stimulation with TTX, TCAs significantly inhibited spontaneous contraction. Afterwards, we tried to find a molecular target for the inhibitory mechanism of TCA, and focused on TRPC4, which has been reported to be important for smooth muscle contraction. Englerin A (EA), TRPC4 agonist, significantly increased the tonic contraction of colonic MMC, whereas Pico145, TRPC4 antagonist, decreased EFS-induced amplitude. In addition, EA significantly increased the spontaneous contraction of circular muscle strips. Then, we measured whether TCA treatment directly modulates TRPC4β current. Pretreatment with TCA completely reduced muscarinic receptor-activated cation current (mIcat) in HEK293 cells expressed with TRPC4β and muscarinic 3 receptor, also, GTPγS-evoked TRPC4β current was also reduced by TCA perfusion. And, these inhibitory effects are observed only when TCA is exposed to extracellular sites. Moreover, the membrane expression level of TRPC4β was not altered during TCA treatment. In hence, TCA acted extracellularly to suppress the opening property of TRPC4, but

did not regulate its expression. Finally, the mIcat was measured in murine colonic myocytes to determine whether the TCA-inhibited TRPC4 current reduced the excitability. CCh-induced myocyte current was significantly reduced by Pico145, as expect, which was also reduced by TCAs to similar level. However, TRPC4 knockout murine myocyte showed neither an increase in current by CCh nor an inhibitory effect by TCA.
**Conclusions:** Our results suggest TRPC4 can have the functional potential as an alternative molecular target for TCAs. As well as symptoms of constipation, inhibition of TRPC4 activity may serve as a mechanism for various side effects of TCA, also including the medical intervention aimed at IBS and IBD therapy.

**Acknowledgement:** This work was supported by the National Research Foundation (NRF) of Korea funded by the Korea government (Grant Nos. NRF-2021R1C1C1006246, NRF-2020R1F1A1050018, NRF-2015R1A63A04058395, and NRF-2021R1A4A2001857). The authors would like to thank Tae-Sik Sung, Ph.D. and Prof. Seung Bum Ryoo for their assistance in human mechanical tension recordings.

**Keywords:** Tricyclic antidepressant, TRPC4, Colonic motility, Constipation

## P21-03-12

### GABA- and glycine-mimetic responses of isopulegol on substantia gelatinosa neurons of trigeminal subnucleus caudalis in mice

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**Purpose:** Isopulegol is a monoterpene alcohol present in essential oils from several plants and is a chemical precursor to menthol. Although it has been demonstrated that various monoterpene compounds have pharmacological effects including anti-nociceptive effects, little is known the orofacial pain modulation and the action mechanism of isopulegol on the substantia gelatinosa (SG) neurons of the trigeminal subnucleus caudalis (Vc), which play an important role in the processing and transmission of orofacial nociceptive information. In this study, we investigated the direct effects of isopulegol on the SG neurons of the Vc and tried to figure out the action mechanism.
**Methods:** After brain removal from immature ICR mice, a transverse section containing the Vc was prepared. To investigate how isopulegol acts on SG neurons in the Vc, we used whole-cell patch-clamp technique.
**Results:** Under the high chloride pipette solution, isopulegol induced repeatable and concentration-dependent inward currents. Isopulegol-induced inward currents were preserved in the presence of tetrodotoxin (voltage-gated $Na^+$ channel blocker), CNQX (non-NMDA glutamate receptor antagonist) and DL-AP5 (NMDA receptor antagonist). However, isopulegol-induced responses were partially inhibited by picrotoxin (GABAA receptor antagonist) and strychnine (glycine receptor antagonist). Moreover, isopulegol increased GABA-mediated and glycine-mediated currents.
**Conclusions:** In conclusion, isopulegol directly acts on SG neurons of the Vc and has inhibitory effects on SG neurons through activation of GABAA receptors and/or glycine receptors. Additionally, isopulegol enhanced the GABA- and glycine-mediated responses. These results indicate that isopulegol has GABA- and glycine-mimetic actions and can modulate orofacial pain by activating inhibitory neurotransmission in the SG area of the Vc.

**Keywords:** Substantia gelatinosa, Isopulegol, Whole-cell patch-clamp technique, GABA, Glycine

## P21-03-13

### Hydrogen peroxide affects the gonadotropin-releasing hormone neuronal activities in mice

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**Purpose:** Gonadotropin-releasing hormone (GnRH) neuron is a key regulators of the hypothalamic-pituitary-gonadal (HPG) axis that plays a pivotal role in the regulation of reproductive physiology and release of gonadotropins in mammals. Reactive oxygen species (ROS) generated due to endogenous and exogenous factors have been reported to alter the reproductive functions by reducing the gonadal hormones and interfering the cross-talks between the HPG axis and other endocrine axes that eventually affects fertility. Kisspeptin, a neuropeptide is a potent stimulator of puberty and fertility because kisspeptin signaling is an essential component of the neuroendocrine reproductive axis. A number of studies have demonstrated that the hindrance of ROS in the various levels affects the HPG axis and the release of gonadotropins. However, how ROS influence the GnRH neuronal activities remains unclear.
**Methods:** Here, we investigated how GnRH neuronal activities and kisspeptin signaling on the GnRH neurons are affected by hydrogen peroxide (H2O2), a long-lived ROS using the brain slice patch-clamp technique.
**Results:** The results show that H2O2 suppressed the GnRH neuronal excitability by hyperpolarizing the majority of GnRH neurons. In addition, H2O2 exposure resulted in the loss of spontaneous as well as kisspeptin evoked neuronal activities on the GnRH neurons suggesting its inhibitory role on GnRH neuron regulation. Furthermore, the increase of endogenous H2O2 by inhibiting glutathione peroxidase resulted in the loss of spontaneous activities on GnRH neurons.
**Conclusions:** These results indicate that H2O2 can suppress the GnRH neuronal activities directly or via kisspeptin signaling suggesting that ROS impact the reproductive axis at the hypothalamic level by regulation of GnRH neuronal activities.

**Keywords:** Gonadotropin-releasing hormone neurons, Brain slice, Patch-clamp technique, Kisspeptin, Hydrogen peroxide

## P21-03-14

### Group I metabotropic glutamate receptor is involved in low $Mg^{2+}$-induced interictal-like epileptiform activity and cell death in rat hippocampal slice

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Group I glutamate metabotropic receptor (mGluR) has been shown to be involved in postsynaptic neuronal excitability. 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 and cell death detected with propodium iodide staining. Exposure to $Mg^{2+}$-free artificial cerebrospinal fluid can induce interictal-like epileptiform activity in rat hippocampal slices. While antagonists of mGluR5 (MPEP, 50 μM) significantly inhibited the frequency of the 0 $Mg^{2+}$-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 U73122 (10 μM) inhibited the frequency of the interictal-like epileptiform activity. Not only 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 also both ryanodine receptor antagonist dantrolene (30 μM) and IP3 receptor

antagonist 2-APB (30 μM) significantly inhibited the frequency of the epileptiform activity. Protein kinase C inhibitor GF109203X (1 μM) and chelerythrine (10 μM) significantly increased 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) did not affect the epileptiform activity. The mGluR5 antagonist MPEP significantly decreased the neuronal cell death. All these results suggest that group I glutamate metabotropic receptor 5 may affect the low $Mg^{2+}$-induced interictal-like epileptiform activity in rat hippocampal slices through phospholipase C, releasing $Ca^{2+}$ from IP3 and ryanodine-sensitive intracellular stores, activation of PKC and TRPC channels, which may be involved in neuronal cell death.

**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:** $Ca^{2+}$, Group 1 metabotropic glutamate receptor, Interictal epileptiform activity, Neuronal cell death, Phospholipase C, Rat hippocampal slice, TRPC channel

## P21-03-15

### TRPC1/4 heteromeric channel's current characteristic is unaffected by mutations in TRPC1 residues lining the pore region

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**Purpose:** TRPC channels consist of 7 subtypes, and it is known that TRPC1 and TRPC4 are able to form a heterotetrameric channel. The heteromeric TRPC1/4 channel has a different I-V curve profile compared to the homomeric TRPC4 channel. Unlike the double rectifying shape of the homomeric channel, the heteromeric channel is outward rectifying with a current smaller in size. The pore region of TRPC1 shares a conserved sequence with TRPC4, and we selected residues that vary between the two (S600, H603, V642 and H646) as candidates for crucial residues affecting the shape of the I-V curve.
**Methods:** Site-directed mutagenesis was used to generate TRPC1 mutant with each residue changed to the one corresponding to TRPC4 sequence. Along with the single mutants, TRPC1 chimeras with the pore region substituted to that of TRPC4 were generated using Gibson Assembly. These mutants were expressed in HEK293 cells with wild type TRPC4 to create a heterotetrameric channel, and the currents were measured using whole cell patch clamp.
**Results:** The results show that the mutant TRPC1 expressing cells still showed wild type TRPC1/4 heteromeric currents, and chimeric mutants were recessive in phenotype.
**Conclusions:** Changing the candidate residues into TRPC4 did not change the characteristics of TRPC1 in a heterotetramer, and further analysis using concatemeric channels to control for expression and stoichiometry will aid in the understanding of the characteristics of a heteromeric TRPC1/4 channel.

**Keywords:** TRPC4, TRPC1, Heterotetramer

## P21-03-16

### Characteristic analysis of mutation in TRPC4 residue

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**Purpose:** With such recent findings of the structure of TRPC4, we hypothesize that some insights into the architecture of the selectivity filter and lower gate could be observed; and we can propose that mutations within this pore region may possibly lead to findings of a critical region.
**Methods:** Four residues of TRPC4 were selected and mutated into TRPC1 by site-directed mutagenesis, and whole-cell patch clamp was conducted to verify that the pore residues of TRPC4 were successfully mutated into TRPC1 by testing the sensitivity to the channel activator, englerin A.
**Results:** When single mutants were tested, a homomeric current of TRPC4 was observed. However, when all four mutants were expressed, the construct produced an IV curve that resembles that of a heteromer, and a punctate distribution at the plasma membrane was also observed as well. It may hint that these four residues may potentially play a role in producing an IV curve of a heteromer.
**Conclusions:** These four residues may potentially play a role in producing an IV curve of a heteromer.

**Keywords:** Electrophysiology, TRPC4, TRPC1, Ion channels, TRPC, Cryo-EM

## P21-03-17

### S2-S3 WW site mediates direct calcium binding and gating of TRPC4 channel

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**Purpose:** Transient receptor potential canonical (TRPC) channels are non-selective calcium-permeable cation channels. Based on previous structural studies, we previously demonstrated that direct calcium binding at S2-S3 linker modifies gating of TRPC4 channel. However, it is not understood how the calcium binding at S2-S3 linker is physically transmitted to the pore region: gating of channel. In this study, we suggest that two continuous tryptophan residues (WW site) located in the S2-S3 linker could be an essential component for intracellular calcium sensing and gating of TRPC4 channel.
**Methods:** We made single mutants in which Try433, Try434 is changed to Ala, Phe, Arg, or Glu, and a WW/AA double mutant from mouse TRPC4β. Wild type and mutants TRPC4 channels were expressed in HEK293 cells for florescence imaging and whole-cell current recording. In electrophysiological experiments, channels were stimulated by (-)-Englerin-A, GTPγS, human Gαi2(Q205L), or by carbachol under the condition where the channels were co-expressed with human muscarinic receptor type 3.
**Results:** Cells expressed with wild type TRPC4 channel showed whole-cell current increase by all activators and showed characteristic double-rectifying current-voltage relationship. All TRPC4 mutants showed whole-cell current responses by (-)-Englerin-A, but among them, W433F, W433E, W434A, W434R, W434E, WW/AA mutants showed decreased whole-cell current responses than the wild type. When stimulated by GTPγS, Gαi2(Q205L), or carbachol, cells expressed with W433F, W434A, W434F, W434R, W434E, WW/AA mutants didn't showed whole-cell current responses. Significantly decreased, but still distinguishable whole-cell current responses were observed in cells expressed with W434F mutant. However, when cells were expressed with W433A, W433R, W433E mutants, they showed increased whole-cell current responses by three activators: GTPγS, Gαi2(Q205L), and carbachol. When intracellular calcium concentration was strictly fixed to near zero value, wild type TRPC4 channels didn't show any whole-cell current responses by Gαi2(Q205L). However, when stimulated by (-)-Englerin-A, whole-cell current responses were observed. Lastly, through florescence imaging, we observed that wild type and mutant TRPC4 channels were all normally expressed and located on the plasma membrane of mammalian cells in a puncta-like pattern.
**Conclusions:** The WW site is considered as an intermediate component that modifies gating of TRPC4 channel after detecting calcium ions. Furthermore, based on present electrophysiological data, we suggest a model in which Try433 and Try434 regulate the force transmission from S2-S3 linker to S4-S5 linker through a π-π interaction. In addition, we found that (-)-Englerin-A may open TRPC4 channel regardless of intracellular calcium concentration.

**Keywords:** TRP channel, Intracellular calcium binding, Channel gating

## P21-03-18

### Non-selective cation currents mediated by Cx43 hemichannel-P2X4 receptor signaling pathway in rat atrial myocytes under shear stress

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**Purpose:** Atrial myocytes are exposed to high shear stress under hemodynamic disturbances associated with arrhythmias. Shear stress triggers spontaneous action potential that is sensitive to gap junction inhibitor or P2X purinergic receptor (P2XR) antagonists. To know if they are activated and contribute to membrane conductance we investigated cellular mechanisms for shear stress-triggered immediate cation entry at resting potentials and possible roles of gap junction channels and P2XR in rat atrial myocytes.
**Methods:** Whole-cell patch clamp and dye flux assay in combination with pharmacological and genetic interventions were used.
**Results:** In the symmetrical Cs+-rich solutions, brief shear exposure triggered inward current (IS,Cs) at -70 mV that was dependent on shear strength and largely enhanced by zero external $Ca^{2+}$. The IS,Cs was eliminated by inhibitions of connexin 43 (Cx43) hemichannel function (50 μM carbenoxolone, La3+ and anti-Cx43 antibodies) or its conditional knockout, but was not affected by pannexin (Px) suppression (probenecid, 10 μM carbenoxolone). Gap junction function was evaluated by the efflux of calcein-red/orange dye through the cell membrane. Shear stress induced significant efflux of the dye, of which rate was accelerated by zero external $Ca^{2+}$ but not altered by Px interventions. The shear-induced dye efflux was suppressed by Cx43 hemichannel inhibition using Gap 19, or negligible in Cx43 conditional KO mouse atrial cells. IS,Cs was eliminated by ATP metabolizing apyrase or P2 receptor antagonism (suramin plus 5-BDBD). A half of the IS,Cs was removed by suppression of P2X4 receptor (P2X4R) (PSB-12054, 5-BDBD, iso-PPADS or anti-P2X4R antibodies). Immunocytochemistry revealed that Cx43 are localized at the cell ends and lateral sites with curvature as a punctate form and that P2X4R are evenly distributed at the cell periphery with negligible colocalization with Cx43.
**Conclusions:** Our data suggest that shear stress triggers Cx43 hemichannels to further gate P2 receptors via ATP, resulting in nonselective cation influx at resting potential in atrial myocytes, and that P2X4R may significantly (about 50%) contributes to the cation influx.

**Keywords:** Cx43, Atrial myocytes, P2X receptor, Shear stress

## P21-04-01

### The vasorelaxant effect of alogliptin, a member of the DPP-4 inhibitor class of anti-diabetic drugs, in rabbit aortic smooth muscle

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**Purpose:** We investigated the vasorelaxant effects of alogliptin, an oral antidiabetic drug in the dipeptidyl peptidase-4 (DPP-4) inhibitor class, using phenylephrine (Phe)-induced pre-contracted aortic rings.
**Methods:** We used rabbit thoracic aortic rings and its arterial tone was tested by using myograghy system.
**Results:** Alogliptin induced vasorelaxation in a dose-dependent manner. Pre-treatment with the voltage-dependent $K^+$ (Kv) channel inhibitor 4-aminopyridine significantly decreased the vasorelaxant effect of alogliptin, whereas pre-treatment with the inwardly rectifying $K^+$ (Kir) channel inhibitor, ATP-sensitive $K^+$ (KATP) channel inhibitor, and large-conductance $Ca^{2+}$-activated $K^+$ (BKCa) channel inhibitor did not alter the effects of alogliptin. Although pre-treatment with the $Ca^{2+}$ channel inhibitor nifedipine did not affect the vasorelaxant effect of alogliptin, pre-treatment with the SERCA pump inhibitors effectively attenuated the vasorelaxant response of alogliptin. Neither cGMP/PKG-related signaling pathway inhibitors nor cAMP/PKA-related signaling pathway inhibitors reduced the vasorelaxant effect of alogliptin. Similarly, the vasorelaxant effect of alogliptin was not changed by endothelium removal or pre-treatment with the NO synthase inhibitor or SKCa and IKCa channel inhibitors.
**Conclusions:** Based on these results, we suggest that alogliptin induced vasorelaxation in rabbit aortic smooth muscle by activating Kv channels and the SERCA pump.

**Keywords:** Alogliptin, Voltage-dependent $K^+$ channel, SERCA pump, Aorta, Vasorelaxation

## P21-04-02

### The inhibitory effect of darifenacin, an anticholinergic agent, on voltage-dependent $K^+$ channels in rabbit coronary arterial smooth muscle cells

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**Purpose:** Darifenacin, an anticholinergic agent, has been used to treat overactive bladder syndrome. This study aimed to investigate the effect of the anti-muscarinic drug darifenacin on voltage-dependent $K^+$ (Kv) channels, vascular contractility, and coronary blood flow in rabbit coronary arteries.
**Methods:** We used the whole-cell patch-clamp technique to evaluate the effect of darifenacin on Kv channels.
**Results:** Darifenacin inhibited the Kv current in a concentration-dependent manner. Applying darifenacin shifted the activation and inactivation curves toward a more positive and negative potential, respectively. Darifenacin slowed the time constants of recovery from inactivation. Furthermore, blockade of the Kv current with darifenacin was increased gradually by applying a train of pulses, indicating that darifenacin inhibited Kv currents in a use-dependent manner. The darifenacin-mediated inhibition of Kv currents was associated with the Kv1.5 subtype, not the Kv2.1 or Kv7 subtype. Applying another anti-muscarinic drug atropine or ipratropium did not affect the Kv current or change the inhibitory effect of darifenacin. Furthermore, darifenacin caused membrane depolarization and decreased coronary blood flow.
**Conclusions:** From these results, we concluded that darifenacin inhibits the Kv currents in concentration- and use-dependent manners. Inhibition of the Kv current with darifenacin occurred by shifting the steady-state activation and inactivation curves regardless of its anti-muscarinic effect.

**Keywords:** Darifenacin, Voltage-dependent $K^+$ channel, Coronary arterial smooth muscle cell, Patch-clamp

## P21-04-03

### Inhibition of voltage-dependent $K^+$ channels by atypical antipsychotic olanzapine in coronary arterial smooth muscle cells

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**Purpose:** Olanzapine, an FDA-approved atypical antipsychotic, is widely used to treat schizophrenia and bipolar disorder. In this study, the inhibitory effect of olanzapine on voltage-dependent $K^+$ (Kv) channels in rabbit coronary arterial smooth muscle cells was investigated.
**Methods:** We used the whole-cell patch-clamp technique to evaluate the effect of olanzapine on Kv channels.
**Results:** Olanzapine inhibited the Kv channels in a concentration-dependent manner with an IC50 value of 7.76 ± 1.80 μM and a Hill coefficient of 0.82 ± 0.09. Although olanzapine did not change the steady-state activation curve, it shifted the inactivation curve to a more negative potential, sug-

gesting that it inhibited Kv currents by affecting the voltage sensor of the Kv channel. Application of 1 or 2 Hz train pulses did not affect the olanzapine-induced inhibition of Kv channels, suggesting that its effect on Kv channels occurs in a use (state)-independent manner. Pretreatment with DPO-1 (Kv1.5 subtype inhibitor) reduced the olanzapine-induced inhibition of Kv currents. In addition, pretreatment with guangxitoxin (Kv2.1 subtype inhibitor) and linopiridine (Kv7 subtype inhibitor) partially decreased the degree of Kv current inhibition. Olanzapine induced membrane depolarization.
**Conclusions:** From these results, we suggest that olanzapine inhibits the Kv channels in a concentration-dependent, but state-independent, manner by affecting the gating properties of Kv channels. The primary Kv channel target of olanzapine is the Kv1.5 subtype.

**Keywords:** Atypical antipsychotic, Olanzapine, Vascular smooth muscle cell, Voltage-dependent $K^+$ channels

## P21-04-04

### The suppression of voltage-dependent $K^+$ channels by an antipsychotic drug pimozide in rabbit coronary arterial smooth muscle cells

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**Purpose:** We investigated the effects of pimozide on voltage-dependent $K^+$ (Kv) channels in rabbit coronary arterial smooth muscle cells.
**Methods:** We used the whole-cell patch-clamp technique to evaluate the effect of pimozide on Kv channels.
**Results:** Pimozide concentration-dependently inhibited the Kv currents with an apparent Kd value of 1.78 ± 0.18 μM and a Hill coefficient of 0.90 ± 0.05. The inhibitory effect on the Kv current by pimozide was highly voltage-dependent in the voltage range of Kv channel activation, and additive inhibition of the Kv current by pimozide was observed in the full activation voltage range. The decay rate of Kv current inactivation was significantly accelerated by pimozide. The pimozide rate constants of association and dissociation were 1.80 ± 0.05 μM-1s-1 and 3.22 ± 0.22 s-1, respectively. Pimozide shifted the steady-state inactivation curve to a more negative potential. The recovery time constant from inactivation increased in the presence of pimozide. Furthermore, pimozide-induced inhibition of the Kv current was augmented by applying train pulses (1 or 2 Hz), suggesting that pimozide inhibited Kv current in a use-dependent manner. Pretreatment with the Kv1.5 channel inhibitor DPO-1 reduced the inhibitory effects of pimozide on Kv currents.
**Conclusions:** We conclude that pimozide inhibits Kv currents in concentration-, voltage-, time-, and use-dependent manners.

**Keywords:** Pimozide, Voltage-dependent $K^+$ channels, Use-dependent, Time-dependent, Voltage-dependent

## P21-04-05

### Vasorelaxation of aortic smooth muscle by sitagliptin via the activation of PKA and voltage-gated $K^+$ channels

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**Purpose:** 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).
**Methods:** We used rabbit thoracic aortic rings and its arterial tone was tested by using myography system.
**Results:** Sitagliptin induced vasorelaxation in a dose-dependent manner but the inhibition of voltage-gated $K^+$ (Kv) channels by pretreatment with 4-aminopyridine (4-AP) effectively reduced the vasorelaxant effect of sitagliptin. Although the application of SQ 22536, which is an adenylyl cyclase inhibitor, also did not change this effect, treatment with KT 5720, a PKA inhibitor, effectively reduced the vasorelaxant effects of sitagliptin. ODQ, which is a guanylyl cyclase inhibitor, and KT 5823, a 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). Furthermore, neither the inhibition of $Ca^{2+}$ channels by pretreatment with nifedipine nor the inhibition of SERCA pumps by pretreatment with thapsigargin changed the effect.
**Conclusions:** Taken together, these results suggest that sitagliptin induces vasorelaxation by activating PKA and Kv channels independent of PKG signaling pathways, other $K^+$ channels, $Ca^{2+}$ channels, SERCA pumps, and the endothelium.

**Keywords:** Sitagliptin, Voltage-gated $K^+$ channels, Protein kinase A, Aorta

## P21-04-06

### Tegaserod, a gastrokinetic agent, inhibits voltage-dependent $K^+$ channels in coronary arterial smooth muscle cells from rabbits

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**Purpose:** We examined the effects of tegaserod on voltage-dependent $K^+$ (Kv) channels in rabbit coronary arterial smooth muscle cells.
**Methods:** We used the whole-cell patch-clamp technique to evaluate the effect of tegaserod on Kv channels.
**Results:** Tegaserod inhibited Kv channels in a concentration-dependent manner with an IC50 value of 1.26 ± 0.31 μM and Hill coefficient of 0.81 ± 0.10. Although tegaserod had no effect on the steady-state activation curves of the Kv channels, the steady-state inactivation curve was shifted toward a more negative potential. These results suggest that tegaserod inhibits Kv channels by influencing their voltage sensors. The recovery time constant of channel inactivation was extended in the presence of tegaserod. Furthermore, application of train steps (1 and 2 Hz) in the presence of tegaserod progressively increased the inhibition of Kv currents suggesting that tegaserod-induced Kv channel inhibition is use (state)-dependent. Pretreatment with a Kv1.5 subtype inhibitor suppressed the Kv current. However, additional application of tegaserod did not induce further inhibition. Pretreatment with a Kv2.1 or Kv7 inhibitor did not affect the inhibitory effect of tegaserod on Kv channels.
**Conclusions:** Based on these results, we conclude that tegaserod inhibits vascular Kv channels in a concentration- and use-dependent manner independent of its own functions.

**Keywords:** Tegaserod, Voltage-dependent $K^+$ channel, Use-dependent, Kv1.5

## P21-04-07

### The vasodilatory effect of trelagliptin via activation of Kv channels and SERCA pumps in aortic smooth muscle

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**Purpose:** We investigated the vasodilatory effects of trelagliptin and its related mechanisms using rabbit aortic rings.
**Methods:** We used rabbit thoracic aortic rings and its arterial tone was tested by using myography system.
**Results:** Trelagliptin induced vasodilation in a dose-dependent manner. Pretreatment with the ATP-sensitive $K^+$ channel inhibitor, large-conduc-

tance $Ca^{2+}$-activated $K^+$ channel inhibitor, and inwardly rectifying $K^+$ channel inhibitor did not affect the vasodilatory effect of trelagliptin. However, pretreatment with the voltage-dependent $K^+$ (Kv) channel inhibitors significantly attenuated the vasodilatory effect of trelagliptin, suggesting that the vasodilatory effect of trelagliptin is associated with Kv channel activation. Although pretreatment with Kv1.5 and Kv2.1 subtype inhibitors did not affect the response to trelagliptin, pretreatment with a Kv7.X subtype inhibitor effectively reduced the vasodilatory effect of trelagliptin. Furthermore, SERCA pump inhibitors also significantly attenuated the vasodilatory effect of trelagliptin. These effects, however, were not affected by pretreatment with $Ca^{2+}$ channel inhibitors, adenylyl cyclase/PKA inhibitors, guanylyl cyclase/PKG inhibitors, or removal of the endothelium.
**Conclusions:** From these results, we concluded that the vasodilatory effect of trelagliptin was associated with the activation of Kv channels (primarily the Kv7.X subtype) and SERCA pump.

**Keywords:** Trelagliptin, Voltage-dependent $K^+$ channel, SERCA pump, Aorta

## P21-04-08

### The state-dependent inhibition of voltage-dependent $K^+$ channels by ziprasidone in coronary arterial smooth muscle cells

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**Purpose:** We investigated the effect of ziprasidone, a widely used treatment for schizophrenia, on voltage-dependent $K^+$ (Kv) channels of coronary arterial smooth muscle cells.
**Methods:** We used the whole-cell patch-clamp technique to evaluate the effect of olanzapine on Kv channels.
**Results:** Ziprasidone dose-dependently inhibited Kv channels with an IC50 value of 0.39 ± 0.06μM and a Hill coefficient of 0.62 ± 0.03. Although ziprasidone had no effect on the steady-state inactivation kinetics of the Kv channels, the steady-state activation curve shifted towards a more positive potential. These results suggest that ziprasidone inhibits Kv channels by targeting their voltage sensors. The recovery time constant of Kv channel inactivation was increased in the presence of ziprasidone. Furthermore, application of train steps (of 1 and 2 Hz) in the presence of ziprasidone led to a progressive increase in the blockade of Kv currents, suggesting that ziprasidone-induced inhibition of Kv channels is use (state)-dependent. Pretreatment with Kv1.5, Kv2.1, and Kv7 subtype inhibitors partially suppressed the ziprasidone-induced inhibition of Kv currents.
**Conclusions:** These results suggest that ziprasidone inhibits vascular Kv channels through its effect on gating properties. The Kv channel-inhibiting action of ziprasidone is concentration- and use (state)-dependent.

**Keywords:** Atypical antipsychotics, Ziprasione, Voltage-dependent $K^+$ channel, Smooth muscle cell

## P21-04-09

### Pathological mechanism of a constitutively active form of stromal interaction molecule 1 in skeletal muscle

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**Purpose:** Stromal interaction molecule 1 (STIM1) is a main protein that, along with Orai1, mediates store-operated $Ca^{2+}$ entry (SOCE) in skeletal muscle. Abnormal SOCE due to mutations in STIM1 is one of the causes of human skeletal muscle diseases. STIM1-R304Q (a constitutively active form of STIM1) has been found in human patients with skeletal muscle phenotypes such as muscle weakness, myalgia, muscle stiffness, and contracture. However, the pathological mechanism(s) of STIM1-R304Q in skeletal muscle have not been well studied.
**Methods:** To examine the pathological mechanism(s) of STIM1-R304Q in skeletal muscle, STIM1-R304Q was expressed in mouse primary skeletal myotubes, and the properties of the skeletal myotubes were examined using single-myotube $Ca^{2+}$ imaging, transmission electron microscopy (TEM), and biochemical approaches.
**Results:** STIM1-R304Q did not interfere with the terminal differentiation of skeletal myoblasts to myotubes and retained the ability of STIM1 to attenuate dihydropyridine receptor (DHPR) activity. STIM1-R304Q induced hyper-SOCE (that exceeded the SOCE by wild-type STIM1) by affecting both the amplitude and the onset rate of SOCE. Unlike that by wild-type STIM1, hyper-SOCE by STIM1-R304Q contributed to a disturbance in $Ca^{2+}$ distribution between the cytosol and the sarcoplasmic reticulum (SR) (high $Ca^{2+}$ in the cytosol and low $Ca^{2+}$ in the SR). Moreover, the hyper-SOCE and the high cytosolic $Ca^{2+}$ level induced by STIM1-R304Q involve changes in mitochondrial shape.
**Conclusions:** Therefore, a series of these cellular defects induced by STIM1-R304Q could induce deleterious skeletal muscle phenotypes in human patients carrying STIM1-R304Q.

**Keywords:** Skeletal muscle, STIM1, Hyper-SOCE, Cytosolic $Ca^{2+}$

## P21-04-10

### Roles of calsequestrin 1 in skeletal muscle

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**Purpose:** Calsequestrin 1 (CASQ1) in skeletal muscle regulates store-operated $Ca^{2+}$ entry (SOCE) by binding to stromal interaction molecule 1 (STIM1). Abnormal SOCE and/or abnormal expression or mutations in STIMs are associated with human skeletal, cardiac, or smooth muscle diseases. However, the functional role of CASQ1 along with SOCE has not been studied well.
**Methods:** To examine the functional relevance of the CASQ1 in the SOCE of skeletal muscle, CASQ1 was expressed in mouse primary skeletal myotubes, and the myotubes were examined using single-myotube $Ca^{2+}$ imaging experiments.
**Results:** The CASQ1 decreased SOCE, increased intracellular $Ca^{2+}$ release for skeletal muscle contraction, and changed intracellular $Ca^{2+}$ distributions.
**Conclusions:** Therefore, in skeletal muscle, CASQ1 plays active roles in $Ca^{2+}$ movement and distribution as well as $Ca^{2+}$ sensing and buffering.

**Keywords:** CASQ1, SOCE, Skeletal muscle

## P21-04-11

### Mechanism of vasomotion in human left gastroepiploic artery and human uterine artery

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**Purpose:** Vasomotion is the oscillatory rhythmic contraction in tone of blood vessel. It gives rise to flow motion of blood which is an oscillation of blood flow into an each organ. It was described in over 100 years ago in vet.

However, neither physiological and pathophysiological implications nor exact mechanism are well understood even in human. Our study was focused to elucidate mechanism of vasomotion and its regulatory factors in human stomach and uterus.
**Methods:** Conventional contractile measuring system, immunoblot, and molecular study were used.
**Results:** Circular muscle of human gastric artery produced sustained tonic contraction by high $K^+$(50 mM). It was blocked by application of nifedipine(2 μM), blocker of L-type $Ca^{2+}$ channel(VDCCL). Stepwise stretch and high K produced nerve-independent spontaneous contraction(vasomotion) of artery. Vasomotion was inhibited by nifedipine(2 μM) and facilitated by Bayk 8644, activator of VDCCL. Blocking of intracellular $Ca^{2+}$ from SR(sarcoplasmic reticulum) also inhibited vasomotion reversibly. Inhibitors of $Ca^{2+}$-activated Cl- channels such as DIDS and/or niflumic acid inhibited human gastric vasomotion. Activation of ATP-sensitive $K^+$ (KATP) channels and application of neuropeptides inhibited vasomotion. In human uterine artery, high $K^+$, oxytocin(OXT) and prostaglandin F2a showed produced nifedipine- and Bayk 8644-sensitive vasomotion in too. Vasomotion and OXT-induced vasomotion were blocked by DIDS and cromakalim. Finally, we identified $Ca^{2+}$-activated Cl- channels, subunits of ATP-sensitive $K^+$ (KATP) channels, and c-Kit positive band in Western blot. Especialy, KATP channels in human left gastroepiploic artery was composed of Kir 6.2 and sulfonylurea receptor 2B (SUR2B).
**Conclusions:** From these results, we found vasomotion sensitive to $Ca^{2+}$-activated Cl- channels in human stomach and uterus. Vasomotion must be important for the regulation of human peripheral and microcirculation even in pacemaker-related autonomic contractile organs.

**Keywords:** Human gastroepiploic artery, Human uterine artery, Vasomotion, $Ca^{2+}$, $Ca^{2+}$-activated Cl- channels, ATP-sensitive $K^+$ (KATP) channel

## P21-04-12

### Activation of cardiac connexin 43 hemichannels by shear stress and subsequent contribution of pannexins in left-side cardiac muscle cells

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**Purpose:** Cardiac myocytes are exposed to shear stress under physiological conditions and hemodynamic disturbances. Shear stress has been thought to trigger global $Ca^{2+}$ waves in atrial myocytes through autocrine activation of P2 receptors by connexin43 (Cx43)-mediated ATP release. We examined whether shear stress activates Cx43 hemichannels and pannexins in atrial and ventricular myocytes from right and left side of heart chambers.
**Methods:** The activities of these hemichannels were measured as an efflux of large fluorescence dye (calcein-red/orange) to permeate these channels using two-dimensional confocal imaging method in single isolated myocytes of murine hearts.
**Results:** Shear stress induced significant dye efflux in atrial and ventricular myocytes with a larger flux in atrial cells than ventricle cells. Atrial shear-induced dye efflux was enhanced by removal of external $Ca^{2+}$ and suppressed by gap 19, 50 μM carbenoxolone or 2 mM La3+, but it was negligible in atrial cells of Cx43 conditional knock-out mice, suggesting a key role of Cx43 hemichannels in shear-induced dye efflux. Shear-induced dye flux was slightly higher in right atrial (RA) cells compared with left atrial (LA) cells, which was consistently observed in ventricles. Pannexin inhibition using probenecid (800 μM) reduced (by ~25%) delayed dye efflux (>1 min) in LA cells only. In contrast, ventricular dye efflux under shear stress was retarded significantly by probenecid with more prominent decrease in its magnitude (by ~25%) in left ventricle, but it was not removed by probenecid.
**Conclusions:** Our data demonstrate functional evidence for activation of Cx43 hemichannels in atrial and ventricular myocytes under shear stress, and distinct contribution of pannexins in the LA and ventricular myocytes under this mechanical stimulus. Functional implication and mechanism for higher Cx43 hemichannel activity in the right-side heart under shear stress as well as more pannexin contribution to the shear response in the left-side heart remain to be understood.

**Keywords:** Cardiac myocytes, Shear stress, Cx43 hemichannels, Pannexin, Left-side heart

## P21-04-13

### Interventricular differences explained by the lower troponin expression in the right ventricle of rats

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**Purpose:** Despite distinctive functional and anatomical difference, a precise understanding of the cardiac interventricular difference in excitation-contraction (E-C) coupling mechanisms is still lacking. Here, we compared the results from the right and left cardiomyocytes (RVCM and LVCM) of rats.
**Methods:** Whole-cell patch clamp technique, IonOptix system and fura-2 fluorimetry were used to measure electrical properties (action potential and ionic currents), single cell contractility and cytosolic $Ca^{2+}$ ($[Ca^{2+}]_i$), respectively. Myofilament proteins were analyzed by Immunoblotting.
**Results:** RVCMs showed significantly shorter action potential duration (APD) and higher density of transient outward $K^+$ current (Ito). However, the triggered $[Ca^{2+}]_i$ change ($Ca^{2+}$ transient) was not different, while the decay rate of the $Ca^{2+}$ transient was slower in RVCM. Although the relaxation speed was also slower, the sarcomere shortening amplitude (ΔSL) was smaller in RVCM. The SERCA activity was approximately 60% lower in RVCM, partly responsible for the slower decay of the $Ca^{2+}$ transient. Immunoblot analysis revealed lower expression of the cardiac troponin complex (cTn) in RVCM, implying a smaller $Ca^{2+}$ buffering capacity (κS), which was proved by in situ analysis. The introduction of the newly found 0.65-fold cTn along with the 1.31-fold Ito and 0.40-fold SERCA into a mathematical model of rat LVCM reproduced the similar $Ca^{2+}$ transient, slower $Ca^{2+}$ decay, shorter APD and smaller ΔSL of RVCM.
**Conclusions:** Taken together, we firstly show the lower expression of cTn proteins in the RVCMs, which gives a clue to explain the inter-ventricular difference in the E-C coupling kinetics.

**Keywords:** Right ventricle, Excitation-contraction coupling, Action potential, $Ca^{2+}$ buffering, Troponin

## P21-05-01

### MLCP downregulation in the monocrotaline-induced pulmonary hypertensive rats impaired the relaxation of pulmonary arteries via T18/S19 diphosphorylation of myosin regulatory light chain (MLC2)

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**Purpose:** The phosphorylation at threonine 18 (T18), serine 19 (S19) or both (T18/S19 diphosphorylation) of myosin regulatory light chain (MLC2) is critical for the contraction of arteries. Other than S19 phosphorylation, T18 phosphorylation requires specific condition such as elevated rho A-dependent kinase (ROCK) or decreased myosin light chain phosphatase (MLCP) activity. The MLCP activity is increased by cGMP-dependent PKG signaling and inhibited by ROCK. While S19 phosphorylation is easily reversible by MLCP, T18 phosphorylation or T18/S19 diphosphorylation is relatively slowly dephosphorylated.
**Methods:** In this study, we investigated the speed of relaxation in rat pulmonary arteries (PAs), which showed stark delay of relaxation (half relaxation time; 19±2.9s vs. 335±59.5s) after a high $K^+$-induced contraction

(80K-contraction) in the monocrotalin-induced pulmonary arterial hypertension (PAH-MCT) model.
**Results:** Interestingly, the diphosphorylation became significant in the PAs from PAH-MCT from the 7th day of monocrotalin injection. Consistently, MLCP (MYPT1) expression was markedly decreased along with the partial increase of ROCK1 and 2. The delayed relaxation was almost completely reversed by ROCK inhibitor (Y27632) whereas not significantly affected by membrane permeable 8-Br-cGMP. Different from the contractile response, recovery of increased $[Ca^{2+}]_i$ in PA smooth muscle cell was not different between control and PAH-MCT. Also, the expressions of $Na^+/Ca^{2+}$ exchanger (NCX1) and SERCA were not changed in PAH-MCT. Furthermore, the delayed relaxation was still observed with L-type $Ca^{2+}$ channel blocker or even with $Ca^{2+}$-free bath solution. Finally, in the control PAs, the pharmacological inhibition of cGMP production by ODQ induced prominent delay of relaxation and MLC2 diphosphorylation as like PAH-MCT. In the presence of ODQ, the application of 8-Br-cGMP largely reversed the delayed relaxation as well as Y27632 application.
**Conclusions:** Taken together, the diphosphorylation of MLC2 accounts for the impaired relaxation of PA in PAH animal via loss of MLCP and elevated ROCK expression.

**Keywords:** Monocrotaline, MLC2 phosphorylation, Pulmonary arteries, PAH

## P21-05-02

### APE1/Ref-1 Inhibits Phosphate-Induced Loss of Vascular Smooth Muscle Cells Phenotype and vascular calcification

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**Purpose:** Vascular calcification described abnormal calcium deposition in vessel walls and is a characteristic feature of atherosclerosis, diabetes mellitus, and end-stage renal disease. Vascular calcification is linked to plaque instability and contributes to increased cardiovascular mortality and poor cardiovascular outcomes for patients.; Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is a multifunctional protein involved in base-excision DNA repair and transcriptional regulation of gene expression, as well as playing a pleiotropic role in controlling cellular responses to oxidative stress.
**Methods:** VSMC cell culture and Induction of calcification in vitro: VSMCs were obtained from thoracic aortas of Sprague–Dawley rats using a tissue explant and enzymatic digestion method. VSMCs were incubated in a calcification medium consisting of DMEM supplemented with 10% FBS, 5 mM Pi (a mixture of NaH2PO4 and Na2HPO4, pH 7.4), and 50 μg/mL ascorbic acid. The medium was replaced with a fresh medium every 2–3 days for 6 days.
Adenoviral transfections: Adenoviruses encoding full-length APE1/Ref-1 (AdAPE1/Ref-1) and a double redox point mutant (C65A/C93A) of APE1/Ref-1 were used as described previously. Cells were infected at the indicated multiplicity of infection (MOI) for 24 h. The total adenoviral transfection was balanced with MOI of Adβgal as a control adenovirus.
Immunoblotting: The cell lysate was cleared by centrifugation at 12,000 ×g for 20 min, and the supernatant was used for immunoblotting. Proteins were resolved on SDS-PAGE and transferred onto a PVDF membrane.
Small interfering RNA for APE1/Ref-1: VSMCs were transfected with 20 nM chemically synthesized siRNA targeting rat APE1/Ref-1 and scrambled siRNA used as a control using Lipofectamine RNAiMAX following the manufacturer's instructions (Invitrogen, San Diego, CA, USA).
Evaluation of VSMC calcification: The calcium content in the supernatant was determined colorimetrically by the O-cresolphthalein method with a calcium assay kit (Biovision, Mountain View, CA, USA). Alizarin red S staining was used to assess the Ca deposition in VSMCs. Cells were stained with 2% alizarin red S and cells were destained with 10% (w/v) cetylpyridinium chloride in 10 mM sodium phosphate, pH 7.0. Von Kossa stain: Aortic sections were treated with a 3% silver nitrate solution, and stained aortas were photographed under light microscopy.
**Results:** We investigated the possible role of APE1/Ref-1 in Pi-induced VSMC calcification. 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. 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. APE1/Ref-1 inhibited Pi-induced osteoblastic differentiation associated with alkaline phosphatase activity and inhibited Pi-exposure-induced loss of the smooth muscle phenotype.
**Conclusions:** APE1/Ref-1 inhibits the phosphate-induced vascular smooth muscle cell and aortic calcification.
APE1/Ref-1 inhibits the phosphate-induced vascular smooth muscle cell phenotype changes.

**Keywords:** APE1/Ref-1, Inorganic phosphate, Vascular smooth muscle cells, Vascular calcification

## P21-05-03

### NOS and angiotensin II receptor subtype profiling in uterine and placental tissues in angiotensin II-induced novel preeclampsia rat model

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**Purpose:** Angiotensin II (Ang II) induced vasoconstriction has been shown to induce preeclampsia (PE) in rats. Here, we aimed to establish Ang II–induced PE rat model, and compare the protein and mRNA expressions of endothelial, neuronal and inducible NOS (eNOS, nNOS, iNOS) as well as angiotensin II type I receptor (AT1R) and type II receptor (AT2R) in uterine and placenta with and without Ang II infusion.
**Methods:** Ang II were infused to non-pregnant (8 weeks) and pregnant SD rats (8 weeks, GD-8) subcutaneously via osmotic minipump (1 μg/kg/min) and rats were sacrificed after 13 days (GD-21). Our results showed that the fetal weight, fetal crown-rump length and placenta weight were reduced significantly in Ang II pregnant rats compared to those in normal pregnant rats without Ang II infusion. Furthermore, immunohistochemistry with eNOS and nNOS results showed that the glomerulus volume was increased by ~30% in Ang II pregnant group, indicating that Ang II infusion in pregnant rat exhibit PE phenotype.
**Results:** Ang II infusion did not affect AT1R, AT2R, nNOS or iNOS protein or mRNA expressions in non-pregnant or pregnant rat uterine tissues. However, eNOS mRNA expression was reduced ($p<0.0001$) but eNOS protein was not affected by Ang II. In placenta, AT1R, AT2R and iNOS protein expressions were not affected by Ang II, but mRNA of AT2R was reduced ($p<0.0001$). Notably, eNOS protein expression was upregulated in Ang II pregnant rat placenta ($P=0.001$), but eNOS mRNA was reduced ($p = 0.0096$). In addition, both the mRNA and protein expressions of nNOS were reduced in placenta of Ang II pregnant rats ($p = 0.0287$ and $p<0.0001$, respectively).
**Conclusions:** These results demonstrate that we have recapitulated the PE model with Ang II infusion in rats. In placenta, the reduced expression of AT2R and nNOS may be the novel mechanism for impaired fetal development.

**Keywords:** Preeclampsia, Ang II,NOS,placenta

## P21-05-04

### Mitochondrial Phosphate Carrier Participates in Superoxide Generation and Vascular Calcification

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**Purpose:** Vascular calcification is a serious complication of hyperphosphatemia, leading to cardiovascular morbidity and mortality. Previous studies unveiled that plasmalemmal phosphate (Pi) transporters, such as PiT-1/2, mediated depolarization, $Ca^{2+}$ influx, oxidative stress and calcific changes in vascular smooth muscle cells (VSMCs). However, pathogenic roles of mitochondrial Pi uptake in calcification related to hyperphosphatemia have not been investigated yet.
**Methods:** Isolated rat aortic ring (ex vivo) or smooth muscle cells (in vitro) were used to identify the molecular mechanism of vascular calcification. Subtotal nephrectomized mice with a high Pi diet were used for in vivo calcification animal model experiments.
**Results:** We have identified that Pi carrier (PiC) is the dominant mitochondrial Pi transporter responsible for high Pi-induced superoxide generation, osteogenic gene upregulation and calcific changes in primary VSMCs isolated from rat aorta. Intriguingly, acute incubation with high Pi condition markedly upregulated PiC abundance via ERK1/2 and mTOR dependent translational activation. Genetic suppression of PiC prevented Pi-triggered ERK1/2 activation, superoxide production and osteogenic differentiation. Calcification of VSMCs in vitro and aortic rings ex vivo was inhibited by knockdown of PiC, but not significant by suppression of other mitochondrial Pi transporters. Pharmacologic blocking with buthylmalonate (BMA) or mersalyl abolished ERK1/2-mTOR activation, superoxide production, osteogenic differentiation and cell death by high Pi. BMA or mersalyl also effectively prevented osteogenic gene upregulation and calcification of aorta from 5/6 subtotal nephrectomized mice with a high Pi diet.
**Conclusions:** We suggest that mitochondrial Pi uptake via PiC is a critical molecular mechanism mediating mitochondrial superoxide generation and pathogenic calcific changes, which could be a potential therapeutic target for vascular calcification related to hyperphosphatemia.

**Keywords:** Hyperphosphatemia, Phosphate carrier, Mitochondrial oxidative stress, Vascular calcification

## P21-05-05

### The Effects of Capsanthin in a Mouse model of Nonalcoholic Fatty Liver Disease

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**Purpose:** We investigated in hepatoprotective function of capsanthin in a mouse model of nonalcoholic fatty liver disease.
**Methods:** Apolipoprotein-E knockout mice were bred with normal diet (ND), Western-type diet (WD), WD with capsanthin (0.5 mg/kg of body weight for everyday; CAP),WD with capsanthin-rich extract (25mg/kg of body weigh for everyday; CRE), or WD with red paprika powder (25mg/kg of body weight for everyday;RPP) for 12weeks. Paprika powder was obtained by freeze-drying of the raon red paprika from Araon Farm (Gyeongsangnam-do, Jinju, Korea). Then, we performed hexane extraction of paprika powder to obtain capsanthin-rich extract.
**Results:** The oral administration of CRE or CAP significantly decreased body weight and hepatic steatosis. In addition, CRE or CAP significantly inhibited cholesterol and low-density lipoprotein levels in mouse plasma. Also, CRE or CAP group mice were reduced blood alanine and aspartate aminotransferase (ALT and AST, respectively), showing a protective effect of CRE or CAP against liver damage. Furthermore, CAP regulated mRNA expression levels of peroxisome proliferator-activated receptor alpha (PPARα), carnitine palmitoyltransferase 1A (CPT1a), acyl-CoA oxidase 1 (ACOX1), and sterol regulatory element binding protein-1c (SREBP1), which are regulated with hepatic fatty acid metabolism.
**Conclusions:** Here, we investigated the hepatoprotective effect of capsanthin in ApoE KO mice induced NAFLD by feeding WD and found that the oral administration of CRE or CAP significantly decreased hepatic steatosis, hepatic injury, and dyslipidemia. As a result, the dietary of capsanthin-rich foods, such as red paprika, may help to the prevention of the hepatic steatosis or steatohepatitis.

**Keywords:** Non-alcoholic fatty liver disease, Capsanthin, Red paprika, Hepatic steatosis

## P21-06-01

### Cell-nonautonomous roles of the nuclear hormone receptor NHR-49 in the nervous system of Caenorhabditis elegans

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**Purpose:** The central nervous system plays a key role in regulating and coordinating whole-body metabolism. In C. elegans, the nuclear hormone receptor NHR-49, known as a functional homolog of mammalian PPARα, is ubiquitously expressed and serve as an important regulator of fat metabolism. In addition to altered lipid composition, nhr-49 mutants display a pleiotropy of defects, including shorter lifespan, impaired starvation response, and increased susceptibility to oxidative stress and pathogenic bacteria. Interestingly, NHR-49 expression in the neuron alone is sufficient to nearly restore lifespan. In light of recent findings of the cell-nonautonomous effects of neurons in cell stress and energy homeostasis in C. elegans, we wondered whether NHR-49 function in the neuron alone could also reverse other known nhr-49 mutant defects. For this study, we focused on the increased susceptibility of nhr-49 mutants to the pathogenic Pseudomonas aeruginosa PA14.
**Methods:** To measure C. elegans lifespan, total of about 100 age-synchronized worms per condition were monitored and counted every 2-3 days starting from adult day 1 until they die. Worms are treated with FudR for the duration of the assay to prevent eggs from hatching.
For survival assays on PA14, overnight culture of PA14 in King's B broth was seeded onto slow-killing plates (NGM with 0.35% peptone) and incubated at 37°C for 24hr, then at room temperature for 24hr. Synchronized worms were transferred to the PA14 plates at L4 stage and maintained at 25°C until they die. Live worms were counted at 6-12h intervals. Same plates were used for the lawn avoidance assays. Worms inside and outside the bacterial lawn were counted at indicated intervals.
**Results:** C. elegans has a two-part strategy to combat infection: innate immunity and behavioral avoidance. Interestingly, contrary to the generally held assumption that nhr-49 mutants are more vulnerable due to defective immunity, our results show that it is mostly due to behavioral defects – inability to avoid the pathogenic bacteria until too late. Restoring NHR-49 in the intestine or neurons each partially restored the avoidance behavior. We then limited NHR-49 expression to a few neuron types, and narrowed down the neurons responsible to cholinergic neurons.
**Conclusions:** We speculate that worms quickly learn to avoid the harmful bacteria through an internal signal alerting the nervous system, that becomes defective in nhr-49 mutants. We are currently testing this hypothesis and trying to identify the signaling mechanisms.

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

## P21-06-02

### Effect of heat stimulation on circulating irisin in humans

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**Purpose:** The aim of the present study is to evaluate whether heat stimulation-induced hyperthermia can increase circulating irisin levels after half-body immersion in hot water. High temperatures lead to oxidative stress and elicit whole-body responses, involving skeletal and cardiac muscle tissues. In addition to irisin, we also analyzed blood creatine kinase and lactate dehydrogenase levels as indicators of heat stimulation-induced oxidative damage.
**Methods:** Tests were performed in a climate chamber under specific control. The experiment was conducted between 2 and 5 p.m. to control for the influence of circadian rhythm on the body temperature. The subject sat in a chair in a relaxed posture for 60 min before the start of the main process. The heat load experiment was carried out by immersing half the body into a bath filled with hot water. Blood sampling was done before immersion and immediately after the experiment. Tympanic and local skin temperature measurements were conducted continuously at 10-s intervals.
**Results:** Levels of irisin, cortisol, creatine kinase, and lactate dehydrogenase were analyzed. Tympanic temperature, mean body temperature and serum irisin levels increased after hot water immersion. The blood levels of cortisol, creatine kinase, and lactate dehydrogenase were also elevated.
**Conclusions:** Heat stimulation might increase the levels of circulating irisin in humans in response to oxidative stress. The molecular mechanism of irisin up-regulation under heat stimulation, its antioxidative activity, quantification of therapeutic gain, and possible side effects need to be investigated before clinical application. However, as a simple indoor practice to alleviate various neuropsychiatric and general diseases, thermotherapy is worth to be investigated further.

**Keywords:** Irisin, Hyperthermia, Oxidative stress, Cortisol, Creatine kinase, Lactate dehydrogenase

## P21-06-03

### Carbon Monoxide Attenuates Monocrotaline-induced Right Ventricle Hypertrophy in Rats

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**Purpose:** Carbon monoxide (CO) which is one of the cytoprotective byproducts of heme oxygenase (HO) and shows pleietrepie bebeficial functions on various animal models has been regarded as a gaseous bioactive substance in numerous body systems. It has been indicated that CO treatment exerts anti-inflammatory, anti-apoptotic, anti-hypertensive, cellular proliferation programs and vasodilatory effects in many experimental models at a low concentration. The purpose of the present study is to explore the effect of CORMs on pulmonary hypertension.
**Methods:** Male rats weighing 180–200 g were given a single subcutaneous injection of 60 mg/kg monocrotaline (MCT) and the rats were treated with CORM-2 (3mg/kg/day) (MCT+CORM-2). The rats were euthanized after 2weeks by decapitation, and the blood, hearts and lung tissue were collected. Body weight and right ventricle, left ventricle plus septum were measured. Lung sections were prepared with HE staining. And right ventricles were prepared for western blot.
**Results:** The ratio of right ventricle/left ventricle plus septum was increased by MCT compared with sham group. However, MCT-induced right ventricle hypertrophy was attenuated by the pretreatment with CORM-2. MCT significantly decreased body weight, but there was no difference on body weight between MCT group and MCT+CORM-2 group. MCT increase right ventricle systolic pressure and pulmonary arterial pressure which were attenuated by administration of CORM-2. Increased Plasma ANP level in MCT group was markedly attenuated in the presence of COMR-2. The percentage of wall thickness of pulmonary arteries was greater in MCT rats than that of control rats. Pretreatment with CORM-2 attenuated wall thickening of the pulmonary arteries in MCT rats. In addition, MCT-induced high HO-1 protein expression was inhibited in MCT+CORM-2 group. More study are on-going to define the signaling pathway and relationship between cardiovascular diseases with HO-1/CO axis.
**Conclusions:** CORM-2 attenuates MCT-induced right Ventricle hypertrophy in rats

**Keywords:** CORM-2, ANP, Hypertrophy, Plasma ANP, HO-1

## P21-06-04

### Particulate matter exposure aggravates IL-17 inflammation in the eye and nose of OVA/Poly(I:C) mouse

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**Purpose:** Recently, social interest in particulate matter (PM) has been increased due to increased PM hazards, but there is not much data about the effects of direct exposure to PM on the nose and eyes.
In this study, IL-17/neutrophil dominant OVA/Poly(I:C) mouse model was used to evaluate the effect of two different size of Titanium dioxide (TiO2) on mucosa of the nose and eyes. In addition, we evaluated whether treatment of IL-17 neutralization antibody could reverse the effect of TiO2 on nose and eyes.
**Methods:** For 21 days, OVA and poly(I:C) were treated in the nasal cavity and conjunctival sac to induce inflammation of nose and eyes. Micro sized TiO2 was exposed using a floating device for 2 hours a day for 7 days during which OVA was challenged, and nano-sized TiO2 were treated with PBS in intranasal or conjunctival sac. After OVA challenge and TiO2 exposure, IL-17 neutralization antibody was injected intraperitoneally. Not only clinical parameters and but also inflammatory parameters were evaluated using qRT-PCR, IHC, ELISA, Sirius Red and immunohistochemistry.
**Results:** Micro- and Nano-TiO2 resulted in a significant decrease in tear break up time and increase in corneal damage. Airborne micro-TiO2 also increased the nasal rubbing and sneezing counts compared with those of the OVA/Poly(I:C) group. Micro-TiO2 exposure increased infiltration of neutrophils and IL-17A+ cells in the conjunctival tissue and the nasal mucosa. In addition, these increased symptoms and inflammation in the eye and nose by Micro-TiO2 exposure were inhibited by the IL-17 neutralizing antibody, suggesting the IL-17 dependency.
**Conclusions:** TiO2 increased IL-17-related inflammation in the eyes and nose of the OVA/Poly(I:C) mice and the IL-17-neutralizing antibody alleviated inflammation. The data might help to develop therapeutic modalities for PM exposure and provide evidence for PM-associated diseases.

**Keywords:** Particulate matter, Nose, Eyes, Titanium dioxide, Interleukin-17

## P21-06-05

### Skeletal muscle-specific FoxO1 deletion improves high-fat diet-induced insulin resistance and increased endurance exercise capacity via enhanced mitochondrial function in mice

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**Purpose:** Forkhead box protein O1 (FoxO1) is a transcription factor that regulates cellular metabolism in insulin-sensitive tissues such as the liver and adipose tissue. On the other hand, FoxO1 in skeletal muscle (SKM), another insulin-sensitive tissue, is well known to regulate muscle mass. However, the metabolic role of FoxO1 in SKM is unclear. In the present study, we investigated whether FoxO1 regulates the energy metabolism of SKM in a high-fat diet (HFD)-induced obesity.
**Methods:** To understand the metabolic role of FoxO1, we generated a muscle-specific inducible FoxO1 knockout (mFoxO1KO) mice using the FoxO1 floxed and the ACTA1-rtTA;tetO-Cre (SKM-specific Cre gene was activated by doxycycline) mice. FoxO1 floxed mice were used as the wild type (WT) to compare KO mice. Eight-week-old male WT and mFoxO1KO mice were fed HFD containing 0.625 mg/kg doxycycline for 16 weeks.
**Results:** We observed that body weight, SKM mass, and total fat mass did not differ between mFoxO1KO and WT in both control and HFD groups. mFoxO1KO improved HFD-induced insulin resistance through enhanced glucose uptake and glycogen synthesis rate in SKM. Microarray analysis revealed that peroxisome proliferator-activated receptor δ (PPARδ) expression increased in mFoxO1KO, which was accompanied by increased fatty acid oxidation and mitochondrial oxygen consumption. mFoxO1KO increased the number and area of mitochondria. Furthermore, mFoxO1KO enhanced the endurance exercise capacity of mice through free fatty acids as a preferred energy source. Increased expression of proteins related to OXPHOS in FoxO1 shRNA-transfected C2C12 cell was abolished by GSK3787 (PPARδ antagonist).
**Conclusions:** In conclusion, we suggest that increased PPARδ expression in mFoxO1KO leads to improved insulin resistance and endurance exercise capacity by enhancing mitochondrial function in HFD-fed mice.

**Keywords:** Foxo1, PPARδ, Insulin resistance, Mitochondria

## P21-06-06

### Peri-lysosomal Calcium overload by Palmitate in Pancreatic β-cells

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**Purpose:** Saturated fatty acids are known to induce lipotoxicity in pancreatic beta cells. Many pathologic mechanisms related to lipotoxicity have been proposed. Recently, defective autophagy upon exposure to saturated fatty acid has been noticed; however, the mechanism underlying the impairment remains unclear.
**Methods:** We identified the association between mTORC1, TRPML1 channel, and autophagy in palmitate-treated isolated mouse islets, dispersed and sorted pancreatic beta cells, and MIN6 cells.
**Results:** : Palmitate incubation increased oxidative stress, ER $Ca^{2+}$ depletion and ER stress, followed by elevated peri-lysosomal $Ca^{2+}$, decreased autophagic flux, and cytotoxicity in beta cells. Palmitate upregulated mTORC1 signaling, which was $Ca^{2+}$/Calmodulin dependent. Simultaneously, TRPML1-mediated lysosomal $Ca^{2+}$ release was abolished by a mTORC1 activator or palmitate treatment. Selective inhibition of mTORC1 by Torin-1 restored the activity of TRPML1 and autophagic flux. Furthermore, there have been links between extracellular $Ca^{2+}$, ROS generation, ER stress, and mTORC1 activation. Mitochondrial ROS scavenger (MitoTEMPO), $Ca^{2+}$ channel blocker (Verapamil) and SERCA activator (CDN1163) have shown protective effects on autophagic suppression in palmitate-treated beta cells.
**Conclusions:** Taken together, our data suggest a novel mechanism in which mTORC1 and TRPML1 play key a critical role in defective autophagy. Pharmacological or genetic modulation to restore autophagic flux would be a hopeful therapeutic application in metabolic diseases.

**Keywords:** Peri-lysosomal Calcium, Palmitate, Pancreatic β-cells

## P21-06-07

### Enhancing β-cells function by Sarco/Endoplasmic Reticulum Calcium ATPase (SERCA) activator

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**Purpose:** Sarco/Endoplasmic Reticulum Calcium ATPases (SERCA) are ubiquitous ER membrane proteins responsible for driving $Ca^{2+}$ from cytoplasm to ER. For many years, diminished SERCA activity and abundance have been implicated in the underlying mechanism of many diseases, especially type 2 diabetes. Accumulating evidence suggests that enhancement of SERCA activity under stress conditions can rescue pathologic progress. CDN1163 has been discovered as a SERCA activator by conducting a high-throughput screen.
**Methods:** Isolated mouse islets, dispersed and sorted pancreatic beta cells, and MIN6 cells were used for identifying the effect of CDN1163 on beta cell function.
**Results:** We observed that pharmacological activation of SERCA by CDN1163 promoted insulin secretion in isolated mouse islets. CDN1163 did not alter SERCA expression, but profoundly upregulated IP3R expression. IP3Rs have been known to reside on MAMs which is a connected area between ER and mitochondria. Increased ER $Ca^{2+}$ content and IP3R abundance led to increased mitochondrial $Ca^{2+}$ uptake, oxygen consumption rate, mitochondrial membrane hyperpolarization, ATP production, and subsequently promoted insulin secretion. Small interfering RNA knockdown of SERCA2 showed the diminish of CDN1163 action in glucose-stimulated insulin secretion.
**Conclusions:** Collectively, our data highlight the mechanism of CDN1163 in modulating organellar $Ca^{2+}$ exerts benefit via SERCA2 to improve beta cell functions. Enhancement of SERCA activity may thus define a promising therapeutic strategy for type 2 diabetes.

**Keywords:** SERCA activator, CDN1163, Pancreatic beta-cells

## P21-06-08

### Relationships between exposed surface area and cutaneous thermal sensitivity to radiant heat exposure

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**Purpose:** The purpose of the present study was to explore the relationship between body surface area to be exposed to radiant heat and cutaneous warmth and hotness thresholds.
**Methods:** Fifteen healthy Korean males (23.7 ± 1.8 y in age, 175.2 ± 5.6 cm

in height, 78.7 ± 17.8 kg in body weight, 25.7 ± 6.1 kg/m in body mass index, and 23.4 ± 7.9% body fat) participated in this study. Warmth and hotness thresholds on the following eight body parts (the forehead, abdomen, forearm, hand, front thigh, front calf, foot, and upper back) were measured using a radiant heating device. Three sizes of heating films were manufactured (Size 20 × 20, 10 × 10, 5 × 5 cm^2) and each heating film was fixed using a wood frame in order to maintain a distance of 10 cm from the skin. The surface temperature of the radiant heating device increased at a constant rate of 1℃/s from 30℃. Subjects pushed a switch when they felt the first warmth and hotness sensation on their skin. All measurements were repeated three times and their averaged value was used as a representative mean (14 subjects × 8 body regions × 3 sizes of films × 3 repetitions = 1,008 trials). In order to test the effects of different sized heating films, a one-way repeated measure ANOVA was used.
**Results:** Film surface temperatures at warmth thresholds for radiant heat showed significant differences according to the three heating film sizes for all body regions (P<0.001): the forehead (69 ± 18, 121 ± 26, and 175 ± 34 ℃ for 400, 100, and 25 cm^2 heating film size, respectively), the abdomen (61 ± 8, 119 ± 30, and 173 ± 35 ℃), the forearm (53 ± 9, 113 ± 24, and 156 ± 34 ℃), the hand (61 ± 12, 119 ± 24, and 170 ± 39 ℃), the front thigh (61 ± 13, 133 ± 36, and 186 ± 41 ℃), the front calf (61 ± 13, 125 ± 27, and 177 ± 42 ℃), the foot (77 ± 21, 152 ± 43, and 199 ± 47 ℃), and the upper back (58 ± 13, 115 ± 22, and 166 ± 33 ℃). Film surface temperatures at hotness thresholds according to the three film sizes showed similar tendencies as the warmth thresholds (P<0.001): the forehead (98 ± 16, 176 ± 38, and 215 ± 25℃), the abdomen (97 ± 15, 188 ± 34, and 217 ± 25 ℃), forearm (82 ± 17, 168 ± 38, and 209 ± 27 ℃), the hand (89 ± 15, 174 ± 31, and 215 ± 20 ℃), the front thigh (94 ± 17, 193 ± 35, and 220 ± 22 ℃), the front calf (93 ± 18, 193 ± 36, and 219 ± 20 ℃), the foot (101 ± 12, 205 ± 32, and 218 ± 20 ℃), and the upper back (87 ± 19, 171 ± 38, and 207 ± 29 ℃). Differences among the body regions were significant in both warmth and hotness thresholds (P<0.05).
**Conclusions:** Larger heating area resulted in lower thermal thresholds, but the relationships differed with body regions. These results suggest that thermal threshold is influenced by the surface area exposed to heat as well as body region.

**Keywords:** Thermal sensitivity, Thermal threshold, Exposed area, Radiation heat, Body region

## P21-06-09

### Body Regional Differences in Cutaneous Warm and Hot Thresholds using a Radiant Heater

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**Purpose:** The aim was to evaluate body regional differences in cutaneous warm and hot thresholds to radiation heat exposure.
**Methods:** The surface temperature of a radiant film heater increased by 0.01 A per 0.7 s (0.9oC/s increase) and the film was fixed using a wood frame to keep a distance of 10 cm from the skin. Fourteen male subjects participated in this study (age: 25 ± 5.1 y, height: 176.6 ± 5.5 cm, body weight: 70 ± 5.8 kg, body surface area (BSA): 1.89 ± 0.11 m2). Cutaneous warm and hot thresholds on the following 17 body regions were measured: the forehead, neck, chest, abdomen, upper back, lower back, upper arm, forearm, palm, back of hand, front thigh, shin, back of foot, buttock, back thigh, calf, and sole. A warm threshold was defined as skin temperature at the first moment of feeling warmth, and a hot threshold was defined as skin temperature at the first moment of feeling hot on the skin to radiant heat exposure. All trials were conducted in a climate chamber (23oC and 50%RH) and subjects were in a fowler's or prone position on a recliner. A one-way ANOVA was used to test the body regional differences, and Tukey's post hoc test was conducted for multiple comparisons. Statistical significance was set at P<0.05.
**Results:** At initial stages, mean skin temperature was 32.1 ± 2.0oC (thermally comfortable). The forehead (34.8 ± 0.2oC), lower back (34.1 ± 1.2oC) and palm (34.3 ± 0.7oC) had the highest values in warm thresholds, whereas the foot (29.8 ± 1.9oC) and sole (28.0 ± 2.1oC) had the lowest values, showing ~ 7oC difference in regional skin temperatures (P<0.001). The order of hot thresholds showed similar tendencies as the order of warm thresholds. The least increases in skin temperature at warm thresholds were the lower back with a rise of 0.19 ± 0.42oC and the abdomen with a rise of 0.26 ± 0.30oC, while the part with the highest increase was the buttock with a rise of 0.89 ± 0.79oC (P<0.05). The smallest increase in skin temperature at hot threshold was also the lower back with a rise of 0.5oC, showing significant differences with the increases on the upper arm (1.46 ± 0.87oC), foot (1.42 ± 0.71oC), buttock (1.57 ± 0.97oC), and sole (1.50 ± 0.99oC) (P<0.001).
**Conclusions:** Cutaneous thermal thresholds to radiant heat exposure at a distance of 10 cm had higher on the forehead, lower back and palm than the values on the foot and sole, which were related to the level of initial skin temperatures.

**Keywords:** Cutaneous thermal threshold, Radiant heat exposure, Thermal sensation, Body regional differences, Skin temperature

## P21-06-10

### The role of FGF signaling in C. elegans' aging

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**Purpose:** Fibroblast growth factors (FGFs) are a group of multifunctional proteins that are involved in proper cell growth, communication, development, and regulating metabolic homeostasis. In C. elegans, there are only two known FGF orthologs, namely egl-17 and let-756, which act on a single FGFR encoded by egl-15. This receptor has two isoforms namely, EGL-15A and EGL-15B, which mediate a variety of functions during early worm development, but not much is known about the roles of FGF signaling during adulthood of C. elegans. Recent literature found that signaling via EGL-17 and EGL-15(A) improves lifespan and oxidative stress in adulthood, but not LET-756. However our data suggests that LET-756 may also play a role in C. elegans' aging
**Methods:** Using a simple lifespan assay, we investigated various aspects of the possible signaling pathway in conjunction with RNAi of let-756 and egl-15 by feeding. We tested the effects of RNAi using the C. elegans wild type and mutant strains that allow for tissue-specific RNAi. We also used temperature-sensitive egl-15 mutants that allow for specific expression of the EGL-15 isoforms. Furthermore, RNAi of downstream effectors of FGF signaling was performed. Lifespan analysis curves were generated and analyzed using OASIS 2.
**Results:** Feeding let-756 RNAi in L4 worms increases maximum velocity of aging worms. In addition, we found that let-756 RNAi treatment starting at L4 worms increases lifespan. Interestingly, we also found that egl-15 RNAi solely in the hypodermis improves lifespan. RNAi of various downstream effectors of FGF signaling also modestly improves lifespan of worms.
**Conclusions:** Our data suggests that FGF signaling in C. elegans via let-756 also plays a role in aging. A partial inhibition in the C. elegans hypodermis improves lifespan especially in the animal's later life stages. It is promising that these findings occur at adulthood and would be more beneficial in understanding aging also in humans. Our future direction includes testing if starting RNAi at a later life stage would induce the same improvement in longevity and if this effect also involves DAF-16, which is an important transcription factor where most aging signaling converges in C. elegans.

**Keywords:** FGF signaling, Let-756, Egl-15, Aging

## P21-06-11

### Cutaneous warmth thresholds to conductive and radiant heat exposure: body regional differences

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**Purpose:** The purpose of the present study was to explore cutaneous warmth thresholds during conductive and radiant heat exposure on 17 body regions
**Methods:** A. Conductive heat exposure: Seven male subjects participated in this study (25.7 ± 7.1 y in age, 176 ± 7.4 cm in height, 70.0 ± 7.5 in body weight, 22.2 ± 1.2 kg/m2 in BMI). All tests were performed in a climate chamber and subjects were seated in a comfortable recliner posture at an air temperature of 23 ℃ and 50%RH. All measurements were conducted using a thermal stimulator (Intercross-210, Intercross Co., Japan, stimulating probe surface area: 2.5 × 2.5 $cm^2$) and repeated three times at each of the 17 body sites (the forehead, neck, chest, abdomen, upper back, lower back, upper arm, forearm, palm, back of hand, front thigh, shin, back of foot, buttock, back thigh, calf, and sole). The values of three repetitions were averaged. A warmth threshold was measured by a methods of limit, which was that the stimuli of the probe started from baseline skin temperature (33°C) and increased at a constant rate of 0.1°C s-1 until the subject reported feeling warmth. Warmth sensation was defined as initially sensed warmth on the skin. Subjects pushed the button of the thermal stimulator as soon as they felt warmth. B. Radiant heat exposure: The surface temperature of a radiant film heater increased by 0.01 A per 0.7 s (0.9oC/s increase) and the film (10 × 10 cm) was fixed using a wood frame to keep a distance of 10 cm from the skin. Fourteen male subjects participated in this study (age: 25 ± 5.1 y, height: 176.6 ± 5.5 cm, body weight: 70 ± 5.8 kg, body surface area (BSA): 1.89 ± 0.11 m2). Cutaneous warmth thresholds on the identical 17 body regions as the conductive heat exposure experiment. A warmth and hotness thresholds were defined as same as the definition in the conductive heat experiment. All trials were conducted in a climate chamber (23oC and 50%RH) and subjects were in a fowler's or prone position on a recliner. A one-way ANOVA was used to test the body regional differences, and Tukey's post hoc test was conducted for multiple comparisons. Statistical significance was set at P<0.05.
**Results:** There were significant differences in warmth thresholds among the 17 body regions for both conductive and radiant heat exposure, showing higher thresholds on the forehead, back and palm when compared to the foot and sole (P<0.05), which were explained higher initial skin temperatures on the forehead, back and palm. For the most body regions, warmth thresholds were higher for the conductive heat exposure than for the radiant heat exposure. The biggest differences were found on the foot (2.6oC-difference) and sole (3.0oC-difference). The results might suggest that the skin was relatively less sensitive to catch conductive heat than radiant heat, but the surface area of heaters was 16 times greater for the radiant heating film than for the conductive heating element and the radiant heater was placed at a 10-cm distance from the skin, while the conductive heating element was contacted to the skin in direct.
**Conclusions:** Therefore, direct comparison in warmth thresholds between conductive and radiant heating was not feasible, but body regional differences in both conductive and radiant heat exposures can be accepted in terms of biological and statistical significance.

**Keywords:** Cutaneous warmth threshold, Conductive heat exposure, Radiant heat exposure, Body regional difference

## P21-06-12

### Effects of intake of caffeine with thermotherapy on active sweat gland density in humans

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**Purpose:** Caffeine is known to be closely associated with sympathetic systems and neurohormones. Our previous studies have reported that caffeine ingestion affects the increase of body temperature in humans. However, very little is known about the combined effect of thermotherapy and caffeine ingestion on body temperature, activated sweat gland density, and serum neurohormones. Therefore, this study aims to investigate the effect of caffeine on blood levels of dopamine (DA), fibroblast growth factor 21 (FGF-21), irisin, serotonin (5-hydroxytryptamine; 5-HT), cortisol, and β-endorphin during thermotherapy in humans.
**Methods:** Blood levels of DA, FGF-21, irisin, 5-HT, cortisol, 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℃) 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 (chest, upper arm, upper back, lower back, abdomen, thigh, forearm, and leg) areas were determined with iodine impregnated paper method.
**Results:** After thermotherapy, the mTb and mTs increased significantly ($p < 0.001$) in caffeine (CAFF) group in comparison to the control (CON) group. In ASGD measurements, CAFF group showed more activation in sweat gland compared to CON group. Changes in circulating DA, FGF-21, irisin, 5-HT, cortisol, and β-endorphin levels also increased more in CAFF group as compared to CON group.
**Conclusions:** Caffeine ingestion with thermotherapy helped increasing bodily temperature in subjects in addition to increased concentrations of serum neurohormones. This suggests the combination of caffeine ingestion with thermotherapy to be a possible treatment for autonomic dysregulation and sympathetic activation.

**Keywords:** Caffeine, Thermotherapy, Sweat gland density, FGF21, Irisin

## P21-06-13

### Sweat gland density and output during passive heat load might be lower in tropical natives than in temperate natives

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**Purpose:** Modification of sweating could be due to changes in activated sweat gland density (ASGD) and/or activated sweat gland output (ASGO). The present study purpose investigates that regional and inter-ethnic differences in ASGD and ASGO during passive heating between tropical natives (African, n = 22) and temperate natives (Republic of Korean, n = 25).
**Methods:** Passive heat load was carried out by immersing the half body into a hot water bath for 30 min. Tympanic temperature (Tty) and skin temperature (Ts) were measured. Mean body temperature (mTb) was calculated. Sudomotor activities including sweat onset time, sweat rate, ASGD, and ASGO were examined in eight regions of the skin.
**Results:** Africans had smaller increase in mTb during passive heating than Koreans. The onset time of sweating was much more delayed in Africans compared to Koreans. In response to thermal load, ASGD and ASGO differed between body regions in Africans and Koreans. In most skin regions, ASGD and ASGO were lower in tropical Africans compared to those in temperate Koreans. Trunk portion including chest, upper back, lower back, abdomen

had greater swear rate, ASGD, and ASGO compared to peripheral segments including upper arm, forearm, leg, and thigh in both ethnic groups. Distribution patterns of ASGD over the body appeared to be similar in both Africans and Koreans at the peak of thermal loading.
**Conclusions:** In conclusion, the present study demonstrates that sudomotor activity in tropical Africans is reduced with lower ASGD and ASGO over the body surface compared to temperate Koreans. Therefore, sweat gland density and output during passive heat load might be lower in tropical natives than in temperate natives

**Keywords:** Sweat gland density, Sweat gland output, Tropical, Temperate, Passive heating

## P21-06-14

### Effects of detention living on the immune index in female youths in the youth detention center

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**Purpose:** The purpose of this study was to investigate the changes in immune indexes during the detention living period of female youths in the youth detention center.
**Methods:** The participants of this study were female youths (n=8), detention living in the youth detention center. Blood was collected before and after 3 months under the same conditions. Immune indexes were determined changes of white blood cell (WBC) neutrophil, lymphocyte, monocyte, eosinophil, and basophil.
**Results:** All immune indexes were decreased after 3 months compared to 3 months before, and the decrease in neutrophil, monocyte and eosinophil levels was statistically significant.
**Conclusions:** In conclusion, youths may show decreased immune indexes during their detention living in the youth detent center. Therefore, it suggests the need for further study on the cause of the decrease in immune indexes and improvement measures.

**Keywords:** Immune index, Youth detention center, WBC, Immune cell

## P21-07-01

### Tas2r108 knock-out induced change in growth and metabolism

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**Purpose:** Taste plays an important roles or survival. Among the five basic tastes, bitter taste is important for suppressing the intake of possible toxic substances such as life-threatening toxic substances. Bitter taste is detected in the vertebrates by type 2 taste receptors (t2rs). Tas2r108 of 35 murine t2rs was found to be most highly expressed in various exocrine tissues as well as the tongue. The physiological function of tas2r108 would be elucidated by pursuing change in arterial blood pressure(BP), bood glucose(BG) and body weight(BW) during 18 month in tas2r108 knock-out mice.
**Methods:** Tas2r108 knock-out mice produced with CRISPR/Cas9 technology. BPs were measured by non-invasive technique on tail. Wild type C57BL/6 mice or tas2r108 knock-out mice from 8 to 78-week-old were used.
**Results:** Tas2r108 knock-out does not elicit much change in expression of tas2rs in taste buds and submandibular glands. From 8 weeks to 78 weeks age, the difference in BPs or BG between WT and KO mice did not found. The BWs of both groups were gradually increased.
**Conclusions:** The results suggest that at least by 18 months tas2r108 KO would not elicit change in metabolism or feeding behavior. However, more continuous research is needed to confirm the exact physiological role of bitter taste.

**Keywords:** Tas2r108, Taste gene, Bitter taste, Metabolism, Life span

## P21-07-02

### Hyperbaric oxygen therapy promotes wound healing in diabetic mice

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**Purpose:** The diabetic wound is frequently impaired in regenerative functions and treatments are challenging. Hyperbaric oxygen therapy (HBOT) is known as an effective treatment for diabetic foot ulcers. However, the most effective HBOT condition and the mechanism for the wound healing process have not yet been elucidated.
**Methods:** HBOT conditions for treating diabetic skin wounds are investigated into 3 different groups (2, 2.5, and 3 ATM) with non-HBOT (room air) conditions in the present study. Skin wounds were produced by a 4 mm biopsy punch in twelve-weeks-old diabetic mice. After wound production, the animals received HBOT for 2 hr 3 days per week for 2 weeks.
**Results:** The wound healing process was evaluated by measuring wound area, epidermal and dermal thickness from H&E stain, collagen portions, and re-epithelization from Masson's trichrome stain analysis, respectively. Histological examination revealed that 2.5 ATM condition treatment exhibited the smallest wound area, thickened epidermis and dermis, elevated collagen composition, and enhanced re-epithelization.
**Conclusions:** These results suggest that 2.5 ATM is the most effective condition of HBOT for wound healing processes. HBOT activated ERK1/2 and NRF2 pathways to accelerate angiogenesis and decreasing inflammation. These results supported that effective HBOT promotes diabetic wound healing through activating ERK1/2-NRF2 pathway.

**Keywords:** HBOT, Skin, Wound healing, Diabetic mice

## P21-07-03

### The Effects of Mitochondria-derived Peptides on Skin Wound Healing

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**Purpose:** Wound healing is the process of tissue repair and regeneration. Mitochondria are known crucial regulators of wound healing. However, the therapeutic effects of mitochondrial-derived peptides (MDPs) and its underlying mechanism are poorly understood in skin tissue
**Methods:** Here, we examined whether MDPs play a critical regulation in the wound healing process. The experiment was conducted by using in vivo hairless skin-wounded mouse model and in vitro human epidermal keratinocytes
**Results:** The results showed humanin and formylated humanin peptide treatment promoted tissue repair through significant reduction of mouse skin wound areas. Histological skin tissue staining analysis showed that MDPs accelerated the healing process by promoting neovascularization. Similarly, both humanin and formylated humanin peptide-treated increased the protein expression level of alpha-smooth muscle actin in keratinocytes. Furthermore, we revealed the effects of MDPs on wound healing

by enhancing the phosphorylation of signal transducer and activator of transcription 3 (STAT3) signaling pathway in human keratinocytes.
**Conclusions:** Together, our study provides an underlying mechanism of MDPs in mouse skin wound healing and proposed MDPs as therapeutics for tissue repair.

**Keywords:** Wound healing, Mitochondrial-derived peptides, STAT3 signaling pathway, Human epidermal keratinocytes

## P21-07-04

### Co-cultures of human conjunctival epithelial cells on PVA scaffolds and conjunctival fibroblasts in PCL scaffolds better mimic tissue architecture and microenvironment in vivo

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**Purpose:** Three-dimensional (3D) culture models based on human derived cells closely recapitulate tissues in vivo, and thus have become essential research tools in cell biology as well as drug discovery and testing. Physiologically mimetic in vitro conjunctival models are required to assess drug delivery and safety of new ocular medicines as an alternative to animal testing. We have previously developed a 3D human conjunctiva model in which human primary conjunctival epithelial cells and fibroblasts were co-cultured using two-layered poly-ε-caprolactone (PCL) micro/nanofibrous scaffolds. However, this model has several inherent drawbacks related with using PCL fibers such as epithelial cell adhesion to extracellular matrix and stratification. The present study was carried out to overcome these drawbacks and to provide another model better mimicking in vivo structure and extracellular microenvironment of conjunctival tissue.
**Methods:** The primary cultures of human conjunctival epithelial cells and fibroblasts were established from surplus tissue from surgical resection in cataract patients. Human conjunctival epithelial cells were seeded on PVA scaffolds and co-cultured for 7 days with fibroblasts which had been grown in the microfibrous layer of PCL scaffolds. Immunofluorescence was performed to assess epithelial cell adhesion to extracellular matrix and stratification.
**Results:** Conjunctival epithelial cells cultured alone on PVA scaffolds reached early confluence but detached after 7 days. However, when co-cultured on fibroblast-grown PCL scaffolds, epithelial cells on PVA scaffolds maintained confluence until 14 days and began to stratify. Conjunctival epithelial cells co-cultured on PVA scaffolds displayed not only discrete junctional localization of ZO-1 but also basal localization of integrin β1 and vinculin. Staining pattern of laminin, a major constituent of the basement membrane, showed the formation of basement membrane and double layering of epithelial cells.
**Conclusions:** Taken together, co-cultures of both human conjunctival epithelial cells on PVA scaffolds and conjunctival fibroblasts in PCL scaffolds create a more closely mimicking in vivo tissue structure and functions, providing a more relevant model to study ocular drug toxicity and delivery.

**Keywords:** Human conjunctival epithelial cells, Human conjunctival fibroblasts, 3D cell co-culture, Polyvinylalcohol (PVA) scaffold, Polycaprolactone (PCL) scaffold.

## P21-08-01

### Hepatic stellate cell-specific HAS2 deficiency attenuates CCl4-induced liver fibrosis

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**Purpose:** Hyaluronan (HA), a major extracellular matrix component, has been used as a serum biomarker for liver fibrosis. HA is a ligand of Toll-like receptor-2/4 (TLR2/4), which can regulate inflammatory and fibrogenic signaling. HA is synthesized by hyaluronan synthases (HAS) and is cleaved from high molecular weight (HMW-HA) to low molecular weight (LMW-HA) by hyaluronidases (HYAL). This study investigated LMW-HA dysregulated by liver fibrosis, its impact on liver inflammation and fibrosis and underlying basis.
**Methods:** The liver tissues obtained from 65 liver fibrosis patients with chronic HBV infection were used to assess HYAL1 and HYAL2 levels. Primary hepatic stellate cells (HSCs) and Kupffer cells (KCs) were treated with HMW-HA or LMW-HA. WT or HSC-specific Has2 knockout mice were injected with carbon tetrachloride (CCl4) intraperitoneally every 3 days for 6 weeks. Mice were subjected to bile duct ligation (BDL). Vehicle or 450 mg/kg 4-methylumbellieferone was orally gavaged once a day for 5 days.
**Results:** We found that HYAL2 was overexpressed in advanced stage of liver fibrosis in patients, which may be responsible for the increase of LMW-HA. LMW-HA treatment increased Tlr2 mRNA expression in hepatic stellate cells (HSCs) and Kupffer cells. In addition, LMW-HA stimulated the mRNA expression of chemokines (Ccl3 and Ccl4), involved in the recruitment and activation of immune cells and HSCs. In contrast, HMW-HA treatment was unable to increase either Ccl3 or Ccl4. Has2 was greatly increased in HSCs isolated from chronic CCl4-induced fibrotic mouse liver compared with controls. The deposition of HA in the liver was attenuated by HSC-specific Has2 deficiency. Furthermore, collagen deposition and macrophage infiltration was reduced in the liver of CCl4-treated HSC-specific Has2 knockout mice compared with CCl4-treated WT mice. HA synthesis inhibitor, 4-methylumbelliferone treatment successfully inhibited BDL-induced Ccl3 and Ccl4 expression.
**Conclusions:** In liver fibrosis, HAS2 and Hyaluronidase 2 are overexpressed. LMW-HA contributes to chemokine production and liver fibrosis. We suggest that targeting HAS2 may be a good strategy for the treatment of liver fibrosis.

**Keywords:** Liver fibrosis, HAS2, CCL3, CCL4

## P21-08-02

### Molecular protective mechanisms of kaempferol in RINm5F islet β-cells under exposure to interleukin-1β

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**Purpose:** Pro-inflammatory cytokines and nitric oxide (NO) have been implicated in both dysfunction and destruction of pancreatic islet β-cells during the development of diabetes mellitus. Kaempferol, a natural flavonoid, has received much attention because of its beneficial health effects. In this study, we investigated the effects and the underlying mechanisms of kaempferol on RINm5F islet β-cells.
**Methods:** RINm5F β-cells were treated with IL-1β in the presence or absence of kaempferol (5-50 μM). The production of NO was detected with the Griess reagent system. iNOS expression was determined with qRT-PCR and Western blot analysis. The transcriptional activity of NF-κB was evaluated by luciferase reporter assay and EMSA. iNOS mRNA and protein stability assay were determined by actinomycin D (Act.D) and cycloheximide (CHX) chase analysis, respectively. Also, to assess the effect of kaempferol on pancreatic β-cells' function, cell viability, apoptosis, and insulin secretion assays were conducted.
**Results:** In pro-inflammatory cytokine interleukin-1β (IL-1β)-stimulated RINm5F β-cells, kaempferol inhibited the production of NO dose-dependently, and reduced the levels of iNOS protein and its mRNA expression. Kaempferol also inhibited NF-κB activation for iNOS induction, IκB phosphorylation and NF-κB p65 nuclear translocation. Kaempferol decreased the expression of iNOS mRNA through both inhibitions of NF-κB DNA binding activity and mRNA stabilization. In addition, kaempferol reduced the stability of iNOS protein in cycloheximide-treated cells and inhibited enzyme activity of iNOS. Kaempferol pretreatment partially preserved cell viability in IL-1β-treated RINm5F β-cells and improved IL-1β-induced reduc-

tion of insulin release.
**Conclusions:** These findings suggest that kaempferol appears to be helpful in protecting islet β-cells, thereby inhibits the incidence and progression of diabetes mellitus.

**Keywords:** Kaempferol, Interleukin-1β, NO, INOS, RINm5F islet β-cells

## P21-08-03

### Plasma APE1/Ref-1 is upregulated in relation to vascular inflammation in ApoE knockout mice

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**Purpose:** Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is an essential multifunctional protein involved in DNA base excision repair as well as in redox regulation of the several functional proteins, such transcriptional factors. However, the role of APE1/Ref-1 in atherosclerosis is unclear.
**Methods:** In ApoE-/- mice fed Western type diet for 20 weeks, we found an increase of neutrophil/lymphocyte ratio (NLR), the endothelial/macrophage activation as atherosclerotic inflammation, and atherosclerotic plaque by Oil Red O staining.
**Results:** APE1/Ref-1 expression is markedly increased in the aortic tissue of ApoE-/- mice fed Western type diet, it expression was co-localized with CD31 and Galectin-3, suggesting the endothelial/macrophage expression of APE1/Ref-1. Surprisingly, the level of plasma APE1/Ref-1 in ApoE-/- mice fed Western type diet showed a significant increase compared to those in normal diet group, and were suppressed by atorvastatin administration. Correlation analysis showed high correlation between plasma APE1/Ref-1 levels and NLR, a marker of systemic inflammation. The cut-off value for APE1/Ref-1 for predicting atherosclerotic inflammation at 4.903 ng/mL showed sensitivity of 100% and specificity of 91%.
**Conclusions:** We conclude that APE1/Ref-1 expression is upregulated in aortic endothelial cells/macrophages of atherosclerotic mice, and that plasma APE1/Ref-1 levels could predict atherosclerotic inflammation.

**Keywords:** APE1/Ref-1, Atherosclerosis, ApoE knockout mouse, Atorvastatin, VCAM-1, Galectin-3, Neutrophil/lymphocyte ratio

## P21-08-04

### Majonoside-R2 postconditioning protects cardiomyocytes against hypoxia/reoxygenation injury

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**Purpose:** Reoxygenation to hypoxic cardiac myocytes can paradoxically induce myocardial injury and affect the recovery processes. Pharmacological postconditioning is an efficient strategy used in clinical practice that protects cardiomyocytes from hypoxia/reoxygenation (HR) injury. Natural products or foods have been known to possess effective cardioprotective properties. Majonoside-R2 (MR2) is a dominant saponin component of Vietnamese ginseng that has several biological effects. In this study, we evaluated the protective effect of MR2 on HR-stimulated cardiomyocytes and investigated the related molecular mechanisms.
**Methods:** H9C2 cardiomyocytes were exposed to HR condition with or without MR2 supplementation. Samples from experimental groups were used to analyze the expression of apoptosis- and activating reperfusion injury salvage kinase (RISK)-related factors in response to HR injury by using enzyme linked immunosorbent assay, real-time polymerase chain reaction, and western blotting. Post-treatment, MR2 enhanced cell viability under HR condition.
**Results:** We found that MR2 suppressed the expression of hypoxia-inducible factor 1-alpha (HIF1α) and transforming growth factor beta 1 (TGFβ1), modulated Akt/GSK3ß/CREB signaling, and suppressed gene expression related to apoptosis (Bcl-xl, Bak, Bax, and Cnx43).
**Conclusions:** Thus, the present findings demonstrate that MR2 protects cardiomyocytes against HR injury by suppressing the expression of HIF1α and activating the RISK pathway.

**Keywords:** Anti-apoptosis, Cardioprotection, Hypoxic injury, Majonoside-R2

## P21-08-05

### Inhibition of mitochondrial calcium uniporter attenuates mouse bone marrow-derived mast cell degranulation induced by beta-1,3-glucan

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**Purpose:** Mast cells are primary mediators of allergic inflammation. Beta-1,3-glucan (BG) protects against infection and shock by activating immune cells. Activation of the BG receptor induces an increase in intracellular $Ca^{2+}$, which may induce exocytosis. However, little is known about the precise mechanisms underlying BG activation of immune cells and the possible role of mitochondria in this process. The present study examined whether BG induced mast cell degranulation and evaluated the role of calcium transients during mast cell activation. Our investigation focused on the role of the mitochondrial calcium uniporter (MCU) in BG-induced degranulation.
**Methods:** The methods used in this study are preparation of bone marrow-derived mast cells, the use of drugs and solutions, mast cell confirmation, BMMC stimulation, tryptase release measurement, dynamic measurements of cytosolic and mitochondrial calcium and membrane potential, monitoring of vesicle release during mast cell degranulation, fluorescence imaging by laser scanning confocal microscopy, and statistical analyses.
**Results:** Bone marrow-derived cells were cultured and analyzed at week 4 for confirmation of mast cell characteristics via microscopic image and flow cytometry analysis and toluidine blue staining, which indicated a high percentage with >95% of the total population as BMMCs. BG-induced degranulation increased both cytosolic and mitochondrial calcium levels in BMMCs, and the inhibition of the mitochondrial calcium uniporter (MCU) by ruthenium red (RuR) attenuated BG-induced mast cell degranulation.
**Conclusions:** This study demonstrated that the mitochondrial calcium uniporter is an important regulator of $Ca^{2+}$-dependent BG-induced mast cell degranulation. BGs are natural polysaccharides that are widely used in various clinical applications including in DNA damage protection, antioxidative therapy, anti-cancer, and immune stimulation. Among these clinical applications, the role of BG in mast cell stimulation and degranulation has been extensively studied due to its importance in cytokine-mediated immune response. The present study identified the crucial role of MCU during $Ca^{2+}$-dependent mast cell degranulation. These results suggest that the mitochondria are essential regulators of mast cell activation and immunomodulation, which is pertinent knowledge for potential therapeutics involving the optimization of BG- induced clinical immune modulation.

**Keywords:** Beta 1,3-glucan, Bone marrow-derived mast cell, Mast cell degranulation, Mitochondrial calcium uniporter

## P21-09-01

### Palmitic acid remodels lipid metabolism in hepatocellular carcinoma

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**Purpose:** Reprogramming in lipid metabolism is attracting increasing recognition as a hallmark of cancer cells. Oncogenic signal and malignant phenotypes are closely correlated with dysregulation of lipids and related enzyme profiles. Palmitic acid (PA) is the most common saturated fatty acid in human body and is also known to induce post-translational lipid modification, palmitoylation. Numerous human proteins are known to undergo palmitoylation, yet its pathophysiological functions remain elusive.
**Methods:** Palmitoylation of plant homeodomain finger protein 2 (PHF2) was assessed using ABE assay and LC-MS. The molecular target of PA and PHF2 was found by proteomics based on LC-MS. The biological role and the mechanism of PA and PHF2 were determined in vitro and a xenograft mouse model. Clinical datasets from public resources and clinical samples from liver cancer patients were assessed.
**Results:** In this study, we highlight the role of palmitoylation as a molecular checkpoint in hepatocellular carcinoma (HCC) progression. PA palmitoylates PHF2 via ZDHHC23, and subsequently palmitoylated PHF2 undergoes ubiquitin-dependent proteasomal degradation. We also uncovered a function of PHF2 as an E3 ubiquitin ligase of sterol regulatory element binding protein 1c (SREBP1c). Palmitoylation-induced PHF2 loss stabilizes SREBP1c protein, thereby enhancing SREBP1c-dependent proliferation and lipogenesis of liver cancer.
**Conclusions:** Overall, this study unravels a previously unexplored lipid reprogramming in HCC by PA/PHF2/SREBP1c axis. Since PA seems to be the center of this axis, we recommend that patients with HCC should carefully adjust the level of dietary lipids, especially PA.

**Keywords:** Palmitoylation, Phf2, Srebp1c, Lipid metabolism, Hepatocellular carcinoma

## P21-09-02

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

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**Purpose:** Vascular endothelial cell senescence is an important cause of cardiac-related diseases. Mitochondrial reactive oxygen species (mtROS) have been implicated in cellular senescence and multiple cardiovascular disorders. CR6 interacting factor 1 (CRIF1) deficiency has been shown to increase mtROS via the inhibition of mitochondrial oxidative phosphorylation; however, the mechanisms by which mtROS regulates vascular endothelial senescence have not been thoroughly explored. The goal of this study was to investigate the effects of CRIF1 deficiency on endothelial senescence and to elucidate the underlying mechanisms.
**Results:** CRIF1 deficiency was shown to increase the activity of senescence-associated β-galactosidase along with increased expression of phosphorylated p53, p21, and p16 proteins. Cell cycle arrested in the G0/G1 phase were identified in CRIF1-deficient cells using the flow cytometry. Furthermore, CRIF1 deficiency was also shown to increase cellular senescence by reducing the expression of Sirtuin 3 (SIRT3) via ubiquitin-mediated degradation of transcription factors PGC1α and NRF2. Downregulation of CRIF1 also attenuated the function of mitochondrial antioxidant enzymes including manganese superoxide dismutase (MnSOD), Foxo3a, nicotinamide-adenine dinucleotide phosphate, and glutathione via the suppression of SIRT3. Interestingly, overexpression of SIRT3 in CRIF1-deficient endothelial cells not only reduced mtROS levels by elevating expression of the antioxidant enzyme MnSOD but also decreased the expression of cell senescence markers.
**Conclusions:** Taken together, these results suggest that CRIF1 deficiency induces vascular endothelial cell senescence via ubiquitin-mediated degradation of the transcription coactivators PGC1α and NRF2, resulting in decreased expression of SIRT3.

**Keywords:** Vascular endothelial cell, Mitochondria, Senescence, Oxidative stress, Antioxidant system

## P21-09-03

### CR6-interacting factor 1 deficiency inhibits BH4 production and induces eNOS uncoupling

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**Purpose:** CRIF1 knockdown or knockout in endothelium shows decreased eNOS activity and NO production. Because of these results, vasodilation was significantly reduced. We investigated about the relationship between CRIF1 deficiency and eNOS uncoupling in endothelial cells
**Methods:** siRNA specific downregulation and endothelial-specific CRIF1 knockout were used to model of CRIF1 deficiency. Western blot and qPCR were used for measuring BH4 biosynthesis protein expression. Fluorescence-HPLC was used for analyzing BH4 content.
**Results:** CRIF1 deficiency inhibits eNOS activity including decreased NO production. Also, CRIF1-deficient cells shown no changes with eNOS substrates, L-arginine compare with control groups. We also meausre the uncoupled eNOS-mediated ROS production by L-NAME, NOS specific inhibitor, supplementation. In control cells, L-NAME treatment did not change ROS levels, but it decreased ROS generation significantly in CRIF1-deleted cells. BH4, eNOS cofactor, level was significantly decreased in CRIF1 downregulation cells, and supplementation of BH4 rescued impaired eNOS activity and NO generation. In BH4 biosynthesis, GCH-1, PTS, SPR and DHFR play an important role and CRIF1 deficiency suppressed those expression via excessive ROS. ROS scavenging with mito-tempo reversed BH4 biosynthesis expression in CRIF1-deleted HUVECs.
**Conclusions:** CRIF1 deficiency induced endothelial dysfunction and eNOS uncoupling via BH4 deficiency and mitochondrial ROS generated through damaged mitochondria plays an important role in inhibition of BH4 biosynthesis.

**Keywords:** BH4, CRIF1, ROS, ENOS uncoupling

## P21-09-04

### Butylated hydroxyanisole reduces the growth of lung cancer and normal fibroblast cells via apoptosis and cell cycle arrest

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**Purpose:** Butylated hydroxyanisole (BHA), a fat-soluble synthetic antioxidant, is widely used as a preservative in food and pharmaceutical products. BHA exerts a variety of effects on tissues and cell functions. However, little is known about its cytotoxicological effects on lung cells. Thus, the objective of the present study was to investigate effects of BHA on cell growth, cell death, and cell cycle distributions of lung cancer cells (Calu-6 and A549), primary normal human pulmonary fibroblast (HPF) cells, and SV40-transformed normal lung WI-38 VA-13 cells.
**Methods:** Lung cancer cells (Calu-6 and A549) and lung normal cells (HPF and WI-38 VA-13) were used for this study. The growth or viability of the cells in response to BHA was assessed by MTT assay. Cell cycle distribution and mitochondrial membrane potential (MMP; ΔΨm) of cancer and normal cells

were measured using FACs analysis.
**Results:** BHA (50–400 μM) dose-dependently inhibited the growth of lung cancer and normal cells with a half maximal inhibitory concentration (IC50) of approximately 200 μM at 24 h. DNA flow cytometry showed that BHA generally induced arrest at G1 phase of the cell cycle in lung cancer and normal cells. Treatment with BHA induced cell death accompanied by (MMP; ΔΨm) loss. Generally, there was no significant difference in susceptibility to BHA between lung cancer and normal cells. Z-VAD, a pan-caspase inhibitor, significantly decreased the number of sub-G1 cells in BHA-treated Calu-6 cells and attenuated the percentages of annexin V-positive cells in BHA-treated A549 cells. Z-VAD also slightly reduced proportions of MMP (ΔΨ m) loss cells in BHA-treated cancer cells.
**Conclusions:** BHA treatment could dose-dependently inhibit the growth of lung cancer and normal fibroblast cells through G1 phase arrest of cell cycle, apoptosis, and/or necrosis.

**Keywords:** Butylated hydroxyanisole, Lung cancer cells, Human pulmonary fibroblast Cell.

## P21-09-05

### Butylated hydroxyanisole inhibits the growth of lung cancer and normal cells accompanied by increased ROS levels and GSH depletion

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**Purpose:** Butylated hydroxyanisole (BHA) which is broadly used as a potent antioxidant and preservative in food, cosmetics, and medicine exerts various effects on tissues and cell functions. The present study investigated the anti-proliferative effect of BHA in Calu-6 and A549 lung cancer cells, and primary normal human pulmonary fibroblasts (HPF) cells and SV40-transformed normal lung WI-38 VA-13 cells by analyzing reactive oxygen species (ROS) and glutathione (GSH) levels.
**Methods:** Lung cancer cells (Calu-6 and A549) and lung normal cells (HPF and WI-38 VA-13) were used for this study. The number of viable cells in cancer and normal cells responding to BHA was counted by tryptophan blue exclusion assay. Determination of intracellular ROS and GSH levels in lung cells were performed using FACs analysis.
**Results:** BHA (50 – 400 μM) decreased the number of live cells in both lung cancer and normal cells at 24 h and the higher doses induced cell death. A pan-caspase inhibitor, Z-VAD, increased the number of live cells in BHA-treated A549 cells and strongly decreased the number of dead cells in BHA-treated Calu-6 cells. BHA (50 – 400 μM) increased ROS levels, including $O_2^{\bullet-}$ in both the Calu-6 and A549 cancer cells at 24 h. BHA also increased the $O_2^{\bullet-}$ levels in HPF and WI-38 VA-13 normal cells but decreased non-specific general ROS levels in both the normal cells. Z-VAD decreased ROS levels, including $O_2^{\bullet-}$ in BHA-treated Calu-6 and A549 cells. Moreover, higher doses of BHA increased the number of GSH-depleted lung cancer and normal cells at 24 h. Z-VAD significantly reduced GSH depletion in BHA-treated Calu-6 and A549 cells.
**Conclusions:** BHA treatment decreased the proliferation of lung cancer and normal cells and induced cell death, which was related to increases in $O_2^{\bullet-}$ levels and GSH depletion.

**Keywords:** Butylated hydroxyanisole, Lung cancer cells, Human pulmonary fibroblast, Cell proliferation, Reactive oxygen species, Glutathione

## P21-09-06

### Apoptotic lung cancer cells suppress migration and invasion of cancer-associated fibroblasts via inhibition of TGF-β1 signaling

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**Purpose:** Cancer-associated fibroblasts (CAFs) are critical in determining tumor invasion and metastasis. Apoptotic cell clearance by phagocytes is essential in tissue homeostasis. Here, we investigated whether direct exposure of UV-irradiated apoptotic lung cancer cells or conditioned medium (CM) from isolated lung CAFs exposed to apoptotic cancer cells inhibits migration and invasion of CAFs themselves.
**Methods:** CAFs were incubated with apoptotic or necrotic lung cancer cells or conditioned medium from CAFs exposed to apoptotic or necrotic cells. And then we analyzed TGF-β1-induced migration and invasion of CAFs using the Transwell assay and related signaling pathways using Western blot analysis and qRT-PCR assay.
**Results:** Direct exposure to apoptotic lung cancer cells, 344SQ cells (ApoSQ) markedly inhibited TGF-β1-induced cell migration and invasion of CAFs themselves, whereas control or necrotic 344SQ cancer cells (NecSQ) did not. Similar to the direct effects of ApoSQ, treatment with CM from CAFs exposed apoptotic lung cancer cells, including ApoSQ and apoptotic A549 cells, showed significant inhibitory effects on TGF-β1-induced migration and invasion of CAFs. However, CM from CAFs exposed to necrotic lung cancer cells had little inhibitory effects. Neither CM from ApoSQ or necrotic 344SQ cells alone nor direct exposure did not influence TGF-β1-induced migration and invasion of CAFs. Interestingly, treatment with ApoSQ, but not NecSQ, reversed the increases in gene and protein expression of well-known the CAF activation markers, such as α-smooth muscle actin, collagen type 1 alpha 1, and fibronectin, by TGF-β1. Direct exposure to ApoSQ partially blocked TGF-β1 signaling, including Smad2/3, FAK, ERK, p38 MAP kinase and Akt pathways, in CAFs. In addition, ApoSQ reversed TGF-β1-induced up-regulation of MMP-2 and MMP-12 expression at mRNA and protein levels in CAFs.
**Conclusions:** Taken together, these findings suggest that interaction between CAFs and apoptotic lung cancer cells can suppress migration and invasion of CAFs via inhibition of TGF-β1 signaling.

**Keywords:** Cancer-associated fibroblasts, Apoptotic lung cancer cells, Migration, Invasion

## P21-09-07

### Butylated hydroxytoluene decreases HeLa, Calu-6, and A549 cell growth via cell death and cell cycle arrest accompanied by increased ROS levels and GSH depletion

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**Purpose:** Butylated hydroxytoluene (BHT) is a widely used synthetic antioxidant. The present study investigated the cytotoxicological effect of BHT on the growth of HeLa cervical cancer cells, and Calu-6 and A549 lung cancer cells in relation to reactive oxygen species (ROS) and glutathione (GSH).
**Methods:** HeLa cervical cancer cells, and Calu-6 and A549 lung cancer cells were used for this study. The growth or viability of the cells in response to BHT was assessed by MTT assay. Annexin V/PI staining, cell cycle distribution and mitochondrial membrane potential (MMP; ΔΨm) in these cells were measured using FACs analysis. We also measured intracellular ROS and GSH levels using FACs analysis.
**Results:** BHT (50–300 μM) inhibited the growth of HeLa, Calu-6, and A549 cells with a half maximal inhibitory concentration (IC50) of approximately 100, 200, and 150 μM, respectively, after 24 h. BHT dose-dependently in-

creased the loss of viability in HeLa cells but not in Calu-6 and A549 cells. In addition, some doses of BHT induced the G1 phase arrest of the cell cycle. Generally, BHT led to dose-dependent increases in sub-G1 cells and annexin V-positive cells, accompanied by MMP (ΔΨm) loss. BHT (50–300 μM) did not significantly increase non-specific ROS levels in cancer cells. However, BHT dose-dependently increased O2•- levels in HeLa cells but not in Calu-6 and A549 cells. Furthermore, BHT efficiently induced GSH depletion in HeLa cells but not in Calu-6 and A549 cells.
**Conclusions:** HeLa cervical cancer cells showed higher susceptibility to BHT, and Calu-6 lung cancer cells were relatively resistant to BHT. BHT treatment decreased the growth of HeLa, Calu-6, and A549 cancer cells and induced their cell death, which was related to increases in O2•- levels and GSH depletion.

**Keywords:** Butylated hydroxytoluene, Cervical cancer cells, Lung cancer cells, Cell growth, Cell death, Reactive oxygen species, Glutathione

## P21-09-08

### Each inhibitor of mitogen-activated protein kinases influences the growth inhibition of Calu-6 and A549 lung cancer cells induced by Auranofin

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**Purpose:** Auranofin as an inhibitor of thioredoxin reductase (TrxR) has many biological properties, including an anti-cancer effect. However, little is known about the toxicological effect of Auranofin in human lung cancer cells in relation to mitogen-activated protein kinase (MAPK) signaling. In this study, we recently demonstrated that Auranofin inhibited the growth of Calu-6 and A549 lung cancer cells through apoptosis. Here, we investigated the effects of Auranofin and MAPK inhibitors on Calu-6 and A549 lung cancer cells in relation to cell growth, cell death, reactive oxygen species (ROS) and GSH levels.
**Methods:** Calu-6 and A549 lung cancer cells were used for this study. The growth or viability of the cells in response to Auranofin and MPAK inhibitors was assessed using the MTT assay and the LDH assay. Annexin V/PI staining and mitochondrial membrane potential (MMP; ΔΨm) of these cells were measured using FACs analysis. We also measured intracellular ROS and GSH levels using FACs analysis.
**Results:** Treatment with Auranofin inhibited the growth of Calu-6 and A549 cells at 24 h. Auranofin -induced apoptosis was accompanied by the loss of (MMP; ΔΨm). Auranofin also increased ROS levels as well as GSH depletion in these cells. All the MAPK (MEK, JNK, p38) inhibitors slightly enhanced cell growth inhibition and death by Auranofin and appeared to augment O2•- levels in Auranofin-treated Calu-6 and A549 cells. MEK inhibitor enhanced the growth inhibition and death by Auranofin. This agent also significantly increased MMP loss, O2•- level and GSH depletion in Auranofin-treated Calu-6 cells. JNK inhibitor significantly decreased cell growth and increased cell death and ROS levels in Auranofin-treated Calu-6 cells. Treatment with p38 inhibitor intensified growth inhibition, cell death, MMP loss and GSH depletion in Auranofin-treated Calu-6 and A549 cells.
**Conclusions:** MAPK inhibitors slightly intensified cell death in Auranofin-treated Calu-6 and A549 cells. The changes of ROS and GSH by Auranofin and MAPK inhibitors were in part involved in cell growth and death in these cells.

**Keywords:** Auranofin, Lung cancer, MAPK, ROS, GSH

## P21-09-09

### Interaction between cancer-associated fibroblasts and apoptotic lung cancer cells inhibits migration and invasion of cancer cells via downregulation of TGF-β1 signaling

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**Purpose:** High levels of cell death can occur within the tumor microenvironment (TME). Paracrine communication between cancer-associated fibroblasts (CAFs) and cancer cells facilitates underlying processes such as cancer cell migration and invasion. Here, we investigated whether interaction between CAFs and UV-irradiated apoptotic cancer cells controls migration and invasion of cancer cells.
**Methods:** Cancer cells were exposed to conditioned medium (CM) from CAFs exposed apoptotic lung cancer cells.
And then we analyzed TGF-β1-induced migration and invasion cancer cells and related signaling pathways.
**Results:** Conditioned medium (CM) from lung CAFs exposed apoptotic lung cancer cells, including mouse 344SQ cells and human A549 cells, or colon cancer cell lines (HCT-116) substantially prevented TGF-β1-induced cancer cell migration and invasion, whereas control or CM derived CAFs exposed to necrotic cancer cells did not. However, neither CM from apoptotic 344SQ cells (ApoSQ) or necrotic 344SQ cells (NecSQ) alone nor direct exposure did not influence TGF-β1-induced migration and invasion of 344SQ cells. Treatment with ApoSQ-exposed CAF CM partially blocked TGF-β1 signaling, including Smad2/3, Src, FAK, ERK, p38 MAP kinase and Akt pathways, in 344SQ cells. In addition, ApoSQ-exposed CAF CM reversed TGF-β1-induced up-regulation of MMP-2 and MMP-12 expression at mRNA and protein levels in 344SQ cells.
**Conclusions:** Taken together, these findings suggest that CAFs exposed to apoptotic cancer cells can prevent migration and invasion of lung cancer cells via down-regulation of TGF-β1 signaling.

**Keywords:** Cancer-associated fibroblasts, Apoptotic cancer cells, Migration, Invasion, Lung cancer cells

## P21-09-10

### CRIF1 knockdown suppresses endothelial cell migration via upregulation of RhoGDI2

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**Purpose:** Rho GDP-dissociation inhibitor (RhoGDI), a downregulator of Rho family GTPases, prevents nucleotide exchange and membrane association. It is responsible for the activation of Rho GTPases, which regulate a variety of cellular processes, such as migration. In addition, Adrenomedullin2 (ADM2) secreted by vascular endothelial cells (ECs) promotes migration and invasion by ECs. Although RhoGDI2 has been identified as a tumor suppressor gene involved in cellular migration and invasion and ADM2 is an autocrine/paracrine factor that regulates vascular tone and other vascular functions, little is known of their roles in EC migration. CR6-interacting factor 1 (CRIF1) is a CR6/GADD45-interacting protein with both nuclear and mitochondrial functions and regulates cell growth.
**Methods:** We examined the expressions of RhoGDI2 and ADM2 in CRIF1-deficient human umbilical vein endothelial cells (HUVECs) and their role in cell migration. Cell migration was measured using the scratch wound healing assay and transwell migration assay.
**Results:** Expression of RhoGDI2 was considerably higher in CRIF1-deficient HUVECs, which suppressed their migration; endogenous ADM2 levels in

CRIF1-silenced HUVECs were elevated as a compensatory mechanism. In addition, the phosphorylation of Akt and CREB was decreased in CRIF1-silenced cells. The Akt-CREB signaling pathway was implicated in the changes in endothelial cell migration caused by CRIF1 downregulation.
**Conclusions:** Depletion of RhoGDI2 or exogenous ADM2 significantly restored cell migration via the Akt-CREB signaling pathway. In conclusion, RhoGDI2 and ADM2 play important roles in the migration of CRIF1-deficient endothelial cells.

**Keywords:** CRIF1, RhoGDI2, Adrenomedullin2, Cell migration, Akt

## P21-09-11

### Autophagy dysfunction in an in vitro and in vivo model of diabetic peripheral neuropathy

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**Purpose:** Diabetic peripheral neuropathy (DPN) is one of the most common and problematic complications of diabetes. Drugs and treatments used to control pain and prevent worsening of symptoms have been introduced but have not been effective. Previous studies have shown that diabetes-induced microvascular damage is a direct cause of DPN by causing nerve ischemia. In addition, although there have been reports on the relationship between autophagy and DPN, studies are still lacking. In this study we investigated the relationship between autophagy and diabetic peripheral neuropathy in animal and cell models, and confirmed the change in autophagy in Schwann cells, which are peripheral neurons.
**Methods:** We treated with streptozotocin to measure glucose for 8 weeks and performed von Frey test to produce a diabetic peripheral neuropathy mouse model. For cell model, glucose was added to the media to set a high-glucose cell model.
**Results:** We identified autophagy-related genes by constructing a diabetic peripheral neuropathy mouse model. In protein expression and fluorescence staining experiments, it was confirmed that the Beclin1 gene increased and the p62 and LC3 I/II ratios were decreased in the diabetic peripheral neuropathy test group compared to the control group. As a result of confirming the Myelin sheath thickness produced by Schwann cells with an electron microscope, it was confirmed that it was reduced in the DPN model compared to the control group. Similarly, in the high-glucose cell model, it was confirmed that the expression of the gene responsible for the autophagy function was increased or decreased compared to the control.
**Conclusions:** High glucose may play a role in autophagy dysfunction in Schwann cells. Therefore, our study suggests that autophagy dysfunction of Schwann cells may contribute to the development of DPN.

**Keywords:** Diabetic peripheral neuropathy, Schwann cell, Autophagy, Hyperglycemia

## P21-09-12

### Upregulation of metabokine and UPRmt in amygdala by treatment of β-Guanidinopropionic acid induces anxiolytic behavior

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**Purpose:** β-Guanidinopropionic acid (β-GPA) is the structural isomer of creatine and acts as a competitive inhibitor of cellular creatine uptake. Reduction of ATP/ADP phosphorylation by inhibition of creatine transporter induces mitochondrial stress response, and sequentially, upregulates of mitochondrial biogenesis. Although UPRmt is closely related to mitochondrial stress response, underline mechanisms that cause β-GPA causes UPRmt are unknown.
**Methods:** qRT-PCR was proceed to measure the mRNA levels of genes related to mitochondrial biogenesis and mitochondrial unfolded protein response (UPRmt) after treatment of β-GPA in glia (astrocyte and microglia) and neuron. Next, mitochondrial oxygen consumption rate (OCR) measured by XF24 analyzer. To test the effect of β-GPA in vivo, open field test was performed to investigated the general behavioral change by β-GPA treatment. To evaluate metabokine association in β-GPA effect, metabokine knock out mice were used to test behavioral changes under the same conditions.
**Results:** Metabokine and UPRmt increase by β-GPA treatment. Mitochondrial respiration increases in astrocyte after β-GPA treatment. β-GPA oral injection of β-GPA mice showed no change of movement distance comparing with vehicle injected groups. However, interestingly, β-GPA injected mice spent more time in the center of the field, which means that anxiety related behavior has decreased. Furthermore, β-GPA treatment did not induce any change in metabokine knock out mice.
**Conclusions:** Inhibition of creatine by blocking creatine transporter with β-GPA treatment induces mitochondrial stress response, specifically metabokine, which affect mitochondrial biogenesis and anxiolytic behavior.

**Keywords:** B-GPA, Creatine, UPRmt, Mitochondria

## P21-09-13

### Mitochondrial creatine kinase phosphorylation in novel tyrosine residues confers cardioprotection against hypoxia/reoxygenation injury

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**Purpose:** Proteomic studies have demonstrated ischemic preconditioning (IPC) can assert cardioprotection during ischemic cardiomyopathy (ICM). Considering IPC occurs briefly, protein expression is also rapidly regulated, indicating the importance of protein modulation by post-translational modifications. This study aimed to identify and analyze novel phosphorylated mitochondrial proteins that can be targeted to address ischemia/reperfusion (I/R) injury.
**Methods:** Sprague-Dawley rat hearts were used in an ex vivo Langendorff system to simulate normal perfusion, I/R, and IPC condition, after which the samples were prepared for phosphoproteomic analysis. Employing human cardiomyocyte AC16 cells, we investigated the cardioprotective role of CKMT2 through overexpression and how site-directed mutagenesis of putative CKMT2 phosphorylation sites (Y159A, Y255A, and Y368A) can affect cardioprotection by measuring CKMT2 protein activity, mitochondrial function, and protein expression changes.
**Results:** Phosphoproteomics revealed dephosphorylation of mitochondrial creatine kinase (CKMT2) during ischemia and I/R in a rat model while preserving its phosphorylated state during IPC. Using human ventricular

cell line AC16, CKMT2 overexpression conferred cardioprotection against hypoxia/reoxygenation (H/R) by increasing cell viability and mitochondrial ATP, preserving mitochondrial membrane potential, and reduced ROS generation, while phosphomutations, especially in Y368, nullified cardioprotection by reducing cell viability and increasing ROS production during H/R. CKMT2 overexpression increased mitochondrial function by mediating the PGC1α/ERRα axis, and these effects were mostly inhibited by Y368A mutation.
**Conclusions:** Regulation of quantitative expression and phosphorylation site Y368 of CKMT2 offers a unique mechanism in future ICM therapeutics.

**Keywords:** Mitochondria, Mitochondria creatine kinase, Phosphorylation, Heart failure

## P21-09-14

### The protective effect of HS 1793 via mitochondrial function regulation from oxidative stress in C2C12 cells

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**Purpose:** HS1793, a novel analogue of resveratrol, was previously determined to be more potent at lower dosages by improving mitochondrial function and increased mitochondrial biogenesis-related proteins. In this study, we focused on targeting the mitochondria to address muscle wasting with HS-1793.
**Methods:** Dosage screening was performed by evaluating for cytotoxicity and cell proliferation. Mitochondrial mass, mitochondrial membrane potential (Δψm), reactive oxygen species (ROS) level, and mitochondria biogenesis-regulated genes and proteins were analyzed to determine the effects on mitochondrial biogenesis.
**Results:** HS-1793 reduced ROS generation, but treatment did not interfere with cellular viability at low dosages. HS-1793 also regulated mitochondrial function by increasing cellular and mitochondrial ATP synthesis function, stabilizing Δψm and decreasing ROS. More importantly, these dysfunction in these parameters were ameliorated by HS-1793 in a simulated oxidative stress model with tBHP. We also observed increase in mitochondrial mass and upregulation in vital mitochondrial biogenesis-related gene PGC1-α as a response to HS-1793 treatment. Moreover, phosphorylation of AKT and mTOR proteins, which are considered as regulators of skeletal muscle function were also increased during the treatment. Finally, HS-1793 also demonstrated protective effects against cisplatin-induced skeletal muscle cell injury by increasing expression of mitochondrial biogenesis-relate markers.
**Conclusions:** Taken altogether, it shows the viability of HS-1793 as a compound that can restore mitochondrial function and render protection in skeletal muscle cells, especially during high oxidative stress levels.

**Keywords:** Reactive oxygen species, Mitochondria, Resveratrol, Skeletal muscle, Oxidative stress

## P21-09-15

### 17β-estradiol increases APE1/Ref-1 secretion via calcium-dependent exosome pathway

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**Purpose:** Apurinic/apyrimidinic endonuclease-1/redox factor-1 (APE1/Ref-1) is a multifunctional protein that can be secreted, and recently suggested as new biomarker for vascular inflammation. However, the endogenous hormones for APE1/Ref-1 secretion and its underlying mechanisms are not defined. Here, the effect of twelve endogenous hormones on APE1/Ref-1 secretion was screened in cultured vascular endothelial cells.
**Methods:** Human umbilical vein endothelial cells (HUVECs) were cultured in endothelial growth medium (EGM-2) and were maintained in humidified atmosphere of 95% air and 5% CO2 at 37 °C. Cell viability and cytotoxicity of HUVECs were analyzed using a RealTime-Glo™ MT cell viability assay kit. Quantification of secreted APE1/Ref-1 levels were determined using a APE1/Ref-1 sandwich enzyme-linked immunosorbent assay (ELISA) kit. To isolate the exosome from the cell culture medium of HUVECs, the medium was changed to medium without fetal bovine serum and exosomes were isolated using an Exoquick-TC isolation kit that precipitates exosomes based on polyethylene glycol precipitation. Immunoblot and immunofluorescence assay were used for detection of proteins.
**Results:** The effect of twelve endogenous hormones on APE1/Ref-1 secretion was screened in cultured vascular endothelial cells. The endogenous hormones that significantly increased APE1/Ref-1 secretion was 17β-estradiol (E2), 5α-dihydrotestosterone, progesterone, insulin, and insulin-like growth factor. The most potent hormone inducing APE1/Ref-1 secretion was E2, which in cultured endothelial cells, E2 for 24h increased APE1/Ref-1 secretion level of 4.56 ± 1.16 ng/mL, compared to a basal secretion level of 0.09 ± 0.02 ng/mL. Among the estrogens, only E2 increased APE1/Ref-1 secretion, not estrone and estriol. Blood APE1/Ref-1 concentrations decreased in ovariectomized (OVX) mice but were significantly increased by the replacement of E2 (0.39 ± 0.09 ng/mL for OVX vs 4.67 ± 0.53 ng/mL for OVX + E2). E2-induced APE1/Ref-1secretion was remarkably suppressed by the estrogen receptor (ER) blocker fulvestrant and intracellular $Ca^{2+}$ chelator, BAPTA-AM, suggesting E2-induced APE1/Ref-1 secretion was dependent on ER and intracellular calcium. E2-induced APE1/Ref-1 secretion was significantly inhibited by exosome inhibitor GW4869. Furthermore, APE1/Ref-1 level in CD63-positive exosome were increased by E2. Finally, fluorescence imaging data showed that APE1/Ref-1 colocalized with CD63-labled exosome in the cytoplasm of cells upon E2 treatment.
**Conclusions:** Taken together, E2 was the most potent hormone for APE1/Ref-1 secretion, which appeared to occur through exosomes that were dependent on ER and intracellular $Ca^{2+}$. Furthermore, hormonal effects should be considered when analyzing biomarkers for vascular inflammation.

**Keywords:** APE1/Ref-1, 17β-estradiol, Endothelial cells, Calcium, Exosome

## P21-09-16

### Knockdown of hematopoietic- and neurologic-expressed sequence 1 stimulated autophagy in colorectal cancer

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**Purpose:** The purpose of our study is investigated the underlying molecular mechanisms by which hematopoietic- and neurologic-expressed sequence 1 (HN1) regulates proliferation, metastasis, apoptosis and autophagy in colorectal cancer cell.
**Methods:** We performed western blot assay, siRNA transfection assay, plasmid transfection assay, WST-1 assay, flow cytometry, wound healing assay, matrigel invasion assay, immunofluorescence, and co-immunoprecipitation in SW480 and SW620 cell llines, and established Xenograft animal model in nude mice.
**Results:** Knockdown of HN1 significantly decreased the viability of colorectal cancer cells, inducing G1 cell cycle arrest and apoptosis. HN1 silencing by siRNA also inhibited the invasion and metastasis of colorectal cancer cells. Additionally, knocking down of HN1 induced autophagy whereas EGF treatment to CRC cells induced HN1 expression. Knockdown of HN1 on EGF treated cells counteracted the effects of EGF induction. Co-immunoprecipitation demonstrated that HN1 regulates colorectal cancer cell proliferation, metastasis and autophagy through directly acting with Akt/

mTOR signaling. Moreover, knockdown of HN1 inhibited tumor growth in xenograft model.
**Conclusions:** Our results suggest that in vivo and vitro 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

## P21-09-17

### Hematopoietic- and eurologic-expressed sequence 1 regulates autophagy and ERstress in hepatocellular carcinoma cell

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**Purpose:** The purpose of our present study is to research underlying mechanism of HN1 in hepatocellular carcinoma cell (HCC).
**Methods:** We performed WST-1 assay, colony formation assay, western blot assay, siRNA transfection, immunofluorescence, co-immunoprecipitation and real time-PCR in HepG2 and SNU449 cell lines.
**Results:** Knockdown of HN1 enhanced cell apoptosis and induced G1 cell cycle arrest. In addition, knockdown of HN1 induced autophagy whereas overexpression of HN1 reduced autophagy. Knockdown of HN1 under starvation condition or Torin 1 treatment further induced autophagy but reversed chloroquine-induced autophagy reduction. Knockdown of HN1 down-regulated mTOR/AKT signaling pathway and Bcl-2/Bax signaling pathway. Knockdown of HN1 increased nuclear-translocation oftranscription factor EB (TFEB), a key transcriptional regulator of lysosome biogenesis and autophagy, under starvation condition or Torin 1 treatment. Moreover, knockdown of HN1 induced ER stress and overexpression of HN1 counteract part of tunicamycin induced-ER stress.
**Conclusions:** Our results suggest that HN1 regulates cell apoptosis, autophagy and ER-stress of hepatocellular carcinoma cells.

**Keywords:** Hepatocellular carcinoma, HN1, Apoptosis, Autophagy, TFEB

## P21-09-18

### Recombinant human BMP-2 induced tumorigenesis in human colorectal cancer cells

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**Purpose:** In our present study, we investigate the role of rhBMP-2 with associated signaling pathway in human colorectal cancer (CRC) cells,HT-29 and HCT116 cells.
**Methods:** We performed flow cytometry, WST-1 assay, western blot assay and colony formation assay in colorectal cancer cell lines.
**Results:** RhBMP-2 significantly suppressed 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. 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 activated Hippo signaling pathway.
**Conclusions:** Therefore, our results indicate that rhBMP-2 suppresses colorectal cell proliferation which is mediated via activation 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

## P21-09-19

### Ursolic acid and Doxorubicin combination therapy enhance the anti-tumor activity in human colorectal cancer by inactivation of Akt signaling

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**Purpose:** Colorectal cancer is the third most common cancer worldwide. Although ursolic acid (UA) and doxorubicin (DXR) have been suggested to reduce the risk of adenocarcinomas in humans, their combined effects on human colorectal cancer cells have never been fully elucidated. Here, we report for the first time that the biological effects of UA and DXR in human colorectal cancer cells.
**Methods:** We used WST-1 assay, soft agar colony formation assay, flow cytometry, wound healing assay and western blot assay in HCT116 and HT29 cell lines.
**Results:** Treatment with UA and DXR substantially increased apoptosis as indicated by increased cleaved polyADP-ribose polymerase (PARP) and cleaved caspase-9 levels. In addition, combination treatment with UA and DXR also strongly inhibited the migration of colorectal cancer cells. Furthermore, combination treatment with UA and DXR strongly blocked the survival Akt/GSK3β signaling pathway, which led to a concomitant reduction of the anti-apoptotic protein cyclinD1, altogether resulting in the activation of intrinsic apoptosis.
**Conclusions:** These results suggest that combination treatment with UA and DXR induce cell apoptosis by suppressing Akt activity and influence the cell migratory properties in human colorectal cancer cells.

**Keywords:** Ursolic acid, Doxorubicin, Colorectal cancer cells

## P21-09-20

### 3,3'-diindolylmethane combination with 5-fluorouracil strength the anti-tumor effect through Akt and Wnt/β-catenin pathway in gastric carcinoma

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**Purpose:** Our study aims to explore whether 3,3'-diindolylmethane (DIM) potentiates chemotherapeutic agents 5-fluorouracil (5-Fu) of gastric cancer cells and investigate the possible mechanisms of this process.
**Methods:** We performed WST-1 assay, soft agar colony formation assay, flow cytometry, wound healing assay, western blot assay, real-time PCR in SN484 and SNU638 cell lines and established xenograft animal model in nude mice.
**Results:** Functionally, the data of MTT assay and colony formation assay revealed that combination treatment could suppress gastric cancer cells viability, proliferation and migration. In addition, DIM combined with 5-Fu significantly induce apoptosis through enhancing the degree of cleavage caspase-9 and cleaved poly ADP-ribose polymerase (PARP). Co-administration of DIM with 5-Fu resulted in a significantly increased the percentage of sub G1 phase and total apoptotic cells. Western blot also showed that MMP-9 and uPA were decreased while E-cad was increased after two drugs combination. DIM and 5-FU alone or in combination treatment could reduce the expression of nuclear β-catenin and p-Akt, c-Myc, cyclin D1 after 48 hours. In vivo study also revealed that DIM combined with 5-Fu significantly reduce tumor growth in mice with a SNU484 tumor xenograft. Therefore, DIM could strengthen the chemotherapy effect of 5-Fu on gastric cancer cells through Akt signaling pathway.
**Conclusions:** Therefore, DIM could strengthen the chemotherapy effect of 5-Fu on gastric cancer cells through Akt signaling pathway.

**Keywords:** 3'-Diindolylmethane, 5-Fluorouracil, Gastric carcinoma, Akt,Wnt

## P21-09-21

### Sirtuin 6 deacetylation TFEB induces cell autophagy in hepatocellular carcinoma

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**Purpose:** Sirtuin (SIRT)6 as a member of the sirtuin family which may be the targets in the treatment of tumors. SIRT6 was highly expressed in human hepatocellular carcinoma (HCC) cells. In this study, we investigated the role of SIRT6 in HCC cell lines, HepG2 and SNU368.
**Methods:** We performed WST-1 assay, soft agar colony formation assay, wound healing assay, western blot assay in HepG2 and SNU368 cell lines and established xenograft animal model in nude mice.
**Results:** 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. TFEB as an essential regulator modulating lysosomal pathways translocation increased in nucleus after sirt6 overexpression through mtor signaling pathway. Autophagy marker LC3-II/LC3-I and P62 was changed after SIRT6 overexpression or knockdown in HCC cells indicated sirt6 may stimulate autophagy in HCC cells. In vitro, knockdown of SIRT6 significantly promoted the tumor growth.
**Conclusions:** SIRT6 suppresses the proliferation, invasion and metastasis also induce autophagy and may play as a tumor suppressor in HCC cells.

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

## P21-09-22

### Role of TGF-β-mTORC1-NOX4 signaling in pathogenic alterations in the retinal pigment epithelium

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**Purpose:** Retinal pigment epithelium (RPE) undergoes characteristic structural changes and epithelial-mesenchymal transition (EMT) during normal aging, which are exacerbated in age-related macular degeneration (AMD). Although the pathogenic mechanisms of aging and AMD remain unclear, transforming growth factor-β1 (TGF-β1) is known to induce oxidative stress, morphometric changes, and EMT as a senescence-promoting factor.
**Methods:** We examined whether intravitreal injection of TGF-β1 into the mouse eye elicits senescence-like morphological alterations in the RPE and if this can be prevented by suppressing mammalian target of rapamycin complex 1 (mTORC1) or NADPH oxidase (NOX) signaling.
**Results:** We verified that intravitreal TGF-β1-inducedstress fiber formation and EMT in RPE cells, along with age-associated morphometric changes, including increased variation in cell size and reduced cell density. In RPE cells, exogenous TGF-β1 increased endogenous expression of TGF-β1 and upregulated Smad3-ERK1/2-mTORC1 signaling, increasing reactive oxygen species (ROS) production and EMT. We demonstrated that inhibition of the mTORC1-NOX4 pathway by pretreatment with 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), an activator of AMP-dependent protein kinase, or GKT137831, a NOX1/4 inhibitor, decreased ROS generation, prevented stress fiber formation, attenuated EMT, and improved the regularity of the RPE structure in vitro and in vivo.
**Conclusions:** These results suggest that intravitreal TGF-β1 injection could be used as a screening model to investigate the aging-related structural and functional changes to the RPE. Furthermore, the regulation of TGF-β-mTORC1-NOX signaling could be a potential therapeutic target for reducing pathogenic alterations in aged RPE and AMD.

**Keywords:** Epithelial-mesenchymal transition, Retinal pigment epithelium, Senescence, TGF-β1, MTORC1-NOX signaling

## P21-09-23

### Autocrine activation of TGF-β mediates transdifferentiation of hepatic stellate cells and liver fibrosis

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**Purpose:** Fibrotic change with excessive deposition of extracellular matrix (ECM) is a hallmark of the pathological consequences of various chronic and/or age-related diseases. In hepatic fibrosis, activated hepatic stellate cells (HSCs) transform into myofibroblast with proliferative and fibrogenic phenotypes. Particularly, transforming growth factor-β (TGF-β) signaling promotes the epithelial-mesenchymal transition (EMT) and inhibits ECM degradation in HSCs. Furthermore, isolated quiescent HSCs can be activated spontaneously during culture on a dish, the molecular mechanisms of which have not been identified. This study aimed to investigate the role of TGF-β in HSC activation related to the pathogenesis of hepatic fibrosis.
**Methods:** We used isolated primary HSCs from balb/C mice for in vitro experiments and thioacetamide (TAA)-injection or bile duct ligation (BDL) for in vivo mouse model of hepatic fibrosis.
**Results:** Culturing on a polystyrene surface for 7 days differentiated quiescent HSCs via the integrin receptor signaling, by which TGF-β was cleaved off from its precursor and released into the extracellular environment. Both extracellular and intracellular $Ca^{2}$+ were required for the spontaneous activation of integrin receptors in HSCs. Active TGF-β released from HSCs substantially phosphorylated Smad-2/-3, followed by ERK1/2 and mTOR phosphorylation, leading to NOX4 upregulation and ROS generation in an autocrine manner. Pharmacological inhibition against each step of TGF-β receptor-ERK1/2-mTOR-NOX4 pathway prevented oxidative stress and spontaneous transdifferentiation of primary HSCs. In vivo mouse model using TAA or BDL, time-dependent activation of ERK1/2-mTOR-NOX4 signaling was detected in liver tissues during fibrogenic progression. Notably, α-Klotho, known to interfere with the binding of TGF-β and its receptor, or trametinib, an inhibitor of ERK1/2 activation, suppressed in vitro transdifferentiation of HSCs. Furthermore, co-injections of trametinib or α-Klotho significantly alleviated TAA-induced liver damage and fibrosis in vivo by attenuating TGF-β-ERK1/2-mTOR signaling.
**Conclusions:** Activation of TGF-β-ERK1/2-mTORC1-NOX4 pathway has a critical pathologic role in hepatic fibrosis, which could be novel therapeutic target against chronic fibrotic diseases.

**Keywords:** Hepatic stellate cells, Hepatic fibrosis, TGF-β1, Integrin receptor

## P21-09-24

### Deficiency of SREBP-1c protects against liver fibrosis in a mouse model of nonalcoholic steatohepatitis

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**Purpose:** The sterol regulatory element binding proteins (SREBPs) are key

transcriptional regulatory proteins that sense the intracellular lipid environment and modulate expression of key genes of fatty acid and cholesterol metabolism to maintain lipid homeostasis. Nonalcoholic steatohepatitis (NASH) is a leading cause of chronic liver disease worldwide and is characterized by lipid accumulation, inflammation, and fibrosis. However, the molecular mechanism by which SREBPs regulate cell signaling pathway in NASH animal model has not been fully addressed.
**Methods:** Both male SREBP-1c knockout mice and their wild-type (WT) littermates (8 weeks old) were divided into two groups and fed a standard chow diet (control group) or high-fat, high-sucrose diet (D12327, Research Diets, New Brunswick, NJ, USA) for 20 weeks.
**Results:** We found that hepatic fat accumulation was decreased in SREBP-1c knockout (KO) mice compared with wild type mice. SREBP-1c KO mice showed reduction of hepatic fibrosis and inflammation.
**Conclusions:** We characterized that biomarkers of liver injury were transcriptionally decreased in SREBP-1c KO hepatocyte. Based on those data, we suggest that SREBP-1c is involved in chronic inflammation and fibrosis by reducing target gene expression in NASH.

**Keywords:** SREBP, NASH, Fibrosis

## P21-09-25

### Autophagy regulation in TREK1 and TREK2 overexpressed Chinese hamster ovary cells

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**Purpose:** Autophagy plays an important role in various pathophysiological conditions such as starvation, hypoxia, oxidative stress, cancer growth and is involved in the clearance of damaged organelles. Two-pore domain potassium (K2P) channels are known to maintain resting membrane potential and regulate cellular homeostasis. The relation of between K2P channels to autophagy regulation has not been well investigated. In this study, TREK1 or TREK2 (TREKs) -overexpressed CHO (Chinese hamster ovary) cells were treated with autophagy inhibitor and activator to observe changes in autophagy-related proteins such as LC3, p62, and Beclin1 ATG5.
**Methods:** For TREK transfection, CHO cell lines were maintained in alpha-MEM supplemented with 10% fetal bovine serum, and approximately 60~80% confluent cell were transfected with TREKs plasmid using lipofectamine reagent and cultured for 24 hours. Electrophysiological recording and immunoblot assay were used to confirm protein expression.
**Results:** CHO cells overexpressed with TREK were treated with an autophagy inhibitor bafilomycin A1 (50 nM) and an autophagy activator (rapamycin 200 nM) to observe changes in LC3, ATG5, ATG12, beclin1 and p62 proteins. The effects of autophagy inhibitors on the accumulation of LC3 II and the increase of p62 and beclin1 were more effective in TREKs-overexpressing cells than in TREKs-non-expressing cells. The LC3 II increased more in TREK1 than TREK2. When TREKs-overexpressed cells were exposed to starvation (serum-free growth medium), a slight accumulation of LC3 II and a slight increase in p62 were observed. Simultaneous treatment with an autophagy inducer and an autophagy inhibitor in CHO cells overexpressing TREK1 did not reduce LC3 II accumulation by autophagy inhibitors, but attenuated LC3II accumulation in CHO cells overexpressing TREK2. No significant autophagy maker protein changes were observed with TREKs overexpression alone.
**Conclusions:** The results suggest that autophagy effects may be different for TREK channels with similar physiological properties, and that autophagy modulators targeting TREK channels need to be screened more carefully.

**Keywords:** TREKs, CHO cell, Autophagy markers, P62, LC3

## P21-09-26

### IL-1 beta secreted by macrophages induces migration in A549 cells

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**Purpose:** Macrophage is known to be involved in cancer progression and migration. In addition, macrophages secrete many cytokines, among which HB-EGF and IL-1β are known to be involved in cancer progression and migration. Cell migration is induced due to actin polymerization or depolymerization, the most representative signals of the upstream signal are the cdc42 and rac1 pathways. It is known that cdc42 and rac1 interact to induce phosphorylation of PAK1 after conversion to GTP, and it has been found that cdc42 alone activates N-WASP after conversion to GTP to activate actin polymerization. In this study, we investigate the effects and mechanisms of macrophage and cytokine on the migration of A549 cells.
**Methods:** We performed WHA (wound healing assay) by treating A549 cells with macrophage culture medium, HB-EGF, and IL-1β. It was confirmed that HB-EGF and IL-1β were secreted from macrophage and TAMs (Tumor-associated macrophages) by ELISA. PAK1 and N-WSAP inhibitors were treated in A549 cells, and the effect of migration inhibition was confirmed with WHA.
**Results:** We show that a culture medium of macrophages and TAM increased the migration of A549 cells, lung cancer cells. In addition, it was confirmed that macrophages and TAM secrete HB-EGF and IL-1b. Increased secretion of HB-EGF and IL-1b further increased the migration of A549 cells. To confirm the migration pathway of A549 cells, WHA was performed using inhibitors of PAK1 and N-WASP. All groups showed a tendency to decrease migration when the inhibitor was treated.
**Conclusions:** The culture medium of macrophage increases the migration of A549 cells. The levels of HB-EGF and IL-1b, which are shown to be secreted from macrophage also increase the migration. Increased migration showed a tendency to be reduced by inhibitors of PAK1 and N-WASP, and consequently suggests the possibility of passing through the PAK1 or N-WASP pathway.

**Keywords:** Cancer, Macrophage, IL-1 beta, Migration

## P21-10-01

### Amphetamine-induced locomotor sensitization is inhibited by alteration of dendritic thin spines in the nucleus accumbens core

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**Purpose:** Psychomotor stimulants like amphetamine (AMPH), when repeatedly administered to rodents, produces behavioral sensitization, which is considered to represent a long-lasting craving for the drugs. The nucleus accumbens (NAcc), an important neuronal substrate mediating drug's rewarding and locomotor activating effects, shows increased dendritic spine densities with the development of sensitization by psychomotor stimulants. These effects may reflect a characteristic of behavioral sensitization that is maintained for long period of time as a form of long-term memory. The ezrin, radixin, and moesin (ERM) proteins play an important role in determining whether spines become mature or immature by controlling their phosphorylation at the C-terminal region.
**Methods:** In the present experiments, we first microinjected lentivirus, encoding a phosphomimetic pseudo-active mutant of radixin (Rdx T564D), in the NAcc core and repeatedly administered AMPH to those rats.
**Results:** We found that AMPH sensitization was not expressed in the rats with Rdx T564D compared to those with GFP control. Furthermore, we found that Rdx T564D increased the thin spine densities selectively more for filopodia-like thin spines, whereas AMPH sensitization by itself, compared

to acute AMPH, increased thin spine densities with a similar ratio of filopodia-like to mature thin spines.
**Conclusions:** These results demonstrate that an increase in mature thin spines is necessary for AMPH sensitization developed, and this effect can be disrupted by Rdx T564D, which drives thin spines to immaturity. The present findings suggest that dendritic thin spines in the NAcc core may be importantly involved in regulating the development of psychomotor stimulant addiction.

**Keywords:** Amphetamine, Locomotor sensitization, Nucleus accumbens, Radixin, Dendritic spine

## P21-10-02

### Genome-wide association study and gene-lifestyle interaction of gout in Korean population

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**Purpose:** Gout is a disease caused by a combination of genetic variation and environment factors. The purpose of this research is to identify single nucleotide polymorphisms (SNPs) and their association with health-related lifestyle on gout using genomic data from Korean Genome and Epidemiology Study (KoGES).
**Methods:** This research is a secondary analysis study that analyzes epidemiologic and genomic information with the utilization of HEXA based on metropolitan area and KARE based on the local community for KoGES. A total of 18,927 people were analyzed, including HEXA's gout group of 438 people and the control group of 18,489 people for the discovery stage. A total of 3,063 people were analyzed, including KARE's gout group of 326 people and control group of 2,737 for the replication stage. After then, a meta-analysis was performed using two cohorts. We analyzed the effects of lifestyle factors such as eating habits, physical activity, alcohol consumption, and smoking on gout. After identifying the association between GWAS-derived SNPs and health-related lifestyle factors, the PRS of SNPs was calculated to confirm the interaction between PRS and health-related lifestyle factors.
**Results:** 15 SNPs related to gout were found, among which rs1481012 of the ABCG2 gene (4:89039082_A/G) located on chromosome 4 was newly discovered (p=2.46E-11). When examining the interaction between SNP and health-related lifestyles, the rs3109823, located in the ABCG2 gene on chromosome 4, is associated with smoking status. rs11936395, located in the SLC2A9 gene on chromosome 4, was significantly associated with average momentum of exercise once. rs11066325 located in PTPN11 on chromosome 12, showed a significant association with the number of exercises per week, smoking status, and drinking status, respectively. It was also found that the rs200888518, located in the APP gene on chromosome 21, and the Amount of drinking once of soju significantly interact with each other. In addition, it was verified that the interaction between PRS and duration of smoking affects gout.
**Conclusions:** This study found novel SNPs related to gout and identified their association with health-related lifestyle in Korean population.

**Keywords:** GWAS, SNP, Gene-lifestyle interaction, Gout, PRS

## P21-10-03

### Sex differences in genetic polymorphisms of dyslipidemia in Korean populations

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**Purpose:** Dyslipidemia is one of the key risk factors causing coronary heart disease that defined as increase or decrease in blood lipid levels, such as LDL-Cholesterol, HDL-Cholesterol, Triglyceride, and Total Cholesterol. Although characteristics of the incidence of dyslipidemia between men and women are clearly distinguished, the exact cause has not been identified in terms of genetics. The study aimed to identify SNPs related to dyslipidemia that show sex differences in Korean cohorts through GWAS analysis.
**Methods:** Genotyping was conducted to determine genotypes of 72,298 people and investigate genotypes for 7,079,946 SNPs from Korean Genome and Epidemiology Study (KoGES) cohort. The sex, age, and BMI figures were set to covariate for genome-wide association analyses and finally significant SNPs were found through the discovery and two of replication stages using logistic regression.
**Results:** GWAS analysis of the entire study found a total of five significant SNPs: rs117026536(LPL), rs651821(APOA5), rs9804646(APOA5), rs9926440(CETP), rs429358(APOE). GWAS analysis of male subjects revealed a total of four significant SNPs. rs9804646 and rs429358 were significant in the entire study, while rs662799 and rs56156922 were significant only in the male subjects. GWAS analysis of female subjects is a total of two significant SNPs, rs651821(APOA5) and rs9804646(APOA5), both of which were significant in the entire study.
**Conclusions:** This is first study to identify a sex difference in the genetic polymorphism of dyslipidemia in Korean populations. In order to elucidate this genetic sex difference on dyslipidemia, further study considering environmental variables will be needed.

**Keywords:** Genome-wide association analysis, Dyslipidemia, Sex-difference, Korean cohorts

## P21-11-01

### A simplification of glucose-insulin model

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**Purpose:** To compose the glucose dynamic model, the glucose-stimulated insulin secretion from the pancreas is an essential part. The previous pancreatic beta-cell model made by Cobelli group, based on the experimental results of Grodsky, well explains intracellular mechanisms but complicate and time-consuming. We would like to develop a simplified and efficient model to represent the main aspects of glucose-stimulated insulin secretion.
**Methods:** In the Cobelli model, glucose-stimulated insulin secretion was represented by intermediate pool(mobilization and docking), readily releasable pool(priming and insulin granules with a certain glucose threshold), and fused pool(secretion). Readily releasable pool(RRP) is described by a time-varying density function, indicating the amount of insulin in beta-cells with a certain threshold. This density function is an integral equation, and in Cobelli model, 500 calculations are required for each time step. We simplify the Cobelli model by omitting the intermediate pool and assumes that the mobilized granules flow directly into RRP. Also, RRP is divided into RRPup and RRPdown depending on glucose stimulus. RRPup is a fraction of the silent granules and RRPdown is the remaining granules triggered to release insulin. When glucose concentration increases, the granules move from RRPup to RRPdown and vice versa. Instead of using the integral equation, the amount of releasable insulin is calculated by switching granules between RRPup and RRPdown.
**Results:** For the verification of the proposed method, we conducted a demonstration that a simplified model is efficient. The simplified model reproduced the experimental results well by fitting. In addition, we could verify the efficiency of our model by comparing the time spent to calculate the same simulation 1000 times. The simplified model performed about 620 times faster.
**Conclusions:** The results suggest that our simplified model improves the Cobelli model and is suitable for simulating glucose-stimulated insulin secretion.

**Keywords:** Glucose-stimulated insulin, Pancreatic beta-cell, Simplified model

## P21-12-01

### The structure-based designing approach revealed TMEMinh001 as a novel inhibitor of ANO1

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**Purpose:** Recent data demonstrate that anoctamin1 (ANO1), a calcium-activated-chloride channel (CaCC), is implicated in several cellular processes such as cell proliferation, cell migration, carcinogenesis, and cancer progression but gained much attention in cancer research with great pace. Accumulating evidence suggests that suppression of epidermal growth factor and calmodulin-dependent protein kinase II (CAMKII) signaling by ANO1 inhibition impede regular tumor growth, which is reported in several research studies. With this regard, combined in-vitro and in-silico approaches are carried out in our study to find a potent small molecule from some compounds that can inhibit ANO1 activity or expression in cancer cells.
**Methods:** 1. Cell culture: FRT cells line stably expressing ANO1 and CFTR. HEK293T cells and PC-9 cells.
2. Ussing Chamber-Based Analysis: Apical membrane currents were measured using the EVC4000 Multi-Channel V/I Clamp and a Data were analyzed using Lab Chart Pro 7.
3. Whole-Cell Patch Clamp Experiments: Recordings were performed at room temperature (RT) using an Axopatch 200 B (Axon Instruments, San Jose, CA, USA). Currents were digitized using the Digidata 1440 A converter (Axon Instruments), and data were filtered at 5 kHz and sampled at 1 kHz.
**Results:** Our electrophysiological study that examined some compounds discovered a novel candidate compound, TMEMinh001, which reduces ANO1 activity in PC-9 cells at IC50 10 μM value. In addition, TMEMinh001 showed the highest docking score and binding free energy than other competitive candidates.
**Conclusions:** Our current study suggests that TMEMinh001 can be a new potential compound against several cancer treatments.

**Keywords:** Anoctamin1, Apoptosis, Cancer treatment, Inhibitor

## P21-12-02

### Auraptene alleviates blood-brain barrier leakage after ischemic stroke by enhancing junction proteins through activation of antioxidant enzymes

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**Purpose:** Blood-brain barrier (BBB) integrity, protecting the brain from the infiltration of pathogens is maintained by junctional proteins in cerebrovascular endothelial cells. BBB disruption is the underlying cause of cerebrovascular disease such as ischemic stroke accompanying secondary brain injury by oxidative stress and mitochondrial dysfunction. BBB disruption allow leukocyte infiltration and neurotoxic molecules which may lead to irreversible fatal neuronal damage. To date, antiplatelet medication and antihypertensive therapy have been used for treatment of ischemic stroke. However, therapeutic agents for preventing severe secondary outcome after ischemic stroke, especially protecting BBB, should be investigated.
**Methods:** Auraptene (AUR), natural compound was treated in cerebrovascular endothelial cells Junctional proteins are investigated after oxygen-glucose deprivation (OGD), ischemic condition with AUR pretreatment. Furthermore, BBB disruption was observed in middle cerebral artery occlusion (MCAO), ischemic stroke mouse model after pre- and post-treatment of AUR by evaluating evans blue leakage assay and TTC staining
**Results:** Treatment of AUR in mouse cerebrovascular endothelial cells enhanced the junctional protein expression, such as occludin, zonula occludens-1 (ZO-1) and vascular endothelial cadherin (VE-cadherin), by increasing the levels of mRNA encoding antioxidant enzymes. In addition, pretreatment of AUR alleviates BBB disruption and brain tissue damage in MCAO ischemic stroke mouse model.
**Conclusions:** This study demonstrated that AUR may be beneficial to prevent ischemic-induced BBB disruption by enhancing junctional proteins through the upregulation of antioxidant enzymes.

**Keywords:** Auraptene, Endothelial cell, Blood-brain barrier, Ischemic stroke, Antioxidant

## P21-12-03

### Unveiling ligand based structural insights targeting SARS-CoV-2 main protease through molecular dynamics

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**Purpose:** Shikonin, a phytochemical isolated from the roots of Lithospermum erythrorhizori, has already been known for its anti-cancer, anti-oxidative stress, anti-inflammatory, anti-viral, and anti-COVID-19 effects. To date, any candidate compound against Main protease (Mpro) of SARS CoV-2 is not discovered yet, and as a result, developing a potential compound to impede Mpro regular function is of particular importance now. A recent report based on a crystallographic investigation revealed a unique shape of shikonin binding to the Main protease (Mpro) crystal, implying that shikonin derivatives could be designed as a possible candidate against Covid.
**Methods:** In Silico structure based durg design is a promising method widely followed nowadays to explore new drug targeting 3D structures of disease causing macromolecule. Towards the goal, the current study employed molecular docking and molecular dynamics simulation to explore new shikonin derivatives that target Mpro of Covid.
**Results:** A total of 25 shikonin derivatives were evaluated, with seven exhibiting higher binding affinity than shikonin and four obtaining the highest binding energy in the MM-GBSA binding energy calculation. According to molecular dynamics simulations, all candidate compounds interact with two conserved His41 and Cys145 residues in the catalytic sites via multiple bonding, implying that these derivatives may be efficient in terminating SARS COV-2 progression via Mpro inhibition.
**Conclusions:** Taken together, the present in silico study concluded that shikonin derivatives might play an effective role against Mpro inhibition.

**Keywords:** SARS COV-2, Shikonin, Molecular docking, Molecular dynamics simulation

## P21-12-04

### N-terminally truncated hERG channels generated by KCNH2 frameshift mutation (c.453delC) induces LQT phenotype in patient-derived iPSC-CMs

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**Purpose:** Patient-specific cardiomyocytes from human induced pluripotent stem cells (hiPSC-CMs) are valuable for studies in the inherited cardiac diseases. A recent study reported a single nucleotide C deletion mutation in the exon 3 of KCNH2 gene (c.453delC-KCNH2, p.151Pfs +15X in hERG) associated with LQT syndrome (Park JK et al., 2013). Since the 453delC-KCNH2 resulted the frameshift of the coding sequences, a premature termination

of translation at the N-terminal region was suggested. However, there is an additional initiation codon next to the mutated residue.
**Methods:** To elucidate the precise mechanism of LQT phenotype, we performed whole-cell patch clamp and immunoblot assay in 453delC-KCNH2 hiPSC-CMs and HEK293 cells transfected with 453delC-KCNH2.
**Results:** The 453delC-KCNH2 hiPSC-CMs showed significantly prolonged action potential duration (APD) and reduced density of the rapidly activating delayed rectifier $K^+$ current (IKr). The density of IhERG in HEK293 cells transfected with 453delC-KCNH2 was 10 % of the wild type (WT) IhERG. However, voltage dependence of activation, voltage dependence of inactivation, and deactivation kinetics of 453delC-KCNH2 were not significantly different from those of WT. To study the interaction between WT and mutant, the equimolar amounts of WT and 453delC cDNA were transfected into HEK293 cells. The current density of WT/453delC channels was half of that from the WT channel alone, indicating insignificant dominant negative effect. Immunoblot analysis of WT channel showed 150 kDa of core-glycosylated form and 180 kDa of fully-glycosylated channel. Interestingly, 453delC-KCNH2 overexpressed cells showed 135 kDa and 160kDa suggesting that the translation of shorter form, i.e. N-terminal truncated hERG, actually occurred with subsequent glycosylation.
**Conclusions:** These results suggest that 453delC-KCNH2 could escape the premature termination via a hidden initiation site. Nevertheless, the markedly reduced IhERG and the prolonged APD indicated functionally impaired state of 453delC-KCNH2, consistent with the LQT2 phenotype.

**Keywords:** Human induced pluripotent stem cells-cardiomyocyte, Long QT syndrome type 2, KCNH2 mutation

## P21-12-05

### Regulation of murine myometrial and gastric smooth muscle contraction by ginger extracts

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**Purpose:** Voltage-dependent L-type $Ca^{2+}$ channel (VDCCL ) and/or T-type $Ca^{2+}$ channel (VDCCT) in murine myometrium was identified in murine stomach and myometrium. Its regulatory functions were characterized by using extracts of ginger. Several ginger extract were used such as methanol extract of ginger, oreoleginginer, and extract from oleoresinginer and so on(Methanol extract of ginger was used to obtain dichloromethane fraction (Gin C)).
**Methods:** Conventional contractile measuring system and ginger extract were used.
**Results:** Spontaneous uterine contractions were enhanced by BayK 8644, a VDCCL activator. However, such effects were inhibited by nifedipine (a VDCCL blocker) and mibefradil (a VDCCT blocker). Mibefradil also inhibited oxytocin (OXT), prostaglandins F2a (PGF2a), and prostaglandins E2 (PGE2)-induced contractions. However, application of BayK 8644 in the presence of mibefradil recovered those contractions in a nifedipine-sensitive manner. These results suggest that both VDCCL and VDCCT are important in the regulation of murine myometrial contractions. Gin C (200 mg/mL) completely inhibited spontaneous contractions of murine uterus reversibly. The inhibition by Gin C on spontaneous contractions independent of L-NAME, $K^+$ channel blockers, and nerve blockers. High $K^+$ (50 mM)-induced contraction in the presence and absence of cyclopizonic acid (CPA) was also completely inhibited by Gin C, respectively. In addition, Gin C inhibited oxytocin (OXT; 10 nM)-induced contraction independent of L-NAME and blockers of protein kinases. Prostaglandin F2a (PGF2a)- and acetylcholine (ACh) produced contractions were also inhibited by Gin C. In murine stomach, ginger extract also increased and decreased contraction too. oleoresinginer and water fraction of ginger extracts produced increase of ACh-induced phasic contractions. These results raise the possibility that Ginger extracts inhibits spontaneous, high $K^+$ -, OXT-, PGF2a and ACh-induced contractions by inhibition of VDCCL in mouse uterine longitudinal smooth muscle. In murine stomach, oleoresinginer and water fraction of ginger extracts increased of ACh-induced phasic contractions.
**Conclusions:** It means extract from ginger have strong effective physiological and functional components for regulation of myometrial and gastric smooth muscle contractility.

**Keywords:** Myometrium, Stomach, VDCCL, VDCCT, Oxytocin, Ginger, Oleoresinginer

## P21-12-06

### Targeted downregulation of Hipp1 ameliorates tau-engendered deficits in Drosophila melanogaster

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**Purpose:** Tauopathies, such as Alzheimer's disease (AD), are neurodegenerative diseases characterized by the deposition of neurofibrillary tangles comprising hyperphosphorylated tau protein in the human brain. Given that abnormal epigenetic alterations in heterochromatin configuration have been documented in AD patients and transgenic animal models of AD, we investigated the roles of novel heterochromatin-associated interactors in tauopathies.
**Methods:** We examined whether tissue-specific downregulation or loss-of-function alleles of heterochromatin-associated interactors can affect tau-induced neurotoxicity using transgenic flies via UAS-Gal4 binary system.
**Results:** Here, we found that knockdown of HP1 and insulator partner protein (Hipp1) ameliorates tau-engendered eye defects, locomotion defects, reduced lifespan, weight loss, and neurodegeneration by preventing hyperphosphorylation of tau. Nonetheless, RNAi-mediated reduction of Hipp1 failed to restore tau-induced heterochromatin loosening; it accelerated abnormal overexpression of heterochromatic genes. Instead, knockdown of Hipp1 restored tau-driven aberrant expression of putative insulator targets and aberrant insulator-mediated epigenetic alterations. HIPP1 may have a role as an insulator binding partner regarding to be implicated in tau-induced neurodegeneration. Moreover, knockdown of Hipp1 in flies overexpressing tau restored the aberrant expression of AD susceptibility genes, Amph and Sox102F.
**Conclusions:** These results suggest that downregulation of Hipp1 expression may be a potential therapeutic target in neurodegenerative diseases; they also provide new insights regarding the roles of insulator proteins in tauopathies.

**Keywords:** Tau, Drosophila, Hipp1, Insulator

## P21-12-07

### Evaluation of image processing and reconstruction procedures for diffusion tensor imaging in ex-vivo rat brain

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**Purpose:** DTI is a relatively novel imaging method which provides information on the structure of white matter. This method is based on measuring diffusion properties of water molecules within each voxel by magnetic resonance imaging (MRI). However, researches on how to process white mat-

ter tractography in the DTI are insufficient. This study aims to establish an image processing and reconstructing procedures.
**Methods:** 27 adult Sprague-Dawley rats were used for this study. The ex-vivo DTI scans were performed on the brain. The processing procedure consisted of 4 steps; motion correction, orientation, artifact elimination, and FOV reduction. The procedure was divided into 3 conditions, and processing was performed differently. The first condition was that the reconstruction alone was performed. The second condition was to conduct reconstruction after performing steps excluding orientation. In the third condition, the image was reconstructed after all processing steps were performed. The data were reconstructed in the Waxholm Space atlas of the Sprague-Dawley rat brain using QSDR. The goodness-of-fit (R2) between the QA maps generated from individual image and the template was calculated.
**Results:** The result showed that the goodness-of-fit (R2) significantly differed across three image processing conditions. Bonferroni post-hoc results revealed that condition applied processing step, except for orientation had a significantly higher goodness-of-fit test than condition performed all the processing steps or condition conducted only reconstruction. In addition, the condition in which all the processing steps were performed showed a higher goodness-of-fit test than the condition in which only the reconstruction was performed.
**Conclusions:** These results show that it is more suitable to reconstruct the image by applying QSDR after performing the three processing steps; motion correction, artifact elimination, and FOV reduction. Applying the procedures established in this study can yield more reliable and valid ex vivo white matter information.

**Keywords:** Diffusion tensor imaging, Magnetic Resonance Imaging, Ex-vivo rat brain, Image processing, Image construction

## P21-12-08

### Development of a 3-dimensional culture model of mouse hair follicles using dermal fibroblast-grown hydrogels

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**Purpose:** The hair follicle, a skin appendage, is a complex and dynamic mini organ that undergoes a lifelong cycle of degeneration and regeneration. Aberrant hair follicle cycling causes most common types of hair loss (alopecia). Hair follicles are a target for not only a vast number of hormones, neurotransmitters and inflammatory mediators but also for drug development to treat hair loss. Therefore, in vitro hair follicle culture models as alternatives to animal testing need to be developed for drug testing as well as elucidating hair follicle biology. With an aim to develop a more physiologically relevant in vitro hair follicle culture model, we performed vibrissae hair follicle organ culture using 3D collagen hydrogels containing dermal fibroblast spheroids.
**Methods:** Vibrissae hair follicles were isolated from 2-week-old CD1 mice and cultured either in traditional liquid 2D condition or in 3D collagen hydrogels with or without derma fibroblast spheroids. After 4 week-culture of hair follicles, the lengths of hair shafts and follicles were measured using a stereo microscope and frozen sections were stained for histology and immunofluorescence.
**Results:** The lengths of hair shafts and hair follicles increased regardless of 2D or 3D culture conditions until 2 weeks. The growth rate of hair shaft was faster in 3D hydrogel environment than 2D liquid medium environment, and the presence of derma fibroblast spheroids within hydrogels further accelerate the growth rate. After 4 weeks of culture, hair follicles cultured in 2D liquid medium were disintegrated, but their integrity was well maintained in 3D hydrogel environment. The presence of dermal fibroblast spheroids within hydrogels reduced the shrinkage of hair bulbs as well as collagen hydrogels.
**Conclusions:** Our approach using collagen hydrogels containing fibroblast spheroids permits hair follicles in a more physiologically relevant extracellular matrix via epidermal–mesenchymal interactions, and enables long-term in vitro culture of hair follicles

**Keywords:** Vibrissae hair follicles, Collagen hydrogels, 3D co-culture, Dermal fibroblasts, Long-term culture

## P21-12-09

### Vasodilatory effect of Alpinia officinarum Hance extract in rat mesenteric arteries

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**Purpose:** Alpinia officinarum Hance (AO) is widely used as herbal medicine in many Asian countries. The rhizome of AO exhibited beneficial effect for anti-inflammatory, anti-oxidant, anti-hyperlipidemic effects. However, no sufficient research data are available on cardiovascular effect of AO. Thus, in this study, we investigate whether AO extract has direct effects in rat mesenteric resistance arteries.
**Methods:** To examine whether AO extract causes vasodilation, we used mesenteric arteries from 12-week-old male Sprague Dawley rats. Isometric tension was recorded for testing vascular functionality using wire myograph system. The Western blot analysis was performed to measure phosphorylation of myosin light chain (MLC20) in vascular smooth muscle cells (VSMCs).
**Results:** AO extract induced vasodilation in concentration-dependent manner and this effect was endothelium-independent. To further investigate the mechanism, we incubated arteries in $Ca^{2+}$-free and high-$K^{+}$ solution, followed by a cumulative addition of CaCl2 (0.01-2.5 mM) with or without AO extract (30 μg/ml). Pre-treatment of AO extract reduced contractile responses induced by cumulative administration of $Ca^{2+}$, which suggests that extracellular $Ca^{2+}$ influx was inhibited by treatment of AO extract. Furthermore, AO extract inhibited phosphorylation of MLC20 in VSMCs.
**Conclusions:** In the present study, we showed that AO extract induced concentration-dependent vasodilation in the rat mesenteric arteries. The vasodilatory effect of AO extract was endothelium-independent. The inhibition of extracellular $Ca^{2+}$ influx was related with AO extract-induced vasodilation, which was associated with decrease in MLC20 phosphorylation. We suggest that AO extract has therapeutic significance and could act as a vasorelaxant.

**Keywords:** Alpinia officinarum Hance, $Ca^{2+}$, Mesenteric arteries, Relaxation, Vasodilation

## P21-12-10

### ASK 최신 의대인증평가에 즈음한 충북대학교 의과대학 생리학교실의 교육 및 실습 지도 경험의 예

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충북의대 생리학교실

**Purpose:** 최근 실시되고 있는 우리나라의 의과대학 인증평가에서는 세계 의과대학의 의대 인증 평가 기준을 따르고 있어서 기존의 평가 방식과는 또 다른 매우 적극적인 교육을 요구하고 있다.
**Methods:** 이에 본 교수진은 지난 10여년 전부터 의과대학생과 교수진이 함께 보다 역동적인 교육을 제공하고자 시행 해 온 교육 방식을 제시해 보고자 한다.
**Results:** 의과대학의 블록 강좌는 이제 '통합강좌,' '기초-기초 통합 강좌' 또는 '기초-임상 통합 강좌'라는 명칭 등으로 개편되었다. 본 통합강좌에서는 일반적인 학과별 강의를 넘어 장기별로 강의가 바뀐 것으로 이 체계는 이미 의과대학의 교수진이나 학생들이 지도하고 배움으로써 충실히 잘 수행되고 있다. 본 교수진은 이러한 시스템을 더 보완하여 학생들이 졸업 후 연구 및 의료환경에 필요한 부분까지도 개발을 할 수 있는 보다 더 능력이 있는 의사로 교육하고 있다. 즉 통합강좌에서는 이론 지식만이 아닌 문제풀이나 증례 지도를 강화하였으며 실습 부분에서도 의예-의학과에 걸친 교수진/학생 매칭 연구 지도 수업에도 참여하고 있다. 이때 학생들에게 더 적극적인 실제 연구 및 개발의 경험을 주기 위해 각종 새로운 연구방법, 아이디어 특허 출원/등록, 논문 작성 및 재학생으로서 국가연구사업에도 함께 참여 하는 등의 지도를 진행하고 있다.

**Conclusions:** 이러한 교육과정은 졸업 후까지도 학생들과 연결이 되어 있으며 지속적인 교육, 공동 논문 작성 및 특허 등록이 이루어 지고 있다. 이러한 성공적인 교육 사례를 보고하고자 한다.

**Keywords:** 의학교육, 교육과 실습, 의대인증평가, 연구 지도 수업, 개발 지도 수업

## P21-12-11

### Effects of chondroT on monosodium iodoacetate (MIA) induced osteoarthritis rats

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**Purpose:** Osteoarthritis is a disease that causes inflammation and pain due to continuous damage to the cartilage part that protects the joint or damage to the structure(bone, ligament, etc.) that forms the joint, and pain in the joint area is the most common symptom. Research using Korean medicine is increasing to treat or prevent osteoarthritis. In previous studies, after selecting medicines with ingredients that can improve osteoarthritis, the newly combined ChondroT was extracted with water to confirm the effectiveness of improving osteoarthritis. In this study, the effectiveness of 30% and 60% alcohol extract was observed to compare and verify the effectiveness of improving osteoarthritis according to the ChondroT extraction method.

**Methods:** The experimental groups were divided into (1) normal group, (2) arthritis induced group, (3) oral administration of Joins tab after arthritis induced, (4) oral administration of ChondroT water extract after arthritis induced(W-CT), (5) oral administration of ChondroT 30% alcohol extract after arthritis induced(30% A-CT), (6) oral administration of ChondroT 60% alcohol extract after arthritis induced(60% A-CT) group. Monosodium Iodoacetate was dissolved in saline to induce arthritis. The left knee was injected with 50μl and the ankle with 25μl. The drug was administered once a day for 10 days from the 8th day after arthritis was induced.

**Results:** In the measurement of allodynia, all treatment groups significantly decreased after treatment. TNF-α, an inflammatory cytokine, was significantly reduced in all treatment groups compared to the control group, and IL-6 was significantly reduced in W-CT and 60% A-CT compared to the control group. IL-10, an anti-inflammatory cytokine, was significantly increased in all treatment groups compared to the control group.

**Conclusions:** ChondroT according to the extraction method was found to have effective effects on TNF-α, IL-6, and IL-10, which are cytokines related to inflammatory pathways, and all three samples of water extract and 30% and 60% alcohol extract in osteoarthritis mice induced by Monosodium Iodoacetate. Since the water extracts showed similar levels to those of 30% and 60% alcohol extracts, it is considered that the extraction method of this material may be performed by the hydrothermal extraction method.

**Keywords:** ChondroT, Osteoarthritis, MIA, Alcohol extract, Water extract

## P21-12-12

### A study on the anti-inflammatory effect of Herbal medicine mix (modified Iksuyongjingo) in LPS-induced inflammatory mice

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**Purpose:** Lipolysaccharide(LPS) causes endotoxemia during intraperitoneal(i.p.) or intravenous(i.v.) injection. Recognition of LPS by TLR4 activates the NF-kB pathway and induces expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1b. Previous studies have confirmed an increase in the expression of IL-6, IL-1b, TNF-α, and IL-10 when inducing inflammation by LPS in rat. Therefore, in this study, an experiment was conducted to confirm the anti-inflammatory effect of the Herbal medicine mix (modified Iksuyongjingo) in the LPS-induced inflammatory mouse model.

**Methods:** The experimental groups were divided into (1) normal group, (2) LPS induced group, (3) oral administration of silymarin, (4) oral administration of 100 mg/kg Iksuyongjingo and (5) oral administration of 200 mg/kg Iksuyongjingo group. In this study, drug oral administration was performed once a day for 7 days, and lipopolysaccharide was injected into the intraperitoneal on the 7th day to cause inflammation.

**Results:** In the blood biochemical test, aminotransferase levels increased in the control group compared to the normal group, and aminotransferase tended to decrease in the drug administration group. IL-1β, a pro-inflammatory cytokine, increased in the control group compared to the normal group, and tended to decrease in the treatment group compared to the control group. As a result of PCR analysis of liver tissue in experimental mice, the expression of TNF-α, an inflammatory cytokine, increased in the control group compared to the normal group, and the drug administration group tended to decrease compared to the control group.

**Conclusions:** The Herbal medicine mix (modified Iksuyongjingo) used in this experiment is expected to have an anti-inflammatory effect in inflammatory model mice induced by LPS. For the subject matter of this study, we intend to continuously search and study the effective path through additional indicator confirmation of the NF-kB pathway and its effect on the expression of cytokine.

**Keywords:** Anti-inflammatory, Herbal medicine mix (modified Iksuyongjingo), Lipolysaccharide(LPS), Cytokine , Aminotransferase

## P21-12-13

### Daeyeongjeon ameliorates particulate matter 2.5-induced lung and vascular injury via NLRP3 dependent inflammasome pathway

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Environmentally generated particulate matter (PM2.5) has been injury to lung, blood vessel and other organs, as focusing on inflammation and oxidative stress tightly linked to respiratory disease such as asthma, bronchial allergy. Diesel exhaust particles (DEP) is a major PM2.5 emitted by motor vehicles and includes polycyclic aromatic hydrocarbons (PAHs). Herbal formula Daeyeongjeon (DYJ) has been used in the clinic to treat menstrual deficiencies, infertility and menopause disorder caused by blood shortages. The present study aimed to investigate that DYJ ameliorated lung and cardiovascular injury and its related mechanisms in PM2.5 stimulation. DYJ was administrated to C57BL/6 mice at dose of 100, 300 mg/kg/day for 2 weeks. In vitro study using Human umbilical vein endothelial cells (HUVEC) was also performed. PM2.5 triggered adhesion molecules and pro-inflammatory cytokines. The expression of inducible CXCL1 and CXCL2 in bronchoalveolar lavage fluid and Muc5ac, ICAM-1, TNF-α, IL-6 mRNA in lung were also attenuated by DYJ. In thoracic aorta, histological changes demonstrated that the administration of DYJ protected vascular damage. PM2.5 increased cell adhesion molecules and inflammasome markers such as NLRP3, Caspase-1, ASC, TNF-α. In HUVECs, treatment with DYJ suppressed PM2.5-induced pro-inflammatory factors and cell adhesion molecule expression in a dose-dependent manner, suggesting a possible role of the inhibition of atherosclerosis. Taken together, this study proved that exposure to PM2.5 induced both lung and vascular inflammation, however, DYJ attenuated this injury via the downregulation of the NLRP-dependent inflammasome signaling pathway. These findings suggest that Daeyeong-

jeon may have potential therapeutic benefit against air pollution-mediated lung and cardiovascular diseases.

**Keywords:** Daeyeongjeon, Particulate matter, NLRP3, CXCL, TNF-α, CAMs

## P21-12-14

### Protective Effect of Gunryeong-tang on Diabetic Cardio-renal Syndrome in db/db Mice

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Diabetes is a group of metabolic problems featuring chronic hyperglycemia. GRT(Gunryeong-tang) is a traditional oriental herbal formula for the treatment of acute and chronic nephritis, which is used to promote water retention and reduce swelling. However, this is no study on the use of GRT to improve cardiorenal function, so this study was investigated whether GRT alleviated diabetic nephropathy and diabetic cardiovascular injury in db/db mice. The db/m mice and db/db mice were physically divided into db/m control, db/db control, db/db treated with Vildagliptin (50 mg/kg/day) or db/db treated with GRT (200 mg/kg/day) and their age-matched littermates were used. Mice were treated with GRT for 8weeks and tested for impact on metabolic derangements and diabetic nephropathy as well as renal fibrosis. GRT significantly improved creatinine (CRE) and blood urea nitrogen (BUN) in plasma. Moreover, GRT reduced the intensity of the periodic acid Schiff (PAS) staining, glomerular dilation and tubular fibrosis in db/db model. GRT inhibited type I collagen and prevented tissue fibrosis by interfering with transforming growth factor beta (TGF-β)-Smad signaling. In addition, cardiac dysfunction was alleviated in diabetic mice following GRT treatment, while myocardial hypertrophy and fibrosis were reduced. Furthermore, GRT depressed the nuclear translocation of nuclear factor-kB (NF-kB) and Smads, and reduced the transcriptional activity of NF-kB and Smads. In particular, the expression levels of transforming growth factor (TGF)- β1 and collagen1, which are target downstream molecules of the NF-kB and Smads signaling pathways, were also reduced in the diabetic heart. Apoptosis of cardiac cells was then confirmed by Western Blot, which revealed that GRT effectively ameliorated apoptosis in the db/db model. Taken together, our results suggest that GRT has a protective effect on the heart and kidneys in the db/db mice, and therefore, GRT will be an excellent treatment option.

**Keywords:** Diabetic nephropathy; fibrosis; myocardial hypertrophy; TGF-β signaling.