UKorea
www.ukorea.ac.uk

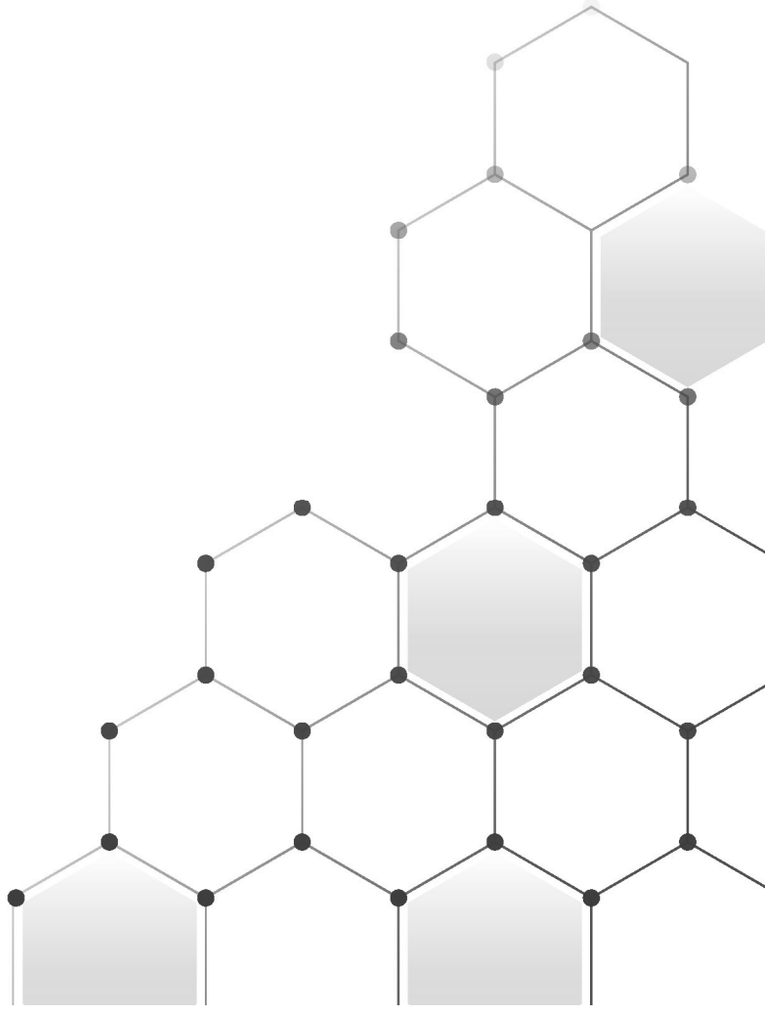
The 11th

UK-KOREA Neuroscience Symposium

20-21 August 2018

Hotel Shilla Stay, Haeundae, Busan, Korea

https://www.ukorea.ac.uk/



ibs 기초과학연구원 Institute for Basic Science

MRC Medical Research Council

UK-Korea Committee 2018

Laura Andreae	(King's College London)
Kei Cho	(King's College London)
Morgan Sheng	(Genentech)
John Isaac	(J&J London Innovation Centre)
Peter St George Hyslop	(University of Cambridge)
Inhee Mook-Jung	(Seoul National University)
Hee-Sup Shin	(IBS)
Kyungjin Kim	(KBRI-DGIST)
Seong-Gi Kim	(IBS-SKKU)
Eunjoon Kim	(IBS-KAIST)

PROGRAM DAY 1 (August 20, 2018) Ballroom (3F)

TIME	PROGRAM
08:00-09:10	Registration
09:10-09:20	**Opening Address** - Kyungjin Kim (KBRI-DGIST) & Mark Palmer (MRC)
Plenary Lecture 1	*Chair: Eunjoon Kim*
09:20-10:00	High resolution fMRI at ultra high fields Seong-Gi Kim (IBS-SKKU)
10:00-10:30	*Coffee Break*
Session 1: Computational Neuroscience	*Chair: Albert Lee*
10:30-11:00	Synaptic plasticity as probabilistic inference Peter Latham (University College London)
11:00-11:30	A simulation-selection model of the hippocampus Min Whan Jung (IBS-KAIST)
11:30-12:00	The statistical structure of hippocampal representations Albert Lee (HHMI, Janelia Farm)
12:00-14:00	*Lunch* Restaurant (2F)
14:00-14:30	[Debate] Algorithm of Neuroscience: Smart challenge for solid conclusion? (30 min) Co-Chairs: Gail McConnell, Peter Latham Panels: Mathew Horrocks, Albert Lee, Morgan Sheng, Daniel Whitcomb, Seong-Gi Kim
14:30-15:50	Group-A Poster Session & *Coffee Break* Meeting Room (5F)
Poster Short-Talks	*Chair: Daniel Whitcomb & Min Whan Jung*
15:50-16:00	Using the power of Dementias Platform UK (DPUK) cohorts to investigate the effects of childhood adversity on adult behavioural, physiological, cognitive and dementia outcomes: A cross-cohort investigation Sarah Bauermeister (University of Oxford)
16:00-16:10	Mossy fiber stimulation induces transient and inhibitory impact on CA3 neuronal activity in freely-moving mice Joonyeup Lee (Center for Synaptic Brain Dysfunctions, IBS)
16:10-16:20	Reactivation in biological and artificial neural networks Gido Van de Ven (University of Oxford / Baylor College of Medicine)
16:20-16:30	Restless days and sleepless nights Haram Park (Center for Synaptic Brain Dysfunctions, IBS / KAIST)
16:30-17:00	*Coffee Break*
17:00-17:10	Activation of distinct estrogen receptors in vitro can mediate the prevention and recovery of Amyloid-β induced synaptotoxicity Iain Watson (King's College London)
17:10-17:20	Neural representations of ensemble coding in occipital and parietal cortex Kyeong-Jin Tark (Center for Neuroscience Imaging Research, IBS)
17:20-17:30	Direct in-cell observation of structural progression of amyloid-β Arctic mutant aggregation Meng Lu (University of Cambridge)
17:30-17:40	In vivo imaging reveals regrowth of serotonin axons following injury in the adult mouse brain Yunju Jin (Center for Cognition and Sociality, IBS)
17:40-17:50	The divergent role of Frizzled receptors in synapse connectivity and plasticity Faye McLeod (University College London)
17:50-18:00	Mouse BOLD fMRI at the ultrahigh-fields of 9.4T and 15.2T: Detection of sensory pathways including thalamic nuclei Won Beom Jung (Center for Neuroscience Imaging Research, IBS)
18:30-20:30	*Welcome Dinner*

PROGRAM DAY 2 (August 21, 2018) Ballroom (3F)

TIME	PROGRAM	
Plenary Lecture 2		*Chair: Inhee Mook-Jung*
09:00-09:40	Molecular and cellular mechanisms of synapse loss in Alzheimer's disease **Morgan Sheng** (Genentech)	
Session 2: Innovative Imaging for Neuroscience		*Chair: Hee-Sup Shin*
09:40-10:10	Optical mesoscopic imaging of the brain with the Mesolens **Gail McConnell** (University of Strathclyde)	
10:10-10:40	Optogenetic control of diverse molecular and cellular processes in the mouse brain **Won Do Heo** (IBS-KAIST)	
10:40-11:10	Optical nanoscopy for the characterisation of protein aggregates in neurodegenerative disorders **Mathew Horrocks** (University of Edinburgh)	
11:10-11:40	*Coffee Break*	
Session 3: Cellular and Molecular Environment of Disease		*Chair: Morgan Sheng*
11:40-12:10	Tauopathies and synapse weakening in the hippocampus **Kei Cho** (King's College London)	
12:10-12:40	Tau-based therapeutic approaches for Alzheimer's disease **Inhee Mook-Jung** (Seoul Natl University)	
12:40-14:40	*Lunch*	Restaurant (2F)
14:40-15:50	Group-B Poster Session & *Coffee Break*	Meeting Room (5F)
Poster Short-Talks		*Chair: Won Do Heo & Albert Lee*
15:50-16:00	CRISPR/Cas9-mediated downregulation of PMP22 ameliorates Charcot-Marie-Tooth disease 1A in mice **Jae Young LEE** (ToolGen Inc.)	
16:00-16:10	Identification of compounds and drug targets that enhance TDP-43 clearance in ALS and FTD **Alinda Fernandes** (King's College London)	
16:10-16:20	MAPK-dependent presynaptic potentiation in the LHb is responsible for depressive behaviors **Hoyong Park** (Konkuk University)	
16:20-16:30	Postsynaptic p47phox controls long-term depression in the hippocampus **Jee Hyun Yi** (University of Bristol / KAIST)	
16:30-17:00	*Coffee Break*	
17:00-17:10	Effects of cell type-specific Shank3 deletion **Taesun Yoo** (Center for Synaptic Brain Dysfunctions, IBS / KAIST)	
17:10-17:20	Alzheimer's disease-like pathology in Cyfip2+/- mice **Anshua Ghosh** (King's College London)	
17:20-17:30	Characterization of synaptic and behavioral phenotypes in mice carrying a de novo Shank3 mutation Q321R **Ye-Eun Yoo** (Center for Synaptic Brain Dysfunctions, IBS / KAIST)	
17:30-17:40	The effects of apolipoprotein E (ApoE) polymorphism on human hippocampal neurogenesis **Hyunah Lee** (King's College London)	
17:40-17:50	Somatostatin interneurons in the anterior cingulate cortex gate mouse observational fear **Arie Kim** (Center for Cognition and Sociality, IBS)	
17:50-18:00	A tauopathy-associated tau fragment causes autophagic dysfunction **Dina Dakkak** (King's College London)	
18:00-18:10	**Closing Remarks** - Hee-Sup Shin (IBS)	
18:30-20:30	*Symposium Dinner*	

August 20, 2018

Ballroom (3F)

Plenary Lecture 1 09:20-10:00

Chair: Eunjoon Kim (IBS-KAIST)

Symposium 10:30-12:00

Session 1: Computational Neuroscience

Chair: Albert Lee (HHMI, Janelia Farm)

Poster Short-Talks 15:50-18:00

Chair: Daniel Whitcomb (University of Bristol) & Min Whan Jung (IBS-KAIST)

Poster Presentation 14:30-15:50

Poster Group-A

August 21, 2018

Ballroom (3F)

Plenary Lecture 2 09:00-09:40

Chair: Inhee Mook-Jung (Seoul Natl University)

Symposium 09:40-11:10

Session 2: Innovative Imaging for Neuroscience

Chair: Hee-Sup Shin (IBS)

Symposium 11:40-12:40

Session 3: Cellular and Molecular Environment of Disease

Chair: Morgan Sheng (Genentech)

Poster Short-Talks 15:50-18:00

Chair: Won Do Heo (IBS-KAIST) & Albert Lee (HHMI, Janelia Farm)

Poster Presentation 14:40-15:50

Poster Group-B

The 11th UK-KOREA Neuroscience Symposium

20-21 August 2018

Hotel Shilla Stay, Haeundae, Busan, Korea

Plenary Lecture

Plenary Lecture 1

Chair: Eunjoon Kim (IBS-KAIST)

Plenary Lecture 2

Chair: Inhee Mook-Jung (Seoul Natl University)

Plenary Lecture 1

High resolution fMRI at ultra-high fields

Seong-Gi Kim

Center for Neuroscience Imaging Research, Institute for Basic Science, Suwon, Korea;
Department of Biomedical Engineering, Sungkyunkwan University, Suwon, Korea

Magnetic resonance imaging (MRI) is a powerful non-invasive imaging tool to visualize brain structure, connectivity, function and chemistry non-invasively. Especially, high-resolution fMRI is increasing used for mapping functional networks in whole brains at a fine scale. In human fMRI studies, one millimeter isotropic resolution has been obtained at 7 Tesla (T) with states-of-the-art methodologies. In animal studies, even higher spatial resolution is needed for matching brain resolution due to the different brain size (e.g., 20cm in humans vs. ~ 2cm in rats), which requires the improvement of fMRI methodologies, and understands fundamental spatial limits. My lab has been working on underlying biophysics, sensitivity, specificity, and limits of fMRI with animal models. In my talk, several issues will be discussed, including fMRI sensitivity at ultrahigh fields of 9.4T and 15.2T, high-resolution fMRI of anesthetized mouse, and a spatial limit of hemodynamic regulation.

Plenary Lecture 2

Molecular and cellular mechanisms of synapse loss in Alzheimer's disease

Morgan Sheng

Genentech

Synaptic dysfunction and synapse loss are hallmarks of Alzheimer's disease (AD) and other tauopathies, yet the underlying molecular pathomechanism remains largely undefined. Here, we used unbiased proteomic analysis of postsynaptic density (PSD) proteins from wild-type versus Tau- P301S transgenic mice before the onset of overt neurodegeneration to identify early tau-dependent changes in the synapse. PSDs from tauopathy mice showed a specific depletion of a set of small GTPase regulatory proteins that regulate postsynaptic actin cytoskeleton, which could contribute to spine and synapse loss. Furthermore, we discovered that C1q, initiator of the classical complement cascade, is strikingly increased in PSDs purified from Tau-P301S hippocampus, and that C1q is localized at synapses. Tau-P301S brains had increased engulfment of synaptic material by microglia. Moreover, C1q-neutralizing antibodies suppressed microglial synapse clearance in neuron-microglia co-cultures and in vivo in Tau-P301S mice, resulting in rescue of synapse density. These findings suggest that tau pathology induces tagging of synapses by C1q, leading to removal of synapses by microglia, and raise the possibility that C1q-neutralizing antibodies might be a potential approach to mitigate synapse loss in AD.

Symposium

Session 1:
Computational Neuroscience

Chair: Albert Lee (HHMI, Janelia Farm)

Session 1: Computational Neuroscience

Synaptic plasticity as probabilistic inference

Peter Latham

University College London

Organisms face a hard problem: based on noisy sensory input, they must set a large number of synaptic weights. However, they do not receive enough information in their lifetime to learn the correct, or optimal weights (i.e., the weights that ensure the circuit, system, and ultimately organism functions as effectively as possible). Instead, the best they could possibly do is compute a probability distribution over the optimal weights. Based on this observation, we hypothesize that synapses represent probability distributions over weights-in contrast to the widely held belief that they represent point estimates. From this hypothesis, we derive learning rules for both supervised and unsupervised learning. This introduces a new feature: the more uncertain the brain is about the optimal weight of a synapse, the more plastic it is. Consequently, the learning rate of each synapse is adjusted on the fly. This framework makes several testable predictions and, combined with the ansatz that more uncertain synapses are more variable, it is consistent with current data.

Session 1: Computational Neuroscience

A simulation-selection model of the hippocampus

Min Whan Jung[1], Hyunjung Lee[2], Yeong Seok Jeong[1], Jong Won Lee[1] & Inah Lee[3]

[1]Center for Synaptic Brain Dysfunctions, Institute for Basic Science
[2]Department of Anatomy, Kyungpook National University School of Medicine
[3]Department of Brain and Cognitive Sciences, Seoul National University

Despite tremendous progress, the neural circuit dynamics underlying hippocampal mnemonic processing remain poorly understood. We proposed a new model of hippocampal function-the simulation-selection model-based on recent experimental findings and neuroecological considerations. Under this model, the mammalian hippocampus evolved to simulate and evaluate arbitrary navigation routes. Specifically, we suggest that CA3 evolved to simulate unexperienced navigation sequences in addition to remembering experienced ones, and CA1 evolved to select from among these CA3-generated sequences, reinforcing those that are likely to maximize reward. We argue that the simulation-selection organization of the hippocampus has evolved in mammals, but not in birds, because of the unique ecological and navigational needs of land animals. Although solid empirical evidence is missing for many aspects of our model, it may account for why the mammalian hippocampus has evolved not only to remember, but also to imagine episodes, and how this might be implemented in its neural circuits.

Session 1: Computational Neuroscience

The statistical structure of hippocampal representations

Albert Lee

HHMI, Janelia Farm

The hippocampus plays a central role in the brain's representation of the external environment and, in humans, the encoding of long-term, consciously recallable memories of daily experience. In the rodent, the phenomenon of place cells and their associated receptive fields is the most prominent feature of the hippocampal representation of space. Our previous work involving intracellular recordings of rodent hippocampal neurons in freely moving animals indicated that these cells differed from each other in their excitability, and that these differences were reflected in the level of place field activity expressed. Subsequent extracellular recordings from populations of hippocampal neurons in rodents exploring large environments allowed us to statistically characterize these differences across cells and develop a simple generative model of hippocampal representations of space. Most recently, we have performed 2-photon calcium imaging of large populations of hippocampal neurons in mice exploring virtual spatial environments. This has allowed us to describe the statistics of place field representations across multiple environments and over long periods of time. The implications of our findings for the mechanisms of memory formation and navigation will be discussed.

The 11th UK-KOREA Neuroscience Symposium

20-21 August 2018

Hotel Shilla Stay, Haeundae, Busan, Korea

Symposium

Session 2:
Innovative Imaging for Neuroscience

Chair: Hee-Sup Shin (IBS)

Session 2: Innovative Imaging for Neuroscience

Optical mesoscopic imaging of the brain with the Mesolens

Gail McConnell

University of Strathclyde

For more than a century, the design of low-magnification microscope objectives has been guided by the angular acuity of the human eye (approximately 1 second of arc). At x4 magnification, this requires a numerical aperture no greater than 0.1 or 0.2, which can be achieved cheaply and easily by simple optical designs. With the advent of confocal and multiphoton microscopy, however, it became apparent that the poor axial resolution of more than 30 microns with low magnification objectives was intolerable for these 3D methods.

To overcome this, we have developed a new and complex objective with a magnification of 4x and an NA of just less than 0.5 which we call the Mesolens. We specified this lens for mammalian embryology, and have shown that it can image every cell of a 6mm-long embryo 3mm thick with sub-cellular resolution if the tissue is cleared appropriately. A by-product of the high NA is that the optical throughput is approximately 20x greater than a conventional 4x objective. The pupil size of the lens is so great that it cannot be used with a conventional microscope frame, so we have built the imaging system around the lens, and use either wide-field camera or point-scanning fluorescence detection to create images. We have used the lens for a number of applications in biology, including imaging of whole e12.5 mouse embryos, and whole adult Drosophila and other insect models without dissection. We have established a mesoscopic imaging centre (http://www.strathclydemesolab.com) to give researchers worldwide access to this new technology.

I will present recent results from imaging of mouse brain tissue, and discuss our plans for future optical mesoscope development and applications at the University of Strathclyde, UK.

Session 2: Innovative Imaging for Neuroscience

Optogenetic control of diverse molecular and cellular processes in the mouse brain

Won Do Heo

[1]Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea
[2]Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon, Republic of Korea

My group has been developing various bio-imaging and optogenetic tools for the study of cell signaling in live cells as well as neuronal functions in vivo. Novel optogenetic toolkit developed by my group is highly advantageous compared with conventional approaches in that it allows finely manipulated signaling pathways in a spatial and temporal resolution, thereby making it possible to dissect and analyze the transient dynamics of signaling processes within a defined period. These tools are very useful not only for imaging based researches in cell biology, but also for the studies in neuroscience. Recently developed optogenetic strategies have brought significant changes the way in which signaling in living cells is studied in neurobiology and other disciplines. Novel optogenetic toolkit my group has been developing are capable of providing what channelrhodopsins could not offer previously, contributing in a disparate perspective of neuroscience. We are applying the new technologies to the study of spatiotemporal roles of signaling proteins and second messengers in synaptic plasticity and learning and memory in normal and disease mouse models.

References

1. Park H*, Kim NY*, Lee S, Kim N, Kim JH, **Heo WD.** Optogenetic protein clustering through fluorescent protein tagging andextension of CRY2. **Nature Communications.** 2017 Jun 23. doi: 10.1038/s41467-017-00060-2.
2. Nguyen MK, Kim CY, Kim JM, Park BO, Lee S, Park H, Heo WD. Optogenetic oligomerization of Rab GTPases regulates intracellular membrane trafficking. **Nature Chemical Biology.** 2016 Apr 11. doi: 10.1038/nchembio.2064. [Epub ahead of print].
3. Kyung T*, Lee S*, Kim JE, Cho T, Park H, Jeong YM, Kim D, Shin A, Kim S, Baek J, Kim J, Kim NY, Woo D, Chae S, Kim CH, Shin HS, Han YM#, Kim D#, **Heo WD#.** Optogenetic control of endogenous Ca(2+) channels in vivo. **Nature Biotechnology (Cover Article).** 2015 Sep 14. doi: 10.1038/nbt.3350.
4. Lee S*, Park H*, Kyung T, Kim NY, Kim S, Kim J, **Heo WD.** Reversible protein inactivation by optogenetic trapping in cells. **Nature Methods.** 2014 Jun;11(6):633-6. doi: 10.1038/nmeth.2940. Epub 2014 May 4.
5. Chang KY*, Woo D*, Jung H, Lee S, Kim S, Won J, Kyung T, Park H, Kim N, Yang HW, Park JY, Hwang EM, Kim D, **Heo WD.** Light-inducible receptor tyrosine kinases that regulate neurotrophin signalling. **Nature Communications.** 2014 Jun 4;5:4057. doi: 10.1038/ncomms5057.

Session 2: Innovative Imaging for Neuroscience

Optical nanoscopy for the characterisation of protein aggregates in neurodegenerative disorders

Mathew Horrocks

University of Edinburgh

The aberrant misfolding and aggregation of soluble proteins into amyloid fibrils characterizes many neurodegenerative disorders, including Parkinson's and Alzheimer's disease. The ability to study such processes has remained difficult due to the heterogeneity and low abundance of the aggregates along the fibril-formation pathway. Many such species are smaller than the diffraction limit of light (~250 nm), and so imaging them in high enough resolution with optical microscopy has been limited. We report here a method, termed ADPAINT (aptamer DNA PAINT), for the characterization of amyloid species at the nanometer scale. Using a combination of DNA PAINT and an amyloid specific aptamer, we demonstrate that this technique is able to detect a whole range of aggregates species along the aggregation pathway of alpha-synuclein, allowing for the earliest formed oligomers as small as 50 nm to be imaged in high detail, both within cells and in the test tube.

The 11th UK-KOREA Neuroscience Symposium

20-21 August 2018

Hotel Shilla Stay, Haeundae, Busan, Korea

Symposium

Session 3:
Cellular and Molecular Environment of Disease

Chair: Morgan Sheng (Genentech)

Session 3: Cellular and Molecular Environment of Disease

Tauopathies and synapse weakening in the hippocampus

Kei Cho

United Kingdom Dementia Research Institute at King's College London

Department of Basic and Clinical Neuroscience,Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom

Functional weakening/reduction of synapse size is thought to correlate with the severity of neurodegenerative diseases. In this context, the most extensively studied set of mechanisms thought to underlie learning and memory are the processes referred to collectively as synaptic plasticity. Changes to the synaptic expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, a family of excitatory glutamate receptors, is considered a major component of synaptic plasticity. The molecular mechanisms of synaptic plasticity specifically, and synaptic connectivity more broadly, can be severely dysregulated by disease. For instance, amyloid-beta (Aβ) oligomer accumulation and phosphorylation of microtubule associated protein tau (pTau) are central components of neurodegenerative diseases such as Alzheimer's disease (AD), and are known to impair the dynamic function of synapses.

Evidence suggests that synaptic dysfunction and aberrant decomposition of dendritic spines occurs prior to Aβ/Tau plaque and tangle formation. Similarly, several strands of research have underscored the importance of mechanisms of synapse weakening, in particular AMPA receptor (AMPAR) endocytosis, to synaptic dysfunction associated with early stage models of neurodegenerative disease. We have previously shown that the caspase-3→Akt1→glycogen synthase kinase-3 beta (GSK-3β)→pTau cascade is involved in Aβ-mediated pathophysiological synaptic dysfunction in the hippocampus. This led us to hypothesise that synapse loss in disease is underpinned by the aberrant activation of synapse weakening signalling. If correct, understanding the mechanisms of synapse weakening and its molecular regulation (e.g., AMPAR endocytosis) is of paramount importance in the quest to determine the initial catalyzing stages of synapse dysfunction and neurodegeneration.

Session 3: Cellular and Molecular Environment of Disease

Tau-based therapeutic approaches for Alzheimer's disease

Inhee Mook-Jung

Department of Biochemistry and Biomedical Sciences, Seoul National University College of Medicine

A large portion of dementia patients are suffering from Alzheimer's disease (AD). AD has two typical pathological phenotypes, neurofibrillar tangle (NFT) and amyloid beta (Aβ) plaques. NFTs are composed of tau protein aggregates. Tau undergoes diverse post translational modifications (PTMs) such as phosphorylation, ubiquitination, glycosylation and acetylation. PTMs are considered as important features of abnormal pathological tau. This study focused on acetylation by inhibiting HDAC6 (histone deacetylase 6) in AD pathology because acetylated tau contributed for AD pathogenesis. Axonal transport deficit caused by Aβ was recovered by up-regulating acetylation level by HDAC6 inhibitor (H6I) in primary hippocampal neuron culture. Acetylation level was increased by intraperitoneal injection of H6I on AD mice model, resulting in significant recovery of memory deficits. H6I also reduced phosphorylated tau in sarkosyl-insoluble fraction and AT 180 immuno-reactive tau in these mice. With these data, we suggest targeting HDAC6 inhibition is a good therapeutic target by reduction of tau burden in AD.

Poster Short-Talks

August 20, 2018

(15:50-18:00)

Chair: Daniel Whitcomb (University of Bristol) & Min Whan Jung (IBS-KAIST)

Abstract A1

Using the power of Dementias Platform UK (DPUK) cohorts to investigate the effects of childhood adversity on adult behavioural, physiological, cognitive and dementia outcomes: A cross-cohort investigation

Sarah Bauermeister, John Gallacher

The University of Oxford

Childhood adversity is a construct encompassing extre8me difficulties and adverse childhood experiences (ACE) such as sexual, physical and emotional abuse and deprivation. Experiencing adversity within childhood alters the life of a child to an extent that it may change biological processes which lead to adverse biomedical health outcomes in adulthood (Mehta et al., 2013), and dementia (Radford et al., 2017). Our aim is to investigate associations between childhood adversity and adult
health-related outcomes, cognition and dementia utilising questionnaire data from DPUK cohorts: Whitehall II, UK Biobank and MRC NSHD.

A preliminary analysis from 123 945 UK Biobank participants was conducted using structural equation modelling. Individual ACE variables formed a latent construct of childhood adversity and multiple adult outcomes were entered, adjusting for socioeconomic status, education and, selectively, age (e.g., BMI, medications, vascular health and cognition). Childhood adversity significantly predicted (all *p*s < .000) higher frequency of alcohol intake, younger sexual activity and onset of smoking, poorer vascular health, increased medication usage and BMI, higher neuroticism, increased self-reported depression and neuroticism, lower levels of overall happiness and poorer cognition. The other cohorts with their rich cognitive data are being analysed to further investigate the effect on adult cognition and dementia outcomes.

References:

Mehta, N.M., Corkins, M.R., Lyman, B., Malone, B., Malone, A., Goday, P.S., Carney, L.N.,… (2013).
Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions.
JPEN J Parenter Enteral Nutr. 37(4):460-481.

Radford, K., Delbaere, K., Draper, B., Mack, H.A., Daylight, G., Cumming, R., Chalkley, S., Monogue, C., & Broe, G.A. (2017). Childhood stress and adversity is associated with late-life dementia in boriginal Australians. Am J Geriatr Psychiatry. 25(10):1097-1106.

Abstract B8

Mossy fiber stimulation induces transient and inhibitory impact on CA3 neuronal activity in freely-moving mice

Joonyeup Lee[1,2], Miru Yun[1,2], Eunjae Cho[2], Jong Won Lee[2], Doyun Lee[3] & Min Whan Jung[1,2]

[1]Department of Biological Sciences, Korea Advanced Institute of Science and technology, Daejeon, Republic of Korea
[2]Center for Synaptic Brain Dysfunctions, Institute for Basic Science, Daejeon, Republic of Korea
[3]Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Republic of Korea

Strong hippocampal mossy fiber synapses are thought to function as detonators, imposing 'teaching' signals onto CA3 neurons during new memory formation. However, such strong inputs may disrupt previously formed neural representations. We found that optogenetic stimulation of mossy fibers can drive CA3 neuronal firing in freely-moving mice, but their effects are overall inhibitory and transient. Spatially restricted mossy fiber stimulation emulating dentate place cell firing, either congruent or incongruent with CA3 place fields, was more likely to suppress than enhance CA3 neuronal activity. Also, changes in spatial firing induced by optogenetic stimulation reverted immediately upon stimulation termination, leaving CA3 place fields unaltered. Our results argue against the standard view that mossy fibers convey teaching signals, and show the robustness of established CA3 spatial representations.

Abstract B1

Reactivation in biological and artificial neural networks

Gido M. van de Ven

[1]MRC Brain Network Dynamics Unit, Department of Pharmacology,
University of Oxford, Oxford OX1 3TH, UK
[2]Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza,
Houston TX 77030, USA

The brain's ability to retain memories over a lifespan is thought to rely on the reactivation of memory-representing cell assemblies. To experimentally test this, for my PhD I performed multi-unit recordings in the hippocampus of mice exploring novel environments. We showed that selectively disrupting reactivation by closed-loop optogenetic silencing of sharpwave/ ripples (SWRs) impaired the later reinstatement of recently-formed place cell assemblies, thereby providing the first direct evidence that reactivation stabilizes new cell assemblies.

To gain deeper insight into the computational role of reactivation, for my postdoc I turned to machine learning. Current state-of-the-art artificial neural networks are my ideal "model organism" as they can perform extremely well on a wide variety of individual tasks, but they struggle to retain old information when trained on new tasks. Could reactivation improve memory consolidation in artificial neural networks? To test this, we equipped deep feedforward networks for classification with symmetrical feedback connections that were trained to have generative capability. We found that interleaving "reactivation" generated by these feedback connections with new task data, substantially reduces the "catastrophic forgetting" of old tasks. Notably, this approach outperforms and is more widely applicable then current deep learning strategies for alleviating catastrophic forgetting.

Abstract B9

Restless days and sleepless nights

Haram Park, Yeonsoo Choi, Hwajin Jung, Hanseul Kweon, Eunjoon Kim

Center for Synaptic Brain Dysfunctions Department of Biology, KAIST

Sleep is an essential condition to life. It has been well known that loss of sleep results in a plethora of symptoms including impaired memory, aggravation, cognitive dysfunction and in extreme cases results in death. Deficiency in sleep is a common comorbity of various neuropsychiatric disorders including ADHD and PTSD. Here we find that the conditional deletion of *Ptprd*, a protein tyrosine phosphatase acting as a major presynaptic hub during synaptogenesis and maintenance, results impaired sleep, memory dysfunction, and hyperactivity. Interestingly, *Ptprd* is a risk gene for Restless Leg Syndrome, in which patients suffer decreased sleep, as well as Attention-Deficit-Hyperactive Disorder. Analysis of brain-wide neuronal activity revealed loss of PTPRD results in decreased synaptic activity in centers of the brain critical to normal sleep architecture, such as the preoptic area of the hypothalamus. Our results reveal the importance of PTPRD in the formation of critical sleep circuits as well as how deletion of PTPRD leads to disrupted sleep architecture and comorbidities of sleep loss.

Abstract A4

Activation of distinct estrogen receptors *in vitro* can mediate the prevention and recovery of Amyloid-β induced synaptotoxicity

Iain Watson[1], Katherine J. Sellers[1], Richard Killick[2], Deepak P. Srivastava[1,3].

[1]Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K.
[2]Department of Old-Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K
[3]MRC Centre for Neurodevelopmental Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K

Estrogens have known powerful influences on learning, memory and synaptic connectivity. Furthermore, animal models have shown estrogens to be neuroprotective against the synaptotoxic effects of oligomeric amyloid-β (AβO). However, it remains unclear whether specific ERs are neuroprotective, and whether estrogen can recover AβO-induced synaptotoxicity. We developed a novel high content screening (HCS) synapse-assay that examined if specific ERs have neuroprotective and neurotrophic effects on AβO-induced synaptotoxicity.

Primary cortical neurons (DIV26) were grown in 96-well plates and treated with AβO(25-35), 17β -estradiol, specific ER agonists: PPT; WAY020070; G1 or vehicle control. Estrogens were treated either concurrently with AβO(25-35), or delayed 30 minutes prior to fixation. Cells were fixed and immunostained for synaptic markers and synaptic density was determined from our HCS synapse assay.

AβO(25-35) treatment robustly reduced synaptic density. Concurrent estrogen treatment with 17β -estradiol and PPT 'prevented' AβO(25-35)-induced synaptic density loss. Delayed treatment of the ER agonists WAY020070 and G1 'recovered' AβO(25-35)-induced synaptic density loss.

In vitro, specific activation of ERα 'prevents' synapse loss caused by AβO(25-35), whereas activation of ERβ or GPER1 'recovered' AβO(25-35) induced synapse loss. Taken together, these data suggest that more in depth studies into the underlying molecular mechanisms exerted by specific ERs against AβO(25-35) synaptotoxicity are warranted.

Abstract A9

Neural representations of ensemble coding in occipital and parietal cortex

Kyeong-Jin Tark[1], Min-Suk Kang[1,2], Sang Chul Chong[4,5], Won Mok Shim[1,3]

[1]Center for Neuroscience Imaging Research, Institute for Basic Science (IBS), South Korea
[2]Department of Psychology, Sungkyunkwan University, South Korea
[3]Department of Biomedical Engineering, Sungkyunkwan University, South Korea
[4]Department of Psychology, Yonsei University, South Korea
[5]Graduate Program in Cognitive Science, Yonsei University, South Korea

The human visual system is able to extract summary statistics from sets of similar items, but the underlying neural mechanism remains poorly understood. Using fMRI and an encoding model, we examined how the neural representation of ensemble coding is constructed and whether it is distinguished from that of individual coding. We found stronger orientation-selective responses to the mean orientation of multiple items than to the orientation of an individual one in extrastriate and parietal cortex, indicating that the ensemble orientation is represented at multiple stages along the visual hierarchy. Such orientation responses to the ensemble were found only when the to-be-averaged feature dimension was attended, implying that attention to the ensemble dimension is required to create neural representations of the ensemble percept. Our findings suggest that the neural representation of the ensemble percept is formed by pooling signals at multiple levels of visual processing from extrastriate to higher-order parietal regions.

Abstract B4

Direct in-cell observation of structural progression of amyloid-β Arctic mutant aggregation

Meng Lu[1,2], Neil Williamson[2], Ajay Mishra[1,2], Claire H. Michel[2], Clemens F. Kaminski[1,2], Alan Tunnacliffe[1], Gabriele S. Kaminski Schierle[1,2]

[1]Cambridge Infinitus Research Centre, Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge CB2 3RA, United Kingdom
[2]Department of Chemical Engineering and Biotechnology, University of Cambridge, West Cambridge Site, Philippa Fawcett Drive, Cambridge, CB3 0AS, United Kingdom

Hereditary Aβ mutations, such as the Arctic Glu22-to-Gly (E22G) mutation, lead to increased intracellular accumulation of β-amyloid and disease onset at a young age. It remains largely unknown, how the Arctic mutation leads to aggressive protein aggregation and increased toxicity. Here, we constructed stable cell models expressing wild-type (WT) and E22G Aβ42 fused to mCherry to study the aggregation kinetics of the Arctic Aβ mutant and its heterogeneous structural forms. Arctic mutant peptides assemble to form fibrils at a much faster rate than WT peptides and rapidly accumulate to form fibril bundles or clusters and later aggresomes. All aggregate species, as revealed by fluorescence-lifetime imaging (FLIM) and 3D Structural Illumination Microscopy (SIM), display a lowered fluorescence lifetime and highly compact structures with a strong affinity among individual fibrils. The aggregates formed by Arctic mutant Aβ are also more resistant to intracellular degradation than their wild-type counterparts.

Abstract B10

In vivo imaging reveals regrowth of serotonin axons following injury in the adult mouse brain

Yunju Jin

Center for Cognition and Sociality Institute for Basic Science KI bldg. A420, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon, Korea

It is widely believed that damaged axons in the adult mammalian brain have little capacity to regrow, thereby impeding functional recovery after injury. Studies using fixed tissue have suggested that serotonin neurons might be a notable exception, but remain inconclusive. We have employed *in vivo* two-photon microscopy to produce time-lapse images of serotonin axons in the neocortex of the adult mouse. Serotonin axons undergo massive retrograde degeneration following amphetamine treatment and subsequent slow recovery of axonal density which is dominated by new growth with little contribution from local sprouting. A stab injury that transects serotonin axons running in the neocortex is followed by local regression of cut serotonin axons and followed by regrowth from the cut ends into and across the stab rift zone. Regrowing serotonin axons do not follow the pathways left by degenerated axons. The regrown axons release serotonin and their regrowth is correlated with recovery in behavioral tests.

Abstract B5

The divergent role of Frizzled receptors in synapse connectivity and plasticity

McLeod F, Bossio A and Salinas PC

Department of Cell and Developmental Biology, University College London, London, WC1E 6BT, UK.

Activity-mediated changes in the strength of glutamatergic synapses, the basis of synaptic plasticity, are critical for learning and memory. Reduced synaptic plasticity and memory loss are key features of Alzheimer's disease (AD). Unravelling the mechanisms that govern synaptic plasticity is essential for therapeutic intervention strategies. Wnt secreted proteins are emerging as key modulators of synaptic connectivity. Our group has established a central role for Wnt signalling in synapse formation and maintenance. Wnt7a promotes synaptic connectivity by signalling pre and postsynaptically. Wnt7a binds to Frizzled 5 (Fz5) receptors to mediate presynaptic assembly. Fz7 is also a receptor for Wnt7a at the synapse. Gain/loss of function experiments demonstrate that Fz7 regulates dendritic spine number and the Wnt7a-mediated increase in spine number and growth. Furthermore, Fz7 is required for spine plasticity and enhanced synaptic strength following long-term potentiation (LTP) induction, one phenomena underlying synaptic plasticity. Therefore, Fz5 and Fz7 differentially mediate the effects of Wnt7a in axons and dendrites respectively and Fz7 signalling is required for structural and functional plasticity. We provide new insight into how synaptic modulators through their receptors regulate synaptic plasticity. Future experiments will focus on how defects in Fz receptors contribute to synaptic failure and memory deficits in AD.

Abstract A12

Mouse BOLD fMRI at the ultrahigh-fields of 9.4T and 15.2T: Detection of sensory pathways including thalamic nuclei

Won Beom Jung[1,2], Hyun-Ji Shim[1,3], Felix Schlegel[1] and Seong-Gi Kim[1,2,3]

[1]Cener for Neuroscience Imaging Research (CNIR), Institute for Basic Science (IBS), Suwon 16419, Republic of Korea.
[2]Department of Biomedical Engineering, Sungkyunkwan University, Suwon 16419, Republic of Korea.
[3]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul 06351, Republic of Korea

Blood oxygenation level dependent (BOLD) fMRI has been used to map functions in entire human brains. Similarly, mapping functional networks in the entire rodent brain during sensory stimulation can provide critical insights of neural plasticity and functional recovery. In anesthetized rodent fMRI studies, a change of BOLD activity in the primary somatosensory cortex (S1) has been observed during functional recovery after injury. However, since the BOLD activity is observed only in S1, it is unknown whether the modification in the S1 BOLD signal is due to changes in local synaptic activities or in thalamic afferents. Lack of thalamic activities may be due to an insufficient sensitivity of BOLD fMRI. To examine this issue, mouse fMRI experiments were performed on the ultrahigh magnetic fields of 9.4T and 15.2T since an increase of BOLD signals with field strength is expected.

C57BL/6 mice were used for fMRI studies under ketamine and zylazine anesthesia. Two different fMRI studies were performed; i) magnetic field strength dependent fMRI on the forepaw stimulation with spatial resolution of 188 × 188 × 500 μm^3 and temporal resolution of 1 s at the 9.4 T (N=7) and 15.2 T (N=7) Bruker MR systems to examine the functional sensitivity, and ii) forepaw vs. hindpaw stimulus fMRI with spatial resolution of 125 × 125 × 500 μm^3 and temporal resolution of 1.5 s at 15.2T (N=7) to determine spatial specificity of ultrahigh-field BOLD fMRI.

While activation at 9.4T was only localized in the contralateral primary forelimb somatosensory cortex, the response at 15.2 T was additionally observed in the thalamus and secondary somatosensory cortex (S2). This indicates that the sensitivity gain by the use of ultrahigh magnetic field allows us to detect macroscopic activities in entire somatosensory pathways. Also, high resolution BOLD fMRI at the ultrahigh field of 15.2T separated activities in the primary somatosensory area and secondary areas in a somatopic manner.

In conclusion, ultrahigh-field fMRI of mouse opens a new research avenue for investigating functional networks in the whole brain noninvasively and repeatedly, allowing investigations of functional development, recovery, and reorganization in diseased and transgenic models.

Funding: This project is funded by the Institute for Basic Science in Korea (IBS-R015-D1)

Poster Short-Talks

August 21, 2018

(15:50-18:00)

Chair: Won Do Heo (IBS-KAIST) & Albert Lee (HHMI, Janelia Farm)

Abstract A8

CRISPR/Cas9-mediated downregulation of *PMP22* ameliorates Charcot-Marie-Tooth disease 1A in mice

Jae Young Lee

Toolgen Inc, R&D Center, Seoul, South Korea

AIMS

Charcot-Marie-Tooth 1A (CMT1A) is the most common inherited neuropathy without a known therapy, which is caused by duplication of the gene encoding the peripheral myelin protein of 22 kDa (PMP22). Overexpression of *PMP22* is thought to cause demyelination and subsequently axonal degeneration in the peripheral nervous system (PNS). Here we investigate whether downregulation of *PMP22* by targeting gene regulatory region of *PMP22* using CRISPR/Cas9 could provide a therapeutic strategy for treating CMT1A

METHODS

In this study, we utilize human *PMP22* overexpressing transgenic mouse model of CMT1A to test the efficacy of CRISPR/Cas9-mediated suppression of *PMP22* expression. For this, CRISPR/Cas9 was designed to target the gene regulatory region of human *PMP22* to normalize overexpressed *PMP22* level. Using primary human Schwann cells, we screened CRISPR-associated guide RNA (gRNA) and a lead gRNA was then tested for their ability to reduce *PMP22* transcripts in mouse model of CMT1A.

RESULTS

Efficient editing of gene regulatory region of *PMP22* was achieved via single intraneural injection of CRISPR/Cas9 in ribonucleoprotein complexes, which downregulated *PMP22* transcripts in sciatic nerves. Treatment led to preservation of both myelin and axons which resulted in improvement in motor nerve conduction velocity and compound motor action potentials. *PMP22* downregulating CRISPR/Cas9 showed no aberrant cleavage of off-target sites predicted by unbiased genome-wide identification.

CONCLUSIONS

These results demonstrate that our approach utilizing CRISPR/Cas9 to target gene regulatory region of *PMP22* efficiently and specifically downregulates PMP22 expression to therapeutic level, providing a compelling therapeutic approach for CMT1A.

Abstract A2

Identification of compounds and drug targets that enhance TDP-43 clearance in ALS and FTD

Alinda R Fernandes[1], Jacqueline C Mitchell[1], Micha el J O'Neill[2], Chris E Shaw[1]

[1]Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, United Kingdom
[2]Eli Lilly and Company Limited, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, United Kingdom

The only marketed drug, Riluzole, prolongs life expectancy in Amyotrophic Lateral Sclerosis (ALS) patients for up to three months. Given the poor prognosis for this disease, accelerating both research-based and pre-clinical studies is critical for ALS drug development. Advancement of effective therapeutic strategies for ALS has largely been hampered due to i) lack of *in vitro* models that are robust and high throughput and (ii) our limited understanding of mechanisms underlying the disease. Current approaches such as transient transfection or patient-derived motor neurons to model ALS are very informative though highly laborious for primary screening of novel candidate compounds. Here, we present a robust high throughput, high content screening meth od to identify and quantify pathological features in an inducible human neuroblastoma SHSY5Y cell line expressing wild-type TDP-43 (GFP-tagged). By delineating nuclear vs cytoplasmic TDP-43 expression combined with high-content analyses, we demonstrate several pathological features observed in sporadic and familial TDP-43 patients, including TDP-43 hyperphosphorylation, increased cytoplasmic TDP-43 mislocalisation as well as altered autophagy (using P62 as a marker) and neurotoxicity. The addition of osmotic and oxidative stressors further exacerbates this phenotype. Further, we use this approach, in combination with mass spectroscopy to identify and validate cytoplasmic TDP-43 protein binding partners which drive pathological aggregation. Nuclear and cytoplasmic lysates from a transgenic mouse model of ALS were extracted and TDP-43 was co-immunoprecipitated.

Subsequently, we demonstrate the effects of TDP-43 associated pathology upon knockdown of a selection of prominent TDP-43 protein binding partners in mouse brain slices derived from ALS mouse models. We anticipate that outcomes from these studies will advance our understanding of TDP-43 disease mechanisms which can be extended for other proteinopathies leading to neurodegeneration.

Abstract B7

MAPK-dependent presynaptic potentiation in the LHb is responsible for depressive behaviors

Hoyong Park[1], Hakyun Ryu[1], Seung-Jae Zhang[1], and ChiHye Chung[1,*]

[1]Department of Biological Sciences, Konkuk University, Seoul 05029, South Korea

The lateral habenula (LHb), recently proposed to be involved in depressive disorders, is a part of clock system in our brain. It was reported that disrupted circadian patterns are one of commonly observed symptoms in human patients with depression. Interestingly, the habenular complex is reported to contain an intrinsic molecular clock and to show rhythmic expression of circadian clock genes and proteins. In addition, previously reported abnormal potentiation of LHb neurons was shown to be mainly due to presynaptic alterations. However, it is unknown that the circadian rhythms in the LHb are impaired in depressive state. Furthermore, the mechanisms of this presynaptic enhancement remain completely unknown. In this study, we showed that the presynaptic release probability potentiation previously observed in the LHb of in animal models of depression is temporarily variable and mediated by altered mitogen -activated protein kinase (MAPK)-dependent signaling upon the activation of glucocorticoid receptors (GRs). Interestingly, either exposure to a stressor or incubation with corticosterone abolishes the circadian termporal oscillatory pattern of synaptic transmission in the LHb in MAPK-dependent but not protein kinase C (PKC)-dependent manner. The selective inhibition of MAPK kinase (MAPKK, MEK) activity in the LHb prevents the presynaptic potentiation of synaptic efficacy after the exposure to stressors and successfully reversed depressive symptoms including behavioral despair and helplessness in animal models of depression. Our study delineates the cellular and molecular mechanisms responsible abnormal presynaptic enhancement of LHb neurons in an animal model of depression, which critically participate in mediating depressive behaviours.

Abstract B2

Postsynaptic p47phox controls long-term depression in the hippocampus

Jee Hyun Yi[1,2,3], Dong Hyun Kim[1], Thomas M. Piers[1], Daniel J. Whitcomb[1,2], Philip Regan[1,2*] and Kwangwook Cho[1,2*]

[1]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, Faculty of Health Sciences,
[2]Centre for Synaptic Plasticity, University of Bristol, Whitson Street, Bristol, BS1 3NY, United Kingdom,
[3]Center for Synaptic Brain Dysfunctions, Institute for Basic Science, Daejeon 34141, Republic of Korea.

It is well documented that reactive oxygen species (ROS) affects neurodegeneration in the brain. Several studies also implicate ROS in the regulation of synapse function and learning and memory processes, although the precise source of ROS generation within these contexts remains to be further explored. Here I show that postsynaptic superoxide generation through PKCζ -activated NADPH oxidase 2 (NOX2) is critical for long-term depression of synaptic transmission (LTD) in the CA1-Shaffer collateral synapse of the rat hippocampus. Specifically, PKCζ-dependent phosphorylation of p47phox at serine 316, the NOX2 regulatory subunit, is required for LTD but has no roles in long-term potentiation (LTP). Therefore, this study suggests that postsynaptic p47phox phosphorylation at serine 316 is a key upstream determinant for LTD and synapse weakening.

Key index words
Reactive oxygen species, PKCζ, NADPH oxidase, Long-term depression

Abstract A10

Effects of cell type-specific *Shank3* deletion

Taesun Yoo,[1,#] Heejin Cho,[1,#] Jiseok Lee,[2,#] Haram Park,[1] Ye-Eun Yoo,[1] Esther Yang,[3] Jin Yong Kim,[3] Hyun Kim,[3] and Eunjoon Kim[1,2,*]

[1]Department of Biological Sciences, Korea Advanced Institute for Science and Technology (KAIST), Daejeon 305-701, Korea

[2]Center for Synaptic Brain Dysfunctions, Institute for Basic Science (IBS), Daejeon 305-701, Korea

[3]Department of Anatomy and Division of Brain Korea 21, Biomedical Science, College of Medicine, Korea University, Seoul 136-705, Korea; #These authors contributed equally to the study; *Corresponding author.

Shank represents a family of postsynaptic scaffolding proteins with three known members: Shank1/ProSAP3, Shank2/ProSAP1, and Shank3/ProSAP2. Shank proteins interact with many other synaptic proteins and are known to regulate excitatory synapse assembly as well as excitatory synaptic transmission and plasticity.

Mutations of Shank3 have been implicated in diverse brain disorders, including autism spectrum disorders (ASD), Phelan-McDermid syndrome (PMS), schizophrenia, intellectual disability, and mania.

A number of different lines of *Shank3*-mutant mice have been generated and characterized in an effort to understand the in vivo functions of Shank3 and identify important mechanisms underlying Shank3-related brain disorders.

Results obtained using these various mouse models, together with additional studies on Shank3 using a variety neurobiological approaches, have further revealed diverse functions of Shank3 in physiological and pathological conditions.

Despite this progress, whether specific cell types that express Shank3 differentially contribute to normal brain functions and behaviors remains largely unclear. Here, we report that Shank3 is expressed in both excitatory glutamatergic and inhibitory GABAergic neurons. Deletion of *Shank3*exons 14-16, encoding the PDZ domain, specifically in glutamatergic or GABAergic neurons differentially alters electrophysiology and behaviors in mice, with GABAergic deletion generally exerting a stronger influence. Our results suggest that Shank3 expression in both glutamatergic and GABAergic neurons contributes to normal brain functions and is associated with Shank3-related brain disorders.

Abstract A3

Alzheimer's disease-like pathology in *Cyfip2*+/- mice

Anshua Ghosh[1], Sachin Tiwari[2], Keiko Mizuno[1], Karl Peter Giese[1]

[1]Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, 5 Cutcombe Road London, SE5 9RT, United Kingdom
[2]MRC Centre for Regenerative Medicine, SCRM Building, The University of Edinburgh, 5 Little France Drive, Edinburgh. EH16 4UU, United Kingdom

Synaptic degeneration is one of the best correlates of impaired memory in Alzheimer's disease (AD). Recent advances in the field have suggested that early changes in the AD brain may involve alterations in protein synthesis at synaptic sites. These changes may be dependent on the *Cy*toplasmic *F*MRP-*I*nteracting *P*rotein 2 (CYFIP2), a highly conserved protein that is abundant in synapses and has been proposed to have functions in regulating protein synthesis of FMRP-regulated mRNAs.

We previously found that CYFIP2 protein expression is reduced by 50% in severe AD post mortem hippocampus. Adult *Cyfip2+/-* mice model the reduced expression, and have elevated Aβ 1-42, increased tau phosphorylation, altered dendritic spine morphology, and a deficit in memory retention.

Aged *Cyfip2* +/- mice have somatodendritically mislocalised PHF-1 and AT-8 phosphorylated tau in CA1 and DG of the hippocampus compared to wild-types. These subregions also show an increase in the number of GFAP-positive cells, suggesting there may be reactive gliosis. Thalamic regions of *Cyfip2+/-* mouse brains show ThioflavinS-positive deposits that resemble diffuse plaques seen in AD.

Taken together, reducing CYFIP2 in the mouse brain is sufficient to recapitulate several aspects of the disease and therefore may be a key mediator of changes in the AD brain.

Abstract A11

Characterization of synaptic and behavioral phenotypes in mice carrying a *de novo Shank3* mutation Q321R

Ye-Eun Yoo[1,2], Taesun Yoo[1,2], Jiseok Lee[1,2], and Eunjoon Kim[1,2]

[1]Center for Synaptic Brain Dysfunctions, Institute for Basic Science
[2]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Korea

A *de novo* point mutation in exon 8 of the *SHANK3* gene (g.51121844A>G) leading to a change in the amino acid 321-Gln to 321-Arg (Q321R) in the N-terminal ankyrin repeats of the SHANK3 protein has been identified in an individual with autism spectrum disorder (ASD). This mutation has been shown to induce changes in excitatory synaptic structure and function in cultured neurons, including actin polymerization, dendritic spine morphogenesis, and excitatory synaptic transmission. However, whether this mutation has any influences on synaptic properties or animal behaviors *in vivo* has not been tested. Here we generated a novel *Shank3* mutant mouse line carrying a Q321R knockin (KI) mutation and characterized synaptic and behavioral phenotypes in the mutant mice. Unlike our expectation, we found that a point mutation did not affect the mouse brain gross morphology and excitatory synaptic transmission in the hippocampus. Homozygous *Shank3* Q321R KI mice showed increased repetitive behavior and anxiolytic behavior, but showed normal social interaction or communication. These results indicate that the aberrant function of synaptic scaffolding protein SHANK3 by ankyrin repeat domain mutation may underlie ASD-related behaviors.

Abstract A5

The effects of apolipoprotein E (ApoE) polymorphism on human hippocampal neurogenesis

Hyunah Lee[1], Sandrine Thuret[1]

[1]Laboratory of Adult Neurogenesis and Mental Health, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Apolipoprotein E (APOE) polymorphism is the most common genetic risk factor for Alzheimer's disease (AD. Growing body of evidence suggests that APOE polymorphism may differentially affect adult hippocampal neurogenesis in the dentate gyrus. However, the impact of APOE isoforms on hippocampal neurogenesis at a cellular/molecular level is not completely understood. In the present study, we performed a time-course characterization of isogenic human induced pluripotent stem cell lines that differ only in APOE genotype by differentiating them into hippocampal neural progenitor cells (NPC) and then dentate gyrus granule cell (DGC)-like neurons. We found that the isogenic lines exhibited differential phenotypes including expression patterns for hippocampal NPC markers and PROX1, the marker for mature DGCs, and expression of Ki-67, a marker for cell proliferation, during DGC differentiation. The gene expression pattern of APOE and immunolabeling of MAP2 and DCX did not significantly differ between APOE3/3 and APOE4/4 cells. Our findings suggest that APOE genotype can impact hippocampal neurogenesis, and that hippocampal neurogenesis can be a potential target for early intervention against AD for APOE4-carriers. We are investigating whether APOE genotype interacts with environmental factors to either exacerbate or ameliorate the phenotypes we have characterized thus far in our model system.

Abstract B11

Somatostatin interneurons in the anterior cingulate cortex gate mouse observational fear

Arie Kim[1,2,*], Sehoon Keum[1,*], Jae Jin Shin[1,3], Jong-Hyun Kim[1,4], Joomin Park[1,2], Hee-Sup Shin[1,2]

[1]Center for Cognition and Sociality, Institute for Basic Science, Daejeon 34047, Republic of Korea
[2]School of Basic Science, University of Science and Technology, Daejeon 34113, Republic of Korea
[3]Department of Brain and Cognitive Science, Seoul National University, Seoul 08826, Republic of Korea
[4]Center for Glia-Neuron Interaction, Brain Science Institute, Korea Institute of Science and Technology, Seoul 02792, Republic of Korea
[*]These authors contributed equally

Empathy is the ability to recognize and share emotions with others. The anterior cingulate cortex (ACC) is critically involved in human empathy and the acquisition of observational fear in mice. However, molecular and cellular mechanisms in the ACC that control observational fear remain to be determined. Here, through behavior-driven forward genetic analyses in inbred strains of mice, we identified that a missense mutation in Neurexin 3 (*Nrxn3*) increased observational fear. Furthermore, mice in which *Nrxn3* was selectively deleted in somatostatin-expressing (SST^+) interneurons showed markedly increased vicarious fear. In acute slices of the ACC of those mice, inhibitory synaptic transmission from SST^+ neurons onto layer 2/3 excitatory neurons was impaired without affecting intrinsic excitability. Concordantly, optogenetic suppression of SST^+ interneurons in the ACC evoked an elevation of vicarious freezing, mimicking the *Nrxn3* ablation in SST^+ neurons, whereas activation of SST^+ neurons obliterated acquisition of observational fear. This study indicates that *Nrxn3* is an essential molecular machinery for inhibitory synaptic transmission in SST^+ neurons and uncovers a novel role of SST^+ neurons-mediated inhibitory circuit in the ACC in gating the top-down computation for the expression of socially incited fear.

Abstract B3

A tauopathy-associated tau fragment causes autophagic dysfunction

Dina Dakkak, Tong Guo, Wendy Noble, Diane P. Hanger

Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

Introduction

Tauopathies are characterised by aggregates of posttranslationally modified tau. We identified a tau fragment, Tau35, in human four-repeat (4R) tauopathy brain and used this to generate a cell model, in which Chinese hamster ovary (CHO) cells stably express Tau35 (CHO-Tau35) or full-length human tau (CHO-FL). Since altered autophagy has previously been reported in several models of tauopathy, we investigated the autophagic status of CHO-Tau35 cells.

Materials and Methods

Markers of the autophagy pathway, including microtubule-associated proteins 1A/1B light chain 3B (LC3) and Beclin-1, were measured in CHO-Tau35 cells on western blots and using immunofluorescence. Experiments were conducted under basal conditions and following stimulation of autophagy using rapamycin. Other markers, including lysosomal associated membrane protein 2(LAMP2), transcription factor EB (TFEB), cathepsin D and lipid staining were assessed using fluorescence microscopy.

Results

The basal amount of LC3-II was significantly lower in CHO-Tau35, compared to CHO-FL and CHO cells. Upon rapamycin treatment, LC3-II remained significantly reduced. LAMP2 staining was reduced in CHO-Tau35 compared to CHO-FL and CHO cells. Parallel decreases were observed in cathepsin D staining and cathepsin D/LAMP2 localisation in CHO-Tau35. Imaging of TFEB revealed a higher proportion of cytoplasmic TFEB in CHO-Tau35. BODIPY staining showed a higher number of lipid droplets in CHOTau35 compared to CHO-FL and CHO cells.

Conclusions

Under both basal and stimulated conditions, levels of LC3 in CHO-Tau35 were reduced, thereby revealing that Tau35 reduces autophagosome formation. Additionally, the limited response of LC3 to rapamycin in CHO-Tau35 suggests that Tau35 is less able to activate autophagy via an mTORdependent mechanism. Reduced nuclear TFEB in CHO-Tau35 suggests impaired lysosomal biogenesis, which is further validated by decreased LAMP2 and cathepsin D in CHO-Tau35.

Poster Presentation

Poster Group-A

Abstract A1

Using the power of Dementias Platform UK (DPUK) cohorts to investigate the effects of childhood adversity on adult behavioural, physiological, cognitive and dementia outcomes: A cross-cohort investigation

Sarah Bauermeister, John Gallacher

The University of Oxford

Childhood adversity is a construct encompassing extre8me difficulties and adverse childhood experiences (ACE) such as sexual, physical and emotional abuse and deprivation. Experiencing adversity within childhood alters the life of a child to an extent that it may change biological processes which lead to adverse biomedical health outcomes in adulthood (Mehta et al., 2013), and dementia (Radford et al., 2017). Our aim is to investigate associations between childhood adversity and adult
health-related outcomes, cognition and dementia utilising questionnaire data from DPUK cohorts: Whitehall II, UK Biobank and MRC NSHD.

A preliminary analysis from 123 945 UK Biobank participants was conducted using structural equation modelling. Individual ACE variables formed a latent construct of childhood adversity and multiple adult outcomes were entered, adjusting for socioeconomic status, education and, selectively, age (e.g., BMI, medications, vascular health and cognition). Childhood adversity significantly predicted (all *p*s < .000) higher frequency of alcohol intake, younger sexual activity and onset of smoking, poorer vascular health, increased medication usage and BMI, higher neuroticism, increased self-reported depression and neuroticism, lower levels of overall happiness and poorer cognition. The other cohorts with their rich cognitive data are being analysed to further investigate the effect on adult cognition and dementia outcomes.

References:

Mehta, N.M., Corkins, M.R., Lyman, B., Malone, B., Malone, A., Goday, P.S., Carney, L.N.,… (2013).
Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions.
JPEN J Parenter Enteral Nutr. 37(4):460-481.

Radford, K., Delbaere, K., Draper, B., Mack, H.A., Daylight, G., Cumming, R., Chalkley, S., Monogue, C., & Broe, G.A. (2017). Childhood stress and adversity is associated with late-life dementia in boriginal Australians. Am J Geriatr Psychiatry. 25(10):1097-1106.

Abstract A2

Identification of compounds and drug targets that enhance TDP-43 clearance in ALS and FTD

Alinda R Fernandes[1], Jacqueline C Mitchell[1], Micha el J O'Neill[2], Chris E Shaw[1]

[1]Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, United Kingdom
[2]Eli Lilly and Company Limited, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, United Kingdom

The only marketed drug, Riluzole, prolongs life expectancy in Amyotrophic Lateral Sclerosis (ALS) patients for up to three months. Given the poor prognosis for this disease, accelerating both research-based and pre-clinical studies is critical for ALS drug development. Advancement of effective therapeutic strategies for ALS has largely been hampered due to i) lack of *in vitro* models that are robust and high throughput and (ii) our limited understanding of mechanisms underlying the disease. Current approaches such as transient transfection or patient-derived motor neurons to model ALS are very informative though highly laborious for primary screening of novel candidate compounds. Here, we present a robust high throughput, high content screening meth od to identify and quantify pathological features in an inducible human neuroblastoma SHSY5Y cell line expressing wild-type TDP-43 (GFP-tagged). By delineating nuclear vs cytoplasmic TDP-43 expression combined with high-content analyses, we demonstrate several pathological features observed in sporadic and familial TDP-43 patients, including TDP-43 hyperphosphorylation, increased cytoplasmic TDP-43 mislocalisation as well as altered autophagy (using P62 as a marker) and neurotoxicity. The addition of osmotic and oxidative stressors further exacerbates this phenotype. Further, we use this approach, in combination with mass spectroscopy to identify and validate cytoplasmic TDP-43 protein binding partners which drive pathological aggregation. Nuclear and cytoplasmic lysates from a transgenic mouse model of ALS were extracted and TDP-43 was co-immunoprecipitated.

Subsequently, we demonstrate the effects of TDP-43 associated pathology upon knockdown of a selection of prominent TDP-43 protein binding partners in mouse brain slices derived from ALS mouse models. We anticipate that outcomes from these studies will advance our understanding of TDP-43 disease mechanisms which can be extended for other proteinopathies leading to neurodegeneration.

Abstract A3

Alzheimer's disease-like pathology in *Cyfip2*+/- mice

Anshua Ghosh[1], Sachin Tiwari[2], Keiko Mizuno[1], Karl Peter Giese[1]

[1]Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, 5 Cutcombe Road London, SE5 9RT, United Kingdom
[2]MRC Centre for Regenerative Medicine, SCRM Building, The University of Edinburgh, 5 Little France Drive, Edinburgh. EH16 4UU, United Kingdom

Synaptic degeneration is one of the best correlates of impaired memory in Alzheimer's disease (AD). Recent advances in the field have suggested that early changes in the AD brain may involve alterations in protein synthesis at synaptic sites. These changes may be dependent on the *Cy*toplasmic *F*MRP-*I*nteracting *P*rotein 2 (CYFIP2), a highly conserved protein that is abundant in synapses and has been proposed to have functions in regulating protein synthesis of FMRP-regulated mRNAs.

We previously found that CYFIP2 protein expression is reduced by 50% in severe AD post mortem hippocampus. Adult *Cyfip2+/-* mice model the reduced expression, and have elevated Aβ 1-42, increased tau phosphorylation, altered dendritic spine morphology, and a deficit in memory retention.

Aged *Cyfip2* +/- mice have somatodendritically mislocalised PHF-1 and AT-8 phosphorylated tau in CA1 and DG of the hippocampus compared to wild-types. These subregions also show an increase in the number of GFAP-positive cells, suggesting there may be reactive gliosis. Thalamic regions of *Cyfip2+/-* mouse brains show ThioflavinS-positive deposits that resemble diffuse plaques seen in AD.

Taken together, reducing CYFIP2 in the mouse brain is sufficient to recapitulate several aspects of the disease and therefore may be a key mediator of changes in the AD brain.

Abstract A4

Activation of distinct estrogen receptors *in vitro* can mediate the prevention and recovery of Amyloid-β induced synaptotoxicity

Iain Watson[1], Katherine J. Sellers[1], Richard Killick[2], Deepak P. Srivastava[1,3].

[1]Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K.
[2]Department of Old-Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K
[3]MRC Centre for Neurodevelopmental Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, U.K

Estrogens have known powerful influences on learning, memory and synaptic connectivity. Furthermore, animal models have shown estrogens to be neuroprotective against the synaptotoxic effects of oligomeric amyloid-β (AβO). However, it remains unclear whether specific ERs are neuroprotective, and whether estrogen can recover AβO-induced synaptotoxicity. We developed a novel high content screening (HCS) synapse-assay that examined if specific ERs have neuroprotective and neurotrophic effects on AβO-induced synaptotoxicity.

Primary cortical neurons (DIV26) were grown in 96-well plates and treated with AβO(25-35), 17β -estradiol, specific ER agonists: PPT; WAY020070; G1 or vehicle control. Estrogens were treated either concurrently with AβO(25-35), or delayed 30 minutes prior to fixation. Cells were fixed and immunostained for synaptic markers and synaptic density was determined from our HCS synapse assay.

AβO(25-35) treatment robustly reduced synaptic density. Concurrent estrogen treatment with 17β -estradiol and PPT ‘prevented’ AβO(25-35)-induced synaptic density loss. Delayed treatment of the ER agonists WAY020070 and G1 ‘recovered’ AβO(25-35)-induced synaptic density loss.

In vitro, specific activation of ERα ‘prevents’ synapse loss caused by AβO(25-35), whereas activation of ERβ or GPER1 ‘recovered’ AβO(25-35) induced synapse loss. Taken together, these data suggest that more in depth studies into the underlying molecular mechanisms exerted by specific ERs against AβO(25-35) synaptotoxicity are warranted.

Abstract A5

The effects of apolipoprotein E (ApoE) polymorphism on human hippocampal neurogenesis

Hyunah Lee[1], Sandrine Thuret[1]

[1]Laboratory of Adult Neurogenesis and Mental Health, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Apolipoprotein E (APOE) polymorphism is the most common genetic risk factor for Alzheimer's disease (AD. Growing body of evidence suggests that APOE polymorphism may differentially affect adult hippocampal neurogenesis in the dentate gyrus. However, the impact of APOE isoforms on hippocampal neurogenesis at a cellular/molecular level is not completely understood. In the present study, we performed a time-course characterization of isogenic human induced pluripotent stem cell lines that differ only in APOE genotype by differentiating them into hippocampal neural progenitor cells (NPC) and then dentate gyrus granule cell (DGC)-like neurons. We found that the isogenic lines exhibited differential phenotypes including expression patterns for hippocampal NPC markers and PROX1, the marker for mature DGCs, and expression of Ki-67, a marker for cell proliferation, during DGC differentiation. The gene expression pattern of APOE and immunolabeling of MAP2 and DCX did not significantly differ between APOE3/3 and APOE4/4 cells. Our findings suggest that APOE genotype can impact hippocampal neurogenesis, and that hippocampal neurogenesis can be a potential target for early intervention against AD for APOE4-carriers. We are investigating whether APOE genotype interacts with environmental factors to either exacerbate or ameliorate the phenotypes we have characterized thus far in our model system.

Abstract A6

Impaired pathways to callous-unemotional traits in children with conduct disorder

Hyungyou Park[1], Arjun Sethi[2,3], Marco Catani[2,3], Michael C. Craig[2,3]

[1]Department of Basic & Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[2]Natbrainlab, Department of Forensic & Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[3]Sacker Institute for Translational Neurodevelopment, Department of Forensic & Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Conduct disorder (CD) is a childhood mental disorder that is characterised by repetitive and persistent patterns of aggressive and antisocial behaviours. Most children with severe CD have callous-unemotional (CU) traits, which consist of lack of empathy and limited prosocial emotions. These functions rely on the normal development of limbic regions in the medial temporal lobe, subgenual area and forebrain. Tractography allows to dissect white matter connections in the living human brain and study anatomical differences associated with abnormal development. In this study we used tractography to analyse the projections from amygdala and temporal paralimbic cortex to the hypothalamic/anterior thalamic nuclei (ventral amygdalofugal pathway, VAF) and subgenual area (medial uncinate fasciculus, MUF) in children with CD. 31 CD boys (of which 17 with CU traits) were compared to 22 age matched neurotypical controls. CD group had statistically significant ($p = 0.001$) increased radial diffusivity in the right MUF compared to controls and this difference was driven primarily by those children with CU traits. These findings are in line with similar results reported adult psychopaths and indicate an abnormality of the temporo-frontal networks underlying prosocial affective behaviour. Furthermore, our results show that these abnormalities can be detected during childhood and are particularly severe in those children at higher risk of developing psychopathy in adult life.

Abstract A7

The roles of fused in sarcoma (FUS) in synaptic dysfunction in hippocampal neurons

Seung Chan Kim[1], Peter St George-Hyslop[2], Daniel J. Whitcomb[1] and Kwangwook Cho[1,3]

[1]Bristol Medical School, University of Bristol, Bristol BS1 3NY
[2]Cambridge Institute for Medical Research, Department of Clinical Neuroscience, University of Cambridge, Cambridge CB2 0XY
[3]UK-Dementia Research Institute at King's College London, Department of Basic and Clinical Neuroscience, King's College London, UK.

Fused in sarcoma (FUS) is a DNA/RNA-binding protein that modulates gene expression by associating with a wide range of transcription-related factors in the nucleus and/or cytoplasm of neurons. Mutations or abnormal expression of FUS have been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Mutations at the nuclear localisation signal (NLS) of FUS have been reported cause the mis-localisation of the protein from the nucleus to the cytoplasm, forming cytoplasmic inclusions. However, it is not known whether aberrant inclusion of FUS affects neuronal function. Accordingly, here we have investigated the synaptic, physiological changes of NLS-mutant FUS (FUSP525L) to discover the missing links between mis-localisation of FUS and neuronal function and morphological structure by using whole cell patch clamp recording and multi-photon imaging. Overexpression of FUS-P525L causes an aberrant propagation of FUS through dendrites compared with wild type FUS-expressing hippocampal neurons. We also found that FUS-P525L expression changes the excitability of neurons, their resting membrane potential, AMPA/NMDA currents and dendritic structures. These findings may represent the pathological consequences of cytoplasmic inclusion of FUS in hippocampal neuron, and provides a new pathological model of FUS-mediated neurodegeneration.

Abstract A8

CRISPR/Cas9-mediated downregulation of *PMP22* ameliorates Charcot-Marie-Tooth disease 1A in mice

Jae Young Lee

Toolgen Inc, R&D Center, Seoul, South Korea

AIMS

Charcot-Marie-Tooth 1A (CMT1A) is the most common inherited neuropathy without a known therapy, which is caused by duplication of the gene encoding the peripheral myelin protein of 22 kDa (PMP22). Overexpression of *PMP22* is thought to cause demyelination and subsequently axonal degeneration in the peripheral nervous system (PNS). Here we investigate whether downregulation of *PMP22* by targeting gene regulatory region of *PMP22* using CRISPR/Cas9 could provide a therapeutic strategy for treating CMT1A

METHODS

In this study, we utilize human *PMP22* overexpressing transgenic mouse model of CMT1A to test the efficacy of CRISPR/Cas9-mediated suppression of *PMP22* expression. For this, CRISPR/Cas9 was designed to target the gene regulatory region of human *PMP22* to normalize overexpressed *PMP22* level. Using primary human Schwann cells, we screened CRISPR-associated guide RNA (gRNA) and a lead gRNA was then tested for their ability to reduce *PMP22* transcripts in mouse model of CMT1A.

RESULTS

Efficient editing of gene regulatory region of *PMP22* was achieved via single intraneural injection of CRISPR/Cas9 in ribonucleoprotein complexes, which downregulated *PMP22* transcripts in sciatic nerves. Treatment led to preservation of both myelin and axons which resulted in improvement in motor nerve conduction velocity and compound motor action potentials. *PMP22* downregulating CRISPR/Cas9 showed no aberrant cleavage of off-target sites predicted by unbiased genome-wide identification.

CONCLUSIONS

These results demonstrate that our approach utilizing CRISPR/Cas9 to target gene regulatory region of *PMP22* efficiently and specifically downregulates PMP22 expression to therapeutic level, providing a compelling therapeutic approach for CMT1A.

Abstract A9

Neural representations of ensemble coding in occipital and parietal cortex

Kyeong-Jin Tark[1], Min-Suk Kang[1,2], Sang Chul Chong[4,5], Won Mok Shim[1,3]

[1]Center for Neuroscience Imaging Research, Institute for Basic Science (IBS), South Korea
[2]Department of Psychology, Sungkyunkwan University, South Korea
[3]Department of Biomedical Engineering, Sungkyunkwan University, South Korea
[4]Department of Psychology, Yonsei University, South Korea
[5]Graduate Program in Cognitive Science, Yonsei University, South Korea

The human visual system is able to extract summary statistics from sets of similar items, but the underlying neural mechanism remains poorly understood. Using fMRI and an encoding model, we examined how the neural representation of ensemble coding is constructed and whether it is distinguished from that of individual coding. We found stronger orientation-selective responses to the mean orientation of multiple items than to the orientation of an individual one in extrastriate and parietal cortex, indicating that the ensemble orientation is represented at multiple stages along the visual hierarchy. Such orientation responses to the ensemble were found only when the to-be-averaged feature dimension was attended, implying that attention to the ensemble dimension is required to create neural representations of the ensemble percept. Our findings suggest that the neural representation of the ensemble percept is formed by pooling signals at multiple levels of visual processing from extrastriate to higher-order parietal regions.

Abstract A10

Effects of cell type-specific *Shank3* deletion

Taesun Yoo,[1,#] Heejin Cho,[1,#] Jiseok Lee,[2,#] Haram Park,[1] Ye-Eun Yoo,[1] Esther Yang,[3] Jin Yong Kim,[3] Hyun Kim,[3] and Eunjoon Kim[1,2,*]

[1]Department of Biological Sciences, Korea Advanced Institute for Science and Technology (KAIST), Daejeon 305-701, Korea

[2]Center for Synaptic Brain Dysfunctions, Institute for Basic Science (IBS), Daejeon 305-701, Korea

[3]Department of Anatomy and Division of Brain Korea 21, Biomedical Science, College of Medicine, Korea University, Seoul 136-705, Korea; #These authors contributed equally to the study; *Corresponding author.

Shank represents a family of postsynaptic scaffolding proteins with three known members: Shank1/ProSAP3, Shank2/ProSAP1, and Shank3/ProSAP2. Shank proteins interact with many other synaptic proteins and are known to regulate excitatory synapse assembly as well as excitatory synaptic transmission and plasticity.

Mutations of Shank3 have been implicated in diverse brain disorders, including autism spectrum disorders (ASD), Phelan-McDermid syndrome (PMS), schizophrenia, intellectual disability, and mania.

A number of different lines of *Shank3*-mutant mice have been generated and characterized in an effort to understand the in vivo functions of Shank3 and identify important mechanisms underlying Shank3-related brain disorders.

Results obtained using these various mouse models, together with additional studies on Shank3 using a variety neurobiological approaches, have further revealed diverse functions of Shank3 in physiological and pathological conditions.

Despite this progress, whether specific cell types that express Shank3 differentially contribute to normal brain functions and behaviors remains largely unclear. Here, we report that Shank3 is expressed in both excitatory glutamatergic and inhibitory GABAergic neurons. Deletion of *Shank3*exons 14-16, encoding the PDZ domain, specifically in glutamatergic or GABAergic neurons differentially alters electrophysiology and behaviors in mice, with GABAergic deletion generally exerting a stronger influence. Our results suggest that Shank3 expression in both glutamatergic and GABAergic neurons contributes to normal brain functions and is associated with Shank3-related brain disorders.

Abstract A11

Characterization of synaptic and behavioral phenotypes in mice carrying a *de novo Shank3* mutation Q321R

Ye-Eun Yoo[1,2], Taesun Yoo[1,2], Jiseok Lee[1,2], and Eunjoon Kim[1,2]

[1]Center for Synaptic Brain Dysfunctions, Institute for Basic Science
[2]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Korea

A *de novo* point mutation in exon 8 of the *SHANK3* gene (g.51121844A>G) leading to a change in the amino acid 321-Gln to 321-Arg (Q321R) in the N-terminal ankyrin repeats of the SHANK3 protein has been identified in an individual with autism spectrum disorder (ASD). This mutation has been shown to induce changes in excitatory synaptic structure and function in cultured neurons, including actin polymerization, dendritic spine morphogenesis, and excitatory synaptic transmission. However, whether this mutation has any influences on synaptic properties or animal behaviors *in vivo* has not been tested. Here we generated a novel *Shank3* mutant mouse line carrying a Q321R knockin (KI) mutation and characterized synaptic and behavioral phenotypes in the mutant mice. Unlike our expectation, we found that a point mutation did not affect the mouse brain gross morphology and excitatory synaptic transmission in the hippocampus. Homozygous *Shank3* Q321R KI mice showed increased repetitive behavior and anxiolytic behavior, but showed normal social interaction or communication. These results indicate that the aberrant function of synaptic scaffolding protein SHANK3 by ankyrin repeat domain mutation may underlie ASD-related behaviors.

Abstract A12

Mouse BOLD fMRI at the ultrahigh-fields of 9.4T and 15.2T: Detection of sensory pathways including thalamic nuclei

Won Beom Jung[1,2], Hyun-Ji Shim[1,3], Felix Schlegel[1] and Seong-Gi Kim[1,2,3]

[1]Cener for Neuroscience Imaging Research (CNIR), Institute for Basic Science (IBS), Suwon 16419, Republic of Korea.
[2]Department of Biomedical Engineering, Sungkyunkwan University, Suwon 16419, Republic of Korea.
[3]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul 06351, Republic of Korea

Blood oxygenation level dependent (BOLD) fMRI has been used to map functions in entire human brains. Similarly, mapping functional networks in the entire rodent brain during sensory stimulation can provide critical insights of neural plasticity and functional recovery. In anesthetized rodent fMRI studies, a change of BOLD activity in the primary somatosensory cortex (S1) has been observed during functional recovery after injury. However, since the BOLD activity is observed only in S1, it is unknown whether the modification in the S1 BOLD signal is due to changes in local synaptic activities or in thalamic afferents. Lack of thalamic activities may be due to an insufficient sensitivity of BOLD fMRI. To examine this issue, mouse fMRI experiments were performed on the ultrahigh magnetic fields of 9.4T and 15.2T since an increase of BOLD signals with field strength is expected.

C57BL/6 mice were used for fMRI studies under ketamine and zylazine anesthesia. Two different fMRI studies were performed; i) magnetic field strength dependent fMRI on the forepaw stimulation with spatial resolution of 188 × 188 × 500 μm^3 and temporal resolution of 1 s at the 9.4 T (N=7) and 15.2 T (N=7) Bruker MR systems to examine the functional sensitivity, and ii) forepaw vs. hindpaw stimulus fMRI with spatial resolution of 125 × 125 × 500 μm^3 and temporal resolution of 1.5 s at 15.2T (N=7) to determine spatial specificity of ultrahigh-field BOLD fMRI.

While activation at 9.4T was only localized in the contralateral primary forelimb somatosensory cortex, the response at 15.2 T was additionally observed in the thalamus and secondary somatosensory cortex (S2). This indicates that the sensitivity gain by the use of ultrahigh magnetic field allows us to detect macroscopic activities in entire somatosensory pathways. Also, high resolution BOLD fMRI at the ultrahigh field of 15.2T separated activities in the primary somatosensory area and secondary areas in a somatopic manner.

In conclusion, ultrahigh-field fMRI of mouse opens a new research avenue for investigating functional networks in the whole brain noninvasively and repeatedly, allowing investigations of functional development, recovery, and reorganization in diseased and transgenic models.

Funding: This project is funded by the Institute for Basic Science in Korea (IBS-R015-D1)

Abstract A13

The ciliopathy gene Tmem138 contributes to intellectual disability and affects neuronal survival

HeeJin Jang[1], JeongHo Lee[1]

[1]Korea advanced Institute of Science and Technology (KAIST)

Joubert syndrome is rare autosomal recessive genetic disorder. It is characterized by appearance of molar tooth sign that is caused the absence or underdevelopment of the cerebellar vermis. Most cells of Joubert syndrome patient show absence of primary cilia or abnormality of cilium structure. The proteins made from cause genes are located in primary cilium. They are either known or thought to affect cell structures called cilia. One of cause genes, Tmem138 is thought to function as vesicular trafficking.

We made Tmem138 conditional knock-out mouse by using Cre-loxP system. Tmem138 is knock-out only in excitatory neuron of cortex and hippocampus by mating Emx1-cre mouse. Though behavioral tests, we found that these mouse have defect in hippocampus-dependent learning and memory. To investigate cause mechanism, we examined adult neurogenesis. We confirmed neuronal survival in dentate gyrus is decreased and apoptosis is increased. In addition to these findings, we found genome instability in Joubert syndrome patient's fibroblasts that have mutation in Tmem138 and hippocampal neuron of Tmem138 KO mouse.

Our findings suggest that Ciliary proteins including Tmem138 can influence neuronal survival in pursuance of adult neurogenesis and the mechanism may explain a role of primary ciliary proteins in the memory function, intellectual disability.

Abstract A14

Optogenetic protein clustering through fluorescent protein tagging and extension of CRY2

Hyerim Park[1,3], Na Yeon Kim[1,3], Sangkyu Lee[2], Nury Kim[2], Jihoon Kim[1] & Won Do Heo[1,2,*]

[1]Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

[2]Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

[3]These authors contributed equally to this work.

*Correspondence should be addressed to W.D.H. (e-mail: wondo@kaist.ac.kr)

Protein homo-oligomerization is an important molecular mechanism in many biological processes. Therefore, the ability to control protein homo-oligomerization allows the manipulation and interrogation of numerous cellular events. To achieve this, cryptochrome 2 (CRY2) from Arabidopsis thaliana has been recently utilized for blue light-dependent spatiotemporal control of protein homo-oligomerization. However, limited knowledge on molecular characteristics of CRY2 obscure its widespread applications. Here, we identify important determinants for efficient CRY2 clustering and introduce a new CRY2 module, named 'CRY2clust', to induce rapid and efficient homo-oligomerization of target proteins by employing diverse fluorescent proteins and an extremely short peptide. Furthermore, we demonstrate advancement and versatility of CRY2clust by comparing against previously reported optogenetic tools. Our work not only expands the optogenetic clustering toolbox but also provides a guideline for designing CRY2-based new optogenetic modules.

Abstract A15

Resting-state fMRI networks in anesthetized rhesus monkey: hyperalgesia -induced effects

Eunha Baeg, Bo-yong Park, Chan-Ung Park, Hyunjin Park, Choong-Wan Woo, Seong-Gi Kim

Center for Neuroscience Imaging Research, Institute for Basic Sciences (IBS), Suwon 16419, Republic of Korea, Departments of Electrical Engineering and Biomedical Engineering, Sungkyunkwan University, Suwon 16419, Republic of Korea, School of Electronic and Electrical Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea, and Department of Electronic, Electrical and Computer Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea.

Resting state coherent fMRI activities of the brain have been reported in humans, non-human primates (NHP) and even rodents. Although its functional role needs to be further verified, it was reported that network synchronizations are modified by learning and cognitive tasks in humans, suggesting that resting state fMRI (rsfMRI) can detect network-level activity changes. We applied rsfMRI to determine whether capsaicin-induced hyperalgesia affects the network synchronization of rsfMRI in anesthetized NHP. The independent component analysis decomposed group-wise rsfMRI data into 10 independent components reliably. Nine components out of ten were selected because of their known relations with human rsfMRI networks and were used to compute connectivity matrices. Electrical stimulation by itself did not affect rsfMRI networks. However, capsaicin application induced centrality changes in sensorimotor related networks, in which networks are the major target of the electrical stimulation. Our result suggests that MION-enhanced rsfMRI in non-human primates is a good approach to understand the underlying mechanisms of network-level changes in functional connectivity because of its superiority in detecting modified functional networks, and the similarity to human network changes.

Abstract A16

Understanding the mechanism of neurodegenerative diseases caused by phospholipid abnormality

Sunkyung Kim[1], Yejin Park[1], Sanghak Jeon[1]

[1]Department of Biology Education, Seoul National University, Seoul 08826, Republic of Korea

Brain is one of the richest organs in lipid content. Phospholipids are important building blocks of cell membranes, which provide an optimal environment for protein interactions, trafficking and function. Recently, we have found various phenotypes related to neurodegenerative disease in the mutation of Drosophlia Phosphatidylserine synthase1(dPtdss1), which functions in the production of Phosphatidylserine(PS). Mutations in Drosophila Ptdss1 gene resulted in reduced life spans, impaired locomotive capacity, increased bang-sensitivity and increase in the size and number of brain vacuoles. It was confirmed that apoptosis and ROS (Reactive Oxygen Species) occurred more severely in the mutants than wild type. Since the dPtdss1 gene encodes PS synthase, it is predicted that phospholipids composition will be altered if an abnormality occurs in this gene. In humans, mutation of the phospholipid synthase causes serious abnormality in development and organ formation, such as Lenz-Majewski syndrome (LMS). Studies have also shown that neurodegeneration occurs when there are mutations in the enzymes involved in phospholipid synthesis pathways, such as phosphatidylserine decarboxylase (PSD), swiss cheese protein, and ethanolamine kinase (EK). In this study, we investigated the mechanism of degenerative phenomenon which focused on mitochondrial abnormality in dPtdss1 mutation. Moreover, we confirmed that the neuroinflammation occurred in our mutants.

Complement C3 phosphorylation by Gene X is critical for synaptic pruning by microglia

Juhyun Lee[1], Seunghyun Lee[2], Shihyun Sung[3], Dohyun Lee[3], Sangjune Kim[3, 4], Eunji Oh[1], Ji-young Seo[1], Se-young Choi[2] and Kyong-Tai Kim[1,3,*]

[1]Division of Integrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang 790-784, Republic of Korea
[2]Department of Physiology, Dental Research Institute, Seoul National University School of Dentistry, Seoul 110-749, Republic of Korea
[3]Department of Life Sciences, Pohang University of Science and Technology, Pohang 790-784, Republic of Korea
[4]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

During postnatal neurodevelopment, some of the excessively formed synapses should be eliminated by 'synaptic pruning' by microglia in order to complete a functional brain connectivity. For synaptic pruning to occur, synapse-to-be-lost should be tagged by opsonins. Especially, complement component C3 (C3) serves as opsonins for synapses in nervous system. Here we show that Gene X, which is expressed in microglia, phosphorylates C3 and enhances its opsonization by releasing the intermolecular thioester bond-containing domain of C3. In Gene X-deficeint mice (Gene XKO), lack of C3 phosphorylation resulted in reduction of opsonization by C3. As a result, synaptic pruning was not efficiently performed as needed, in turn, Gene X KO mice showed impaired hippocampal learning and sociability due to delayed neurodevelopment. Similar to Gene XKO mice, 2p15-p16.1 microdeletion syndrome of human, which includes deletion of Gene X, showed impairment of neurodevelopment. Thus, our findings can be one of the possible explanations of 2p15-p16.1 microdeletion syndrome.

Abstract A18

Synchronized type-2 theta oscillations in the reciprocal cingulo -amygdala circuits are required for observational fear

Seong-Wook Kim[1], Minsoo Kim[1], Gireesh Gangadharan[1], Jinhee Baek[1], Charles Latchoumane[1], Taesup Cho[1], Junweon Byun[1,2], Duk-Soo Kim[3], Yeon-Soo Kim[4], Ji Su Ma[5], Masahiro Yamamoto[5], Yong Ryoul Yang[6], Pann-Ghill Suh[6], and Hee-Sup Shin[1,2]

[1]Center for Cognition and Sociality, Institute for Basic Science (IBS), 70 Yuseong-daero 1689-gil, Yusung-gu, Daejeon, 305-811 Republic of Korea
[2]IBS School, University of Science and Technology, Daejeon 305-333, Republic of Korea
[3]Department of Anatomy, College of Medicine, Soonchunhyang University, Cheonan-Si, Republic of Korea
[4]Graduate School of New Drug Discovery & Development, Chungnam National University
[5]Department of Immunoparasitology, Research Institute for Microbial Diseases, Osaka University, Suita, Osaka 565-0871, Japan
[6]School of Life Science, Ulsan National Institute of Science and Technology, Ulsan, Republic of Korea

Observational fear relies on the coordinated activity in the cingulo-amygdala circuits, yet the underlying neural mechanism and substrates allowing long-range functional connections during observational fear expression remains unclear. Here, we found that mice with a knockout or right anterior cingulate cortex (ACC)-specific knockdown of phospholipase C-β1(PLC-β1) showed impaired observational fear, whereas silencing of PLC-β1 in the left ACC, prelimbic, and infralimbic cortex had no effect. In the local field potential recording, power and phase synchrony of low-frequency theta rhythms in the range of 4-8 Hz were decreased in the ACC and basolateral amygdala (BLA) of ACC-specific PLC-β1 knockdown observers during observational fear. Suppressed type-2 theta rhythms by optogenetic inhibition of medial septal GABAergic neurons projecting to the hippocampus decrease freezing level during observational fear. Furthermore, optogenetic inhibition of the reciprocal excitatory connections between the ACC and the BLA suppressed observational fear without affecting classical fear conditioning. Thus, these results suggest that type-2 theta oscillations in the reciprocal cinguloamygdala circuits drive observational fear.

Key words
Observational fear, Type-2 theta rhythms, Anterior cingulate cortex, Basolateral amygdala, Phospholipase C-β1

Abstract A19

Dynamics of neurovascular coupling between excitatory neurons and adjacent vessels during seizure events revealed by *in vivo* two-photon imaging

Hyun Kyoung Lim[1,2], Na-yeon You[1,3], Sungjun Bae[1,3], Seong-Gi Kim[1,3], Minah Suh*[1,3]

[1]Center for Neuroscience Imaging Research, Institute for Basic Science (IBS)
[2]Department of Biological Sciences, Sungkyunkwan University
[3]Department of Biomedical Engineering, Sungkyunkwan University Suwon 16419, South Korea

Epileptic seizures involve the most hyperactive and hypersynchronous neuronal activities, which result in the most dramatic functional hyperemia. Earlier studies showed large increases of cerebral blood volume and metabolism in the epileptic focus using PET, SPECT, fMRI, and intrinsic optical signal (IOS) imaging. However, there has been a controversy over the observations as negative blood oxygen level-dependent (BOLD) fMRI response was also observed in the epileptic focus in experimental seizure models and human epilepsy. But to date, a detailed examination has not been carried out to answer this controversy.

We proposed to investigate fine details of the interaction between neuronal responses and cerebrovascular dynamics during recurrent seizures in acute 4-aminopyridine (4-AP) seizure model at mesoscale as well as microscale. With concurrent measurement of local field potentials (LFP), cerebral blood volume (CBV) changes, single vascular dynamics (arterioles & venules) and fMRI BOLD responses were observed. Thy1-GCaMP6f mice were also used to investigate how individual neuronal activities were reflected in LFP signals. In accord with large increases of CBV and BOLD responses, arterioles near the seizure focus dilated right after the ictal onset and maintained their maximum dilation until seizure termination. Unlike arterioles, venules changed very little in response to the onset or termination. Furthermore, arterioles were observed to have a constricted tone during interictal periods with reduced gamma band power (30-100 Hz) and the following seizure-induced dilation showed a strong negative correlation with the degree of constriction. The following CBV increase and the arteriole dilation were most closely associated with increased alpha band (8-13 Hz) power at seizure onset while gamma band power showed the strongest correlation when a seizure was in progress. The GCaMP signals indicated two distinct activity patterns in that the seizure-induced activation propagated from a focus to its surroundings during the initial phase while individual neurons of a broad region showed synchronous activities during the later. Our findings provide useful insights into neurovascular basis of perfusion-based imaging signals in the epileptic state and may have implications for further research of epileptic brain using non-invasive imaging techniques. This study is important for the adequate interpretation of the signals such as blood oxygen level-dependent (BOLD) fMRI, which is widely used in clinical research and surgical operations.

Abstract A20

Mitochondrial calcium promotes constriction of mitochondrial inner compartment as a priming event for efficient mitochondrial division in neuron

Bongki Cho[1], Hyo Min Cho[2], Youhwa Jo[2], Hee Dae Kim[3], Myungjae Song[4], Cheil Moon[1], Hyongbum Kim[4], Kyungjin Kim[1,5], Hiromi Sesaki[6], Im Joo Rhyu[2], Hyun Kim[2], and Woong Sun[2*]

[1]Department of Brain & Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology, Republic of Korea
[2]Department of Anatomy, Korea University College of Medicine, Republic of Korea
[3]Department of Biological Sciences, Seoul National University, Republic of Korea
[4]Department of Pharmacology, Yonsei University College of Medicine, Republic of Korea
[5]Korea Brain Research Institute, Republic of Korea
[6]Department of CellBiology, Johns Hopkins University School of Medicine, USA

Neurons require proper regulation of mitochondrial function for their development, function, survival and plasticity. The process is mediated by morphological change, which is controlled by balance between fusion and division. While mitochondrial fusion is completed by sequential fusion of outer- (OMM) and inner-membrane by Mfn1/2 and Opa1, mitochondrial division is solely executed by cytosolic OMM -constricting machineries including Drp1. Although some event in mitochondrial inner compartment for mitochondrial division has been proposed, the precise underlying mechanism has not been yet elucidated. In this study, we found spontaneous, transient and repetitive constriction of mitochondrial inner compartment (CoMIC) in neuronal process, and dissected its molecular mechanism as a priming event for efficient mitochondrial division. Although the CoMIC is spatiotemporally linked with mitochondrial division, it appears independently of OMM-constricting machineries. Instead, the CoMIC is initiated and potentiated by mitochondrial influx of Ca^{2+}, which induces two synergistic processes; 1) mitochondrial bulging and depolarization by mitochondrial influx of K^{+}, and 2) transient disorganization of OMM-IMM contact by accumulation of short Opa1. Furthermore, the mitochondrial influx of Ca^{2+} indirectly promotes efficient mitochondrial division by triggering the CoMIC. Taken together, we first suggest a Ca^{2+}-driven priming event on mitochondrial inner compartment for efficient mitochondrial division.

Abstract A21

Physiological character of silent synapse after chronic cocaine exposures by D1 MSN specific NR2B suppression

Hyun Jin Kim[1], Joung-Hun Kim[1,*]

[1]Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang, Gyungbuk, 37673, Korea

Addiction is psychological symptom accompany with consequences of behavioral expression for seeking reward even though negative feedback. Addictive substances are surround our lives, among these, addictive drugs are powerful but harmful to our health. When after exposure to the addictive drugs, various cellular and molecular mechanisms dynamically occur in our brain. Excitatory inputs to the medium spiny neurons (MSNs) of nucleus accumbens (NAc), which is critical area for behavioral responses to the addictive drugs, are dramatically changes after repeated exposure to cocaine or addictive drugs. The generation of silent synapse which only has NMDAR including NR2B subunit and lacking of AMPAR is the most prominent plasticity of glutamatergic transmission to the MSN, especially D1 MSN, in NAc after chronic cocaine exposure. In addition, silent synapses highly correlated locomotor sensitization and conditioned place preference (CPP). However, there is little information on the role of NR2B subunits for silent synapses and addiction like behaviors. Here, using viral mediated conditional knock down (cKD) technique and optogenetics, we assessed whether the cKD of NR2B subunit alters the, physiological and behavioral aspects in the D1 MSN of NAc shell area. Locomotor sensitization after 5days of non-contingent cocaine exposure, NR2B cKD virus injected mice show increased locomotor activity. In contrast, % silent synapse was reduced but generated the silent synapses. Moreover, we found evidences the contribution of distinct other NMDAR subunits (i.e. NR2C) through the selective antagonists tests in NR2B deleted D1 MSNs. In addition, the result of CPP was impaired on NR2B cKD mice. Together, these results indicate that NR2B is not critical for the generation of silent synapses but strongly contribute to the glutamatergic changes, like synaptic plasticity, for the acquisition of associated memory formation when after cocaine exposure.

Abstract A22

Characterization of *in vivo* functions of BCR

Eunkyung Lie[1], Eunjoon Kim[1,2]

[1]Center for Synaptic Brain Dysfunctions, Institute for Basic Science (IBS), Daejeon 305-701, Korea
[2]Department of Biological Sciences, Korea Advanced Institute for Science and Technology(KAIST), Daejeon 305-701, Korea

Rac1, one of the protein of Rho family small GTPases, is involved in spine and synapse remodeling. Abnormal Rho activity affects brain dysfunctions which could induce several psychiatric disorders. Breakpoint cluster region (BCR), as a Rac GTPases-activating protein, known to generate a hybrid protein as combined with c-Abl tyrosine kinase in Philadelphia chromosome-induced chronic myeloid leukemia. Relatively little papers suggested that the relation between deficit of BCR protein and brain dysfunctions. Here, we reported the characterized BCR knock-out (KO) mice to explore in vivo functions of bcr–/– mice.

Abstract A23

MicroRNAs as modulators of circadian gene *Period2* oscillation

Inah Park[1], Han Kyoung Choe[1], Youngshik Choe[2], Kyungjin Kim[1,3]

[1]Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu 42988, Korea
[2]Department of Neural Development and Disease, Research Division, Korea Brain Research Institute (KBRI), Daegu 41068, Korea
[3]Korea Brain Research Institute (KBRI), Daegu 41068, Korea

Circadian clock controls an organism's biological rhythm and regulates physiological conditions in response to external time cues. Most living organisms have their own time-keeping mechanism that is maintained by transcriptional-translational auto-regulatory feedback loops involving several core clock genes such as *Periods, Cryptochromes, Clock*, and *Bmal1*. Recent discoveries have found the relevance between changes in circadian oscillation and post-transcriptional modification by microRNAs (miRNAs). However, the specific mechanisms of miRNAs on circadian oscillation remain unclear. To understand modulatory functions of miRNAs on circadian rhythm, several *in silico* algorithms were used and identified miR-24-3p and miR-25-3p as promising candidates targeting *Per2* mRNA. Luciferase reporter assay validated that miR-24-3p and miR-25-3p repressed the expression of the luciferase reporter containing predicted miRNAs binding sites of 3' untranslated region (UTR) of *Per2* mRNA. Furthermore, real-time bioluminescence analyses using PER2::LUC transgenic mouse confirmed that PER2 protein oscillation patterns were sensitive to the level of selected miRNAs in vitro and ex vivo. Overexpression of either miR-24-3p or miR-25p-3p resulted in dampening and period lengthening of PER2::LUC oscillation, while inhibition of either miR-24-3p or miR-25-3p increased the relative amplitude of PER2::LUC oscillation. In summary, both miR-24-3p and miR-25-3p are involved in fine-tuning of circadian rhythmicity through regulating PER2 oscillation at the post-transcriptional level.

Analyzing the endogenous calcium oscilllation of kisspeptin neurons and its effect on GnRH neurons

Doyeon Kim[1,2], Jeongah Kim[1,3], Inah Park[1], Sangwon Jang[1], Mijung Choi[1], Kyojin Ku[1], Gi Hoon Son[4], Han Kyoung Choe[1], Kyungjin Kim[1,5,*]

[1]Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu, Korea
[2]Interdisciplinary Program in Neuroscience, College of Natural Sciences, Seoul National University, Seoul, Korea
[3]Department of Biological Sciences, College of Natural Sciences, Seoul National University, Seoul, Korea
[4]Department of Biomedical Sciences, College of Medicine, Korea University, Seoul, Korea
[5]Korea Brain Research Institute (KBRI), Daegu, Korea

Kisspeptin in the hypothalamus acts as an important regulator of mammalian reproduction by synchronizing gonadotropin-releasing hormone (GnRH) pulse generator. Mainly located in the arcuate nucleus (ARC) and the anteroventral periventricular nucleus in the hypothalamus, kisspeptin neurons are poised to generate GnRH pulse and surge. Our group previously reported that intermittent administration of kisspeptin elicits synchronization of GnRH promoter activity and pulsatile secretion of GnRH. However, the driving force which produces pulsatile kisspeptin output still remains unknown. We hypothesized that kisspeptin neurons would sustain their own rhythm, with information received from neurotransmitter or hormonal inputs integrated. To address the hypothesis, we analyzed endogenous intracellular calcium dynamics from ARC kisspeptin neurons *ex vivo*. Subsequently, we imaged fluorescent and luminescent signals from organotypic slice culture of *Kiss1-IRES-Cre;GnRHp-dsLuc* mouse transduced with adeno-associated virus encoding RGECO, a genetically encoded calcium indicator. Calcium oscillation in ARC kisspeptin neurons was highly synchronized and appeared to have 240~300s period, which was abolished by IP_3 receptor blocker and induced by neurokinin B agonist. Analysis of kisspeptin neurons' endogenous calcium oscillation and their regulatory factors would elucidate the mechanism underlying pulsatile kisspeptin secretion. Further, monitoring their effects on GnRH neurons would help understand the neural network regulating GnRH pulse generator.

Abstract A25

Novel peptide drug candidates reduce *Aβ* oligomers and plaques

Seungyeop Baek[1,2], Sejun Lee[1], Jiyoon Kim[3], Seung-Hoon Yang[3], Donghee Lee[1], Taeho Ko[1], Daeun Kwak[1], Kyeonghwan Kim[1], Illhwan Cho[1], Yoonseong Son[1], Gyoonhee Han[2*], and Youngsoo Kim[1*]

[1]Department of Pharmacy, Yonsei University, Yeonsu-gu, Incheon 21983, Republic of Korea
[2]Department of Biotechnology, Yonsei University, Seoul 03722, Republic of Korea
[3]Korea Institute of Science and Technology (KIST), Seoul 02792, Republic of Korea

Alzheimer's disease (AD) is the most common neurodegenerative disorder. One of the main causes of AD is the aggregation of amyloid-β (Aβ) peptides and an increase of amyloid plaques in the brain. Recently, many drug candidates focusing on the amyloid clearance mechanism are reported. We designed a peptide drug candidate to bind and dissociate Aβ aggregates. We hypothesized that this peptide can disaggregate Aβ plaques, which reduces the prevalence of amyloid plaques in APP/PS1 (2xTg-AD) transgenic mice models. We injected the peptide drug eight-times intravenously into 10-month-old 2xTg-AD mice for 4 weeks. Mice were sacrificed three days after the final injection. We collected blood from the inferior vena cave and brain. The brain was sliced at 30 μm and stained with thioflavin S (ThS), in order to visualize the β-sheet-rich Aβ plaques. In the results, we observed a significant decrease in plaque number and total plaque area in drug-injected 2xTg-mice, compared to vehicle-injected mice. We propose an alternative prospective use of the peptide drug candidate as a therapeutic reagent for AD.

Abstract A26

Organoselenium-based fluorescent probes for detection of biological analytes related to neurodegenerative diseases

Donghyeon Kim[1,2], David G. Churchill[*1,2]

[1]Molecular Logic Gate Laboratory, Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea.
[2]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea.

Organoselenium molecular probes show great promise in the detection of biological analytes such as reactive oxygen species (ROS) and biothiols in living biological systems. These biological species are considered to play important roles for normal physiological processes; an overproduction or deficiency of them can indicate neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). 1 ROS have important roles in biological systems such as an apoptosis, a gene expression and an activation of cell signalling cascades. If the ROS level in cells exceed the antioxidant capacity, it can cause the damage to lipids, proteins and DNA and lead to cellular death resulting in neurodegenerative diseases. 2 Biothiols such as cysteine(Cys), homocysteine (Hcy) and glutathione (GSH) also have significant roles in biological system. Especially, GSH is an important antioxidant that protects the cell from oxidative damage and maintains biological homeostasis. Therefore, the abnormal high level of GSH can demonstrate that cells are under the condition of oxidative stress which is responsible for or observed in AD and PD. 3 The details of synthesis, screening, biological studies and applications of phenyl selenium-based small molecule probes will be discussed in this presentation.

1. (a) Hyman, L. M.; Franz, K. J, *Coord. Chem. Rev*. **2012**, *256*, 2333; (b) Feng, Y.; Cheng, J.; Zhou, L.; Zhou, X.; Xiang, H. *Analyst* **2012**, *137*, 4885.
2. (a) Hancock, J. T.; Desikan, R. and Neill, S. J. *Biochem. Soc. Trans.*, **2001**, 29, 345. (b) Waris, G. and Ahsan, H.; Carcinog, J. **2006**, 5, 14.
3. (a) Townsend, D. M.; Tew, K. D.; Tapiero, H. *Biomed. Pharmacother*. **2003**, *57*, 145; (b) Helbling, B.; Overbeck, J. V.; Lauterburg, B. H. *Eur. J. Clin. Invest*. **1996**, *26*, 38.

An astrocytic membrane protein, MLC1 inhibits cell motility for stable cell communication

Junmo Hwang[1], Hyun-Ho Lim[1]

[1]Department of Structure & Function of Neural Network, Korea Brain Research Institute (KBRI), Daegu, Korea

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) disease is a rare type progressive leukodystrophy in children. Mutation of MLC1 mainly lies behind of this disorder leading vacuolation of myelin and astrocyte, subcortical cysts, brain edema, and macrocephaly. Recent studies indicate that functional interactions between MLC1, GlialCAM, and ClC-2 channel is important to regulate neuronal, glial, and vascular homeostatic interactions, however, the physiological role of MLC1 on the cellular communication is poorly understood. Thus, we have been trying to reveal the molecular function of MLC1 on the cell to cell interaction. Expression of MLC1 drastically altered cell morphology; disappearance of lamellipodia and increase in filopodia. Moreover, wound healing assay and live cell time-lapse imaging revealed that cell motility was significantly suppressed by MLC1. These changes in cell morphology and motility seemed to be correlated with altered cellular actin dynamics. Interestingly, patient-derived MLC1 mutants did not affect cell morphology and motility and the expression pattern of mutants were mainly accumulated in the intracellular organelles. These data suggested that expression of MLC1 on the plasma membrane might change actin dynamics, cell shape and cell motility. Indeed, we found that MLC1 shows heteromorphic intracellular distribution patterns during the course of expression. Plasma membrane-localized MLC1 (PM-MLC1) induced stationary movement, however, intracellular organelle-localized MLC1 (IO-MLC1) showed normal cell motility. These results indicate that MLC1 is important to regulate cell motility and stabilizing cell-cell interaction. In MLC disease patients, misallocation of mutant MLC1 could related with unstable cell communication resulting in disturbed homeostasis of neuro-glia-vascular interaction.

Keywords

Neurovascular unit; MLC1; Cell motility; Actin branching; Cell communication

Towards reversible probing of oxidative stress in biology of neurodegenerative disease research

Woo Hyun Lee[1,2], Tesla Yudhistira[1,3], Youngsam Kim[1,2], David G. Churchill*[1,2,4]

[1]Molecular Logic Gate Laboratory, Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea

[2]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea

[3]Lembaga Pengelola Dana Pendidikan (LPDP), Indonesia Endowment Fund for Education, Kementrian Keuangan Republik Indonesia, Gedung Ali Wardhana Lt. 2 Kementerian Keuangan Jl. Lap. Banteng Timur No. 1 Jakarta 10710, DKI Jakarta, Negara Kesatuan Republik Indonesia.

[4]Visiting Associate Professor, Schulich Faculty of Chemistry at Technion - Israel Institute of Technology (2017-2018).

Selenium as an element is extremely versatile in biology. Organoselenium compounds, as well as organic forms of sulfur and tellurium are also emergent species in the interest of better understanding redox chemistry. In this presentation we detail the synthesis and characterization of a variety of probes and medicinal compounds and explain what information we have accumulated so far from which (live) cell assays and animal studies, to date. As a laboratory, we are interested in understanding more about neurodegenerative disease research on the molecular level. Organoselenium molecular probes show great promise in the detection of a variety of biological analytes in living biological systems. The valence of the element can rise to 4, and also in some cases to 6, allowing for significant optical changes to occur in the responsive media. The analytes of interest relate to ROS but also involve biothiols. Overproduction, or deficiencies of ROS and related species such as biothiols (reductants) can be indicative of, or may play a decisive role in, cancer formation and neurodegenerative disease disorders such as Alzheimer's (AD) and Parkinson's disease (PD).1 Such goals in molecular detection, sensing, and imaging require extensive small molecule (fluorophore) design which can also involve metal ion binding. The selective and reversible determination of these species is required for a better understanding of their role in biological systems, possible therapeutic potential of medicinal compounds, and towards molecular detection of the disease and in the early diagnosis of disease. Recent examples from our own laboratory, through collaborative work, as well as from other researchers will be profiled. Thus, the details of synthesis, screening, biological studies and general application of many recent sulfur/selenium-based small molecular probes prepared in our group will be highlighted in this presentation.[2-5]

1. Hyman, L. M.; Franz, K. J, *Coord*. *Chem*. *Rev*. **2012**, *256*, 2333.
2. “Novel intramolecular pi-pi-interaction in a BODIPY system by oxidation of a single selenium center: geometrical stamping and spectroscopic and spectrometric distinctions.” Kim, Youngsam; Jun, Taehong; Mulay, Sandip V.; Manjare, Sudesh T.; Kwak, Jinseong; Lee, Yunho; Churchill, David G. DALTON TRANSACTIONS Volume: 46 Issue: 12 Pages: 4111-4117.
3. “Substituent Effects in BODIPY in Live Cell Imaging.” Mulay, Sandip V.; Yudhistira, Tesla; Choi, Minsuk; Kim, Youngsam; Kim, Jinjoo; Jang, Yoon Jeong; Jon, Sangyong; Churchill, David G.; CHEMISTRY-AN ASIAN JOURNAL Volume: 11 Issue: 24 Pages: 3598-3605.
4. “Enhanced Fluorescence Turn-on Imaging of Hypochlorous Acid in Living Immune and Cancer Cells.” Mulay, Sandip V.; Choi, Minsuk; Jang, Yoon Jeong; Kim, Youngsam; Jon, Sangyong; Churchill, David G. CHEMISTRY-A EUROPEAN JOURNAL Volume: 22 Issue: 28 Pages: 9642-9648
5. “Diselenide-based probe for the selective imaging of hypochlorite in living cancer cells.” Kim, Youngsam; Choi, Minsuk; Manjare, Sudesh T.; Jon, Sangyong; Churchill, David G.; RSC ADVANCES Volume: 6 Issue: 38 Pages: 32013-32017

The 11th UK-KOREA Neuroscience Symposium

20-21 August 2018

Hotel Shilla Stay, Haeundae, Busan, Korea

Poster Presentation

Poster Group-B

Reactivation in biological and artificial neural networks

Gido M. van de Ven

[1]MRC Brain Network Dynamics Unit, Department of Pharmacology,
University of Oxford, Oxford OX1 3TH, UK
[2]Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza,
Houston TX 77030, USA

The brain's ability to retain memories over a lifespan is thought to rely on the reactivation of memory-representing cell assemblies. To experimentally test this, for my PhD I performed multi-unit recordings in the hippocampus of mice exploring novel environments. We showed that selectively disrupting reactivation by closed-loop optogenetic silencing of sharpwave/ ripples (SWRs) impaired the later reinstatement of recently-formed place cell assemblies, thereby providing the first direct evidence that reactivation stabilizes new cell assemblies.

To gain deeper insight into the computational role of reactivation, for my postdoc I turned to machine learning. Current state-of-the-art artificial neural networks are my ideal "model organism" as they can perform extremely well on a wide variety of individual tasks, but they struggle to retain old information when trained on new tasks. Could reactivation improve memory consolidation in artificial neural networks? To test this, we equipped deep feedforward networks for classification with symmetrical feedback connections that were trained to have generative capability. We found that interleaving "reactivation" generated by these feedback connections with new task data, substantially reduces the "catastrophic forgetting" of old tasks. Notably, this approach outperforms and is more widely applicable then current deep learning strategies for alleviating catastrophic forgetting.

Abstract B2

Postsynaptic p47phox controls long-term depression in the hippocampus

Jee Hyun Yi[1,2,3], Dong Hyun Kim[1], Thomas M. Piers[1], Daniel J. Whitcomb[1,2], Philip Regan[1,2*] and Kwangwook Cho[1,2*]

[1]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, Faculty of Health Sciences,
[2]Centre for Synaptic Plasticity, University of Bristol, Whitson Street, Bristol, BS1 3NY, United Kingdom,
[3]Center for Synaptic Brain Dysfunctions, Institute for Basic Science, Daejeon 34141, Republic of Korea.

It is well documented that reactive oxygen species (ROS) affects neurodegeneration in the brain. Several studies also implicate ROS in the regulation of synapse function and learning and memory processes, although the precise source of ROS generation within these contexts remains to be further explored. Here I show that postsynaptic superoxide generation through PKCζ -activated NADPH oxidase 2 (NOX2) is critical for long-term depression of synaptic transmission (LTD) in the CA1-Shaffer collateral synapse of the rat hippocampus. Specifically, PKCζ-dependent phosphorylation of p47phox at serine 316, the NOX2 regulatory subunit, is required for LTD but has no roles in long-term potentiation (LTP). Therefore, this study suggests that postsynaptic p47phox phosphorylation at serine 316 is a key upstream determinant for LTD and synapse weakening.

Key index words
Reactive oxygen species, PKCζ, NADPH oxidase, Long-term depression

Abstract B3

A tauopathy-associated tau fragment causes autophagic dysfunction

Dina Dakkak, Tong Guo, Wendy Noble, Diane P. Hanger

Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

Introduction

Tauopathies are characterised by aggregates of posttranslationally modified tau. We identified a tau fragment, Tau35, in human four-repeat (4R) tauopathy brain and used this to generate a cell model, in which Chinese hamster ovary (CHO) cells stably express Tau35 (CHO-Tau35) or full-length human tau (CHO-FL). Since altered autophagy has previously been reported in several models of tauopathy, we investigated the autophagic status of CHO-Tau35 cells.

Materials and Methods

Markers of the autophagy pathway, including microtubule-associated proteins 1A/1B light chain 3B (LC3) and Beclin-1, were measured in CHO-Tau35 cells on western blots and using immunofluorescence. Experiments were conducted under basal conditions and following stimulation of autophagy using rapamycin. Other markers, including lysosomal associated membrane protein 2(LAMP2), transcription factor EB (TFEB), cathepsin D and lipid staining were assessed using fluorescence microscopy.

Results

The basal amount of LC3-II was significantly lower in CHO-Tau35, compared to CHO-FL and CHO cells. Upon rapamycin treatment, LC3-II remained significantly reduced. LAMP2 staining was reduced in CHO-Tau35 compared to CHO-FL and CHO cells. Parallel decreases were observed in cathepsin D staining and cathepsin D/LAMP2 localisation in CHO-Tau35. Imaging of TFEB revealed a higher proportion of cytoplasmic TFEB in CHO-Tau35. BODIPY staining showed a higher number of lipid droplets in CHOTau35 compared to CHO-FL and CHO cells.

Conclusions

Under both basal and stimulated conditions, levels of LC3 in CHO-Tau35 were reduced, thereby revealing that Tau35 reduces autophagosome formation. Additionally, the limited response of LC3 to rapamycin in CHO-Tau35 suggests that Tau35 is less able to activate autophagy via an mTORdependent mechanism. Reduced nuclear TFEB in CHO-Tau35 suggests impaired lysosomal biogenesis, which is further validated by decreased LAMP2 and cathepsin D in CHO-Tau35.

Abstract B4

Direct in-cell observation of structural progression of amyloid-β Arctic mutant aggregation

Meng Lu[1,2], Neil Williamson[2], Ajay Mishra[1,2], Claire H. Michel[2], Clemens F. Kaminski[1,2], Alan Tunnacliffe[1], Gabriele S. Kaminski Schierle[1,2]

[1]Cambridge Infinitus Research Centre, Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge CB2 3RA, United Kingdom
[2]Department of Chemical Engineering and Biotechnology, University of Cambridge, West Cambridge Site, Philippa Fawcett Drive, Cambridge, CB3 0AS, United Kingdom

Hereditary Aβ mutations, such as the Arctic Glu22-to-Gly (E22G) mutation, lead to increased intracellular accumulation of β-amyloid and disease onset at a young age. It remains largely unknown, how the Arctic mutation leads to aggressive protein aggregation and increased toxicity. Here, we constructed stable cell models expressing wild-type (WT) and E22G Aβ42 fused to mCherry to study the aggregation kinetics of the Arctic Aβ mutant and its heterogeneous structural forms. Arctic mutant peptides assemble to form fibrils at a much faster rate than WT peptides and rapidly accumulate to form fibril bundles or clusters and later aggresomes. All aggregate species, as revealed by fluorescence-lifetime imaging (FLIM) and 3D Structural Illumination Microscopy (SIM), display a lowered fluorescence lifetime and highly compact structures with a strong affinity among individual fibrils. The aggregates formed by Arctic mutant Aβ are also more resistant to intracellular degradation than their wild-type counterparts.

Abstract B5

The divergent role of Frizzled receptors in synapse connectivity and plasticity

McLeod F, Bossio A and Salinas PC

Department of Cell and Developmental Biology, University College London, London, WC1E 6BT, UK.

Activity-mediated changes in the strength of glutamatergic synapses, the basis of synaptic plasticity, are critical for learning and memory. Reduced synaptic plasticity and memory loss are key features of Alzheimer's disease (AD). Unravelling the mechanisms that govern synaptic plasticity is essential for therapeutic intervention strategies. Wnt secreted proteins are emerging as key modulators of synaptic connectivity. Our group has established a central role for Wnt signalling in synapse formation and maintenance. Wnt7a promotes synaptic connectivity by signalling pre and postsynaptically. Wnt7a binds to Frizzled 5 (Fz5) receptors to mediate presynaptic assembly. Fz7 is also a receptor for Wnt7a at the synapse. Gain/loss of function experiments demonstrate that Fz7 regulates dendritic spine number and the Wnt7a-mediated increase in spine number and growth. Furthermore, Fz7 is required for spine plasticity and enhanced synaptic strength following long-term potentiation (LTP) induction, one phenomena underlying synaptic plasticity. Therefore, Fz5 and Fz7 differentially mediate the effects of Wnt7a in axons and dendrites respectively and Fz7 signalling is required for structural and functional plasticity. We provide new insight into how synaptic modulators through their receptors regulate synaptic plasticity. Future experiments will focus on how defects in Fz receptors contribute to synaptic failure and memory deficits in AD.

Abstract B6

The impairment of cortical postsynaptic muscarinic acetylcholine receptor (mAChR) function in amyloid-β-mediated pathophysiology.

Jee Hyun Yi[1], Daniel J. Whitcomb[1] and Kwangwook Cho[1,2]

[1]Bristol Medical School, University of Bristol, Bristol, BS1 3NY
[2]UK-Dementia Research Institute at King's College London, Department of Basic and Clinical Neuroscience, King's College London, SE5 9NU, U.K.

The pathophysiology of Alzheimer's disease (AD), the predominant form of dementia, involves cognitive impairment and progressive neurodegeneration, driven in part by amyloid-β. Postmortem study suggests that aberrant synaptic loss in the cortex is a hallmark of AD, specifically the reduction of cholinergic innervation. Within the context of therapeutic applications, acethylcholinestrase (AChE) inhibitors are beneficial for cognitive enhancement in AD patiens. Arguably, however, AChE inhibitors have a tolerated dose problem and side effects in long-term trials, and limited clinical outcomes within certain stages of AD. Therefore, it is of interest to determine whether this is due to dysfunction of available mAChR in the synapse.

We investigated the dysregulation of mAChR function by amyloid-β-mediated patholophysiology in rat cortical brain slices *in vitro*. We found that amyloid-β causes a loss in surface expression of mAChR, and this was mirrored by decrements to carbachol-induced postsynaptic holding current change shown using whole cell patch clamping. Utilising the genetically-encoded calcium indicator GCaMP in organotypic cultured cortical slices, we found the impairment of mAChR function was associated with a reduction in mAChR-mediated calcium signal. Intriguing, these effects were reversed through inhibition of metabotropic glutamate receptor subtype 5 (mGluR5). Together, these findings tentatively suggest a mechanisitc interplay between mAChR and mGluR5, and this could serve as a crucial target in the restoration of mAChR function in AD pathology.

Abstract B7

MAPK-dependent presynaptic potentiation in the LHb is responsible for depressive behaviors

Hoyong Park[1], Hakyun Ryu[1], Seung-Jae Zhang[1], and ChiHye Chung[1,*]

[1]Department of Biological Sciences, Konkuk University, Seoul 05029, South Korea

The lateral habenula (LHb), recently proposed to be involved in depressive disorders, is a part of clock system in our brain. It was reported that disrupted circadian patterns are one of commonly observed symptoms in human patients with depression. Interestingly, the habenular complex is reported to contain an intrinsic molecular clock and to show rhythmic expression of circadian clock genes and proteins. In addition, previously reported abnormal potentiation of LHb neurons was shown to be mainly due to presynaptic alterations. However, it is unknown that the circadian rhythms in the LHb are impaired in depressive state. Furthermore, the mechanisms of this presynaptic enhancement remain completely unknown. In this study, we showed that the presynaptic release probability potentiation previously observed in the LHb of in animal models of depression is temporarily variable and mediated by altered mitogen -activated protein kinase (MAPK)-dependent signaling upon the activation of glucocorticoid receptors (GRs). Interestingly, either exposure to a stressor or incubation with corticosterone abolishes the circadian termporal oscillatory pattern of synaptic transmission in the LHb in MAPK-dependent but not protein kinase C (PKC)-dependent manner. The selective inhibition of MAPK kinase (MAPKK, MEK) activity in the LHb prevents the presynaptic potentiation of synaptic efficacy after the exposure to stressors and successfully reversed depressive symptoms including behavioral despair and helplessness in animal models of depression. Our study delineates the cellular and molecular mechanisms responsible abnormal presynaptic enhancement of LHb neurons in an animal model of depression, which critically participate in mediating depressive behaviours.

Abstract B8

Mossy fiber stimulation induces transient and inhibitory impact on CA3 neuronal activity in freely-moving mice

Joonyeup Lee[1,2], Miru Yun[1,2], Eunjae Cho[2], Jong Won Lee[2], Doyun Lee[3] & Min Whan Jung[1,2]

[1]Department of Biological Sciences, Korea Advanced Institute of Science and technology, Daejeon, Republic of Korea
[2]Center for Synaptic Brain Dysfunctions, Institute for Basic Science, Daejeon, Republic of Korea
[3]Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Republic of Korea

Strong hippocampal mossy fiber synapses are thought to function as detonators, imposing 'teaching' signals onto CA3 neurons during new memory formation. However, such strong inputs may disrupt previously formed neural representations. We found that optogenetic stimulation of mossy fibers can drive CA3 neuronal firing in freely-moving mice, but their effects are overall inhibitory and transient. Spatially restricted mossy fiber stimulation emulating dentate place cell firing, either congruent or incongruent with CA3 place fields, was more likely to suppress than enhance CA3 neuronal activity. Also, changes in spatial firing induced by optogenetic stimulation reverted immediately upon stimulation termination, leaving CA3 place fields unaltered. Our results argue against the standard view that mossy fibers convey teaching signals, and show the robustness of established CA3 spatial representations.

Abstract B9

Restless days and sleepless nights

Haram Park, Yeonsoo Choi, Hwajin Jung, Hanseul Kweon, Eunjoon Kim

Center for Synaptic Brain Dysfunctions Department of Biology, KAIST

Sleep is an essential condition to life. It has been well known that loss of sleep results in a plethora of symptoms including impaired memory, aggravation, cognitive dysfunction and in extreme cases results in death. Deficiency in sleep is a common comorbity of various neuropsychiatric disorders including ADHD and PTSD. Here we find that the conditional deletion of *Ptprd*, a protein tyrosine phosphatase acting as a major presynaptic hub during synaptogenesis and maintenance, results impaired sleep, memory dysfunction, and hyperactivity. Interestingly, *Ptprd* is a risk gene for Restless Leg Syndrome, in which patients suffer decreased sleep, as well as Attention-Deficit-Hyperactive Disorder. Analysis of brain-wide neuronal activity revealed loss of PTPRD results in decreased synaptic activity in centers of the brain critical to normal sleep architecture, such as the preoptic area of the hypothalamus. Our results reveal the importance of PTPRD in the formation of critical sleep circuits as well as how deletion of PTPRD leads to disrupted sleep architecture and comorbidities of sleep loss.

Abstract B10

In vivo imaging reveals regrowth of serotonin axons following injury in the adult mouse brain

Yunju Jin

Center for Cognition and Sociality Institute for Basic Science KI bldg. A420, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon, Korea

It is widely believed that damaged axons in the adult mammalian brain have little capacity to regrow, thereby impeding functional recovery after injury. Studies using fixed tissue have suggested that serotonin neurons might be a notable exception, but remain inconclusive. We have employed *in vivo* two-photon microscopy to produce time-lapse images of serotonin axons in the neocortex of the adult mouse. Serotonin axons undergo massive retrograde degeneration following amphetamine treatment and subsequent slow recovery of axonal density which is dominated by new growth with little contribution from local sprouting. A stab injury that transects serotonin axons running in the neocortex is followed by local regression of cut serotonin axons and followed by regrowth from the cut ends into and across the stab rift zone. Regrowing serotonin axons do not follow the pathways left by degenerated axons. The regrown axons release serotonin and their regrowth is correlated with recovery in behavioral tests.

Abstract B11

Somatostatin interneurons in the anterior cingulate cortex gate mouse observational fear

Arie Kim[1,2,*], Sehoon Keum[1,*], Jae Jin Shin[1,3], Jong-Hyun Kim[1,4], Joomin Park[1,2], Hee-Sup Shin[1,2]

[1]Center for Cognition and Sociality, Institute for Basic Science, Daejeon 34047, Republic of Korea
[2]School of Basic Science, University of Science and Technology, Daejeon 34113, Republic of Korea
[3]Department of Brain and Cognitive Science, Seoul National University, Seoul 08826, Republic of Korea
[4]Center for Glia-Neuron Interaction, Brain Science Institute, Korea Institute of Science and Technology, Seoul 02792, Republic of Korea
[*]These authors contributed equally

Empathy is the ability to recognize and share emotions with others. The anterior cingulate cortex (ACC) is critically involved in human empathy and the acquisition of observational fear in mice. However, molecular and cellular mechanisms in the ACC that control observational fear remain to be determined. Here, through behavior-driven forward genetic analyses in inbred strains of mice, we identified that a missense mutation in Neurexin 3 (*Nrxn3*) increased observational fear. Furthermore, mice in which *Nrxn3* was selectively deleted in somatostatin-expressing (SST^+) interneurons showed markedly increased vicarious fear. In acute slices of the ACC of those mice, inhibitory synaptic transmission from SST^+ neurons onto layer 2/3 excitatory neurons was impaired without affecting intrinsic excitability. Concordantly, optogenetic suppression of SST^+ interneurons in the ACC evoked an elevation of vicarious freezing, mimicking the *Nrxn3* ablation in SST^+ neurons, whereas activation of SST^+ neurons obliterated acquisition of observational fear. This study indicates that *Nrxn3* is an essential molecular machinery for inhibitory synaptic transmission in SST^+ neurons and uncovers a novel role of SST^+ neurons-mediated inhibitory circuit in the ACC in gating the top-down computation for the expression of socially incited fear.

Abstract B12

Different mutational rates and mechanisms in human cells at pregastrulation and neurogenesis

Taejeong Bae[1], Livia Tomasini[2], Jessica Mariani[2], Bo Zhou[3], Alexander E Urban[3], Alexej Abyzov[1], Flora M Vaccarino[2]

[1]Mayo Clinic, Health Sciences Research, Rochester, MN
[2]YaleUniversity, Child Study Center, New Haven, CT
[3]Stanford University, Psychiatry and Genetics, Palo Alto, CA

As evidence accumulates, it is becoming revealed that the genome of each cell in the human body is not identical, a phenomenon called somatic mosaicism. A few recent studies showed accumulation of post- zygotic mutations in cells of the healthy human body. Growing single cells, directly collected from three fetal brains, we established 31 clones of neuronal progenitors, and conducted whole genome sequencing on DNA of each clone. Across the three brains, we detected 183-399 mosaic single nucleotide variations (SNVs) per cell at 15-21 weeks post-conception. On a coarse scale mosaic SNVs were distributed uniformly across the genome, and showed similar pattern to the mutational signatures in cancer, suggesting a possible role of background mutagenesis there. SNVs with a frequency of >2% in brain were shared with the spleen, revealing they have occurred before gastrulation. Reconstruction of mutational history of SNVs during the first five post-zygotic cell divisions estimated a mutation rate of 1.3±0.15 per division per cell. The mutation rate shifted towards oxidative stress-related mutations and increased to ~ 8.6 per division per cell in neuronal progenitors. This suggests that neurogenesis is more mutagenic than early embryogenesis while both periods are more mutagenic than adulthood.

Abstract B13

Measuring glutamate released from individual presynaptic terminals reveals release probability-dependent modulation of exocytic patterns at hippocampal synapses

Yujin Kim*, Soohyun Kim, Unghwi Lee, Sunghoe Chang**

*: presenter
**: corresponding author

Department of Physiology and Biomedical Sciences, Neuroscience Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, South Korea

The number of synaptic vesicles released in response to an action potential at presynaptic terminals determines synaptic weight and reliability. Although previous electrophysiological and optical methods have shown quantal mode of vesicular release, the actual amount of glutamate and the number of released vesicles per exocytic event at single hippocampal synapses remained unknown. To address it, we measured amounts of released glutamate by imaging an axon-targeting glutamate sensor iGluSnFRpre at individual presynaptic boutons of cultured hippocampal neurons. Quantal analysis uncovered quantal or multi-quantal release of glutamate as well as sub-quantal release especially when release probability (P_r) was low. Increasing P_r with high external calcium or by paired-pulse stimulation switched vesicular release into a preferentially multivesicular mode. Our data provide strong evidence that exocytic patterns are not an intrinsic property of each synapse, but actively modulated depending on P_r. This modulation contributes to synaptic reliability at these synapses as well as to synaptic strength.

Abstract B14

Searching for neural substrate underlying rule-observance behavior of competing mice in social conflict

Junweon Byun, Abdelrahman Alkahwaji, Il-Hwan Choe, Ko Keun Kim, Sol Park, Isaac Kim, Jaeseung Jeong & Hee-Sup Shin

Korea University of Science and Technology (UST), Daejeon, South Korea
Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon, South Korea
Korea Institute for Advanced Science and Technology (KAIST), Daejeon, South Korea

Violating social rules might bring immediate individualistic profit, whereas orderly resolution by consent rules requires patience, but enhances long-term mutual benefit. However, the neural circuits mediating these socio-economical strategies are remained unclear. Here, we developed modified two-armed maze that uses wireless electrical brain stimulation as reward. First, the mice were individually operant-trained to initiate and then receive the reward at the signaled arm. Then, two mice were coupled and had to cooperate to initiate reward but then to compete over reward allocation. Mice develop and observe a rule of reward zone allocation that increases the total amount of reward and reward equity between the pair. Now we are investigating on the role of medial prefrontal cortex (mPFC) in reward zone allocation by using chemogenetic DREADD system and in vivo unit recordings. These results will provide a framework for understanding the circuit basis of interactive social behavior.

Abstract B15

Spectral reflectometry on the myelinated axon

Junhwan Kwon, Moonseok Kim, Hyejin Park, Bokman Kang, Yongjae Jo, Jae-Hwan Kim, Oliver James, Seok-Hyun Yun, Seong-Gi Kim, Minah Suh, Myunghwan Choi*

Center for Neuroscience Imaging Research (CNIR)
Institute for Basic Science (IBS)
Sungkyunkwan University, Suwon, Republic of Korea

Oligodendrocyte in the mammalian nervous system provides axonal integrity and facilitate fast electrical conduction by warping axon with multilayered membrane, called myelin. Individual leaflet of myelin sheath is in a few nanometers and small changes on myelin sheath can effect substantial changes in conduction speed and may thus alter neuronal circuit in CNS. So far, conventional imaging modality is not sufficient to provide resolution (optical microscopy) or in vivo imaging (electron microscopy). Here, we report a new optical imaging technique providing a spatial resolution beyond diffraction-limit by using intrinsic reflective property on the myelinated axon in *vivo* without exogenous labeling. This technique provides new avenues to observe myelin dynamics in a nanoscale in vivo.

Abstract B16

New Suggestion of GIT1 Hetero type for more reliable ADHD mouse model than KO type

Yoo Sung Kim[1], Junsung Woo[2], C. Justin. Lee[2], Bo-Eun Yoon[1*]

[1]Department of Molecular biology, Dankook University, Cheonan, Chungnam 31116, Korea
[2]Center for Neuroscience and Functional Connectomics, Korea Institute of Science and Technology (KIST), Seoul 02792, Korea

About one of ten school-aged children are suffering by Attention-Deficit/Hyperactivity Disorder (ADHD) and this ratio is increasing each year. However, mechanisms of ADHD are still remains unknown. Although G-protein coupled receptor kinase-interacting protein-1 knock-out (GIT1 KO) mice has been reported that shows ADHD likes behavior, actually, GIT1 KO mice are highly lethal in prenatal period and have small brain and body size than wild type (WT). GIT1 hetero (HET) mice are known to be show no difference with WT. However, we observed that GIT1 HET shows decreased GABA level to GIT1 KO mice, and diminished tonic GABA current from cerebellum than WT mice. Therefore, we make a new suggestion that GIT1 HET mice can be a more reliable ADHD mouse model for clinical application.

Key words
GIT1, tonic GABA, ADHD, cerebellum

Abstract B17

Astrocyte-mediated neuroprotection in YAC128 mouse model of Huntington's disease by transplanted human iPSC-derived neural precursor cells

Ji Woo Choi,[1] Hyun Jung Park,[1] Ji Yeon Kim, [1] Jihwan Song,[1*]

[1]CHA Stem Cell Institute, Department of Biomedical Science, CHA University, 335 Pangyo-ro, Bundang-gu, Seongnam-si 13488, Gyeonggi-do, Republic of Korea

Huntington's disease (HD) is a hereditary autosomal dominant disease, in which medium spiny neuron present in the striatum is selectively degenerated caused by the neurotoxicity from extended CAG repeat sequences at the N-terminus of huntingtin protein. In addition, dysfunction of astrocytes exacerbates neurological symptoms of HD through the decrease of glutamate uptake or growth factors release. The purpose of this study is to investigate the astrocyte differentiation and neuroprotective effects of human iPSC-derived neural precursor cells (iPSC-NPCs) following transplantation into YAC128 transgenic mouse model of HD. We detected hNu-positive transplanted cells at 1, 3, 5, 12 weeks post-transplantation and found that hNu-positive cells co-localized MAP2 (a neuronal marker) or GFAP (an astrocyte marker). Using immunohistochemical and western blot analyses, we detected the release of BDNF, especially from the human GFAP-positive cells. In addition, we also observed the increase of EAAT, a marker for glutamate transporter, in the human GFAP-positive cells. These results strongly suggest that the transplanted cells increased the glutamate reuptake in the human GFAP-positive cells, thereby reducing the glutamate toxicity in the host brain. Transplanted animals showed improvement of motor and cognitive functions. Taken together, these results strongly suggest that the transplanted iPSC-NPCs led to neuroprotection by the astrocyte-mediated modulation of glutamate excitotoxicity or release of growth factors, providing a new possibility that astrocytes may play a major role in the cell therapy of HD.

Abstract B18

Pathway-specific synapse formation by NGL-1 in CA1 pyramidal neuron

Yeonsoo Choi, Haram Park, Hwajin Jung, Hanseul Kweon, Eunjoon Kim

Center for Synaptic Brain Dysfunctions Department of Biology, KAIST

NGL-1 (Netrin-G ligand 1) is a postsynaptic adhesion molecule present only in the mammal brain and shows an expression pattern that, interestingly, is mostly complementary to its family member NGL-2. We focused on the role of NGL-1 in hippocampal CA1 pyramidal neuron where the exclusive expression pattern of NGL-1 and NGL-2 can be found; NGL-1 in SLM and NGL-2 in SR. Unlike NGL-2 KO mice, we found electrophysiological alteration in both SR and SLM when NGL-1 was ablated. Short term plasticity was reduced in both pathways and SR region showed decreased input/output. Such impairment likely caused memory deficits shown in NGL-1 KO mice. In order to understand why the deletion of NGL-1 affects SR region as well as SLM, we underwent western blot analysis with microdissected SR and SLM lysates. Interestingly, upon NGL-1 deletion, distribution of NGL-2 along the CA1 apical dendrite was schewed toward SLM, lossing its specific expression pattern. These results highlight the importance of NGL-1 in forming pathway-specific synapse formation.

Abstract B19

miR-200c deficiency promotes hyperphosphorylation of tau through up-regulation of 14-3-3γ in 5xFAD mouse model of Alzheimer's disease

Hyunjun Park[1], Eunjoo Nam[2,3], Yoo-hun Suh[2,3], Keun-A Chang[1,2,3]

[1]Department of Health Sciences and Technology, GAIHST, Gachon University, Incheon, Republic of Korea
[2]Departmenet of Phamacology, Gachon University of Medicine and Science, Incheon, Republic of Korea
[3]Neuroscience Research Institute, Gachon University, Incheon, Republic of Korea

Alzheimer's disease (AD) is a neurodegenerative disease characterized by impaired cognitive function and the deposition of extracellular amyloid plaques and tau phosphorylation. microRNAs (miRNAs) are non-coding RNA molecules with a length of 18-25 nucleotides, which serve as post-transcriptional regulators of gene expression. Recently, a number of dysregulated miRNAs have been identified, but one stands out due to its levels early in disease and in diverse biological samples, as well as its central role in multiple pathways involved in AD. The purpose of this study was to identify miRNAs that are abnormally expressed in AD and to search whether abnormally expressed miRNAs affect AD pathology. In vivo study, we found that miR-200c reduced in the hippocampus of 4-month-old 5xFAD mouse using a microarray and RT-qPCR. 14-3- 3γ protein was increased in the hippocampus of the 5xFAD mouse brain. 14-3-3 family is known to phosphorylate microtubule-associated tau protein by GSK-3β. Thus, we confirmed that GSK-3β and Tau phosphorylation is increased in the hippocampus of the 5xFAD mouse brain. In vitro study, miR-200c was found to regulate 14-3-3γ using the dual-luciferase reporter gene assay in HEK-293 cells. In addition, 14-3-3γ and GSK-3β protein was increased, though transfection of the miR-200c inhibitor in primary hippocampal neurons. Our in vivo and in vitro results suggests that dysregulation of miR- 200c expression contributes to tau hyperphosphorylation in AD.

Abstract B20

Chronic stress induces neurovascular coupling dysfunction in the mouse somatosensory cortex via a GABA-mediated pathway

Kayoung Han[1,2*], Bok-Man Kang[1,3], Hyunwoo Ryu[1,3], Junsung Woo[4,5,6], Hyunji shim[1,2], Won Beom Jung[1,3], Junghyun Hanhn[1], Justin C Lee[4,5,6,7],SeongiKim[1,2,3], and Minah Suh[1,2,3]

[1]Center for Neuroscience Imaging Research (CNIR), Institute for Basic Science (IBS),
[2]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul 06351, Korea
[3]Department of Biomedical Engineering, Sungkyunkwan University, Suwon 16219, Korea,
[4]Center for Neuroscience, Korea Institute of Science and Technology (KIST), Seoul 02792,
[5]Functional Connectomics, Korea Institute of Science and Technology (KIST), Seoul 02792,
[6]Center for Glia-Neuron Interaction, Korea Institute of Science and Technology (KIST), Seoul 02792,
Department of neuroscience
[7]Division of Bio-Medical Science&Technology, KIST school, Korea University of Science and Technology, Seoul 02792, Korea

Neurovascular coupling is refered as the relationship between local neuronal activity and cerebral blood flow changes. The magnitude and spatial location of blood flow changes are tightly linked to the elaborate interplay among excitatory neurons, inhibitory neurons and vascular units. Several reports suggest that the disruption of neurovascular coupling is preceded the progression of disease. However, which neuronal component changes in pathological condition leading to abnormal neurovascular coupling remain unclear. In this study, we investigated the relationship between neuronal activity and cerebral arterioles' dynamics in chronically stressed animals with *in vivo* and *ex vivo* study. We induced depressive-like behaviors in mouse using chronic immobilization protocol. First, we utilized functional magnetic resonance imaging (fMRI) to confirm whether hypo-perfusion was occurred in chronically stressed model. Following sensory stimulation, we observed that the blood-oxygen-level-dependent (BOLD) signal was significantly decreased in chronic stressed group compared to control group. To examine the underlying mechanism of hypo-perfusion in chronic stressed condition, we utilized the acute brain slice which have better accessibility for dissecting complex signaling between neurons and blood vessels. In acute brain slices, we used a focal electrical stimulation and drugs related with glutamatergic or GABAergic pathway to investigate underlying events of neurovascular dysfunction in the brain slices. Following a focal electrical stimulation, there was a considerable vasodilation in most of arterioles in controls, whereas vasoconstriction is clear in most arterioles of stressed group. NMDA stimulation evoked arteriole vasodilation with no difference in degree in both control and chronically stressed group. However, GABA receptor agonist stimulation induced noticeably dissimilar responses in controls and stressed group. When GABA agonist applied there was a considerable vasoconstriction in arterioles in controls, but no changes in arterioles in stressed group. In addition, we measured neural activity with a patch clamp recording to confirm whether GABAergic signaling was damaged in chronically stressed condition. The results indicated that the amplitude of excitatory postsynaptic currents (EPSCs) was not notably different between controls and stressed models, but the amplitude of inhibitory postsynaptic currents (IPSCs) was significantly reduced in stressed mouse. This study suggest that chronic stress induced altered vaso-dynamics of arterioles. Our results also indicate that these alteration in vaso-dynamics are affected not by an NMDA-mediated pathway but by a GABA-mediated pathway.

This work was supported by IBS-R015-D1

Abstract B21

Effects of Rheb(S16H) transduction of dopaminergic neurons against neurotoxic inflammation *in vivo*

Sehwan Kim[1], Sang Ryong Kim[1,2,#]

[1]School of Life Sciences, BK21 plus KNU Creative BioResearch Group, Kyungpook National University, Daegu 41566, Korea.
[2]Brain Science and Engineering Institute, Kyungpook National University, Daegu 41944, Korea.
#Corresponding authors: Sang Ryong Kim, PhD. Phone: +82-53-950-7362; Fax: +82-53-943-2762; E-mail: srk75@knu.ac.kr

We recently reported that adeno-associated virus serotype 1 (AAV1) transduction with constitutively active ras homolog enriched in brain with a mutation of serine to histidine at position 16 [Rheb(S16H)] into murine nigral dopaminergic (DA) neurons could induce the production of neurotrophic factors, resulting in neuroprotective effects on the nigrostriatal DA system in animal models of Parkinson's disease (PD). To further investigate whether AAV1-Rheb(S16H) transduction has a neuroprotective potential against neurotoxic inflammation, which is well known as a potential event related to PD pathogenesis, we examined the effects of Rheb(S16H) expression in nigral DA neurons under a neurotoxic inflammatory environment induced by prothrombin kringle-2 (pKr-2), which has been reported as an endogenous microglial activator. Our observations showed that Rheb(S16H) transduction could play a role in the neuroprotection of the nigrostriatal DA system against pKr-2-induced neurotoxic inflammation, even though there were similar levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β), in the AAV1-Rheb(S16H)-treated substantia nigra (SN) compared to the SN treated with pKr-2 alone, and that the neuroprotective effects may be mediated by the activation of neurotrophic signaling pathways following Rheb(S16H) transduction of nigral DA neurons. We conclude that AAV1-Rheb(S16H) transduction of neuronal populations to activate the production of neurotrophic factors and intracellular neurotrophic signaling pathways may offer promise for protecting adult neurons against extracellular neurotoxic inflammation.

Keywords
AAV1-Rheb(S16H); Microglia; Neuroinflammation; Neurotrophic factor

Acknowledgments
This study was supported by grants from the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare (HI15C1928 and HI16C2210), and the National Research Foundation of Korea (NRF- 2017R1A2B4002675).

Abstract B22

Mood regulation and circadian rhythm in midbrain dopaminergic neurons in a 6-hydroxydopamine-treated mouse model of Parkinson's disease

Jeongah Kim[1,2], Doyeon Kim[1,3], Sangwon Jang[1], Mijung Choi[1], Han Kyoung Choe[1], Gi Hoon Son[4], Kyungjin Kim[1*]

[1]Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology (DGIST) and Korea Brain Research Institute (KBRI), Daegu, Korea.
[2]Department of Biological Sciences, College of Natural Sciences, Seoul National University, Seoul, Korea.
[3]Interdisciplinary Program in Neuroscience, College of Natural Sciences, Seoul National University, Seoul, Korea
[4]Department of Biomedical Sciences, College of Medicine, Korea University, Seoul, Korea.

Parkinson's disease (PD) is a neurodegenerative disease characterized by degeneration of dopaminergic (DAergic) neurons in the substantia nigra. PD patients are known to suffer from mood disorders and sleep disturbances with motor deficits. We have recently demonstrated that REV-ERBα, a circadian nuclear receptor, serves as a molecular link between mood regulation and circadian nature of DAergic system in the midbrain. Therefore, we aimed to examine how circadian rhythm is related to mood regulation in a PD mouse model. A neurotoxin 6-hydroxydopamine (6-OHDA) was injected into left dorsal striatum, and mood-related behaviors were assessed at two time points: dawn and dusk. While vehicle-injected mice exhibited daily oscillation of mood-related behaviors, these patterns were disappeared in 6-OHDA-injected mice with increased anxiety- and depressive-like behaviors only at dawn. 6-OHDA treatment induced circadian disturbances of locomotor activity and body temperature. 6-OHDA injection eliminated rhythmic expression of tyrosine hydroxylase, a rate-limiting enzyme of DA biosynthesis, with DAergic neuronal loss in the midbrain. Interestingly, a local administration of REV-ERB antagonist, SR8278 into midbrain recovered mood disorders shown in 6-OHDA-injected mice with partial alleviation of motor deficits. Taken together, these results suggest a novel therapeutic potential of REV-ERBα in circadian rhythm-related mood disorders of PD patients.

Abstract B23

Divergent mechanisms and functions of translational dysregulation induced by brain somatic mosaicisms

Jang Keun Kim[1], Jun Cho[3], Hyongbum (Henry) Kim[8,9], Dong-Seok Kim[6,7], V. Narry Kim[4,5], Jeong Ho Lee[1,2]

[1]Biomedical Science and Engineering Interdisciplinary Program, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea
[2]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea
[3]Department of Microbiology and Immunobiology, Harvard Medical School, Boston MA 02115, U. S. A
[4]Center for RNA Research, Institute for Basic Science, Seoul 08826, Republic of Korea
[5]Department of Biological Sciences, Seoul National University, Seoul 08826, Republic of Korea
[6]Epilepsy Research Institute, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[7]Department of Neurosurgery, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[8]Department of Pharmacology, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[9]Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul 03722, Republic of Korea

Hyperactivation of mTOR kinase, which is a major translation regulator, is a common molecular hallmark in various human diseases such as epilepsy, autism, and cancers. In particular, brain somatic mosaicisms activating mTOR directly lead to focal malformations of cortical development (FMCD), which is the most common cause of childhood intractable epilepsy. Here, our comprehensive translational profiling in genome edited cells and FMCD mouse models reveals that somatic activating mutations in MTOR cause the aberrantly increased translation of specific mRNAs not overlapping with acute mTOR inhibition-sensitive mRNAs such as 5' terminal oligopyrimidine (5' TOP) mRNAs that mainly encode ribosoma proteins. The increased translation of mTOR mutation-sensitive genes is mediated by the activation of translation and implicated in the molecular pathogenesis of FMCD underlying epilepsy, dysmorphic neurons, and defective neuronal migration. In patients' brain tissues, we validated the increased expression of novel mTOR mutation-sensitive genes underlying FMCD phenotypes. Furthermore, we rescued intractable epilepsy and other pathologies by inhibiting aberrant translation in our FMCD mouse models. Thus, our study elucidates the divergence of translational landscape and molecular pathogenesis caused by brain somatic mosaicisms in MTOR as well as novel therapeutic targets of FMCD.

Abstract B24

Activity-dependent local translation of GluA1 is regulated by hnRNP A2/B1

Youngseob Jung[1], Ji-Young Seo[1], Hye Guk Ryu[2], Do-Yeon Kim[3], Kyung-Ha Lee[4], Kyong-Tai Kim[1,5,*]

[1]Division of Integrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang, Gyeongbuk 37673, Republic of Korea
[2]Department of Life Sciences, Pohang University of Science and Technology, Pohang, Gyeongbuk 37673, Republic of Korea
[3]Department of Pharmacology, School of Dentistry, Brain Science and Engineering Institute, Kyungpook National University, Daegu 41940, Republic of Korea.
[4]Division of Cosmetic Science and Technology, Daegu Haany University, Gyeongbuk 38610, Republic of Korea
[5]Lead Contact
*Correspondence: ktk@postech.ac.kr

AMPA receptor subunit GluA1 is essential for induction of synaptic plasticity. Mounting evidence demonstrates the regulations of AMPA receptor expression, but underlying molecular mechanisms of the GluA1 protein synthesis elicited by synaptic activity are not fully understood. Here, we show that brain-derived neurotrophic factor (BDNF) stimulation results in the increase of GluA1 local translation. We also demonstrate that heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 interacts with GluA1 mRNA and mediates internal translational initiation of GluA1 in hippocampal neuronal dendrites. Moreover, we directly visualize newly synthesized GluA1 in neuronal compartments. Furthermore, the BDNF-induced GluA1 local translation as well as GluA1 total and surface expressions are significantly inhibited in the hnRNP A2/B1 deficient neuron. Taken together, hnRNP A2/B1-mediated translational regulation of GluA1 mRNA provides novel aspect for activity-dependent local expression of AMPA receptor.

A unified developmental model of functional maps in the primary visual cortex

Jaeson Jang[1*], Min Song[1,2*] & Se-Bum Paik[1,2]

[1]Department of Bio and Brain Engineering
[2]Program of Brain and Cognitive Engineering, Korea Advanced Institute of Science and Technology, Daejeon 34141, Republic of Korea

[*]Contributed equally
Jaeson Jang: jaesonjang@kaist.ac.kr,
Min Song: night@kaist.ac.kr,
Se-Bum Paik: sbpaik@kaist.ac.kr

In higher mammals, the primary visual cortex (V1) is organized into various maps of visual functions such as ocular dominance, preferred orientation, and spatial frequency. These cortical functional maps are thought to take an important role in visual information processing, thus have been extensively studied for decades. Recently, it was also reported that the topography of these functional maps is correlated (Nauhaus et al., 2016), so that the contours of the orientation and the spatial frequency maps intersect orthogonally (Nauhaus et al., 2012). This may imply an efficient tiling of functional columns for information processing, but it is still unclear how this systematic organization of multiple maps can arise in the cortex. To address the issue, here we introduce a novel model that the functional maps can be seeded altogether from the regularly structured retinal afferents and show that this unified evolution process can result in the observed topographical correlations among the maps. Our developmental model is based on the previous notion that a quasi-periodic orientation map can be seeded by the moiré interference between hexagonal lattices of ON and OFF retinal ganglion cells (RGCs) (Paik and Ringach, 2011). The key assumption was that the orientation tuning of a V1 neuron can be generated by the anisotropic receptive fields from the ON and OFF RGCs afferents. Expanding this single map model, we suggest that the ON and OFF RGC afferents from the retina can also induce ocular dominance and spatial frequency tuning. We found that the spatial organization of ON and OFF RGC mosaics could result in the observed quasi-periodic variation of ocular dominance. In addition, we found that competition between contra- and ipsilateral inputs to binocular V1 neurons could produce the architecture of spatial frequency tuning in mono- and binocular regions (Nauhaus et al., 2016). As a result, we successfully reconstructed the orthogonal relationships between orientation, ocular dominance, and spatial frequency maps, as reported in experiments (Hübener et al., 1997; Nauhaus et al., 2012). Our results suggest a unified developmental model of various functional maps in visual cortex.

Abstract B26

Impairment of NHE6 recruitment to synaptic vesicle by SCAMP5 deficiency decreases quantal size at glutamatergic synapses

Unghwi Lee[1], Daehun Park[1], Soohyun Kim[1], Sunghoe Chang[1,2,3,*]

[1]Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, Seoul 110-799, South Korea
[2]Neuroscience Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul 110-799, South Korea
[3]Biomembrane Plasticity Research Center, Seoul National University College of Medicine, Seoul 110-799, South Korea.

The quantal size of synaptic vesicle (SV) is regulated by a chemical gradient (ΔpH) and membrane potential (Δψ) generated by the vacuolar H+-ATPase. The relative roles of ΔpH and Δψ vary with the type of neurotransmitters, and uptake of glutamate is known to more depend on the electrical component of Δψ than ΔpH. Monovalent cation/H+ exchanger plays an important role in establishing Δψ, and thus the proper sorting of this protein to SV is of utmost importance for regulating the quantal size of glutamate release, but the underlying mechanism that mediates the sorting of this protein to SV remains poorly understood. In this study, we demonstrated that sorting of (Na+/K+)/H+ exchanger 6 (NHE6) to SV is regulated by its interaction with Secretory carrier membrane protein 5 (SCAMP5) at hippocampal excitatory synapses. We showed that the 2/3 loop domain of SCAMP5 interacts with the C-terminal region of NHE6 and depletion of endogenous SCAMP5 by shRNA or overexpression of 2/3 loop mutant hinders the sorting of NHE6 to SV in cultured rat hippocampal neurons. Using optical imaging with a fluorescent glutamate sensor iGluSnFR, we demonstrated that the amount of glutamate released spontaneously or by stimulation decreased with SCAMP5 knockdown (KD). This result was further corroborated by the electrophysiological recording in which SCAMP5 KD results in a decreased miniature excitatory postsynaptic current (mEPSC), thus supporting that disturbed localization of NHE6 to SVs reduces presynaptic quantal size. Together, our results suggest that SCAMP5 has a critical role in proper sorting of NHE6 to SVs and subsequent regulation of quantal size at glutamatergic synapses. Non-sense mutations of NHE6 found in neurodevelopmental disorders such as X-linked intellectual disability and Christianson syndrome could be related with the failure in localization of NHE6 to SVs due to absence of interaction with SCAMP5.

Abstract B27

Improving functional correlation tensor using anatomically-guided multivariate regression

Kyoung-seob Byeon[1,2], Bo-yong Park[1,2], Hyunjin Park[2,3*]

[1]Department of Electronic, Electrical and Computer Engineering, Sungkyunkwan University, Suwon, 16419, Korea
[2]Center for Neuroscience Imaging Research, Institute for Basic Science (IBS), Suwon, 16419, Korea
[3]School of Electronic and Electrical Engineering, Sungkyunkwan University, Suwon, 16419, Korea
Email: present4us@skku.edu[1,2], by6860@sby6860@skku.edu[1] and hyunjinp@skku.edu[2,3*]

Functional correlation tensor (FCT) is a tensor model that resembles the diffusion tensor (DT) and it is calculated using the resting-state functional magnetic resonance imaging (rs-fMRI). The FCT can mimic the water diffusivity in the brain without actually acquiring diffusion tensor imaging. Previous studies developed the FCT, but they showed relatively weak correlation between FCT and DT. In this study, we proposed an anatomically-guided multivariate regression framework render FCT more similar to the real DT. We used 146 rs-fMRI data from the enhanced Nathan Kline Institute-Rockland Sample database. The FCT was calculated in a voxel-wise manner and it was defined as the sum of the unit directional vectors weighted with the correlation coefficients of the time series between a voxel and its 26 neighbor voxels. The multivariate regression model was constructed by setting the FCT of six directions, the intensity value of the T1-weighted data, and the mean value of the neighbor voxels of the T1-weighted data of a given voxel as independent variables, and the DT as the dependent variable. The training and testing of the multivariate regression model were performed using four-fold cross-validation. The 50 regions of interest (ROIs) were defined using the ICBM DTI-81 atlas and the functional anisotropy (FA) values were calculated from the enhanced FCT and DT for each ROI. The correlation between the FA values that derived from the FCT and DT was calculated. The 31 ROIs of the corpus callosum, fornix, medial lemniscus, cerebral peduncle, internal capsule, external capsule, corona radiata, posterior thalamic radiation, sagittal stratum, cingulate gyrus and uncinate fasciculus showed significant ($p < 0.05$) correlation (mean r-value = 0.4562). We demonstrated that combining both the functional and structural information improved the quality of the FCT model.

Abstract B28

Hypothalamic peptide hormone A, a mitokine, controls appetite via leptin signaling

Yunseon Jang[1,2,3], Jeongsu Han[1,2,3], Soo Jeong Kim[1,2,3], Min Joung Lee[1,2,3], Ilhwan Ryu[1,2,3], Xianshu Ju[1,2], Min Jeong Ryu[1,2,4], Jun Young Heo[2,3*] and Gi Ryang Kweon[1,2,4*]

[1]Department of Medical Science
[2]Department of Biochemistry
[3]Medical Research Center
[4]Research Institute for Medical Science, Chungnam National University School of Medicine, Daejeon, South Korea, 35015

Hypothalamic regulation of appetite governs whole body energy balance. Satiety is regulated by endocrine factors including leptin and impairment of its induction causes obesity. Peptide hormone A (PA), a mitokine, is induced by high fat diet in liver of mice and promotes lipolysis in periphery. However, its role in hypothalamus to control food intake is unknown. We demonstrated that PA is expressed in proopiomelanocortin (POMC) expressing neurons located in arcuate nucleus (ARC) of hypothalamus which is a target of leptin and has an anorectic effect. PA expression was promoted by leptin-induced STAT3 phosphorylation. Intracerebroventricular injection of PA significantly reduced food intake via increasing α-melanocyte -stimulating hormone (α-MSH) content in hypothalamus. We also found that hypothalamic injection of PA significantly decreased body weight of high fat diet- induced obese mice which showing leptin insensitivity. We suggest that hypothalamic PA provokes anorectic melanocortin pathway activation and mediates leptin signaling to prevent obesity. (2014R1A6A1029617, 2016R1A2B4010398, 2016R1D1A1B03932766, 2017R1A5A2015385, 2017R1A6A3A1102936)

Keywords
Hypothalamus, Peptide A, appetite, α-MSH, POMC