Neural signature driving affective empathy (Plenary Lecture)

Hee-Sup Shin

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Gene therapy for ALS and Motor neuron disease -Are we there yet?

Chris Shaw

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Characterising the protein aggregates in neurodegenerative disease.

David Klenerman and Yusuf Hamied

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Abstract

We have developed a suite of sensitive biophysical methods to detect and characterise the low levels of heterogeneous protein aggregates present in human biofluids such as cerebrospinal fluid (CSF) and serum. Our methods, which I will briefly review, can measure the number, size and shape and the composition of the aggregates present as well as their capability to permeabilise a lipid membrane or trigger inflammation. I will then describe how we have applied these methods to the CSF and serum of controls and patients with Alzheimer's and Parkinson's disease. Both control and patient samples contain aggregates. Most of the aggregates present are smaller than 50 nm but the aggregates range in size from 20-200 nm. There is no detectable increase in aggregate number with the development of disease but we observe an increase in the proportion of larger aggregates and in the proportion of a-synuclein aggregates in Parkinson's disease patients. In particular, in Alzheimer's disease the formation of increased numbers of protofilaments in CSF correlates with an increase in aggregate induced inflammation via Toll-like receptor 4. These changes in aggregate size and composition have potential as biomarkers for early disease diagnosis. Our results also highlight the difficulty in targeting the heterogeneous protein aggregates for therapy and suggest that targeting inflammation and Toll-like receptor 4 in particular may be a better strategy.

What would happen in the dopamine system after antipsychotic discontinuation in first-episode psychosis?

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Abstract:
Recent meta-analysis revealed that elevated presynaptic striatal dopaminergic function is a robust feature of psychosis like schizophrenia. Considering increased dopaminergic capacity in psychotic disorders, it is not surprising that antipsychotic drugs, which primarily block dopaminergic neurotransmission, are mostly effective in the treatment of psychosis. However, it remains obscure what would happen to presynaptic dopaminergic function with antipsychotic treatment. This is an important issue addressing whether the current antipsychotic drugs are correcting the primary dopaminergic abnormality or not. In addition, it can give a clue regarding the mechanism of relapse in psychotic disorders.
We measured presynaptic dopamine capacity using [18F]DOPA PET before and after the antipsychotic discontinuation in first episode psychosis. The binding potential of [11C]raclopride were also measured after the discontinuation. Heathy controls had [18F]DOPA and [11C]raclopride scans at the corresponding date.
I will present the results of the project above as an example of a clinical study conducted in Korea.

Molecular mapping of stress circuits

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Abstract
Mammals exhibit instinctive reactions to danger by releasing stress hormones. Hypothalamic corticotropin releasing hormone neurons (CRHNs) control stress hormone levels, but how diverse stressors converge on CRHNs to induce stress responses is not well understood. Here, we used single cell transcriptomics to define CRHN receptors for neurotransmitters and neuromodulators and then viral tracing to localize subsets of upstream neurons expressing cognate receptor ligands. Surprisingly, one subset comprised POMC (pro-opiomelanocortin)-expressing neurons in the hypothalamic arcuate nucleus, which are linked to appetite suppression. The POMC neurons were activated by one stressor, physical restraint, but not another, a predator odor. Chemogenetic activation of POMC neurons induced a stress hormone increase and their silencing inhibited the stress hormone response to physical restraint, but not predator odor. Together, these results indicate that hypothalamic POMC neurons, which are implicated in appetite suppression, also play a major role in the stress hormone response to a specific type of stressor. We also found that two different odorants can block stress hormone responses to both physical restraint and predator odor. Both odorants activate GABAergic inhibitory neurons presynaptic to CRHNs in the hypothalamic ventromedial nucleus. Stimulation of those neurons inhibits restraint-induced stress hormone increase, mimicking a blocking odorant. Conversely, their silencing prevents odorant blocking of the response. Notably, we also observed odor blocking of stressor activation in neurons presynaptic to CRHNs in the bed nucleus of the stria terminalis. Together, these findings indicate that selected odorants can block stress responses via two routes: a direct route in which blocking odor signals directly inhibit CRHNs and an indirect route in which they inhibit stressor activation of neurons presynaptic to CRHNs and prevent them from transmitting stress signals to CRHNs.

Key words: corticotropin releasing hormone neurons (CRHNs), stress hormones, single cell transcriptomics, viral tracing, odor blocking

miRNA-target interaction and its application in drug abstinence (Poster presentation)

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Abstract
Abstinence from prolonged drug use prompts drug withdrawal syndrome. Molecular adaptations within the dorsal striatum have been considered the main hallmark of drug abstinence. Here we explored striatal miRNA–target interaction and its impact on circulating miRNA marker as well as behavioral dysfunctions in methamphetamine (MA) abstinence. In nonhuman primates, MA abstinence triggered a lasting upregulation of miR-137 in the dorsal striatum but a simultaneous downregulation of circulating miR-137. In mice, aberrant increase in striatal miR-137-dependent inhibition of SYNCRIP essentially mediated the MA abstinence-induced reduction of circulating miR-137. Specifically, the MA abstinence-mediated reduction of circulating miR-137 was caused by the deficit in SYNCRIP-dependent miRNA sorting into the exosomes in the dorsal striatum. Applying our findings to theragnosis, we demonstrated that circulating miR-137 is a potential blood-based marker of MA abstinence in human patients, and that striatal SYNCRIP is a potential therapeutic target for aberrant behavioral bias towards egocentric spatial learning in MA-abstinent mice. Taken together, our data revealed that striatal miRNA-target interaction could be exploited for the development of theragnosis against drug withdrawal syndrome.

Consequence of hypomethylation of FUS in dynamics of dendritic FUS condensate in hippocampal CA1 neurons (Poster Presentation)

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Abstract: The hypomethylation of the RNA-binding protein Fused in Sarcoma (FUS) and formation of irreversible condensates have been found in hippocampus of sporadic frontotemporal lobar degeneration (FTLD) post-mortem samples. While the level of FUS hypomethylation has been shown to alter its ability to undergo Liquid-Liquid Phase Separation (LLPS) thereby forming condensates. However the behaviour of these FUS condensates in the neurons are poorly understood. Here, by mimicking FUS hypomethylation, we observed mislocalisation and aberrant formation of FUS condensates in CA1 neuronal dendrites, accompanied by impaired synaptic transmission and dendritic spine plasticity. Interestingly, this form of FUS condensate exhibited abnormally rapid movement and single spine activity caused a local increase of synaptic FUS condensates. Furthermore, neuronal activity caused recruitment of FUS condensates and accelerated the movement of condensates through the dendrites. Our study suggests that activity-dependent aberrant movement of FUS condensates contributes to synaptic dysfunction and may be implicated in FUS-mediated pathophysiology.

Donepezil regulates Ab pathology but not tau pathology in 5xFAD mice (Poster Presentation)

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Abstract

Donepezil, a cholinesterase inhibitor, is currently used for treatment of Alzheimer's disease (AD) by regulating Ab pathology and cognitive function. However, whether donepezil can alter tau pathology in 5xFAD mice (a mouse model of AD) is not well studied. Therefore, in this study we first examined the effects of donepezil on Ab and tau pathology in 5xFAD mice. In the present study, we found that 1 mg/kg donepezil treatment significantly reduced Ab plaque number in the cortex and hippocampus DG region in 5xFAD mice. In addition, donepezil-treated 5xFAD mice significantly decreased Ab-induced microglial activation but had less effect on Ab-mediated astrocyte activation. Surprisingly, 1 mg/kg donepezil treatment did not alter tau phosphorylation at Ser202/Thr205 (AT8), Thr212/Ser214 (AT100), and Thr 231 in 5xFAD mice. Moreover, we found that donepezil-treated 5xFAD mice significantly increased tau phosphorylation at Thr212 and tau kinase p-CDK5 levels in the hippocampus. Taken together, these data suggest that donepezil suppressed Ab pathology but not tau pathology in 5xFAD mice.

Keywords: Alzheimer's disease; tau; tau kinase; amyloid beta; 5xFAD mice; donepezil

Mental Health on the Autism Spectrum

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Abstract:

Children and adults on the autism spectrum show elevated rates of mental health conditions, notably anxiety and depression. Because of their greater exposure to negative life events (e.g. bullying), and particular cognitive characteristics (e.g. detail-focused processing), we hypothesised that autistic people might be at heightened vulnerability to develop trauma-related psychiatric problems or Post-Traumatic Stress Disorder (PTSD). In this talk I will briefly summarise our work to date on PTSD symptoms in autistic adults. Reasons for the high rates of PTSD and other mental health conditions in autism will be considered, as well as implications and future research directions.

GABAergic-like dopamine synapses in health and Parkinsonism

Jae-Ick Kim

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Abstract:
Dopamine synapses play a crucial role for volitional movement and reward-related behaviors, while dysfunction of dopamine synapses causes various psychiatric and neurological disorders. Despite this significance, true biological nature of dopamine synapses remains poorly understood in the brain. Here we show that dopamine transmission is strongly correlated with GABA co-transmission across the brain and dopamine synapses are structured and function like GABAergic synapses with marked regional heterogeneity. In addition, GABAergic-like dopamine synapses are uniquely clustered on the dendrites and GABA transmission at dopamine synapses has distinct physiological properties. Interestingly, knockdown of neuroligin-2, a key postsynaptic protein at GABAergic synapses, unexpectedly does not weaken GABA co-transmission but instead facilitates it at dopamine synapses in the striatal neurons. More importantly, the attenuation of GABA co-transmission precedes deficits in dopaminergic transmission in an animal model of Parkinsonism. Our findings reveal unknown spatial and functional nature of GABAergic-like dopamine synapses in health and disease.

The effects of epigenetic age and its acceleration on surface area, cortical thickness, and volume in young adults (Poster Presentation)

Yong Jeon Cheong

Korea Brain Research Institute

Abstract:

DNA methylation age has been used in recent studies as an epigenetic marker of accelerated cellular aging, whose contribution to the brain structural changes was lately acknowledged. We aimed to characterize the association of epigenetic age (i.e. estimated DNA methylation age) and its acceleration with surface area, cortical thickness, and volume in healthy young adults. Using the multi-tissue method (Horvath, 2013), epigenetic age was computed with saliva sample. Epigenetic age acceleration was derived from residuals after adjusting epigenetic age for chronological age. Multiple regression models were computed for 148 brain regions for surface area, cortical thickness, and volume using epigenetic age or accelerated epigenetic age as a predictor and controlling for sex. Epigenetic age was associated with surface area reduction of the left insula. It was also associated with cortical thinning and volume reduction in multiple regions, with prominent changes of cortical thickness in the left temporal regions and of volume in the bilateral orbital gyri. Finally, accelerated epigenetic age was negatively associated with right cuneus gyrus volume. Our findings suggest that understanding the mechanisms of epigenetic age acceleration in young individuals may yield valuable insights into the relationship between epigenetic aging and the cortical change and on the early development of neurocognitive pathology among young adults.

AD protective variant PLCγ2_P522R enhances Aβ clearance, protects synapses and boosts microglia metabolic fitness. (Poster Presentation)

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Abstract

A rare P522R coding variant in the microglial gene PLCG2 has been identified as protecetive against late onset Alzheimer's disease, but the impact of this variant on disease relevant processes is not well understood. We used CRISPR edited hiPSC derived microglial cells to investigate the impact of PLC ☐ 2P522R on microglial capacity to uptake amyloid ☐ (A ☐) and synapses, and found that heterozygous expression of the variant resulted in increased clearance of A ☐, while preserving synapses. This was associated with the upregulation of a number of genes, including the anti-inflammatory cytokine IL-10, and the synapse-linked CX3CR1, as well as alterations in mitochondrial function, and increased cellular motility. These findings suggest that PLC ☐ 2P522R may result in increased surveillance by microglia, as well as priming them towards an anti-inflammatory state, with an increased capacity to respond to varying energy demands.

Dysfunction of striatal MeCP2 is associated with cognitive decline in a mouse model of Alzheimer's disease (Poster Presentation)

Sangjoon Lee, Tae Kyoo Kim, Ji Eun Choi, Yunjung Choi, Minsu You, Jeewon Ryu, Yoo Lim Chun, Suji Ham, Seung Jae Hyeon, Hoon Ryu, Hye-Sun Kim, Heh-In Im

Korea Institute of Science and Technology (KIST)

Abstract: Cerebral Methyl-CpG binding Protein 2 (MeCP2) is involved in several psychiatric disorders that are concomitant with cognitive dysfunction. However, the function of striatal MeCP2 and its association with Alzheimer's disease (AD) has been largely neglected due to the absence of amyloid plaque accumulation in the striatal region until the later stages of AD. Considerable evidence indicates that neuropsychiatric symptoms related to cognitive decline are involved with striatal dysfunction. To this respect, we investigated the epigenetic function of striatal MeCP2 paralleling the pathogenesis of AD. We investigated the brain from amyloid precursor protein (APP)/presenilin1 (PS1) transgenic mice. Striatal MeCP2 expression was increased in the younger (6 months) and older (10 months) ages of APP/PS1 mice, and the genome-wide occupancy of MeCP2 in the younger APP/PS1 showed dysregulated binding patterns in the striatum. Notably, defective cognitive phenotypes and abnormal neuronal activity in old APP/PS1 mice were rescued through the knock-down of striatal MeCP2. We found that the MeCP2-mediated dysregulation of the epigenome in the striatum is linked to the defects in the AD animal model, and that this alteration is initiated even in the very early stages of AD pathogenesis. Together, our data indicates that MeCP2 may be a potential target for the diagnosis and treatment of AD at asymptomatic and symptomatic stages

Astrocytic urea cycle detoxifies Aβ-derived ammonia while impairing memory in Alzheimer's disease (Poster Presentation)

Yeon Ha Ju, Mridula Bhalla, Seung Jae Hyeon, Ju Eun Oh, Seonguk Yoo, Uikyu Chae, Jae Kwon, Wuhyun Koh, Jiwoon Lim, Yongmin Mason Park, Junghee Lee, Il-Joo Cho, Hyunbeom Lee, Hoon Ryu#, and C. Justin Lee#

Korea Institute of Science and Technology (KIST)

Abstract: Alzheimer's disease (AD) is one of the foremost neurodegenerative diseases, characterized by beta-amyloid (Aβ) plaques and significant progressive memory loss. In AD, astrocytes are proposed to take up and clear Aβ plaques. However, how Aβ induces pathogenesis and memory impairment in AD remains elusive. We report that normal astrocytes show non-cyclic urea metabolism, whereas Aβ-treated astrocytes show switched-on urea cycle with upregulated enzymes and accumulated entering-metabolite aspartate, starting-substrate ammonia, end-product urea, and side-product putrescine. Gene-silencing of astrocytic ornithine decarboxylase-1 (ODC1), facilitating ornithine-to-putrescine conversion, boosts urea cycle and eliminates aberrant putrescine and its toxic by-products ammonia, H2O2, and its end-product GABA to recover from reactive astrogliosis and memory impairment in AD model. Our findings implicate that astrocytic urea cycle exerts opposing roles of beneficial Aβ detoxification and detrimental memory impairment in AD. We propose ODC1-inhibition as a promising therapeutic strategy for AD to facilitate removal of toxic molecules and prevent memory loss.

Multi-spine boutons, memory, and Alzheimer's disease (Poster Presentation)

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Abstract:
Introduction: Synaptic changes are thought to underlie learning and memory, with synapse loss being considered the best correlate of memory impairment in Alzheimer's disease (AD). Multiple synapses, such as multi-spine boutons (MSBs), have been linked to learning and memory, but are often overlooked in AD research.

Methods: We have used 3-dimensional electron microscopy, which provides sufficient resolution to unequivocally identify and classify established synapses, to address whether MSBs are affected by memory formation in a mouse model, and if MSBs change in post-mortem AD brain.

Results: MSBs account for approximately 20% of all synapses in mouse CA1 stratum radiatum, and their abundance does not change after contextual fear conditioning (CFC). However, CFC seems to decrease the number of synapses per MSB, hence their complexity. Further, AD does not change the abundance of MSBs in transentorhinal cortex and stratum pyramidale, but their complexity may be increased. Please note that in these brain regions, synapse number is conserved after CFC and in AD, respectively.

Conclusions: Our results suggest that changes in MSBs complexity occur in AD brain, which are the opposite of learning-induced alterations in MSB complexity. The decreased MSB complexity seen after CFC may be needed for memory retrieval, therefore the increased complexity seen in AD is expected to impair memory, most likely the retrieval process, as too many neurons become inter-connected. Further, pre-and-post-synaptic profiles appear to degenerate independently, at least in some brain areas, in AD.

Partitioning the effects of psychiatric risk variants on synaptic dynamics

Nicholas E Clifton

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Abstract:

The search for much-needed new treatments for schizophrenia and related disorders has been hampered by complex underlying genetics and a poor understanding of the genetic effects on cell biology. My work incorporates novel methods for studying cell biology during brain development and exploits recent discoveries in DNA sequencing that have revealed a subset of genetic variants that substantially increase the risk of schizophrenia. I present relationships between the expression of genes involved in particular biological pathways and stages of brain development, then refine these relationships using common and rare genomic data to pinpoint where and when neuronal systems are most vulnerable to the effects of genetic variants conferring risk for psychiatric disorders.

The role of the protein quality control system in TDP43 proteinopathy

Hyung Jun Kim

Korea Brain Research Institute

Abstract: