

**Neuroscience Symposium 2016
&
Annual Scientific Conference of
The Hong Kong Society of Neurosciences**

**Nature and Nurture in
Brain Functions**

18 May 2016 (Wednesday)

**Cheung Kung Hai Conference Centre
Faculty of Medicine Building
The University of Hong Kong**



State Key Laboratory of Brain and Cognitive Sciences
(The University of Hong Kong)

腦與認知科學國家重點實驗室 (香港大學)



Neuroscience Research Centre
The University of Hong Kong

Organized by:

HKU State Key Laboratory of Brain and Cognitive Sciences
HKU Strategic Research Theme on Neuroscience
HKU Neuroscience Research Centre
HKU School of Biomedical Sciences
The Hong Kong Society of Neurosciences

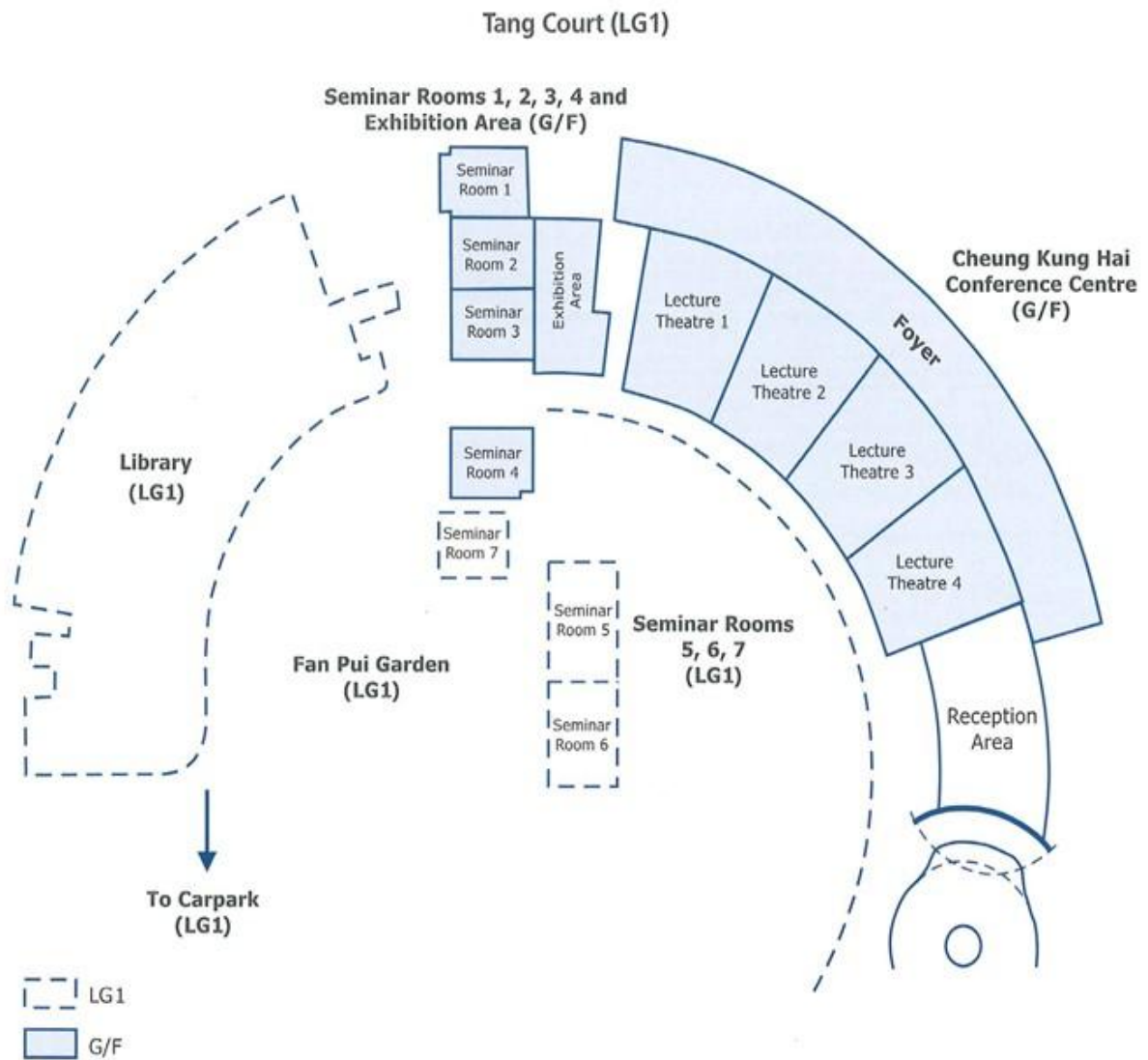


Neuroscience
Strategic Research Theme
The University of Hong Kong



THE HONG KONG SOCIETY
OF NEUROSCIENCES

Symposium Venues



Lecture Theatres 1-4: Cheung Kung Hai Conference Centre, G/F, William MW Mong Block

Seminar Rooms 1-3: G/F, Laboratory Block

Exhibition Area: G/F, Laboratory Block

Welcome Message

On behalf of The State Key Laboratory of Brain and Cognitive Sciences (SKLBCS), HKU and The Hong Kong Society of Neurosciences (HKSAN), we bid you a warm welcome to the joint neuroscience symposium on *Nature and Nurture in Brain Functions!*

This is the first time that the SKLBCS and HKSAN are holding hands to organize a joint symposium. We share a common interest in brain research, yet at the same time many of the approaches employed by our members are diverse and complementary in nature. It is thus most fitting to have this gathering for science as well as friendship. We are especially privileged to have four distinguished investigators from US, UK and Australia to deliver plenary lectures. Equally exciting are talks to be given by a cadre of outstanding local investigators. The afternoon session, which is the annual scientific meeting of HKSAN, features several young investigators symposia and poster sessions presented by local and overseas researchers.

It is our hope that this symposium will nourish old friendship, enable new relationship, catalyze scientific collaboration and promote neuroscience welfare of Hong Kong and beyond. To all attendees, we appreciate very much your contribution and hope you will enjoy your time in the meeting.

Pak Chung Sham
Co-Director,
The State Key Laboratory of Brain & Cognitive Sciences, HKU

Wing-Ho Yung
President,
Hong Kong Society of Neurosciences

Organizers

Organizing Committee:

Chairpersons: SHUM Daisy Kwok Yan, The University of Hong Kong
LAI Kwok-On, The University of Hong Kong

Members: CHANG Raymond Chuen Chung, The University of Hong Kong
HE Jufang, City University of Hong Kong
KE Ya, The Chinese University of Hong Kong
LO Amy Cheuk Yin, The University of Hong Kong
MA Eddie Chi Him, City University of Hong Kong
PARK HYOKEUN, Hong Kong University of Science and Technology
YUNG Ken Kin Lam, Hong Kong Baptist University

The symposium is jointly organized by:

HKU State Key Laboratory of Brain and Cognitive Sciences
HKU Strategic Research Theme on Neuroscience
HKU Neuroscience Research Centre
HKU School of Biomedical Sciences
The Hong Kong Society of Neurosciences

Meeting information

Date: 18th May 2016

Venue: Cheung Kung Hai Conference Centre, Faculty of Medicine Building
The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong

Official Language: English

Meeting Secretariat:

Mr. Kenny Leung

School of Biomedical Sciences, The University of Hong Kong

21 Sassoon Road, Pokfulam, Hong Kong

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Acknowledgements

We gratefully acknowledge the sponsorship from the following companies:

Bioprobes Limited

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Scientific Programme

8:00 – 8:30 am **Registration (Centre Lobby) & Poster Posting (Exhibition Area)**

SKL Neuroscience Symposium

8:30 – 8:45 am **Welcome Address** at LT2

8:45 – 9:20 am **Plenary Lecture I** at LT2

Chairperson:

SHAM Pak Chung, The University of Hong Kong

Speaker:

TAM Patrick (*PL1*)

Embryology Unit, Children's Medical Research Institute and School of Medical Sciences, Sydney Medical School, University of Sydney, New South Wales, Australia.

Title:

Early development of embryonic brain: Impact of WNT signalling activity

9:20 – 9:55 am **Plenary Lecture II** at LT2

Chairperson:

YUNG Wing-Ho, The Chinese University of Hong Kong

Speaker:

DAN Yang (*PL2*)

Howard Hughes Medical Institute, Department of Molecular and Cell Biology, University of California, Berkeley, USA.

Title:

Neural Circuits Controlling Sleep

9:55 – 10:25 am **Coffee/Tea Break and Exhibition Booth Viewing**

10:25 am	Symposium I	at LT2
	<u>Chairpersons:</u> KE Ya, The Chinese University of Hong Kong YUNG Ken Kin Lam, Hong Kong Baptist University	
10:25 – 10:45 am	<u>Invited Speakers:</u> CHANG Wing Chung, The University of Hong Kong (S1) <i>Reinforcement learning deficits in patients with first-episode schizophrenia-spectrum disorder</i>	
10:45 – 11:05 am	CHEUNG Vincent Chi Kwan, The Chinese University of Hong Kong (S2) <i>Mechanisms of muscle coordination and their implications for neurorehabilitation</i>	
11:05 – 11:25 am	LI Miaoxin, The University of Hong Kong (S3) <i>Revisit associated genes of Schizophrenia in an existing whole-genome meta-analysis dataset</i>	
11:25 – 11:45 am	SCHNUPP Jan, City University of Hong Kong (S4) <i>Coding for multiple features of complex sounds: sound source pitch, timbre, and location</i>	
11:45 – 12:20 pm	Plenary Lecture III	at LT2
	<u>Chairperson:</u> CHAN Ying-Shing, The University of Hong Kong	
	<u>Speaker:</u> YAU King-Wai (PL3) The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University, USA	
	<u>Title:</u> <i>Physical/Biochemical Limitations in Visual and Olfactory Transductions</i>	
12:20 – 12:50 pm	Lunch & Poster Posting	
12:50 – 1:50 pm	Poster Session I (odd numbers)	at Exhibition Area

Annual Scientific Conference of the Hong Kong Society of Neurosciences

1:50 – 2:00 pm	Hong Kong Society of Neurosciences Opening	at LT2
2:00 pm	Symposium II	at LT2
	<u>Chairpersons:</u> LAI Kwok-On, The University of Hong Kong MA Eddie Chi Him, City University of Hong Kong	
	<u>Invited Speakers:</u>	
2:00 – 2:20 pm	PARK HYOKEUN, Hong Kong University of Science and Technology (S5) <i>Synaptic Dysfunction in a Huntington's disease</i>	
2:20 – 2:40 pm	LAU Geoffrey, City University of Hong Kong (S6) <i>Regulation of parvalbumin inhibitory circuit function by TrkB signaling</i>	
2:40 – 3:00 pm	YAU SONATA SUK YU, Hong Kong Polytechnic University (S7) <i>Chronic minocycline treatment improves hippocampal NMDA receptor function, dendritic atrophy and memory processing in Fragile X Syndrome mice</i>	
3:00 – 3:20 pm	LEE CHI WAI, The University of Hong Kong (S8) <i>Regulation of acetylcholine receptor trafficking in neuromuscular development and disease</i>	
3:20 – 4:20 pm	Coffee/Tea Break & Exhibition Booth Viewing	
3:20 – 4:20 pm	Poster Session II (even numbers)	at Exhibition Area

Young Investigator Oral Presentations (Parallel Sessions)

4:20 pm **Oral Presentations I** at LT2

Chairpersons:

CHANG Raymond Chuen Chung, The University of Hong Kong
PARK HYOKEUN, Hong Kong University of Science and Technology

Speakers:

- 4:20 – 4:30 pm LAU Eva On-Chai, The Chinese University of Hong Kong (**OP1**)
Functional Role of TRPC5 Channels In Aortic Baroreceptors
- 4:30 – 4:40 pm CHONG Chi Ho, The University of Hong Kong (**OP2**)
Lrrc7 mutant mice model developmental emotional dysregulation
- 4:40 – 4:50 pm KWAN Pui Yi, The University of Hong Kong (**OP3**)
The Regulatory Roles of Semaphorin 3A and Chondroitin Sulfates on Perineuronal Nets in the Developing Vestibular Circuitry
- 4:50 – 5:00 pm WALKER Steven, The Chinese University of Hong Kong (**OP4**)
A high throughput screening system for visualizing therapeutic drugs of neurodegenerative diseases
- 5:00 – 5:10 pm TSUI Yat Ping, The University of Hong Kong (**OP5**)
Schwann cells demonstrated lineage plasticity in culture to acquire oligodendrocyte phenotypes
- 5:10 – 5:20 pm CHENG Sally Shuk Yee, The University of Hong Kong (**OP6**)
Differential roles of the ubiquitin-proteasome system and autophagy in experimental models of Alzheimer's disease
- 5:20 – 5:30 pm KUMAR Gajendra, City University of Hong Kong (**OP7**)
Lycium Barbarum Polysaccharides accelerates axonal regeneration after peripheral nerve injury

4:20 pm **Oral Presentations II** at LT3

Chairpersons:

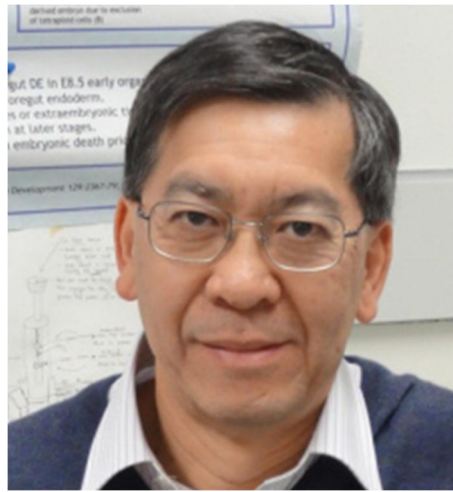
LO Amy Cheuk Yin, The University of Hong Kong
YAU SONATA SUK YU, Hong Kong Polytechnic University

Speakers:

- 4:20 – 4:30 pm JIANG Qiufen, The University of Hong Kong (**OP8**)
Antidepressant reinstates the plasticity in the adult vestibular nucleus
- 4:30 – 4:40 pm CHINE Virendra Bhagawan, City University of Hong Kong (**OP9**)
Protection against paclitaxel-induced peripheral neuropathy by targeted overexpression of human heat shock protein 27 in neurons

- 4:40 – 4:50 pm HUNG Clara Hiu-Ling, The University of Hong Kong (**OP10**)
The Dynamic Mitochondrial Network in Neurodegeneration
- 4:50 – 5:00 pm DUAN Zhigang, The University of Hong Kong (**OP11**)
Kinesin-1 regulates extrasynaptic NMDAR targeting and its reduction can confer neuroprotection
- 5:00 – 5:10 pm WU Ka-Chun, The Chinese University of Hong Kong (**OP12**)
PGC-1 rescues PINK1 deficiency-induced disease phenotypes in a Drosophila model of Parkinson's disease
- 5:10 – 5:20 pm LAI Hei Ming, The University of Hong Kong (**OP13**)
A simple method for all to rapidly evaluate neuronal architectures in situ in three dimensions
- 5:20 – 5:30 pm TETTEH Hannah, City University of Hong Kong (**OP14**)
Synaptic plasticity of interlamellar CA1 network in the hippocampus
- 5:30 – 6:05 pm **Plenary Lecture IV** at LT2
Chairperson:
SHUM Daisy Kwok Yan, The University of Hong Kong
- Speaker:
HÄUSSER Michael (**PL4**)
Wolfson Institute for Biomedical Research, University College London, UK
- Title:
Active dendrites in grid cells
- 6:05 – 6:15 pm **Awards Presentation & Closing Remarks** at LT2

Plenary Speakers



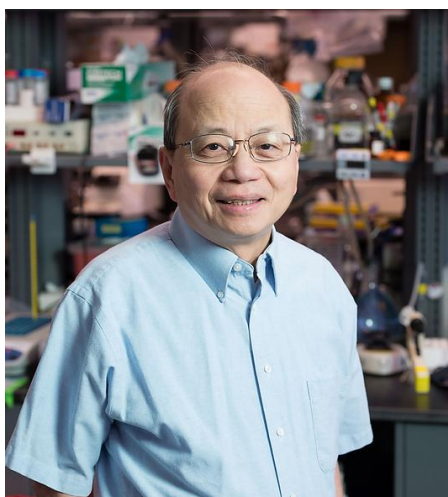
Professor Patrick Tam is the Deputy Director and Head of the Embryology Research Unit at the Children's Medical Research Institute, Senior Principal Research Fellow of the National Health and Medical Research Council of Australia (NHMRC), Professor in the School of Medical Sciences, Sydney Medical School at University of Sydney and the Mok Hing-Yiu Distinguished Visiting Professor in the School of Biomedical Sciences of University of Hong Kong

Patrick Tam's research focuses on the systems-based investigation of the gene regulatory network underpinning the cellular and molecular mechanisms of body patterning during mouse development and the biology of embryo-derived stem cells. He pioneered the application of micromanipulation and embryo culture for analyzing mouse embryos and examining the development of the head and embryonic gut. The embryological analysis undertaken by his team at CMRI has enabled the construction of a series of fate-maps revealing the organization of the basic body plan of the early embryo. The in-depth knowledge of cell differentiation during early embryogenesis laid the foundation for elucidating the genome activity that drive cell lineage development and directing the differentiation of stem cells into clinically useful cell types for therapy in regenerative medicine.

Patrick Tam is an Editor of *Development* and member of the editorial board of journals including *Developmental Biology*, *Developmental Cell*, *Developmental Dynamics*, *Differentiation and Genesis*. He was a Guest Editor of *BioEssays* and *Current Opinion of Genetics and Development* and co-edited with James Nelson and Janet Rossant, a special issue of *CSH Perspectives in Biology* and the accompanying book on "Mammalian Development". He serves on the scientific advisory board / council of Stem Cell Australia, RIKEN Centre for Developmental Biology, Max Planck Institute for Molecular Genetics, Eskitis Institute for Drug Discovery and the HKU School of Biomedical Sciences, and is currently a member of the Embryo Research Licensing Committee of the NHMRC. He was awarded the President's Medal of the Australia and New Zealand Society of Cell and Developmental Biology, and elected to the Fellowship of the Institute of Biology, the Australian Academy of Sciences, the Australian Academy of Health and Medical Sciences, the Royal Society of Biology and the Royal Society of London.



Prof. Dan is a Howard Hughes Medical Institute Investigator and Professor of the Department of Molecular and Cell Biology, University of California, Berkeley, USA. where she has been a faculty member since 1997. She was a physics major at Beijing University and received her Ph.D. training in Biological Sciences at Columbia University, where she worked on cellular mechanisms of neurotransmitter secretion and synaptic plasticity with Mu-ming Poo. She did postdoctoral research on information coding in the visual system at Rockefeller University and Harvard Medical School with Clay Reid, Joseph Atick, and Torsten Wiesel. Dan has received the Alfred P. Sloan Research Fellowship, Beckman Young Investigator Award, and Society for Neuroscience Research Awards for Innovation in Neuroscience. Using a combination of electrophysiology, imaging, and computational methods, Dan's lab provided important insights into the microcircuits underlying visual cortical computation and cellular mechanisms for functional plasticity. More recently, Prof. Dan's research interest aims to elucidate what circuits in the mammalian brain control sleep, and the mechanisms by which the frontal cortex exerts top-down executive control. To achieve these research goals, a variety of state-of-the-art techniques which include optogenetics, electrophysiology, imaging, and virus-mediated circuit tracing are used.



King-Wai Yau was born in China and grew up in Hong Kong. After high school and a year of medical school in Hong Kong University, he came to the US and received an A.B. in physics from Princeton (1971, University Scholar; Phi Beta Kappa; Sigma Xi) and a Ph.D. in neurobiology from Harvard (1975) under John Nicholls. He did postdoctoral work with Denis Baylor at Stanford, developing the suction-pipette-recording method that revolutionized the study of retinal rods and cones, including its ability to detect a rod's response to a single photon. He spent 1979-81 at Cambridge, England with Sir Alan Hodgkin, during which time he became intrigued by the problem of rod/cone phototransductions. In 1981, he moved to Department of Physiology and Biophysics at University of Texas Medical Branch at Galveston, where he contributed greatly to solving this problem. He rose to full professor in 1985, and, a year later, relocated to Johns Hopkins as Professor of Neuroscience and HHMI Investigator.

At Hopkins, Yau investigated rod/cone phototransductions in ever greater detail. He also expanded over time into molecular biology, olfactory transduction, ion-channel molecular physiology, and mouse genetics. In 2002, he and David Berson of Brown University discovered intrinsically-photosensitive retinal ganglion cells expressing the visual pigment, melanopsin, and mediating mostly subconscious, non-image vision. He characterized their light responses in great detail, including likewise observing their single-photon response and recently solving their phototransduction mechanism. Most recently, he discovered yet additional retinal ganglion-cell photoreceptors expressing another visual pigment, neuropsin. Yau also solved a 50-year-old puzzle regarding the spontaneous activation of visual pigments in darkness, providing a rationale for why natural pigments and the associated color vision do not extend into infrared. Together with colleagues Jeremy Nathans and Valeria Canto Soler at Hopkins, he has been engaged in some translational work, such as discovering bestrophin being a member of a novel family of Ca^{2+} -activated anion channels and causing human macular degeneration when mutated, and showing human stem cells developing into an entire retina in culture with sign of photosensitivity.

Yau received England's Rank Prize in Optoelectronics (with Denis Baylor and Trevor Lamb) in 1980, Friedenwald Award from Association of Research in Vision and Ophthalmology (1993), Alcon Award in Eye Research twice (1994, 2005), Magnes Prize from Hebrew University of Jerusalem (1996), Balazs Prize (2006) and RRF Paul Kayser International Prize (2016), the latter two from International Society for Eye Research, Portugal's António Champalimaud Vision Award (with Jeremy Nathans) in 2008, CNIB Chanchlani Global Vision Award, Canada (2012), and the tri-yearly National Academy of Sciences Alexander Hollaender Award in Biophysics (2013). Yau is a member of National Academy of Sciences and a Fellow of American Academy of Arts and Sciences.



Michael Häusser is Professor of Neuroscience at University College London and a Principal Research Fellow of the Wellcome Trust. He received his PhD from Oxford University under the supervision of Julian Jack. He subsequently worked with Nobel Laureate Bert Sakmann at the Max-Planck-Institute for Medical Research in Heidelberg and with Philippe Ascher at the Ecole Normale Supérieure in Paris. He established his own laboratory at UCL in 1997 and became Professor of Neuroscience in 2001. He was elected a Fellow of the Royal Society and a Fellow of the Academy of Medical Sciences. He is interested in understanding the cellular basis of neural computation in the mammalian brain using a combination of experiments and theory, with a special focus on the role of dendrites. His group has helped to pioneer several new optical approaches for probing the function of neural circuits in the intact brain.

PL1

EARLY DEVELOPMENT OF EMBRYONIC BRAIN: IMPACT OF WNT SIGNALLING ACTIVITY

Patrick P. L. Tam

Embryology Unit, Children's Medical Research Institute and School of Medical Sciences, Sydney Medical School,
University of Sydney, New South Wales, Australia.

The embryonic brain is the first major body part to be constructed during embryogenesis. The allocation and the assembly of the progenitor tissues, which start at gastrulation, are accompanied by the spatiotemporal activity of transcription factors and signalling pathways that drives lineage specification, germ layer formation and morphogenetic tissue movement. The assembly of progenitor tissues and regionalization of the embryonic brain rely on the function of the LIM-domain transcription factor and its interacting partners. These factors constitute the central nodes of a gene regulatory network (GRN) which intersects with the activity of the WNT signalling pathway that underpins head formation. It is predicted that the key functional output of this gene network through the stringent modulation of the level of signalling activity impacts on the inductive activity that are essential for cell differentiation and tissue modelling.

PL2

NEURAL CIRCUITS CONTROLLING SLEEP

Yang Dan

Howard Hughes Medical Institute, Department of Molecular and Cell Biology, University of California, Berkeley, USA

I will summarize our work over the past five years on understanding the neural mechanisms controlling sleep. Using optogenetic manipulation, optrode recording, and cell-type-specific calcium imaging, we identify neuronal types that play critical roles in the generation of rapid-eye-movement (REM) sleep and non-REM sleep. Local synaptic interactions between cell types are measured by recordings in brain slices, and long-range connections are mapped using a variety of viral tools.

PL3

PHYSICAL/ BIOCHEMICAL LIMITATIONS IN VISUAL AND OLFACTORY TRANSDUCTIONS

King-Wai Yau

The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University, USA

Vision is initiated in the rod and cone photoreceptors in the retina, where absorbed photons activate a G-protein-coupled signaling pathway (with the visual pigment being the G-protein-coupled receptor, or GPCR) to transduce light energy into an electrical signal that the brain can understand. The rod photoreceptors, which mediate dim-light vision, are exceedingly efficient in signaling light, being capable of transmitting a single-photon-absorption signal to the postsynaptic neuron in the retina -- in other words, right down to the physical limit of light. One reason for this high sensitivity is attributed to the high amplification during rod phototransduction at the step of interaction between rhodopsin and its downstream G protein, transducin; namely, one rhodopsin molecule during its active lifetime is reputedly capable of activating ~1,000 transducin molecules. Given this high gain, and considering that rod phototransduction is the prototypical GPCR signaling pathway, the signature of high amplification in G-protein signaling was born and has become a textbook dogma. The question is thus: Is this concept really universally valid, considering that practically all other GPCR pathways are activated by ligands rather than light? In olfactory transduction, which is a GPCR pathway driven by odor chemicals, we have found that this concept of high amplification is indeed far from being true; namely, a typical receptor-odorant complex has a low probability of activating even a single downstream G-protein molecule, owing largely to the rapid dissociation of the odorant molecule from the receptor. Hence, the limitation of signaling in this case comes from the intrinsic biochemistry. We think this "low" amplification is likely the norm for ligand-driven G-protein signaling, because most ligands do not have high affinity for their cognate receptors. In other words, the high amplification in rod phototransduction is likely an exception.

PL4

ACTIVE DENDRITES IN GRID CELLS

Michael Häusser

Wolfson Institute for Biomedical Research, University College London, UK

How neurons in layer II of medial entorhinal cortex integrate their synaptic inputs to form the dual temporal and rate code of grid cell firing is unknown. Here we use a combination of 2-photon glutamate uncaging, in vivo patch clamp recordings, and computational modelling to show that the dendrites of grid cells are highly excitable, generating dendritic spikes and supralinear input-output curves, which can sharpen the precision of the temporal code and enhance the robustness of the rate code. Active dendrites may therefore constitute a key cellular mechanism for ensuring reliable spatial navigation.

S1

REINFORCEMENT LEARNING DEFICITS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA-SPECTRUM DISORDER

Wing Chung Chang

Department of Psychiatry and State Key Laboratory of Brain & Cognitive Sciences, LKS Faculty of Medicine,
The University of Hong Kong.

Numerous studies have identified reinforcement learning (RL) deficits in schizophrenia. Most have focused on chronic patients with longstanding antipsychotic treatment, however, and studies of RL in early-illness patients have produced mixed results, particularly regarding gradual/procedural learning. No study has directly contrasted both rapid and gradual RL in first-episode psychosis (FEP) samples. We examined probabilistic RL in 34 FEP patients and 36 controls, using Go/NoGo (GNG) and Gain vs. Loss-Avoidance (GLA) paradigms. Our results were mixed, with FEP patients exhibiting greater impairment in the ability to use positive, as opposed to negative, feedback to drive rapid RL on the GLA, but not the GNG. By contrast, patients and controls showed similar improvement across the acquisition. Finally, we found no significant between-group differences in the post-acquisition expression of value-based preference in both tasks. Negative symptoms were modestly associated with RL measures, while the overall bias to engage in Go-responding correlated significantly with psychosis severity in FEP patients, consistent with striatal hyperdopaminergia. Taken together, FEP patients demonstrated more circumscribed RL impairments than previous studies have documented in chronic samples, possibly reflecting differential symptom profiles between first-episode and chronic samples. Our finding of relatively preserved gradual/procedural RL, in briefly-medicated FEP patients, might suggest spared or restored basal ganglia function. Our findings of preserved abilities to use representations of expected value to guide decision-making, and our mixed results regarding rapid RL, may reflect a lesser degree of prefrontal cortical functional impairment in FEP than in chronic samples. Further longitudinal research, in larger samples, is required.

S2

MECHANISMS OF MUSCLE COORDINATION AND THEIR IMPLICATIONS FOR NEUROREHABILITATION

Vincent Chi Kwan Cheung

School of Biomedical Sciences, The Chinese University of Hong Kong

Stroke is a leading cause of adult disability worldwide. The efficacy of most assistive technologies for reversing post-stroke motor impairment, especially for chronic survivors, has remained limited. A new technology that facilitates recovery at the level of general motor control beyond that achievable by standard care must be based on true biological mechanisms of control. We propose that one theory of how the CNS coordinates muscle activations can be the basis of a new rehabilitation strategy. There is strong evidence suggesting that CNS activates groups of muscles together as neuromotor modules - the rudimentary building blocks of movement. The CNS produces complex muscle patterns by flexibly combining several modules together. Here, we aim to use this modular framework to understand the complex muscle-pattern changes that underlie motor recovery in stroke survivors, and harness this knowledge to develop a new rehabilitation. Electromyographic activities (EMGs) from upper-limb muscles of stroke survivors were recorded, before and after intervention; motor modules were identified from the EMGs using specialized algorithms. Preliminary results from chronic survivors indicate that enhanced motor recovery is associated with the activation of a specific muscle synergy in the affected arm after rehabilitation - a "marker" of post-training recovery. Our results raise the possibility of providing rehabilitative training by facilitating the emergence of the marker module through muscle-signal feedback provided to the subject. Overall, our research may be a step towards developing a stroke rehabilitation with specific targets of intervention that is likely to significantly improve general motor control of the arm.

S3

REVISIT ASSOCIATED GENES OF SCHIZOPHRENIA IN AN EXISTING WHOLE-GENOME META-ANALYSIS DATASET

Miaoxin Li

Centre for Genomics Sciences, Department of Psychiatry, and State Key Laboratory of Brain and Cognitive Sciences,
The University of Hong Kong

Whole genome meta-analysis summary statistics of many human diseases are publicly available at present. These resources provide a valuable opportunity to mine extra association signals by gene-based genetic association analyses. However, gene-based genetic association analysis by existing approaches is not immune to genotype dependency among genes and often results in many indirectly associated genes which are functionally irrelevant to a disease. We proposed a novel statistical approach for genetic association mapping that evaluates gene-based and conditional gene-based association using summary statistics. Not only did the proposed approach outperform existing approaches for gene-based association analysis but it is also able to isolate independently associated genes without using individual level genotypes and phenotypes. We applied the proposed gene-based and conditional gene-based association to a large Schizophrenia meta-analysis study. It turned out only 22% or 150 genes were independently significant among 674 significant genes according to conventional gene-based p-value. The functional implication of these isolated genes were suggested by their intensive co-expression (nominal $p = 2.5E-6$; Bonferroni correction $p = 4.5E-5$) and different expression trend between cases and controls (nominal $p = 9.2E-6$, Bonferroni correction $p = 5.5E-5$), in a Schizophrenia related brain region, the superior temporal cortex. Our results highlight how summary statistics of large-scale meta-analyses can be effectively re-analyzed in gene-based units to mine extra association signals.

S4

CODING FOR MULTIPLE FEATURES OF COMPLEX SOUNDS: SOUND SOURCE PITCH, TIMBRE, AND LOCATION

Jan Schnupp

Department of Biomedical Sciences, City University of Hong Kong

When listening to speech sounds, our brains must compute a number of features from the sound wave, including the pattern of so called formant spectral peaks which determine the sound's timbre and identify its phonetic identity, as well as the voice pitch and sound source direction. Furthermore, these computations need to be achieved in a manner which is "noise robust", given that adding background noise to a speech stream disrupts our ability to process speech less than might be expected. Little is known about how these processing steps are accomplished in the human brain, but given that many of the fundamental aspects of vocal communication are generic across all mammals, we have been conducting a number of studies in ferrets, rats, gerbils and mice which aim to shed light on the neural processing of vocalisations and speech sounds in the ascending auditory pathway, and in this talk I will present some of the highlights of our recent work.

S5

SYNAPTIC DYSFUNCTION IN A HUNTINGTON'S DISEASE

Hyokeun Park

Division of Life Science, Hong Kong University of Science and Technology

Huntington's disease is a genetic autosomal neurodegenerative disease. People with larger than 40 CAG repeats in the Huntingtin gene will probably suffer from this disease. The mutant huntingtin protein is believed to lead significant dysfunction in neurons, leading to progressive neuronal death in the striatum and cortex. However, the detailed mechanisms of neurodegeneration in these vulnerable regions remain unknown. We have investigated the release and transport of synaptic vesicles and BDNF containing vesicles, and mobility of mitochondria in Striatal and Cortical neurons. We found significant changes in exocytosis of FM 1-43 and BDNF-pHluorin. These changes cause the defects in release of neurotransmitters and BDNF probability. We also found defects in the transport of vesicles and mobility of mitochondria. These defects in release and mobility of organelles severely affect healthy of neuron and can lead to neuronal death in Striatum and Cortex.

S6

REGULATION OF PARVALBUMIN INHIBITORY CIRCUIT FUNCTION BY TRKB SIGNALING

C. Geoffrey Lau

Department of Biomedical Sciences, City University of Hong Kong

Neural activity modulates the development and plasticity of neurons, in part, by release of intercellular signaling molecules. Signaling by neurotrophins such as the brain-derived neurotrophic factor (BDNF) is known to modulate development of interneurons, but how it affects their synaptic and circuit function remains unclear. Here we examined the impact of TrkB, a BDNF receptor, on the function of parvalbumin-expressing (PV) interneurons by selectively deleting this gene in these cells. In the mouse olfactory cortex, TrkB deletion impairs multiple aspects of PV neuronal function including synaptic excitation, intrinsic excitability and innervation pattern of principal neurons. Impaired PV cell function resulted in aberrant spiking patterns in principal neurons in response to stimulation of sensory inputs. By modulating PV circuit plasticity and development, TrkB plays a critical role in shaping the evoked pattern of activity in a cortical network.

S7

CHRONIC MINOCYCLINE TREATMENT IMPROVES HIPPOCAMPAL NMDA RECEPTOR FUNCTION, DENDRITIC ATROPHY AND MEMORY PROCESSING IN FRAGILE X SYNDROME MICE

Suk Yu Yau

Department of Rehabilitation Sciences, Hong Kong Polytechnic University

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability, and is the leading known single-gene cause of autism spectrum disorder. FXS patients display varied behavioral deficits ranging from mild to severe cognitive impairment, mood disorder to language problem. Minocycline, which can alleviate social behavioral deficit and improving verbal functioning in FXS patients, is currently the only prescribed and targeted treatment for FXS. However, whether minocycline can improve cognitive impairment associated with FXS, such as hippocampal-dependent learning and memory, has not yet been reported. Here we tested if chronic treatment with minocycline improves deficits in hippocampal dentate gyrus (DG)-dependent cognitive behavioral tasks via promoting N-methyl-D-aspartate receptor (NMDAR)-dependent functional and structural plasticity in the DG. Chronic minocycline treatment significantly reversed impairments in two cognitive tasks in FXS mice, including novel object recognition and categorical spatial tasks. Whole cell patch clamping revealed that minocycline treatment significantly increased NMDA receptor function in the dentate granule cells, in concurrent with an increase in PSD-95 and NMDAR subunits including NR2B and NR2A in the DG synaptoneurosome of FXS mice. Furthermore, dendritic analysis showed that minocycline treatment significantly increased dendritic complexity of dentate granule cells of FXS mice. These findings indicate that synaptic plasticity and cognitive deficits in FXS mice can be improved by minocycline, which may provide therapeutic basis of pro-cognitive effect of minocycline in FXS.

S8

REGULATION OF ACETYLCHOLINE RECEPTOR TRAFFICKING IN NEUROMUSCULAR DEVELOPMENT AND DISEASE

Chi Wai Lee

School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong

Synapses are specialized cell membrane domains that facilitate neuronal communication. The nerve-muscle synapse, neuromuscular junction (NMJ), has been considered as the best model for the study of synaptogenesis due to its large size, simplicity and accessibility. In the postsynaptic membrane, acetylcholine receptors (AChRs) are highly concentrated for effective communication between presynaptic and postsynaptic cells. Over the past decades, a significant progress has been made to understand the signaling molecules and their signaling pathways involved in the anchoring and clustering of AChRs in the postsynaptic membrane at developing NMJs. However, the mechanisms underlying the dynamic trafficking of AChRs to/from the postsynaptic membrane remain unclear. Using *Xenopus* primary culture system together with molecular manipulation techniques, we found that actin depolymerizing factor (ADF)/cofilin regulated actin-dependent vesicular trafficking of AChRs to the postsynaptic membrane. Active ADF/cofilin was concentrated in small puncta adjacent to AChR clusters and was spatiotemporally correlated with the formation and maintenance of surface AChR clusters. Furthermore, during the pathogenic mechanisms of AChR endocytosis in myasthenia gravis, the disappearance of ADF/cofilin was closely correlated to the disassembly of AChR clusters induced by the treatment of pathogenic antibodies. Taken together, our results have revealed that spatiotemporally restricted ADF/cofilin-mediated actin dynamics regulate AChR trafficking during the assembly and disassembly of neuromuscular synapses in development and disease, respectively.

OP1

FUNCTIONAL ROLE OF TRPC5 CHANNELS IN AORTIC BARORECEPTORS

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Aortic baroreceptor is the mechanosensor to detect blood pressure in aortic arch. Upon changes in arterial blood pressure, the baroreceptor nerve terminal on the aortic arch adventitia will be activated, resulting in action potentials that propagate to the cardiovascular control centre in the brain. However, the molecular identity of the baroreceptor mechanosensors is not well understood.

TRP channels are a superfamily of non-selective cation channels that can be divided into seven subfamilies: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP, and TRPV. Many TRP isoforms have been reported to be sensors for diverse source of external and/or internal stimuli. Recently, one of the isoforms, TRPC5, has been reported to be hypo-osmolarity and pressure sensitive.

In the present study, the expression of TRPC5 channels in the aortic baroreceptor nerve terminal, which is located on the aortic arch and in the ganglion region (nodose ganglion) was demonstrated by immunohistochemistry. RT-PCR and immunoblot studies confirmed the expression of TRPC5 channels in the aortic baroreceptor. Electrophysiological studies showed that hydrostatic pressure could activate single-channel and whole-cell current in cultured baroreceptor neurons and the current displayed a double rectifying *I-V* relationship, which is typical of TRPC5. Furthermore, *trpc5* knockout mice manifested a significant reduction in aortic depression nerve activity and baroreflex regulation upon blood pressure elevation when compared with wild-type mice. Moreover, knockout of TRPC5 also resulted in blood pressure instability in mice.

Taken together, our study provides the evidence that TRPC5 is involved in pressure sensing of aortic baroreceptor neuron and is participated in the aortic baroreceptor function.

OP2

LRR7 MUTANT MICE MODEL DEVELOPMENTAL EMOTIONAL DYSREGULATION

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LRR7 (*Leucine-rich repeat containing 7*) encodes for Densin-180, a scaffold protein in the postsynaptic density. *LRR7* has been reported as a risk allele for childhood emotional dysregulation and autism spectrum disorder. Knockout mice were reported to have defects related to mental illnesses and abnormal spin development. To further define the role of *LRR7* in behavioural control we made use of our transgenic mice line carrying a hypomorphic allele of *Lrrc7*. Mutant mice exhibited features of childhood emotional dysregulation, including excessive following and fighting at juvenile stage. Behavioural tests in young adults confirm increased anxiety, abnormal social behavior and defective spatial working memory in mutants. To reveal the molecular defects, we examined the dendritic complexity of hippocampal neuros in adult brain and in primary neurons from embryos. Mutant mice showed reduced dendritic complexity in both cases. Using primary neurons, we demonstrated that there was a reduced surface localization of mGlu5 receptor. Furthermore, augmentation of mGlu5 with CDPPB rescued the defects of neurite growth. To test for therapeutic potential of augmenting mGlu5 signaling in developmental emotional dysregulation, we tried acute injection of CDPPB and found that the treatment could alleviate the anxiety-like behavior and excessive social interaction of mutant mice. Our data suggested that *Lrrc7* mutant mice provide a valuable model for developmental emotional dysregulation and identify a novel role of *LRR7* as a scaffold for the regulation of mGlu5 trafficking and activity. Our data also highlight a novel role of mGlu5 signaling in early neuron morphogenesis.

OP3

THE REGULATORY ROLES OF SEMAPHORIN 3A AND CHONDROITIN SULFATES ON PERINEURONAL NETS IN THE DEVELOPING VESTIBULAR CIRCUITRY

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Perineuronal nets (PN) were crucial for restricting neuronal plasticity during development. Our study of the central vestibular nucleus (VN) found consolidation of PN around GABAergic interneurons as from postnatal day (P)9 of Sprague Dawley (SD) rats. This was accompanied by progressive localization of semaphorin 3A (Sema3A) to chondroitin sulphate moieties (CS) of PN. We hypothesized that PN-CS binding of Sema3A limits the action of Sema3A as a plasticity-inducing factor in the VN.

We tested for structural plasticity in VN explant cultures, treated with Chondroitinase ABC (ChABC) and/ or Sema3A. Parallel cultures were fixed for assessment of neurite arborization and growth. Increase in these parameters suggested involvement of CS and Sema3A in the structural plasticity of VN neurons.

To study the impact of PN-CS/Sema3A at the circuit level, the SD rats were assessed for the emergence of negative geotaxis as a readout for graviception. We observed negative geotaxis as early as P9, in correlation with consolidation of PN around GABAergic neurons in the VN. ChABC/Sema3A-treated rats showed delayed emergence of negative geotaxis, similar to effects of bicuculline but contrasting those of muscimol. Delayed emergence of negative geotaxis also correlated to the postponed formation of PN after ChABC treatment. Our results suggest that trapping of plasticity-inducing Sema3A onto PN-CS translates to the closure of plasticity in the graviceptive circuit. [Grant Support: HKRGC17125115M & 777911M]

OP4

A HIGH THROUGHPUT SCREENING SYSTEM FOR VISUALIZING THERAPEUTIC DRUGS OF NEURODEGENERATIVE DISEASES

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Brain diseases including neurodegenerative disorders pose one of the major challenges to the health care system worldwide particularly in regions, such as Hong Kong, that are facing a rapidly aging population. Development of new, more effective drug treatments to cope with neural diseases is a burning issue. However, current drug screening systems and procedures, especially for those targeting brain diseases, have severe limitations. To identify novel therapeutics, we have designed a two phase system which integrates our current understanding of zebrafish behavior and novel neural imaging techniques to identify neural active compounds for treating disorders like epilepsy. The first phase focuses on identifying behavioral differences in mass for quick screening of drugs. The second phase integrates OLEDs into a multiphoton imaging platform as means to establish a framework for the effects of drugs on a behaving model. Utilizing a preliminary design of this system, we were able to statistically and reproducibly differentiate between epileptic, healthy and drug suppressed epilepsy. In vivo neural imaging provided an avenue for distinguishing differences between currently available therapeutic drugs with the potential of identifying newer drugs in the future.

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OP5

SCHWANN CELLS DEMONSTRATED LINEAGE PLASTICITY IN CULTURE TO ACQUIRE OLIGODENDROCYTE PHENOTYPES

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Schwann cells and oligodendrocytes are myelin-forming glial cells found in the peripheral and central nervous systems, respectively. Despite being similar in function, the two cell types have distinct developmental origins. In cultured Schwann cells, however, we serendipitously observed expression of the oligodendrocyte lineage fate determining factor Olig2. Purified Schwann cell cultures were prepared from neonatal rat sciatic nerves. Olig2-positive Schwann cells (OL2-SCs) were detected at 25-30 DIV. By 50-60 DIV, OL2-SCs acquired polydendritic morphology typical of oligodendrocyte precursors. This was accompanied by a decline in Schwann cell marker expression. The OP-like cells were termed Schwann cell-derived oligodendrocyte precursors (SC-OP). We therefore hypothesized that the peripheral nervous system environment is essential for the maintenance of Schwann cell identity. Co-culture of OL2-SCs with dorsal root ganglia neurons prevented conversion in SC-OPs. In contrast, SC-OPs co-cultured with dorsal root ganglia neurons continued differentiation into mature oligodendrocyte-like cells with myelin basic protein-positive segments along multiple axons. Our results revealed "lineage switching" capability of Schwann cells isolated from the peripheral nervous system. Preservation of Schwann cell identity *in vitro* requires signalling cues derived from peripheral neurons.

OP6

DIFFERENTIAL ROLES OF THE UBIQUITIN-PROTEASOME SYSTEM AND AUTOPHAGY IN EXPERIMENTAL MODELS OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a progressive neurodegenerative disease and most prevalent form of dementia today. Current therapeutics are only capable of alleviating symptoms without targeting the root of the problem, as the pathogenesis of AD is still not completely clear. As pathological hallmarks of AD include the accumulation of β -amyloid ($A\beta$) and hyperphosphorylated tau protein aggregates, the current study examines whether impairments in protein degradation pathways, namely the ubiquitin-proteasome system and autophagy-lysosomal pathway, may play important roles in contributing to AD pathogenesis.

Using primary cortical neuronal culture exposed to oligomeric $A\beta$ as an *in vitro* model and triple transgenic (3xTg) AD mice as an *in vivo* model, this study examines longitudinal changes in protein degradation pathways and its relationship to tau accumulation and aggregation. How modulations of ubiquitin, a signaling protein involved in both proteasomal and autophagic degradation of target proteins, can mediate tau expression and aggregation was also explored.

An initial impairment in proteasomal activity with a subsequent activation of the autophagy-lysosomal pathway was found both *in vitro* and *in vivo*. This corresponded with the changes in lysine residue 48 and 63- specific ubiquitin expression, which signals for proteasome and autophagic degradation of target proteins, respectively. Impairments in protein degradation resulted in an accumulation and aggregation of phosphorylated and non-phosphorylated forms of tau with the expression of ubiquitin mutants signaling for autophagic degradation attenuating this accumulation.

In conclusion, this study shows the progression of the decline in proper protein degradation both *in vitro* and *in vivo* with modulation in ubiquitin signaling as a possible new therapeutic target for AD.

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OP7

LYCIUM BARBARUM POLYSACCHARIDES ACCELERATES AXONAL REGENERATION AFTER PERIPHERAL NERVE INJURY

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Lycium Barbarum Polysaccharides (LBP) are the bioactive components of *Lycium barbarum* berries (Wolfberry), an upper class Chinese medicine in Chinese Pharmacopoeia used for centuries. Its pharmacological properties i.e. antioxidant, immunomodulation and neuroprotective are relevant to peripheral nerve regeneration, but not yet investigated. In the present study, we aimed to evaluate the effect LBP on sciatic nerve crush injury mouse model and assess the motor and sensory recovery using a battery of neurobehavioral, electrophysiological and immunohistochemistry tests. Male mice (C57BL/6, 8-10 weeks) were divided into three groups; LBP (100 mg/kg, p.o), Pre + post & post treatment and PBS (vehicle control). Neurobehavioral tests were performed on alternate days and electrophysiological test at every week till full recovery. Based on our neurobehavioral results, axons and neuro-muscular junctions (NMJ) quantifications were performed after 17 days of LBP (100 mg/kg, p.o) administration. The results showed that LBP treatment improves the sensory and motor function recovery after injury. LBP treated group (pre+post & post treatment) showed significant increased in score of pinprick, toe spread, sciatic functional index, four limbs and hind limb grip strength as compared with control ($p < 0.05$). Immunohistochemistry analysis exhibited significant increased in NF200 positive axon in the sciatic nerve 5 to 25 mm distal to injury site and NMJ numbers in lateral planter muscle in ipsilateral side ($P < 0.05$). Electromyography amplitude of gastrocnemius and interossius was significantly increased ($p < 0.05$) in LBP treated mice as compared with control. In conclusion, LBP treatment promotes the regeneration of peripheral nerve after injury.

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OP8

ANTIDEPRESSANT REINSTATES THE PLASTICITY IN THE ADULT VESTIBULAR NUCLEUS

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Antidepressant fluoxetine is known to restore ocular dominance plasticity in adulthood. We hypothesize that fluoxetine can also reinstate the plasticity in the adult vestibular nucleus (VN), including both behavioral and neuronal plasticity. In previous work, a critical period was revealed before P14 when the sensory inputs from the VN shaped the adult navigation behavior. In the present study, we demonstrated that, with orally administration of fluoxetine during P21-28, perturbation in GABAergic transmission in the VN even at P21 could still lead to deficits in spatial navigation of adults, suggesting the restoration in behavioral plasticity induced by fluoxetine. Then, neuronal plasticity in the VN of young adult rats was investigated after fluoxetine treatment. Using whole-cell patch-clamp, we found that the frequency of miniature inhibitory post-synaptic currents (mIPSCs) was significantly decreased after 7-day treatment of fluoxetine, while the proportion of cells exhibiting long-term depression (LTD) mediated by IPSC was increased. This result indicated a reduction in the inhibitory neurotransmission, causing an increase in the ratio of excitation to inhibition (E/I ratio) in the VN of P28 rats, even to a value that was comparable to that within the critical period. What's more, fluoxetine accelerated neurogenesis in the VN with a significant increase in the number of BrdU⁺ neurons, among which a majority also expressed parvalbumin (PV⁺). Taken together, our findings indicate that fluoxetine is able to restore navigation plasticity in adulthood by modulating neuronal plasticity in the VN of young adult rats, in which the balance between excitation and inhibition is re-organised and the neurogenesis is promoted. [Supported by HKU 761812M]

OP9

PROTECTION AGAINST PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY BY TARGETED OVEREXPRESSION OF HUMAN HEAT SHOCK PROTEIN 27 IN NEURONS

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Cancer patients withdraw their lifesaving chemotherapy due to chemotherapy induced peripheral neuropathy (CIPN). Paclitaxel is widely used to treat breast, ovarian and lung cancers. Our previous studies revealed that Paclitaxel disrupted microtubule organization in mouse primary dorsal root ganglion neuron assessed by atomic force microscopy and confocal imaging. In addition, development of allodynia with loss of intra-epidermal nerve fibers (IENFs), axonal degeneration and demyelination with reduced sensory nerve action potential (SNAP), nerve conduction velocity (NCV) and compound muscle action potential (CMAP) have been reported in animal model of CIPN. Heat shock protein 27 (Hsp27) is a chaperone protein which demonstrated anti-apoptotic and anti-oxidative activities. We have generated transgenic mouse lines which highly express human Hsp27 (hHsp27 Tg) in both sensory and motor neurons. Paclitaxel was injected intraperitoneally to hHsp27 Tg and their littermate (LM) mouse to induce peripheral neuropathy and Cremophore/Ethanol was injected as vehicle (VH) control. Assessment of mechanical and cold allodynia showed that hHsp27 overexpression significantly protects against paclitaxel induced peripheral neuropathy compared to VH control. Similarly, hHsp27 Tg group showed significant protection in IENF density, myelin basic protein and neuromuscular junctions analysis than in LM. Moreover SNAP, NCV and CMAP recordings showed better electrophysiological properties in hHsp27 Tg mice than LM indicating better axonal transport due to less mitochondrial damage. qPCR analysis for mitochondrial proteins showed significant downregulation in LM but not in hHsp27 Tg. Overall, overexpression of hHsp27 showed marked protection against Paclitaxel induced peripheral neuropathy and this may open new therapeutic approach to treat CIPN.

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OP10

THE DYNAMIC MITOCHONDRIAL NETWORK IN NEURODEGENERATION

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Mitochondrial fragmentation due to fission/fusion imbalance has often been linked to mitochondrial dysfunction and apoptosis in neurodegeneration. It is traditionally believed that once the morphology of mitochondria shifts away from its physiological tubular form, mitochondria becomes defective and downstream apoptotic signalling pathways are triggered. In this study, we explored the dynamic changes in mitochondrial network in neurodegeneration.

Our study showed that at early stages of neurodegeneration, beta-amyloid (Ab) induced morphological changes in mitochondria where they become granular shape which was distinct from the conventional round and fragmented mitochondria in terms of both morphology and function. In addition, we demonstrated that accumulation of mitochondrial reactive oxygen species triggered granular mitochondria formation, while mitoTEMPO (a mitochondria-targeted superoxide scavenger) restored tubular mitochondrial morphology within Ab-treated neurons. Interestingly, modulations of mitochondria fission and fusion by genetic and pharmacological means not only attenuated the induction of granular mitochondria but also diminished mitochondrial superoxide levels in Ab-treated neurons.

This study demonstrates a unique reciprocal relationship between mitochondrial dynamics and reactive oxygen species and provides a new possible therapeutic target at early stages of neurodegenerative disease pathogenesis. This study is supported by HMRF02131956, HKU Alzheimer's Disease Research Network, and generous donation from Ms. Kit-Wan Chow.

OP11

KINESIN-1 REGULATES EXTRASYNAPTIC NMDAR TARGETING AND ITS REDUCTION CAN CONFER NEUROPROTECTION

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The cellular response to brain injury mediates the fate of the neuron. Previous studies to identify neuronal responses that could be protective indicated intracellular transport as a potential target, but the underlying mechanisms are still unknown. Here, we showed that a decreased level of kinesin-1, a microtubule-dependent molecular motor, confers neuroprotection by reducing extrasynaptic N-methyl-D-aspartate receptor (NMDAR) targeting and functioning. We found that kif5b, the heavy chain of kinesin-1, was down-regulated by ischemic preconditioning. A loss of 50% of Kif5b protected the neurons against excitotoxic insult and ischemia provoked neurodegeneration through the hypofunction of NMDARs. Kinesin-1 forms complex with NMDAR *in vivo* and the tail of Kif5b directly binds with the NR2B cytoplasmic tails. Decreased kinesin-1 reduces the formation of this complex *in vivo*, prevents NMDAR concentrating at extrasynaptic sites and inhibits calcium influx mediated by extrasynaptic NMDAR activation to confer neuroprotection. *De novo* upregulation of the reduced Kif5b level abolished such protection effects. Our findings reveal that kinesin-1 reduction benefits and protects the neurons against neurodegeneration by reducing the cellular response to NMDAR mediated excitotoxic insult, which is likely to be an intrinsic event in the early stage of neurodegeneration. This finding could lead to the development of therapeutic strategies that fine-tune the intracellular transport machinery to postpone or halt neurodegeneration.

OP12

PGC-1 RESCUES PINK1 DEFICIENCY-INDUCED DISEASE PHENOTYPES IN A DROSOPHILA MODEL OF PARKINSON'S DISEASE

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PTEN-induced putative kinase 1 (PINK1) is a serine/threonine kinase critical to mitochondria quality control. Deficiency in PINK1 causes mitochondrial dysfunction and early-onset Parkinson's disease (PD). Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) is regarded as the master regulator of mitochondrial biogenesis and cellular energy metabolism. Recently, overexpression of PGC-1 α has resulted in contradictory outcomes in neurotoxin-induced PD models. In this study, we overexpressed the PGC-1 α fly homolog, PGC-1, in the well-established PINK1-deficient fly model of PD to examine whether PGC-1 overexpression may modify PINK1 deficiency-induced disease phenotypes and the underlying mechanisms. Our data indicated that, in PINK1-deficient flies, PGC-1 overexpression improved survival rate and motor deficits, revealed by negative geotaxis test, as early as 10d post-eclosion at which no loss of dopaminergic neurons was detected by whole-mount immunohistochemistry. Further investigation revealed that PGC-1 overexpression preserved mitochondrial morphology and mitochondrial membrane potential in 10d PINK1-deficient flies. Consistently, ATP depletion and impaired mitochondrial complex I activity in 10d PINK1-deficient flies were also found to be rescued upon PGC-1 overexpression. To conclude, our findings suggested that PGC-1 overexpression may have therapeutic effects in PINK1 deficiency-induced early-onset PD possibly via functional rescue of mitochondria. Manipulation of endogenous PGC-1 α in dopaminergic neurons, which is possible via a number of FDA-approved drugs, can be a promising and readily translatable treatment strategy.

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OP13

A SIMPLE METHOD FOR ALL TO RAPIDLY EVALUATE NEURONAL ARCHITECTURES *IN SITU* IN THREE DIMENSIONS

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Detailed evaluation of neuronal architectures and interconnections has been a challenge and the key to understand how the brain functions. Building on the theories and principles of traditional histochemistry, tissue clearing, and diffusion models, we developed a novel yet simple method for all to evaluate neuronal architectures in 3D in intact tissues, without the use of additional equipment, specialized chemicals, and difficult techniques. We believe with the introduction of such simple yet powerful methodology, key questions regarding the brain can be resolved more rapidly, and would help uncover the structural basis of neurocognitive functions.

OP14

SYNAPTIC PLASTICITY OF INTERLAMELLAR CA1 NETWORK IN THE HIPPOCAMPUS

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The connections along the longitudinal axis of the CA1 hippocampal cells have been known to be highly insignificant therefore most studies have looked at the transverse orientations of the CA3 and/or CA1 regions. Recently though, a study has shown that the CA1 pyramidal neurons are well-organized and have a longitudinally projecting synaptic network that supports plasticity including long-term potentiation. This triggered an interest in the cellular processing within the longitudinal CA1 hippocampal region. This study aimed to investigate the involvement of the CA1 pyramidal cells along the longitudinal axis in long term synaptic plasticity. Here we studied long-term synaptic plasticity in CA1 longitudinal plane using in vitro and in vivo recordings. We found that the longitudinal network has NMDAR dependent long-term potentiation (LTP). Meanwhile, there is no apparent long-term depression (LTD) under the frequently used LTD induction protocols. This result implicates a unique functional property in the longitudinal projection, stimulating a further research regarding how the longitudinal network contributes to information processing.

CHRONIC EXPOSURE TO PACIFIC CIGUATOXIN-1 DELAYS MOTOR FUNCTIONAL RECOVERY AND REDUCES MOTOR CORTEX NEURONAL ACTIVITY AFTER PERIPHERAL NERVE INJURY

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Ciguatera fish poisoning (CFP) is a common foodborne illness caused by consumption of tropical reef fish containing ciguatoxins (CTXs). Neurological symptoms in CFP patient such as muscle weakness last for several months. However, underlying mechanism for persistent symptoms after P-CTX-1 exposure remains largely unknown. In the present study, we investigate the effect of P-CTX-1 chronic exposure on motor function after injury. Male adult C57BL/6 mice were injected with sub-lethal dosage of P-CTX-1 (0.26ng/g, i.p) or vehicle control (PBS solution with 1% Tween 60) on day 0 and 3. We observed delayed motor functional recovery for first two weeks and then restored to baseline. Sciatic nerve crush was performed after four months of exposure and neurobehavioral & electrophysiological assessments were performed for 2 months. P-CTX-1 treated group exhibited significant decrease in toe spread score, hind limb & four-limb grip strength, retention time on rota-rod as compared with vehicle control ($p < 0.05$). However, sensory recovery as assessed by pinprick test was delayed for four days. Electromyography amplitude of gastrocnemius and lateral planter muscle were significantly decreased in P-CTX-1 treated group as compared to vehicle treated during initial recovery period. Single cell recording of motor cortex neuron performed at the end of experiment exhibited significant decreased in firing rate in P-CTX-1 treated group as compared to vehicle. In conclusion, this study suggests that chronic exposure of P-CTX-1 cause motor deficit by delaying the peripheral nerve regeneration and affecting the motor cortex neuronal spontaneous activity.

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A SMALL HEAT SHOCK PROTEIN PROTECTS AGAINST GUILLAIN-BARRÉ SYNDROME IN MICE

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Guillain-Barré syndrome (GBS) is a peripheral system disorder in which host immune system causes neuropathy. Molecular mimicry between the gangliosides on the peripheral nerves and the lipooligosaccharide of microorganisms initiates the autoimmune response. Several case reports confirmed the GBS symptoms after the swine influenza vaccine and *Campylobacter jejuni* infection. Recent reports observed Zika virus infection also induced GBS symptoms. Majority of the GBS patients experienced neurological symptoms such as paresthesia, muscle weakness, pain and areflexia. Our previous studies reported heat shock protein (Hsp) 27 accelerated the axonal regeneration in mice after peripheral nerve injury. We showed that forced overexpression of human (h) Hsp27 could overcome anti-ganglioside mediated nerve regeneration inhibition. Passive transfer of anti-ganglioside antibodies (GD1a/GT1b-2b)/IB7 into hHsp 27 transgenic (Tg) mice and littermates was done to study their functional recovery. In our chronic animal model (90 days) we observed improved sensory and motor functional recovery in hHsp27 Tg mice as compared to littermates. Our electromyography and histology data showed that hHsp27 Tg mice demonstrated marked improvement of muscle function in terms of increased compound muscle action potential (CMAP) and neuromuscular junction (NMJ) reinnervation. To further investigate we used sub acute animal model (30 days) in which CMAP and muscle mass index was improved in hHsp27 Tg mice as compared to littermates. NMJ and axon quantification showed higher number of innervated NMJ and axon number in hHsp 27 Tg mice. Our future work is to elucidate the molecular pathway of hHsp27 involved in overcoming the inhibitory effect of anti-gangliosides.

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NOVEL STRATEGY FOR PROMOTING AXONAL REGENERATION AND REPAIR IN THE NERVOUS SYSTEMS

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Injuries to the nervous system remain major obstacles in clinical medicine resulting in poor functional recovery. Damaged central nervous system (CNS) neurons cannot regenerate their axons largely due to the limited intrinsic growth capacity of injured neurons and extrinsic inhibitory microenvironment. By contrast, peripheral nervous system (PNS) neurons can regenerate their damaged axons at extremely slow rate of axonal regrowth (1-2mm/day). The slow regeneration of axons largely limited the functional recovery in patients with brachial plexus nerve injury (i.e. proximal PN injury) in which axons require to grow a long distance for muscle reinnervation. In recent years, there is emerging evidence suggesting that low-dose of ionizing radiation (LDIR) including X-ray is beneficial to living organisms via induction of adaptive response. LDIR activates the DNA repair mechanism and enhances the innate immunity, and thus promotes the overall fitness of irradiated individuals. Here, we examined whether LDIR of X-ray exhibits hormetic effects on promoting nerve repair after injury to the nervous system. In PNS, we demonstrated that LDIR of X-ray promotes neurite outgrowth of cultured peripheral neurons (i.e. dorsal root ganglions). Moreover, LDIR of X-ray accelerates axonal regrowth after sciatic nerve crush injury *in vivo*. In CNS, LDIR of X-ray promotes the migration of microglia towards the injury site after stab wound injury in postnatal cortex, which facilitate rapid degradation of CSPG. Further studies on the underlying molecular mechanism of LDIR on nervous system repair will shed new light on understanding the intrinsic machinery essential for successful regeneration after nervous system injuries.

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SMALL MOLECULE APPROACH TO DIFFERENTIATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS TO SENSORY NEURONS

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In this study, we took an alternative approach and selected five small molecule inhibitors (SMIs) of key signaling pathways to test out a new protocol for the derivation of sensory neurons from human iPSCs. Within 8 days of the differentiation protocol, iPSC-derived sensory neurons were achieved at >80% efficiency. The derived cells were positive for cytoskeletal markers common to neurons, Tuj-1 and neurofilament, and specific markers for sensory neurons, Islet, peripherin and Brn3a. Whole-cell patch-clamp recordings of the neurons showed firing in response to membrane depolarization, capable of generating action potentials sensitive to tetrodotoxin. In co-culture with rat Schwann cells in myelinating medium, axon bundles of the derived sensory neurons underwent myelination, showing internodal segments that were positive for myelin basic protein. The phenotype of the iPSC-derived sensory neurons was sustainable in Neurobasal medium supplemented with maintenance growth factors but without SMIs. Our rapid and efficient induction protocol promises controlled production of sensory neurons from human iPSCs as a pool for developmental studies and disease modeling.

THE KINESIN MOTOR PROTEIN KIF5B REGULATES RNA TRAFFICKING AND DENDRITIC SPINE MORPHOGENESIS IN HIPPOCAMPAL NEURON

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Protein synthesis in neuron can occur locally near individual synapses of the postsynaptic neuron, which may serve to translate synaptic activity into the formation of persistent synaptic connections and mature dendritic spines. To achieve local protein synthesis, specific mRNAs must first be transported to the neuronal dendrites. The anterograde transport of selective cargoes, including mRNAs, protein complexes and organelles to distal dendrites, is carried out by the Kinesin Superfamily (KIFs) of molecular motors. Among them, the three members of the KIF5 family (KIF5A, KIF5B & KIF5C) are present in the ribonucleoprotein complexes (RNPs) that transport dendritic mRNAs. However, it is not clear whether individual KIF5 perform redundant or distinct functions in the transport of RNPs and the regulation of synapse structure. Here we performed time-lapse confocal imaging using the RNA dye SYTO 14 and the Mitotracker CMXRos to monitor the dynamics of RNPs in dissociated hippocampal neurons derived from wild-type or KIF5B heterozygous knockout mice. Consistent with previous studies, majority of the RNPs were stationary, and the motile RNPs exhibited discontinuous movement which was either oscillatory (bi-directional movement over short distances) or unidirectional (moving one direction over long distances). Interestingly, KIF5B heterozygous neurons contained significantly fewer stationary RNPs, and higher proportion of RNPs displayed unidirectional movement. We further found that knock down of KIF5B expression in rat hippocampal neurons using short hairpin RNA (shRNA) led to the loss of mature spines and a significant increase in the number of immature filopodia. These findings suggest that the kinesin KIF5B is crucial for the transport and docking of selective mRNAs, which may subsequently regulate the maturation of dendritic spines.

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STRUCTURAL INSIGHTS INTO SUBTYPE SELECTIVITY OF HUMAN MELATONIN RECEPTOR

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Both MT₁ and MT₂ melatonin receptors have been associated with circadian rhythm regulation and have emerged as attractive drug targets for treatment of chronobiological disorders. The two receptors have been suggested to act in a complementary way in the SCN to modulate the sleep-wake cycle. Studies in mice suggested that MT₁ activation suppresses SCN neuron firing, while MT₂ receptors are involved in entraining the circadian rhythmic activity of SCN neurons. However, the high conservation of the melatonin binding pocket has made the development of subtype-selective compound challenging. With the discovery of MT₂ selective isoquinolinone derivatives, the proximity of a MT₂ selective ligand binding site on melatonin receptor was examined through mutagenesis studies. The potential ligand binding site of melatonin receptor was predicted using computational approaches and seven conserved residues (Asn¹⁷⁵, His²⁰⁸, Trp²⁶⁴, Asn²⁶⁸, Gly²⁷¹, Tyr²⁹⁴ and Tyr²⁹⁸) were selected as targets for site-directed mutagenesis. Comparison of the functional activities of melatonin and isoquinolinones on wild-type and point-mutated melatonin receptors revealed differences in their respective binding sites that contribute to a role in selectivity at this receptor family. This study also report identification of a subset of residues that form a hydrophobic binding cavity for accommodating the selectivity conferring aromatic substituent of isoquinolinone compound, which provide new insights into the development subtype selective melatoninergics for treating circadian rhythm sleep disorders.

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P7

REPEATED TACTILE STIMULATION PROMOTES HIPPOCAMPAL NEUROGENESIS AND REDUCES DEPRESSION-LIKE BEHAVIORS

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Base on the clinical usage of tactile stimulation and tactile stimulation has been shown neurogenic effect in spinal cord, which promotes proliferation of progenitor cells in the spinal cord in mouse, but the theoretical basis and underlying biological mechanisms in the brain remain unknown. Tactile stimulation, a kind of mechanosensory stimulation, used to apply as a rehabilitative treatment to decrease hypersensitivity, enhances recovery of cognitive functions and emotion. In current study, we investigate the influence of repeated tactile stimulation on hippocampal neurogenesis, dendritic maturation of new neuron and affective behaviors in the brain. Young adult Sprague-Dawley rats treated with supraphysiological dose of corticosterone (40mg/kg), which induced anxiety and depression-like behaviors and suppressed hippocampal neurogenesis. Depression- and anxiety- like behavior reduced while the treatment of repeated tactile stimulation was delivered by brushing the back, forelimbs, hindlimbs and whisker pad of rats with a force at 200mN, with a duration of 5 minutes per day for two weeks. The present finding shows enhance dividing cell proliferation, neuronal differentiation and dendritic complexity. The findings indicate that tactile stimulation may be an enhancer for the regulation of neurogenesis in the brain and improving the recovery of social/emotional problems because of increased number of positive social interaction. These results demonstrate novel knowledge on the regulation of neurogenesis and mechanism of treatment related to tactile stimulation. Further study suggests that molecular mechanism will be examined through blocking neurogenesis for determining the necessary of neurogenesis.

P8

A PUTATIVE MECHANISM FOR THE DEVELOPMENT OF REM SLEEP BEHAVIOR DISORDER IN A CHRONIC MODEL OF PARKINSON'S DISEASE

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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia that is characterized by elaborated motor behaviors and dream enactments during REM sleep. According to clinical observations, RBD is associated with several alpha-synuclein neurodegenerative diseases such as Lewy body dementia and Parkinson's disease (PD), and often occurring prior to their diagnosis. Since the cause of RBD is not fully understood, being a potential biomarker of PD, investigating the cause of RBD and its relationship with PD would provide insight into the pathogenic process of PD. Here we show that in a chronic model of PD, rats with daily injection of rotenone exhibited key RBD features, including elevated sleep muscle tone, sleep fragmentation and EEG slowing, at different time points. We found that alpha-synuclein aggregation and apoptosis were detectable relatively early in the pontine tegmentum area, including sublateralodorsal tegmental nucleus, that is known to regulate REM sleep. In contrast, alpha-synuclein aggregation and neuronal degeneration in another downstream brain-stem region, the gigantocellular ventricular reticular nucleus, occurred at a later time point. These results are consistent with a progressive degeneration in the descending pathway that controls REM sleep and associated muscle atonia induced by accumulation of alpha-synuclein. These findings provide the foundation for further investigation into the generation of RBD and its relationship to neurodegenerative diseases.

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KINESIN-1 REGULATES EXTRASYNAPTIC NMDAR TARGETING AND ITS REDUCTION CAN CONFER NEUROPROTECTION

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The cellular response to brain injury mediates the fate of the neuron. Previous studies to identify neuronal responses that could be protective indicated intracellular transport as a potential target, but the underlying mechanisms are still unknown. Here, we showed that a decreased level of kinesin-1, a microtubule-dependent molecular motor, confers neuroprotection by reducing extrasynaptic N-methyl-D-aspartate receptor (NMDAR) targeting and functioning. We found that kif5b, the heavy chain of kinesin-1, was down-regulated by ischemic preconditioning. A loss of 50% of Kif5b protected the neurons against excitotoxic insult and ischemia provoked neurodegeneration through the hypofunction of NMDARs. Kinesin-1 forms complex with NMDAR *in vivo* and the tail of Kif5b directly binds with the NR2B cytoplasmic tails. Decreased kinesin-1 reduces the formation of this complex *in vivo*, prevents NMDAR concentrating at extrasynaptic sites and inhibits calcium influx mediated by extrasynaptic NMDAR activation to confer neuroprotection. *De novo* upregulation of the reduced Kif5b level abolished such protection effects. Our findings reveal that kinesin-1 reduction benefits and protects the neurons against neurodegeneration by reducing the cellular response to NMDAR mediated excitotoxic insult, which is likely to be an intrinsic event in the early stage of neurodegeneration. This finding could lead to the development of therapeutic strategies that fine-tune the intracellular transport machinery to postpone or halt neurodegeneration.

ROLE OF DELETED IN LIVER CANCER 2 (DLC2) IN DIABETES-ASSOCIATED NEUROPATHY

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Diabetes mellitus (DM), characterized by hyperglycemia, represents one of the main threats to human health in the 21st century. One of the major complications of diabetes is diabetic neuropathy but few effective treatment options exist for this disease. Previously we found mice deficient in DLC2, a RhoA specific GTPase-activating protein, to have increased sensitivity to thermal and inflammatory stimuli compared to wild type (DLC2^{+/+}) in acute pain tests. Here, we hypothesize that DLC2 may also play a protective role in chronic inflammatory pain associated with diabetes. To address this, multiple low dose streptozotocin (MLDS) treatment was used to induce diabetes in DLC2^{-/-} and DLC2^{+/+} mice, and nociceptive behavior were measured. Interestingly, non-diabetic and diabetic DLC2^{-/-} mice showed more severe hyperalgesia compared to the corresponding DLC2^{+/+} mice. In addition, diabetic DLC2^{-/-} mice also showed earlier onset of painful response than diabetic DLC2^{+/+} mice. Diabetic and non-diabetic DLC2^{-/-} mice showed more small sensory nerve ending density in the skin. Meanwhile, the dorsal root ganglia of these mice had higher gene expression of voltage-gated sodium channel *SCN1A* compared to diabetic DLC2^{+/+} mice, while phosphorylated ERK was elevated in non-diabetic DLC2^{-/-} mice and diabetic mice of both genotypes compared to non-diabetic DLC2^{+/+} mice. The DLC2^{-/-} mice are a useful model to investigate the glucose metabolism and diabetic painful neuropathy since DLC2^{-/-} mice display lower blood glucose level with MLDS treatment, but have more severe chronic inflammatory pain response. We also hypothesize that increased RhoA activity and pERK levels may lead to increased *SCN1A* transcription and activation, leading to a heightened pain response in diabetic DLC2^{-/-} mice.

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MC4R ACTIVATION ALLEVIATES AMYLOID-BETA-INDUCED SYNAPTIC DYSFUNCTION

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Activation of melanocortin 4 receptor (MC4R), which is well known for its role in regulating energy homeostasis, enhances synaptic plasticity in mouse hippocampus via the cAMP/PKA-dependent pathway. In Alzheimer's disease, impaired hippocampal synaptic plasticity is suggested to be induced by soluble amyloid-beta. Here, we show that treatment of cultured hippocampal neurons with amyloid-beta reduced synaptic transmission, and the reduction could be reversed by MC4R activation. Furthermore, the rescue action of MC4R at synapses was mediated via the cAMP/PKA-dependent signaling pathway. Treatment of acute mouse hippocampus slices with MC4R agonist abolished the amyloid-beta-induced impairment in cAMP/PKA signaling and synaptic plasticity. Hence, our findings collectively indicate that MC4R activation alleviates the amyloid-beta-induced synaptic deficit in hippocampal neurons in a cAMP/PKA-dependent manner. Further mechanistic studies of the causative link between MC4R/cAMP/PKA signaling with synaptic dysfunctions observed in AD may provide insights into the potential development of MC4R as a molecular target of the disease.

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MANIPULATION OF DIFFERENT CORTICAL NEURON SUBTYPES WITH OPTOGENETICS

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Optogenetics is widely used to investigate the function of neural systems via manipulation of activities in specific neuronal subtypes. Our long-term goal is to manipulate the plasticity of excitatory-inhibitory balance in the neocortical circuitry responsible for spatial processing and relevant behaviors. To achieve this, we have to express functional channelrhodopsin-2 (ChR-2) and halorhodopsin (NpHR) in excitatory and inhibitory neurons of the neural circuits. To target excitatory neurons, we took the advantage of calcium kinase II (CamK II) promoter that is known to drive gene product that is characteristic for these neurons. After the injection of viral-based vector for ChR-2 or NpHR in the neocortex of rats for 3 weeks, we showed that blue light triggered an inward current in ChR-2-positive neurons whereas green light induced an outward current in NpHR-positive neurons. On the other hand, inhibitory neurons, as visualized by YFP expression in vesicular GABA transporter (VGAT)-Venus transgenic mice, rarely expressed ChR-2 protein, indicating high selectivity of this optogenetic virus for excitatory neurons. Instead, we used parvalbumin (PV) promoter to drive specific expression of light-sensitive channels in PV neurons, a subtype of GABAergic neurons, of Cre-PV-transgenic mice. Blue light exerted an excitatory action on ChR-2-expressing neurons whereas green light triggered an inhibitory current in NpHR-positive neurons. That these light-gated channels were predominantly expressed in PV neurons suggests high selectivity of the virus for PV neurons. Overall, we have established a platform in expressing functional ChR-2 and NpHR in target neuron phenotypes, paving the way for future studies in animal behavior.

P13

DYNAMICS OF CHONDROITIN SULFATION IN THE RAT BRAIN DURING DEVELOPMENT AND VESTIBULAR COMPENSATION

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Chondroitin sulfate (CS) regulates neuronal plasticity by restricting neurite growth and synapse formation. Sulfation on C-2 of glucuronic acid, C-4 and/ or C-6 of N-acetylgalactosamine of the repeating disaccharide units contributes to the heterogeneity and functions of CS. However, the regulation of CS sulfation in the brain is still poorly understood. We hypothesized that the abundance of different sulfated CS moieties changes in coordination with plastic changes in the brain.

With fluorophore-assisted carbohydrate electrophoresis, we found that in both the cortex and the brainstem during postnatal development, mono-4-sulfated chondroitin moiety increased while mono-6-sulfated moiety decreased progressively to an undetectable level in adults. Di-2, 4 and 2, 6-sulfated moieties were not detectable in early postnatal stages but small amount could be found at later stages. We set forth to find changes in CS moieties in a plastic event in adult rat. Following unilateral labyrinthectomy in adult rats, we observed immediate deficits in posture, motor and ocular functions. Time taken for functional recovery reflected compensatory rewiring of the brainstem network. During the recovery period, expression of the mono-6-sulfated chondroitin moiety resumed, reminiscent of that in the early postnatal period. Real time PCR also revealed differences in the expression of chondroitin sulfotransferases between the left and right vestibular nucleus during early stage of vestibular compensation.

Taken together, the developmental changes in CS sulfation and the rise of mono-6-sulfated moiety during vestibular compensation suggest a role of CS sulfation pattern in neuronal plasticity.

P14

DIFFUSION DYNAMICS OF ACHR RECEPTORS ON LIVE MUSCLE CELL MEMBRANE

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The dynamic structure of a cell membrane allows it to become an effective platform for various biological functions, such as signal transduction, molecule transportation and endocytosis. We report here a single-molecular tracking experiment on a quantum-dot-labeled transmembrane protein, acetylcholine receptor (AChR), in cultured *Xenopus* muscle cells. We carried out a complete statistical analysis on a large set of AChR trajectories with more than 500 cells examined. Various drug treatments were used to perturb F-actin and scaffold proteins and examine their roles in regulating the motion of the AChRs. The diffusion dynamics of AChRs was characterized by three quantities: the mean-square displacement $\overline{\Delta r^2(t)}$, the probability density function $P(Dx)$ of instantaneous displacement $Dx(t)$ and the probability distribution $f(d)$ of instantaneous diffusion coefficient d . After a careful analysis, we conclude that (1) AChRs show a hindered motion by the surrounding membrane molecules at short time and become diffusive at long time. (2) The mobile AChRs have a broad distribution in diffusion coefficient d with a long exponential tail, which is universal and independent of different sample conditions. (3) The exponential distribution $f(d)$ leads to an exponential distribution $P(Dx)$. Our measurements of membrane diffusion based on a large number of single molecular trajectories provide a complete statistical description of dynamic heterogeneity on live cell membrane. By combining all the experimental results available, we propose a dynamic picket-fence model of membrane organization involving slow active remodeling of the underlying cortical actin network to explain the observed non-Gaussian statistics and dynamic heterogeneity. (Work was supported by the Research Grants Council of Hong Kong SAR.)

THE ROLE OF TAU PROTEIN AND INFLAMMATION WITHIN COGNITIVE DYSFUNCTION INDUCED BY LAPAROTOMY IN YOUNG ANIMAL

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Objectives: Postoperative cognitive dysfunction (POCD) is characterized by impairment of memory, concentration, language comprehension, social integration and learning difficulties after surgery. Abnormal tau protein phosphorylation is known to be associated with this disorder and more commonly with Alzheimer's Disease. This study investigates the contribution of surgical trauma as compared with anaesthesia exposure alone to the development of this condition.

Methods: Adult wild type C57BL/6N male mice (3-month-old, 25 ± 2 g) were divided into control (CON), sevoflurane only (SEVO) and laparotomy (LAP) groups. Cognitive function was assessed by Y-maze analysis and Novel Objective Recognition test (NOR), and locomotor activity by the Open Field test on postoperative day 14. Inflammatory cytokine mRNA expression from the liver, frontal cortex and hippocampus were assessed by q-PCR at 4h and 24h postoperatively. Brain tissues were collected for Western-Blot analysis and immunofluorescent staining. Normalized band intensities were analyzed by One-Way ANOVA followed by Turkey's post hoc test. All data were expressed as mean \pm standard deviation (SD), and $p < 0.05$ was considered as statistically significant.

Results: No difference in the frequency of crossing the square and central duration was seen between groups. Latency and error number were significantly increased in LAP compared with SEVO ($n=10-11$, $p < 0.01$ and $p < 0.05$ respectively) in Y-maze test; the discrimination index in NOR was significantly lower in LAP compared with SEVO ($n=7-10$, $p < 0.001$). Hepatic mRNA levels of IL-1 β , TNF- α , IL-8 and MCP-1 were significantly increased at 4h in LAP compared with SEVO. IL-1 β was elevated in the frontal cortex, as was IL-8 in the hippocampus at 4h in LAP ($n= 6-8$, $p < 0.05$). Immunofluorescent positive intensity of GFAP labeled astrocyte was higher in LAP compared with SEVO at the CA1 region of hippocampus. There were also more activated microglia (IBA-1 labeled) in CA1 and DG regions in hippocampus. There was a significant reduction of phosphorylated tau (S396, T205, S404, and AT180) in both SEVO and LAP at 24 h, with no difference between them. However, significantly hyperphosphorylation of tau protein was then in the frontal cortex and hippocampus of LAP at 14d.

Concluding remarks: Neuroinflammation induced by laparotomy activates astrocytes and microglia, increases tau hyperphosphorylation that finally impaired the cognition with long-term effect.

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OREXIN MODULATES INHIBITORY SYNAPTIC TRANSMISSION OF VESTIBULAR NUCLEAR NEURONS IN RATS

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Orexin is a neuromodulator known to be produced by lateral hypothalamic neurons, which send projections to the hippocampus, brainstem and cerebellum. In the hippocampus, orexin is known to modulate long-term synaptic plasticity, thereby contributing to social memory. We hypothesized that orexin modulates synaptic transmission in the vestibular nucleus (VN), thus regulating behavioral expression. To understand the impact of orexin on synaptic transmission within the VN, we employed an established *in vitro* electrophysiological technique to study the action of orexin on the excitability of neurons in the medial vestibular nucleus (MVN) of rats at postnatal day 14. Whole-cell patch-clamp results indicated that treatment with orexin led to reductions in amplitude and frequency of miniature inhibitory postsynaptic current (mIPSC). This suggests that orexin decreases both the presynaptic release of inhibitory transmitters and postsynaptic depolarization in MVN neurons. We thus demonstrated that orexin attenuates synaptic inhibition on MVN neurons. We further tested whether orexin-modulated mIPSC is mediated by GABA_A receptors or glycine receptors. With the use of bicuculline and strychnine, we observed that orexin decreased mIPSC mediated by GABA_A receptors, but not glycine receptors. Taken together, our findings provided us with fundamental knowledge about the modulatory role of orexinergic transmission in the VN. This forms the basis for further investigation on the involvement of orexin in long-term synaptic plasticity of the central vestibular system. [Supported by N_HKU735/14]

ABLATION OF TRANSCRIPTION FACTOR IN CEREBELLAR PURKINJE CELLS DELAYS MOTOR FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY

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Brain neurocircuitry system is highly organized and motor efferent signal from motor cortex and cerebellum control locomotion and fine tuning of movement. Deep cerebellar nuclei (DCN) in cerebellum acts as a signal relay center, receiving inputs from the Purkinje cells (PCs), mossy fibers, and climbing fibers and sending out signal to the motor cortex via thalamus. PCs are the only output neurons of the cerebellar cortex suggesting that PC activity are crucial for DCN firing. Previous studies showed that ablation of this transcription factor in PCs resulted in ataxia due to the abnormal formation of PC dendritic spines in the mutant mice. We therefore hypothesized that ablation of a transcription factor in PC cells affect the functional recovery after peripheral nerve injury. In the present study, we performed sciatic nerve crush on these mutant mice and observed functional recovery by using a battery of neurobehavioral and electrophysiological tests parameters. Neurobehavioral tests were performed on alternate day and electromyography (EMG) of gastrocnemius (GCM) and lateral planter muscle (LPM) on every week after injury for 8 weeks. The results of present study showed that mutant mice exhibited delay in motor functional recovery by significant decreased in toe spreading motor test score, four limbs and hind limb grip strength, EMG amplitude of GCM and LPM as compared with control mice ($p < 0.05$). However, there was no significant change in recovery of sensory function (pinprick test). In conclusion, ablation of transcription factor in PC cells of cerebellum delay motor functional recovery after injury.

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INTERACTION OF PLATELETS WITH BRAIN-SPECIFIC GLYCOLIPIDS PROMOTES NEUROINFLAMMATION DURING TRAUMATIC BRAIN INJURY

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Interaction of neuronal and blood or immune cells is a hallmark of different neurodegenerative disorders such as traumatic brain injury (TBI), stroke, multiple sclerosis and Alzheimer's disease. Platelets, or thrombocytes, provide fast response after the injury, initiating inflammation and regeneration, while their role in neurological diseases is still unclear.

Our research group had found that platelets could interact with brain-specific sialated glycolipids, gangliosides within neuronal and astroglial lipid rafts. This interaction resulted in platelet activation and degranulation and promoted experimental autoimmune encephalitis in mice [1]. The current work describes the mechanisms and functional role of platelet – brain specific glycolipid interactions during TBI in wild type (WT) and ST3KO mice that lack of major brain gangliosides within brain lipid rafts. We found that ST3KO mice developed reduced level of microglia activation and leukocyte infiltration in the CNS after TBI comparing to WT animals. ST3KO mice exhibited substantial increased neuronal loss and more severe hemorrhage than WT mice.

Intracerebral injection of WT lipid rafts promoted TBI-induced neuroinflammation and reduced hemorrhage in ST3KO mice. Second, we found that platelet-derived factors, such as platelet activating factor, histamine and serotonin played an essential role in regulation of hemorrhage and neuroinflammation after brain trauma.

Our study determined the essential role of platelet-brain-specific glycolipid interaction in regulation of neuroinflammation and neuronal damage after TBI and, potentially, other neurodegenerative disorders.

1. Sotnikov et al. Platelets recognize brain-specific glycolipid structures, respond to neurovascular damage and promote neuroinflammation. PLOS ONE. 2013; 8 (3); e58979.

COMBINATION OF UNIAXIALLY ALIGNED CHITOSAN NANOFIBER AND IMMOBILIZED CHONDROITINASE ABC IMPROVES AXONAL REGROWTH

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After spinal cord injury, axonal regrowth is often restricted due to upregulation of chondroitin sulfate proteoglycans (CSPGs) at the lesion site. Although delivery of the soluble recombinant chondroitinase ABC (ChABC) to the site enhanced prospects of axonal regrowth through the lesion, the enzyme activity was short-lasting due both to loss by diffusion and diminished half-life at physiological temperature. We attempted to address the problems by cross-linking recombinant ChABC to chitosan microbeads with use of genipin. Chitosan was chosen because of its high biocompatibility and appropriate biodegradability. Immobilized ChABC demonstrated CS-cleaving activity both in biochemical assay and in astrocyte cultures that had been activated by transforming growth factor beta (TGF- β) to secrete CSPGs. Cortical neurons seeded on such ChABC-treated cultures extended neurites that were 5 times those on the null-treated control cultures. In an attempt to guide re-growing axons across the lesion site, uniaxially aligned chitosan nanofibers were prepared by electrospinning onto tissue culture plastic. Dorsal root ganglia (DRG) explant (E14-15 rats) seeded onto the nanofibers demonstrated that both neurons and Schwann cells on exit from the explant aligned with the nanofibers. The neurites of DRG neurons maintained on the nanofiber substratum were 5 times longer than those on control substratum without nanofibers. Taken together, the results suggest that delivering immobilized ChABC to the lesion site and bridging the site with use of uniaxial chitosan nanofiber-based conduit improve axonal regrowth in post-traumatic spinal cord injury.

MODULATORY EFFECTS OF OREXIN ON THE FUNCTIONAL MATURATION OF CENTRAL VESTIBULAR SYSTEM IN MOTOR COORDINATION AND SPATIAL RECOGNITION

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Orexin is a hypothalamic neuropeptide that is known to be involved in animals' balance and motor coordination. To test whether neonatal perturbation of orexinergic synapses in the vestibular nucleus (VN) exerts any effect on the maturation of vestibular-related behaviors, we blocked/activated orexin receptors in the VN of postnatal day (P) 1 rats by implanting polymer (Elvax) slices loaded with orexin receptor antagonist (SB334867) or agonist ([Ala11, D-Leu 15]-orexin-B) onto the dorsal surface of VN for slow release of the drug to the underlying VN. Specific behavioral tests including negative geotaxis (a graviceptive response), surface righting (ability to correct body orientation to erect position) and air righting were performed on these rats at different stages of postnatal development until adulthood. Neonatal treatment with antagonist accelerated acquisition of negative geotaxis and surface righting from P7 to P6, as well as air righting from P21 to P16. In contrast, neonatal treatment with agonist delayed acquisition of negative geotaxis by 4 days and surface righting by 1 day. These findings reveal the unique role of orexin on functional maturation of the vestibular system. Moreover, neonatal treatment of the VN with agonist impaired the performance of both motor coordination (as revealed by rotarod test and balanced beam test) and spatial navigation (as indicated by dead reckoning/ path integration) at the adult stage. On the contrary, antagonist treatment enhanced the performance in spatial navigation. These findings suggest that neonatal modulation of orexinergic transmission in the neonatal VN perturbs the maturation of spatial recognition. [Supported by NSFC/RGC N_HKU 735/14]

MOTOR TRAINING REDUCES PSYCHOMOTOR RETARDATION VIA GLIOGENESIS IN RATS WITH DEPRESSION-LIKE BEHAVIOUR

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Adult-born oligodendrocytes are found to be continuously produced in rodent's brain. The functional role of these cells has been highly correlated to motor-related activities of the healthy animals, such as in learning a new motor skill. In correlating these cells with the control of motor-related activities, it has not been investigated under a pathological condition. Psychomotor retardation (PMR) is one of the key symptoms found in depression. Consistent with the impairments shown in rodent's motor performance, the proliferation and the survival of adult-born oligodendrocytes are altered under corticosterone-induced stress paradigm. Furthermore, we have found that these proliferating cells could possibly be involved in the neural circuitry of motor activity as these cells were activated (co-expressed with an immediate-early gene marker, *egr-1*) upon motor stimulation. However, the activation level was found to be lowered under stress. Therapeutic rotarod training can reverse the above altered components. Surprisingly, the above changes were shown to be obvious in layer I of the motor cortex. Therefore, the current study has provided evidence on the functional involvement of adult-born oligodendrocytes in contributing to the motor impairments found in depressed animals. Also, layer I may possibly be a novel site of investigation in relation with the PMR symptom.

HEPCIDIN AS A POTENTIAL PROGNOSTIC BIOMARKER OF PARKINSON'S DISEASE

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Parkinson's disease (PD), characterized by dopaminergic neuron loss in the substantia nigra pars compacta (SNc) and motor deficits, is the second most common neurodegenerative disease incapacitating millions of patients in the world. It has been viewed that iron accumulation in SN is the major pathological event in PD. However, the exact causes of the degeneration of neurons in SNc are still obscure, and there is no effective cure for PD. Hepcidin is the main iron regulatory peptide in periphery and central nervous system, and we previously found that its expression is decreased in late stage of rotenone-induced PD model in SN. Therefore, we hypothesized that hepcidin is a potential prognostic marker for PD progression. To testify our hypothesis, we made use of the rotenone induced *in vivo* and *in vitro* model. Adult SD rats received daily intraperitoneal injection of rotenone for 30 days while control animals received vehicle injection. SH-SY5Y neuronal cells were treated with low dosage of rotenone for 3 days. The results present that rotenone induced progressive motor deficits and TH+ neuron loss in SN in rats, assessed 10 days and 30 days after rotenone administration. Total iron content in SN and the level of serum iron was altered slightly at 10 days, while elevated drastically at 30 days. Concurrently, hepcidin level had no significant change at early phase of PD model, and decreased significantly in advanced stage. Similarly, hepcidin is decreased after 3 days but not 1 day of rotenone treatment in SH-SY5Y cells, accompanied by progressive iron accumulation in cells. In addition, in several neuron-microglia co-culture systems, hepcidin is reduced time-dependently when treated with rotenone. In conclusion, hepcidin is decreased with the PD progression in rotenone-induced PD models. Therefore, hepcidin may be a biomarker for tracing the course of disease.

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THE ROLES OF PTEN PDZ-BD DOMAIN IN NEURONAL FUNCTION AND ALZHEIMER'S DISEASE

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Phosphatase and tensin homolog (PTEN), a critical regulator of neuronal morphology and migration, has been linked to autism and ischemic neuronal injuries. PTEN has been implicated in N-methyl-D-aspartate receptor (NMDAR)-mediated long-term depression (LTD). The carboxyl-terminal Postsynaptic density-95/Dlg1/ZO1 binding domain (PDZ-BD) of PTEN is required for LTD, and this is mediated through the direct binding to a PDZ-containing signaling scaffold protein, PSD-95. In Alzheimer's Disease (AD), pathogenic β -amyloid peptides are known to induce LTD in hippocampal neurons. Thus the hypothesis is that β -amyloid induces synaptic malfunction in Alzheimer's disease (AD) can be relieved by blocking PTEN-mediated Long-term synaptic depression. To further evaluate the *in vivo* relevance of PTEN PDZ-BD in AD, we crossed the AD mouse strain, 5XFAD (APP^{SweF10L}, PSEN1^{*M146L*L286V}) with the PTEN PDZ-BD knockout (KO) mice. 5xFAD mice in PTEN PDZ-BD KO genetic background have improved working memory in radial arm maze (RAM) test. Based on this result, inhibiting the interaction between PTEN and PSD-95 may be a potential approach in treating AD. For this, we identified the second PDZ domain (PDZ-2) of PSD95 to interact with the PDZ-BD of PTEN. To facilitate the identification of drug-like compounds that can block the interaction between PTEN and PSD-95, an efficient screening platform has been developed based on the fluorescence polarization methodology. The major goals of this thesis proposal are to define the mechanistic role of PTEN PDZ-BD in AD and to identify potential targeted therapeutics that can alleviate β -amyloid neurotoxicity.

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ELECTROPHYSIOLOGICAL PROPERTIES OF MOUSE PRIMARY MOTOR CORTEX NEURONS BY *IN VIVO* WHOLE-CELL PATCH-CLAMP RECORDING

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The primary motor cortex (M1) is responsible for motor execution and also contributes to acquisition of new motor skills. Most previous studies, however, have focused on recording extracellular activity *in vivo* or intracellular properties *in vitro* in M1. Properties of these neurons like the *in vivo* intrinsic membrane excitability and synaptic inputs, which are important in understanding neuronal integration leading to their outputs, are less well addressed. We therefore applied *in vivo* whole-cell patch-clamp technique to record from neurons in M1, focusing on layer V. We characterized the electrophysiological properties of these neurons in normal mature mice under anesthesia. Neurons were approached and patched blindly and the recording depth recorded, and confirmed by post-mortem biocytin avidin-biotinylated complex method that also revealed their morphology. A total of 11 neurons were patched successfully and lasted for at least 20 mins. Based on their intrinsic firing patterns and morphology, these neurons were classified as fast-spiking interneurons (n=3), and regular-spiking (n=7) or burst-firing (n=1) pyramidal neurons. Putative pyramidal neurons have relatively low spontaneous action potential firing rates (0.72 ± 0.37 Hz, n=5) compared with interneurons (4.92 ± 1.15 Hz, n=3, $P < 0.05$) and longer decay time (8.82 ± 2.59 ms, n=6, compared with 3.34 ± 0.57 ms, n=3, $P < 0.05$). Spontaneous synaptic potentials are often observed in both types of neurons. Interestingly, interneurons tend to have a higher power in the beta- (20-30 Hz) and gamma-band (30-90 Hz). These results provide the baseline properties for further investigation on the roles of M1 neurons in normal and pathological conditions.

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AXONAL TRAFFICKING OF HEPARANASE 1

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Heparanase 1 (HPA1) is the mammalian β -D-endoglycosidase that degrades heparan sulfate (HS). It is synthesized as a latent form (proheparanase) that lacks enzymatic activity. Proheparanase will be secreted to the extracellular environment before it is reuptake by the cells via heparan sulfate proteoglycan (HSPG). The internalized proheparanase will then be processed to the mature form that displays enzymatic activity in lysosome. Neurons, unlike other mammalian cells, have highly arborized morphology. However, it is still unknown how neuronal heparanase may be transported and processed. In cultured hippocampal neuros, we found axonal localization of heparanase 1. Axonal heparanase distributes along the neurofilament as shown by image from structure illumination microscopy, suggesting its active axonal trafficking, which was further confirmed by the presynaptic rather than postsynaptic localization of heparanase. Similar to other mammalian cells, neuronal heparanase, predominantly the latent form, can also be released. The exocytosed heparanase however, show low affinity for heparin. In addition, we found, unexpectedly, that even the purified recombinant heparanase, when exogenously added, fail to bind to heparan sulfate at the cell surface significantly, indicating that heparanase may not be extensively internalized by the neurons. This is confirmed by sparse co-localization between heparanase and early endosome. Additionally, we also identified the activity-regulated expression of HPA1. Specifically, long term suppression or increase of neuronal activity will result in decrease of increase of HPA1 expression respectively. Collectively, our data suggests a novel trafficking pathway of HPA1 and suggest that HPA1 may be involved in the process of homeostatic plasticity.

HMGB1 AMELIORATES IRON ACCUMULATION AND DOPAMINERGIC NEURON LOSS IN LPS-INDUCED INFLAMMATION

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It has been established that inflammation and iron accumulation in the midbrain substantia nigra (SN) both play important roles in the pathogenesis of Parkinson's disease (PD). However, the exact cause of iron dyshomeostasis in SN in PD is still unknown. High mobility group box 1 protein (HMGB1) is a pivotal early cytokine mediator of inflammation in the central nervous system as well as other organs. Moreover, HMGB1 is accumulated in SN and its neutralization can ameliorate pathogenesis in rodent PD model. Therefore, we hypothesize that inflammation is the cause of iron accumulation in dopaminergic neurons. Specifically, HMGB1-mediated inflammation results in iron accumulation in dopaminergic neurons and SN. To address this question, we unilaterally injected lipopolysaccharide (LPS) into SN in SD rats to induce inflammation. HMGB1 neutralizing antibody was co-injected with LPS in some rats. The animals were sacrificed at 12h, 24h or 72h after surgery. LPS caused dopaminergic neuron loss 72h after injection but not at 12h and 24h. Also, there were severe iron accumulation at 24h but not 12h after LPS injection in both SN pars compacta and SN pars reticulata subdivisions, accompanied by iron import proteins DMT1+, DMT1- and transferrin receptor overexpression in dopaminergic neurons. These results suggest that iron accumulation occurs before dopaminergic neuron loss. At 12h and 24h after LPS injection we found astrocytes and microglia activation, which were accompanied by HMGB1 overexpression in astrocytes, microglia and neurons, suggesting that inflammation is the cause of iron accumulation. Anti-HMGB1 neutralizing antibody, but not anti-TNF-alpha neutralizing antibody, more extensively suppressed microglia activation, iron accumulation in SN, and DMT1 overexpression in dopaminergic neurons. Our data demonstrate that iron accumulation in SN in PD may be attributed to inflammation. The results also implicate HMGB1 as a pivotal mediator of inflammation-induced iron accumulation, which may be a promising target for treating PD.

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THE PSEUDOKINASE CaMKv IS REQUIRED FOR THE ACTIVITY-DEPENDENT MAINTENANCE OF DENDRITIC SPINES

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Abstract

The stabilization of dendritic spines depends on afferent synaptic inputs and requires changes in actin cytoskeleton dynamics and protein synthesis. However, the underlying molecular mechanism remains unclear. Here, we identified calmodulin kinase-like vesicle-associated (CaMKv), a pseudokinase of the CaMK family with unknown function, as a synaptic protein crucial for dendritic spine maintenance. CaMKv mRNA localizes at dendritic spines, and its protein synthesis is regulated by neuronal activity. CaMKv function is inhibited upon phosphorylation by cyclin-dependent kinase 5 (Cdk5) at Thr-345. Furthermore, CaMKv knockdown in hippocampal CA1 pyramidal neurons in vivo impairs synaptic transmission and plasticity, resulting in hyperactivity and spatial memory impairment in mice. These findings collectively indicate that the precise regulation of CaMKv through activity-dependent synthesis and post-translational phosphorylation is critical for dendritic spine maintenance. Thus, this study reveals an unusual signaling pathway involving a pseudokinase that regulates synaptic transmission and brain function.

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THE ROLE OF ADIPOCYTE FATTY ACID BINDING PROTEIN IN ISCHEMIC STROKE

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Stroke is the one of the main cause of death and permeability disability in the worldwide. Emerging evidence shows that a lot of metabolic diseases such as hypertension, type 2 diabetes, metabolic syndrome and hypercholesterolemia all contributes to the increased susceptibility of ischemic stroke.

Adipocyte fatty acid binding protein (A-FABP) is a lipid chaperon adipokine that mainly expressed in adipocytes and macrophages. Serum A-FABP level is shown to have a strong correlation with many cardiometabolic diseases.

Previous clinical evidence suggest that serum A-FABP is significantly increased in ischemic stroke patients and has a positively correlation with the severity of ischemic stroke. However, the role of A-FABP in pathogenesis of ischemic stroke is rarely studied.

In this study, we investigate the pathological role of A-FABP in ischemic stroke with using A-FABP KO mice and their wildtype (WT) littermates.

THE EPILEPSY AND INTELLECTUAL DISABILITY-RELATED GENE TBC1D24 ENCODES A NOVEL SYNAPTIC PROTEIN THAT REGULATES DENDRITIC SPINE MORPHOGENESIS IN NEURON

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The majority of excitatory synapses are located on dendritic spines of the postsynaptic neuron. Spine formation and turnover is considered as an important mechanism underlying brain development as well as learning and memory. Several missense mutations of the human *tbc1d24* gene have been associated with epilepsy and intellectual disability. However, the physiological role of the TBC1D24 protein remains largely unexplored. Here we report an essential role of TBC1D24 in regulating the density and morphology of dendritic spines in hippocampal neurons. We found that TBC1D24 protein was enriched in the synaptic plasma membrane fraction of adult mouse brains. Immunocytochemistry further revealed that TBC1D24 was present in close proximity to dendritic spines and the postsynaptic scaffold protein PSD-95. Notably, the expression of TBC1D24 in hippocampal neurons was bi-directionally regulated in response to elevation and blockade of neuronal activity. Using short-hairpin RNA (shRNA) to knock down its expression in mature hippocampal neurons, we demonstrated that the maintenance of dendritic spines critically depends on TBC1D24. Moreover, the small GTPase ARF6 was identified as the downstream mediator of TBC1D24 in the regulation of spine morphogenesis. These findings suggest that TBC1D24 is involved in activity-dependent spine morphogenesis in the postsynaptic neuron, and defects in spine development might contribute to the pathophysiology of intellectual disability in individuals harboring the loss-of-function gene mutations.

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THE ROLE OF TRANSFERRIN RECEPTOR 2 IN THE PATHOGENESIS OF PARKINSON'S DISEASE

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Iron accumulation in the substantia nigra is a common feature in Parkinson's disease (PD), the second most common neurodegenerative disease that results in severe motor disability in patients. However, how abnormal iron metabolism contributes to the development of PD is poorly understood. With growing lines of evidence pointing to a convergence between abnormal iron metabolism and mitochondrial dysfunction in the pathogenesis of the disease, we hypothesize that misregulation of iron transport proteins in mitochondria may underlie the selective degeneration of dopaminergic neurons in PD. Here we studied transferrin receptor 2 (TfR2), a novel iron transporter with a mitochondrial targeting sequence. Immunohistological examination results demonstrated that TfR2 was increased in dopaminergic neurons in substantia nigra of rotenone-induced PD model. Utilizing lentivirus-based expression system we packaged a TfR2 overexpression lentivirus. The cDNA of TfR2 was amplified by PCR and then ligated into a shuttle plasmid pLIG with EGFP-tag. The positive recombinant plasmids named as Lenti-TfR2 were co-transfected with pCMV-VSVG, pMDL-G/P-RRE, pRSV-REV into HEK293T cells. The lentivirus were harvested and the titers were measured. We unilaterally injected 3 μ l (1.5×10^8 copies) of TfR2 overexpression lentivirus in the substantia nigra in 3 month-old Sprague-Dawley (SD) rats, which were sacrificed after 1 month for immunostaining. Tyrosine hydroxylase immunoreactivity in the substantia nigra revealed a significant dopaminergic neuronal loss and iron increase in the model. Additionally, MES 23.5 neuronal cells treated with rotenone and 6-hydroxydopamine showed an increase of TfR2 which was colocalized with the mitochondrial marker Hrp75. We concluded that TfR2 was increased in mitochondria of dopaminergic neurons in PD models, and TfR2 overexpression induced dopaminergic neuron loss and iron increase in rats.

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EFFECTS AND MECHANISMS OF SARSASAPOGENIN ON A β PRODUCTION IN HT-22 CELLS CULTURED WITH HIGH GLUCOSE

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Objective To investigate effects and potential mechanisms of sarsasapogenin (Sar), an active component purified from *Rhizoma Anemarrhenae*, on high glucose-induced amyloid-beta peptides (A β) overproduction in HT-22 cells. **Methods** HT-22 cells were divided into normal glucose (NG, 25 mmol/L D-glucose), high glucose (HG, 75 mmol/L D-glucose), osmotic pressure control (NG + 50 mmol/L mannitol), solvent control (HG + 0.1% dimethylsulfoxide), HG co-treated with low, middle, high dose of Sar (1, 5, 25 μ mol/L Sar), and peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist (10 μ mol/L pioglitazone), a positive control group. After treatment for 24 h, A β 42 level and activated PPAR- γ level in HT-22 cells were determined by using both immunofluorescence and Western blot methods, and protein expression of β -site A β precursor protein cleaving enzyme 1 (BACE1) by Western blot as well as BACE1 activity by fluorospectrophotometry. Cell viability was assayed by using a CCK-8 kit. **Results** Elevated A β 42 level as well as BACE1 protein and activity was found in HG-treated HT-22 cells, which was markedly attenuated by three doses of Sar and pioglitazone. Moreover, HG induced a decrease in nuclear protein expression of PPAR- γ in HT-22 cells, which was reversed by pioglitazone and middle dose of Sar. Additionally, cell viability was significantly decreased in HG-treated HT-22 cells, which was suppressed by three doses of Sar. **Conclusion** High glucose could induce an increase in A β levels and a decrease in cell viability in HT-22 cells, while co-treated with Sar improved these results, which was mediated through activation of PPAR- γ and subsequent down-regulation of BACE1.

Key words A β ; high glucose; HT-22 cells; PPAR- γ ; sarsasapogenin

A POTENTIAL ROLE OF NMDA RECEPTOR-DEPENDENT EXPRESSION OF STRIATIN-4 IN DENDRITIC SPINE MATURATION

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Most excitatory synapses are located in dendritic spines of the postsynaptic neuron. Immatures spines, such as stubby spines or filopodia, do not possess a distinct spine head, while mature spines appear as mushroom-shaped with large heads, or thin spines with elongated necks and small heads. Spine maturation requires local dendritic protein synthesis in response to synaptic activity. Dysregulated mRNA trafficking and local protein synthesis can lead to altered spine morphology in neurodevelopmental disorders such as Fragile-X syndrome and autism. Nonetheless, the molecular mechanism underlying activity-dependent spine maturation is not fully understood. Striatin-4 (Zinedin) was identified in transcriptomic studies as an mRNA transcript present in hippocampal neuropil and a putative cargo of the RNA-binding protein FMRP. Interestingly, certain striatin-interacting proteins, namely mammalian STE20-like protein kinase 3 (MST3) and cortactin-binding protein 2 (CTTNBP2), are encoded by autism risk genes. Despite previous studies demonstrating Striatin-4 enrichment in dendritic spines, the function of Striatin-4 in neuron remains unknown. Here we found that Striatin-4 mRNA and protein expression in cortical and hippocampal neurons was regulated by neuronal activity and NMDA receptors. Notably, Striatin-4 was preferentially expressed in mature dendritic spines, and blockade of NMDA receptor by APV led to reduced Striatin-4 expression and a concomitant switch of mature spines to the immature stubby spines and filopodia. Striatin-4 knockdown in hippocampal neurons by shRNA also led to mature spines loss and increased proportions of the stubby spines and filopodia. These findings suggest that NMDA receptor-dependent synthesis of striatin-4 is crucial for dendritic spine maturation.

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LHX1/5 CONTROL DENDRITOGENESIS AND SPINE MORPHOGENESIS OF PURKINJE CELLS VIA REGULATION OF ESPIN

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Purkinje cells (PCs), the sole output neurons in cerebellar cortex, have extensively branched dendrites to receive different cerebellar inputs and serves as an integration centre in cerebellar cortex. Defects in the dendritic development of PCs thus disrupt cerebellar circuitry and cause ataxia. However, the molecular mechanism of dendritic development remained unclear. Our group found that the specific inactivation of both *Lhx1* and *Lhx5* in postnatal PCs resulted in ataxic mutant mice with abnormal dendritic development in PCs. The PCs of *Lhx1/5* mutants had reduced expression of Espin, a novel F-actin cytoskeleton regulator. We later identified that Espin expression was transcriptionally activated by *Lhx1/5*. Downregulation of Espin in the mutants caused F-actin mislocalization, hence impaired the dendritogenesis and maturation of dendritic spines in PCs. The mutant PCs therefore failed to innervate with the pre-synaptic inputs properly, leading to aberrant electrophysiological properties. By overexpressing Espin in the mutant PCs, we were able to rescue the normal dendritogenesis and spine morphogenesis in the mutant PCs. Our findings give evidences for a novel pathway controlling dendritic development in which *Lhx1/5*, through regulating Espin expression, govern dendritogenesis and spine morphogenesis in postnatal PCs.

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PLANT-DERIVED PENTACYCLIC TRITERPENOID CELASTROL ATTENUATES OXYGEN GLUCOSE DEPRIVATION-INDUCED DISRUPTION OF ENDOTHELIAL TIGHT JUNCTION VIA INDUCING THE EXPRESSION OF OCCLUDIN, CLAUDIN-5 AND ZO-1

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Background: The integrity and functions of blood-brain barrier (BBB) are regulated by the expression and organization of tight junction proteins.

Objective: The present study was designed to explore whether plant-derived triterpenoid celastrol could regulate tight junction integrity in murine brain endothelial bEnd3 cells.

Methods: We disrupted the tight junctions between endothelial bEnd3 cells by oxygen glucose deprivation (OGD). We investigated the effects of celastrol on the permeability of endothelial monolayers by measuring transepithelial electrical resistance (TEER). To clarify the tight junction composition, we analyzed the expression of tight junction proteins by RT-PCR and Western blotting techniques.

Results: We found that celastrol recovered OGD-induced TEER loss in a concentration-dependent manner. Celastrol induced occludin, claudin-5 and ZO-1 in endothelial cells. As a result, celastrol effectively maintained tight junction integrity and inhibited macrophage migration through endothelial monolayers against OGD challenge. Further mechanistic studies revealed that celastrol induced the expression of occludin and ZO-1 via activating MAPKs and PI3K/Akt/mTOR pathway. We also observed that celastrol regulated claudin-5 expression through different mechanisms.

Conclusion: The present study demonstrated that celastrol effectively protected tight junction integrity against OGD-induced damage. Thus, celastrol could be a drug candidate for the treatment of BBB dysfunction in various neurological diseases.

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NEUROPROTECTIVE EFFECTS OF GSK-J4 AGAINST OXIDATIVE STRESS IN PARKINSON'S DISEASE MODEL

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Free iron that accumulates in the substantia nigra of Parkinson's disease (PD) patients drives oxidative stress and leads to selective destruction of dopaminergic neurons. Therefore, removal of excess labile iron from the substantia nigra provides a new therapeutic strategy for the treatment of PD. GSK-J4 is a newly discovered epigenetic regulator with the ability to cross blood-brain barrier. Recently, we found that only a trace amount of GSK-J4 was sufficient to reduce cellular iron selectively in SH-SY5Y neuronal cells. Here we investigated the effects of GSK-J4 on 6-OHDA induced PD model. Calcein-AM assay showed that GSK-J4 reduced labile iron accompanied by reduced ferritin, an iron storage protein, in SH-SY5Y. MTT assay and TUNEL staining showed GSK-J4 pretreatment could prevent 6-OHDA-induced cell death and cell apoptosis. Interestingly, GSK-J4 was also found to show iron-dependent catalase-like anti-oxidant activity in our cell-free catalase activity assay, suggesting that GSK-J4 may act as a novel catalase mimetic after binding iron. Consistently, GSK-J4 suppressed hydrogen-peroxide-induced cell death in SH-SY5Y. In addition, GSK-J4-treated cells also showed lower levels of reactive oxygen species and malondialdehyde. These findings indicated that GSK-J4 can be an antioxidant rescuing oxidative stress-induced toxicity. Besides, brain-derived neurotrophic factor in SH-SY5Y cells was increased in the presence of GSK-J4. In parallel, GSK-J4 pre-treatment could rescue dopaminergic neuron loss and motor defects in 6-OHDA-induced PD model. Taken together, we identified that GSK-J4 possess a potent and selective effect in regulating iron level in neuronal cell line and displays a protective effect in 6-OHDA-induced PD model via oxidative stress reduction.

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ALTERED DENDRITIC SPINE PLASTICITY IN A MOUSE DEPRESSION MODEL

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Depressive disorder is a most prevalent psychiatric disorder worldwide and is estimated to be affecting 350 millions of the global population. In the prefrontal cortex (PFC) of depression patients, hypofunction is accompanied with structural deficits, including decreased cell number, neuronal atrophy and decreased number of spine synapses. In rodents, chronic stress exposure induces depressive-like behaviour and results in structural impairment of dendrites of layer 2/3 and 5 pyramidal neurons in PFC, including reduced dendritic spine density and atrophy of apical dendrites. However, it is unclear whether dendritic deficits contribute to depression development. Ketamine, a NMDA receptor blocker, is found to exert rapid, lasting antidepressant effect at a single, sub-anaesthetic dose. Ketamine can also rapidly reverse chronic stress-induced synaptic deficit. Yet, data on the effect of ketamine on dendritic spine plasticity in long-term is lacking. In this study, we used *in vivo* two-photon transcranial imaging of Thy1-YFP H line mice to investigate dendritic spine plasticity in the chronic restraint stress (CRS) depression model. We found that CRS increased dendritic spine elimination and reduced spine formation of layer V pyramidal neurons in the frontal association cortex. In addition, CRS-induced alterations in spine plasticity precede the onset of behavioural symptoms. Importantly, we found that ketamine treatment counteracted the effects of stress on dendritic spine plasticity.

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AN AUTOMATED APPARATUS FOR STIMULUS-REWARD BEHAVIORAL STUDIES IN RODENTS

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Animal behavior studies based on stimulus-reward experiments are common in neuroscience research. Manual operation of such experiments is usually inaccurate, prone to mistakes, time-consuming, and also difficult for procedures involving presentation of complex acoustic or optical stimuli and synchronization with data acquisition such as electrophysiological recordings. Here, we designed and implemented an automated setup for behavior studies for conduction of different kinds of complex stimulus-reward experiments by software settings. The apparatus includes six components: 1) a black container for a rat/mouse with a loudspeaker and at most eight LEDs of six colors, 2) at most eight touch buttons driven by electrical motors to move in/out of the box, 3) a liquid food delivery module with a pinch valve controlling the liquid flow, 4) a human-machine interface consisting of a display screen and eight keys for the user's operation, 5) a communication interface that sends data to and receives commands from a computer, and 6) a microcontroller that controls the whole system by executing experimental procedures step by step. Using this setup, programmable procedures are controlled by the microcontroller for training or testing of rodents. Parameters such as the color, duration and timing of light stimuli, or the frequency, duration and patterns of sound are adjustable by software. In our investigation of the ability of the rats to discriminate different sound stimuli, the apparatus works stably and reliably. The setup would also be useful for other studies such as learning and memory behaviors, with less manual operation and higher efficiency.

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DLC1, A RHO GTPASE-ACTIVATING PROTEIN, IS ESSENTIAL FOR CRANIAL NEURAL CREST DEVELOPMENT

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The neural crest is a transient population of multipotent progenitor cells, which emerges from the dorsal neural tube during early vertebrate development. These cells migrate extensively throughout the body to differentiate into a variety of cell types. The Sox (SRY-related HMG box) family of transcription factor, Sox10, has been implicated in cranial neural crest migration and differentiation via an as-yet unclear mechanism. Here, we revealed that *Dlc1*, a Rho-GTPase-activating protein (RhoGAP) that negatively regulates specific Rho family proteins (RhoA-C), is expressed at the anterior neural plate border region, and later becomes restricted in the premigratory and migrating cranial neural crest cells. Indeed, overexpression of *Dlc1* inhibited RhoA and promoted Rac1 activity consistent with their mutual antagonism that also underlies the transition from neural crest delamination to migration, but the total amount of migratory neural crest cells positive for HNK1 in the transfected cranial region remained unchanged compared to the vector control. By contrast, dominant-negative (DN) inhibition of *Dlc1* function in cranial neural tube reduced expression of neural crest specifier, *Sox9*, whereas expression of *Snail2*, *Sox10* and *FoxD3* remained unaltered. In addition, embryos electroporated with DN-*Dlc1* exhibited reduced expression of HNK1, and defects in cranial ganglia formation. Furthermore, we found *Sox10* was sufficient to induce ectopic *Dlc1* expression. Consistently, epistasis analysis showed that *Dlc1* functions downstream of Sox10 in neural crest migration. Together, our findings reveal an essential requirement for DLC1 to function in the transcriptional cascade downstream of Sox10 to regulate cranial neural crest migration and differentiation likely through the regulation of Rho GTPases activity.

TARGETED DELIVERY OF ANTRODIN B-LOADED POLY (LACTIC-CO-GLYCOLIC ACID) NANOPARTICLES TO NEURONS PROMOTES FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY

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Targeted drug delivery by using biodegradable nanoparticles showed substantial improvements in drugs with poor solubility and bioavailability *in vivo*. Our studies showed a traditional Chinese medicine, *Antrodia cinnamomea* (Niu-Chang-Chih in Chinese) extract promoted functional recovery after peripheral nerve injury in mice. We identified antrodin B as an active ingredient from *A. cinnamomea* extract which increased neurite outgrowth from adult mouse dissociated dorsal root ganglia (DRG) neurons and from DRG explants. However, the effect of antrodin B *in vivo* is limited. We therefore developed poly (lactic-co-glycolic acid) (PLGA) based nanoparticles (NPs) delivery system for targeted delivery of antrodin B to the site of injury after a sciatic nerve crush in mice. We first examined if the antrodin B-loaded PLGA-NPs exhibit the same promoting effect as the PLGA-NP free antrodin B *in vitro*. Antrodin B-loaded PLGA-NPs showed significantly increased neurite outgrowth from dissociated DRG neurons. Local administration of antrodin B-loaded PLGA-NPs to sciatic nerve crush injury site in adult mice significantly accelerated sensory axonal regrowth (up to 40%) as assessed by nerve pinch test. Functional recovery monitoring assays, such as Pinprick assay revealed significant and earlier return of sensory function in mice treated with antrodin B-loaded PLGA-NPs. Also, Toe-spreading motor assay indicated significant improvement and earlier motor function regain in treatment group as compared with control groups. Taken together, our findings suggest antrodin B as a potential candidate for nerve repair. Further studies to reveal underlying mechanism of accelerated axonal growth by antrodin B are yet to be investigated.

THE EFFECT OF OXYRESVERATROL ON ENDOPLASMIC RETICULUM STRESS IN PARKINSON'S DISEASE.

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Parkinson's disease (PD) results from a loss of dopaminergic neurons and the presence of intracytoplasmic inclusions known as Lewy bodies (LB), culminating in a loss of motor function. While the risk factors are multifactorial in nature, there is no breakthrough curative therapy for PD. Oxysresveratrol (OXY) is a potent antioxidant found in Mulberry fruits. We have previously reported the neuroprotective potential of OXY in an *in vitro* parkinsonian model. The aim of this study is to investigate the effects of OXY on specific pathways implicated in PD.

Human neuroblastoma SH-SY5Y cells were stably transfected to express the A30P familial mutant of alpha synuclein (α S), which is the main constituent of LBs. Forty eight hours after treatment with OXY, we observed a reduction in the misfolded, oligomeric species of α S. A build-up of misfolded protein leads to stress in the endoplasmic reticulum (ER), subsequently activating the unfolded protein response (UPR). Therefore, our next aim was to study the effects of OXY on this pathological pathway in a PD model. SH-SY5Y cells were treated with 6-hydroxydopamine, a parkinsonian mimetic toxin, after pre-treatment with OXY. Activation of signaling molecules involved in the UPR were then assessed. The results showed that OXY does indeed modulate the UPR, in turn mitigating ER stress. This gives us an idea of the underlying mechanism by which OXY exerts neuroprotective effects in PD.

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HNRNPA1 IS CRUCIAL FOR THE SURVIVAL OF NEURAL PROGENITORS IN MOUSE DEVELOPING SPINAL CORD

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Heterogeneous nuclear ribonucleoprotein A1(HNRNPA1) regulates many cellular processes such as RNA metabolism, cell cycle, gene regulation and telomere maintenance. Mutations of *HNRNPA1* has been implicated in the neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA). However, the roles of HNRNPA1 in the central nervous system remain largely unknown. Our expression analyses in mouse showed that HNRNPA1 is expressed in the neural progenitors in the ventricular zone of the developing neural tube and in the motor neurons in the adult spinal cord, leading to the hypotheses that HNRNPA1 is important in both neurogenesis at the embryonic stages and the maintenance of the neurons at the adult stages. To address this, we analyzed our *hnrnpa1*^{ct/ct} spontaneous mouse mutant which resembles to the null mutant due to no detectable *hnrnpa1* transcript and HNRNPA1 protein in the mutant. Interestingly, we observed the thinning of the neuroepithelium in the neural tube of the *hnrnpa1*^{ct/ct} mutant starting from 10.5dpc with the reduced expression of Sox2 and Sox9 which mark the neural progenitors. We further found that the thinning of the neuroepithelium could be mainly due to the apoptosis of the neural progenitors in the neural tube at 9.5dpc. This supports the notion that HNRNPA1 is crucial for the survival of the neural progenitors. However, the mechanism of how the loss of *hnrnpa1* leads to apoptosis of the neural progenitors remains to be elucidated in the future.

CHONDROITIN SULPHATE-DERIVED DISACCHARIDES: A POTENTIAL DRUG FOR AXONS REGROWING ACROSS THE GLIAL SCAR

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Chondroitin sulphate (CS) moieties enriched in the glial scar can be cleaved by chondroitinase ABC (ChABC) delivered to the site, resulting in improved outcomes in axonal regrowth and functional recovery. We postulate that the disaccharide products generated during digestion play parts in the enhancement of axonal growth. With a co-culture model of astrocytes and cortical neurons, treated with recombinant ChABC (rChABC) combinations, washed of digestion products and then treated with selected CS disaccharides, neurite growth-promoting effects of CS disaccharides were revealed. By contrast, control treatments with sucrose or CS tetrasaccharides did not promote neurite growth. Among the different CS disaccharides, DdiUA-2S was found superior in the enhancement of neurite growth. Without the pre-treatment of rChABC, the growth-promoting effect was less pronounced and the differences among the CS disaccharides with regard to growth-promoting effects were insignificant. Evidence is thus provided for (1) the role of ChABC activities, in disrupting the barrier to axonal growth, and (2) possible supplementation with the neurite growth-promoting CS disaccharides means to overcome the axonal growth barrier at the glial scar.

GAMMA-SECRETASE CLEAVES STROMAL INTERACTION MOLECULE 1 INDUCES CAPACITATIVE CALCIUM ENTRY DEFICITS IN FAMILIAL ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most common form of dementia and mounting evidence suggests calcium (Ca²⁺) disruption is its proximal pathogenic origin. Ca²⁺ dysregulation observed in cells expressing familial Alzheimer's disease (FAD)-causing presenilins (PS) has been attributed to the exaggerated Ca²⁺ release and the attenuated store-operated Ca²⁺ entry (also known as capacitative Ca²⁺ entry, CCE). Several mechanisms have been proposed for the exaggerated Ca²⁺ release, yet the underlying molecular mechanisms for attenuated CCE remain elusive.

In this study we employed Ca²⁺ imaging, FRET microscopy, in situ proximity ligation assay, in vitro γ -secretase cleavage assay and primary neuronal culture to delineate the mechanism for CCE attenuation and its linkage to AD pathology. We showed that the attenuation of CCE depends upon PS-associated γ -secretase activity. PS1 and STIM1 interact in human neuroblastoma SH-SY5Y cells, and mutant PS1 enhances γ -secretase cleavage of STIM1 in the transmembrane domain that has high similarity with amyloid precursor protein. Furthermore, FAD PS1-induced CCE attenuation destabilizes mature dendritic spines that are rescued by γ -secretase inhibition or overexpression of STIM1. Our results suggest a molecular mechanism of CCE deficits in which FAD-mutant PS1 enhances γ -secretase cleavage of STIM1, reducing recruitment of Orail that results in impaired CCE. These findings indicate a physiological role of PS1/ γ -secretase in modulating the availability of STIM1 for CCE, and suggest that identification of STIM1 as a substrate of γ -secretase provides a novel therapeutic target for the treatment of AD.

ROLE OF EXCHANGE PROTEIN DIRECTLY ACTIVATED BY CAMP 1 & 2 (EPAC1 & EPAC2) IN INFLAMMATORY PAIN

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3'-5'-cyclic adenosine monophosphate (cAMP) is a key mediator of nociceptor signaling. There is evidence that Epac mediates cAMP signaling under inflammatory conditions, however, the significance of the two isoforms of Epac, Epac1 and Epac2, in inflammatory pain is unclear. In the present study, Epac1 (Epac1^{-/-}) and Epac2 (Epac2^{-/-})-deficient mice were used to study the role of Epac in formalin-induced inflammatory pain. Here, we report that Epac1^{-/-} and Epac2^{-/-} mice display significantly lower nociceptor behavior compared to the wild-type (Epac1^{+/+}; 2^{+/+}) mice under formalin-induced inflammatory conditions. Cyclooxygenase-2 (Cox-2) protein was significantly overexpressed in the ipsilateral sciatic nerve of the Epac1^{+/+}; 2^{+/+}, but not Epac2^{-/-} mice. Cox-2 is rapidly induced due to inflammation and is known to sensitize nociceptors leading to increased pain sensitivity. Collectively, these data suggest that Epac2 deficiency alleviates pain by preventing Cox2 induction. Furthermore, phosphorylated ERK protein expression was found to be significantly reduced in the ipsilateral DRG of Epac2^{-/-} mice, suggesting that the Epac2 deficiency leads to suppression of formalin-induced ERK phosphorylation in the DRG. Our findings indicate the involvement of both Epac1 and Epac2 in inflammation-induced hyperalgesia in animals, and suggest that Epac could potentially be a novel therapeutic target for the treatment of pain.

SOX9 IS CRITICAL FOR SUPPRESSION OF NEUROGENESIS BUT NOT INITIATION OF GLIOGENESIS IN THE CEREBELLUM

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The high mobility group (HMG) family transcription factor Sox9 is critical for induction and maintenance of neural stem cell pool during development of many different organs (CNS). In the spinal cord and retina, Sox9 is the master determinant that defines glial fate choice by mediating the neurogenic-to-gliogenic fate switch. On the other hand, the genetic repertoire governing the maintenance and fate decision of neural progenitor pool in the cerebellum has remained elusive. By using the Cre/loxP strategy, we specifically inactivated Sox9 in the mouse cerebellum. Surprisingly, the self-renewal capacity and multipotency of neural progenitors at the cerebellar ventricular zone (VZ) were not perturbed upon Sox9 ablation. Instead, the mutants exhibited an increased number of VZ-derived neurons including Purkinje cells and GABAergic interneurons. Interestingly, we observed continuous neurogenesis from Sox9-null VZ at late gestation, when normally neurogenesis from the VZ should cease to occur and gives way for gliogenesis. Unexpectedly, glial cell specification at the cerebellar VZ was not affected upon Sox9 ablation. Our findings suggest Sox9 may mediate the neurogenic-to-gliogenic fate switch in mouse cerebellum by modulating the termination of neurogenesis, and therefore indicate a functional discrepancy of Sox9 between the development of cerebellum and other major neural tissues.

CHARACTERIZATION OF GERMLINE PTEN MISSENSE MUTATIONS ASSOCIATED WITH AUTISM SPECTRUM DISORDERS

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Phosphatase and tensin homolog deleted on chromosome ten (PTEN) was initially identified as a tumor suppressor and possessed lipid phosphatase activity. Subsequently, PTEN was shown to play important roles in neurogenesis and synaptic plasticity. During central nerve system (CNS) development and neural stem cell differentiation, PTEN is tightly regulated in expression level and subcellular localization. Germline mutations in the *PTEN* gene have been shown to cause autism spectrum disorders (ASD), which is a neurodevelopmental disorder characterized by impairments in social interaction and communication. About 1 to 5% of ASD patients have germline PTEN mutation. These mutations scattered along the phosphatase domain and C2 domains of PTEN. To study what changes to the function of the PTEN protein that are responsible for ASD, a panel of germline PTEN mutants reported in ASD was characterized. Our results showed that a significant fraction of the phosphatase domain mutants still retained comparable protein expression levels when compared with wild-type. However, all the C2 domain mutants have drastic reduction in their protein levels. There were corresponding decreases in C-tail phosphorylation in these C2 domain mutants and this may cause protein instability. Also, both in vivo and in vitro assays showed that most ASD PTEN mutants have decreased lipid phosphatase activity. By immunofluorescence analysis, most ASD PTEN mutants have decreased nuclear localization.

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ASTROCYTIC REGULATION OF PERINEURONAL NET FORMATION

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Perineuronal nets (PNN) are dense chondroitin sulphate proteoglycan (CSPG)-rich structures that surround the cell body and proximal dendrites of a subset of neurons in the central nervous system. PNN formation is associated with consolidation and hard-wiring of neuronal circuits. Removal of the chondroitin sulphate component of PNN is accompanied by reinstatement of functional plasticity. Little is known about the spatial regulation of PNN formation. This project aims to reveal cues for PNN formation.

In an indirect co-culture of cortical neurons and astrocytes, we show that astrocytes suppressed both maturation of GABAergic transmission and PNN formation. This is consistent with reports that inhibition of GABA synthesis results in decrease number of PNN (Harauzov, et al. J. Neurosci. 2010). We hypothesis that astrocytes inhibit PNN formation to regulate local PNN density. Using tissue clearing and deep brain imaging techniques, a systematic analysis of the distribution of PNN in the adult rat cortex will be conducted to test this hypothesis.

On the single cell level, it was reported that PNN-bearing neurons formed more synaptic connections than non-PNN-bearing neurons (Geisslar, et al. J. Neurosci. 2013). We reason that synaptic input could promote PNN formation. Since the difference in synapse number might also be reflected by increased dendritic arborization, we compared the morphometric parameters of PNN-bearing inhibitory neurons against non-PNN-bearing neurons to investigate whether dendritic structure could be used as a predictor for PNN formation.

FUNCTIONAL ASSESSMENT OF MT₂ MELATONIN RECEPTOR VARIANTS THAT ARE ASSOCIATED WITH TYPE 2 DIABETES

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Melatonin, a pleiotropic neurohormone secreted in the pineal gland, plays a major role in circadian rhythm regulation through the activation of MT₁ and MT₂ receptors. There is increasing evidence to suggest that melatonin may also participate in the regulation of glucose metabolism. Interestingly, several Genome Wide Association Studies (GWAS) have revealed a possible correlation between rare MT₂ receptor mutants and the risk of Type 2 diabetes (T2D). The occurrence of single nucleotide polymorphisms (SNPs) in the gene encoding the MT₂ receptor (*MTNR1B*) increases the risk of developing T2D in the European population. It was speculated that the SNPs rendered functionally defective MT₂ receptors. Among the 40 non-synonymous *MTNR1B* variants reported, we have selected five MT₂ receptor variants (A52T, A74T, R138C, L166I, and R222H) for assessing their functional integrity in terms of cellular signal transduction in HEK 293 cells. In calcium mobilization and ERK phosphorylation assays, A52T, A74T, L166I, and R222H receptor mutants exhibited approximately 30% reduction in potency and efficacy upon the treatment of melatonin, while R138C displayed a complete loss of agonist-induced response. By detecting calcium mobilization as up-regulator of insulin secretion, we have investigated the different glucose-stimulated insulin secretion pattern from pancreatic β -TC6 cells after prolonged and short-term melatonin treatment. The application of highly selective MT₂ ligands may help to elucidate the influence of MT₂ receptor variants on the function of pancreatic β cells.

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DOPAMINERGIC TREATMENT PROMOTES MOTOR RECOVERY AND IMPROVES PERILESIONAL PLASTICITY AFTER ISCHEMIC STROKE

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Accumulating clinical evidence has shown that dopaminergic treatment for chronic patients with ischemic stroke enhances sensorimotor functions, however the mechanisms involved are poorly understood. Based on our recent findings that dopamine in the motor cortex is critical for motor skill learning, we tested the hypothesis that dopaminergic treatment can enhance cortical neuroplasticity and promote functional recovery.

In rodent models of focal ischemic stroke induced by photothrombosis, we assessed the integrity of cortical dopaminergic system and found that it was significantly disrupted by focal stroke. Through a 3-week daily treatment of levodopa (15 mg/kg) / benserazide (15 mg/kg), we recapitulated its beneficial effects on sensorimotor function, and further identified that the improvement was more pronounced in training-dependent motor tasks. Morphological and biochemical examination of the perilesional area provided evidence that neuroplasticity markers, dendritic arborisation and synaptic plasticity were increased by the treatment. Further examination of neuronal activity through *in vivo* multielectrode recording revealed that motor cortical regions adjacent to the infarct had restored capability for synaptic plasticity. Finally, pharmacological blockade of either D1 or D2 receptors at the perilesional region abolished the beneficial effects. This signified that dopaminergic action at the peri-infarct area is the core mechanism of the treatment. With evidence that dopamine replacement can enhance functional recovery by coalescing connections across the cortex, we postulate that modulating dopaminergic transmission is a promising therapeutic strategy for stroke rehabilitation.

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CIRCULATING MICRORNAS IN PLASMA AS NOVEL BIOMARKERS FOR ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most common and complex neurodegenerative disorder. Although it has been over a hundred years since AD was originally described, the exact underlying mechanism remains largely elusive and no curative drugs are available for AD treatment. Early diagnosis of AD is believed to be essential for effective administration of drugs targeting. However, there are still no perfect biomarkers for AD diagnosis. Recent findings suggest that microRNAs (miRNAs) in the circulating system act as potential biomarkers for AD.

In the present study, we extracted total RNAs from the plasma of 12 Chinese AD patients and 6 normal controls. Eight miRNA candidates (miR-29a, -125b, -146b, let-7f, -181a, -30c, -128 and -16) were selected and their expression profiles in plasma were measured using qRT-PCR (quantitative reverse transcription polymerase chain reaction). Our data demonstrated that plasma miR-128 was significantly down-regulated in AD patients compared with control subjects. Moreover, plasma miR-128 levels significantly correlated with protein markers in cerebrospinal fluid (CSF) and Mini Mental State Examination (MMSE) scores of the subjects. Importantly, plasma miR-128 showed good accuracy to distinguish AD patients from control subjects based on receiver operating characteristic (ROC) curve analysis.

In conclusion, our results indicated that miR-128 in plasma could be a potential non-invasive biomarker of AD.

Notes

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