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投稿學會：台灣基礎神經科學學會	編號: P2-16

Neuroprotection of flavone compounds quercetin and apigenin against Aβ toxicity via inhibition of Aβ aggregation and activation of TRKB signaling in Aβ-GFP SH-SY5Y cells

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Abstract

Alzheimer's disease (AD), presented with progressive memory loss and cognitive decline, is a common neurodegenerative disease. The pathogenesis of AD is caused by abnormal accumulation of misfolded amyloid β (Aβ), which leads to neurodegeneration via a number of possible mechanisms such as down-regulation of brain-derived neurotrophic factor-tropomyosin-related kinase B (BDNF-TRKB) signaling pathway. Emerging evidence indicate deterioration of brain BDNF-TRKB signaling in AD and enhancement of TRKB signaling for a promising AD treatment strategy. 7,8-Dihydroxyflavone (7,8-DHF), a TRKB agonist, demonstrate potential to enhance BDNF-TRKB pathway in various neurodegenerative diseases. In this study, the potential of two 7,8-DHF analogous compounds, quercetin and apigenin, as TRKB agonists were examined, using 7,8-DHF as a control. These compounds were tested for solubility, and predicted for oral bioavailability and blood brain barrier permeability. Then human 293 reporter cells expressing cAMP-response-element (CRE) motifs-driving GFP were established to test these three compounds for enhancing cAMP-response-element binding protein (CREB)-mediated transcription. All three compounds significantly increased the transcriptional activity of CREB. Neuroprotective effects of the potential TRKB agonists were further examined in human SH-SY5Y cells expressing Aβ-GFP. Quercetin and apigenin reduced Aβ-aggregation, oxidative stress, caspase 1 and acetylcholinesterase activities, as well as improved NRF2 expression and neurite outgrowth in Aβ-GFP-expressing SH-SY5Y cells. Treatment with these compounds also phosphorylated TRKB-mediated signaling, up-regulated their downstream BCL2 apoptosis regulator (BCL2) and BDNF, and reduced the expression of BCL2 associated X, apoptosis regulator (BAX). The neurite outgrowth promotion of 7,8-DHF, quercetin and apigenin was counteracted by knockdown of TRKB. Using tryptophan fluorescence quenching assay, we confirmed the direct interaction between quercetin/apigenin and TRKB extracellular domain. Therefore, in addition to the known 7,8-DHF, the neuroprotective effects of quercetin and apigenin also mediate through TRKB signaling. Our results demonstrate how quercetin and apigenin are likely to work as TRKB agonists in Aβ-aggregation reduction and neuroprotection, providing insight into the possible applications of flavones in AD treatment.

投稿學會：台灣基礎神經科學學會	編號: P2-17

In Vitro Efficacy and Molecular Mechanism of Curcumin Analog in Pathological Regulation of Spinocerebellar Ataxia Type 3

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Abstract

Different from nuclear factor erythroid-2-related factor 2 (Nrf2) activators, the mechanism of action of curcumin analog, ASC-JM17 (JM17), in pathological regulation of Spinocerebellar ataxia type 3 (SCA3) including polyglutamine neurotoxicity and oxidative stress remains unknown. Presently, we compared actions of JM17 with those of known Nrf2 activators, omaveloxolone (RTA-408) and dimethyl fumarate (DMF), using human neuroblastoma SK-N-SH cells with stable transfection of full-length ataxin-3 protein with 78 CAG repeats (MJD78) to clarify the resulting pathological mechanism by assaying mitochondrial function, mutant ataxin-3 protein toxicity, and oxidative stress. JM17, 1 μM, comprehensively restored mitochondrial function, decreased mutant protein aggregates, and attenuated intracellular/mitochondrial reactive oxygen species (ROS) levels. Although JM17 induced dose-dependent Nrf2 activation, a low dose of JM17 (less than 5 μM) still had a better antioxidant ability compared to the other Nrf2 activators and specifically increased mitochondrial superoxide dismutase 2 in a Nrf2-dependent manner as shown by knockdown experiments with siRNA. It showed that activation of Nrf2 in response to ROS generated in mitochondria could play an import role in the benefit of JM17. The supporting result was showed by the presence of JM17 distribution not only observed in nuclei but also in mitochondria. It reflected the possibility that JM17 may simultaneously regulate mitochondrial function through Nrf2-independent pathways. In summary, this study presents the diversified regulation of JM17 in a pathological process and helped develop more effective therapeutic strategies for SCA3.

投稿學會：台灣基礎神經科學學會	編號: P2-18

Elevation of CaMKI expression in neurons of the deep cerebellar nuclei of mice with Niemann-Pick disease type C

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Abstract

Niemann-Pick disease type C (NPC) is caused by a deficiency of the NPC1 or NPC2 gene, leading to endosomal and lysosomal storage of unesterified cholesterol and sphingolipids. Cerebellar ataxia, related to Purkinje cells dysfunction, is one of the major symptoms of NPC. In this study, single-nucleus RNA sequencing (snRNA-Seq) and immunohistochemistry were used to explore the pathological changes in neurons of the deep cerebellar nuclei (DCN), the sole signal output of the cerebellum, in Npc1 knockout mice. snRNA-Seq analysis revealed a generalized reduction in gene expression levels, but an elevated level of Camk1d in the mice with NPC. Camk1d was found to be the major Ca2+/calmodulin-dependent protein kinase (CaMK) gene expressed in the DCN neurons. Immunohistochemistry of the DCN neurons revealed prominent GM2 accumulation in the late endosomes and elevated CaMKI expression in the submembranous space. No GM2 lipid rafts staining could be found. Interestingly, CaMKI expression was elevated in the wild-type mice treated with a CaMK inhibitor KN-93. Together, our data suggest that dysfunction of CaMKI, probably due to the disruption of lipid rafts, leads to its overexpression in the DCN neurons of mice with NPC. Clinical implications of the current findings will be discussed.

投稿學會：	編號: P2-19

Biochemical characterization of a genetic modifier that modulates the onset of disease in SCA3

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Abstract

Spinocerebellar ataxia type 3 (SCA3) is an inherited neurological disorder caused by the expression of mutant ATXN3 gene containing a segment of CAG repeat expansion, producing pathogenic protein with a long stretch of polyQ track that is aggregation-prone and detrimental to neurons. While an inverse correlation between CAG repeat length and age of disease onset (AO) in SCA3 has been readily reported, individuals with variation in a predicted AO are often observed, suggesting the existence of genetic modifiers that influence the disease progression of SCA3 and pathogenicity of mutant ATXN3. Here, we demonstrated that mutant ATXN3 protein is regulated by Protein inhibitor of activated STAT1 (PIAS1) through a post-translation mechanism. PIAS1 functions as a SUMO E3 ligase of ATXN3, enabling to increases ATXN3 protein half-life by preventing its UB-mediated proteasome degradation and enrich mutant protein accumulation in the insoluble fraction of protein lysates. In addition, PIAS1 genetic knockdown causes a decrease of mutant ATXN3 protein abundance and rescues impaired mobility and longevity in a Drosophila model of SCA3. Besides, by characterizing a PIAS1 gene variant identified from a subset of SCA3 patients with late disease onset, we showed that the variant exhibits a biochemical defect in SUMOylation of mutant ATXN3 protein, resulting in a decrease of protein aggregates and cell death in cultured neurons. Our findings indicate that PIAS1 is a genetic modifier of SCA3 and it might serve as a therapeutic target to delay or prevent the incidence of the disease.

投稿學會：台灣基礎神經科學學會	編號: P2-20

A computational model for dendritic pruning in the cerebellum induced by intercellular interactions

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Abstract

The cerebellum is involved in coordinating motor functions as well as in cognition and emotion. Major neurons in this complex information processor maturate postnatally in mammalian brains. During the postnatal development phase, each Purkinje cell neuron, the sole output from the cerebellar cortex, selects a primary dendritic tree among multiple young branches. Meanwhile, a large population of granule cells, the most copious neurons in the brain, migrates from the surface to the bottom of the cortex. This cortex layer reconstruction by granule cells creates a highly crowded environment for the Purkinje cell to grow dendrites. Although intensive interactions between Purkinje cell dendrites and migrating granule cells have been recognized, the involvement of the granule cells in the primary dendritic selection rules is still unclear. In order to investigate their interactions under strong control of maturation parameters, we constructed a computational model representing migrations of about 3,000 granule cells and dendritic development of 48 Purkinje cells in a 3D cube. By varying environmental or dendritic pruning conditions, roles of the selection processes in elaborating primary trees were found. A new version of the NeuroDevSim software (developed by Computational Neuroscience Unit at OIST) is used for its capability to simulate interactions among large populations for shaping neuronal morphology. This study presents the first computational model that simultaneously simulates populations of growing Purkinje cells and the dynamics of migrating granule cells. The model can bridge the gap in understanding the developmental course of early neonatal Purkinje cell dendrites from the aspect of cellular interactions, and may provide new insights into how the cerebellar cortex develops into a normal or abnormal structure.

投稿學會：台灣基礎神經科學學會	編號: P2-21

Chinese herbal medicine Coptis chinensis up-regulates β-glucosylceramidase and autophagy to reduce α-synuclein aggregation and neuronal vulnerability

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease characterized by progressive loss of dopaminergic (DAergic) neurons in the substantia nigra (SN) and presence of proteinaceous inclusions immunoreactive for α-synuclein. Mutations in lysosomal enzyme β-glucosylceramidase (GBA) are the major genetic risk factor for PD, and impaired GBA activity may cause an accumulation of α-synuclein. Coptis chinensis (C. chinensis) is one of the fundamental herbs widely used in traditional Chinese medicine to treat human diseases. This study examined the association of GBA L444P mutation with Taiwanese PD in 1016 cases and 539 controls. In addition, the neuroprotective effects of C. chinensis and its active constituents, isoquinoline alkaloids berberine, coptisine and palmatine in PD were assessed. Case-control study of L444P revealed that subjects with TC genotype had a 3.93-fold increased risk of PD (95% CI: 1.37–11.24, P = 0.006) compared to subjects with TT genotype. By promoter reporter assay in HEK-293 cells and endogenous GBA protein analysis, C. chinensis and constituents displayed potential to enhance GBA expression. In addition, C. chinensis and constituents induced autophagy in DsRed-LC3-expressing 293 cells. C. chinensis and constituents further reduced α-synuclein aggregation and protected SH-SY5Y cells against α-synuclein-induced neurotoxicity by up-regulating GBA expression and autophagy. Our findings indicate the potential of C. chinensis and active constituents berberine, coptisine and palmatine to protect DAergic neurons in PD..

投稿學會：台灣基礎神經科學學會	編號: P2-22

Early dysbiosis and dampened gut microbe oscillation precede motor dysfunction and neuropathology in a mouse model of alpha-synucleinopathy

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Abstract

The pathological hallmark of Parkinson's disease (PD), neuronal α-synuclein accumulations named Lewy body, has been identified within the gut enteric nervous system early in the disease process. Studies have shown different gut microbiomes in PD patients compared to healthy controls. However, when the gut microbiota shift toward dysbiosis in the PD process remains unclear. Here, we investigate the gut microbiota in PD rodent models using 16s rRNA next-generation sequence, and their locomotor function and neuropathology longitudinally. Compared to non-transgenic littermate controls, the altered gut microbiota of the SNCA p.A53T mice can be detected starting at 2 months old, while motor deficits were observed as early as 8 months old. Notably, the diurnal oscillation of the gut microbiome was dampened throughout PD progression starting from 4 months old. Similar changes in altered gut microbiota were also observed in another PD genetic mouse model carrying the LRRK2 p.G2019S mutation at 2 months old. Finally, using metagenomic sequencing, we found that Parabateroides Merdae and Ruminococcus torques were enriched in human PD patients. Interestingly, genera Parabacteroides and Ruminococcaceae were also enriched in both PD mouse models. These findings revealed the altered gut microbiota communities and oscillations preceding the occurrence of neuropathy and motor dysfunction in the PD process. Furthermore, a common host and gut microbe interaction may be conserved in mammals such as humans and rodents.

投稿學會：台灣基礎神經科學學會	編號: P2-23

Long-term deep-brain stimulation of the subthalamic nucleus stabilizes dendritic spine dynamics in the motor cortex in Parkinsonian mice

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease that represents motor dysfunction such as akinesia and bradykinesia, as well as impaired cognitive functions such as learning and memory. Previous studies have shown that at the cellular level, dopamine depletion leads to increased formation and elimination of dendritic spines, where excitatory synapses are located, in the primary motor cortex (M1). Since the structural dynamic of dendritic spines is critical in learning and memory, the instability of dendritic spines in M1 under Parkinsonian conditions could impair motor skill learning. Deep-brain stimulation (DBS) is one of the clinical therapies to acutely ameliorate PD symptoms. However, how DBS affects spine dynamics and neural circuit reorganization remains elusive. Here we show that the structural dynamic of dendritic spines in the M1 is stabilized by long-term DBS of the subthalamic nucleus (STN-DBS) in Parkinsonian mice. We combine activity-dependent genetic labeling (TRAP2) with optogenetic STN-DBS to label stimulation-modulated cortical neurons. We further investigate the structural dynamics of the dendritic spine in M1 pyramidal neurons using longitudinal in vivo two-photon microscopy in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. We found that dopamine depletion-induced elevation of dendritic spine turnover rate can be reduced after long-term bilateral STN-DBS in M1 pyramidal neurons. Dopamine-depleted mice receiving bilateral STN-DBS 4-6 hrs per day showed a tendency of improved performance on single-pellet reaching tasks. Our results suggest that long-term STN-DBS might improve motor learning by stabilizing the synaptic connections in the M1 cortical neurons in PD mice.

投稿學會：台灣基礎神經科學學會 | 編號: P2-24

Investigating the neural dynamics in the primary motor cortex under deep-brain stimulation of the subthalamic nucleus in Parkinson's disease

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Abstract

Deep-brain stimulation (DBS) delivered through the electrodes implanted in the subthalamic nucleus (STN) has been a clinical treatment to ameliorate Parkinson's disease (PD)-associated motor symptoms, e.g., bradykinesia, tremor, rigidity, and postural instability. However, the underlying mechanism for DBS to alter our brain dynamics and subsequently alleviate the symptoms remains elusive. Specifically, the contribution of the motor cortex to the therapeutic effect of DBS is controversial. The electrophysiological recording is frequently adopted to study the activity of cortical neurons during STN-DBS. However, electrophysiological recording is limited in determining cell types and large-scale spatial information. Here, we show the method combining optogenetics and the technique of Targeted Recombination in Active Populations (TRAP2) to achieve cell-type specific stimulation and analysis the distribution pattern of DBS-activated neurons in different layers of the M1 of PD mice. In addition, a pipeline of labeling two cell populations under two DBS conditions is established by integrating the TRAPping and c-fos technique. This tool can help specify the DBS-responsive neurons at either DBS-effective or non-effective stimulation frequencies. In this way, we identified the critical neurons for achieving the therapeutic effect of STN-DBS. We found the labeled neurons showing layer- and stimulation-protocol specificity. We further combine two-photon calcium imaging to monitor the neural activity in the M1 in real-time upon STN-DBS in behaving mice. Our results provide insight into which M1 neuron populations have a dominant role in contributing to the therapeutic effect of DBS and restoring PD motor symptoms.

投稿學會：台灣基礎神經科學學會	編號: P2-25

The investigation to the neural activity topography in the cortico-basal ganglia circuit under deep-brain stimulation of subthalamic nucleus

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Abstract

The subthalamic nucleus deep-brain stimulation (STN-DBS) shows significant therapeutic effects on alleviating the motor deficits in patients with Parkinson's disease (PD). However, its underlying mechanism is remained controversial. STN serves as the excitatory component within the basal ganglia circuitry, which is critical for the excitation-inhibition balance in motor control. While the neural activities in the nuclei of the basal ganglia and the motor cortex recruited by STN-DBS has been demonstrated, the sub-regional information of the activity is remained insufficient. In this study, we combined the genetic tool, Target Recombination in Active Population (TRAP2), with optical STN-DBS to identify the spatial distribution of neural activities that are correlated with the stimulation. Here we show that high-frequency STN-DBS is sufficient to recruit a population of neurons in the deep layers of primary motor cortex (M1). Interestingly, these deep-layer TRAPped neurons are spatially independent of the neurons in M1 layer 5 which projects axons to the STN as the target of stimulation. We also characterized the topographic distribution of the neural activity in STN, globus pallidus externus (GPe) and substantia nigra pars reticulata (SNr), and identified the activity alterations correlated with DBS under physiological or parkinsonian condition. In summary, we have established the STN-DBS TRAP system, which allows us to address the brain-wide neural activity under DBS and extract profound spatial information. These pieces of information provided hints for investigating the circuit mechanism of STN-DBS and for achieving precise therapeutic manipulations in PD.

投稿學會：台灣基礎神經科學學會 | 編號: P2-26

Development and integration of new behavior approach with large-scale recordings to study neural activity in sensorimotor cortices during forelimb movements in mice

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Abstract

The primary motor cortex is essential for skilled forelimb movements. While the primary somatosensory cortex collects the sensory feedback about movement outcomes, that can be used for motion correction or response to unexpected stimuli. However, how the sensory feedback is used by the sensorimotor cortices to produce precise movements is not entirely clear. To address this question, we trained mice to perform skilled forelimb motor tasks and simultaneously recorded the neural activity. To separate neural activity caused by the sensory feedback from other activities, we designed “active” and “passive” motor tasks. In the active tasks, the mice need to control a robotic manipulandum with their forelimbs to target different points in space in front of them for receiving rewards. In the passive tasks, the forelimb is moved by the manipulandum replicating trajectories of the active tasks. Taking advantage of the small size of the mouse brain, we recorded thousands of neurons in the sensorimotor cortices, including the primary motor cortex, the somatosensory cortex, and the premotor cortex, using a high-density multi-electrode array. With this approach, we will be able to extend the knowledge about the role of each of the brain areas in skilled forelimb movements. Moreover, we will be able to investigate the interactions between these areas and the flow of information between them, that was not been studied before due to technological limitations.

投稿學會：台灣基礎神經科學學會 | 編號: P2-27

Mapping the downstream brain regions engaged by zona incerta afferent input from the substantia nigra

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Abstract

Recent studies have shown that the zona incerta (ZI) is engaged in modulating defensive behaviors. Previous studies in the lab has revealed that stress or threats engage substantia nigra-to-zona incerta (SN-to-ZI) input to promote defensive behavior. How the SN-to-ZI input recruits its downstream regions to regulate defensive behavior remains unclear. To address this question, we first employed anterograde viral tracing method to map the downstream projections of SN-innervated ZI cells. We detected axonal projections of the SN-innervated ZI cells in several subcortical brain regions, such as the caudate putamen, ventral pallidum, lateral habenula (LHb), superior colliculus, mesencephalic reticular formation (mRT) and periaqueductal gray (PAG). To further examine the functional recruitment of SN-to-ZI input, we combined excitatory optogenetic manipulation and activity-dependent c-Fos staining to map involved brain regions that may mediate regulation of defensive behavior. By employing ImageJ semiautomatic cell counting analysis, we obtained objective counting results indicating that significantly more PAG and LHb neurons were recruited when the SN-to-ZI input was activated. On the other hand, mRt neurons were significantly less active. Further investigation will be required to examine the causal roles of these brain regions in mediating defensive behavior.

投稿學會：台灣認知神經科學學會	編號: P2-28

Evaluating the different stages of Parkinson's disease using resting-state EEG with Holo-Hilbert Spectral Analysis

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Abstract

The major pathology of Parkinson's Disease (PD) occurs in subcortical structures, however, dopaminergic cortical-subcortical connectivity amid the basal ganglion, the thalamus and frontal lobes are also affected. These abnormalities can be revealed by electroencephalography (EEG). Nevertheless, conventional time-frequency analysis of EEG signals cannot comprehensively divulge the nonlinear properties of neural activities and interactions. Thus, a novel and established Holo-Hilbert Spectral Analysis (HHSA) was applied to reveal nonlinear features in EEG. The resting state EEG of 99 PD patients and 59 healthy controls (HCs) were recorded and analyzed via HHSA. PD patients demonstrated reduction of β bands in frontal and central regions, and reduction of γ bands in central, parietal and temporal regions. Compared to early PD (EPD) patients in stages 1 and 2 (n = 80), late PD (LPD) patients in stages 3 and 4 (n = 19) demonstrated reduction of β bands in posterior central region, and increased θ and δ2 bands in left parietal regions. θ and β bands in all brain regions were positively correlated with the scores of Hamilton's depression rating scale (HAM-D). Machine learning algorithms were then applied using three prioritized HHSA features, with the best result appearing in the 'Bag' algorithm with an AUC of 0.90, followed by "LogitBoost" with an AUC of 0.89, and "GentleBoost" with an AUC of 0.88, and AUC of other algorithms greater than 0.7. The application of each algorithm to testing data showed that 'Bag" demonstrated the highest level of accuracy (0.81), followed by "Tree" (0.80), "LogitBoost" (0.79) and "SVM" (0.74). These results support the potential of implementing machine learning algorithms with HHSA features of EEG as diagnostic tools for PD.

投稿學會：台灣基礎神經科學學會 | 編號: P2-29

Functional involvement of the peduncular part of lateral hypothalamus by the midbrain afferent inputs in stress

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Abstract

Being able to signal threat and react to potential danger are critical skills for organisms to survive. Recent studies have shown that the ventral tegmental area is tuned to salient aversive stimuli and elicit coping defensive responses. Similarly, substantia nigra is also reported to modulate defensive behavior. Nevertheless, how the two midbrain structures engage respective downstream circuits to cope with threats remains less clear. Here, we describe both VTA and substantia nigra (SN) innervate the peduncular part of the lateral hypothalamus (PLH), a region that is linked to stress and feeding regulation. To further understand their possible functions, we then employed anterograde tracing technique to map the downstream brain regions innervated by midbrain-innervated PLH cells. Moreover, we demonstrated that both VTA and SN afferent inputs to the PLH were selectively tuned to restraint stress. Consistent with this finding, causal optogenetic examinations revealed that photoactivation of midbrain-to-PLH pathway is sufficient to cause aversion. We are currently investigating the possible roles of midbrain-to-PLH inputs in regulating feeding and defensive behaviors.

投稿學會：台灣基礎神經科學學會 | 編號: P2-30

Perinatal Blockade of Neuronal Glutamine Transport Sex Differentially Alters Glutamatergic Synaptic Transmission and Organization of Neurons in the Ventrolateral Ventral Media Hypothalamus of Adult Rats

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Abstract

Brain sex differentiation in term of synaptic mechanism associated with feminization has not been ascertained. Perinatal female rats rely heavily on glutamine (Gln) supplied by the Gln-glutamate (Glu) cycle (GGC), a metabolic pathway between astrocyte and neuron, for sustaining glutamatergic synaptic transmission in neurons of ventrolateral ventral media nucleus of the hypothalamus (vlVMH) compared to that of the male pups. Since VMH is a brain nucleus that mainly regulate female sexual behavior, and increase Glu release of perinatal hypothalamic neurons enhances dendrite spine number permanently, which is associated with brain and behavioral defeminization, we hypothesized that perinatal interruption of the GGC may alter glutamatergic synaptic transmission of adult rats. Perinatal rats of both sexes received intracerebroventricular (icv) injection of a neuronal Gln uptake blocker, alpha-(methylamino) isobutyric acid (MeAIB, 5 mM), and were raised until adulthood. Whole-cell voltage-clamp recording of miniature excitatory postsynaptic currents (mEPSCs) and evoked EPSCs (eEPSCs) of vlVMH neurons in acute slices obtained from the adult rats, followed by post-hoc examination of morphology of the recorded neurons were conducted. It was found that perinatal MeAIB treatment sex differentially increased mEPSC frequency of the male rats, while sex differentially decreased mEPSC amplitude and synaptic Glu release of the female rats. The pretreatment sex differentially decreased eEPSC amplitude of the male rats, yet it increased AMPA/NMDA current ratio of the female rats. Post-hoc examination of the labeled neurons revealed sex differences on the morphology with vehicle-pretreated male rats showed more extent arborized neurites and longer process length compared to that of the female group. The perinatal MeAIB treatment sex differentially reversed the neurite profiles within the level of their sex counterpart with vehicle-pretreatment. It is concluded that perinatal blockade of neuronal Gln transport sex differentially alters glutamatergic synaptic transmission and organization of vlVMH neurons of adult rats, and these changes may be associated with brain and behavior feminization and/or de-feminization of rats.

投稿學會：台灣基礎神經科學學會 | 編號: P2-31

DEFECTIVE STORE OPERATED CALCIUM ENTRY CHANNEL AND CALCIUM RELATED PATHWAYS IN A RAT MODEL OF INTRACEREBRAL HEMORRHAGE

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Abstract

Objective: Intracerebral hemorrhage (ICH) is a type of cerebral stroke and could occur after an ischemic stroke. Endoplasmic reticulum (ER) stress has been implicated as a significant factor that exacerbates the injury after ICH. One of the major Ca2+ channels from the extracellular matrix to the cytosol is via a channel formed by the oligomerization of ER luminal proteins stromal interaction molecule 1 & 2 (STIM1/2) and plasma membrane protein Ca2+ release-activated Ca2+ channel protein 1 (ORAI1). Collectively the oligomerization is called store-operated Ca2+ entry (SOCE). Since SOCE is one of the major pathways to intracellular Ca2+ homeostasis, it might play a direct or indirect role in ICH outcomes. Materials & Methods: Male Sprague-Dawley rat ICH was induced by intrastriatal infusion of bacterial collagenase VII-S. The protein & gene expression of SOCE proteins and Ca2+ binding ER stress-associated proteins glucose-regulated protein (GRP)-78 were analyzed with western blotting and RT-qPCR, respectively. Neurological deficits, hematoma expansion, and brain edema/BBB permeability were used to evaluate the outcome of neuroinflammation. Ca2+-related pathways were identified and analyzed with the help of RNA sequencing data analysis, gene ontology, and gene set enrichment analysis. Results: At 3 hours post-ICH, the SOCE protein STIM1 and GRP78 (Ca2+-dependent chaperone protein) were downregulated significantly. STIM1 levels were restored on day three post-ICH, indicating the disturbance of SOCE at 3 hours. Annotating the RNA sequencing results (n=4 for ICH-1 day, n=2 for normal) with rat genome and analyzing with gene set enrichment analysis (GSEA) revealed defective Ca2+ signaling pathways in the Kyoto encyclopedia of genes and genomes (KEGG). Further gene ontology (GO) analysis explained the deficiency of Ca2+-dependent protein binding and Ca2+ channel activity pathways in the molecular functions (MF) category. In addition, GSEA further elucidated upregulated ER-mediated unfolded protein response (UPR) pathway, which explains the defective Ca2+ channel might increase the UPR pathway increasing the ER stress. Conclusion: In this study, we figured out the defective Ca2+ channel and further exacerbation of ER stress using molecular biology techniques and RNA sequencing data analysis in a rat model of ICH.

投稿學會：台灣基礎神經科學學會	編號: P2-32

CCL5 protects cortical neuron function by regulating M2 microglia activation after mild traumatic brain injury

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Abstract

Cytokines and chemokines play important roles in inflammation and repair system activation following brain injury as traumatic brain injury (TBI). After TBI, activated M1-like microglia produces proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6, which promotes neuroinflammation and leads to neuron degeneration. On the other hand, another type of microglia shows anti-inflammation function by releasing anti-inflammation molecules and activating repair system to protect neurons, as M2-like microglia. However, the mechanism of regulating microglia polarization after TBI is unclear. C-C Motif Chemokine Ligand 5 (CCL5 also called RANTES) has been reported increasing in the plasma of TBI patients and animals. Our laboratory found that CCL5 has a neuroprotective function by activating GPX1 at early stage to reduce oxidative stress in hippocampal neurons after mild TBI. CCL5 might contribute to the balance of oxidative stress and inflammation response after brain injury. Therefore, we want to find out whether CCL5 is involved in regulating microglia polarization after injury. In the current study, we induced mild brain injury in both C57B/6 (wildtype, WT) mouse and CCL5 knockout (CCL5-KO) mouse by a weight-drop model. Neurological function as motor and sensory functions were analyzed by mNSS score, rotarod, beam walking, and adhesive removal test. The performance of motor and sensory function in both WT and CCL5-KO mice were reduced after brain injury which were recovered after 7 days post-injury (dpi) in WT group but 14 days in CCL5-KO mice group. The activation of different chemokines in cortical tissue was analyzed by RT-qPCR. Pro-inflammation cytokines - IL-1β and IL-6 was found increased in CCL5-KO mice comparing WT mice at 4 & 14 dpi. On the contrary, M2-like microglia markers - IL-10 and Arg-1, and CCL5 were increased in WT mice cortical tissue at 4 dpi. The number of Iba1+ cells was increased in both WT and CCL5-KO mice at 28 dpi. Also, we used microglia cell line BV2 to investigate CCL5 whether directly activated M2-like gene expression under oxidative stress. BV2 cell were treated with H2O2 and CCL5, M1 and M2 gene was analysis by RT-QPCR. we found that CCL5 promoted M2-like micgroglia marker and reduced M1-like microglia marker expression under oxidative stress. An intranasal (i.n.) delivery of CCL5 was applied to rescue the neurological dysfunction in CCL5-KO with mild TBI. The motor and sensory functions were successfully recovered in mice with i.n. CCL5 after 4 dpi. Also, pro-inflammation cytokines were reduced and anti-inflammation cytokines were increased in mice cortex tissue with i.n. CCL5. In summary, CCL5 has an important function in regulating microglia polarization during post-injury days 4-7 which alters immune response and protects neurons.

投稿學會：台灣基礎神經科學學會	編號: P2-33

Glial determinant gene Sox9 plays essential roles in the recovery of white matter injury

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Abstract

The restoration of lost myelin plays an essential role in the maintenance of normal central nervous system (CNS) function and recovery after injury. Reactive astrocytes play an essential role in limiting inflammation-mediated damage during the acute phases of injury. Though essential early on, reactive astrocytes are associated with multiple sclerosis (MS) disease progression; however, their underlying biology and contributions to MS remain enigmatic. Sox9 is a transcription factor playing a critical role in glial development and astrocyte differentiation. We found that Sox9 is expressed in reactive astrocytes in MS lesions, and Sox9 expression is upregulated in the reactive astrocytes in mouse brain. To examine the role of Sox9 in the recovery of white matter injury (WMI), we generated astrocyte- and oligodendrocyte-specific Sox9 knockout (KO) mice. Behavior tests showed that removal of Sox9 function in astrocytes does not result in defects in motor coordination or memory in health mice. However, the remyelination after WMI is impeded when Sox9 is specifically removed from astrocytes. In addition, in vitro experiments showed that loss of Sox9 expression in cultured astrocytes resulted in the significantly decrease of the proliferation but not the migration ability. To find the possible mechanism, we used RNA-Seq and ChIP-Seq to determine the possible target of Sox9 in astrocytes. Beta-1,4-galactosyltransferase 6 (B4GALT6), a key mediator enzyme of astrocyte activation, was identified as a possible candidate. Expression of B4GALT6 is observed in reactive astrocytes but not in normal astrocytes, and the expression is diminished in Sox9 KO mice. Our findings suggest that Sox9 regulates proper astrocyte activation through B4GALT6 after WMI. We will further examine the effect of Sox9 removal in Experimental autoimmune encephalomyelitis mouse model to further elucidate the role of Sox9 in chronic astrocyte activation..

投稿學會：台灣基礎神經科學學會	編號: P2-34

Cisd2 ameliorates cognitive impairment and attenuates Aβ-mediated neuroinflammation in Alzheimer's mouse model

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Abstract

Aging and age-related diseases are urgent and important national health issues in Taiwan and worldwide. Alzheimer's disease (AD), the most common type of dementia in elderly, is associated with deterioration in memory and loss of cognitive function. However, medication for AD is an unmet need currently. Our previous studies revealed that elevated expression of Cisd2, which is a prolongevity gene, can slow down aging in wild-type mice and ameliorate neurodegeneration and cognitive impairment in AD mouse model. In this study, we aim to provide evidence that Cisd2 is likely a novel therapeutic target for AD and to decipher the mechanisms underlying the beneficial effects of Cisd2 on AD. Here, we apply a genetic and pharmaceutical (Cisd2 activator PZ-19b) approaches are used to investigate whether maintaining Cisd2 protein at a higher level is able to attenuate Aβ-mediated neuronal loss and neuroinflammation as well as ameliorate cognitive impairment and memory decline in the 5xFAD mice, which overexpress 5 mutations of Familial AD, namely 3 mutations of APP and 2 mutations of PS1, driven by neural-specific mouse Thy1 promoter. Our study revealed the following results. Firstly, Cisd2 is down-regulated to less than 35% in the hippocampus of 5xFAD mice compared with WT mice. Secondly, upregulation of Cisd2 achieved by transgenic overexpression or Cisd2 activator PZ-19b treatment can significantly ameliorate cognitive and spatial memory decline of 5xFAD mice. Thirdly, RNA sequencing revealed that the hippocampal transcriptomic profiling has undergone extensive alterations; remarkably, cell death and immune responses are in the top pathways associated with AD pathogenesis. Intriguingly, it seems that the abnormality of transcriptomic profiling can be reversed by the treatment of Cisd2 activator PZ-19b; moreover, the profile of inflammatory-related cytokines is also down-regulated after PZ-19b treatment. Finally, molecular imaging and pathway analyses indicated that pentose phosphate pathway and antioxidant responses are dysregulated in 5xFAD mice; while these metabolic dysregulations appear to be improved by Cisd2 up-regulation. These findings suggest that Cisd2 plays a protective role on AD pathogenesis and highlight Cisd2-based therapies as a potential disease-modifying strategy for AD.

投稿學會：台灣基礎神經科學學會 | 編號: P2-35

A novel point mutation in the nucleotide-binding domain of V-ATPase subunit ATP6V1B2 is associated with human microcephaly

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Abstract

A Taiwanese patient born with autosomal dominant microcephaly has de novo mutation in ATP6V1B2 (V1B2) gene, which encodes a subunit of V1 subcomplex of the vacuolar-type ATPase (V-ATPase). It has been shown that mutations of V1B2 can lead to a variety of dominant disorders such as dominant deafness-onychodystrophy (DDOD), Zimmermann-Laband syndrome-2 (ZLS2), epilepsy, and/or microcephaly. How mutations in a single gene can lead to drastically different phenotypes remains elusive. Using the in vitro neuronal differentiation model, we observed that the expression of microcephalic V1B2 mutations compromises neuronal differentiation while those causing ZLS2 do not. In addition, the microcephalic V1B2 mutations do not affect lysosomal acidification. Interestingly, ATP6V1B2 localizes to late endosomes and Golgi apparatus in embryonal carcinoma cells and the microcephalic mutations disrupts this localization. Our data suggest that V1B2 plays a role in the function of late endosome and/or Golgi apparatus which in turn regulates neuronal differentiation and brain development.

投稿學會：台灣基礎神經科學學會	編號: P2-36

De Novo Loss-of-function KCNA3 and KCNA6 Variants Cause Early Onset Developmental Epilepsies

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Abstract

Epilepsy is characterized by abnormal electrical brain activity in central nervous system which leads to seizure or unusual behaviors. During a period of seizure, part of neurons undergoes synchronous firing and the firing frequency is much higher than usual. It is well known that ion channels are essential for maintaining neuronal membrane potential and their mutations would lead to epilepsies in humans. Potassium ion channels are responsible for regulating neuronal membrane potential and modulating the neuronal excitability; mutations in several shaker-type (Kv1) potassium channels, such as KCNA1 and KCNA2, have been shown to cause early onset epilepsies. In this study, we identified novel de novo mutations in two additional Kv1 channels using whole exome sequencing from Taiwanese patients suffering from early onset epilepsies. One mutation resides in KCNA3 and the other in KCNA6. Both wild-type and mutant KCNA3/6 exhibit membrane localization, which indicates that these mutations do compromise the protein association. Electrophysiological studies using the whole-cell patch-clamp technique detect loss-of-function effect in these variants, which could impair the repolarization of the membrane potential and lead to hyperexcitability. Our findings expand the list of Kv1 family genes that associates with early onset epileptic encephalopathy.

投稿學會：台灣神經罕見疾病學會	編號: P2-37

NEXMIF encephalopathy: A Synaptopathy causing Epilepsy and Intellectual Disability

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Abstract

NEXMIF (Neurite Extension And Migration Factor), previously called KIAA2022, is required for neuronal migration and dendritic growth. It also regulates the N- cadherin expression, thus may play a role in the cell-cell adhesion. Pathogenic variants in NEXMIF gene have been reported to cause development and epileptic encephalopathy (DEE), autism and intellectual disability (ID); but it has not been reported in Taiwan yet. Herein, we reported two cases of NEXMIF encephalopathy, both were female with intellectual disability in addition to seizures. Clinically, both had adolescent to adult-onset epilepsy with moderate ID. EEG showed multifocal epileptiform discharges and photosensitivity in one of them. Brain MRI showed a bottom of sulcus dysplasia in left frontal lobe of uncertain significance. Both pathogenic variants were novel single nucleotide variants, one cause nonsense and one cause frameshift with premature truncation. This is in accordance with the literature where “loss of function” underlies the pathogenesis. Recently, NEXMIF knock-out animal model demonstrated aberrant synaptic function, which suggests that NEXMIF encephalopathy is an example of “synaptopathy”.

投稿學會：台灣生物精神醫學暨神經精神藥理學會 | 編號: P2-38

Examining the genetic overlap between methamphetamine use disorders and other psychiatric disorders

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National Health Research Institutes

Abstract

Background: There has been evidence that methamphetamine (MA) use disorder is heritable and probably highly polygenic. Shared genetic factors may explain the high comorbidity between MA use and other psychiatric disorders. Previous studies also suggest possible shared etiological mechanisms between MA-induced psychosis and primary psychosis. We aimed to examine whether MA use disorders are genetically correlated with other psychiatric disorders using a polygenic risk score (PRS) approach. Methods: A total of 143 patients with MA use were recruited. Genome-wide single nucleotide polymorphism (SNP) genotyping, demographic, and clinical information were obtained. Healthy controls were 77,520 individuals, who self-reported no history of psychosis, with genome-wide genotypic data available from Taiwan Biobank. We calculated genome-wide PRS for five major psychiatric disorders, including schizophrenia (SCZ), bipolar disorder (BPD), major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and alcohol dependence (AD), and tested their associations with MA use and MA-induced psychosis. Results: MA use was significantly associated with ADHD-PRS with a P-value threshold of 0.05 and AD-PRS with a P-value threshold of 0.05 and 0.1. None of SCZ-PRS, BPD-PRS, and MDD-PRS was associated with MA use. MA-induced psychosis was significantly associated with SCZ-PRS with a P-value threshold of 0.001, 0.005, and 0.05. Conclusions: MA use was genetically correlated with ADHD and AD, while MA-induced psychosis was genetically correlated with SCZ.

投稿學會：台灣生物精神醫學暨神經精神藥理學會 | 編號: P2-39

Heart Rate Variability in the Social Stress Task in Adolescents with Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder Who Have Various Experiences of Victimization and Perpetration of Peer Bullying

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Abstract

Objective: Previous research has found that individuals with autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) are the risk groups of involving in peer bullying. The autonomic nervous system (ANS) was related to emotional regulation in individuals with ASD and ADHD, and the heart rate variability (HRV) was the common index for ANS. The aims of this study were to examine HRV at baseline, at the watching a bullying video stage, and the recovery stage in adolescents with ASD and adolescents with ADHD who had various experiences of involving peer bullying. Method: Thirty adolescents with ASD and 55 adolescents with ADHD aged between 11 and 18 participated in this study. The experiences of victimization and perpetration of peer bullying were assessed using the Chinese version of the School Bullying Experience Questionnaire. The lead-II electrocardiography and blood pressure were measured during the baseline stage, the watching a bullying video stage, and recovery stage for 5 minutes each. Two-way repeated measure ANOVAs were examined the GROUP and STAGE interaction effects in HRV indices, and examined the group differences in HRV reactivity and HRV recovery for the ADHD and ASD group with various experience of victimization and perpetration of peer bullying. Results: The current study demonstrated a lower low-frequency power (LF) of HRV at baseline in the ASD group compared to that in the ADHD group. Participants in both ASD and ADHD groups activated HRV while they countered a social stress task (watching bullying video) compared to their resting baseline, especially in normal to normal intervals (SDNN), very low frequency (VLF), and total power of HRV. The ASD nonvictim and nonperpetrator experiences had higher HRV reactivity and HRV recovery compared with the ADHD nonvictim and nonperpetrator, respectively, whereas there was no difference in HRV reactivity between ASD and ADHD victims and in HRV recovery between the ASD and ADHD perpetrators. Conclusions: HRV is an indicator presenting the various psychological and physical states across ASD and ADHD adolescents with various experiences of involving peer bullying.

投稿學會：台灣基礎神經科學學會 | 編號: P2-40

Arginine vasopressin modulates ion balance and social behavior during hypo-osmo adaptation in zebrafish

Chih-Wei Fu, Sok-Keng Tong, Ming-Yi Chou

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Abstract

Arginine vasopressin (AVP) is a conserved and osmo-regulatory hormone across vertebrates. Besides, AVP is a neurotransmitter that released into many regains of brain and regulates social and aggressive behavior. Previous study showed the function of AVP in the Cl- content and H+ regulation and ionocyte proliferation after hypo-osmo stress. AVP also regulates the calcitonin gene-related peptide (cgrp) and calcitonin receptor-like 1 (crlr1) expression for Cl- regulation. However, the effects of AVP signaling on central nervous system during osmo-adaption remain largely unclear. To better evaluate the effects on central nervous system, adult zebrafish were conduct series behavior test after de-ionic water treatment. Zebrafish exhibited higher level social preference after de-ionic water incubation. The biting number was decreased in mirror biting test. Our results suggested AVP might modulate ionocyte differentiation and proliferation, and affect Cgrp and Crlr1 for Cl- homeostasis. Moreover, AVP transmission after osmo-stimulation might modulate aggressive behavior and social behavior. We reveal the central and peripheral effects of AVP, providing new and comprehensive insight to the response after osmo-stress.

投稿學會：台灣計算神經科學學會	編號: P2-41

Automated neuropil segmentation of fluorescent images for Drosophila brains

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Abstract

The connectomic study is one of the most important research domains in today's neuroscience. Connectomic analysis usually involves warping and registration of individual brain images into a standard brain template. However, warping and registration often produce large errors (1~3μm error) and hence severely reduce the accuracy of the connectomic analysis. To address this issue, we develop a method to segment neuropils automatically for individual fluorescent images of Drosophila brains from the FlyCircuit database. The segmented neuropils can serve as local landmarks and using these landmarks we are able to achieve ultra-accurate registration between brain images and the standard template. Our method includes two stages. In the first stage we use the YOLOv4 model to detect neuropils and rapidly extract small-scale 3D images. In the second stage, we use the fully convolutional network (FCN) model for neuropil segmentation. Our preliminary result showed that the Intersection over Union (IoU) score of the first stage was 90.89%. Moreover, the accuracy of AL and MB neuropils prediction was 99.2%. We have manually reviewed 500 random brain fluorescence images, and only 4 required threshold adjustment to remove redundant masks. In the second stage, we only used one brain 3D image as a training set, and the model was able to significantly segment the 3D boundaries of the AL and MB neuropils. Segmentation of other neuropils will be carried out soon. Our method will greatly improve imaging registration accuracy, allowing the construction of high-precision connectome and detailed neural network models of the Drosophila brain.

投稿學會：台灣計算神經科學學會 | 編號: P2-42

Sparse Edge Encoder (SEE) for natural images

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Abstract

The well-known function of the (spatial) receptive field of the retinal ganglion cell is edge detection, which is useful for image enhancement. As the retina plays the role of the first stage visual information processing, the important information should be compressed by the receptive field operation. Here we discovered a sparse coding method to sort out the pixel-priority by a local filter, the original image can be reconstructed efficiently by less than 40% original pixel information with the PSNR higher than 27dB. This result provides us a new understanding of retinal edge detection, especially the efficient visual information processing for natural images, implies that useful information might be filtered out by our retina when processing the non-natural images.

投稿學會：台灣基礎神經科學學會 | 編號: P2-43

MOCAT: Combination of long-term tissue preservation and volumetric organ-level imaging in cellular resolution

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Abstract

Whole brain volumetric imaging, instead of tissue section imaging, is necessary for studying the complicated function involving cooperation between brain regions. The development of tissue clearing and immune-labeling methods combined with light-sheet microscopy in this decade facilitates whole brain volumetric imaging and offers spatial information that is difficult to collect via traditional tissue sections. However, the current tissue clearing and labeling approaches require freshly prepared samples. Studies also proved the difficulty of tissue clearing of long-period fixed organs. The disfavor for long-termed preserved specimens reduces the flexibility for sample transportation and experiment design and therefore narrows the application. Here, we present MOCAT, a solution filling the gap between long-term preservation of brain tissue and whole brain immune labeling and imaging. Using MOCAT, the spatial information of biomarkers could be preserved long-term in paraffin wax-embedded (or formalin-fixed paraffin-embedded, FFPE) mouse brains and retrieved later. The volumetric images collected from FFPE mouse brains show the same pattern as freshly prepared samples and are as capable as images of fresh samples for image segmentation via commercial software and AI-driven models. MOCAT satisfies the need for long-term tissue storage before performing volumetric imaging and has the potential to be used on the human clinical sample in the future..

投稿學會：台灣基礎神經科學學會	編號: P2-44

Molecular Modeling and Mechanism Studies of Potential Small Molecule TRKB Agonists in ΔK280 Tau Folding Reporter Cell

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Abstract

The binding of matured brain-derived neurotrophin factor (BDNF) to its high-affinity tropomycin-related kinase receptor B (TRKB) induces dimerization of TRKB which subsequently activates signaling cascades critical for neuronal survival, development and synaptic plasticity. BDNF-TRKB pathway may be a potential therapeutic target of AD since reduced BDNF levels were found in Alzheimer's disease (AD) brains. Small-molecule BDNF mimetics that selectively target the TRKB receptor may provide a strategy to overcome limitations of BDNF such as poor blood-brain barrier penetration and low plasma stability. Administration of selective TRKB agonist 7,8-dihydroxyflavone (7,8-DHF) improves spatial memory and minimizes dendrite loss in the hippocampus of AD mice. In addition, our previous study showed a novel synthetic chalcone-coumarin hybrid LM-031 could modify AD progression in streptozocin-induced hyperglycemic 3 × Tg-AD mice. LM-031 suppresses apoptosis and promotes neuron survival by targeting HSPB1 to reduce Tau misfolding and activating NRF2 and CREB pathways. In this study, four analogous compounds of LM-031, LMDS-1, -2, -3 and -4, were selected through virtual screening to expand chemical space of potential TRKB agonists. BDNF has been shown to bind to leucine-rich motif (LRM) and the second Ig-like (Ig-2) domain (or d5 domain) in the extracellular domain (ECD) of TRKB. In molecular modeling, docking conformation between potential agonist compounds and 7,8-DHF (as reference) with TRKB d5 domain (PDB 1hcf) was compared. Also, Pichia-expressed complete (including LRM and d5) wild type ECD of TRKB were purified and applied on tryptophan fluorescence quenching assay to investigate the binding of potential agonist compounds to TRKB ECD. Moreover, we tested these compounds on our ΔK280 TauRD-DsRed SH-SY5Y AD cell models to examine the molecular mechanisms. Among them, LMDS-1 and -2 exert neuroprotection through activating BDNF-TRKB-CREB signaling pathway. And both LMDS-1 and -2 have higher binding activity to TRKB than 7,8-DHF. Combining modeling computation, tryptophan fluorescence quenching assay and AD cellular experiments results, the derived compounds could be possible therapeutic candidates in AD, while still need more experiments to verify.

投稿學會：台灣基礎神經科學學會 | 編號: P2-45

A practical guide to in vivo electrophysiology in the brain of the minipig

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Abstract

In translational medicine, the use of large animals to study brain disorders facilitates the development of clinical trials. Minipigs are relatively inexpensive and easy-to-obtain large animals; and are suitable as an animal model for brain disorders such as epilepsy, stroke, and Parkinson's disease. However, there is less information on the brain atlas of the minipigs, which is quite challenging for researchers to investigate the functions of the specific nucleus. In the present study, we describe a method for in vivo electrophysiology using the minipig's brain. T1-weighted imaging under a 3T MRI scanner can identify the anatomical structures of the porcine brain such as cortices, hippocampus, thalamus, hypothalamus, and basal ganglia. By adjusting the top of the skull to horizontal during MRI image processing and the minipig's head to horizontal on the stereotaxic frame, the MRI anatomical images can be used as a reference atlas for electrode trajectory planning. The bregma of the minipig's skull, although not as reliable as in rodents, is still a good orientation point in individual minipigs. As an example, the action potential of the subthalamic nucleus were recorded in parkinsonian minipigs, which had a spontaneous firing frequency of approximately 30 Hz. The local field potential of the subthalamic nucleus in parkinsonian minipigs showed abnormal beta oscillation. The post-surgical MRI images, CT images, and gross sections showed that the electrodes had insertion into the target nucleus. This study provides a practical guide to the use of the minipigs for in vivo electrophysiological recordings.

投稿學會：	編號: P2-46

U(1) dynamics in neuronal activities

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Abstract

Neurons convert the external stimuli into action potentials, or spikes, and encode the contained information into the biological nerve system. Despite the complexity of neurons and the synaptic interactions in between, the rate models are often adapted to describe neural encoding with modest success. However, it is not clear whether the firing rate, the reciprocal of the time interval between spikes, is sufficient to capture the essential feature for the neuronal dynamics. Going beyond the usual relaxation dynamics in Ginzburg-Landau theory for statistical systems, we propose the neural activities can be captured by the U(1) dynamics, integrating the action potential and the ``phase" of the neuron together. The gain function of the Hodgkin-Huxley neuron and the corresponding dynamical phase transitions can be described within the U(1) neuron framework. In addition, the phase dependence of the synaptic interactions is illustrated and the mapping to the Kinouchi-Copelli neuron is established. It suggests that the U(1) neuron is the minimal model for single-neuron activities and serves as the building block of the neuronal network for information processing.

投稿學會：台灣認知神經科學學會 | 編號: P2-47

Gamma-related EEG connectivity indexes for variant TMS treatment efficacy in Treatment-Resistant Depressed patients

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Abstract

The investigation of effective electrophysiological biomarkers for transcranial magnetic stimulation (TMS) treatment efficacy in Major Depression is one of the critical issues in the field. Gamma oscillation has been proposed as a critical index for MDD, however, fewer studies have been reported. The present study aimed to investigate the gamma-related electroencephalography (EEG) indexes under resting state as biomarkers for repetitive TMS (rTMS) and intermittent theta burst stimulation (iTBS) treatment in treatment-resistant depression (TRD). A total of 61 TRD eligible participants were recruited and were randomly assigned to either prolong iTBS (piTBS) (N=19), 10-Hz rTMS (N=20), or sham group (N=22). Each participant went through clinical assessments and resting state EEG with eye-closed recording both before and after ten sessions' treatment phase. The evaluation of efficacy was defined by the changes in scores on the Hamilton depression rating scales (HDRS-17) between the baseline phase and the phase completing the treatment. The advanced analytical method to calculate the EEG brain connectivity, namely Holo-Hilbert cross-frequency phase clustering (HHCFPC), was applied. The results showed that theta-gamma connectivity and gamma connectivity decreased after piTBS in the responder compared to the sham group. In addition, theta-gamma connectivity was correlated to the improvement of symptoms. That is, the more decrement in theta-gamma connectivity, the more improvement of symptoms in TRD. On the other hand, the increment of beta-gamma connectivity was investigated in non-responder who received rTMS in comparison with the sham group. However, the index did not correlate with the antidepressant efficacy. Given these patterns of results, different mechanisms of rTMS and iTBS in TRD treatment can be indicated. Furthermore, theta-gamma connectivity could be one of the powerful EEG predictors for iTBS treatment efficacy.

投稿學會：台灣計算神經科學學會 | 編號: P2-48

Investigating neural activity on recognition mathematics functions graph for students with different mathematics prior knowledge: an ERP study

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Abstract

The reason that students with excellent prior knowledge in mathematics perform well on math exams is due to two factors: first, their knowledge reserves are richer, and second, they may also advantage from possessing better working memory. Recognizing function graphs is an important skill in mathematical learning, however, the neural activity associated with judging functional graphs remains to be further investigated. According to ERP studies on recognizing graphs, N1 and LPP are related to recognizing graphs information and working memory processing, respectively. Therefore, N1 and LPP are used as neurophysiological indicators to understand how students process function graphs in this study. The main goal of this study was to determine whether there were differences in the neural activity (N1, LPP) between students with high and low prior mathematical knowledge, and the electrode location of the scalp (C3, Cz, C4) was considered. First, the SAT-M test was administered to 125 high school students, and it allowed researchers to distinguish between those with high and low mathematical knowledge (HG=32, LG=36). Second, the "graphs-functions" identification task was tested for HG and LG students. For analysis, the T-test was used in behavior data, and a mixed 2 X 3 ANOVA was performed in EEG data. The behavior results showed the accuracy of HG was significantly higher than LG, but there was no significant difference in reaction time. ERP results, in the N1 peak, only the main effect of mathematical prior knowledge was significant, revealing that HG has a shorter latency compared with LG. In the LPP amplitude, the main effect of lateral was significant, and the amplitude of the midline is greater than the other two sides, while the main effect of mathematical prior knowledge was significant, showing that HG has a larger amplitude compared with LG. In conclusion, students with high prior knowledge may identify function graphs more quickly, and they also seem to mobilize more working memory during the stage of temporarily storing graph information, which may be helpful for the evaluation of subsequent functions.

投稿學會：台灣神經學學會	編號: P2-49

Different cerebro-cerebellar functional connectivity of cerebellar efferent and afferent loops associated with visuomotor learning ability

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Abstract

The cerebellum and motor cortex are involved in visual-motor coordination. However, inconsistency results of the cerebellar cortex and deep cerebellar nucleus was noted. There are two different afferent and efferent cerebro-cerebellar pathways based on their anatomical locations and connections. By setting regions of interest (ROIs) in the cerebellum cortex and the deep cerebellar nucleus, we measured the cerebro-cerebellar connections of the afferent cerebro-ponto-cerebellar pathways and the dentato-cortical connections of the efferent dentato-thalamo-cortical pathways. To investigate how different cerebellar afferent and efferent connectivity influence the visuomotor coordination abilities, we separated the functional connectivity into distinct afferent and efferent connectivity among the cerebro-cerebellar loops. We examined the baseline resting-state FC of different cerebellar afferent and efferent pathways and their relationship to visuomotor learning abilities. Our results showed that the accuracy improvement positively correlated with the higher baseline FC in the afferent cerebro-cerebellar pathways (L M1-R CbC), and the stability improvement negatively correlated with the lower baseline FC in the cerebellar-cerebral efferent pathways (L M1-R DCN and L M1-L DCN). The functional dissociation of the cerebellar cortex and deep cerebellar nucleus and their connections indicate distinct mechanisms in the cerebellum for visuomotor learning.

投稿學會：台灣神經學學會	編號: P2-50

Phenotype and Clinical Screening Tool Study for Diabetic Neuropathy

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Abstract

Aims and Introduction: To identify the phenotypes of diabetic neuropathy and subdivide the patients with diabetes Materials and Methods: We enrolled diabetic individuals with or without clinical symptoms compared with healthy subjects. To analyze the prevalence of Sngception/cramps and proprioception impairment, we designed the Rapid Sngception and Balance Questionnaire (RSBQ, 8 items), and two clinical neurological examinations (finger-to finger test and Romberg's test) for proprioception were conducted under the subjects' eyes opening and closing. Diabetic neuropathy (DN) was defined by the Toronto Consensus Panel on Diabetic Neuropathy. Results: Clinical data base from single center revealed (n= 29): Sngception is a unique symptom distinct from pain. Estimated 25% subjects with diabetes suffered from Sng. In minor proportion (22%) of participants in this survey, Sngception presented or aggravated by low intensity exercise. Cramp is frequently noticed as well (50%). Balance impairment (29%), floating sensation (15%), and feeling unbalance in dark environment (18%) may be underestimated in clinical practice and result in fall (6%) in patient with severe neuropathy, Conclusion: These results are the first survey of Sngception and possible Sng related discomfort in patients with diabetes. Impaired balance is an early symptom but progress in the advance disease stage.

投稿學會：台灣計算神經科學學會 | 編號: P2-51

Exploring the neural processing mechanisms of biological and non-biological hand pain in adults: An ERP study from the empathy-for-pain experimental paradigm

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Abstract

The technologies of biomimetic morphology for social robots are becoming more and more developed, blurring the boundary between living things and agents. The impact of how humans perceive the simulated social robots on human-computer interaction should be concerned. Empathy plays an important role in social interaction with others. Previous cognitive neuroscience research has shown that pain context tasks would induce neural responses of empathy for others' pain. Therefore, the aim of the present study was to explore the empathy with living things and agents investigated for the neural responses of abiotic hands (robot, doll) and biological hands (human) by measuring ERPs in the empathy-for-pain experimental paradigm. Electroencephalography was performed on 30 healthy adults who observed human-, robot- and doll-hand pictures in painful or non-painful situations. Participants were divided into two groups: the typical empathy group (TE) and the extensive empathy group (EE), based on their pain empathy for agents (robot and doll) rating. The effects of animacy, pain, and empathy on late P3 at Fz with a three-factor mixed design ANOVA were analyzed in this study. The results showed a statistically significant difference in the amplitude of animacy among the three conditions. Holm's Test revealed that the late P3 amplitude of the robot condition was greater than the human condition. The main effects of pain and empathy were not significant. There was a statistically significant interaction between animacy and empathy. Further analysis revealed that late P3 amplitudes of the robot and doll conditions were larger than the human condition in TE. In conclusion, adults could distinguish pain from non-pain situations based on the rating of pain empathy, but the results of ERPs showed that some adults' empathy performance was not different between the two situations. Generally, people have empathy for pain only humans. However, some adults seemed to have over-extensive pain empathy with robots and dolls. They empathized with humanoid robots and dolls in late top-down processing similarly to human others. This study enriched the comprehension of the neurological mechanisms implicated in human empathy and provided evidence of function for late responses of pain empathy towards humans, robots, and dolls.

投稿學會：台灣疼痛醫學會	編號: P2-52

The clinical characteristics of the sng and pain represent in cancer patients

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Abstract

Extensive studies have been conducted on pain medicine to assess the degrees and patterns of pain and how to mitigate it. Nevertheless, the insufficient and barely existent research on “Sng,” a Taiwanese phrase for soreness sensation, warrants more studies to enhance our understanding of sng. Therefore, we sought to determine the validity of assessing cancer-related pain and sng synonymously as opposed to two disparate sensations. In this retrospective study, 61 Taiwanese male and female cancer patients aged 40-80 were reviewed and analyzed at the National Taiwan University Cancer Center from May 2021 to July 2022. The subject with a pain scale over 3 responded to an MD Anderson Symptom Inventory (MDASI) questionnaire during their in-hospital stay for routine assessment to measure the patient-reported outcomes (PRO) corresponding to a wide array of discomforts and sensations. The patients also filled out sng assessments forms, which allowed us to map out pain and sng locations, frequencies, and magnitudes portrayed with color gradients overlaid onto anatomical diagrams to understand these patterns better. We revealed that patients experienced the most severe pain in the abdominal area and sng in the middle to lower back. In addition, 50 of 61 patients reported pain and sng alleviation under analgesics. Two of the four patients who received modern-day intervention for cancer pain, such as neurolysis, reported noticeable pain/sng alleviation. However, the sample size needs to be more significant to bolster the credibility of a claim vouching for these treatments. Even though sng and pain correlate with specific symptoms, only around half of the patients reported the simultaneous perception of both; therefore, synonymity between the two is weak. In conclusion, cancer patients reported pain and sng in different regions. However, analgesics effectively reduce pain and sng and do not seem to be limited by or correlated with the location or form of cancer.

投稿學會：台灣基礎神經科學學會	編號: P2-53

The role of spinal astrocytes in hyperalgesic priming in the acid induced muscle pain

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Abstract

The mechanisms that lead to transition of acute pain to chronic pain still poorly understood, Astrocytes are known as multifunctional cells entirely filling the space between neurons in the central nervous system (CNS), in the CNS astrocytes are active modulators of the brain and spinal cord physiology by carrying out maintaining homeostasis and modulating synaptic transmission, The exact role of astrocytes in hyperalgesic priming remain unknown, Here, we examined whether spinal astrocyte activation is involved in the hyperalgesic priming induced by intramuscular acid ph4.0 injection in mice, the chronic pain induced by 2nd acid injection were attenuated gradually by single intrathecal (i.t) injection of the astrocytes inhibitor L-alpha- aminoadipate (L-AA) prior 1st acid injection, while the same dose of i.t of L-AA did not affect the acute pain induced by 1st acid injection and no changes in the pain threshold when co-injected with 2nd acid injection, the involvement of astrocyte activation was evidenced by the findings that spinal Glial fibrillary acidic protein (GFAP) protein expression and number of activated astrocytes increased in the spinal dorsal horn of mice 4 hours after 1 st acid injection in compare with saline pH7.2 group. Previously shown that 1st acid induces a phosphoERK (pERK) 2 hours after acid injection, also (pERK) inhibitor (U0126) disrupt the priming formation, in our findings we showed that spinal pERK expression restricted to vesicular glutamate transporter-2 (Vglut2) neurons in the superficial dorsal horn area. we also found that i.t injection of (U0126) the inhibitor of ERK activation abolished the upregulation of spinal GFAP at 4 hours after the 1st acid injection when compared with the same dose of U0124 as control, these results together led us to examine whether astrocytic glutamate transporters glutamate-aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1) contribute in hyperalgesic priming, based on our current results, it could be considered that excitatory inputs from nociceptors stimulated by acid injection to the pERK/Vglut2 neurons release glutamate neurotransmitters and increase the excitability in the spinal cord which cause mechanical hypersensitivity, these excited superficial dorsal horn neurons from nociceptors involved in synchronizing astrocytic glutamate transporters GLT-1 and GLAST responses to form the priming signal.

投稿學會：台灣基礎神經科學學會	編號: P2-54

Hypoxia associated with Evoked Muscle Pain in lumbar radiculopathy (LR)

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Abstract

Chronic pain is a common complaint among patient in lumbar radiculopathy (LR). There is no effective treatment for the pain characteristics associated with LR and its mechanisms are not well studied. In chronic pain conditions, pain becomes the primary concern rather than a symptom, so that understanding the pain mechanism in chronic pain conditions is critical for better treatment outcome. Ralf Baron provides an ideal approach for chronic pain conditions, in which pain is analyzed on the basis of mechanism. In this pain-mechanism-based approach, the pain mechanisms play pivotal roles for examining and classifying patients and ultimately obtaining a better treatment outcome. Both clinical study and animal study are keystones for the development of this approach. From the bedside, detailed symptoms interview and quantitative sensory tests could suggest the underlying pain mechanisms. From the bench, the pain mechanisms are further revealed by the evidence from animal studies. Deep pain with a non-dermatomal distribution is a typical presentation in patients with LR, but muscle pain is rarely studied in animal LR model. Muscle afferent could be sensitized to evoke muscle pain by ischemia and hypoxia of DRG presented in animal LR model with nerve constriction. Besides, different nerve constriction sites in proximity of DRG had significant differential impacts on pain behaviors and the histochemistry changes of DRG neurons. Thereby, this study was aimed to assay evoked muscle pain in mice LR models with different nerve constriction sites in proximity to DRG, and to establish the association between the histochemistry changes of DRGs, especially hypoxia, and evoked muscle pain. Methods Clinical study: 3 groups were recruited: patients with 1) central spinal stenosis (CS)-related LR, 2) lateral spinal canal stenosis (LS)-related LR and 3) healthy subjects. Animal study: To exploring the mechanism of evoked muscle pain, 3 mice LR models of nerve constriction at different anatomical site in proximity to DRG10 were conducted: 1) proximal group: constriction about 0.2 mm proximal to DRG; 2) distal group: constriction about 0.2 mm distal to DRG and proximal to dorsal ramus of L4 spinal nerve; and 3) spinal nerve group: constriction about 0.2 mm distal to dorsal ramus of L4 spinal nerve. Both clinical study and animal study were measured the reliability of muscle pressure pain threshold (MPPT) for the development of chronic pain. For DRG pathological study, animals were sacrificed and the DRGs were harvested 1 day after the surgery. Results Clinical study Compared to healthy participants, dMPPT of patients with LR did not present significant difference in tibialis anterior (TA), lateral head (GEL) and medial head (GEM) of gastrocnemius muscle (GE). Patients were sub-grouped based on the LS or CS, because our previous work showed LS was associated with more sensory deficits, suggesting more severe nerve injury in LS. Patients with LS-related LR showed significant higher VAS for leg pain than those with CS-related LR. Patients with LS-associated LR presented significant decrease of MPPT in TA and GEM, but not in GEL. Animal study Interestingly, compatible to the clinical scenarios of LS-related LR patients, distal group presented decrease of MPPT in both GE and TA muscle. We next investigate the pathological changes of DRG at acute stage. HO-1(+), is activated under conditions of hypoxia, is significantly increased in DRG neurons of the distal and spinal nerve groups. Therefore, the ratios of ATF3(+) DRG neurons was not significantly different between group. Further examination of different nerve constriction sites on the expression of IB4, CGRP and N52 in DRG neurons 1 day after nerve constriction, we found that increased ratios of N52(+) DRG neurons in distal and spinal nerve groups were resulted from the N52 expression of IB4 and CGRP subpopulations and also the cell size of N52(+) DRG neurons were different among groups. Conclusion This study demonstrated the presence of evoked muscle pain in mice model of LR with nerve constriction distal to DRG. The different nerve constriction sites had significant differential impacts on pain behaviors and the histochemistry changes of DRG neurons. Hypoxia and the expression of NF-H of DRG neurons were associated with the evoked muscle pain.

投稿學會：台灣基礎神經科學學會	編號: P2-55

Neurological basis of statin -induced sngception

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Abstract

Sng (pronounced as 'səng') is a Taiwanese word that solely describes soreness, where in English, usage of soreness and pain is dubious. Somatosensory sensation of sng, sngception is triggered by mechanical stimulation or tissue acidosis. Perceptually sng is different from 'traditional' pain, even though they may have overlapping mechanism. It can be described as a type of hyper-mechanosensitivity that includes a tenderness or stiffness of muscle. Unfortunately, the neurological mechanisms involved in sngception is unknown. Previous studies have loosely connected sngception with acid sensitivity of deep tissue, specifically involving the Acid Sensing Ion Channels (ASICs). However, this connection has only widened the gap in our understanding of ASIC's role in nociception and anti-nociception and their involvement in sngception. Nonetheless, the question of this special sensation is hovering around mechanosensitivity changes. Here we developed a statin induced sng-like muscle hypersensitivity mouse model. The goal of this study is to understand mechanism of sngception using a novel approach of statin class drug-induced sng. Clinical studies have already shown that statin class drugs induce soreness in human subjects. Our experiments show that systemic administration of statin can induce similar hyper-mechanosensitivity of muscles in mice. This study investigates statin modulated mechanosensitive ion channels and relevant intracellular cascade mechanism involved in statin induced sng in murine peripheral nervous system.

投稿學會：台灣基礎神經科學學會	編號: P2-56

In vitro and In vivo investigating of ASIC1a protein and glucose interaction

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Abstract

Asic1a, an ion channel protein encoded by ASIC1 gene, is thought to be a PH sensitive receptor localized on the specific cell surface in both central and peripheral neuron system. Which can form the protein complex with ASIC2, ASIC3 and ASIC4 at homomeric or heteromeric composition, to achieve PH sensitivity in different range. With our understand in molecular and structure level, however, the physiological function of ASIC1a protein remain unclear in decades. Recently years, increasing evidence suggest that this protein may act as a mechanotransduction and nociceptor in the animal model. Functional disruption of ASIC1a protein also showed the high relation to pain, neurological and even psychiatric disease. In our previous studies, we illustrated that ASIC1a channel play a key role in the mechanism of prolotherapy, a common therapy used in many pain-related diseases, by involving in the dextrose-induced pERK response. Moreover, our evidence showed that ASIC1a protein change the PH sensitivity after dextrose stimulation. This evoke some interesting question about the functional and structure property of ASIC1a protein. For instance, does ASIC1a protein interact with dextrose by sensing of hypertonic pressure, or directly binding to glucose molecular? In this study, we design a series of mutagenesis protein of ASICa1 base on structure prediction, then test them in vitro and in vivo to answer these question. Our studies may help to reveal more potential physiological function or therapeutic target usage of ASIC1a protein.