program book contents

Popular science talk

人類意識的科學研究

Po-Jang Hsieh(謝伯讓)
Associate Professor, National Taiwan University

Ph.D.Dartmouth College

Abstract

每天早上起床後，意識經驗就如影隨形的伴隨著我們，直到晚上入睡無夢時，意識經驗才會消失。「意識」這個現象，每個人都非常熟悉，因為意識經驗每日每夜都會這樣不斷地再現和消失。但是，對於意識的本質，我們卻又始終摸不著頭緒。

人為什麼會有意識？它是如何產生？意識的本質又是什麼？數千年來，許多偉大的哲學家和思想家，都想要解開意識之謎。大部份的現代神經科學家，都認為意識是大腦活動的產物。基於這樣的假設，科學家們便試圖在腦中尋找意識的神經關聯。

有哪些科學方法可以用來尋找意識的神經關聯？三個關於意識的主要科學研究方向分別是：一，「失去意識」後的大腦變化；二，意識「內容」變化時的大腦反應；三，無意識的資訊如何被大腦處理。我將逐一介紹這三個研究方向中的最新進展。

Selected recent publications:

1. Feng, Y.-J., Hung, S.-M. and Hsieh, P.-J.* (2022). Detecting spontaneous deception in the brain. Human Brain Mapping. 2022; 1–13.
2. Chen, Y.-K. Cheng, T. and Hsieh, P.-J.* (2022). P3b does not reflect perceived contrasts. eNeuro. 0387-21. 2022 1–14.
3. Lin, Y., Tsao, Y. and Hsieh, P.-J.* (2022). Neural correlates of individual differences in predicting ambiguous sounds comprehension level. Neuroimage. 251 (119012).
4. Hung, S.-M. and Hsieh, P.-J.* (2022). Mind wandering in sensory cortices. Neuroimage: Reports. 2 (1).
5. Hung, S.M. and Hsieh, P.-J.* (2021). Subliminal temporal integration of linguistic information under discontinuous flash suppression. Journal of Vision. 21: 27

Popular science talk

Cephalopods as model animals for neuroscience research: historical perspectives and modern approaches

頭足類動物對神經科學研究的影響

Chuan-Chin Chiao(焦傳金)
Director General, National Museum of Natural Science
Distinguished Professor, Department of Life Science,
National Tsing Hua University

Ph.D.University of Maryland, Baltimore County

Abstract

自亞里斯多德時代（公元前384-322年）以來，頭足類動物就讓科學家們著迷。然而，真正是英國神經解剖學家 JZ Young 在 1930 年代將魷魚作為神經科學研究的模式動物，這才使得頭足類動物成為 1940 年代和 1950 年代研究神經傳導的一群獨特動物。Alan Hodgkin 和 Andrew Huxley（1963 年諾貝爾生理學或醫學獎）對動作電位的著名研究就是利用魷魚的巨大軸突來進行的。此外，利用魷魚的巨大突觸，Bernard Katz（1970 年諾貝爾生理學或醫學獎）發現鈣離子負責突觸前神經元釋放神經遞質。1980 年代，Ron Vale 和他的同事利用魷魚的巨大軸突來研究快速軸突運輸，並確定了運動驅動蛋白的角色與功能。除了這些細胞神經科學的研究，章魚與烏賊在 1960 年代也被用於研究學習和記憶的神經機制。近年來頭足類動物的研究出現了許多新的工具，如基因體學、轉錄體學、RNA編輯等。除此之外，頭足類動物的各種複雜行為，如感知、認知、記憶都是非常值得深入探索的領域。在本次的演講中，我也將分享研究烏賊分辨數量的能力與影響攝食決策的因素，並證明它們確實是有趣且聰明的動物。現在是頭足類研究的新紀元，歡迎所有生物學家一起來探索他們的潛力。

Selected recent publications:

1. Chung T.-T., Darmaillacq A.-S., Dickel L., and Chiao C.-C. The effect of unexpected rewards on decision making in cuttlefish. Scientific Reports 12: 2514 (2022).
2. Kuo T.-H. and Chiao C.-C. Learned valuation during forage decision-making in cuttlefish. Royal Society Open Science 7: 201602 (2020).
3. Wu J. J.-S., Hung A., Lin Y.-C., and Chiao C.-C. Visual attack on the moving prey by cuttlefish. Frontiers in Physiology 11:548 (2020).
4. Huang Y.-H., Lin S.-J., Lin L.-Y., and Chiao C.-C. Do cuttlefish have fraction number sense? Animal Cognition 22:163-168 (2019).
5. Yang T.-I. and Chiao C.-C. Number sense and state-dependent valuation in cuttlefish. Proceedings of the Royal Society B (2016) Aug 31;283(1837). pii: 20161379. doi: 10.1098/rspb.2016.1379.

TSfN 跨領域神經科學國際研討會
TSfN Interdisciplinary Neuroscience Congress

Neural Mechanisms for Retrieving Episodic Memory of Face-Scene Composite Images with Differential Associative Strength

Gary C.-W. Shyi (襲充文)
National Chung Cheng University

Gary C.-W. Shyi (1, 2), Vivian T.-Y. Peng (2), Cody L.-S. Wang (1), Peter K.-H. Cheng (2, 3), & S.-T. Tina Huang (1, 2)
Department of Psychology, National Chung Cheng University, Chiayi, Taiwan
PhD Program in Cognitive Sciences, National Chung Cheng University,

Abstract

Seeing faces against different scenes represents a modal experience of daily life. The associative strength between a face and a scene, however, can vary depending upon how different faces are encountered against disparate scenes. Here we examined the neural mechanisms that may underlie the retrieval of episodic memory for face-scene composite images of differential associative strength. During encoding, participants were shown face-scene composite images where a specific face was associated with a specific scene, a single face associated with multiple scenes, or multiple repetitions of a specific pairing between a face and a scene. During recognition, participants were shown face-scene images and asked to judge whether the specific pairing of face and scene was presented during encoding or was a re-combined version from those presented during encoding. They performed the recognition test while their brains were scanned with fMRI. The behavioral results showed that participants performed best with the fixed pairing between faces and scenes of multiple repetitions, followed by those faces paired with multiple scenes, and worst on the singly paired face and scene images. Brain imaging results indicate that for retrieving singly paired face-scene images, the parahippocampal place area (PPA) and the region at the intersection between hippocampus cortex (HPC) and PPA were highly activated. In addition, dorsolateral prefrontal cortex (dlPFC) was highly activated, implicating that the singly paired face-scene images may require the assistance of top-down activation from the PFC. For retrieving episodic memory of a face paired with multiple scenes, again the intersection between HPC and PPA was highly activated. In addition, regions for face processing including FFA and IFG were highly activated, reflecting the consequence of a single face associated with multiple scenes. Finally, for multiple repetitions of specific face-scene pairings, in addition to brain regions activated in the two former conditions, those that were specific for processing of faces (e.g., amygdala and inferior frontal gyrus) and those specific for processing scenes (e.g., PPA & HPC) were highly activated. Taken together, our findings indicate that the activations of brain regions in retrieving episodic memory for face-scene composite images are modulated by their associative strength.

Mental effort to retain verbal items in auditory working memory

Ming Lo (羅明)
Speech and Hearing Science Research Institute, Children's Hearing Foundation

Ming Lo1, Yi-Xiu Lin1, Yi-Jui Lee1, Shiou-Yuan Chen2
羅明1, 林怡秀1, 李翊瑞1, 陳修元2
1. Speech and Hearing Science Research Institute, Children's Hearing Foundation 2. Department of Early Childhood Education, University of Taipei

Abstract

Working memory (WM) allows us to actively hold and manipulate items in mind over short periods of time. Recent research suggests that WM capacity represents a limited resource that can be allocated flexibly across items. According to resource allocation models, fewer items can be stored if more processing is in demand because short-term storage and processing of items share a common pool of mental resource. Children have a smaller digit span (DS: the number of auditory digits that one can reproduce correctly) than adults, and the difference could be due to that cost of mental effort to retain items in WM is higher in children. In the present research electroencephalography (EEG) is employed with a DS task, in order to examine the subtler change of mental effort that occurs before a recall response. Specifically, strength of theta oscillations is used as the EEG-based measure of deliberate allocation of mental resource to encode and maintain verbal items in WM. Theta oscillations should be enhanced when additional amount of mental resource is consumed to memorize a string of spoken digits. Sixteen children (mean age 5.5 years) and 16 adults (mean age 26.5 years) performed an auditory-manual DS task, and change of theta oscillations is measured at a forehead site on the scalp. Linear regression analysis showed that, in the children group, frontal theta power in response to a string of digits increased significantly ($b=0.63$, $p<.05$). The enhancement of frontal theta power was, however, less obvious in the adult group ($b=0.21$, $p=.14$). Consistent with the EEG data, the digit span was smaller in the children than the adults (6.3 vs. 7.9, $t=5.32$, $p<.01$). Moreover, the accuracy of recognition responses showed that the children were more likely to make errors in recollection such as missing, adding and replacement, as compared to the adults (15% vs. 2%, $t=6.23$, $p<.01$). The current results support the idea that additional mental effort is required for children to retain verbal items in a DS task. This finding is also consistent with that the prefrontal cortex undergoes maturation during childhood.

TSfN 跨領域神經科學國際研討會 TSfN Interdisciplinary Neuroscience Congress

TMS disrupts ethical standards in personal situations and accelerates moral judgment

Yuju Chou (周育如)
National Dong Hwa University

Chia-Yu Yu and Yuju Chou
余佳佑, 周育如
National Dong Hwa University

Abstract

This study aims to use Transcranial Magnetic Stimulation (TMS) to disrupt brain regions and inspect the causal roles of moral judgment. Moral judgments involve multiple brain regions and are associated with different types of ethical dilemmas. It is found that the right dorsolateral prefrontal cortex (r-DLPFC) is related to the factor of Personalization. Thus, this study manipulates the variables "Personalization" and "Personal-perspective" in moral stories. Thirty-two participants were recruited for this study. While participants were reading stories and making moral judgments, a non-invasive TMS was discharged to disrupt the right dorsolateral prefrontal cortex (r-DLPFC) or the right temporoparietal junction (r-TPJ). Then, the experiment analyzed the changes in moral scores and reaction time (RT) with the random application of real and sham TMS. The results presented that, first, under the TMS condition, there was an interaction between Personalization and Personal-perspective. While personal stories with severe harm presented changes in moral scores and the tendency to be "more tolerant" towards both self and others, impersonal stories with minor injury only presented the same tendency towards others, the third-person perspective. Secondly, TMS on the r-TPJ had a greater influence on moral judgments than on the r-DLPFC. Thirdly, moral judgment was a sophisticated mechanism, as "inappropriate" might stand for "slightly inappropriate" or "more inappropriate". Last, TMS accelerated moral judgment. However, if only the data of moral judgments longer than 2,501 milliseconds were analyzed, the TMS effect on RT reached marginal significance.

TSfN 跨領域神經科學國際研討會
TSfN Interdisciplinary Neuroscience Congress

A midbrain circuit for coordinated saccade and pupil responses: implications for cognitive and arousal modulation of pupil size

Chin-An Wang (汪勁安)
Institute of Cognitive Neuroscience, College of Health Science and Technology, National Central University

Abstract

Pupil size is becoming a popular index in basic and clinical investigation, because it is modulated by various sensory, cognitive, and affective processes. Recent research has shown similar modulations by bottom-up saliency, top-down cognitive, and arousal processes between saccade and pupillary responses. The superior colliculus (SC), a midbrain structure causally linked to eye movements and attention, is implicated underlying these pupil modulations because SC responses are modulated similarly by these processes. The SC receives multisensory, cognitive, and arousal inputs from multiple cortical and subcortical areas such as the frontal eye field and locus coeruleus, and projects directly to premotor brainstem circuit to initiate the orienting response including eye/head/body movement, attention shifts, and pupillary responses. It is likely that multisensory, cognitive, and arousal signals, known to be integrated in the SC, can drive coordinated saccade and pupillary responses.

Deciphering emotional versus non-emotional components between positive and negative expectancy modulation of pain

Hsin-Yun Tsai (蔡昕芸)
Taiwan International Graduate Program - Interdisciplinary Neuroscience, Academia Sinica and National Taiwan University

Hsin-Yun Tsai and Ming-Tsung Tseng
蔡昕芸 曾明宗
1. Taiwan International Graduate Program - Interdisciplinary Neuroscience, Academia Sinica and National Taiwan University, Taipei City, Taiwan 2. Graduate Institute of Brain and Mind Science, College of Medicine, National Taiwan University, Taipei City, Taiwan

Abstract

Positive expectations (i.e., expecting decreased pain) and negative expectations (i.e., expecting increased pain) toward noxious stimulations respectively alleviating and exacerbating human pain perceptions; however, psychological factors involved in pain expectations remain unclear. By applying the functional magnetic resonance imaging technology, we aim to investigate emotional versus non-emotional neural mechanisms underlying pain expectations. Thirty-one participants were instructed to use emotion regulation strategies to down-regulate expectation-related emotions in a cue-based expectancy paradigm. As indicated by subjective emotional ratings and skin conductance responses, participants successfully reduced their anxiety toward negative expectations and pleasantness toward positive expectations when applying emotion regulation strategies. We observed that expectancy effects on pain were diminished when emotions reduced. Additionally, the reduction in emotional ratings significantly predicted the expectancy effect, supporting an emotional component in the pain expectation. The non-emotional neural mechanism, which was unbiased by emotional states, for positive and negative expectations respectively engaged the anterior insular cortex and the rostral anterior cingulate cortex, with these two regions exhibiting interrelated activation. The emotional mechanism was dissociable between positive and negative expectations: positive expectations involved the medial orbital frontal cortex (mOFC) tracking the pleasantness and co-activating with the periaqueductal gray (PAG); by contrast, negative expectations recruited the amygdala and thalamus subserving the modulation of anxiety on the nociceptive processing. Furthermore, emotions also modified the encoding of aversive prediction error in the mOFC for positive expectations and PAG for negative expectations. Taken together, the current study identifies that emotional modulations on the nociceptive processing and prediction error signalling subserve the emotional mechanism underlying pain expectations.

The α6GABAA receptor - A novel drug target for fibromyalgia?

Myles Stephen Sant-Cassia (麥佑思)
TIGP in Chemical Biology and Molecular Biophysics, National Taiwan University and Academia Sinica

Myles Sant-Cassia1,3, Chih-Cheng Chen5, Cheng-Han Lee5, Chen Chun Yeh2, Daniel Knutson6, James Cook6, Lih-Chu Chiou1,2,4*
1Taiwan International Graduate Program in Chemical Biology and Molecular Biophysics, National Taiwan University and Academia Sinica, Taipei, Taiwan. 2Graduate Institute of Pharmacology, 3Graduate Institute of Biochemical Sciences, 4Graduate Institute of Brain and Mind Science, National Taiwan University Taipei, Taiwan. 5Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan. 6Department of Chemistry and Biochemistry, Milwaukee Institute for Drug Discovery, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, WI, 53211, USA.

Abstract

Fibromyalgia is a complex disorder, affecting 2-4% of the global population, and characterized by chronic widespread musculoskeletal pain, fatigue, mood disturbance, and memory impairment. Its pathogenesis remains unclear but central sensitization with changes of several neurotransmitters has been proposed. Among these, impaired GABAergic transmission is noteworthy. Neuroimaging studies have demonstrated that patients with fibromyalgia had lower GABA levels in the cerebrospinal fluid and insular cortex. Furthermore, optogenetic manipulation to inhibit GABAergic neurons in the dorsal horn induces mechanical hyperalgesia. Recently, we have demonstrated that targeting the α6 subunit-containing GABAA receptor (α6GABAAR) using a pyrazoloquinolinone Compound 6, an α6GABAAR-highly selective positive allosteric modulator (PAM), can rescue migraine-like pain and orofacial pain in animal models. In this study, we aim to determine whether α6GABAAR PAMs may relieve fibromyalgia-like pain in both the intermittent cold stress (ICS) and dual acidic-saline model. In ICS mice, daily i.p. treatment with Compound 6, but not its vehicle, on days 9 to 12 significantly inhibited mechanical allodynia without tolerance at both 3 and 10 mg/kg in female mice. This anti-allodynic effect of Compound 6 was also observed in male mice but only at 10 mg/kg. Similarly, in mice receiving dual acidic-saline (pH 4.0) injections, as compared with normal saline (pH 7.4) injections, Compound 6 (10 mg/kg, i.p.) administered on days 6 to 9 also effectively inhibited mechanical allodynic responses without tolerance in male mice. The present study indicates that Compound 6 can inhibit mechanical allodynia in animal models mimicking fibromyalgia at the same dose range that is effective in animal models of schizophrenia, essential tremor, migraine, and orofacial pain, via acting as an α6GABAAR-selective PAM. It is devoid of benzodiazepine-like side effects, such as sedation, and addiction potential. Thus, α6GABAAR-selective PAMs have the potential to be a novel therapy of fibromyalgia. This study also for the first time supports that the α6GABAAR may an important role in the pathogenesis of fibromyalgia. The higher susceptibility in female mice with fibromyalgia-like pain is in line with the higher prevalence of fibromyalgia in women than men. The association between α6GABAAR and this sex difference are yet to be elucidated.

Risk of type 1 diabetes mellitus in offspring of mothers with major psychiatric disorders

Yichun Liu (劉怡君)
Changhua Christian Children's Hospital

Yi-Chun Liu 1,2,3, Yin-To Liao 4, Vincent Chin-Hung Chen 5,6, and Yi-Lung Chen 3,7
劉怡君 廖尹鐸 陳錦宏 陳儀龍
1 Department of Psychiatry, Changhua Christian Children's Hospital, Changhua 500, Taiwan; 2 Department of Psychiatry, Changhua Christian Hospital, Changhua 500, Taiwan 3 Department of Healthcare Administration, Asia University, Taichung 413, Taiwan 4. Department of Psychiatry, Chung Shan Medical University and Chung Shan Medical University Hospital, Taichung 402,Taiwan 5 School of Medicine, Chang Gung University, Taoyuan 333, Taiwan 6 Department of Psychiatry, Chiayi Chang Gung Memorial Hospital, Chiayi 613, Taiwan 7 Department of Psychology, Asia University, Taichung 413, Taiwan

Abstract

Type 1 diabetes mellitus (T1D) is an autoimmune disease which involved abnormal Th17 function. Several major psychiatric disorders have also been linked to dysregulated immune processes mediated by Th17 cells. Th 17 cells play an essential role in pregnancy maintenance. No study aimed to examine the impact of maternal psychiatric disorders on the risk of developing T1D in offspring. We aimed to investigate the association between mothers with major psychiatric disorders and the risk of T1D in their offspring. We linked the Taiwan National Health Insurance Research Database to the Maternal and Child Health Database for the analysis and identified 2,556,640 mother-child pairings. There were no statistically significant differences in the risk of developing T1D in offspring whose mother had any major psychiatric disorders after adjusting covariates in the Cox regression model ((adjusted hazard ratio (aHR) = 0.86, 95% CI (confidence interval) 0.60-1.23). In subgroup analysis, we found aHRs 0.87, 95% CI 0.60-1.25 in the major depression group, and elevated aHRs 1.81, 95% CI 0.86-3.80 in the bipolar disorder group. There were fewer than 3 cases of T1D in the schizophrenia/schizoaffective disorder group, so we did not present the results in the Cox regression model. Our study highlights the potential relationship between mothers with bipolar disorder and T1D in offspring.

O2-8

Inhibitory Effects of SUPT4H/SUPT5H Complex Formation on Mutant Huntingtin Gene Expression and HD-associated Phenotypes

Yun-Yun Wu (吳昀芸)
INational Yang Ming Chiao Tung University

Yun-Yun Wu 1,2, Ning Deng 3, , Yanan Feng 3, Wen-Chieh Hsieh 1, Jen-Shin Song 4, Yu-Shiuan Lin 1, Ya-Hsien Tseng 1, Wan-Jhu Liao 1, Yi-Fan
吳昀芸1,2,鄧甯3, 封雅栟3, 謝文傑1, 宋政勳4, 林妤軒1, 曾雅嫻1, 廖婉竹1,朱逸凡5, 劉育丞 6, 張恩誠1, 劉珈榮1, 許世宜5, 蘇銘燦7, 郭紘志8, 史坦恩3, 鄭子豪1,2,9
1. Institute of Biochemistry and Molecular Biology, National Yang Ming Chiao Tung University. 2. Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica. 3. Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305. 4. Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes,. 5. Department of Life Science and Institute of Genome Sciences, National Yang Ming Chiao Tung University. 6. Institute of Biomedical Informatics, National Yang Ming Chiao Tung University. 7. Department of Life Science, National Taiwan Normal University. 8. Institute of Cellular and Organismic Biology, Academia Sinica,. 9. Brain Research Center, National Yang Ming Chiao Tung University.

Abstract

Huntington’s disease (HD) is an inherited neurodegenerative disorder, caused by CAG tri-nucleotide repeat expansion in the coding sequence of huntingtin (HTT) gene. Accumulated evidence indicate that the pathogenesis of HD is stemming from the toxic gain-of-function mechanism of mutant HTT. Various approaches are applied and aimed to lower mutant HTT for development of therapeutic intervention. In our earlier studies, we discovered a novel biochemical feature conferred by the transcription elongation complex SUPT4H/SUPT5H, which empowers RNA polymerase II to transcribe over DNA region containing a long stretch of CAG tri-nucleotide repeats. In line with this finding, in the context of HD, we demonstrated that SUPT4H genetic knockdown resulted in a lowering of mutant HTT expression in striatal neuronal cells and an alleviation of motor function deficits in a mouse model of HD. Here, using two independent cell-based reporter assays and small molecule libraries, we performed high-throughput screening and identified a nucleoside compound enabling to interfere with the complex formation of SUPT4H and SUPT5H. This small molecule effectively inhibits the expression of mutant HTT in a variety of HD cultured cell models, including Q111 striatal neuronal cells derived from HD mice and terminally differentiated GABAergic neurons derived from iPSCs of HD patients. In addition, an increased cellular susceptibility to oxidative stress caused by mutant HTT was reversed by the nucleoside compound in human GABAergic neurons. Moreover, alleviation of a neurodegenerative phenotype caused by mutant HTT expression was observed in a Drosophila model of HD. Our findings suggest that the SUPT4H/SUPT5H protein complex is a potential therapeutic target to lower the synthesis of mutant HTT and prevent the pathological progression of HD.

Kv4.3-F227del mutant protein disturbs protein biogenesis machinery, causes Purkinje cell death and results in spinocerebellar ataxia in SCA22

JIA-HAN LIN (林佳翰)
National Yang-Ming Chiao-Tung University

Jia-Han Lin 1,2 Hao-Chih Hung 2 Cheng-Heng Kao 3 Bing-Wen Soong 1,4,5 Ting-Fen Tsai 2,6
林佳翰 洪浩植 高承亨 宋秉文
1. Faculty of Medicine, National Yang-Ming Chiao-Tung University, Taipei, Taiwan 2. Department of Life Sciences and Institute of Genome Sciences, National Yang-Ming Chiao-Tung University, Taipei, Taiwan 3. Center of General Education, Chang Gung University, Taoyuan, Taiwan 4. Department of Neurology, Shuang Ho Hospital, Taipei, Taiwan; 5. Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan 6. Institute of Molecular and Genomic Medicine, National Health Research Institutes, Zhunan, Taiwan

Abstract

Background: Spinocerebellar ataxia type 22 (SCA22) is a dominant-inherited neurodegenerative disease featuring motor disorder, loss of balance, slurred speech, and dramatic cerebellar atrophy. In previous studies of Dr. Bing-Wen Soong, an in-frame-three-nucleotide deletion, c.679_681delTTC p.F227del, in potassium voltage-gated channel subfamily D member 3 (KCND3) gene had been identified as the disease causative mutation in several Taiwanese families. Methods: To elucidate the pathogenic mechanisms of SCA22, we generated a mouse model with Kcnd3-F227del Knock-in (KI) allele to simulate the pathogenesis of human SCA22. We performed behavioral, histological, and molecular experiments to evaluate the pathogenic phenotypes of SCA22 and investigate the specific disease mechanisms. Results: The Kcnd3-F227del carrying mice exhibit abnormal coordination and locomotion, suggesting our mouse model can faithfully simulate human SCA22 pathogenesis. Additionally, declined Purkinje cell density in the cerebellum of SCA22 mice is also observed. The neuroinflammatory responses accompanying Purkinje cell loss can deteriorate and accelerate neuron degeneration, resulting in a vicious cycle. Furthermore, we discovered that Kv4.3-F227del mutant protein might accumulate massively in the endoplasmic reticulum (ER) and Golgi apparatus. We also found that the retention of Kv4.3-F227del in ER and Golgi apparatus can induce severe ER stress and abnormal organelle structures, which may lead to the death of cerebellar neurons and eventually contribute to the occurrence of the ataxia phenotypes. Moreover, the destruction of ER and Golgi apparatus, both crucial organelles for the transportation, modification, and maturation of membrane proteins, can interrupt the trafficking of the other SCA-associated channel proteins, such as Kv3.3. Conclusion: Our findings suggest that the Kv4.3 mutant protein can induce ER stress and jeopardize the protein secretory pathway, which will eventually cause Purkinje cell loss, neuroinflammation, and SCA manifests in mice. Understanding the specific pathogenic mechanisms of SCA22 can give us new insights into the SCA channelopathies and pave the way to potential medications for the disease.

Induction of Cleaved PGAM5 Promotes Mitochondrial Biogenesis and Neurite Re-growth after Traumatic Brain Injury

Min-Zong Liang
National Tsing Hua University

Min-Zong Liang, Shao-Lung Lo, Ting-Hsuan Lu, and Linyi Chen
Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan

Abstract

Traumatic brain injury (TBI) affects 70 million individuals worldwide every year. However, there is currently no effective therapy to promote neuronal regeneration after TBI. Our previous study showed that mitochondria transplantation restored mitochondrial function and enhanced neuronal regeneration of injured hippocampal neurons. We also found a subset of WNT ligands were upregulated during neurite re-growth. This current study aims to investigate the regulation of WNT signaling and mitochondrial biogenesis after TBI. Our results showed that mitochondrial phosphoglycerate mutase 5 (PGAM5) was up-regulated after TBI both in vitro and in vivo. Given that cleaved form of PGAM5 activates WNT signaling to increase mitochondrial biogenesis in cancer cells, we hypothesized that PGAM5 might regulate WNT signaling and mitochondrial biogenesis in response to TBI. To this end, our finding showed TBI-increased PGAM5 promoted mitophagy and repressed neurite re-growth of injured cortical neurons. To further investigate the transcriptional regulation responsible for the elevated PGAM5, we have predicted the enhancer regions of Pgam5 through our previously developed algorism based on specific histone marks. Increased enhancer RNA transcripts of enhancer subregion e6-1-a suggests an active enhancer region for increasing transcription of Pgam5. We also found that TBI induced the cleavage and release of PGAM5 from the mitochondria. Besides, the upregulation of mitochondrial biogenesis coactivator PGC1α and mitochondrial transcription factor TFAM in response to TBI suggests an enhanced mitochondrial biogenesis. To confirm the enhanced mitochondrial biogenesis was regulated by cleaved PGAM5, we overexpressed cleaved PGAM5 and constitutively active PARL, which is known to cleave PGAM5, and found increased TFAM expression. Moreover, overexpressing cleaved PGAM5 and activated PARL increased neurite re-growth of injured cortical neurons. Together, our findings demonstrate that PGAM5 regulates mitochondrial biogenesis and neurite re-growth after TBI. Elevated PGAM5 enhances mitophagy and induction of PGAM5 cleavage promotes mitochondrial biogenesis and neurite re-growth.

Effect of normobaric hyperoxia on spinal cord oxygenation and cardiorespiratory function following cervical spinal cord injury

Meng-Yun Chen (陳孟云)
National Sun Yat-sen University

Meng-Yun Chen, Yen-Ting Lin, Kun-Ze Lee
陳孟云，林彥霆，李昆澤
Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

Abstract

Cervical spinal cord injury is typically associated with cardiorespiratory dysfunction due to damages of bulbospinal respiratory and vasomotor pathways, and cervical phrenic motoneurons. Hyperbaric hyperoxia following injury can prevent ischemia and hypoxia of tissue and consequent secondary injuries, but this approach may also induce several complications. Accordingly, the present study was aimed to evaluate the therapeutic efficacy of acute normobaric hyperoxia on spinal cord oxygenation and cardiorespiratory function following cervical spinal cord injury. Male Sprague-Dawley adult rats were received sham surgery or contusion at C3/4 spinal cord for the following studies. In the first study, the spinal cord oxygenation and cardiorespiratory function of anesthetized and spontaneously breathing rats were measured in response to normobaric hyperoxia (50% O2 + 50% N2) and normoxia (21% O2 + 79% N2) at the acute injured stage. The result demonstrated that mid-cervical contusion significantly reduced the spinal cord oxygenation, arterial oxygen partial pressure and mean arterial blood pressure, which could be alleviated by acute hyperoxia. These results lead us to design the second study to examine whether acute hyperoxia can prevent respiratory and metabolic dysfunction following injury. The contused animals were exposure to hyperoxia or normoxia for 4 hours immediately after injury. The respiratory behavior, oxyhemoglobin saturation and metabolism of unanesthetized rats were measured at 1 and 7 day post-injury. The result demonstrated that the body weight, oxyhemoglobin saturation, respiratory and metabolic function recovered better in contused animals received hyperoxia at 1 day post-injury. But recovery of respiratory function and metabolism is comparable between contused animals received hyperoxia or normoxia at 7 days post-injury. These data suggested that acute hyperoxia treatment can maintain spinal oxygenation level and prevent cardiorespiratory dysfunction during acute mid-cervical contusion. We proposed that adjuvant normobaric hyperoxia combined with other hemodynamic optimization strategies during acute spinal cord injury may be able to prevent secondary damage of spinal cord injury and improve functional recovery.

Brain region specific effect of alpha-synuclein in Parkinson Disease Dementia

Yu-Ting Huang (黃予庭)
Chang Gung University

Yu-Ting Huang, Yu-Yin Lee, Jin-Chung Chen*
黃予庭，李育穎，陳景宗教授
Chang Gung University

Abstract

Parkinson's disease (PD) belongs to a neurodegenerative disease with characteristic phenotype of movement disorder, some patients show other symptoms likes anxiety, depression and cognitive malfunction that called the Parkinson's disease non-motor symptoms. dementia encodes the most serious symptom among the non-motor symptoms, Parkinson's disease dementia (PDD). PD is mainly caused by the degeneration of the dopamine neuron in the substantia nigra pars compacta (SNpc) of the midbrain. Clinically, abnormal aggregation of α-synuclein was found everywhere in patient's brain, whereas alpha- synuclein-enriched Lewy bodies signal a neuronal death. Among the complications in Parkinson's disease, The motor dysfunction combined with dementia seriously affect the patient's quality of life, but the cause of dementia in Parkinson's disease is rarely explored, and whether the dementia correlation with the immune system, including the microglia and the astrocyte. In this study, to mimic the symptoms the PDD, mice were injected with AAV-a-Syn bilaterally into the SNpc and injected the alpha-synuclein PFF (pre-formed fibril) in the HIP, our results showed that after 6 months viral injection in the SNpc, the mice exhibited motor dysfunction along with anxiety, depression-like behavior and deficit in working memory and recognition. In addition, mice showed higher concentration of α-Syn by the Single-photon emission computed tomography (SPECT) and the serum α-Syn level detected by SPR biosensor in 10-12 months after viral injection. In the RNA analysis, we found increase the human α-Syn RNA expression that decrease the mice α-Syn, and also increase the NR2A and the complement C3 expression. In the protein level, we found the expression of syn211 increase in the SN, STR and the HIP, and phosphorylated ser129 in α-Syn in the SNc, also activate the GFAP and the iba1. In the intra-HIP PFF injection, the mice show high phosphorylated ser129 in α-Syn in the HIP that cause the memory behavior defect. Collectively, our finding provides the model of PD dementia by the α- synuclein aggregation. The biochemical and mechanism will be performed in the future by the Next Generation Sequencing, NGS. We want to find the correlation mechanism between the dementia and the immune system cause by the α-Syn aggregation.

Suppressing pathological neural oscillation in Parkinsonian rats with a wireless, closed-loop neuromodulator

Hsin Chen
National Tsing Hua University

H. Chen, C.T. Kuo, Y.S. Kuo, B.H. Chang, S.R. Yeh
陳新, 郭芷婷, 郭聿修, 張博勳, 葉世榮
Electrical Engineering & Life Science, National Tsing Hua University

Abstract

The high-voltage spindle (HVS) is a spike-and-wave, neural oscillation that has been identified as a pathological signature related to the dopamine depletion in Parkinsonian rats. It is of great interests to investigate whether suppressing HVSs helps to improve the motor deficits associated with the HVS, or even to delay the progression of the Parkinson's disease. As each HVS episode occurs randomly and lasts for only a few seconds, an adaptive neuromodulator is demanded for predicting the onset of HVSs and suppressing the HVSs by deep-brain stimulation at precise timing. This presentation will introduce a wireless, closed-loop neuromodulator consisting of a lightweight(~4g) neuro-interfacing headstage and a wireless data hub. The proposed algorithm for detecting the HVS is based on the autoregressive modelling at interval (ARt), and the algorithm is realized in the headstage for triggering stimulation to the subthalamic nucleaus whenever the onset of HVS is detected. The algorithm is proved able to predict the onset of HVS with high precision (96\%) and short latency (61ms), and the wireless neuromodulator facilitates experiments with freely-moving Parkinsonian rats. In parallel, the recorded neural activity is transmitted wirelessly to the data hub, wherein the Kalman-filter framework is implemented to re-estimate optimal model parameters for detecting the HVS reliably. The re-estimated parameters are then uploaded to the headstage regularly, so as to adapt the ARt model in response to the uncertain changes of neural activities from one day to another. Such machine-learning capability is also crucial for applying the ARt model to detecting HVSs in different brain regions or different rats. The adaptive neuromodulator is proved able to suppress HVSs with high efficacy. The latest data collected from our animal experiments will be presented for discussion. The intriguing finding also indicates that precise control on the timing of brain stimulation is crucial for increasing stimulation efficacy while reducing stimulation dosage and thus its side-effects. Moreover, the proposed algorithm and adaptive neuromodulator is applicable to detecting different pathological signatures (oscillation) of other neural disorders.

The Monoclonal TDP-43 Antibody Against the Oligomeric TDP-43 Mitigates Neuropathology

Yuh Shen Lye
Genomic Research Center, Academia Sinica

Yuh Shen Lye, Yun-Ru (Ruby) Chen
Genomic Research Center, Academia Sinica

Abstract

The cytoplasmic mislocalization and aggregation of the TAR DNA-binding protein 43 (TDP-43) are the histopathological hallmark of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTLD). Studies show the TDP-43 oligomers antibody revealed that TDP-43 oligomers presented in the forebrain of the FTLD transgenic mice as well as FTLD-TDP patients. Interestingly, the ALS-linked TDP-43 mutant (TDP-43Q331K) mice model shows the impairment of motor performance as early as 3 months without the formation of cytoplasmic inclusion nor loss of TDP-43. Those studies emerge antibody therapeutic approaches to prevent the neuropathology in the transgenic mice model. Therefore, we study the target and therapeutic efficacy of TDP-43 oligomer antibody in the transgenic mice model. To study the efficacy of the antibody, we delivered TDP-43 oligomer antibody on the TDP-43Q331K mice by i.v. injection weekly for 1mg/kg and IgG2a injection was served as an antibody control. The animal motor performance was evaluated by rotarod for a month after injection. Interestingly, we observed TDP-43 oligomers in the spinal neurons. We also demonstrated TDP-43 oligomer antibody injection ameliorate the motor performance deficits and mitigate the reduction of spinal neurons. We found that antibody treatment increases the astrogliosis with A2 neuroprotective phenotypes. These results suggest astrocytes may play a role on the antibody treatment.

JM17 for Treatment of Spinal-bulbar Muscular Atrophy and Neurodegenerative Disorders

Tsung-Pin Pai (白宗彬)
AnnJi Pharmaceutical Co., Ltd.

Tsung-Pin Pai, Yen-Ting Liu, Chen-Lung Chen, Tzu-Chi-Chen, Che-Chuan Yang, Yiumo Michael Chen
白宗彬, 劉彥廷, 陳承龍, 陳咨錡, 楊哲權, 陳耀武
AnnJi Pharmaceutical Co., Ltd.

Abstract

Spinal-bulbar muscular atrophy (SBMA) is an inherited genetic neuromuscular disorder caused by abnormal aggregation of polyQ-expanded androgen receptor (AR). Currently, there is no effective or approved treatment for SBMA. JM17, a novel Nrf2 activator, has been shown to mitigate SBMA phenotypes in a mouse model by promoting AR degradation mediated by Nrf1 and Nrf2 pathways. JM17 displayed a higher potency in activating Nrf2-mediated antioxidant genes compared to DMF, a well-known Nrf2 activator approved for multiple sclerosis. Our study suggested a mechanism of JM17 disrupting Nrf2 interaction with its key regulator Keap1 to increase the stability of Nrf2 protein. RNA sequencing study in SBMA fibroblast confirmed a transcriptome signature consistent with Nrf1 and Nrf2 activation in expression of proteasome subunits and antioxidant enzymes, respectively. Moreover, JM17 was shown to protect neuronal N2a cells from H2O2-induced challenge; reduce apoptosis of the cells with defective mitochondrial respiratory chain; suppress pro-inflammatory cytokines, TNF-a, IL-1b, and IL-17a in mouse bone-marrow derived macrophage splenocytes efficiently; inhibit activation of human T-cells and human brain-derived microglia cell line. Altogether, these results suggested JM17 has pleiotropic activities and potential for treating other neurological disorders associated with oxidative stress and inflammation. A first-in-human Phase I study revealed an excellent safety and pharmacokinetic profile of JM17. Enrollment of the first-in-patient trial will be initiated by the end of 2022 to assess the safety of JM17 and its pharmacodynamic effects in muscles.

	順序編號	英文姓名	中文姓名	Title
02-1	2	Gary C.-W. Shyi	襲充文	Neural Mechanisms for Retrieving Episodic Memory of Face-Scene Composite Images with Differential Associative Strength
02-2	2	Ming Lo	羅明	Mental effort to retain verbal items in auditory working memory
02-3	2	Yuju Chou	周育如	TMS disrupts ethical standards in personal situations and accelerates moral judgment
02-4	2	Chin-An Wang	汪勁安	A midbrain circuit for coordinated saccade and pupil responses: implications for cognitive and arousal modulation of pupil size
02-5	2	Hsin-Yun Tsai	蔡昕芸	Deciphering emotional versus non-emotional components between positive and negative expectancy modulation of pain
02-6	2	Myles Stephen Sant-Cassia	麥佑思	The α6GABAA receptor - A novel drug target for fibromyalgia?
02-7	2	Yichun Liu	劉怡君	Risk of type 1 diabetes mellitus in offspring of mothers with major psychiatric disorders
02-8	2	Yun-Yun Wu	吳昀芸	Inhibitory Effects of SUPT4H/SUPT5H Complex Formation on Mutant Huntingtin Gene Expression and HD-associated Phenotypes
02-9	2	JIA-HAN LIN	林佳翰	Kv4.3-F227del mutant protein disturbs protein biogenesis machinery, causes Purkinje cell death and results in spinocerebellar ataxia in SCA22
02-10	2	Min-Zong Liang		Induction of Cleaved PGAM5 Promotes Mitochondrial Biogenesis and Neurite Re-growth after Traumatic Brain Injury
02-11	2	Meng-Yun Chen	陳孟云	Effect of normobaric hyperoxia on spinal cord oxygenation and cardiorespiratory function following cervical spinal cord injury
02-12	2	Yu-Ting Huang	黃予庭	Brain region specific effect of alpha-synuclein in Parkinson Disease Dementia
02-13	2	Hsin Chen		Suppressing pathological neural oscillation in Parkinsonian rats with a wireless, closed-loop neuromodulator

O2-14	2	Yuh Shen Lye		The Monoclonal TDP-43 Antibody Against the Oligomeric TDP-43 Mitigates Neuropathology
O2-15	2	Tsung-Pin Pai	白宗彬	JM17 for Treatment of Spinal-bulbar Muscular Atrophy and Neurodegenerative Disorders
P2-16	2	Ya-Jen Chiu		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
P2-17	2	Jui-Chih Chang	張瑞芝	In Vitro Efficacy and Molecular Mechanism of Curcumin Analog in Pathological Regulation of Spinocerebellar Ataxia Type 3
P2-18	2	Chen Tsu-I	陳子翊	Elevation of CaMKI expression in neurons of the deep cerebellar nuclei of mice with Niemann-Pick disease type C
P2-19	2	Yi-Ching Chang	張奕晴	Biochemical characterization of a genetic modifier that modulates the onset of disease in SCA3
P2-20	2	Mizuki Kato		A computational model for dendritic pruning in the cerebellum induced by intercellular interactions
P2-21	2	Chih-Hsin Lin		Chinese herbal medicine Coptis chinensis up-regulates β-glucosylceramidase and autophagy to reduce α-synuclein aggregation and neuronal vulnerability
P2-22	2	Ashley Hsieh	謝媛媛	Early dysbiosis and dampened gut microbe oscillation precede motor dysfunction and neuropathology in a mouse model of alpha-synucleinopathy
P2-23	2	Han-Yuan Yeh	葉瀚元	Long-term deep-brain stimulation of the subthalamic nucleus stabilizes dendritic spine dynamics in the motor cortex in Parkinsonian mice
P2-24	2	Yu-Ting Hu	胡昱庭	Investigating the neural dynamics in the primary motor cortex under deep-brain stimulation of the subthalamic nucleus in Parkinson's disease
P2-25	2	Bing-Shiuan Wu	吳秉軒	The investigation to the neural activity topography in the cortico-basal ganglia circuit under deep-brain stimulation of subthalamic nucleus
P2-26	2	Iryna Andriivna Bilous	伊琳娜	Development and integration of new behavior approach with large-scale recordings to study neural activity in sensorimotor cortices during forelimb movements in mice.
P2-27	2	Shi-Hong Chiu	邱士紘	Mapping the downstream brain regions engaged by zona incerta afferent input from the substantia nigra

P2-28	2	Isobel Timothea French	范 慧 珊	Evaluating the different stages of Parkinson’ s disease using resting-state EEG with Holo-Hilbert Spectral Analysis
P2-29	2	HAU-JIE YAU		Functional involvement of the peduncular part of lateral hypothalamus by the midbrain afferent inputs in stress
P2-30	2	Shu-Ling Liang	梁淑鈴	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
P2-31	2	Mohammed Thangameeran Shaik Ismail		DEFECTIVE STORE OPERATED CALCIUM ENTRY CHANNEL AND CALCIUM RELATED PATHWAYS IN A RAT MODEL OF INTRACEREBRAL HEMORRHAGE
P2-32	2	Manhau Ho		CCL5 protects cortical neuron function by regulating M2 microglia activation after mild traumatic brain injury
P2-33	2	Teng-Wei Peter Huang	黃騰緯	Glial determinant gene Sox9 plays essential roles in the recovery of white matter injury
P2-34	2	Ching-Cheng Lin		Cisd2 ameliorates cognitive impairment and attenuates Aβ-mediated neuroinflammation in Alzheimer’s mouse model
P2-35	2	ting han kuo		A novel point mutation in the nucleotide-binding domain of V-ATPase subunit ATP6V1B2 is associated with human microcephaly
P2-36	2	ChiaHua Lo		De Novo Loss-of-function KCNA3 and KCNA6 Variants Cause Early Onset Developmental Epilepsies
P2-37	2	Shih-Ying Chen	陳詩穎	NEXMIF encephalopathy: A Synaptopathy causing Epilepsy and Intellectual Disability
P2-38	2	Yen-Feng Lin	林彥鋒	Examining the genetic overlap between methamphetamine use disorders and other psychiatric disorders
P2-39	2	Cheng-Fang Yen		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

P2-40	2	Chih-Wei Fu		Arginine vasopressin modulates ion balance and social behavior during hypo-osmo adaptation in zebrafish
P2-41	2	KAIYI HSU	許楷翊	Automated neuropil segmentation of fluorescent images for Drosophila brains
P2-42	2	Mei Ian Sam	岑美茵	Sparse Edge Encoder (SEE) for natural images
P2-43	2	Ya-Hui Lin	林亞慧	MOCAT: Combination of long-term tissue preservation and volumetric organ-level imaging in cellular resolution
P2-44	2	Te Hsien Lin		Molecular Modeling and Mechanism Studies of Potential Small Molecule TRKB Agonists in ΔK280 Tau Folding Reporter Cell
P2-45	2	Hsiao-Chun Lin		A practical guide to in vivo electrophysiology in the brain of the minipig
P2-46	2	Chia-Ying Lin		U(1) dynamics in neuronal activities
P2-47	2	Yi-Chun Tsai		Gamma-related EEG connectivity indexes for variant TMS treatment efficacy in Treatment-Resistant Depressed patients
P2-48	2	Jing-Fong Wang	王靖烽	Investigating neural activity on recognition mathematics functions graph for students with different mathematics prior knowledge: an ERP study
P2-49	2	Yicheng Lin	林易徵	Different cerebro-cerebellar functional connectivity of cerebellar efferent and afferent loops associated with visuomotor learning ability
P2-50	2	Yi-Chen Lin	林奕辰	Phenotype and Clinical Screening Tool Study for Diabetic Neuropathy
P2-51	2	Pin-Han Jeffrey Wang	王品涵	Exploring the neural processing mechanisms of biological and non-biological hand pain in adults: An ERP study from the empathy-for-pain experimental paradigm
P2-52	2	Wen-Ying Lin	林文瑛	The clinical characteristics of the sng and pain represent in cancer patients
P2-53	2	Mohamed Abbas AbdelAziz	莫罕	The role of spinal astrocytes in hyperalgesic priming in the acid induced muscle pain

P2-54	2	郁雯　尤		Hypoxia associated with Evoked Muscle Pain in lumbar radiculopathy (LR)
P2-55	2	Md Tauhid Siddiki Tomal		Neurological basis of statin -induced sngception
P2-56	2	Yu-Chen Lee	李育辰	In vitro and In vivo investigating of ASIC1a protein and glucose interaction.

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

Ya-Jen Chiu, Yu-Shan Teng, Guey

Department of Life Science, National Taiwan Normal University

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

Jui-Chih Chang1,2, Yu-Ling Wu2,†, Hardy Chan3, Mingli Hsieh4 and Chin-San Liu2,5,6,7*

1Center of Regenerative Medicine and Tissue Repair, 2Vascular and Genomic Center, 5Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan 3Allianz Pharmascience Limited, Taipei 10682, Taiwan 4Department of Life Science, Life Science Research Center, Tunghai University, Taichung, Taiwan 6Graduate Institute of Integrated Medicine College of Chinese Medicine, China Medical University, Taichung, Taiwan 7Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan.

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

Tsu-I Chen, Pei-Chun Hsu, Ni-Chung Leea, Yu-Han Liua, Hao-Chun Wang, Yen-Hsu Lua, Yin-Hsiu Chien, Wuh-Liang Hwu

Department of Pediatrics and Medical Genetics, National Taiwan University Hospital.

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

Yi-Ching Chang1, Yao-Chou Tsai1, En-Cheng Chang1, Yu-Chien Hsu1, Yi-Ru Huang1, Yu-Shuen Tsai3, Yi-Chung Lee2,4, Yi-Chu Liao4, Ming-Tsan Su5, Ueng-Cheng Yang3, Yijuang Chern6, Bing-Wen Soong7,8, Tzu-Hao Cheng1,2

1Institute of Biochemistry and Molecular Biology, National Yang Ming Chiao Tung University, Taipei, 11221, Taiwan, 2Brain Research Center, National Yang Ming Chiao Tung University, Taipei, 11221, Taiwan, 3Center for Systems and Synthetic Biology, National Yang Ming Chiao Tung University, Taipei, 11221, Taiwan, 4Department of Neurology, Taipei Veterans General Hospital, Taipei, 11221, Taiwan, 5Department of Life Science, National Taiwan Normal University, Taipei, 11677, Taiwan, 6Institute of Biomedical Sciences, Academia Sinica, Taipei 11529, Taiwan, 7Department of Neurology, Shuang Ho Hospital , Taipei, 23561, Taiwan , 8Taipei Neuroscience Institute, Taipei Medical University , Taipei, 23561, Taiwan

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.

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

Mizuki Kato , Erik De Schutter

Computational Neuroscience Unit, Okinawa Institute of Science and Technology Graduate University

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

Chih-Hsin Lin1, Chih-Ying Chao1, Yih-Ru Wu1*, Guey-Jen Lee-Chen2*

1 Department of Neurology, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, Taoyuan 33302, Taiwan 2 Department of Life Science, National Taiwan Normal University, Taipei 11677, Taiwan

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

Ashley Hsieh, Feng Liang, Cheng-Yu Chen, Yun-Pu Li, Yi-Ci Ke, En-Pong Ho, Chih-Fan Jeng, Chin-Hsien Lin, Shih-Kuo Chen

National Taiwan University.

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

Han-Yuan Yeh1,2, Rui-Ni Wu1,2, Bing-Yen Wu1,2, and Yu-Wei Wu1,2,3

1. Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan 2. Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei 115, Taiwan 3. Department of Life Science, College of Life Science, National Taiwan University, Taipei 106, Taiwan

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.

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

Yu-Ting Hu1, Rui-Ni Wu2, Han-Yuan Yeh2,3, Bing-Shiuan Wu1, Yu-Wei Wu1,2,3*

1Department of Life Science, College of Life Science, National Taiwan University, Taipei 106, Taiwan 2Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan 3Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei 115, Taiwan

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.

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

Bing-Shiuan Wu1, Yu-Ting Hu1, Rui-Ni Wu2, Han-Yuan Ye

1. Department of Life Science, College of Life Science, National Taiwan University, Taipei 106, Taiwan 2. Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan 3. Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei 115, Taiwan

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.

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

Iryna Bilous, Yen-Yuan Chen, Shuo-Yen Chueh, Poulomi A

Taiwan International Graduate Program in Molecular Cell Biology, National Defence Medical Centre and Academia Sinica, Taipei 112, Taiwan
Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei, Taiwan Genome and Systems Biology Degree Program, Academia Sinica and National Taiwan University, Taipei 10617, Taiwan
Department of Life Science, College of Life Science, National Taiwan University, Taipei, Taiwan

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.

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

Shi-Hong Chiu (1), Yung-Hsia Li (2), Ping-Chen Ho (3) and Hau-Jie Yau (3)

(1) School of Medicine, National Taiwan University. (2) Morrison Academy Taipei. (3) Graduate Institute of Brain and Mind Sciences, National Taiwan University

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.

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

Kuo-Hsuan Chang3, Wei-Kuang Liang1,4, Chi-Hung Juan1,4*

1Institute of Cognitive Neuroscience, National Central University, Taoyuan, Taiwan; 2TIGP in Interdisciplinary Neuroscience, National Central University and Academia Sinica, Taipei, Taiwan 3Department of Neurology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan. 4Cognitive Intelligence and Precision Healthcare Research Center, National Central University, Taoyuan, Taiwan.

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.

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

Yi-Jie Yang and Hau-Jie Yau

Graduate Institute of Brain and Mind Sciences, National Taiwan University

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.

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

Shu-Ling Liang 1, 3*, Rou-Shayn Chen 2, 3, Wen-Lin Liao 4

1, * Department of Physiology and Pharmacology, College of Medicine, Chang Gung University, Taoyuan, 33302, Taiwan 2, Division of Movement Disorders, Department of Neurology, Chang Gung Memorial Hospital at Linkou, Taoyuan, 33302, Taiwan 3, Neuroscience Research Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, 33302, Taiwan 4, Institute of Neuroscience, National ChengChi University, Taipei, 116011, Taiwan

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.

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

Shaik Ismail Mohammed Thangameeran1, Hock-Kean Liew2,3,4, Sheng-Tzung Tsai5,6, Cheng-Yoong Pang1,2,3

1-Institute of Medical Science, Tzu Chi University, Hualien 970, Taiwan 2-Department of Medical Research, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien 970, Taiwan 3-Neuro-Medical Scientific Center, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien 970, Taiwan 4-PhD Program in Pharmacology and Toxicology, Tzu Chi University, Hualien 970, Taiwan 5-Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien 970, Taiwan 6-School of Medicine, Tzu Chi University, Hualien 970, Taiwan

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

Manhau Ho, Chia Yen Chen, Szu-Yi Chou

Ph.D. Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University and National Health Research; 2Graduate Institute of Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan

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

Teng-Wei Huang, Brittney Lozzi, Yi-Ting Cheng, Debosmita Sardar, Benjamin Deneen

Graduate Institute of Biomedical Sciences, China Medical University, Taiwan Neuroscience and Brain Disease Center, China Medical University, Taiwan Center for Cell and Gene Therapy, Baylor College of Medicine, TX, US

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

Ching-Cheng Lin1#, Hsin-Che Lee1#, Ting-Kuan Chu1, Hsiu-Yun Chen1, Chia-Hao Su2, 3, 4, Ting-Fen Tsai1, 5, 6*

1 Department of Life Sciences and Institute of Genome Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan 2 Department of Biomedical Imaging and Radiological Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan 3 Center for General Education, Chang Gung University, Taoyuan, Taiwan 4 Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan 5 Center for Healthy Longevity and Aging Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan 6 Institute of Molecular and Genomic Medicine, National Health Research Institutes, Miaoli, Taiwan

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.

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

Ting-Han Kuo 1, Meng-Han Tsai 2,3, Eric Hwang 1*

1 Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan. 2 Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan. 3 School of Medicine, Chang Gung University, Taoyuan City, Taiwan

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.

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

Chia-Hua Lo1, Meng-Han Tsai5-7, Ya-Jean Wang8-9, Eric Hwang1-4*

1 Institute of Molecular Medicine and Bioengineering, National Yang Ming Chiao Tung University 2 Department of Biological Science and Technology, National Yang Ming Chiao Tung University 3 Institute of Bioinformatics and Systems Biology, National Yang Ming Chiao Tung University 4 Center for Intelligent Drug Systems and Smart Bio-devices (IDS2B), National Yang Ming Chiao Tung University 5 Department of Neurology, Division of Epilepsy, Kaohsiung Chang Gung Memorial Hospital 6 School of Medicine, College of Medicine, Chang Gung University 7 Department of Medical Research, Genomics and Proteomics Core Laboratory 8 Center for Neuropsychiatric Research, National Health Research Institutes 9 Department of Senior Service Industry Management, Minghsin University of Science and Technology

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

Shih-Ying Chen, Chen-Rui Ho, Yan-Ting Lu, Chih-Chiang Lin, Meng-Han Tsai

Department of Neurology & Medical Research, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University, Taiwan

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

Yen-Feng Lin, Chia-Lin Hsu, Ming-Chyi Huang

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.

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

Cheng-Fang Yen

Department of Psychiatry, Kaohsiung Medical University Hospital, and School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

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

Department of Life Science, National Taiwan University

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.

Automated neuropil segmentation of fluorescent images for Drosophila brains

Kai-Yi Hsu, Chi-Tin Shih, Nan-Yow Chen, Chung-Chuan Lo

Institute of Systems Neuroscience, National Tsing Hua University, Hsinchu, Taiwan

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.

Sparse Edge Encoder (SEE) for natural images

Mei Ian Sam, Hsiu-Hau Lin

Department of Physics, National Tsing Hua University, Hsinchu 300, Taiwan

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.

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

Ya-Hui Lin 1,2, Li-Wen Wang 1,2, Yan-Hui Chen 3, Chi-Shiun Chiang 2, Shang-Hsiu Hu 2, Bi-Chang Chen 4 and Li-An Chu 1,2,*

1 Brain Research Center, National Tsing Hua University 2 Department of Biomedical Engineering and Environmental Science, National Tsing Hua University 3 Institute of Biomedical Sciences, Academia Sinica 4 Research Center for Applied Sciences, Academia Sinica

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..

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

Te-Hsien Lin, Ya-Jen Chiu, Ying-Chieh Sun, Guey-Jen Lee-Chen*

Department of Life Science, National Taiwan Normal University, Taipei, Taiwan

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.

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

Hsiao-Chun Lin, Yi-Hui Wu, Ming-Dou Ker

National Yang Ming Chiao Tung University

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

Chia-Ying Lin, Ping-Han Chen, Hsiu-Hau Lin, Wen-Min Huang

Department of Physics, National Tsing Hua University, Hsinchu 300044, Taiwan

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.

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

Yi-Chun Tsai1, Cheng-Ta Li1,4-6, Wei-Kuang Liang1,2, Norden E. Huang3, Chi-Hung Juan1,2*

1 Institute of Cognitive Neuroscience, National Central University, Jhongli, Taiwan 2 Cognitive Intelligence and Precision Healthcare Center, National Central University, Taiwan 3 Key Laboratory of Data Analysis and Applications, First Institute of Oceanography, SOA, 266061 Qingdao, China 4 Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan 5 Institute of Brain Science, National Yang-Ming Chiao-Tung University, Taipei, Taiwan 6 Division of Psychiatry, Faculty of Medicine, National Yang-Ming Chiao-Tung University, Taipei, Taiwan

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

Jing-Fong Wang 1,2 & Tzu-Hua Wang 1,2

1 Department of Education and Learning Technology, National Tsing Hua University, Hsinchu, Taiwan 2 Research Center for Education and Mind Sciences, National Tsing Hua University, Hsinchu, Taiwan

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 $\times$ 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

Yi-Cheng Lin, Yun R. Lien, Shang-Hua N. Lin, Yi-Chia Kung, Chu-Chung Huang, Ching-Po Lin, Li-Hung Chang

Institute of Neuroscience, National Yang Ming Chiao Tung University, Taipei, Taiwan

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

Yi-Chen Lin1, 2, Jia-Ying Sung1, 3, Chih-Cheng Chen4

1 Department of Neurology, Taipei Municipal Wanfang Hospital, Taipei Medical University 2 The PhD Program for Translational Medicine, College of Medical Science and Technology, Taipei Medical University and Academia Sinica 3 Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University 4 Institute of Biomedical Sciences, Academia Sinica 5 Department of Life Science, National Taiwan University, Taipei, Taiwan.

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.

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

Pin-Han Wang 1, Peter Kuan-Hao Cheng 2, Jung-Tai King 3, Chia-Hui Chiu 4*

1 Department of Early Childhood Education, National Tsing Hua University, Hsinchu 300, Taiwan 2 Research Center for Education and Mind Sciences, National Tsing Hua University, Hsinchu 300, Taiwan 3 Institute of Neurosciences, National Yang-Ming Chiao Tung University, Taipei 112, Taiwan 4 Department of Early Childhood Education, University of Taipei, Taipei 100, Taiwan *Corresponding author

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

Derek Chan, Wun-Jyun Wang, Yi-Jung Sung, Wen-Ying Lin

National Taiwan University Cancer Center, University of Chicago

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.

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

Mohamed Abbas 1,2, Wei-Hsin Chen1, Shun-Fen Tzeng3 and Chien-Chang Chen1

1 Taiwan International Graduate Program in Molecular Medicine, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan, 2 College of Medicine, National Cheng Kung University, Tainan 701, Taiwan, 3 Department of Life Sciences, National Cheng Kung University, Tainan, Taiwan

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.

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

Jiann-Her Lin, Yu-Wen Yu, Yu-Chia Chuang, Cheng-Han Lee, Chih-Cheng Chen.

1Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan 2Division of Neurosurgery, Department of Surgery, School of Medicine, Taipei Medical University, Taipei, Taiwan 3Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan 4Taiwan Mouse Clinic-National Comprehensive Mouse Phenotyping and Drug Testing Center, Academia Sinica, Taipei, Taiwan 5Taipei Neuroscience Institute, Taipei Medical University, Taipei, Taiwan

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

Md Tauhid Siddiki Tomal, Chih Cheng Chen

1 Interdisciplinary Neuroscience Program in Taiwan International Graduate Program, Academia Sinica, Taipei 115, Taiwan 2 Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan 3 Life Science School, National Yang-Ming University, Taipei 112, Taiwan

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

Yu-Chen, Lee

Institute of Biomedical Sciences, Academia Sinica

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.

Sonodynamic therapy: the novel application of 5-ALA in malignant brain tumors

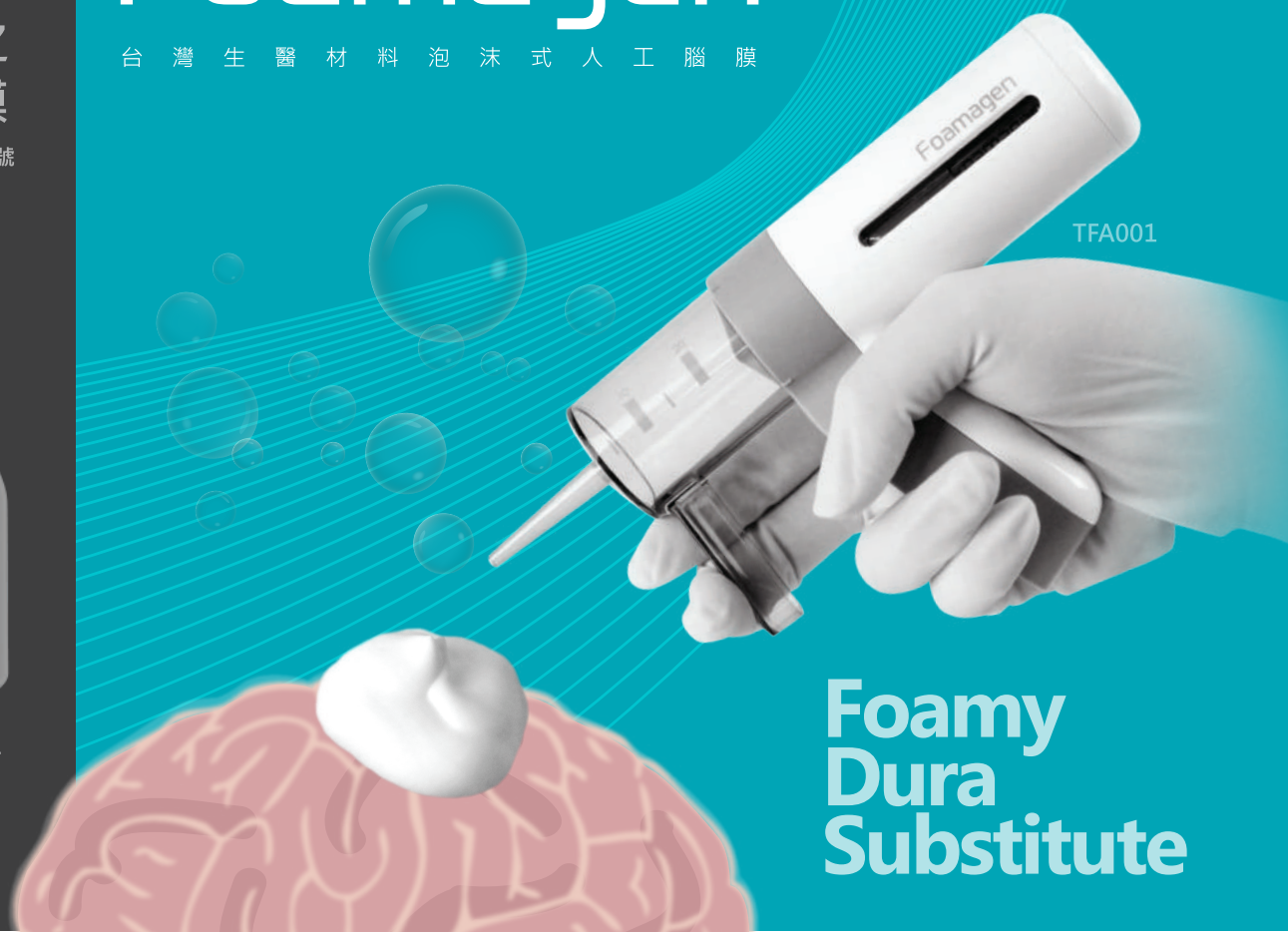
Glioblastoma multiforme (GBM) is a severe disease affects approximate 600 patients per year in Taiwan. The infiltrative growth of the tumor limits the resection rate of tumor and results a poor outcome for approximate 15 months. Thus, a precise guidance leads to recognize tumor cells from normal tissues may be beneficial for GBM treatment. It is well known that 5-aminolevulinic acid (5-ALA) induces the accumulation of fluorescent porphyrins in tumor cell, and may serve as an excellent tool to improve intraoperative decision-making and guide tumor resection. For glioma treatment, 5-ALA is not only an indicator for operation guidance, but also the key component of sonodynamic therapy (SDT) while combine with focused ultrasound. 5-ALA is reported to induce photodynamic effect by employing photo excitation to trigger tumor-targeting cytotoxicity, and is considered as a new anticancer targeting therapy route. However, using light to trigger the photodynamic effect is less practical because its limited tissue penetration ability, therefore craniotomy should be proceeded prior to light excitation. It had been proven the similar cytotoxicity can be triggered by mechanical sheer stress induced by ultrasound. By using transcranial focused ultrasound, the noninvasive SDT for GBM treatment is achievable. Here we will report the current works on *in vitro* and *in vivo* studies for demonstrating the therapeutic effectiveness of SDT in the treatment of cancer. The potential of SDT as a novel non-invasive brain tumor treatment system is highly promising, and the further application will be beneficial to brain tumor patients.

國內首家
榮獲衛福部
許可製造之
人工腦膜

衛部醫器製字第006200號

Foamagen

台灣生醫材料泡沫式人工腦膜



成份： 醫療級第一型膠原蛋白

適應症： Foamagen 泡沫式人工腦膜可被應用在以下的手術上:

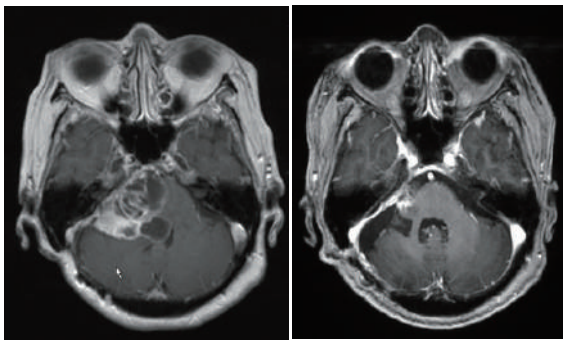
1. 頭骨凸面手術： 通常手術後用來覆蓋大範圍缺損的腦膜，如外傷切除、攣縮之腦膜缺損。

2. 後顱窩手術：一般用作硬腦膜植入使用。

適用單位： 神經外科

滅菌方式： γ-ray 照射

【手術前】 【手術後三個月】



型號	規格
FB01	Foamagen泡沫式人工腦膜鋼瓶，提供單瓶10毫升的容量、無菌包裝，產品內容保證無菌、無熱原，除非包裝已拆封或破損。
TFA001	“台灣生醫材料” 人工腦膜注射器一組。

藥商名稱/地址:
台灣生醫材料股份有限公司 / 新竹科學工業園區新竹縣竹北市生醫路1段188號 Tel: +886-3-668-3088 ; Fax: +886-3-668-3099

Ko-Ting Chen, MD, PhD (陳科廷) Assistant professor, Neurosurgeon, department of neurosurgery, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
PhD program of Biomedical Engineering, College of Engineering, Chang Gung University

Insight of anti-epileptic drug selection in seizure control – a neurosurgical perspective

Ko-Ting Chen1

1Department of Neurosurgery, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

Seizure is frequently presented in neurosurgical scenes. Seizure may be the initial presentation of patients with spontaneous intracerebral hemorrhage, after traumatic head injury, and newly found brain tumors. Besides, the incidence of post-craniotomy seizure has been reported to be as high as 20% without prophylaxis. Lacosamide is a third-generation anti-epileptic drug (AED) selectively affects sodium channel slow inactivation, which reduces the long-term availability of sodium channels and therefore reduce the pathologically hyperexcitability while leaving the physiological activity intact. Lacosamide has both intravenous and oral forms clinically, with 1:1 conversion without dose adjustment needed. Besides, a very low drug-drug interaction makes it a safe utilization for patients with complex underlying diseases. Furthermore, recent studies have demonstrated a less psychological side effects compared with other sodium channel-targeted AEDs. In this talk, I will share the consideration of choosing AEDs from a neurosurgical perspective, in the meantime, provide relevant evidence regarding the pros and cons of lacosamide in neurosurgical scenes.

VIMPAT®
維帕特™ 輸液溶液 膜衣錠 lacosamide

2020 年 2 月起
適應症放寬，適用於 4 歲以上局部癲癇發作患者[1]

完整的照護
療效看得見[1] 用藥少負擔

52.9% 的兒童病人每 28 天* 的局部癲癇發作頻率至少減少 50%

老年病人及輕度至中度腎功能不全病人，無須調整劑量

*從基準期到維持期間

參考資料：1. Vimpat 中文仿單

維帕特 10 毫克/毫升輸液溶液 I 維帕特 50 / 100 / 150 / 200 毫克膜衣錠
衛部藥輸字第 026283 號 I 衛部藥輸字第 026284 / 026285 / 026286 / 026287 號

【適應症】1. 四歲以上有或無次發性全身發作的局部癲癇發作病人的單一藥物治療。2. 四歲以上之 (1) 複雜性局部癲癇發作 (complex partial seizure) 與 (2) 單純或複雜性局部發作之合併有次發性全身發作 (simple or complex partial seizure with secondary generalization) 癲癇病人之輔助治療 (add-on therapy)。【劑量和服用方法】體重 50 公斤或以上的兒童與青少年，以及成人：◎單一藥物治療：建議起始劑量為每天兩次每次 50 毫克 (100 毫克/天)，一週後提高至 100 毫克每天兩次的初始治療劑量 (200 毫克/天)。根據反應和耐受性，維持劑量可進一步每週增加 50 毫克每天兩次 (100 毫克/天)，至每日最大建議劑量 200 毫克每天兩次 (400 毫克/天)。針對已達到 400 毫克/天劑量且須使用額外抗癲癇藥品的病人，應遵守下方輔助療法的建議用量。◎輔助治療：建議起始劑量為每天兩次 50 毫克，應在一週後提高至 100 毫克每天兩次的初始治療劑量。根據反應和耐受性，維持劑量可以進一步每週增加 50 毫克每天兩次 (100 毫克/天)，至每日最大建議劑量 200 毫克每天兩次 (400 毫克/天)。◎開始以 Lacosamide 的速效劑量來治療：Lacosamide 的治療亦可一開始以 200 毫克的單一速效劑量，約 12 小時後以 100 毫克每天兩次 (200毫克/天) 的維持劑量來治療。應考量如上述的個別的反應與耐受性，進行後續劑量調整。當醫師決定須快速達到 Lacosamide 的穩定血漿濃度與治療效果時，病人可開始接受速效劑量。應於醫療監測下給予速效劑量，並考量到可能增加嚴重心臟心律不整與中樞神經系統不良反應的發生率。◎停用藥物：按照目前的臨床情況，如果要停止服用 Lacosamide，建議逐步減量 (如以 200 毫克/週的減少量來降低每日劑量)。對發生嚴重心臟心律不整病人，應進行臨床效益/風險評估，且必要時應停用 Lacosamide。◎從單一抗癲癇藥物 (AED) 轉換成 Lacosamide 單一藥物治療：針對已接受單一 AED 治療且將轉換成 Lacosamide 單一藥物治療的病人，在達到 Lacosamide 治療劑量且至少持續 3 天前，不應停用併用 AED。建議用至少 6 周的時間逐步停用併用抗癲癇藥物。【特殊族群】◎腎功能不全：對於輕度至中度腎功能不全病人，無須調整劑量。重度腎功能不全 [以 Cockcroft-Gault 公式估算之成人肌酸酐廓清率 (CL_{CR}) 低於 30 毫升/分鐘；以 Schwartz 公式估算兒童病人的 CL_{CR} 低於 30 毫升/分鐘/1.73 公尺^2]、或末期腎臟疾病病人，建議減少最大劑量的 25%。血液透析可有效清除血漿中的 Lacosamide。4 小時的血液透析治療後，應考慮補充最多 50% 的劑量。◎肝功能不全：針對輕度或中度肝功能不全病人，建議減少最大劑量的 25%。Lacosamide 不建議用於重度肝功能不全的病人。◎兒童族群：醫師應根據體重和劑量開立最合適的劑型與包裝規格。體重 50 公斤以上的青少年與兒童：體重 50 公斤以上的青少年與兒童的劑量與成人相同。體重低於 50 公斤的兒童 (4 歲以上) 與青少年：1. 單一藥物療法：建議的起始劑量為 2 毫克/公斤/天，一週後應提高至 4 毫克/公斤/天的初始治療劑量。根據反應和耐受性，維持劑量可以進一步每週增加 2 毫克/公斤/天。劑量應逐漸增加至達到最佳反應。對於體重低於 40 公斤的兒童，建議最大劑量為 12 毫克/公斤/天 (最多 400 毫克/天)。對於體重為 40 公斤到不滿 50 公斤的兒童，建議最大劑量為 10 毫克/公斤/天 (最多 400 毫克/天) 。2. 輔助療法：建議的起始劑量為 2 毫克/公斤/天，一週後應提高至 4 毫克/公斤/天的初始治療劑量。根據反應和耐受性，維持劑量可進一步每週增加 2 毫克/公斤/天。劑量應逐漸調整，至達到最佳反應。對於體重小於 20 公斤的兒童，由於清除率較成人高，建議最大劑量達 12 毫克/公斤/天。對於體重為 20 公斤到不滿 30 公斤的兒童，建議最大劑量為 10 毫克/公斤/天，而體重為 30 公斤到不滿 50 公斤的兒童，建議最大劑量為 8 毫克/公斤/天。【禁忌症】對本品主成分或任何完整仿單第 7.1 節所列之賦形劑過敏者。已知患有 2 級或 3 級房室阻斷 (second-or third-degree AV block)。【警語和注意事項】頭暈：Lacosamide 治療會伴隨頭暈，可能會增加意外傷害或跌倒的發生。心臟節律和傳導：在臨床研究中觀察到 Lacosamide 具劑量相關性的延長 PR 間期。Lacosamide 對潛在心律不整前期如已知有傳導或嚴重心臟疾病 (例如有心肌缺血/梗塞、心臟衰竭、結構性心臟疾病或心臟鈉離子通道疾病) 的病人或者是正接受會影響心臟傳導的藥物 (如抗心律不整或鈉離子阻斷劑) 治療的病人與老年病人應謹慎使用。在這些病人，投予超過 Lacosamide 400 毫克/天之前，及 Lacosamide 劑量調整達到穩定狀態後，建議考慮 ECG 檢查。【副作用】最常見 (≥10%)使用 Lacosamide 治療的不良反應為頭暈、頭痛、噁心、複視。強度通常為輕度至中度。有些是劑量相關，可以透過減少劑量緩解。中樞神經系統和胃腸道不良反應的發生率及嚴重程度通常隨著時間下降。在所有的對照研究中，由於不良反應造成的停藥率，於服用 Lacosamide 病人為 12.2%，於服用安慰劑病人為 1.6%。因不良反應所導致停止 Lacosamide 治療最常見的原因是頭暈。非常常見 (≥ 1/10) 的不良反應：神經系統疾病：眩暈、頭痛。眼睛視力異常：複視。胃腸道疾病：噁心。【使用指引】膜衣錠：歐盟，無特殊需求。輸液溶液：歐盟：藥用產品為單次使用，未使用的輸液應丟棄。有顆粒物或變色產品，不可使用。Lacosamide 輸液與以下稀釋劑混合，存放在玻璃或 PVC 袋中，溫度最高可達 25°C，確認至少有 24 小時物理相容性和化學安定性。稀釋劑：Sodium chloride 9 毫克/毫升 (0.9%) 注射液。Glucose 50 毫克/毫升 (5%) 注射液。乳酸林格液注射液。

【仿單版本日期】
維帕特 10 毫克 / 毫升輸液溶液 Lacosamide 2021 年 9 月，CCDS V3。
維帕特 50 / 100 / 150 / 200 毫克膜衣錠 Lacosamide 2021 年 7 月，CCDS V3。
本藥須由醫師處方，處方使用前請參閱仿單說明

北市衛藥廣字第 110080092 號

掃描 QR code
取得數位版本

台灣優時比貿易有限公司
UCB Pharmaceuticals (Taiwan) Ltd.
台北市松山區敦化北路88號12樓之2
(02)8979-6177

TWHK-P-VI-EPOS-2200027 EXP.202306

Neuroimmune Dysfunction and Neurodegeneration

Eric JinshengHuang(黃金生)
Professor and Vice Chair of Research, Department of Pathology, University of California, San Francisco (UCSF)

Ph.D.Weill Cornell Graduate School of Medical Sciences
M.D. National Taiwan University

Abstract

Neuroimmune dysfunction is a cardinal feature of neurodegenerative diseases. But how immune dysregulation in the brain contributes to neurodegeneration remains unclear. My research focuses on dominant mutations in the human Progranulin (GRN) gene – a leading cause of frontotemporal dementia (FTD). Patients with GRN mutations have much lower progranulin (PGRN) protein levels in the cerebrospinal fluid (CSF) and serum, suggesting that haploinsufficiency in PGRN could be a major cause of disease. To model the impacts of PGRN deficiency, we show that mice with a complete loss of PGRN (Grn-/-) and those that carry humanized GRNR493X mutation exhibit age-dependent microgliosis that preferentially affects the thalamocortical circuit, where it promotes excessive synaptic pruning, neuronal degeneration, and TDP-43 proteinopathy in the thalamocortical circuits. My lecture will discuss our recent strategies to further uncover how PGRN deficiency contributes to neurodegeneration. Our approaches include blocking both complement pathways and proinflammatory cytokines to mitigate neuroinflammation caused by PGRN deficiency. In addition, we use proteomic and lipidomic approaches to uncover the essential role of Progranulin in intracellular vesicle trafficking and how these defects impede lysosome-mediated lipid degradation and secretion, leading to lipid-mediated toxicity during the late phase of neurodegeneration in the Grn-/- mouse model. Finally, to determine the contributions of the glial pathology to human disease, we perform single cell transcriptomic analyses in the thalamocortical circuits in Grn-/- mice and in FTD patients with GRN mutations. This approach provides a comprehensive understanding of the impacts of glial pathology to neurodegeneration in mice and human.

Selected recent publications:

1. Martens LH, Zhang J, et al. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J Clin Invest. 2012 Nov 1;122(11):3955-9.
2. Lui H, Zhang J, et al. Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. Cell. 2016 May 5;165(4):921-35.
3. Kao AW, McKay A, Singh PP, Brunet A, Huang EJ. Progranulin, lysosomal regulation and neurodegenerative disease. Nature Rev Neurosci. 2017 Jun;18(6):325-333.
4. Nguyen AD, Nguyen TA, Zhang J, et al.. Murine knockin model for progranulin-deficient frontotemporal dementia with nonsense-mediated mRNA decay. Proc Natl Acad Sci U S A. 2018 Mar 20;115(12):E2849-E2858.
5. Zhang J, Velmeshev D, Hashimoto K, Huang HY, et al. Neurotoxic microglia promote TDP-43 proteinopathy in progranulin deficiency. Nature. 2020 Dec;588(7838):459-465.

跨領域神經科學國際研討會

What are brain circuit therapeutics and how do we map and modulate them with Deep TMS

Shan H. Siddiqi, MD
Washington University School of Medicine in St. Louis
Psychiatry Department, Brigham and Women's Hospital
Instructor in Psychiatry, Harvard Medical School
Director, Psychiatric Neuromodulation ResearchCenter for Brain Circuit Therapeutics

Harvard Medical School

Abstract

Topics:

Overview and history of brain circuit mapping and modulation.

Finding the right TMS target.

Common brain circuit modulation with TMS, DBS, and Brain Lesions.

What's on the horizon?

Selected recent publications:

1.Siddiqi, S. H., Schaper, F. L., Horn, A., Hsu, J., Padmanabhan, J. L., Brodtmann, A., & Fox, M. D. (2021). Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. Nature human behaviour, 5(12), 1707-1716.

2.Siddiqi, S. H., Weigand, A., Pascual-Leone, A., & Fox, M. D. (2021). Identification of personalized transcranial magnetic stimulation targets based on subgenual cingulate connectivity: an independent replication. Biological psychiatry, 90(10), e55-e56.

3. Cash, R. F., Weigand, A., Zalesky, A., Siddiqi, S. H., Downar, J., Fitzgerald, P. B., & Fox, M. D. (2021). Using brain imaging to improve spatial targeting of transcranial magnetic stimulation for depression. Biological psychiatry, 90(10), 689-700.

4.Siddiqi, S., Taylor, S., Cooke, D., George, M., Pascual-Leone, A., & Fox, M. (2019). Distinct symptom-specific treatment targets for antidepressant neuromodulation. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 12(2), 537.

5. Padmanabhan, J. L., Cooke, D., Joutsa, J., Siddiqi, S. H., Ferguson, M., Darby, R. R., & Fox, M. D. (2019). A human depression circuit derived from focal brain lesions. Biological psychiatry, 86(10), 749-758.

Plenary session speech

Peripheral sodium channels and human pain – recent progress in analgesic therapies.

John N Wood and The Molecular Nociception Group

John N WoodPhD FRS
Professor of Molecular Neurobiology
Molecular Nociception group
Wolfson Institute for Biomedical Research

Abstract

Human genetics have provided us with useful insights into novel validated analgesic drug targets, but the harvest has been poor. SCN9A encoding voltage-gated sodium channel Nav1.7 is required for pain in mice and humans, but small molecule antagonists have not proved useful. We have found that this is due to a key role in neurotransmitter release for this channel within the spinal cord. Opioid signalling within sensory neurons is massively enhanced in the absence of Nav1.7 and this blocks nociceptive transmission. Gene therapy targeting Nav1.7 in the periphery thus has many attractions over centrally acting antagonists that are likely to have side effects, given the broad expression of Nav1.7 with the central nervous system and its known role in the hypothalamus (PMID: 27315482).

Nav1.8 is another appealing analgesic target, but has been linked to Brugada syndrome with sudden death caused by cardiac dysfunction. Recent studies (PMID: 33910361) have now shown that a C-terminal fragment of Nav1.8 only produced in the heart potentiates cardiac sodium channel Nav1.5 function. This information allows cardiac side effects to be avoided with either carefully designed small molecules or gene therapy. A quarter of a century after the cloning of Nav1.8, antagonists have proved to be excellent analgesics in Phase 2 trials of acute pain, providing more relief than opioids.

Basic mechanistic studies highlightthe importance of basic science in translational advances.

Acknowledgements
We thank past and present group members for their insights and Wellcome, AZ, Versus Arthritis, UKRI and the EU for their support.

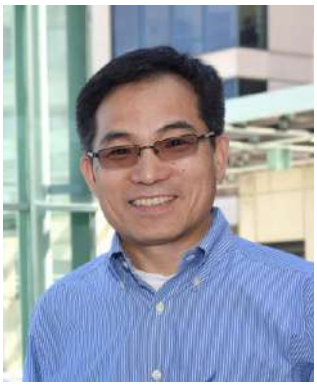
Selected recent publications:

1. Donald Iain MacDonald, Shafaq Sikandar, Jan Weiss, Martina Pyrski, Ana P. Luiz, Queensta Millet, Edward C. Emery, Flavia Mancini Gian D. Iannetti, Sascha R.A. Alles, Manuel Arcangeletti, Jing Zhao, James J Cox, Robert M. Brownstone, Frank Zufall, and John N. Wood The mechanism of analgesia in NaV1.7 null mutants Neuron. 2021 May 5;109(9):1497-151
2. Alles SRA, Nascimento F, Luján R, Luiz AP, Millet Q, Bangash MA, Santana-Varela S, Zhou X, Cox JJ, Okorokov AL, Beato M, Zhao J, Wood JN.Sensory neuron-derived NaV1.7 contributes to dorsal horn neuron excitability. Sci Adv. 2020 Feb 19;6(8): PMID: 32128393
3. Donald Iain MacDonald, Ana P. Luiz, Queensta Millet, Edward C. Emery and John N. Wood Silent cold-sensing neurons drive cold allodynia in neuropathic pain states Brain 2021 Jul 28;144(6):1711-1726.
4. Luiz AP, MacDonald DI, Santana-Varela S, Millet Q, Sikandar S, Wood JN, Emery EC. Cold sensing by Nav1.8-positive and Nav1.8-negative sensory neurons. Proc Natl Acad Sci U S A. 2019 Feb 26;116(9):3811-3816
5. Raouf R, Lolignier S, Sexton JE, Millet Q, Santana-Varela S, Biller A, Fuller AM, Pereira V, Choudhary JS, Collins MO, Moss SE, Lewis R, Tordo J, Henckaerts E, Linden M, Wood JN. Inhibition of somatosensory mechanotransduction by annexin A6. Sci Signal. 2018 Jun 19;11(535).

跨領域神經科學國際研討會

Neural regeneration through cell fate reprogramming in vivo

Chun-Li Zhang(張春立)
Professor
Department of Molecular Biology
Center for Regenerative Science and Medicine
UT Southwestern Medical Center
Dallas,Texas, USA



Ph.D., UT Southwestern Medical Center

Abstract

Neural injury or neurodegeneration frequently leads to irreversible loss of neurons; however, the adult mammalian central nervous system (CNS) has largely lost the ability to produce new neurons. A key question in the regeneration field is how to generatenew neurons for functional reconstruction in the adult CNS. Our lab has taken an in vivo reprogramming approach, which is to engineer the fate of resident glial cells to let them become neurogenic. In this talk, I will focus on two types of glial cells, astrocytes and NG2 glia. Our results show that resident astrocytes or NG2 glia can be in vivo reprogrammed to produce new neurons in the adult mouse brain or spinal cord. Importantly, these glia-generated new neurons can become mature, make synaptic connections, and may contribute to functional recovery in a mouse model of spinal cord injury. Further development in this reprogramming approach may lead to a regeneration-based therapeutic strategy for many of the neurological diseases.

Selected recent publications:

1. Zhang Y, Li B, Cananzi S, Han C, Wang W, Zou Y, Fu Y, Hon G, Zhang CL. A single factor elicits multilineage reprogramming of astrocytes in the adult mouse striatum. Proc Natl Acad Sci U S A. 2022 Mar 15;119(11):e2107339119. doi: 10.1073/pnas.2107339119. PMID: 35254903.
2. Wang LL, Serrano C, Zhong X, Ma S, Zou Y, Zhang CL. Revisiting astrocyte to neuron conversion with lineage tracing in vivo. Cell. 2021 Oct 14;184(21):5465-5481.e16. doi: 10.1016/j.cell.2021.09.005. PMID: 34582787.
3. Yu Y, Shen T, Zhong X, Wang LL, Tai W, Zou Y, Qin J, Zhang Z, Zhang CL. NEK6 is an injury-responsive kinase cooperating with STAT3 in regulation of reactive astrogliosis. Glia. 2021 Oct 13. doi: 10.1002/glia.24104. PMID: 34643969
4. Tai W, Wu W, Wang LL, Ni H, Chen C, Yang J, Zang T, Zou Y, Xu XM, Zhang CL. In vivo reprogramming of NG2 glia enables adult neurogenesis and functional recovery following spinal cord injury. Cell Stem Cell. 2021 May 6;28(5):923-937.e4. doi: 10.1016/j.stem.2021.02.009. PMID: 33675690.
5. Ding B, Tang Y, Ma S, Akter M, Liu ML, Zang T, Zhang CL. Disease modeling with human neurons reveals LMNB1 dysregulation underlying DYT1 dystonia. J Neurosci. 2021 Jan 15:JN-RM-2507-20. doi: 10.1523/JNEUROSCI.2507-20.2020. PMID: 33468570

Neurofilament light chain: emerging evidence in neuropsychiatric disorders

Yu-Li Liu(劉玉麗)
Investigator, Center for Neuropsychiatric Research, National Health Research Institutes, Miaoli County, TAIWAN

Ph.D., East Tennessee State University

Abstract

Neurofilament light chain (NFL) is a protein located mainly in the axon region of myelinated brain neuron. This small protein has been studied intensively for its characteristic of sending brain neuronal damage messages toward the peripheral blood. It makes diagnoses of brain injuries possible through taking peripheral blood rather than cerebral spinal fluid. Using single molecule array method for NFL concentration measurement as an in vitro diagnostic device for neurodegenerative diseases, such as dementia, amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease, has already been approved in Europe. Recent studies have also shown that peripheral blood NFL level may indicate the severity of psychiatric diseases, including schizophrenia, major depressive disorder, and substance use. In this report session, the researchers will report the discovery of NFL in psychiatric diseases and its role in the pathological symptom. I will summarize recent literature reports on NFL that reveal its potential applications for both basic and clinical research.

Selected recent publications:

1. Huang, MC, Chung, RH, Lin, PH, Kuo, HW, Liu, TH, Chen, YY, Chen, ACH, **Liu, YL**. (correspondence) (2022) Increase in plasma CCL11 (Eotaxin-1) in patients with alcohol dependence and changes during detoxification. Brain Behavior and Immunity. 99:83-90.

2. Chen, MH, **Liu, YL**, Kuo, HW, Tsai, SJ, Hsu, JW, Huang, KL, Tu, PC, Bai, YM. (2022) Neurofilament light chain is a novel biomarker for major depression and related executive dysfunction. Int J Neuropsychopharmacol.25(2):99-105.

3. Chang, HM, Chen, PY, Fang, CP, Liu, TH, Wu, CT, Hsu, YC, Kuo, HW, **Liu, YL,** (correspondence), Huang, MC. (2021/7) Increased nectin-4 levels in chronic ketamine abusers and the relationship with lower urinary tract symptoms. Environ ToxicolPharmacol. 87:103714.

4. **Liu, YL**, Bavato, F., Chung, AN, Liu, TH, Chen, YL, Huang, MC, Quednow, B. B. (2021) Neurofilament light chain as novel blood biomarker of disturbed neuroaxonal integrity in patients with ketamine dependence. World J Biol Psychiatry. 27:1-9.

5. Fang, CP, Liu, TH, Chung, RH, Tsou, HH, Kuo, HW, Wang, SC, Liu, CC, Liu, SC, Chen, ACH, **Liu, YL**. (correspondence) (2020) Genetic variants in NECTIN4 encoding an adhesion molecule are associated with continued opioid use. PLoS One. 15(6), e0234549.

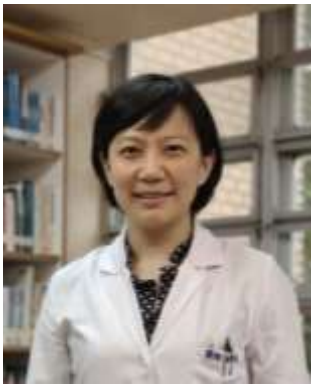
Exploring the role of neurofilament light chain in addiction

Ming-Chyi Huang(黃名琪)

Chief and Staff Psychiatrist, Department of Addiction Sciences, Taipei City Psychiatric Center, Taipei City Hospital, Taipei, TAIWAN

Adjunct Professor, Department of Psychiatry, Taipei Medical University, Taipei, Taiwan

M.D., Ph.D.,



Abstract

Substance use disorders have been associated with persistent neurocognitive impairment and structural brain abnormalities. Because brain imaging facilities are not universally available for healthcare systems, it may be feasible to look for a reliable and adequate substitute indicator for clinicians to evaluate and monitor the neurotoxicity severity. We examined the level of NFL in patients with ketamine dependence (KD) and alcohol dependence (AD) the explored its relationship with clinical characteristics. We found significantly increased NFL levels following chronic and heavy ketamine or alcohol use. In patients with KD, we found pronounced increase of NFL levels in the those comorbid with MDD. The observation warrants further investigation of a potential neuroaxonal vulnerability of depressed patients to prolonged ketamine exposure. In addition, NFL level might be a novel indicator for AD and reflect clinical severity in craving and psychological symptoms (anxiety and depression). Also, the aldehyde dehydrogenase gene polymorphism rs671 seemed to influence the level of NFL. These observations collectively indicate NFL levels may serve as a potential indicator for neurotoxicity related to addictive disorders.

Selected recent publications:

1. **Huang, MC,** Chung, RH, Lin, PH, Kuo, HW, Liu, TH, Chen, YY, Chen, ACH, Liu, YL. (correspondence) (2022) Increase in plasma CCL11 (Eotaxin-1) in patients with alcohol dependence and changes during detoxification. *Brain Behavior and Immunity*.Jan;99:83-90.

2. Liu, YL, Bavato, F., Chung, AN, Liu, TH, Chen, YL, **Huang, MC*,**Quednow, B. B. (2021) Neurofilament light chain as novel blood biomarker of disturbed neuroaxonal integrity in patients with ketamine dependence. *World J Biol Psychiatry*. 27:1-9.

3. **Huang MC,** Chen CH, Chen LY, Chang HM, Chen CK, Lin SK, Xu K. (2020) Chronic Ketamine Abuse Is Associated with Orexin-A Reduction and ACTH Elevation. *Psychopharmacology*, Jan, 237 (1), 45-5

4. Cheng WJ, Chen CH, Chen CK, **Huang MC***, Pietrzak RH, Krystal JH, Xu K. (2018) Similar psychotic and cognitive profile between ketamine dependence with persistent psychosis and schizophrenia. *Schizophr Res*, 2018 Sep;199:313-318

5. Wang LJ, Chen CK, Lin SK, Chen YC, Xu K, **Huang MC***. (2018) Cognitive profiles of ketamine-dependent patients in comparisons to healthy controls and methamphetamine abusers. *Psychopharmacology*, Jul; 235(7):2113-21.

Neurofilament Light Chain Is a Novel Biomarker for Major Depression and Related Executive Dysfunction

Mu-Hong Chen
Attending Psychiatrist, Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

Department of Psychiatry, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

M.D., Ph.D., National Yang Ming Chiao Tung University.

Abstract

Background: Evidence suggests that major depressive disorder is related to neuroaxonal injury and that neurofilament light chain (NfL) is a biomarker of neuroaxonal injury. In addition, proinflammatory cytokines have been reported to be associated with major depression and neuroaxonal injury. **Methods:** Forty patients with major depression and 40 age- and sex-matched healthy control subjects were enrolled for the measurement of NfL and proinflammatory cytokines and assessment of executive function. General linear models were used to examine the association between NfL levels, proinflammatory cytokine levels, and executive function. **Results:** Patients with major depressive disorder exhibited significantly higher NfL levels ($p = 0.007$) than the control subjects. NfL levels were positively related to log-transformed levels of tumor necrosis factor (TNF)-α ($p = 0.004$). Higher levels of NfL ($p = 0.002$) and TNF-α ($p = 0.013$) were associated with greater deficits in executive function. **Discussion:** NfL was a novel biomarker for major depressive disorder and related executive dysfunction. Further studies are necessary to elucidate the role of NfL in the pathophysiology of major depression and related cognitive impairment.

Selected recent publications:

1. **Chen MH**, Chang WC, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, Huang WS, Su TP. Functional dysconnectivity of frontal cortex to striatum predicts ketamine infusion response in treatment-resistant depression. Int J Neuropsychopharmacol. 2020 Jul 30:pyaa056.

2. **Chen MH**, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, Hong CJ, Tu PC, Cheng CM, Su TP. Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression. J Clin Psychiatry. 2020 Nov 10;81(6):20m13232.

3. **Chen MH**, Kao CF, Tsai SJ, Li CT, Lin WC, Hong CJ, Bai YM, Tu PC, Su TP. Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. Genomics. 2020 Dec 25:S0888-7543(20)32077-2.

4. **Chen MH**, Cheng CM, Gueorguieva R, Lin WC, Li CT, Hong CJ, Tu PC, Bai YM, Tsai SJ, Krystal JH, Su TP. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. Neuropsychopharmacology. 2019 Aug 17.

5. **Chen MH,** Liu YL, Kuo HW, Tsai SJ, Hsu JW, Huang KL, Tu PC, Bai YM. Neurofilament Light Chain Is a Novel Biomarker for Major Depression and Related Executive Dysfunction. Int J Neuropsychopharmacol. 2022 Feb 11;25(2):99-105.

The Interplay of Stress, Inflammation, and Nutrition in Depression

Kuan-Pin Su(蘇冠賓)

Professor and Deputy Superintendent, An-Nan Hospital, China Medical University, Tainan, Taiwan

PI, Mind-Body Interface (MBI-Lab), Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

M.D., Kaohsiung Medical College, Kaohsiung, Taiwan

Ph.D. Institute of Psychiatry, King's College London, UK

Abstract

The increasing global burden calls for the development of novel approaches to tackle unmet needs in prevention and treatment of depression underlying biological, psychological and social dysregulations. Depressed patients with chronic low-grade inflammation might be classified as a subgroup of major depressive disorder (MDD); therefore, looking for antidepressant therapies from anti-inflammatory pathways could improve treatment effectiveness for this subgroup of patients. Omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) are anti-inflammatory both in peripheral organs and central nervous systems and have clinically applied in the treatment and prevention of depression, cardiovascular diseases, dyslipidaemia, diabetes and arthritis. Anthropological studies suggest that human beings evolved to a modern diet with less than one-tenth of omega-3 to omega-6 PUFAs intake ratio, which leads to a constitutional bias toward chronic systemic inflammatory status to explain dramatically increasing of depression and chronic medical illnesses in modern world. The presentation is to provide our recent clinical and pre-clinical studies and an overview about the role of inflammation in "mind-body" comorbidity and present anti-inflammatory mechanisms by which n-3 PUFAs may orchestrate the molecular and cellular functions and facilitate the therapeutic pathways in chronic medical illnesses and depression.

Selected recent publications:

1. Yang CP, Chang CM, Yang CC, Pariante CM,Su KP*. Long COVID and long chain fatty acids (LCFAs): Psychoneuroimmunity implication of omega-3 LCFAs in delayed consequences of COVID-19. **Brain Behavior and Immunity** 2022 Apr 4;103:19-27.

2. Cheng SW, Li JX, Chien YC, Chang JP, Shityakov S, Huang SY, Galecki P, Su KP*. Genetic Variations of Ionotropic Glutamate Receptor Pathways on Interferon-α-induced Depression in Patients with Hepatitis C Viral Infection. **Brain Behavior and Immunity** 2021 Mar; 93:16-22.

3. Yang B, Lin L, Bazinet RP, Chien YC, Chang JPC, Satyanarayanan SK, Su HX, Su KP*. Clinical efficacy and biological regulations of omega-3 PUFA-derived endocannabinoids in major depressive disorder. **Psychotherapy and Psychosomatics** 2019;88(4):215-224.

4. Bosini A, Nicolaou A, Camacho-Munoz MD, Kendall A, Di Benedetto MG, Giacobbe J, **Su KP***. Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. **Molecular psychiatry** 2020Nov;26(11):6773-6788.

5. Lin YW, Wu AIC, Su HX, **Su KP***. Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: The common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids. **Brain Behavior and Immunity** 2020 Oct; 89: 604-614.

Loss of Functionof Shaker type Potassium Channels caused Epileptic Encephalopathy

Meng-Han Tsai(蔡孟翰)
Professor, Department of Neurology

Director, Division of Epilepsy and Brain Function

Director, Genomics and Proteomics Core Laboratory

Deputy Director, Department of Medical Research

M.D. Ph.D.Kaohsiung Chang Gung Memorial Hospital,

Chang Gung University, Taiwan

Abstract

Potassium (K+) channels are essential for the regulation of neuronal membrane potential and electrophysiological excitability. The Shaker-type potassium channels (Kv1) family contains 8 members including Kv1.1-Kv1.8. Six were prominently expressed in the CNS (Kv1.1-6). Hitherto, two of the Kv1 genes(*KCNA1* and *KCNA2*)have been reported to cause human epilepsies. In this study, we identified three patients with de novo missense pathogenic variants in three additional Shaker-type channel genes (*KCNA3*, *KCNA4*, and *KCNA6*). All variants were located in important functional domains such as the selectivity filter or the S6 hinge responsible for gating. Clinically, they presented as early-onset epileptic encephalopathy which subsided after the infantile period. Electrophysiological studies demonstrated loss of function effects in two of the variants, which could impair repolarization of the action potentials causing hyperexcitable neuronal activities. The disease course coincided with the age-related expression of these genes. Our findings expand the list of potassium channels genes, especially the Shaker-type, that cause human epilepsies.

Selected recent publications:

1. Pathogenic Variants in CEP85L Cause Sporadic and Familial Posterior Predominant Lissencephaly. M.-H. H. Tsai, A. M. Muir, W.-J. J. Wang, Y.-N. N. Kang, K.-C. C. Yang, N.-H. H. Chao, et al. *Neuron* 2020 Vol. 106 Issue 2 Pages 237--245.e8

2. Impairment in dynein-mediated nuclear translocation by BICD2 C-terminal truncation leads to neuronal migration defect and human brain malformation. M. H. Tsai, H. Y. Cheng, F. S. Nian, C. Liu, N. H. Chao, K. L. Chiang, et al. *Acta neuropathologica communications* 2020 Vol. 8 Issue 1 Pages 106

3. PRRT2 missense mutations cluster near C-terminus and frequently lead to protein mislocalization. M. H. Tsai, F. S. Nian, M. H. Hsu, W. S. Liu, Y. T. Liu, C. Liu, et al. *Epilepsia*2019 Vol. 60 Issue 5 Pages 807—817.

4. Etiology of hippocampal sclerosis: evidence for a predisposing familial morphologic anomaly. M. H. Tsai, H. R. Pardoe, Y. Perchyonok, G. J. Fitt, I. E. Scheffer, G. D. Jackson, et al. *Neurology* 2013 Vol. 81 Issue 2 Pages 144-9

5. Clinical genetic study of the epilepsy-aphasia spectrum. M. H. Tsai, D. F. Vears, S. J. Turner, R. L. Smith, S. F. Berkovic, L. G. Sadleir, et al. *Epilepsia* 2013 Vol. 54 Issue 2 Pages 280-7.

EpileptogenesisIn Cerebral Cavernous Malformations: Genomic Landscape, Biomarkers And Neuroplasticity

Yo-Tsen Liu(劉祐岑)MD, PhD
台北榮民總醫院神經醫學中心神經內科癲癇科主治醫師

Division of Epilepsy, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan.

國立陽明交通大學醫學系兼任副教授

School of Medicine, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan.

Abstract

Cerebral cavernous malformation (CCM), characterized by enlarged, blood-filled endothelial compartments within the venous-capillary vascular bed, is the most frequent epileptic substrate of cerebral vascular malformations.Epilepsy is the leading clinical manifestation of CCM, observed in 50% of patients.However, the clinical behavior of a CCM lesion could be highly variable and it is quite challenging to predict the epilepsy risk and outcome of different lesions.The uncertainty thus leads to the consensus of ideal treatment for CCMremains inconclusive.Familial CCM and some sporadic cases caused by loss-of-function mutations in one of the three genes, *CCM1*, *CCM2* and *CCM3*, with the hallmark of multiple lesions, have significant higher risk of CCM-related epilepsy (CRE).Recently, the substantial contribution of somatic mutations to the epileptogenetic mechanism of CCM has been recognized.Understanding the genomic landscape is essential to decipher the mechanisms of the development and progression of CRE. It is also important to search biomarkers from the transcriptome, proteome and connectome of CCM which can correlate with the patient's seizureoutcome and other clinical relevant phenotypes. Further, the key molecules shaping the CCM microenvironments and the whole picture of the crosstalk between abnormal vasculogenesis and altered neuronal plasticity could be unraveled. The goal is to improve precision treatment of CCM.

Selected recent publications:

1. Clinical characteristics and long-term outcome of cerebral cavernous malformations-related epilepsy. Shih YC, Chou CC, Peng SJ, Yu HY, Hsu SPC, Lin CF, Lee CC, Yang HC, Chen YC, Kwan SY, Chen C, Wang SJ, Lin CJ, Lirng JF, Shih YH, Yen1 DJ, Liu YT*. Epilepsia, April 19, 2022 accepted.

2. Novel Lissencephaly-Associated DCX Variants in the C-terminal DCX Domain Affect Microtubule Binding and Dynamics. Lin JR#, Cheng JF#, **YT Liu**, Hsu TR, Lin KM, Chen C, Lin CL, Tsai MH, Tsai JW*, Epilepsia, Feb 22, 2022 accepted.

3. Cellular secretion and cytotoxicity of transthyretin mutant proteins underlie late onset amyloidosis and neurodegeneration. R B Ibrahim, SY Yeh, KP Lin, F Ricardo, TY Yu, CC Chan, JW Tsai*#, **YT Liu***#. Cell Mol Life Sci. 2020 Apr;77(7):1421-1434.

4. Biophysical characterization and pharmacological modulation of Transthyretin Ala97Ser mutant. **YT Liu**, YJ Yen, F Ricardo, Y Chang, PH Wu, SJ Huang, KP Lin*, TY Yu*. Ann Clin Transl Neurol. 2019 Oct;6(10):1961-1970. doi: 10.1002/acn3.50887. Epub 2019 Sep 10.

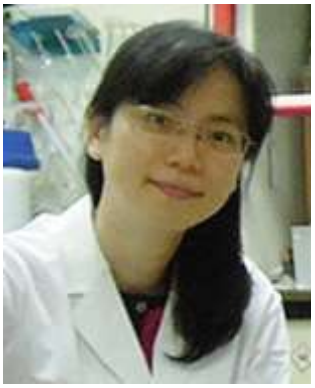
5. PRRT2 mutations lead to neuronal dysfunction and neurodevelopmental defects. **Liu YT**, Nian FS, et al, Soong BW*, Tsai JW*. Oncotarget. 2016 Jun 28;7(26):39184-39196.

Deciphering age-dependent neuronal hyperexcitability caused by CDKL5 deficiency

Wenlin Liao (廖文霖)

Professor, Institute of Neuroscience, National Cheng-Chi University

Ph.D. National Yang-Ming University



Abstract

Cyclin-dependent kinase-like 5 (CDKL5) is a serine-threonine kinase, localized primarily in the nucleus to control gene expression and neuronal development by regulating protein phosphorylation. Mutations in *CDKL5* gene cause CDKL5 deficiency disorder (CDD), a developmental and epileptic encephalopathy characterized by severe early-onset seizures, developmental delay and intellectual disability. Despite well-defined genetic cause, children with CDD are resistant to most of the anti-epileptic drugs and the pathogenic mechanisms for early-onset seizures in CDD remain unclear.

Through longitudinal EEG recordings coupled with videotaping in preweaning mouse pups, we found that *Cdkl5* null pups displayed increased EEG discharges at postnatal day 12 (P12) compared to their wild-type (WT) littermate controls. The increased burst discharges in mutants returned to the comparable pattern of WT mice after P14, suggesting that CDKL5 deficiency may increase neuronal excitability in an age-dependent manner. Through electrophysiological study and whole-genome RNA sequencing, we further revealed that CDKL5 ablation increases firing rate of neurons and down-regulates genes for tangential migration in dorsal hippocampus at P7. By contrast, the transcript levels of marker genes for GABAergic interneurons, such as parvalbumin and somatostatin, were up-regulated in cortical tissue of mutants at the age of P17 and 3-month, consistent to the increased number of parvalbumin-positive neurons found in the primary motor cortex of adult *Cdkl5* null mice. Our results demonstrate that CDKL5 is required to preserve gene expression essential for interneuronal migration during early postnatal age. Loss of CDKL5 may affect tangential migration of interneurons that leads to hyperexcitability soon after birth. Our discoveries may provide a basis to develop therapeutics for early-onset seizures in developmental disorders, including CDD.

Selected recent publications:

1. Su SH, Kao FC, Huang YB, **Liao W** (2015) MeCP2 in the rostral striatum maintains local dopamine content critical for psychomotor control. *The Journal of Neuroscience*, 35:6209-6220.

2. Kao FC, Su SH, Carlson GC, **Liao W** (2015) MeCP2-mediated alterations of striatal features accompany psychomotor deficits in a mouse model of Rett syndrome. *Brain Structure and Function*, 220: 419-434

3. Jhang CL, Huang TN, Hsueh YP and **Liao W** (2017) Mice lacking cyclin-dependent kinase-like 5 manifest autistic and ADHD-like behavior. *Human Molecular Genetics*, 26(20): 3922-34.

4. **Liao W** (2019) Psychomotor Dysfunction in Rett Syndrome: Insights into the Neurochemical and Circuit Roots. *Developmental Neurobiology*, 79(1): 51-59.

5. Jhang CL, Lee HY, Chen JC and **Liao W** (2020) Dopaminergic loss of cyclin-dependent kinase-like 5 recapitulates methylphenidate-remediable hyperlocomotion in mouse model of CDKL5 deficiency disorder. *Human Molecular Genetics*, 29(14): 2408-19.

Cellular and molecular mechanisms for malformations in cortical development

Jin-Wu Tsai(蔡金吾)

Distinguished Professor, Institute of Brain Science (IBS), College of Medicine, National Yang Ming Chiao Tung University (NYCU), Taiwan

Dean of Research and Development, NYCU, Taiwan

Adjunct Professor, Department of Biological Science & Technology, NYCU, Taiwan

Ph.D., Columbia University

Abstract

Neural developmental disorders are divesting neurological diseases resulting from defects in neural progenitor proliferation, neuronal migration and connections during development. These defects may lead brain malformations, including microcephaly, lissencephaly, double cortex, and focal cortical dysplasia. The patients often suffer from epilepsy, developmental delay, and cognitive impairments. To date, the genetic causes of a number of brain malformations have been identified, such as LIS1, DCX, ARX, TUBA1A, NDE1, KATNB1, and CDK5. Using in utero electroporation to knock down these genes and monitoring cellular and subcellular events with live cell imaging in brain slices, we found that LIS1 together with dynein facilitates centrosomal and nuclear movements during neuronal migration. Using whole exome sequencing (WES) in a cohort of patients with cortical malformation, we further identified variants in novel genes, CEP85L and BICD2, that cause lissencephaly. However, many genetic mutations involved in cortical malformations still remain unidentified. Recently, we developed an in vivo genetic screen paradigm that utilizes in utero electroporation of transposons into mouse embryos to induce insertional mutations in neural stem cells (i.e., radial glial cells; RGCs). We identified 33 potential genes, many of which have been previously implicated in neuronal development and related disorders, including holoprosencephaly, microcephaly and mental retardation. Bioinformatics analysis demonstrated that these candidate genes are highly associated with neuronal development and various neuronal disorders. In this presentation, molecular mechanisms of thesegenes in cortical malformation will be discussed.

Selected recent publications:

1. Lin JR, Cheng JF, Liu YT, …, Tsai JW* (2022) Novel lissencephaly-associated *DCX* variants in the C-terminal DCX domain affect microtubule binding and dynamics, ***Epilepsia***, *in press*.

2. Tsai MH, Muir AM, WangWJ, Kang YN, Yang KC, Chao NH, Wu MF, …, Dobyns WB, BerkovicSF, SchefferIE, Tsai JW*, MeffordHC* (2020) Pathogenic variants in CEP85L cause sporadic and familial posterior predominant lissencephaly. ***Neuron***, 106(2):237-245.

3. Tsai MH, Cheng HY, Nian FS, Liu C, Chao NH, Chiang KL,…,Tsai JW* (2020) Impairment in dynein-mediated nuclear translocation by BICD2 C-terminal truncation leads to neuronal migration defect and human brain malformation. ***Acta NeuropatholCommun***, 8(1):106.

4. Chang CH, ZaniniM, ShirvaniH, Cheng JS, Yu H, Feng CH, Mercier AL, Hung SY, Forget A, …, Spassky N, Tsai JW*, Ayrault O* (2019) Atoh1 controls primary cilia formation to allow for SHH-triggered granule neuron progenitor proliferation. ***DevCell***, 48(2):184-199.e5.

5. Lu IL, …,Tsai JW* (2018) Identification of genes associated with cortical malformation using a transposon-mediated somatic mutagenesis screen in mice. ***Nat Commun***, 9(1):2498.

Application of hUCMSC Exosomes in Neuropathic Pain and Spinal Cord Injury Models

Jen-Kun Cheng(鄭仁坤)
Senior Attending Anesthesiologist,

Mackay Memorial Hospital

Professor/Discipline Director of Anesthesiology,

Mackay Medical College

M.D., National Yang-Ming Medical College

Ph.D., National Taiwan University

Abstract

In the past decades, exosomes derived from mesenchymal stem cells have been used as therapeutics in various fields. Recently, we first demonstrated the antinociceptive effects of human umbilical cord mesenchymal stem cell (hUCMSC) exosomes, given intrathecally, in the L5/6 spinal nerve ligation neuropathic pain model. The therapeutic effects were associated with anti-inflammatory and neurotrophic effects of exosomes. We then further tested locally applied exosomes, embedded in alginate scaffold, in the pain model and found similar analgesic and neurotrophic effects. To further extent the application of exosomes, we examined the use of exosomes, embedded in gelfoam, in T9 spinal cord hemisection injury model. Our recent work demonstrated the nerve regenerative and motor function-improving potential of hUCMSC exosomes in the spinal cord injury model.

Selected recent publications:

1. Poongodi R, Chen YL, Yang TH, Huang YH, Yang KD, Lin HC, **Cheng JK** (2021) Bio-Scaffolds as Cell or Exosome Carriers for Nerve Injury Repair. *International Journal of Molecular Sciences* 22:13347.
2. Hsu JM, Shiue SJ, Yang KD, Shiue HS, Hung YW, Pannuru P, Poongodi R, Lin HY,**Cheng, J. K** (2020) Locally applied stem cell exosome-scaffold attenuates nerve injury-induced pain in rats. *Journal of Pain Research* 13:3257-68.
3. Shiue SJ, Rau RH, Shiue HS, Hung YW, Li ZX, Yang KD, **Cheng, JK** (2019) Mesenchymal stem cell exosomes as a cell-free therapy for nerve injury–induced pain in rats. *Pain*, 160: 210-23.
4. Shiue SJ, Peng HY, Lin CR, Wang SW, Rau RH, **Cheng JK** (2017) Continuous intrathecal infusion of cannabinoid receptor agonists attenuates nerve ligation-induced pain in rats. *Regional Anesthesia and Pain Medicine* 42:499-506.
5. Chen YL, Tsaur ML, Wang SW, Wang TY, Hung YC, Lin CS, Chang YF, Wang YC, Shiue SJ**Cheng JK** (2015) Chronic intrathecal infusion of mibefradil, ethosuximide and nickel attenuates nerve ligation-induced pain in rats. *British journal of anaesthesia* 115:105-11.

Nutrition interventionfor neuropathic,muscular and acute pain

Jen-Yin, Chen(陳貞吟)
Professor and Chair

Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan

Ph.D.National Chung Hsing University

Abstract

Vitamin D and vitamin C are essential micronutrients for human health. In cell and animal models, vitamin D has concentration-dependent anti-inflammatory effects through inhibiting the production of nitric oxide. Nitric oxide increases phosphorylated N-methyl-D-aspartate receptors in spinal dorsal horn neurons leading to central sensitization and mechanical allodynia. Vitamin D deficiency induces excessive reactive oxygen species resulting in cold pain,produces a marked dysbiosis and alters nociception via molecular mechanisms involving the endocannabinoid and related mediator signaling system. Clinically, we discovered that patients with neuropathic pain had a high prevalence of hypovitaminosis D which was associated with increased spontaneous cold pain and brush-evoked painbased onthe DN4 questionnaire. Vitamin C exerts antinociception and neuromodulation. Spontaneous pain symptoms include tingling, prickling, pins and needles sensation, as wellas electric shock, bursting, jumping, shooting, stabbing and burning pain. We discovered that the patients' plasma vitamin C concentrations were negatively correlated with spontaneous pain and with tingling, prickling or pins and needles sensation by the LANSS Questionnaire.Intravenous high-dose vitamin C relieved spontaneous pain effectively but not brush-evoked pain in patients with neuropathic pain. We will describe the findings in patients with muscular pain as well.A pneumatic tourniquet involving a previous exsanguination is often used in total knee arthroplasty. The procedures induce muscle ischemia leading to tissue acidosis and aching sensation (soreness,sngception). Sngception depends on the proton-sensing neurons and is a specific somatosensory function that transmits the aching sensation from the peripheral to the central nervous system when the tissue acidosis. High-dose vitamin C pretreatment reduces exercise-induced muscle soreness, oxidative stress and with little loss on muscle function.The benefits of intravenous high-dose vitamin C in patients with total knee arthroplasty will be reported.

Selected recent publications:

1. Hung KC, Wang LK, Lin YT, Yu CH, Chang CY, SunCK, **Chen JY** (2022) Association of preoperative vitamin D deficiency with the risk of postoperative delirium and cognitive dysfunction: A meta-analysis. *Journal of Clinical Anesthesia* 79:110681.
2. **Chen JY**, Lin YT, Wang LK, HungKC, LanKM, Ho CH, ChangCY (2019). Hypovitaminosis D in postherpetic neuralgia-High prevalence and inverse association with pain: A retrospective study. *Nutrients*11:2787.
3. Wang LK, Lin YT, Hung KC, Chang CY, Wu ZF, Hu ML, **Chen, JY** (2020). Plasma Vitamin C Concentrations Were Negatively Associated with Tingling, Prickling or Pins and Needles Sensation in Patients with Postherpetic Neuralgia. *Nutrients* 12:2384.
4. Wang LK, Chuang CC, **Chen, JY** (2018) Relief of acute herpetic pain by intravenous vitamin C: The dosage may make a difference. *Annals of Dermatology* 30:262-63.
5. **Chen JY**, Chu CC, Lin YS, So EC, Shieh JP, Hu ML (2011). Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia. *British journal of nutrition* 106:700-07

New advances in myofascial pain syndrome

Li-Wei Chou(周立偉)

Professor and Director, Departmentof PhysicalTherapy and Graduate Institute of Rehabilitation Science, China Medical University, Taiwan.

Director, Departmentof PhysicalMedicineandRehabilitation, Asia University Hospital, AsiaUniversity,Taiwan.

M.D., Ph.D.China Medical University

Abstract

Myofascial pain syndrome, characterized by the presence of myofascial trigger points (TrPs), is recognized as a common source of musculoskeletal pain. Myofascial TrP is a hyperirritable spot within a taut band of skeletal muscle that is painful on compression, stretch, overload, or contraction of the tissue which usually responds with a referred pain that is perceived distant from the spot.Several needling therapies are proposed for treatment of myofascial pain syndrome. In fact, two different needling applications can be used to inactivate TrP: wet needling (injections) or dry needling.Fu's subcutaneous needing (FSN) is one of the newly invented dry needling methods. The treated target is tightened muscle (the muscle including TrPs). The soft tissue pain diseases might be treated via FSN combined the special techniques (swaying movement and reperfusion approach).

The application of TrP needlingtherapy is able to reduce this excitability by reducing peripheral nociception from the TrP, by reducing dorsal horn neuron activity, and by modulating brainstem areas. However, effects are only seen at short-term and effect sizes are small, pointing to a particular role that TrPs play within the complex chronic pain experience.When providing needling therapy to chronic pain patients, therapists are advised to integrate contemporary pain neurosciences when providing the treatment. This implies applying evidence-based recommendations; therefore, TrP needling therapy can be part of, but should never be, the only treatment plan for individuals with chronic pain. A comprehensive management program should include neuroscience pain education,exercise programs,self-management (including graded activity),stress management (psychological),sleep management,and other individuallytailored aspects of self-management.

Selected recent publications:

1. Huang CH, Lin CY, Sun MF, Fu Z, **Chou LW** (2022) Efficacy of Fu's Subcutaneous Needling on Myofascial Trigger Points for Lateral Epicondylalgia: A Randomized Control Trial. *Evidence-Based Complementary and Alternative Medicine* 2022:5951327.

2. Dommerholt J, Hooks T, Thorp JN, **Chou LW** (2019) A critical overview of the current myofascial pain literature–July 2020. *Journal of Bodywork and Movement Therapies* 24:307-20.

3. **Chou LW,**Hong CZ (2019) Needling Therapy for Myofascial Low Back Pain. *Journal of the Formosan Medical Association* 23:335-45.

4. Hsieh YL, Hong, CZ, Liu SY, **Chou LW**, Yang, CC (2016) Acupuncture at distant myofascial trigger spots enhances endogenous opioids in rabbits: a possible mechanism for managing myofascial pain. *Acupuncture in Medicine* 34:302-09.

5. **Chou LW**, Hsieh YL, Kuan TS, Hong CZ (2014) Needling therapy for myofascial pain: recommended technique with multiple rapid needle insertion. *BioMedicine* 4:13.

Mechanism of prolotherapy and ultrasound in chronic muscle pain

Der-Sheng Han(韓德生)

Medical Director, National Taiwan University Hospital Beihu Branch.

Clinical Associate Professor, Department of Physical Medicine and Rehabilitation, College of Medicine, National Taiwan University.

Director, Taiwan Academy of Physical Medicine and Rehabilitation

Director, Taiwan Osteoporosis Association

Director, Taiwan Society of Neurorehabilitation

Education Committee, ISPRM

PhD.Graduate Institute of Clinical Medicine, National Taiwan University, Taiwan.

Abstract

Prolotherapy is widely used in pain control and tissue repair in pain medicine. The classical mode is injection with hypertonic dextrose in muscle or perimysium. However, the analgesic mechanism is still not known. Here we successfully established dextrose-mediated analgesia in a mouse model of fibromyalgia. The analgesic effects of dextrose injections were evaluated in a mouse model of fibromyalgia, in which bilateral chronic mechanical hyperalgesia was induced by unilateral intramuscular acid injection. The injectant (dextrose), dose (≥ 5%) and volume (>10 uL) but not osmolarity were essential for the prolotherapy. Further studies showed that activation of acid-sensingion channel 1a (ASIC1a), neural activation, and the release of substance P from muscle afferents were required in the dextrose-induced analgesia. Both pharmacological blockade and genetic deletion of ASIC1a or substance P as well as lidocaine abolished the dextrose-induced analgesia in mice with chronic hyperalgesia. Moreover, intramuscular dextrose injection induced phosphorylated extracellular signal-regulated kinase (pERK) expression in dorsal root ganglia neurons expressing substance P; the pERK expression was inhibited by the ASIC1a antagonist PcTx1. The optimal settings for prolotherapy in fibromyalgia-like pain are dextrose- and volume-dependent, and the peripheral analgesia involves ASIC1a and substance P signaling in muscle afferents. We suggest a possible mechanism of action of dextrose prolotherapy in noninflammatory muscle pain such as fibromyalgia and provides insights for treating other types of chronic pain.

Selected recent publications:

1. **Han DS**, Lee CH, Shieh YD, Chang CT, Li MH, Chu YC, Wang JL, Chang KV, Lin SH, Chen CC (2022) A role for substance P and acid-sensing ion channel 1a in prolotherapy with dextrose-mediated analgesia in a mouse model of fibromyalgia. *Pain*163:E622-33.

2. Hsu WH[*], **Han DS**[*], Ku WC[*], Chao YM, Chen CC[#], Lin YL[#](2022) Metabolomic and proteomic characterization of sng and pain phenotypes in fibromyalgia.European Journal of Pain 26:445-62. ([*]equal contribution, [#]correspondence)

3. Chang KV, Hung CH, Sun WZ, Wu WT, Lai CL, **Han DS[*]**, ChenCC[*] (2020) Evaluating soreness symptoms of fibromyalgia: Establishment and validation of the Revised Fibromyalgia Impact Questionnaire with Integration of Soreness Assessment. *Journal of the Formosan Medical Association* 119:1211-18.([*] co-correspondence)

4. **Han DS**, Lee CH, Shieh YD, ChenCC (2019) Involvement of substance P in the analgesic effect of low-level laser therapy in a mouse model of chronic widespread muscle pain. *Pain Medicine*20:1963-70.

5. Lin JH[*], Hung CH[*], **Han DS**[*], Chen ST, Lee CH, Sun WZ, Chen CC (2018) Sensing acidosis: nociception or sngception? *Journal of Biomedical Science*25:85. ([*] equal contribution)

Inflammation and Nutrition in Child Mental Health: Focus on ADHD

Jane Pei-Chen Chang
Director,Child Psychiatry Division, Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

Assistant Professor, College Medicine, China Medical University, Taichung, Taiwan

M.D., China Medical University, Taichung, Taiwan

M.Sc., China Medical University, Taichung, Taiwan

Ph.D., Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, UK

Abstract

Inflammation and deficiency of omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been suggested to play a role in attention deficit hyperactivity disorder (ADHD). Studies have suggested that children with ADHD tend to have higher inflammatory biomarkers and less intake and lower blood levels of n-3 PUFAs. This talk will provide a brief overview focused on personalized medicine of n-3 PUFAs in ADHD with the most updated research findings supported by cross-sectional studies, meta-analyses and randomised controlled trials.

Selected recent publications:

1. **Chang JP,*** Su KP, Mondelli V, Pariante CM. Cortisol and Inflammatory Biomarker Levels in Youths with Attention Deficit Hyperactivity Disorder (ADHD): Evidence from a Systematic Review with Meta-analysis. Translational Psychiatry. 2021; 11(1):430.

2. **Chang JP.** Personalised medicine in child and adolescent psychiatry: Focus on omega-3 polyunsaturated fatty acids and ADHD. Brain, Behavior and Immunity-Health. 2021; 16:100310.

3. **Chang JP**, Su KP, Mondelli V, Satyanarayanan SK, Yang HT, Chiang YJ, Chen HT, Pariante CM. High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels. Translational Psychiatry. 2019; 9:303.

4. **Chang JP**, Su KP, Mondelli V, Pariante CM. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder (ADHD): A Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. Neuropsychopharmacology. 2018, 43:534-545.

5. **Chang JP**, Mondelli V, Satyanarayanan SK, Chiang YJ, Chen HT, Su KP, Pariante CM. Cortisol, inflammatory biomarkers and neutrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan. Brain, Behavior and Immunity. 2020;88:105-113.

Effects of Anthocyanin-rich Mulberry Milk on Working Memory and Mental Wellbeing in Healthy Working Population

Pongsatorn Paholpak
Associate Profressor, Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Research Institute for High Human Performance and Health Promotion, Khon Kaen University, Khon Kaen, Thailand

MD. Khon Kaen University

Abstract

Anthocyanins from various types of berries have been investigated for positive effects on cognitive, mood, anxiety, and stress symptoms. Our group conducted an open-labelled study in 300 healthy volunteers to consume either 1 or 2 servings of the anthocyanin-rich mulberry milk daily for 6 weeks. We monitored performances on 7 computerized working memory tests, General Health Questionnaire-28 (GHQ-28), Hospital Anxiety and Depression Scale (HADS), saliva activity levels of acetylcholinesterase (AchE), monoamine oxidase (MAO), and cortisol at the baseline and after 6 weeks. We found significant improvement of performances on all working memory tasks, significantly decreased GHQ-28 and HADS total scores and all their subscales, and significantly decreased activity levels of AchE, MAO-A, MAO-B, and cortisol in both groups (all $p < 0.05$). We speculated that a daily consumption of anthocyanin-rich mulberry milk improved psychological and somatic symptoms via suppressions of AchE, MAO and cortisol activity.

Selected recent publications:

1. Thukham-Mee WWattanathorn J, **Paholpak P**, Rangseekajee P, Piyavhatkul N.The Positive Modulation Effect of a 6-Week Consumption of an Anthocyanin-Rich Mulberry Milk on Working Memory, Cholinergic, and Monoaminergic Functions in Healthy Working-Age Adults . Oxid Med Cell Longev. 2021 Aug 31;2021:5520059. doi: 10.1155/2021/5520059. eCollection 2021

2. Rangseekajee P, Aphisitphinyo S, Paholpak P, Piyavhatkul N, Vadhanavikkit P, Manasawee K, **Paholpak P**.Mobile Application for Monitoring Behavioral and Psychological Symptoms of Dementia in Patients with Moderate to Severe Dementia. Geriatr Gerontol Int. 2021 Apr 13. doi: 10.1111/ggi.14164 PMID: 33851502

3. .Fong SS, **Paholpak P**, Daianu M, Deutsch MB, Riedel BC, Carr AR, Jimenez EE, Mather MM, Thompson PM, Mendez MF.The attribution of animacy and agency in frontotemporal dementia versus Alzheimer'sdisease. Cortex. 2017 Jul;92:81-94. doi: 10.1016/j.cortex.2017.03.019. Epub 2017 Apr 8. PMID: 28458182

4. Person-Based Versus Generalized Impulsivity Disinhibition in Frontotemporal Dementia Alzheimer Disease.**Paholpak P**, Carr AR, Barsuglia JP, Barrows RJ, Jimenez E, Lee GJ, Mendez MF.J Geriatr Psychiatry Neurol. 2016 Sep 19. DOI: 10.1177/0891988716666377 PMID: 27647788

5. **Paholpak P**, Li-Jung L, Carr DR, Jimenez E, Barrows RJ, Sabodash V, Mendez MF. Prolonged Visual Facial Grasp in Frontotemporal dementia..J Alzheimers Dis. 2016 May 7;53(1):327-35. doi: 10.3233/JAD-150864.PMID: 27163801

Brain Ageing: Potential Avenue for Antioxidant Compounds?

Hanafi Ahmad Damanhuri
Associate Professor, Department of Biochemistry, Faculty of Medicine, The National University of Malaysia

Ph.D., Macquarie University, Australia

Abstract

Brain aging is a continuous and complex multifactorial process manifested by physiological and cognitive deterioration, ultimately leading to death. Brain aging influences mental health and affects individuals' ability to carry out their daily routines. For the past decades, research has been conducted to understand how the ageing process affects the brain, from the molecule to the functional perspective. Despite the aggressive effort, many more questions are being raised and fail to clearly explain how the actual process occurs during brain ageing. It was further supported by the fact that the numbers of drugs or natural products extract results in inconclusive findings in delaying brain ageing progression in various contexts. Several questions remain unsolved and require extensive investigation. The controversies and relevant issues will be discussed further in the presentation.

Selected recent publications:

1. Aslina Pahrudin Arrozi, Wan Zurinah Wan Ngah, Hanafi Ahmad Damanhuri and Suzana Makpol (2021) Modulatory Effects of Alpha- and Gamma-Tocopherol on the Mitochondrial Respiratory Capacity and Membrane Potential in an In Vitro Model of Alzheimer's Disease. Frontiers in Pharmacology 12: 69883 (1-11).
2. Nur Fathiah Abdul Sani, Ahmad Imran Zaydi Amir Hamzah, Zulzikry Hafiz Abu Bakar, Yasmin Anum Mohd Yusof, Suzana Makpol, Wan Zurinah Wan Ngah and Hanafi Ahmad Damanhuri(2021) Gene expression profile in different age groups and its association with cognitive function in healthy Malay adults in Malaysia. Cells 10: 1611 (1-25).
3. Nur Zuliani Ramli, Mohamad Fairuz Yahaya, Ikuo Tooyama and Hanafi Ahmad Damanhuri (2020) A mechanistic evaluation of antioxidant nutraceuticals on their potential against age-associated neurodegenerative diseases. Antioxidants 9 (10): 1019 (1-39).
4. Zulzikry Hafiz Abu Bakar, Hanafi Ahmad Damanhuri, Suzana Makpol, Wan Mohd Aizat, Nur Fathiah Abdul Sani, Ahmad Imran Zaydi Amir Hamzah, Khairun Nain Nor Aripin, Mohd Dzulkhairi Mohd Rani, Nor Azila Noh, Rosdinom Razali, Musalmah Mazlan, Hamzaini Abdul Hamid, Mazlyfarina Mohamad and Wan Zurinah Wan Ngah (2019) Effect of Age on the Protein Profile of Healthy Malay Adults and its Association with Cognitive Function Competency. Journal of Alzheimer's Disease 70: S43–S62.
5. Wan Nurzulaikha Wan Nasri, Suzana Makpol, Musalmah Mazlan, Ikuo Tooyama, Wan Zurinah Wan Ngah and Hanafi Ahmad Damanhuri (2019) Tocotrienol Rich Fraction (TRF) Supplementation Modulate Brain Hippocampal Gene Expression In APPswe/PS1dE9 Alzheimer's Disease Mouse Model. Journal of Alzheimer's Disease 70: S239–S254.

Inflammatory Cytokines in and Cognitive Function of Adolescents with First-Episode Schizophrenia, Bipolar Disorder, or Major Depressive Disorder

Mu-Hong Chen
Attending Psychiatrist, Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

Department of Psychiatry, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

M.D., Ph.D., National Yang Ming Chiao Tung University.

Abstract

Background: Few studies have explored the complex relationship of pro- and anti-inflammatory cytokines with cognitive function in adolescents with first-episode schizophrenia, bipolar disorder, or major depressive disorder. **Methods:** In total, 26, 35, and 29 adolescents with first-episode schizophrenia, bipolar disorder, and major depressive disorder, respectively, and 22 age- and sex-matched controls were included in the current study. Cytokines, namely interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP), were assessed. The Wisconsin Card Sorting Test (WCST) and the working memory task were administered to assess cognitive function. **Results:** Using generalized linear models with adjustment for demographic data and clinical symptoms, patients with bipolar disorder were found to exhibit the highest levels of CRP ($p = 0.023$), IL-6 ($p = 0.022$), and TNF-α ($p = 0.011$) and had the lowest IL-2 levels ($p = 0.034$) among the four groups. According to the results of the WCST and working memory task, adolescents with schizophrenia exhibited the lowest performance in cognitive function. In addition, among the assessed cytokines, only CRP levels ($p = 0.027$) were negatively associated with WCST scores. **Discussion:** Dysregulated pro- and anti-inflammatory cytokines and impaired cognitive functioning were observed in first-episode adolescent-onset schizophrenia, bipolar disorder, and major depressive disorder. The altered cytokine profiles may play important roles in the pathophysiology of schizophrenia, bipolar disorder, and major depressive disorder.

Selected recent publications:

1. **Chen MH**, Chang WC, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, Huang WS, Su TP. Functional dysconnectivity of frontal cortex to striatum predicts ketamine infusion response in treatment-resistant depression. Int J Neuropsychopharmacol. 2020 Jul 30:pyaa056.

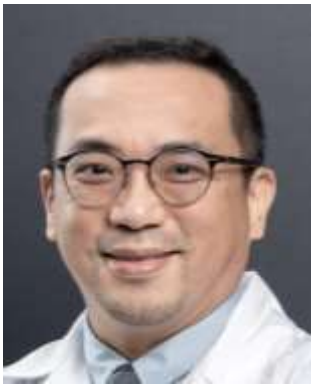
2. **Chen MH**, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, Hong CJ, Tu PC, Cheng CM, Su TP. Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression. J Clin Psychiatry. 2020 Nov 10;81(6):20m13232.

3. **Chen MH**, Kao CF, Tsai SJ, Li CT, Lin WC, Hong CJ, Bai YM, Tu PC, Su TP. Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. Genomics. 2020 Dec 25:S0888-7543(20)32077-2.

4. **Chen MH**, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, Tu PC, Bai YM, Mao WC, Su TP. Is one or two infusions better in the first week of low-dose ketamine treatment for medication-resistant depression? A post hoc pooled analysis of randomized placebo-controlled and open-label trials. J Psychiatr Res. 2021 Nov 3;144:448-454.

5. **Chen MH**, Cheng CM, Gueorguieva R, Lin WC, Li CT, Hong CJ, Tu PC, Bai YM, Tsai SJ, Krystal JH, Su TP. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. Neuropsychopharmacology. 2019 Aug 17.

HF–Age–Gender (HAG) Index as a Biomarker for Sleep Disorder in mTBI



John Chung-Che Wu(吳忠哲)
Current title and affiliation

Assistant Professor

Division of Neurosurgery, Department of Neurosurgery, Taipei Medical University Hospital,

Division of Neurosurgery, Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University

M.D., Ph.D., Taipei Medical University

Abstract

Biomarkers are emerging as a useful tool for prediction of outcomes in TBI. To identify a screening tool for poor self-reported sleep quality in the first week after mild traumatic brain injury (mTBI) for sleep disorder at 12 weeks, data from 473 mTBI participants were collected and follow-ups were performed at 12 weeks. Patients were then divided into two groups according to the Pittsburgh Sleep Quality Index based on whether or not they experienced poor sleep quality at 12 weeks post-mTBI. The analysis was performed on personal profiles and heart rate variability (HRV) in the 1st week. An analysis of the non-invasive patient data for mTBI patients who did and did not complain of poor sleep quality revealed several factors relevant to the delayed onset of poor sleep quality, including age, gender, and HRV measurements. The HRV–age–gender (HAG) index has a 100% sensitivity (cut-off, 7; specificity, 0.537) to predicting whether the patient will experience poor sleep quality after mTBI at the 12-week follow-up. The HAG index allows identifying the patients with mTBI who have no initial sleep quality complaints but are prone to developing poor self-reported sleep quality at 12 weeks.

Selected recent publications:

1. Wang YJ, Wong HSC, **Wu CC**, Chiang YH, Chiu WT, Chen KY and Chang WC. The functional roles of IGF-1 variants in the susceptibility and clinical outcomes of mild traumatic brain injury. J Biomed Sci. 2019 Dec 2;26(1):94.

2. **Wu CC**, Ekanem TI, Phan NN, Loan DTT, HouSY, Lee KH, Wang CY. Gene signatures and prognostic analyses of the Tob/BTG pituitary tumor-transforming gene (PTTG) family in clinical breast cancer patients.Int. J. Med. Sci. 2020; 17(18): 3112-3124.

3. Tsai YT, **Wu CC**, Ko CY, Hsu TI, Chang WC, Lo WL, Chuang JY. Correlation between the expression of cancer stem cell marker BMI1 and glioma prognosis. Biochem Biophys Res Commun. 2021 Apr 23;550:113-119.

4. Kao TJ, **Wu CC**, Phan NN, Liu YH, TaHDK, Anuraga G, Wu YF, Lee KH, Chuang JY, Wang CY. Prognoses and genomic analyses of proteasome 26S subunit, ATPase (PSMC) family genes in clinical breast cancer. Aging (Albany NY). 2021 Jul 30;13.

5. Ma HP, Ou JC, Chen KY, Liao KH, Kang SJ, Wang JY, Chiang YH, **Wu JCC**. Screening for Poor Self-Reported Sleep Quality at 12 Weeks in Post-Mild Traumatic Brain Injury Patients Using the HF-Age-Gender (HAG) Index. Brain Sci. 2021 Oct 20;11(11):1369.

Visual working memory decline in aging and potential neuromodulatory treatment

Philip Tseng(曾祥非)

Professor and Director, Graduate Institute of Mind, Brain and Consciousness, Taipei Medical University

Vice Dean, College of Humanities and Social Sciences, Taipei Medical University

Ph.D.University of California, Santa Cruz

Abstract

Visual working memory (VWM) is a cognitive faculty that allows us to remember visual information from one fixation to another.However, VWM capacity is far from perfect, and research has demonstrated a high degree of individual difference in VWM performance. Perhaps due to its imperfection and fragility, VWM capacity has been shown to be highly sensitive to one's neurological development and frontoparietal functioning, and can be a sensitive marker to many factors such as aging, and neurodegenerative diseases, etc. In this talk I will explore the possibility of applying VWM to research in traumatic brain injury, as well as some of the brain stimulation techniques such as transcranial electric stimulation and sensory stimulation that have been known to facilitate VWM performance, that may be of interest to clinicians working with TBI patients.

Selected recent publications:

1. Sahu PP &**Tseng P** (2021). Frontoparietal theta tACS nonselectively enhances encoding, maintenance, and retrieval stages in visuospatial working memory. Neuroscience Research, 172, 41-50.

2. **Tseng P**, Iu K-C, & Juan CH (2018). The critical role of phase difference in theta oscillation between bilateral parietal cortices for visuospatial working memory. Scientific Reports, 8:349.

3. Wu YJ, Lin CC, Yeh CM, Chien ME, Tsao MC, **Tseng P**, Huang CW, & Hsu KS (2017). Repeated transcranial direct current stimulation improves cognitive dysfunction and synaptic plasticity deficit in the prefrontal cortex of streptozotocin-induced diabetic rats. Brain Stimulation, 10(6), 1079-1087.

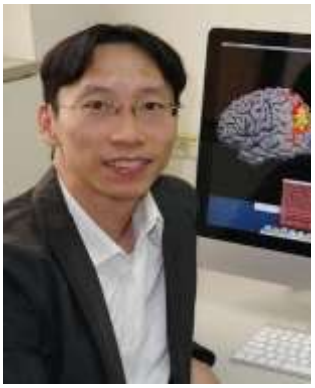
4. Juan CH, **Tseng P**, & Hsu TY (2017). Elucidating and modulating the neural correlates of visuospatial working memory via noninvasive brain stimulation. Current Directions in Psychological Science, 26(2), 165-173.

5. **Tseng P**, Hsu TY, Chang CF, Tzeng OJL, Hung DL, Muggleton NG, Walsh V, Liang WK, Cheng SK, & Juan CH (2012). Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. Journal of Neuroscience, 32, 10554-10561.

Task-related fMRI reveals age-related neuro-functional differences in younger and older adult decision processes

Joshua Goh(吳恩賜)

Associate Professor,Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University



Ph.D.University of Illinois, Urbana-Champaign

Abstract

The ability of the human brain to make appropriate decisions given the context undergoes notable changes with age. This is a puzzling phenomenon since both younger and older adults are faced with the same contextual scenarios, yet differences in decision behaviors reflect age-related influences in the underlying neural processes that culminate in the chosen actions or responses. In a series of studies, our lab has applied the use of psychological value-based decision-making in lottery choices and complex rule contingency decision-making in functional magnetic resonance imaging experiments applied on younger and older adults. Our findings highlight drastic differences in neural network systems engaged by younger and older adults as they process value-based decisions as well as non-linear rule-mappings. Crucially, in these fMRI tasks, we found a shift from rapid, simplifying heuristic-like processing in younger adult striatum and prefrontal operations to slower, more biased processing in older adult medial and lateral frontal systems. These findings delineate how the human brain reorganizes its decision-making neural circuits in the face of neurobiological changes and lifespan experiences with age.

Selected recent publications:

1. Goh, J. O. S.*, Su, Y. S., Tang, Y. J., McCarrey, A. C., Tereschenko, A., Elkins, W., Resnick, S. M. (2016). Frontal, striatal, and medial temporal sensitivity to value distinguishes risk-taking from risk-aversive older adults during decision-making. Journal of Neuroscience, 36(49), 12498-12509.

2. Su, Y. S., Chen, J. T., Tang, Y. J., Yuan, S. Y., McCarrey, A. C., Goh, J. O. S.* (2018). Age-Related Differences in Striatal, Medial Temporal, and Frontal Involvement During Value-Based Decision Processing. Neurobiology of Aging, 69:185-198.

3. Chen, C. C., Su, Y. S., Tu, Y. Z., Goh, J. O. S.* (2019). Default-mode network activation underlies accurate contextual processing of exclusive disjunctions in older but not younger adults, NeuroImage, 201, 116012.

Sleep disturbance and its impacts on cognitive deficits following traumatic brain injury

Hsiao-Yean(Shannon) Chiu(邱曉彥)

Associate Professor and Deputy director of School of Nursing,

College of Nursing, Taipei Medical University

Supervisor, Department of Nursing, Taipei Medical University Hospital

RN, Ph.D.Taipei Medical University

Abstract

Traumatic brain injury (TBI) is one of the most common neurological disorder, which can be classified as mild, moderate or severe types, and may have wide-ranged physical and psychological sign and symptoms. On the other hand, with increasing life expectancy in modernsocieties, the epidemiological pattern of TBI has changed in recent decades,with an increasing proportion of TBI survivors fallinginto the older age group (one-third ofTBI survivors). In general, TBI has becomea major public health concern for young and older adults.Note that some symptoms could appear immediately after brain trauma, while others days or weeks later. Among these symptoms, sleep disturbance is one of the most common complaint in the population. In the lecture, I will review our past study findings regarding the sleep patterns of TBI survivors at acute and chronic stages. During acute stage, sleep duration seems play a critical role in recovering cognitive impairment caused by head trauma; in the chronic stages, psychological factors such as depression may contribute to the development of sleep disturbance following TBI. Furthermore, I will describe the association between post-TBI sleep disturbance and cognitive impairment and illustrate possible nonpharmacological interventions targeting sleep disturbance following TBI.

Selected recent publications:

1. Chen PY, Hsieh SH, Lin CK, Wei L, Su YK, Tsai PS, **Chiu HY.** Mental fatigue mediates the relationship between cognitive functions and return to productive activity following traumatic brain injury. *Brain Injury*. 2022; 31;1-7.

2. Chung JW, Liu D, Wei L, Wen YT, Lin HY, Chen HC, **Chiu HY.** Postconcussion symptoms after an uncomplicated mild traumatic brain injury in older adults: frequency, risk factors, and impact on quality of life. *Journal of Head Trauma Rehabilitation*. 2021; doi: 10.1097/HTR.0000000000000733.

3. Tsai YC, Liu CJ, Huang HC, Lin JH, Chen PY, Su YK, Chen CT, **Chiu HY.** A meta-analysis of dynamic prevalence of cognitive deficits in the acute, subacute, and chronic phases following traumatic brain injury. *Journal of Neuroscience Nursing*. 2021; 53:63-68.

4. Wei L, Wen YT, Thompson HJ, Liu CY, Su YK, Chen PY, Chen CY, Chuang YH, Lin YJ, Chen, CT, Chen CC, Chiu HT, **Chiu HY**. Sleep disturbances following traumatic brain injury in older adults: a comparison study. *Journal of Head Trauma Rehabilitation*. 2020; 35(4):288-295.

5. Chen PY, Tsai PS, Chen NH, Chaung LP, Lee CC, Chen CC, Chiu HT, Lu YJ, Wei KC, **Chiu HY.** Trajectories of sleep and its predictors in the first year following traumatic brain injury. *Journal of Head Trauma Rehabilitation.* 2015, 30(4): E50-55.

Current Status of Opioid Prescribing for Cancer and Non-Cancer Pain in Taiwan

Chih-Peng Lin (林至芃)

Associate Professor, Department of Anesthesiology, National Taiwan University College of Medicine

President, Taiwan Pain Society

M.D.; Ph.D. National Taiwan University

Abstract

Opioids are the mainstay treatment for severe pain, both cancer pain and non-cancer pain. However, over the past two decades, North America, Oceania and European countries experienced a marked increase of opioid prescribing in especially chronic non-cancer pain that resulted in “opioid epidemic”.

In Taiwan, those patients with cancer diagnosis can be prescribed with opioid without too much limitation. However, lack of different strong opioid options remains major barrier to adequate cancer pain management in Taiwan until late 2014. Our recent studies demonstrated that approximately 50% of cancer patients used analgesics, 50% of which were opioids; the proportions were stable in the pass 2 decades. However, the annual cumulative opioid dose significantly decreased while the annual cumulative strong opioid use per patient increased significantly. In parallel, the annual cumulative weak opioids use per patient decreased. Among extended-release strong opioids, the use of transdermal fentanyl significantly decreased after oxycodone and hydromorphone were introduced. These finding implied that increased therapeutic options in strong opioid prescriptions led opioid prescription patterns to evolve towards international cancer pain management guidelines and may facilitate more efficient opioid titration and rotation and thus decrease, not increase, the opioid usage.

On the contrary, opioid prescription for non-cancer pain is strictly limited in Taiwan. According to Controlled Drugs Management Information System of Taiwan Food and Drug Administration data, we have only less than 500 chronic non-cancer pain patients were prescribed with long term strong opioids. Most of the strong opioid prescription were used in acute pain service. Specifically, weak opioid tramadol is categorized as schedule 4 controlled substance that is not strictly regulated. So the utilization of tramadol prescribed to patients without cancer diagnosis increased drastically in the past decades.

Selected recent publications:

1. Wu TC, Hsu CH, Sun WZ, Chen HM, Lin CP*, Shao YY*: Impact of expanded strong opioid availability on opioid prescription patterns in patients with cancer: A population-wide cohort study in Taiwan. Lancet Reg Health West Pac. 2021 Aug 26;16:100255.

2. Chen TC, Wang TC, Lin CP, Bonar K, Ashcroft DM, Chan KA, Chen LC: Increasing tramadol utilisation under strict regulatory control of opioid prescribing - A cross-sectional study in Taiwan from 2002 through 2016. Journal of Formosan Medical Association, 2021 Feb;120(2):810-818

3. Lin CP, Hsu CH, Fu WM, Chen HM, Lee YH, Lai MS, Shao YY: Key opioid prescription concerns in cancer patients: A nationwide study. Acta Anaesthesiol Taiwan 2016 Jun;54(2):51-6

4. Wang JJ, Teng SF, Chu YR, Chu CC, Ho CH, Chu LL: Evaluation of opioid consumption trends for pain in Taiwan and comparison with neighboring Asian countries. J Food Drug Anal. 2022 Mar 15;30(1):104-110.

5. Wang JJ, Chu YR, Teng SF, Chu CC, Ho CH, Chu LL: Prevalence of opioid prescriptions in Taiwan (2008-2018). J Chin Med Assoc. 2022 May 1;85(5):603-609.

Mesoporous polydopamine nanoparticles attenuates morphine tolerance in neuropathic pain rats: Morphine sparing effect

Chih-Shung Wong (汪志雄)

Director, Department of Medical Education, Cathay General Hospital
Director, Department of Anesthesiology, Cathay General Hospital
Chairman, Cathay General Hospital IRB
Chairman, Cathay General Hospital, IACUC

MD. National Defense Medical Center
Ph.D. Duke University

Abstract

In 2017, more than 70,000 died from drug overdoses, making a leading cause of injury-related death in the US. Of those deaths, almost 68% involved a prescription or illicit opioid. More than 25 million US adults are affected by daily pain and 2 million individuals have an opioid use disorder, most starting with opioids prescription, then to addiction. NIH initiates the HEAL in 2018; it focuses on 2 primary goals, improving treatments for opioid misuse and addiction, and enhancing strategies for pain management. Study showed that ultra-restrictive opioid prescription protocol provided adequate postoperative pain control without any negative health consequences; this radical opioid-sparing for postoperative pain is expected to reduce health care costs and limited opioids circulating in communities. Ultimately protect patients and their family members from opioid misuse and abuse. Good perioperative pain management is a key matter to enhance surgery recovery and limited CPSP, opioid-sparing is advised; it can be achieved by potentiate the effect of opioids, reduce dosage and duration with MMA. Antioxidation is considered an efficient strategy to eliminate excessive ROS for neuropathic pain. Nanoparticles with natural enzyme-like activities have been developed, which enhanced biological stability with improved half-life, multi-functionality and ease of preparation. We, by using of PSNL model, developed nanocarriers, which provided antioxidative effect to enhance morphine's antinociception with prolong action. MPDA-nanocarrier effectively scavenges ROS and alleviated neuropathic pain with prolonged duration.

Selected recent publications:

1. Kuthati Y, Busa P, Davuluri VNG, Wong CS*. Manganese oxide nanozymes ameliorate mechanical allodynia in a rat mode of partial sciatic nerve-transection induced neuropathic pain. Int J Nanomed 2019:14:10105-10117.

2. Kuthati Y, Navakanth RV, Pabby P, Tummala S, Davuluri VNG, Wong CS*. Scope and applications of nanomedicines for the management of neuropathic pain. Molecular Pharmaceutics, DOI: 10.1021/acs.molpharmaceut.9b01027, 2020.

3. Kuthay Y, Busa P, Tummala S, Rao VN, Davuluri VNG, Ho YP, Wong CS*. Mesoporous polydopamine nanoparticles attenuates morphine tolerance in neuropathic rats by inhibition oxidative stress and restoration of endogenous antioxidant system. Antioxidants 2021, 10, 195 https//doi.org/10.3990/antiox100201195.

4. Kuthati Y, Rao VN, P, Busa P, Wong CS.* Teneligliptin exerts antinociceptive effects in rat model of partial sciatic nerve transection induced neuropathic pain. Antioxidants **2021**, 10, 1438.

5. Busa P, Kuthati Y, Huang NC, Wong CS.* New advances on pathophysiology of diabetes neuropathy and pain management: potential role of melatonin and DPP-4 inhibitors. Frontier Pharm Doi:10.3389/fphar.2022.864088.

The striatal dopamine transporter, novelty seeking and cognitive flexibility in patient with opioid dependence

San-Yuan Huang (黃三原)

Professor, Department of Psychiatry,
National Defense Medical center

Executive Director, Taiwan social addiction

M.D.; Ph.D. National Defense Medical center

Abstract

Novelty seeking (NS) is a core personality trait that primes the susceptibility to drug addiction. Striatal dopamine activity contributes to cognitive flexibility, an important cognitive strategy to inhibit impulsivity and compulsive drug seeking behavior. Evidence supports the association between dopamine and NS, which is higher in opioid-dependent patients. Moreover, repeated opioid exposure can cause cognitive deficits including poor cognitive flexibility and impaired impulse control. However, in opioid-dependent patients, the link between NS, striatal dopamine activity, and cognitive flexibility is still unclear. We recruited 22 opioid-dependent individuals and 30 age- and sex-matched healthy controls. Single-photon emission computed tomography with [99mTc]TRODAT-1 as a ligand was used to measure the striatal dopamine transporter (DAT) availability. The Trial Making Test (TMT) was performed to assess cognitive flexibility. We found that in opioid-dependent patients, the striatal DAT availability was lower and negatively associated with TMT Part B ÷ Part A. Moreover, an inverted-U shape significantly matched the scores of NS as a function of the striatal DAT availability, with maximum NS potential in the midrange of the DAT availability. An extra sum-of-squares F test was conducted, indicating that a quadratic model fitted the association between the DAT and NS better than a linear model did. In brief, in opioid-dependent patients, the striatal DAT availability is nonlinearly linked to NS and linearly linked to cognitive flexibility. The role of the striatal DAT in the transition from controlled to compulsive opioid use warrants further research.

Selected recent publications:

1. Tsou CC, Chou HW, Ho PS, Kuo SC, , ***Huang SY (correspondence).**DRD2 and ANKK1 genes associate with late-onset heroin dependence in men.. World J Biol Psychiatry. 2019 Oct;20(8):605-615.
2. Huang CC, Kuo SC, Yeh TC, Yeh YW, Chen CY, Liang CS, Tsou CC, Lin CL, Ho PS, ***Huang SY (correspondence).** OPRD1 Gene Affects Disease Vulnerability and Environmental Stress in Patients with Heroin Dependence Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar 8;89:109-116 (accepted on 25 Aug 2018) ICF 4.185（28/142 Psychiatry）
3. Tsou CC, Kuo SC, Chen CY, Lu RB, Wang TJ, ***Huang SY (correspondence).**. NGF gene polymorphisms are not associated with heroin dependence in a Taiwanese male population. Am J Addict. 2018 Sep;27(6):516-523
4. Kuo SC, Yeh YW, Chen CY, Huang CC, Ho PS, Liang CS, Lin CL, Yeh TC, Kuo SC, Yang BZ , Lu RB, ***Huang SY (correspondence).** Differential effect of the DRD3 genotype on inflammatory cytokine responses during abstinence in amphetamine-dependent women Psychoneuroendocrinology. 2018 Nov;97:37-46.
5. Yen CH, Mei-Chen Shih, MS, Cheng-Yi Cheng, …...Lu RB, ***Huang SY (correspondence) Differential cytokine levels between early withdrawal and remission states in patients with alcohol dependence.** Psychoneuroendocrinology. 2017 Mar. 20;76:183-191.

Development of Novel Therapeutic Drugs for Treatment and Prevention of Opioid Addiction

Chia-Hung Hsieh (謝佳宏)

Professor, Graduate Institute of Biomedical Sciences

China Medical University

Abstract

The opioids addiction is a serious global problem that affects the health, social, and economic welfare of all societies. Methadone or Buprenorphine is a long-acting synthetic opioid agonist medication that can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. However, those who take these drugs are still addicts and the heroin relapse rate is relatively high. Therefore, there is no cure for opioids addiction until now. Opioids addiction continue to be global unmet medical needs. Recently, we found that Scla711 (xCT), which encodes system x_c^-, knockout mice lack the heroin or methadone-seeking and craving behaviors compared to wild-type mice while mice were habituated to receive the heroin or methadone administration, indicting system x_c^- has a critical role in the process of opioids addiction. Importantly, the wild-type mice with heroin or methadone-dependence treated with the inhibitor of system x_c^-, sulfasalazine (SSZ)) suppressed the heroin or methadone-seeking and craving behaviors. Moreover, we also finished the PI-initiated clinical trials for SSZ in treatment of patients with opioid addiction. Our results indicate that oral administration of SSZ is able to promote the detoxification and inhibit the opioid craving and withdrawal symptoms in patients with opioid addiction. Moreover, our big data analysis also demonstrates that long-term use of SSZ decreased incidence rate of opioid-addictive disorders in human. These findings show the inhibitors of system x_c^- represent new class of therapeutics against opioids addiction.

Selected recent publications:

1. Wei ST, Huang YC, Hsieh ML, Lin YJ, Shyu WC, Chen HC, Hsieh CH*. Atypical chemokine receptor ACKR3/CXCR7 controls postnatal vasculogenesis and arterial specification by mesenchymal stem cells via Notch signaling. Cell Death Dis. 2020;11(5):307. IF=9.705, R/C=45/203, CELL BIOLOGY

2. Chiang CS, Lin YJ, Lee R, Lai YH, Cheng HW, Hsieh CH*, Shyu WC*, Chen SW*. Combination of fucoidan-based magnetic nanoparticles and immunomodulators enhances tumour-localized immunotherapy. Nature Nanotechnology. 2018;13:746–754. IF=40.523, R/C=2/109, NANOSCIENCE & NANOTECHNOLOGY.

3. Huang MW, Lin YJ, Chang CW, Lei FJ, Ho EP, Liu RS, Shyu WC, Hsieh CH*. RGS4 Deficit in Prefrontal Cortex Contributes to the Behaviors related to Schizophrenia via System xc–-mediated Glutamatergic Dysfunction in Mice. Theranostics. 2018; 8(17): 4781–4794. IF=11.6, R/C=13/139, MEDICINE, RESEARCH& EXPERIMENTAL.

4. Lin YJ, Shyu WC, Chang CW, Wang CC, Wu CP, Lee HT, Chen LJ, Hsieh CH*. Tumor Hypoxia Regulates Forkhead Box C1 to Promote Lung Cancer Progression. Theranostics. 2017; 7(5): 1177–1191. IF=11.6, R/C=13/139, MEDICINE, RESEARCH& EXPERIMENTAL.

5. Hsieh CH*, Lin YJ, Chen WL, Huang YC, Chang CW, Cheng FC, Liu RS, Shyu WC*. HIF-1α triggers long-lasting glutamate excitotoxicity via system xc- in cerebral ischaemia-reperfusion. J Pathol. 2017. doi: 10.1002/path.4838. IF=9.883, R/C=4/77 ,PATHOLOGY.

Roles of Neutrophils in Glioma

Ya-Jui Lin (林亞銳)

Attending Neurosurgeon
Brain tumor Division, Department of Neurosurgery,
Chang-Gung Memorial Hospital, Linkou Medical Center

Ph.D. candidate, Graduate Institute of Natural Products, Chang Gung University

Abstract

Neutrophils, which are the most abundant circulating leukocytes in humans, are the first line of defense against bacterial and fungal infections. Recent studies have reported the role and importance of neutrophils in cancers. Glioma are the most common primary malignant tumors of the brain. The tumor microenvironment (TME) in the brain is complex and unique owing to the brain-blood barrier or brain-tumor barrier, which may prevent drug penetration and decrease the efficacy of immunotherapy. However, there are limited studies on the correlation between glioma and neutrophils. Here, we reviewed the current knowledge on the correlation between neutrophil-to-lymphocyte ratio and prognosis of glioma, and the implications of tumor-associated neutrophil (TAN) phenotypes and the functions in glioma microenvironment as well. Definitely, we also look into the potential effects of various treatments on TANs and the ability of neutrophils to function as a nanocarrier of drugs to the brain TME. Indeed, further studies are needed to elucidate the complex interactions between neutrophils, other immune cells, and glioma cells inside TME.

Selected recent publications:

1. **Lin YJ**, Wei KC, Chen PY, Lim M, Hwang TL. Roles of Neutrophils in Glioma and Brain Metastases. Front Immunol. 2021 Aug 13;12:701383.
2. Chen KT, Chai WY, **Lin YJ**, Lin CJ, Chen PY, Tsai HC, Huang CY, Kuo JS, Liu HL, Wei KC. Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors. Sci Adv. 2021 Feb 5;7(6):eabd0772.
3. **Lin YJ**, Mashouf LA, Lim M. CAR T Cell Therapy in Primary Brain Tumors: Current Investigations and the Future. Front Immunol. 2022 Feb 21;13:817296.
4. **Lin YJ**, Huang CY, Shen YC, Wei KC, Chuang CC, Hsu PW, Huang YC, Hwang TL, Chen PY. A manzamine-derived compound as a potential therapeutic agent for glioma by inducing apoptosis and cell cycle arrest. Am J Cancer Res. 2022 Apr 15;12(4):1740-1751.
5. Chen CH, **Lin YJ**, Lin YY, Lin CH, Feng LY, Chang IY, Wei KC, Huang CY. Glioblastoma Primary Cells Retain the Most Copy Number Alterations That Predict Poor Survival in Glioma Patients. Front Oncol. 2021 Apr 26;11:621432.

Multiple Novel approach for GBM therapy

Cheng-Yu Tsai (蔡政宇)

Attending Staff, Division of Neurosurgery, Chung-Ho Memorial Hospital, Kaohsiung Medical University

Ph.D. Program in Environmental and Occupational Medicine, College of Medicine, Kaohsiung Medical University and National Health Research Institutes

Abstract

Glioblastoma multiforme is one of the most malignant tumors, and it has an aggressive pattern and a high recurrence rate. Despite multimodalities treatment with surgery and concomitant radiation and chemotherapy, patients with GBM still have a poor prognosis, with a mean survival of <15 months. We used the multiple bioinformatics algorithms tools for multiple modality approach. The goals and aims from novel approach for new drug development and drug repurposing. Simultaneously, biomarker prediction could be fully assessed and applied. Moreover, we performed basic research methods to confirm the big data results and reach the satisfied conclusions. Herein, we presented three studies for demonstration for GBM therapy.

Selected recent publications:

1. **Cheng-Yu Tsai,** Huey-Jiun Ko, Joon-Khim Loh, Aij-Lie Kwan, Tsung-Hsien Chuang, Yi-Ren Hong. **(2021)** Ionizing Radiation Induces Resistant Glioblastoma Stem-Like Cells by Promoting Autophagy via the Wnt/β-Catenin Pathway. Life 11 (5), 451.

2. **Cheng-Yu Tsai,** Huey-Jiun Ko, Shean-Jaw Chiou, Tsung-Hsien Chuang, Chi-Ying F Huang, Joon-Khim Loh, Yi-Ren Hong. **(2021)** NBM-BMX, an HDAC8 Inhibitor, Overcomes Temozolomide Resistance in Glioblastoma Multiforme by Downregulating the β-Catenin/c-Myc/SOX2 Pathway and Upregulating p53-Mediated MGMT Inhibition. International journal of molecular sciences 22 (11), 5907.

3. Huey-Jiun Ko, **Cheng-Yu Tsai,** Shean-Jaw Chiou, Joon-Khim Loh, Yi-Ren Hong. **(2021)** The Phosphorylation Status of Drp1-Ser637 by PKA in Mitochondrial Fission Modulates Mitophagy via PINK1/Parkin to Exert Multipolar Spindles Assembly during Mitosis. Biomolecules 11 (3), 424.

4. Cheng-Jung Ho, **Cheng-Yu Tsai,** Yi-Ren Hong, Chihuei Wang. **(2022)** Compound cellular stress maximizes apoptosis independently of p53 in glioblastoma. Cell Cycle, 1-13.

5. **Cheng-Yu Tsai,** Shean-Jaw Chiou, Huey-Jiun Ko, Aij-Li Kwan, Joon-Khim Loh, Yi-Ren Hong. **(2022)** Deciphering the evolution of composite-type GSKIP in mitochondria and Wnt signaling pathways PloS one 17 (1), e0262138.

Translational Research of Glioma Tumor Therapy: Magic Bullet of Targeting Drug Delivery? Precision Medicine? Tumor Microenvironment? Energy Metabolism?

Feng-Ting Huang (黃楓婷)

Associate Professor, Department of Biochemical Science and Technology, College of Life Science, National Taiwan University.

Ph.D. University of Southern California, USA

Abstract

Among the broad range of tumors, malignant tumors in the central nervous system (CNS) represent the greatest challenge for effective drug delivery due to the blood-brain barrier (BBB). Nanotechnologies may have great clinical potential in overcoming this formidable obstacle in traditional brain cancer treatment. Nanoparticles are purposely constructed on the nanometer scale, and nanoparticles can penetrate more deeply into inflammatory sites, the epithelium and tumors. Moreover, nanoparticles can be loaded with various chemotherapeutic drugs and modified with targeting molecules to provide the targeted delivery of drugs to tumors. Ferritin, the natural iron storage protein complex, self-assembles into a uniform cage-like structure. Human H-ferritin (HFn) has been shown to transverse the BBB by binding to transferrin receptor 1 (TfR1), which is abundant in endothelial cells and overexpressed in tumors, and enters cells via endocytosis. Ferritin is easily genetically modified with various functional molecules, justifying that it possesses great potential for development into a nanocarrier drug delivery system. Hence, with modifications of versatile molecules on ferritin, the tumor-targeting or the tumor microenvironment (TME)-targeting ferritin nanocarrier can be established and encapsulated with various types of drugs/small molecules to specifically deliver them to the GBM tumor or GBM TME, respectively.

Selected recent publications:

1. Huang CW, Hsieh WC, Hsu ST, Lin YW, Chung YH, Chang WC, Chiu H, Lin YH, Wu CP, Yen TC*, **Huang FT*** (2017) The Use of PET Imaging for Prognostic Integrin α2β1 Phenotyping to Detect Non-Small Cell Lung Cancer and Monitor Drug Resistance Responses. *Theranostics* 7(16):4013-4028.

2. Huang CW, Chang YH, Lee HH, Wu JY, Huang JX, Chung YH, Hsu ST, Chow LP, Wei KC, **Huang FT*** (2020) Irisin, an exercise myokine, potently suppresses tumor proliferation, invasion and growth in glioma. *FASEB J*, 34(7):9678-9693.

3. Huang CW, Chuang CP, Chen YJ, Wang HY, Lin JJ, Huang CY, Wei KC, **Huang FT*** (2021) Integrin α2β1-targeting ferritin nanocarrier traverses the blood-brain barrier for effective glioma chemotherapy. *Journal of Nanobiotechnology* 19(1):180.

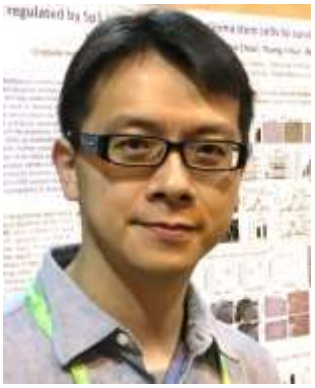
4. Lin JJ, Chuang CP, Lin JY, **Huang FT***, Huang CW* (2021) Rational Design, Pharmacomodulation, and Synthesis of [^{68}Ga]Ga-Alb-FAPtp-01, a Selective Tumor-Associated Fibroblast Activation Protein Tracer for PET Imaging of Glioma. *ACS Sensors* 6: 3424-3435.

The role of histone deacetylases in promoting glioblastoma process

Jian-Ying Chuang (莊健盈)

Professor, Ph.D. Program in Medical Neuroscience, Taipei Medical University
Vice Dean, College of Medical Science and Technology, Taipei Medical University

Ph.D. National Cheng-Kung University



Abstract

Glioblastoma is associated with poor prognosis and high mortality. Although the use of first-line temozolomide (TMZ) can reduce tumor growth, therapy-induced stress drives stem cells out of quiescence, leading to chemo-resistance and glioblastoma recurrence. Histone deacetylases (HDACs) are known to involve in multiple different stages of tumor development; however, how HDACs contribute to more malignant transformation and adaptation of glioblastoma cells to evade drug treatment is not known. Here we observed that HDAC1/HDAC2/HDAC6 are highly overexpressed in TMZ-resistant glioblastoma cells and glioblastoma stem-like tumorspheres. These HDACs can activate Sp1 transcription factor to promote self-renewal of the malignancy by upregulating BMI1 and telomerase reverse transcriptase (TERT), as well as to induce the DNA damage response and repair (DDR) pathway by altering the transcription of various DDR genes. In addition, we also identified a lncRNA, *LINC00461*, as a novel downstream target of HDAC6, and highlighted that the HDAC6/RNA-binding proteins (CCR4-NOT)/*LINC00461* axis increases glioblastoma cell proliferation by maintaining the expression of cell-cycle-related proteins via a sponge function of tumor-suppressive miRNAs. Importantly, HDAC1/HDAC2/HDAC6 expression is associated with poor clinical outcome in both glioblastoma and low-grade gliomas. However, treatment with azaindolylsulfonamide (MPT0B291), a potent HDAC6 inhibitor with partial efficacy against HDAC1/2, induced G2/M arrest and senescence in both TMZ-resistant cells and stem-like tumorspheres. Our study uncovers a previously unknown regulatory mechanism in which the HDACs-mediated Sp1 activation and *LINC00461* expression enable to induce maintains the stem cell population to fuel tumor growth and therapeutic resistance.

Selected recent publications:

1. Chang KY, Hsu TI, Hsu CC, ……, Chuang CK, Kao TJ, **Chuang JY***. (2017 Oct). Specificity protein 1-modulated superoxide dismutase 2 enhances temozolomide resistance in glioblastoma, which is independent of O ^{6}-methylguanine-DNA methyltransferase. *Redox Biol*, 13:655-64.

2. Chen TC[#], **Chuang JY**[#], Ko CY, ……, Chan H, Chang WC, Hsu TI. (2020 Feb). AR Ubiquitination Induced by the Curcumin Analog Suppresses Growth of Temozolomide-Resistant Glioblastoma through Disrupting GPX4-Mediated Redox Homeostasis. *Redox Biol*, 30:101413.

3. Yang WB, Hsu CC, Hsu TI, ……, Chen RM, Chang WC*, **Chuang JY***. (2020 Oct). Increased activation of HDAC1/2/6 and Sp1 underlies therapeutic resistance and tumor growth in glioblastoma. *Neuro Oncol*, 22(10):1439-1451.

4. Yang WB, Wu AC, Hsu TI, ……, Chang WC, Ko CY, **Chuang JY***. (2021 Sep). Histone deacetylase 6 acts upstream of DNA damage response activation to support the survival of glioblastoma cells. *Cell Death Dis*, 12(10):884.

5. Wu AC, Yang WB, Chang KY, ……, Chang WC, Chen PY*, **Chuang JY***. (2022 Feb). HDAC6 involves in regulating the lncRNA-microRNA-mRNA network to promote the proliferation of glioblastoma cells. *J Exp Clin Cancer Res*, 41(1):47.

Cell Therapy in Parkinson Disease

Kuo-Hsuan Chang (張國軒)

Professor, School of Medicine, Chang Gung University

Consultant Neurologist, Department of Neurology, Chang Gung Memorial Hospital-Linkou Medical Center

MD., PhD., Imperial College London

Abstract

Medication using levodopa, surgery including deep brain stimulation, and rehabilitation have all been established as current therapeutic strategies for Parkinson's disease (PD). Strong therapeutic effects have been demonstrated by these treatment methods, but they have been unable to stop the progression of the disease. Therefore cell therapy might be a key for modification of PD progression by reimplementing or regenerating dopaminergic neurons. Cell therapy for PD began with the transplantation of fetal nigral dopamine-containing neurons that improved motor abnormalities in the PD rodent models with good survival of grafts and axonal outgrowth. Thirty years have passed since the 2 clinical trials using fetal nigral transplantation for PD patients were reported and demonstrated unsatisfactory results. However, some patients receiving fetal nigral cell transplantation showed a continuous improvement of motor symptoms for over a decade. Therefore, a new European Union–funded multicenter clinical trial of fetal nigral cell transplantation, TRANSEURO trial, has been carried out recently. The advancement of biotechnology represented by pluripotent stem cells, mesenchymal stem cells and neural stem cells also brings a new hope to apply cell therapies in treating PD. Transplantation of these cell sources has already proven to reduce parkinsonian symptoms in rodent and primate models. Here we will discuss the history and implications for cell therapies for PD, the advantages and disadvantages of these treatments along with the results of relevant trials. Apart from confronting future with optimism in cell therapies, ethical and safety issues should be seriously concerned, with hope separated from hype.

Selected recent publications:

1. **Chang KH**, Cheng ML, Tang HY, Huang CY, Wu HC, Chen CM (2022). Alterations of sphingolipid and phospholipid pathways and ornithine level in the plasma as biomarkers of Parkinson's disease. Cells 11, 395.

2. **Chang KH**, Huang CY, Ou-Yang CH, Ho CH, Lin HY, Hsu CL, Chen YT, Chou YC, Chen YJ, Chen Y, Lin JL, Wang JK, Lin PW, Lin YR, Lin MH, Tseng CK, Lin CH (2021). In vitro genome editing rescues parkinsonism phenotypes in induced pluripotent stem cells-derived dopaminergic neurons carrying LRRK2 p.G2019S mutation. Stem Cell Res Ther 12(1):508.

3. Cheng YC, Chan YH, Hu CJ, Lu YC, Saek T, Hosoya M, Fujioka M, Okano H, Weng SM, Hsu CJ, **Chang KH** (2019). Generation of a human iPS cell line (CGMH.SLC26A4919-2) from a Pendred syndrome patient carrying SLC26A4 c.919-2A>G splice-site mutation. Stem Cell Res. 40: 101524 (Corresponding author)

4. Chiu CC, Wang HL, Weng YH, Chen RS, Chen CM, Yeh TH, Lu CS, Chen YJ, Huang YZ, **Chang KH** (2019). Generation of induced pluripotent stem cells from a young-onset Parkinson's disease patient carrying the compound heterozygous PLA2G6 p.D331Y/p.M358IfsX mutations. Stem Cell Res. 40: 101552

5. **Chang KH***, Lee-Chen GJ, Huang CC, Lin JL, Chen YJ, Wei PC, Lo YS, Yao CF, Kuo MW, Chen CM (2019). Modeling Alzheimer's Disease by Induced Pluripotent Stem Cells Carrying APP D678H Mutation. Mol Neurobiol. 56:3972-3983

Stem cell therapy – a new drug development experience sharing from Steminent

ChihYuan Ho (何智元)

Director of Clinical and Business Development, Steminent Biotherapeutics Inc.

Ph.D., University College London

Abstract

Cell-based therapies have been attracting much attention for their potential to provide promising approach for the treatment of unmet medical needs and are considered the fourth pillar of healthcare. Recently, extensive interest has focused on the application of stem cell-based therapies in tissue repair and disease treatments. Among different types of stem cells, mesenchymal stem cells (MSCs) are considered multipotent, which means they are able to differentiate into more than one type of cell and are proved to possess multiple mechanism of actions that are critical for many disease treatments. The unique characteristics of MSCs make them the most studied and applied stem cell type in clinical development.

Research of MSCs in neurodegenerative diseases have revealed encouraging evidence for their therapeutic potentials through multiple mechanism of actions. In the talk, I will share general observations from our clinical trials of stem cell therapy for spinocerebellar ataxia and also discuss the challenges for stem cell new drug development.

Selected recent publications:

1. Yoneda T, Choi BH, Gupta PK, Ho CY, Tsui YP, Wang LM, Fujiwara Y, Karasawa H, Moriya Y, Bando K, Kamiyama Y, Kanki M, Omura K, Watanabe T, Bae Y, Chou FC, Ham DS, Lee JY, Liu G, Liu Y, Ooi J, Tsurumaki Y. Non-clinical assessment of cell therapy products: the perspective from five Asian countries/regions based on regulatory guidelines and the underpinning rationales. Cytotherapy. 2021 Oct;23(10):874-885.

2. Coathup MJ, Blunn GW, Campion C, Ho CY, Hing KA. The effect of increased microporosity on bone formation within silicate-substituted scaffolds in an ovine posterolateral spinal fusion model. J Biomed Mater Res B Appl Biomater. 2017 May;105(4):805-814.

3. Ho CY, Sanghani A, Hua J, Coathup M, Kalia P, Blunn G. Mesenchymal stem cells with increased stromal cell-derived factor 1 expression enhanced fracture healing. Tissue Eng Part A. 2015 Feb;21(3-4):594-602.

4. Chan O, Coathup MJ, Nesbitt A, Ho CY, Hing KA, Buckland T, Campion C, Blunn GW. The effects of microporosity on osteoinduction of calcium phosphate bone graft substitute biomaterials. Acta Biomater. 2012 Jul;8(7):2788-94.

5. Lien CY, Chih-Yuan Ho K, Lee OK, Blunn GW, Su Y. Restoration of bone mass and strength in glucocorticoid- treated mice by systemic transplantation of CXCR4 and cbfa-1 co-expressing mesenchymal stem cells. J Bone Miner Res. 2009 May; 24 (5): 837-48.

創新標靶基因編輯CRISPR/Cas9:在視網膜疾病上的應用
Application of Genomic Editing Technology in Retinal Diseases

Shih-Hwa Chiou(邱士華)

Current title and affiliation
Director, Department of Medical Research, Taipei Veterans General Hospital
Distinguished Chair Professor, The Institute of Pharmacology / The Institute of Clinical Medicine & Gemonic Center, National Yang-Ming University, Taiwan
Appointment Researcher, Genomics Research Center, Academia Sinica, Taiwan
Ph.D.Institute of Clinical Medicine, National Yang-Ming University

Abstract

In recent years, due to advances in regenerative medicine and stem cell technology, as well as the use of health big data, cell therapy has broken through the barriers and bottlenecks in the treatment of many diseases and physiological research in the past, creating various possibilities for personalized precision medicine, and has become the focus of global medical competition. It is also a key policy direction for the government to promote innovative medical care in Taiwan.

The Ministry of Health and Welfare of the Executive Yuan promulgated the "Measures for the Administration of the Implementation or Use of Specific Medical Technical Inspection Instruments " (referred to as the Special management method) in 107, and formulated a draft of the "Regulations on the Administration of Regenerative Medicine Preparations " to promote Taiwan's regenerative medicine industry and emerging organisms. The basis for technological development. In recent years, Taiwan and Japan have been promoting economic structural reforms and industrial innovation measures. It is hoped that this exchange of Taiwanese clinical trials will help Japan’s successful experience in implementing the regenerative medicine industry and provide more complete domestic regenerative medicine products. Benefit the domestic public.

In the future, multi-center and cross-field clinical treatment can be carried out in Taiwan, which is expected to improve the treatment level for Taiwan's stem cell industry.

Selected recent publications:

1. Oncogenic circRNA C190 Promotes Non-Small Cell Lung Cancer via Modulation of the EGFR/ERK Pathway.Ishola AA, Chien CS, Yang YP, Chien Y, Yarmishyn AA, Tsai PH, Chen JC, Hsu PK, Luo YH, Chen YM, Liang KH, Lan YT, Huo TI, Ma HI, Chen MT, Wang ML, Chiou SH.Cancer Res. 2022 Jan 1;82(1):75-89.(IF=12.701;RANK=20/310;ONCOLOGY)

2. METTL3-dependent N6-methyladenosine RNA Modification Mediates the Atherogenic Inflammatory Cascades in Vascular Endothelium. Chien CS, Li Julie YS, YC, Wang ML, Aliaksandr A Yarmishyn, Tsai PH, Juan CC, Phu Neugyn, Cheng HM, Huo TI, **Chiou SH ***, Chien Shu ****Proc. Natl. Acad. Sci. USA*** 2021 118 (7) e2025070118 (IF= 9.412; RANK=8/71;Multidisciplinary Sciences)

3. Supramolecular Nanosubstrate-Mediated Delivery System Enables CRISPR/Cas9 Knockin of Hemoglobin Beta Gene for Hemoglobinopathies. Yang P, Chou SJ, Li J, Hui W, Liu W, Sun N, Zhang RY, Zhu Y, Tsai ML, Lai HI, Smalley M, Zhang X, Chen J, Romero Z, Liu D, Ke Z, Zou C, Lee CF, Jonas SJ, Ban Q, Weiss PS*, Kohn DB*, Chen K*, **Chiou SH***, Tseng HR*.***Science Advances*** 2020 Oct 23;6(43):eabb7107 (IF=13.116;RANK=4/71; MULTIDISCIPLINARY SCIENCES)

4. Dual Supramolecular Nanoparticle Vectors Enable CRISPR/Cas9-Mediated Knockin of Retinoschisin 1 Gene—A Potential Nonviral Therapeutic Solution for X-Linked Juvenile Retinoschisis. SJ Chou,Yang P, Ban Q, Yang YP, Wang ML, Chien CS, Chen SJ, Sun N, Zhu Y, Wang F, Zhang RY, Nguyen VQ, Liu Wnfei, Chen M, Jonas SJ, Weiss PS, Tseng HR*, **Chiou SH*.*****Advanced Science*** 2020 April 16;7(10):1903432 (IF=15.804;RANK=9/103; NANOSCIENCE & NANOTECHNOLOGY)

5. Ash2l interacts with Oct4-stemness circuitry to promote super-enhancer-driven pluripotency network. Tsai PH, Chien Y, Wang ML, Hsu CH, Laurent B, Chou SJ, Chang WC, Chien CS, Li HY, Lee HC, Huo TI, Hung JH, Chen CH, **Chiou SH*** Nucleic Acids Res 2019 Sep 26. (IF= 11.147;RANK= 15/297; BIOCHEMISTRY & MOLECULAR BIOLOGY)

From bench to bedside, a study of mesenchymal stem cell-like cells in the blood

Hong-Lin Su(蘇鴻麟)
Professor

Department of Life Sciences

National Chung Hsing University

Ph.D.Institute of Life Sciences, National Defense Medical Center

Abstract

The sustained therapeutic effects and tissue repairment are two significant advantages of cell therapy. Besides the hematopoietic stem cells, stem cells-orientated clinical applications require cell purification, amplification or differentiation. These cellular processes require sophisticated techniques and comprehensive regulations to fulfill strict quality controls and assurance. In order to provide a practical and feasible cell resource for clinical application, we introduce a method to produce a mesenchymal stem cell-like population in the blood that shows strong immunomodulation and tissue repairment activity. These cells are evaluated in animal models and several clinical trials at multiple centers, such as late-stage osteoarthritis, discogenic pain and carpal tunnel syndrome, as a disease-modified drug for long-term pain relief and tissue regeneration.

Selected recent publications:

1. Huang, M,H,, Chou, Y,W,, Li, M.H., et al. (2019). Epigenetic targeting DNMT1 of pancreatic ductal adenocarcinoma using interstitial control release biodegrading polymer reduced tumor growth through hedgehog pathway inhibition..*PharmacologicalResearch.* 139, 50-61.

2. Chang, C. Y. Chen, S. M. Lu, H. E. et al. (2015). Nbutylidenephthalide attenuates Alzheimer's disease-like cytopathy in Down syndrome induced pluripotent stem cell-derived neurons. *Scientific Reports*, 5, 8744.

3. Chen, S.M., Lee, M.S., Chang, C.Y., et al. (2015). Prerequisite Oct4 maintenance potentiates the neural induction of differentiating human embryonic stem cells and induced pluripotent stem cells. *Cell Transplantation.*, 24(5), 829-44.

4. Sun, C. K. Lee, F. Y. Kao, Y. H. et al. (2015). Systemic combined melatonin-mitochondria treatment improves acute respiratory distress syndrome in the rat. *Journal of Pineal Research* , 58(2):137-150. (SCI, 3/83, Physiology).

5. Shen, C.I., Lee, H.C., Kao, Y.H., Wu, C.S., Chen, P.H., Lin, S.Z., Lai, P.S., Su, H.L. (2014). EpCAM induction functionally links to the Wnt-enhanced cell proliferation in human keratinocytes .*Cell Transplantation*, 23: 1031-1044.

Translational neurosciences of personalized medicine for omega-3 fatty acids in depression

Kuan-Pin Su(蘇冠賓)

Professor and Deputy Superintendent, An-Nan Hospital, China Medical University, Tainan, Taiwan

PI, Mind-Body Interface (MBI-Lab), Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

M.D., Kaohsiung Medical College, Kaohsiung, Taiwan

Ph.D.Institute of Psychiatry, King's College London, UK

Abstract

Depression is one of the leading causes of morbidity and mortality in medicine. Current available treatments clearly do not meet clinical needs, while clinicians and researchers are facing the huge challenge of developing effective depression treatments despite of the advance of neurosciences. Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have a range of neurobiological activities in modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity, by which could contribute to the antidepressant effects. The committee of the International Society for Nutritional Psychiatry Research (ISNPR) organized an expert panel and conducted a Delphi-process to develop a consensus-based practice guideline for clinical use of n-3 PUFAs in MDD. Evidence from epidemiological, pre-clinical, and clinical studies have revealed that omega-3 PUFAs play an important role in the treatment and prevention of certain subgroups of clinical depression. According to biological specificity and safety consideration, omega-3 PUFAs is a potential antidepressant treatment for pregnant women, children, adolescents, and inflammation-related depression. Omega-3 PUFAs are well tolerated and accepted by general populations for health promoting. Thus, more research on stratifying depression is needed to justify the clinical application of omega-3 PUFAs as one of the first-line antidepressant treatments in specific populations with depression.

Selected recent publications:

1. Guu TW, Mischoulon D, Sarris J, Hibbeln J, McNamara RK, Hamazaki K, Freeman MP, Maes M, Matsuoka Y, Belmaker RH, Jacka FN, Pariante CM, Berk M, Marx W, **Su KP***. International Society for Nutritional Psychiatry Research (ISNPR) Practice Guidelines for Omega-3 Fatty Acids in the Treatment of Major Depressive Disorder. **Psychotherapy and Psychosomatics** 2019;88(5):263-273.

2. Yang B, Lin L, Bazinet RP, Chien YC, Chang JPC, Satyanarayanan SK, Su HX, **Su KP*.** Clinical efficacy and biological regulations of omega-3 PUFA-derived endocannabinoids in major depressive disorder. **Psychotherapy and Psychosomatics** 2019;88(4):215-224.

3. Bosini A, Nicolaou A, Camacho-Munoz MD, Kendall A, Di Benedetto MG, Giacobbe J, **Su KP***. Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. **Molecular psychiatry** 2020Nov;26(11):6773-6788.

4. Lin YW, Wu AIC, Su HX, **Su KP***. Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: The common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids. **Brain Behavior and Immunity** 2020 Oct; 89: 604-614.

5. Lin PY, Cheng C, Satyanarayanan SK, Chiu LT, Chien YC, Chuu CP, Lan TH, **Su KP***. Omega-3 fatty acids and blood-based biomarkers in Alzheimer's disease and mild cognitive impairment: A randomized placebo-controlled trial. **Brain Behavior and Immunity** 2022 Jan;99:289-298.

Fish oil alleviates LPS-induced inflammation and depressive-like behavior in mice via restoration of metabolic impairments

HuanXing Su(蘇煥興)
Professor,Institute of Chinese Medical Sciences, University of Macau

Ph.D.,University of Hong Kong

Abstract

Fish oil (FO) pre-treatment could improve the lipopolysaccharides (LPS)-induced depressive-like behavior in mice but did not alter the expression of stress hormones associated with the hypothalamic-pituitary-adrenal (HPA) axis. The exact mechanisms underlying the protective effects of FO remain elusive. Here we applied the metabolomic technique to investigate the potential involvement of FO metabolites in ameliorating depressive-like behaviors in LPS-injected mice. It revealed that LPS-injection stimulated systemic inflammation, exhausted the nicotinamide adenine dinucleotide (NAD) level in the brain, decreased energy metabolism and impaired neuronal function, which collectively contributed to depressive-like behaviors in mice. FO treatment enhanced the production of neuroprotective metabolites including taurine, hypotaurine and tyramine, decreased the generation of neurotoxic agents such as ADPR, glutamate accumulation and oxidized glutathione, and prevented the NAD exhaustion in the brain, which might underlie the beneficial effects of FO against LPS-induced inflammation and depressive-like behaviors.

Selected recent publications:

1. Peng Y, Shi Z, Kumaran Satyanarayanan S, He C, Li P, Wan JB, **Su H***. Fish oil alleviates LPS-induced inflammation and depressive-like behavior in mice via restoration of metabolic impairments. Brain Behav Immun. 2020 Nov;90:393-402.

2. Ke M, Chong CM, Zeng H, Huang M, Huang Z, Zhang K, Cen X, Lu JH, Yao X, Qin D*, **Su H***. Azoramide protects iPSC-derived dopaminergic neurons with PLA2G6 D331Y mutation through restoring ER function and CREB signaling. Cell Death Dis. 2020 Feb 18;11(2):130.

3. Yan L, Xie Y, Satyanarayanan SK, Zeng H, Liu Q, Huang M, Ma Y, Wan JB, Yao X, Su KP, **Su H***. Omega-3 polyunsaturated fatty acids promote brain-to-blood clearance of β-Amyloid in a mouse model with Alzheimer's disease. Brain Behav Immun. 2020 Mar;85:35-45.

4. Tan Y, Ke M, Huang Z, Chong C, Cen X, Lu JH, Yao X*, Qin D*, **Su H***. Hydroxyurea facilitates manifestation of disease relevant phenotypes in patients-derived iPSCs-based modeling of late-onset Parkinson's disease. Aging and disease. 2019 Oct 1;10(5):1037-1048.

5. Luo C, Ren H, Yao X, Shi Z, Liang F, Kang JX, Wan JB, Pei Z, Su KP, **Su H***. Enriched Brain Omega-3 Polyunsaturated Fatty Acids Confer Neuroprotection against Microinfarction. EBioMedicine. 2018 Jun;32:50-61

Diagnosis and quantification of symptoms of psychiatric disorders by digital phenotyping

Taishiro Kishimoto
Professor, Hills Joint Research Laboratory for Future Preventive Medicine and Wellness, Keio University School of Medicine, Tokyo Japan

M.D. Ph.D. Keio University School of Medicine

Abstract

One of the biggest challenges in the field of psychiatry is the lack of biomarkers. As a result, diagnosis or assessment of disease severity are done through conversations between patients and psychiatrists. Such approaches, which can be influenced by the experience of the evaluator, lack objectivity and reproducibility, and make research and clinical trials difficult. Recently, the utilization of digital phenotype, i.e. behavioral data from smartphones and wearable devices, has become a worldwide trend in the psychiatry field.

Our group has been developing technologies for diagnosing (screening) and assessing the severity of mental disorders using such digital phenotypes. Specifically, we have developed technologies for screening and severity assessment of depression using a wristband-type wearable device, screening technology for depression using Holter ECG, screening technology for dementia using natural language processing.

In this presentation, the research projects above will be presented and the prospects for using digital phenotype will be discussed.

Selected recent publications:

1. **Kishimoto T**, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. Lancet Psychiatry. 2021 May;8(5):387-404.

2. Shiga K, Izumi K, Minato K, Sugio T, Yoshimura M, Kitazawa M, Hanashiro S, Cortright K, Kurokawa S, Momota Y, Sado M, Maeno T, Takebayashi T, Mimura M, **Kishimoto T**. Subjective well-being and month-long LF/HF ratio among deskworkers. PLoS One. 2021 Sep 7;16(9): e0257062.

3. Horigome T, Sumali B, Kitazawa M, Yoshimura M, Liang KC, Tazawa Y, Fujita T, Mimura M, **Kishimoto T**. Evaluating the severity of depressive symptoms using upper body motion captured by RGB-depth sensors and machine learning in a clinical interview setting: A preliminary study. Comprehensive Psychiatry. 2020 Feb 20;98:152169.

4. Tazawa Y, Liang KC, Yoshimura M, Kitazawa M, Kaise Y, Takamiya A, Kishi A, Horigome T, Mitsukura Y, Mimura M, K**ishimoto T**. Evaluating depression with multimodal wristband-type wearable device: screening and assessing patient severity utilizing machine-learning, Heliyon. 2020 Feb 4;6(2):e03274. doi: 10.1016/j.heliyon.2020.e03274. PMID: 32055728; PMCID: PMC7005437.

5. **Kishimoto T**, Hagi K, Nitta M, Kane JM, Correll CU. Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. World Psychiatry. 2019 Jun;18(2):208-224.

Associations of leptin, C-reactive protein and corticostriatal connectivity in bipolar disorder

Po See Chen
Professor,Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Director, Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Ph.D., National Cheng Kung University

M.D., Kaohsiung Medical University

Abstract

Bipolar disorder (BD) and metabolic disturbance represent a chronic state of low-grade inflammation and corticostriatal circuitry alterations. Herein, we aimed to investigate whether plasma leptin, an adipokine that plays a key role in the interplay of metabolism and inflammation, is associated with corticostriatal connectivity in patients with BD. Twenty-eight BD I patients, 36 BD II patients and 66 healthy controls were enrolled and completed the Hamilton Depression Rating Scale, the Young Mania Rating Scale, and the Recent Life Change Questionnaire. Fasting plasma leptin and C-reactive protein (CRP) levels were measured, and corticostriatal connectivity was examined using functional magnetic resonance imaging (fMRI). The relationships between leptin, CRP and body mass index (BMI) identified in the controls and BD II patients were absent in the BD I patients. We did not find a significant group difference in the leptin level; nevertheless, the negative correlation between leptin level and corticostriatal connectivity (ventrolateral prefrontal cortex and inferior temporal gyrus) observed in the healthy controls was absent in the BD patients. The disproportionate increase in leptin level with increasing BMI in BD indicated a potential inflammatory role of white adipose tissue in BD. Furthermore, higher CRP levels in BD I patients might induce leptin resistance. Collectively, our results implied vulnerability to inflammatory and metabolic diseases in patients with BD, especially BD I.

Selected recent publications:

1. Wei SY, Tseng HH, Chang HH, Lu TH, Chang WH, Chiu NT, Yang YK, **Chen PS**: Dysregulation of oxytocin and dopamine in the corticostriatal circuitry in bipolar II disorder. Translational Psychiatry 2020 Aug;10:281~1-281~8.
2. **Chen PS**, Jamil A, Tseng HH, Wei SY, Liu LC, Nitsche MA, Kuo MF: Nonlinear Effects of Dopamine D1 Receptor Activation on Visuomotor Coordination Task Performance. Cerebral Cortex 2020 Oct;30(10):5346-5355.
3. Chang HH, Tseng HH, Chang WH, Huang KC, Lu TH, Yang YK, **Chen PS**: Peripheral insulin sensitivity predicting cognitive function in euthymic bipolar disorder patients. CNS Spectr. 2021 Mar 11;1-6.
4. Hsueh YS, Lin CY, Chiu NT, Yang YK, **Chen PS**, Chang HH: Changes in striatal dopamine transporters in bipolar disorder and valproate treatment. European Psychiatry 2021 Jan 8;64(1):e9~1-e9~7.
5. Tseng HH, Chang HH, Wei SY, Lu TH, Hsieh YT, Yang YK, **Chen PS**: Peripheral inflammation is associated with dysfunctional corticostriatal circuitry and executive dysfunction in bipolar disorder patients. Brain, Behavior, and Immunity 2021 Jan;91:695-702.

Cortical maps following peripheral nerve reconstruction

Yu-Cheng Pei, MD PhD (裴育晟)
Current title and affiliation

Professor and Attending Physician at Department of Physical Medicine and Rehabilitation and School of Medicine

復健部部長、主治醫師、教授

Chang Gung Memorial Hospitalat Linkou/Chang Gung University

林口長庚紀念醫院/長庚大學

Abstract

The conventional dogma indicates that the removal of sensory inputs to the sensory cortex results in massive reorganization in the brain, but recent studies support a different theory by showing a stability of cortical topography without reorganization. It is important to understand the neuronal mechanisms underlying neuroplasticity after deafferentation. To this end, we designed anexperimental model that deliberately induces aberrant reinnervation of peripheral nerve to evaluate the change of cortical topography and direction tuning in neurons in the somatosensory cortex (S1BF).

We applied two-photon calcium imaging on awake animal and developed a long-term brain window method to chronically record the topographicalreorganization of neuronal selectivity.In addition, electrophysiological recording of spiking activities was applied at multiple time points after reinnervation surgery to observe the chronological changes of neuronal tuning over time. After the induction of aberrant reinnervation in the periphery,whisker-wise topography in S1BF was systematically shiftedand the shift can be predicted by the pattern of aberrant inputs. A proportion of barrels whose original whisker inputs were absent also responded to whisker stimulations and, most importantly,tuned to whiskers of the same row, a property suggesting a mechanism of lateral sprouting.Onemonth after reinnervation surgery, a proportion of neurons showed extremely strong direction selectivity, a property we dubbed as “nascent tuning”. Interestingly, the proportion of neurons with nascent tuning gradually decreased afterwards, implying that nascent tuning is mediated by the early restoration of sensory inputs after the reinnervation surgery.

Selected recent publications:

1. Pu SW, et al. Decoupling Finger Joint Motion in an Exoskeletal Hand: A Design for Robot-assisted Rehabilitation. IEEE transactions on industrial electronics. 2020 Jan. 67(1) 686-697.
2. Pei Y, et al. Neural mechanisms of tactile motion integration in primary somatosensory cortex. Neuron. 2011; 69(3):536-547.
3. Pei Y, et al. Shape invariant coding of motion direction in primary somatosensory cortex. PLoS Biology. 2010;8(2):e1000305.
4. Pei Y, et al. The tactile integration of local motion cues is analogous to its visual counterpart. Proc Natl Acad Sci USA. 2008 Jun 10;105(23):8130-5.

Habitual physical activity mediates the acute exercise-induced modulation of anxiety-related amygdala functional connectivity

Yawei Cheng(鄭雅薇)
Current title and affiliation

Distinguished Professor/Director

Institute of Neuroscience, National Yang Ming Chiao Tung University

M.D. College of Medicine, Chang Gung University

Ph.D.Institute of Neuroscience, National Yang Ming Chiao Tung University

Abstract

Aerobic exercise, in relation to physical activity, has been shown to have beneficial effects on anxiety. However, the underlyig neural mechanism remains elusive. Using a within-subject crossover design, this fMRI study examined how exercise (12-min treadmill running versus walking) mediated amygdala reactivity to explicit and implicit (backward masked) perception of emotional faces in young adults (N = 40). Results showed that acute exercise-induced differences of state anxiety (STAI-S) varied as a function of individual's habitual physical activity (IPAQ). Subjects with high IPAQ levels showed significant STAI-S reduction (P< .05). Path analyses indicated that IPAQ explained 14.67% of the variance in acute exercise-induced STAI-S differences. Running elicited stronger amygdala reactivity to implicit happiness than fear, whereas walking did the opposite. The exercise-induced amygdala reactivity to explicit fear was associated with the IPAQ scores and STAI-S differences. Moreover, after running, the amygdala exhibited a positive functional connectivity with the orbitofrontal cortex and insula to implicit happiness, but a negative connectivity with the parahippocampus and subgenual cingulate to implicit fear. The findings suggest that habitual physical activity could mediate acute exercise-induced anxiolytic effects in regards to amygdala reactivity, and help establish exercise training as a form of anxiolytic therapy towards clinical applications.

Selected recent publications:

1. Chen YC, Chen C, Martínez RM, Fan YT, Liu CC, Chen CY, Cheng Y* (2021) An amygdala-centered hyper-connectivity signature of threatening face processing predicts anxiety in youths with autism spectrum conditions. *Autism Research* 14 (11):2287-99

2. Chen C, Martínez RM, Cheng Y* (2020) The key to group fitness: the presence of another synchronizes moral attitudes and neural responses during moral decision-making. *NeuroImage* 213: 116732.

3. Chen C, Martínez RM, Liao TT, Chen CY, Yang CY, Cheng Y* (2020) An integrative analysis of 5HTT-mediated mechanism of hyperactivity to non-threatening voices. *Communications Biology* 3: 113.

4. Chen YC, Chen C, Martínez RM, Etnier J, Cheng Y* (2019) Habitual physical activity mediates the acute exercise-induced modulation of anxiety-related amygdala functional connectivity. *Scientific Reports* 9: 19787.

5. Chen C, Hu CH, Cheng Y* (2017) Mismatch negativity stands at the crossroads between explicit and implicit emotional processing. *Human Brain Mapping* 38(1): 140-150.

The function of cortical layers in the sensory cortex

Chun-I Yeh(葉俊毅)
Assistant Professor, Department of Psychology,Neurobiology and Cognitive Science Center, and Graduate Institutes of Brain and Mind Sciences at College of Medicine, National Taiwan University,Taiwan

PhD, University of Connecticut

Abstract

In macaques and humans, the cerebral cortexoccupies >70% of the brain volume (<30% in rodents), and consists of six distinct layers of neurons that differ in both morphology and neurophysiology. A main question in cortical neurophysiology is to understand the function of cortical layers and how incoming information is transformed through different layers to form perceptions. Measuring neural activity simultaneouslyacross cortical layers will be critical for revealing the computational roleand effect of each cortical layer. We did this by applying a multiple-electrode array (8 parallel shanks x 8 contacts each shank, 200 um spacing, Neuronexus) to simultaneously record from different layers of macaque monkey primary visual cortex V1. We studied both physiological responses to sensory stimuli and synchronous responses of pairs of cells according to their laminar location. We used different stimulus ensembles to measure response properties of V1 neurons and found that both receptive-field dissimilarity and response bias were smaller for neurons in the granular layerthan those in the supragranular layer. Analysesof spike triggered local field potential (st-LFP) signals also revealed laminar difference:the lateral space constant of the st- LFP was significantly shorter and lateral propagation speed of the st-LFP was significantly slower in the in thesupragranular layer than in the granular and infragranular layers. Moreover, the preferred frequency of gamma oscillation differs between the supragranularlayer and the granular layer.These results provide some insight about general rules of cortical processing across different laminar structures.

Selected recent publications:

1. Yeh CI, Xing D, Williams PE, Shapley RM (2009). Stimulus ensemble and cortical layer determine V1 spatial receptive fields. Proceedings of the National Academy of Sciences of the United States of America, 106, 14652-14657.

2. Yeh CI, Xing D, Shapley RM (2009). “Black” responses dominate macaque primary visual cortex V1. Journal of Neuroscience, 29, 11753-11760.

3. .Xing D, Yeh CI, Gordon J, Shapley RM (2014). Cortical brightness adaptation when darkness and brightness produce different dynamical states in the visual cortex. Proceedings of the National Academy of Sciences of the United States of America, 111, 1210-1215.

4. Huang WN, Wu HY, Pei YC, Yeh CI (2019). Response asymmetry of red and green in macaque primary visual cortex. Society for Neuroscience Abstract No 143.09.

5. Han C, Wang T, Yang Y, Wu Y, Li Y, Dai W, Zhang Y, Wang B, Yang G, Cao Z, Kang J, Wang D, Li L, Yu H, Yeh CI, Xing D (2021). Multiple gamma rhythms carry distinct spatial frequency information in primary visual cortex. Public Library of Science: Biology 19: e3001466.

Interactive dynamics of the sensorimotor cortices during dexterous forelimb movement in mice

Yu-Wei Wu(吳玉威)
Assistant Research Fellow

Institute of Molecular Biology, Academia Sinica, Nangang, Taiwan

Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Nangang, Taiwan

Adjunct Assistant Professor

Department of Life Science, College of Life Science, National Taiwan University, Taipei, Taiwan

Ph.D.University College London

Abstract

Understanding how the primary motor cortical (M1) neural activity coordinates to achieve fine movement control is a central challenge in comprehending brain function. The M1 neural activity state can be described as a dynamic system, and its spiking patterns are strongly influenced by external inputs from other brain regions, such as the somatosensory cortex (S1) and the pre-motor cortex (M2), and the thalamus. However, the spatiotemporally detailed interactive dynamics across sensorimotor cortices are largely unexplored due lacking an adequate method. Here, we established a large-scale in vivo cortical extracellular electrophysiology platform consisting of a microwire bundle and a CMOS multielectrode array (MEA) (Obaid *et al*., 2020) to concurrently record the M1, M2, and S1spiking activity during a forelimb food-pallet reaching movement. We conducted spike sorting and monitored over 2000 units across multiple cortices chronically with this platform. We applied a machine learning framework, Latent Factor Analysis via Dynamical Systems or LFADS (Pandarinat*et al*., 2018), to search for low-dimensional neural states' dynamics and provide high-quality denoised spike rates across the M1, M2, and S1. Our results reveal the interactive dynamics undying the movement kinematic variables. In addition, using the denoised firing rates, we decoded the neural dynamics and predicted forelimb positions with high performance (R^2> 0.9), suggesting this framework is also suitable to apply in brain-computer interfaces (BCIs).

Selected recent publications:

1. Obaid A*, Hanna M*, **Wu YW* (co-first author)**, Kollo M*, Racz R, Angle MR, Muller J, Wray W, Franke F, Blackbill N, Chichilinsky EJ, Hierlemann A, Ding JB, Schaefer AT, Melosh NA (2019) Massively parallel microwire arrays integrated with CMOS chips for neural recording. ***Science Advances*** 6(12) eaay2789

2. **Wu YW*(co-corresponding author)**, Gordleeva S, Tang X, Shih PY, Dembitskaya Y, Semyanov A* (2019) Morphological profile determines frequency of spontaneous calcium events in thin astrocytic processes. ***Glia*** 67(2):246-262

3. Du K*, **Wu YW* (co-first author)**, Lindroos R, Liu Y, Rózsa B, Katona G, Ding JB, Kotaleski JH (2017) Cell-type specific inhibition of the dendritic plateau potential in striatal spiny projection neurons. ***Proceedings of the National Academy of Sciences (PNAS)*** 114(36): E7612-E7621.

4. Guo L*, Xiong H*, Kim JI*, **Wu YW* (*co-first author)**, Lalchandani RR, Cui Y, Shu Y, Xu T, Ding JB (2015) Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. ***Nature Neuroscience*** 18(9):1299-309

5. **Wu YW**, Kim JI, Tawfik VL, Lalchandani RR, Scherrer G, Ding JB (2015) Input- and cell type-specific Endocannabinoid-Dependent LTD in the striatum. ***Cell Reports*** 10(1):75-87