Plenary Session Speech (II)

HCN2 ion channels: critical drivers of pain

Speaker: Peter McNaughton

Professor of Pharmacology, King's College London, UK

Ph.D., Balliol College, Oxford, UK

Location: 生物醫學科學研究所 B1B會議室
Institute of Biomedical Sciences (IBMS) B1B

Time: Sept. 12 13:55-14:40
Video presentation

Abstract

We would all like to avoid pain – but acute pain (the pain felt shortly after injury) is essential for life, because it is a critical warning system that protects us from damage. Chronic pain, by contrast, is a long-lasting pain that often serves no useful purpose.

HCN (Hyperpolarization-activated, Cyclic Nucleotide gated) ion channels are activated both by membrane hyperpolarization and by inflammatory mediators that activate G-protein coupled receptors and elevate the intracellular level of cAMP. When activated, HCN channels generate an inward current that can depolarize a nerve cell to threshold and initiate action potential generation. In nociceptive (pain-sensing) neurons these action potentials transmit a sensation of pain up to conscious levels. We found that genetically deleting the HCN2 isoform in nociceptors abolished the neuropathic pain caused by nerve injury (ref 5). Similar results were obtained with an HCN ion channel blocker. Critically, there was no effect on acute pain thresholds. These results show that HCN2 is a critical driver of chronic pain.

In more recent work we have extended the idea that HCN2 may drive abnormal excitability of sensory neurons to other pathologies – painful diabetic neuropathy, arthritis, migraine and tinnitus, with promising results in all these apparently distinct conditions (refs 2, 3 and unpublished work).

We conclude that HCN2 is a critical target for the development of novel analgesics. A challenge has been to develop selective blockers that will inhibit HCN2 ion channels without interfering with the closely-related HCN4 ion channels that are important in regulating the heart rate

Selected recent publications:

1. Vilar, Bruno, Tan, C-H and McNaughton, P. A. (2020). The TRPM2 ion channel is a heat detector in somatosensory neurons. Nature (in press)

2. Tsantoulas C, Lainez S, Wong S, Mehta I, Vilar B & McNaughton PA. (2017). Hyperpolarization-activated cyclic nucleotide-gated 2 (HCN2) ion channels drive pain in mouse models of diabetic neuropathy. Science Transl Med 9, eaam6072.

3. Tsantoulas, C., Mooney, E.R. & McNaughton, P.A. (2016). HCN ion channels: basic science opens up possibilities for therapeutic intervention in neuropathic pain. Biochem J. 473, 2717-36.

4. Tan, C.-H. & McNaughton, P.A. (2016). The TRPM2 ion channel is required for sensitivity to warmth. Nature 536, 460-63.

5. Emery EC, Young GT, Berrocoso EM, Chen L, & McNaughton PA (2011). HCN2 ion channels play a central role in inflammatory and neuropathic pain. Science 333, 1462-1466.

Plenary Session Speech (II)

Blood biomarkers for Alzheimer's disease: tools for screening, diagnosis and therapy monitoring.

Speaker: Kaj Blennow

Location:生物醫學科學研究所 B1C會議室
Institute of Biomedical Sciences (IBMS) B1C

Time: Sept. 12 13:55-14:40

Abstract

Kaj Blennow is MD, and holds a Specialist Competence in General Psychiatry and in Clinical Chemistry. He is Professor and Academic Chair in Neurochemistry at University of Gothenburg, and Head of the Clinical Neurochemistry Lab at Sahlgrenska University Hospital, Gothenburg, Sweden. Prof. Blennow holds the Torsten Söderberg Professorship at the Royal Swedish Academy of Sciences.

Dr. Blennow has published more than 1200 original research papers and 150 review articles in peer-reviewed journals. Many papers wer published in New Engl J Med, Lancet, Lancet Neurol, Nature Med, JAMA, PNAS, Science Transl Med etc.. The numbers of citation with his papers is more than 8000 and the H-index of 133.

He is President of the Society for CSF analysis and Clinical Neurochemistry, head of the Alzheimer's Association QC program for CSF biomarkers and Chair of the International Federation of Clinical Chemistry (IFCC) working group on CSF proteins.

He has received several scientific awards, such as The CINP Award (1992), the IPA Research Award (1993), the Alois Alzheimer Research Award (2001), the ECNP Clinical Research Award (2010), the Henry Wisniewski Lifetime Achievement Award in Alzheimer's Disease Research (2011), and the International Foundation for Research in Alzheimer's Disease European Grand Prix in Research (2013), and the Söderberg Price in Medicine at the Swedish Society for Medicine (2016), and the Nordic Prize in Medicine.

Selected recent publications:

Diagnostic and prognostic value of serum NfL and p-Tau181 in frontotemporal lobar degeneration. Alberto Benussi, Thomas Karikari, Nicholas J. Ashton, Stefano Gazzina, Enrico Premi et al. Journal of neurology, neurosurgery, and psychiatry, Journal article 2020

Plasma phospho-tau181 in presymptomatic and symptomatic familial Alzheimer‘s disease: a longitudinal cohort study A. O'Connor, Thomas Karikari, T. Poole, Nicholas J. Ashton, Juan Rodriguez et al. Molecular Psychiatry, Journal article 2020

Cerebrospinal Fluid 7-Ketocholesterol Level is Associated with Amyloid-beta(42) and White Matter Microstructure in Cognitively Healthy Adults A. Iriondo, M. Garcia-Sebastian, A. Arrospide, M. Arriba, S. Aurtenetxe et al. Journal of Alzheimers Disease, Journal article 2020

Maximizing Safety in the Conduct of Alzheimer‘s Disease Fluid Biomarker Research in the Era of COVID-19 S. E. Schindler, G. A. Jicha, P. T. Nelson, C. D. Keene, Kaj Blennow et al. Journal of Alzheimers Disease, Journal article 2020

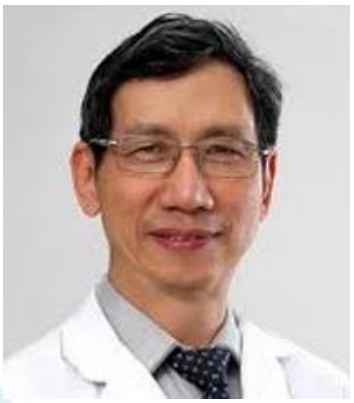
Serum Hepcidin Levels in Cognitively Normal Older Adults with High Neocortical Amyloid-beta Load P. Chatterjee, M. Mohammadi, K. Goozee, T. M. Shah, H. R. Sohrabi et al. Journal of Alzheimers Disease, Journal article 2020

Plenary Session Speech (II)

Intranasal infusion of mitochondria in treatment of 6-hydroxydopamine-lesioned rat models of Parkinson's disease via the rostral migratory stream

Speaker: Chin-San Liu (劉青山)
Chief, Vascular and Genomic Research Center and Vice-Superintendent,
Changhua Christian Hospital, Taiwan.
Ph.D., National Yang-Ming University, Taiwan
M.D., China Medical University, Taiwan

Location:跨領域大樓
Interdisciplinary Research Building for Science and Technology (IRB)
Time: Sept. 12 13:55-14:40



Abstract

The potential therapy via intranasal mitochondria-delivery system is emerging as a noninvasive option for resilience of damaged dopamine neuron. Thus, we validated mitochondrial transplantation using unilateral nasal infusion in treatment of unilaterally 6-hydroxydopamine-induced rat model of Parkinson's disease (PD). The biochemical and physical data were measured during whole panel study. The delivered mitochondria labeled with BrdU was observed in the rostral migratory stream, called subventricular zone-olfactory trigone connection, in ipsilateral and contralateral hemisphere contained TH-positive fibers, but it was absent in region of substantia nigra (SN). Either infused mitochondria with pep-1 conjugation or mitochondria alone dominantly reduced the apomorphine-induced rotational behavior of PD rats and improved locomotive activity to compare with the treated control of sham and pep-1 alone. The survival of tyrosine hydroxylase-positive dopaminergic (DA) neurons in SN and their input axons in striatum was increased simultaneously. The mechanism could be associated with the elevated expression of mitochondrial complex I protein in soma of DA neuron located lesioned SN. Mitochondrial transplantation conjugated with pep-1, compared to naked mitochondria or sham group, can reduce pro-inflammatory reaction in brain tissue especially the interleukin 1 alpha and interleukin 12. Conclusion: Nose-to-brain delivery system is a valid and potential approach for mitochondrial transplantation in treatment of PD with safety and non-invasive procedures.

Selected recent publications:

1. Liu SW, Chang JC, Chuang SF, Liu KH, Cheng WL, Chang HJ, Chang HS, Lin TT, Hsieh CL, Lin WY, Hsieh M, Kuo SJ, Liu CS* (2019) Far-infrared Radiation Improves Motor Dysfunction and Neuropathology in Spinocerebellar Ataxia Type 3 Mice. Cerebellum 18:22-32.

2. Chang JC, Chang HS, Wu YC, Cheng WL, Lin TT, Chang HJ, Kuo SJ, Chen ST, Liu CS* (2019) Mitochondrial transplantation regulates antitumour activity, chemoresistance and mitochondrial dynamics in breast cancer. J Exp Clin Cancer Res 38:30.

3. Lin YT, Chen ST, Chang JC, Teoh RJ, Liu CS*, Wang GJ* (2019). Green extraction of healthy and additive free mitochondria with a conventional centrifuge. Lab Chip 18:3862-69.

4. Hsiao YH, Li CW, Chang JC, Chen ST, Liu CS*, Wang GJ* (2018) Chemical-Free Extraction of Functional Mitochondria Using a Microfluidic Device. Inventions 3:68.

5. Chang JC, Wu SL, Hoel F, Cheng YS, Liu KH, Hsieh M, Hoel A, Tronstad KJ, Yan KC, Hsieh CL, Lin WY, Kuo SJ, Su SL, Liu CS* (2016) Far-infrared radiation protects viability in a cell model of Spinocerebellar Ataxia by preventing polyQ protein accumulation and improving mitochondrial function. Sci Rep 6:30436.

Plenary Session Speech (II)

Characterizing autism spectrum disorder by the longitudinal and endophenotypic approaches of brain structures and functions

Speaker: Susan Shur-Fen Gau (高淑芬)

Professor, Department of Psychiatry, National Taiwan University Hospital & College of Medicine, National Taiwan University, Taiwan.

Ph.D., Yale University

Location: 分子生物研究所
Institute of Molecular biology (IMB)

Time: Sept. 12 13:55-14:40

Abstract

Autism spectrum disorder (ASD) is a clinically and genetically heterogeneous neurodevelopmental disorder with an unknown pathogenetic mechanism and a lack of effective early detection and treatment for ASD. This presentation aims to characterize ASD based on endophenotype (sibling design) and longitudinal approaches of the neuropsychological and brain images data collected at NTU. Comparing the neuropsychological, neuroanatomy, white-matter (WM) tracts microstructural properties, and intrinsic functional connectivity (iFC) among ASD probands, unaffected siblings (US) and typically developing controls (TDC), results suggest that verbal and spatial working memory, atypical neuroanatomy and iFC surrounding the MCC, several white-matter tracts related to social communication and interactions with aberrant integrity, maybe potential endophenotypic markers for ASD. Our longitudinal neuropsychological data showed that despite significant improvement in attention and most executive functions with time except cognitive flexibility and inhibition control, ASD still suffered from impaired focused attention, cognitive flexibility, executive functions, and visual memory than TDC at follow-up. Our longitudinal iFC results suggest a clinically meaningful relationship between the atypical development of frontoparietal structural connections and the dynamics of the ASD phenotype through early adulthood. Our longitudinal whole-brain structural results provide evidence to support the atypically developmentally increasing fractional anisotropy of several WM tracts in ASD than TDC during follow-up using the normative model method, and altered within- and between-cortical changes of the regions relating to the social and language networks predicting improving ASD phenotype across a crucial developmental phase. These findings highlight several potential markers searching for the etiologies and future outcomes of ASD.

Selected recent publications:

Lin, H. Y., Kesseler, D., Tseng, W. I. & Gau, S. S. Compensatory functional segregation related to the salience network in unaffected siblings of youths with ADHD. *J Am Acad Child Adolesc Psychiatry (in press)* (2020).

Shang, C. Y., Lin, H. Y. & Gau, S. S. The norepinephrine transporter gene modulates intrinsic brain activity, visual memory, and visual attention in children with attention-deficit/hyperactivity disorder. *Mol Psychiatry*, doi:10.1038/s41380-019-0545-7 (2019).

Hearne, L. J. *et al*. ADHD symptoms map onto noise-driven structure-function decoupling between hub and peripheral brain regions. *Mol Psychiatry* **31**, 019-0554 (2019).

Lin, H. Y., Tseng, W. I., Lai, M. C., Chang, Y. T. & Gau, S. S. Shared atypical brain anatomy and intrinsic functional architecture in male youth with autism spectrum disorder and their unaffected brothers. *Psychol Med.* **47**, 639-654. (2017).

Chien, Y. L., Chen, Y. J., Hsu, Y. C., Tseng, W. I. & Gau, S. S. Altered white-matter integrity in unaffected siblings of probands with autism spectrum disorders. *Hum Brain Mapp.* **38**, 6053-6067. (2017).