Peroxisome proliferator-activated receptor gamma participates in the acquisition of brain ischemic tolerance induced by ischemic preconditioning via glial glutamate transporter 1 in vivo and in vitro

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Front cover: Ischemic preconditioning (IPC) could induce neuron ischemic tolerance. However, the mechanism is not very clear. This study explores whether PPARγ participates in the induction of neuron ischemic tolerance by IPC via regulating GLT-1. At first, we found that cerebral IPC up-regulated PPARγ and GLT-1 expressions in astrocytes in CA1 hippocampus, and induced neuron ischemic tolerance in rats. Then the molecular mechanism of PPARγ contributed to neuroprotection induced by IPC through regulating GLT-1 was verified in astrocyte-neuron co-cultures. Inhibiting PPARγ by its selective antagonist T0070907 or PPARγ siRNA significantly attenuated GLT-1 up-regulation and neuroprotection induced by IPC. Consistently, pre-administration of T0070907 inhibited GLT-1 up-regulation and neuron ischemic tolerance induced by cerebral IPC in rats. In conclusion, it reveals that PPARγ participates in the acquisition of neuron ischemic tolerance induced by IPC via regulating GLT-1.

Image content: The image is a representative photograph of thionin staining showing the histological change in CA1 hippocampus at 7d after brain ischemic insult. This image shows that ischemic insult, global brain ischemia for 8min, led to obvious neuronal death, which appeared neuronal pyknosis in CA1 hippocampus.
Synaptic vesicle generation from activity-dependent bulk endosomes requires a dephosphorylation-dependent dynamin–syndapin interaction

Giselle Cheung, Michael A. Cousin

Activity-dependent bulk endocytosis is the dominant pathway via which synaptic vesicles (SVs) are generated during intense neuronal activity. Calcineurin is essential for SV generation from bulk endosomes and we aimed to determine its mechanism. We found that SV generation was inhibited by: disruption of calcineurin interactions, inhibition of dynamin-I activity and disruption of dynamin-I–syndapin-I interactions. This revealed that 1) calcineurin localization at bulk endosomes, 2) dynamin-I GTPase activity and 3) calcineurin-dependent dynamin-I–syndapin-I interactions are all essential. We propose that a calcineurin-dependent dephosphorylation cascade requiring dynamin-I GTPase and syndapin-I lipid-deforming activity is essential for SV generation from bulk endosomes.
Pro-inflammatory role of high-mobility group box-1 on brain mast cells via the RAGE/NF-κB pathway

Qing-Qing Qian, Xiang Zhang, Yi-Wei Wang, Jia-Wen Xu, Hong-Quan Dong, Na-Na Li, Yan-Ning Qian, Bo Gui

We proposed that RAGE/NF-κB mediated MC activation is involved in the pro-inflammatory effect of HMGB-1 in CNS. In the in vivo study, i.p. injection of HMGB-1 promoted the release of inflammatory factors and destroyed the integrity of the BBB in the hippocampus. I.c.v injection of cromoglycate (stabilizer of MCs) partially inhibited these effects. We think these findings would provide a new theory for the mechanism of HMGB-1-induced neuroinflammation.
**Age- and disease-specific changes of the kynurenine pathway in Parkinson’s and Alzheimer’s disease**

Freek J. H. Sorgdrager, Yannick Vermeiren, Martijn Van Faassen, Claude van der Ley, Ellen A. A. Nollen, Ido P. Kema, Peter P. De Deyn

To study the role and diagnostic potential of the kynurenine (Kyn) pathway in age-related neurodegenerative disease, time-linked serum, and cerebrospinal fluid (CSF) samples from Alzheimer’s disease (AD) patients, Parkinson’s disease (PD) patients and age-matched cognitively healthy controls were retrospectively selected. Kyn metabolites and large neutral amino acids (LNAAs), which compete with Kyn metabolites to cross the blood–brain barrier, were analyzed by mass spectrometry. Age-related increases of several Kyn metabolites were similar in controls, AD, and PD. Concentrations of kynurenic acid (KA), which plays a role in glutamate toxicity and neuronal development, were strongly reduced in CSF of PD and AD patients.
**High mobility group box 1 (HMGB1) as a novel frontier in epileptogenesis: from pathogenesis to therapeutic approaches**

Yam Nath Paudel, Bridgette D. Semple, Nigel C. Jones, Iekhsan Othman, Mohd. Farooq Shaikh

High-mobility group box protein 1 (HMGB1) is an emerging target against epileptic seizures. HMGB1 is getting attention as an initiator and amplifier of neuroinflammation in epileptogenesis via TLR4 activation. This review highlighted the role of HMGB1 in epileptogenesis and argued on the challenges of HMGB1 as a therapy. HMGB1 targeted therapy has demonstrated admirable outcome in experimental epilepsy but clinical proofs are not yet registered. Disulphide form of HMGB1 is well studied and targeting HMGB1/TLR4 axis would represent a novel treatment option. Moreover, designing a disulphide-HMGB1 antagonist is capable of preventing HMGB1 translocation and BBB disruption as a potential anti-epileptic therapeutic strategy is a future need.
Loss of insulin-like growth factor-1 signaling in astrocytes disrupts glutamate handling

Disha Prabhu, Sariya M. Khan, Katherine Blackburn, Jessica P. Marshall, Nicole M. Ashpole

Front cover: Insulin-like growth factor 1 (IGF-1) promotes growth and excitability of neurons. The role of IGF-1 in regulating the function of astrocytes is still not clearly understood. Astrocytes form the major cell type in the brain, and regulate glutamate handling in the brain, thereby protecting neurons and other cells. Our study uses a combination of pharmacological and genetic techniques of manipulating IGFR signaling to examine whether IGF-1 acts through its cognate receptor IGFR to alter the handling of glutamate by astrocytes in the brain. Our study showed that short-term inhibition of IGFR resulted in a significant decrease in glutamate transporter availability on the cell surface, thereby decreasing the uptake of glutamate in vitro. Additionally, we saw long-term inhibition of IGFR resulted in significant reductions in glutamate uptake by decreasing mRNA expression of glutamate transport machinery. Reduced glutamate transporter mRNA was also observed in mice lacking astrocytic IGFR. Together, these data suggest that reduced IGF-1 signaling will favor an accumulation of extra-synaptic glutamate, which may contribute to neurodegeneration in disease states where IGF-1 levels are low.

Image content: The image shows GFAP positive primary astrocytes in culture (purple) with their nuclei stained with DAPI (blue), thereby validating our astrocyte cultures.
Subcellular NAMPT-mediated NAD+ salvage pathways and their roles in bioenergetics and neuronal protection after ischemic injury

Xiaowan Wang, Zhe Zhang, Nannan Zhang, Hailong Li, Li Zhang, Christopher P. Baines, Shinghua Ding

We investigated whether neuronal mitochondria have an endogenous NAD+ salvage pathway and the roles of subcellular compartmental NAD+ salvage pathways in bioenergetics and neuronal protection after ischemia. Using multiple approaches, we found that both NAMPT and NMNAT3 are expressed in neuronal mitochondria, and are localized in the matrix. We further found that mitochondrial NAD+ salvage pathway has a larger effect on basal and ATP production-related oxygen consumption than nuclear and cytoplasmic NAD+ pathways, while nuclear and cytoplasmic NAD+ pathways have a larger effect on glycolytic flux. Moreover mitochondrial, cytoplasmic, and non-subcellular compartmental over-expressions of NAMPT have a comparable effect on neuronal death in ischemia. Our findings provide novel insights into the roles of subcellular NAD+ salvage pathways in bioenergetics and neuronal protection in ischemia.
**Effects of the presence and absence of amino acids on translation, signaling, and long-term depression in hippocampal slices from Fmr1 knockout mice**

Spencer K. Cooke, Jacob Russin, Kristen Moulton, Jeffrey Nadel, Inna Loutaev, Qinhua Gu, Zheng Li, Carolyn Beebe Smith

Previous studies of protein synthesis, long-term depression (LTD), and signaling pathways in hippocampal slice preparations indicate effects of the absence of FMRP in Fmr1 KO mice. One of the conditions of these studies was amino acid starvation, a condition that has powerful effects on activation and translation of proteins involved in regulating protein synthesis. Our studies demonstrate that in hippocampal slices from Fmr1 KO mice incubated in amino acid-enriched medium, LTD and translation rates are similar to control mice, but following mGluR5 activation, eIF2α phosphorylation is increased and P70S6 kinase phosphorylation is decreased compared to control mice. Results suggest tissue attempts to compensate for the absence of regulation of translation by FMRP.
Post-ischemic salubrinal administration reduces necroptosis in a rat model of global cerebral ischemia

Enrique Font-Belmonte, Irene F. Ugidos, María Santos-Galdiano, Paloma González-Rodríguez, Berta Anuncibay-Soto, Diego Pérez-Rodríguez, Jose Manuel Gonzalo-Orden, Arsenio Fernández-López

Necroptosis is a regulated cell death, closely related with pathologies with an important inflammatory response, but its role in global cerebral ischemia is uncertain. Phospho-MLKL levels prove the existence of a necroptosis response in the cerebral cortex after 72 h of reperfusion. This response is consistent with a strong response in the endoplasmic reticulum (ER) stress. The treatment with salubrinal decreases ER stress and reduces or blocks the necroptosis response highlighting the close relation between them. Necroptosis and ER stress are not observed at this time in CA1 hippocampal area.
Microglia and the aging brain: are senescent microglia the key to neurodegeneration?

Dafina M. Angelova, David R. Brown

The most important risk factor for neurodegenerative diseases like Alzheimer’s disease is aging. While the potential role aberrant microglia play in neurodegeneration has been studied for some time, new evidence suggests that that microglial aging might be more important. When microglia become senescent they lose many of their supportive roles and compromise neuronal survival. This review focuses on senescent microglia. New models of senescent microglia could advance study of aging and neurodegeneration.
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