Journal of Neurochemistry
JNC The Official Journal of the International Society for Neurochemistry

JNC Highlights July 2020

Latest Research and Reviews

The following articles are part of Volume 154, Issue 1

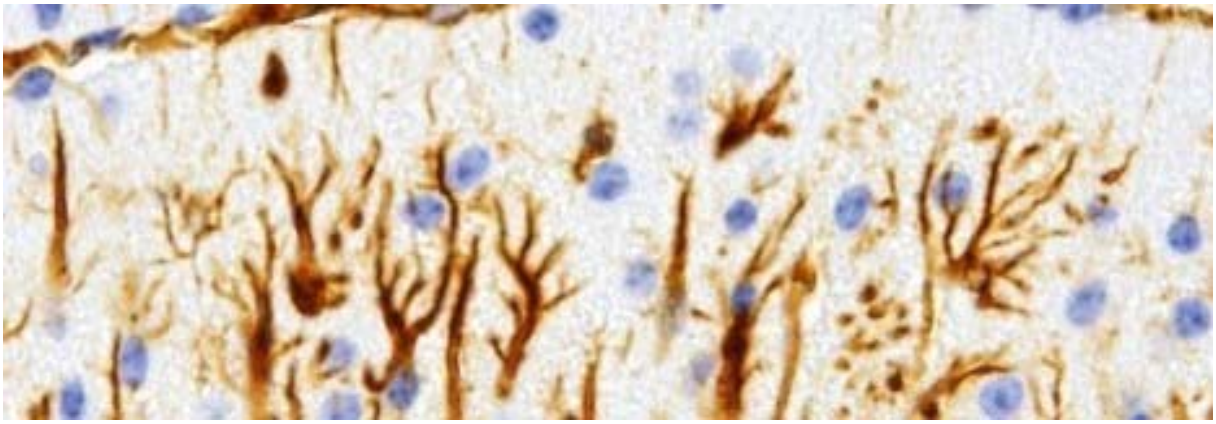
Cover Image

[Glial pathology in a novel spontaneous mutant mouse of the Eif2b5 gene: a vanishing white matter disease model]

Mika Terumitsu-Tsujita, Hiroki Kitaura, Ikuo Miura, Yuji Kiyama, Fumiko Goto, Yoshiko Muraki, Shiho Ominato, Norikazu Hara, Anna Simankova, Norihisa Bizen, Kazuhiro Kashiwagi, Takuhiro Ito, Yasuko Toyoshima, Akiyoshi Kakita, Toshiya Manabe, Shigeharu Wakana, Hirohide Takebayashi, Hironaka Igarashi

Front cover: Vanishing white matter disease (VWM) is an autosomal recessive neurological disorder caused by mutation(s) in any subunit of eukaryotic translation initiation factor 2B (eIF2B), an activator of a translation initiation factor, eIF2. *Toy* mouse is a spontaneous mutant mouse strain that was identified by its small body, abnormal gait, male and female infertility, epileptic seizures, and shortening of the lifespan. A missense mutation of the *Eif2b5* gene (C>G, I98M) was identified in the *toy/Eif2b5*^{I98M} mice. Histopathological analysis showed increased number of GFAP positive astrocytes and translocation of cerebellar Bergmann glia in the *Eif2b5*^{I98M} brain.

Image content: Sagittal sections of *Eif2b5*^{I98M} cerebellum were immunostained using the glial fibrillary acidic protein (GFAP) antibody (brown). Counterstaining was carried out using hematoxylin (deep blue-purple). Bergmann glia were mislocalized to the molecular layer and were abnormally oriented with intense and thick GFAP-positive processes.



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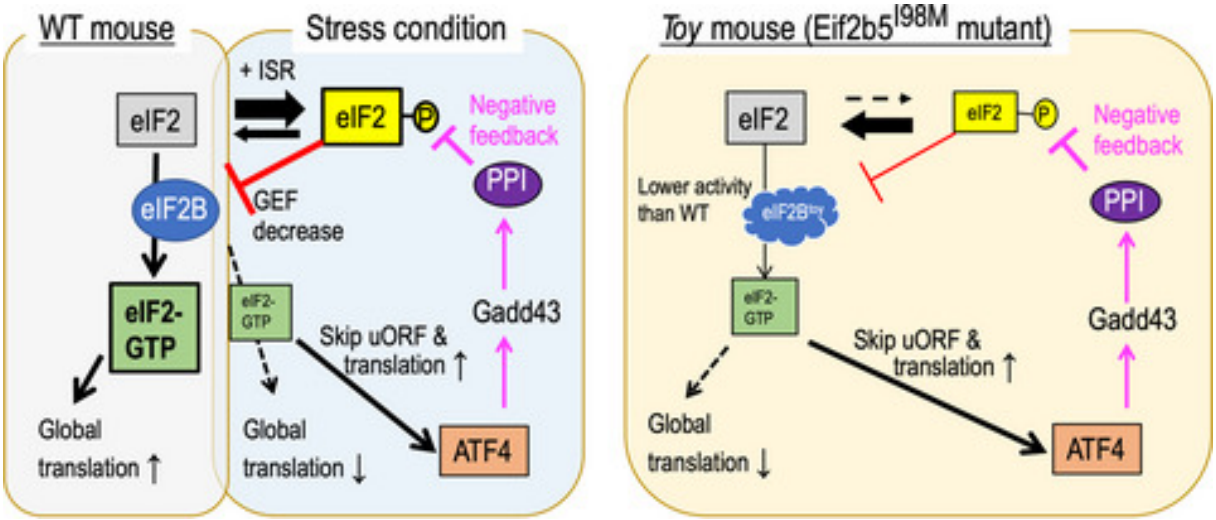
Original Articles

Glial pathology in a novel spontaneous mutant mouse of the Eif2b5 gene: a vanishing white matter disease model

Mika Terumitsu-Tsujita, Hiroki Kitaura, Ikuo Miura, Yuji Kiyama, Fumiko Goto, Yoshiko Muraki, Shiho Ominato, Norikazu Hara, Anna Simankova, Norihisa Bizen, Kazuhiro Kashiwagi, Takuhiro Ito, Yasuko Toyoshima, Akiyoshi Kakita, Toshiya Manabe, Shigeharu Wakana, Hirohide Takebayashi, Hironaka Igarashi

Schematic of wild-type and *toy* mutant mice. In wild-type mice, global translation is up-regulated via GEF activity of eIF2B complex. In integrated stress response (ISR) condition, global translation is down-regulated via decreased GEF activity of eIF2B complex by direct binding of phosphorylated eIF2, which is an inhibitor of eIF2B complex. Up-regulated translation of ATF4 transcription factor by readthrough of upper open reading frame (uORF) initiates negative feedback pathway, which results in decrease of phosphorylated eIF2. *Toy* mutant mice have a point mutation in *Eif2b5* gene, which results in missense mutation (I98M) and decreased GEF activity of eIF2B complex. In *toy* mice, Up-regulated translation of ATF4 transcription factor is also observed.



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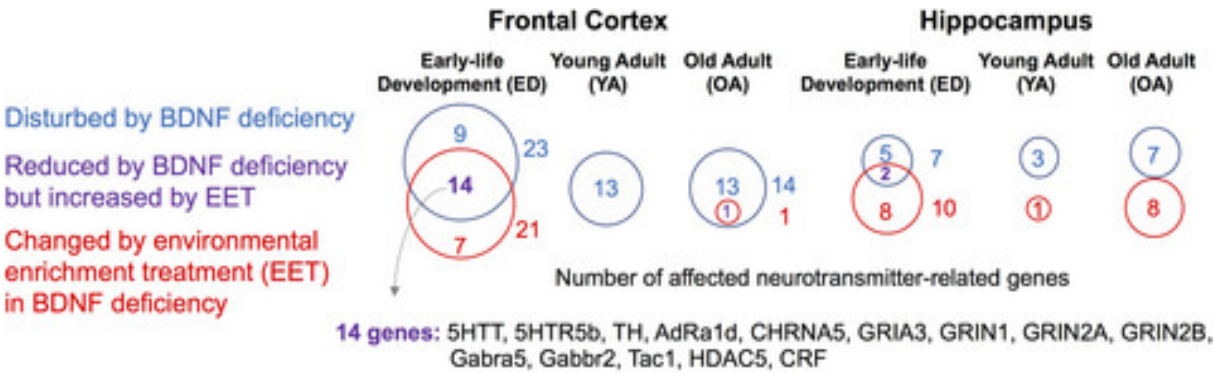
BDNF deficiency and enriched environment treatment affect neurotransmitter gene expression differently across ages

Brittany E. Dong, Hao Chen, Kazuko Sakata

We report the age dependency of how BDNF deficiency (with promoter IV defect, KIV) and enriched environment treatment (EET) affect the expression of 81 neurotransmitter-related genes. BDNF deficiency reduced the expression of the largest number of neurotransmitter genes at early-life development (ED), particularly in the frontal cortex (FC). The EET effects were more specific to BDNF deficiency, largest at ED in the FC but more universal across ages in the hippocampus. These effects were reflected by the density of gene co-expression network. Our results highlight the importance of early-life EET for BDNF deficiency, which occurs under chronic stress.



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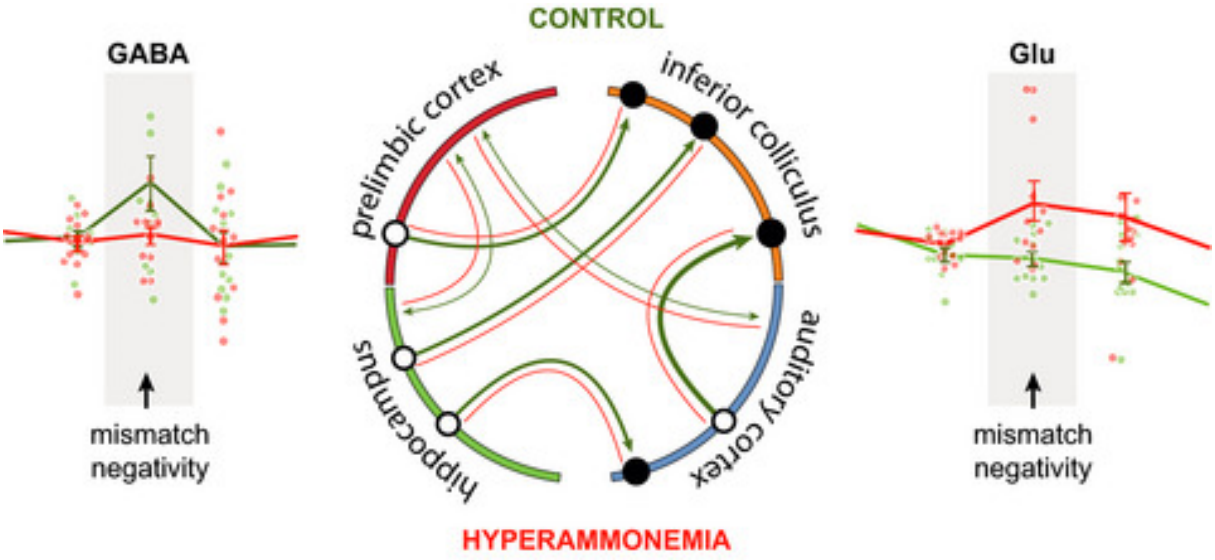
Hyperammonemia alters the mismatch negativity in the auditory evoked potential by altering functional connectivity and neurotransmission

Raquel García-García. Juan F. Guerrero, Manuel Lavilla-Miyasato, Jose R. Magdalena, Juan F. Ordoño, Marta Llansola, Carmina Montoliu, Vicent Teruel-Martí, Vicente Felipo

We propose an approximation to the neuronal correlate that explains the alteration of auditory mismatch negativity (NMM) as a possible cognitive disorder derived from the minimal hepatic encephalopathy (MHE). The aims of this work mainly are to analyze the functional connectivity between the involved areas in MMN under MHE; and to analyze if this altered response is associated with alterations neurotransmission. The results show that rats with MHE show reduced MMN response in hippocampus. This is associated with altered functional connectivity in the network involved in the generation of the MMN as a consequence of an altered glutamate and GABA neurotransmission in hippocampus.



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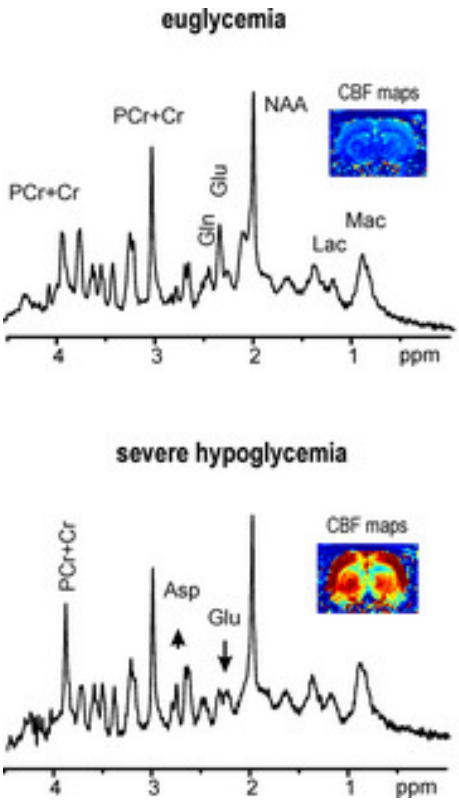
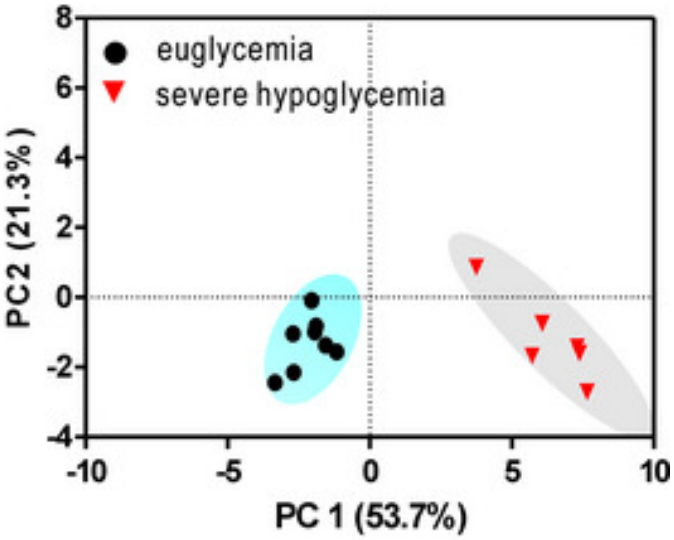
Metabolic and perfusion responses to acute hypoglycemia in the rat cortex: A non-invasive magnetic resonance approach

Hongxia Lei, Rolf Gruetter

We propose the overall high-field ^{1}H MR Spectroscopy (^{1}H-MRS) neurochemical profile as a metabolic signature for acute hypoglycemia severity in rat cortex. In addition to perfusion MR imaging (CBF maps), ^{1}H-MR spectra of rat cortex after three phases of hypoglycemia showed a specific metabolic pattern, distinct from that of euglycemia conditions. Partial-Least-Squares discriminant analysis (PLS-DA) on the overall neurochemical profiles revealed metabolic signatures of acute hypoglycemia severity, i.e. severe hypoglycemia versus. euglycemia.





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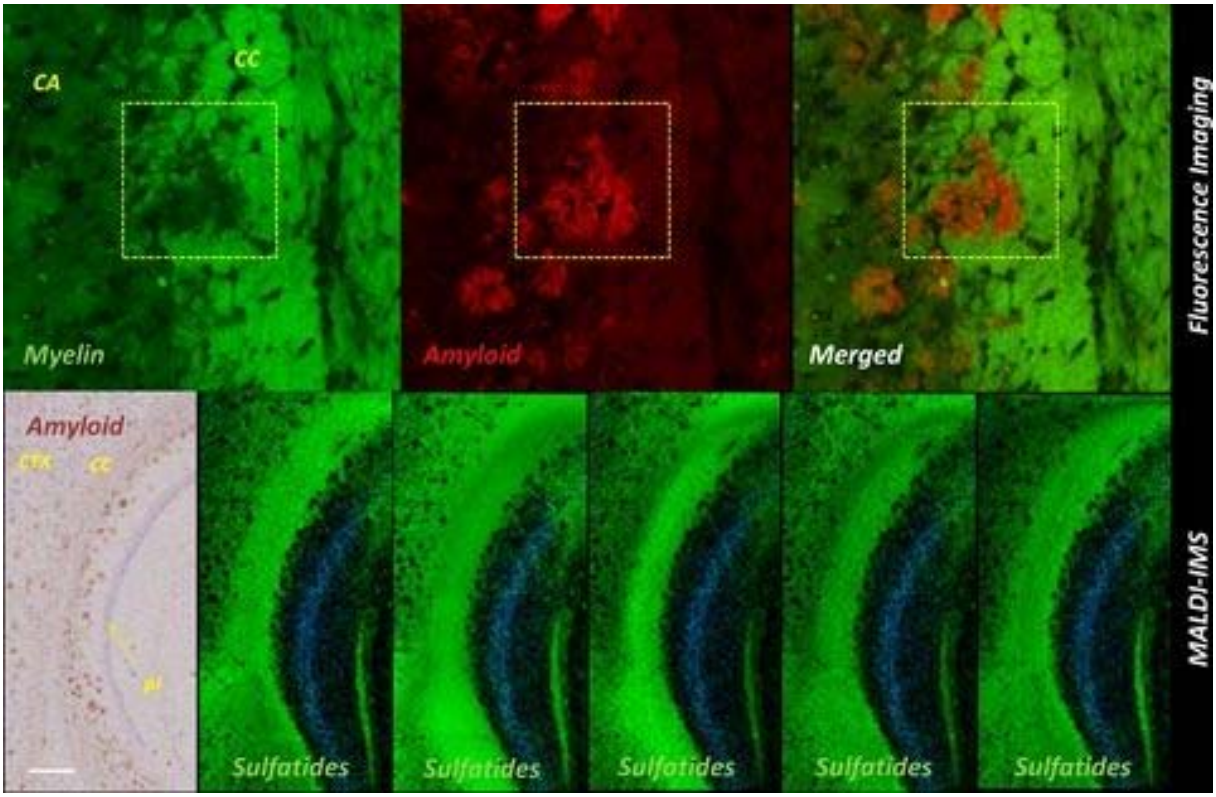
Brain region-specific amyloid plaque-associated myelin lipid loss, APOE deposition and disruption of the myelin sheath in familial Alzheimer's disease mice

Open Access

Ibrahim Kaya, Eva Jennische, Stefan Lange, Ahmet Tarik Baykal, Per Malmberg, John S. Fletcher

We examined focal myelin lipid alterations and the disruption of the myelin sheath in amyloid plaques in 5XFAD mice. MALDI imaging mass spectrometry revealed Aβ plaque-associated depletion of multiple myelin-associated lipid species, prominently sulfatides. Double staining with fluoromyelin and amyloid-specific antibody reveal amyloid plaque-associated myelin sheath disruption on the edges of corpus callosum which is specifically correlated with plaque-associated myelin lipid loss only in this region. Further, apolipoprotein (APOE) which is implicated with the depletion of sulfatides in the AD brain is deposited in all the Aβ plaques which suggest plaque-associated APOE might mediate sulfatide depletion.



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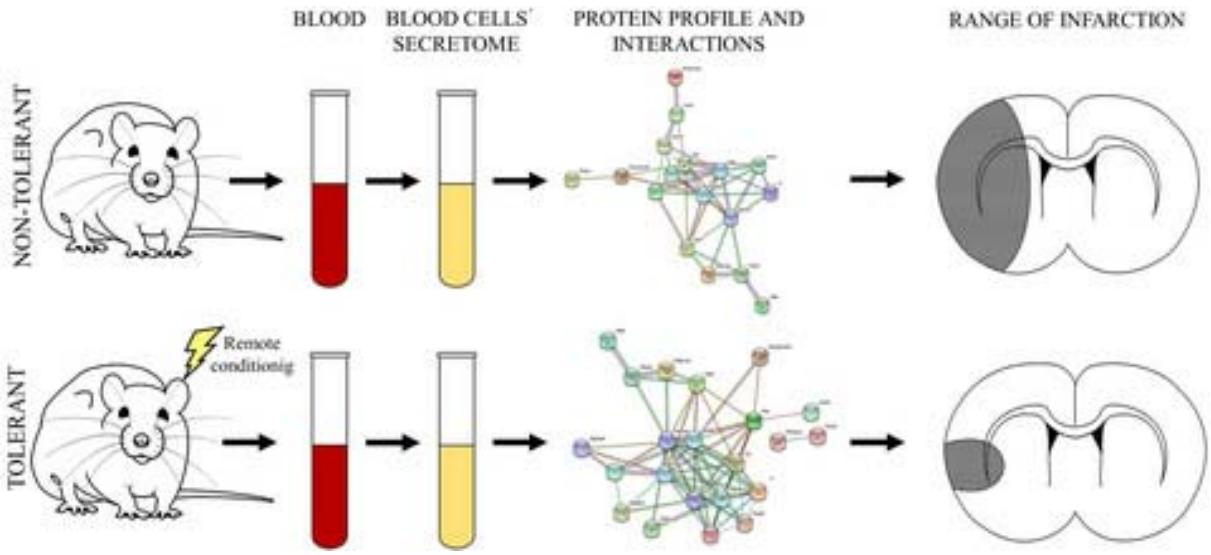
Rapid remote conditioning mediates modulation of blood cell paracrine activity and leads to the production of a secretome with neuroprotective features

Petra Bonova, Jana Jachova, Miroslava Nemethova, Lubica Macakova, Martin Bona, Miroslav Gottlieb

Blood cells are capable of paracrine activity and can react to extracellular stimuli. Proper priming can affect the biological processes of blood cells and force them to modulate their paracrine activities. Stimulated blood cells can release a mixture of bio-reactive proteins that are capable of mediating neuroprotective mechanisms agains toxic glutamate conditions and brain ischemia.



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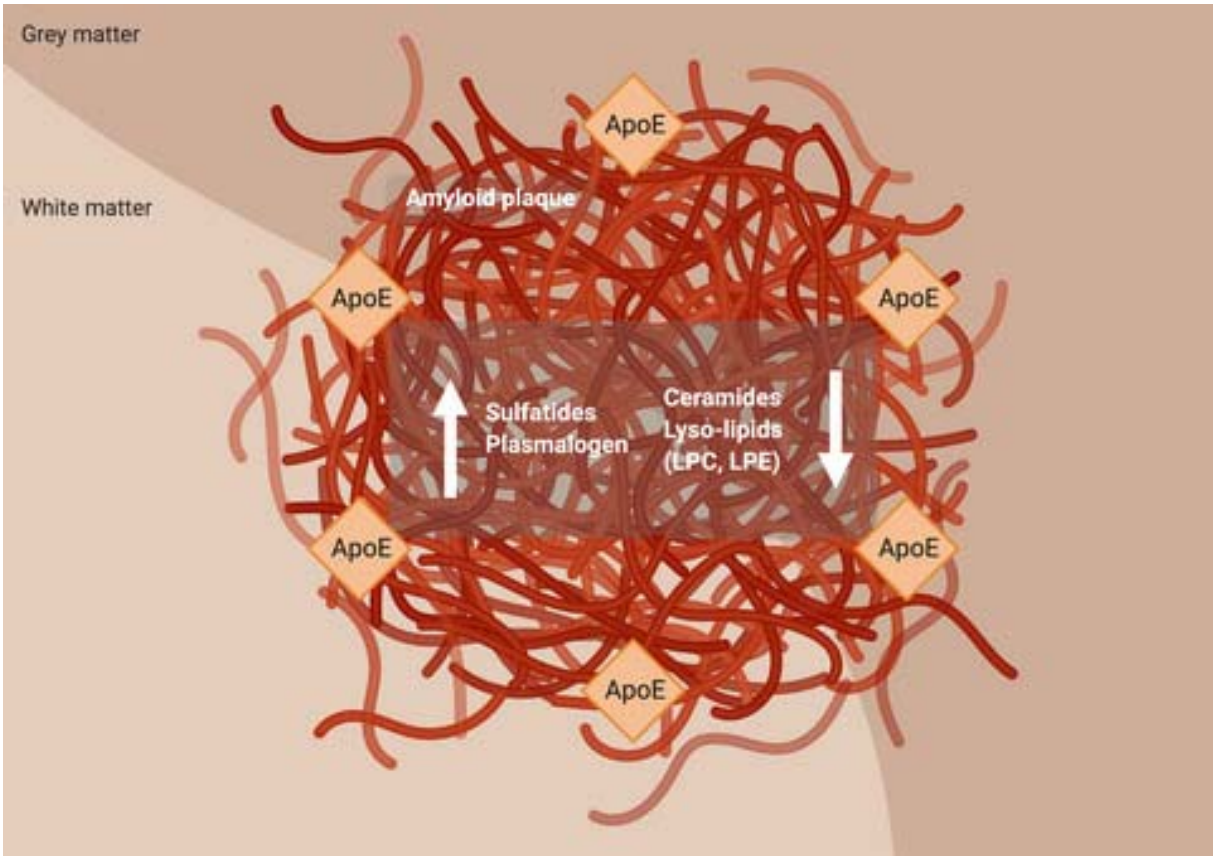
Editorial Highlight

The lipid component of Alzheimer's disease research

Free Access

Lisa Marie Munter

This editorial highlights the work by Kaya et al. suggesting that focal lipid perturbations occur at the amyloid plaque, a pathological hallmark of Alzheimer's disease. The disruption of lipid homeostasis could form the basis of myelin degeneration in Alzheimer's disease, possibly through the recruitment of the apolipoprotein E (ApoE), a strong risk factor of the disease.



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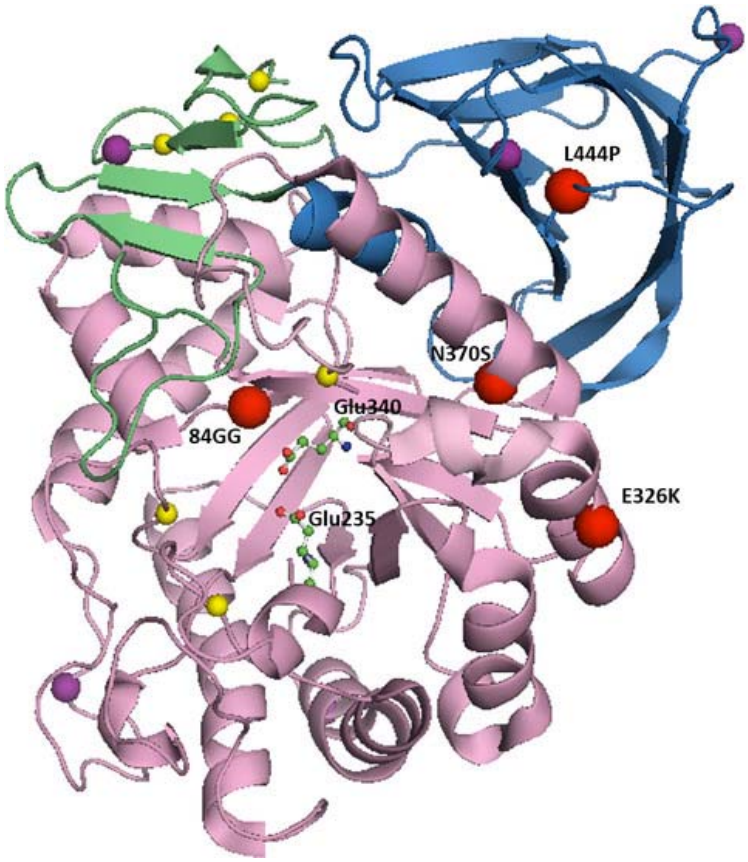
Review articles

The biochemical basis of interactions between Glucocerebrosidase and alpha-synuclein in GBA 1 mutation carriers

Free Access

Marco Toffoli, Laura Smith, Anthony H. V. Schapira

The discovery of genes involved in familial as well as sporadic forms of Parkinson disease (PD) constitutes an important milestone in understanding its pathopysiology and potential treatment. Among these genes, *GBA1* is one of the most common and well-studied, but it is still unclear how mutations in *GBA1* can translate into an increased risk of developing PD. In this review, we analyzed the literature and tried to give a comprehensive overview of the biochemical and structural relationship between GBA1 and PD to better understand the recent advancements in the therapy of PD.



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The following articles are part of Volume 154, Issue 2

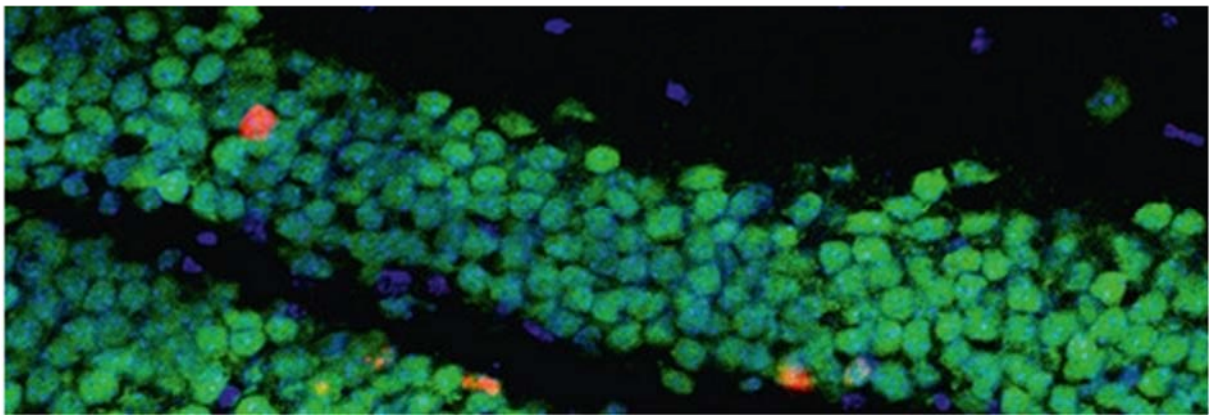
Cover Image

[Activation of liver X receptor promotes hippocampal neurogenesis and improves long-term cognitive function recovery in acute cerebral ischemia-reperfusion mice]

Lili Chen, Dan Song, Beibei Chen, Xuemei Yang, Oumei Cheng

Front cover: Cerebral ischemia results in the loss of hippocampal pyramidal neurons and induces cognitive dysfunction. Cerebral ischemia itself can induce endogenous neurogenesis, but it is generally far from enough, and only a little percentage of NSCs can successfully differentiate into new neurons. So, promoting endogenous neurogenesis will be a promising treatment for the ischemic brain damage. In this study, we demonstrated that LXRs activation can ameliorate long-term cognitive dysfunction caused by cerebral ischemia by increasing neurogenesis, which possibly through the Wnt/β-catenin signaling pathway activation. Our findings suggest that LXRs activation may have potential therapeutic effects on clinical treatment of cerebral ischemia.

Image content: Confocal microscopy image of the hippocampal DG region immunolabeled for NeuN (green immunofluorescence staining) and BrdU (red immunofluorescence staining). Nuclei are shown in blue (Dapi signal). The BrdU+ / NeuN+ double-labeled cells represent neural stem cells differentiate into neurons.



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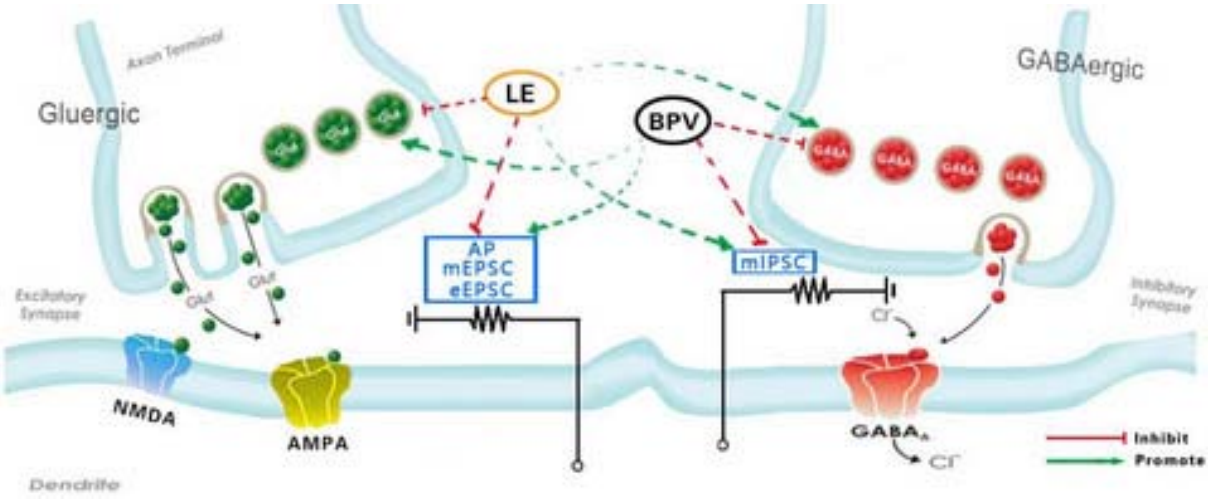
Original Articles

Intravenous lipid emulsion modifies synaptic transmission in hippocampal CA1 pyramidal neurons after bupivacaine-induced central nervous system toxicity

Open Access

Hao Nie, Zhixia Bai, Zhenzhou Li, Li Yan, Xue-Xin Chen

Bupivacaine (BPV) can affect the synthesis and release of glutamic acid and gamma-aminobutyric acid in pre-synaptic membrane. Changes the intensity of synaptic excitation or inhibition. This indirectly affects the electrical changes that occur when neurotransmitters bind to the post-synaptic membrane. Including action potential (AP); miniature excitatory/inhibitory post-synaptic currents (mEPSCs/mIPSCs); evoked excitatory post-synaptic currents (eEPSCs). Lipid emlusion (LE) can change this process.



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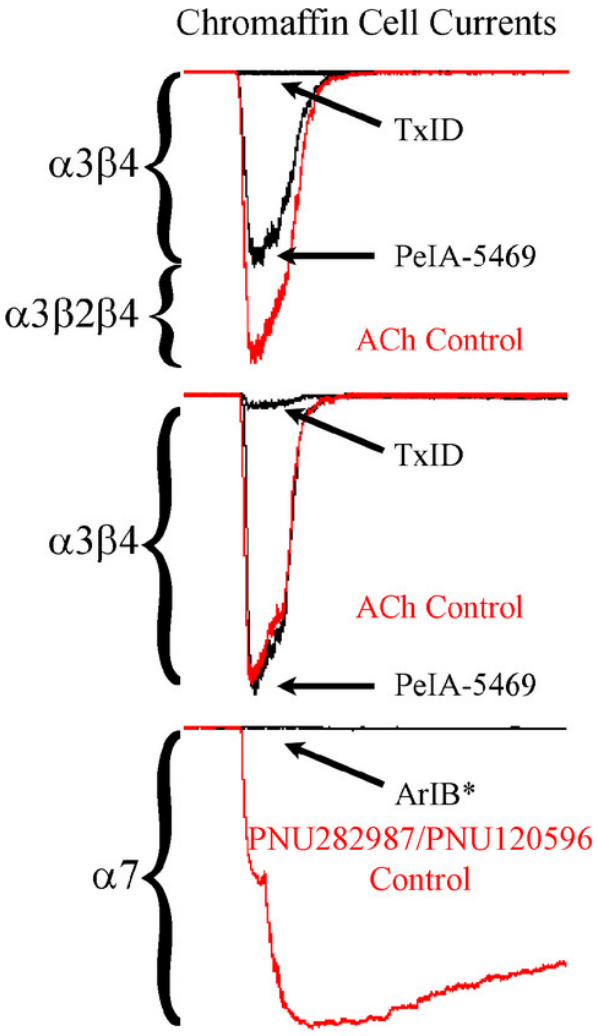
Expression of α3β2β4 nicotinic acetylcholine receptors by rat adrenal chromaffin cells determined using novel conopeptide antagonists

Arik J. Hone, Lola Rueda-Ruzafa, Thomas J. Gordon, Joanna Gajewiak, Sean Christensen, Tino Dyhring, Almudena Albillos, J. Michael McIntosh

Adrenal chromaffin cells are an important secretory cell type and responsible for the homeostasis of a host of physiological functions. The nicotinic acetylcholine receptors (nAChRs) expressed by these cells are critical players in the secretion-coupling response and the release of catecholamines and other neurotransmitters into the bloodstream. Despite decades of use as a model system, the nAChRs subtypes expressed by rat chromaffin cells have not been fully elucidated. Here we report that chromaffin cells express three main nAChR subtypes: α3β2β4, α3β4, and α7. This study provides significant advances in our understanding of the nAChR expression profile of rat chromaffin cells.



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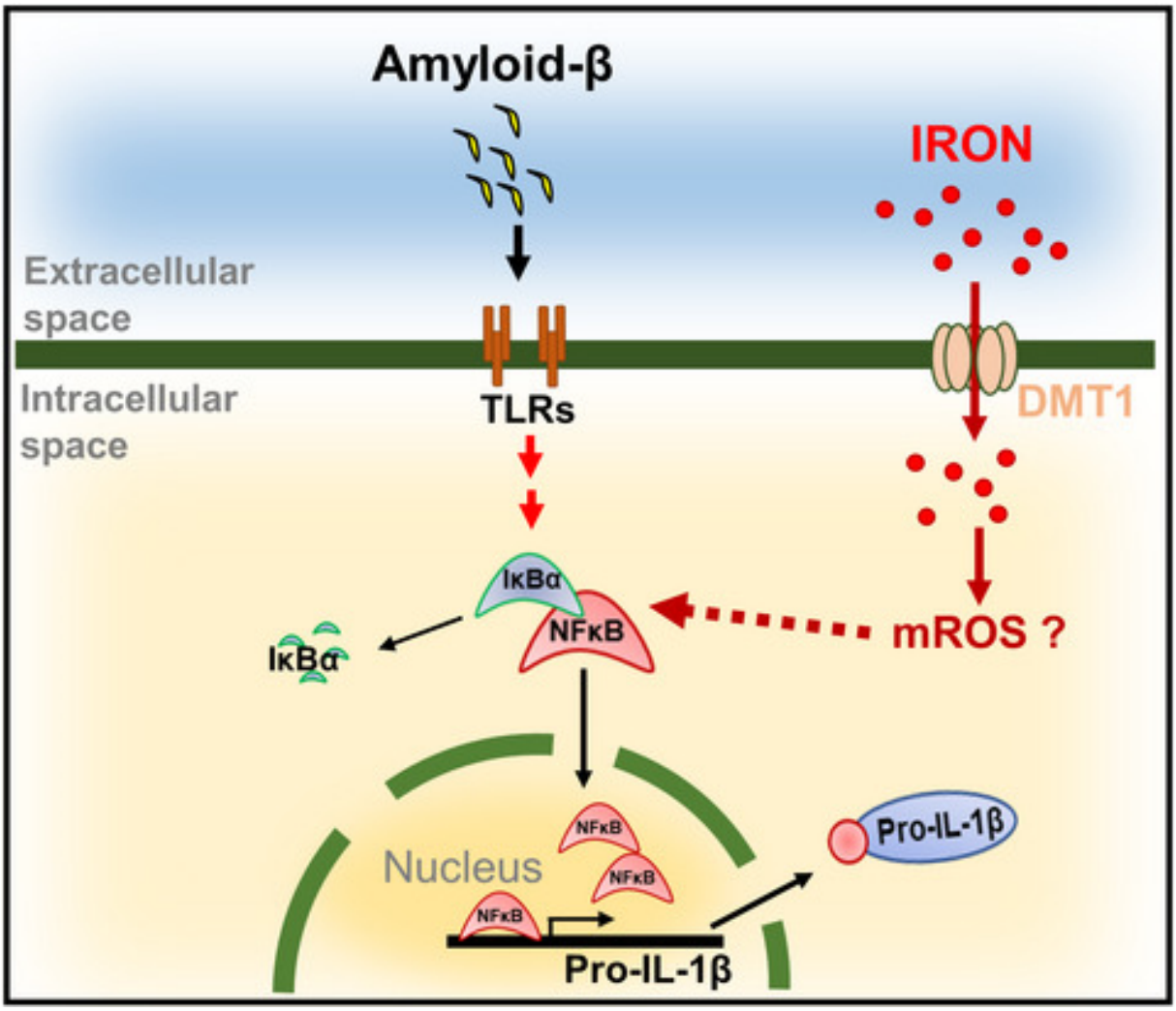
Iron potentiates microglial interleukin-1β secretion induced by amyloid-β

Israel C. Nnah, Chih-Hao Lee, Marianne Wessling-Resnick

The dysregulation of microglial iron homeostasis and cytokine production are implicated in Alzheimer's disease. Our results support the hypothesis that Aβ stimulates microglial cell expression of the pro-inflammatory cytokine IL-1β by activating NF-κB signaling. We show that iron enhances Aβ activation of NF-κB signaling to further promote synthesis of IL-1β. These effects are suppressed by depletion of the iron transporter DMT1. ROS scavengers also reduce induction of IL-1β, suggesting that the potentiating effects of iron are at least in part because of cellular ROS production.



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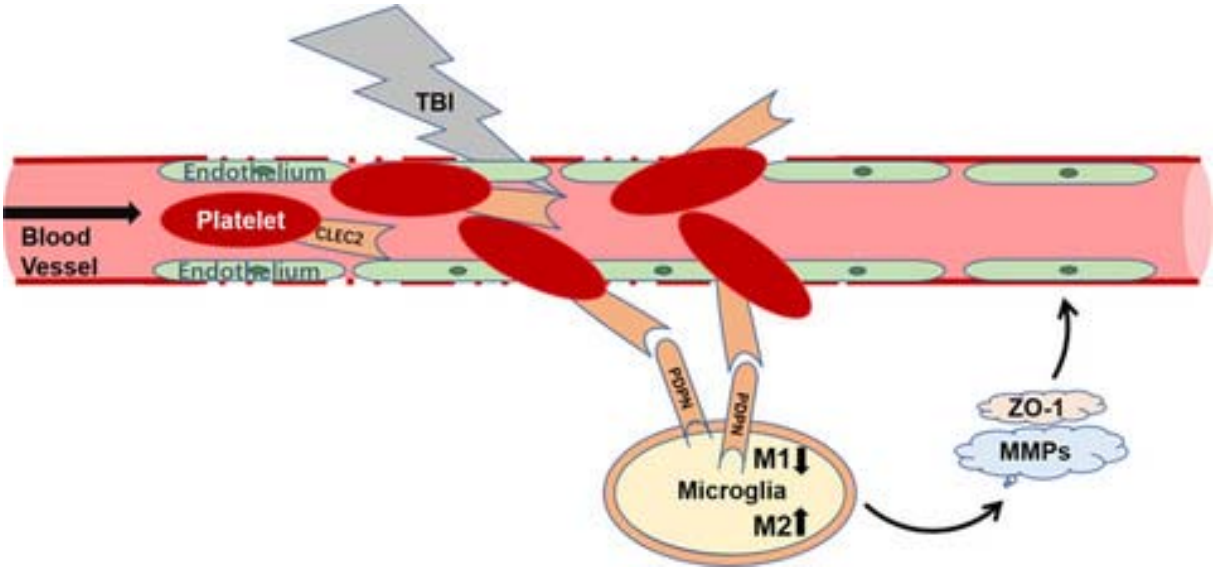
Platelet regulates neuroinflammation and restores blood–brain barrier integrity in a mouse model of traumatic brain injury

Cheng Gao, Haochen Wang, Tao Wang, Chengliang Luo, Zufeng Wang, Mingyang Zhang, Xiping Chen, Luyang Tao

Based on the alteration of inflammatory process under the condition of platelet C-type lectin-like 2 receptor (CLEC-2) conditional deletion, we proposed the following cascade for platelet CLEC-2 mediated restoration of blood brain barrier integrity: The infiltrated platelets, which mostly expressed CLEC-2, regulated microglial polarization through interacting with podoplanin expressed by itself and restored the integrity of blood brain barrier. We assume these findings should provide a new strategy for the treatment of traumatic brain injury.



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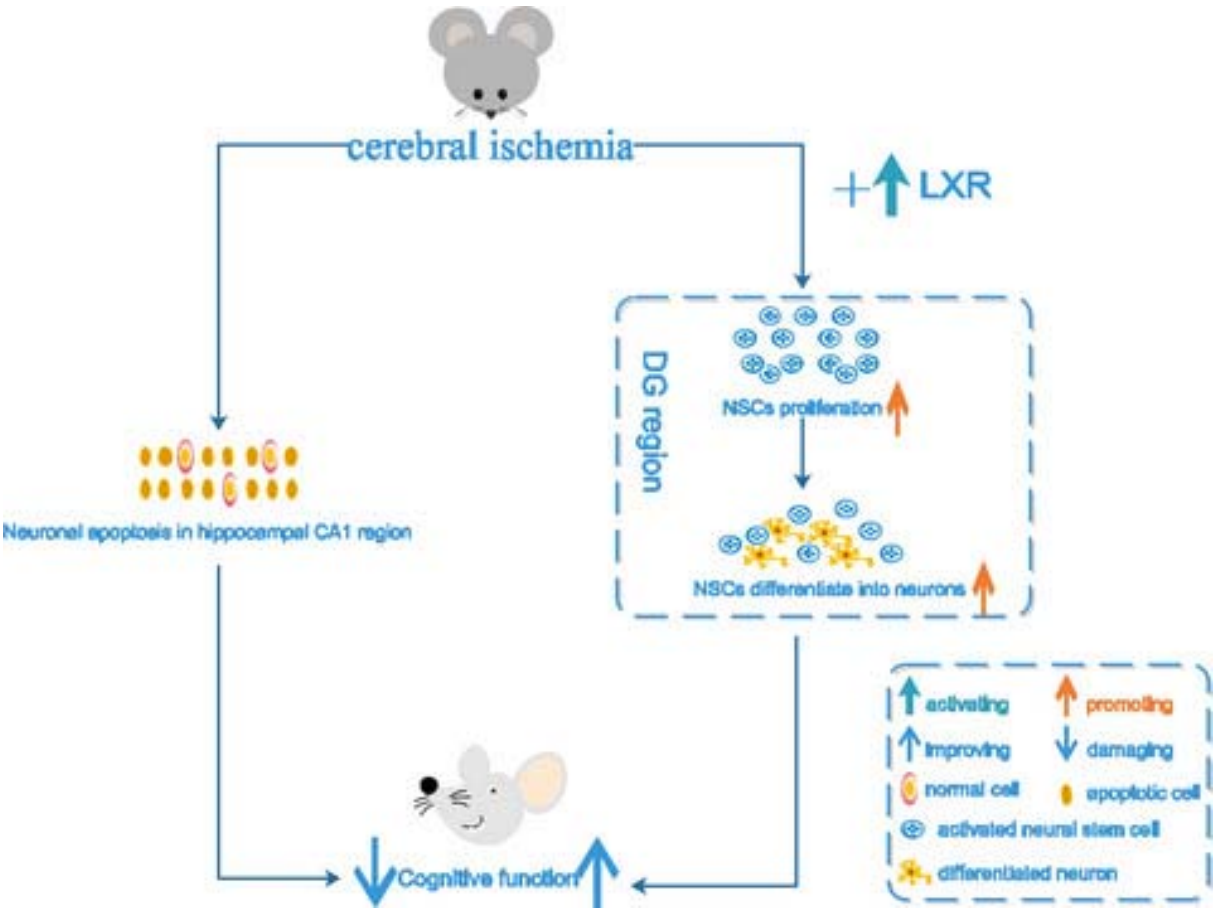
Activation of liver X receptor promotes hippocampal neurogenesis and improves long-term cognitive function recovery in acute cerebral ischemia-reperfusion mice

Lili Chen, Dan Song, Beibei Chen, Xuemei Yang, Oumei Cheng

Cerebral ischemia leads to loss of hippocampal pyramidal neurons and causes cognitive dysfunction. In this study, we treated cerebral ischemia mice with TO90 (LXRs synthetic agonist) and found that BrdU+ cells, DCX+ cells, and BrdU+/NeuN+ cells in the hippocampal DG region were significantly increased, and the expression of Wnt/β-catenin signaling pathway-associated proteins were increased, and the Morris water maze experiments showed that the spatial learning and memory abilities of mice were improved. Our findings suggest that LXRs activation may have potential therapeutic effects on clinical treatment of cerebral ischemia.



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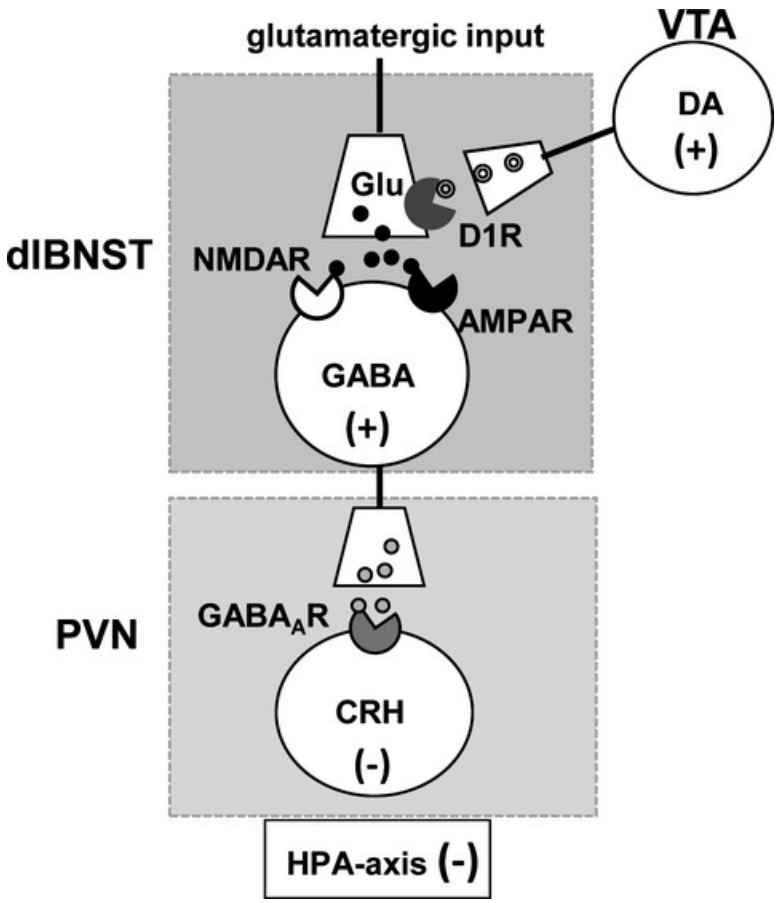
Dopaminergic afferents from midbrain to dorsolateral bed nucleus of stria terminalis inhibit release and expression of corticotropin-releasing hormone in paraventricular nucleus

Tingting Di, Ya Wang, Yajie Zhang, Sha Sha, Yanying Zeng, Ling Chen

Dopaminergic (DA) afferents from midbrain ventral tegmental area (VTA) to dorsolateral bed nucleus of stria terminalis (dlBNST) through enhanced D1-like dopaminergic receptor (D1R)-mediated presynaptic glutamate (Glu) release and induction of NMDA receptor (NMDAR)-dependent long-term potentiation (LTP) can increase activation of postsynaptic GABAergic neurons (GABA). The increase in activation of GABAergic neurons in dlBNST produces GABAA receptor (GABAAR)-induced inhibition for corticosterone (CORT) release and expression in hypothalamic paraventricular nucleus (PVN), leading to down-regulation of hypothalamic-pituitary-adrenal (HPA) axis activity. (+): increased activity; (-) reduced activity.



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Review articles

Regulation of NMDA glutamate receptor functions by the GluN2 subunits

Free Access

Marta Vieira, Xuan Ling Hilary Yong, Katherine W. Roche, Victor Anggono

The N-methyl-D-aspartate glutamate receptors (NMDARs) mediate calcium-dependent signalling that underpins multiple forms of synaptic plasticity. Different GluN2 (GluN2A-D) subunits confer NMDARs with distinct ion channel properties and intracellular trafficking pathways. This review article summarizes the current knowledge of the molecular mechanisms that regulate the trafficking of GluN2-containing NMDARs, focusing on the roles of several key-binding partners.