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

JNC Highlights August 2020

Latest Research and Reviews

The following articles are part of Volume 154, Issue 3 – Pages 235-348

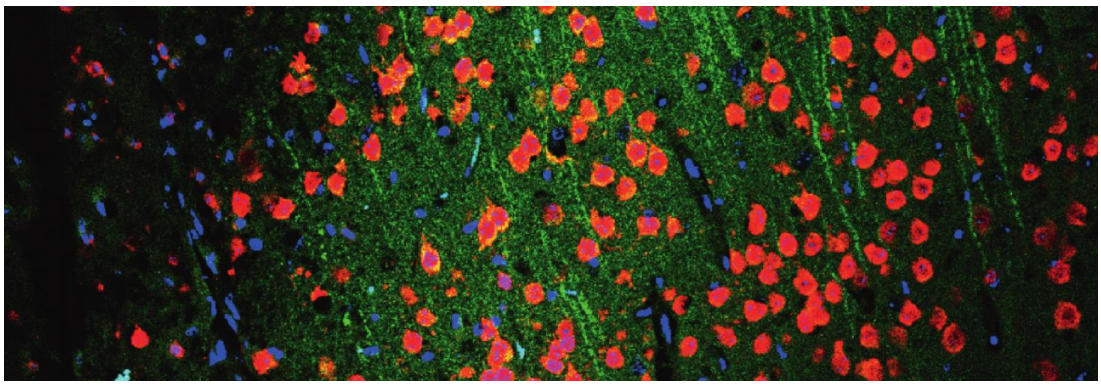
Cover Image

Valproic acid affects neuronal fate and microglial function via enhancing autophagic flux in mice after traumatic brain injury

Xiao, Jian, Zheng, Zhilong; Wu, Yanqing; Li, Zhengmao; Ye, Luxia; Lu, Qi; Zhou, Yajiao; Yuan, Yuan; Jiang, Ting; Xie, Ling; Liu, Yanlong; Chen, Daqing; Ye, Junming; Nimlamool, Wutigri; Zhang, Hongyu

Front cover: Appropriate levels of autophagy can promote the removal of abnormal proteins or damaged organelles, while hyperactivated autophagy can induce autophagic apoptosis. However, it was reported that autophagic flux may be blocked after traumatic brain injury (TBI), which may further cause brain cells apoptosis. Here, we found that daily intraperitoneal injection of valproic acid (VPA) after TBI for three days may contribute to lysosomal function recovery to reverse TBI-induced autophagic flux blockage, which is accompanied by reduced inflammatory response and decreased brain cell apoptosis. Furthermore, 3-methyladenine (3-MA) administration for inhibiting autophagy in VPA-treated injured mice abolished VPA-induced neuroprotective and anti-inflammatory effects, which results in significantly reduced neurite expression when immunofluorescent staining with anti-NeuN and anti-MAP2 antibodies in the somatosensory cortical region. Our findings support that VPA treatment after TBI contributes to functional recovery via enhancing autophagic flux.

Image content: Immunofluorescence staining was performed at 3 days post injury on VPA-treated injured mice with 3-MA pretreatment. DAPI (blue cannel), MAP2 (green cannel) and NeuN (red cannel) were utilized to mark the brain cells nuclear, neurites and neurons in mouse brain tissue, respectively. The tissue was mounted after incubation with the corresponding secondary antibody and captured by a Nikon ECLIPSE 80i microscope. Pretreatment with 3-MA in VPA-treated mice suffering from TBI resulted in significant down-regulation of neuronal neurite expression in the somatosensory cortex around the lesion, indicating that 3-MA pretreatment partially abolished VPA-induced neuroprotective effect after TBI.



Read the full article *'Valproic acid affects neuronal fate and microglial function via enhancing autophagic flux in mice after traumatic brain injury'* by Z. Zheng, Y. Wu, Z. Li, L. Ye, Q. Lu, Y. Zhou, Y. Yuan, T. Jiang, L. Xie, Y. Liu, D. Chen, J. Ye, W. Nimlamool, H. Zhang, J. Xiao, (*J. Neurochem*. 2020, vol. 154 (3), pp. 284–300) on doi:10.1111/jnc.14892

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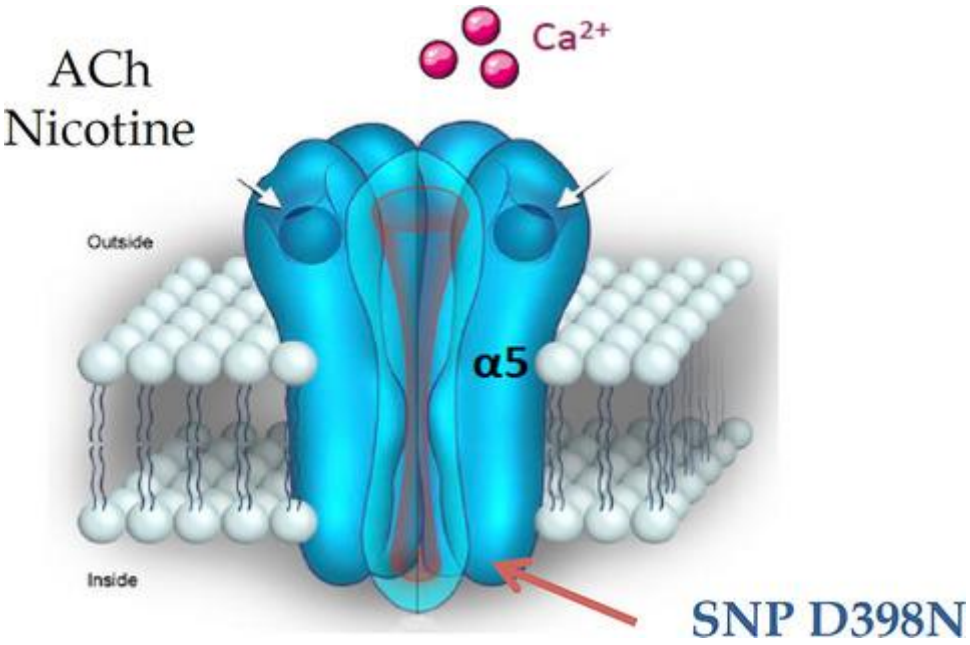
Review articles

The nicotinic receptor alpha5 coding polymorphism rs16969968 as a major target in disease: Functional dissection and remaining challenges

Free Access

Uwe Maskos

We review the functional consequences of a human coding polymorphism, rs16969968, of the nicotinic acetylcholine receptor (nAChR) alpha5 subunit. An aspartate to asparagine change in position 398 (D398N) is frequently found in many human populations, and has been linked to several diseases in large-scale genome-wide association studies (GWAS). In many model systems, the mutation changes the properties of the resulting nAChR, resulting in partial loss-of-function phenotypes.



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Original Articles

Relating ligand binding to activation gating in P2X2 receptors using a novel fluorescent ATP derivative

Open Access

Christian Sattler, Ralf Schmauder, Tina Schwabe, Andrea Schweinitz, Christopher Unzeitig, Frank Schwede, Maik Otte, Klaus Benndorf

Besides the fundamental importance as energy currency of life, adenosine triphosphate (ATP) has a pivotal role as signaling molecule activating purinergic receptors which are involved in many life processes, for example, synaptic transmission, pain, and inflammation. We synthesized a novel fluorescent ATP derivative and characterized its function on wild-type and mutated P2X2 channels with enhanced apparent affinity. This allowed us to correlate ligand binding to channel activation and to identify and quantify cooperativity already for the first and second binding step as well as to determine the binding of ATP at the channel binding sites.

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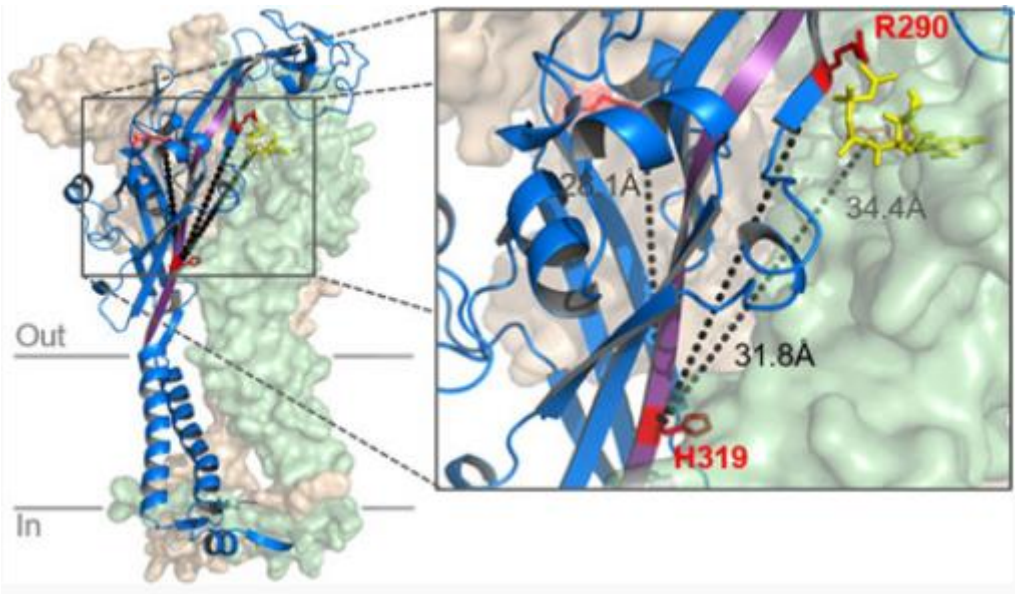

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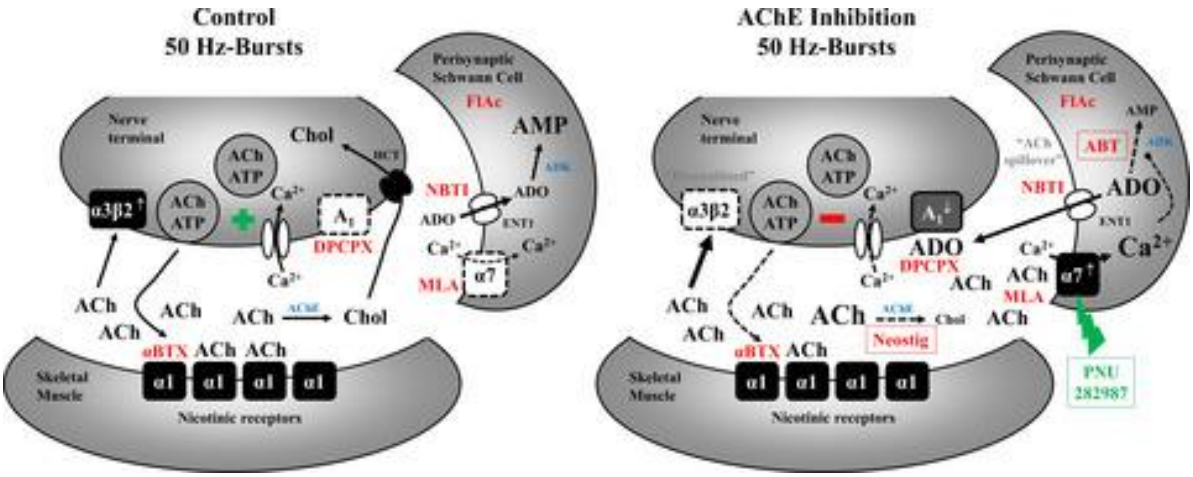
Nicotinic α7 receptor-induced adenosine release from perisynaptic Schwann cells controls acetylcholine spillover from motor endplates

José B. Noronha-Matos, Laura Oliveira, Ana R. Peixoto, Liliana Almeida, Lilian Martins Castellão-Santana, Célia R. Ambiel, Wilson Alves-do Prado, Paulo Correia-de-Sá

This study highlights a novel aspect of the fine-tuning control of neuromuscular transmission by adenosine underscoring its role as the more likely gliotransmitter mediating perisynaptic Schwann cells (PSCs)-nerve terminal communication at the tripartite neuromuscular synapse. Using myographic, neurochemical, and fluorescence video-microscopy techniques, we show here that α7 nicotinic acetylcholine receptors (nAChR) control tetanic-induced ACh spillover from the motor endplate by favoring adenosine outflow from PSCs via NBTI-sensitive ENT1 transporters and retrograde activation of presynaptic A1 inhibitory receptors. [Ca2+]i influx through the α7nAChR pore triggers downstream inhibition of adenosine kinase (ADK) forcing adenosine outflow from PSCs via ENT1.



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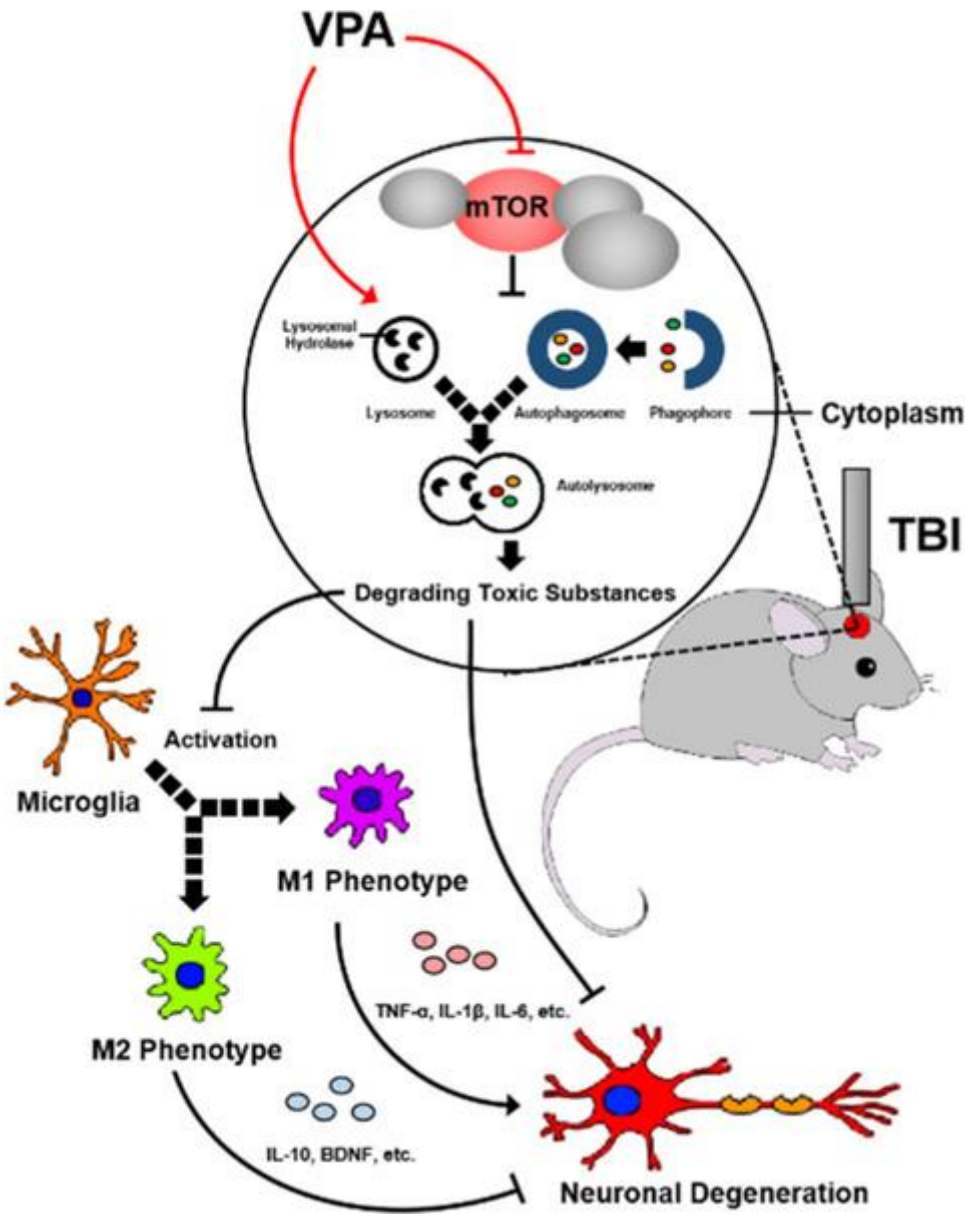
Valproic acid affects neuronal fate and microglial function via enhancing autophagic flux in mice after traumatic brain injury

Zhilong Zheng, Yanqing Wu, Zhengmao Li, Luxia Ye, Qi Lu, Yajiao Zhou, Yuan Yuan, Ting Jiang, Ling Xie, Yanlong Liu, Daqing Chen, Junming Ye, Wutigri Nimlamool, Hongyu Zhang, Jian Xiao

We proposed that daily intraperitoneal injection of valproic acid (VPA) in mice for three days after traumatic brain injury (TBI) can reverse TBI-induced lysosomal functional damage and inhibit mammalian target of rapamycin (mTOR) phosphorylation to enhance autophagic flux in mice brain. In addition, increased autophagic flux inhibits excessive activation of microglia and promotes the polarization of activated microglia to M2 phenotype. It is revealed that VPA treatment may stabilize the central nervous system (CNS) microenvironment by enhancing autophagic flux in the brain and thereby affecting microglial activation and polarization to support the recovery of neurological function after TBI.

Cover Image for this issue: doi: 10.1111/jnc.14755.



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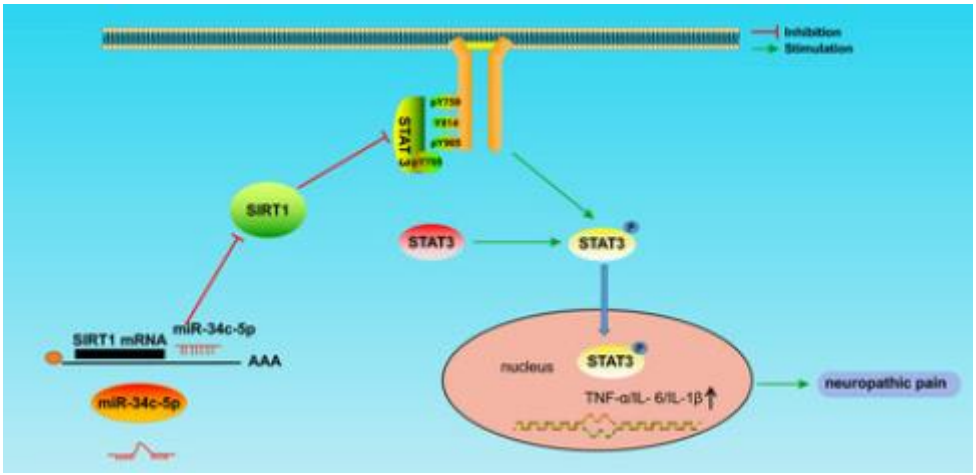
Down-regulation of microRNA-34c-5p alleviates neuropathic pain *via* the SIRT1/STAT3 signaling pathway in rat models of chronic constriction injury of sciatic nerve

Yanshuai Mo, Benjuan Liu, Shuang Qiu, Xueqin Wang, Lina Zhong, Xiao Han, Fuli Mi

This study aims to clarify the effects of miR-34c-5p-mediated SIRT1/STAT3 signaling pathway on neuropathic pain in rat models with chronic constriction injury (CCI) of sciatic nerve. MicroRNA-34c-5p (miR-34c-5p) targets and down-regulates the expression of sirtuin-1 (SIRT1), consequently promoting the activation of signal transducer and activator of transcription 3 (STAT3) signaling pathway and increasing the expression of interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-α (TNF-α), which ultimately leads to neuropathic pain. These findings may serve as novel clues for the molecular mechanism behind neuropathic pain. These results establish the miR-34c-5p/SIRT1/STAT3 axis as a potential physiologically validated target for neuropathic pain management.



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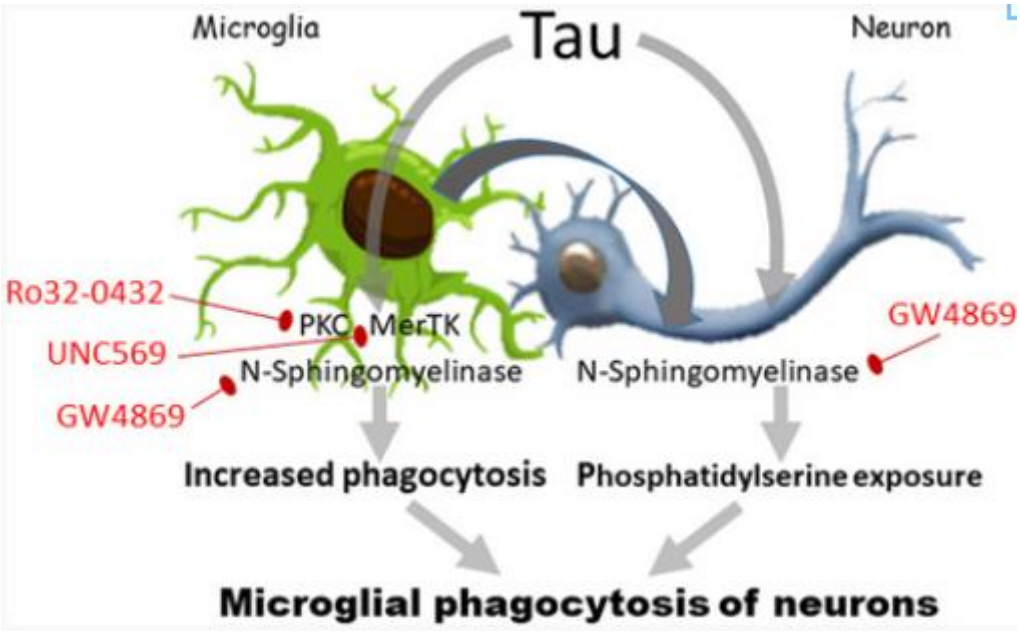
Extracellular tau induces microglial phagocytosis of living neurons in cell cultures

Katryna Pampuscenko, Ramune Morkuniene, Tomas Sneideris, Vytautas Smirnovas, Rima Budvytyte, Gintaras Valincius, Guy C. Brown, Vilmante Borutaite

Microtubule-associated protein tau is found in neurons, but can be also secreted. Effects of extracellular tau on neuronal viability are not clear. We show here that extracellular addition of tau stimulated phagocytic activity of microglia and caused microglia-dependent exposure of phosphatidylserine on neurons leading to loss of neurons in mixed neuronal-glial cultures prepared from rats' cerebella. Inhibitors of protein kinase C (Ro 32–0432) and neutral sphingomyelinase (GW4869) blocked tau-induced phagocytic activity of microglia. In neurons, GW4869 blocked phosphatidylserine exposure. Both inhibitors, as well as Mer-tyrosine-kinase inhibitor UNC569 or elimination of microglia prevented extracellular tau-induced neuronal loss. The data suggest that extracellular tau induces primary phagocytosis of stressed neurons by activated microglia, and identifies multiple ways in which the neuronal loss induced by tau can be prevented.



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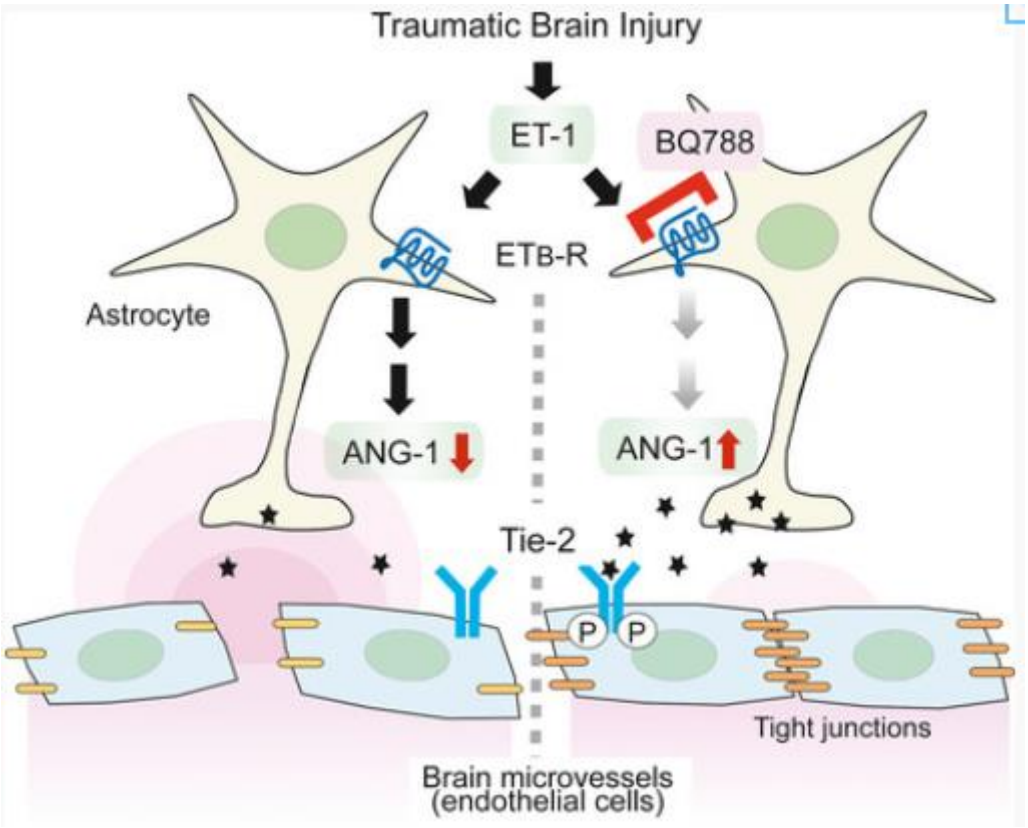
Angiopoietin-1/Tie-2 signal after focal traumatic brain injury is potentiated by BQ788, an ET_B receptor antagonist, in the mouse cerebrum: Involvement in recovery of blood–brain barrier function

Shotaro Michinaga, Ayami Tanabe, Ryusei Nakaya, Chihiro Fukutome, Anna Inoue, Aya Iwane, Yukiko Minato, Yu Tujiuchi, Daisuke Miyake, Hiroyuki Mizuguchi, Yutaka Koyama

The mechanisms underlying the BBB function recovery induced by BQ788, an endothelin ET_B receptor antagonist, were examined in a mouse traumatic brain injury (TBI) model. In this model, BQ788 increased angiopoietin-1 (ANG-1) expression and phosphorylation of Tie-2, which was accompanied by recovery of BBB function. These results suggest that activation of the angiopoietin-1/Tie-2 signal underlies the ability of BQ788 to recover BBB function.



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The following articles are part of Volume 154, Issue 4 – Pages 349-457

Cover Image

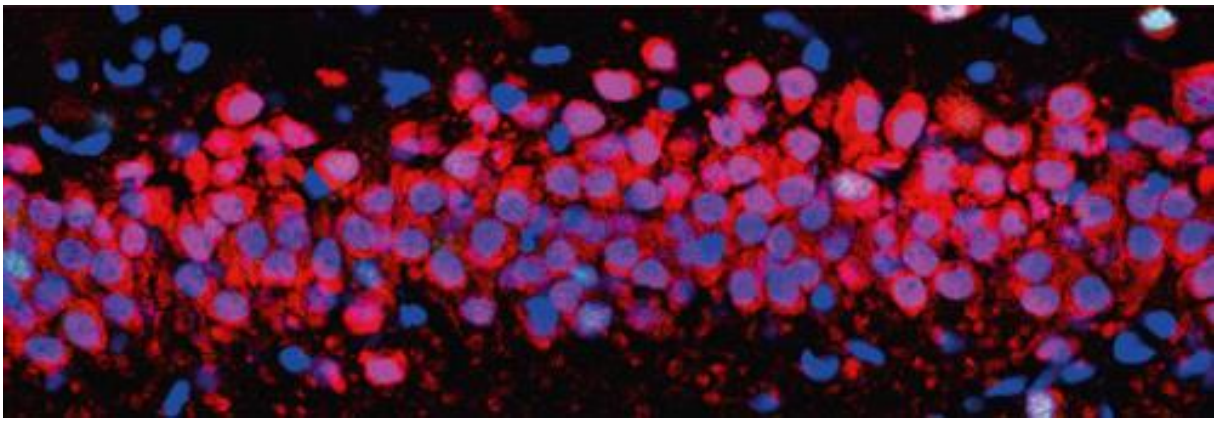
Involvement of homodomain interacting protein kinase 2-c-Jun N-terminal kinase/c-Jun cascade in the long-term synaptic toxicity and cognition impairment induced by neonatal Sevoflurane exposure

Open Access

Lirong Liang, Rougang Xie, Rui Lu, Ruixue Ma, Xiaoxia Wang, Fengjuan Wang, Bing Liu, Shengxi Wu, Yazhou Wang, Hui Zhang

Front cover: The long term neurotoxicity of neonatal general anesthetics exposure is an important issue in the field of child. Sevoflurane is one of the most widely used pediatric anesthetics. Its effects on synapse development and cognition remain poorly understood. In the present study, researchers investigated the long term synapotoxicity of neonatal Sevoflurane exposure and roles of homeodomain interacting protein kinase 2 (HIPK2), a stress activating kinase involved in neuronal survivaol and synaptic plasticity, and its downstream JNK/c-Jun signaling in this process. The data showed that neonatal Sevoflurane exposure results in impairment of memory, enhancement of anxiety, reduction of excitatory synapses and synaptic proteins in the hippocampus of adult rats without significant changes of hippocampal neuron numbers. Up-regulation of HIPK2 and JNKc/c-Jun was observed in hippocampal granular neurons quickly upon Sevoflurane exposure and persisted to adult. A64, antagonist of HIPK2, could significantly rescue the cognition impairment, decrease of long term potentiation, reduction of spine density and activation of JNK/c-Jun induced by Sevoflurane. JNK antagonist SP600125 partially restored synapse development and cognitive function without affecting the expression of HIPK2. In conclusion, HIPK2-JNK/c-Jun signaling may play a key role in the long term synaptic toxicity and cognition impairment of neonatal Sevoflurane exposure, and may serve as a potential target for reducing the synaptic toxicity of Sevoflurane in the future.

Image content: The image shows that there are few c-Jun-positive cells (green, faintly visible) among the granular neurons (red) which colocated in the nucleus (blue) in the hippocampus of Sevoflurane treated rats with co-administration of A64, an antagonist of HIPK2, indicating that c-Jun may act downstream of HIPK2 in mediating the synaptic toxicity of Sevoflurane.



Read the full article *'Involvement of homodomain interacting protein kinase 2-c-Jun N-terminal kinase/c-Jun cascade in the long-term synaptic toxicity and cognition impairment induced by neonatal Sevoflurane exposure'* by L. Liang, R. Xie, R. Lu, R. Ma, X. Wang, F. Wang, B. Liu, S. Wu, Y. Wang, H. Zhang, (*J. Neurochem*. 2020, vol. 154 (4), pp. 372–388) on doi:10.1111/jnc.14910

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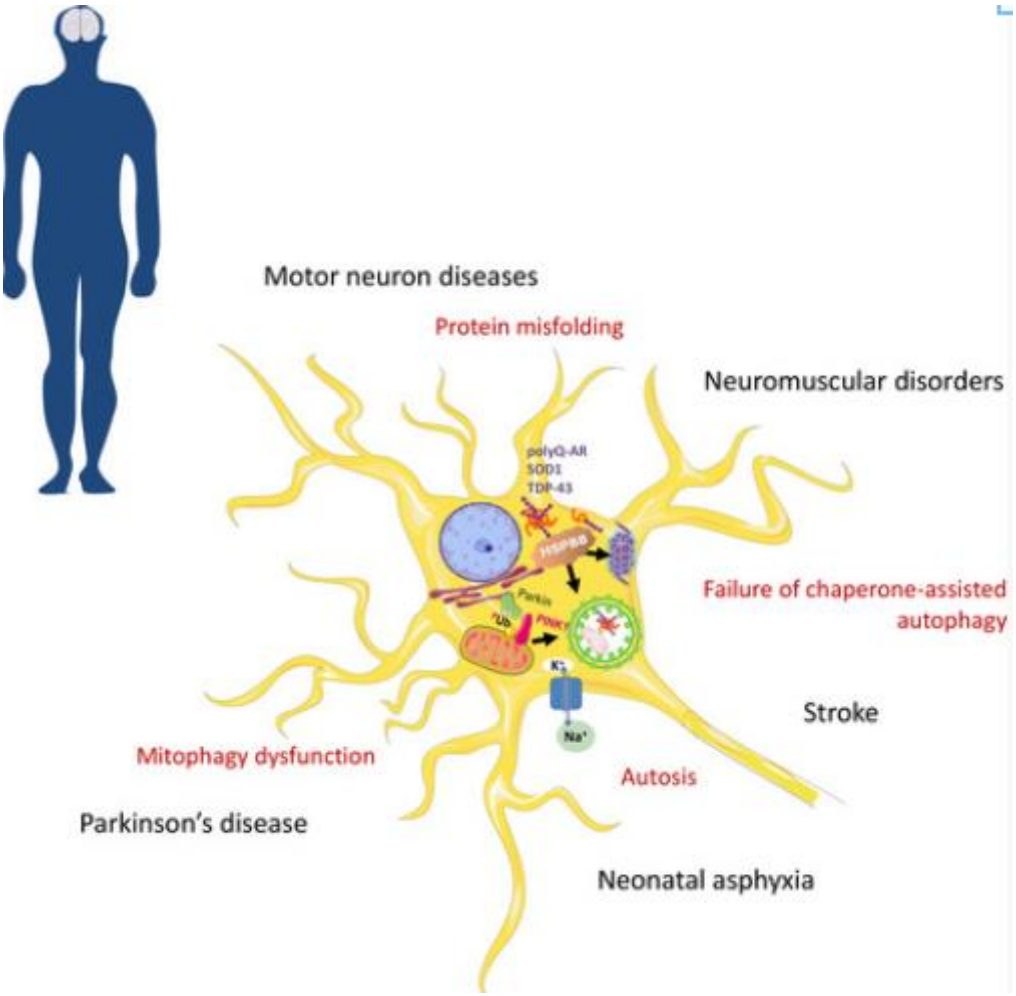
Review articles

Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases

Free Access

Olga Corti, Klas Blomgren, Angelo Poletti, Philip M. Beart

Autophagy is a process whereby damaged or abnormal components, such as proteins or organelles, are degraded in the cell. In this manuscript, we use specific examples to illustrate how alterations in this process are involved in various pathological conditions of the brain, reviewing selected mechanisms associated with its detrimental enhancement or impairment. Further, we provide prospects for therapy and discuss key issues to be considered when exploring therapeutic avenues based on the manipulation of autophagy.



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Original Articles

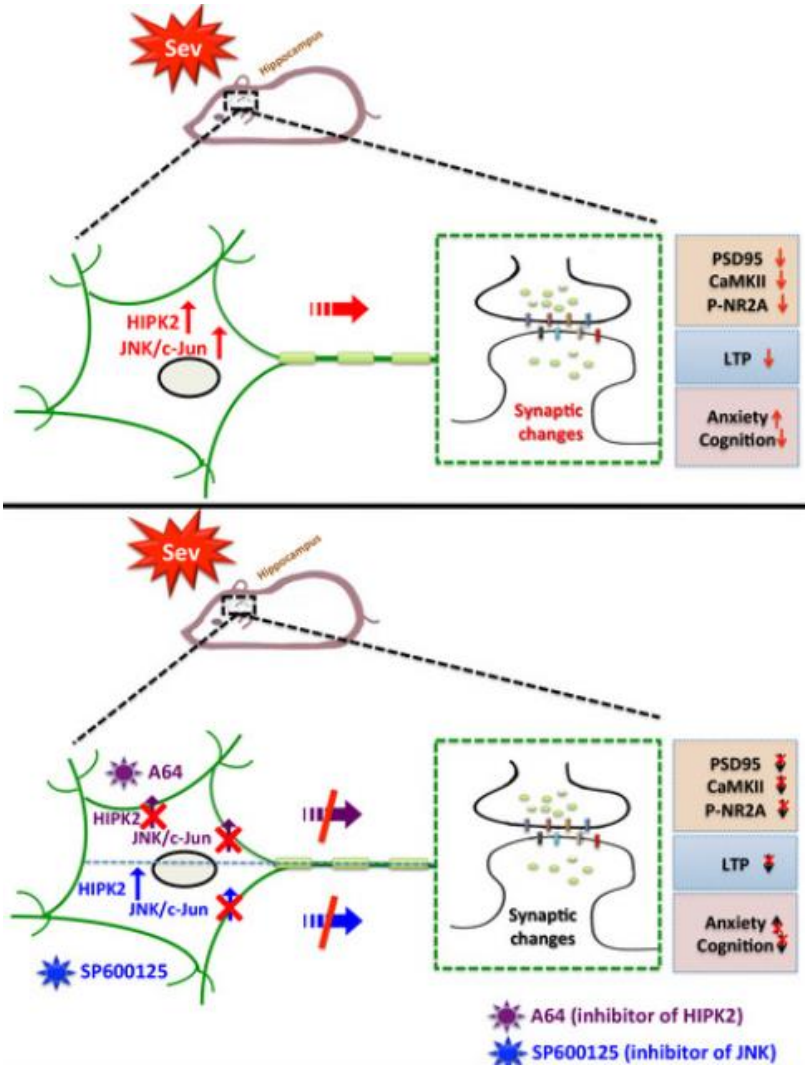
Involvement of homodomain interacting protein kinase 2-c-Jun N-terminal kinase/c-Jun cascade in the long-term synaptic toxicity and cognition impairment induced by neonatal Sevoflurane exposure

Open Access

Lirong Liang, Rougang Xie, Rui Lu, Ruixue Ma, Xiaoxia Wang, Fengjuan Wang, Bing Liu, Shengxi Wu, Yazhou Wang, Hui Zhang

Sevoflurane is one of the most widely used pediatric anesthetics. Its long-term effects on synapse development and cognition remain poorly understood. Here, we report that neonatal Sevoflurane exposure results in impairment of memory, enhancement of anxiety, reduction in excitatory synapses in the adult hippocampus with up-regulation of HIPK2 and JNK/c-Jun signaling. A64, antagonist of HIPK2, could significantly rescue the cognition impairment, synaptic dysfunction, and JNK/c-Jun activation. JNK antagonist SP600125 partially restored synapse development and cognitive function without affecting HIPK2. These data revealed a novel role of HIPK2-JNK/c-Jun cascade in the long-term synaptic toxicity of neonatal Sevoflurane exposure.

Cover Image for this issue: doi: 10.1111/jnc.14757.



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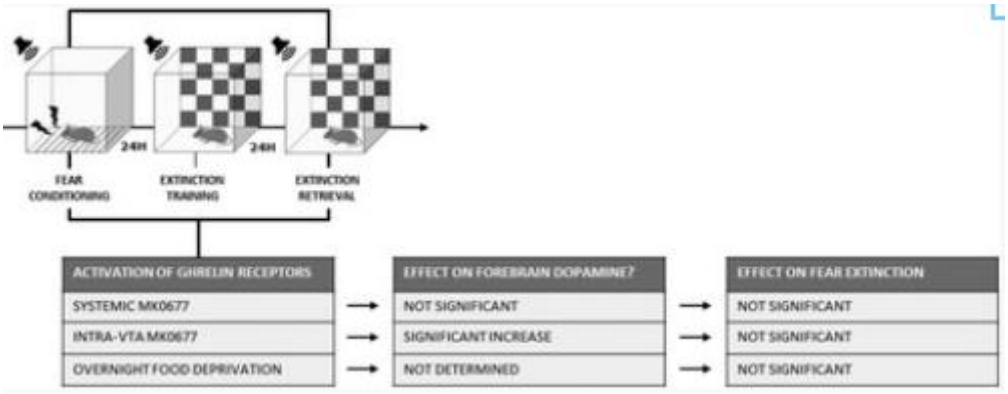
Effects of ghrelin receptor activation on forebrain dopamine release, conditioned fear and fear extinction in C57BL/6J mice

Anouk Pierre, Andries Van Schuerbeek, Wissal Allaoui, Sven Van Laere, Nicolas Singewald, Ann Van Eeckhaut, Ilse Smolders, Dimitri De Bundel

We explored the effects of ghrelin receptor activation on auditory fear processing and forebrain dopamine release. Systemic administration of MK0677 had no significant effect on auditory fear processing and did not significantly affect dopamine release. Local administration of MK0677 into the ventral tegmental area significantly increased dopamine release but did not significantly affect fear extinction. In addition, overnight food deprivation had no significant effect on fear extinction either. We conclude that the effects of manipulation of the ghrelin system on fear processing are subject to boundary conditions that remain poorly understood.



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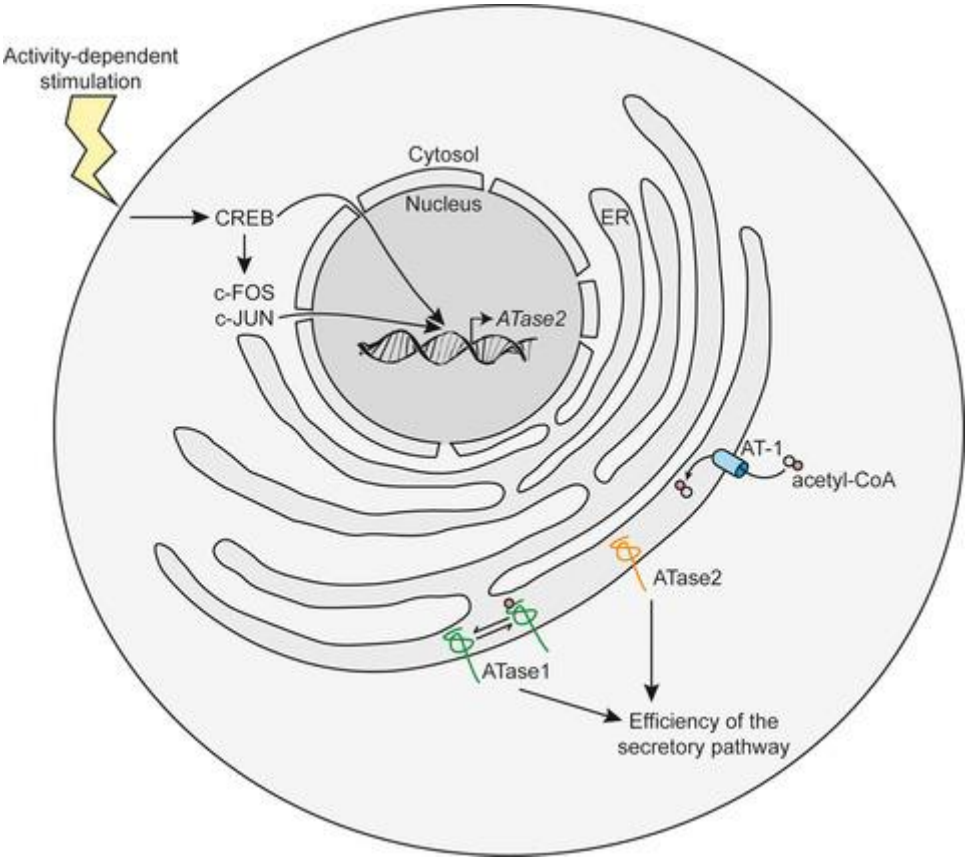
The endoplasmic reticulum acetyltransferases ATase1/NAT8B and ATase2/NAT8 are differentially regulated to adjust engagement of the secretory pathway

Michael J. Rigby, Yun Ding, Mark A. Farrugia, Michael Feig, Giuseppe P. Cortese, Heather Mitchell, Corinna Burger, Luigi Puglielli

Characterizing the regulation of the endoplasmic reticulum (ER)-based acetylation machinery can reveal important information regarding its biology and role in neurophysiology. We discovered that one of the two acetyltransferases, ATase1, can be regulated via acetylation. On the other hand, ATase2 was found to be primarily regulated transcriptionally by the immediate-early gene cascade, and the expression of ATase2 increased following activity-dependent processes. Finally, both ATase1 and ATase2 modulated the flux of glycoproteins through the secretory pathway. Our results demonstrate mechanistic ways for the cell to regulate the efficiency of the secretory pathway, which has implications in neuron function and beyond.



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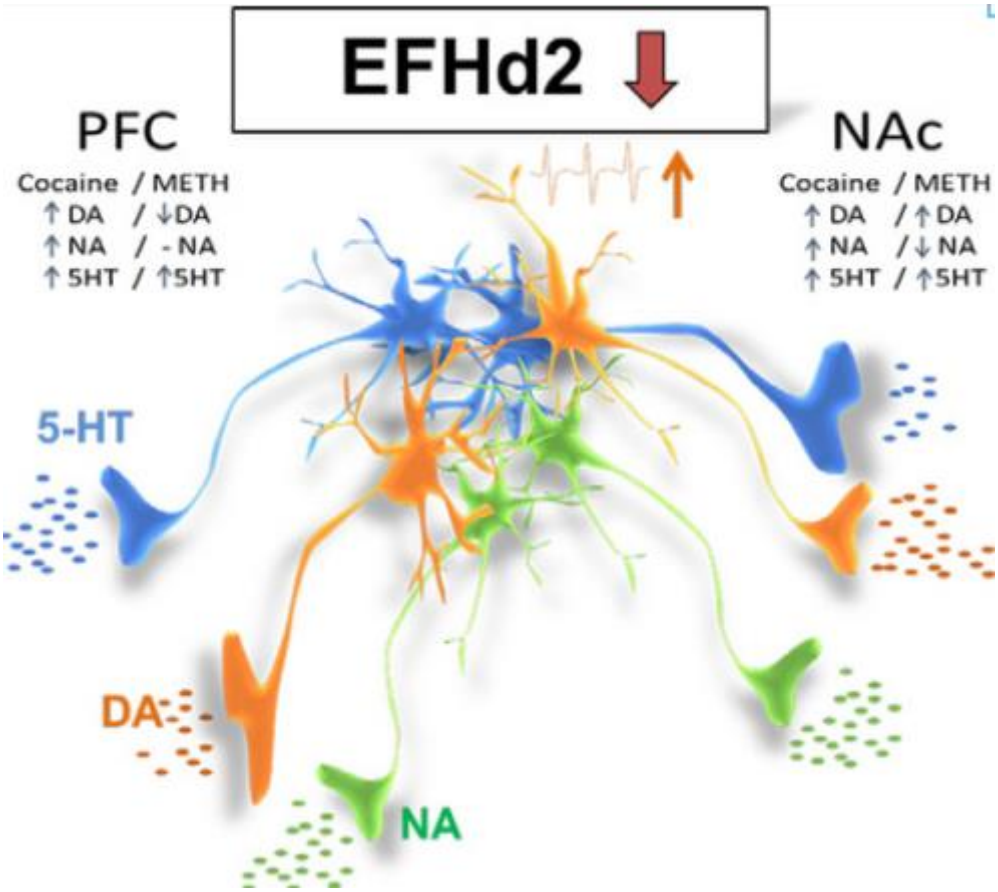
Swiprosin1/EFhd2 is involved in the monoaminergic and locomotor responses of psychostimulant drugs

Open Access

Georgios Kogias, Fang Zheng, Liubov S. Kalinichenko, Johannes Kornhuber, Christian Alzheimer, Dirk Mielenz, Christian P. Müller

Natural resilience factors provide a protection for the development of psychostimulant addiction at molecular level. Here, we describe how Swiprosin-1/Efhd2 exerts its resilience effects after methamphetamine or cocaine administration. Efhd2 limits the psychostimulant-induced increase in extracellular dopamine, serotonin and noradrenaline activity and reduces acute locomotor activation. Dopaminergic effects are mediated by direct action on basal and induced cell firing in the mesencephalon.



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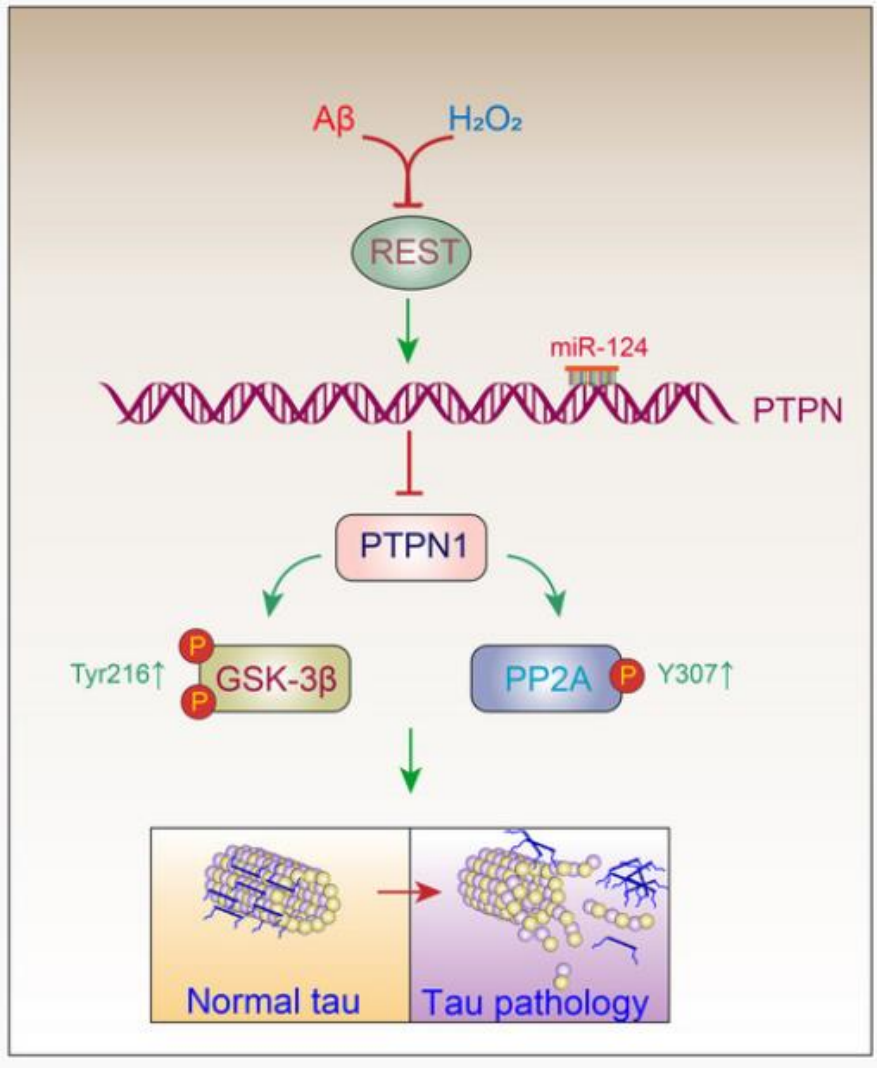
Correcting abnormalities in miR-124/PTPN1 signaling rescues tau pathology in Alzheimer's disease

Tong-Yao Hou, Yang Zhou, Ling-Shuang Zhu, Xiong Wang, Pei Pang, Ding-Qi Wang, Zhen-Yu Liuyang, Hengye Man, Youming Lu, Ling-Qiang Zhu, Dan Liu

Disruption of miRNA signals had been implicated in Alzheimer's disease (AD). We previously reported that aberrant miR-124/PTPN1 signaling induces the synaptic disorders in AD. In this study, we further investigated the potential role of miR-124/PTPN1 in the tau pathology of AD. We found that artificially replicated disturbance of miR-124/PTPN1 results in the tau pathology while correcting this abnormality rescued the tau pathology and learning/memory impairments in the P301S mice. Our study extends the critical role of miR-124/PTPN1 in the pathogenesis and provides the potential therapeutic target for AD.



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