Journal of Neurochemistry
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JNC Highlights June 2020

Latest Research and Reviews

The following articles are part of Volume 153, Issue 3

Cover Image

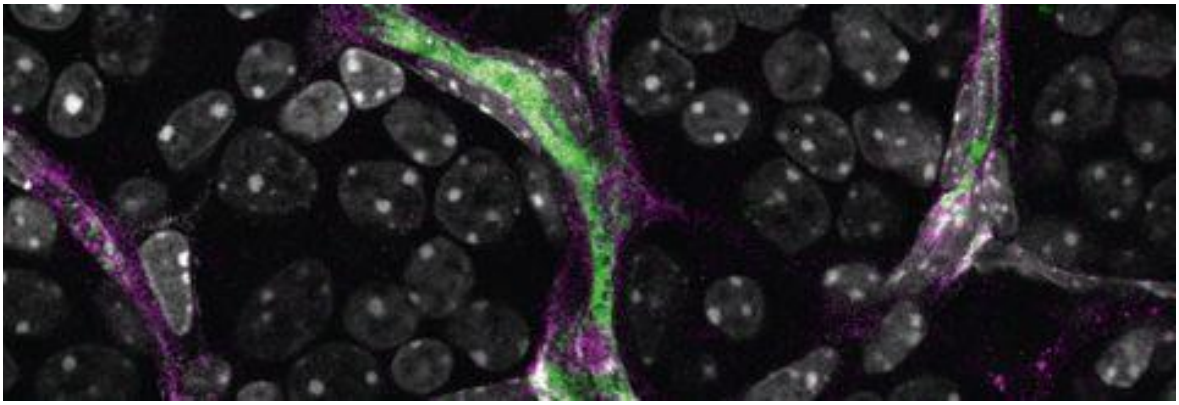
Open Access

VEGF-Trap is a potent modulator of vasoregenerative responses and protects dopaminergic amacrine network integrity in degenerative ischemic neovascular retinopathy

Jesús E. Rojo Arias, Matina Economopoulou, David A. Juárez López, Anica Kurzbach, Kwan H. Au Yeung, Vanessa Englmaier, Marie Merdausl, Martin Schaarschmidt, Marius Ader, Henning Morawietz, Richard H. W. Funk, József Jászai

Front cover: Ocular microvasculopathies compromise vision in diseases as retinopathy of prematurity and proliferative diabetic retinopathy. Using the oxygen induced retinopathy mouse model, we investigated the effects of aflibercept in modulating the aberrant retinal microvascular response to ischemia.

Image content: In this image, a magnified view of a flat-mounted retina from a 17 day old mouse subjected to the oxygen-induced retinopathy protocol and subsequently treated with aflibercept is shown. FITC-labeled dextran (150 kDa) was injected intra-peritoneally to animals 2 hours prior to sacrifice and was detected in the retinal microvasculature residing primarily within the vascular lumen (green). By contrast, immunolabeling of the tissue with an anti-human IgG antibody (magenta) and visualization of cell nuclei with DAPI (white) revealed that Aflibercept is also detected in blood vessel walls, suggesting it can be transported across retinal endothelial cells under ischemic conditions. Albeit slow in nature, this controlled transport might be central to achieving the functional benefits in vision we report in our study.



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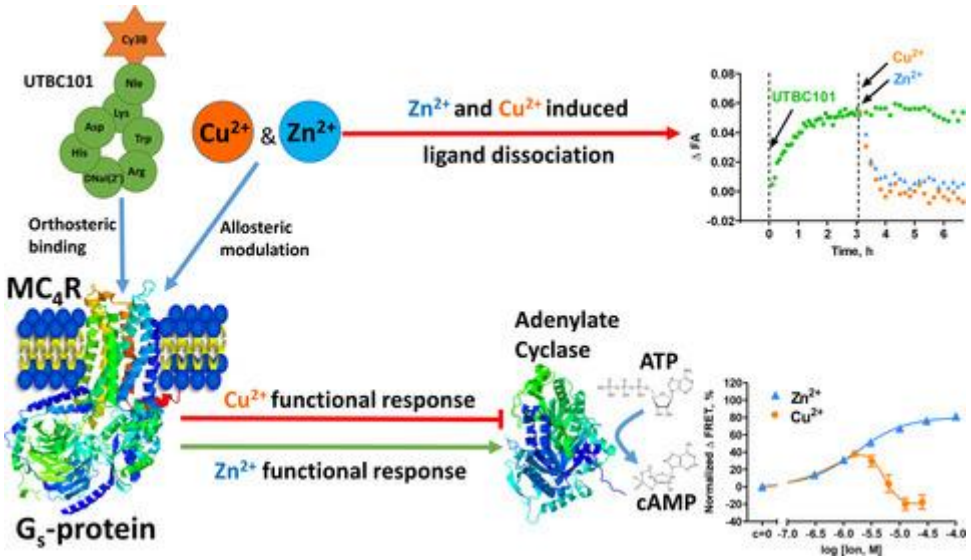
Original Articles

[The constitutive activity of melanocortin-4 receptors in cAMP pathway is allosterically modulated by zinc and copper ions]

Reet Link, Santa Veiksina, Maris-Johanna Tahk, Tõnis Laasfeld, Päärn Paiste, Sergei Kopanchuk, Ago Rinken

We have studied how different metal ions modulate the activity of melanocortin-4 receptors (MC4R), which plays an important role in energy homeostasis, sexual functions, neuroprotection, and neurogenesis. Herewith we show that submillimolar Ca^{2+} is indispensable for the high-affinity ligand binding to MC4R, whereas Zn^{2+} and Cu^{2+} are negative allosteric modulators of the ligand binding. In functional assays, Zn^{2+} causes MC4R-dependent activation of the cAMP pathway, whereas Cu^{2+} reduces this activity even below the basal intrinsic activity. Obtained results indicate that Zn^{2+} and Cu^{2+} function as MC4R agonists or inverse agonists, respectively, at physiologically relevant low micromolar concentrations.



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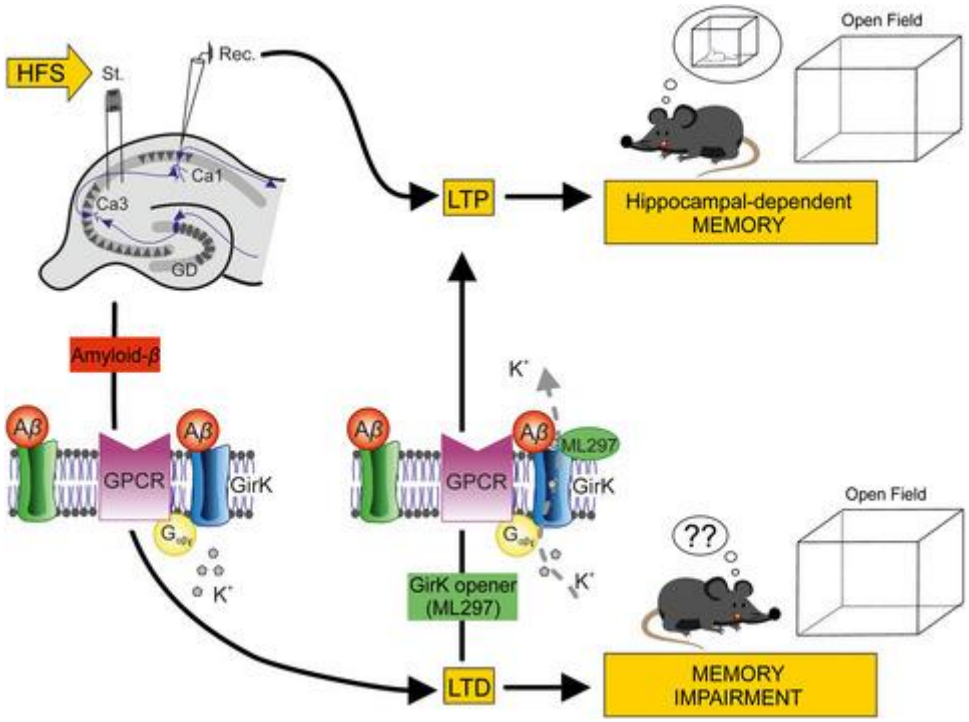
Hippocampal long-term synaptic depression and memory deficits induced in early amyloidopathy are prevented by enhancing G-protein-gated inwardly rectifying potassium channel activity

Open Access

Irene Sánchez-Rodríguez, Souhail Djebari, Sara Temprano-Carazo, David Vega-Avelaira, Raquel Jiménez-Herrera, Guillermo Iborra-Lázaro, Javier Yajeya, Lydia Jiménez-Díaz, Juan D. Navarro-López

Disruption of hippocampal synaptic plasticity by amyloid-β (Aβ) peptides is thought to be responsible for learning and memory impairments in early Alzheimer's disease. Here we describe an Aβ-mediated deleterious synaptic mechanism that modifies the threshold for the induction of hippocampal LTP and/or LTD and underlies memory alterations in amyloidosis models. We also propose a potential intervention to prevent such synaptic impairment through G-protein-gated inwardly rectifying potassium (GirK) channels activation.



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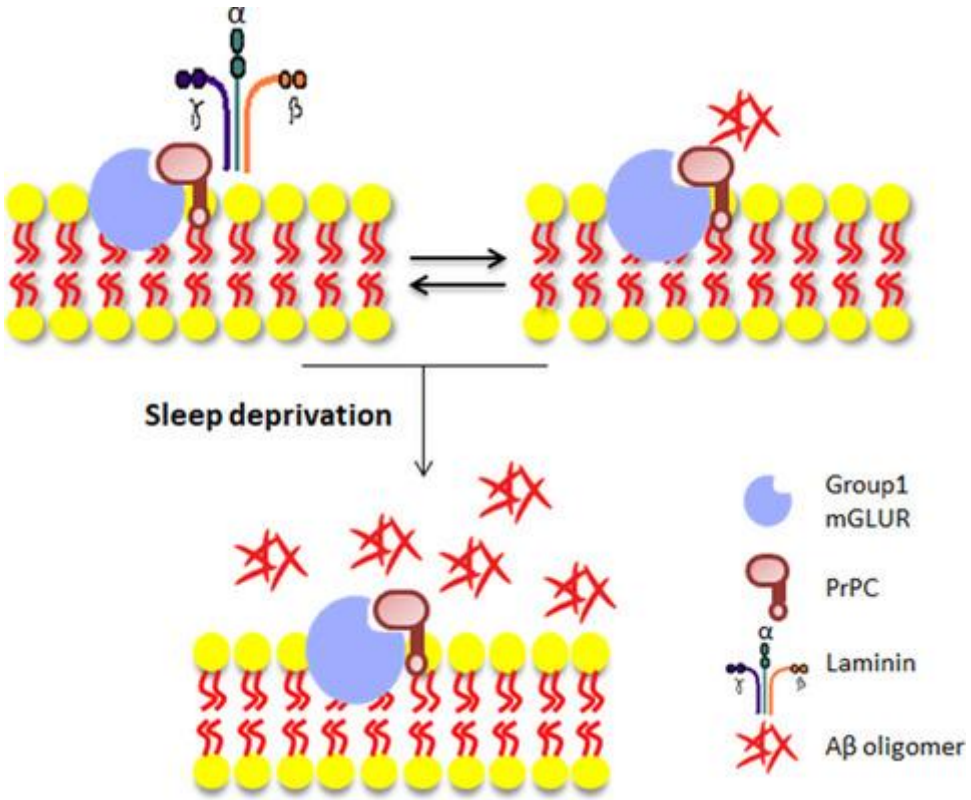
Sleep deprivation regulates availability of PrPC and Aβ peptides which can impair interaction between PrPC and laminin and neuronal plasticity

Open Access

Marcio H. M. da Luz, Jessica M. V. Pino, Tiago G. Santos, Hanna K. M. Antunes, Vilma R. Martins, Altay A. L. de Souza, Ricardo J. S. Torquato, Kil S. Lee

Pleiotropic functions of PrPC in intracellular signaling depend on co-receptors (ex: mGluR1) and ligands such as laminin and Aβ oligomers. In this study, we observed that sleep deprivation reduces PrPC levels and increases Aβ peptides levels. Our results also indicate that Aβ oligomers compete with laminin for PrPC binding and impair neuritogenesis dependent of PrPC–laminin interaction, which is important for synaptic plasticity and memory consolidation. Thus, reduction in PrPC level, accumulation of Aβ peptides, and consequent disruption of PrPC–laminin binding might be a part of molecular mechanisms that lead to low cognitive performance in sleep deprived individuals.



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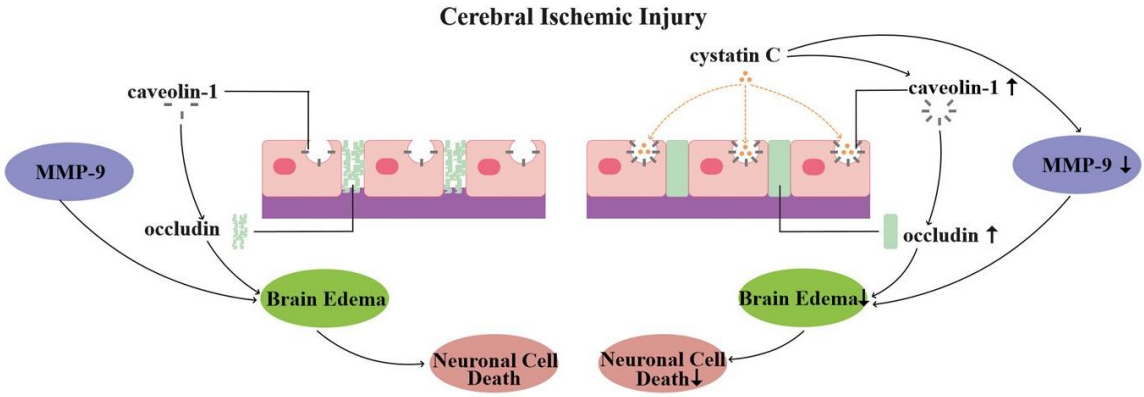
Cystatin C improves blood–brain barrier integrity after ischemic brain injury in mice

Bo Yang, Junjie Xu, Liuhui Chang, Zhigang Miao, Dara Heang, Yuwei Pu, Xun Zhou, Lingwei Zhang, Hong Xie

We report that Cystatin C reduces the permeability of the blood–brain barrier (BBB) by up-regulating the expression of caveolin-1 and occludin in ischemic brain injury. Enhancing the permeability of the BBB leads to increased MMP-9 and the death of bEnd.3 cells, which can be counteracted by ameliorating the BBB disruption and might represent a new therapeutic strategy for cerebral ischemic injury. The diagram shows that pretreatment with cystatin C increases caveolin-1 and occludin expression in ischemic brain injury (right side of diagram). Left side of the diagram: cerebral ischemia-reperfusion-induced injury increases cystatin C and caveolin-1, which may be a compensatory reaction; but it fails to rescue the degradation of occludin.



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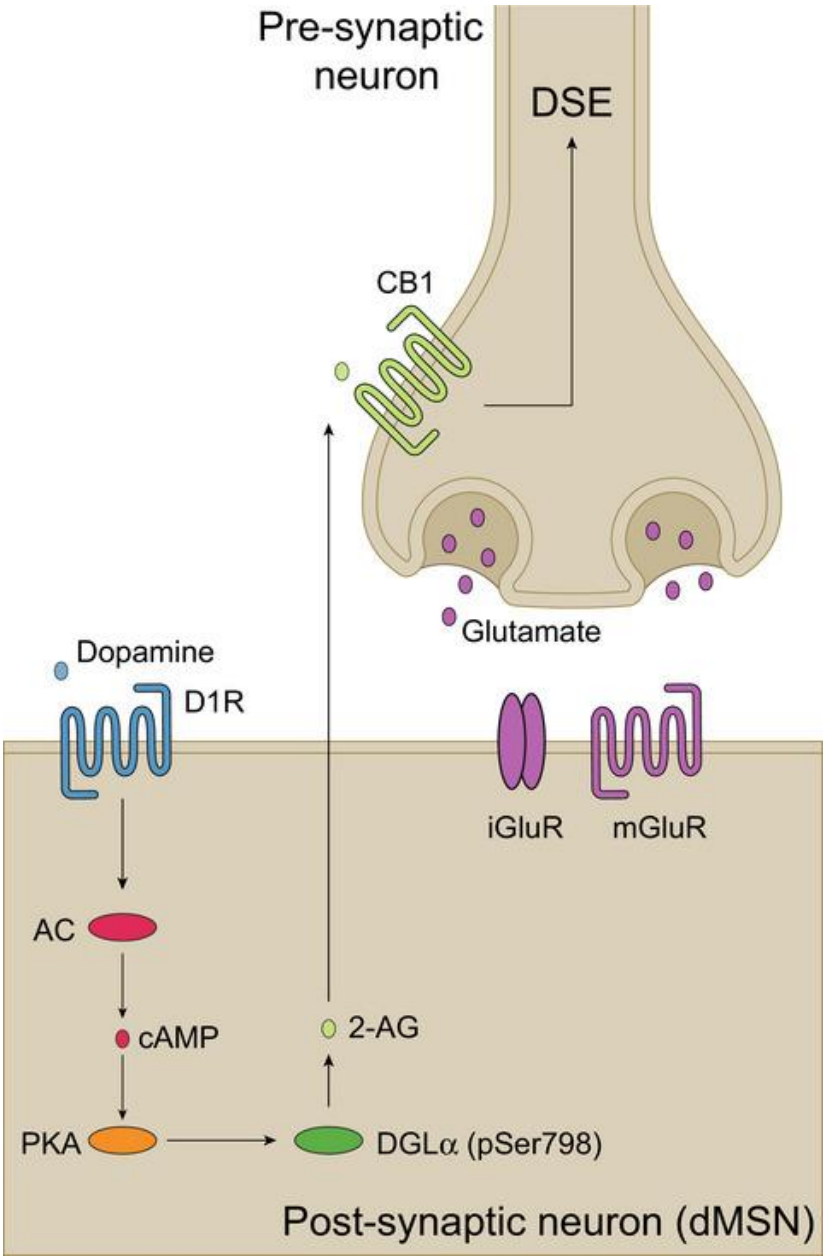
Editorial Highlight

Dopamine D1 receptor signaling and endocannabinoid cooperate to fuel striatal plasticity

Renato Socodato

Dopamine (released from the substantia nigra) binds to and activates D1 receptors in striatal MSN (the direct pathway; dMSN). The canonical D1 pathway (cAMP dependent) leads to the downstream activation of PKA. Active PKA phosphorylates DGL at Ser798, enhancing the synthesis of 2-AG. Secretion of 2-AG in the corticostriatal pathway activates pre-synaptic CB1 receptors, which can modulate synaptic plasticity such as DSE, leading to a decrease of glutamate release from the excitatory pre-synaptic neuro.



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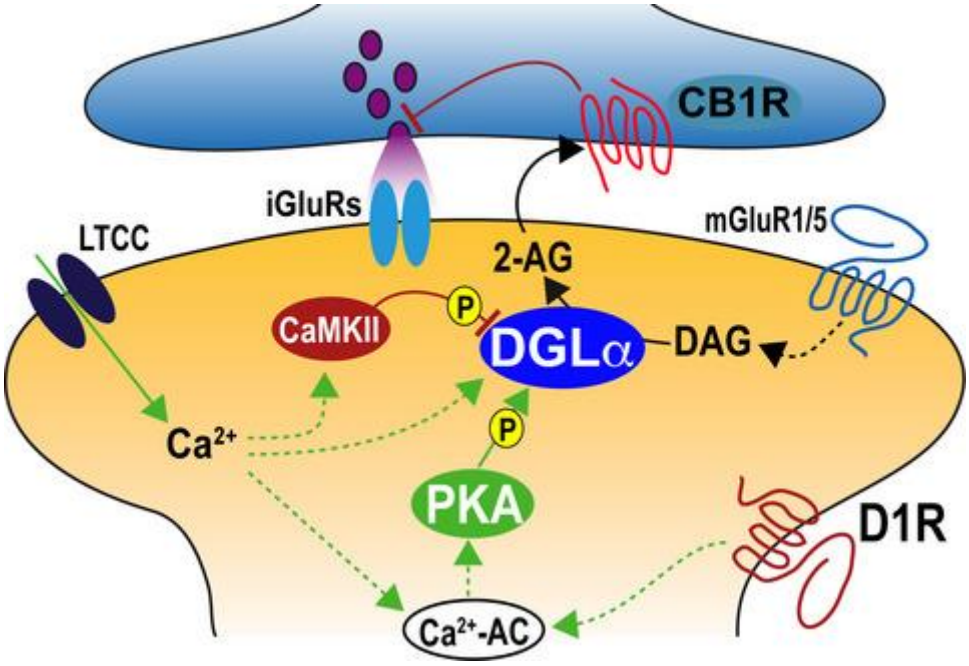
Highlighted Article

Cyclic AMP-dependent protein kinase and D1 dopamine receptors regulate diacylglycerol lipase-α and synaptic 2-arachidonoyl glycerol signalling

Brian C. Shonesy, Jason R. Stephenson, Christian R. Marks, Roger J. Colbran

Post-synaptic synthesis of a major brain endocannabinoid, 2-arachidonoyl glycerol (2-AG), from diacylglycerol (DAG) by diacylglycerol lipase-α (DGLα) is stimulated by L-type voltage-gated calcium channels (LTCC) and/or metabotropic glutamate receptors (mGluR1/5). Shonesy et al show that cyclic AMP-dependent protein kinase (PKA) phosphorylates Ser798 in DGLα to increase activity. Their data indicate that D1-dopamine receptors (D1R) stimulate adenylyl cyclase (Ca^{2+}-AC) and PKA to enhance synaptic 2-AG production by DGLα and short-term depression of glutamatergic transmission, which depends on pre-synaptic endocannabinoid 1 receptors (CB1R). Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) was previously shown to phosphorylate distinct sites in DGLα to restrain synaptic 2-AG synthesis.



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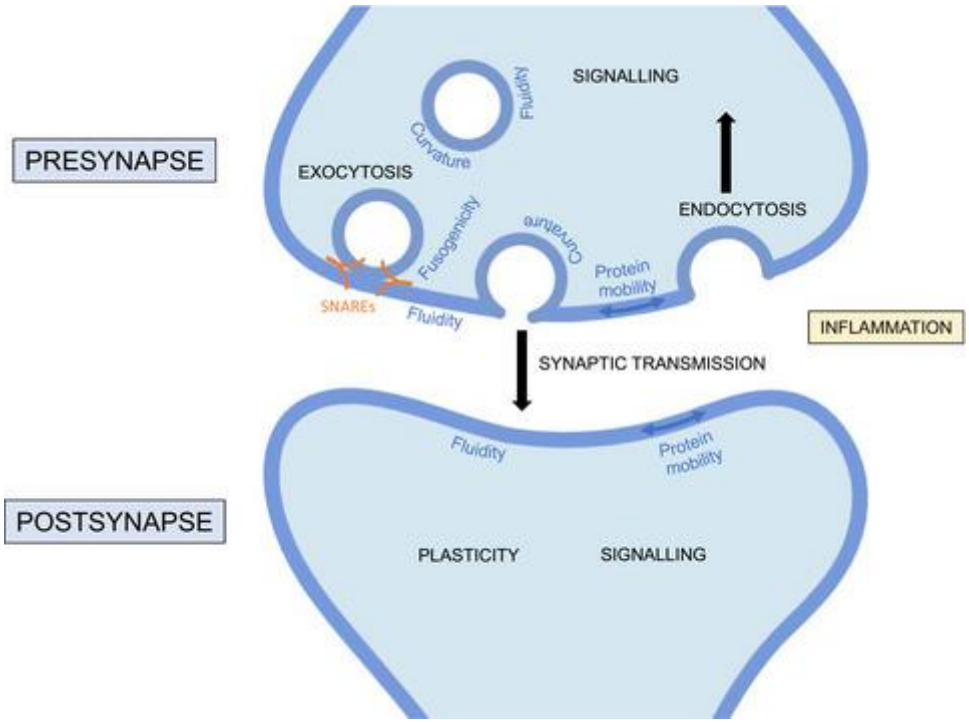
Review article

Phospholipases in neuronal function: A role in learning and memory?

Free Access

Merja Joensuu, Tristan P. Wallis, Saber H. Saber, Frédéric A. Meunier

Neurotransmission and synaptic plasticity underlie cognition and memory formation, and involve tightly regulated dynamic modulation of phospholipid membrane composition, fluidity, curvature and surface chemistry in concert with protein–protein, protein–lipid and lipid–lipid interactions at the pre- and post-synapse. Phospholipases are crucial players in this process, capable of dramatically changing the phospholipid landscape and their metabolites thereby contributing to SNARE-mediated exo- and endocytosis, synaptic transmission, synaptic plasticity, pre- and post-synaptic signalling and inflammation. This review discusses the role of phospholipases expressed in the human brain in these processes, and the diseases associated with their dysregulation.



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The following articles are part of Volume 153, Issue 4

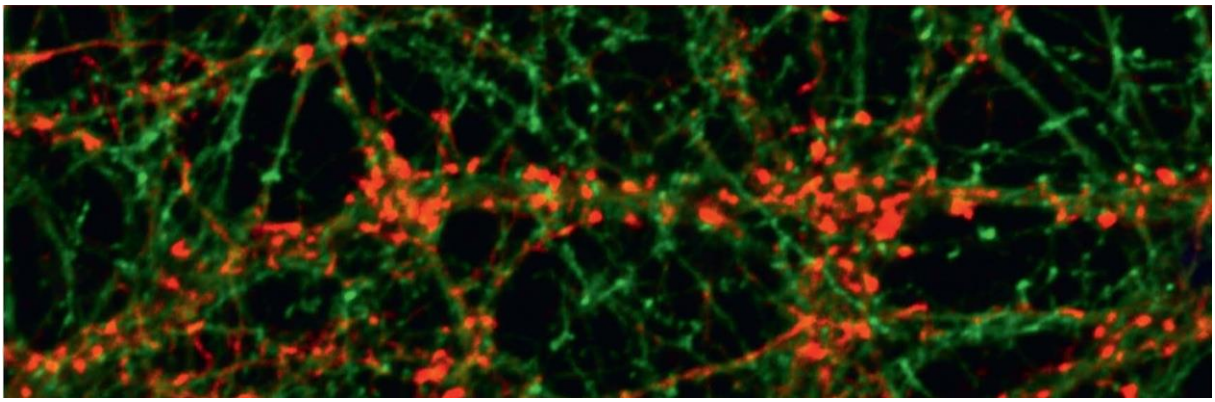
Cover Image

Insulin-regulated aminopeptidase inhibitor-mediated increases in dendritic spine density are facilitated by glucose uptake

Benjamin Seyer, Shanti Diwakarla, Peta Burns, Anders Hallberg, Alfhild Grönbladh, Mathias Hallberg, Siew Yeen Chai

Front cover: Inhibition of insulin-regulated aminopeptidase (IRAP) activity improves spatial working and recognition memory in rodents. However, the mechanism of its cognitive-enhancing effect remains unknown. There is a close correlation between dendritic spine density and learning in vivo. Dendritic spines are small protrusions from the dendrites of neurons that serve as contacts with neighboring axons and contain all of the molecular machinery required for synaptic plasticity and long term potentiation, i.e. the storage of memories.

Image content: Primary rat hippocampal cultures were exposed to varying concentrations of the IRAP inhibitor HFI-419 on 14, 17 and 20 div, a period of time when peak dendritic spine formation occurs. At 21 div, hippocampal cells were fixed and immunostained against β-III tubulin (1:500, green) and drebrin (1:500, red) to visualize neuronal processes and dendritic spines, respectively. Nuclei were counterstained with DAPI (blue). Cultures treated with HFI-419 had an increased number of total spines when compared with vehicle-treated cells, suggesting that IRAP inhibition may exert its memory enhancing effects by increasing dendritic spine density. Scale bar = 10 µm.



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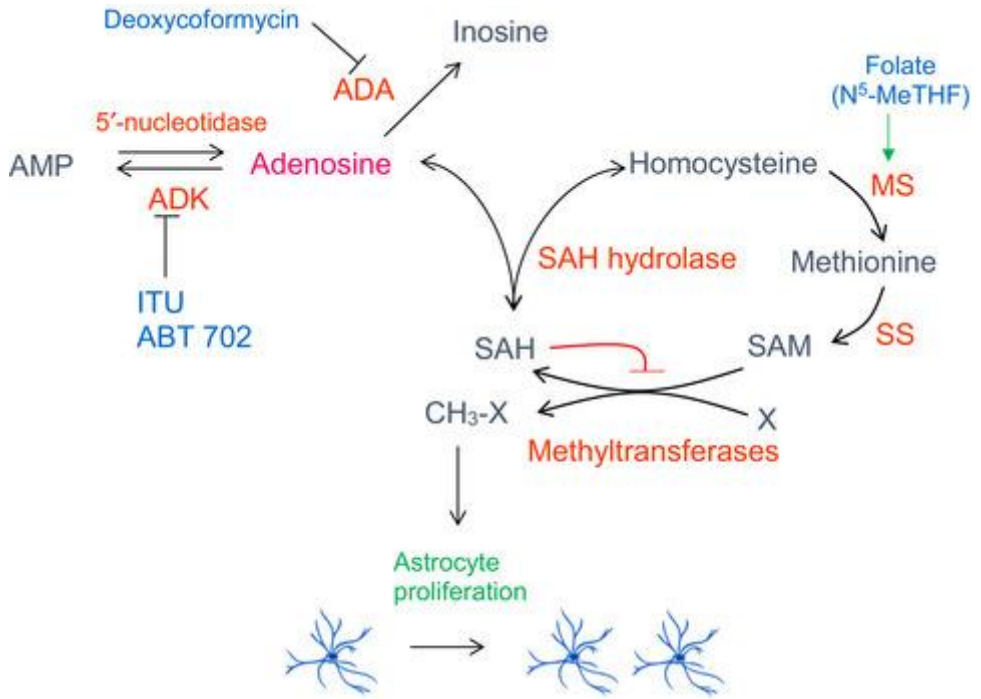
Original Articles

Adenosine inhibits human astrocyte proliferation independently of adenosine receptor activation

Helena Marcelino, Vanda C. Nogueira, Cecília R.A. Santos, Patrícia Quelhas, Tiago M.A. Carvalho, João Fonseca-Gomes, Joana Tomás, Maria J. Diógenes, Ana M. Sebastião, José F. Cascalheira

Brain adenosine reaches micromolar concentrations in stressful situations. Astrocytes uncontrolled proliferation plays a role in neurodegeneration and glioma. The effect of increased adenosine concentration on astrocytes proliferation was addressed in present work. Human astrocytes (HA) were treated for 3 days with test drugs. 30 µM-Adenosine caused a receptor-independent inhibition of HA proliferation/viability. The adenosine effect was potentiated by homocysteine, mimicked by two adenosine kinase inhibitors (ABT-702 and ITU) and attenuated in the presence of folate or SAM. Results suggest that adenosine reduces HA proliferation by a receptor-independent mechanism probably involving reversal of SAH hydrolase-catalysed reaction.



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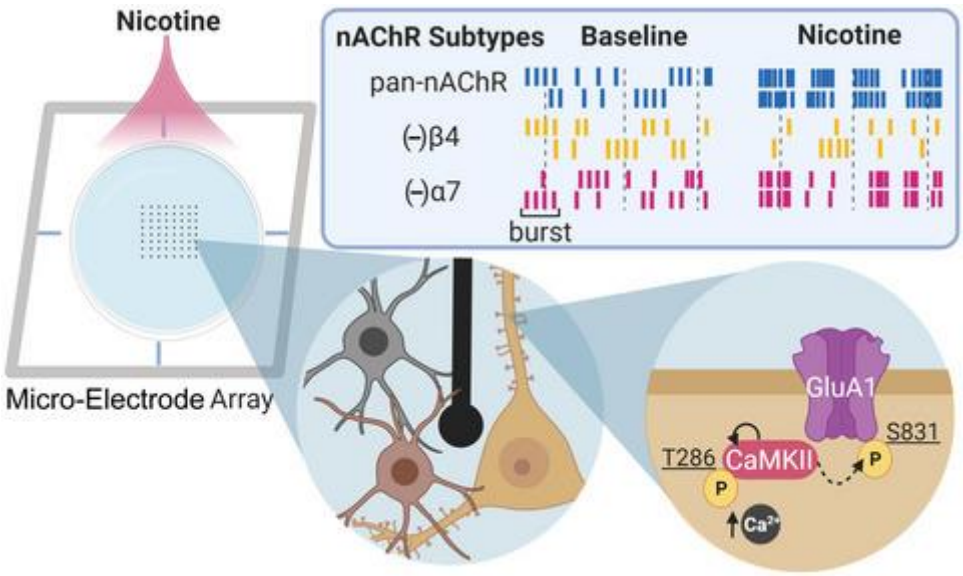
[Activation of nicotinic acetylcholine receptors induces potentiation and synchronization within in vitro hippocampal networks]

Sarra Djemil, Xin Chen, Ziyue Zhang, Jisoo Lee, Mikael Rauf, Daniel T. S. Pak, Rhonda Dzakpasu

Nicotinic acetylcholine receptor (nAChR) activation within the hippocampus is capable of shifting the excitatory–inhibitory ratio. We found that pan-activation of nAChRs using nicotine potentiates cultured hippocampal networks through β4-containing nAChRs, and this effect is augmented by the activation of α7 nAChRs. Furthermore, nicotine exposure promotes threonine 286 autophosphorylation of CaMKII and serine 831 phosphorylation of the AMPA receptor subunit GluA1. These findings highlight the impact of cholinergic signaling in generating network-wide potentiation in the form of enhanced spiking and bursting dynamics as well as elevated synchrony that coincide with molecular correlates of memory such as increased phosphorylation of CaMKII and GluA1.



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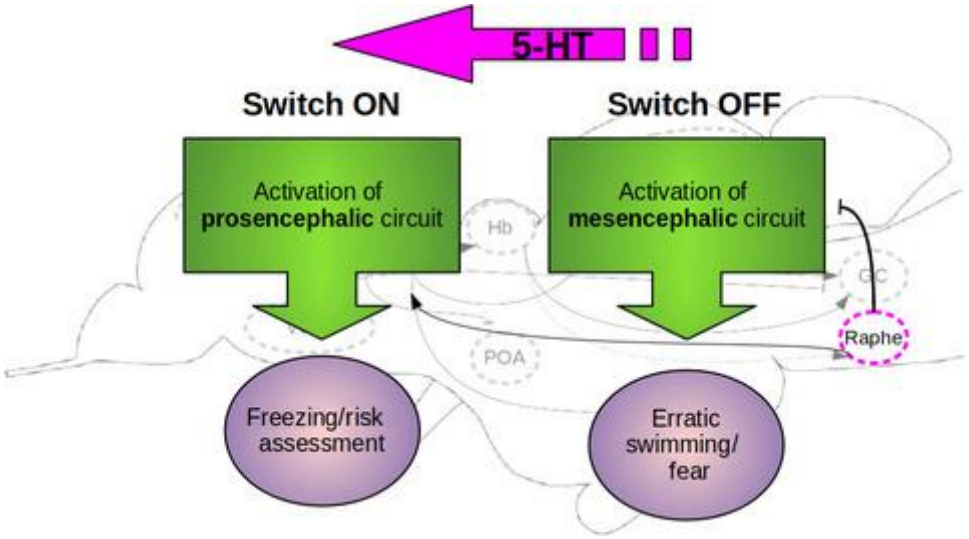
[Phasic and tonic serotonin modulate alarm reactions and post-exposure behavior in zebrafish]

Monica Lima-Maximino, Maryana Pereira Pyterson, Rhayra Xavier do Carmo Silva, Gabriela Cristini Vidal Gomes, Sueslene Prado Rocha, Anderson Manoel Herculano, Denis Broock Rosemberg, Caio Maximino

Hypothetical mechanism of the serotonergic signaling in zebrafish defensive behavior during and after exposure to conspecific alarm substance (CAS). CAS elicits responses dominated by erratic swimming, which decreases as the substance's concentrations decline. After CAS exposure, the behavioral response is dominated by freezing. Serotonin (5-HT) shifts responding from the first to the second (represented by the purple arrow, as well as by the arrows connecting the raphe to the “switch” green boxes), putatively by switching control from the mesencephalic aversive circuit (“switch OFF”) to the prosencephalic aversive circuit (“switch ON”).



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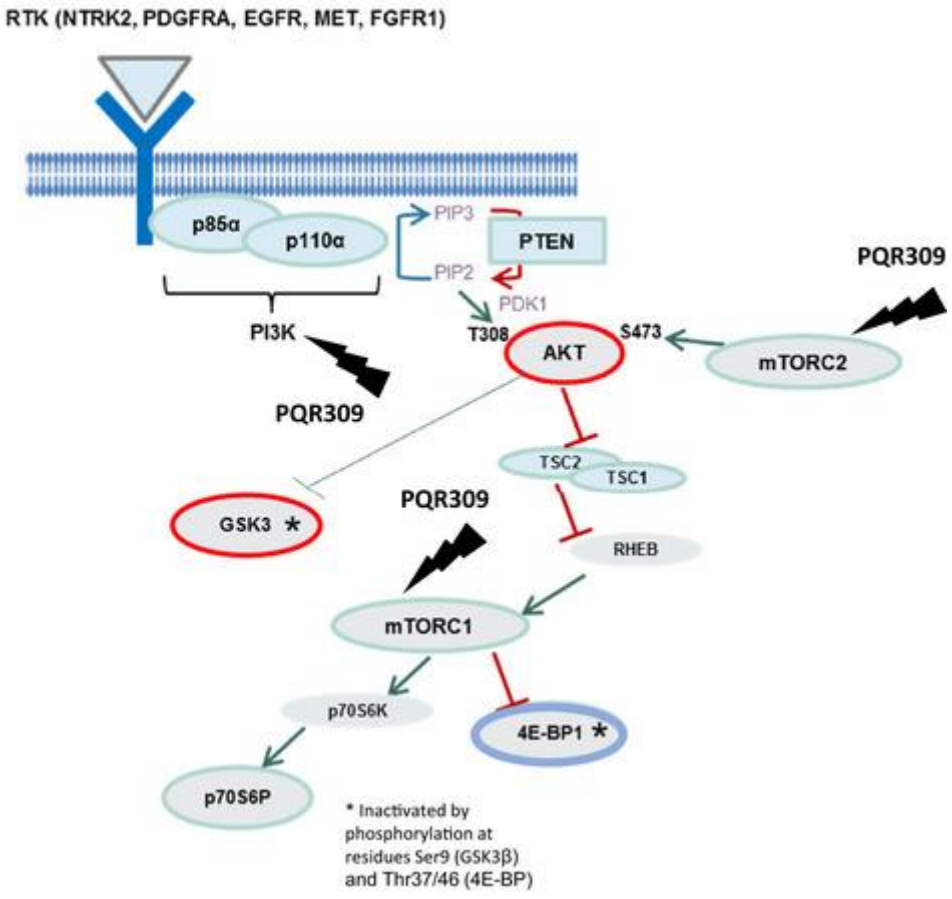
Synergistic growth inhibition mediated by dual PI3K/mTOR pathway targeting and genetic or direct pharmacological AKT inhibition in human glioblastoma models

Caroline von Achenbach, Michael Weller, Kerstin Kaulich, Dorothee Gramatzki, Angela Zacher, Doriano Fabbro, Guido Reifenberger, Emese Szabó

Molecular genetic aberrations in the PI3K/AKT/mTOR pathway are common in glioblastoma. We hypothesized that molecular profiling in combination with *in vitro* drug sensitivity testing may allow to identify signatures associated with sensitivity or resistance to PI3K/mTOR pathway inhibition. Cell lines with high basal levels of phosphorylated (active) AKT, low levels of phosphorylated (inactive) protein translation repressor 4E-BP1, and high levels of Ser9-phosphorylated (inactive) GSK3β were more sensitive to PQR309, a dual pan-PI3K/mTOR antagonist *in vitro* .



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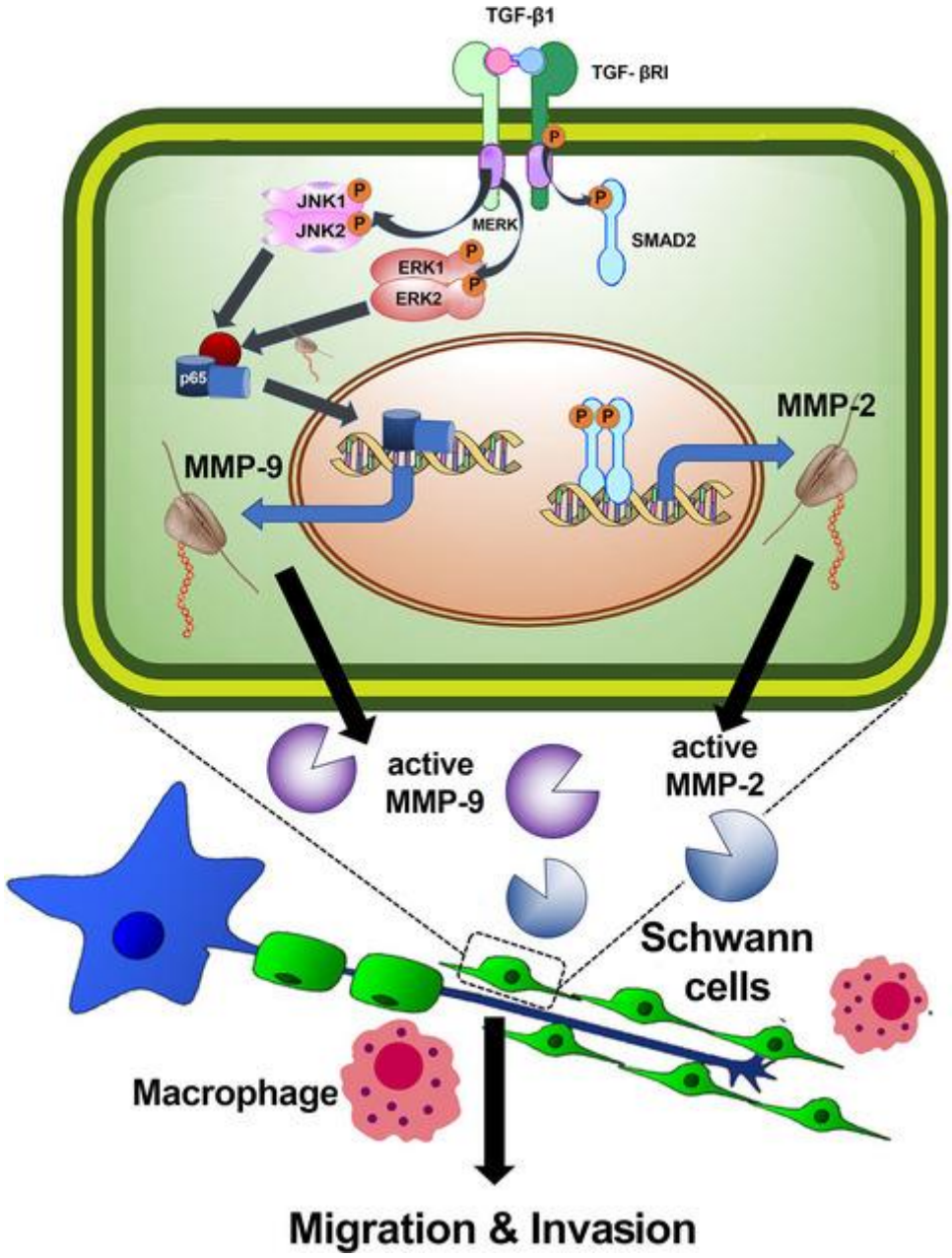
TGF-β1 activates RSC96 Schwann cells migration and invasion through MMP-2 and MMP-9 activities

Antonella Muscella, Carla Vetrugno, Luca Giulio Cossa, Santo Marsigliante

Following peripheral nerve injury, Schwann cells remodel the extracellular matrix allowing axonal regrowth. We investigated the role of TGF-β1 in migration and invasion of RSC96 Schwann cells. Signaling along the TGF-β1 pathway activates SMAD2 that enhances transcription of matrix metalloproteinase MMP-2. Furthermore, TGF-β1 activates MAPKs ERK1/2 and JNK1/2 that control p65/NFkB, which enhances the transcription of MMP-9. Secretion of metalloproteinases thus plays an important role in the motility capacity of Schwann cells.



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Review articles

Synucleinopathies: Where we are and where we need to go

Open Access

Inês Caldeira Brás, Antonio Dominguez-Meijide, Ellen Gerhardt, David Koss, Diana F. Lázaro, Patrícia I. Santos, Eftychia Vasili, Mary Xylaki, Tiago Fleming Outeiro

This article is related to the Special Issue Synuclein which was solicited from the Synuclein Meeting 2019. Every 2 years for about 12 years, the Synuclein Meetings bring together leading experts in the field of Synuclein and related human conditions with the goal of discussing and advancing the research. Here, we provide a summary of the topics discussed in each session and highlight what we know, what we do not know, and what progress needs to be made in order to enable the field to continue to advance. Alpha-synuclein (aSyn) is implicated in several neurodegenerative disorders of the brain and in this review we cover various aspects of aSyn biology and pathobiology, as depicted in the various circles.