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

JNC Highlights March 2020

Latest Research and Reviews

The following articles are part of Volume 152, Issue 3

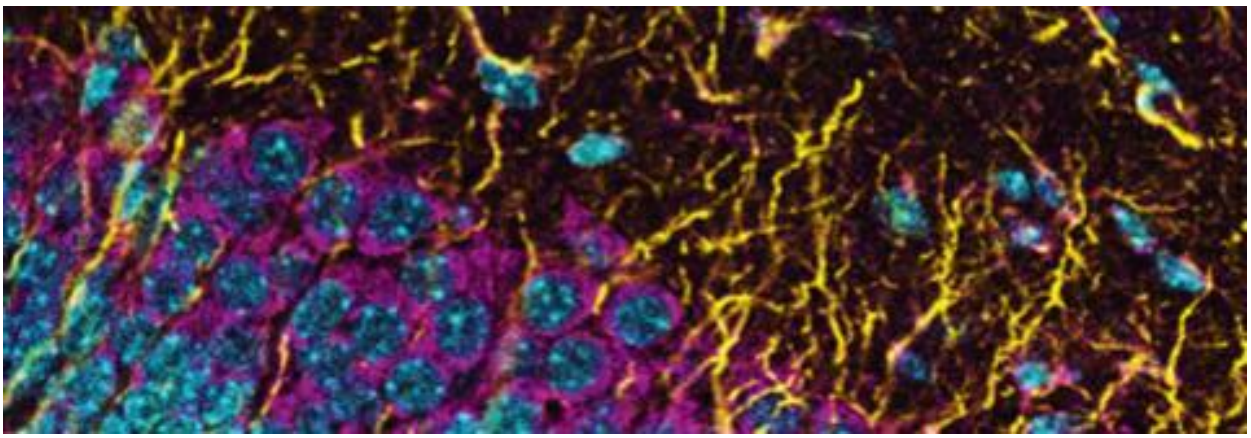
Cover Image

Transferrin and H-ferritin involvement in brain iron acquisition during postnatal development: impact of sex and genotype

Brian Chiou, Elizabeth B. Neely, Dillon S. Mcdevitt, Ian A. Simpson, James R. Connor

Front cover: Proper iron delivery is crucial for normal brain development and function. Here, we demonstrate H-ferritin, traditionally considered an iron storage protein, to be a significant iron delivery protein during development. Our study profiles the cellular uptake mechanism for H-ferritin in the brain, demonstrating that sex and genotype play a major role in iron uptake. Furthermore, our study uncovers the regional and cellular distribution of Tim-2, the murine receptor for H-ferritin. These findings together shed light on the basic mechanisms surrounding iron delivery to the brain, thus providing a promising new direction in the treatment of iron deficiency.

Image content: Confocal image of P7 mouse brains immunolabeled for astrocytes (GFAP, yellow) and Tim-2 (magenta). Nuclei are shown in cyan (DAPI). Tim-2 signal is co-localized with GFAP signal as well as in the surrounding microvasculature and neurons.



Journal of Neurochemistry
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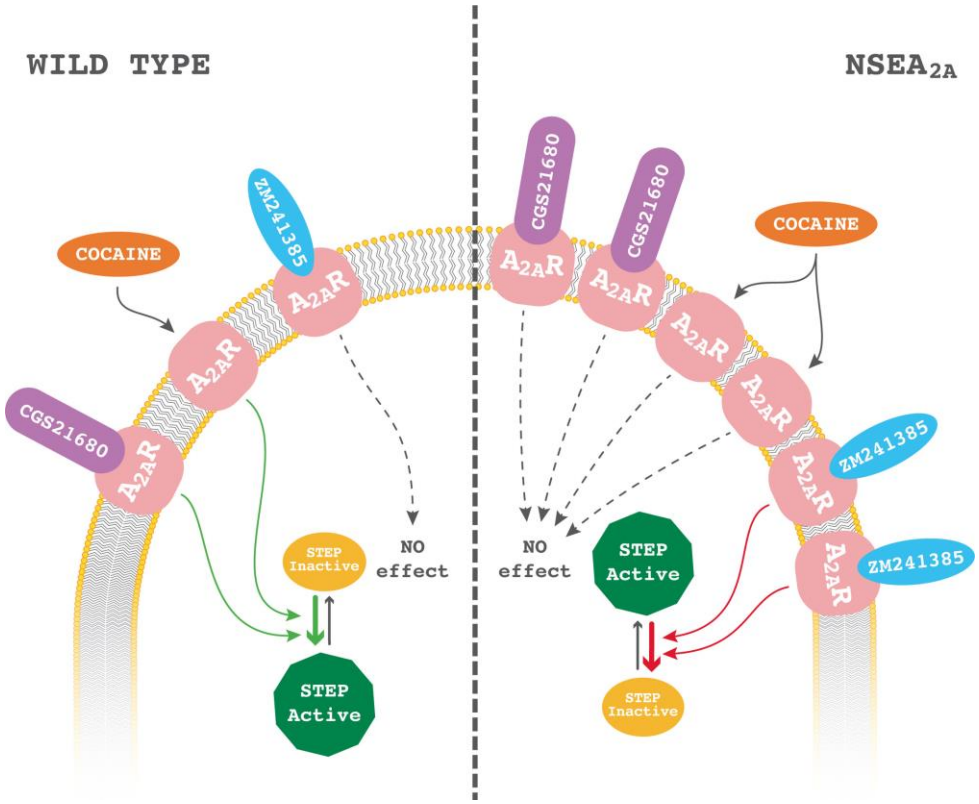
Original Articles

The activity of the Striatal-enriched protein tyrosine phosphatase in neuronal cells is modulated by adenosine A2A receptor

Cinzia Mallozzi, Rita Pepponi, Sergio Visentin, Valentina Chiodi, Paul J. Lombroso, Michael Bader, Patrizia Popoli, Maria Rosaria Domenici

We previously demonstrated that a tonic activation of A2ARs is required for cocaine-induced synaptic depression and increased activity of the protein tyrosine phosphatase STEP. Thus, we investigated the relationship between A2AR and STEP in the striatum of a transgenic rat strain over-expressing A2AR (NSEA2A). STEP activity is increased in NSEA2A compared to WT. The A2AR agonist CGS21680 up-regulates STEP activities in WT but not in NSEA2A, while the A2AR antagonist ZM241385 restores STEP activities in NSEA2A, having no effects in WT. While cocaine-induced STEP activation in WT, it failed to increase it in NSEA2A rats. The present study identified a novel interaction between A2AR and STEP.



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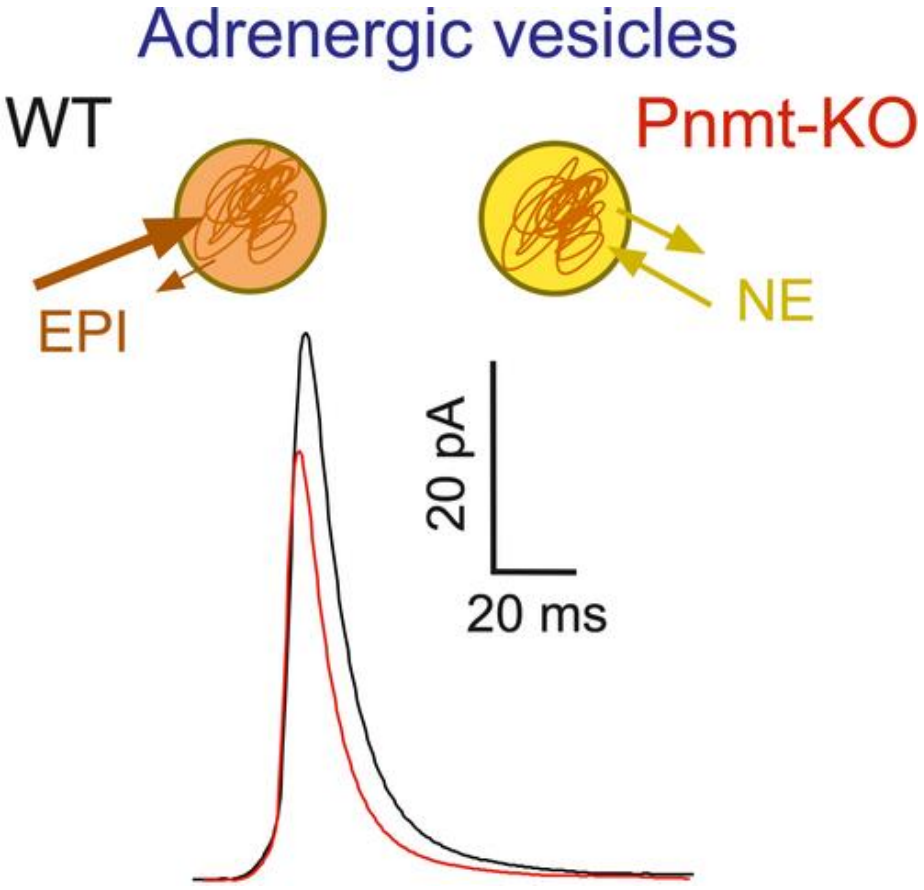
Adrenergic chromaffin cells are adrenergic even in the absence of epinephrine

Ayoze González-Santana, Leandro Castañeyra, Rebeca Baz-Dávila, Judith Estévez-Herrera, Natalia Domínguez, Iago Méndez-López, J. Fernando Padín, Agustín Castañeyra, José-David Machado, Steven N. Ebert, Ricardo Borges

The absence of functional phenylethanolamine-N-methyltransferase (Pnmt) results in a mouse without epinephrine (EPI). In the adrenal gland, this is only partially compensated by an increase in the adrenal content of norepinephrine (NE). This can be explained because secretory vesicles of adrenergic cells are optimized for storage and release EPI resulting in lower accumulation of the only available catecholamine, NE. The quantal exocytosis characteristics and the functional responses to stimuli suggest that adrenergic cells are still of adrenergic linage in spite of the lack of EPI.



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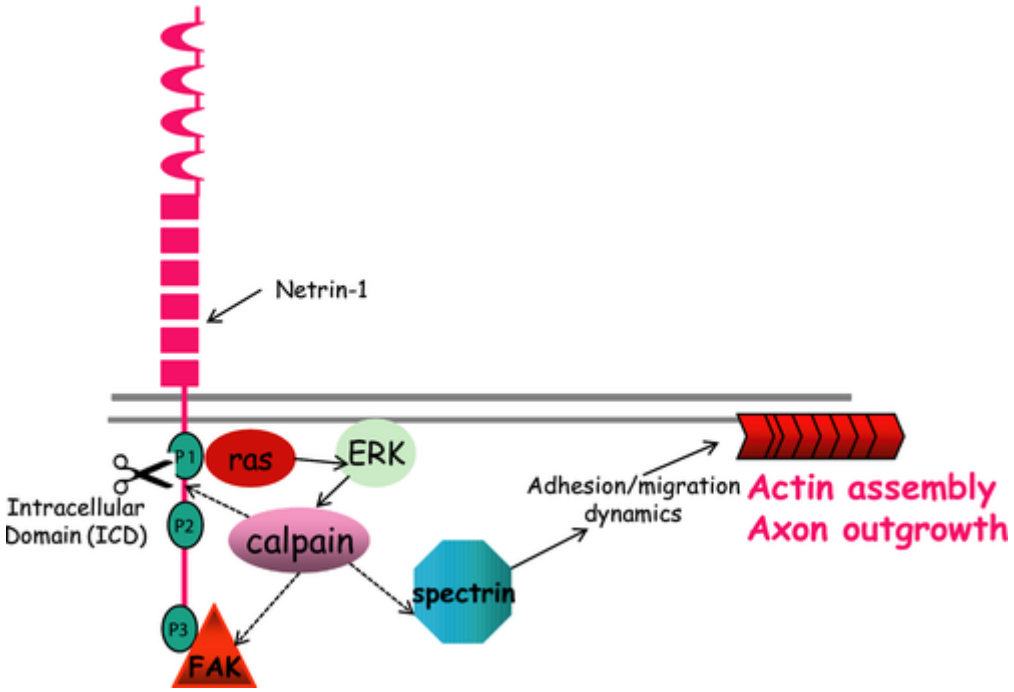
The calcium-activated protease calpain regulates netrin-1 receptor deleted in colorectal cancer-induced axon outgrowth in cortical neurons

Philippe M. Duquette, Nathalie Lamarche-Vane

The calcium-activated protease calpain is involved in the cleavage of cytoskeletal proteins, which plays an important role during adhesion turnover and cell migration. However, its function during neuronal development remains unclear. Our study revealed that the axon guidance cue netrin-1 activated calpain in cortical neurons in an extracellular-regulated kinase 1/2-dependent manner, which in turn induced the cleavage of the cytoskeletal proteins spectrin and focal adhesion kinase concomitantly with the intracellular domain of its receptor deleted in colorectal cancer. We propose that these intracellular events may control adhesion/migratory dynamics as an important mechanism to regulate netrin-1/deleted in colorectal cancer -mediated axon outgrowth in developing neurons.



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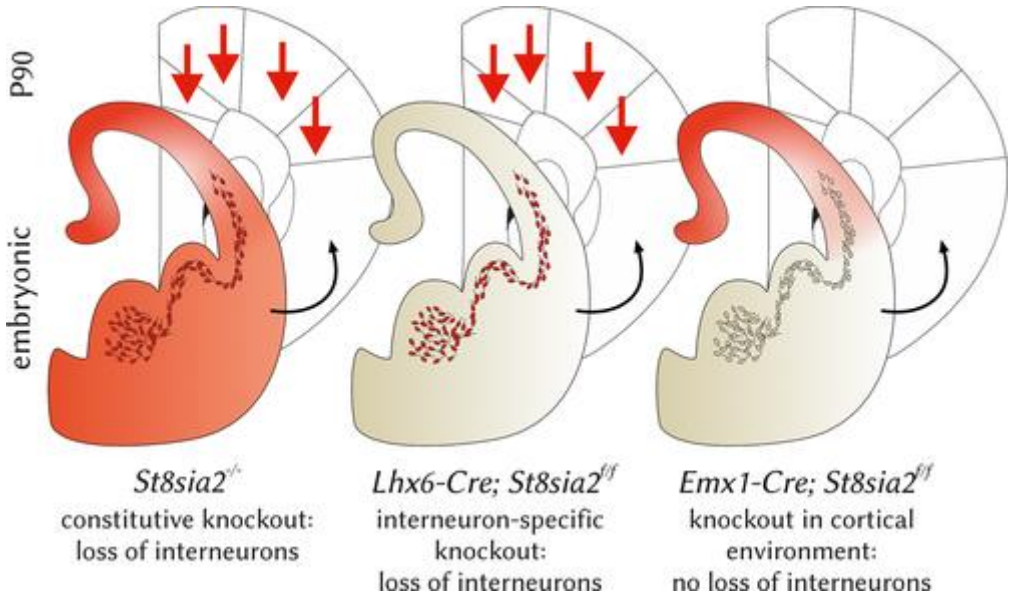
Cell-autonomous impact of polysialic acid-producing enzyme ST8SIA2 on developmental migration and distribution of cortical interneurons

Open Access

Ute E. Schuster, Charlotte Rossdam, Iris Röckle, Miriam Schiff, Herbert Hildebrandt

The enzyme ST8SIA2 is implicated in brain development and variants of the human ST8SIA2 gene have been linked to mental disorders like schizophrenia and autism. Here we use constitutive and conditional St8sia2 knockout mouse models to demonstrate that the specific deletion of ST8SIA2 in cortical interneurons is sufficient to disturb developmental migration and distribution of these cells in the same way as the ablation of ST8SIA2 in the entire organism. These findings provide mechanistic insight into a possible link between variations in ST8SIA2 and alteration of cortical inhibition as observed in schizophrenia and autism.



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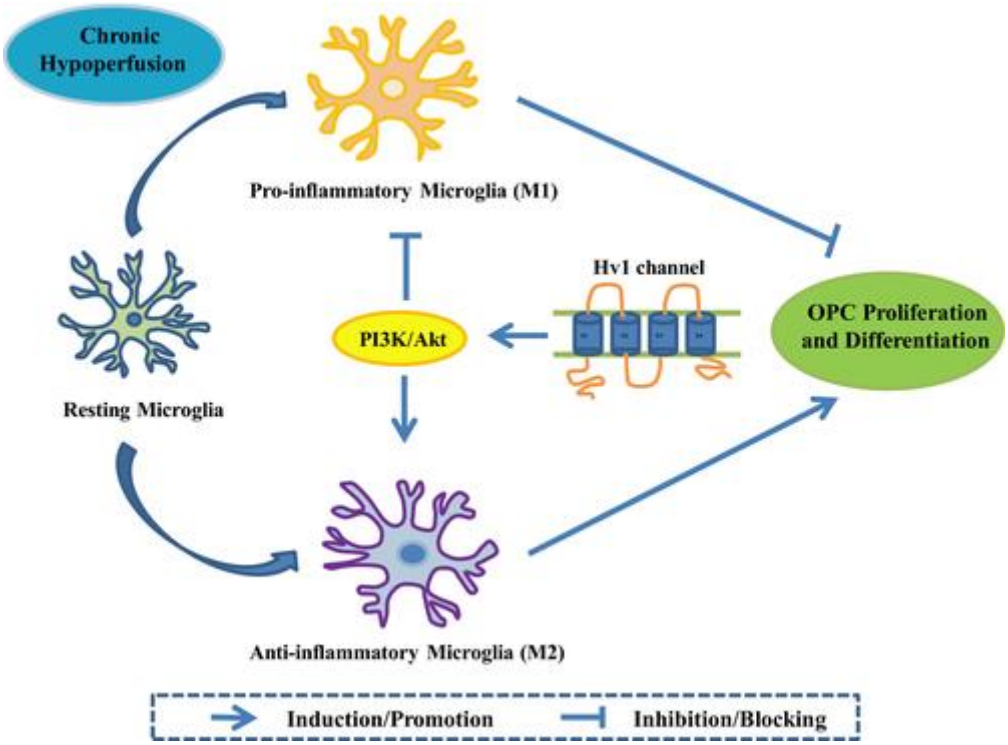
Microglial Hv1 proton channels promote white matter injuries after chronic hypoperfusion in mice

Ying Yu, Xiang Luo, Chunyu Li, Fengfei Ding, Minghuan Wang, Minjie Xie, Zhiyuan Yu, Bruce R. Ransom, Wei Wang

Voltage-gated proton channel (Hv1) is expressed in microglia and contributes to nicotinamide adenine dinucleotide phosphate oxidase complex (NOX)-dependent production of reactive oxygen species (ROS). Recent findings have shown that Hv1 is involved in regulating luminal pH of M1-polarized microglial phagosomes and inhibits endocytosis in microglia. Some studies reported that Hv1 enhances brain damage from ischemic stroke. We proposed the following mechanism for microglia mediated white matter injuries induced by chronic hypoperfusion: chronic hypoperfusion via bilateral common carotid artery stenosis evokes microglia activation, voltage-gated proton channel Hv1 facilitates ROS and pro-inflammatory cytokines production of microglia and promotes an M2-dominant microglia polarization through PI3K/AKT signaling, and then impairment of oligodendrocyte precursor cells proliferation and differentiation is induced. We think these results indicated that microglial Hv1 is a promising therapeutic target for reducing ischemic white matter injuries and cognitive impairment.



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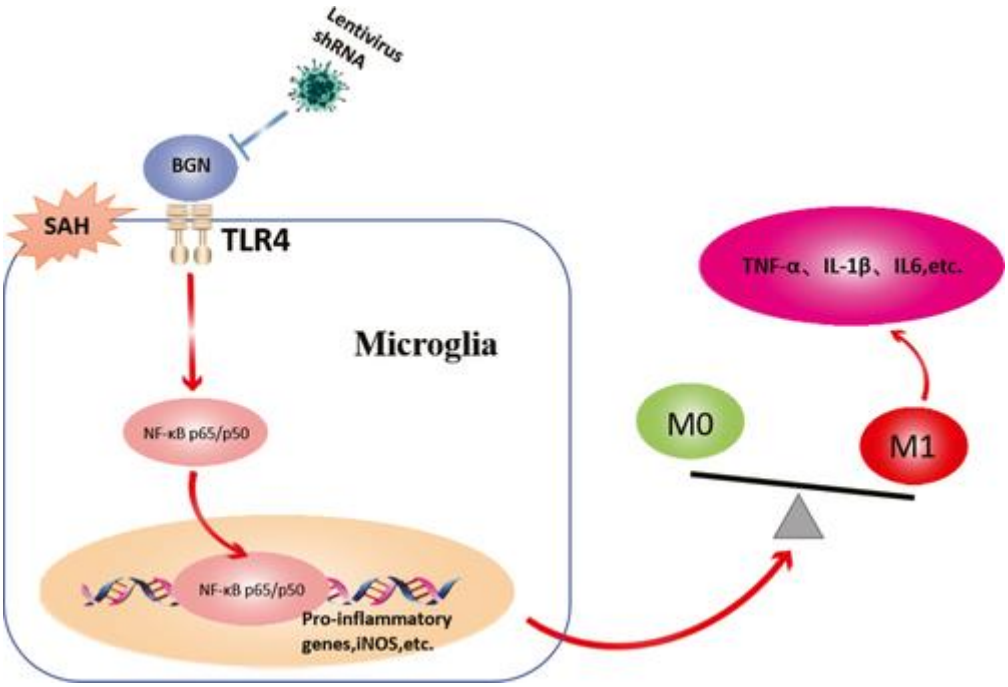
Biglycan regulates neuroinflammation by promoting M1 microglial activation in early brain injury after experimental subarachnoid haemorrhage

Yuke Xie, Jianhua Peng, Jinwei Pang, Kecheng Guo, Lifang Zhang, Shigang Yin, Jian Zhou, Long Gu, Tianqi Tu, Qiancheng Mu, Yuyan Liao, Xianhui Zhang, Ligang Chen, Yong Jiang

Biglycan, a small leucine-rich proteoglycan, functions as an endogenous ligand of Toll-like receptor 4 (TLR4) and could potently induce nuclear factor-kappa B (NF-κB) transcription. Our findings describe that biglycan is a critical regulator of M1 microglial polarization and mediates neuroinflammation via TLR4/NF-κB signaling pathway in early brain injury (EBI) following subarachnoid hemorrhage (SAH) in mice. Knockdown of biglycan exerts neuroprotective effects against EBI, providing a novel strategy for SAH treatment.



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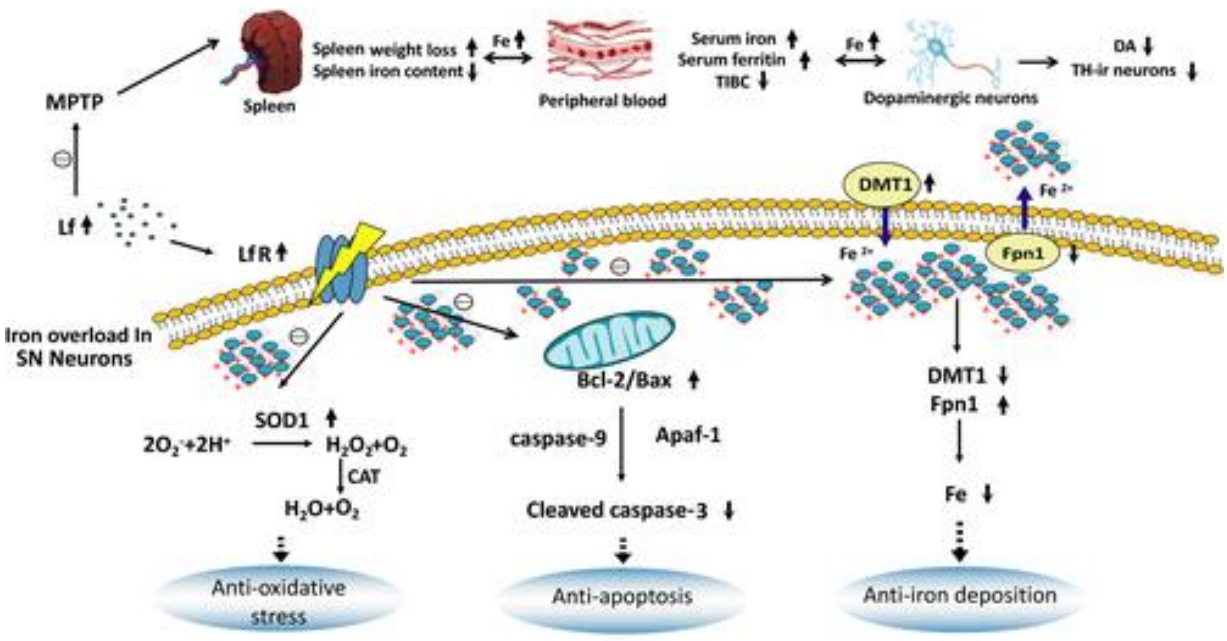
Lactoferrin protects against iron dysregulation, oxidative stress, and apoptosis in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease in mice

Huiying Liu, Hao Wu, Ning Zhu, Zijie Xu, Yue Wang, Yan Qu, Jun Wang

Lactoferrin (Lf) and lactoferrin receptor (LfR) both are found increased in dopaminergic neurons in Parkinson's disease (PD). Increased secretion of Lf associated with excessive iron accumulation in the substantia nigra (SN) of PD raised the question of whether Lf is beneficial or harmful to PD. We investigated the protective effects of iron-free Lf (apo-Lf) and iron-saturated Lf (holo-Lf) in a 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. In the central nervous system, results show that Lf antagonized MPTP-induced dopamine (DA) depletion in striatum, iron deposition, oxidative, and apoptotic processes in SN. Lf treatment down-regulated iron import protein divalent metal transporter (DMT1) and up-regulated iron export protein ferroportin1 (FPN1), attenuating MPTP-induced accumulation of nigral iron. In the peripheral system, Lf alleviated MPTP-induced increases in serum iron and ferritin, and decreases in serum total iron-binding capacity (TIBC), loss of spleen weight, and reduction in spleen iron content. As a conclusion, Lf has neuroprotective effects on MPTP-induced PD model mice, and its mechanism may be related to the anti-iron dysregulation, anti-oxidative stress, and anti-apoptosis, with apo-Lf showing greater efficacy. Therefore, Lf might be a promising therapeutic substance for PD.



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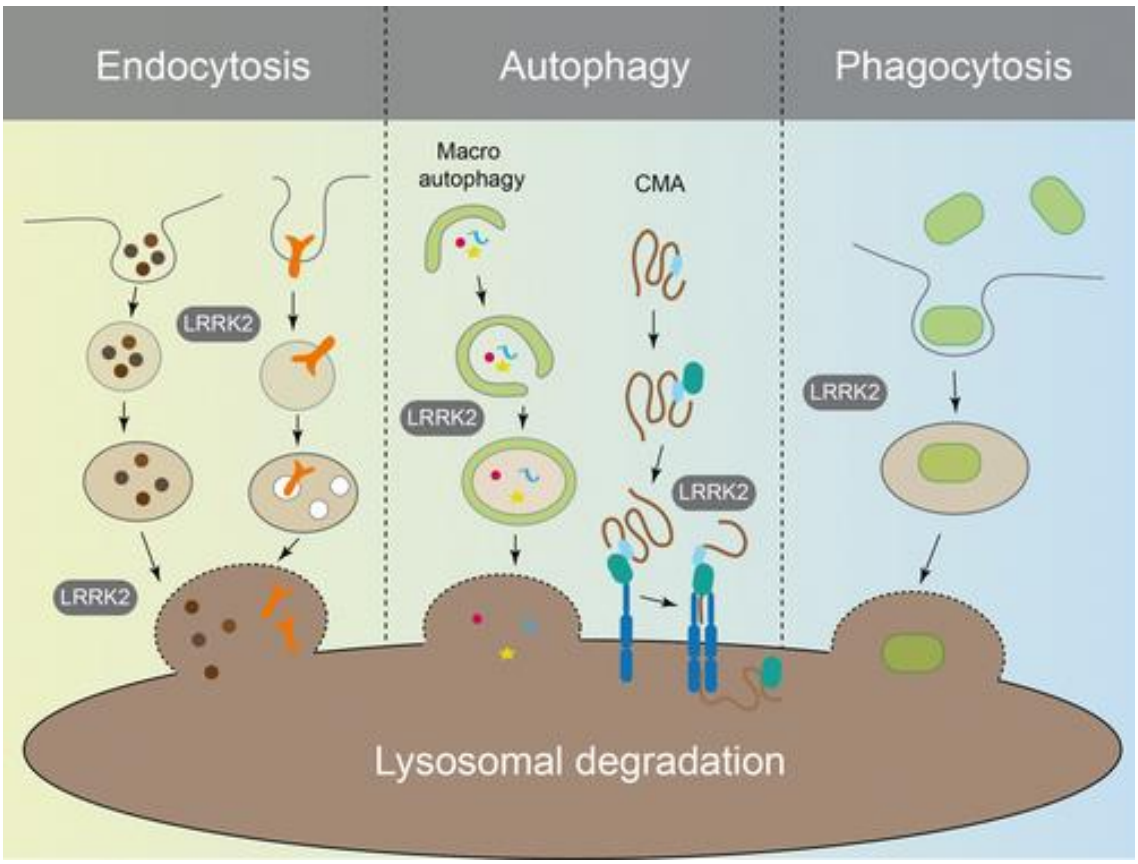
Review article

Leucine-rich repeat kinase 2 and lysosomal dyshomeostasis in Parkinson disease

Free Access

Susanna Cogo, Claudia Manzoni, Patrick A. Lewis, Elisa Greggio

Several neurodegenerative disorders are associated with alterations in the autophagy and endo-lysosomal pathways. In Parkinson disease, mounting evidence links Leucine-rich repeat kinase 2 (LRRK2) to intracellular vesicle traffic, autophagy and lysosomal function. In this review, we discuss the rapidly increasing roles proposed for LRRK2 at the intersection with lysosome biology and how disease-associated mutations affect lysosomal-based degradative pathways in neuronal and non-neuronal cells.



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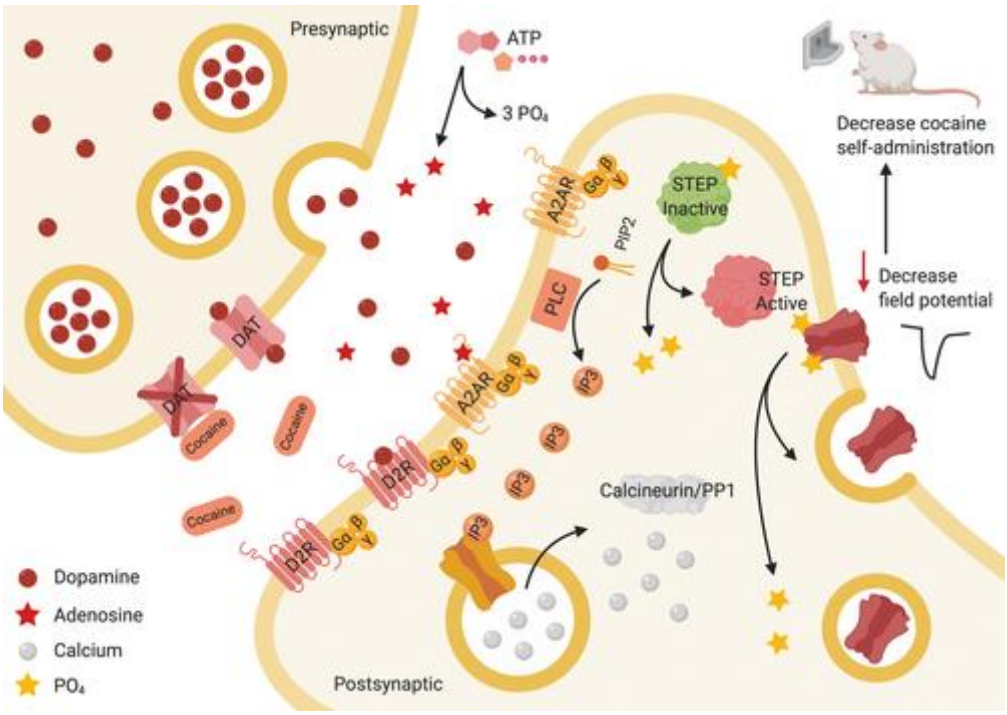
Editorial Highlight

Adenosine STEPs on synaptic function

Robert P. Yasuda

This Editorial highlights a manuscript by Mallozzi et al. (2019) that details the biochemical pathway that cocaine uses to cause synaptic depression. This pathway requires the adenosine A2A receptor and STEP phosphatases. Activation of the adenosine A2A receptor leads to an increase in intracellular calcium, activation of STEP by dephosphorylation, inhibition of excitatory ionotropic glutamate receptors by dephosphorylation of phospho-tyrosine residues and subsequent internalization of the ionotropic glutamate receptors. This adenosine A2A receptor pathway could lead to potential drug targets for neurologic and neuropsychiatric disorders.



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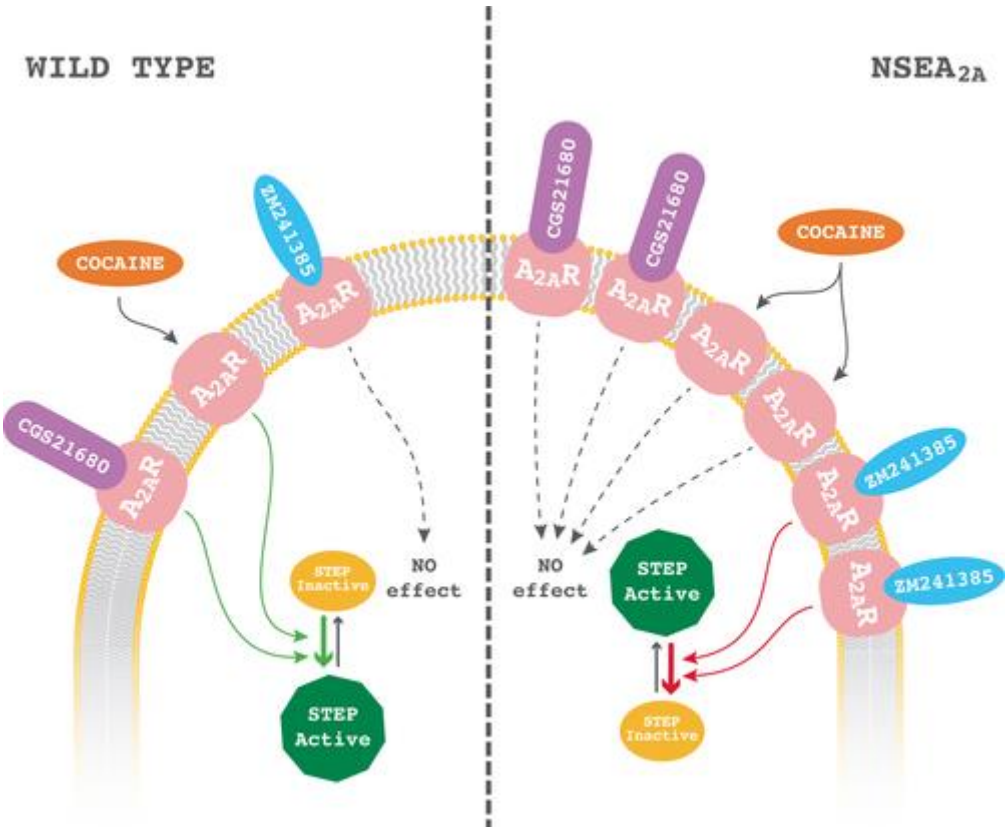
Highlighted Article

The activity of the Striatal-enriched protein tyrosine phosphatase in neuronal cells is modulated by adenosine A2A receptor

Cinzia Mallozzi, Rita Pepponi, Sergio Visentin, Valentina Chiodi, Paul J. Lombroso, Michael Bader, Patrizia Popoli, Maria Rosaria Domenici

We previously demonstrated that a tonic activation of A_{2A}Rs is required for cocaine-induced synaptic depression and increased activity of the protein tyrosine phosphatase STEP. Thus, we investigated the relationship between A_{2A}R and STEP in the striatum of a transgenic rat strain over-expressing A_{2A}R ($NSEA_{2A}$). STEP activity is increased in $NSEA_{2A}$ compared to WT. The A_{2A}R agonist CGS21680 up-regulates STEP activities in WT but not in $NSEA_{2A}$, while the A_{2A}R antagonist ZM241385 restores STEP activities in $NSEA_{2A}$, having no effects in WT. While cocaine-induced STEP activation in WT, it failed to increase it in $NSEA_{2A}$ rats.The present study identified a novel interaction between A_{2A}R and STEP.



Journal of Neurochemistry

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The following articles are part of Volume 152, Issue 4

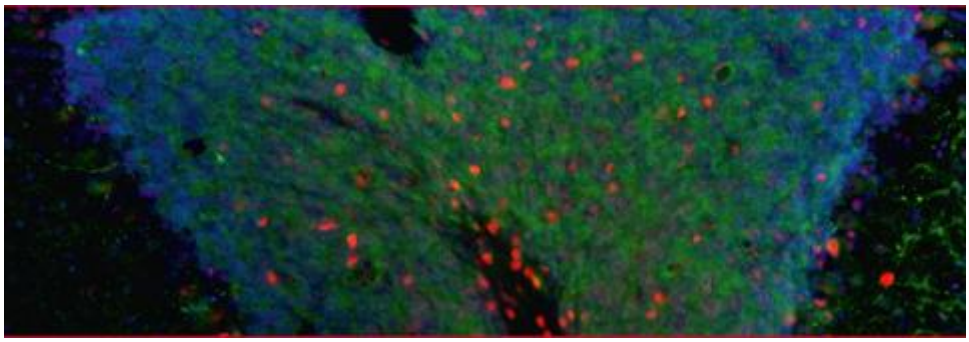
Cover Image

Marine bacterial extracts as a new rich source of drugs against Alzheimer's disease

Beika Zhu, Zhongrui Li, Pei-Yuan Qian, Karl Herrup

Front cover: Mature neurons in the healthy central nervous system are considered to be permanently post-mitotic cells. In several neurodegenerative diseases, however, ectopic neuronal cell cycle events are found associated with regions of neuronal death. In the paper by Zhu et al., the authors use abnormal neuronal cell cycle activity as a screen to test natural compounds derived from marine bacteria for their potential in preventing it and thus acting as neuroprotective agents.

Image content: This image shows cerebellar Purkinje cells in one-month old mouse model of ataxia-telangiectasia, a neurodegenerative disease. Note that many of the Purkinje cells, the cells at risk for death in the human disease, are abnormally expressing the cell cycle related protein PCNA (red immunostaining), suggesting they have initiated an abnormal cell cycle event, just as they do in the human disease. Neurons in the granule cell layer are also positive, as are oligodendrocytes in the white matter, suggesting that these cell types too are at risk for death. The neuronal marker MAP2 (green) shows the neuronal cell bodies. Cell nuclei are stained with the nuclear marker, DAPI.



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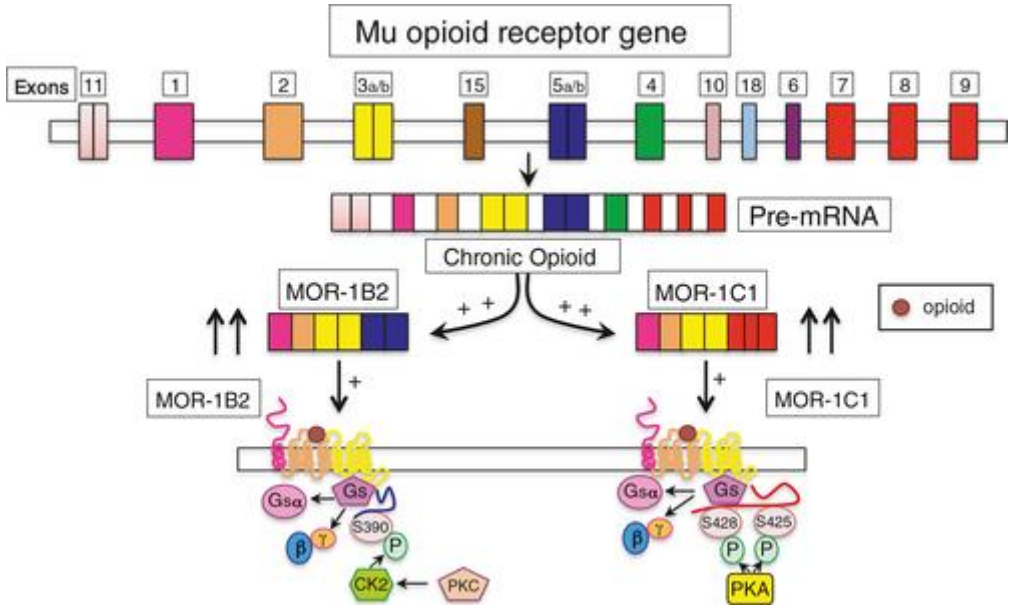
Original Articles

Phosphorylation of unique C-terminal sites of the mu-opioid receptor variants 1B2 and 1C1 influences their Gs association following chronic morphine

Sumita Chakrabarti, Nai-Jiang Liu, Alan R. Gintzler

Chronic morphine induced C-terminal phosphorylation of mu opioid receptor splice variants, MOR-1B2 at S390 (a casein kinase 2 site) and S425 (a protein kinase A site) in MOR-1C1, both absent in MOR-1, enhances their interaction with Gsα. Chronic morphine induced upregulation of MOR-1B2 and MOR-1C1 (as we reported in rat spinal cord) together with their phosphorylation and resulting enhanced Gsα interaction provides a mechanistic underpinning for our previous finding of augmented stimulatory MOR Gs signaling in opioid tolerance and also suggests novel targets for opioid tolerance abatement.



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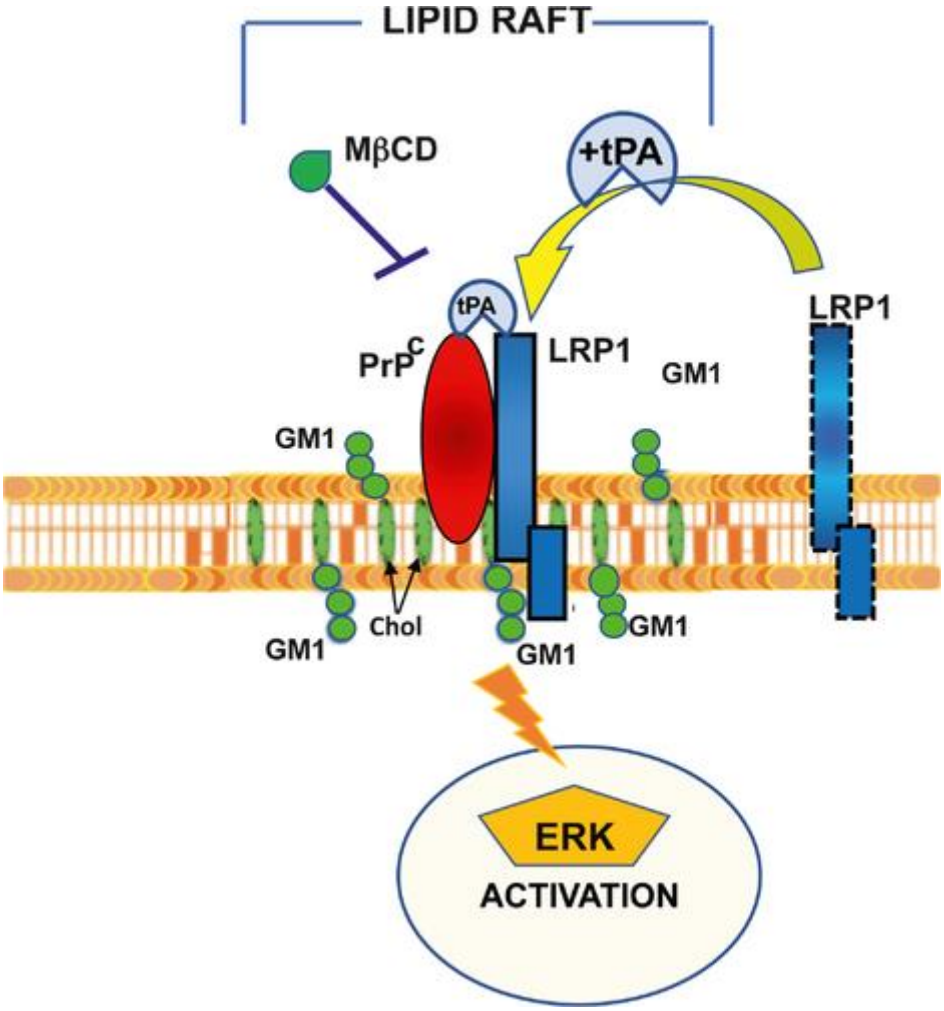
A multimolecular signaling complex including PrPC and LRP1 is strictly dependent on lipid rafts and is essential for the function of tissue plasminogen activator

Vincenzo Mattei, Valeria Manganelli, Stefano Martellucci, Antonella Capozzi, Elisabetta Mantuano, Agostina Longo, Alberto Ferri, Tina Garofalo, Maurizio Sorice, Roberta Misasi

Prion protein (PrPC) localizes stably in lipid rafts microdomains and is able to recruit downstream signal transduction pathways by the interaction with promiscuous partners. It is known that tissue plasminogen activator (tPA) functions by binding a prion–plasminogen complex and forming activated plasmin and that tPA acts as a ligand for LRP1 (lipoprotein receptor-related protein 1), leading to receptor recruitment in lipid rafts and inducing neurodifferentiation signaling.In this research we show that:Knocking-down PrP or LRP1 by siRNA impairs ERK phosphorylation induced by tPA.Perturbation of lipid raft inhibits the binding of tPA to LRP1/PrP complex .Inhibition of the interaction among PrP and LRP1 alters signaling mediated by tPA.Thus we can say that PrP, LRP1 and tPA work in a single complex whose activity depends on lipid raft.



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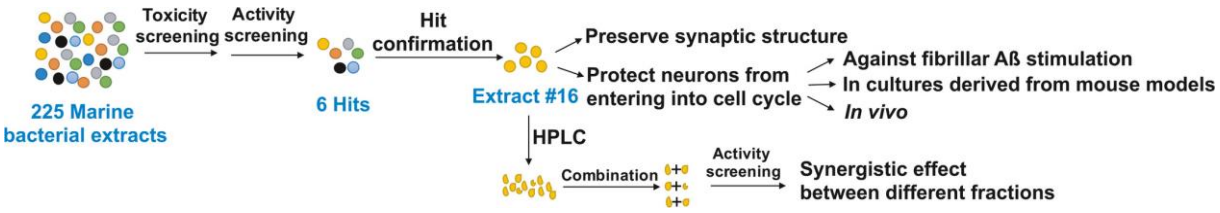
Marine bacterial extracts as a new rich source of drugs against Alzheimer's disease

Beika Zhu, Zhongrui Li, Pei-Yuan Qian, Karl Herrup

Using a model based on reducing Alzheimer's disease-associated neuronal cell cycle events, we have screened a largely unexplored source of compounds with therapeutic potential – the natural products created by diverse strains of marine bacteria. Two hundred and twenty-five bacterial extracts from different strains were tested for both toxicity and neuroprotective properties by crystal violet and In-cell Western – first in HT22 cells and in mouse primary neuronal cultures. We found that we could directly assay even a crude bacterial extract in our E16 mouse cortical neuronal cultures and screen for activities that prevent cell cycle reentry and preserve synaptic structure. Our findings showcase a new effective and efficient assay system and validate the use of marine natural compounds as a novel source for new drugs to fight Alzheimer's disease.



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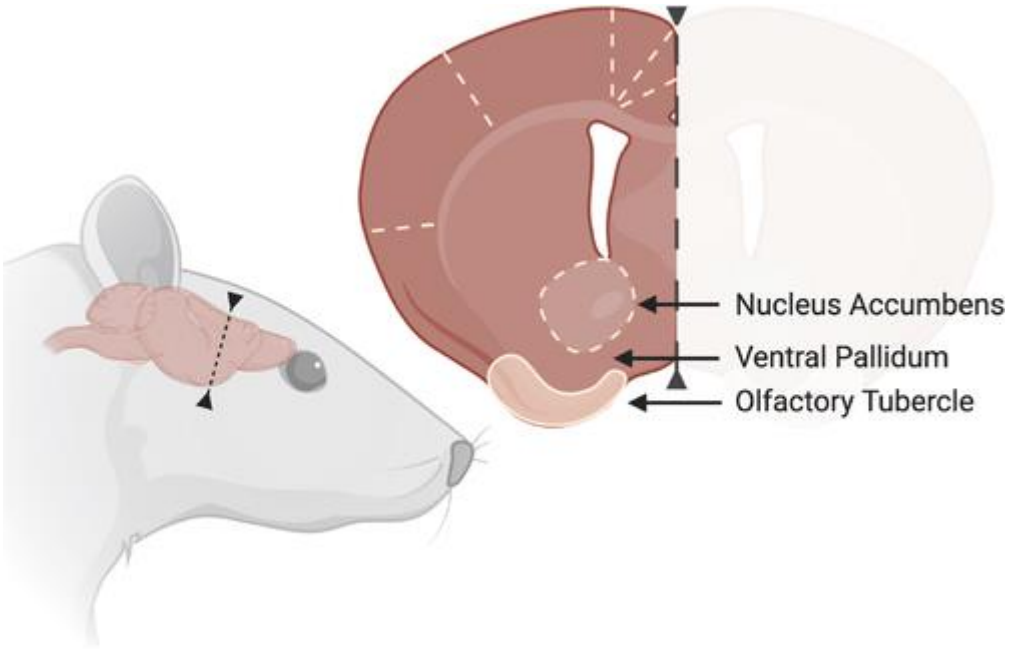
Review articles

Neurochemical organization of the ventral striatum's olfactory tubercle

Free Access

Hillary L. Cansler, Katherine N. Wright, Lucas A. Stetzik, Daniel W. Wesson

The olfactory tubercle is a structure within the ventral striatum that has received relatively little attention. In this review, we provide a detailed summary of the olfactory tubercle's rich neurochemistry, including the neurotransmitters present as well as their associated receptors, transporters and putative functions. In addition, we briefly review the literature pertaining to neurochemical changes in the olfactory tubercle in neurodegenerative disorders. This review will serve to aid future research into the olfactory tubercle and the ventral striatum as a whole. The figure is based in part upon (Xiong & Wesson, 2016) and was re-drawn by Marco Bazelmans in BioRender (https://biorender.com/).



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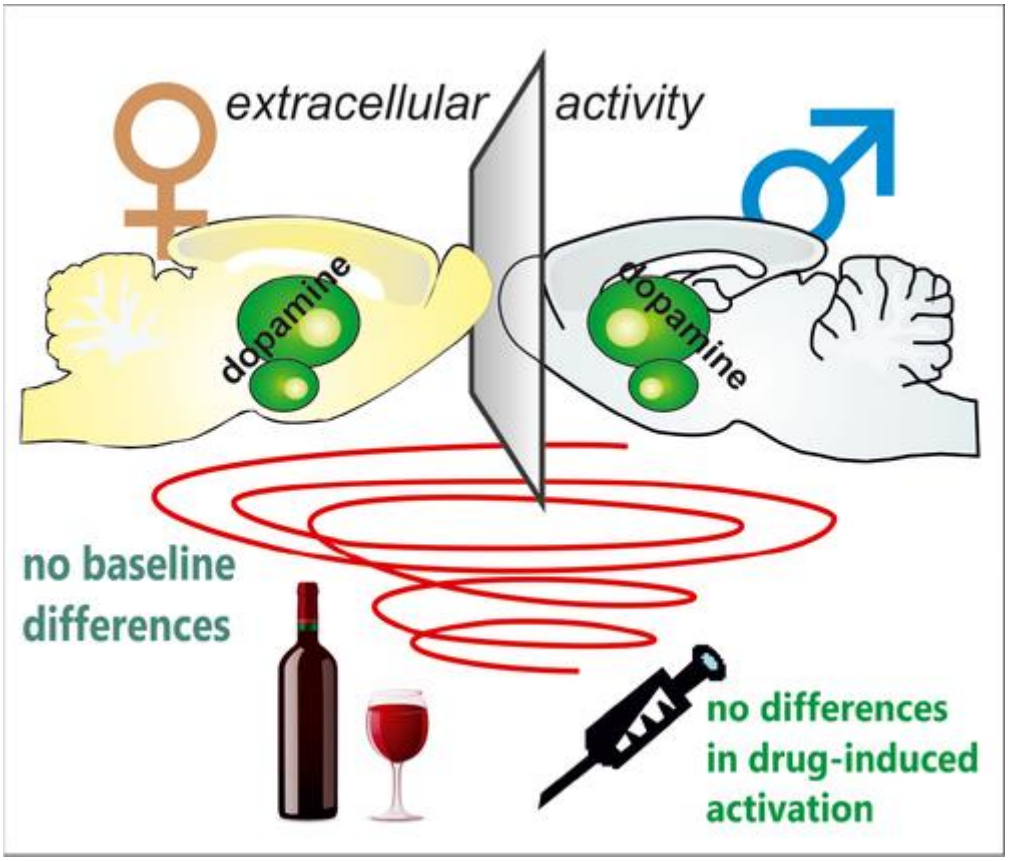
Editorial Highlight

Everything you always wanted to know about sex and dopamine, but were afraid to ask

Open Access

Christian P. Müller

This Editorial highlights a study by Egenrieder and colleagues published in the current issue of Journal of Neurochemistry. A meta-analysis of in vivo microdialysis data that the authors carried out, controlling for methodological differences between studies, suggests only very little sex differences in extracellular dopamine levels in the nucleus accumbens and caudate putamen between male and female rodents. This is an unexpected finding that may constitute but the beginning of a system's analysis of dopaminergic sex differences.



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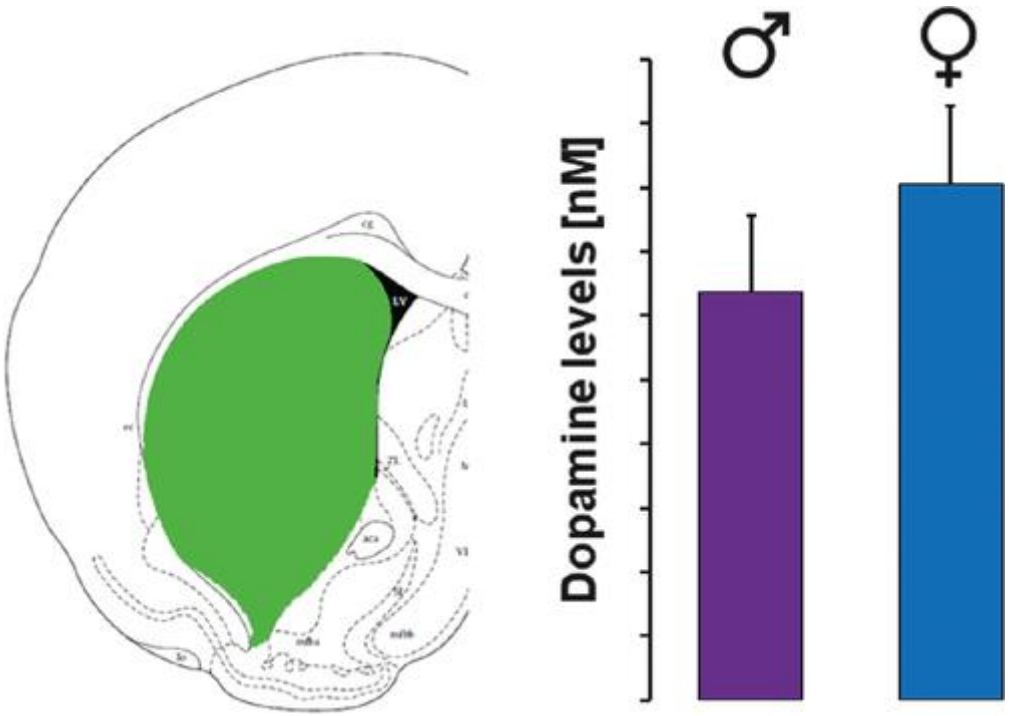
Highlighted Article

No basal or drug-induced sex differences in striatal dopaminergic levels: a cluster and meta-analysis of rat microdialysis studies

Lisamon Egenrieder, Ekaterina Mitricheva, Rainer Spanagel, Hamid R. Noori

Our meta-analysis of in vivo microdialysis experiments suggests that basal dopamine levels as well as the effects of drugs of abuse on dopaminergic overflow in nucleus accumbens and caudate putamen of adult rats are not sex-dependent. Previously reported sex differences in the CPu seem to be a result of ovariectomy and may only to a lesser, non-significant degree be attributed to a sexual duality. However, our study does not exclude the possibility of sex differences in other spatiotemporal scales of consideration or other components of reward circuitry.



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