Journal of Neurochemistry
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JNC Highlights April 2020

Latest Research and Reviews

The following articles are part of Volume 152, Issue 5

Cover Image

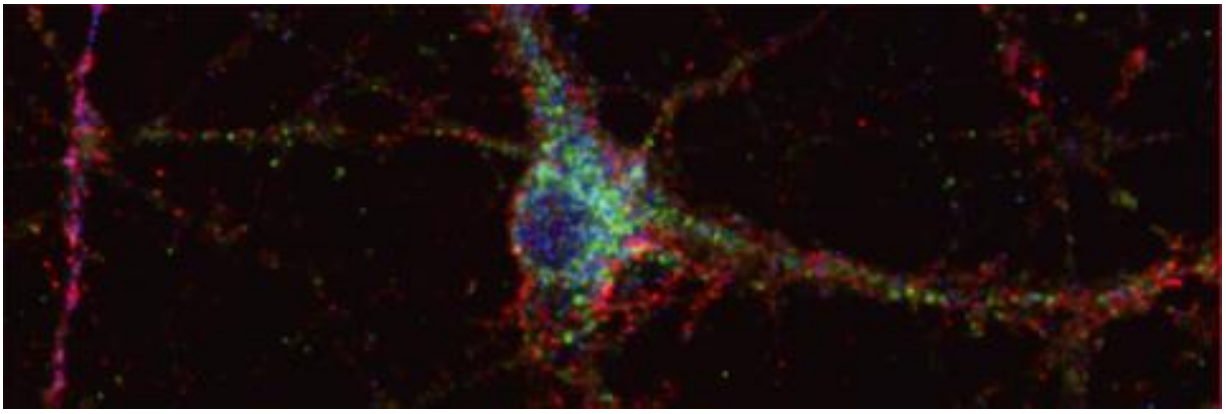
Open Access

NYX-2925 induces metabotropic N-methyl-d-aspartate receptor (NMDAR) signaling that enhances synaptic NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

M. Scott Bowers, Luisa P. Cacheaux, Srishti U. Sahu, Mary E. Schmidt, Joseph A. Sennello, Katherine Leaderbrand, M. Amin Khan, Roger A. Kroes, Joseph R. Moskal

Front cover: N-methyl-d-aspartate receptors (NMDARs) mediate a number of physiological and pathophysiological processes. We sought to determine if the novel NMDAR modulator NYX-2925, discovered by Aptinyx Inc. and currently in Phase 2 clinical development for chronic pain conditions, increases glutamatergic neurotransmission.

Image content: The rat primary hippocampal neuron depicted on the cover was treated with NYX-2925 at concentrations that increase synaptic levels of GluN2B-containing NMDARs via a novel ion-flux independent mechanism, which in turn, increases the ability of chemical long-term potentiation to increase synaptic levels of GluA1-containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Green: PSD-95 positive puncta, Red: GluA1 positive puncta, Blue: MAP-2 positive puncta.



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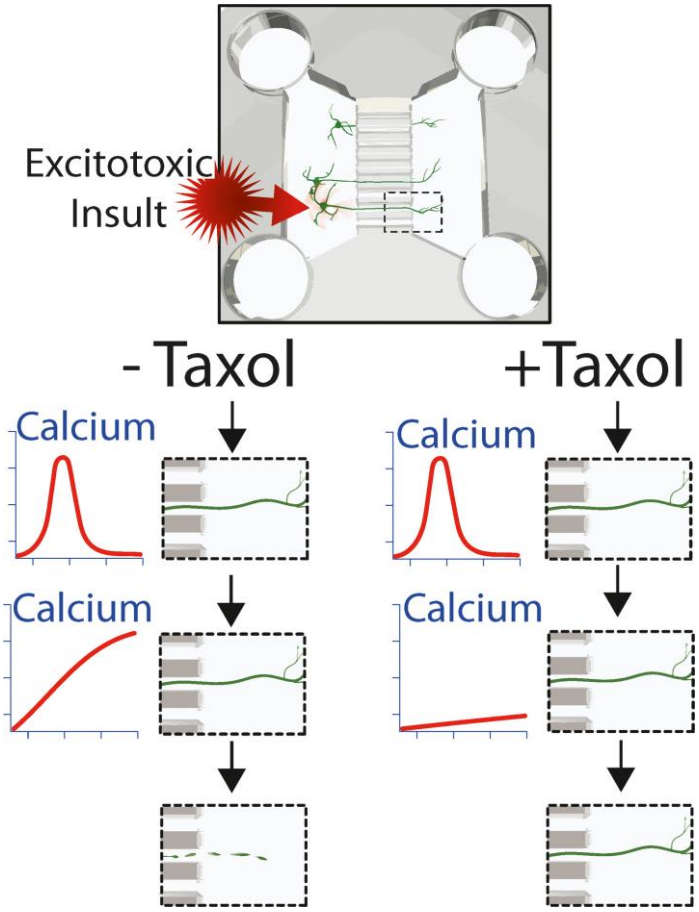
Original Articles

Microtubule-dependent processes precede pathological calcium influx in excitotoxin-induced axon degeneration

N. Tian, K. A. Hanson, A. J. Canty, J. C. Vickers and A. E. King

We investigated the relationship between calcium-signalling and microtubule stability in axons undergoing degeneration following an excitotoxic insult. Kainic acid applied to the cell body of primary mouse cortical neurons resulted in a biphasic calcium response in the axon, with an initial benign calcium transient followed by a second gradual rise in axonal calcium, which was associated with axonal loss. Application of the microtubule stabilizing drug taxol to the axons did not affect the initial calcium transient, but reduced the second calcium influx, suggesting that microtubule-associated events are involved upstream of calcium dysregulation.



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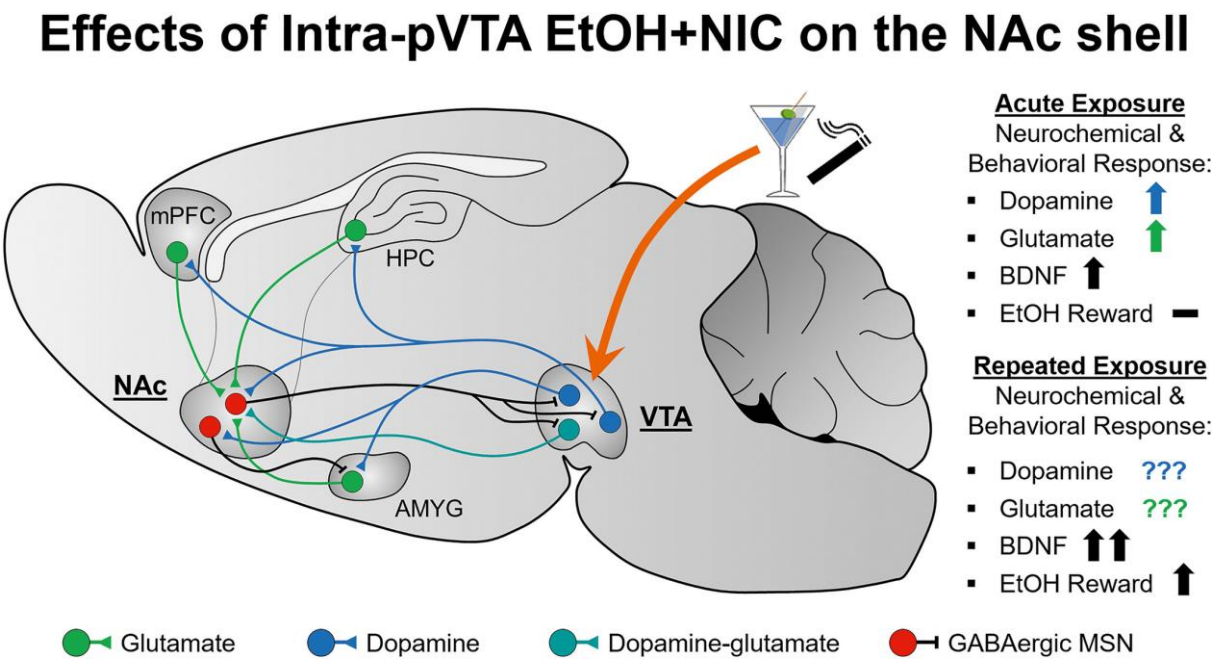
Co-administration of ethanol and nicotine heightens sensitivity to ethanol reward within the nucleus accumbens (NAc) shell and increasing NAc shell BDNF is sufficient to enhance ethanol reward in naïve Wistar rats

R. A. Waeiss, C. P. Knight, E. A. Engleman, S. R. Hauser and Z. A. Rodd

Alcohol use disorder (AUD) often presents as a polydrug disorder where > 85% are estimated to smoke. EtOH and nicotine (NIC) are self-administered directly into the posterior ventral tegmental area (pVTA). Microinjections of EtOH+NIC into the pVTA produces simultaneous increases of BDNF, glutamate, and dopamine and enhances the sensitivity to EtOH reward within the nucleus accumbens (NAc) shell. Additionally, rats pretreated with BDNF in the NAc shell were more sensitive to EtOH reward. The data highlight the importance of investigating AUD under polydrug conditions to identify neuroadaptations in the search for potential treatment targets.



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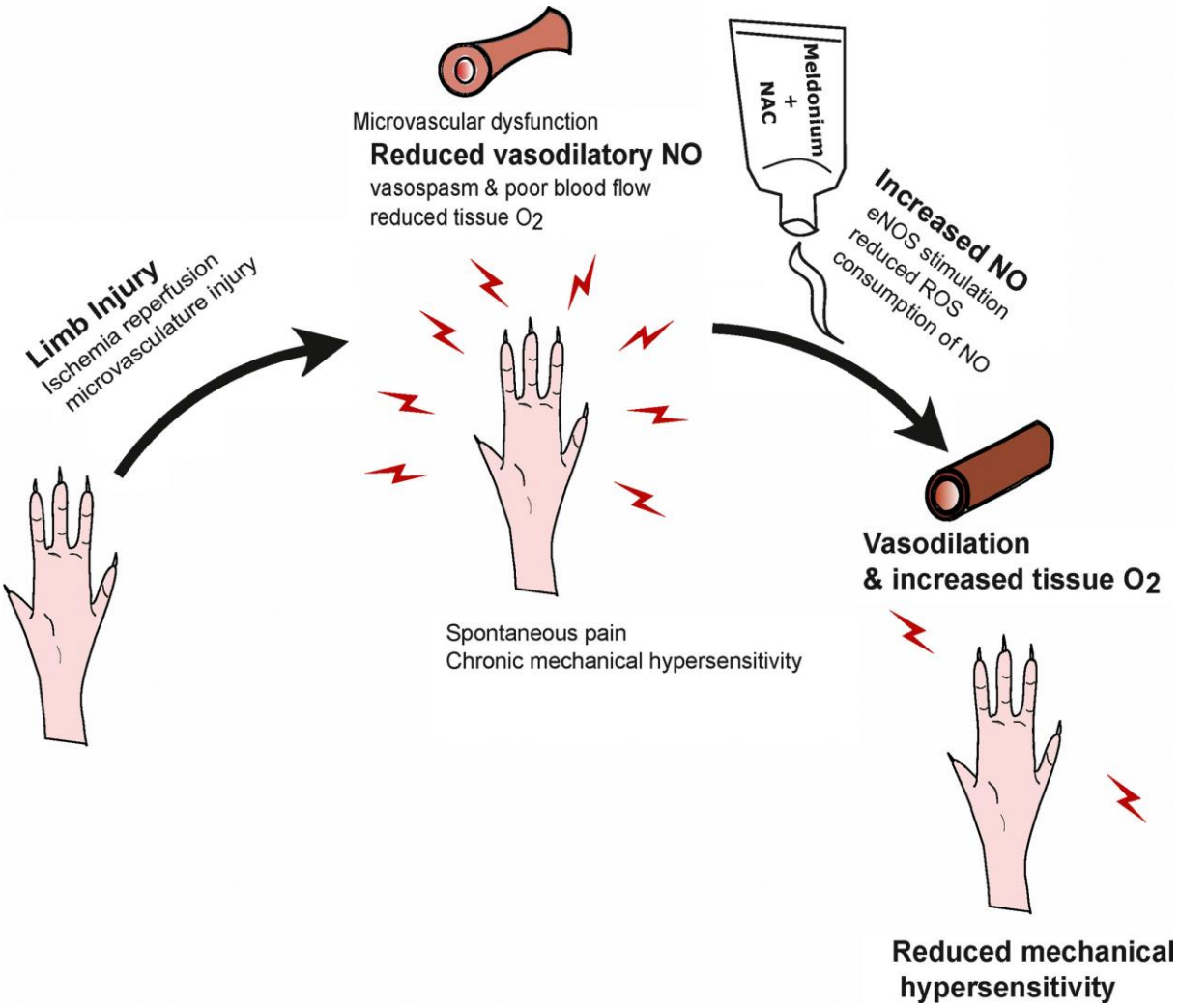
Topical combination of meldonium and N-acetyl cysteine relieves allodynia in rat models of CRPS-1 and peripheral neuropathic pain by enhancing NO-mediated tissue oxygenation

O. A. Fulas, A. Laferriere, R. S. Stein, D. S. Bohle and T. J. Coderre

Spontaneous pain and chronic mechanical hypersensitivity of both complex regional pain syndrome (CRPS) and peripheral neuropathic pain (PNP) depend partly on microvascular injury following ischemia reperfusion injury of either multiple limb tissues (CRPS) or an injured nerve (PNP). Microvascular dysfunction in these syndromes is maintained by reduced vasodilatory nitric oxide (NO), which contributes to vasospasms, poor blood flow, and reduced tissue oxygenation (O_2). Topical treatment with a combination of meldonium and N-acetylcysteine (NAC) reduced mechanical hypersensitivity in animal models of CRPS and PNP by increasing NO, that produced vasodilation and increased tissue O_2.



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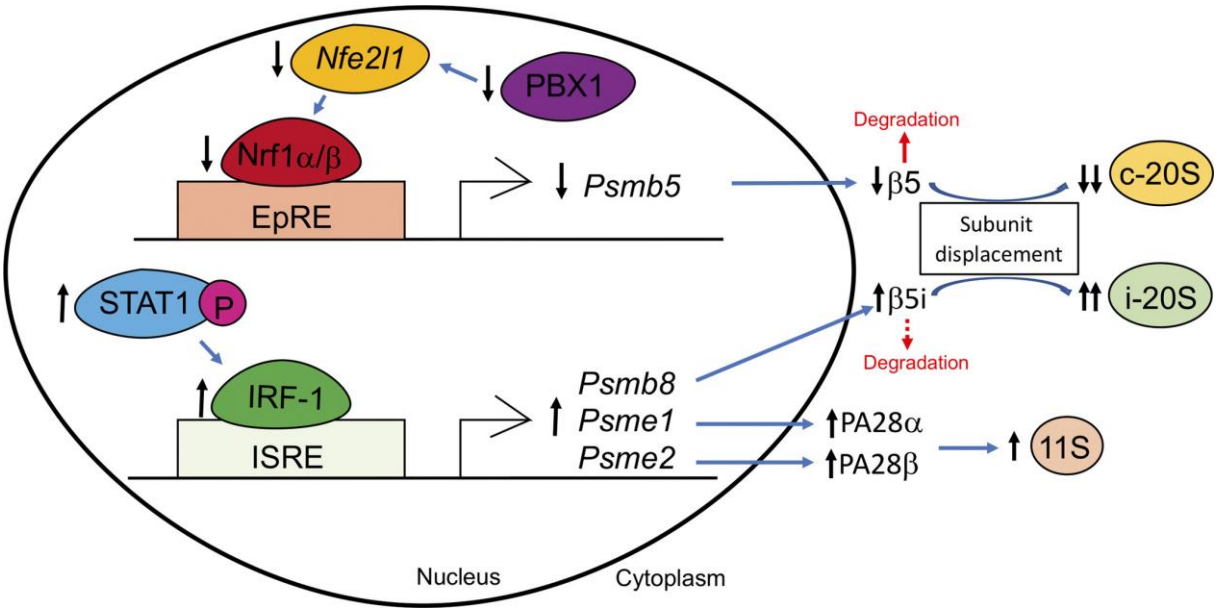
Decreased levels of constitutive proteasomes in experimental autoimmune encephalomyelitis may be caused by a combination of subunit displacement and reduced Nfe2l1 expression

K. L. Shanley, C-L. Hu and O. A. Bizzozero

Proteasome composition in experimental autoimmune encephalomyelitis (EAE) is determined by a number of signaling pathways. Here we show that the number of immunoproteasomes is increased in neurons and astrocytes from mice EAE spinal cords at the peak of the disease and is probably due to a rise in phosphorylated signal transducer and activator of transcription 1 (p-STAT1) and interferon regulatory factor-1 (IRF-1) levels. Immunoproteasome over-expression is accompanied by a decrease in constitutive proteasomes levels, which correlates with low expression of nuclear factor (erythroid-derived 2)-like 1 (Nrf1) and is likely caused by reduced pre-B-cell leukemia homeobox-1 transcription factor (PBX1) signaling. The displacement of constitutive subunits by their inducible counterparts may also be responsible for alterations in proteasome composition. The present work provides insights into the dynamics of proteasome expression in EAE and is the first to explore Nrf1 signaling in an inflammatory demyelinating disorder.



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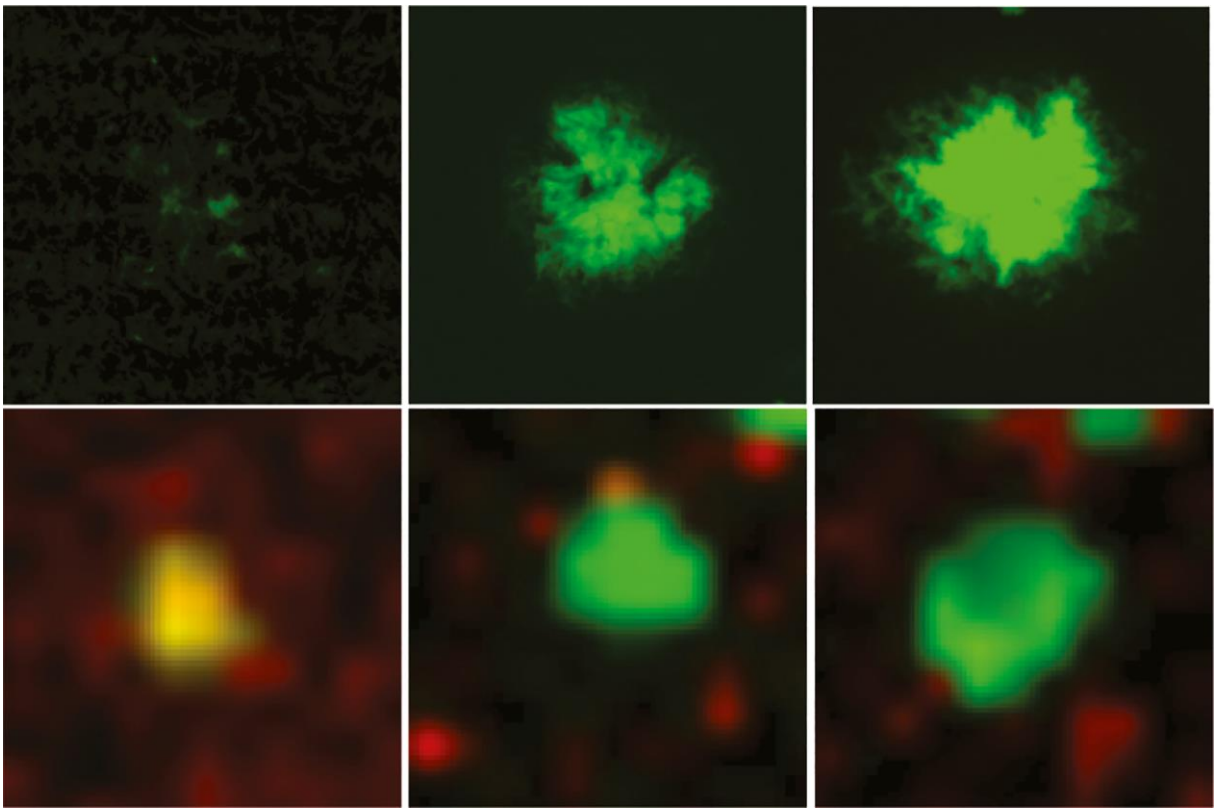
Chemical imaging of evolving amyloid plaque pathology and associated Aβ peptide aggregation in a transgenic mouse model of Alzheimer's disease

W. Michno, P. Wehrli, S. R. Meier, D. Sehlin, S. Syvänen, H. Zetterberg, K. Blennow and J. Hanrieder

One of the major hallmarks of Alzheimer's disease (AD) pathology is the formation of extracellular amyloid β (Aβ) plaques. As plaque pathology precipitates long before any clinical symptoms occur, targeting the Aβ aggregation processes provides a promising target for early interventions. We used an emerging, chemical imaging modality – MALDI imaging mass spectrometry – to delineate evolving Aβ pathology with high molecular specificity at the single plaque level. We identified that early plaques contain higher levels of Aβ1–42 while plaque maturation was characterized by increased deposition of Aβ1–40, and development of cored plaque morphology.



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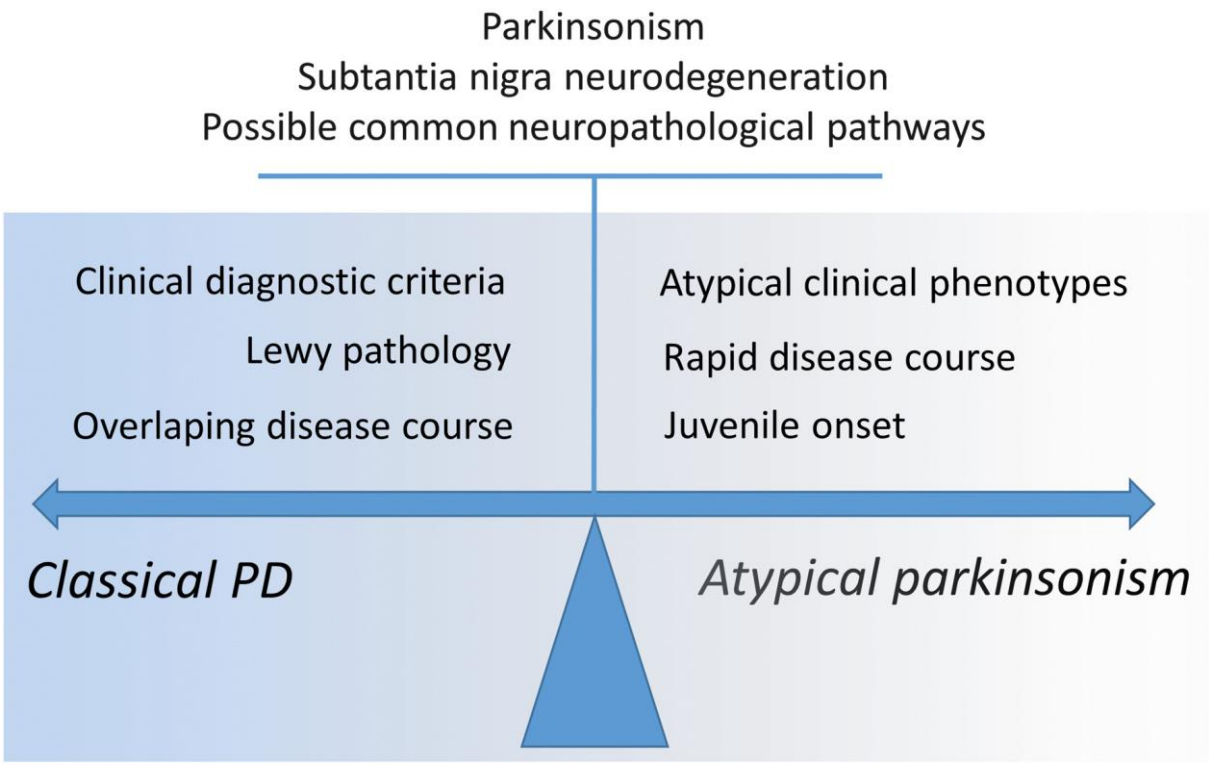
Review article

Are genetic and idiopathic forms of Parkinson's disease the same disease?

Free Access

L. Correia Guedes, T. Mestre, T. F. Outeiro and J. J. Ferreira

With advancing knowledge on genetic forms of Parkinson's disease (PD) and parkinsonism, it is important to critically discuss the association of rare and atypical forms to PD. Here, we present our views on arguments for merging or separating genetic and idiopathic forms of PD and parkinsonisms as the same or different disease entities and discuss potential implications of possible common physiopathological backgrounds for future research, care and development of new therapeutic strategies.



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The following articles are part of Volume 152, Issue 6

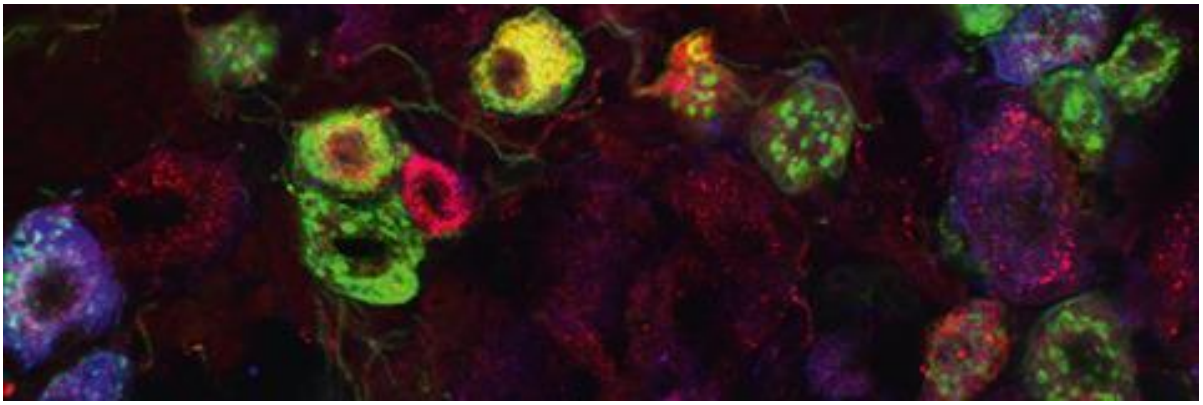
Cover Image

[Cutaneous inflammation differentially regulates the expression and function of Angiotensin-II types 1 and 2 receptors in rat primary sensory neurons]

Sergio G. Benitez, Alicia M. Seltzer, Diego N. Messina, Mabel R. Foscolo, Sean I. Patterson, Cristian G. Acosta

Front cover: Type-2 receptors for angiotensin II had been implicated in chronic pain. We examined its role in inflammatory pain and demonstrated that its expression changed in different neuronal subpopulations of the dorsal root ganglia at different times after cutaneous inflammation. Furthermore, this receptor works co-operatively with the type-1 receptor for angiotensin II via regulation of the neuritogenic activity of Angiotensin II on non-peptidergic isolectin B4 binding and peptidergic trkA-expressing dorsal root ganglion neurons. These findings have important implications for the clinical use of angiotensin-II receptor blockers in the treatment of pain.

Image content: Triple immunofluorescence confocal micrograph showing L5 adult dorsal root ganglion neurons expressing the type 2 receptor for angiotensin II (in red), binding of isolectin B4 (in green) and expression of trkA (in blue). Scale bar represents 30 µm.



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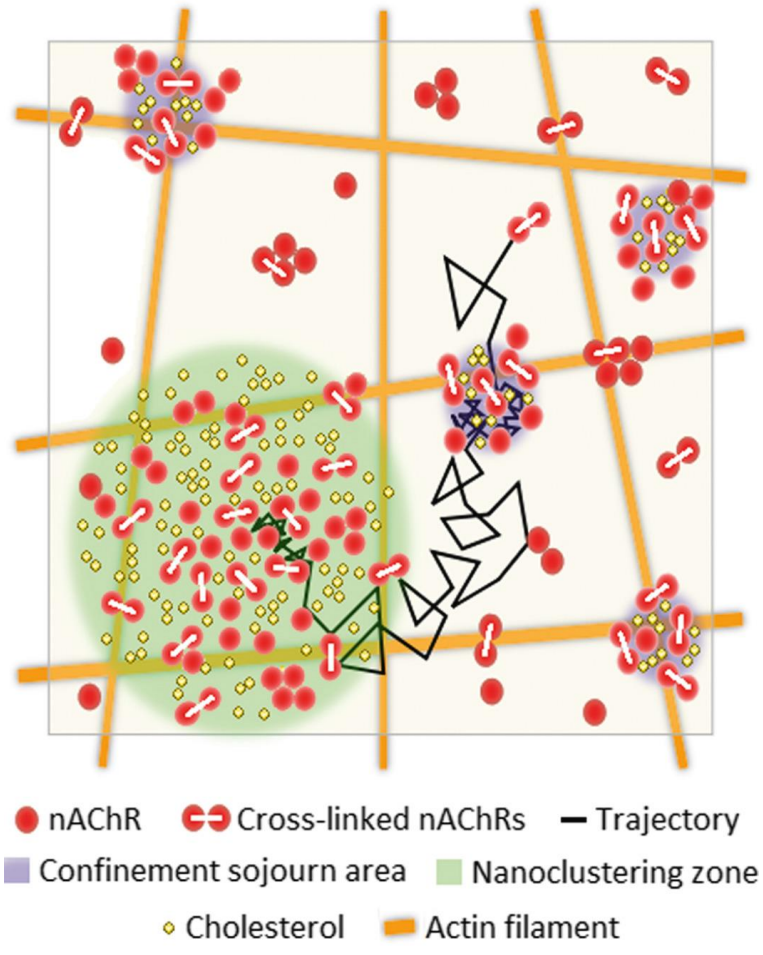
Original Articles

Antibody-induced crosslinking and cholesterol-sensitive, anomalous diffusion of nicotinic acetylcholine receptors

A. Mosqueira, P. A. Camino and F. J. Barrantes

Using monoclonal antibodies to experimentally mimic the muscle autoimmune disease myasthenia gravis, we characterized the interplay between antibody-induced crosslinking of the nicotinic acetylcholine receptor and membrane cholesterol levels by combining STORM superresolution microscopy and single-molecule tracking. The two modulate the nanoclustering and the diffusion of the receptor protein in the membrane, in a clear example of how biophysical studies of a key neurotransmitter receptor can shed light on the physiopathological basis of antigenic modulation, with implications for autoantibody-mediated diseases.



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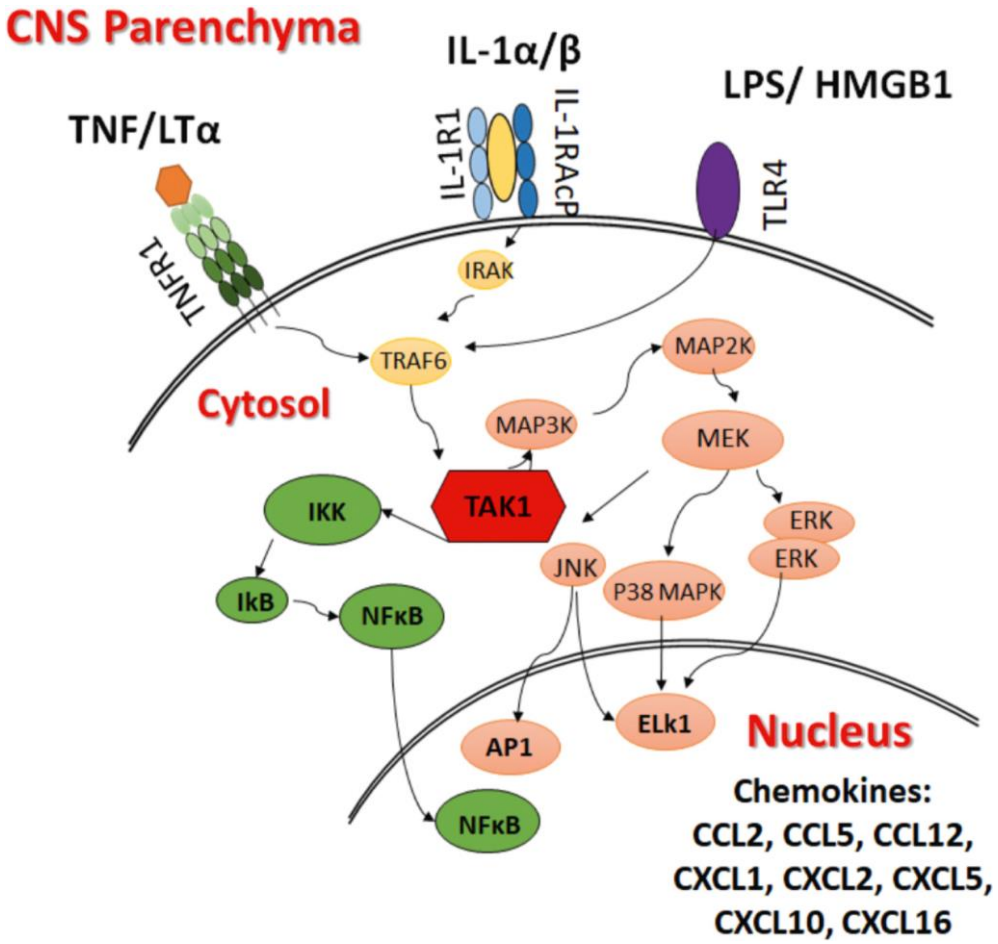
TAK1 inhibition in mouse astrocyte cultures ameliorates cytokine-induced chemokine production and neutrophil migration

K. Soto-Díaz, M. B. Juda, S. Blackmore, C. Walsh and A. J. Steelman

Chemokines facilitate cell trafficking. Using primary mouse cultures we found that astrocytes readily increase production of chemokines in response to TNF and IL-1 stimulation. Chemokine secretion following a cytokine challenge was sufficient to promote neutrophil migration in vitro and was dependent on TAK1 activation. These data suggest that TAK1 signaling in astrocytes may represent a key pathway in the promotion of immune cell trafficking to the brain during neuroinflammatory events.



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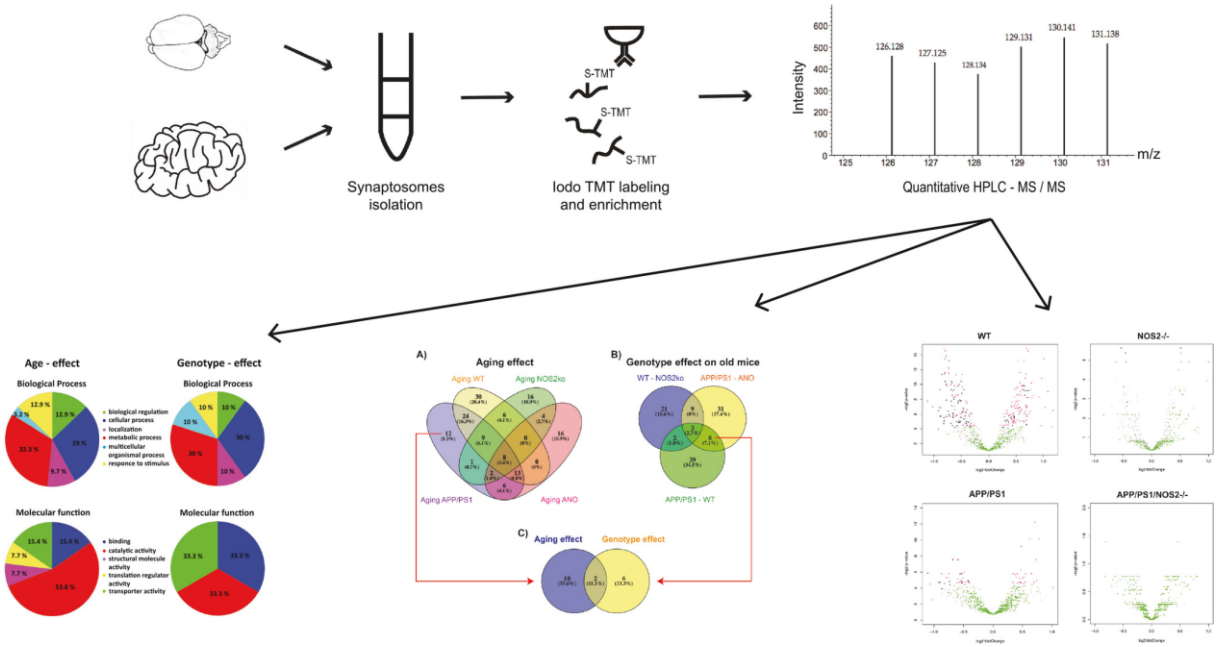
Quantitative proteomics of synaptosome S-nitrosylation in Alzheimer's disease

Open Access

T. S. Wijasa, M. Sylvester, N. Brocke-Ahmadinejad, S. Schwartz, F. Santarelli, V. Gieselmann, T. Klockgether, F. Brosseron and M. T. Heneka

Loss of synapses and neuroinflammation constitute early events in pathogenesis of Alzheimer's disease (AD). Both events might be linked if inflammation- induced mediators affect the synapses or synaptic proteins, potentially providing new biomarker candidates. This proteomics study quantified S-nitrosylated synaptosomal proteins as a fingerprint of neuroinflammation-induced nitric oxide release. Synaptosomes were isolated from human AD patient brain tissue, as well as APP/PS1 mice at 3 and 12 months of age, followed by mass spectrometry. Differentially nitrosylated proteins were evaluated and the 10 most promising targets for biomarker validation were discussed.



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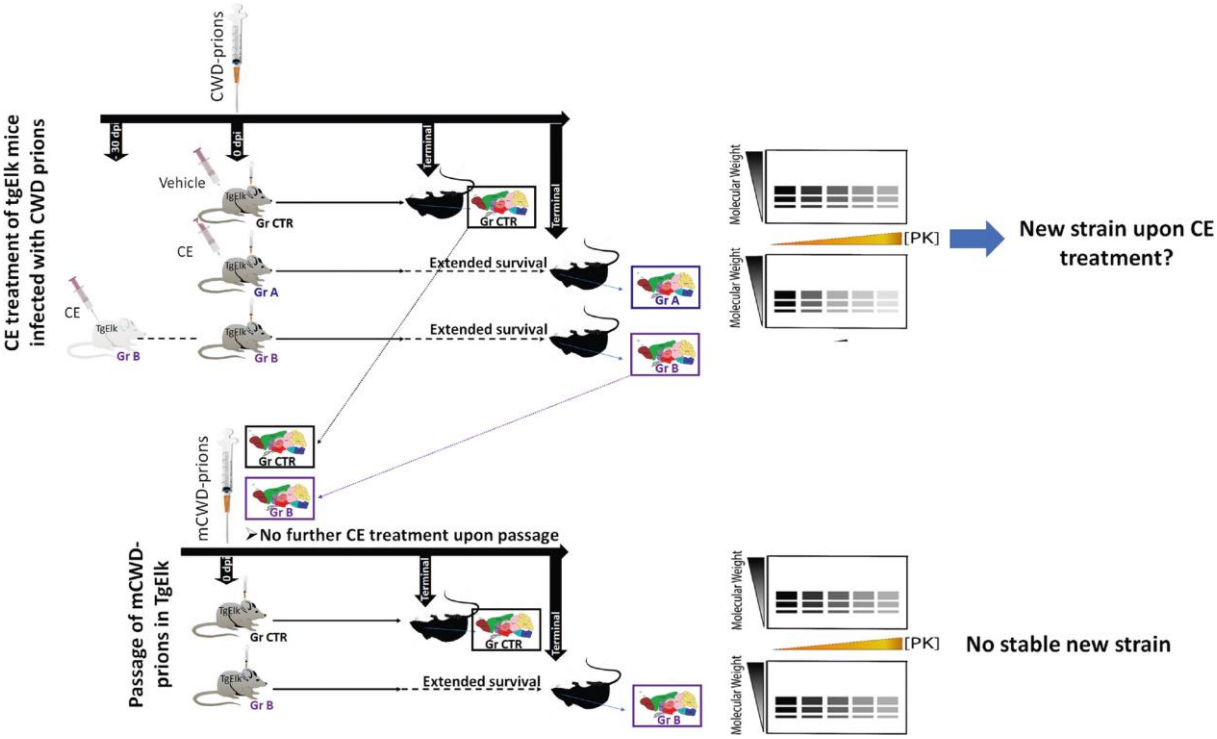
Cellulose ether treatment in vivo generates chronic wasting disease prions with reduced protease resistance and delayed disease progression

Open Access

S. Hannaoui, M. I. Arifin, S. C. Chang, J. Yu, P. Gopalakrishnan, K. Doh-ura, H. M. Schatzl and S. Gilch

Chronic wasting disease (CWD) is a prion disease affecting free-ranging and farmed cervids, with substantial lateral transmission and effective shedding, making its containment nearly impossible. This poses a significant concern for public health, economy and ecology. Here we demonstrate that cellulose ether (CE) treatment of CWD infected transgenic mice (TgElk) prolongs survival and modifies the biochemical and biological properties of prions, resulting in reduced protease resistance along with delayed clinical disease. Therefore, CE treatment could be a good strategy to reduce CWD spreading, limiting its potential of transmission to cerid and non-cervid animals and potentially to humans.



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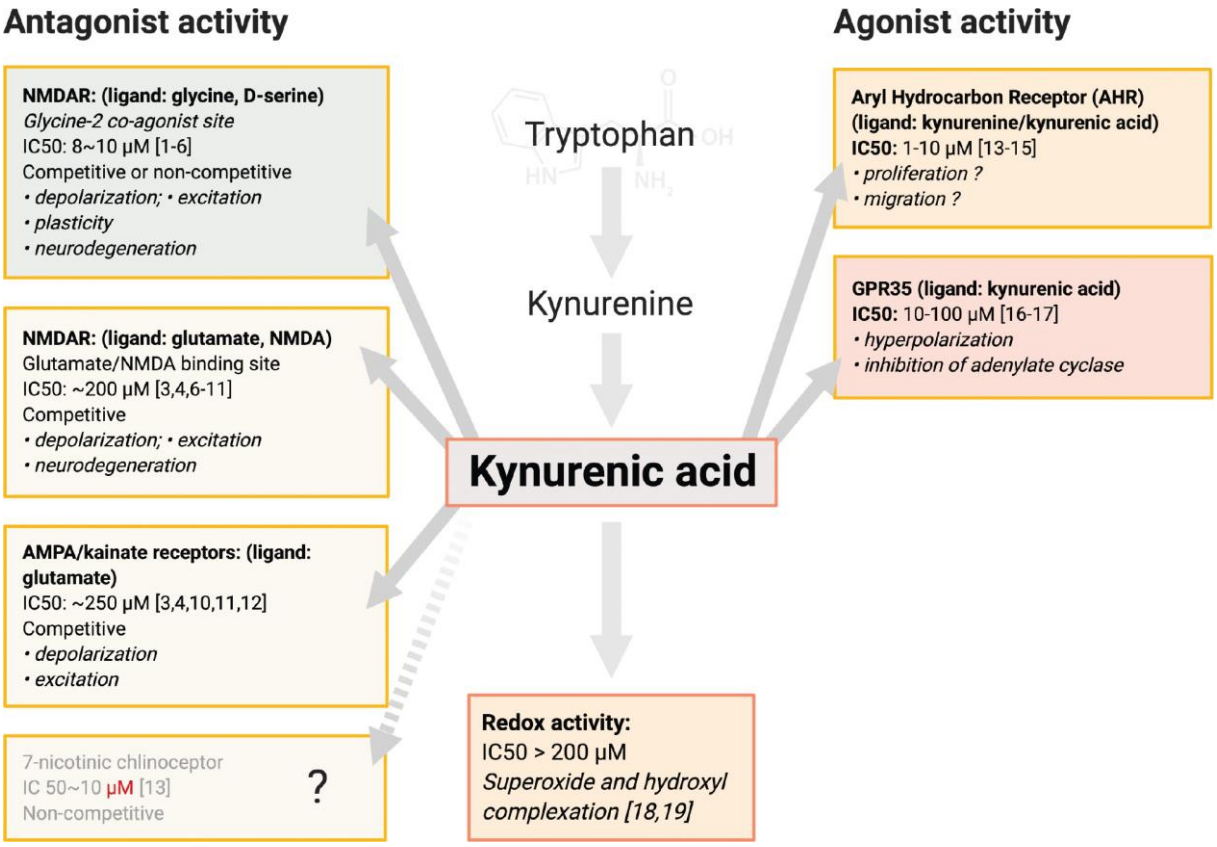
Review articles

Does kynurenic acid act on nicotinic receptors? An assessment of the evidence

Open Access

T. W. Stone

Kynurenic acid has well-established activity as an antagonist at glutamate receptors, especially the glutamate and glycine co-agonist binding sites, with possibly relevant actions on Aryl Hydrocarbon Receptors and the GPR35 binding site. A single proposal that it also acts on acetylcholine nicotinic receptors is analysed and discussed in the light of at least 12 failures to reproduce the activity, and a wide range of pharmacological arguments. It is concluded that there is no confirmed, reliable evidence for any effect at nicotinic acetylcholine receptors.



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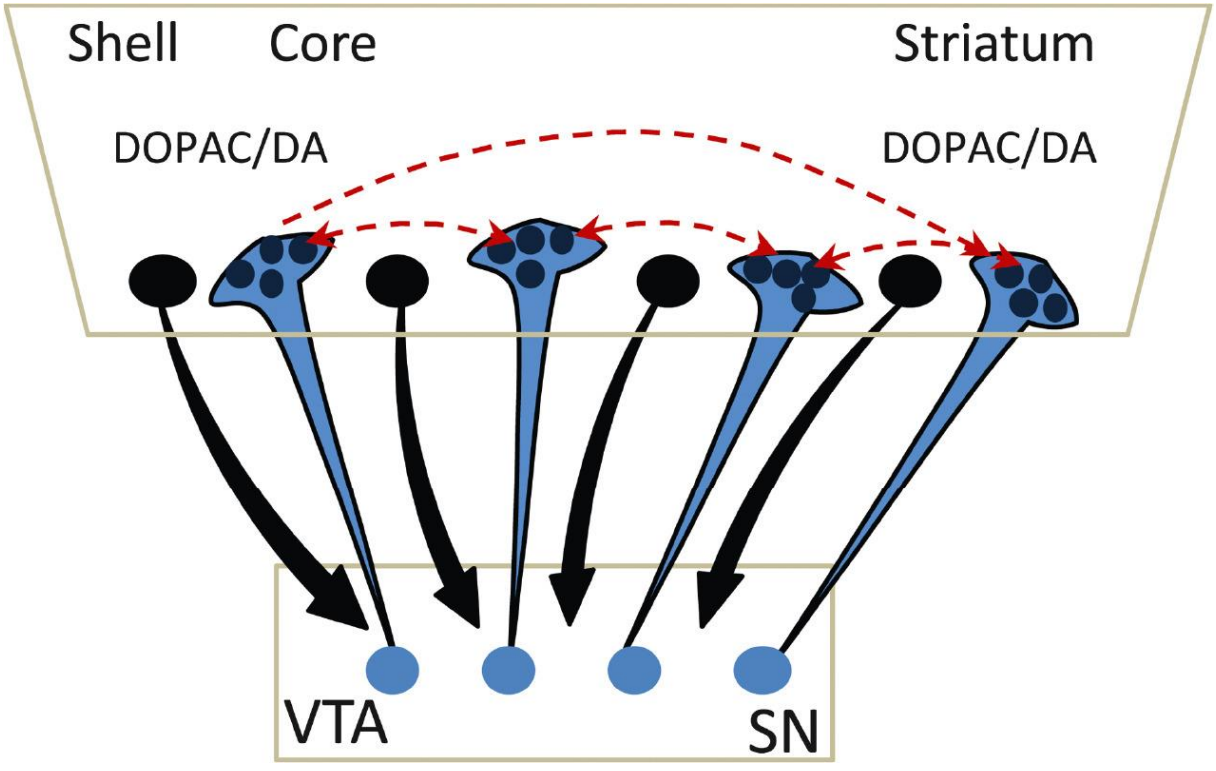
Editorial Highlight

Old neurochemical markers, new functional directions?

P. De Deurwaerdere, S. Gaetani and R. A. Vaughan

This Editorial highlights a study of Hörtnagl et al. (2019) that describes the post-mortem distribution of neurochemical markers for dopamine and other neurotransmitters in precisely-dissected sub-regions of human caudate nucleus and putamen, presenting a new quantitative description of marker heterogeneity across striatal sub-territories and providing evidence for a regional organization of dopaminergic metabolism. Correlation analyses of transmitter measurements between the tissue markers within sub-regions indicates the potential for biochemical activity of dopaminergic neurons (blue) at terminals to be indirectly influenced by distal dopaminergic projections (red arrows). This highlight addresses the possibility to use these “old neurochemical markers” to investigate functional relationships between striatal territories and beyond via multiple correlative analyses.



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Highlighted Article

Distinct gradients of various neurotransmitter markers in caudate nucleus and putamen of the human brain

Open Access

H. Hörtnagl, C. Pifl, E. Hörtnagl, A. Reiner and G. Sperk

Caudate nucleus (CN) and putamen (PUT) of the dorsal striatum are involved in higher brain functions and part of the extrapyramidal motor system. We demonstrate a pronounced regional diversity in the distribution of dopamine (DA), serotonin, γ-aminobuturic acid, and choline acetyltransferase, for example, DA levels continuously increase from rostral to caudal PUT, whereas their rostro-caudal distribution is bell-shaped in the CN, and the highest levels are associated with the lowest turnover in the most central area of CN and PUT. The described gradients might be relevant for comparing tissue samples from healthy and diseased striatum and directing intrastriatal therapy of diseases.