



JNC Highlights November 2020

Latest Research and Reviews

The following articles are part of Volume 155, Issue 1 – Pages 1-110

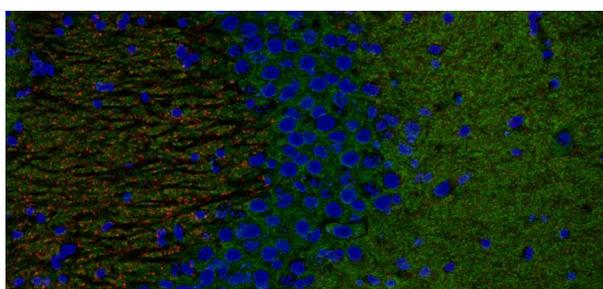
Cover Image

[Amyloid-beta 1–42 induced glutamatergic receptor and transporter expression changes in the mouse hippocampus](#)

Jason H.Y. Yeung, Beatriz Calvo-Flores Guzmán, Thulani H. Palpagama, Jayarjun Ethiraj, Ying Zhai, Warren P. Tate, Katie Peppercorn, Henry J. Waldvogel, Richard L.M. Faull, Andrea Kwakowsky

Front cover: Alzheimer's Disease (AD) is the leading type of dementia worldwide. Glutamate is the main excitatory neurotransmitter in the brain and plays an essential role in the function and health of neurons and neuronal excitability. This is the first comprehensive anatomical study to characterize the subregion- and cell layer-specific effect of beta-amyloid (A β 1-42) on the expression of specific glutamate receptors and transporters in the mouse hippocampus, using immunohistochemistry with confocal microscopy. Our data demonstrate heterogeneous expression changes in glutamatergic signaling components in an in vivo A β 1-42-injected mouse model of AD. These changes have the ability to alter normal glutamatergic signaling and could contribute to AD pathology. Due to the pivotal role of the glutamatergic system in regulating synaptic activity, any disruption to its composition could have consequences for normal neuronal function. These findings also indicate that A β 1-42 induces brain region and layer specific expression changes of the glutamatergic receptors and transporters, suggesting complex and spatial vulnerability of this pathway during AD neuropathology.

Image content: The image shows glutamate receptor GluA1 subunit (green) and glutamate transporter vGluT1 (red) immunoreactivity in CA3 region of the mouse hippocampus. Nuclei were counterstained with Hoechst dye (blue).



Read the full article 'Amyloid-beta 1–42 induced glutamatergic receptor and transporter expression changes in the mouse hippocampus' by J. H. Y. Yeung, B. C.-F. Guzmán, T. H. Palpagama, J. Ethiraj, Y. Zhai, W. P. Tate, K. Peppercorn, H. J. Waldvogel, R. L. M. Faull, A. Kwakowsky, (*J. Neurochem.* 2020, vol. 155 (1), pp. 19–62) on doi:[10.1111/jnc.15099](https://doi.org/10.1111/jnc.15099)



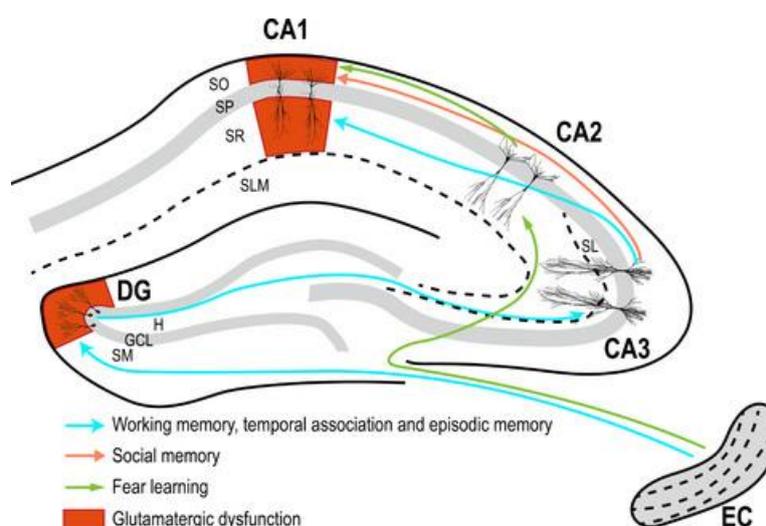
Editorial Highlight

Toward a dissection of β -Amyloid localized effects on glutamatergic hippocampal repertoire

J. Alfredo Méndez Arturo Ortega

Free Access

Hippocampal excitatory glutamatergic transmission is critically involved in cognitive functions such as learning and memory. A severe impairment of spatial memory is associated with the Alzheimer's disease characteristic augmentation of soluble Amyloid-beta1-42 which in turn leads to glutamatergic neurotransmission dysfunction. As the molecular basis of such correlations has not been completely understood, this Editorial highlights a study in the current issue of the Journal of Neurochemistry in which Yeung and coworkers provide an elegant anatomical study that sheds light into this problematic. Through a rigorous immunohistochemical approach, a sub-regional expression pattern of ionotropic glutamate receptors and vesicular transporters was determined in control and beta amyloid-injected mouse hippocampus. The selected areas participate in information processing and thus, in memory formation. Furthermore, the authors discuss their findings in the context of cognitive deficits present in Alzheimer's disease patients delivering an easy to follow analysis of plausible molecular events that disturb proper glutamate signaling. This study takes an important step towards a better understanding of the complexity of Amyloid-beta1-42 and glutamatergic neurotransmission interactions.





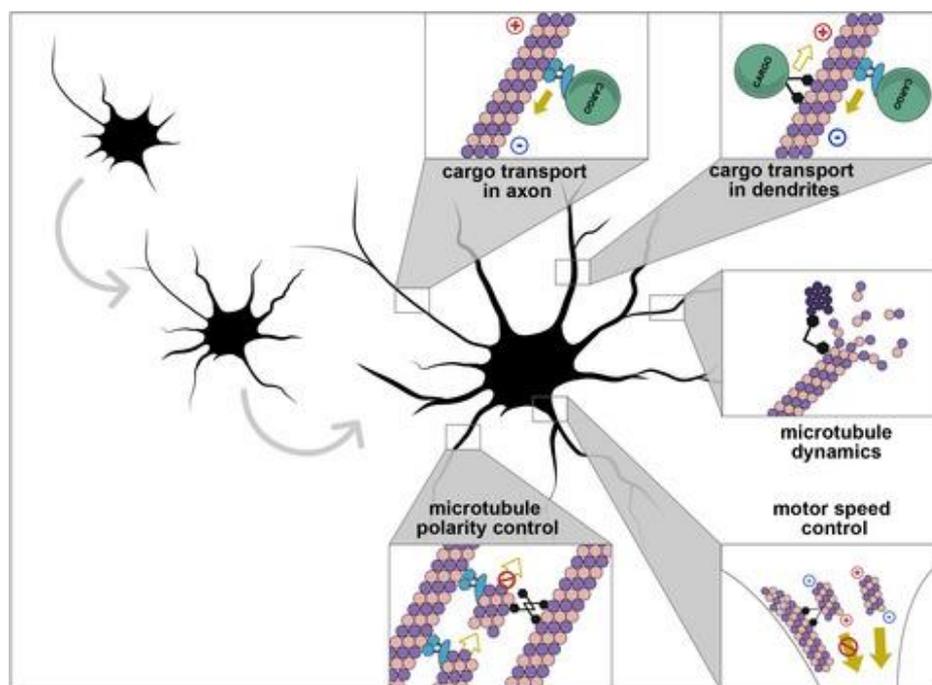
Review articles

[Role of dynein–dynactin complex, kinesins, motor adaptors, and their phosphorylation in dendritogenesis](#)

Free Access

Aleksandra Tempes, Jan Weslawski, Agnieszka Brzozowska, Jacek Jaworski

One of the characteristic features of different classes of neurons is the shape of their dendritic arbors. To properly develop dendritic trees, neurons need to accurately control the intracellular transport of various cellular cargo which relies on motor proteins. This review focuses on the contribution of the dynein–dynactin complex, kinesins, their adaptors, and the phosphorylation of these proteins in dendritogenesis. We review not only the effects of the motor activity of these proteins in dendrites on dendritogenesis but also lesser-known aspects of their contribution, for example, dynein-driven axonal transport or regulation of MT dynamics, polarity, and other motors speed.





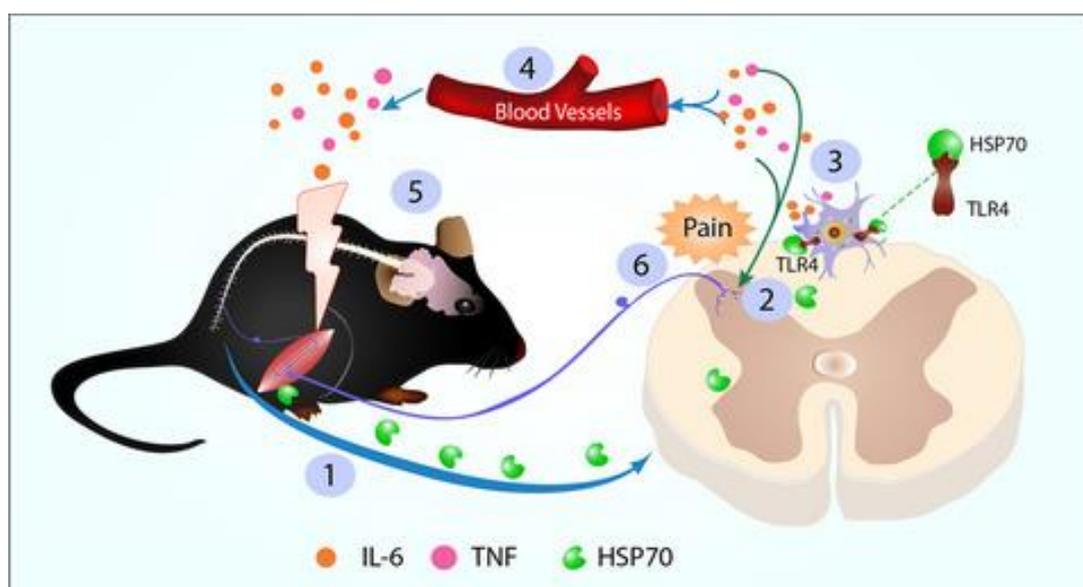
Original articles

**Involvement of the Hsp70/TLR4/IL-6 and TNF- α pathways in delayed-onset muscle soreness**

Rafaela Silva dos Santos, Flávio Protasio Veras, David Wilson Ferreira, Morena Brazil Sant'Anna, Pablo Christiano Barboza Lollo, Thiago Mattar Cunha, Giovane Galdino



Few studies have investigated delayed-onset muscle soreness (DOMS), and most have found proinflammatory cytokine involvement. This study was the first to further demonstrate that exercise increases Hsp70 in muscle and spinal cord (1), which activates TLR4 in the spinal microglia (2) and therefore releases pronociceptive cytokines as TNF- α and IL-6 (3), that through the blood veins (4) activate muscle nociceptors (5), or released by microglia contribute to spinal sensitization of DOMS (6).



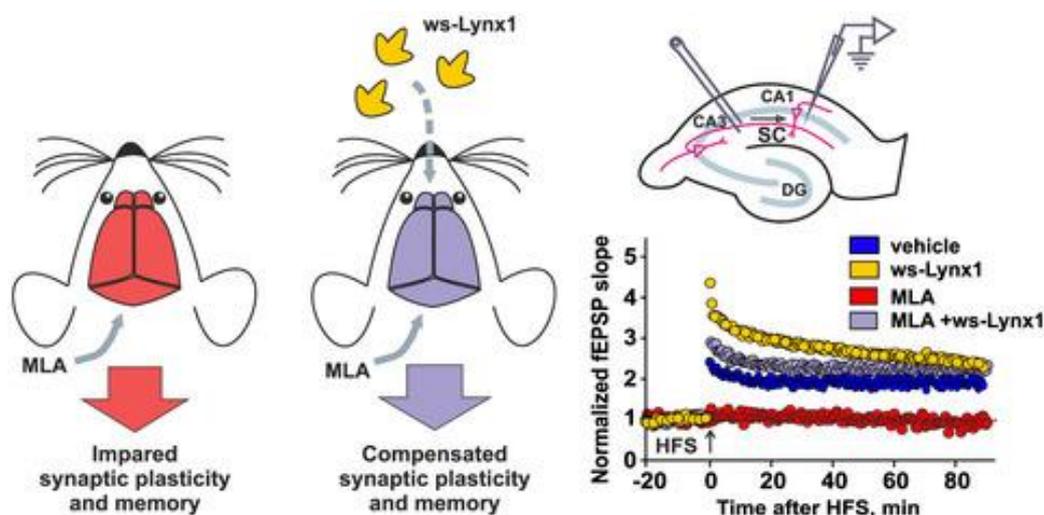


Water-soluble variant of human Lynx1 positively modulates synaptic plasticity and ameliorates cognitive impairment associated with $\alpha 7$ -nAChR dysfunction

Zakhar O. Shenkarev, Mikhail A. Shulepko, Maxim L. Bychkov, Dmitrii S. Kulbatskii, Olga V. Shlepova, Nathalia A. Vasilyeva, Alexander A. Andreev-Andrievskiy, Anfisa S. Popova, Evgeniya A. Lagereva, Eugene V. Loktyushov, Sergey G. Koshelev, Morten S. Thomsen, Dmitry A. Dolgikh, Sergey A. Kozlov, Pavel M. Balaban, Mikhail P. Kirpichnikov, Ekaterina N. Lyukmanova



Lynx1 is a GPI-tethered regulatory protein colocalized with nicotinic acetylcholine receptors (nAChRs) in the brain. We studied the water-soluble Lynx1 variant lacking GPI-anchor (ws-Lynx1). At 2 μ M, ws-Lynx1 potentiates $\alpha 7$ -nAChRs in the rat primary visual cortex L1 interneurons. At higher concentrations, ws-Lynx1 inhibited $\alpha 7$ -nAChRs. In C57BL/6 mice, ws-Lynx1 penetrated the blood-brain barrier upon intranasal administration and accumulated in the cortex, hippocampus, and cerebellum. Chronic ws-Lynx1 treatment prevented the olfactory memory, motor learning, and long-term potentiation impairment induced by methyllycaconitine (MLA). Ws-Lynx1 enhances synaptic plasticity and may constitute useful hit for treatment of cognitive deficits associated with the cholinergic system dysfunction.

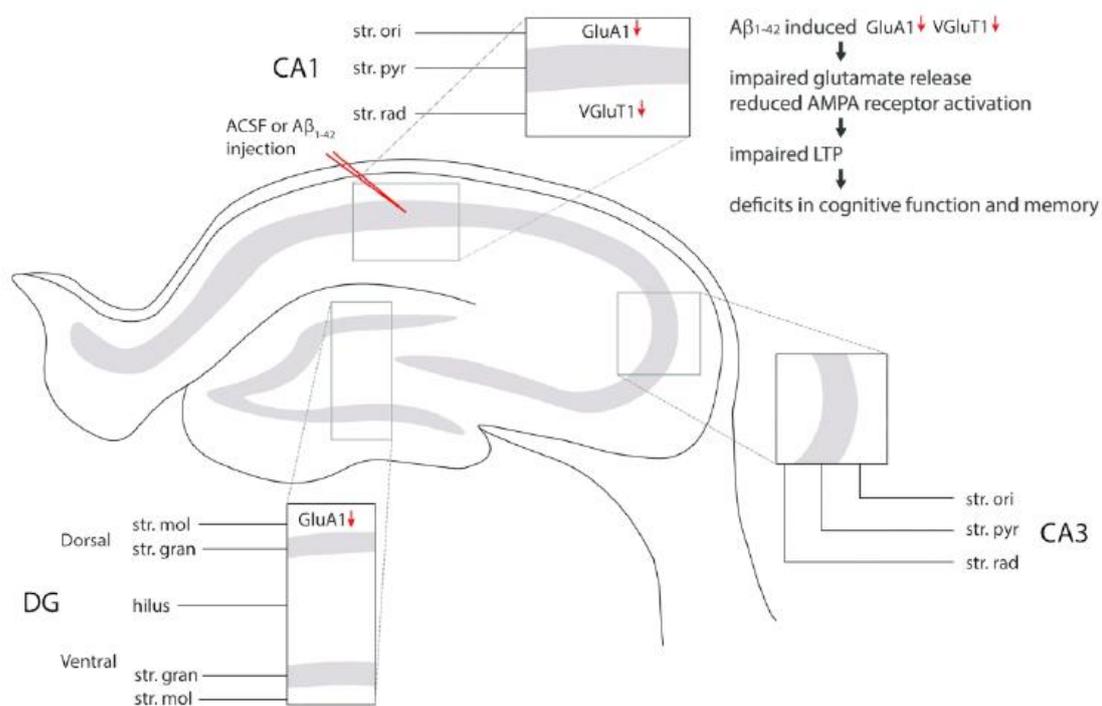




Amyloid-beta₁₋₄₂ induced glutamatergic receptor and transporter expression changes in the mouse hippocampus

Jason H.Y. Yeung, Beatriz Calvo-Flores Guzmán, Thulani H. Palpagama, Jayarjun Ethiraj, Ying Zhai, Warren P. Tate, Katie Peppercorn, Henry J. Waldvogel, Richard L.M. Faull, Andrea Kwakowsky

These findings indicate that A β ₁₋₄₂ induces region- and layer-specific expression changes in the hippocampus of the glutamatergic receptors and transporters, suggesting complex and spatial vulnerability of this pathway during development of AD neuropathology. These changes have the ability to alter normal glutamatergic signaling and could contribute to AD pathology. A better understanding of glutamatergic receptor and transporter changes in AD could lead to new pharmacological approaches to target specific components of the signaling pathway.

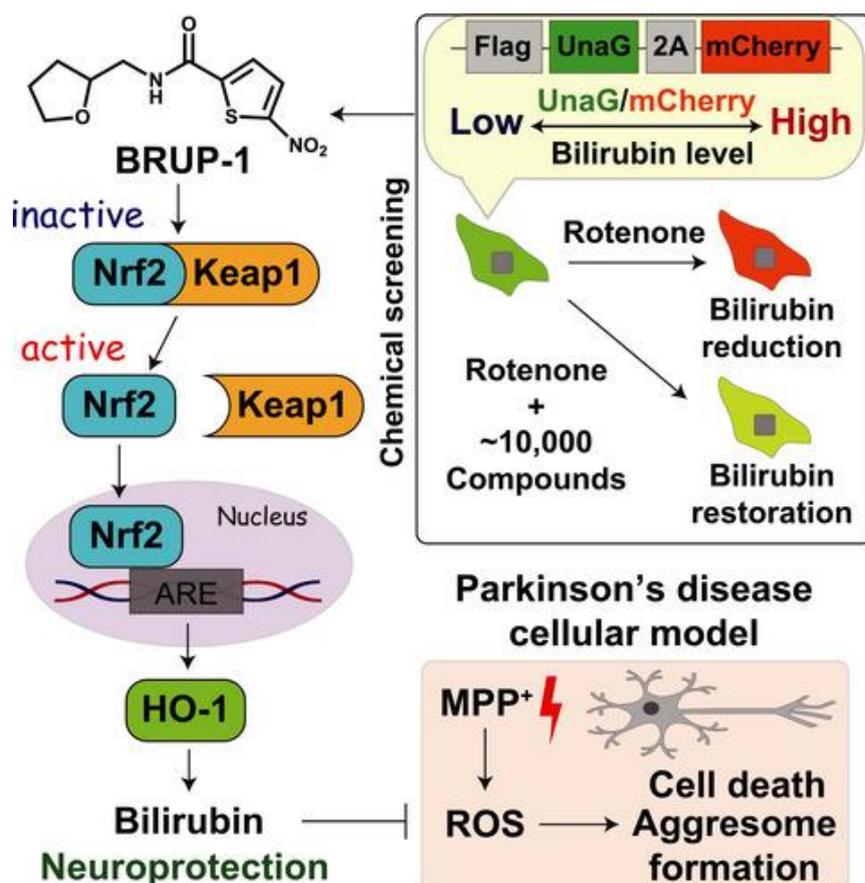




BRUP-1, an intracellular bilirubin modulator, exerts neuroprotective activity in a cellular Parkinson's disease model

Tetsushi Kataura, Shinji Saiki Kei-ichi Ishikawa, Wado Akamatsu, Yukiko Sasazawa, Nobutaka Hattori, Masaya Imoto

Since bilirubin levels were decreased in patients with Parkinson's disease (PD), we searched for compounds that restore bilirubin levels by using a ratiometric bilirubin probe, Flag-UnaG-2A-mCherry, and identified BRUP-1. We also found that BRUP-1 inhibited the binding of Keap1 to Nrf2 leading to the activation of Nrf2-HO-1 pathway, thereby increasing bilirubin level. BRUP-1 showed potent neuroprotective activity through the activation of Nrf2-HO-1-bilirubin pathway in a PD model using neuronal PC12D cells. Neuroprotective activity of BRUP-1 was also shown in iPSC-derived neurons, which suggests that chemical modulation of heme metabolism using BRUP-1 may be beneficial for treatment of PD.

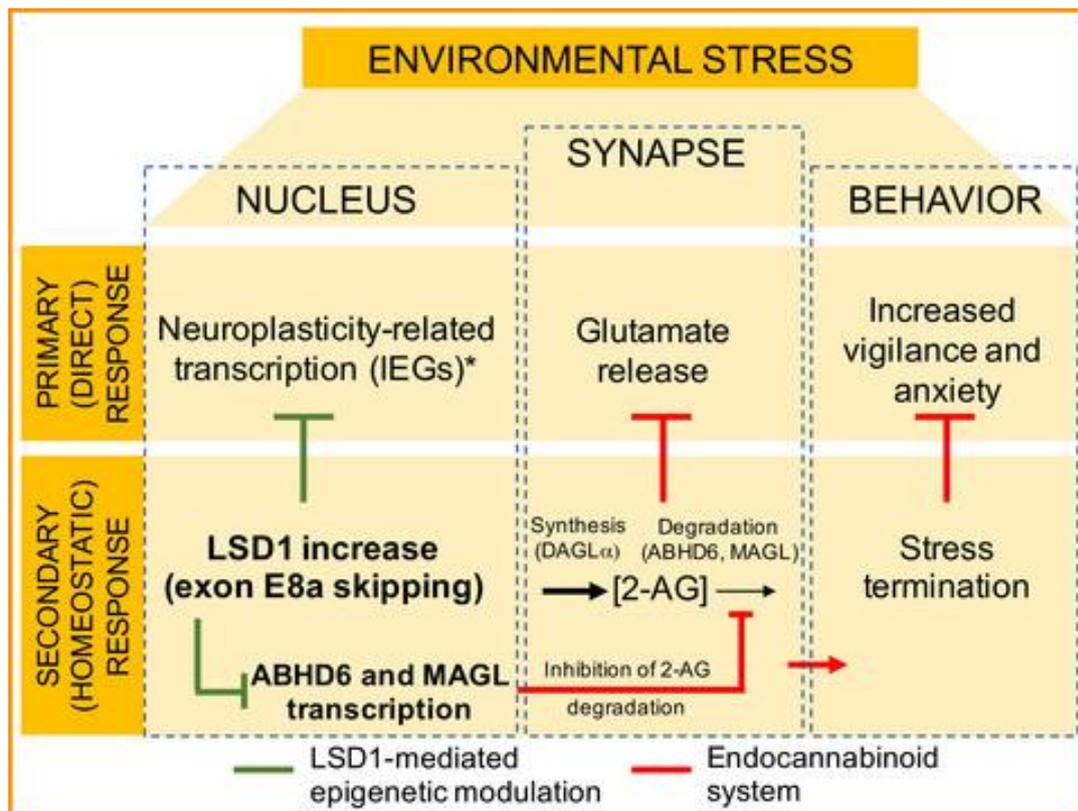




Termination of acute stress response by the endocannabinoid system is regulated through lysine-specific demethylase 1-mediated transcriptional repression of 2-AG hydrolases ABHD6 and MAGL

Alessandra Longaretti Chiara Forastieri Marina Gabaglio Tiziana Rubino Elena Battaglioli Francesco Rusconi

Environmental stress engages physiological responses primed by synaptic activation. In the nucleus direct psychosocial stress effects induce a program of neuroplasticity-related gene expression instrumental to memory consolidation of the negative experience. On the behavioral point of view, stress response directly elicits anxiety arousal and increased vigilance. A slower homeostatic response to stress entails nuclear, synaptic, and behavioral adaptations instrumental to stress response termination. We show that direct targets of LSD1 transcriptional repression at the nuclear level are 2-AG degrading enzymes ABHD6 and MAGL. In response to stress their expression is reduced helping to maintain active 2-AG concentrations via LSD1-mediated mechanism.





The following articles are part of Volume 155, Issue 2 – Pages 111-224

Cover Image

[Respiratory syncytial virus tropism for olfactory sensory neurons in mice](#)

Bertrand Bryche, Maxence Frétaud, Audrey Saint-Albin Deliot, Marie Galloux, Laura Sedano, Christelle Langevin, Delphine Descamps, Marie-Anne Rameix-Welti, Jean-François Eléouët, Ronan Le Goffic, Nicolas Meunier

Front cover: While the respiratory syncytium virus (RSV) is mainly known for the damage it causes in the respiratory tract, it could also impact the central nervous system. We explored globally the impact of RSV in the mouse nasal cavity and showed that RSV can infect olfactory sensory neurons, giving the virus access to the central nervous system by entering the olfactory bulb. Our study also yielded a 3D atlas of the nasal cavity in mice, providing tools to improve our understanding of virus tropism in the upper respiratory tract.

Image content: The present image is a periodic acid–Schiff reaction (PAS)-stained coronal section of the mice nasal cavity.



Read the full article '*Respiratory syncytial virus tropism for olfactory sensory neurons in mice*' by B. Bryche, M. Frétaud, A. Saint-Albin Deliot, M. Galloux, L. Sedano, C. Langevin, D. Descamps, M.-A. Rameix-Welti, J.-F. Eléouët, R. Le Goffic, N. Meunier, (*J. Neurochem.* 2020, vol. 155 (2), pp. 137–153) on doi:[10.1111/jnc.14936](https://doi.org/10.1111/jnc.14936)

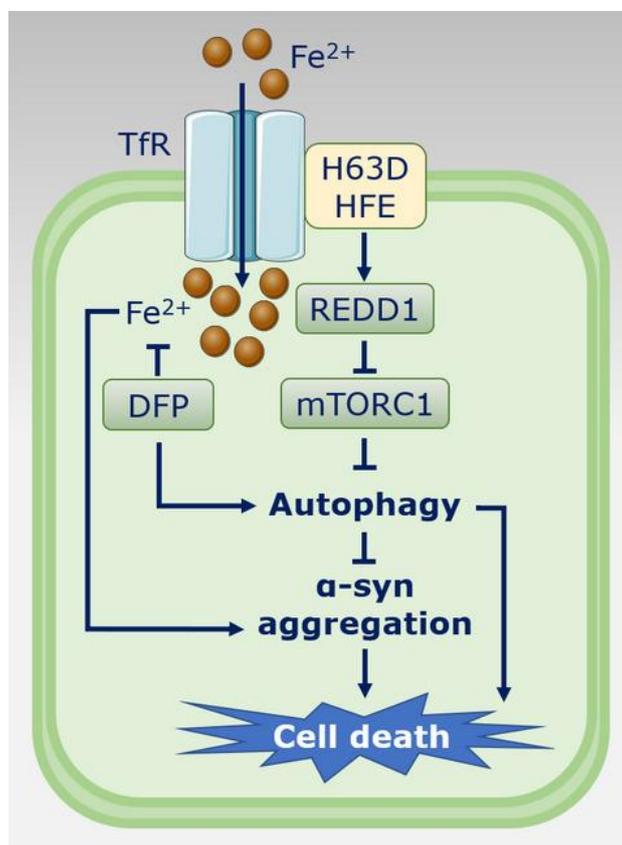
Editorial Highlight

[Iron promotes the clearance of \$\alpha\$ -synuclein: An Editorial for 'H63D variant of the homeostatic iron regulator \(HFE\) gene alters \$\alpha\$ -synuclein expression, aggregation, and toxicity' on page 177](#)

 Free Access

Qing-Zhang, Tuo Peng Lei

Iron accumulation is a pathological feature of Parkinson's disease (PD), and iron chelation therapy is in a trial for PD. This Editorial highlights a recent Journal of Neurochemistry paper by Kim et al. In their latest work, they have reported that H63D HFE variant that causes iron retention can increase REDD1 and subsequently inhibit mTORC1 to induce autophagy. This process promotes the clearance of α -syn and can be regulated by iron chelator deferiprone. Therefore, PD patients with the H63D HFE variant may respond differently to iron chelation therapy. Considering high prevalence of H63D HFE variants (approximately 5%–22%), pre-screening of PD patients for the H63D HFE variant may be warranted before iron chelation therapy.



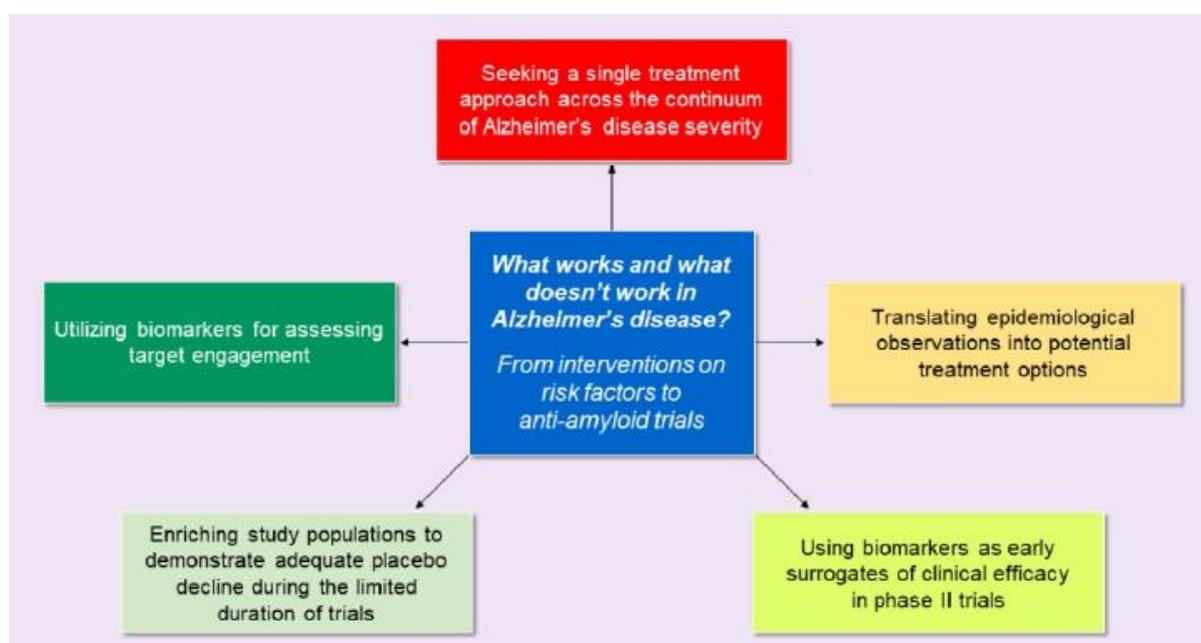


Review articles

What works and what does not work in Alzheimer's disease? From interventions on risk factors to anti-amyloid trials Free Access

Szofia Bullain, Rachelle Doody

In this review, we summarize past approaches to finding an anti-amyloid- β monoclonal antibody capable of altering the disease course in Alzheimer's disease (AD). Key learnings from the field have helped shape the current AD clinical development programs, including translating epidemiological observations into potential treatment options, evaluating therapies across the AD continuum, using biomarkers to assess target engagement and as a surrogate of efficacy, and enriching study populations. Because of the underlying complex pathophysiology of AD, disease-modifying therapies targeting both amyloid-dependent and -independent mechanisms may be needed to provide clinical benefit across the disease continuum.



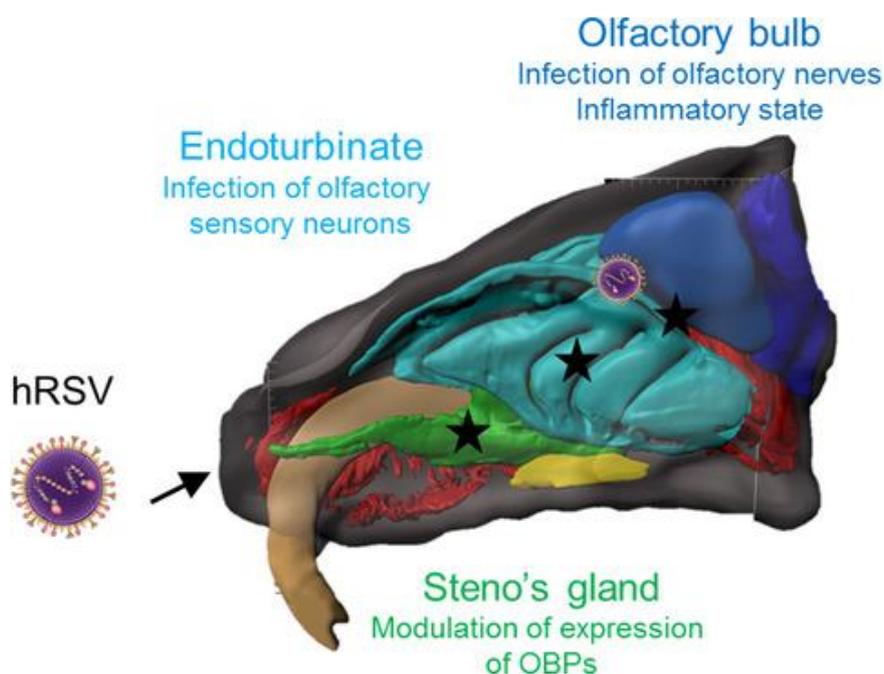


Original articles

**Respiratory syncytial virus tropism for olfactory sensory neurons in mice**

Bertrand Bryche, Maxence Frétaud, Audrey Saint-Albin Deliot, Marie Galloux, Laura Sedano, Christelle Langevin, Delphine Descamps, Marie-Anne Rameix-Welti, Jean-François Eléouët, Ronan Le Goffic, Nicolas Meunier

While the respiratory syncytium virus (RSV) is mainly known for its damaged in the respiratory tract, it could also impact the central nervous system. We explored globally the impact of RSV in the mouse nasal cavity and showed that RSV can infect olfactory sensory neurons giving access to the central nervous system by entering the olfactory bulb. Our study also provides a 3D atlas of the nasal cavity in mice giving tools to improve our understanding of virus tropism in the upper respiratory tract.

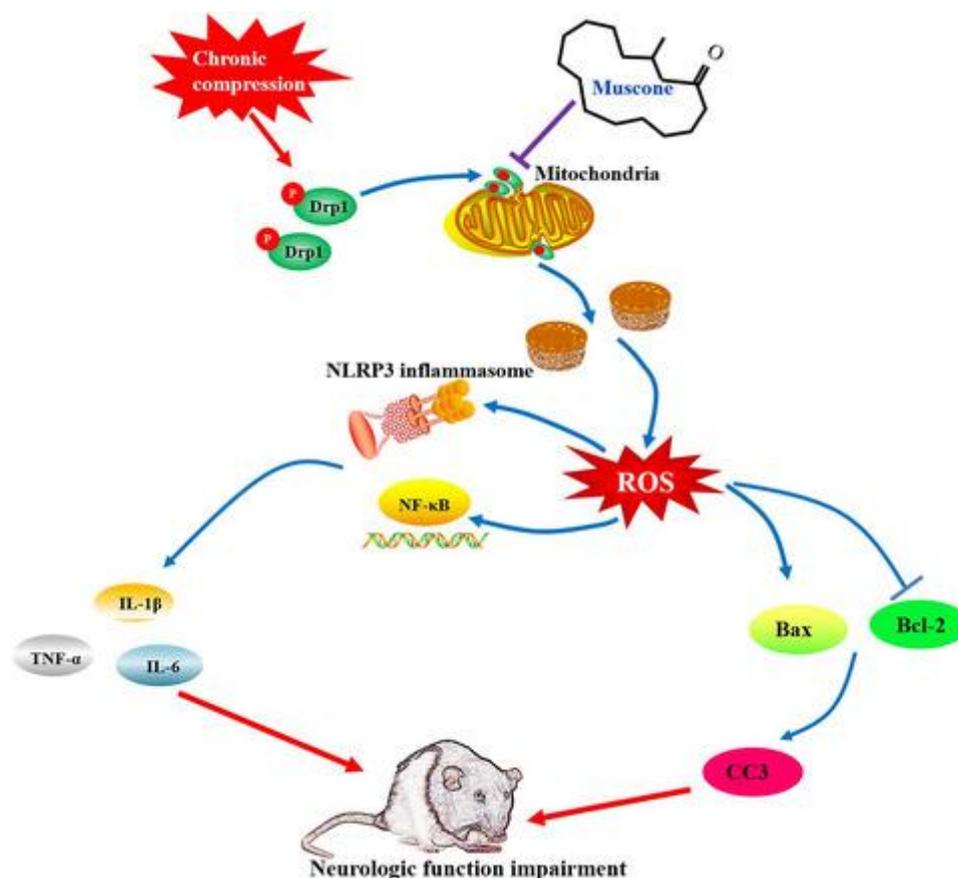




Muscone suppresses inflammatory responses and neuronal damage in a rat model of cervical spondylotic myelopathy by regulating Drp1-dependent mitochondrial fission

Long-yun Zhou, Min Yao, Zi-rui Tian, Shu-fen Liu, Yong-jia Song, Jie Ye, Gan Li, Yue-li Sun, Xue-jun Cui, Yong-jun Wang

Cervical spondylotic myelopathy (CSM) is a common cause of disability with few treatments. Muscone, the ingredient from an animal product, exhibits anti-inflammatory and neuroprotective effects for which the underlying mechanisms remain obscure. In this study, we explored the effects of muscone on a classic CSM rat model, microglial and neuronal cell. Results indicated that muscone could attenuate both inflammatory responses and neuronal damage in a rat CSM model and in vitro. Such effects may be associated with its role on mitochondrial dynamics and downstream signaling, suggesting that mitochondrial dynamics and muscone may be new highlights for the treatment of CSM.

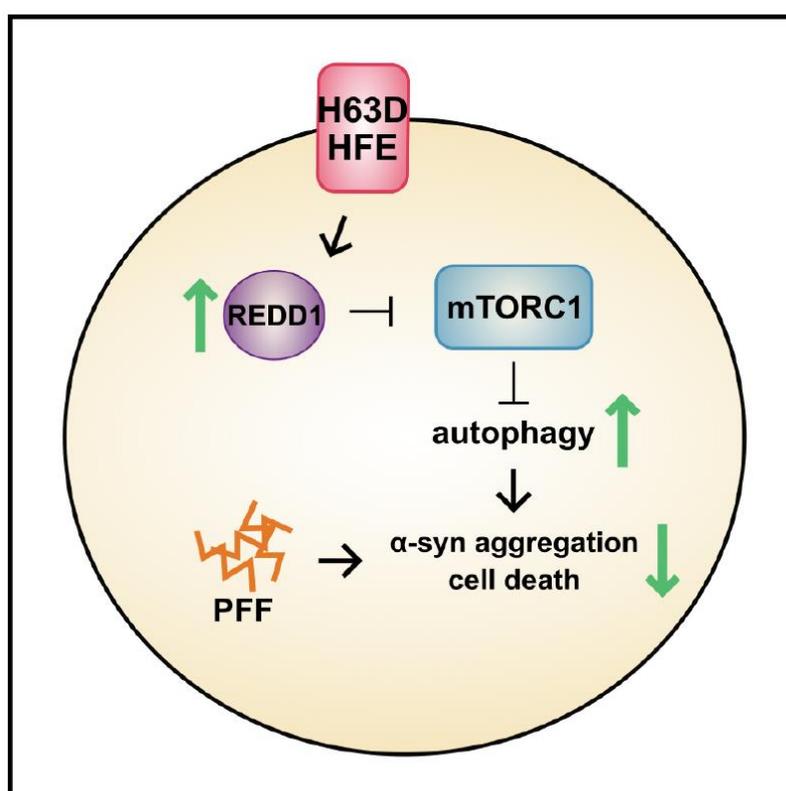




H63D variant of the homeostatic iron regulator (HFE) gene alters α -synuclein expression, aggregation, and toxicity

Yunsung Kim, Mark C. Stahl, Xuemei Huang, James R. Connor

Iron plays a complex role in pathogenesis of Parkinson's disease. H63D variant of the homeostatic iron regulator, HFE, increases intracellular iron levels by promoting uptake. Expression of H63D HFE was shown to decrease α -synuclein levels and protect SH-SY5Y cells from pre-formed fibril mediated toxicity through the induction of autophagy. Increased REDD1 expression was found to inhibit mTORC1, the major negative regulator of autophagy. Furthermore, H67D Hfe mice injected with preformed fibrils had better preservation of motor functions. Our findings argue that HFE genotype may explain the variability in disease progression and therapeutic responses in Parkinson's disease.





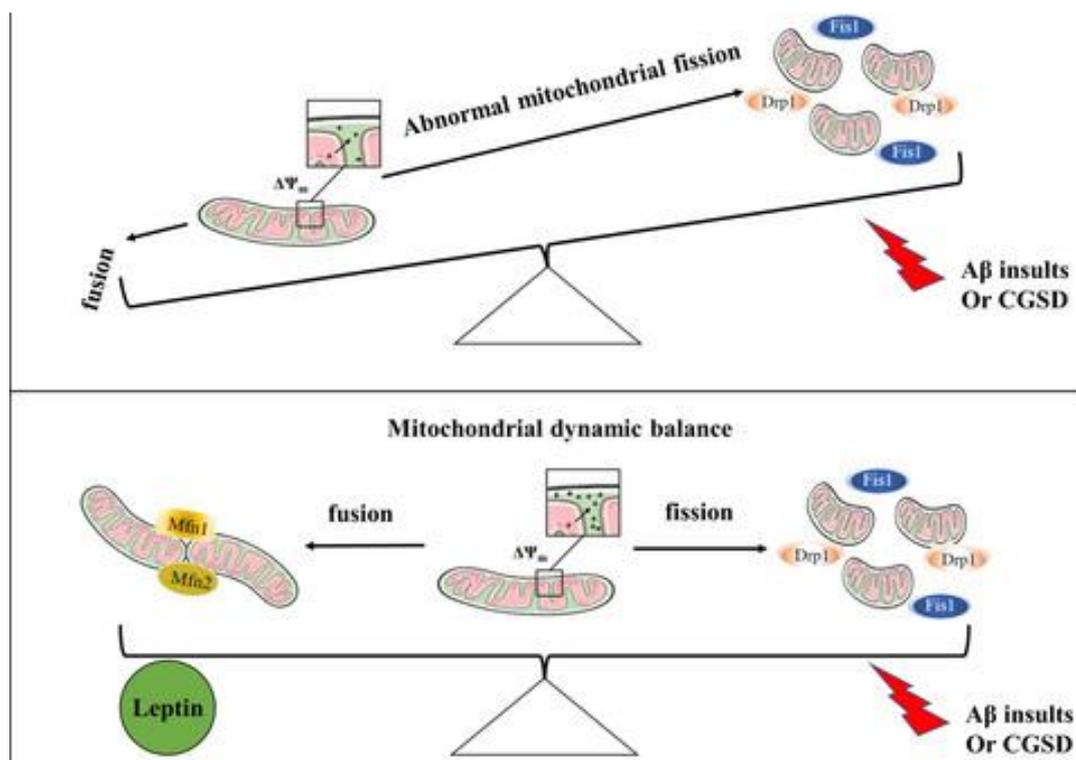
Neuroprotective actions of leptin facilitated through balancing mitochondrial morphology and improving mitochondrial function

Open Access

Ying Cheng, Matthew Buchan, Karina Vitanova, Laura Aitken, Frank J. Gunn-Moore, Rona R. Ramsay, Gayle Doherty



The amelioration of mitochondrial dysfunction in neurodegeneration such as Alzheimer's disease, is an established strategy in the search for treatments for these disorders. In this study, we demonstrate that the anti-obesity hormone, leptin, can benefit mitochondrial dynamics and function through supporting mitochondrial membrane potential and balancing the expression of fission and fusion proteins, while boosting the expression and activity of mitochondrial antioxidant enzymes MAOB. Thus leptin's neuroprotection may be facilitated through the regulation of mitochondrial function and dynamics.

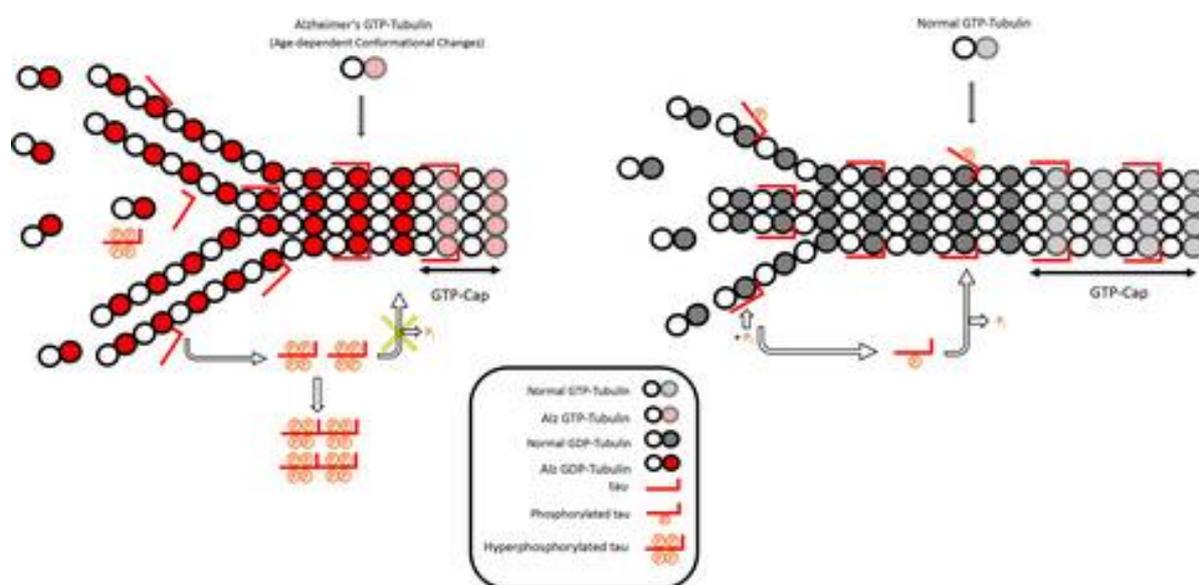




Conformational change and GTPase activity of human tubulin: A comparative study on Alzheimer's disease and healthy brain

Shima Rajaei, Saeed Karima, Hessam Sepasi Tehrani, Somayeh Shateri, Somayeh Mahmoodi Baram, Meisam Mahdavi, Farzad Mokhtari, Alimohammad Alimohammadi, Abbas Tafakhori, Abolfazl Amiri, Vajiheh Aghamollaii, Hamid Fatemi, Masoumeh Rajabibazl, Farzad Kobarfard, Ali Gorji

Axonal microtubule disintegration and neuronal death are characteristics of Alzheimer's disease. GTP-cap which is comprised of GTP-tubulin is highly important in microtubule dynamic instability. We proposed that in Alzheimer's disease age-dependent conformational changes of tubulin causing altered intrinsic tubulin GTPase activity and decreased GTP-cap length precedes tau detachment and its subsequent hyperphosphorylation. Human tubulin was purified from normal young adult, normal aged and Alzheimer's brains. Prolonged lag phase, increased critical concentration and GTPase activity concurrent with profound conformational changes and contracted intermolecular MT-tau distances were found in Alzheimer's brains compared with normal young and aged ones.



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