

ADONTAGE

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Tau pathology, BDNF/TrkB neurotrophic system and adenosine A_{2A} receptors

Context and objectives

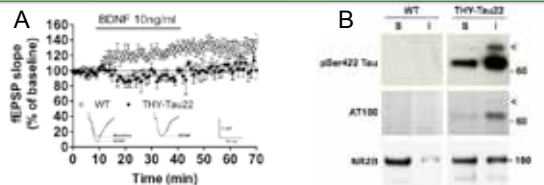
Brain Derived Neurotrophic Factor (BDNF) is highly expressed in the hippocampus where it plays, through the activation of its cognate TrkB receptor, a critical role in synaptic plasticity processes underlying learning and memory. A_{2A} receptors are GPCR previously viewed as modulators of hippocampal synaptic response as well as of BDNF production and involved in various neurodegenerative disorders (1-5). Aim of the present project was originally to identify whether A_{2A} receptors could modulate the BDNF/TrkB system in control mice as well as in a in-house transgenic mouse model (THY-Tau22) mimicking the Alzheimer's disease (AD)-like Tau pathology. Indeed, Tau pathology is instrumental in AD and little is known about its relationships with BDNF/TrkB system and A_{2A} receptors. However, we could not find relationship and the project was logically re-focused to identify how Tau pathology impacts on the BDNF/TrkB system and A_{2A} receptors as well as whether modulation of BDNF/TrkB system or A_{2A} receptors could influence THY-Tau22 mice physiopathology.

Tau-related physiopathology

THY-Tau22 mice overexpress a human mutated Tau protein and were originally shown to exhibit progressive development of hippocampal Tau pathology and memory defects. Recently, we have demonstrated that spatial and contextual memory defects were likely related to long-term depression impairments (6). Our data also indicated that while hippocampal neuronal survival and synaptic markers were spared (6), Tau pathology promoted strong hippocampal inflammation (7) as well as alterations in the septo-hippocampal transport associated with hippocampal accumulation of Nerve Growth Factor and cholinergic neuron degeneration, all possibly accounting for cognitive deficiencies (8,9,10). We finally demonstrated that neither BDNF or TrkB expressions were strikingly altered by Tau pathology and that hippocampal A_{2A} receptor expression and synaptic function was preserved (11,12,13).

Tau pathology and the BDNF/TrkB system

Using physiological and biochemical tools, we demonstrated that hippocampal Tau pathology is associated with the early loss of BDNF-induced synaptic enhancement, due to the defective coupling of TrkB with the NMDA receptor (Fig.A). Indeed, whereas TrkB expression and activatability remained unaltered, we observed a significant reduction of NMDA-induced fEPSP depression in the hippocampus of THY-Tau22 mice, suggesting decreased NMDA receptor function.



In accordance, we observed an increase in the level of the NMDAR subunit NR2B in the insoluble protein fraction rich in pathological Tau species (Fig.B), along with a reduced phosphorylation of this subunit at the Y1472 residue. Our results suggest that the impairment of BDNF-induced synaptic enhancement mediated by defective NR2B function could contribute to the cognitive deficits observed in AD and other Tauopathies. However, challenging mice by long-term physical exercise that strongly increases hippocampal BDNF levels however prevented memory alterations in THY-Tau22 mice. This was accompanied by a decrease in hippocampal Tau pathology and a prevention of the loss of choline acetyltransferase expression within the medial septum. These data supported that since TrkB activatability is not impaired in THY-Tau22 mice, BDNF could promote beneficial function against Tau pathology through pathways independent from NMDA-dependent plasticity.

Tau pathology and A_{2A} receptors

To investigate the potential role of A_{2A} receptors towards Tau pathology, the latter were invalidated in THY-Tau22 mice. This resulted in the prevention of memory and anxiety defects, reduction of hippocampal Tau phosphorylation as well as of plasmatic Tau levels. We also demonstrated that these improvements were associated with reduction of the hippocampal inflammatory status.

Conclusions & perspectives

Our data provide new insights on how Tau pathology may impact on synaptic processes underlying memory. Further cellular and molecular works are needed to understand these processes. In addition, we originally give the proof-of-concept that modulating A_{2A} receptors is of therapeutical interest for AD and Tauopathies. This will be confirmed using pharmacological approaches and underlying mechanisms will be uncovered using new transgenic mouse models of cell-specific A_{2A} receptor up- and down-regulations.

Publications

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