Involvement of bradykinin B2 receptor in NGF neuroprotective activity

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Nerve Growth Factor (NGF) is a neurotrophin acting on cholinergic neurons of the CNS and on sympathetic and sensory neurons. NGF represents a validated therapeutic candidate, as demonstrated in different neurodegenerative pathological conditions, due to its crucial actions in long-lasting cholinergic maintenance, and as a direct anti-amyloidogenic factor.

It is well known that NGF profoundly regulates gene expression of bradykinin (BK) receptors in TrkA-expressing dorsal root ganglion sensory neurons (DRGs), facilitating nociceptive signals.

Biological effects of BK are produced by two G protein coupled transmembrane receptors: the constitutive receptor B2 (B2R), and the inducible receptor B1 (B1R), over-expressed during chronic inflammatory conditions. Interestingly, the involvement of these receptors in neurodegenerative diseases has been recently demonstrated. During the neurodegenerative process, B1R seems to be involved in memory degeneration, while B2R acts as a neuroprotective factor, pointing to BRs as potential therapeutic target in Alzheimer's disease (AD).

However, the involvement of BK receptors in the neuroprotective activity of NGF has never been demonstrated in central, not-sensory neurons.

To this aim, we investigated this topic by treating cultured rat cortical neurons (CNs) with NGF (100ng/ml) for 3 days and subsequently depriving them of NGF. The intracellular mechanisms whereby NGF alters BK receptors expression were investigated by measuring steady-state B2R and B1R mRNA levels by microarray analysis. This study showed a B2R mRNA up-regulation after NGF treatment and, conversely, an up-regulation of B1R mRNA in NGF deprived condition

B2R up-regulation, following NGF treatment has been further confirmed at a protein level by Western blot analysis.

Moreover, electrophysiology recordings showed that pre-treatment of hippocampal slices with NGF (100ng/ml for 1 hour) was able to enhance LTP at CA1 hippocampal synapses. Notably, application of BK (100nM) mimicked the NGF-mediated facilitatory action on CA1-LTP. The effect of NGF was prevented by pre-treatment of slices with the B2 receptor antagonist HOE140 (1µM) further suggesting that NGF modulates synaptic plasticity via interaction with B2R.

These results indicate that B2R, endowed with neuroprotective activity, plays a role in NGF mechanism of action.