**p75NTR in Huntington’s disease: beyond the basal ganglia**

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Huntington’s disease (HD) is a fatal neurodegenerative disorder with a characteristic phenotype including chorea and dystonia, uncoordinated fine movements, cognitive decline and psychiatric disturbances. Even though the clinical diagnosis of HD relies on the manifestation of motor abnormalities, the associated memory impairments have been growing in prominence. Indeed, cognitive deficits are evident along all the disease process even in the prodrome before any motor diagnosis is given.

These clinical signs have been mainly attributed to corticostriatal dysfunction being deficits of neurotrophic support, caused by either reduced levels of brain-derived neurotrophic factor (BDNF) [1] or decreased TrkB and aberrant p75NTR signalling [2, 3], one of the major pathogenic mechanism involved. However, in recent years has emerged the idea that cognitive decline in HD is likely a reflection of a widespread brain circuitry defect rather than a basal ganglia dysfunction per se. In this regard, in our recent studies we shed new light on the contribution of the hippocampal circuitry to synaptic and memory decline in HD. We demonstrated hippocampal dysfunction in a precise genetic HD mouse model that expresses endogenous levels of mutant huntingtin, HdhQ7/Q111 mice, manifested as alterations in spatial, recognition and associative memories.

To get insight into the molecular mechanisms underlying such defects, we focused on p75NTR since growing evidence indicate that p75NTR plays an antagonistic role in synaptic plasticity. We demonstrated up-regulation of p75NTR in the hippocampus of distinct HD mouse models and in human brain without evident changes in the cortex, which extends our previous data showing increased p75NTR expression in the HD striatum [4]. In agreement with a critical role of aberrant p75NTR expression in hippocampal dysfunction we found preserved spatial, recognition and associative memories in new double-mutant mice expressing mutant huntingtin but “physiological” levels of p75NTR levels (HdhQ7/Q111:p75+/- mice).

How aberrant p75NTR levels may mediate synaptic and memory deficits in HD is an intriguing question. On one hand, our results indicated that p75NTR directly or indirectly regulate the expression of different synaptic-related proteins previously implicated in HD synaptic and/or cognitive deficits, such as CBP, CamKII, GluA1 or BDNF since memory improvements in double mutant HdhQ7/Q111:p75+/+ mice correlated with a recovery of the expression and/or phosphorylation of these molecules. On the other, the loss of dendritic spines in CA1 pyramidal neurons exhibited by HdhQ7/Q111 mutant mice was also prevented by normalization of p75NTR levels. Altogether, these data suggest that synaptic and memory deficits in HD could be related with a reduction in proteins involved in synaptic function and in the number and complexity of hippocampal dendritic spines in agreement with a role of p75NTR as a negative regulator of dendritic spine dynamics and synaptic activity.

We further built on work showing that p75NTR contributes to synaptic dysfunction and memory decline in HD by deregulation of RhoA activity, a small GTPase with complex effects on spines and thereby in synaptic plasticity [5]. Interestingly, such increase was reversed in double mutant HdhQ7/Q111:p75+/- mice suggesting a direct link between aberrant p75NTR activity, dendritic spine loss and aberrant RhoA activity. In agreement with our findings Plotkin and colleagues [3] have demonstrated that plasticity in indirect pathway spiny projection neurons (iSPNs) from BACHD mutant mice can be rescued by inhibition of the p75NTR-RhoA signalling suggesting that early corticostriatal dysfunction in HD could also be attributable to a correctable defect in BDNF signalling. Altogether, this evidence strongly suggests that, in the early stages of the disease, p75NTR antagonism should be considered an effective therapeutic strategy for restoring BDNF neuroprotective and synaptic functions. However, remains to be investigated whether therapeutic approaches targeting p75NTR inhibition should also integrate TrkB activation to produce the most favourable benefits on motor and cognitive impairments.

Moreover, we have recently demonstrated that fingolimod, a compound used as an immunomodulator in Multiple Sclerosis patients, restores hippocampal synaptic plasticity and improves memory function in a mouse model of Huntington disease acting through down-regulation of TNFa and p75NTR [6]. These last evidence open the question whether p75NTR dysregulation is triggered by neuroinflammation at very early stages and whether modulation of the inflammatory response of microglia and astroglia in HD may contribute to antagonize the deleterious effects of aberrant p75NTR-induced RhoA activity in synaptic plasticity. So far, our studies strongly implicates p75NTR-RhoA hippocampal dysfunction on cognitive decline in HD stressing the
need to explore therapeutic strategies that target the identified pathways, not only in the striatum but also in other brain areas besides the basal ganglia which has been underestimated and are strongly involved in HD cognitive pathology

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**Keywords:** Huntington’s disease, cognitive deficits, hippocampus, p75 receptor, RhoA

**Received:** December 03, 2015

**Published:** December 17, 2015

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