

Neuroprotective role of CB1 cannabinoid receptor in Huntington's disease and experimental models

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Research questions and background

Understanding the mechanisms of neural cell generation and survival is a pivotal issue for characterizing the aetiology and progression of neurodegenerative diseases and, therefore, for designing rational therapies for their treatment. In this context, during the last decade our group has studied how the endocannabinoid system modulates these processes, as well as the potential therapeutic value of cannabinoid receptors as neuropharmacological targets. The CB1 cannabinoid receptor is the most abundant G protein-coupled receptor in the brain and, specifically, is very highly expressed in the basal ganglia, in which it plays a critical role in the control of motor behaviour. A remarkable down-regulation of CB1 receptors occurs in the basal ganglia of patients and animal models of Huntington's disease (HD), a devastating disorder primarily characterized by the degeneration of medium-sized spiny neurons (MSNs). MSNs belonging to the direct (D1 dopamine receptor-expressing MSNs) or indirect (D2 dopamine receptor-expressing MSNs) corticostriatal pathways have different neurochemical and functional properties, so the corticostriatal input-mediated excitotoxic death of striatal MSNs, as well as an imbalance between D1-MSN and D2-MSN-dependent circuitry, may be key factors in the symptomatic and pathological alterations of HD. Previous projects from our group provided direct evidence for the neuroprotective activity of the CB1 receptor in a HD animal model (Blázquez et al. *Brain* 134, 119-136, 2011) that is mediated by the PI3K/mTORC1-induction of BDNF (Blázquez et al., *Cell Death Differ*, 2015 doi: 10.1038/cdd.2015.11). The CB1 receptor is found in the basal ganglia at the synapses of two opposing neuronal populations: the excitatory/corticostriatal projections and inhibitory/MSNs. Particularly CB1 receptor expression located on glutamatergic corticostriatal terminals appears to be an indispensable player in the neuroprotective activity of (endo)cannabinoids in HD models (Chiarlone et al., *Proc Natl Acad Sci U S A*. 111:8257-62, 2014).

Methods and tissues used

Ongoing studies in human samples provided by the Netherland Brain Bank are oriented to determine the precise evolution of CB1 receptor expression and distribution in the two aforementioned neuronal populations along different grades of progression of Huntington's disease.

There are not publications derived yet from the samples kindly provided by the NBB.