Neurosteroids as potential neuroprotective agents in Parkinson’s disease: implications for new therapeutic strategies.

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Research question and background
The main aim of this study is to clarify if neurosteroid biosynthetic pathway changes we found in a previous study (Luchetti et al 2010) might be a causative factor in the PD neurodegenerative process. Additionally we aim to test which neurosteroid might be a good candidate for neuroprotective action in PD brains. We will therefore ask the following specific questions about the biosynthesis and metabolism pathways of steroids in the CNS of PD:

1. How does neurosteroid synthesis change in the SN in the early stages of PD and before neurodegeneration begins?
2. Are the changes in neurosteroid synthesis in the SN of PD patients directly related to PD-specific neuropathological changes (neuronal stress, neuronal death and α-synuclein accumulation)?
3. Are neurosteroids neuroprotective in PD brain?

Methods and tissues used
Immunohistochemistry and qPCR will be used to correlate these with neuropathological PD hallmarks (e.g. α-synuclein), neuronal stress (e.g. Hsp70) and neuronal death (e.g. SMI-32, c-Jun). Frozen and paraffin embedded tissue from substantia nigra (SN), and prefrontal cortex of 8 Parkinson’s disease (PD) patients and 8 matched controls (CTR), is provided by the Netherlands Brain Bank. Part of frozen tissue will be used to quantify neurosteroids by gas chromatography mass spectrometry (GC/MS). Functional effects of different neurosteroids in the neurodegenerative process will be tested in a unique human post-mortem organotypic slice culture assay from PD prefrontal cortex, developed in our laboratory. Neurosteroid-induced gene expression changes will be evaluated using immunohistochemistry and qPCR, for neurotrophic factors, anti-inflammatory molecules and enzymes synthesizing neurotransmitters.

Results and conclusion
Preliminary qPCR results on human post-mortem organotypic slice culture assay are available for the 5 PD and 4 CTR (from 10 PD and 5 CTR already obtained). qPCR and GC/MS on frozen tissue and immunohistochemistry on paraffin tissue are ongoing.

Reference: