RAAV 2/7-MEDIATED OVEREXPRESSION OF A-SYNUCLEIN IN RAT BRAIN INDUCES RAPID DOPAMINERGIC DYSFUNCTION


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Introduction: Regulation of α-synuclein levels within the brain is thought to play a critical role in Parkinson's disease pathogenesis. In pathological conditions, the protein is present in a fibrillar, aggregated form inside cytoplasmic inclusions called Lewy bodies. We aimed to generate a robust animal model for Parkinson's disease by overexpression of A53T mutant α-synuclein in the rat substantia nigra using rAAV vectors.

Methods: Pseudotyped rAAV2/7 vectors encoding A53T α-synuclein were stereotactically injected into rat substantia nigra. Animals were analyzed at different time points using the cylinder test and immunohistochemistry. A group of animals was followed up in time by 18F-FECT-microPET imaging to monitor dopamine transporter binding and by microMRI to visualize axon degradation and cell death. To further validate our model, another group of rats was treated with FK506 daily during 1 month.

Results and conclusion: Immunohistochemical analysis at different time points after injection showed reproducible progressive loss of approximately 80% of the dopaminergic neurons at 4 weeks after injection. These changes were accompanied by a significant motor impairment which could be reversed by the administration of L-dopa. Furthermore, differences in the vector dose used allowed modulating the degree and onset of the pathology. In conclusion, targeted overexpression of α-synuclein in the SN using rAAV2/7 provides a fast and reproducible animal model for PD. This model offers interesting possibilities for testing of new experimental drugs, such as α-synuclein-based compounds. In this perspective, we are currently investigating the effect of FK506 on α-synuclein aggregation and cell death in the rat brain.