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AAV-Mediated Human A-Synuclein Expression in a Rat Model of Parkinson's Disease –Further Characterization of PD Phenotype, Fine Motor Functional Effects as Well as Neurochemical and Neuropathological Changes over Time

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Abstract : Targeted over-expression of human α-synuclein using viral-vector mediated gene delivery into the substantia nigra of rats and non-human primates has been reported to lead to dopaminergic cell loss and the formation of α-synuclein aggregates reminiscent of Lewy bodies. We have previously shown how AAV-mediated expression of α-synuclein is seen in the chronic phenotype of the rats over 16 week follow-up period. In the context of these findings, we attempted to further characterize this long term PD related functional and motor deficits as well as neurochemical and neuropathological changes in AAV-mediated α-synuclein transfection model in rats during chronic follow-up period. Different titers of recombinant AAV expressing human α-synuclein (A53T) were stereotaxically injected unilaterally into substantia nigra of Wistar rats. Rats were allowed to recover for 3 weeks prior to initial baseline behavioral testing with rotational asymmetry test, stepping test and cylinder test. A similar behavioral test battery was applied again at weeks 5, 9,12 and 15. In addition to traditionally used rat PD model tests, MotoRater test system, a high speed kinematic gait performance monitoring was applied during the follow-up period. Evaluation focused on animal gait between groups. Tremor analysis was performed on weeks 9, 12 and 15. In addition to behavioral end-points, neurochemical evaluation of dopamine and its metabolites were evaluated in striatum. Furthermore, integrity of the dopamine active transport (DAT) system was evaluated by using 123I- β-CIT and SPECT/CT imaging on weeks 3, 8 and 12 after AAV- α-synuclein transfection. Histopathology was examined from end-point samples at 3 or 12 weeks after AAV- α-synuclein transfection to evaluate dopaminergic cell viability and microglial (Iba-1) activation status in substantia nigra by using stereological analysis techniques. This study focused on the characterization and validation of previously published AAV- α-synuclein transfection model in rats but with the addition of novel end-points. We present the long term phenotype of AAV- α-synuclein transfected rats with traditionally used behavioral tests but also by using novel fine motor analysis techniques and tremor analysis which provide new insight to unilateral effects of AAV α-synuclein transfection. We also present data about neurochemical and neuropathological end-points for the dopaminergic system in the model and how well they correlate with behavioral phenotype.

Keywords : adeno-associated virus, alphasynuclein, animal model, Parkinson’s disease
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