A53T ALPHA-SYNUCLEIN PROMOTES A RAPID NEURODEGENERATION AND MOTOR DEFICIT FOLLOWING AAV VECTOR MEDIATED EXPRESSION IN THE RAT SUBSTANTIA NIGRA.

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Hereditary forms of Parkinson's disease can be caused by duplication, triplication and missense mutations in the alpha-synuclein encoding gene (e.g. A53T). Adeno-associated viral (AAV) vector mediated expression of alpha-synuclein in different forms provides a means for studying alpha-synuclein-induced motor deficits and pathology in animal models. Attempts with different AAV serotypes generate mixed results. This study investigates the effects of AAV serotype 5 with insert for human wildtype alpha-synuclein (AAV5-CBA-alpha-synuclein$^{1x1013vg/ml}$) and AAV serotype 1/2 with insert for human A53T alpha-synuclein (AAV1/2-CMV-A53T-alpha-synuclein$^{>5x1012vg/ml}$) delivery to the rat substantia nigra$^{(SN)}$ and assesses motor behavioural deficits and dopamine neuronal cell loss. AAV empty-vector, AAV-enhanced-green-fluorescent-protein$^{(eGFP)}$ and phosphate buffered saline$^{(PBS)}$ were included as controls. Male and female rats received a unilateral stereotaxic injection into the SN. Vector-mediated expression of alpha-synuclein was assessed at multiple timepoints post-injection, and behavioural tests of motor function and immunohistochemical analysis of dopaminergic cell loss were conducted. AAV5 successfully transduced and expressed alpha-synuclein in nigral dopaminergic neurons 12 weeks post-injection, with forelimb-use asymmetry and impaired skilled forelimb function evident, however there was no significant nigral dopaminergic cell loss. Dopamine cell loss was apparent in the AAV5-eGFP group, compared to both the AAV5 alpha-synuclein and PBS groups. Motor behavioural deficits became evident 3 weeks post-AAV1/2 A53T delivery with alpha-synuclein expression and dopaminergic cell loss evident in the SN 4 weeks post-vector delivery. In conclusion, delivery of AAV1/2 to express human A53T alpha-synuclein in the rat SN provides a rapid and progressive course of alpha-synuclein aggregation, accompanied by dopaminergic nigrostriatal degeneration and associated motor deficits.