α-Synuclein A53T Mice Present with Progressive Motor Decline

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Background

Aggregation of α-Synuclein (α-Syn) plays a central role in Parkinson's disease (PD). α-Syn over-expressing mice are therefore a suitable model to study α-Syn production, sequestration and deposition and the possible influences of drugs on these parameters. Point mutations in α-Syn (e.g. A53T, A30P, E46K) have been identified in rare forms of familial PD and are reported to accelerate its oligomerization and aggregation. In subjects affected by the α-Syn A53T mutation, the age of onset is much earlier than for sporadic PD. The development of new PD drugs halting the production of α-Syn aggregates and the resulting neurodegeneration is thus the main focus in PD research. To be able to test these new drugs, appropriate animal models are needed.

Methods

We characterize transgenic mice over-expressing mutated human α-Syn-A53T under control of the human PDGF-β promoter on a C57Bl/6 background ["A53T" mice (Hashimoto et al., 2003: Ann NY Acad Sci 991:171-88)]. Male and female A53T mice and non-transgenic littermates were tested at 3, 6 and 9 months in a test battery, including the Irwin test, open field, rotarod, challenging beam walk, two choice swim test and fear conditioning task. A quantitative immunohistological analysis of human α-Syn (15G7, Enzo Life Sciences, USA) and pan α-Syn (4D6, abcam, UK) levels was performed *ex vivo*.

Results

Starting at 6 months of age, A53T α-Syn transgenic mice display severe motor deficits as analyzed with the rotarod (Fig. 1) and the challenging beam walk (Fig. 2). Analysis of animals in the two choice swim test and the fear conditioning task up to an age of 9 months, revealed no cognitive deficits (Fig. 3). These data are unbiased by any changes in general health and activity (data not shown). Throughout different regions of the mouse brain, expression and distribution of endogenous (murine) and transgenic (human) α-Syn isoforms are altered (Fig. 4).

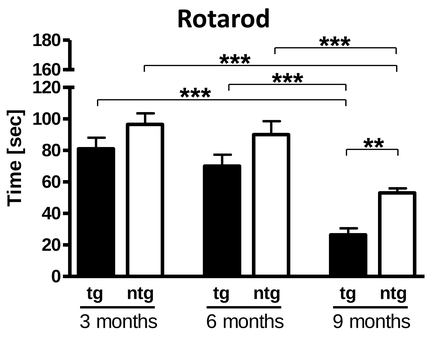


Fig. 1: Rotarod of A53T α-Syn transgenic mice. Time on the rotarod of 3, 6 and 9 months old transgenic (tg) and non-transgenic (ntg) mice (n = 12). **P<0.01 (two-way ANOVA); asterisks in graph represent results of *post hoc* analysis. Age-dependent decline and transgene-associated impairment of motor coordination interact, resulting in shorter time on the rotarod of tg mice at 9 months.

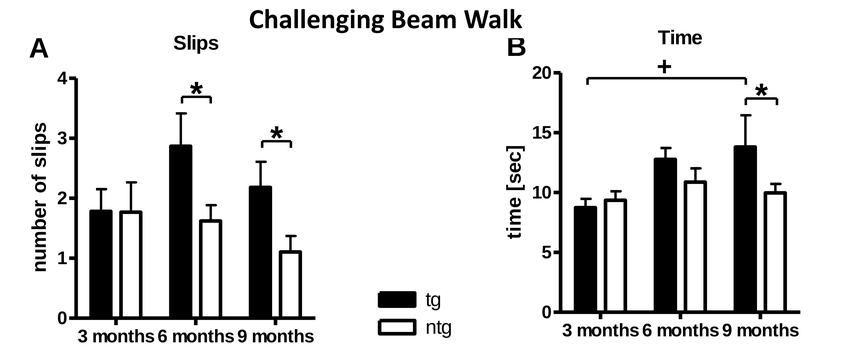


Fig. 2: Challenging beam walk of A53T α-Syn transgenic mice. Number of slips (A) and time to traverse (B) of 3, 6 and 9 months old transgenic (tg) mice compared to non-transgenic (ntg) littermates (n = 12). *P<0.05. * significant differences between genotypes within one age (t-test); + significant differences in progression (two-way ANOVA).

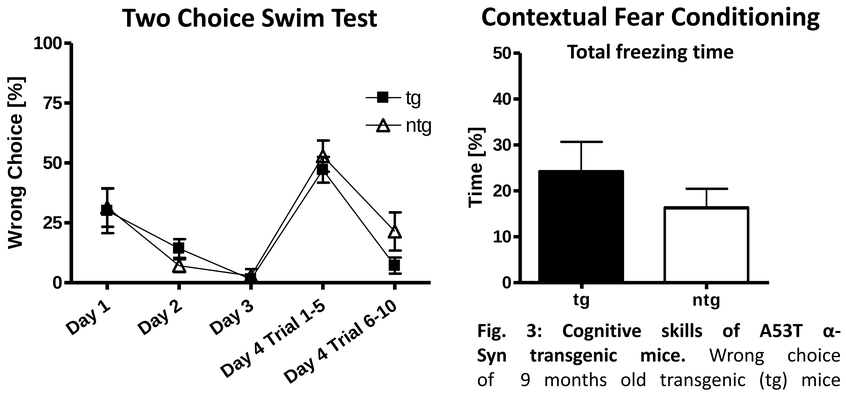
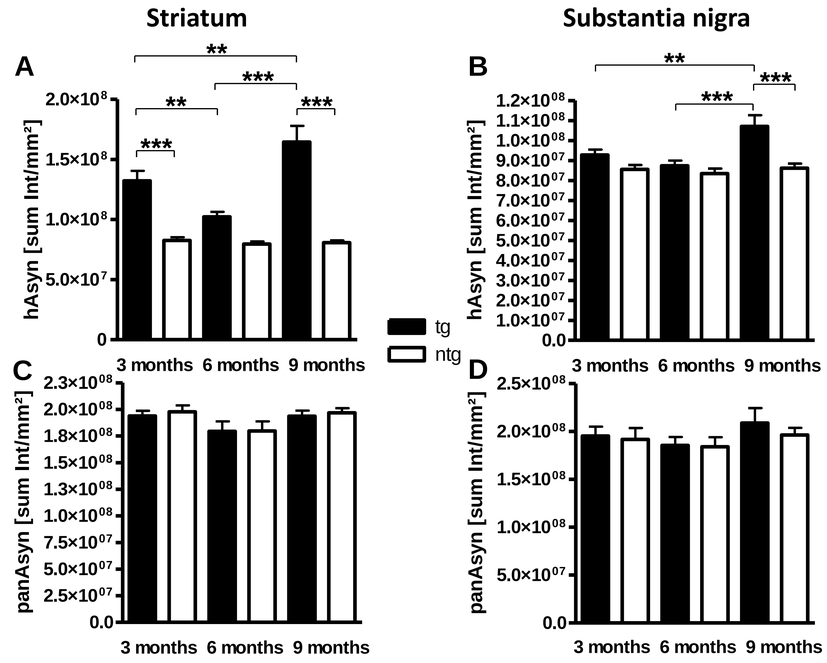


Fig. 3: Cognitive skills of A53T α-Syn transgenic mice. Wrong choice of 9 months old transgenic (tg) mice compared to non-transgenic (ntg) littermates (n = 12) in the two choice swim test (A) and time spent in the dark compartment in percent of 9 months old tg mice compared to ntg littermates (n = 12) in the contextual fear conditioning test (B). A: Analyzed by two-way ANOVA. B: Analyzed by t-test.

Conclusions

Behavioral motor deficits occur in parallel with an increase of human α-Syn accumulation in the dopaminergic system. The A53T α-Syn transgenic mouse is a suitable model for α-Syn dependent familial Parkinson's disease research, since it illustrates major behavioral hallmarks of PD. This model imitates critical clinical features of PD, and it therefore represents a valuable tool for both basic research related to PD as well as for efficacy tests investigating new compounds against PD.



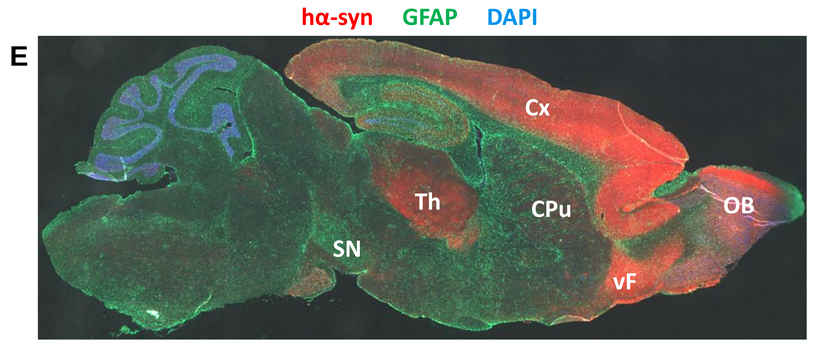


Fig. 4: Immunofluorescence of α-Syn isoforms. Quantification of human α-Syn (**A,B**) and pan α-Syn (**C,D**) in the striatum (CPu) and the substantia nigra (SN) of 3, 6, and 9 months old A53T α-Syn mice compared to non-transgenic littermates. Note the age-dependent increase of A53T α-Syn in either brain area. (**E**) Multichannel immunofluorescence labeling shows the staining pattern of human α-Syn (*red channel*), astrocytes (GFAP, *green*), and the nuclear dye DAPI *(blue)*. Note the very strong expression of A53T α-Syn in the neocortex (Cx), thalamus (Th), ventral forebrain (vF), and olfactory bulb (OB). **P<0.01, ***P<0.001; one-way ANOVA with *post-hoc* analysis.

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We would be happy to test your compound in our α-synuclein A53T transgenic mouse!
Please contact us to support your drug development program.

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