Progressive motor deficits in α-synuclein A53T mice as a model of Parkinson's disease

Havas D.[1], Amschl D.[1], Neddens J.[1], Windisch M.[1], Römer H.[2], Masliah E.[3], Hutter-Paier B.[1]

[1]QPS-Austria, Parkring 12, 8074 Grambach, Austria,[2] Karl-Franzens Univ., Inst. of Zoology, 8010 Graz, Austria,[3] Univ. of California San Diego, Dep. of Pathology, La Jolla, CA, USA

Background

Aggregation of α-Synuclein (α-Syn) plays a central role in human 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

Here, 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 [1]). Male and female A53T mice and non-transgenic littermates were tested at three age groups (3, 6 and 9 months) in a behavioral test battery, including the Irwin test, Open Field, Challenging Beam Walk, RotaRod, Two Choice Swim Test and Fear Conditioning Task. A quantitative histological analysis of human (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 Challenging Beam Walk test (Fig. 1) and the RotaRod test (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 were 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) expression of α-syn isoforms was altered (Fig. 4).

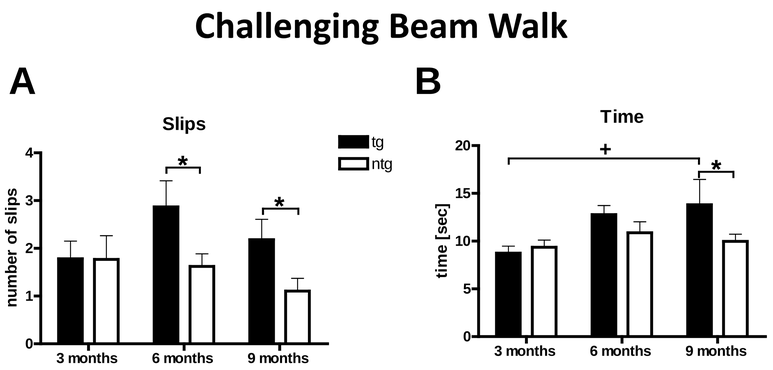


Fig. 1: Challenging Beam Walk of A53T α-Syn transgenic mice. Number of slips (A) and time to traverse (B) of 3, 6 and 9 months old transgenic (tg) mice compared to non-transgenic (ntg) littermates (n = 12). *P<0.05. * significant differences between genotypes within one age (t-test); + significant differences in progression (Two-Way ANOVA).

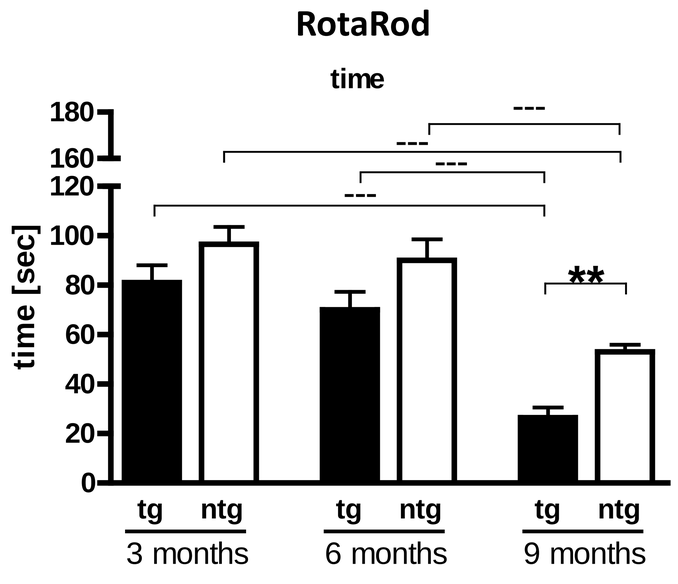


Fig. 2: RotaRod of A53T α-Syn transgenic mice. Time on the RotaRod of 3, 6 and 9 months old transgenic (tg) mice compared to non-transgenic (ntg) littermates (n = 12). **P<0.01. (Two-Way ANOVA).

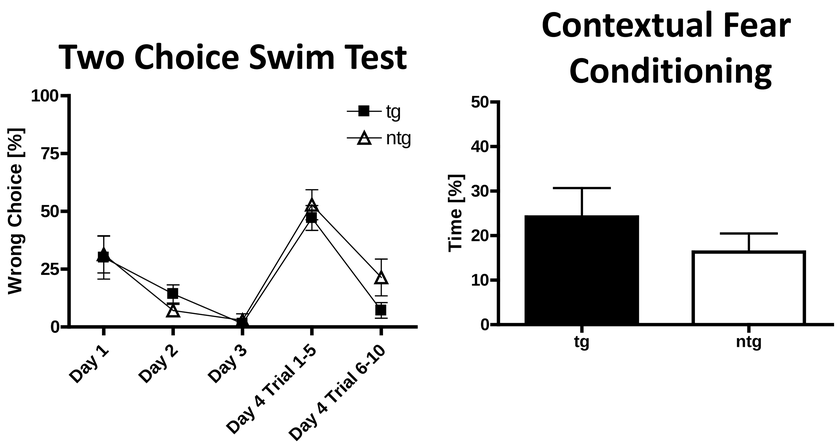
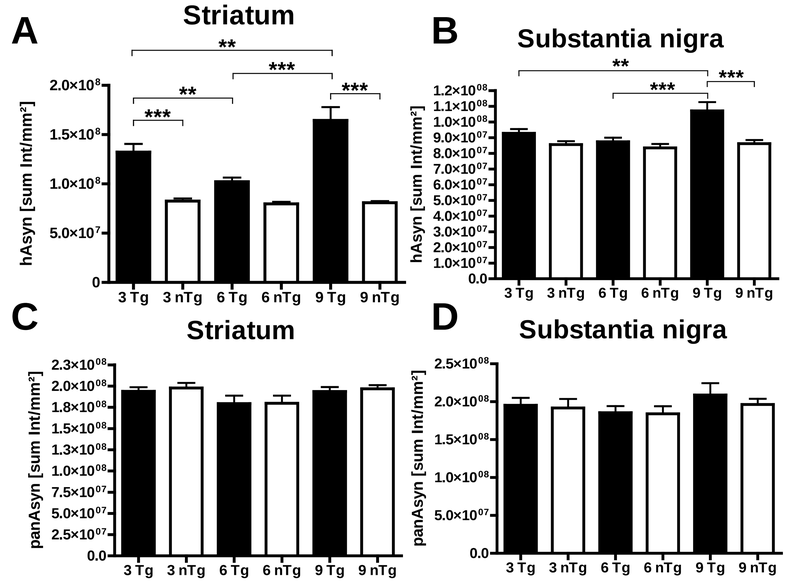


Fig. 3: Cognitive skills of A53T α-Syn transgenic mice. Wrong choice of 9 months old transgenic (tg) mice compared to non-transgenic (ntg) littermates (n = 12) in the Two Choice Swim test (A) and time spent in the dark compartment in percent of 9 months old tg mice compared to ntg littermates (n = 12)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

[1] Hashimoto M, Rockenstein E, Masliah E. Transgenic models of alpha-synuclein pathology: past, present, and future. Ann N Y Acad Sci. 2003 Jun;991:171-88. PMID:12846986



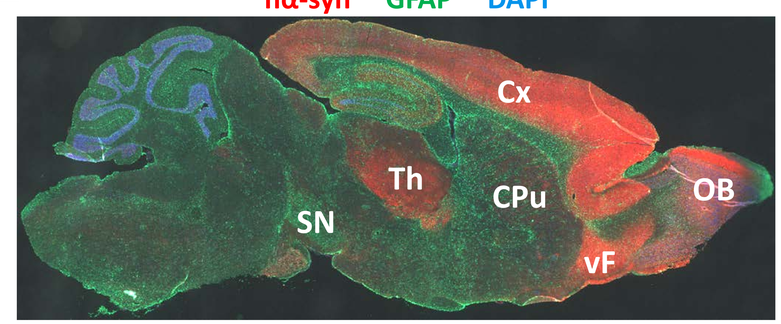


Fig. 4: Quantification of human (A,B) and pan α-Syn (C,D) in the striatum (CPu) and the substantia nigra (SN) of 3, 6, and 9 months old A53T α-Syn transgenic mice compared to non-transgenic littermates. Note the age-dependent increase of A53T α-Syn in either brain area. (E) Multichannel immunofluorescence labeling shows the staining pattern of human α-Syn (*red channel*), astrocytes (GFAP, *green channel*), and the nuclear dye DAPI *(blue channel)*. 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.

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. Because this model imitates critical clinical features of PD, it represents a valuable tool for fundamental PD research as well as for efficacy tests investigating new compounds against PD.

CONTACT
Birgit Hutter-Paier, PhD
Director Neuropharmacology Department
Birgit.Hutter-Paier@qps.com