Acute and chronic ER-stress-induced animal models of Parkinson's disease

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BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to impairments of motor and cognitive functions. Although the etiology is still not known, α-synuclein aggregation plays an important role in PD pathogenesis, which may be associated to some pathological processes such as endoplasmic reticulum (ER) stress.

Rotenone is a well-known ER stressor able to reproduce many critical features of PD in animal models. In the present study, we aim to characterize and compare the behavioral hallmarks of ER stress-induced mouse models using different treatment protocols with rotenone.

MATERIALS and METHODS

For a chronic model, 2 months old C57BL/6JRj mice were orally daily treated with rotenone (30 mg/kg) or vehicle (4% CMC and 1.25% chloroform) and weekly subjected to beam walk test and RotaRod test for 15 weeks.

For an acute model, 2 months old C57BL/6JRj mice were injected with rotenone at different concentrations directly into the right striatum: 3 µg and 5.4 µg of rotenone in a final volume of 1.5 µL. All animals were weekly subjected to the D-amphetamine-induced rotation test and beam walk test for 4 weeks.

RESULTS – chronic model

Evaluation of the chronic model for motor deficits in the beam walk test showed a tendency of a higher number of slips while crossing the different tested beams for rotenone-treated animals when comparing to the vehicle-treated group after 4 weeks of daily oral treatment (Figure 1). Further analysis of animals in the RotaRod test showed significant differences in the latency to fall off the rotating rod after 11, 12 and 13 weeks of treatment (Figure 2). The observed trend to fall earlier from the RotaRod was maintained until week 15 of treatment.

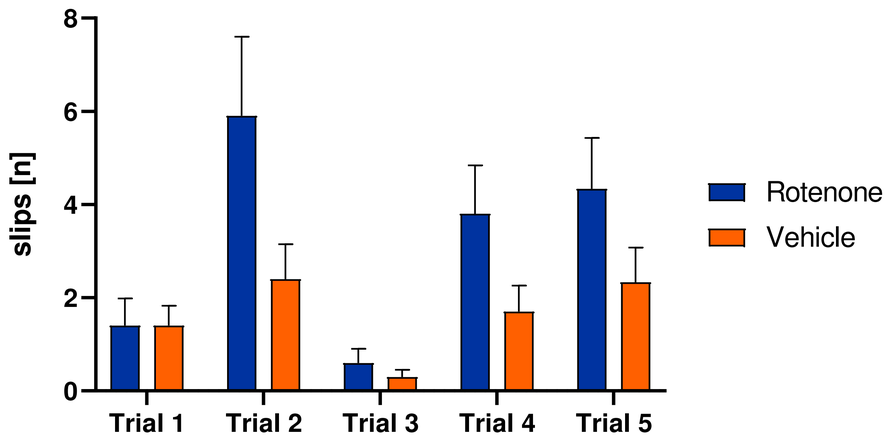

Figure 1 : Beam walk test of the chronic model after 4 weeks of daily oral treatment with rotenone (30 mg/kg). Number of total slips (n) while crossing the different beams 1 - 5. Trial 1: 13 mm square beam; trial 2: 10 mm square beam; trial 3: 28 mm round beam; trial 4: 16 mm round beam; trial 5: 11 mm round beam. Graph shows mean ± SEM. Each trial was evaluated independently by an unpaired t-test assuming a Gaussian distribution. n= 10 /group.

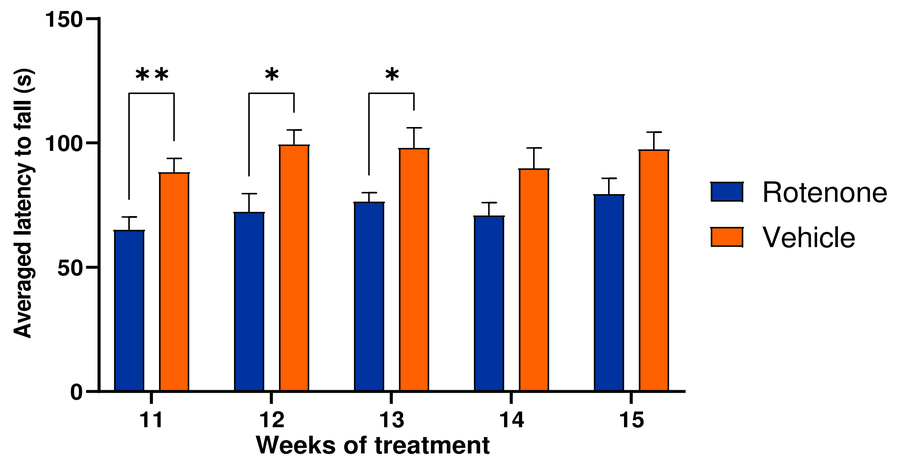

Figure 2: RotaRod test of the chronic model after oral rotenone (30 mg/kg/day) treatment. Latency to fall off the RotaRod in treatment weeks 11 to 15. The latency to fall from the accelerating RotaRod was measured in three trials per day. Graph shows mean + SEM of the performed three trials over time. Two-way ANOVA with Fisher´s LSD test; * p<0.05, **p<0.01. n = 10 per group.

RESULTS – acute model

Evaluation of the acute rotenone mouse model for motor deficits in the beam walk test resulted in a higher number of total slips for the rotenone-injected mice over time, which was concentration dependent (Figure 3). When analyzing the type of slips, there was a significant increase in the number of contralateral slips when crossing a 10 mm squared beam after 1 and 4 weeks (Figure 4A and 4B, respectively), suggesting a unilateral lesion in the brain.

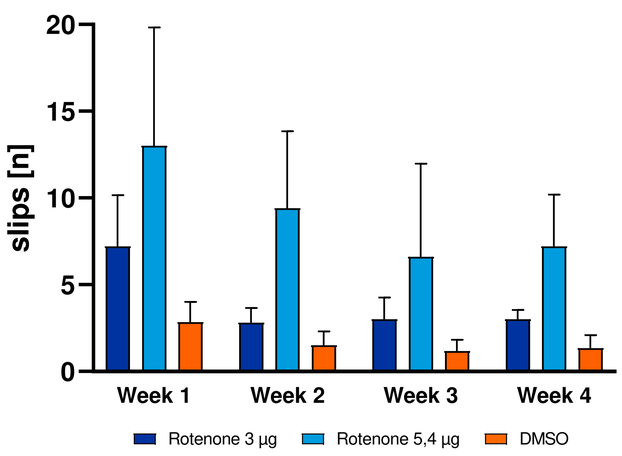

Figure 3: Beam walk analysis after inducing ER stress in the stiatum. Number of total slips (n) when crossing a 13 mm square beam over time. Graph shows mean ± SEM. Two-way ANOVA followed by Fisher´s LSD test. n = 5-6/ group.

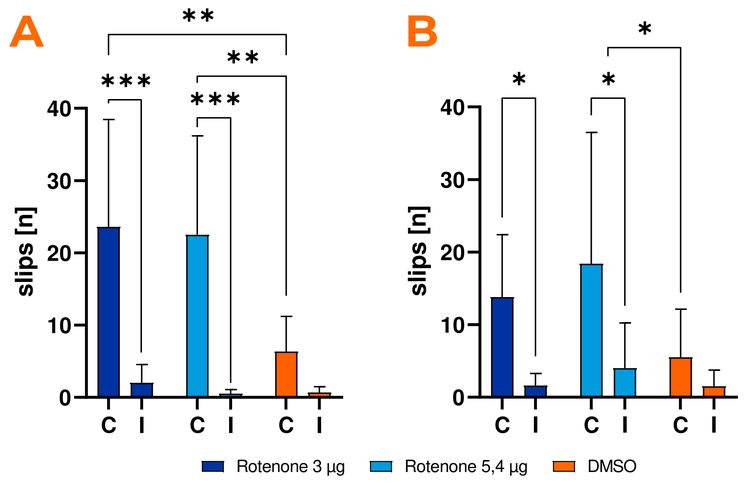

Figure 4: Analysis of the slips performed in the beam walk test when crossing a 10 mm square beam. Number of contralateral and ipsilateral slips A) 1 week after surgery and B) 4 weeks after surgery. Graphs show mean ± SEM of slips. Two-way ANOVA followed by Fisher´s LSD test. *p<0.05, **p<0.01, ***p<0.001. n = 5-6/ group. C: contralateral slips; I: ipsilateral slips.

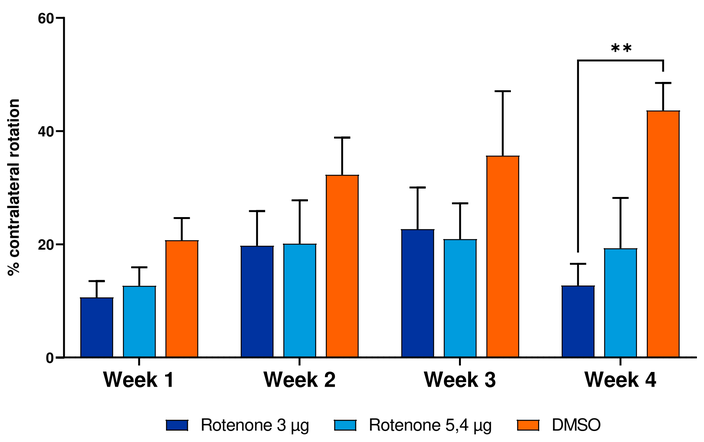

Figure 5: D-amphetamine (2.5 mg/kg, i.p.) induced rotation test analysis. Percentage of contralateral rotations over time. D-amphetamine was injected 5 minutes prior to the test and all animals were recorded for 40 minutes. Graph shows mean ± SEM. Two-way ANOVA, followed by Fisher´s LSD test. **p <0.01. n = 5-6/ group.

Even though the results for the acute model are very promising, a bigger group size is needed for more statistically significant and robust results. Moreover, histological analysis are currently performed to confirm the unilateral lesion and correlate data with behavioral results.

SUMMARY and CONCLUSION

The chronic rotenone model shows a weak motor phenotype over time. Further histological analyses are currently performed to evaluate rotenone-induced histological features such as reduction of tyrosine hydroxylase protein. In contrast, the acute model showed stronger motor impairments, but further histological analyses are currently performed to confirm the unilateral lesion.

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