Pathological hallmarks of a genetic and an induced Gaucher disease mouse model

**BACKGROUND**

Gaucher disease is the most common lysosomal storage disease. The neuronal disease variant is characterized by aggregated protein accumulations in the brain and associated neurological manifestations. The disease is autosomal recessively inherited and modeled by 4L/PS-NA mice that express low levels of prosaposin and saposins, as well as β-glucosidase (GCase) with a point mutation at V394L/V394L. Additionally, the disease can be modeled by treating mice with Condurotol-beta-Epoxide (CBE) a specific inhibitor of GCase activity.

To use these models for compound tests against the Gaucher disease a detailed characterization of these mice is needed. We thus analyzed 4L/PS-NA mice for their neuro- and non-neuropathic features and CBE-treated wildtype mice for their neuropathic phenotype.

**MATERIALS AND METHODS**

4L/PS-NA mice were tested behaviorally in the Wire Suspension test at the age of 8, 12, and 18 weeks as well as in the Rota Rod test at 12 and 18 weeks of age. Wildtype mice lacking endogenous α-synuclein (C57BL/6JLoaHsd) were treated for 15 days daily intraperitoneally with 100 mg/kg CBE starting at 6 months of age. One day after the last treatment, animals were investigated in the Open Field test and on the second day in the Beam Walk test.

Furthermore, brain tissue of both models was analyzed for neuroinflammation by histological methods. The 4L/PS-NA mouse model was additionally examined for visceral symptoms.

**RESULTS**

**4L/PS-NA mouse model**

- **Wire Suspension and Rota Rod Impairment in 4L/PS-NA mice.**
- Representative images of GFAP (red), IBA-1 (green) and DAPI (blue, merge only) labeling of the hippocampal CA1 region in 18 weeks old 4L/PS-NA mice and control mice. GFAP (B) and IBA-1 (C) immunoreactive (IR) area in percent in the cortex of 5, 12 and 18 weeks old 4L/PS-NA mice compared with controls. Two-way ANOVA followed by Bonferroni’s post hoc test. Mean + SEM, n=5, differences between genotypes/age groups: *p<0.05, **p<0.01.

**Neuroinflammation**

- **GFAP IR area [%]**
- **Vehicle**
- **CBE**

**CBE-induced mouse model**

- **Behavioral Phenotype**
- **Open Field**
- **Beam Walk**

**Neuroinflammation**

- **Vehicle**
- **CBE**

**CONCLUSION / SUMMARY**

In summary, 4L/PS-NA mice present with highly increased glial activation in the brain that is accompanied by strong motor deficits suggesting that 4L/PS-NA mice are a good model to study chronic neuropathic type 3 Gaucher disease. Additionally, 4L/PS-NA mice present early alterations in visceral organs and thus further mimicking the non-neuropathic phenotype of Gaucher disease. Treatment with CBE causes no motor deficits but strong neuroinflammation, suggesting that this induced model has in total a weaker phenotype compared to the 4L-NA mouse model.