Neuroinflammation in Mouse Models of Two Different Lysosomal Storage Diseases

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BACKGROUND

Lysosomal Storage Diseases (LSDs) are a group of metabolic disorders that are caused by defects in the lysosomal pathway. All LSDs are characterized by an abnormal accumulation of lysosomal substrates. In some diseases accumulations can only be observed in visceral organs while in other diseases also the brain is affected causing secondary pathologies like neuroinflammation. Neuroinflammation is thus valuable for the evaluation of compound effects. We therefore compared neuroinflammatory pathology in three LSD mouse models.

MATERIALS and METHODS

All models were analyzed for activated microglia and astrocytosis in distinct brain regions using quantitative image analysis of immunostainings. The following models were evaluated:

I: 4L/PS-NA transgenic mice as model of Gaucher disease express low levels of prosaposin and saposins, as well as a functionally impaired β-glucosidase with a homozygous point mutation at V394L.

II: CBE-treated mice as model of Gaucher disease.

III: NPC1$^{-/-}$ mice as model of Niemann-Pick type C1 disease. Animals are homozygous for the recessive NIH allele of the Niemann Pick type C1 gene and have a premature truncation of the protein deleting 11 out of 13 transmembrane domains leaving the first two transmembrane domains intact.

RESULTS

4L/PS-NA mice

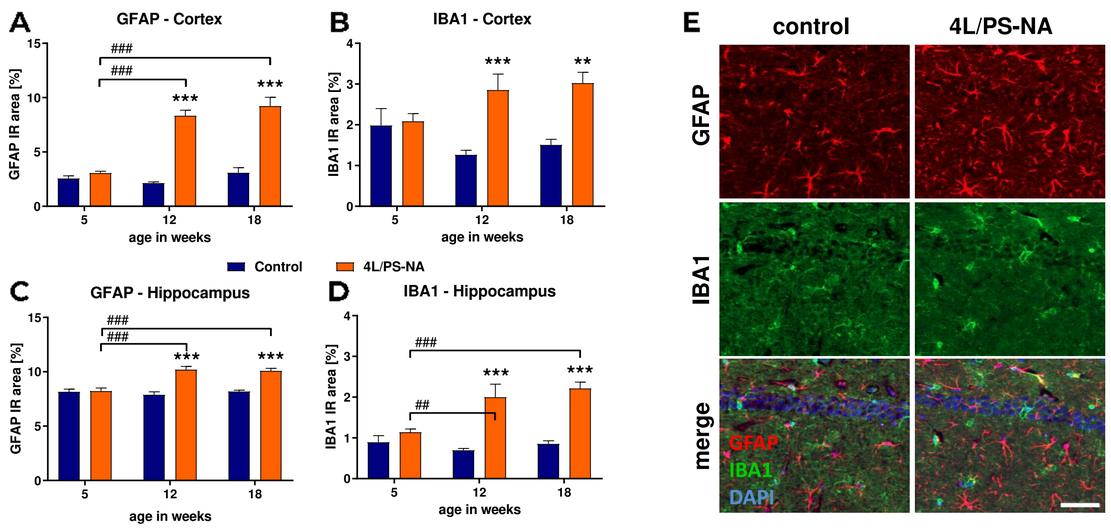


Figure 1. Quantification of astrocytosis and activated microglia in 4L/PS-NA mice over age. The cortex (**A, B**) and hippocampus (**C, D**) of 4L/PS-NA mice were analyzed for astrocytosis (GFAP; **A, C**) and activated microglia (IBA1; **B, D**) immunoreactive area (IR) in percent at the age of 5, 12 and 18 weeks compared to control littermates. Two-way ANOVA followed by Bonferroni's *post hoc* test. n = 5 per group. Mean + SEM. *differences between genotypes; #differences between age groups; *p<0.05; **p<0.01; ***p<0.001. **E**: Representative images of GFAP, IBA1 and DAPI labeling of the hippocampal CA1 region in 18 week old 4L/PS-NA and control mice. Scale bar: 50 µm.

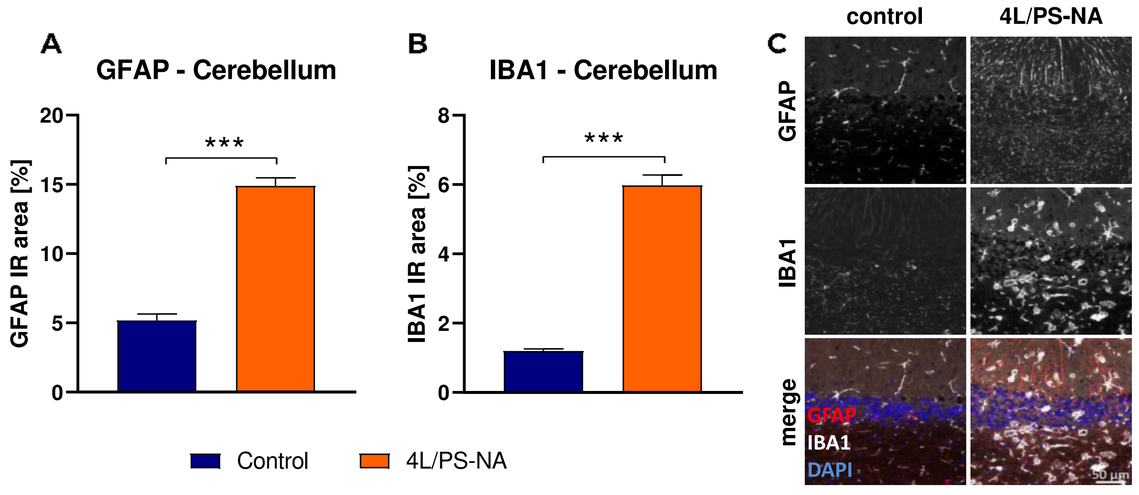


Figure 2. Quantification of astrocytosis and activated microglia in the cerebellum of 4L/PS-NA mice. The cerebellum of 4L/PS-NA mice was analyzed for astrocytosis (GFAP; **A**) and activated microglia (IBA1; **B**) immunoreactive area (IR) in percent at the age of 18 weeks compared to control littermates. Unpaired Student's t-test. n = 5 per group. Mean + SEM. ***p<0.001. **C**: Representative images of GFAP, IBA1 and DAPI labeling of the cerebellum in 18 week old 4L/PS-NA and control mice. Scale bar: 50 µm.

RESULTS

CBE-treated mice

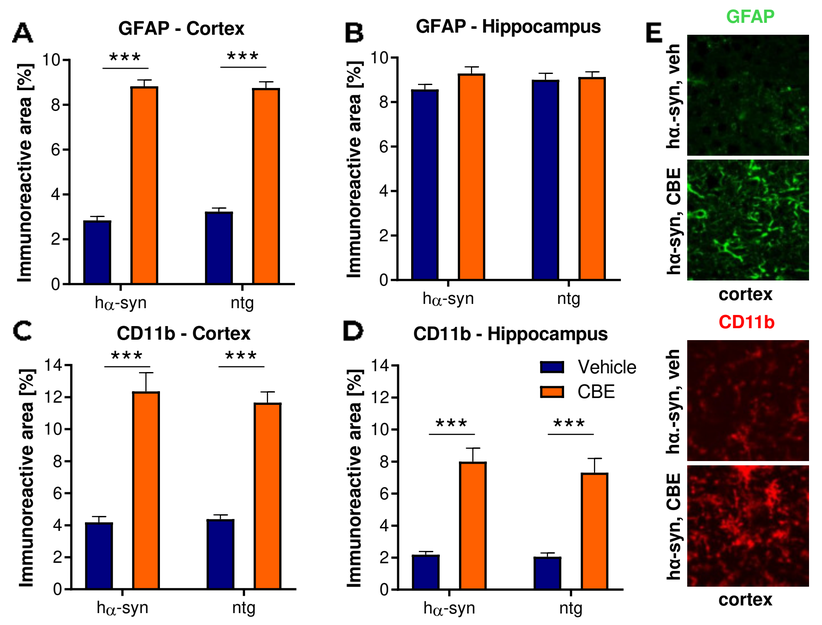
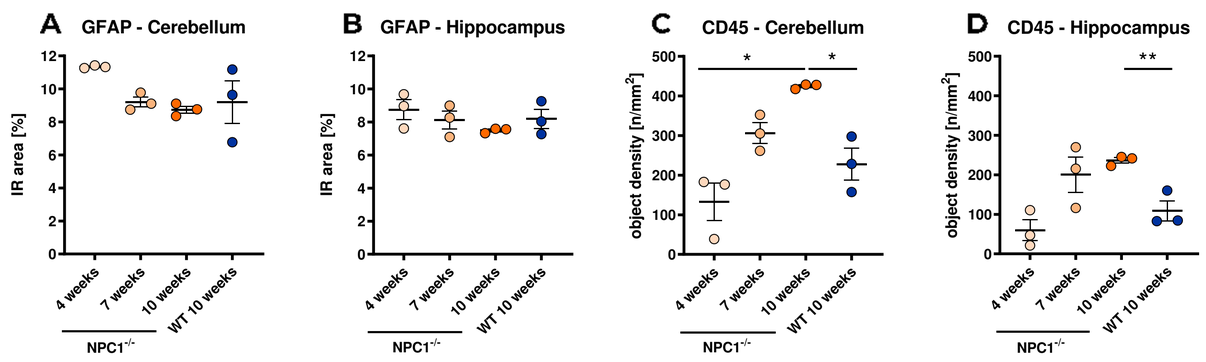


Figure 3: Quantification of astrocytosis and activated microglia in D-Line transgenic mice (PDGF promoter driving wild type α-synuclein) and non-transgenic (ntg) littermates after CBE treatment. GFAP (**A, B**) and CD11b (**C, D**) immunoreactive area in percent in the cortex (**A, C**) and hippocampus (**B, D**). Mean + SEM; n = 12 per group; Two-way ANOVA with Bonferroni's *post hoc* test; ***p<0.001.

NPC1$^{-/-}$ mice



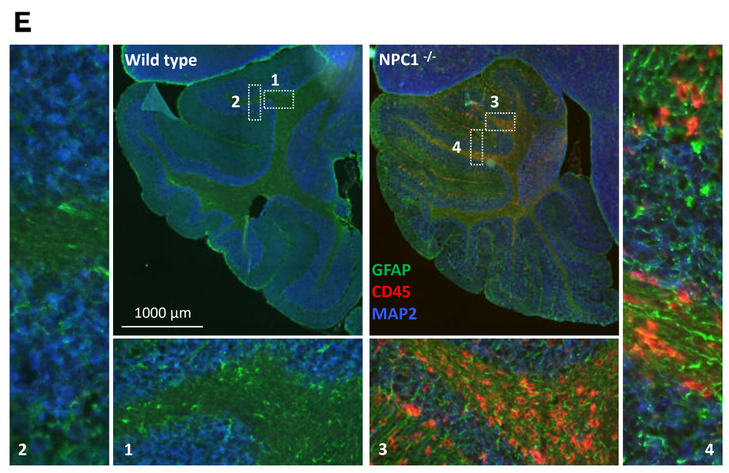


Figure 4. Neuroinflammation in NPC1$^{-/-}$ mice. The cerebellum (**A, C**) and hippocampus (**B, D**) of NPC1$^{-/-}$ mice were analyzed for astrocytosis (GFAP; **A, B**) and activated microglia (CD45; **C, D**) at the age of 4, 7 and 10 weeks. 10 week old wild type animals served as controls. (n = 3 per group). One-way ANOVA. Differences between 10 week old mice were analyzed by unpaired Student's t-test for CD45 expression in the cerebellum and hippocampus. Mean ± SEM. *p<0.05, **p<0.01.

SUMMARY and CONCLUSION

Our results suggest that CBE-treated mice are a valuable model of cortical neuroinflammation while 4L/PS-NA and NPC1$^{-/-}$ mice are models of cortical and subcortical neuroinflammation.

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