Neuroinflammation in Mouse Models of Two Different Lysosomal Storage Diseases

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, 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 CI disease. Animals are homozygous for the recessive NIH allele of the Niemann-Pick type CI gene and have a premature truncation of the protein deleting 11 out of 13 transmembrane domains leaving the first two transmembrane domains intact.

RESULTS

Our results show severe neuroinflammation in the cortex, hippocampus and cerebellum of 4L/PS-NA by GFAP and IBA1 labelling. In CBE-treated D-Line (PDGF promoter driving wild type α-synuclein) and wild type mice strong astrocytosis could be detected in the cortex, while activated microglia could be observed in the cortex and the hippocampus. In NPC1-/- mice neuroinflammation was measurable by CD45 activated microglia labelling in the hippocampus and cerebellum.

CBE-treated mice

4L/PS-NA mice

NPC1-/- mice

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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