

Introduction

In Alzheimer's disease (AD), astrocytes have been shown to respond to both soluble amyloid beta ($A\beta$) and phosphorylated tau, as well as to amyloid plaques and neurofibrillary tangles, leading to chronic brain astrogliosis. Importantly, astrocytes are the primary brain cells that synthesize apolipoprotein E (apoE), strongly linking these star-shaped glia with the strongest genetic risk factor for AD (i.e. APOE4 allele). On the other hand, previous lipidomics and mechanistic studies from our laboratory have demonstrated that (1) the content of brain sulfatide, a myelin enriched lipid, is dramatically reduced at the earliest clinically recognizable stage of AD; (2) brain sulfatides are transported by apoE in an isoform-specific manner; and (3) $A\beta$ mediates sulfatide deficiency in an apoE-dependent manner. Seeking to better understand the consequences of sulfatide deficiency in AD, we characterized the brains of sulfatide depleted animals, i.e. cerebroside sulfotransferase (CST) knockout mice.

Abstract

Sulfatide and astrocytes both play important roles in maintaining CNS homeostasis, however, the association between them remains unclear. To gain insights into the underlying consequences and mechanisms of severe ST deficiency in regards to astrocyte homeostasis, we exploited CST knockout mice and found substantial astrogliosis, as evidenced by a dramatic increase in gene and protein expression levels of myelin-associated glial fibrillary acidic protein (GFAP) within both white and gray matter regions. Mechanistic studies showed that although apoE is necessary for sulfatide deficiency to occur in apoE4, AD, and aging, our data from apoE knockout and apoE/CST double knockout mice demonstrated that once ST depletion occurs, apoE is dispensable for astrogliosis. Furthermore, we show that sulfatide deficiency induces astrogliosis via the activator of transcription 3 (STAT3) pathway, independently of Smad2/3 activation. Thus, we provide novel insights into the molecular mechanisms by which sulfatide deficiency induces astrogliosis in vivo.

Materials and Methods

The animals include CST wildtype, heterozygote, and knockout mice. As well as CST and ApoE double knockout mice. Brain samples were analyzed by Western blot, immunofluorescence, real-time PCR, and mass spectrometry.

Results

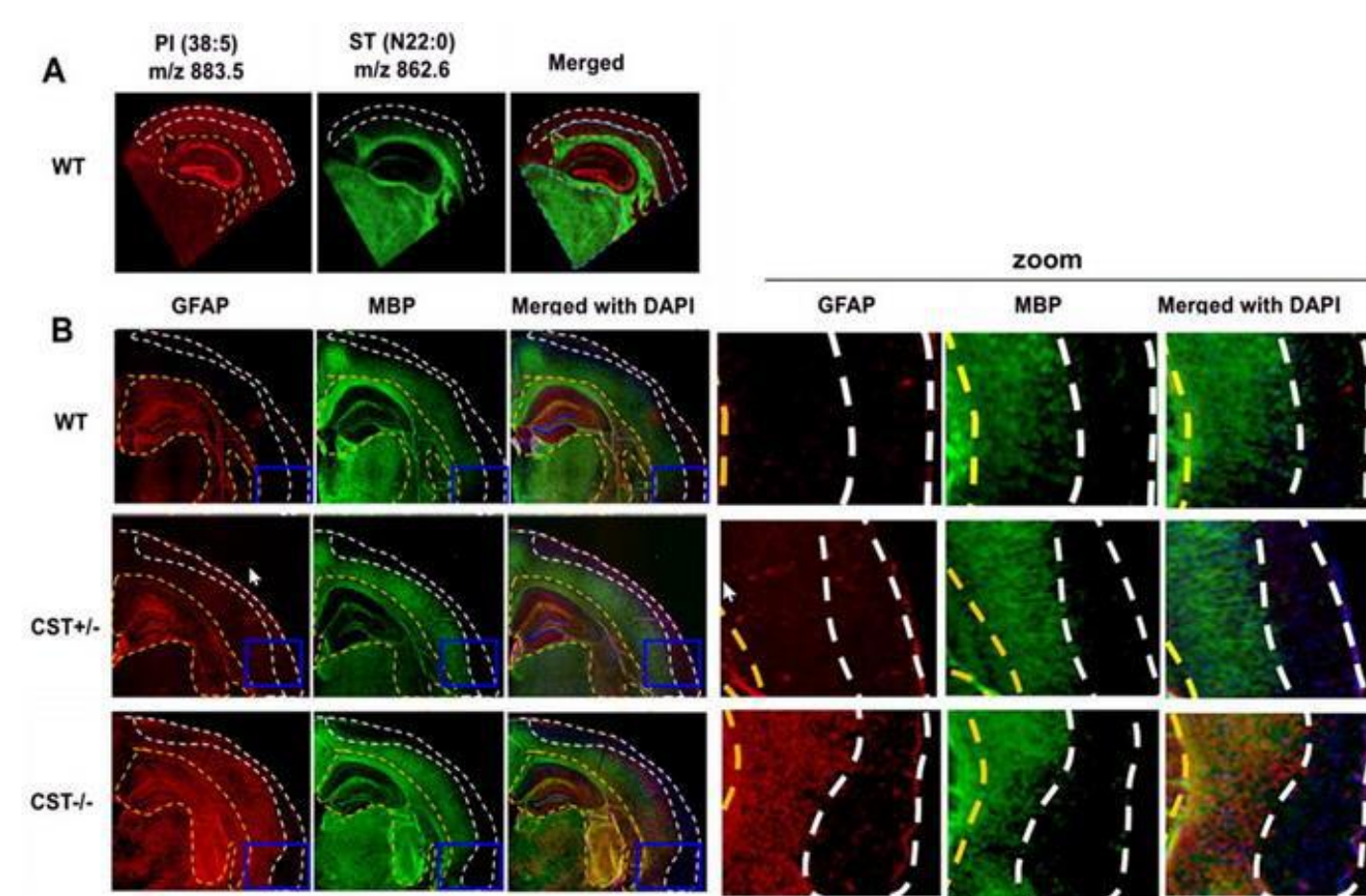


Figure 1. Sulfatide depletion leads to chronic reactive astrogliosis in the brain of CST^{-/-}, primarily within myelin-rich regions. Sulfatide and MBP are primarily found in the myelin.

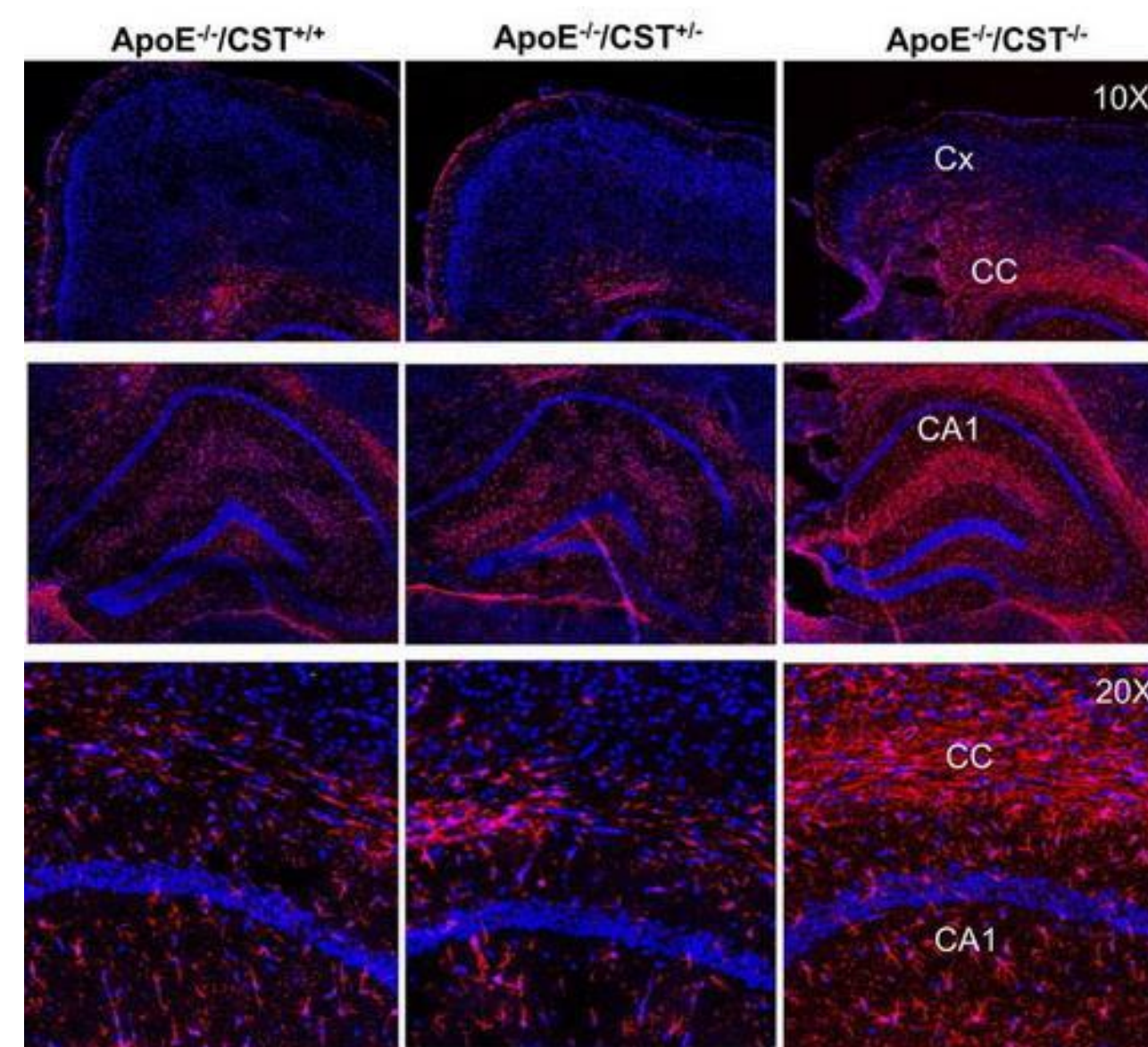


Figure 2. Sulfatide depletion induces astrogliosis independently of ApoE.

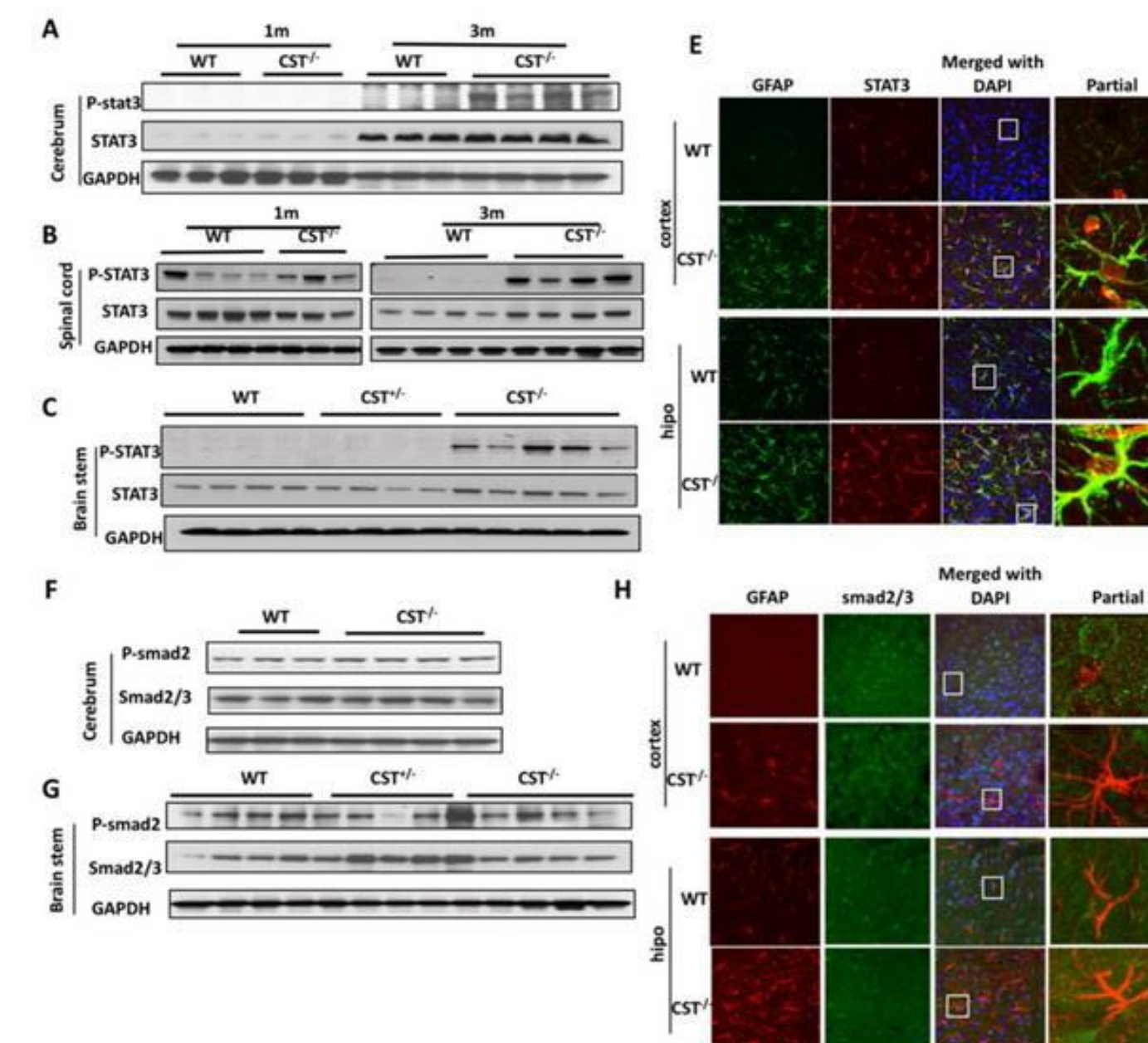


Figure 3. Sulfatide depletion induces astrogliosis via activation of STAT3 but not Smad2/3.

Conclusions

1. We found that sulfatide depletion leads to chronic reactive astrogliosis. Histological characterization revealed activation of fibrous astrocytes within myelin regions. Finally, CST/apoE double KO mice revealed that sulfatide depletion induces astrogliosis in an apoE-independent manner.
2. Our results strongly suggest that sulfatide deficiency represents a novel mechanism by which widespread astrogliosis is chronically induced in AD brains. Taken together, our results from this and other studies advise that sulfatide repletion could be an effective therapeutic strategy to treat AD.

References

1. Han, X., et al. (2002). "Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis." *J Neurochem* 82(4): 809-818.
2. Khakh, B. S. and M. V. Sofroniew (2015). "Diversity of astrocyte functions and phenotypes in neural circuits." *Nat Neurosci* 18(7): 942-952.