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Neuronal SphK1 acetylates COX2 and contributes to pathogenesis in a model of Alzheimer's Disease

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Although many reports have revealed the importance of defective microglia-mediated amyloid phagocytosis in Alzheimer's disease (AD), the underlying mechanism remains to be explored. Here we demonstrate that neurons in the brains of patients with AD and AD mice show reduction of sphingosine kinase1 (SphK1), leading to defective microglial phagocytosis and dysfunction of inflammation resolution due to decreased secretion of specialized pro resolving mediators (SPMs). Elevation of SphK1 increased SPMs secretion, especially 15-R-Lipoxin A4, by promoting acetylation of serine residue 565 (S565) of cyclooxygenase2 (COX2) using acetyl-CoA, resulting in improvement of AD-like pathology in APP/PS1 mice. In contrast, conditional SphK1 deficiency in neurons reduced SPMs secretion and abnormal phagocytosis similar to AD. Overall, these results reveal a novel mechanism of SphK1 pathogenesis in AD that leads to defective microglial phagocytosis due to impaired SPMs secretion, and suggests that SphK1 in neurons has acetyl-CoA dependent cytoplasmic acetyltransferase activity towards COX2.

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