CRITICAL ROLE OF BRAIN-SPECIFIC GANGLIOSIDES IN THE PATHOGENESIS OF TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE

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Major brain glycosphingolipids, also called brain gangliosides, are localized within neuronal lipid rafts (NLR) of neuronal axons and synapses and their role in neurodegenerative diseases remains unknown. Here, we compared the outcome of traumatic brain injury (TBI) and Alzheimer's disease (AD) pathology in wild-type and glycosphingolipid-deficient animals. The St3gal5 gene encodes for ST3 β-galactoside alpha-2, 3-sialyltransferase 5, which is responsible for the biosynthesis of complex a- and b- and c- series gangliosides in the brain. We found that uninjured st3gal5-deficient mice exhibit normal cognitive and social behaviors, but do exhibit some very mild motor deficits. After TBI, st3gal5-deficient animals exhibit marked deficits in cognitive and motor functions, which was associated with increased hemorrhage and neuronal damage owing to the failure of NLR-induced platelet activation and serotonin (5-HT) secretion. The decrease in NLR-induced platelet-derived platelet activating factor (PAF) release also resulted in reduced microglial activation and central nervous system macrophage infiltration in the st3gal5-deficient animals after TBI. Further investigation demonstrated that the interaction of platelets with NLR stimulated neurite growth, increased the number of dendritic spines, and increased neuronal activity during TBI. To understand the role of gangliosides in Alzheimer's disease pathology we crossed st3gal5-deficient mice with 5XFAD transgenic mice that overexpress three mutant human amyloid proteins AP695 and two presenilin PS1genes. We found that st3gal5-deficient 5XFAD mice had a significantly reduced burden of amyloid depositions, low level of neuroinflammation, and did not exhibit neuronal loss or synaptic dysfunction as compared to wild-type 5XFAD mice. St3gal5-deficient 5XFAD mice also performed significantly better in a cognitive test than wild-type 5XFAD control group. Finally, the treatment of wild-type 5XFAD mice with the sialic acid-specific Limax flavus lectin resulted in substantial improvement of AD pathology. Thus, our study establishes an important role for major brain glycolipids in the regulation of neuroinflammation, neuronal plasticity, synaptic functions and cognitive ability after a neuronal injury during TBI- and AD-related neurodegeneration.