Lowering Synaptogyrin-3 Expression Rescues Tau-Induced Memory Deficits and Synaptic Loss in the Presence of Microglial Activation

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Abstract

Background: Tau is implicated in multiple neurodegenerative disorders, including Alzheimer’s disease. Synaptic loss and neuroinflammation are characteristic features of tauopathies, but it is unclear if these pathological events are causally linked and whether they are relevant for cognitive decline. Mutations and/or hyperphosphorylation of Tau leads its accumulation at synapses, where Tau binds to synaptic vesicle-associated protein Synaptogyrin-3 resulting in clustering of vesicles and impaired synaptic function. Given that Synaptogyrin-3 is uniquely present at presynaptic terminals, this allows us to decipher the contribution of pre-synaptic Tau to overall Tau-induced pathology.

Method: We generated a synaptogyrin-3 knockout mouse line using CRISPR-Cas9 technology. Synaptogyrin-3-/- and +/- mice are viable and fertile and do not show overt phenotypes. We bred synaptogyrin-3-3/- mice with human Tau P301S-expressing mice (PS19 line) and aged the offspring. We used several techniques, including electrophysiology, behavioral tests, immunohistochemistry and electron microscopy, to determine the effects of lowering Synaptogyrin-3 expression in a tauopathy mouse model.

Result: We found that heterozygous knockout of Synaptogyrin-3 in Tau P301S mice was sufficient to rescue synaptic plasticity and working memory defects. Moreover, lowering Synaptogyrin-3 expression prevented synaptic degeneration and loss of synaptic markers in Tau P301S mice. Interestingly, proliferation and activation of astrocytes and microglia are observed in Tau P301S; synaptogyrin-3-3/- mice to the same extent as in their Tau P301S littermates.

Conclusion: Our results indicate that Tau induces synaptic loss and neuroinflammation independently, and that neuroinflammation is not sufficient to cause synaptic loss. In addition, pre-synaptic defects caused by Tau are enough to drive defects in working memory.