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Previews

Targeting pre-synaptic tau accumulation: a new strategy to counteract tau-mediated synaptic loss and memory deficits

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Synaptic tau accumulation is believed to promote synaptic loss, which contributes to cognitive deficits in Alzheimer's disease and tauopathies. In this issue of *Neuron*, Largo-Barrientos et al. report that synaptic loss can be mitigated by lowering Synaptogyrin-3, a known mediator of tau binding to synaptic vesicles.

Tau is a microtubule-associated protein that is present predominantly in the axonal compartment of neurons. In physiological conditions, the main function of tau is to regulate microtubule assembly and stabilization and to modulate axonal transport. Moreover, several other physiological functions have been characterized, showing that tau influences neuronal excitability as well as diverse cellular processes including cell morphogenesis, cellular signaling, and apoptosis. Tau can become pathological when it aggregates. Its aggregation is facilitated by post-translational modifications such as hyperphosphorylation and acetylation that notably impair its ability to bind to microtubules and facilitate its aggregation. Consequently, accretion of monomers and oligomers of misfolded tau leads to accumulation, oligomerization, and aggregation in the somatodendritic compartment of neurons. Such pathological forms of tau can also excessively localize to synaptic terminals. Tau aggregates in the form of neurofibrillary tangles (NFTs) are a pathological feature of a group of neurodegenerative diseases called tauopathies such as progressive supranuclear palsy, corticobasal degeneration, certain forms of frontotemporal dementia, and Alzheimer's disease (AD). Importantly, tau pathology correlates with synapse loss and cognitive decline in AD and other tauopathies. Tau can localize to synaptic terminals under normal as well as in pathological conditions, but there are more hyperphosphorylated tau species in synapses in AD and other tauopathies (Fein et al., 2008). Accumulation of pathological tau in the synapse can disrupt synaptic function and drive synaptic degeneration (Hoover et al., 2010). However, the mechanism underlying this phenomenon is not fully understood. Impairment of microtubule transport or altered synaptic structure has been suggested to drive tau-mediated synapse loss, and more recently, it has been shown that components of the complement system can tag tau-affected synapses, resulting in microglial engulfment and synapse loss. The presence of tau-pathology-mediated microgliosis and astrogliosis is a prominent hallmark of AD and other tauopathies, and recent evidence suggests that microglia are required for tau-mediated neurodegeneration (Shi et al., 2019). Despite this connection between tau, synapses, and inflammation, we do not yet understand whether and how specific interactions between synaptic proteins and pathological tau present at the synapse are related to the initiation of the synaptic events that lead to downstream neurodegeneration or whether synaptic degeneration and inflammation are always linked.

The article by Largo-Barrientos et al. (2021) in this issue of *Neuron* provides important data to address these issues. This study presents the first explicit demonstration of tau pathology inducing synaptic loss via the involvement of a specific synaptic protein. Further, this effect may occur independently of suppressing microglial and astrocyte activation. In this manuscript, the authors focused on Synaptogyrin-3, a synaptic-vesicle-associated protein uniquely found in pre-synaptic terminals that was previously characterized as a mediator of tau binding to synaptic vesicles (Liu et al., 2016; McInnes et al., 2018). Largo-Barrientos et al. employed a well-characterized mouse model of tauopathy harboring the P301S human tau mutation, PS19 mice. By 9 months of age, this model develops strong tau hyperphosphorylation and aggregation, neurofibrillary tangle deposition, and gliosis, as well as neuronal loss, brain atrophy, and loss of synaptic proteins in specific brain regions including the hippocampus, entorhinal cortex, and piriform cortex. The authors first confirmed in this model the pre-synaptic accumulation of tau and Synaptogyrin-3 in mossy fibers of the hippocampus by immunohistochemical staining and western blot of biochemically isolated fractions of synaptic vesicles. They also performed array tomography on post-mortem brain tissues, indicating more tau and Synaptogyrin-3 in pre-synaptic terminals in AD brains compared to healthy controls.

As Synaptogyrin-3 has been shown to contribute to tau-pathology-induced synaptic impairment (McInnes et al., 2018), they next hypothesized that decreasing Synaptogyrin-3 expression in PS19 mice would mitigate tau-mediated synapse loss and dysfunction. The authors generated PS19-*synaptogyrin*-$3^{+/-}$ mice and evaluated electrophysiological synaptic functions in 6–7-month-old mice. While lowering Synaptogyrin-3 did not affect short-term plasticity of mossy fibers in PS19 mice, this reduction preserved long-term plasticity such that it was now similar to that found in wild-type (WT)

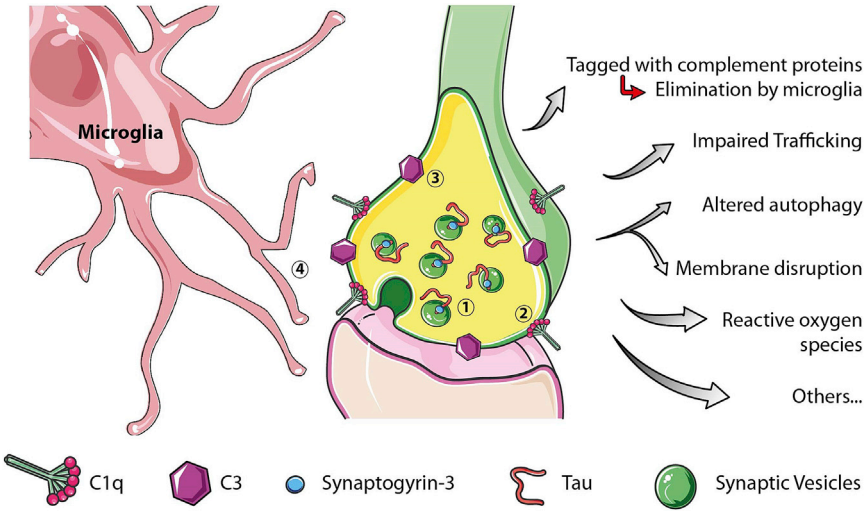

Figure 1. Possible mechanisms by which pre-synaptic tau accumulation led to synaptic loss
Interaction between Synaptogyrin-3 and tau results in tau accumulation in the synapse, which could impair trafficking, alter autophagy, disrupt the membrane, promote the production of reactive oxygen species, and induce synaptic tagging of C1q, resulting in synapse engulfment by microglia.

mice. Importantly, this protective effect from Synaptogyrin-3 reduction on synaptic plasticity was accompanied by improved working but not spatial memory in 6–7-month-old PS19 mice evaluated with 2 versions of the Morris Water Maze. These data suggest that tau/Synaptogyrin-3 co-localization in pre-synaptic terminals drives, at least in part, impairment of synaptic function and resulting working memory deficit in PS19 mice.

But what about synaptic loss? Does the preserved synaptic function and working memory induced by lower Synaptogyrin-3 coincide with reduced tau-mediated synaptic loss? Using immunohistochemical staining, western blot, and transmission electron microscopy, the authors evaluated pre- and post-synaptic integrity of mossy fibers in 8–9-month-old PS19 and PS19-*synaptogyrin*-$3^{+/-}$ mice. The authors did not specify why they used older mice for this experiment, but we can hypothesize that synaptic loss is more pronounced in PS19 mice at this age. Largo-Barrientos et al. clearly demonstrated synaptic loss in PS19 mice, while lowering Synaptogyrin-3 in these mice preserved synaptic integrity at mossy fiber synapses consistent with the effects observed on synaptic function and working memory. An interesting question that comes out of these studies is if the preservation of synaptic integrity results in an overall attenuation in synaptic and neuronal loss as well as the concomitant brain atrophy observed in cortical and hippocampal regions at later ages in this model. Indeed, the PS19 model offers important advantages by being one of the rare mouse models to mimic tau-mediated hippocampal and regional cortical synapse and neuronal loss, brain atrophy, and ventricular enlargement in a similar pattern as is seen in both the genetic form of frontotemporal dementia it is modeling as well as potentially the AD brain. While no clear evidence exists to support that NFTs are able to directly contribute to structural and functional synaptic changes (Rocher et al., 2010), one might wonder whether lowering Synaptogyrin-3 can affect other forms and levels of tau such as tau hyperphosphorylation and aggregation in these mice.

Finally, Largo-Barrientos et al. investigated if tau-induced astrocyte and microglia activation can be affected by lowering Synaptogyrin-3. Indeed, as mentioned before, tau pathology is known to result in disease-associated astrocyte and microglia activation linked with synaptic engulfment by microglia (Vogels et al., 2019). However, preserved synaptic function and integrity at mossy fiber synapses due to lowering Synaptogyrin-3 in PS19 mice appeared independent from glial activation as measured by the authors. PS19 and PS19-*synaptogyrin*-$3^{+/-}$ mice exhibited similar numbers of astrocytes and microglia, as well as disease-associated microglia gene expression. The authors concluded that tau-induced synaptic loss and glial activation can be disassociated and that synapse degeneration can be mitigated even with surrounding neuroinflammation. Importantly, because only some homeostatic and disease-associated microglial genes were assessed, gene expression from isolated astrocytes or microglia might uncover novel changes masked by bulk RNA qPCR. This will be an important area to focus on in future studies, given that other work does suggest the clear involvement of microglia in neurodegeneration. If astrocytes and microglia are indeed not involved in the mechanism of the tau-mediated synaptic loss that is mediated by Synaptogyrin-3, some cellular processes that the Synaptogyrin-3/synaptic tau interactions might be enhancing to stimulate synaptic loss include impaired axonal trafficking, altered autophagy, membrane disruption, enhancement of reaction oxygen species production, and others (Figure 1). These possibilities could be explored in future studies.

Recent studies point out that microglia can engulf and excessively prune tau positive synapses via a complement-dependent mechanism leading to synapse loss. In particular, C1q, the initiator of the classical complement pathway and produced by microglia in the brain, is upregulated in AD and tauopathy patients and is detected with hyperphosphorylated tau in synapses of AD patients and PS19 mice (Dejanovic et al., 2018; Vogels et al., 2019). C1q tags tau-affected synapses leading to deposition of complement component 3 (C3) and microglial engulfment and phagocytosis of synapses (Dejanovic et al., 2018; Wu et al., 2019). Importantly, Wu et al. demonstrated that deleted C3 partially rescued neurodegeneration and synaptic function in PS19 mice independently of microglial and astrocyte activation, similar to the findings of Largo-Barrientos et al. One could hypothesize that synaptic vesicles positive for hyperphosphorylated tau can cluster at the pre-synaptic terminal through tau interaction with Synaptogyrin-3 (1), leading to synaptic tagging of C1q (2) and downstream synaptic deposition of C3 (3) and finally synapse engulfment and phagocytosis by microglia (4) (Figure 1). This hypothesis will require further studies

to clearly understand the mechanism underlying tau-mediated synapse loss.

Determining the impact of synaptic tau accumulation on synaptic loss and cognitive impairment is critically important, especially since no curative treatment exists today for AD and other tauopathies. While most therapeutic strategies focus on tau pathology (and amyloid pathology for AD), targeting the synapse could also be an attractive strategy. Antibodies against C1q have been shown to reduce tau-pathology-mediated synaptic engulfment by microglia (Dejanovic et al., 2018). Moreover, one of the corresponding authors of this publication is an applicant on patent application related to identification of Synaptogyrin-3 as a target for treating or inhibiting progression of tauopathies or symptoms of tauopathies. We can therefore hope for future molecules that can target the interaction between tau and Synaptogyrin-3 and be tested in animal models and hopefully in humans. Moreover, several other synaptic proteins interacting with tau could also be assessed as potential targets to mitigate the tau-induced synaptic engulfment by microglia. A careful analysis of these targets will, however, be required, since most of these molecules play critical roles in synaptic function. Altogether, the findings of Largo-Barrientos et al. provide a novel area to look into for new therapeutic strategies to counteract tau-pathology-mediated synaptic loss and concomitant behavioral impairment in AD and other tauopathies.

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Xenopus models suggest convergence of gene signatures on neurogenesis in autism

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Willsey et al. dissect phenotypes associated with *in vivo* disruption of ten ASD-associated genes using a hypothesis-free, parallelized approach in *Xenopus tropicalis*. These studies continue to implicate cortical neurons in ASD pathogenesis and suggest a convergence on functions related to neurogenesis.

For many years in human genetics, the search for specific genes associated with autism spectrum disorder (ASD) and related neurodevelopmental disorders (NDDs) was a daunting challenge. As some of the barriers to gene discovery have dissolved with the power of new genomics technologies, large-scale studies have unambiguously identified hundreds