Synaptic Release of Pathological Tau Is Calcium- and SNAP25-Dependent, and Blocked by BoNT-A Activity

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The spreading of pathological Tau species across interconnected brain regions is a main feature of Alzheimer's disease (AD) and other tauopathies. Emerging evidence supports the trans-neuronal propagation of pathological Tau at synaptic sites, in a process stimulated by neuronal activity. However, the molecular mechanisms have not yet been fully elucidated.

We recently measured the axonal release of human Tau (hTau) overexpressed in primary mouse hippocampal neurons cultured in microfluidic devices.[1] The selective cleavage of SNAP25 by botulinum neurotoxin type A (BoNT-A) significantly reduced the release of hTau carrying the pathological mutation P301S, but not the wild-type form. Similarly, we confirmed the release of hyperphosphorylated and seeding-competent Tau from synaptosomes isolated from rTg4510 mouse forebrains, which overexpress hTau-P301L, and human post-mortem AD brains.[2] Whereas BoNT-A prevented Tau release, BoNT/D-mediated VAMP/synaptobrevin cleavage proved ineffective. Hence, we demonstrated that synaptic Tau release is a SNAP25-dependent mechanism, which does not require VAMP/synaptobrevin. This finding implies that exocytosis of synaptic vesicles is not essential for pathological hTau release.

On these premises, we now aim at characterizing the membranous compartment(s) that harbor pathological Tau at presynaptic sites and mediate Tau release, thus identifying critical regulators of this process. At the same time, we are developing a mouse model of Tau spreading in the visual system to test the effect of BoNT-A in preventing pathological Tau propagation in vivo,[3] further confirming the role of SNARE proteins in this process.

Overall, our strategy will provide further insights on the molecular mechanisms regulating Tau propagation and spread of disease, paving the way for the development of new therapeutic approaches to treat tauopathies.

Keywords: Tau; Alzheimer's disease; Synapse; SNAP25; Botulinum neurotoxins

References

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