Why kiss-and-hop explains that tau does not stabilize microtubules and does not interfere with axonal transport (at physiological conditions)

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Abstract

Tau is a microtubule-associated protein that is enriched in the axonal process of neurons. Post-translational modifications of tau have been implicated in the development of tauopathies characterized by defects in axonal transport, neuronal atrophy, and microtubule disassembly. Although tau is almost quantitatively bound to microtubules under physiological conditions, it does not significantly affect axonal transport. Furthermore, acute or chronic tau deficiency does not result in significant destabilization of neuronal microtubules, challenging the classical view that disease-related tau modifications directly cause axonal microtubule collapse. We discuss how the rapid interaction kinetics of the tau-microtubule interaction, which we previously termed the kiss-and-hop interaction, explains why tau does not affect microtubule-dependent axonal transport but still allows tau to modulate microtubule polymerization. In contrast, tau modifications that slow down the kinetics of the tau-microtubule interaction and increase the residence time of tau at a microtubule interaction site can disrupt axonal transport and cause dendritic atrophy. We discuss the consequences of such a gain-of-toxicity mechanism in terms of the development of disease-modulating drugs that target the tau protein.