Tau-Hyperphosphorylation Suppresses Unidirectional Transport by Motor Proteins

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Synaptic vesicle transport by motor proteins along microtubules is a crucial active process underlying neuronal communication. It is known that microtubules are destabilized by tau-hyperphosphorylation, which causes tau proteins to detach from microtubules and form neurofibril tangles. However, how tau-phosphorylation affects transport dynamics of motor proteins on the microtubule remains unknown. In this talk, we will show that long-distance unidirectional motion of vesicle-motor protein multiplexes (VMPMs) in living cells is suppressed under tau-hyperphosphorylation, with the consequent loss of fast vesicle-transport along the microtubule. The VMPMs in hyperphosphorylated cells exhibit seemingly bidirectional random motion, with dynamic properties far different from VMPM motion in normal cells. We establish a parsimonious physicochemical model of VMPM's active motion that provides a unified, quantitative explanation and predictions for our experimental results. Our analysis reveals that, under hyperphosphorylation conditions, motor-protein-multiplexes have both static and dynamic motility fluctuations. The loss of the fast vesicle-transport along the microtubule can be a mechanism of neurodegenerative disorders associated with tau-hyperphosphorylation. Time permitted, we will also talk about initial-distance dependent synaptic vesicle motion toward fusion sites in stimulated neurons.