Abstract

The microtubule associated protein tau is known for its role in modulating microtubule dynamics in the neuron and has been implicated in numerous neurodegenerative disorders such as Alzheimer's disease. There are six known isoforms of tau in the human brain; however, it is unclear what role these specific isoforms play. Recently tau has also been shown to be involved in the regulation of kinesin-mediated axonal transport. Although it is known tau strongly inhibits kineisn motility, the mechanism by which this occurs has not currently been elucidated. We demonstrate that tau cooperatively binds the microtubule and regulates kinesin binding in an isoform specific manner, with the 4RL-tau isoform sterically blocking kinesin binding and the 3RS-tau allosterically modulating kinesin binding. The 3RS-tau isoform modulates 2.5 tubulin dimers per microtubule binding repeat and reduces kinesin's on-rate for these modulated tubulins by approximately 50 percent. This change in on-rate biases kinesin binding to populations of microtubules that are not affected by tau. These facts have far reaching physiological implications, in neurons, where the microtubule concentration is high as compared to tau. We propose a model in which the 3RS-tau can direct transport by creating subpopulations of microtubules which kinesin does not bind while the 4RL-tau acts as a stop signal for transport.