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In vivo control mechanisms of motor-cargo movement on microtubules

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Within axons, molecular motors transport essential components required for neuronal growth and viability. Although many levels of regulation must exist for proper anterograde and retrograde transport of vital proteins, little is known about these mechanisms. Previous work suggested that the amyloid precursor protein (APP) functions as a kinesin-1 receptor during transport. However, how APP vesicle motility is regulated is unclear. Using genetics and *in vivo* imaging in *Drosophila* we showed that reduction of presenilin (PS) substantially increased anterograde and retrograde APP vesicle velocities. Strikingly, PS deficiency had no effect on an unrelated cargo vesicle containing synaptotagmin, which is powered by a different kinesin motor. Increased PS-mediated velocities required functional kinesin-1 and dynein motors. We also found that these PS-mediated effects on motor protein function were mediated via a pathway that involves glycogen synthase kinase-3β (GSK-3β). PS genetically interacted with GSK-3β in an activity dependent manner. Excess of active GSK-3β perturbed transport by causing axonal blockages, which were enhanced by reduction of kinesin-1 or dynein, while excess of non-functional GSK-3β had no effect. Strikingly, GSK-3β-activity dependent transport defects were enhanced by reduction of PS. Collectively, our findings suggest that PS and GSK-3β are required for normal motor protein function, and we propose a model in which PS likely regulates GSK-3β activity during transport. These findings have important implications for our understanding of the complex regulatory machinery that must exist *in vivo* and how this system is coordinated during vesicle motility on microtubules.