Dynamic association of Tau with neuronal membranes is regulated by phosphorylation

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Tau is an abundant cytosolic protein which regulates cytoskeletal stability. In cell lines, transfected tau is both cytosolic and associated with the plasma membrane. We have found that a significant proportion of tau is located in the membrane fraction of rat and mouse cortical neurons and this form of tau is dephosphorylated, at least at the Tau-1, AT8 and PHF-1 epitopes. Surface biotinylation of neurons revealed tau is associated with plasma membrane. To determine whether tau phosphorylation regulates its membrane association, we inhibited the tau kinases casein kinase 1 (CK1) or glycogen synthase kinase-3 prior to membrane isolation. Kinase inhibition decreased tau phosphorylation and increased the amount of tau in the membrane fraction; this effect was blocked by the protein phosphatase inhibitor okadaic acid. Mutation of serine/threonine residues in the N-terminal half of tau to glutamate, to mimic a permanent state of phosphorylation, prevented its membrane localization in transfected CHO cells. Inhibiting CK1 in neurons lacking the tyrosine kinase fyn induced tau dephosphorylation but did not increase its membrane association. We conclude that dynamic trafficking of tau to the neuronal membrane is regulated by tau phosphorylation and is dependent upon fyn expression.