

EFFECT OF HYPERPHOSPHORYLATION ON TAU PATHOLOGY AND FUNCTION *IN VIVO*

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In Alzheimer's disease (AD) and other tauopathies, hyperphosphorylated tau proteins aggregate and form intraneuronal neurofibrillary tangles in affected neurons. The hyperphosphorylation of tau by the deregulation of kinases and/or phosphatases has been proposed to dissociate tau from microtubules (MT), induce MT destabilization, and promote aggregation. Using anesthesia-induced hypothermia as a well characterized model of tau hyperphosphorylation *in vivo*, we investigated whether hyperphosphorylation impacts tau in wild-type (WT) and transgenic mice (TG).

We found that following anesthesia-induced hypothermia, MT-free tau was hyperphosphorylated, which impaired its ability to bind MT and promote MT assembly. MT-bound tau was more resistant to hyperphosphorylation compared to free tau and tau did not dissociate from MT in WT mice. In TG mice, anesthesia led to increased levels of phospho-tau, and detachment of tau from microtubules. Surprisingly, dissociation of tau from MT did not lead to depolymerization of tubulin, and there was no disturbance of axonal MT networks. These results indicate that, *in vivo*, a sub-population of tau bound to MT does not easily dissociate under conditions that extensively phosphorylate tau. Tau remaining on the MT under these conditions is sufficient to maintain MT network integrity. Interestingly, the level of aggregated tau was increased one week following anesthesia in TG mice, suggesting that hyperphosphorylation precipitates changes in the brain that provoke later development of tauopathy. Our results suggest that anesthesia-induced hypothermia could lead to an acceleration of tau pathology *in vivo* that could have significant clinical implications for patients with early stage, or overt neurofibrillary tangle pathology.