Annonacin, a natural lipophilic mitochondrial complex I inhibitor, increases phosphorylation of tau in the brain of FTDP-17 transgenic mice.

Both genetic and environmental factors likely contribute to the neuropathology of tauopathies, but it remains unclear how specific genetic backgrounds affect the susceptibility towards environmental toxins. Mutations in the tau gene have been associated with familial tauopathies, while annonacin, a plant-derived mitochondrial inhibitor, has been implicated in an environmental form of tauopathy. We therefore determined whether there was a pathogenic synergy between annonacin exposure and the expression of the R406W-tau mutation in transgenic mice. We found that annonacin exposure caused an increase in the number of neurons with phosphorylated tau in the somatodendritic compartment in several brain areas in R406W(+/-) mice as opposed to mice that had only the endogenous mouse tau (R406W(-/-)). Western blot analysis demonstrated a concomitant increase in total tau protein without increase in tau mRNA, but reduced proteasomal proteolytic activity in R406W(+/-), but not R406W(-/-) mice, upon annonacin-treatment. Phosphorylated tau levels exceeded the increase in total tau protein, along with increased levels of different tau kinases, foremost a striking increase in the
p25/p35 ratio, known to activate the tau kinase Cdk5. In summary, we observed a synergistic interaction between annonacin exposure and the presence of the R406W-tau mutation, which resulted in reduced degradation, increased phosphorylation and redistribution of neuronal tau.