Chronic consumption of Annona muricata juice triggers and aggravates cerebral tau phosphorylation in wild-type and MAPT transgenic mice.

Abstract:
In the pathogenesis of tauopathies, genetic and environmental factors have been identified. While familial clustering led to the identification of mutations in MAPT encoding the microtubule-associated protein tau, the high incidence of a sporadic tauopathy endemic in Guadeloupe was linked to the plant-derived mitochondrial complex I inhibitor annonacin. The interaction of both factors was studied in the present work in a realistic paradigm over a period of 12 months. Mice over-expressing either human wild-type tau or R406W mutant tau as well as non-transgenic mice received either regular drinking water or commercially available tropical fruit juice made of soursop (Annona muricata L.) as dietary source of neurotoxins. HPLC-MS analysis of this juice identified several Annonaceous acetogenins, mainly annonacin (16.2 mg/L), and 41 isoquinoline alkaloids (18.0 mg/L, mainly asimilobine and reticuline). After 12 month of juice consumption, several brain regions showed an increased number of neurons with phosphorylated tau in the somatodendritic compartment of R406W mice and, to a much lesser extent, of non-transgenic mice and
mice over-expressing human wild-type tau. Moreover, juice drinking was associated with a reduction in synaptophysin immunoreactivity, as well as an increase in 3-nitrotyrosine (3NT) reactivity in all three genotypes. The increase in 3NT suggests that Annona muricata juice promotes the generation of reactive nitrogen species. This study provides first experimental evidence that long-lasting oral ingestion of a widely consumed environmental factor can induce somatodendritic accumulation of hyperphosphorylated tau in mice expressing rodent or human wild-type tau, and can accelerate tau pathology in R406W-MAPT transgenic mice.