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Human 3R and 4R tau expression improves function and decreases axonal injury following traumatic brain injury in mice

Clinical traumatic brain injury and closed head injury (CHI) in mice damage the brain in many ways, yet the axonal cytoskeleton is particularly vulnerable. Tau protein expression may alter the extent of brain injury since tau crosslinks and stabilizes axonal microtubules. Adult humans express six tau protein isoforms with either three (3R) or four (4R) microtubule binding sites yet adult mice express only 4R isoforms. 3R tau containing microtubules are more flexible since 3R binds tubulin with lower affinity than 4R. Recent studies show tau in synapses with pre- and post- synaptic functions. I tested whether 3R tau expression alters outcomes following CHI. Cognition and brain damage following CHI is examined in C57/BL6 wildtype mice (WT) that express murine 4R tau or in human tau locus knock-in (MAPTKI) mice that express human 3R and 4R tau. CHI produces similar initial injury in WT and MAPTKI mice as measured by righting reflex. At 14 days post injury, Active Place Avoidance (APA) evaluates spatial memory in WT and MAPTKI mice. Injured MAPTKI mice acquire APA, whereas injured WT mice are impaired. APA acquisition is hippocampal-dependent so hippocampal injury was compared in WT and MAPTKI mice. Injured WT and MAPTKI mice have similar hippocampal neuronal loss. Injured WT mice have a selective 4R tau loss compared to injured MAPTKI mice. 3R tau expression is unaffected in injured MAPTKI mice. Injured WT mice lose 4R tau in major hippocampal axons including the perforant path and mossy fiber. Injured WT mice lower 4R tau expression in CA1 stratum radiatum and CA3 stratum lucidum suggesting loss of synaptic tau. These data suggest that despite similar initial injury, CHI causes axonal and synaptic 4R tau loss in WT mice compared to MAPTKI mice. APA deficits in injured WT mice likely arise due to impaired axonal transport and synaptic dysfunction. These data also suggest that 3R tau expression improves brain function by limiting hippocampal injury following CHI.