2023 Annual Research Day – Oral session
April 19th, 2023, 2:00 p.m. – 4:30 p.m., PHAB 2A

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Impact of Tau Isoform Expression on Memory and Phosphorylated Tau Accumulation after Traumatic Brain Injury

Tau is a microtubule associated protein involved in many neurodegenerative diseases, including traumatic brain injury (TBI). Tau forms abnormally phosphorylated tau aggregates (pTau) after TBI. The tau gene (MAPT) contains 6 different isoforms that have either 3 (3R) or 4 (4R) microtubule binding sites. Adult mouse brains express only 4R tau and human brains express both 3R and 4R. The impact of tau isoform expression on pTau accumulation and memory after a traumatic brain injury is still unknown. This study uses male and female C57/Bl6 mice (WT), and mice with a knock-in of the human tau locus (MAPTKI), which express 3R and 4R tau at WT levels. Mice receive a single closed head injury (CHI) and are evaluated for spatial memory using Barnes maze at 7 days post injury (DPI). Following behavioral testing, immunohistochemistry assessed either beta-amyloid or pTau accumulation with antibodies against 3 different tau phosphorylation sites (S396, S404 S214). Previous studies show male WT mice have memory deficits at 7DPI but not at 60DPI. CHI increases pTau expression in oligodendrocytes in corpus callosum, thalamus, and cortex (n=8) at 14DPI. pTau+ oligodendrocyte density progressively increases in white matter but decreases in grey matter by 180DPI (n=10). Beta-amyloid is present in corpus callosum of injured mice at 14DPI but not 180DPI. Unlike WT, injured male (n=8) or female (n=9) MAPTKI mice at 7DPI retain Barnes maze similarly to sham-injured mice. This is despite a 2-fold increased pTau+ cell density in cortex, corpus callosum, and thalamus. Studies of MAPTKI mice at later time points after CHI may reveal whether the 14DPI increase in pTau negatively affects memory, and whether there is greater accumulation of pTau or beta-amyloid. Understanding a potential role of tau isoforms in TBI could inform the development of targeted therapies aimed at reducing the accumulation of hyperphosphorylated tau and improving cognitive outcomes.