Is Chronic Pain an Initiator of Tauopathy?

Karin N Westlund High, PhD[1] • Danielle N Lyons, PhD[1] • Liping Zhang, PhD[1]

[1]*Physiology, University of Kentucky*

Background: The hallmark of frontotemporal dementia (FTD) is abundance of tau protein in specific vulnerable brain regions leading to progressive impairment in cognition, emotional and social behavior, language and executive function. Although progressive spread of tau neuropathology from frontal and hippocampal cortex is mapped in humans, no animal models appropriately replicate tauopathy. Understanding basic mechanisms during initial stages of tau pathology is fundamentally important to designing new strategies for early intervention.

Purpose/Hypothesis: We are addressing the question of how chronic pain produces vulnerability for tauopathy by investigating the link between neuronal overactivation of the pain circuitry and intracellular stress responses that cause expression of dysfunctional tau proteins and result in neurotoxicity. Our goal is comprehensive understanding of molecular and cellular mechanisms during the transition of chronic pain that produce risk for tauopathy to allow us to identify novel therapeutic targets. Our current novel hypothesis is that chronic pain conditions produce early features of tauopathy which over time promote hippocampal stem cell and medial prefrontal cortical neuron loss.

Methods: Our time sequenced studies utilize animal models that allow study of the transition from persistent to chronic pain. Hypersensitivity is accompanied by anxiety- and depression-like behaviors. Neuropathological analysis at multiple time points over a 6 month period is providing a unique understanding that chronic pain is a generator causal in intracellular organelle stress.

Results: Chronic neuropathic pain induces expression of dysregulated endoplasmic reticulum (ER) stress sensor protein pPERK (phosphorylated promoter protein kinase R (PKR)-like ER kinase and hyperphosphorylated PHF-1 tau protein within 3 weeks that accumulates over 6 months in wild type, genetically unmodified mice and rats. ER stress sensor pPERK is a suppressor of protein translation linked to tau pathogenesis. Hyperphosphorylated PHF-1 tau and pPERK signaling pathway proteins are indicative of cellular oxidative stress, neuronal damage and potential neurotoxicity. pPERK inhibitor treatment reduces expression of PHF -1 tau and pPERK proteins, identifying pPERK pathway signaling as a potential therapeutic target for prevention of long-term neuropathological consequences of chronic pain.

Conclusion: These pre-clinical animal models are useful for study of persisting nerve injury as a risk factor in the earliest stage of pre-tauopathy development and for targeting stabilization of pPERK signaling to mitigate vulnerability for pre-dementia neuropathology. Relevance is underscored by the fact that 100 million patients with chronic pain in the US may be at risk for tau pathology and dementia.