Alcohol consumption during early adulthood in a preclinical mouse model of Alzheimer's disease leads to gait impairments, dysregulated circadian rhythm, alterations in tauopathy and brain-region-specific transcriptional alterations.

NM Maphis, D Furlano, SA David, and DN Linsenbardt

Alzheimer's disease (AD) is a leading cause of cognitive dysfunction and death in the US attributable in part to the accumulation and spread of pathologically modified tau (pTau). Recently, excessive alcohol use, particularly binge drinking, has emerged as a risk factor for the development of AD. However, the neurobiological consequences underlying how excessive alcohol exposure might lead to the accumulation and/or progression of pTau and associated neurobehavioral deficits has not been fully explored. We used the binge-alcohol drinking paradigm, 'drinking-in-the-dark' (DID), in the P301S mouse model of tauopathy to test the hypothesis that excessive voluntary alcohol consumption during young adulthood would exacerbate pTau-induced alterations in behavioral decline as a consequence of the recruitment of unique neurobiological genes/gene networks. We found that excessive alcohol use in the P301S mice altered the presentation of pTau, shortened circadian rhythm, impaired right hind paw gait characteristics, and led to brain-region-specific transcriptional alterations. Of particular interest, we identified a well-characterized thyroid transport gene, Transthyretin (*Ttr*), recently found to regulate microtubule dynamics and has a strong connection to Alzheimer's, that was downregulated in the hippocampus of alcohol consuming P301S males compared with alcohol consuming male nTg littermates. These findings support alcohol consumption as a factor that interacts with pTau and pTau-associated behavioral decline as well as reveals some potential targetable neurobiological mechanisms underlying these changes.

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Department of Neurosciences, New Mexico Alcohol Research Center, School of Medicine and Health Sciences Center, University of New Mexico, Albuquerque, NM 87131, USA
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Non Technical:
Excessive alcohol consumption has been identified as a risk factor for developing Alzheimer's disease. Our work seeks to understand how the pattern and amount of alcohol consumption could drive tau tangle formation in the brain and other consequences, like difficulty walking and sleeping. In order to study this, we exposed a rodent model that has tau tangles in its brain to a voluntary drinking task, during a short period in the dark.