

Project Summary

Alcohol use disorder (AUD) is associated with the emergence of negative emotional states that can influence the motivational properties of alcohol. Pain represents one such motivational state hypothesized to drive AUD severity (Egli, Koob, and Edwards, 2012), and this relationship is particularly concerning since there are limited treatments for either chronic pain or AUD. Ascending nociceptive circuitry and excessive alcohol exposure alters the function of central brain stress and reinforcement systems, including the central amygdala (CeA). Related neuroadaptations may underlie negative reinforcement mechanisms driven by persistent pain in the context of AUD. We have discovered the emergence of a significant mechanical and thermal nociceptive hypersensitivity (or hyperalgesia) in alcohol-dependent male rats and our current aim is to interrogate valid animal models of excessive drinking and hyperalgesia toward the elucidation of neuropharmacological mechanisms contributing to these conditions in alcohol dependence. Our previous work implicated the stress neuropeptide vasopressin in the transition to dependence in male rats via its actions on V1b receptors (V1bRs; Edwards et al., 2012). While V1bR antagonists reduce excessive drinking in rodents and facilitate abstinence in alcohol-dependent individuals (Ryan et al., 2016), additional evidence suggests that they may also reduce stress-induced hyperalgesia (Bradesi et al., 2009). Pain-related affective responses are also enhanced via vasopressin signaling through CeA V1a receptors (V1aRs, Cragg et al., 2016), although the contribution of this receptor system to excessive drinking or hyperalgesia in the context of alcohol dependence is unexplored. As two key stress-regulatory systems, vasopressin and glucocorticoid signaling may closely interact, with each system driving the other's activity in a bidirectional fashion. Elucidation of this link could be critical to understanding the efficacy of glucocorticoid receptor antagonist therapy in reducing excessive drinking in preclinical and clinical models (Vendruscolo et al., 2015). Our primary hypothesis is that blockade of either of two subclasses of central vasopressin receptors (V1bRs or V1aRs) in a key pain- and reinforcement-related brain area (CeA) will reduce both excessive drinking and hyperalgesia in alcohol-dependent animals. Our secondary hypothesis is that blockade of vasopressin V1bR signaling will reduce GR phosphorylation in the CeA of alcohol-dependent animals, while blockade of GR transcription activity will also reduce vasopressin system gene expression in the CeA. We also propose an investigation of sex as a factor in these relationships given the substantial human sex differences in alcohol withdrawal and pain. A better understanding of the central brain mechanisms of alcohol dependence-related behaviors (excessive drinking and hyperalgesia) will provide substantial insight into neurobiological mechanisms of dependence and may reveal novel treatment opportunities for AUD and persistent pain in the context of AUD.