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"Translational Investigation of Sex Differences in Alcohol Analgesic Efficacy: Comparison Across Preclinical and Clinical Domains"

Although chronic pain affects over 220 million Americans and significantly contributes to both the development and maintenance of alcohol use disorder (AUD), there is an alarming gap in knowledge regarding the mechanisms underlying the anti-nociceptive effects of alcohol. The goals of the current project were to: 1) relate self-reported pain rating in people living with HIV (PLWH) and 2) investigate neuroadaptations in the phosphorylation status of excitatory and inhibitory protein markers produced by alcohol in the central amygdala (CeA) and the insula in an animal model of chronic inflammatory pain. Towards our first goal, we asked participants in the New Orleans Alcohol Use in HIV (NOAH) cohort of PLWH to complete the SF-36 Survey to report their pain symptoms and pain interference and measured their phosphatidyl-ethanol (PEth) levels to access their recent alcohol use within the past two to three weeks. Individuals who recently used alcohol (PEth+) reported fewer pain symptoms and less pain interference compared to people without recent alcohol use (PEth-), suggesting that recent alcohol use reduces pain symptoms and pain interference in PLWH. To further investigate potential mechanisms of alcohol-induced pain relief, we utilized the complete Freund's adjuvant (CFA) model of inflammatory pain and intraperitoneal ethanol injection in adult female and male Wistar rats. Using Western blotting, we quantified phosphorylation levels of γ-aminobutyric acid (GABA) type B receptor 2 ($GABA_BR2$), glutamate (Glu) receptor type 1 (GluR1) subunit A1 at S845, and the intracellular signaling molecule ERK. We identified a significant interaction between CFA exposure and acute ethanol administration to alter ERK phosphorylation in the CeA of male, but not female, rats. Conversely, there was a significant interaction between CFA and acute alcohol to alter GluR1 and ERK phosphorylation status in the female, but not male, insula. These findings suggest that both the CeA and insula may contribute to the anti-nociceptive effects of acute alcohol in animals in chronic pain and that there may be sex differences in the changes in the brain's nociceptive systems. Ongoing investigations are clarifying sex differences in these relationships, and future preclinical investigations will build on our clinical findings by examining how acute and chronic alcohol regulates HIV-specific pain. This research will help elucidate the mechanism of analgesic action of alcohol in the context of chronic inflammatory pain states across sexes with the goal of identifying the corticolimbic system as a novel target for treating pain in AUD patients.