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“Long-term effects of adolescent alcohol exposure on inflammatory pain response and neuronal activation”

Introduction: Adolescence is a critical period of brain maturation marked by heightened neuroplasticity, making the brain particularly susceptible to environmental influences, including alcohol exposure. Adolescent intermittent ethanol (AIE) exposure has been shown to produce long-lasting alterations in pain processing that persist into adulthood, including mechanical and thermal hypersensitivity. Chronic alcohol use and pain also exhibit a bidirectional relationship, in which alcohol exposure can exacerbate pain while heightened pain states may contribute to continued alcohol use and increased vulnerability to alcohol use disorder (AUD). To better define the neurobiological mechanisms underlying this relationship, we examined behavioral responses to a noxious stimulus after AIE and subsequently assessed neuronal activation in brain regions involved in pain processing and modulation. These regions included the bed nucleus of the stria terminalis (BNST), periaqueductal gray (PAG), central amygdala (CeA), and basolateral amygdala (BLA).

Methods: Adolescent intermittent ethanol (AIE) vapor exposure consists of two 4-day cycles of 16hr in the chamber and 8hr out of the chamber with a 3-day no-exposure interval, spanning postnatal day (PND) 28 to 39. Male and female C57BL/6J mice were exposed to chambers filled with volatilized ethanol or water vapor, producing blood ethanol concentrations in the range of 150-185mg/dL. Following AIE exposure, mice were allowed to mature into adulthood (~PND 70). Adult mice then received unilateral intraplantar injections of formalin into the hindpaw to induce an inflammatory pain response. Pain-related behaviors were recorded for 60min following injection and were subsequently quantified. Mice were perfused 130min after formalin injection, and brains were collected, sectioned, and processed for immunohistochemistry staining of cFos, a marker for neuronal activation. Quantification of cFos-positive cells were performed within the BNST, BLA, CeA, and PAG.

Results: AIE significantly enhanced formalin-evoked nociceptive behavior during the tonic phase II response, indicating that adolescent alcohol exposure produces a persistent increase in inflammatory pain sensitivity in both male and female mice. Quantification of cFos-positive neurons revealed significantly decreased neuronal activation in the BLA of AIE-exposed mice compared with air controls ($p=0.0132$). In contrast, no significant differences in cFos-positive neuronal activation were observed between AIE and air-exposed groups in the BNST, CeA, or PAG.

Conclusions: These findings suggest that adolescent alcohol exposure produces long-lasting alterations in pain processing that contribute to heightened inflammatory pain sensitivity in adulthood. Decreased cFos activation within the BLA further suggests that this region, which is involved in threat evaluation, stress processing, and affective components of pain, may contribute to downstream pathways involved in AIE-induced enhancement of nociceptive responses. Ongoing studies are aimed at replicating these findings in larger cohorts and defining the neural circuitry underlying AIE-associated changes in adult pain sensitivity.