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**“Kappa Opioid/Dynorphin Expression in Adult Female Mice with Adolescent Opioid Exposure and Adult Chronic Intermittent Ethanol Treatment.”**

Adolescence is a very vulnerable period of transition to adulthood for humans in which the brain undergoes critical development and maturation physically, emotionally, and socially. Adolescent opioid exposure (AOE) directly affects the brain's reward system and results in elevated risk of prolonged opioid abuse. While opioids are prescribed for pain symptoms, alcohol is also used to self-medicate pain. In spite of efforts to cope with pain with alcohol use, alcohol use and withdrawal can induce hyperalgesia thus facilitating the cycle of future alcohol use. Chronic opioid use and withdrawals has also been found to increase pain sensitivity and potentially contributes to opioids' lack of long-term effectiveness.

The bed nucleus stria terminalis (BNST) is a sexually dimorphic structure located within the ventral forebrain that is involved in the anxiety and addiction circuitry and in pain. The oval and dorsolateral regions of the BNST are involved in the body's emotional processing and regulation and in stress response. The dynorphin/kappa opioid receptor (KOR) system is an important factor in BNST stress signaling also involved in addictive behaviors and pain. This experiment investigated the relationship between mechanical and heat sensitivity in female mice with combined AOE and adult intermittent ethanol vapor exposure (CIE) and the activation of dynorphin and KOR in the BNST.

Adult and adolescent alcohol exposure have been found to produce long-lasting mechanical hypersensitivity in male and female mice with persistent effects following AOE. When AOE was combined with CIE, we found that female mice given AOE+CIE produced more long-lasting mechanical and heat hypersensitivity than CIE alone. Interestingly, this difference was not seen in male mice. In the current work, female brains were collected following the behavioral analysis above. These brains were sliced and RNAscope in situ hybridization was utilized to detect the expression of c-Fos mRNA (indicating cellular activity), dynorphin (which is associated with stress, pain, and addiction), and KOR (which are activated by dynorphin) in individual cells across the oval and dorsolateral BNST regions. QuPath image analysis was employed to count the total number of cells and detect cells containing positive channels. Combined AOE and CIE exposure exhibited decreased expression of positive cFos mRNA, dynorphin mRNA, and KOR in the dorsolateral BNST compared to mice exposed to saline in adolescence and CIE, although these differences were not significant. Future studies will explore whether a larger cohort will provide significant differences of c-Fos, dynorphin, and kappa opioid receptor mRNA expression in the dorsolateral and oval BNST.