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"Modeling Early Life Risk Factors for Alcohol Use Disorder Later in Life"

Introduction: Alcohol Use Disorder (AUD) is a public health and economic burden. Early life stress (ELS) and adolescent alcohol exposure are major risk factors for AUD. The ventral tegmental area (VTA), a component of the brain's reward system, is sensitive to these influences. Within the VTA, G protein-gated inwardly rectifying potassium channels (GIRK), specifically GIRK2, help regulate dopamine neuron activity and shape how the brain responds to alcohol. This study sought to establish preclinical models of ELS and adolescent alcohol exposure to investigate their impact on GIRK2 expression in dopaminergic neuros of the VTA.

Methods: To model ELS, C57BL/6J mouse pups were subjected to the limited bedding and nesting (LBN) paradigm from postnatal day p4-p11. Maternal behavior was recorded during the light and dark cycles and the time spent at the nest was analyzed. After p11, damns and pups were returned to standard housing conditions and allowed to age into adulthood. Immunohistochemistry was performed on VTA-containing sections from ELS and control mice sacrificed during adulthood to evaluate GIRK2 and tyrosine hydroxylase (TH) expression.

To model adolescent alcohol exposure, mice were exposed to alcohol using one of two paradigms beginning at p30. Voluntary consumption was measured using the Drinking-in-the-Dark (DID) paradigm four days a week over a two-week period with a 3-day break in between drinking sessions. A separate protocol, adolescent intermittent exposure to ethanol vapor (AIE), was used to produce similar levels of intoxication in mice to investigate lasting effects of alcohol exposure on behavior into adulthood. Behavioral assays included marble burying tests to assess anxiety-like behavior and von Frey testing to assess mechanical nociception.

Results: Preliminary data indicates altered maternal behavior in the LBN paradigm, with LBN dams spending decreased time on the nest in the light cycle and increased time on the nest in the dark cycle compared to controls in standard housing. LBN pups showed decreased body weight at p11 and p21 compared to the controls. Immunohistochemistry indicates lower level of GIRK2 and TH co-expression in the VTA of offspring with a history of ELS compared to unstressed controls. Adolescent mice demonstrated voluntary ethanol intake in the DID paradigm. AIE mice showed increased marble burying behavior compared to controls when tested four weeks after alcohol exposure, indicative of heightened anxiety-like responses. These mice also demonstrated a decreased paw withdraw threshold when tested three weeks after their last ethanol vapor session, indicating mechanical hyperalgesia

Conclusions: We demonstrated alterations in the VTA of adult offspring with a history of ELS, as well as increased anxiety-like behavior and nociception in adult mice with a history of AIE. Future studies will focus on combined ELS and AIE to understand how the two may increase the risk for AUD.