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“Mesoamygdala contribution to alcohol withdrawal-associated anxiety”

Background and Objectives: Humans with alcohol use disorder (AUD) often experience anxiety during withdrawal (WD), which is associated with greater risk of relapse. Previous work has demonstrated activation of central amygdala (CeA)-projecting ventral tegmental area (VTA) neurons during alcohol WD in a rat model of alcohol dependence, raising the possibility that this circuit contributes to WD-associated behavior. We tested this by using a chemogenetic strategy to inhibit the VTA-CeA circuit and evaluating anxiety-like behavior during WD.

Methods: We used a dual virus approach to selectively transfect CeA-projecting VTA neurons with an inhibitory DREADD and modeled alcohol dependence using a chronic intermittent exposure (CIE) to ethanol vapor paradigm. Following 4 weeks of vapor exposure, rats were tested for anxiety-like behavior in an elevated plus maze (EPM) during WD. To inhibit the VTA-CeA circuit, DCZ (0.1 mg/kg, i.p.) was administered 30 minutes prior to behavioral testing. Brains were then sectioned to confirm virus placement and stained to confirm inhibition of cells using phosphorylation of pyruvate dehydrogenase (pPDH).

Results: We first assessed whether vapor exposure parameters are related to behavioral outcomes. Average BACs across cohorts were aggregated and used to determine a threshold for inclusion in future studies, defined as the lower quartile (≤ 130 mg/dL). We applied this threshold to our analysis of rats following chemogenetic inhibition of the VTA-CeA circuit during WD. Preliminary data suggests that inhibition of the VTA-CeA circuit in alcohol dependent rats tested during WD may rescue increased anxiety-like behavior, although this did not achieve statistical significance. To confirm cell type-specific inhibition following DCZ administration, we stained VTA-containing sections for pPDH, a marker of cellular inhibition. We found a greater number of pPDH+, mCherry expressing (i.e., virus-containing) VTA neurons of Gi-expressing rats compared to inactive virus controls.

Discussion: Our data indicate that inhibiting the CeA-projecting VTA circuit may rescue increased anxiety-like behavior associated with alcohol WD. Further tests with a larger data set to perform a full statistical analysis is necessary to verify the current findings. Additionally, future experimentation is necessary to see whether CeA-projecting VTA neurons have collateral projections which may influence behavior. Ongoing work is utilizing a brain clearing and whole-brain imaging strategy to see if CeA-projecting VTA neurons project elsewhere in the brain. If other regions are identified as being involved, these previous experiments can be repeated with site-specific drug and virus administration to test the role of these regions. Our ultimate goal is to better understand the neurobiology underlying alcohol withdrawal-associated increases in anxiety, potentially allowing for improved therapeutic options for individuals with AUD.