Investigating Epigenetic Mechanisms of Acute Ketamine Treatment in Rats Exposed to Early Life Adversity

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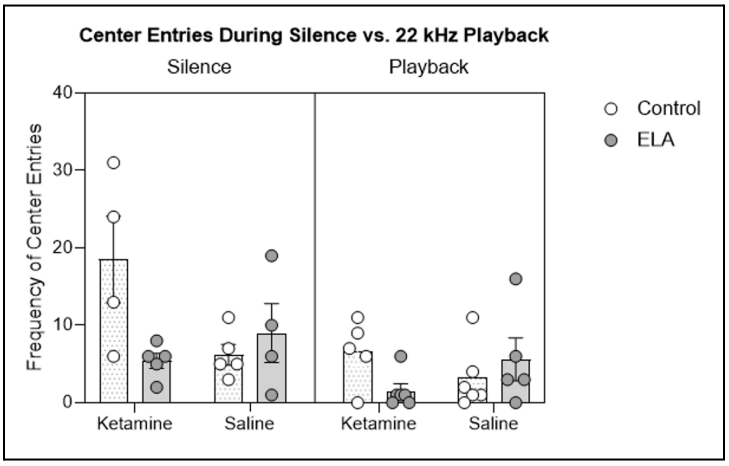
Early life adversity (ELA) is often defined as experiences of abuse, economic hardship, and/or neglect during childhood. There is evidence to suggest that those with a history of childhood adversity have long-lasting structural changes during brain development[1], and are more likely to develop psychiatric disorders in later life, particularly anxiety disorders and major depression disorder[2]. While there are current treatments for anxiety and depression, many patients are still classified as "treatment-resistant", meaning that they have not significantly improved upon standard treatment (such as SSRI/SNRIs). Acute low-dose ketamine treatment has been recently found to have promising qualities as a potential treatment for depression and anxiety[3,4,5], especially for those who are resistant to common treatments[6]. However, the mechanism by which ketamine produces its antidepressant action is still largely unknown. A better understanding of its mechanism of action would allow us to provide more appropriate, background-informed care and identify promising alternative treatments.

While the mechanisms behind its potentially antidepressant/anxiolytic effects are not well-studied, one theory is that ketamine increases the output of excitatory pathways by dysregulating inhibitory interneurons[7,8], such as parvalbumin-containing (PV+) interneurons. PV+ interneurons have been found to be vulnerable to early-life adversity experiences. A change in the inhibitory tone from the prefrontal cortex (executive control) to the amygdala (fear/emotion) could result in atypical behavioral responses to perceived threats.

Epigenetic modifications have been implicated as a pathway through which specific protein expression levels could vary, and therefore inhibit or decrease the function that the protein is originally intended to serve. One specific epigenetic mechanism of interest is DNA methylation. There is evidence to suggest that DNA methylation is involved with the inhibition-excitation imbalance in the brain that is often present in MDD patients[10]. DNA methylation has been associated with emotional dysfunction developed following ELA[11,12] and previous research from the Honeycutt lab suggests that epigenetic changes may be partly responsible for the dysregulation of PV+ prefrontal cortex interneurons following ELA[9].

The purpose of this study is to investigate ketamine's potential epigenetic antidepressant mechanism of action. To study this, we use a translational model of caregiver deprivation in rats. The rat pups are separated from their mothers for 3-4 hours a day from day 2 to day 21. Then, at around day 55, they receive a single 10mg/kg dose of ketamine and undergo anxiety behavioral testing 5-6 days after treatment. Half of the animals are given a saline injection to control for the experience of receiving a subcutaneous injection without the potential therapeutic effects of the drug. Brain collection happened 7 days after treatment. The prefrontal cortex and hippocampus from one hemisphere were frozen for future DNA extraction and other DNA methylation assays



Preliminary data from work this summer do not reveal a statistically significant effect of acute ketamine treatment on anxiety-like behavior in male rats with a history of early life adversity compared to the control groups (control/ketamine, control/saline, and ELA/saline). However, this could be due to the relatively small sample sizes. Further work during the school year will increase group sizes and provide a clearer picture of behavioral outcomes, as well as the addition of sex as another variable. Additional upcoming work is the processing of brain tissue from these subjects collected during the summer to investigate DNA methylation patterns in the brain regions of interest (with a focus on PV+ interneurons in the prefrontal cortex).

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