Effects of a Single Ketamine Dose on the Potentiated Startle Response in the Wistar-Kyoto Rat Model of Affective Dysfunction

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Summary: Ketamine, a non-competitive NMDA receptor antagonist, has emerged as a novel antidepressant in the last decade due to its swift therapeutic response, especially in patients with treatment-resistant disorders. Unlike the commonly used medications such as serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and serotonin/norepinephrine reuptake inhibitors (SNRIs) among others, ketamine's effects persist from one week to months following a single dose (Murrough et al. 2013; Yang et al. 2015; Gass et al. 2019). While used solely as an anesthetic for more than 50 years (Deka et al., 2022), ketamine has now piqued interest as an effective treatment for posttraumatic stress disorder (PTSD; Dames et al., 2022), as well as the only known drug that reduces suicidal ideation and inhibits depressive-like symptoms regardless of any comorbid psychiatric and personality disorders present (Ahmed et al. 2023).

The project utilized the Wistar-Kyoto rat strain known for its genetic profile that exhibits depressive and anxiety-like symptoms comparable to those seen in human patients alongside a reduced response rate to antidepressant treatment (Will et al. 2003; McAuley et al. 2009). Furthermore, as ketamine is known to interact with estrogen, our research has focused solely on female subjects to remedy lack of evidence regarding the drug's effects during the four stages of the estrous cycle (Lehmann et al. 1999; Wright et al. 2016).

Our experimental paradigm included 40 female Wistar-Kyoto rats injected interperitoneally with ketamine doses of 5, 10, and 15 mg/kg or a comparable dose of saline for the control group. To test the effects on behavior, we have habituated the subjects to the SR-LAB Startle Response System for three days before drug administration, then tested the animals 24 hours and seven days after the injection. The SR-LAB system included randomized acoustic pulses of 95, 105, and 115 dB, with the Wistar-Kyotos' degree of startle being recorded by the built-in sensors. After the second test, the rats' brains were collected to conduct immunohistochemistry analysis to look into activation patterns of the basal lateral amygdala, hippocampus, and prefrontal cortex – brain regions responsible for anxiety and fear modulation (Gildawie et al. 2020). We performed staining for 8-hydroxy-2'-deoxyguanosine (8-OHdG) and parvalbumin (PV), a marker of oxidative damage and a Calcium-binding protein crucial in in anxious behaviors respectively, to further investigate ketamine's potential neuroprotective effects (Gürler et al. 2014; Xiao et al. 2017).

While we are yet to process the immunohistochemistry data, behavioral trials demonstrate a decreasing trend in startle response with increasing ketamine dose. An example is provided in Figure 1, which displays a significantly suppressed average startle response in rats administered the 15 mg/kg dose. Thus, we have demonstrated that ketamine indeed does have anxiolytic effect on behavior in a genetic model of treatment-resistant anxiety and PTSD and will continue to analyze the data pertaining to neurobiological markers during the 25-26 academic year.

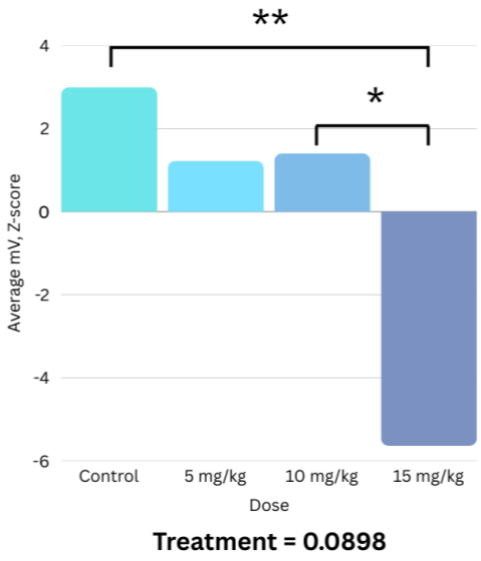

Figure 1. Effect of ketamine dosage on average startle response in Wistar-Kyoto rats. ** corresponds to $p < 0.001$, * to $p < 0.05$.

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