Differentiating the Role of (2*R*,6*R*)-Hydroxynorketamine in Ketamine's Rewarding Effects

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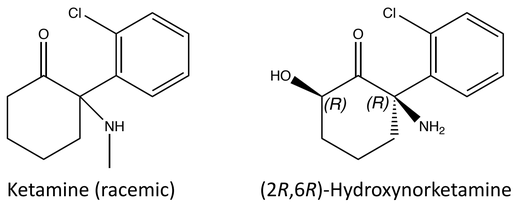
Introduction

Ketamine has shown effectiveness in treating major depressive disorder, with a single dose providing rapid alleviation of depressive symptoms[1]. However, its potential for abuse has prompted an exploration of metabolite (2*R*,6*R*)-hydroxynorketamine (2*R*,6*R*-HNK) which may offer antidepressant effects with reduced risk of addiction[2,3]. To assess this metabolite's role in the observed effects of ketamine we implemented the DISSECTIV method, in which we generated vaccines against 2*R*,6*R*-HNK to block the molecule from entering the central nervous system[4] (Figure 1). Ketamine self-administration was performed to quantify drug seeking behavior with and without actions from 2*R*,6*R*-HNK.



Ketamine (racemic) (2*R*,6*R*)-Hydroxynorketamine

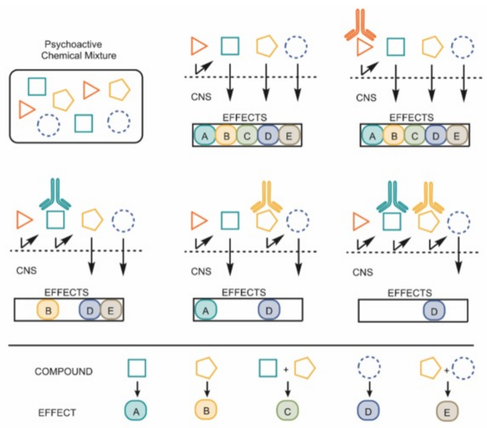


Figure 1. Schematic of the DISSECTIV method.

Methods

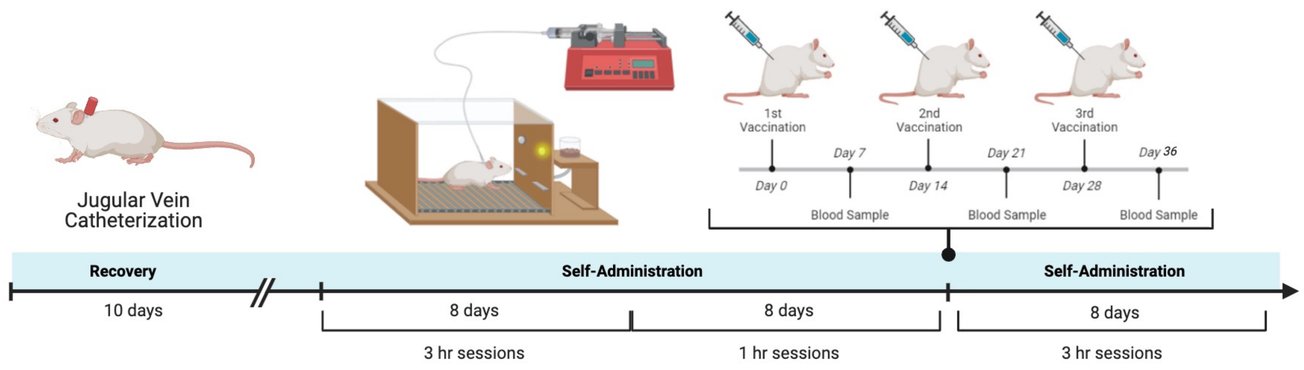


Figure 2. Experimental Timeline. 6 to 8-week-old male Sprague Dawley rats (n=6) underwent jugular vein catheterization, followed by FR1 ketamine self-administration. Right-lever presses administered a 1mg/kg ketamine infusion alongside the shine of a cue light, both lasting 4 seconds. Inactive lever presses did not provide drug infusions nor visual cues. 2*R*,6*R*-HNK-CRM vaccination began 1 week after the final self-administration session and blood samples were taken after each of the three vaccinations. Following the final vaccination, rats performed ketamine self-administration again.

Results

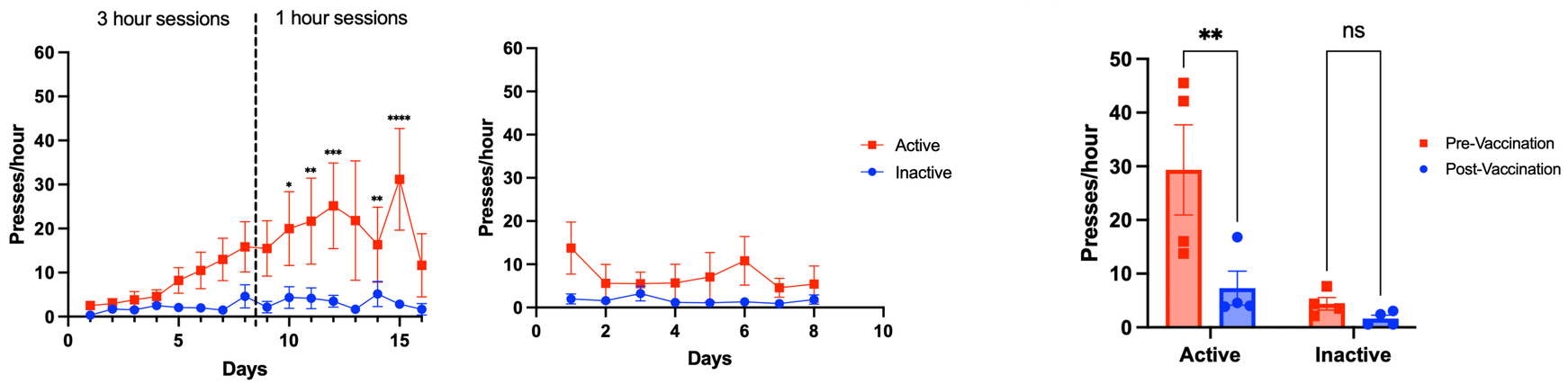


Figure 3. Ketamine Self-administration Pre- and Post- 2*R*,6*R*-HNK Vaccination (A) Rats learned to self-administer ketamine pre-vaccination. We observed an interaction between time and active lever presses per hour with significant differences between day 1 and day 10-15 (p = 0.0215-<0.0001). (B) Rats decreased active lever pressing activity following 2*R*,6*R*-HNK vaccination (p = 0.0049)

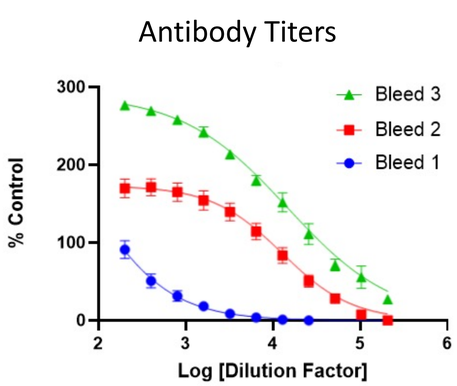


Figure 4. Antibody Titers from Rats Vaccinated with 2*R*,6*R*-HNK-CRM. Midpoint titers increased following each vaccination, demonstrating a good immunologic response.

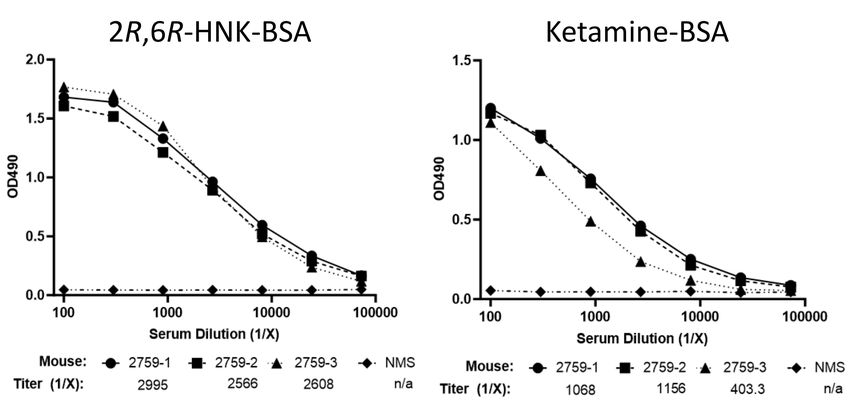


Figure 5. Antibody Titers from Mice Vaccinated with 2*R*,6*R*-HNK-CRM. Greater numbers of antibody titers were generated for 2*R*,6*R*-HNK than for ketamine.

Conclusions and Future Work

Our undergoing study demonstrates drug seeking behavior for racemic ketamine which was decreased following 2*R*,6*R*-HNK vaccination.

Results may be due to cross-reactivity of our 2*R*,6*R*-HNK vaccine with ketamine. We will quantify drug concentrations in the central nervous system and serum by LC-MS analysis.

We are currently developing monoclonal antibodies that more specifically bind to 2*R*,6*R*-HNK. In the future we hope to run self-administration studies using monoclonal antibodies in place of vaccination to control for variable immune responses and achieve higher specificity.

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