Using an advanced operant behavioral task to assess the effects of chronic SERCA activation on attention and impulsivity in mice

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Introduction

Calcium (Ca^{2+}) is a critical cellular messenger that has been implicated in a wide variety of biological processes. Indeed, dysregulation of Ca2+ homeostasis has been proposed as a central mechanism in neurodegenerative diseases such as Alzheimer's and Parkinson's disease [1]. Notably, the sarco-endoplasmic reticulum Ca2+ ATPase 2 (SERCA2), which maintains proper endoplasmic reticulum (ER) calcium stores, has been identified as a key player in both normal Ca^{2+} homeostasis and in neuropathology [1,2]. Further, our lab has demonstrated that chronic activation of SERCA2 via the drug CDN1163 exerts distinct behavioral and neurochemical effects in naïve mice [3]. Recent studies have shown that chronic activation SERCA2 via the drug CDN1163 can alleviate cognitive functioning symptoms in transgenic mouse models of Alzheimer's disease, demonstrating its therapeutic potential [4]. However, no studies to date have investigated the effects of CDN1163 on memory, attention, or executive functioning in naïve mice. To this aim, we employed a state-of-the-art operant behavioral task, the 5-choice serial reaction time task (5-CSRTT), to investigate the effects of CDN1163 on attention and impulsivity. ***(For experiments investigating the effects of CDN1163 on long term memory, see Carter Moore's presentation!)***

Methodology

- **Animals –** C57BL/6J mice (N=24) were housed in a reversed 12-hour light and dark cycle for the duration of the experiments. Mice were food restricted to 90% of free-feeding body weight to enhance motivation for the task. All operant behavioral sessions lasted 30 minutes and were completed in a 9-hole operant chamber (Lafayette) (Figure 1).
- **Magazine Training and Fixed Ratio 1 –** Mice were first trained to pair the illuminated central hole with delivery of a reward solution (Yoohoo Milk) in the magazine tray. Following magazine training, FR1 training was administered, which required a single nose-poke into the central illuminated hole to acquire reward. FR1 was administered for 17d.
- **5-CSRTT Training –** Following FR1 completion, mice were trained on the full 5-CSRTT task, in which any of the 5 odd-numbered holes illuminated in a semi-random order. Following constant stimulus duration 5-CSRTT, mice were trained to baseline performance on the titration paradigm, in which task difficulty is adjusted by animal performance within during a session.
- **Titration Testing and CDN1163 administration –** 1h prior to the acute session, mice received a single dose of vehicle or CDN1163 (20mg/kg). Each day thereafter, mice were tested prior to drug administration for 16 additional days to assess chronic effects of CDN1163 on attention and impulsivity. Accuracy, omissions, and median stimulus duration were used as indices of attention, while premature responses indicated impulsive behavior. All titration data was analyzed via 2- or 3-way ANOVA.

Results and Conclusions

- No significant differences between CDN1163 and Veh-treated mice were found in either acute or chronic titration testing (Figures 3,4).
- Given these findings, pharmacological activation SERCA2 via CDN1163 appears to have no effect on attention or impulsivity in naïve mice.
- These findings add to the growing knowledge base of the behavioral effects of CDN1163 in both naïve and neurodegenerative disease animal models

References

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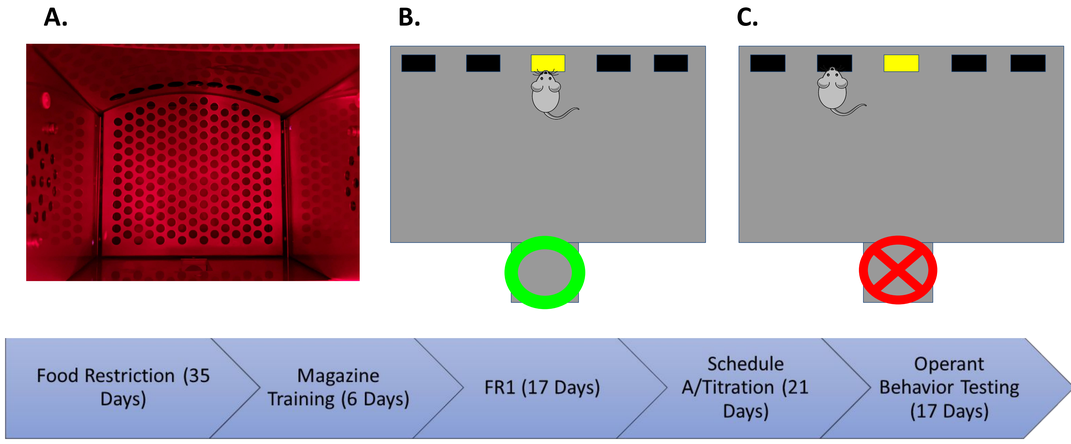

Figure 1: Operant behavior testing chamber. When a mouse nose-pokes the lit hole, reward is dispensed (B). When a Mouse nose-pokes the incorrect hole or omits a response, no reward is dispensed (C).

Figure 2: Project Timeline

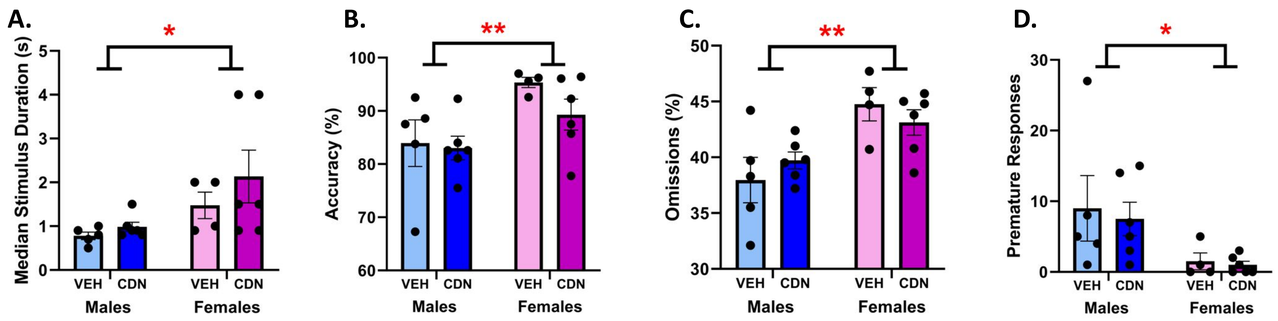

Figure 3: Acute Administration of CDN1163. No significant differences in measures of attention (Average Median Stimulus Duration, Accuracy) or impulsivity (Total Premature responses). *p>0.05; **p<0.01 statistically significant differences between male and female mice.

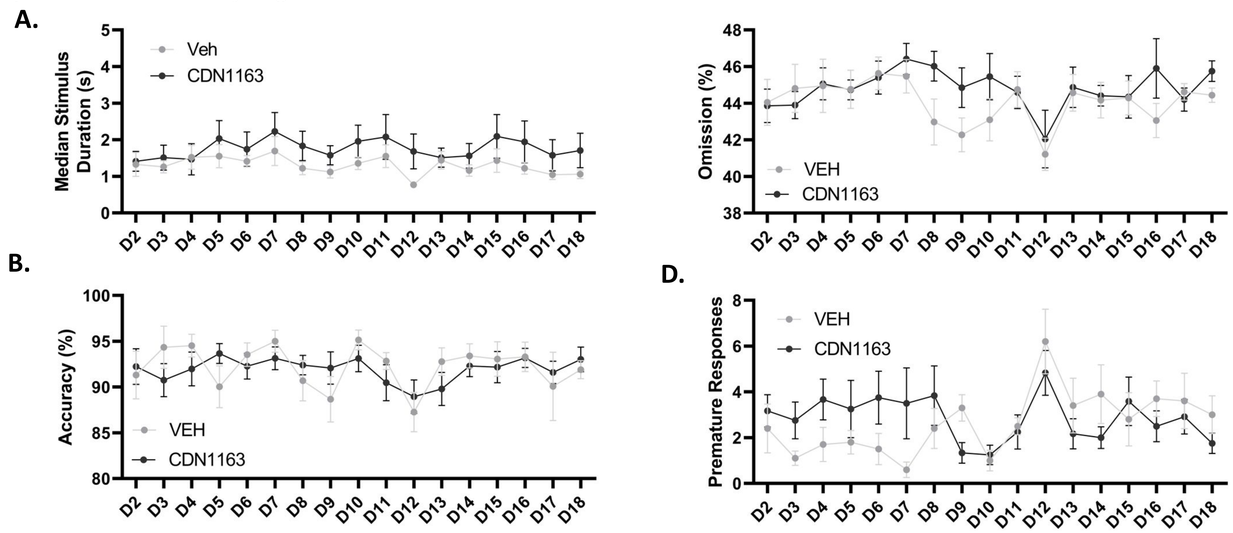

Figure 4: Chronic Administration of CDN1163. No significant differences between treatment groups in measures of attention (Average Median Stimulus Duration, Accuracy) or impulsivity (Total Premature responses).

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