Characterization of Motor Performance in a Mouse Model of Autism Fed a Ketogenic Diet in Early Adolescence

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Background

The ketogenic diet (KD) has long been used to control epilepsy, but more recently has also been shown to improve symptoms of Autism Spectrum Disorder (ASD) (D'Andrea et al., 2019). ASD is a highly prevalent disorder, characterized partially by repetitive behavior (NIH, 2022). Genetics, environmental conditions, and resultant injury to the brain, have been linked to an increased risk for ASD. KD is thought to work as an anti-inflammatory and has been shown to decrease repetitive behavior in a mouse model of ASD (Bechard and McElderry, 2023); but, how KD works within ASD is not well understood. This project works with a mouse model of ASD to determine if early KD intervention prevents the development of ASD behaviors in mice, and explores if glial fibrillary acidic protein (GFAP), a marker of inflammation, may be how KD helps ASD (Matta et al., 2019; Hu et al., 2020).

Mouse Model

Subjects were females from a population of FVBN/J mice that have a mutation that causes approximately half of the individuals within a given litter to develop a stereotypic spinning behavior as adults (at ~14 weeks for females).

Diet Intervention

Diets began at weaning (21 days of age). We fed KD (~75% fat), for 3 weeks to half of the mice (n = 11 females) and the other half of the offspring ate standard chow (n = 9 females). After the 3 weeks, all mice were returned to standard chow and remained on chow across behavioral phenotyping.

Hypothesis

We hypothesized that the mice would demonstrate increased motor performance and decreased repetitive behavior when fed KD in early adolescence, compared to the mice that ate standard chow.

Results

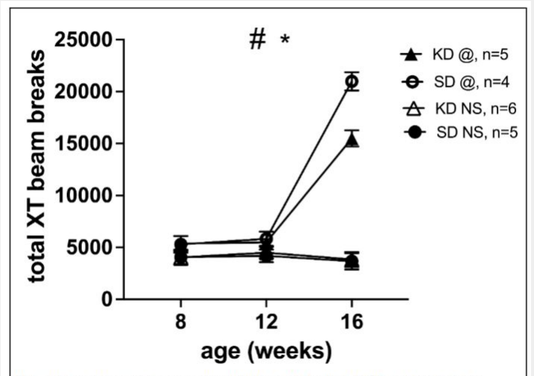

Figure 2 locomotor activity demonstrated by the total number of XT beam breaks in an automated locomotor box at 8, 12, and 16 weeks of age.

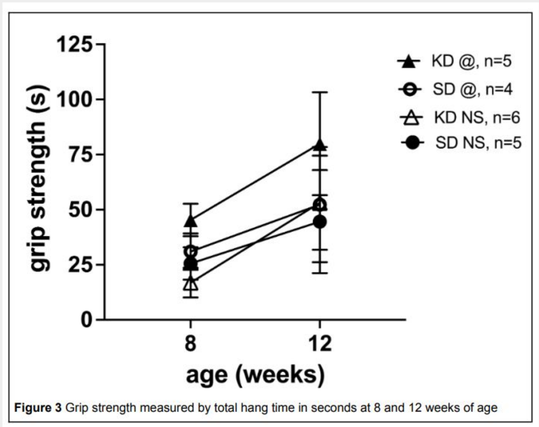

Figure 3 Grip strength measured by total hang time in seconds at 8 and 12 weeks of age

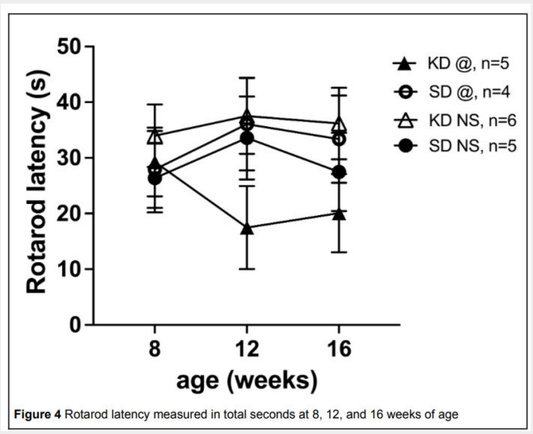

Figure 4 Rotarod latency measured in total seconds at 8, 12, and 16 weeks of age

Methods

Locomotor: : assesses the repetitive behavior in the mice through quantification of the repetitive behavior of the mice by counting the number of beam breaks that correlates with spinning
Grip Strength: measurement of muscle coordination and endurance by testing grip strength with a hanging wire. Latency to let go was recorded.
Rotarod: tests motor coordination and endurance by measuring the time and distance the mouse is able to keep their balance on a rotating rod.
Statistical analyses: For each dependent variable, we used a Repeated Measures ANOVA with Age (week 8, 12, 16) as the within-subject variable and Diet (KD vs SD) and Repetitive Behavior status (spinner vs non-spinner) as between-subject variables.

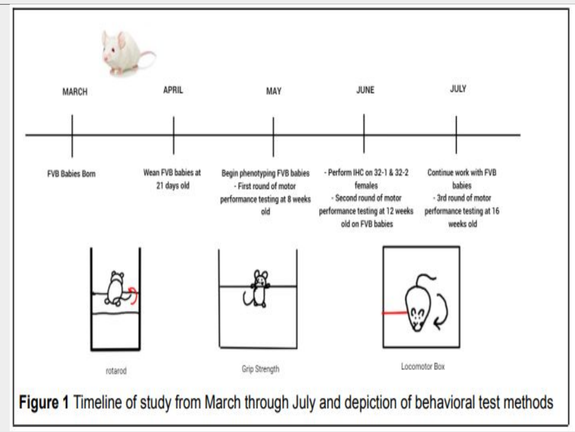

Figure 1 Timeline of study from March through July and depiction of behavioral test methods

Discussion and Future Directions

We saw the prevention of repetitive behavior development associated with KD but no change in strength or coordination. We were only able to see a difference in locomotor activity between diet groups of spinners as a result of the increased locomotor activity caused by the stereotypic behavior. where, mice that don't develop this behavior remain consistent in locomotor activity. It is therefore plausible that KD intervention targeted just the spinning behavior and effectively reduced the development of it. This may be a result of reducing the accumulation of neuroinflammation with age or influence on dopamine and adenosine signaling. Thus, a future hypothesis is that there would be an increased expression of glial proteins (e.g. GFAP) in the mice that have developed repetitive behavior and a decrease of that marker following KD intervention.

References

Bechard and McElderry (2023); 273: 114386; Brady et al. (2022); 422: 113748; CDC (2022); D'Andrea et al. (2019); 13: 5; El-Rashidy et al. (2017); 32: 1935-41; Elamin et al. (2017); 10: 377; Hu et al. (2020); 2020: 8396708; Jagadish et al. (2019); 32- 7; Mandecka and Regulska-Ilow (2022); 73: 247-58; Matta et al. (2019); 79: 75-90; Newell et al. (2016); 7: 37