



Effects of S-equol on obesity-associated depression and anxiety in male and female mice

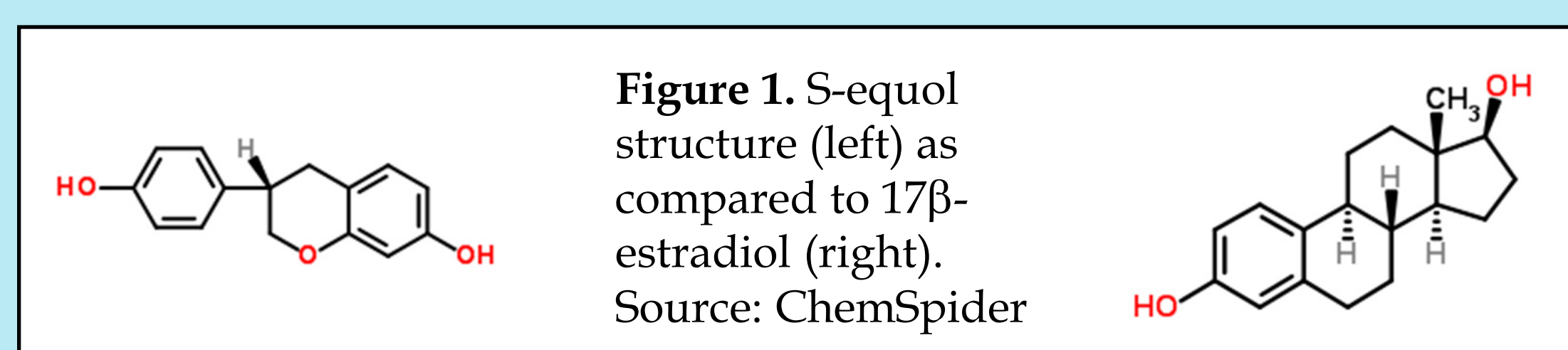


Karlee E. Cochran^{1,2}, Erin N. Bax^{1,2}, Jiude Mao^{1,2}, Cheryl S. Rosenfeld^{1,2,3}

¹Biomedical Sciences, University of Missouri, Columbia, MO; ²Bond Life Sciences Center, University of Missouri, Columbia, MO; ³Thompson Center for Autism and Neurobehavioral Disorders, University of Missouri, Columbia, MO

Introduction

S-equol is a non-steroidal estrogen metabolized from daidzein by intestinal microbiota. Previous studies attribute beneficial neurological and metabolic effects of this metabolite, including anti-depressive and anti-obesity effects¹. A correlation exists between obesity and mood disorders²; therefore, the question remains whether S-equol (**Figure 1**), which has a similar chemical structure as 17 β -estradiol (E2, **Figure 1**), can potentially mitigate the effects of obesity-induced depressive-like or anxiety-like behaviors. With both obesity and mood disorders on the rise, we sought to examine the potential ability of S-equol to improve depressive- or anxiety-like behaviors in a diet-induced mouse model of obesity (DiO).

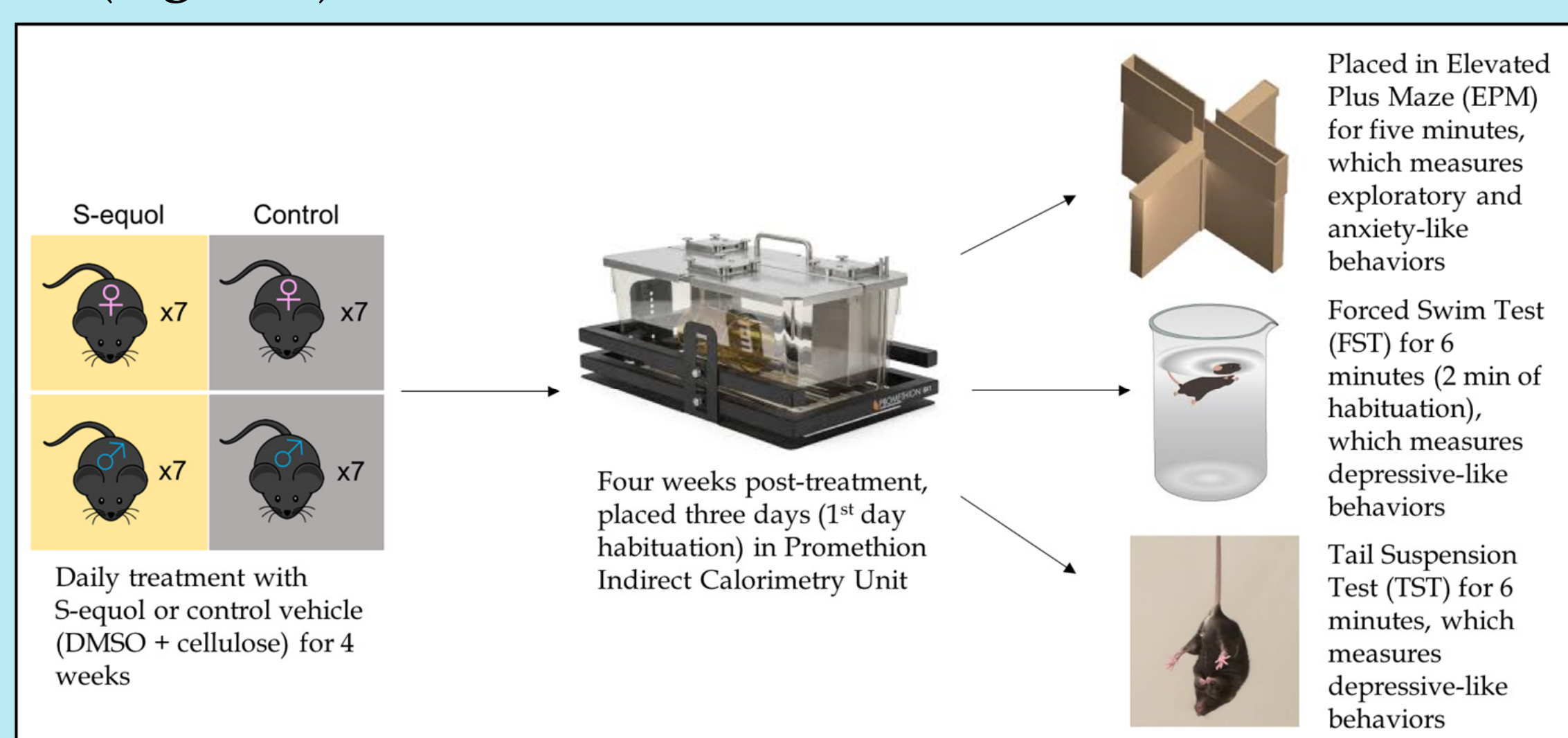


Hypothesis

We hypothesized that mice treated with S-equol would have reduced depressive- and anxiety-like behaviors compared to those not receiving this supplementation.

Methods

- Twenty-eight C57 mice were placed on a high fat diet (HFD) and randomly assigned to 4 groups: 7 females on S-equol, 7 females on control, 7 males on S-equol, and 7 males on control. The mice were six weeks old at start of studies.
- The mice were orally dosed (10 mg S-equol daily/kg body weight) for the total duration of the studies (8 weeks).
- Beginning at four weeks post-treatment, the following tests were performed: Metabolic Chamber, elevated plus maze (EPM), forced swim test (FST), and tail suspension test (TST) (**Figure 2**).



S-equol Treatment Reduces Depressive- and Anxiety-like Behaviors

Elevated Plus Maze Results

Duration of Exploratory Behavior

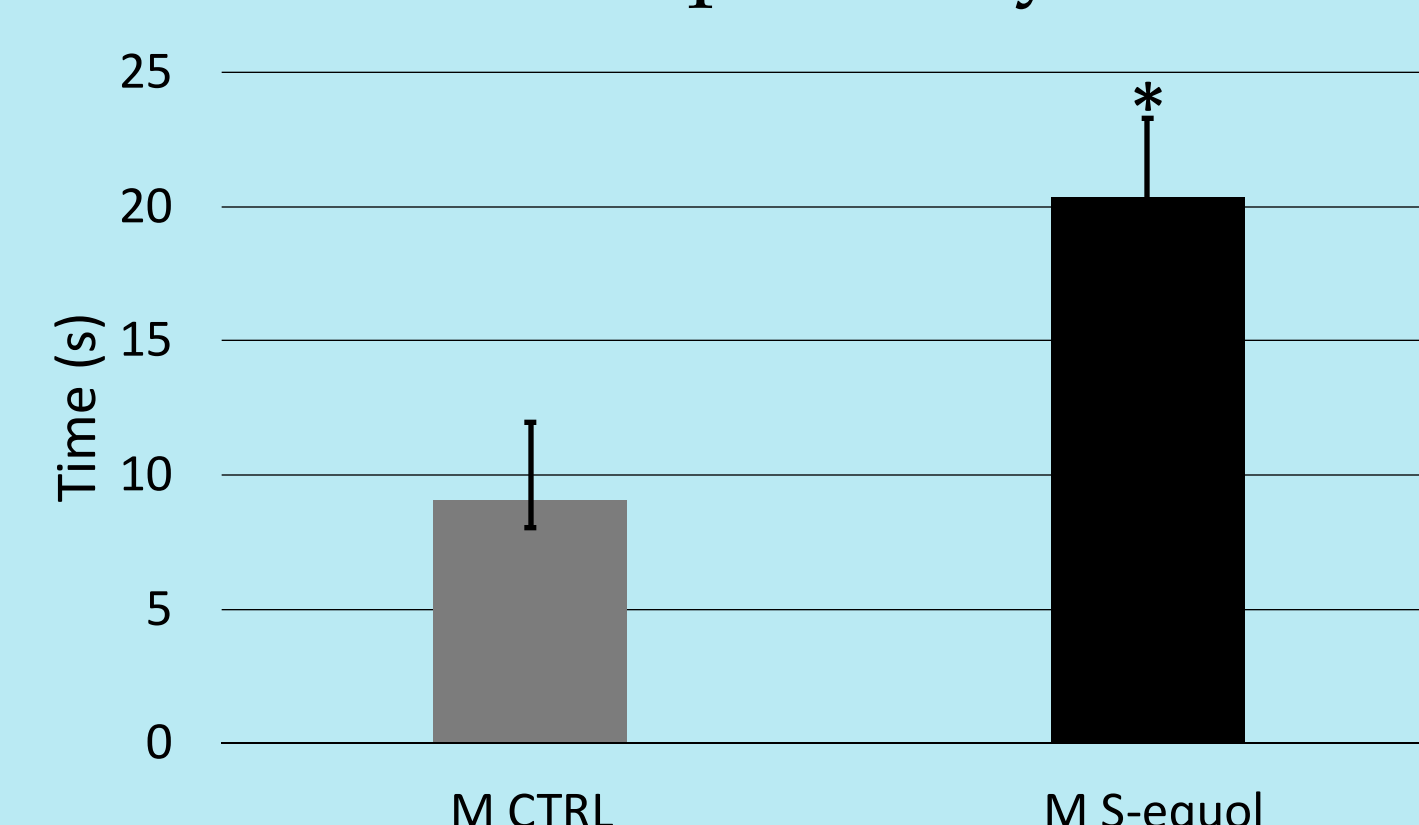


Figure 3. Male (M) S-equol mice had higher total exploratory behavior times (i.e. head dipping & rearing) than Male Control (CTRL) mice, suggestive of less anxiety during the maze testing. *p=0.01.

Tail Suspension Test Results

Duration of Time Spent Mobile

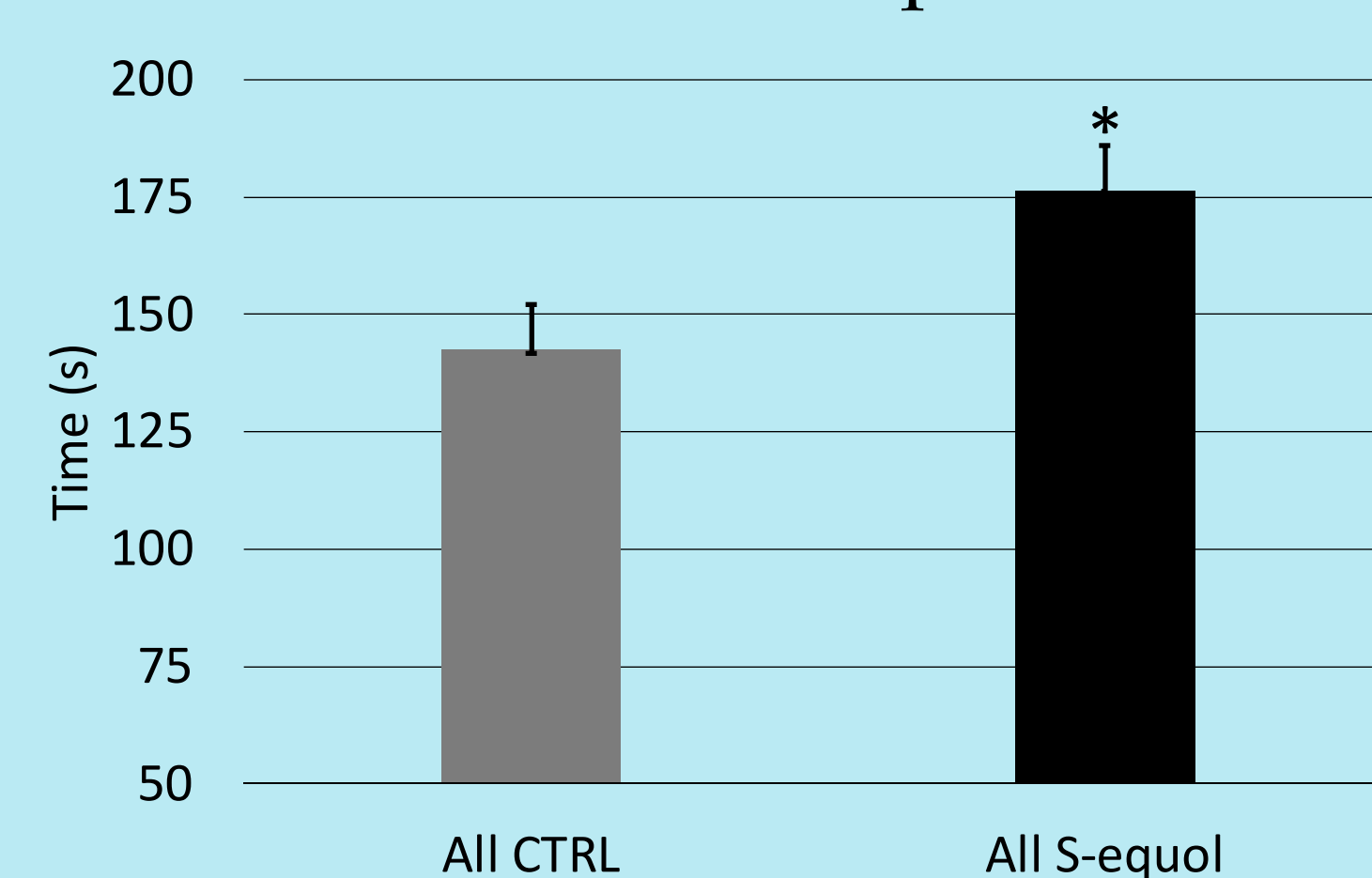


Figure 4. S-Equol mice (Males + females, M+F) spent more time mobile than Control mice (M+F), indicating reduced depressive-like behaviors. *p=0.02.

Metabolic Chamber Results

Meters Traveled

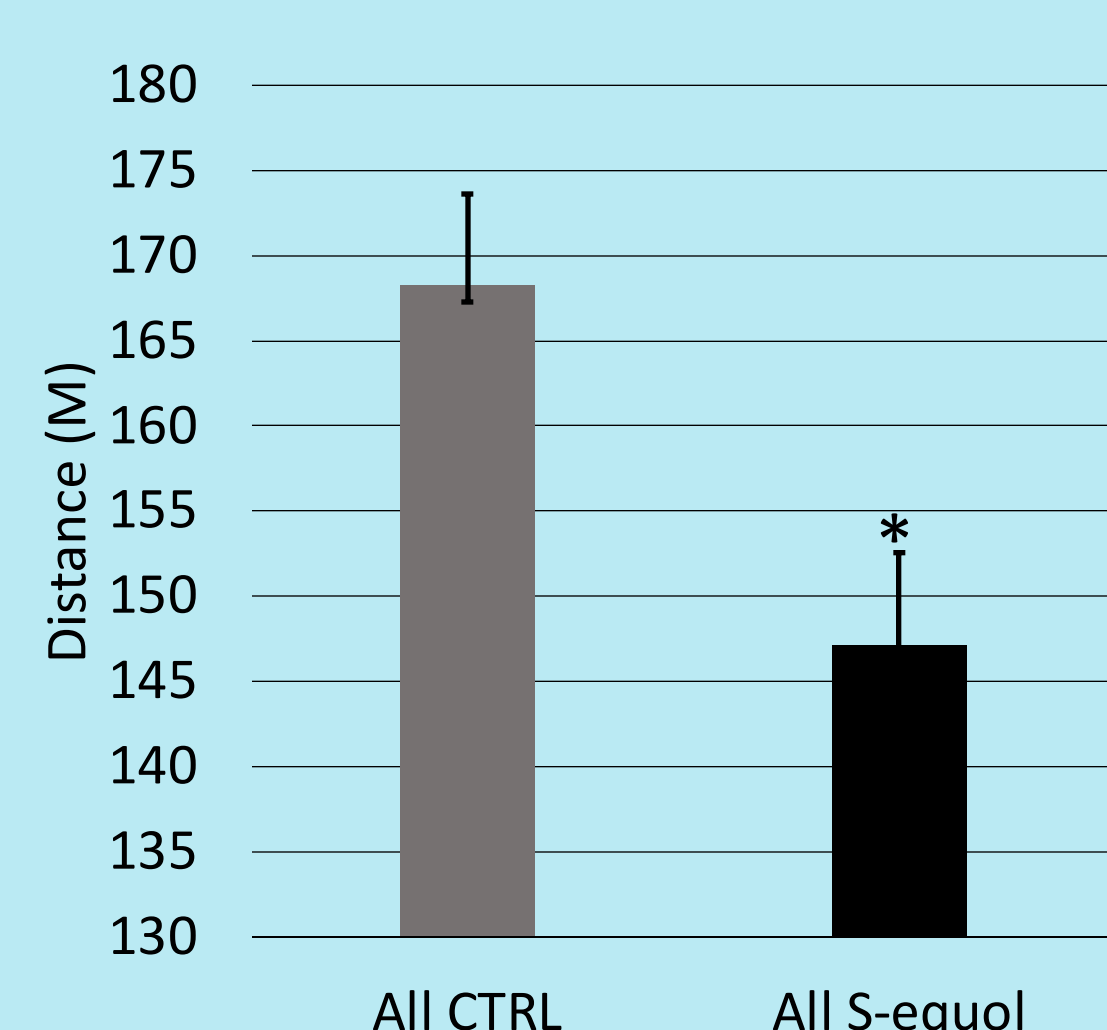


Figure 5. Control mice (M+F) traveled more distance than S-equol mice (M+F) over the two-day period spent in the metabolic chamber. *p=0.006.

% of Time Spent Sleeping

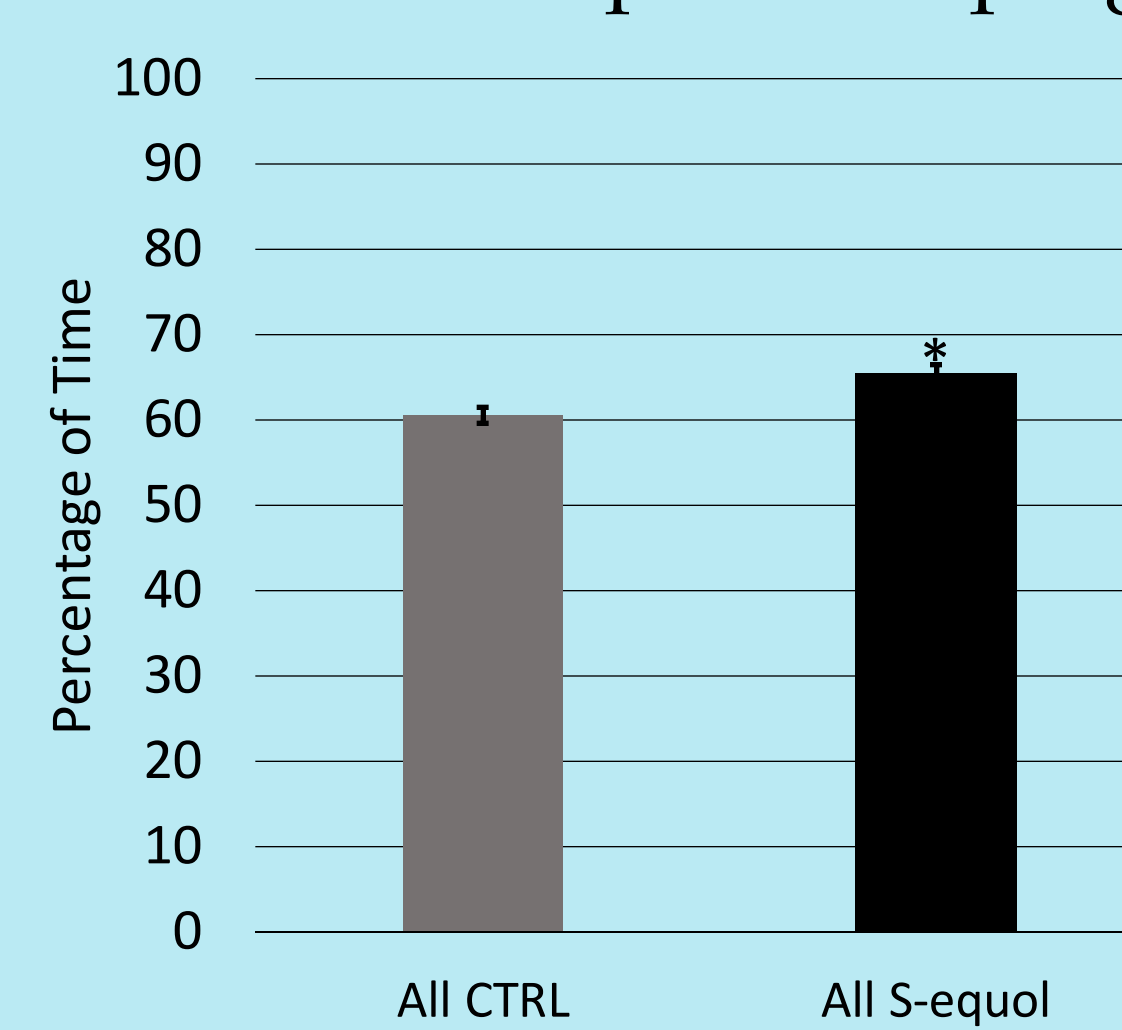


Figure 6. S-equol mice (M+F) spent more time sleeping than Control mice (M+F) over the two-day period spent in the metabolic chamber. *p=0.0003.

Conclusions & Future Aims

- The behavioral tests suggest that mice fed a HFD and treated with S-equol showed reduced anxiety-like behaviors as indicated by increased exploratory behaviors in a novel setting (EPM test), reduced depressive-like behaviors as evidenced by increased time spent mobile in the TST, and reduced anxiety-like behaviors as shown by percentage of time spent sleeping in the metabolic chamber.
- In contrast, mice fed a HFD and vehicle alone (CTRL) traveled more distance when tested in the indirect calorimetry unit, which approximates the homecage setting. Such behavior could, however, suggest increased overall anxiety-like behaviors.
- To test this possibility further, animals could be tested in an open field test, which also measures anxiety-like behaviors.
- Another possibility is that mice treated with S-equol are less active and correspondingly sleep more in the homecage setting, which may indicate such treatment affects their motivation to engage in voluntary physical activity.
- Future studies will also examine for gene expression differences in the amygdala, which regulates emotive behaviors, and nucleus accumbens, primary brain region mediating motivation to engage in voluntary physical activity.

References

1. Blake, C, et al. (2011). Neuromodulation by soy diets or equol: Anti-depressive & anti-obesity like influences, age- & hormone-dependent effects. *BMC Neuroscience* 12(28). doi:10.1186/1471-2202-12-28.
2. Mcelroy, Susan & Kotwal, Renu & Malhotra, Shishuka & Nelson, Erik & Keck, Paul & Nemeroff, Charles. (2004). Are mood disorders and obesity related? *The Journal of Clinical Psychiatry*. 65. 634-51, 730. doi:10.4088/JCP.v65n0507.



Acknowledgments

This research was funded by NIEHS 1R01ES025547-A1 to Cheryl S. Rosenfeld. Student support was provided by the University of Missouri College of Veterinary Medicine Office of Research. Special thanks to Rebecca Welly, Dr. Victoria Vieira-Potter, and other students in the laboratory.