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Project Title:	Circadian Rhythm Disruption and Gravitational Disturbance in a Lunar Mission Analog: Consequences for Muscle Function During and After the Mission		
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Space Biology Special Category:	None		
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	<p>Mechanical loading is the primary stimulus required for the maintenance and health of the musculoskeletal system. Exposure to microgravity or reduced gravity results in rapid bone loss and muscle atrophy, especially in the lower limbs. In recent years, the clock system in the skeletal muscle has been recognized to play a critical role in key aspects of muscle physiology, ranging from structural maintenance to functional regulation. On Earth, perturbations of the circadian rhythm affect muscle function and are associated with the development of sarcopenia. Reciprocally, studies have demonstrated that muscle activity can directly modulate the expression of muscle clock genes in a time-dependent fashion, and recent data suggest that the circadian clock could influence skeletal muscle adaptation in response to exercise training. Since Artemis astronauts will experience alterations in muscle condition and circadian rhythm simultaneously, it is critical to develop ground-based studies that will closely mimic this situation. While these stressors will occur temporarily, their effects may linger, and negatively influence muscle recovery after return from the mission. In this ground-based Early Career Investigator (ECI) proposal, I hypothesize that light cycle disturbances induced by a model of Chronic Jet Lag (CJL) will severely impact the peripheral muscle clock and, combined with altered gravity, will lead to additive negative effects during the disuse period. Moreover, I hypothesize that circadian disruption will have long-lasting effects that will significantly impair muscle recovery during the reloading period.</p> <p>SA1: To characterize the impact of circadian disturbance and partial gravity in a lunar analog in male and female rats. 60 adult outbred rats (30/sex) will undergo 7 days of exposure to partial weight-bearing at 20% of normal loading (PWB20) to simulate lunar gravity. 1 group will be exposed to a regular light cycle (LD), 1 group will be kept in constant light to induce circadian free-running (LL), and the experimental group will be exposed to CJL using a 6h phase advance every other day.</p> <p>SA2: To determine and compare the long-term effects of circadian disturbance and altered gravity during muscle recovery in males and females. 20 animals (10/sex) will be exposed to the same PWB20+CJL paradigm as in Aim 1. Animals will be allowed to recover for 7 days at normal loading (1g) and under a standard light cycle (LD).</p> <p>For this work, I plan on first assessing muscle health and function through regular testing including grip strength, fatigue resistance, force production, and muscle quality. I will also monitor circadian parameters and rest/activity over several 24h periods. Finally, I will perform biomolecular assays in the suprachiasmatic nucleus and soleus muscle, targeting specific genes involved in circadian rhythm entrainment, muscle function, and inflammation.</p> <p>This promising pilot study will help assess the additive effects of circadian disturbance in animals exposed to partial gravity and will help determine the existence of sex-based differences in response to spaceflight stressors. Moreover, I will determine sex-based differences during muscle recovery following disuse, and the long-term impact of circadian disturbance on muscle health and function. This study, which includes phenotypical and molecular outcomes, will assess the contribution of muscle clock genes and pathways to muscle health. Finally, targeted molecular assessment will help me use my diverse background (metabolism, neuromuscular, circadian) to explore other systems of interest that may be linked to muscle health and function (e.g., metabolic signaling pathways), and help characterize the key players that could be targeted with pharmacological approaches to provide new and effective countermeasures in future studies.</p>
Task Description:	
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>This research explores the combined effect of partial gravity and circadian disturbances on muscle health and if it impacts recovery. This work may help provide insights regarding the health and performance of the Artemis astronauts, and may lead to the development of new strategies and countermeasures for people on Earth experiencing shift-work or chronic jet lag</p>
Task Progress:	<p>This work has been delayed due to the Principal Investigator (PI) moving to another institution. We previously reported notable sex differences in young adult rats where, when exposed to mechanical unloading, females had a better ability to maintain musculoskeletal health than males. In our study, using 6 month old outbred animals coming from a different strain and under regular light cycles, we have replicated these findings. We also were able to detect notable differences regarding several circadian output parameters such as body temperature and grip strength.</p> <p>Our experiments in disturbed light conditions are currently ongoing.</p>
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