Project title: Investigating the disruptions within the core clock genes in the hindlimb unloading murine model, to develop novel strategies and countermeasures in space environments.
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Main Abstract: The loss of muscle mass and force is a hallmark of space flight (SF) [1] impairing crew performance and requiring rehabilitation upon return to Earth. Combined with microgravity-induced insulin resistance and low-grade inflammation, muscle atrophy increases the risk of chronic disease. Since SF shares adaptations with physical inactivity and disuse, extensive research has investigated the mechanisms underlying muscle mass and strength loss [1]. However, current countermeasures fail to fully prevent muscle atrophy and force loss [2] highlighting the need for deeper insight into the cellular and molecular mechanisms involved.

Microgravity also induces cephalad fluid shift determining intracranial pressure increase and structural brain changes post-flight, including ventricular enlargement and white matter alterations. Perivascular spaces are key anatomical components of the glymphatic system which controls, during the sleep, the clearance of waste products in the central nervous system, and is under circadian regulation [3]. Disrupted circadian rhythms in microgravity contribute to sleep disturbances [4], which are well documented in astronauts and compromise neurobehavioral function [5]. Moreover, terrestrial studies have shown that sleep deprivation hampers the brain's ability to clear molecules, suggesting that similar glymphatic dysfunction might occur in astronauts [6].

The Hindlimb Unloading (HU) model is a widely used model to simulate both the cephalad fluid shift and musculoskeletal disuse observed during spaceflight. Previous studies show that HU rapidly activates a transcriptional atrophy program (within 1 day), leading to measurable muscle loss within the first 3 days and progressing with prolonged disuse (14 days) [7]. Mitochondrial dysfunction and PGC1α downregulation are key contributors [8]. Importantly, key genes involved in this metabolic impairment are also under circadian regulation [9]. Moreover, long-term and acute HU model impacts at the central level on neuroelectrophysiological signals of brain cells [10].
Recent studies have mainly focused on the disruption of core clock genes, frequently overlooking the multifactorial nature of these disturbances in space environments.

Aims: This project aligns with this context and aims to investigate the impact of circadian clock desynchronization on muscle atrophy and its central nervous system implications by using the HU model

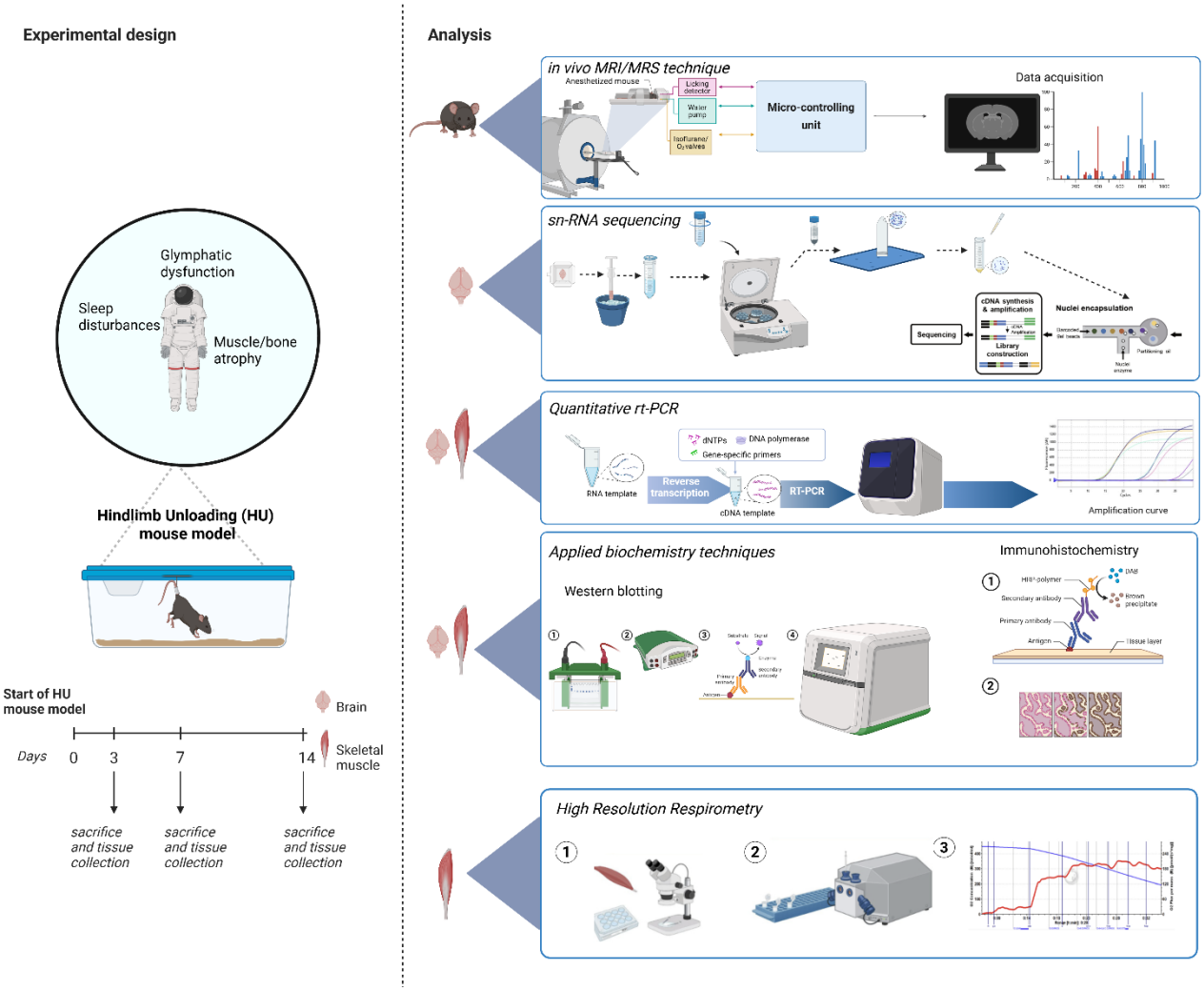
This project will investigate the circadian-regulation of muscle atrophy by examining time-dependent changes in core clock and genes involved in the transcriptional atrophic program. The circadian-driven glymphatic system dynamics will be further explored by imaging techniques encompassing the study of brain fluid dynamics and brain metabolite alterations by magnetic resonance.
The HU model will be applied at three distinct time points (3, 7, and 14 days) to capture the progression from early to potentially irreversible changes.

This project aims to address the following questions:

1. What are the temporal dynamics of circadian gene dysregulation and metabolic alterations in skeletal muscle during unloading?
2. Can reloading reverse core clock gene dysregulation and its downstream effects, and if so, what is the time course of recovery?
3. How does cell-to-cell communication change in the HU model?
4. To what extent is the dynamics of cerebral fluid distribution altered under unloading condition?
5. What is the impact on brain functionality?

Techniques: Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), single nucleus RNA sequencing, molecular biology techniques (quantitative rt-PCR), applied biochemistry techniques (Western Blot, immunohistochemistry), High Resolution Respirometry.

Graphical Abstract



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