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	POSTDOCTORAL FELLOWSHIP Musculoskeletal loss and the associated functional impairment affect broadly, including the elderly, patients with chronic diseases such as cancer, and astronauts. Microgravity in space breaks tissue homeostasis in skeletal muscle by activating proteolysis and inflammatory pathways, leading to muscle atrophy. SIRT1, a NAD+-dependent protein deacetylase, is a critical gene regulating metabolism and tissue homeostasis in skeletal muscle. Notably, activating SIRT1 inhibits protein degradation in skeletal muscle by counteracting the ubiquitin proteasome pathway. In addition, our recent results showed that activating SIRT1 by nicotinamide mononucleotide (NMN), an NAD+ precursor, reverses functional decline in skeletal muscle of aged mice by mimicking exercise. All of this evidence suggests that maintaining high NAD+ levels in muscle tissues is a practical and safe intervention strategy for preventing muscle atrophy. The goal of this proposal is to test if boosting NAD+ mitigates unloading-induced musculoskeletal loss. Specifically, we will investigate the following objectives. Objective 1: Determine the effect of NMN on mitigating unloading-induced musculoskeletal loss. We will use hindimb		
Task Description:	suspension (HS) in mice to simulate microgravity-induced muscle unloading. Our hypothesis is NMN administration during unloading mitigates muscle atrophy, bone loss, and functional impairment. We will also investigate if NMN alleviates slow-to-fast fiber type shift caused by muscle unloading, which significantly reduces fatigue resistance of the slow-twitch muscles.		
	Objective 2: Determine if NMN improves the effectiveness of exercise during unloading. As an exercise mimetics, NAD+ promotes the beneficial effects of exercise by activating SIRT1. We propose that raising NAD+ levels during exercise confers additive benefits than what exercise does alone. We will test if NMN administration augments the effectiveness of exercise and further mitigate musculoskeletal loss.		
	It is not clear why the current extensive exercise protocols are not sufficient to fully prevent muscle atrophy in space. This proposal will further elucidate the role of SIRT1 in the maintenance of skeletal muscle and bone, and test a very promising strategy to resist muscle atrophy during unloading. It will benefit human space exploration and the humans on Earth that suffer from muscle atrophy.		
Rationale for HRP Directed Researc	h:		
Research Impact/Earth Benefits:	In addition to spaceflight-caused muscle atrophy, aging, and many chronic diseases, such as cancer cachexia, all can lead to accelerated decline of muscle mass and strength and, as a result, increase the risk of physical disability and mortality. Thus, reducing the burden of muscle loss in aging and chronic conditions has broad and substantial public health benefits.		
	FINAL REPORTING OCTOBER 2020: Fellowship ended early7/31/2020.		
	During the entire funding period, we accomplished the following:		
	1) We established the hindlimb suspension mouse model in our lab.		
	2) We tested the effect of nicotinamide mononucleotide (NMN) on muscle weight during hindlimb suspension.		
	3) We analyzed slow-to-fast fiber type shift in unloaded muscles treated with NMN.		
	4) We examined the effect of NMN on bone mineral density and morphology using micro-computed tomography (µCT).		
	5) We compared the effect of NMN on muscle weight and slow-to-fast fiber type shift in young and old mice.		
	Detailed findings will be included in forthcoming manuscript.		
	ANNUAL REPORT FEBRUARY 2020		
Task Progress:	We have established the hindlimb suspension mouse model in our lab based on the literature. In a modified cage, the tail of the mouse was unloaded with a 30 degree angle between the torso and the floor of the cage. The mouse had easy access to the food and the water and freedom to move within the cage. The distance between the mice and the food was adjusted so that the mice could not step on the food with their hind legs. The mice adapted to the system within 2-3 days.		
	Using the suspension apparatus we have built, we tested the effect of NMN administration on muscle weight during hindlimb unloading. 6-month-old male C57BL/6J mice, which are equivalent to 20-30-year-old humans, were randomly allocated into six groups. Three groups were ambulatory (Ctrl), and three groups were hindlimb suspended (HS) for 14 days. Both Ctrl groups and HS groups were treated with vehicle (Ctrl-0 and HS-0) or NMN at 400 mg/kg/day (Ctrl-400 and HS-400) or 800 mg/kg/day (Ctrl-800 and HS-800) in drinking water 3 days before and during the two weeks of hindlimb suspension. We observed similar levels of muscle atrophy as previously published in hindlimb muscles of the HS-0 mice compared to the Ctrl-0 mice, including soleus, gastroenemius, tibialis anterior (TA), extensor digitorum longus (EDL), and quadriceps, validating our animal model.		
	To quantify the effect of NMN administration on preventing unloading-induced muscle atrophy, we calculated the relative muscle weight compared to the control groups after hindlimb suspension. 400 mg/kg/day of NMN treatment reduced muscle weight loss in soleus, gastrocnemius, and EDL. However, due to a higher variation in the vehicle-treated group, the difference was not statistically significant in soleus and gastrocnemius. The reasons for the higher variation in the HS-0 group remain unclear. We will increase the n value in the future experiments to increase statistical power. 800 mg/kg/day of NMN treatment did not alleviate muscle atrophy except in quadriceps, suggesting that 800 mg/kg/day NMN is beyond the dose to confer beneficial effect, at least in the hindlimb suspension model.		
	Bone mineral loss is also a major health threat to the astronauts during spaceflight. To assess the effect of NMN administration on bone mineral density and structure, we dissected and fixed the tibias and femurs to analyze bone mineral density and morphology. The samples are currently under investigation using micro-CT and immunofluorescence staining.		
	Slow-to-fast fiber type transition significantly decreases fatigue resistance of the slow-twitch muscles, which impairs		

the ability of muscles to sustain continuous work. At the molecular level, we detected a significant downregulation of a slow-twitch fiber gene Myl2, and an upregulation of a fast-twitch fiber gene Myh1 in the soleus after hindlimb suspension. We are currently quantifying the expression of the slow- and fast-twitch fiber genes in the NMN-treated mice. Considering that SIRT1 deacetylates and activates PGC-1a, a governor of the formation of slow-twitch fibers, we expect that activating SIRT1 by NMN administration will alleviate slow-to-fast transition and may preserve the fatigue resistance of the slow-twitch muscles.

Bibliography Type:

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