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TARGETING SR STRESS TO MITIGATE DISUSE-INDUCED MUSCLE ATROPHY DURING SIMULATED MICROGRAVITY.

Abstract

Mechanical loading is necessary for the development and maintenance of musculoskeletal system. Removal of loading via microgravity, paralysis and prolong bed rest leads to rapid loss of muscle mass and strength. Typically, the muscle atrophy and weakness sets up by 5-6 days of unloading and progressively become worse. To date, no effective pharmacological therapy exists to boost muscle mass and force during prolong unloading, partly because the mechanisms are poorly understood. Dysfunction of protein folding by Endo/Sarco-plasmic reticulum (ER/SR), a condition called ER/SR stress is implicated in diseases of various cell types, but its contribution to muscle detriment during mechanical unloading remains elusive. Recent evidence suggest that the chronic activation of SR stress and its downstream signaling pathways, the unfolded protein response (UPR) in the skeletal muscle is associated with various catabolic degenerative diseases and myopathies. Mitigating SR stress prevents muscle atrophy and/or weakness in congenital myopathies but such intervention has not been tested during mechanical unloading. Further, some component of UPR might be protective to muscle health which require proper dissection of relative role(s) of individual UPR arms in muscle impairment. However, establishing a direct causality between SR stress and muscle detriment during unloading requires measuring muscle mass and force in conditions with or without chronic SR stress, which has not been done to date. Due to difficulty of performing experimental interventions in humans, various animal models have been developed to recapitulate disuse muscle atrophy such as denervation, prolong sedation and cast immobilization. These experimental models induce muscle loss but fail to mimic conditions of prolong bed rest or space flight due to off-target effects of nerve injury, anesthetic drugs or mechanical strain by cast. Here, we are using a mouse model of hind-limbs suspension as an experimental model for microgravity-induced muscle loss. Hind-limbs suspension has an advantage over other models in recapitulating microgravity conditions because it induces muscle atrophy by mechanical unloading while still allowing limb movement. Currently, the mice hind-limbs are being subjected to 1 4 weeks of mechanical unloading and are injected with pan-SR stress inhibitors or inhibitors of individual UPR arms. We are measuring the degrees of activation of SR stress and its downstream effects on skeletal muscle biochemical and functional health at various time points of unloading. The gastrocnemius muscle from the hind-limbs is used for investigations because of large body of literature on the response of this muscle to disuse. We report no significant change in the body mass of the unloaded mice when compared to control group. However, there was significant atrophy (p ¡ 0.05) of the gastrocnemius muscles when compared to loaded control, starting at 6 days of unloading. Reduced muscle mass was partly due to significant reduction in the cross-sectional area (CSA) of single muscle fibers (p ¡ 0.05) in the gastrocnemius muscles, while the total fiber count was unchanged. The grip strength of the hind-limbs, adjusted to body mass was significantly reduced (p ¡ 0.05) when compared to loaded controls. These changes were accompanied by increased protein expression of SR chaperons GRP94 and BiP which relate to increase in the SR stress. Currently we are investigating the effect(s) of inhibition of pan-SR stress and individual UPR on the biochemical and functional properties of gastrocnemius muscles. Since currently no pharmacological drug exists to offset skeletal muscle atrophy and weakness associated with prolong disuse, our studies might offer novel therapeutic targets to skeletal muscle impairment during

conditions of prolong mechanical unloading such as microgravity.