IAF MICROGRAVITY SCIENCES AND PROCESSES SYMPOSIUM (A2)
Life and Physical Sciences under reduced Gravity (7)

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MITIGATION OF SR STRESS PREVENTS DISUSE MUSCLE ATROPHY IN A MOUSE MODEL OF SIMULATED MICROGRAVITY.

Abstract

Mechanical unloading of skeletal muscle is associated with contractile dysfunction and atrophy in a plethora of conditions such as microgravity, paralysis, and prolonged bed rest leads. The experimental mouse model of hind-limb unloading (HU) mimics several features of muscle unloading including atrophy and weakness. To date, no effective pharmacological therapy exists to boost muscle mass and strength during prolonged unloading. Dysfunction of protein folding by muscle endo/sarcoplasmic reticulum (ER/SR), a condition called ER/SR stress is implicated in several diseases, but its contribution to muscle impairment in unloading is not known. We hypothesized that SR stress is a major contributor to muscle impairment in HU mice, while mitigating SR stress with pharmacological inhibitors restore muscle mass and strength in these conditions. To test this hypothesis, four-month-old, male c57Bl6/j mice were subjected to HU for three weeks, which resulted in a 21 percent reduction in gastrocnemius muscle mass and 25 percent reduction in grip strength than the ground-based control mice. At the molecular level, the muscles showed an activation of essential markers of SR stress including SR chaperons GRP94, BiP and their downstream targets at the protein and/or mRNA levels. Treatment with 4-PBA, an SR stress inhibitor (100mg/Kg BW/d via I/P injections) partially restored the muscle mass and strength in these

mice along with reduced activation of the markers of SR stress. These changes were associated with reduced expressions of the markers of apoptosis and inflammation, the downstream targets of SR stress in the gastrocnemius muscles of HU mice. Taken together, our findings suggest that SR stress may play a pivotal role in muscle impairment in simulated microgravity, while pharmacological mitigation of SR stress may be an attractive molecular target to restore muscle mass and strength in these conditions. We are currently conducting transcript analysis to dissect further mechanistic linkage between SR stress and muscle detriment in simulated microgravity.