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PHARMACOLOGICAL INHIBITION OF ER STRESS MITIGATES TESTICULAR PATHOLOGY IN HIND-LIMB UNLOADED MICE.

Abstract

Reduced physical activity and cephalic fluid shift are common occurrences in prolonged bed rest and space flight and can lead to testicular dysfunction. Experimental mouse model of hind-limbs-unloading (HU) mimics spaceflight and bed rest and recapitulates several features of testicular anomalies in such conditions including disruption of tubular architecture and associated histological changes that together contribute to male infertility. However, an effective pharmacological intervention to these changes remain elusive, partly because molecular mechanisms are poorly understood. Disruption of protein folding by endoplasmic reticulum (ER) or ER stress is a common etiology in several diseases but its contribution to testicular pathology is not known. We hypothesize that HU is associated with activation of ER stress and subsequent disruption of normal testicular histology in a time-dependent manner, while treatment with 4-Phenylburtyrate (4-PBA; an ER-stress inhibitor) will reverse these changes to normal levels. To test this hypothesis, 4-months-old male c57B16/j mice were subjected to 14 and 28-days of HU. A significant

reduction in thickness and organization of seminiferous tubular epithelium and discontinuation of germ cell layers was seen after 14 days of HU. We also observed a significant increase in the tubular and luminal diameter along with a reduction in the density of spermatozoa at 14 days. These changes were further intensified at 28 days of HU and were associated with signature alterations in the Raman spectroscopic analysis of the HU testis. Importantly, treatment with 4-PBA for 3-4 weeks (100mg/kg BW/d via intraperitoneal injections) partially reversed most of the pathological changes in mouse testis. Collectively, our findings reveal the pivotal role of ER stress in triggering testicular pathology in conditions mimicking spaceflight and present 4-PBA as a potential therapeutic agent to prevent and/or reduce testicular disruption in such cases. Currently, we are characterizing the associated molecular phenotype in testicular disruption by mapping the global transcriptome and detailed Raman spectroscopic alterations in mouse testes under HU with and without 4-PBA treatment.