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PHARMACOLOGICAL RESTORATION OF ER PROTEIN HOMEOSTASIS REDUCED LIVER INJURY IN A MOUSE MODEL OF SIMULATED MICROGRAVITY

Abstract

Microgravity environment in spaceflight has detrimental effects on several body organs due to prolonged inactivity and cephalic fluid shift. Hepatic injury and metabolic alterations are a common consequence of exposure to microgravity environment; however, the molecular characterization of these changes is poorly understood. Prolonged dysregulation of protein folding by endoplasmic reticulum (ER), a condition called ER stress is implicated in several diseases. However, its contribution to hepatic injury and metabolic alterations in microgravity is not known. We have recently developed a mouse model of microgravity or hindlimb unloaded (HU) mouse, which recapitulates several systemic consequences of spaceflight including hepatic injury and metabolic compromise. Here, we hypothesized that HU-induced hepatic alterations are associated with activation of ER stress, while pharmacological inhibition of ER stress can partially restore hepatic and metabolic health. To test this hypothesis, we subjected four-month-old, male c57Bl6/j mice to HU for periods ranging from two to four weeks, followed by collection and analysis of hepatic tissues for histological and molecular evaluation. HU resulted in significant apoptosis of hepatocytes along with disruption of hepatic architecture, when compared to the control ground-based mice. We

also found an upregulation of the essential markers of ER stress including ER chaperons BiP and GRP94. Treatment with 4-PBA, an ER stress inhibitor (100mg/Kg BW/d via I/P injections) incompletely restored hepatic morphology along with markers of ER stress to the normal levels. These changes were mirrored in the Raman spectroscopic analysis of the global molecular phenotypes of liver tissues. Taken together, our findings suggest that the ER stress may play a pivotal role in microgravity-induced hepatic injury while pharmacological inhibition of ER stress may partially restore liver health in HU. Presently we are confirming and extending our findings by performing a global transcriptomic and Raman spectroscopic analysis of the liver tissues in HU with or without 4-PBA treatment.