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ENDOPLASMIC RETICULUM STRESS INDUCES VASCULAR ENDOTHELIAL INFLAMMATION AND APOPTOSIS DURING MICROGRAVITY SIMULATION

Abstract

Exposure to microgravity results in vascular remodeling and cardiovascular deconditioning in astronauts, which poses a threat to spaceflight safety and the health in astronauts. To elucidate the mechanism for this condition, we investigated whether endoplasmic reticulum (ER) stress during simulated microgravity induced endothelial inflammation and apoptosis of human umbilical vein endothelial cells (HUVECs). Microgravity was simulated by clinorotation in present study. We examined the biomarkers of ER Stress (CHOP and GRP78), protein abundance of endothelial/inducible NO synthase (eNOS/iNOS), pro-inflammatory cytokines, NF-κB/NLRP3 inflammasomes and detected the apoptosis in HUVECs. We found that the levels of CHOP and GRP78, pro-inflammatory cytokines (TGF-β, IL-6, TNF-, IL-8 and IL-2) and eNOS/iNOS protein were upregulated by clinorotation. These alterations were partially restored by ER stress inhibitors TUDCA and 4-PBA. ER stress inhibitors and NOS inhibition with L-NAME dramatically suppressed the activation of NF-κB/NLRP3 pathway and the pro-inflammatory cytokines production. The protein abundance of pro-caspase1, caspase-1 and apoptosis-associated speck-like protein (ASC) was upregulated by clinorotation, which suggested an increase of apoptosis in HUVECs. The increased apoptosis of HUVECs by clinorotation was significantly suppressed by inhibiting ER stress, NOS activity and NF-κB/NLRP3 pathway. Therefore, simulated microgravity results in ER stress in HUVECs, and thereafter activates iNOS/NO/NF-κB/NLRP3 inflammasome signaling pathway, which plays key roles in regulating endothelial inflammation and apoptosis.