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MITOPHAGY REGULATES CIRCADIAN RHYTHMS DISTURBANCE INDUCED BY SIMULATED SPACE ENVIRONMENTS

Abstract

Long-term spaceflight leads to disrupted circadian rhythms and increased oxidative stress in astronauts, triggered by factors such as microgravity, isolation, and radiation environments, ultimately having a detrimental effect on their health and performance. Recent studies show that oxidative stress plays a crucial role in regulating the circadian rhythms by activating clock proteins in response to external environmental changes. Our previous study has demonstrated that the core antioxidant protein NRF2 regulates the clock protein CLOCK to modulate circadian rhythms. Hence, oxidative stress might be an important mechanism for altering circadian rhythms during spaceflight conditions. In the present study, we established a tail suspension combined isolation (TSI) model to simulate the space microgravity and confined environment. The results indicated that the TSI environments imposed circadian disruption of core body temperature, heart rate, activity, and serum hormones rhythms of rats. In TSI model rats' SCN, a central pacemaker in circadian rhythms, core circadian gene NR1D1 showed higher protein level along with decreased BMAL1 level. Mechanistically, reduced causative mitophagy, subsequent mitochondrial dysfunction and enhanced oxidative stress were observed in the SCN of TSI models. We also found the autophagosome marker LC3 can directly bind to NR1D1 via the LC3-interacting region (LIR) motifs and induced the degradation of NR1D1 in a mitophagy-dependent manner. Defects in mitophagy led to the reversal of NR1D1 degradation, thereby suppressing the expression of BMAL1. The antioxidant urolithin A (UA) demonstrated a beneficial effect in counteracting circadian rhythm disorders caused by the TSI environment through promoting mitophagy and reducing oxidative stress levels. In summary, these findings implicate defects in mitophagy under simulated space environments might be the cause of disrupted circadian rhythms in rats. The antioxidant UA could regulate the circadian rhythms of the SCN by degrading NR1D1, making mitophagy activation a potential target for improving circadian rhythm disturbances during long-term spaceflight. Keywords: Space flight; Simulated space environments; Circadian rhythms; Oxidative stress; Mitophagy