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GENOMICS AND PROTEOMICS ANALYSIS OF HIPPOCAMPUS REVEALS POTENTIAL MECHANISMS UNDERLYING SPATIAL MEMORY DEFICIENCY INDUCED BY LONG-TERM SIMULATED MICROGRAVITY

Abstract

Spaceflight produces profound effects on central nervous system function due to microgravity reflecting stress in the brain. It has been demonstrated that simulated microgravity may lead to cognitive dysfunction. However, the underlying mechanism remains unclear. In present study, tail-suspension rats were employed to explore the effects of 28 days of simulated microgravity on hippocampus-dependent learning and memory capability and the underlying mechanisms. We found that 28-day tail-suspension rats displayed decline of spatial learning and memory ability in Morris water maze test, and oxidative stress in hippocampus was increased after simulated microgravity in consideration of the decreased expression of Nrf2 and declined activities of T-SOD, CuZn-SOD, GSH-PX and T-AOC. Using RNA-seq based genomics and iTRAQ-based proteomics analysis, a total of 849 genes and 147 proteins were found to be differentially expressed in hippocampus. Further analysis showed these differentially expressed genes and proteins involved in different molecular function categories, and participated in many biological processes (such as metabolism, immunity, cytoskeleton, synaptic transmission, apoptosis, transcription regulation). Based on the results of further RT-PCR and western blot verification, we found the expression of HIF-1α and HIF-2α, the master regulators of oxygen homeostasis, were significantly increased. The expression of PDK1, LDHA and VEGF, three well-defined downstream targets of HIF-1α, were up-regulated in hippocampus after 28 days of simulated microgravity exposure. Brain oxygen saturation and blood flow were also significantly reduced. Additionally, the expression of GluR1and GluR4 involved in metabotropic glutamate receptor group III pathway and ionotropic glutamate receptor pathway were significantly induced by simulated microgravity. Moreover, an increased concentration of glutamic acid was also found in hippocampus while the concentration of 5-HT, dopamine, γ- GABA and epinephrine were decreased. Further HE and Nissl staining showed the number of hippocampal neurons was declined; The expression of apoptosis related molecules, Bax and caspase-3, were significantly increased in hippocampus after 28 days of simulated microgravity exposure. These findings indicate that simulated microgravity might cause an alteration in oxygen homeostasis, and result in glutamate excitotoxicity in hippocampus, which may provide novel insight into better understanding of how simulated microgravity affects the function

of hippocampus and a new direction to the development of countermeasure for brain dysfunction during spaceflight.

Key words: spaceflight; simulated microgravity; cognitive dysfunction; hippocampus; oxygen homeostasis; excitotoxicity