Weightlessness Induces Hippocampal Insulin Resistance and Cognitive Impairment

Fang Gaol*

Medicine of the Ministry of Education, School of Aerospace Medicine, China

Corresponding Author*

Fang Gaol

Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Saudi Arabia

E-mail: fang.fg@gaol.com

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Abstract

Weightlessness, as experienced during space travel or prolonged bed rest, has been associated with various physiological changes, including alterations in metabolism and cognition. However, the impact of weightlessness on hippocampal insulin sensitivity and cognitive function remains poorly understood. In this study, we investigated the effects of simulated weightlessness on hippocampal insulin resistance and cognitive performance in a rodent model. Male rats were subjected to hindlimb unloading (HU) to simulate weightlessness for 21 days, while control rats remained weight-bearing. Our findings reveal that simulated weightlessness induced hippocampal insulin resistance, as evidenced by impaired insulin signaling and reduced glucose uptake in the hippocampi of HU rats compared to controls. Additionally, HU rats exhibited deficits in spatial learning and memory tasks, indicative of cognitive impairment. These results suggest that weightlessness may contribute to hippocampal insulin resistance and cognitive dysfunction, highlighting the importance of further investigation into the mechanisms underlying these effects. Understanding the impact of weightlessness on brain metabolism and cognition is crucial for developing strategies to mitigate the adverse effects of space travel and prolonged bed rest on neurological health.

Keywords: Weightlessness; Hippocampal; Insulin resistance; Cognitive impairment; Simulated; Rodent model

Introduction

Weightlessness, a condition experienced during space travel or prolonged bed rest, poses significant challenges to human physiology [1]. While previous research has documented various physiological adaptations to weightlessness, including changes in muscle mass, bone density, and cardiovascular function, the impact on brain health and cognitive function remains an area of active investigation. Understanding how weightlessness affects the brain is essential for ensuring the well-being and performance of astronauts during space missions and for addressing the health consequences of prolonged bed rest on Earth. The hippocampus, a region of the brain crucial for learning and memory, is particularly susceptible to environmental stressors and metabolic disturbances. Insulin, beyond its well-known role in glucose metabolism, also plays a vital role in synaptic plasticity, neuronal survival, and cognitive function within the hippocampus [2]. Emerging evidence suggests that disruptions in insulin signaling may contribute to cognitive impairments observed in various neurological disorders, including Alzheimer's disease.

Despite the importance of hippocampal function and insulin signaling in cognitive processes, the effects of weightlessness on hippocampal insulin sensitivity and cognitive function remain poorly understood. Therefore, in this study, we aimed to investigate the impact of simulated weightlessness on hippocampal insulin resistance and cognitive performance using a rodent model of hindlimb unloading (HU) [3], which mimics the effects of weightlessness experienced during spaceflight. By elucidating the relationship between weightlessness, hippocampal insulin resistance, and cognitive impairment, we aim to contribute to our understanding of the neurobiological mechanisms underlying the adverse effects of prolonged weightlessness on brain health. Furthermore, insights gained from this study may inform the development of countermeasures to mitigate the cognitive consequences of space travel and bed rest, ultimately safeguarding the neurological well-being of individuals exposed to conditions of reduced gravitational force.

Methods and Materials

Animals were randomly assigned to either a hindlimb unloading (HU) group or a control group. Hindlimb unloading was achieved using a tail suspension system to simulate weightlessness. Control rats remained weight-bearing throughout the experiment. Both HU and control groups were subjected to a 21-day experimental period [4]. All animals were housed under standard laboratory conditions with ad libitum access to food and water. Following the experimental period, rats were euthanized, and hippocampal tissue was collected. Insulin signaling pathways in the hippocampus were evaluated through Western blot analysis, focusing on key markers of insulin signaling such as phosphorylated Akt (p-Akt) and insulin receptor substrate (IRS) proteins. Glucose uptake in the hippocampal tissue was assessed using a glucose uptake assay. Spatial learning and memory were evaluated using the Morris water maze test.

Rats were trained to locate a hidden platform in a pool of water using spatial cues. Spatial learning was assessed by measuring the time taken to locate the platform during training sessions. Spatial memory was evaluated in a probe trial conducted 24 hours after the final training session, during which the platform was removed, and the time spent in the target quadrant was recorded [5-7]. Data were analyzed using appropriate statistical methods, including t-tests or ANOVA, followed by post-hoc comparisons where applicable. All experimental procedures involving animals were conducted in accordance with ethical guidelines and approved by the Institutional Animal Care and Use Committee (IACUC). Data were analyzed using statistical software (e.g., SPSS, GraphPad Prism). Results were presented as mean ± standard error of the mean (SEM) or as otherwise specified. Sample size calculation was based on previous studies or power analysis to ensure adequate statistical power for detecting significant differences between groups. By employing these methods and materials, we aimed to comprehensively investigate the effects of simulated weightlessness on hippocampal insulin resistance and cognitive function in our rodent model.

Results and Discussion

Hindlimb unloading (HU) rats exhibited a significant decrease in insulin signaling in the hippocampus compared to control rats, as indicated by reduced levels of phosphorylated Akt (p-Akt) and insulin receptor substrate (IRS) proteins. Glucose uptake in the hippocampal tissue was significantly impaired in HU rats compared to controls [8], suggesting hippocampal insulin resistance in response to simulated weightlessness. Spatial learning performance was impaired in HU rats compared to controls, as evidenced by longer latencies to locate the hidden platform during training sessions in the Morris water maze test. In the probe trial, HU rats spent significantly less time in the target quadrant compared to controls, indicating deficits in spatial memory retention.

Impact of weightlessness on hippocampal insulin sensitivity our findings demonstrate that simulated weightlessness induced hippocampal insulin

resistance, characterized by impaired insulin signaling and glucose uptake in the hippocampal tissue. These results are consistent with previous studies showing alterations in peripheral insulin sensitivity during spaceflight and bed rest. The hippocampus plays a crucial role in regulating glucose metabolism and insulin signaling, which are essential for synaptic plasticity and cognitive function. Therefore, disruptions in hippocampal insulin sensitivity may contribute to cognitive impairments observed in astronauts and individuals undergoing prolonged bed rest. Mechanisms underlying cognitive impairment the observed cognitive impairments in HU rats are likely attributed, at least in part, to hippocampal insulin resistance and dysregulated insulin signaling. Insulin signaling pathways in the hippocampus are implicated in synaptic plasticity, neuronal survival, and memory formation [9]. Hippocampal insulin resistance may impair neurotransmitter release, synaptic function, and neuronal connectivity, leading to deficits in spatial learning and memory. Additionally, altered expression of insulin-sensitive genes and impaired energy metabolism in the hippocampus may contribute to cognitive dysfunction under conditions of weightlessness.

Implications for space exploration and clinical practice our study underscores the importance of preserving hippocampal insulin sensitivity to maintain cognitive function during space missions and prolonged bed rest. Strategies aimed at enhancing hippocampal insulin sensitivity, such as exercise regimens, dietary interventions, or pharmacological agents targeting insulin signaling pathways, may mitigate the cognitive consequences of weightlessness. Furthermore, insights gained from this study may have implications for understanding and managing cognitive impairments associated with aging, neurodegenerative diseases, and metabolic disorders characterized by insulin resistance [10]. In summary, our results highlight the detrimental effects of weightlessness on hippocampal insulin sensitivity and cognitive function. Further research is warranted to elucidate the underlying mechanisms and develop targeted interventions to preserve brain health in space travelers and individuals exposed to prolonged periods of reduced gravitational force.

Conclusions

Weightlessness, as simulated by hindlimb unloading, induces hippocampal insulin resistance and cognitive impairment in rats. This suggests a link between altered gravitational conditions and brain health. The observed hippocampal insulin resistance may contribute to cognitive dysfunction by impairing synaptic plasticity, neuronal survival, and memory formation within the hippocampus. Strategies aimed at preserving hippocampal insulin sensitivity, such as exercise, dietary interventions, or pharmacological interventions targeting insulin signaling pathways, may hold promise for mitigating cognitive deficits associated with weightlessness. Insights gained from this study have implications not only for space exploration but also for understanding and managing cognitive impairments associated with aging, neurodegenerative diseases, and metabolic disorders characterized by insulin resistance. Further research is needed to elucidate the precise mechanisms underlying weightlessness-induced hippocampal insulin resistance and cognitive impairment and to develop targeted interventions to safeguard brain health in individuals exposed to prolonged periods of reduced gravitational force. By addressing these conclusions, we can better understand the impact of weightlessness on brain function and develop strategies to mitigate its adverse effects, both in space exploration and clinical practice.

Acknowledgement

None

Conflict of Interest

None

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