Effects of Microgravity on the Hypothalamic-Pituitary-Adrenal Axis and Cellular Immunodeficiency: Implications for Long-term Space Missions

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Microgravity is one of the most significant physiological challenges extraterrestrial life imposes upon the human body. Numerous anecdotal and experimental accounts of elevated psychological stress and immunodeficiencies have been reported. Yet, their precise physiological reasons and correlations to space's unique physical factors remain to be investigated. This paper examines data from two research articles examining stress-responsive hormone secretions and the changes in expression levels of genes pertinent to innate immunity (CD69, CD25, STAT5, and STAT1) to extrapolate physiological patterns under simulated microgravity. Such results highlight the necessity of creating efficient measurement techniques to mitigate the harmful effects of microgravity on psychological and immune health.

Introduction

The 2020s is a crucial decade in which both governmental organizations and private corporations recognize the immense scientific and economic potential behind space exploration. To further promote such explorations, astronauts must first assess the prospects of vitality and its risks in extraterrestrial environments. This task might be highly burdensome to astronaut health, as they must adapt and survive in an outcast climate with physical factors alien to those of Earth, including hazardous radiation, microgravity, and perpetual darkness. Health issues about prolonged extraterrestrial life usually occur through physical symptoms such as organ failure and cancer development. However, we must not overlook investigating physiological stress about extraterrestrial physical conditions in light of the growing awareness of the significance of such.

As anecdotal reports of psychological stress have existed since the first missions of human spaceflight, researchers and experts have long recognized human spaceflight as a progenitor for detriments in mental health. For instance, experiments such as Project Mercury in the early 1960s, though unaware of precise physiological reasons, demonstrate deteriorated psychological capabilities in extraterrestrial environments[1]. In light of progressions in scientific knowledge and the accumulation of genomic data through investigations such as the Twins Study, recent analyses of the causality between human spaceflight and psychological stress have increasingly proceeded toward neurophysiological bases[2].

Due to its regulation in the orientation of various interstitial and extracellular fluids, gravity has been one of the most significant driving factors of physiological evolution. Consequently, exposure to altered gravitational fields yields catastrophic adverse effects on human physiology, including functional declines in the central nervous system and other biological pathways governing emotional and cognitive functions[3]. In a six-month study aboard the International Space Station (ISS), astronauts exhibited significant cognitive and motor skills dysfunctions compared to baseline measurements taken at ground level[2,4]. Microgravity can be simulated for experimental purposes through a method known as Head-Down Tilt Bedrest (HDTB), where individuals lay on a flat surface tilted at various angles.

Recent studies aim to utilize biomarkers contingent to such in analyzing and determining physiological inevitabilities of psychological stress during human spaceflight, regarding the intimate interdependence between the HPA axis and the immune system and microgravity's potential as a disruptive agent[5,6,7]. Therefore, the objective of this paper is to summarize such physiological pathways and to review changes in expression levels of several indices related to them based on recent studies, including a 2001 study by Choukèr et al.[5], and a 2021 study by Spatz et al.[7]. Furthermore, this review might be expedited to identify proper biomarkers to be analyzed to detect the onset of psychological stress in real-time.

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

All psychological stress responses begin with the stria terminalis (BNST) bed nucleus, a complex neuroanatomic structure significantly involved with psychological stress response[8].

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The most significant pathways activated by stress stimuli interpreted by the BNST is the hypothalamic-pituitary-adrenal (HPA) axis, stimulating the stress-responsive hormones glucocorticoids and catecholamines, contributing against psychological stress through different means[9]. Glucocorticoids direct energy expenditure and metabolic responses to dissipating prolonged stress[10]. Conversely, catecholamines induce physical adaptations such as increased heart rate and oxygen intake to modulate immediate fight-or-flight responses[11].

The HPA axis is a neuroendocrine pathway composed of the hypothalamus, anterior pituitary, and adrenal cortex for psychological stress response initiated by corticotropin-releasing hormone (CRH) release from the BNST's hypothalamic paraventricular neurons (PVN). The PVN, projecting to the median eminence, releases CRH and other peptides, such as vasopressin (AVP), to the anterior pituitary through the hypophysial portal plexi of veins. Such peptides bind to corticotropin-releasing hormone R1 receptors (CRHR1), a type of G-protein coupled receptors, and activate adenylate cyclase, stimulating the transcription and eventual differentiation of proopiomelanocortin (POMC), a precursor hormone to ACTH, via a mechanism dependent on cAMP/protein kinase A[10]. Released ACTH interacts with melanocortin 2 receptors (MC2R) in the zona fasciculata of the adrenal cortex, elevating adenylate cyclase-dependent intracellular cAMP levels[12]. Such interactions elevate cholesterol levels and precursor substances for steroid hormones such as mineralocorticoids and glucocorticoids, with the latter eventually secreted to redirect energy expenditures for stress mitigation. In the absence of psychological stress, the HPA axis halts itself via negative feedback to prevent further changes in energy usage.

On the other hand, the autonomic nervous system is a component of the peripheral nervous system that regulates various involuntary physiological processes such as heart rate, blood pressure, respiration, digestion, and sexual arousal[13]. Like the HPA axis, the autonomic nervous system is activated upon receiving stress stimuli from the BNST through PVN neurons. The autonomic nervous system involves two components integral to inducing such effects: the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous initiates the fight-or-flight response, whereas the parasympathetic system enacts negative feedback. When activated, the sympathetic nervous system stimulates secretory glands embedded in the adrenal medulla to release the catecholamines epinephrine, norepinephrine, and dopamine, which circulate throughout the body and bind to various adrenergic receptors in target organs[14]. Catecholamines induce responses preparing the body for fight-or-flight through multiple means, such as binding to beta-adrenergic receptors in the heart to tachycardia, stimulating bronchioles for increased respiration, and enhancing blood flow in essential organs while restricting it in hindering regions such as the gastrointestinal tract[15].

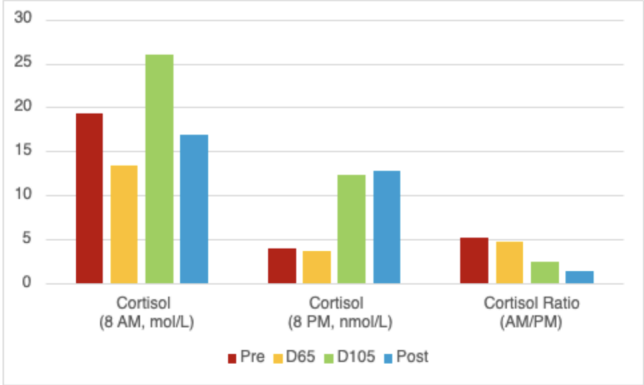

Figure 1-1. Morning and evening cortisol concentrations throughout experimentation

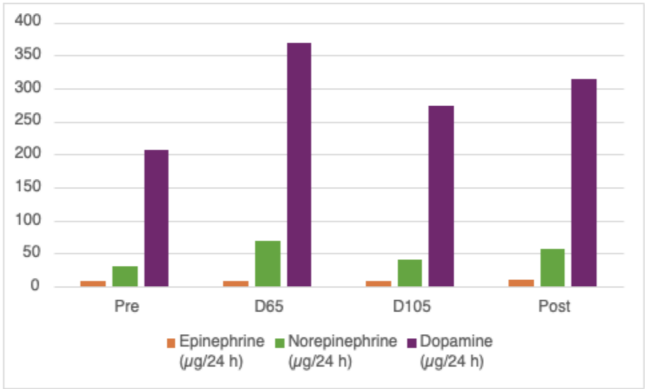

Figure 1-2. Catecholamine concentrations throughout experimentation

In the 2001 study by Choukèr et al., six healthy male astronauts were subject to 120 days of 6° HDTB. Biomarker data about HPA axis activity were sourced prior to HDTB (Pre), on the 65th day of HDTB (D65), on the 105th day (D105), and following HDTB termination (Post)[5].

Glucocorticoids, conveniently known as cortisol, are the steroid hormones secreted by the HPA axis to redistribute energy expenditure for stress mitigation[16]. As observed by the decreasing cortisol ratio between 8 AM and 8 PM, cortisol secretion elevates much more at night than in the morning towards the latter days of the trial. Since extraterrestrial environments are in perpetual darkness, cortisol secretion during human spaceflight is projected to incline significantly due to microgravity.

On the other hand, none of the catecholamines secreted by the sympathetic nervous system (epinephrine, norepinephrine, dopamine) exhibited particular patterns of fluctuation correlated to the progression of the experiment[17]. Such results suggest that microgravity profoundly impacts the HPA axis, not the autonomous nervous system, despite their common roots in

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Table 1. Saliva cortisol and urine catecholamine secretion (Values are means ± SE; n=6 subjects)[5]

	Pre	D65	D105	Post
Cortisol (8 AM, mol/L)	19.33 ± 5.90	13.42 ± 1.63	25.99 ± 4.9	16.95 ± 1.81
Cortisol (8 PM, nmol/L)	3.91 ± 1.62	3.7 ± 0.89	12.28 ± 2.32	12.73 ± 3.07
Cortisol Ratio (AM/PM)	5.24 ± 1.11	4.73 ± 1.31	2.45 ± 0.59	1.41 ± 0.16
Epinephrine (μg/24 h)	7.78 ± 1.85	7.78 ± 1.85	8.09 ± 1.96	9.72 ± 2.55
Norepinephrine (μg/24 h)	30.87 ± 5.63	70.05 ± 33.3	40.93 ± 10.07	57.48 ± 5.97
Dopamine (μg/24 h)	207 ± 34.34	369 ± 86.4	274.28 ± 71.66	314.08 ± 25.33

the BNST. Thus, microgravity's influence reaches the HPA axis after functional divergence from the autonomous nervous system[5]. Specific physiological mechanisms of causation are yet to be determined, in addition to confirming that the patterns are solely attributed to microgravity.

Immune Homeostasis

Breaches in immune homeostasis are significant stressors that require many redirections of energy metabolism, and as a result, immune responses are major triggers for the HPA axis. Cytokines are signaling proteins exchanged between immune cells in coordinating defensive reactions such as inflammation, which differentiate into functional groups depending on whether they trigger innate or adaptive immunity. In addition to directly responding to inflammatory agents, cytokines can bind to receptors ubiquitous throughout all levels of the HPA axis and stimulate its activation without interfering with the BNST. In return, glucocorticoids redirect energy for immune cells to effectively combat stressors and thus suppress further cytokine releases, preventing the brain from hyperactivation[18]. Glucocorticoids also cause shifts from cellular (Th1/inflammatory) immunity to humoral (Th2/anti-inflammatory) types, being actively involved in immunomodulation[19]. Immune responses also release proinflammatory mediators that excite or lower thresholds of afferent nociceptive and afferent vagal nerve fibers and, when stimulated powerfully enough, activate the sympathetic nervous system to release catecholamines[15]. During an immune response, activated immune cells release proinflammatory mediators, such as cytokines and chemokines, which coordinate defensive reactions and inflammation. Those catecholamines bind to adrenergic receptors on the surface of immune cells, though with varying nature, density, and sensitivity, and enhance immune activity. For example, natural killer cells exhibit both high-density and high-affinity $\beta 2$-adrenergic receptors, B cells possess such in high density but low affinity, and T cells have such in the lowest density[20]. The sympathetic nervous system also directly regulates the immune system; sympathetic fibers descending from the brain into primary and secondary lymphoid tissues secrete various substances capable of binding to immune receptors.

Immunosuppressive Effect of Microgravity on Human Blood Cells

As previously established, the HPA axis is significantly intertwined with the immune system where immunodeficiencies induce changes in cytokine levels. Through a high-dimensional mass cytometry, this study was able to determine functional downregulation in immune cell response across various types of leukocytes under microgravity simulated through the Rotating Wall Vessel[7].

CD69 is shown to be downregulated across all of the included T cells that it governs (CD4+Tmem, CD4+Tnaive, CD8+Tcells)[7]. Likewise, the T cells contingent to the CD25 gene (CD8+Tmem, CD8+Tcells, CD56midCD16+NKcells) are also downregulated. Since CD69 is an early activation marker of T cells and CD25 is the alpha chain of the IL-2 receptor responsible for T cell proliferation, T cell assembly and immunity execution will inevitably be severely impeded under microgravity[21,22]. Additionally, CD8+Tnaive harbors a unique pattern in that it is governed by two genes (STAT5 and STAT1), which partake significantly in cytokine signaling pathways[7].

Natural Killer (NK) cells, another integral aspect of the innate immune system encompassing the CD56mid and CD16+ lymphocytes, show downregulated CD25 expression like its T-cell counterparts, suggesting issues with their activation and function[23].

In conclusion, the data in Table 2 indicate that microgravity inhibits activations of genes pertinent to integral T cells and

Gene	Cell Type	Significance of gene
CD69	$CD4^{+}T_{mem}$	Early activation marker of T cells[21]
	$CD4^{+}T_{naive}$	
	$CD8^{+}$Tcells	
CD25	$CD8^{+}T_{mem}$	Alpha chain of IL-2 receptor responsible for T cell proliferation[22]
	$CD8^{+}$Tcells	
	$CD56^{mid}CD16^{+}$NKcells	
STAT5	$CD8^{+}T_{naive}$	Regulation of lymphocyte differentiation and related transcriptional pathways[23]
STAT1		Cytokine activity transduction[24]

Table 2. Downregulation of genes governing immune function under microgravity.
(Values are means ± SE; n=6 blood samples)

lymphocytes, resulting in immunosuppression and the loss of ability to maintain immune homeostasis in space.

Conclusion

The presented data indicates that concentrations of stress-responsive hormones increased, whereas genes pertinent to T cell and NK cell activation exhibited downregulation under microgravity. Such results suggest that extraterrestrial microgravity is a physiological trigger of psychiatric stress and immunosuppression. However, despite the intricate relationship between the HPA axis and the immune system, whether the observed patterns between the physiological systems have any direct causation remains unknown. Notably, the data indicates that HPA axis activity increased while immunosuppression also took place, resulting in the exchange of fewer cytokines; as aforementioned, cytokines are recognized as physical sources of stress and thus enhance HPA axis activity. Ultimately, data examining simultaneous changes in the activities of the HPA axis and the immune system will be necessary to elucidate a more comprehensive understanding of their intricate relationship and how it is affected by microgravity or if such a psychological relationship exists.

On the other hand, the National Aeronautical Space Agency (NASA), aware of the psychological challenges many astronauts face and thus invested in alleviating such, is committed to developing non-invasive and multi-dimensional wearable devices tracking astronauts' stress in real-time. Current methods of stress assessment among astronauts aboard the International Space Station (ISS) include in situ analyses of saliva samples or biometric sensors tracking vital signs[4,24]. Still, NASA is currently under development of a multifaceted sensory platform aimed at detecting deep stress anxiety. The device aims to monitor molecular analytes in human sweat, including the aforementioned stress hormones, along with substances such as glucose, lactate, sodium, potassium, pH, sweat rate, and other vital signs[25]. Ultimately, a holistic wearable device that efficiently alerts both astronauts and administrators on Earth of impending risks would be necessary for a comprehensive analysis of physiological stress and its prolonged physiological risks and appropriate responsive measures to be taken.

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