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Role of Epigenetics in Predicting the Impact of Hyper Gravity on Cardiovascular Tissues During Space Flight

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1. Abstract

The safety of hyper gravity exposure on heart muscle is still missing. Here, we attempt to provide a brief overview of epigenomic and epigenetic mechanisms in light of transcriptional regulation by DNA methylation and its role in cardiovascular disease (CVD). The objective is to identify some of the complex changes that these tissues undergo that are relevant to the experiences of astronauts who are subjected to long-term space travel and following their subsequent return to earth. A comprehensive understanding of the different vascular equilibria defined by gene expressions that are induced in gravity and microgravity and the transitions between them may result in the design of better countermeasures.

2. Introduction

Gravity is a universal force on the earth's surface and every known organism evolved and developed under the same gravitational force thus their developmental and physiological processes majorly rely upon gravity [1]. While any deviation from earth's standard gravity will influence development and physiology. Therefore, altered gravity is considered a powerful physical cue that exerts deep modeling effects on both anatomy and function of living organisms [2-13]. Alteration in gravitational forces can be through decreasing force, microgravity, or hypo gravity, or by increasing force, known as hyper gravity. The change of the force in either direction could potentially alter the normal physiology of a living organism. Previously hypo gravity/ microgravity remains the subject of various scientific research and has been widely studied [14]. Despite, being known as a major influencing factor that triggers the biochemical signals involved in molecular cascades that result in altered cell migration, proliferation, and differentiation, and thus in variations in tissue/organ architecture and function [15], few researchers have reported about the hyper gravity and its effects on human physiology have been least discussed to date.

Besides, several occupational hazards range from space flight training to Jet fighter pilots, experiencing high gravitational acceleration forces in the cephalocaudal direction (+Gz). Due to the lack of knowledge about the acute or long-term consequences of the exposure to altered gravity, astronauts had Initially made their journey to space without any prior qualitative and quantitative knowledge of the possible side effects because these changes were never known in the evolutionary history of living matter. This abnormal environment in space that can potentially cause unique alterations in astronauts' physiology requires further attention from clinicians and scientists. This indicates that each mission requires careful consideration and well-planned protection of the crew to ensure the safety during extraterrestrial missions, peculiarly, the Mars exploration mission or during the construction of lunar bases, etc., Hence, indicating the requirement of well-designed in vitro cellular and molecular models to enhance the basic knowledge about the underlying molecular events which could potentially aid devising an effective clinical strategy. The work presented here deals with the consequences of hyper gravity on body functions, namely the cardiovascular system. There are several aspects through which hyper gravity affects the cardiovascular

system. For instance, hyper gravity could not only cause structural and functional alterations in the visceral organs which lead to the impairment of visceral circulation but also cause variation in the cerebral and coronary blood flow [11, 12]. This ultimately leads to the combination of hyper gravity-induced cardiovascular reflex responses, emotional stress causing sympathetic vasoconstriction, and the increased peripheral vascular resistance of visceral beds. Besides, hyper gravity has been known to cause weaker cardiovascular circulation in developing embryos and which could result in cardiac hypertrophy. [11-13].

Herein, we provide a brief overview of the biological effects of hyper gravity of human cardiovascular system in the context of DNA methylation and its role in cardiovascular disease, to shed the light on epigenetic epidemiological studies relevant to cardiovascular health and disease and discuss the limitations, challenges, and future directions during the space flight.

3. Hyper Gravity and CVD

Cardiac hypertrophy is a cardiac enlargement condition, which results in an attempt to maintain necessary cardiac output to supply nutrients to the developing body. Since hyper gravity has been known to cause significant effects on the development of the ventricular myocardial wall, neuromuscular responsiveness, and equilibrium organs. This ultimately increases the workload and cardiac stress and thus leads towards cardiac hypertrophy, thus causing an increase in the size of the heart, particularly within the ventricle, as a response to this gravitational stress. It could also attribute to the hindered ability of the heart to pump nutrients throughout the body which ultimately affects the developing organism negatively. For instance, it has been reported that C57BL6J mice cardio myocytes exposed to hyper gravity at 2g for 30days, exhibited a significant reduction in the transverse stiffness by 16% by decreasing the alpha-actinin content in the protein membranous fraction. Moreover, in a mouse model, strong hyper gravity (15 g, 5 min) negatively impacts the heart [16]. Thus, indicating that further knowledge is required to understand the biological responses to hyper gravity, which is to date largely deficit since the body of evidence in the literature comprises significantly different and hardly relatable hyper gravity conditions. Therefore, predicting the clinical effects of hyper gravity is motivated by the possibility.

The development in preclinical and clinical research studies at the molecular level has significantly contributed to reducing the rate of mortality caused by CVD, which is attributed to the management of clinical risk factors, secondary and tertiary prevention, as well as improvements in quality of care and treatment. However, until now, primary prevention remains a challenge [1] due lack of comprehensive understanding about the interaction between genetic and environmental factors that ultimately contribute to CVD development. Besides, in the context of changes regarding the gravitational environment such as hyper gravity, it is a prerequisite to unravel that how cardio myocytes in response to mechanical force could resolve the barrier for mechanical force flight in space.

Though heart failure is seen as a complex disease caused by a combination of a mechanical disorder, cardiac remodeling, and neuro hormonal activation. Thus, targeting the systematic biological approach which integrates with genes and molecules, interprets the relationship of the molecular networks with modular functional units, and explains the interaction between mechanical dysfunction (i.e., gravitational alteration) and cardiac remodeling could aid in predicting the novel therapeutic strategy [1].

It is accepted that early (initial) mechanical stresses applied in the myocytes and/or mechanical changes in the left ventricular cavity comprise the primary initiating causes for cardiac remodeling and neuro hormonal activation [1,17]. While mechanical changes consist are the major cause of cardiac remodeling [18, 19]. For instance, in human cardiac myocyte, the changes leading to left ventricular dysfunction has attributed to the reduction of the gene expression of myosin heavy chain, increase in the myosin heavy chain expression, along with modifications in cytoskeletal proteins, which results in desensitization of adrenergic signaling [20-22]. Collectively, these changes diminish cardiac myocyte contractility cell shortening and reduce responsiveness to adrenergic signaling [23]. Thus, suggesting that changes in the environment have a significant effect on the genetics and physiological function of an organism as explained under the umbrella of epigenetics. In the next section, we will discuss the correlation between alteration in the gravitational environment and its long term

4. Epigenetics in Space and its Correlation with the CVD

In space missions, astronauts experience a period of cardiovascular adaptation to hyper gravity and microgravity. However, following their return to 1G from prolonged space flight (Zero-G) unpredictable cardiovascular events have been reported. These responses and their subsequent long-term effects are poorly understood. Whole-genome, methylome, and transcriptome are functionally interrelated; therefore, creating a comprehensive network and understating of changes in methylation pattern in response to alteration in the gravitational environment is essential to probe the genetic and physiological changes in CVD as a result of hyper gravity.

Epidemiological studies have demonstrated that genetic, environmental, behavioral, and clinical factors contribute to cardiovascular disease development. How these risk factors interact at the cellular level to cause cardiovascular disease is not well known. Epigenetic epidemiology enables researchers to explore critical links between genomic coding, modifiable exposures, and the manifestation of disease phenotype (v.imp). Although DNA methylation is potentially an important mechanism underlying these associations. However, there is limited knowledge about in vivo time course of DNA methylation pattern establishment in cardiomyocytes17,18.

In the past decade, there has been a significant increase in the number of epidemiological studies investigating cardiovascular risk factors and outcomes concerning DNA methylation, but many gaps remain in our understanding of the underlying cause and biological implications [24].

On the other hand, recently understanding of the epigenetic mechanisms has shown its link to the internal genetic landscape and the external environmental influences, which might provide better mechanistic insight into the cause of CVD. This further explains the mechanism through which mechanical forces bring changes in the pattern of DNA methylation. Besides, vascular adaptation and changes in DNA methylation patterns have also been indicated to adapt through gene transcription. Therefore, gravitational experimental design on earth should be designed to investigate the variation at gene expression at the structural and regulatory level in cardiovascular tissues have indicated to be associated with acute and prolonged exposure to hyper gravity (3G) [25]. Though experiments have already been performed on mice at the NASA Ames large diameter centrifuge facility at Moffett Field in California. Moreover, complex changes experienced by cardiac tissue after hyper gravity exposure in vitro study design should be relevant to the experiences of astronauts subjected to long-term space travel and following their subsequent return to earth. Hence, a comprehensive understanding of the different vascular equilibria defined by gene expressions in response to hyper gravity could aid in designing a better countermeasure. However, conclusive evidence on the safety of hyper gravity treatment on heart muscle is still missing. In the present study, we attempt to study epigenomic and epigenetic mechanisms, particularly transcriptional regulation by DNA methylation, in response to hyper gravity [26].

Before space exploration, no known biological organism ever was or could have been, exposed to an extraterrestrial environment. However, during the early years of the 'space age', test animals have been elucidated to unravel the complex process of CVD. Thus, focusing on DNA methylation, particularly concerning how it relates to CVD and selecting appropriate technology, to balance genome coverage, resolution, accuracy, specificity, throughput, and the cost is the basic prerequisite to ensure the safety of astronauts at the clinical level. Besides, the advantages of sequencing-based methods include comprehensive and highly accurate assessment of epigenetic changes i.e., DNA methylation, as well as assessment of allele-specific and repetitive element DNA methylation states. Thus, we suggest that understanding the epigenetic of CVD, particularly the epigenome can serve as a modifiable target or intervention, physicians could directly translate such knowledge into practice [27].

Further insight indicates that epigenetic mechanisms contributing to aberrant DNA methylation have been associated with several diseases including cancer,2,3 diabetes,4,5 or psychiatric disorders.6-8. While DNA methylation, by the addition of a methyl group in the 50 carbon of cytosine, alters the structure of the DNA molecule resulting in possible modifications of gene expression patterns. Thus, aberrant DNA methylation through its transcriptional consequences may have an important role in human disease (DNA methylation abnormalities). Accordingly, a growing number of studies provided evidence of cardiovascular epigenetic which could aid in countering the cardiovascular consequences of spaceflight i.e., increased arterial stiffness from aging on earth, which can cause high blood pressure and organ damage. Thus providing a novel concept on cardiovascular structural and functional adaptations to long-duration space flight [28].

5. Conclusive Remarks

Although the major limitation for designing hyper gravity experiments in vitro for CVD has been attributed to its limited regenerative capacity, however, cardio myocytes respond to these challenges of changes in the environment during development and disease with characteristic gene expression programs, i.e., epigenetic processes. Hence understanding the modulators of cardiac gene expression in development and disease in the context of hyper gravity possess the potential to open a new era of space biology and its clinical implications.

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