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Advances in China Space Medical Experiment Research

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Abstract In 2021, China Space Station (CSS) was assembled and constructed in-orbit, which provided a broad space platform for space medicine and space life sciences research. Space medicine focuses on the systematic risks that restrict long-term manned spaceflight. It carries out systematic research on the impact and countermeasure technology of long-term weightlessness on astronauts' health, space radiation on astronauts' health, behavior and ability, advanced on-orbit monitoring and medical disposal technology, and traditional space medical application technology by the space medicine experiment platform on human body and cell. It has accumulated valuable data on space environmental effects and human factors research, established a "human system risk" research system, obtained new knowledge and discoveries of space medicine, and explored countermeasure technologies of new characteristics. Moreover, a series of achievements have been made in the basic research on the mechanism of the special space environmental effect, which provides a solid foundation for the implementation of space missions.

Key words Space medical experiment, Weightlessness, Radiation, Behavior, Traditional medicine

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1 Introduction

In 2021, China Space Station (CSS) was assembled and constructed in-orbit, which provided a broad space platform for space medicine and space life sciences research. Space medicine focuses on the systematic risks that restrict long-term manned spaceflight. It carries out systematic research on the impact and countermeasure technology of long-term weightlessness on astronauts' health, space radiation on astronauts' health, behavior and ability, advanced on-orbit monitoring and medical disposal technology, and traditional space medical application technology by the space medicine experiment platform on human body and cell. It has accumulated valuable data on space environmental effects and human factors research, established a "human system risk" research system, obtained new knowledge and discoveries of space medicine, and explored countermeasure technologies of new characteristics. Moreover, a series of achievements have been made in the basic research on the mechanism of the special space environmental effect, which provides a solid foundation for the implementation of space missions.

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2 Overview of Space Medical Experiment Field during the Construction Period of China Space Station

During the construction period of China space station, our work mainly focused on the "human system risk" mechanism and key scientific issues that restrict long-term manned spaceflight, with the aim to build a space laboratory with cutting-edge and open innovation, overall planning, fast-track development, economic feasibility and maximizing application benefits. Five research directions were envisioned and designed, including the impact of long-term weightlessness on astronauts' health and countermeasure technology, the impact of space radiation on astronauts' health and countermeasure technology, astronaut behavior and capabilities, advanced on-orbit monitoring and medical treatment technology, space application technology of traditional medicine, to study the characteristics of long-term manned spaceflight, explore the advanced health countermeasure technology, provide theoretical medical support and technical reserves for long-term healthy life and efficient work on orbit, and promote the wellbeing of the public.

2.1 Space Medical Experiment Platform of China Space Station

In the space medical experiment field, we focus on the "human system risk" that restricts long-term spaceflight, systematically plan and construct research equipment at different levels, such as behavior, physiology, cell and molecule, and built advanced and highly integrated space experiment platform.

The space medicine experiment platform mainly includes a human system research cabinet and a medical sample analysis experiment cabinet, which are composed of comprehensive management equipment, physiological research equipment, operational capacity research equipment, medical sample preparation and analysis equipment, as well as body fluid detection equipment. It can collect and analyze data of the muscle structure function such as EEG, cardiovascular function and ultrasonic image, electromyography, muscle circumference, plantar stress, joint mobility, human sports biomechanics, basic cognition, biological rhythm, visual function and other behavior and cognitive function. It supports the research on physiology, sports biomechanics and behavior such as heart, cerebrovascular, muscle, bone, nerve and biological rhythm. It is able to study cellular and molecular mechanisms such as cell cultivation and in-orbit observation, as well as body fluid metabonomics, and to collect, process and store body fluid samples in orbit.

The experimental platform has been verified by Shenzhou-12 and Shenzhou-13 flights, and it effectively ensured the smooth progress of experimental projects in the space medicine experiment field. As a follow-up, the advanced theories and technologies of space medicine will be closely followed, and the capacity of experimental facilities will be continuously updated and expanded.

2.2 Project Operation and Management in Space Medicine Experiment Field

On 19 March 2018, China Manned Space Engineering Office released the first batch of project guidelines of the space station project in the space medical experiment field and the relevant project guidelines were also released globally through the United Nations Office for Outer Space Affairs (UNOOSA). As the overall institution in space medical experiment field, China Astronaut Research and Training Center is responsible for organizing the mission study and project approval, which will be implemented after being approved by the China Manned Space Engineering Office. All human experimental projects shall pass the review of the ethics committee.

3 Main Research Progress in the Space Medicine Experiment Field

We have carried out a series of studies focusing on the effects of weightlessness, radiation and other factors in the long-term spaceflight environment and mission conditions on astronauts' health and behavioral ability, as well as the application of traditional medicine in space.

3.1 Effect of Long-term Weightlessness on Astronauts' Health and Countermeasure Technology

We have carried out a series of studies on cardiovascu-

lar function, bone metabolism, muscle function, brain function, visual function, nutritional metabolism, epigenetics and cytological mechanism under weightlessness.

3.1.1 Weightless Cardiovascular Research

Aiming at the scientific questions on cardiovascular function change in space environment, this project analyzes the spatial-temporal characteristics of long-term flight on the autonomic nerve response of the cardiovascular system, and explores the role of gravity in the dynamic adaptation of cardiovascular structure and function.

The project systematically studied the autonomic nerve regulation function, cardiac structure and function, vascular structure and function, long-term rhythm change of cardiovascular function, comprehensive cardiovascular regulation function, cardiovascular function regulating hormone and factors during long-term spaceflight, and comprehensively and accurately described the changes of cardiovascular physiological function of individual crew members at all stages.

3.1.2 Research on Bone Metabolism Countermeasure

Aiming at the medical problem of bone loss in space, this project explored the change law of bone-related physiological system, the characteristics of tissue interaction and steady-state regulation mechanism during long-term spaceflight, and carried out the research on the influence law of weightlessness on bone-related physiological system, the role and mechanism of mechanical load change in the interaction regulation between bone and other tissues and organs. Through the integrated analysis of bone metabolism and glucose and lipid metabolism, the characteristic spectrum of individual bone glucose metabolism during a 180-day flight was obtained, which laid a foundation for explaining the regulatory mechanism of bone loss during long-term spaceflight and establishing new bone loss prevention measures.

3.1.3 Research on Muscle Adaptation and Gait Analysis

Aiming at the medical problem of muscular atrophy during long-term spaceflight, this project carries out the research on the occurrence and development of weightless muscular atrophy and the intervention effect of sport-specific countermeasures, which will clarify the characteristics of human sports biomechanics changes and the dynamic change law of exercise adaptability under long-term spaceflight. This study may provide theoretical and data support for the formulation of effective antimuscular atrophy exercise programs for long-term missions.

A non-invasive measurement method of muscle structure and function was established. Through the analysis and research of Achilles tendon stiffness, lower limb electromyography, joint angle, plantar pressure, muscle function and gait, the biomechanical changes of lower limb muscles under long-term weightlessness were obtained.

3.1.4 Brain Functional Network Research

Aiming at the medical problems of brain function changes in long-term spaceflight, this project studies the effects of microgravity on brain blood flow, brain structure and brain function, striving to understand the relationship between brain hemodynamic changes and brain high-level function changes, and explore the effects of long-term weightlessness on brain structure and function changes, brain hemodynamics, and the correlation between autonomous regulation function of brain blood flow and high-level function changes of brain, which can provide theoretical support and technical reserves for the follow-up missions of long-term stay in low earth orbit, manned lunar landing and deep space exploration.

This project has carried out millimeter level analysis of the whole brain parenchyma and ventricular volume, established an individualized brain function image data processing and analysis method, studied the changes of brain function, metabolism and functional network in the resting state under the space flight environment, and accumulated data on the volume changes of brain tissue and brain parenchyma under spaceflight.

3.1.5 Research on Visual Function

Aiming at neuro-ocular syndrome during spaceflight, this project studied the adaptation characteristics and time course changes of intraocular pressure, retrobulbar optic nerve cerebrospinal fluid pressure, visual function, and revealed the physiological effects, coupling relationships and physiological regulation mechanisms of visual function, intraocular pressure, retrobulbar optic nerve peripheral cerebrospinal fluid pressure. Using a visual

function measuring instrument, optometer, orbital B-ultrasound and other equipment, we monitored the change patterns of visual function and cerebrospinal fluid pressure around the retrobulbar optic nerve during long-term flight, verified the hypothesis of ophthalmic cranial pressure gradient under weightlessness, and provided the theoretical basis and technical support for reducing the probability of space flight related neuro-ophthalmic syndrome.

3.1.6 Research of Metabolomics, Methylation and Transcriptomics

This project has established a metabolome research method based on Raman spectrum detection technology, which can analyze the nutritional level in real time. Through the urine metabolite information before, during and after the flight, through the enrichment analysis of differential metabolite pathways, the screening and identification of differential compounds, the relationship between the changes of metabolic pathways and the changes of intestinal flora were studied.

We have established the relevant network links between methylation, transcriptome and multiple physiological systems, found the epigenetic gene sets and biological pathways closely related to health risks, studied their internal links with glucose and lipid metabolism, bone and muscle metabolism, cardiovascular system function, oxidative stress and immune function, and established the "methylation-phenotype" correlation characteristics and "transcriptome-phenotype" correlation characteristics spectrum in long-term spaceflight.

3.1.7 Stem Cell Research

Microgravity affects the key signal regulation network of human cardiomyocytes. Therefore, it is necessary to clarify the mechanism of dysfunction under microgravity environment of the cardiovascular system, find possible intervention targets, and create conditions for subsequent experimental research such as drug screening.

This project has established a space-based experimental system of pluripotent stem cells. The effects of weightlessness on the structure, excitation contraction coupling and function in humanized cardiomyocytes were studied by using a beating cardiomyocyte model induced by pluripotent stem cells derived from human urine and a calcium transient fluorescence signal detection system. The changes of myocardial cell structure, survival, energy metabolism and gene expression under spaceflight were obtained. The 3D culture system of skin stem cells under microgravity was constructed, and the effects of microgravity on the dryness, aging and cytoskeleton of skin stem cells, as well as the changes of MAPK, PPAR and other signaling pathways in skin stem cells were obtained. We have understand the influence of microgravity on the biological function of stem cells in the process of skin defect repair and its regulatory pathway, in order to provide basic data for the study of skin accessory organ damage repair under microgravity environment, and can provide an efficient treatment scheme for skin trauma in long-term spaceflight.

3.2 Research on the Impact of Space Radiation on Astronauts' Health and Countermeasure Technology

Focusing on the scientific problem of possible damage to humans under space radiation environment, research on screening of radiation sensitive indicators, research on the mechanism and countermeasure of space radiation nerve damage, and research on the mechanism of space radiation visual damage have been carried out.

3.2.1 Study on Screening of Radiation Sensitivity Indexes

Focusing on the possible damage of long-term spaceflight radiation to humans, this project studied the biological effects and mechanism of space radiation damage to hematopoietic stem cells and peripheral blood cells through chromosome aberration, micronucleus and RNA sequencing, and explored the establishment of sensitive biological indicators and sensitive screening index system of space radiation damage, so as to provide an important biological reference for deep space exploration crew selection and early warning of radiation damage.

3.2.2 Radiation Nerve Injury Research

This project focuses on the possible abnormal protein metabolism and cellular inflammatory response of neurons under the space radiation environment, tried to clarify the impact of ionizing radiation on sensitive RNA metabolism and epigenetic regulation, screen radiation damage non-coding RNA markers in urine or urine exosomes, study the effect of nerve dysfunction under the

space radiation condition and possible molecular mechanism, and carry out targeted drug countermeasure of space radiation nerve dysfunction.

3.2.3 Radiation Vision Research

Aiming at the damage effect of the combined effect of radiation and weightlessness on the human central nerve system, this project discusses the characteristics of EEG changes related to the combined effect of space radiation and weightlessness through the localization research of EEG spectrum, characteristic spectrum and EEG topographic map, and understands the impact of space environmental effect on the central nerve system under the condition of on-orbit flight, and provides data of evaluation and early warning research on the injury effect of central nerve system under radiation and weightlessness.

3.3 Research on Astronaut' Behavior and Ability

Focusing on the impact of space mission conditions on task operation and performance ability, research has been carried out on eye-hand coordination, brain fatigue, biological rhythm monitoring, cognitive based adaptive automated human-machine cooperation technology, in-orbit brain load assessment technology, sleep area lighting and astronauts' sleep quality, the impact of biological rhythm on the alert level, and mindfulness meditation intervention technology.

3.3.1 Eye-hand Coordination Research

Facing the requirements of typical operation tasks in manned spaceflight, this project designs and constructs the evaluation system, technology and method of eye-hand coordination fine motion control capability applicable to multiple scenarios such as in orbit and ground-based, obtains the data of in orbit three-dimensional space gesture operation, rhythm keys, touch screen clicks, studies the characteristics and mechanism of the changes in the stability, accuracy and coordination of fine operation control in orbit, which can provide a reference for follow-up program and human-machine interaction (HMI) design.

3.3.2 Research on Mental Fatigue and Mental Load

Aiming at the problems of mental fatigue, mental load and operational ability guarantee under the working conditions during long-term space missions, this project studied the influence of sleep structure and quality of long-term on-orbit missions on mental fatigue, obtained the brain wave characteristic data related to the rapid detection of mental fatigue, and developed a fatigue intervention instrument based on transcranial electrical, magnetic and sound fusion stimulation. Through the research of real-time brain load monitoring technology in space mission, the recognizable level, cross time robustness and on-orbit applicability of brain load monitoring are verified.

3.3.3 Research on Biorhythm Monitoring, Guidance and Lighting and Sleep

Focusing on the compound environmental factors of weightlessness and isolation limitation in long-term flight, this project studies the changes of human sleep quality and biological rhythm under long-term flight conditions. Based on the characteristics of sleep-waking rhythm, heart rate rhythm, sleep quality and methylation, the coupling relationship between biological rhythm and related physiological effects and physiological regulation mechanism during long-term weightlessness were studied, which provides basic scientific data for the re-adaptation characteristics of human physiological rhythm system and the screening of guiding intervention targets during long-term flight. Aiming at the influence of biological rhythm on alertness, this project attempts to establish the grading standard of alertness level, and explores the alertness intervention technology based on mindfulness meditation training. It has verified the effect of short wave illumination on the guidance and intervention of biological rhythm. Using the most advanced LED and intelligent control technology, we has customized the experimental lighting fixtures in the sleeping area during space flight, formulated the illumination strategy of "early wake-up and late induction", and preliminarily verified the effectiveness of improving sleep quality.

3.3.4 Research on Human-machine Collaboration

This project constructed an adaptive automatic "man in the loop" human-robot collaboration method based on the functional state of real-time operation, verified the effectiveness of human-machine task collaboration dynamically according to the functional state of humans in the process of human-machine operation in-orbit, and

explored the influence law of long-term on-orbit residence on the operator functional state detection method based on physiological parameters and the adaptive human-machine task collaboration method. It provides an experimental basis for the future long-term on-orbit adaptive human-machine collaboration method.

3.4 Research on Space Application Technology of Traditional Medicine

Focusing on the scientific problem of monitoring and protecting the changes of the overall functional state of the body under the space environment, the research direction of space application technology of traditional medicine has carried out the research on four diagnostic methods of traditional Chinese medicine, portable acupoint stimulation and "Hang Tian Kang Yang Gong".

3.4.1 Research on the Four Diagnoses of Traditional Chinese Medicine (TCM)

Through the ground-based simulated weightlessness experiment, this project establishes the monitoring and analysis method of TCM health status representation information with syndrome elements as the core and machine learning algorithm, and defines the diagnostic and evaluation indicators of TCM health status in space environment; Through space-based experiments, the four diagnostic data of spaceflight are obtained, and the characteristic parameters of four diagnostic methods of TCM and their correlation with cardiovascular related physiological indicators are analyzed, in order to explain the characteristics and laws of the overall functional state in different flight stages.

3.4.2 Research on Acupoint Stimulation and Hang Tian Kang Yang Gong

Aiming at the problems of cardiovascular dysfunction and muscular atrophy during long-term flight, this project develops portable acupoint stimulation devices, and carries out the research on the regulation effect and regulation mechanism of portable acupoint stimulation devices, so as to provide a theoretical basis for the application of traditional Chinese medicine in the countermeasure of weightlessness physiological effects in orbit flight. In view of the possible adverse effects of long-term spaceflight on the overall health state, we create a Chinese space fitness exercise with the basic concept of calming down, improving psychological capital, improving sleep, and increasing muscle strength, explore new measures to maintain the overall functional status, and give play to the role of comprehensive health regulation and promotion.

4 Exploration and Research for Further Flight

Low metabolic regulation, as a future-oriented human potential development technology, is expected to become an effective means to solve the long-term spaceflight healthy survival support technology, and is a new field of body health assurance research. In July 2021, a 21-day complete fasting (adequate water) human low metabolism experiment was carried out to analyze the physiological, psychological, emotional, nutritional status, cardiovascular function, brain cognition, EEG balance function, functional nuclear magnetic resonance, basic metabolism, skin, body composition and other changes under the ultra-long complete fasting. The results show that the human can physically and psychologically tolerate complete fasting for up to 21 days, fasting for 3–6 days can form a new energy metabolism steady state, the psychological state is basically stable, the level of basic metabolism is reduced, and there is no significant change in brain cognitive function.

In view of the risk associated with space medicine, we carried out research on cardiovascular function, muscle function, bone metabolism, nerve function, found specific markers reflecting the physiological function, established targeted detection methods, and verified effective protection methods. Cardiovascular studies have shown that the hemodynamic response of high angle short-term tilt test scheme was consistent with the effect induced by the traditional low angle long-term tilt test scheme[1]. The molecular mechanism study showed that Calpain mediated myocardial abnormalities in mice in simulated microgravity by activating p38 and ERK1/2 MAPK pathways[2]. The study of muscular atrophy showed that resistance exercise during bed rest could significantly improve the muscular atrophy of some lower limbs, but it is necessary to strengthen the targeted training of hamstring and tibialis anterior muscles and design richer resistance training movements[3]. Bone loss

studies have shown that GABAergic circuits in the ventromedial hypothalamus mediated chronic stress-induced bone loss[4]. Calcium chloride channel protein ANO1 regulated the differentiation and function of osteoclasts through RANKL-RANK mediated signaling pathway. ANO1 knockout mice can resist the bone loss in tail suspended and estrogen deficient mice[5]. In addition to weightless factor, long-term closed environmental factor can also affect bone metabolism, which is related to changes in glucose and lipid metabolism[6]. Cognitive function research found that 28-day tail suspension simulated weightlessness can cause changes in hippocampal mitochondrial morphology and metabolic function, which may be related to the decline of cognitive function caused by space microgravity environment[7]. The change of miR-383-5p level and its regulation of target gene AQP4 are also one of the potential molecular mechanisms of hippocampal cognitive impairment induced by microgravity[8]. Aromatherapy can significantly alleviate the memory impairment of tail suspended mice[9]. The study of neural function found that the hippocampal neurons of tail suspended rats were damaged after cell dimension regulation, and the pyramidal cells were more sensitive than the intermediate neurons[10]. The microelectrode array biosensor modified with nanocomposites detected that under the condition of sleep deprivation, the release of domaine increased in the cortex and caudate putamen in rats, the activity of nerve spikes increased, and the local field potential increased significantly, suggesting the adaptive response of the brain to sleep deprivation[11]. The 90-day head down bed rest simulated weightlessness study found that the acupoint electrophysiological signals are specific and can more accurately reflect the changes of neural function[12].

In the research on the impact of space radiation factors on body health, it was found that MAFG protein played an important role in the regulation of radiation damage[13], and *Atg*7 gene knockout was an important factor leading to the disorder of nucleosome assembly in mouse myeloid cells[14].

In terms of behavior and ability research, research on cognitive ability, mental load, sleep, mood, alertness and biological rhythm regulation has been carried out. In terms of cognitive ability research, it was found that the bilateral inferior parietal lobules were the neurophysiological basis for the maintenance of interpersonal cooperation ability[15]; attention bias or emotional disengagement was the underlying mechanism of the impact of psychological resilience on emotional experience[16]; eye control highlighting technology enables both serial and parallel processing in visual search[17]. In terms of mental load research, the mental load detection method based on EEG and functional near-infrared spectroscopy has been optimized to improve the detection accuracy[18]. In the research on the effect of lighting on sleep, it was found that the impact of short-term light on subjective feelings and comfort was related to the time of light. At 500 lx illumination, the comfort was better in the morning and afternoon[19]. In terms of emotion regulation research, it was found that working memory training can improve emotion regulation and activate spontaneous emotion regulation strategies[20]. In the research on vigilance, it was found that sleep restriction can cause disturbance of the body's biological rhythm and decreased vigilance[21]. In terms of biorhythm research, by summarizing recent studies, it was believed that biorhythm was an important factor that cannot be ignored in the maintenance of body health in the spaceflight environment. Rhythm disorders can cause sleep disorders, and have a negative impact on the musculoskeletal system, nervous system, cardiovascular system and endocrine system. System and other adverse effects, resulting in a decline in human cognition and ergonomics[22]; among them, long-term closed environments and non-24-hour cycles in Mars may affect human emotions, and there are differences in the impact of positive and negative factors on emotions[23]; According to recent research, it is believed that the change of redox level is an important factor for the change of biological rhythm in the space-specific environment[24].

In the application of traditional medical methods, research on the countermeasure effects of traditional Chinese medicine and acupoint stimulation on the physiological effects of weightlessness in spaceflight has been carried out. The physiological effects of weightlessness are divided into liver disease syndrome, heart disease syndrome, limb meridian disease syndrome and "Qi and

blood" disease syndrome. The general pathogenesis of weightlessness effect is the deficiency of liver, spleen and kidney, mainly "Yin" deficiency, and there are syndromes such as disorder of "Qi and blood", "Qi" deficiency and "blood" stasis. It was found that traditional Chinese medicine is effective on simulated weightlessness animal model and head down bed rest model[25]. Research results suggest that acupoint stimulation can effectively prevent cardiovascular dysfunction under weightless conditions and maintain human orthostatic endurance[26–28].

5 Conclusion

The space station platform provides a unique chance for new understanding and discovery of space medicine. Focusing on relevant cutting-edge hot spots and key issues, the basic forward-looking and exploratory research can provide theoretical support and technical reserves for longer-term continuous on-orbit stay, manned lunar landing and interstellar flight.

In the follow-up mission of the China Space Station, we will continue to focus on the forward-looking and exploratory development of space human body research, devote ourselves to biotechnology such as biochip, nanotechnology, stem cell/organ chip, tissue engineering, and omics research, and carry out research and development on the mechanism and protection of restructure in the special space environment, the pathogenesis and protection of space-earth comorbidity, miniaturization, integration, intelligence, high-precision diagnosis and treatment equipment, as well as theoretical and technical research on the change mechanism of human-machine-environment interaction, so as to produce original research results, which will promote the development of space medicine and serve the public health.

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