ISSN 0362-1197, Human Physiology, 2021, Vol. 47, No. 7, pp. 716–734. © Pleiades Publishing, Inc., 2021.
Russian Text © The Author(s), 2020, published in Aviakosmicheskaya i Ekologicheskaya Meditsina, 2020, Vol. 54, No. 6, pp. 5–26.

Gravity as a Factor in Evolutionary Adaptation of Animals to Living on the Earth

O. L. Vinogradova[a, *], E. S. Tomilovskaya[a], and I. B. Kozlovskaya[a, †]

[a] *Institute of Biomedical Problems, Russian Academy of Sciences, Moscow, Russia*

**e-mail: ovin@imbp.ru*

Received August 19, 2020

Abstract—The review considers the current ideas about the role of the gravitational factor in activities of the sensorimotor and cardiovascular systems, as well as new basic problems and questions of space medicine and physiology. The review presents data on animal embryonic development in weightlessness, evolution of the motor and cardiovascular systems, and characteristics of their functions in conditions of normal and altered gravity. Much attention is paid to the results of unique studies with ground-based gravitational unloading models: head-down bed rest, dry immersion and hindlimb suspension, in which the mechanisms that regulate various body systems under conditions of altered gravity were studied. Terrestrial organisms have learned to live in the gravitational field. Almost all of their body systems are gravity dependent. However, the extent and mechanisms of this dependence remained unclear for a long time. Space flights opened up the possibility of studying the activity of living systems in the absence of gravity. Changes in activity of sensory systems are among the main factors that mediate the effect of weightlessness on the motor system. Under the Earth's conditions, the afferent support of motor control is polyreceptive and involves vision, the vestibular apparatus, and support and muscular proprioception. In microgravity, activity of some channels is completely eliminated (support afferentation), distorted (vestibular apparatus), or weakened (proprioception). Similar processes occur in the cardiovascular system: loss of the gravity-dependent pressure gradient causes profound changes in the structure and function of the heart and vessels, including both resistive and capacitive ones. It is still an open question as to how much the various changes occurring in the cardiovascular system are associated with the disappearance of the gravity-dependent pressure gradient. Some questions of gravitational physiology are impossible to answer in space flights experiments. Various methods were therefore developed to simulate the effects of gravitational unloading on the Earth. New knowledge on the mechanisms of changes occurring in the sensorimotor system was gotten by comparing space flight data and data obtained in model experiments. A basic problem of gravitational physiology of the cardiovascular system is the degree of correspondence between changes observed in laboratory animals or under model conditions (bed rest, immersion, and hindlimb suspension) and changes recorded in humans during real space flights. The problem is specially discussed in the review. Many issues remain unresolved in the light of future inter-planetary missions, including the problems of post-flight readaptation of the motor and cardiovascular systems to normal gravity conditions. Another problem is preventing losses of strength, endurance, and orthostatic stability. The development and improvement of countermeasures for preventing the negative effects of space flight is impossible without understanding the mechanisms that underlie the observed changes.

Keywords: evolution, gravity, sensorimotor system, cardiovascular system, embryogenesis

DOI: 10.1134/S0362119721070124

EVOLUTION

Charles Darwin [1], who formulated the theory of evolution, stated that humans would never understand the role of gravity in evolution because they are unable to get rid of the Earth's gravity. Space flights opened the possibility for such investigations, and studies in the field greatly contributed to understanding the role that gravity played in evolution of the structure and function of terrestrial organisms, including mammals and humans. Flight and ground-based simulation experiments showed that substantial functional changes occur in various body systems when the gravitational load is reduced. Gravity, which is inherent in the Earth from its birth, affected evolution of all terrestrial organisms and is included in their vital systems as a factor that ensures the living in the Earth's gravitational field. At the same time, biological studies in microgravity showed that the effect of gravity on vital activities is selective and depends on the body size (mass) of an organism, the complexity of its structural and functional organization, and the presence of specialized mechanosensitive receptors. At first glance,

† Deceased.

the effect must be insignificant in the case of aquatic animals because their existence in an aquatic environment should minimize the effect of the gravity factor, equalizing the forces that act on different sides of the body. The functions of aquatic animals in microgravity are therefore of particular interest to study in comparative physiology. Embryonic development in microgravity is a similarly important problem because embryos develop in an aquatic environment.

EMBRYONIC DEVELOPMENT OF INSECTS, CRUSTACEANS, AND LOWER VERTEBRATES IN MICROGRAVITY

Studies with fish and amphibian embryos showed that microgravity does not hinder the development of lower vertebrate embryos in general [2], but its effect becomes detectable at critical developmental stages, such as the mid-blastula stage [3, 4]. Moreover, the function of the vestibular system, which is one of the main gravity-sensitive systems, is not affected in organisms developing in microgravity conditions (the vestibulo–ocural reflex is initially increased and then returns to its normal level in the majority of *Fundulus heteroclitus* fishes; a similar dynamics is characteristic of intracellular and extracellular potentials in the afferent nerve of the utriculus). At the same time specific locomotor aberrations are observed in adults. Studies of locomotion and spatial orientation in fish showed that characteristic changes in the form of looping, or swimming in circles, arise in the locomotion pattern in microgravity [5]. Similar changes in locomotion pattern were observed in *Xenopus laevis* tadpoles [2] and small crustaceans of the class Ostracoda [6]. No explanation was found for the observations. However, it is evident that the locomotion pattern substantially changes in a space flight in aquatic organisms, although they are suspended in an aquatic environment and should seemingly not be affected by microgravity conditions. Another interesting observation was made: the capability of light-dependent orientation is lost in Ostracoda in microgravity.

Experiments with repeated exposure to space flight conditions of the fruit fly *Drosophila melanogaster* showed that successful reproduction is preserved during multiple changes in gravitational conditions (three generations in microgravity during a 44-day space flight, the fourth generation on the Earth, and the fifth generation in a 12-day space flight). At the same time, exposure to flight conditions increased transcription of metabolic genes and genes coding cuticle components and decreased transcription of genes involved in morphogenesis, cell differentiation, and organization of the cytoskeleton. It is important to note that the transcriptome changes increased during repeated exposure to microgravity [7].

AVIAN EMBRYO DEVELOPMENT IN MICROGRAVITY

American researchers [8, 9] showed that chicken embryos successfully develop in microgravity, but only when brought in space at the developmental stage of 7–10 days. On the other hand, studies of the embryo development in Japanese quail were carried out onboard the Mir space station from 1990 to 1999 and showed that avian embryo development is possible in the absence of the gravity factor [4]. Live quail chicks hatched in space flight conditions for the first time in the above experiments, supporting the idea that the avian embryo development is independent of the gravity factor.

The full embryonic cycle was completed by 23% of embryos in microgravity and 53% of embryos in a synchronous control group. Seven embryos failed to hatch because their heads were oriented to face the pointed end of the egg. Microgravity did not hinder the embryonic development, but affected the hatching process. The chicks that had completed the total embryonic cycle in microgravity displayed all signs of normal development. However, the hatched chicks were unable to independently hold themselves in place and the experimentators had to clasp them to the "floor." The chicks fixed in this manner felt better and pecked food more intensely. The chicks, whose movements were restricted from the very beginning, made attempts at orienting in space relative to an immobile object. A behavioral analysis of the newborn chicks showed that orientation in space, which is ensured by gravity on the Earth, is an important prerequisite to their innate behavioral reactions. Chicks are incapable of independent life in microgravity [4].

MAMMALIAN EMBRYONIC DEVELOPMENT IN MICROGRAVITY

A series of experiments was carried out by Russian and American researchers during flights of Kosmos biological satellites and Shuttle spacecrafts. The results showed that rodent embryos developed normally when exposed to microgravity in the last one-fourth of pregnancy, but important disabilitues were observed in the further development and behavior of animals [10, 11]. In particular, the vestibular function was impaired [12], but was then restored in the Earth's gravity conditions. Early embryonic development from fertilization to the mid-blastula stage seems to be the most vulnerable to microgravity [4].

Thus, the available data demonstrate that embryonic development is principally possible in space, but sequels of embryonic exposure to microgravity arise unfortunately during further development and need comprehensive investigation. The male reproductive system attracted particular interest in recent years. Upregulated expression of the Tet2 demethylase gene and downregulation of Hdac1 histone deacetylase were observed in the testes and vas deferens of mice in a real space flight onboard the International Space Station (ISS) with a duration of 21–24 days. The changes might be considered as the events that could affect expression of target genes upon a return to the Earth [13].

EVOLUTION OF THE MOTOR SYSTEM AND GRAVITY

The first vertebrates that populated the water column lived in support-lacking conditions. As mentioned above, fish and other marine vertebrates are adapted to supportless environments.

A principal reorganization occurred in the motor system as animals moved onto the ground. To successfully exist in new terrestrial conditions, animals had to have a strong bone skeleton that holds the body above the ground, a reliable muscular system that ensures coordinated movements and changes in position in space, sensory systems that provide diverse information about the environment, and complex control systems.

The motor system is the most gravity-dependent system of the body. Following the Russian researcher Bernshtein [14], activity that ensures targeted interactions with the environment is the most general feature of living organisms. Encountering various environmental factors, a living organism fights them, overcomes their resistance, or adapts to take advantage of the useful environmental elements. Gravity was a factor that played a leading role in evolution of the mammalian motor system. The role was so important that evolution of the motor system may be defined as evolution of the fight against gravity. As a result, mammals acquired a strong skeleton, a powerful muscular system, a sensory system, and a system that controls movements [4].

The relationship of musculoskeletal system evolution with gravity may be considered as a particular case of relationship between an organism and its environment. The idea was repeatedly voiced by the majority of evolutionists, starting from J.-B. Lamarck and Ch. Darwin. Gravity is commonly thought to play the most basic role among all abiotic environmental factors.

Evolution of the weight bearing/support function manifests itself in the complication of the geometry of the skeleton and the shape of muscular structures in terrestrial animals. A role of mechanical laws in adaptive evolution of the musculoskeletal system is supported by direct relationship of the body size with the specific muscle mass and bone mass in terrestrial animals and lack of these relationship in aquatic animals. Moreover, the specific bone mass shows more than a threefold decrease in certain mammals that returned into an aquatic environment in the course of their evolution [15].

The form-forming role of gravity, apparently, was realized throughout the evolutionary process. For example, an internal bone skeleton that is structurally and functionally combined with the muscular system to form an integral locomotor four-pedal apparatus appeared first in the phylogeny of amphibians. The general body shape and symmetry type in animals were shown to be derivatives of the mode of their spatial movements, which, in turn, depend on the intensity and direction of the Earth's gravity. The development of symmetric musculoskeletal structures does not start until an appreciable weight is acquired by an animal body [4].

A weight load is not the only factor that determined evolution of the motor system in terrestrial animals. Dynamic stimulation was another external mechanical factor, arising in parallel with improving functions of the muscular system in terrestrial animals. S.E. Shnol [16] proposed a "kinetic perfection" principle, assuming that the correspondence of various movements to certain mechanical (kinetic) criteria (velocity, maneuvering capability) determined progressive evolution of the motor system. This process eventually led to the advent of modern movement types realized with the help of specialized motor fibers.

Indeed, as vertebrates further evolved on the ground, a peripheral muscle tone mechanism (acetylcholine contracture) started to hinder the performance of motor tasks, which increased in complexity and required the body not only to be maintained on the ground surface, but also to maneuver, to quickly change its posture, and to stabilize its posture prior to starting a movement [16].

With the advent of a rigid skeleton and limbs that strongly limit the working lengths of muscles, tonic muscles, whose tension is independent on the initial length, changed to cross-striated muscles, which have a phasic contraction type, a mechanism of spreading action potential, and a high contraction velocity [14].

In studies performed mostly by Russian researchers, two components were isolated and descried in the muscular part of the motor system: continuous low-intensity tension, which arises because muscles are involved in regulating posture in the gravitational field, and an alternating (dynamic/phasic) component, which ensures locomotor activity and translocations in space [4]. It is obvious that the first component is determined by the presence of gravity and works to counteract gravity [17].

Thus, it is possible to state that the structural and functional integrity of the musculoskeletal system in the process of its evolution is a result of convergence of several factors: the gravitational force, which determined the relationship between the bone mass and body size in terrestrial animals; physicochemical factors, which determined the modern organization of the muscular system; and a set of static and dynamic loads, which determined the trend in improving the organization of the motor system.

EVOLUTION OF THE CARDIOVASCULAR SYSTEM AND GRAVITY

The cardiovascular system in terrestrial animals is among systems with the strongest gravity dependence. Active mechanisms preventing the passive downward movement of blood under the influence of gravity should have arisen in the process of evolution. Special problems exist in large animals that hold their heads high above the ground because the pressure substantially varies among different body levels, depending on the distance from the heart, and is adjusted to match the weight of the fluid column that separates a given region from the heart level or, more accurately, the level of a hydrodynamically indifferent point (a hydrostatic pressure gradient). The question arises as to what mechanisms the body utilizes to minimize the adverse effect of the gravity factor on the cardiovascular system. To answer, consider the function of the cardiovascular system in giraffes and large tree snakes because the situation is especially intricate in these terrestrial animals with the head held very high above the ground.

Snakes include species that differ in susceptibility to the effect of gravity. There are aquatic species on the one hand and, on the other, large tree snakes, which are continuously exposed to repeated effects of gravitational stress. Snakes provide a unique model to study the effect of gravity on the cardiovascular system because their body shape predisposes to a higher gravity sensitivity and their behavioral features determine a higher or lower susceptibility to the effect of gravity. Comparative physiological studies in aquatic and tree snakes showed that the heart is closer to the body center in aquatic animals, being 45% of the body length away from the heart, while tree snakes have the heart closer to the head, at 15% of the body length in extreme cases. An intermediate heart position is observed in the snake species that do not move on trees or live in both aquatic and terrestrial habitats.

The cardiorespiratory system is sensitive to gravity in all mammals, but this sensitivity is especially high in snakes. The lung is elongated in snakes, and its respiratory part has an extremely well developed vascular network (a vascular segment). The vascular segment is very short in tree snakes, starting at the heart and extending over approximately 20% of the body length. In aquatic snakes, the lung parenchyma enriched in blood vessels may extend over the total length of the body cavity. Calculations showed that the fluid filtration in lung tissues of reptiles is two orders of magnitude higher than in the mammalian lung [18]. It is therefore of immense importance that the additional hydrostatic pressure, which is proportional to the height of the blood column in lung vessels, does not exceed a threshold at which lung edema develops. It is therefore clear why the lungs are relatively short in tree snakes. When marine snakes with their long lungs are suspended head up outside water, severe edema develops with ruptured capillaries in the lower lung regions [19].

Two questions arise when a physiologist observes a standing giraffe. First, why do its legs not get swelled? Second, why does the giraffe not die from stroke when lowering its head? Studies revealed several essential features in the giraffe cardiovascular system. A. Hargens and others showed that leg arteries have a thick wall and a narrow lumen, capillaries have low permeability, the skin and subcutaneous fascia are thick and tight, and the muscle pump helps to move the blood towards the heart during locomotion. Experiments with anesthetized giraffes were carried out by Danish researchers and showed that, when a giraffe moves its head down, the carotid artery remains unchanged in dimensions, while the jugular vein increases several folds so that up to 5 liters of blood accumulate in neck veins. This accumulation facilitates a decrease in blood pressure and protects head vessels from damage [20].

Surprisingly, only scarce literature data describe how the changes that arise in response to gravity depend on the body size [21]. A. Andreev-Andrievskiy et al. [22] used the allometric approach and showed with the example of hematological parameters and body fluid volumes that different parameters differently depend on the body size. Upon 3-day hindlimbs suspension, a decrease in red blood cell count is independent of the body size, while an increase in intracellular fluid volume shows such a dependence in animals that differ in size, but are similar in body structure and physiology (mice–rats–rabbits) [22].

ROLE OF GRAVITY IN THE FUNCTIONS OF VARIOUS BODY SYSTEMS IN THE EARTH'S CONDITIONS

Animals spread out on land in the Carboniferous Period of Paleozoic era, and this was an important event in the animal kingdom. Animals came to be exposed to gravity, which pulls the body to the ground and hinders its movements. The animal body had to adapt to new environmental conditions and to develop adaptive mechanisms. As mentioned above, special systems were formed to counteract gravity and to allow the body to maintain its posture and to move in conditions of the Earth's gravity, including the skeletal system, the muscular system, and the motor control system. In addition, special sensory systems developed to inform the body of the gravity effect, including support receptors, otoliths, and sensors that assess the axial load.

Apart from the systems that counteract gravity, there are gravity-dependent systems in terrestrial animals. These are the cardiovascular and respiratory systems and, to a certain extent, all visceral organs. Data on gravitational sensitivity were obtained even for individual cells by now. The cytoskeleton and especially its actin filaments are sensitive to gravity in mechanosensitive cells. At the same time, it remains unclear how cells integrated in a whole body respond to gravity [23].

MOTOR SYSTEM

The role of the gravity factor in the function of the motor system was studied most comprehensively to date. A special system of antigravity (postural) muscles works to maintain an upright posture in the gravitational field. The system includes extensors of the trunk and limbs (legs in humans): back, neck, anterior thigh, and posterior shin muscles, which work as extensors to keep the respective joints extended [17]. Maintenance of an upright posture is a continuous fight against an abortive forward fall because the center of gravity of the body is in front of the ankles. Continuous, well-adjusted low-intensity activity of the postural muscles is necessary for preventing the body from falling. Physiological and morphological specifics of the postural muscles match well their functional tasks. The muscles consist mostly of slow motor units, can produce a long-lasting contraction without fatigue (slow muscles), are supplied with energy via aerobic processes, are abundantly supplied with blood, and have a high myoglobin content (red muscles).

To control the motor system activity, it is necessary to have information about the environment, the position of the body in space, etc. Sensory systems, which allow spatial orientation in humans, are classified into gravity dependent and gravity independent. The former include support receptors, which are found mostly in weight-bearing plantar areas; vestibular receptors and, primarily, the otolith system; and sensors that assess the axial load. The gravity-independent systems include audition and vision.

Support reception is the least understood among all of the above receptor inputs. Support receptors, or deep skin sensitivity receptors, include Meissner's corpuscles in skin papillae and Vater–Pacini bodies in deeper connective tissue structures [24]. The latter are found in the weight-bearing plantar areas and occur at the highest density in the regions of the heel, the tarsus, and the cushion of the great toe. Spinal [25] and cortical [26] projections are currently known for support afferents. Roll et al. [26] showed that support and muscular afferentation zones overlap morphologically and are coupled functionally in regulating posture and locomotion. It is known that the axial load is assessed by the body. Recent studies showed that molecular sensors of muscle fibers of axial muscles and, possibly, proprioceptors are involved in this process [27].

Sensing balance is the function of the vestibular system. The system includes two receptor structures, labyrinths and the otolith apparatus. The labyrinths are sensitive to accelerations (head rotations and sharp movements); the otoliths, to the body position in the gravitational field. The otolith apparatus is the most gravity-sensitive structure in the body because afferent information results from the pressure that calcium concrements incorporated in the otolith membrane (the pressure depends on their weight) put pressure on hairs of receptor cells [28]. The vestibular system is responsible for orientation in space, controlling the balance, and stabilization of the image on the eye retina. The image is stabilized because the eyeballs move in the direction opposite to that of head movement; i.e., the vestibular system is involved in gaze fixation on the objects that suddenly appear or move in the field of vision [29].

CARDIOVASCULAR SYSTEM

In the Earth's gravity conditions, the cardiovascular system provides the most illustrative example of the effect of gravity on the body. When a human stands still, the pressure in leg vessels is substantially higher than in vessels of the upper part of the body because there is a gradient of hydrostatic pressure. The blood can consequently accumulate in capacitive vessels of the legs to a considerable volume (up to 800 mL). This would not take place if the vessel walls were rigid. It should be noted that an additional hydrostatic pressure is present at both arterial and venous ends of the limb vascular system, and the blood flow observed at rest remains almost unchanged upon a transition to an upright posture. On the other hand, when the body position abruptly changes from horizontal to vertical, the venous return to the heart decreases, and the decrease may result in dizziness due to insufficient blood supply to head tissues. Thus, hemodynamic parameters substantially differ between the standing and lying positions in humans. The central venous and right atrial pressures are decreased in a standing human, the stroke volume is reduced accordingly, the heart output is lower in spite of the increase in heart rate, and the total peripheral resistance is increased. It is of interest that, during walking, all parameters return into the ranges similar to those observed in the lying position. The change is due to the function of the muscle pump; i.e., a high pressure is produced in contracting muscles and helps to push the blood out of them.

The body minimizes the adverse effect of gravity on the cardiovascular system with the help of regulatory systems, primarily by activation of sympathetic traffic to the vessels. Features of vascular system adaptation to abrupt changes in body position were described above with the examples of the cardiovascular systems of giraffes and tree snakes.

The above examples show convincingly that various systems of the body are substantially affected by gravity in humans living on the Earth. Gravity affects the structure and function of the motor system, the nervous system parts that are involved in motor control, the cardiovascular system, the kidney (fluid-and electrolyte balance), and the hormonal system. However, the interaction of the body with gravity was almost not investigated until recently. Lack of studies was possibly due to lack of social demand, but the situation changed as the space flight era started.

EFFECTS OF CHANGES IN GRAVITATIONAL LOADING (SPACE FLIGHTS AND GROUND-BASED MODELS)

The first space flights made it clear that lack of gravity dramatically affects the human body, causing motion sickness (an analog of sea sickness) due to a sensory conflict, head tissue edema, muscular atony, atrophy of skeletal and heart muscles in later periods, postural alterations, etc. [4]. The majority of acute changes are alleviated at later stages of a flight, and cosmonauts adapt to life in microgravity. However, readaptation to gravity after the return from a space flight is a substantial problem. Readaptation is no less painful as adaptation to microgravity and is even more painful in the case of certain body systems. It is enough to say that many cosmonauts find it difficult to maintain an upright posture and to perform locomotion after flight [4]. Preventing adaptation to microgravity is among the main problems of space medicine, aiming to make it easier to cosmonauts to subsequently return to the Earth's conditions. The problem acquired particular significance in the past years as the possibility of interplanetary missions came to be considered.

Knowledge of how microgravity affects the body comes from several sources. Space flights provide a large body of information. However, it is important to note that this information relates mostly to phenomenology rather than to the mechanisms of the observed phenomena. Physicians and physiologists make every effort to reduce the effect of microgravity on the body, thus hindering the acquisition of necessary knowledge. Therefore ground-based models of microgravity effects on various systems of the body were consequently developed from the very advent of gravitational physiology in order to study the effects on the Earth.

SIMULATION OF GRAVITATIONAL UNLOADING CONDITIONS FOR COMPREHENSIVE RESEARCH ON THE EARTH

A parabolic flight reproduces the space flight conditions most precisely, but for a very short period of time. An airplane ascends and gathers speed, the engines are then shut down, and the plane is in free fall with weightlessness conditions being created for 20–25 s. The procedure is repeated several times in one flight. Many principally important data were obtained in parabolic flights to characterize the most acute, immediate changes that arise in the body in microgravity.

Water immersion, that is, suspension of a human in water is among the most efficient means to simulate the microgravity conditions. Several immersion modes are used to simulate the microgravity conditions, head-out immersion and dry immersion being the most common. In the former case, a subject stands in a vertical tank, which is gradually filled with water. Substantial changes occur in the functions of various body systems as the tank is filled. The duration of a subject's exposure to immersion does not exceed a few hours. Suit immersion is used to train cosmonauts for working outside of a spacecraft. Dry immersion was developed at the Institute of Biomedical Problems in the 1960s [30] (for s recent review, see [31, 32]). A subject lies in a large tank filled with thermally neutral water, which is covered with water-/proof fabric. The area of the piece of fabric is far greater than the water surface area. The subject is separated from water by fabric and is suspended in water column, rather than lying on fabric as in a hammock. The duration of exposure to dry immersion in studies is usually 3–7 days; the maximal duration is 56 days. This model most closely reproduces mechanical unloading and lack of support, which are characteristic of microgravity. The support is nearly uniformly distributed over the body surface in immersion conditions, and the central nervous system perceives the environment as supportless.

Head-down bed rest (HDBR) with a tilt of –6° is the most common method to model the effects of microgravity [33]. The HDBR duration is usually 30–90 days. HDBR of the longest duration, 370 days, was carried out at the Institute of Biomedical Problems from 1986 to 1987 [34]. While the above methods are used most frequently to model the microgravity conditions, there are other unloading methods, such unilateral limb suspension [35]. Hindlimb suspension is used in experiments with laboratory rodents. The hindlimbs do not touch the floor, but the animal can move using its forelimbs in the cage [36, 37]. Food and water are provided ad libitum. The suspension duration is usually 3–30 days. Working with various models, it is important to understand which body systems are affected. For example, the vestibular system is not directly affected in the above models other than suit immersion. Effects on the vestibular system are achieved using other means, including a slow rotation room, centrifugation, etc.

ADVANTAGES AND LIMITATIONS OF THE MODELS WITH THE EXAMPLE OF CHANGES IN CARDIOVASCULAR SYSTEM

New data on the mechanisms of changes arising in the sensorimotor system were obtained by comparing in-flight data with data from model experiments. For example, data on changes in the order of motor unit recruitment upon a transition to gravitational unloading conditions are of principal importance for the gravitational physiology of the motor system. The data were obtained in ground-based model experiments [38] (dry immersion and HDBR) and confirmed in a space flight [39].

However, such a success is not always the case. An issue that needs separate consideration and is of basic importance for the gravitational physiology of the cardiovascular system is to what extent the changes observed in model conditions in humans (HDBR, dry immersion) and in laboratory animals (suspension) match the changes observed in cosmonauts during real space flights. The American physiologist M. Delp was the first to raise and discuss the issue in detail with the example of cerebral blood flow. Changes in cerebral circulation are now intensely discussed in the literature in connection of vision impairments in astronauts. Experiments with rat hindlimb suspension, which are used to model gravitational unloading in laboratory animals, showed many times that an increase in vasoconstrictor effects and a hypertrophy-type remodeling of head vessels develop as a result of suspension [40, 41]. The effects are commonly thought to arise because the transmural pressure increases in head vessels of suspended animals as a result of a body fluid redistribution [42], which is similarly observed in cosmonauts. However, the effect is not observed in suspended mice [43]. Moreover, a decrease in both constrictor and dilator responses was detected in isolated cerebral arteries of mice after a flight in recent studies of long-duration space flights [43, 44]. The question arises as to what factors are responsible for these substantial differences. Does the difference mean that data from model experiments with laboratory animals are incomparable with in-flight data or that mice provide an inadequate model to simulate the changes that occur in human cerebral arteries during a space flight?

It is clear that a cranial shift in body fluid distribution during suspension is negligible in mice because of their small body size. In this context, mice are inferior to rats in modeling the human body fluid shift. However, a redistribution of body fluids towards the head and the respective changes in blood pressure are probably not the only factors that determine the changes observed in microgravity. A role may be played as well by other factors, such as the duration of a space flight, background radiation, the composition of the spacecraft atmosphere, etc. Discrepant data on the cerebral blood flow in cosmonauts were reported in the literature, but an increase in blood flow was detected in the majority of relevant studies. A French–Russian team [45] observed an appreciable increase in linear blood flow velocity in the middle cerebral artery and a decrease in cerebral vascular resistance in cosmonauts. The findings agree with a decrease in vasoconstrictor effects that was observed in mice during a flight. It is important to note that the same researchers showed using the same methods that the linear blood flow velocity decreases and the resistance increases in HDBR conditions, as well as in suspended rats [46]. Similar data were obtained by comparing the post-flight and HDBR data by another well-known research team [47, 48]. The available ground-based models of gravitational unloading in rats and mice are efficient in modeling the changes in certain regions of the vasculature, for example, in mesenteric vessels [49], but are unsuitable in the case of other regions and cerebral vessels in particular. Model experiments do not always reproduce the changes observed in a flight, nor do they work similarly for all vascular regions. The limitations of studying the cerebral blood flow in ground-based models seem to be applicable to HDBR as well.

Does the above mean that an insignificant effect is only exerted by a body fluid redistribution due to elimination of gravity? It can hardly be so. Many factors act simultaneously in the body, and one of them is improper to consider in isolation from the others. As for the cerebral blood flow, the pressure must increase in a cosmonaut's cerebral vessels as a result of the body fluid redistribution. However, the question as to how the extravascular intracranial pressure changes as a result is still a matter of discussion [50]. If changes in this pressure are similar to changes in intravascular pressure, as M. Delp assumes, then the transmural pressure remains the same. This situation is most likely observed in the case of mouse cerebral vessels.

Thus, different research teams observed different or even opposite changes in cerebral blood flow in real space flights and ground-based models of gravitational unloading. This means that the factors that determine cerebral circulation in a flight are still impossible to adequate simulate on the Earth.

In spite of the limitations characteristic of the available models of microgravity conditions, data on the state of vessels from model experiments are of immense importance for understanding the mechanisms whereby mechanical (share stress and stress due to vascular wall dilation) and chemical (metabolites) factors mediate adaptation of vessels. In other words, data from model experiments help us to interpret the vascular responses observed in space flights.

CHANGES IN MOTOR SYSTEM, MOTOR CONTROL, AND ITS SENSORY SUPPORT IN CONDITIONS OF ALTERED GRAVITATIONAL LOADING

Studies in real or simulated hypogravity showed that gravity is tightly incorporated in the development of the mammalian motor system. It is important to note that it is not possible to identify any mechanism whose activity would not be significantly disrupted by the elimination of gravity.

Data from experiments performed in space flights and ground-based models led to the development of a concept of microgravitational motor syndrome, including views of muscle detraining and hypogravitational ataxia syndromes, and a concept that considers the nature of motor alterations and distortions in the functions of other body systems in microgravity and relates the microgravity-induced changes to alterations in the functions of the postural muscular system [4, 51]. This system, which arose as the result of evolutionary development during the transition of living organisms to life on the ground, keep its exclusive dependence on gravity. The support input plays a crucial (nonreplaceable) role in regulating its activity in mammals. When the input is reduced or eliminated, changes in the order of motor unit recruitment arise in extensor pools of the spinal cord (the initial recruitment order from slow to fast motor neurons is changed to the opposite one) and activity of extensor slow motor units decreases consequently; this decrease cannot be compensated by other sensory inputs [4, 51].

Changes in different physiological parameters under the influence of microgravity begin differently. The most acute changes, which occur almost immediately with the exposure to microgravity, affect the posture maintenance/muscle tone, the vestibular system (motion sickness), the distribution of body fluids, and the cardiovascular system. Extensor tone is lost very quickly, and its lost is followed by muscular atrophy after a while. Skeletal alterations are the last to arise. Clinical observations showed that a decrease in the weight-bearing load on the skeleton leads to changes in calcium metabolism, calcium is progressively excreted from the body, and osteopenia or even osteoporosis develops. Similar changes arise in microgravity. A detailed description of changes in bone tissue is available in reviews [4, 52, 53].

The distribution of changes in bone tissue density over the body deserves particular attention. Bones of the lower limbs are affected to the greatest extent in microgravity, changes starting from pelvic bones and increasing downwards. These regions account for 90% of mineral calcium losses. In contrast, the bone density may even increase in the head region. This distribution arises almost in parallel with changes in body fluid distribution and the blood filling of various body regions [54] and is possibly associated with volume and ion regulation [55, 56].

Back pain is a common consequence of exposure to microgravity, being often observed in crew members in the first days of space missions and subjects exposed to dry immersion or HDBR to model the microgravity effects on the Earth [32, 57, 58]. Pain syndrome is often thought to be due to possible changes in the topography of output sensory roots of the spinal cord [58, 59]. It is possible that with prolonged exposure, the consolidation of these changes contributes to the development of disorders of the structure of the intervertebral discs with the development of myalgia and neuralgia. In particular, Scheuring and colleagues [59] diagnosed herniation of nucleus pulposus of cervical and lumbar intervertebral discs in 10% of astronauts in the postflight period. The nature of the changes is unclear, although a dramatic decrease in the tone of back extensor muscles at the onset of microgravity was identified as one of the possible causes in recent studies [60].

Load on the skeleton and body posture-maintaining muscles is eliminated in microgravity, as there is no need to maintain the upright posture. This leads to changes in the function of the receptors that are sensitive to the support reaction and respond to the axial load, changes in the function of the vestibular system, a decrease of motor activity, and alterations in the biomechanics of movements. A half-embryonic flexed posture is assumed by the human body because an uprignt posture is no longer necessary to maintain. This is associated with a substantial decrease in the contribution that extensor muscles make to motor activity. In fact, ground-based dry immersion experiments showed repeatedly that a substantial decrease in tone occurs in the shin extensors, soleus and gastrocnemius muscles as early as the first two hours of exposure and reaches its maximum approximately 6 h later. The tone of the tibialis anterior muscle remained almost unchanged [51]. Monkeys performed the task to hold a lever during a space flight onboard the Bion biosatellite. The soleus muscle was involved in the task performance on the Earth, while a gradual change from the soleus to the gastrocnemius muscle was observed in task performance over several days of the flight; i.e., activity switched from a slow postural muscle to a mixed locomotor muscle [39]. Perhaps it is precisely as a result of the disappearance of "functional duties" (posture mantenance) and a dramatic decrease in the mechanical/resistive load that slow motor units (MUs) are turned off from work, they are replaced by the fast MUs, i.e. the order of MU recruitment is changed [38, 61]. In addition to atony, atrophy gradually develops in muscle fibers that express a slow isoform of myosin heavy chains and are components of slow MUs [27, 62]. Substantial changes at the molecular level were found to occur in m. soleus fibers in experiments with rats. Only few of the changes are listed below. Muscle fibers lose cytoskeletal molecules, that leads to a significant decrease in the efficiency of actin–myosin interactions and a decrease of calcium sensitivity, resulting in a decrease in the maximal contractile response of a fiber. In addition, lack of support decreases the efficiency of protective mechanisms (nitric oxide synthase (NOS)) and activity of AMP-activated protein kinase, which acts as a metabolic sensor in the cell [63].

A transformation of a certain portion of slow muscle fibers into fast fibers is one of the most overt changes that occur in postural muscles in real or simulated gravitational unloading. The transformation results from the changes that arise in expression of myosin heavy chain genes and are mediated, in particular, by inhibition of the calcineurin/NFATc1 (nuclear factor of activated T cells) signaling pathway, epigenomic changes, and the effects of specific microRNAs [63].

It should be noted that intense research were recently launched to study the molecular mechanisms of changes that arise in various body systems in response to a dramatic decrease in gravity. Experimental data are intensely accumulating. Many interesting findings were made. For example, Atomi [64] studied the role of individual elements involved in maintaining the integrity and efficient function of the cytoskeleton, which plays an important role in maintaining the cell shape, producing tension, etc. Intracellular and extracellular stimuli act through the cytoskeleton to provide signals to the nucleus and thereby to modulate gene expression. A pronounced decrease in muscle mass is specifically associated with a decrease in B-crystallin level in suspended rats. B-crystallin acts as a chaperone for tubulin and thus prevents calcium-induced disassembly of microtubules. On the other hand, physical exercise promotes constitutive B-crystallin expression, which helps to maintain dynamic homeostasis of microtubules as an element of the cytoskeleton. Following Atomi, the relationship between the chaperone expression level and the regulation of cytoskeletal dynamics in slow postural muscles is an important element in evolution of the motor system.

It is of interest to note that, in contrast to microgravity, artificial hypergravity produces the postural muscle effects that substantially vary depending on the animal body size/weight, the respective support load, and the muscle composition specifics. For examples, studies in rats and primates (rhesus monkeys) did not detect changes in muscle fiber size in slow and fast shin extensors (the soleus and medial gastrocnemius muscles) after 2-week exposure to 2G [65, 66]. On the other hand, 4-week exposure of mice to 3G hypergravity increased the shin muscle sizes and the cross-sectional area of m. soleus fibers [67]. It should be noted that the changes observed in mice did not develop when the vestibular system was damaged, indicating that the processes are directly associated with vestibular influences. However, more recent studies by Russian researchers showed that centrifugation at 2G for 3 weeks did not produce any significant change in protein synthesis rate and the level of phosphorylation/activation of key anabolic markers (AKT, p70s6k, 4E-BP1, GSK-3β, and eEF2) in the mouse soleus muscle [68]. The differences are certainly possible to attribute to the differences in duration and intensity of hypergravitational exposure and in muscle composition (m. soleus is a mixed muscle in mice). Still the effect of body size on how the gravitational factor affects the body is an interesting and important problem of comparative physiology.

Changes in the function of sensory systems occupy an important place among the factors that mediate the effect of microgravity on the motor system. Afferent support of the motor control systems is broad and diverse on the Earth, including vision, the vestibular system, and support and motor afferent inputs. In microgravity the activity of some channels is completely eliminated, others are distorted, and others are significantly weakened. Support afferentation is fully eliminated (no weight, no afferent input), profound distortions arise in the function of the otolith apparatus and lead to serious disorders in the function of vestibular system in the whole, proprioceptive afferent input is weakened because the weight-bearing load is absent, and atony develops as a result. Vision is the only sensory system that displays no apparent change. However, the function of the system of vision is also distorted as far as oculomotor reactions are concerned because the system closely interacts with the vestibular system. On the Earth, the eyeballs rotate in the direction opposite to that of head rotation to stabilize the image on the eye retina. The precision and speed of gaze fixation on a visual object are ensured by the mechanism of the vestibular–ocular reflex. Its function is distorted in microgravity: the head rotation velocity decreases and eye counterrotation fails either to occur or to match the head rotation pattern [69]. The tracking function of the eyes is also impaired, and a smooth tracking of a target replaces with saccadic eyeb movements [4].

Results from cytochemical and morphometric studies performed in rats in a 14-day space flight indicated that a space flight decreases the regulatory influences from Purkinje cells of the superior central lobule of the cerebellum on giant neurons of the dorsocaudal region of Deiters's nucleus. The results additionally supported the hypothesis that a space flight-induced decrease in the inhibitory influence of nodular Purkinje cells on the medial vestibular nucleus is a cause of the changes that are observed in integration of vestibular and visual signals (velocity storage) in mammals during and after a flight [70].

The above changes in the functions of sensory systems can be reproduced in ground-based model experiments. Studies of the effects of head-out immersion on the vestibular–ocular and tonic neck reflexes in *Macaca mulatta* monkeys were carried out at the Institute of Biomedical Problems and showed that the effects depend on the level to which the animal body is immersed in water. Unfavorable changes in gaze fixation characteristics were observed 5 h after the start of immersion to the sternal level and were similar to the changes detected in a space flight: the eye saccade amplitude and the vestibular–ocular reflex coefficient increased, while the maximal head rotation speed decreased. When monkeys were immersed to the neck level, changes observed after 5-h exposure were greater and were accompanied by changes in the organization of head movements during gaze fixation. The findings make it possible to assume that support unloading is possibly a space flight factor that decreases the speed and accuracy of gaze fixation. Water immersion of monkeys provides an adequate model to study the mechanisms whereby microgravity affects the coordination of eye and head movements during gaze fixation [71]. The above changes may eventually affect the precision of movements.

The role that vestibular influences play in controlling activity of postural muscles was additionally investigated by studying the effects of galvanic vestibular stimulation (GVS) in humans [72]. A distinct dichotomy was revealed between the effects of vestibulospinal inputs to motor neurons of axial muscles (the muscles that straighten the vertebral column) and those of leg muscles. Studies provided important information on the integration of vestibular inputs to the sensorimotor system and confirmed that different mechanisms control the axial and leg muscles. EMG responses of the lower limbs to vestibular stimulation are associated to a greater extent with the support factor rather than with the body position. Responses of the axial muscles to vestibular stimulation are direct, well reproducible, and independent on the sensory context according to the experimental findings. The dichotomy observed between the responses of the axial and shin muscles can be interpreted by assuming that individual motor patterns exist for performing different tasks in particular sensory support conditions.

In spite of the numerous changes in the functions of body systems, cosmonauts efficiently perform many working operations and physical exercises during a flight. This would be impossible without a profound functional reorganization of the motor control system and the regulation of the cardiovascular system.

Effects of space flights on the brain were detected in fact in recent studies with modern neurovisualization methods [73, 74]. Ten crew members who participated in long-duration missions with a mean duration of 189 days were examined by magnetic resonance imaging (MRI) of the brain to measure the gray matter and spinal fluid volumes before flight and 7–9 and 180–209 days after landing [74]. Similar studies were performed in parallel in 12 volunteers who did not participate in space missions. The gray matter volume was significantly reduced in the cosmonauts after the flight. The greatest decrease (up to 3.3%) was observed in the orbito-frontal and temporal areas of the cerebral cortex shortly after landing and was gradually alleviated (to 1.2% relative to the preflight level) within 6 months after the flight. The fluid volume in the brain, including the ventricles, was increased, and maximal changes (up to 12.9%) were observed in the third cerebral ventricle. The volumes of the cerebral ventricles returned to the baseline values 6 months after the flight, but the fluid volume in the subarachnoid space remained elevated even relative to the values observed in the first days after landing. No significant change in morphometric parameters was observed in the control group at the same time points. The results make it possible to conclude that reversible functional rearrangements arise in the human brain during long-term exposure to microgravity and are compensated in terms of cell composition within 6 months after landing. Changes in intracranial fluid volume persist for longer periods and seem to require additional rehabilitation. In addition, studies with functional MRI confirmed the intense reorganization of functional connections between different areas of the brain in 11 cosmonauts examined after landing. Disseminated focal activation was detected, and weaker connections were observed between the cerebral cortex and vestibular nuclei and between the cerebellum and several other areas involved in motor control [75]. It is of interest that similar, to an extent, changes in the function of neuronal networks were detected in mollusks. The snail Helix lucorum perceives activation of the statocyst (an organ of balance) as a signal of danger (a fall from the forage plant or an attack of a bird) and responds by a general motor activation reaction. The plasticity of vestibular sensory neurons of the statocyst was recently studied after 30-day exposure to microgravity onboard the Bion-M1 biological space apparatus [76]. The results suggest individual sensitivity adjustments for each hair cell rather than a directionality common for the whole statocist, in contrast to earlier assumptions. This fine sensitivity adjustment is weakened to a substantial extent in post-flight animals, suggesting a plastic, rather than strictly determined, system of connections for neuronal micronetwork of the statocyst. The effect of individual adjustment of sensory neurons of the statocyst may play an important biological role in the snail, which has an asymmetric massive shell and is prone to rest on vertical surfaces above the ground level.

Rearrangements of connections between various structures of the brain were analyzed in cosmonauts after flights and were found to tend to the centers that ensure orientation in space and directionality of movements [75]. The findings confirmed the hypothesis of vestibular neglect developing in space flight conditions. The hypothesis has been developed by Prof. I.B. Kozlovskaya's school for several years. On the other hand, stronger connections were observed after flights between the insular cortex of the two hemispheres and between the insula and other brain regions. The insular lobes are responsible for integrating sensory signals of different modalities and play a key role in the recovery of the motor control system during rehabilitation after stroke or craniocerebral injury. Thus, rearrangements were observed in connections between various cortical areas and other brain regions involved in processing, integrating, and analyzing sensory information and generating motor commands. The range of adaptive changes in brain blood flow is narrowed to accompany the above changes.

In-flight experiments with cell cultures and laboratory animals showed that the wave propagation speed in excitable media of neural tissue is affected by gravity. Certain regions of the active zone of hippocampal neurons are significantly reduced, while dendrite branching and the spine number significantly increase, substantial depolarization (3 mV) is observed for the resting potential of human neuronal cells, and the speed of action potential propagation decreases at the axonal level. All of these changes arise very quickly and are fully reversible after a return into the Earth's gravity conditions [77].

Intense studies are carried out to understand the molecular mechanisms of the changes that arise in brain structures in microgravity. In 2013, a 30-day mission of the Bion-M1 biosatellite was flown with C57BL/6N mice onboard. Molecular changes in brain areas were compared with functional changes in motor system in a series of works reported by Novosibirsk researchers. A long-duration flight exerted a slight inhibitory effect on the genetic control of the serotoninergic system of the brain in mice [78]. In particular, a decrease in expression was observed for the gene coding for the hypothalamic 5-HT2A receptor and was interpreted as a reaction that decreases the efficiency of the stress response.

Signs of higher apoptosis in the hippocampus were observed in the mice after the flight. In particular, the signs included upregulation of the gene for the BAX pro-apoptotic protein and simultaneous compensatory upregulation of the gene for the Bcl-XL anti-apoptotic protein [79].

Changes in gene expression were observed after the flight in the nigrostriatal system, which plays an important role in regulating the muscle tone and maintaining posture and balance. The changes were possibly associated with a decrease in afferent input [78]. For example, expression of the main dopamine synthesis enzyme TH substantially decreased in the substantia nigra, and expression of the dopamine catabolism enzyme COMT decreased in the striatum. A decrease in expression of the dopamine receptor D1 was additionally detected in the striatum and hypothalamus. The studies by this team provide an example of how changes detected in the function of the motor system at the functional and morphological levels gradually receive a molecular explanation.

The reaction of brain circulation to a cranial shift in liquid distribution and subsequent in-flight hypovolemia is intensely discussed in the literature. As mentioned above, a redistribution of body fluids increases the intravascular pressure. However, it is unclear how the intracranial pressure changes in this case [50]. If the intracranial pressure increases to the same extent as the intravascular pressure does, then the transmural pressure will remain unchanged. An increase in intracranial fluid volume and a higher resistance to venous outflow were observed in both earlier impedance studies and recent studies with high-tech methods [74, 80]. The latter change agrees with an increased jugular vein diameter, which is a usual finding. Data on in-flight brain circulation are discrepant, but there is convincing evidence that perfusion of brain tissue is increased. A higher blood flow velocity in the carotid artery and a lower vascular resistance were detected in a rhesus monkey during a short-duration flight onboard the Kosmos-1514 biosatellite [81]. Arbeille et al. [45] found that two-component dynamics of changes in blood flow velocity in the middle cerebral artery is observed in cosmonauts during a long-duration space flight. The blood flow velocity was increased and the vascular resistance decreased in the first week of the flight, and then the blood flow velocity grew lower and fluctuated around the initial level [45]. Iwasaki et al. [47] reported similar findings from a short-duration flight. Indirect evidence to increased perfusion of head tissues is provided by the above increase in the mineral density of cranial bones, which are not exposed to higher mechanical loading in flight, but increase in density and volume [52, 56].

On the other hand, a decrease in cerebral blood supply in astronauts was observed in other studies [82, 83]. Decreases in both constrictor and dilator responses were observed in experiments with isolated cerebral arteries of mice after a flight, i.e., exposure to space flight conditions reduced the range of adaptive changes in cerebral circulation in mice, and this might cause disorders in brain functions [43, 44]. Caution is certainly necessary to exercise when using data from experiments with animals to discuss the problems related to humans. Still the regulation of the cerebral vascular tone is a pressing problem. American astronauts complained of impaired visual acuity in flight in the recent years. Static visual acuity is not impaired in all appearances, while remote vision and dynamic visual acuity (that is, visual acuity of a moving person) are affected [84, 85]. A possible mechanism of the effect was associated with a higher intracranial pressure [86]. Russian researchers [87] think that the vision problems are at least partly attributable to excessive physical exercise, which American astronauts do to prevent the adverse changes in muscular and bone tissues (see below).

CHANGES IN CARDIOVASCULAR SYSTEM AND ITS REGULATION. WHAT ROLE DOES LACK OF A GRAVITY-DEPENDENT PRESSURE GRADIENT PLAY?

Acute changes that arise in human cardiovascular system in real microgravity conditions were described as fluids shift towards the head, which arises because a hydrostatic pressure gradient no longer exists, while the mechanisms that prevent a fluid accumulation in the lower limbs are still working [88]. Outer signs of these changes include facial puffiness, a feeling of nasal stiffness, and a visible decrease in leg volume. Simultaneously with a blood shift, Starling forces in capillaries change towards higher absorption of the interstitial fluid into the intravascular space [89]. The two effects increase the heart preload and filling, as well as the circulating plasma volume. The changes must increase the stroke volume according to Starling's law. The atria are extended and the stroke volume and cardiac output increased, in fact, during parabolic and space flights according to electrocardiography and rebreathing data [90, 91]. Recent studies onboard the ISS showed that a higher cardiac output can persist during a long-duration flight [92]. A redistribution of fluids and the blood similarly occur in model experiments, an increase in cardiac output during head-out immersion being greater than during HDBR [93]. A comparison of data from 3-day dry immersion and 21-day HDBR did not detect any difference in systemic hemodynamic parameters; i.e., the changes develop faster in the case of dry immersion [94].

A cosmonaut's body responds to central volume expansion by reducing the circulating blood volume, which decreases as early as the first days of a flight and is gradually stabilized at a level 10–15% lower than the initial level, that is, between the values characteristic of the body in a vertical and a horizontal position [95]. Similar changes are observed in HDBR [96]. Causes of fluid losses in HDBR were identified in ground-based model experiments and were associated with the hormonal regulation. The changes in plasma/blood volume that occur in a space flight are the same as in model experiments, but are determined by other, still unidentified mechanisms [92].

A 30% decrease in intercellular fluid volume was detected in rhesus monkeys in a 7-day flight onboard the Kosmos biosatellite [97]. Smaller animals with lower changes in hydrostatic pressure (rats) displayed far lower changes in circulating blood and intercellular fluid volumes [98]. In mice with their negligibly low gradient of hydrostatic pressure, the circulating blood volume remains unchanged and the extracellular fluid volume increases slightly [22]. The changes are probably due to an increase in capillary filtration, at least in the front part of the trunk.

A distinct distribution pattern is commonly assumed in the literature for changes in the morphological and physiological properties of vessels; i.e., the vascular wall increases in thickness and contractile responses increase in strength in the cranial direction. The changes are associated with a hydrostatic pressure gradient, which results from the redistribution of body fluids [40]. At the same time, there are ample data the substantial region-specific changes arise in the reactivity of vessels to constrictor and dilator stimuli [41, 99]. The mesenteric region , which is at the level of the hydrodynamically indifferent point, is of interest in that there are no pressure fluctuations due to a cranial shift of body fluids in the region. Still a decrease in the adrenergic constrictor reactions of both mesenteric arteries and veins was observed [100]. A decrease in the reactivity of vascular smooth muscles to adrenergic stimuli is therefore not related to hydrodynamic mechanical changes in this case, but is determined by other factors. The atrial and brain natriuretic peptides were assumed to act as such factors, the peptides affect the ryanodine receptors (by downregulating mRNA expression) and thus reduce the release of intracellular calcium.

Central hemodynamic parameters do not significantly change in flight, and recordings depend on the external factors (spacecraft dimensions, which limit motor activity, and the state of the environment), the intensity of motor activity, and the methods used to record the data and to compare them with preflight data (lying vs. sitting position, measurements at certain time points vs. 24-h monitoring). Studies with 24-h monitoring more often detect a decrease in heart rate as compared with an active ground-based control [101]. A somewhat lower blood pressure is also detected in this case [92].

As discussed above, the volume load of the heart decreases in humans in both real and simulated microgravity, and the decrease must lead to atrophic changes. In fact, MRI studies showed that the masses of the two ventricles, the ventricle wall thicknesses, and the end-diastolic volume decrease progressively in both model experiment with 12-week HDBR and a 10-day space flight (the left ventricular mass tended to decrease) [102]. It is important that the ratio between the end-diastolic volume and stroke volume remained unchanged even after a 3-month flight [103]; i.e., the contractile function of the heart was seemingly not affected. The Soviet physician-cosmonaut O.Yu. Atkov obtained the most convincing evidence for intact heart contractility in prolonged exposure to microgravity in a 9-month space flight. He showed that the ejection fraction measured at rest or during ergometer cycling does not decrease but even grows higher in spite of the in-flight decreases in end-diastolic volume and stroke volume. Similar findings were made in one-year HDBR [34, 104].

The question arises as to how the regulation of the cardiovascular system changes in microgravity. Data on baroreflex sensitivity, which is inferred from the baroreflex amplitude characteristics, are discrepant, which may be related to the methods used for its assessment. Spontaneous baroreflex measurements by the method of sequences or a heart rate variability analysis did not detect any changes in baroreflex-mediated regulation of the cardiac rhythm during long-duration space flights [105, 106]. When a neck chamber was used to change the blood pressure in the carotid sinus region, a decrease in carotid baroreflex sensitivity was detected in both HDBR and in-flight studies [107]. On the other hand, an analysis of baroreflex activity by phase relationship between oscillations in blood pressure and in heart rate showed that the coupling of these oscillations decreases dramatically during 21-day dry immersion [108]. It should be noted that changes in reflex develop later, but persist longer than changes in blood volume.

Several research teams used microneurography and obtained direct data on the sympathetic regulation of muscular vessels in real and simulated microgravity conditions [109–111]. The prominent Japanese researcher T. Mano and colleagues [112] presented the most comprehensive picture of how muscle sympathetic nerve activity (MSNA) changes in response to gravitational unloading. Studies by his colleagues showed that MSNA inhibition accompanies short-term exposure to gravitational unloading, be it head-out immersion or a parabolic flight [113, 114]. Longer exposure to gravitational unloading (from 3-day dry immersion to 120-day HDBR) increases the basal MSNA level [109, 111]. The character of changes in MSNA was associated with changes in hemodynamics system. In the case of short-term gravitational unloading, central volumes of the circulatory system are overfilled and the body responds by dilation of peripheral vessels. In contrast, the circulating blood volume decreases during long-term gravitational unloading, and the decrease is accompanied by vasoconstriction.

Thus, considerable changes arise in the function and regulation of the cardiovascular system in microgravity conditions. The changes are adaptive and allow the body to live actively with minimal limitations in the new conditions. However, readaptation to the Earth's conditions proceeds with great difficulties after landing. The earliest flights showed already that cosmonauts can hardly maintain upright posture for an appreciable period of time after landing and may faint. The phenomenon is related to changes in motor control system (see above) and is determined by the severe problems arising in the cardiovascular system and its regulation. The term "deconditioning" is used now for the problems arising in the cardiovascular system after landing and include orthostatic intolerance, greater reactions of the heart rate and blood pressure to physical loading, etc.

Intense studies of the causes of post-flight orthostatic intolerance and a development of measures to alleviate the adverse sequels of living in microgravity started with the advent of the era of manned space flights. It should be emphasized that many issues are understood in post-flight orthostatic intolerance after 50 years of research, but there is still no means to overcome it.

Several causes of post-flight orthostatic intolerance are obvious. Indeed, the body becomes disaccustomed to periodic blood shifts to the lower limbs due to transitions to upright posture, the circulating plasma volume decreases to a considerable extent, and changes arise in the regulatory system. Venous compliance increases in gravitational unloading conditions because properties of the vein wall change [115] and the "muscular corset" weakens as a result of tone loss and subsequent atrophy of the muscular bed [116]. Regulatory changes that arise in gravitational unloading also seem to substantially affect post-flight orthostatic intolerance. Experiments with 120-day HDBR performed in the Institute of Biomedical Problems in 1997 showed that an increase in MSNA in response to a transition to upright posture becomes higher than the pre-HDBR level as early as 60 days of hypokinesia and further increases by day 120. An adverse reaction of blood pressure to a transition to upright posture develops in parallel: the blood pressure decreases progressively as HDBR continues [110]. Thus, long-term HDBR dramatically changes the response to a transition to upright posture: the blood pressure drops while sympathetic influences on peripheral vessels increase. A decreasing sensitivity of blood vessels to sympathetic influences may be responsible for the observed effect.

There is no data to directly confirm the above assumption. Indirect evidence is provided by the observation that the constrictor reaction of blood vessels to a negative pressure (–45 mm Hg) applied to the lower part of the body gradually decreases during a 6-month flight [117]. Experiments with suspended rats yielded ample data to demonstrate that region-specific changes arise in vascular responses to constrictor and dilator stimuli in modeled gravitational unloading [40, 99]. To summarize, a set of factors acts to cause post-flight orthostatic intolerance, and changes in regulatory systems occupy an important place in the set. That is, the baroreflex sensitivity decreases, sympathetic influences on muscular vessels during standing increase, and the response of vessels to sympathetic influences seem to weaken. The changes are possible to characterize as a dramatic distortion of the response to a disturbing factor.

PREVENTION OF ADVERSE CHANGES CAUSED BY EXPOSURE TO MICROGRAVITY CONDITIONS

Systematic studies of countermeasures to prevent the adverse effects of microgravity on the human body started in the 1970s. Note that a large part of data on the consequences of human body exposure to space flight factors had already been accumulated by that time. Newly forming views suggested that a loss of the support load triggers unfavorable changes in the motor system. Based on available knowledge, running on a treadmill with a special loading bungee system was proposed as a main preventive measure at that time. Locomotor training is still a core element of the Russian countermeasure system [118]. It is important to note that interval running was included as a main component of locomotor exercise as early as the 1970s. Interval running is now thought to provide the most advanced method of aerobic training and is successfully used in sports and restorative cardiology [119]. A locomotor training regimen was developed in model experiments [34, 118]. The regimen is a 4-day cycle wherein exercises of each day are aimed at preserving orthostatic tolerance and a particular physical property, such as force-velocity properties and endurance [4]. Resistive exercise with loading devices are used to maintain the muscle properties. The so-called passive countermeasures occupy a special place in the countermeasure system used onboard orbital stations. The passive means are not time consuming and are often compatible with everyday activities of cosmonauts. The Chibis suit is one of the means. The suite applies a negative pressure to the lower part of the body and helps to prevent a dramatic decrease in orthostatic tolerance during preparation to returning on the Earth. The Penguin loading suite for permanent wearing creates the axial load on muscles and the skeleton. Low- and high-frequency electromyostimulators ensure training for leg, back, and neck muscles. A compensator of support unloading provides mechanical stimulation of the soles support zones in a locomotion mode. There are additionally pressing cuffs, water-salt supplements, etc. [4, 118].

Many issues are still unsolved in the light of future interplanetary missions. Problems of post-flight readaptation of the motor and cardiovascular systems to the gravity conditions occupy an important place among them. The problems include measures to fight losses in strength and endurance and orthostatic intolerance, which arise after landing. The dynamics of readaptation of the motor system in the acute period immediately following the landing is now a focus of research, while little attention was paid to the problem earlier. Intense studies are carried out to improve the efficiency of countermeasures by combining different means, such as physical exercise with a negative pressure applied to the lower part of the body [120], use of centrifuges to create artificial gravity [121], etc. The countermeasure means and methods used in space flights were described in detail in special reviews [4, 118].

Many measures designed to prevent the negative effects of space flight factors on the human body found application in medicine and rehabilitation on the Earth. Special publications focused on the use of modified "space" appliances, such as the Adel and Regent axial loading suites, the Korvit support unloading compensator, electromyostimulation approaches, and the dry immersion model [32, 122–124]. It should be noted in conclusion that understanding the mechanisms of the observed phenomena is essential for developing and improving the system to prevent the negative effects of a space flight on the human body. There is good reason to think that Russian researchers substantially contributed to the development of gravitational physiology in general and the understanding of these mechanisms in particular.

CONCLUSIONS

(1) The development of the animal kingdom on ground is a sequence of changes that arose during evolution to ensure maximal fitness to living in the gravitational field. Using the development of various systems in various animals, it is possible to trace how the gravity factor, physical and chemical characteristics that determine the organization of a given organism, and its size and behavior converged to shape the adaptive structural and functional features of the motor and cardiovascular systems and their control.

(2) Gravitational physiology as a particular research field is still in its infancy, but its achievements are commonly recognized, primarily in the field of motor control. The achievements include the following. The postural and phasic components were isolated in the muscular system, the muscle tone concept was developed, and support afferentation was demonstrated to play a role in controlling locomotion. A clear overview was obtained for the changes that arise in the human cardiovascular system and are associated with the gravity factor, starting from changes in hydrostatic pressure gradient. Substantial alterations in the regulation of hemodynamics and vascular tone were observed in microgravity.

(3) Recent studies with the use of high-tech methods revealed microgravity-dependent rearrangements of connections between various cortical areas and other brain structures involved in analyzing and integrating sensory information and generating motor commands. The rearrangements seem to occur while the range of adaptive changes in cerebral circulation is narrowed. A refined topology was obtained for the effects of the support and vestibular factors on the axial postural muscles and postural muscles of the limbs.

(4) Important factors were identified to trigger the changes in the motor and cardiovascular systems of the human body in response to changes in gravity. Comparative physiological studies in other objects, such as animals that are similar in body structure, but differ in body size, reveal the interesting features that were earlier masked by potent factors, such as support reactions, the hydrostatic pressure gradient, and others. The vestibular system was shown to play a substantial role in increasing the extensor muscle sizes in hypergravity, and body size-dependent changes were observed for hematological parameters and body fluid volumes.

(5) Recent studies provided for a better understanding of the intricate mosaic of changes that arise in the body upon exposure to a changed gravity factor. Interesting avenues of research in the nearest future

are to separate the region of influence of support reactions and that of vestibular influences and to identify the factors that act together with the pressure gradient to trigger adaptive changes in the cardiovascular system on exposure to changes in gravity.

FUNDING

This work was supported by the Russian Foundation for Basic Research (project no. 19-115-50259).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

This work does not contain any studies involving animals or human subjects performed by any of the authors.

REFERENCES

1. Darwin, Ch., *On the Origin of Species by Means of Natural Selection*, London: John Murrey, 1859.
2. Neubert, J., Briegleb, W., Schatz, A., and Hertwig, I., The response of structure and function of the gravireceptors in a vertebrate to near weightlessness, *Acta Astronaut.*, 1988, vol. 17, no. 2, pp. 257–262.
3. Franz-Odendaal, T.A. and Edsall, S.C., Long-term effects of simulated microgravity and vibration exposure on skeletal development in zebrafish, *Stem Cells Dev.*, 2018, vol. 27, no. 18, pp. 1278–1286. https://doi.org/10.1089/scd.2017.0266
4. *Kosmicheskaya meditsina i biologiya* (Space Medicine and Biology), Grigor'ev, A.I. and Ushakov, I.B., Eds., Voronezh, 2013.
5. Von Baumgarten, R.J., Simmonds, R.C., Boyd, J.F., and Garriott, O.K., Effects of prolonged weightlessness on the swimming pattern of fish aboard "Skylab-3," *Aviat., Space Environ. Med.*, 1975, vol. 46, no. 7, pp. 902–906.
6. Fischer, J. and Laforsch, C., The influence of gravity and light on locomotion and orientation of *Heterocypris incongruens* and *Notodromas monacha* (Crustacea, Ostracoda), *NPJ Microgravity*, 2018, vol. 4, p. 3. https://doi.org/10.1038/s41526-017-0037-5
7. Ogneva, I.V., Belyakin, S.N., and Sarantseva, S.V., The development of *Drosophila melanogaster* under different duration space flight and subsequent adaptation to earth gravity, *PLoS One*, 2016, vol. 11, no. 11, p. e0166885. https://doi.org/10.1371/journal.pone.0166885
8. Fermin, C.D., Martin, D., Jones, T., et al., Microgravity in the STS-29 space shuttle discovery affected the vestibular system of chick embryons, *Histol. Histopathol.*, 1996, vol. 11, pp. 407–426.
9. Kenion, R.V., Kerschmann, R., Sgarioto, R., et al., Normal vestibular function in chicks after partial exposure to microgravity during development, *J. Vestibular Res.*, 1995, vol. 5, pp. 289–298.
10. Serova, L.V., Ol'berts, Dzh., and Apanasenko, Z.I., Growth and development of rats during their first month of life, in *Ontogenez mlekopitayushchikh v nevesomosti* (Ontogenesis of Mammals in Weightlessness), Gazenko, O.G., Ed., Moscow, 1988, pp. 82–88.
11. Steller, J.G., Alberts, J.R., and Ronca, A.E., Oxidative stress as cause, consequence, or biomarker of altered female reproduction and development in the space environment, *Int. J. Mol. Sci.*, 2018, vol. 19, pp. 3729–3755. https://doi.org/10.3390/ ijms19123729
12. Ronca, A.E., Fritzsch, B., Bruce, L.L., and Alberts, J.R., Orbital spaceflight during pregnancy shapes function of mammalian vestibular system, *Behav. Neurosci.*, 2008, vol. 122, pp. 224–232.
13. Ogneva, I.V., Usik, M.A., Loktev, S.S., et al., Testes and duct deferens of mice during space flight: cytoskeleton structure, sperm-specific proteins and epigenetic events, *Sci. Rep.*, 2019, vol. 9, no. 1, p. 9730. https://doi.org/10.1038/ s41598-019-46324-3
14. Bershtein, N.A., The dexterity and its development, in *Fizkul'tura i sport* (Physical Training and Sports), Moscow, 1991.
15. Oganov, V.S., Study of skeleton gravitational physiology and problem of osteoporosis, *Russ. J. Physiol.*, 2003, vol. 89, no. 3, pp. 347–355.
16. Shnol', S.E., *Fiziko-khimicheskie factory biologicheskoi evolyutsii* (Physical and Chemical Factors of Biological Evolution), Moscow, 2013.
17. Gurfinkel', V.S., Kots, Ya.M., and Shik, M.L., *Regulyatsiya pozy cheloveka* (Regulation of Human Pose), Moscow, 1965.
18. Smits, A.W., Fluid balance in vertebrate lungs, in *Comparative Pulmonary Physiology Current Concepts*, Wood, S.C., Ed., New York: Marcel Dekker, 1989, pp. 503–537.
19. Lillywhite, H.B., Cardiovascular adaptations to gravity: Lessons from comparative studies of snakes, in *Adaptation Biology and Medicine*, Vol. 4: *Current Concepts*, Hargens, A., Takeda, N., and Singal, P.K., Eds., New Delhi, 2005, pp. 68–81.
20. Brondum, E., Hasenkam, J.M., Secher, N.H., et al., Jugular venous pooling during lowering of the head affects blood pressure of the anesthetized giraffe, *Am. J. Physiol.: Regul. Integr. Comp. Physiol.*, 2009, vol. 297, no. 4, pp. R1058–R1065.
21. Pace, N., Rahlmann, D.F., and Smith, A.H., Scaling of metabolic rate on body mass in small laboratory mammals, *J. Gravitational Physiol.*, 1981, vol. 19, pp. 213–216.
22. Andreev-Andrievskiy, A.A., Popova, A.S., Lagereva, E.A., et al., Fluid shift versus body size: changes of hematological parameters and body fluid volume in hindlimb-unloaded mice, rats and rabbits, *J. Exp. Biol.*, 2018, vol. 221, art. ID jeb182832. https://doi.org/10.1242/jeb.182832
23. Buravkova, L.B., *Mekhanizmy kletochnoi gravichuvstvitel'nosti* (Mechanisms of Cellular Gravity Sensitivity), Moscow, 2018.
24. Otelin, A.A., Mirkin, A.S., and Mashchanskii, V.F., *Tel'tsa Fatera–Pahcini. Strukturno-funktsional'nye osobennosti* (Fatter–Pacini Corpuscles: Structural and Functional Peculiarities), Leningrad, 1976.
25. Perrier, J.-F., D'Incamps, B.L., Kouchtir-Devanne, N., et al., Cooperation of muscle and cutaneous afferents in the feedback of contraction to peroneal mo-

toneurons, *J. Neurophysiol.*, 2000, vol. 83, pp. 3201–3208.

26. Roll, R., Kavounoudias, A., and Roll, J.P., Cutaneous afferents from human plantar sole contribute to body posture awareness, *Neuroreport*, 2002, vol. 13, no. 15, pp. 1957–1961.
27. Shenkman, B.S. and Kozlovskaya, I.B., Cellular responses of human postural muscle to dry immersion, *Front. Physiol.*, 2019, vol. 10, p. 187. https://doi.org/10.3389/fphys.2019.00187
28. Morita, H., Kaji, H., Ueta, Y., and Abe, Ch., Understanding vestibular-related physiological functions could provide clues on adapting to a new gravitational environment, *J. Physiol. Sci.*, 2020, vol. 70, no. 17. https://doi.org/10.1186/ s12576-020-00744-3
29. Barnes, G.R., The role of vestibular system in head-eye coordination, *J. Physiol. (London)*, 1975, vol. 246, no. 2, p. 99.
30. Shul'zhenko, E.B. and Vil'-Vil'ams, I.F., The possibility of long term water immersion by the "dry" immersion method, *Kosm. Biol. Aviakosm. Med.*, 1976, no. 10, pp. 82–84.
31. Navasiolava, N.M., Custaud, M.-A., Tomilovskaya, E.S., et al., Long-term dry immersion: review and prospects, *Eur. J. Appl. Physiol.*, 2011, vol. 111, pp. 1235–1260. https://doi.org/10.1007/s00421-010-1750-x
32. Tomilovskaya, E., Shigueva, T., Sayenko, D., et al., Dry immersion as a ground-based model of microgravity physiological effects, *Front. Physiol.*, 2019, vol. 10, p. 284. https://doi.org/10.3389/fphys.2019.00284
33. Kakurin, L.I., Lobachik, V.I., Mikhailov, V.M., and Senkevich, Y.A., Antiorthostatic hypokinesia as a method of weightlessness simulation, *Aviat., Space Environ. Med.*, 1976, vol. 47, pp. 1083–1086.
34. *Godichnaya antiortostaticheskaya gipokineziya (ANOG)—fiziologicheskaya model' mezhplanetarnogo kosmicheskogo poleta: Monografiya* (One-Year Antiorthostatic Hypokinesia (ANOG): Physiological Model of Interplanetary Space Flight: Monograph), Grigor'ev, A.I. and Kozlovskaya, I.B., Eds., Moscow, 2018.
35. Hackney, K.J. and Ploutz-Snyder, L.L., Unilateral lower limb suspension: integrative physiological knowledge from the past 20 years (1991–2011), *Eur. J. Appl. Physiol.*, 2011, vol. 112, pp. 9–22. https://doi.org/10.1007/s00421-011-1971-7
36. Il'ina-Kakueva, E.I. and Novikov, V.E., Skeletal muscles of rats under conditions of physiological effects of weightlessness simulation, *Kosm. Biol. Aviakosm. Med.*, 1985, vol. 19, no. 3, pp. 56–60.
37. Globus, R.K. and Morey-Holton, E., Hindlimb unloading: rodent analog for microgravity, *J. Appl. Physiol.*, 2016, vol. 120, vol. 1196–1206. https://doi.org/10.1152/japplphysiol.00997.2015
38. Shigueva, T.A., Zakirova, A.Z., Tomilovskaya, E.S., and Kozlovskaya, I.B., Effects of support unloading on recruitment order of motor units, *Aviakosm. Ekol. Med.*, 2013, vol. 47, no. 2, pp. 50–53.
39. Roy, R., Hodgson, J.A., Aragon, J., et al., Recruitment of the Rhesus soleus and medial gasrocnemius before, during and after spaceflight, *J. Gravitational Physiol.*, 1996, vol. 3, no. 1, pp. 11–16.
40. Zhang, L.-F., Vascular adaptation to microgravity: what have we learned? *J. Appl. Physiol.*, 2001, vol. 91, pp. 2415–2430.
41. Zhang, L.-F., Region-specific vascular remodeling and its prevention by artificial gravity in weightless environment, *Eur. J. Appl. Physiol.*, 2013, vol. 113, pp. 2873–2895. https://doi.org/10.1007/s00421-013-2597-8
42. Colleran, P.N., Wilkerson, M.K., Bloomfield, S.A., et al., Alterations in skeletal perfusion with simulated microgravity: a possible mechanism for bone remodeling, *J. Appl. Physiol.*, 2000, vol. 89, pp. 1046–1054.
43. Taylor, C.R., Hanna, M., Behnke, B.J., et al., Spaceflight-induced alterations in cerebral artery vasoconstrictor, mechanical, and structural properties: implications for elevated cerebral perfusion and intracranial pressure, *FASEB J.*, 2013, vol. 27, pp. 2282–2292.
44. Sofronova, S.I., Tarasova, O.S., Gaynullina, D., et al., Spaceflight on the Bion-M1 biosatellite alters cerebral vasomotor and mechanical properties in mice, *J. Appl. Physiol.*, 2015, vol. 118, no. 7, pp. 830–838.
45. Arbeille, P., Fomina, G., Roumy, J., et al., Adaptation of the left heart, cerebral and femoral arteries, and jugular and femoral veins during short- and long-term head-down tilt and spaceflights, *Eur. J. Appl. Physiol.*, 2001, vol. 86, pp. 157–168.
46. Wilkerson, M.K., Lesniewski, L.A., Golding, E.M., et al., Simulated microgravity enhances cerebral artery vasoconstriction and vascular resistance through endothelial nitric oxide mechanism, *Am. J. Physiol.: Heart Circ. Physiol.*, 2005, vol. 288, pp. H1652–H1661.
47. Iwasaki, K.I., Levine, B.D., Zhang, R., et al., Human cerebral autoregulation before, during and after spaceflight, *J. Physiol.*, 2007, vol. 579, pp. 799–810.
48. Zhang, R., Zuckerman, J.H., Pawelczyk, J.A., and Levine, B.D., Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress, *J. Appl. Physiol.*, 1997, vol. 83, pp. 2139–2145.
49. Wilkerson, M.K., Muller-Delp, J., Colleran, P.N., and Delp, M.D., Effects of hindlimb unloading on rat cerebral, splenic, and mesenteric resistance artery morphology, *J. Appl. Physiol.*, 1999, vol. 87, pp. 2115–2121. https://doi.org/10.1152/jappl.1999.87.6.2115
50. Zhang, L.-F. and Hargens, A.R., Spaceflight-induced intracranial hypertension and visual impairment: pathophysiology and countermeasures, *Physiol. Rev.*, 2018, vol. 98, no. 1, pp. 59–87. https://doi.org/10.1152/physrev.00017.2016
51. Kozlovskaya, I.B., Sayenko, I.V., Miller, T.F., et al., Erratum to: New approaches to countermeasures of the negative effects of microgravity in long-term space flights [ActaAstronautica 59 (2006) 13–19], *Acta Astronaut.*, 2007, vol. 60, no. 8, pp. 783–789.
52. Oganov, V.S. and Grigor'ev, A.I., The mechanisms of osteopenia and specific metabolism of human bone tissue in weightless conditions, *Ross. Fiziol. Zh. im. I.M. Sechenova*, 2012, vol. 98, no. 3, pp. 395–409.
53. Vico, L. and Hargens, A., Skeletal changes during and after spaceflight, *Nat. Rev. Rheumatol.*, 2018, vol. 14, no. 4, pp. 229–245.

54. Norsk, P., Cardiovascular and fluid volume control in humans in space, *Curr. Pharm. Biotechnol.*, 2005, vol. 4, pp. 325–330.
55. Gazenko, O.G., Grigor'ev, A.I., and Natochin, Yu.V., Water-salt balance homeostasis and space flight, in *Problemy kosmicheskoi biologii* (Problems of Space Biology), Moscow, 1986, vol. 54.
56. Hargens, A.R. and Vico, L., Long-duration bed rest as an analog to microgravity, *J. Appl. Physiol.*, 2016, vol. 120, pp. 891–903.
57. Cao, P., Kimura, S., Macias, B., et al., Exercise within lower body negative pressure partially counteracts lumbar spine deconditioning associated with 28-day bed rest, *J. Appl. Physiol.*, 2005, vol. 99, pp. 39–44.
58. Sayson, J.V., Lotz, J., Parazynski, S., and Hargens, A.R., Back pain in space and post-flight spine injury: mechanisms and countermeasure development, *Acta Astronaut.*, 2013, vol. 86, pp. 24–38.
59. Johnston, S.L., Campbell, M.R., Scheuring, R., and Feiveson, A.H., Risk of herniated nucleus pulposus among U.S. astronauts, *Aviat., Space Environ. Med.*, 2010, vol. 81, no. 6, pp. 566–574.
60. Rukavishnikov, I.V., Amirova, L.E., Kukoba, T.B., et al., Effects of gravitational unloading on back muscles tone, *Hum. Physiol.*, 2017, vol. 43, no. 3, pp. 291–300.
61. Kozlovskaya, I.B. and Kirenskaya, A.V., Mechanisms of disorders of the characteristics of fine movements in long term hypokinesia, *Neurosci. Behav. Physiol.*, 2004, vol. 34, no. 7, pp. 747.
62. Shenkman, B.S., Nemirovskaya, T.L., Cheglova, I.A., et al., Morphological characteristics of human m. vastuslateralis under supportlessness environment, *Dokl. Ross. Akad. Nauk*, 1999, vol. 364, no. 4, pp. 563–565.
63. Shenkman, B.S., From slow to fast: hypogravity-induced remodeling of muscle fiber myosin phenotype, *Acta Nat.*, 2016, vol. 8, no. 4, pp. 47–59.
64. Atomi, Y., Gravitational effects on human physiology, in *High Pressure Bioscience: Basic Concepts, Applications and Frontiers*, Subcellular Biochemistry Series, vol. 72, Dordrecht: Springer-Verlag, 2015, pp. 627–659. https://doi.org/10.1007/978-94-017-9918-8_29
65. Roy, R., Roy, M., Talmadge, R., et al., Size and myosin heavy chain profiles of rat hindlimb extensor muscle fibers after 2 weeks at 2 G, *Aviat., Space Environ. Med.*, 1996, vol. 67, no. 9, pp. 854–858.
66. Tavakol, M., Roy, R., Kim, J.A., et al., Fiber size, type, and myosin heavy chain content in rhesus hindlimb muscles after 2 weeks at 2 G, *Aviat., Space Environ. Med.*, 2002, vol. 73, no. 6, pp. 551–557.
67. Kawao, N., Morita, H., Obata, K., et al., The vestibular system is critical for the changes in muscle and bone induced by hypergravity in mice, *Physiol. Rep.*, 2016, vol. 4, no. 19, p. e12979. https://doi.org/10.14814/phy2.12979
68. Mirzoev, T., Tyganov, S., Petrova, I., et al., Divergent anabolic signalling responses of murine soleus and tibialis anterior muscles to chronic 2 G hypergravity, *Sci. Rep.*, 2017, vol. 7, pp. 3514. https://doi.org/10.1038/s41598-017-03758-x
69. Tomilovskaya, E.S., Berger, M., Gerstenbrand, F., and Kozlovskaya, I.B., Effects of long-duration space flights on characteristics of the vertical gaze fixation reaction, *J. Vestibular Res.*, 2013, vol. 23, no. 1. https://doi.org/10.3233/VES-130470
70. Krasnov, I.B. and Krasnikov, G.V., Purkinje cells of the vestibular and proprioceptive parts of the rat cerebellum after a 14-day space flight, *Aviakosm. Ekol. Med.*, 2009, vol. 43, no. 4, pp. 43–47.
71. Badakva, A.M., Miller, N.V., and Eron, Yu.N., Effects of water immersion on reaction of gaze fixation in monkeys, *Aviakosm. Ekol. Med.*, 2007, vol. 41, no. 2, pp. 49–53.
72. Guillaud, E., Faure, C., Doat, E., et al., Ancestral persistence of vestibulospinal reflexes in axial muscles in humans, *J. Neurophysiol.*, 2020, vol. 123, no. 5, pp. 2010–2023.
73. Roberts, D.R., et al., Effects of spaceflight on astronaut brain structure as indicated on MRI, *N. Engl. J. Med.*, 2017, vol. 377, pp. 1746–1753.
74. van Ombergen, A., Jillings, S., Jeurissen, B., et al., Brain ventricular volume changes induced by long-duration spaceflight, *Proc. Natl. Acad. Sci. U.S.A.*, 2019, vol. 116, no. 21, pp. 10531–10536.
75. Pechenkova, E., Nosikova, I., Rumshiskaya, A., et al., Alterations of functional brain connectivity after long-duration spaceflight as revealed by fMRI, *Front. Physiol.*, 2019, vol. 10, p. 761. https://doi.org/10.3389/fphys.2019.00761
76. Aseyev, N., Vinarskaya, A., Roshchin, M., et al., Adaptive changes in the vestibular system of land snail to a 30-day spaceflight and readaptation on return to Earth, *Front. Cell. Neurosci.*, 2017, vol. 11, p. 348. https://doi.org/10.3389/fncel.2017.00348
77. Mann, V., Sundaresan, A., and Chaganti, M., Cellular changes in the nervous system when exposed to gravitational variation, *Neurology*, 2019, vol. 67, no. 3, pp. 684–691. https://doi.org/10.4103/0028-3886.263169
78. Popova, N.K., Kulikov, A.V., Kondaurova, E.M., et al., Risk neurogenes for long-term spaceflight: dopamine and serotonin brain system, *Mol. Neurobiol.*, 2015, vol. 51, no. 3, pp. 1443–1451.
79. Naumenko, V.S., Kulikov, A.V., Kondaurova, E.M., et al., Effect of actual long-term spaceflight on BDNF, TrkB, p75, BAX and BCL-X_L genes expression in mouse brain regions, *Neuroscience*, 2014, vol. 284, pp. 730–736.
80. Turchaninova, V.F., Egorov, A.D., and Domrachev, M.V., Central and regional hemodynamics in long space flights, *Kosm. Biol. Aviakosm. Med.*, 1989, vol. 23, pp. 19–26.
81. Sandler, H., Krotov, V.P., Hines, J., et al., Cardiovascular results from a rhesus monkey flown aboard the Cosmos 1514 spaceflight, *Aviat., Space Environ. Med.*, 1987, vol. 58, pp. 529–536.
82. Blaber, A.P., Goswami, N., Bondar, R.L., et al., Impairment of cerebral blood flow regulation in astronauts with orthostatic intolerance after flight, *Stroke*, 2011, vol. 42, pp. 1844–1850.
83. Zuj, K.A., Arbeille, P., Shoemaker, J.K., et al., Impaired cerebrovascular autoregulation and reduced CO_2 reactivity after long duration spaceflight, *Am. J. Physi-*

ol.: Heart Circ. Physiol., 2012, vol. 302, pp. H2592–H2598.

84. Peters, B.T., Miller, C.A., Brady, R.A., et al., Dynamic visual acuity during walking after long-duration spaceflight, *Aviat., Space Environ. Med.*, 2011, vol. 82, no. 4, pp. 463–466.
85. Danilichev, S.N., Pronin, S.V., Shelepin, Yu.E., et al., Optical and psychophysical studies of the visual system of cosmonauts before and after long orbital flights, *J. Opt. Technol.*, 2019, vol. 86, no. 11, pp. 691–696. https://doi.org/10.1364/JOT.86.000691
86. Mader, T.H., Gibson, C.R., Pass, A.F., et al., Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight, *Ophthalmology*, 2011, vol. 118, p. 2058–2069. https://doi.org/10.1016/j.ophtha.2011.06.021
87. Bogomolov, V.V., Kuzmin, M.P., and Danilichev, S.N., Intracranial hypertension in astronauts in the conditions of long-term microgravity, *Aviakosm. Ekol. Med.*, 2015, vol. 49, no. 4, pp. 54–58.
88. Marshall-Goebel, K., Laurie, S.S., Alferova, I.V., et al., Assessment of jugular venous blood flow stasis and thrombosis during spaceflight, *JAMA Network Open*, 2019, vol. 2, no. 11, p. e1915011. https://doi.org/10.1001/jamanetworkopen.2019.15011
89. Norsk, P., Role of arginine vasopressin in the regulation of extracellular fluid volume, *Med. Sci. Sports Exercise*, 1996, vol. 28, no. 10, suppl., pp. S36–S41.
90. Videbaek, R. and Norsk, P., Atrial distension in humans during microgravity induced by parabolic flights, *J. Appl. Physiol.*, 1997, vol. 83, pp. 1862–1866.
91. Buckey, J.C., Jr., Gaffne, F.A., Lane, L.D., et al., Central venous pressure in space., *J. Appl. Physiol.*, 1996, vol. 81, pp. 9–25.
92. Norsk, P., Asmar, A., Damgaard, M., and Christensen, N.J., Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight, *J. Physiol.*, 2015, vol. 593, no. 3, pp. 573–584.
93. Shiraishi, M., Schou, M., Gybel, M., et al., Comparison of acute cardiovascular responses to water immersion and head-down tilt in humans, *J. Appl. Physiol.*, 2002, vol. 92, pp. 264–268.
94. Amirova, L.E., Navasiolava, N.M., Rukavishvikov, I.V., et al., Cardiovascular system under simulated weightlessness: head-down bed rest vs. dry immersion, *Front. Physiol.*, 2020, vol. 11, pp. 395. https://doi.org/10.3389/fphys.2020.00395
95. Huntoon, C., Human physiology in microgravity: spacelab SLS-1 metabolic results, *Proc. FASEB Meeting*, Anaheim, CA, 1992.
96. Fortney, S.M., Hyatt, K.H., Davis, J.E., and Vogel, J.M., Changes in body fluid compartments during a 28-day bed rest, *Aviat., Space Environ. Med.*, 1991, vol. 62, pp. 97–104.
97. Gazenko, O.G. and Ilyin, E.A., Physiological investigations of primates onboard biosatellites Cosmos-1514 and Cosmos-1667, *Physiologist*, 1987, vol. 30, pp. S31–S35.
98. Deever, D.B., Young, R.S., Wang, S., et al., Changes in organ perfusion and weight ratios in post-simulated microgravity recovery, *Acta Astronaut.*, 2002, vol. 50, pp. 445–452.
99. Tarasova, O.S., Kalenchuk, V.U., Borovik, A.S., et al., Simulated microgravity induces regionally distinct neurovascular and structural remodeling of skeletal muscle and cutaneous arteries in the rat, *Front. Physiol.*, 2020, vol. 11, pp. 675. https://doi.org/10.3389/fphys.2020.00675
100. Behnke, B.J., Stabley, J.N., McCullough, D.J., et al., Effects of spaceflight and ground recovery on mesenteric artery and vein constrictor properties in mice, *FASEB J.*, 2013, vol. 27, pp. 399–409.
101. Fritsch-Yelle, J.M., Charles, J.B., Jones, M.M., and Wood, M.L., Microgravity decreases heart rate and arterial pressure in humans, *J. Appl. Physiol.*, 1996, vol. 80, no. 3, pp. 910–914.
102. Perhonen, M.A., Franco, F., Lane, L.D., et al., Cardiac atrophy after bed rest and spaceflight, *J. Appl. Physiol.*, 2001, vol. 91, pp. 645–653.
103. Henry, W.L., Epstein, S.E., Griffith, J.M., et al., Effect of prolonged space flight on cardiac functions and dimensions, in *Biomedical Results from Skylab*, Washington, DC: Natl. Aeronaut. Space Adm., 1977, pp. 366–371.
104. Atkov, O., Bednenko, V.S., and Fomina, G.A., Ultrasound techniques in space medicine, *Aviat., Space Environ. Med.*, 1987, vol. 58, pp. A69–A73.
105. Hughson, R.L., Shoemaker, J.H., Blaber, A.P., et al., Cardiovascular regulation during long-duration spaceflights to the International Space Station, *J. Appl. Physiol.*, 2012, vol. 112, pp. 719–727.
106. Baevsky, R.M., Baranov, V.M., Funtova, I.I., et al., Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station, *J. Appl. Physiol.*, 2007, vol. 103, pp. 156–161.
107. Eckberg, D.L., Halliwill, J.R., Beigthol, L.A., et al., Human vagal baroreflex mechanisms in space, *J. Physiol.*, 2010, vol. 588, pp. 1129–1138.
108. Borovik, A.S., Orlova, E.A., Tomilovskaya, E.S., et al., Phase coupling between baroreflex oscillations of blood pressure and heart rate changes in 21-day dry immersion, *Front. Physiol.*, 2020, vol. 11, pp. 455. https://doi.org/10.3389/fphys.2020.00455
109. Iwase, S., Sugiyama, Y., Miwa, C., et al., Effects of three days dry immersion on muscle sympathetic activity and arterial blood pressure in humans, *J. Auton. Nerv. Syst.*, 2000, vol. 79, nos. 2–3, pp. 156–164.
110. Kamiya, A., Iwase, S., Kitazawa, H., et al., Baroreflex control of muscle sympathetic nerve activity after 120 days of 6° head-down bed rest, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2000, vol. 278, pp. R445–R452.
111. Ertl, A.C., Diedrich, A., Biaggioni, I., et al., Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space, *J. Physiol.*, 2002, vol. 538, pp. 321–329.
112. Mano, T., Iwase, S., and Toma, S., Microneurography as a tool in clinical neurophysiology to investigate peripheral neural traffic in humans, *Clin. Neurophysiol.*, 2006, vol. 117, no. 11, pp. 2357–2384.
113. Miwa, C., Mano, T., Saito, M., et al., Aging reduces sympatho-suppressive response to head-out water im-

mersion in humans, *Acta Physiol. Scand.*, 1999, vol. 158, no. 1, pp. 15–20.

114. Iwase, S., Mano, T., Cui, J., et al., Sympathetic outflow to muscle in humans during short periods of microgravity produced by parabolic flight, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 1999, vol. 277, pp. R419–R426.

115. Thornton, W.E., Hoffler, G.W., and Rummel, J.A., Anthropometric changes and fluid shifts, in *Biomedical Results from Skylab*, Johnston, R.S. and Dietlein, L.F., Eds., Washington, DC: Natl. Aeronaut. Space Adm., 1977, vol. 377, pp. 330–338.

116. Convertino, V.A., Doerr, D.F., Mathes, K.L., et al., Changes in volume, muscle compartment, and compliance of the lower extremities in man following 30 days of exposure to simulated microgravity, *Aviat., Space Environ. Med.*, 1989, vol. 60, no. 7, pp. 653–658.

117. Herault, S., Fomina, G., Alferova, I., et al., Cardiac, arterial and venous adaptation to weightlessness during 6-month "Mir" spaceflights with and without thigh cuffs (bracelets), *Eur. J. Appl. Physiol.*, 2000, vol. 81, pp. 384–390.

118. Kozlovskaya, I.B., Yarmanova, E.N., Yegorov, A.D., et al., Russian countermeasure systems for adverse effects of microgravity on long-duration ISS flights, *Aerospace Med., Hum. Perform.*, 2015, vol. 86, suppl. 1, pp. 24–31.

119. Meyer, T., Kindermann, M., and Kindermann, W., Exercise programs for patients with chronic heart failure, *Sports Med.*, 2004, vol. 34, no. 14, pp. 939–954.

120. Watkins, W., Hargens, A.R., Seidl, S., et al., Lower-body negative pressure decreases noninvasively measured intracranial pressure and internal jugular vein cross-sectional area during head-down tilt, *J. Appl. Physiol.*, 2017, vol. 123, no. 1, pp. 260–266.

121. Kotovskaya, A.R., Vil'-Vil'yams, I.F., and Luk"yanyuk, V.Yu., The creation of artificial gravity using a short radius centrifuge for medical support of interplanetary manned flights, *Aviakosm. Ekol. Med.*, 2003, vol. 37, no. 5, pp. 36–40.

122. Semenova, K.A., *Vosstanovitel'noe lechenie detei s perinatal'nym porazheniem nervnoi sistemy i s detskim tserebral'nym paralichom* (Rehabilitation of Children with Perinatal Damage to the Nervous System and Cerebral Palsy), Moscow, 2007.

123. Saenko, I.V., Chernikova, L.A., and Kozlovskaya, I.B., Space technologies in neurorehabilitation, in *Vosstanovitel'naya nevrologiya: innovatisonnye tekhnologii v neiroreabilitatsii* (Reconstructive Neurology: Innovative Technologies in Neurorehabilitation), Chernikova, L.A., Ed., Moscow, 2016, pp. 294–330.

124. Poltavskaya, M.G., Sviridenko, V.P., Kozlovskaya, I.B., et al., Comparison of the efficacy of neuromuscular electrostimulation and interval exercise training in early rehabilitation of patients hospitalized with decompensation of chronic heart failure, *Hum. Physiol.*, 2018, vol. 44, no. 6, pp. 663–672.

Translated by T. Tkacheva