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Contribution of Space-related Research to Advances in the Field of Medicine

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The main interest of space-neurophysiology is to gain reliable data on processes of physiological adaptation affecting the human standard of performance during microgravity (G_0) exposure. Since all terrestrial life forms are adapted to earth gravity (G_1), microgravity exposure (G_0) is a challenge in order to gain more insight into neurophysiological functions. One of the first symptoms man in space may experience is neurological, namely that of space sickness, a mismatch of vestibular, optic, and proprioceptive input [1-3]. Depending on the duration of G_0 exposure, disturbances of motor performance, coordination and accuracy of movements, structural changes of muscles, bone density, blood and body fluid alterations, and vegetative disorders limit the activities of man in space.

Of the many disturbances induced by a decrease in gravitational load, the disorders and effects on the function of the musculoskeletal and motor regulatory systems are of major significance. These resemble the symptoms of posterior funiculus pathologies, hereditary spinocerebellar degenerations or those of the Bed Rest Syndrome (BRS). Thus, the understanding of the neurophysiological facts may help to understand the pathology, a predisposition for therapeutic consequences. The equipment and technology developed for microgravity experiments are utilized as diagnostic as well as therapeutic tools in patients.

THE HISTORY OF A COOPERATION

An agreement on scientific-technical cooperation termed "Development of Neurological Approaches to the Study of Acute and Chronic Effects of Microgravity on the Human Body" between the Institute of Biomedical Problems (IBMP), Moscow, and the University Hospital of Neurology, Innsbruck, was signed in 1986. According to the tasks of this cooperation, sensomotor system adaptation processes to simulated microgravity were investigated. Special equipment was developed in order to be utilized as countermeasures to muscle protein degredation (SUC project) [4, 5] and for the measurement of eye, head, and upper limb movements in response to visual and acoustic cues. The latter equipment investigates the processing between vestibular, proprioceptive and visual input (MONIMIR project) [6].

In all ground-based experiments, microgravity was simulated by dry-water immersion model (DWI), which according to Shulzenko and Vil Viliams [7] highly resembles the unloading effects of G_0. The MONIMIR project was part of the common space mission in 1991 (AUSTROMIR project).

REAL / SIMULATED MICROGRAVITY

Neurological G_0 research is largely performed in simulated microgravity in ground-based laboratories, since prior to real G_0 exposure all tests have to be prepared in simulated microgravity, and as a consequence of financial considerations, only a few experiments can be carried out in real microgravity. Within a G_1 environment, real G_0 can be provoked for a few seconds by parabolic flights. During long period 5° - 6° head-down tilt bed rest (BR) [8,9], similar changes occur as those observed in G_0. Another method of simulation G_0 is the DWI model, which consists of a water-filled pool covered with a thin foil that increases the surface tension of water, so that a volunteer in supine position cannot sink. Although he or she caves in, floating and movements are similar to those under water but face and nterior parts of the body are outside (Figure 1).

PHYSIOLOGICAL ADAPTATIONS / PATHOLOGIES

A transfer to microgravity particularly affects neurological functions leading to space illusions, disturbances of the vestibular system, autonomic nervous system, and the sensomotor system. These symptoms are denoted as Space Adaptation Syndrome, characterized by motion sickness, vegetative disregulation, movement disorders (hypermetry, dysmetry), optomotor dysregulation, and slight proprioceptive input disturbances.

Prolonged exposure to G_0 induces several neurological fuctional deficits with signs of brainstem disfunction (spontaneous nystagm, pursuit eye movement disturbances, postural and gait disturbances), altered biomechanics of movements, and muscle morphology. Motion sickness improves within a relatively short period, while disfunction of the proprioceptive system deteriorates with prolonged G_0 exposure. False perception of joint position, changed vibratory sensibility, disturbances of coordinated movements of eyes, head and extremities, cerebellar and spinal ataxia occur.

Secondary disfunctions include disturbed body scheme control, reduced vigility, and higher cortical functions. Vegetative disorders cause orthostatic dysfunction and have additional influence on cardiac and circulatory system function. During prolonged G_0 exposure, the Space Adaptation Syndrome gives way to the Cosmonaut Syndrome, characterized by more pronounced proprioceptive disturbances, cerebellar atxia (spinal ataxia), muscle atrophy with morphological changes, polyneuropathy like symptoms, reduced vigility, disturbances of higher cortical functions, and veg-

FIGURE 1
Dry-water immersion model. A water-filled pool covered with a thin foil, which increases the surface tension of water, thus subjects in supine position cannot sink.

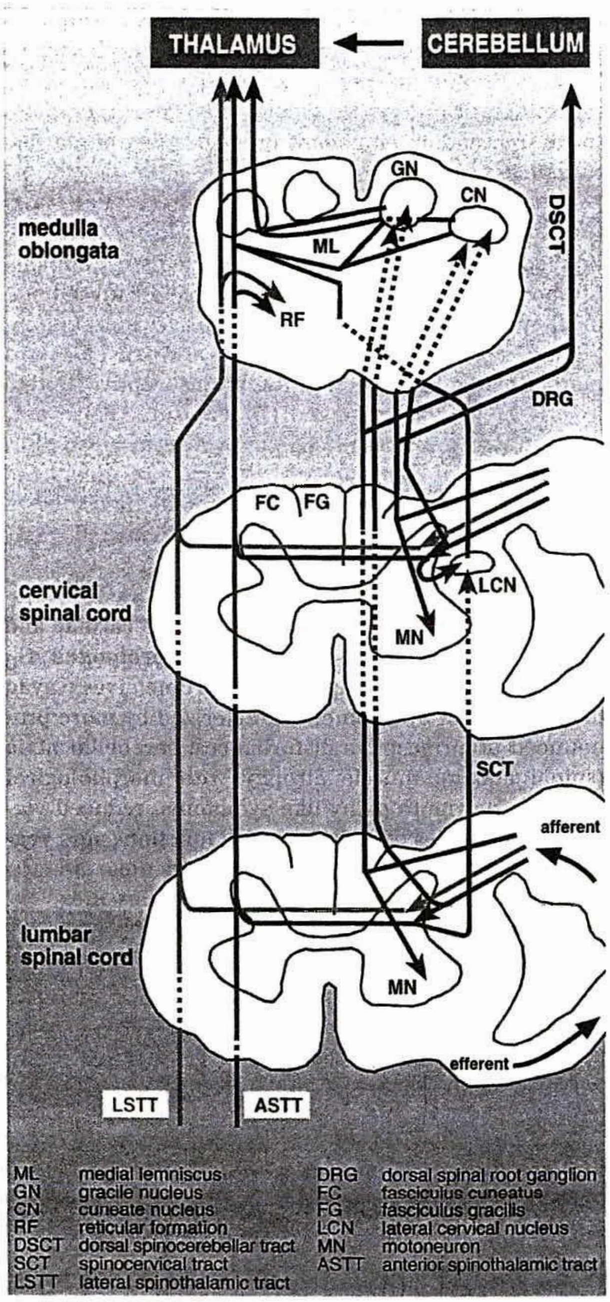

FIGURE 2
Scheme of spinal afferents to brainstem and thalamus.

etative disorders.

The Cosmonaut Syndrome is similar to the BRS occurring in patients, who in case of neurological disorders such as brain injury, apallic syndrome (vegetative state), or subarachnoid hemorrhage, are forced to bedrest for a long period of time. These changes, denoted as tertiary lesions, are particularly drastic in the case of an apallic syndrome (vegetative state) and dramatically prolong hospitalization and rehabilitation. Also, women on complete antepartum hospital bed rest have increased muscle and cardiovascular disfunctions, prolonging post-partum recovery [10, 11].

NEUROPHYSIOLOGICAL CONSIDERATIONS OF AFFERENTS

The sensomotor system is bound to a constant inflow of information via the afferent part of an afferent/efferent neuron loop system. Even simple motor functions such as the monosynaptic reflex are initiated by an excitatory input from specific muscle and tendon receptors. The more complicated a motor function, the higher the cerebral centers involved in initiating a function and gaining influence at the spinal level. For accurate function, all of these systems are dependent on an information inflow about the *ad hoc* position of joints, muscle tone, pressure distribution and sensations, which are characterized by quality, intensity, time, and distribution.

In clinical terms, a differentiation of these sensations in exteroceptive (afferents from skin receptors) and proprioceptive sensitivity (afferents from receptors in muscles, joints, tendons and vestibular system) is common. From the neurophysiologic viewpoint, this bipartition is defined as lemniscal, mediating informations on localization, time and intensity of stimuli (proprioceptive) and extralemniscal system, mediating sensations of deep pressure, touch, pain, and temperature. Specific receptors in muscles (nuclear chain and nuclear bag fibers), tendons (Golgi organs), joints and skin (Krause end bulb, Meissner and Pacinian corpuscle, Merkel disc, free nerve endings, Ruffini terminals) mediate to spinal cord neurons via the pseudounipolar neurons of the dorsal root (primary afferents).

Proprioceptive inputs (lemniscal system) reach the ventrobasal complex of thalamus via the ipsilateral posterior funiculus, or project directly to ipsilateral motoneurons, or terminate via spinocervical tract in the ipsilateral lateral cervical nucleus, located in the upper cervical segments. Afferents from quickly adapting cutaneous receptors ascend without any spinal synaptic contact directly to gracile and cuneate nuclei. Both nuclei as well as the nucleus Z, which represents a relay for muscle spindle afferents, send their axons via the medial lemniscus to the ventrobasal complex of thalamus, where they synapse with neurons of the thalamocortical tract (to primary sensomotor cortex).

The extralemniscal fibers arise from neurons in the posterior horn of the spinal cord and ascend in the contralateral ventral and lateral spinothalamic tract, to terminate in the ventral posterolateral nucleus (VPL, neospinothalamic) thalami, the posterior and intralaminar (paleospinothalamic) nuclei of thalamus. The receptive fields of the spinothalamic neurons are, contrary to those of the lemniscal system, relatively large, thus transmitting information with less specificity. The spinoreticulothalamic pathway important in generalized arousal reaction, ascends via the spinothalamic tracts to the reticular formation of the brainstem, and projects to the intralaminar nuclei of thalamus. Proprioceptive input reach simultaneously the spinocerebellum via funiculus posterior or spinocerebellar tract (additionally Gowers and Flechsing tract), connecting to the nuclei thalami, and also reach the vestibular nuclei (Deiters). The latter connections are of major importance for vestibulomotor rapid reactions to maintain equilibrium. The fibers of the spinocerebellar tract conduct with approximately 415 ft. per second. This represents the highest conducting velocity, which is, considering the function of the spinocerebellar fibers in maintaining equilibrium, necessary to gain rapid influence on muscle tone.

The labyrinth information is mediated mainly to the vestibular nuclei of Roller and Schwalbe (pons, medulla oblongata), which are also closely connected to the reticular formation of the medulla oblongata as well as spinal cord structures, or directly reach the vestibulocerebellum and/or cerebellar nucleus fastigii. Pro-prioceptive input from neck receptors in the cervical spine is mediated to the cuneate nucleus and ascends as cuneocerebellar tract to cerebellum.

Thus, vestibular and proprioceptive information are connected in order to gain rapid influence on primitive spinal level or brainstem motor pattern. Close relationships to the other sensory functions also exist, above all to the visual and the acoustic system, demonstrating an influence on primitive but also more complex motor patterns.

In conclusion, primitive motor reactions as well as complex cortical motor programs are dependent on peripheral input to control the performance of the program. Visual, vestibular, extero, and proprioceptive inputs are essential because they supply the necessary information about posture and locomotion, and are analysed and compared with the program. Motor function is disturbed if neuronal motor centers are blinded by deafferentation (Figure 2).

RESULTS OF SOME EXPERIMENTS PHYSIOLOGICAL ADAPTATIONS / PATHOLOGIES

MONIMIR project

The awareness of body posture and movement is based on the processing of sensory input, with a leading role of the proprioceptive information originating from muscles. The central nervous system is enforced to reprocess all the inputs and adapt the motor commands to the new environmental conditions. Since microgravity induces a modification of central interpretation of afferent input from the vestibular system and from proprioception [12], arm pointing in microgravity during altered head-to-trunk position offers possibilities for studying the mechanisms of adaption of sensorimotor control in detail. One spatial characteristic of these goal-directed arm movements (GDAs) in G1 and G0 is a slant of the moving plane of the arm during horizontal pointing. GDAs were learned and reproduced by 10 cosmonauts in one short-term (7 days, A), eight long-term (4 to 8 months), and one super-long-term flight (14 months, B).

Measurements took place preflight and on the second and fifth day of flight (A), and approximately every month inflight (B). Post-flight tests were on the second

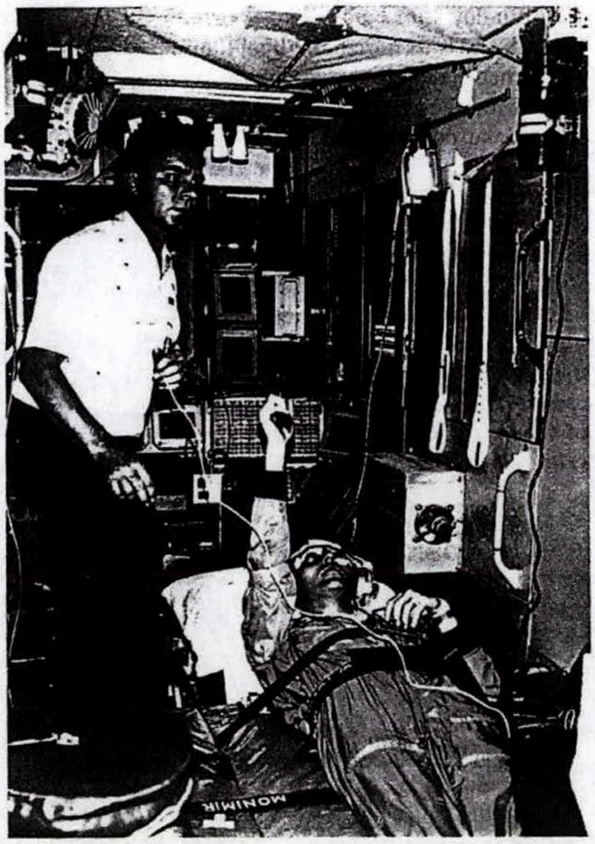

FIGURE 3
Experiment MONMIR in the MIR simulator. The cosmonaut is fixed to the floor and points with the arm fized lamp (laser beam) to flashing LEDs on the LED matrix at the ceiling. Head and arm position/movement is recorded by infrared markers and infrared scanner cameras.

and fifth day after landing. The cosmonauts learned to point to LEDs in horizontal line, then bent the head to the right side (maneuver II) and repeated the movement with eyes closed. The position of head and arm was measured by two infrared scanning cameras. The arm pointer was placed in the right hand, the LEDs-matrix in front of the subject. In the space lab MIR the cosmonauts were fixed in supine position on the floor by belts (Figure 3).

The analysis of the GDAs during changed head-to-trunk positions revealed that, with eyes closed, bending the head sidewards in microgravity and rotation of the head pre- and post-flight is correlated with considerable counterclockwise slant of the movement plane of the arm for short-term and long-term spaceflight (Figure 4). In the short-term flight (A) significant effects were seen (70° slant in maneuver H position) with almost no remaining effect seen in the investigation on the second day after landing. The long-term cosmonaut showed optimization of visually controlled arm movements but no improvement without visual guidance.

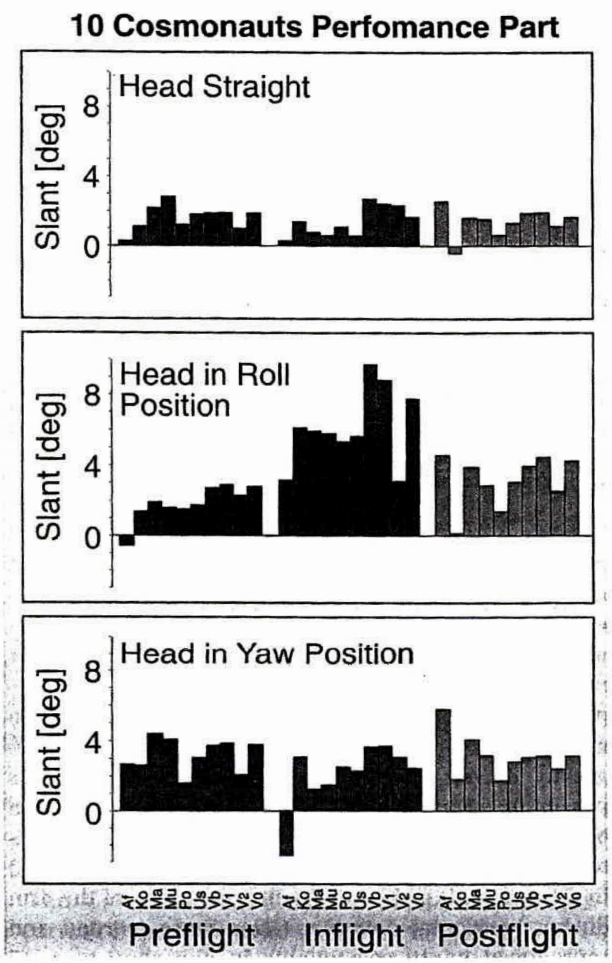

FIGURE 4
Slant of the movement plane of the arm for each of 10 cosmonauts (pre-, in-, post-flight) for three head-to-trunk positions. Positive values correspond with counterclockwise slant of the movement plane during horizontal pointing with eyes closed.

Thus, head position with respect to the trunk plays an important role in encoding target position. It seems that without visual guidance the distorsion induced by rotation or lateral bending of the head disturbs the hypothezised "body scheme" (Schilder) for different reasons. As a consequence a significant contralateral tilt of the internal representation of the horizontal coordinate occurs. Loss of background information due to reduced proprioception inflight causes the development of a changed strategy for movement control even with eyes open.

SUC (Support Unloading Compensator) project

The neurological alterations secondary to a 72 hours exposure to DWI vs. BR with a recompensation time of 96 hours between the two experiments were investigated in 10 healthy volunteers (V_{1-10} ; mean age 27.9 SD 6.3) and in six volunteers (V_{11-16}; mean age 23.3 SD 5.3) exposed to 72 hours of DWI only. Except earlier results seen in DWI, both, DWI and BR experiments reveal identical data.

The main findings of this study involved a change in reflex amplitude, exteroceptive and proprioceptive afferences (afferent input), signs of disintegrated cerebellar function as well as frontal signs. With regard to reflexes, an increase in reflex amplitude was observed in the first 24 to 48 hours, which then in 11 ($p < 0.02$) of the study persons dropped below the original value after 72 hours. Parallel thereto all of these volunteers also showed a decrease in muscle tone (Figure 5). The accentuation and decrease in reflex amplitude is a phenomenon reported by Kozlovskaya et al. [13,14] observed in examinations after short- and long-term exposure to real and simulated microgravity. This decrease in reflex amplitudes may represent a change of afferent inputs, thus influencing the closed control loop of the motor system.

A disturbance in coordination, as defined by the occurrence of minor ataxia was observed first in three persons after 34,2 SD 4,1 hours, and after 72 hours in seven, with increasing symptoms within the 2 hours following DWI (Figure 5). Deficits of coordination may be the consequence of decreased afferences to the cerebellar nucleii. After G0 exposure increased, cell activity was found in nerve cells of rat Nucl.Deiters, a relay within the vestibular nuclei, and closely connected to cerebellar structures. The possible influence of proprioceptive input from the lower limbs, which decreases during microgravity exposure with reactive hyperactivity thereafter, should be considered in this connection.

Additionally, an increased lipid content was described in the whole layer of rat Purkinje cell dendrites, Golgi cells, basket and stellate cells, receiving terminations of the primary and secondary vestibular fibres via mossi fibers. This increased lipid content is interpreted by Kuhlmann and Robins as an indicator of increased functional activity and may be due to hyperactivity response to primary hypoactivity (Figure 5).

The occurrence of frontal signs, observed in 11 subjects (69 percent), was first believed to be an increased stress reaction. The examination of the adrenergic system, however, did not support this hypothesis. A further hypothesis, namely a changed sleeping profile, was also not confirmed in the four examined cases [15].

The pathophysiological basis of the BRS syndrome [16,17] is also a disturbance of the proprioceptive feedback from the extremities, the trunk, and the cervical spine in addition to disturbances of the autonomic nervous system. In its severest form, the BRS in coma patients may be accompanied by other complications and may develop into a severe defect stage.

Prolonged bed rest and immobilization inevitably lead to several musculoskeletal complications such as atrophy, loss of muscle strength and endurance or/and morphological changes [18-21]. All of these complications are much easier to prevent than to treat. These pathologies are well known in long-period bedridden patients as well as after prolonged exposure to real as well as to simulated microgravity.

A 120-hour exposure to DWI leads to a diffuse lesioning mainly of slow twitch fibers in antigravitational muscles [22], documented by an increase of muscle enzymes such as serum creatine kinase activity (CK activity) and mass (CK mass), myoglobin and myosin heavy chain fragments (MHC). The measurement of serum CK-activity is a common method of determining muscle injuries. An eccentric lengthening exercise causes a large delayed increase in CK activity and mass. Concentric shortening exercise, however, results in a small or even no increase of plasma CK activity. Peak values then usually occur within the first 24 hours. CK is a key enzyme of muscular metabolism that exists predominantly as a soluble sarcoplasma protein in muscle fibres and is found in all skeletal muscle fibres in similar concentrations (including cardiac muscle).

Myoglobin is an oxygen-binding sarcoplasmic protein found in striated muscle fibers. Its concentrations are higher in human slow-twitch fibers than in fast-twitch fibers. Myosin is a hexameric structurally bound contractile protein containing four light and two heavy chains. Myosin heavy chain fragments (MHC) can be cleaved into its subfragments by enzymes. The rod portion can be further degraded to form light-meromyosin and subfragments II. MHC fragments are measured by ERIA-immune radiometric assay, and the antibody used reacts owing to the strong structural similarity between beta type cardiac MHC and slow twitch muscle MHC with both, but not with alpha-type MHC or fast twitch-muscle MHC.

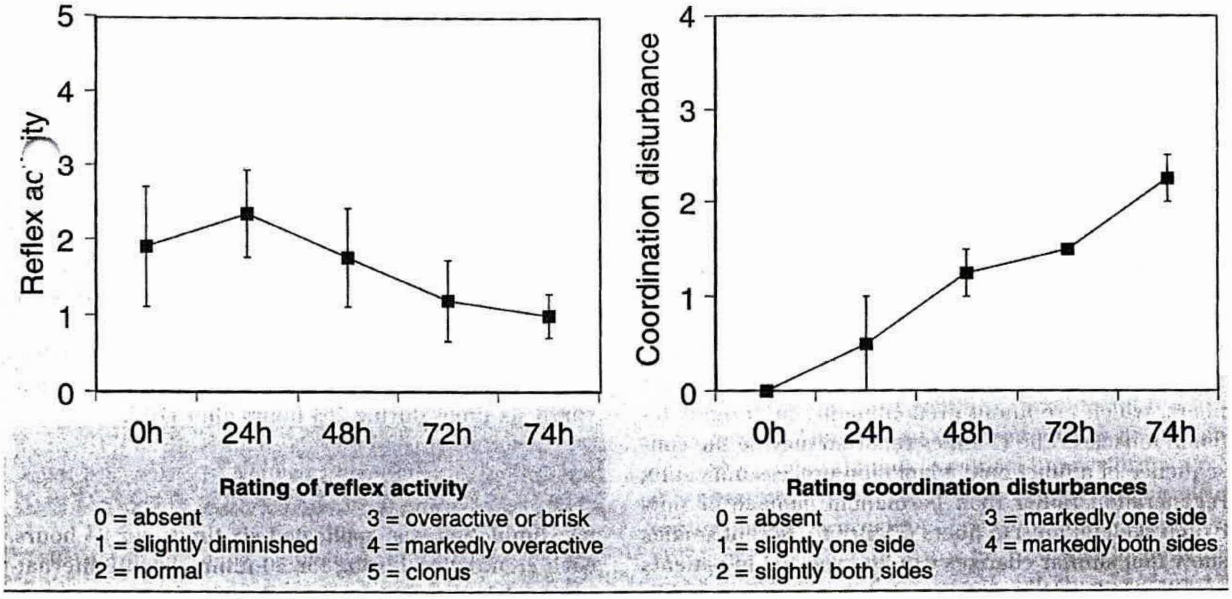

FIGURE 5

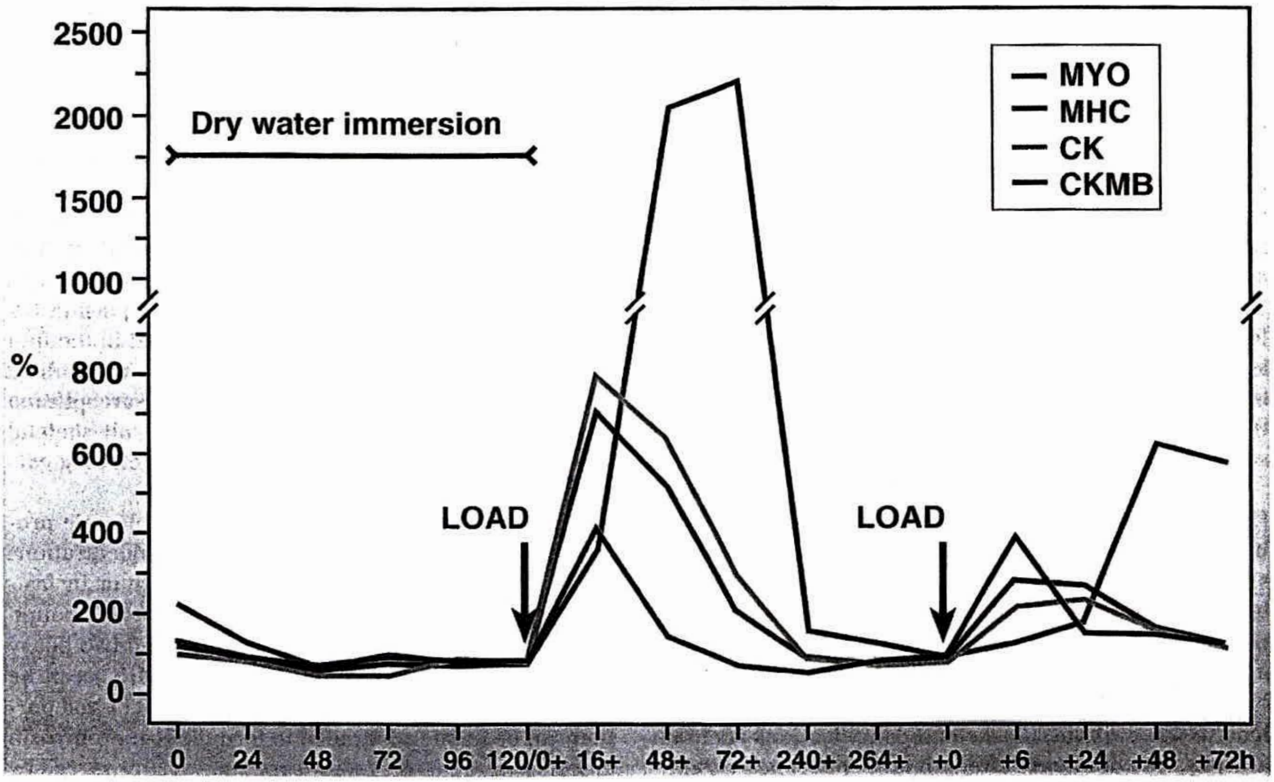

FIGURE 6
Pattern of skeletal muscle proteins (myoglobin Myo; myosin heavy chain fragments Mhc; creatine kinease enzyme activity CK; creatine kinase MB isoenzyme mass CK-MB), which were measured in the plasma of healthy volunteers. The concentrations are shown as percent increases from baseline values. Immobilization (DWI) lasted for 120 hours followed by a standardized isometric muscle load. After a regeneration period of 14 days, the same procedure of muscle load was performed but with a twofold increased isometric load. In contrast to muscle load 14 days after DWI, the exercise 2 hours after dry water immersion exposure leads to a dramatic increase of muscle protein in plasma.

These muscle enzymes were measured in plasma samples after a 120-hour DWI exposure and a defined muscle load of 40 isometric contractions of quadriceps femoris muscle at different times. Especially the contractile protein MHC, mostly present in slow muscle fibers [23] of antigravitational muscles, increases dramatically with a peak 72 hours after loading. Maximal efflux of soluble proteins as CK [24] and myoglobin was observed earlier, mostly 16 hours after exercise. The isometric loads 14 days after DWI exposure showed a significant lower response to loading. The increase of MHC suggests that total immobilization leads to a temporary hidden and diffuse lesioning of slow twitch fibers, which are found predominantly in antigravitational muscles. The changes reported may be the consequence of a functional adaptation process indicating regeneration rather than permanent damage of slow twitch skeletal muscle fibers (Figure 6). Recent studies show that similar changes can be expected in patients mobilized after long duration BR.

Symptomatic subjects reported an amelioration of space motion symptoms by application contact force [1]. Basing on the data obtained in the prior experiments, a boot was developed in order to stimulate plantar mechanoreceptors as countermeasure to deafferentation. To investigate the influence of receptor stimulation by simulating standing we investigated the effect of 72 hours of DWI exposure on muscle enzymes in four healthy volunteers (group A) in whom this boot (SUC-Support Unloading Compensator) simulated standing, vs. a group of four volunteers (group B) without this device. Both groups remained in DWI for 72 hours, quadriceps femoris muscle load two hours thereafter; CK activity, CK mass, and MHC were measured six times during 264 hours after DWI.

To simulate standing, a boot with alternatingly inflatable 13 chambers in the sole was developed (Figure 7). During the 72 hours of DWI exposure, plantar stimulation was applicated six times per 24 hours, each stimulation lasting for 30 minutes with alternating right/left pressure application. This procedure was analogous to a pre-experiment measurement of plan-

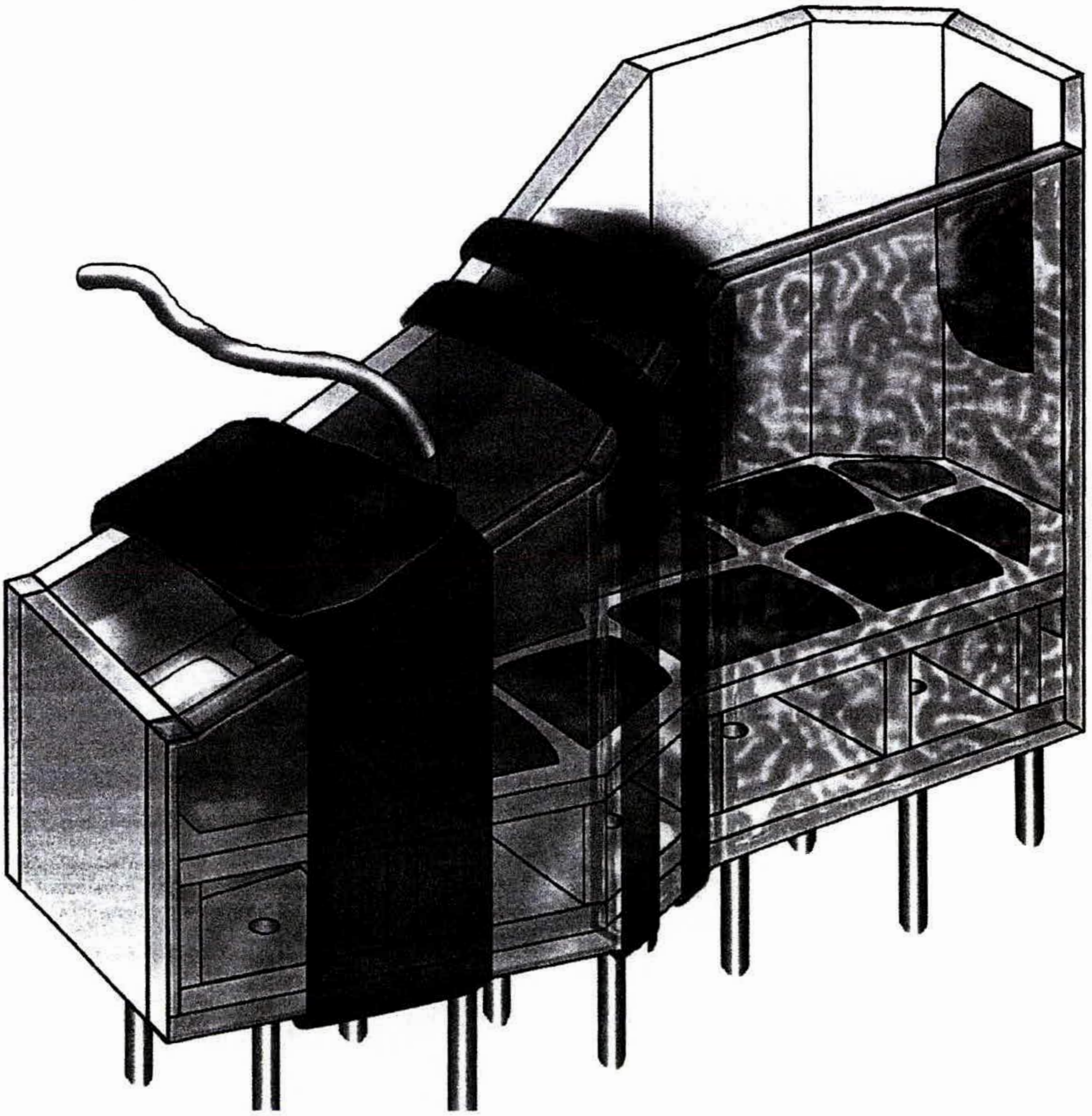

FIGURE 7
Total view of SUC; 13 pneumatic alternatingly inflatable chambers in order to simulate standing.

tar pressure distribution during 30 minutes of standing. Reduced levels of serum CK activity, mass and MHC in group A, as compared with group B, indicated a less diffuse lesioning of mainly antigravitational muscles (Figure 8).

CONCLUSION

Research in space neurology is a completely new field in modern neuroscience. It furnishes new information about sensory motor functions, especially the proprioceptive system. The results of experiments in simulated microgravity can be used to design new diagnostic and therapeutic programs for certain neurological conditions.

Purposive movement is one of the most fundamental and one of the most complex functions of the nervous system. The cortical motor programs are dependent on peripheral input to control the performance of the program. Visual, vestibular, extero, and proprioceptive inputs are essential because they supply the necessary information about posture and locomotion, and are analyzed and compared with the program. Via the dorsal root pathways, the brain receives informa-

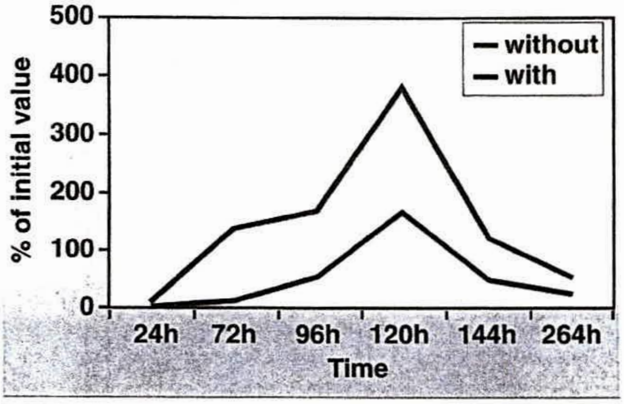

FIGURE 8
MHC in percentage of inital value with/without SUC.

tion from the head, trunk, and the upper and lower extremities.

The basis of these changes is discussed to be a collapse of sensory input from the extremities, trunk and the cervical spine, with subsequent motor dysfunction, functional adaptation of muscle, as well as disorders of the autonomic nervous system, symptoms, which can be observed in bedridden patients after even 2 to 3 weeks of immobilization. In both, adaptation to G_0 and BR the deafferentation mainly of proprioceptive input seems to be of major significance. The data of countermeasures activating afferent input is encouraging enough to continue these investigations.

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