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IIIIII Microgravity Experiments by Aircraft Parabolic Flights Ⅱ IIIIII
(Review)

Effects of Exposure to Microgravity on Neuromuscular Systems: A Review

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Abstract

Parabolic flight lasting 20–30 s and short-term exposure to microgravity for several weeks have been used to examine changes in the neuromuscular system. Previous studies have shown that short-term exposure to microgravity induces an atrophy of fibers, shifting of fiber type from slow-twitch to fast-twitch with synthesis of new fiber types, decreased oxidative enzyme activity, and down-regulation of the mRNA expression of heat shock proteins in the antigravity skeletal muscles of rats. These changes are similar to those observed after decreased muscular activity and loading levels on Earth. Recent studies using long-term exposure to microgravity for several months have also revealed a decreased oxidative capacity of gamma and alpha motoneurons in the spinal cord of mice, as well as degenerative changes in the skeletal muscles. In this article, we reviewed changes in the neuromuscular system in response to parabolic flight of an airplane and short- and long-term exposures to microgravity on orbit around Earth. We especially focused on the oxidative capacity of spinal motoneurons that innervate muscle fibers.

Keywords: microgravity, neuromuscular system, oxidative capacity, parabolic flight, skeletal muscle fiber, spinal motoneuron

1. Introduction

The motor (neuromuscular) unit is comprised of spinal motoneurons and the skeletal muscle fibers that they innervate. There is a high probability of plasticity in the motor units following development, aging, decreased and increased muscular activity and loading levels, hormone treatment, chronic metabolic diseases, and exposures to hypobaric hypoxia, hyperbaric oxygen, and microgravity[1)].

Skeletal muscles are comprised of heterogeneous types of fibers that possess different functional and metabolic properties. Muscle fibers are classified as type I (slow-twitch and fatigue-resistant), type IIA (fast-twitch and fatigue-resistant), and type IIB (fast-twitch and fatigable) based on their ATPase activity after preincubation at different pH values[2)]. Oxidative enzyme activity is higher in type I and type IIA fibers, whereas glycolytic enzyme activity is higher in type IIA and type IIB fibers. The distribution of fiber types correlates with the contraction speed and strength and fatigue resistance of individual skeletal muscles. Skeletal muscles are classified into 2 types: slow and fast, with different normal activity patterns. Slow muscles, e.g., the adductor longus and soleus muscles, exhibit activity of relatively low intensity and long duration, which is required for performing functions against gravity, such as walking and maintaining posture. In contrast, fast muscles, e.g., the extensor digitorum longus and plantaris muscles, exhibit activity of relatively high intensity and short duration, which is required for functions where strength and power are essential. In general, fiber characteristics in skeletal muscles correspond well with the cell body sizes and oxidative enzyme activities of the spinal motoneurons that innervate the muscle fibers.

Spinal motoneurons in the dorsolateral region of the ventral horn of the spinal cord are classified into gamma and alpha. Gamma motoneurons have small cell body sizes, high mitochondrial densities, and oxidative capacities, and innervate intrafusal fibers in the muscle spindle, while alpha motoneurons innervate extrafusal fibers that constitute the main mass of skeletal muscle[3-5)]. Each alpha motoneuron has a single axon that branches to supply a variable number of fibers in the skeletal muscle, forming a muscle unit. The motoneuron group innervating a single muscle is called a motor pool. Motor units are categorized into 2 types based on their properties: slow and fast. The alpha motoneurons belonging to the slow-type motor units have medium cell body sizes and high oxidative capacities than those belonging to the fast-type motor unit[3)]. In general, there is an inverse relationship between cell body size and oxidative capacity in a population of motoneurons[3,6,7)].

The metabolic properties of motoneurons are related to their target muscle fibers, indicating that there is a matching of size and metabolic properties of the motoneurons and the muscle fibers that they innervate.

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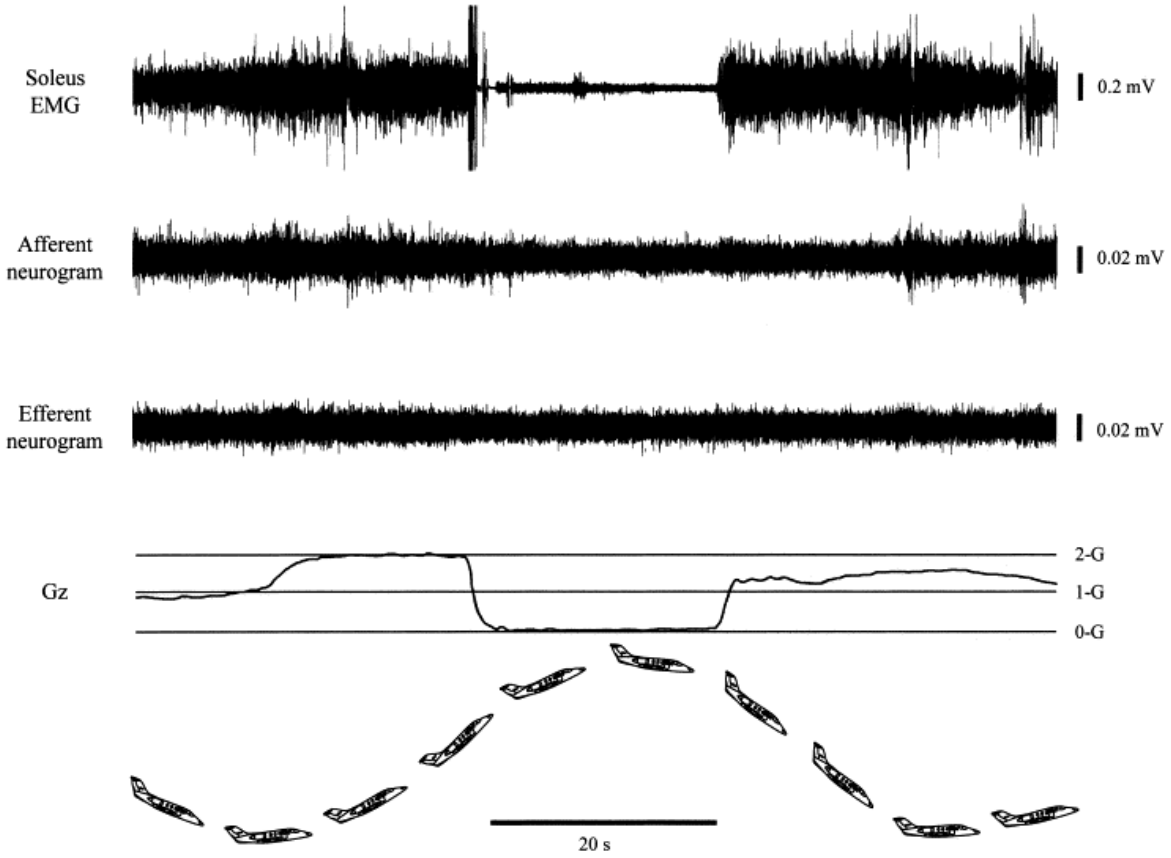

Fig. 1. Typical patterns of soleus electromyogram (EMG) and afferent and efferent neurograms at the L5 segment of the rat spinal cord during parabolic flight. The time-course changes in gravity (Gz) levels and patterns of parabolic flight are indicated. (Kawano et al., Neuroscience, 114: 1133-1138, 2002)

In this article, we reviewed changes in the neuromuscular system in response to parabolic flight and short- and long-term exposures (weeks and months, respectively) to microgravity. We especially focused on the oxidative capacity of spinal motoneurons that innervate skeletal muscles.

2. Parabolic Flight

Electromyograms (EMGs) and both afferent and efferent neurograms were examined under 20 s of microgravity induced by the parabolic flight of an airplane. The EMG from the soleus muscle and both afferent and efferent neurograms at the lumbar 5th segment of the spinal cord of adult rats were recorded during parabolic flight[8]. The soleus EMG activities gradually increased when the gravity level was elevated from 1 G to 1.5 G and thereafter to 2 G during the ascending phase of the parabolic flight (**Fig. 1**). The EMG activities immediately decreased when the rats were exposed to microgravity during the descending phase. The EMG activities were maintained at this low level during the 20 s of microgravity conditions. The EMG activities were restored when the gravity level was increased to 1.5 G and thereafter 1 G during the descending and recovery phases. The afferent neurogram was affected in the same direction as observed in the soleus EMG, although the magnitude of the reduction during microgravity conditions was minor relative to those in the soleus EMG. The level of the efferent neurogram was only slightly decreased during microgravity conditions. Although the afferent input is closely associated with gravity-dependent muscular activity, this relationship is not clearly evident in the efferent activity.

Responses of the Hoffman-reflex in the soleus muscle were examined during parabolic flight[9]. The amplitude of the M-wave during hyper- and microgravity was similar to that obtained at 1 G. In contrast, the amplitude of the H-wave was increased when the participants were exposed to microgravity. Therefore, the H/M ratio was elevated during parabolic flight. An acute exposure to microgravity may increase the excitability of the soleus motor pool.

Fluid shifts toward the upper body cause differences in the blood flow of the upper and lower limbs under microgravity compared to that under normal gravity conditions. A recent study[10] examined the difference in blood flow under the skin of

the upper and lower limbs of participants in a sitting position under different gravity levels generated by parabolic flight. The blood flow of both the upper and lower limbs increased immediately after 0 G. Thereafter, the blood flow of both the upper and lower limbs returned to the normal level observed under 1 G. The blood flow of the upper limbs remained at the normal level during 0 G and after 1.5 G, while the blood flow of the lower limbs decreased during 0 G. The decreased blood flow of the lower limbs recovered to the normal level after 1.5 G. It is suggested that reduced blood flow induced by fluid shifts under microgravity conditions is associated with atrophy of skeletal muscles, especially antigravity muscles of lower limbs, which was observed in a previous study[11].

3. Short-term Exposure to Microgravity

Short-term exposure to microgravity for several weeks induces adaptations in the neuromuscular system. Short-term exposure to microgravity may induce an altered supraspinal function such as that which occurs within the vestibular system, which could disrupt a specific group of neurons. These changes on orbit are not observed by decreased muscular activity and loading levels on Earth[11,12].

Atrophy of fibers, a shifting of fiber type from slow-twitch (type I) to fast-twitch (type II), along with the de novo synthesis of type IIx, decreased oxidative enzyme activity, and down-regulation of the mRNA expression of heat shock proteins (HSPs), e.g., HSP27, HSP70, and HSP84, are observed in the skeletal muscles of rodents following short-term exposure to microgravity[11,12]. Furthermore, these changes are more marked in the slow muscles, such as the soleus muscle, than in the fast muscles, such as the extensor digitorum longus and plantaris muscles. Additionally, greater weight loss was observed in the hindlimb muscles than in the forelimb muscles[13]. These changes are also observed after decreased muscular activity and loading levels on Earth[14-16]. Adequate blood flow, which continuously delivers nutrients and oxygen to individual cells and tissues, is necessary to maintain the function and metabolism of skeletal muscles and their fibers, particularly antigravity slow muscles and the high-oxidative fibers, in the hindlimbs. The soleus, plantaris, and extensor digitorum longus muscles in the hindlimbs of rodents have smaller fiber sizes and higher oxidative capacities than the biceps brachii and triceps brachii muscles in the forelimbs[17,18], indicating that skeletal muscles and their fibers in the hindlimbs require more nutrients and oxygen from the capillaries to maintain their function and metabolism than do muscles and fibers in the forelimbs. Therefore, there is a possibility that decreased blood flow, which may be more pronounced in the hindlimbs under microgravity conditions because of fluid shifts toward the upper body, is associated with muscle atrophy in the hindlimbs.

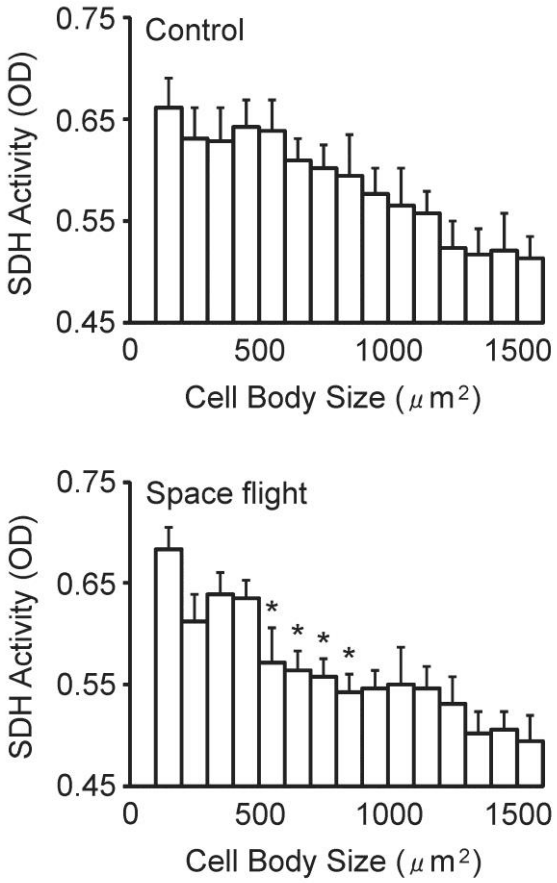

Fig. 2. The relationship between cell body size and succinate dehydrogenase (SDH) activity of motoneurons in the retrodorsal region of the ventral horn at L5 and L6 segments in the rat spinal cord of control (up) and space flight (down) rats. Values are indicated as the mean and standard deviation of 5 rats. OD, optical density. *p<0.05 compared with the control with same cell body sizes. (Ishihara et al., Acta Anat, 157: 303-308, 1996)

Previous studies[19-21] have shown that the oxidative capacity of medium-sized alpha motoneurons, but not gamma or large-sized alpha motoneurons, in the dorsolateral region of the ventral horn in the lumbar segment of the rat spinal cord was decreased after short-term exposure to microgravity (**Fig. 2**). These medium-sized alpha motoneurons were slow-type and innervated the high-oxidative fibers in the hindlimb muscles that atrophy and shift their fiber types following short-term exposure to microgravity. In contrast, there were no changes in the oxidative capacity of alpha motoneurons in the ventromedial region of the ventral horn in the lumbar segment of the rat spinal cord after short-term exposure to microgravity[22] (**Fig. 3**). These motoneurons were fast-type and innervated the perineal muscles that were constituted only of low-oxidative type II fibers[5].

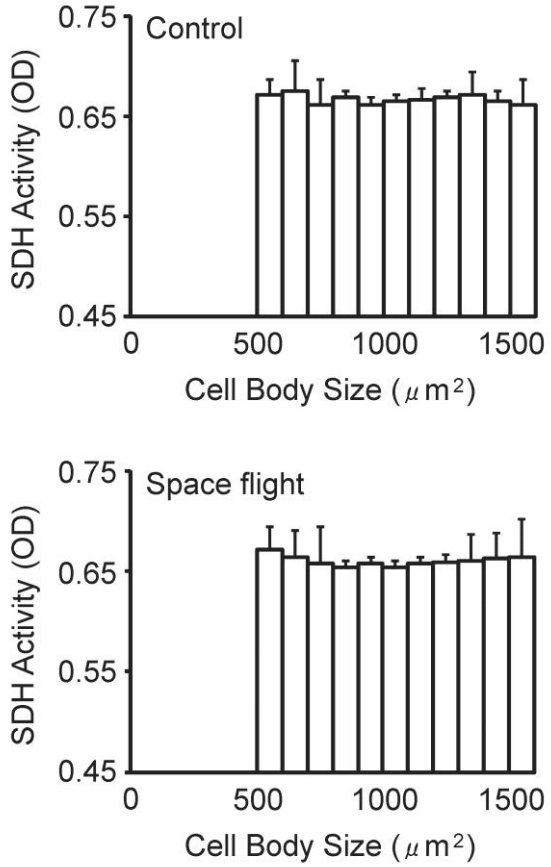

Fig. 3. The relationship between cell body size and succinate dehydrogenase (SDH) activity of motoneurons in the dorsomedial region of the ventral horn at L5 and L6 segments in the rat spinal cord of control (up) and space flight (down) rats. Values are indicated as the mean and standard deviation of 5 rats. OD, optical density. (Ishihara et al., Muscle Nerve, 23: 303-308, 1996)

The oxidative capacity of alpha motoneurons in the dorsolateral region of the ventral horn in the cervical segment, but not in the lumbar segment, of the rat spinal cord did not change after short-term exposure to microgravity[23]. The alpha motoneurons in the cervical segment may be less responsive to short-term exposure to microgravity than those in the lumbar segment. The alpha motoneurons in the cervical segment innervate the forelimb muscles, e.g., the biceps brachii and triceps brachii muscles, which are mainly composed of type II fibers with low oxidative enzyme activity[24]. The alpha motoneurons in the cervical segment are recruited only for relatively brief periods at high activation levels; thus, exposure to microgravity would have little impact on these alpha motoneurons. These findings collectively indicate that oxidative capacity of the slow-type alpha motoneurons innervating high-oxidative fibers in the skeletal muscles with gravity-dependent functions is decreased by short-term exposure to microgravity.

The dorsal root ganglion contains sensory neurons with different cell body sizes and levels of oxidative capacity[25,26]. Decreased oxidative capacity in large-sized sensory neurons in the lumbar segment of the rat spinal cord, without changes in cell body size, was observed after short-term exposure to microgravity[27] (**Fig. 4**). These changes may reflect a decrease in the functional activity of group Ia and II afferents, which project to skeletal muscles, suggesting that the afferent flow from the hindlimb muscles to spinal motoneurons is inhibited and/or disturbed by exposure to microgravity.

These findings clearly demonstrate that the microgravity environment produces effects on the neural elements of the motor unit that are not observed in other models of decreased muscular activity and loading levels on Earth[28].

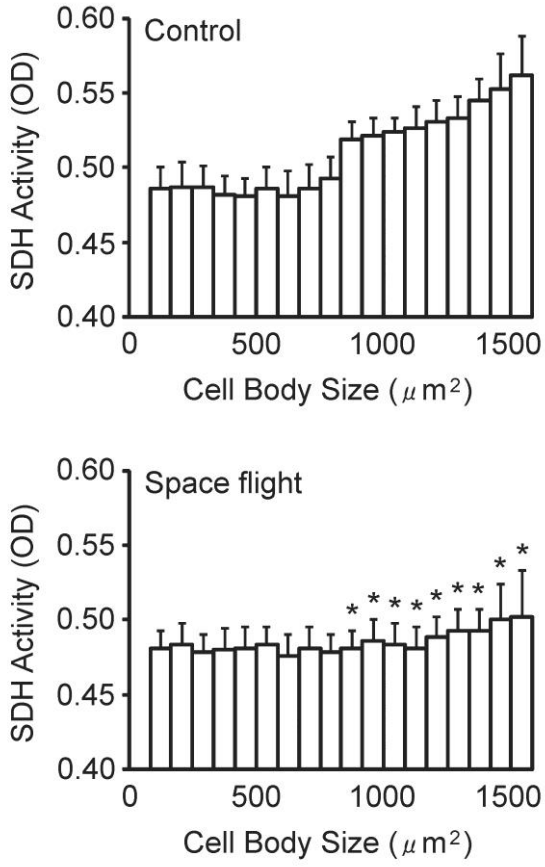

Fig. 4. The relationship between cell body size and succinate dehydrogenase (SDH) activity of sensory neurons in the dorsal root ganglion at the L5 segment in the rat spinal cord of control (up) and space flight (down) rats. Values are indicated as the mean and standard deviation of 5 rats. OD, optical density. *p<0.05 compared with the control with same cell body sizes. (Ishihara et al., Neuroscience, 81: 275-2, 1997)

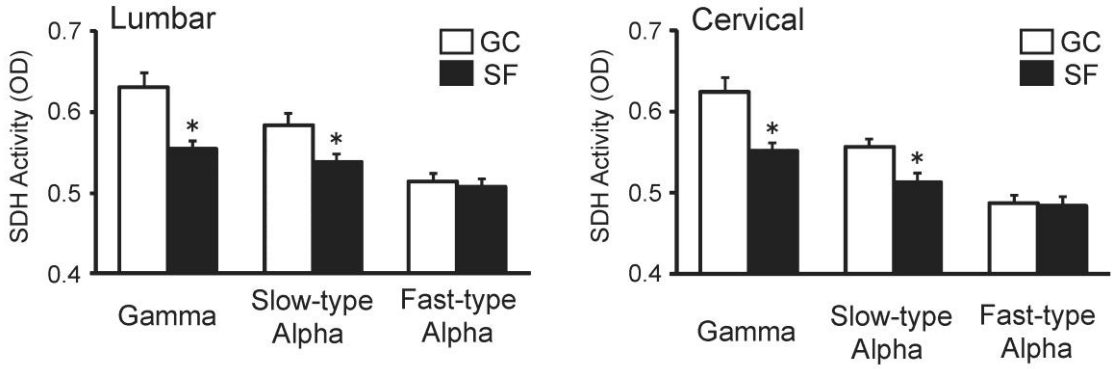

Fig. 5. Succinate dehydrogenase (SDH) activity of gamma and slow- and fast-type alpha motoneurons in the dorsolateral region of the ventral horn in the lumbar (left) and cervical (right) segments of the spinal cord of ground-based control (GC, n = 4) and space flight (SF, n = 3) mice. Values are indicated as the mean and standard deviation. OD, optical density. *p<0.05 compared with GC. (Ishihara et al., Neurochem Res, 38: 2160-2167, 2013)

4. Long-term Exposure to Microgravity

Cell body size and oxidative capacity of motoneurons in the dorsolateral region of the ventral horn in both the lumbar and cervical segments of the mouse spinal cord were assessed after long-term exposure to microgravity for 13 weeks and compared with those of ground-based controls[29] (**Fig. 5**). No changes in the cell body size of motoneurons were observed in either segment after exposure to microgravity, but oxidative capacity of small-sized (<300 μm^2) gamma and medium-sized (300–700 μm^2) alpha motoneurons belonging to the slow-type motor unit, which have higher oxidative capacity than large-sized (>700 μm^2) alpha motoneurons belonging to the fast-type motor unit, was lower than that of ground-based controls in both segments. It is concluded that exposure to microgravity for longer than 3 months induced decreased oxidative capacity of both gamma and slow-type alpha motoneurons. In particular, the decreased oxidative capacity of gamma motoneurons was observed only after long-term exposure to microgravity. These results contradict those observed in alpha motoneurons in the cervical segment of the rat spinal cord after short-term exposure to microgravity[19-21]. Long-term exposure to microgravity may affect fiber properties in the forelimb muscles as well as the hindlimb muscles. Nevertheless, drawing any firm conclusion concerning the degree of fiber atrophy and type-shift of the forelimb muscles is difficult because data concerning fiber profiles after long-term exposure to microgravity are insufficient.

There is significant interest in observing whether the oxidative capacity of gamma motoneurons in the dorsolateral region of the ventral horn in the lumbar and/or cervical segments of the spinal cord responds to long-term exposure to microgravity. Decreased oxidative capacity of gamma motoneurons in the dorsolateral region of the ventral horn in both the lumbar and cervical segments was observed after long-term exposure to microgravity[29]. In contrast, oxidative capacity of gamma motoneurons in the spinal cord was not changed after short-term exposure to microgravity[19-21]. Unfortunately, there are no data currently available concerning changes in the properties of intrafusal fibers in the muscle spindle, which are innervated by gamma motoneurons, after short- and long-term exposures to microgravity.

5. Conclusions

Long-term exposure to microgravity for several months caused a decreased oxidative capacity of gamma motoneurons in the dorsolateral region of the ventral horn in both the lumbar and cervical segments of the spinal cord without inducing corresponding changes in cell body size. A decreased oxidative capacity of slow-type alpha motoneurons in the dorsolateral region of both the lumbar and cervical segments was also observed after long-term exposure to microgravity. The changes in the gamma motoneurons of the ventral horn in the lumbar and cervical segments and in the slow-type alpha motoneurons of the ventral horn in the cervical segment were not observed after short-term exposure to microgravity for several weeks. Finally, long-term exposure to microgravity proved to have a significant effect on the oxidative capacity, but not on the cell body size, of selected motoneurons, i.e., the gamma and slow-type alpha motoneurons, in the spinal cord.

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