Role of muscle spindle in weightlessness-induced amyotrophy and muscle pain

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Abstract: To date, the medium and long-term space flight is urgent in need and has become a major task of our manned space flight program. There is no doubt that medium and long-term space flight has serious damaging impact upon human physiological systems. For instance, atrophy of the lower limb anti-gravity muscle can be induced during the space flight. Muscle atrophy significantly affects the flight of astronauts in space. Most importantly, it influences the precise manipulation of the astronauts and their response capacity to emergencies on returning to the atmosphere from space. Muscle atrophy caused by weightlessness may also seriously disrupt the normal life and work of the astronauts during the re-adaptation period. Here we summarize the corresponding research concentrating on weightlessness-induced changes of muscular structure and function. By combining research on muscle pain, which is a common clinical pain disease, we further provide a hypothesis concerning a dynamic feedback model of “weightlessness condition $\Rightarrow$ muscular atrophy $\Leftrightarrow$ muscle pain”. This may be useful to explore the neural mechanisms underlying the occurrence and development of muscular atrophy and muscle pain, through the key study of muscle spindle, and furthermore provide more effective therapy for clinical treatment.

Keywords: weightlessness; amyotrophy; muscle spindle; muscle pain

1 Introduction

Medium and long-term space flight has serious damaging impact upon human physiological systems^[1,2]. In particular, long-term weightless environment of space flight can apparently cause atrophy of lower limb eccentric anti-gravity muscle in humans^[3]. Muscle atrophy significantly affects the efficiency of the astronauts in space. Most importantly, muscular dystrophy will impair the precise manipulation and emergency response capacity of the astronauts on returning to the atmosphere from space. In addition,

muscle atrophy caused by weightlessness may seriously affect the normal life and work of the astronauts after the re-adaptation. Till now, the exact mechanism of muscle atrophy during weightlessness or simulated weightlessness condition is still unclear. Clarifications of the mechanism of muscle weight loss due to the plasticity changes and the mechanism of muscular dystrophy are important to develop more effective prevention and treatment of muscle atrophy in the weightless environment and to provide the theoretical treatment during clinical experience.

2 Role of muscle spindle in weightlessness-induced amyotrophy

In a long period, the research concerning potential mechanism of muscular atrophy during weightless condition has been conducted extensively, and some progresses have been achieved. However, most of the studies have been concen-

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trated on weightlessness-induced changes on extrafusal muscle fibers, not on muscle spindle^[4-6]. It cannot be ignored that in relation to extrafusal muscle fibers, muscle spindle is an important receptor in skeletal muscle to detect any changes in skeletal muscle fiber length, tension, movement direction, speed and speed changes, and the rate of change^[7].

It is well-known that muscle spindles are special sensory receptors within the belly of muscle, which primarily detect changes in the length of muscle. Due to the non-ignoring gravity on the earth, muscle spindles consistently convey any variations of length information to the central nervous system to regulate the contraction of muscles, and thus maintain the body posture, by activating motor neurons *via* the stretch reflex to resist muscle stretch. Based on the previous experiments, we hypothesize that weightlessness-induced changes or damage of muscle spindle may be the promoter for amyotrophy. Our series of experiments using extracellular recordings reveal that un-loading-induced weightlessness could elicit time-related changes in electrophysiological characteristics of soleus muscle spindles. In rats, significant time-dependent decreases in frequency of spontaneous firings and in the response to ramp-and-hold stretch of soleus muscle spindles were found on day 7 and day 14 after tail-suspension in rats^[8]. Moreover, all the intrafusal, but not extrafusal fibers showed immunoreactivity to MF30, which increased obviously after 14-d tail-suspension. This suggests that the expression level and patterns of myosin heavy chain (MHC) in intrafusal fibers of rat soleus muscle change after simulated weightlessness^[9].

In control rats, the intrafusal muscle fibers were regular and the nerve endings were intact and clear in the soleus spindles of control rats during the physiological state. Besides, no obvious changes were observed in muscle spindles of 7-d tail-suspended rats, while in 14-d tail-suspended rats, intrafusal muscle fibers became irregular, with rough and vague nerve endings. The distinct retrograde changes of muscle spindles and nerve endings were observed in 21-d tail-suspended rats. Degeneration and rupture were found in nerve endings, which made them unclear and pale in staining^[10]. Furthermore, detailed study shows that the disturbance of calcium homeostasis in intrafusal fibers exposed

to hindlimb unloading condition may gradually affect the structure and function of muscle spindle^[11].

In contrast to the decreased muscle spindle afferent discharges of rat soleus muscles, no decrease in muscle spindle activity could be further observed after the application of sinusoidal vibration (frequency: 100 Hz, duration: 300 ms) onto the muscle spindle after the 7-d tail-suspension^[12]. In addition, some Chinese medicines, such as ligustrazine and radix astragali, can selectively excite and enhance the afferents of muscle spindle, thus producing counter-effects on weightlessness-induced muscle atrophy^[13].

Taken together, it is suggested that maintenance of the structure and the function of muscle spindle within physiological range may provide us with a promising route to well understand weightlessness-induced amyotrophy and to develop better clinical therapies.

3 Supraspinal activities in weightlessness-induced amyotrophy

It is well-known that the muscle spindle mediates type II afferent information to the major projection area 3a of the cerebral cortex, which mainly project type II afferents information to the cerebral cortex. From muscle and cerebral cortex, the projection fibers issue the sensory information for effective integration *via* the pyramidal and the extra-pyramidal activities of descending α/γ spinal motor neuron adjustment, which results in the body posture and movement of fine adjustment.

In recent years, studies have proved that the central nervous system has one important feature, the synaptic plasticity, during its exposure to sufficient extra stimuli. Undoubtedly, the functions of muscle spindle and the central nervous system will be influenced by such changes. During weightlessness or simulated weightlessness conditions, the structure and the function of the central nervous system change in a series of patterns. Only after 30-min simulated weightlessness, glia cells exhibited damaged cytoskeleton, destructed cell morphology, and DNA fragmentation, *etc.* After 14 d, in rat hind limb somatosensory cortex, GABA-immunopositive area showed a reduction in the number of nerve cells, and the nerve endings of envelop-

ing layer Vb pyramidal cells and dendritic cells were also significantly reduced^[14]. Another group has also reported that after weightlessness/simulated weightlessness, D2 receptors that are in charge of positioning, launching and regulation of muscle movement, are down-regulated^[15]. The results suggest that during the exposure to weightlessness/simulated weightlessness conditions, the plasticity of the central nervous system changes accordingly to the governing afferents of muscle spindle on functional status of muscle activities.

However, changes in the central nervous system by any kinds of impact on intrafusal and extrafusal muscle fibers leading to abnormalities in muscle function and muscle atrophy have not yet been well reported. It has been demonstrated that dorsal spinocerebellar tract (DSCT) is a major

pathway for muscle spindle afferent projection to the supraspinal centers. DSCT neurons and muscle spindle receptors constitute one of the main pathways to directly govern the formation of synaptic contacts from the lower part of lower limbs, and the trunk of some larger projection, as well as the higher central downlink systems (such as rubrospinal tract and corticospinal tract) of the regulation^[16].

DSCT neurons in cerebellar efferent fibers project to the spinal cord and brainstem reticular formation through the regulations of muscle spindle and the γ sensitivity of spinal motor neurons to regulate muscle tension. It has been reported that DSCT neurons play a pivotal role in reflex activities, through the maintenance of muscle bulk and tension into the process. It can be seen as the proprioceptive information of the lowest integration site in the central^[17] (Fig. 1).

Fig. 1 Diagram of relationship between muscle spindle and weightlessness-induced muscular atrophy concerning different ascending and descending central pathways governing the spinal cord activity. " $\downarrow$ " means the action of decline.

4 Relation between weightlessness-induced amyotrophy and muscle pain

In humans, pain is caused by a variety of exogenous and endogenous noxious stimuli in the body, and is transmitted through the peripheral and the central nervous systems in the brain. At present, pain has become a national issue of research. Based on the different causes, pain can simply be divided into somatic pain and visceral pain. Somatic pain originates from the body skin (skin/cutaneous), muscle, and articular (joint), and it is worth noting here that the basic research involving physical pain is commonly conducted by employing skin or cutaneous pain model (such as pain caused by subcutaneous injection of chemical agents). The proportion of pain research involving muscles, joints and ligaments is still small. There is no doubt that skin pain model is simple and easy to observe the indicative behaviors, and the results have good repeatability. However, pain from less simple clinical skin regions makes it easier to give accurate diagnosis and treatment. In this way, on the basis of animal experiments and clinical studies of human pain, an effective complementary method is needed. This increases the gap between basic research and clinical usage, and further influences the explorations of the mechanism of pathological pain and clinical application^[18].

It should be clearly recognized that the type of clinical pathological pain is very complex and also the pain for these cases (such as muscle pain, especially from unreasonable exercise-induced, chronic, and nonsuppurative inflammation of the muscles). On one hand, patients often feel unbearable pain with the psychological changes (such as anxiety and insomnia). On the other hand, clinicians are often faced with difficulties to give accurate diagnosis and treatment, which are caused by the great spiritual and economic burdens on individuals and the society. Although the basis of muscle pain research is closer to clinical applications, comparable human and animal studies are few.

More recently, studies have shown that intramuscular injection of hypertonic saline can excite type III and type IV nociceptive afferent fibers in muscle. Besides, supraspinal structures control the spinal cord motor neuron activities to

influence the muscle spindle activity^[19,20]. Using laser doppler flowmetry and thermography, we have found that both blood flow and skin temperature at the injection area and contralateral non-injection area increase significantly following the ipsilateral intramuscular injection of hypertonic saline, indicating the involvement of spinal and supraspinal organizations^[21]. Our recent study in conscious rats has further revealed that descending facilitatory, but not inhibitory controls, govern such bilateral muscular hyperactivities during the exposure to ipsilateral acute muscle pain (unpublished data). Previous studies have demonstrated that exciting muscle spindle can inhibit nociceptive activities of spinal dorsal horn wide-dynamic range (WDR) neurons^[22-23]. Supraspinal structures, such as red nucleus, participate in muscle spindle-mediated inhibition of spinal WDR neuronal responses^[24]. Functional impairment of ionotropic, but not metabotropic glutamate (NMDA and non-NMDA) receptors, is important in red nucleus-modulated muscle atrophy including decreased activities of muscle spindle^[25]. Excitation of muscle spindle can significantly reverse the decrease in Fos protein expression during hindlimb unloading-simulated weightlessness condition^[26]. Combining different studies, here we speculate that in the weightlessness/simulated weightlessness or muscle pain conditions, muscle spindle afferent impulses triggered by the environment will be correspondingly decreased, thus further increasing the muscle atrophy and muscle pain (Fig. 2). Accordingly, we put forward the “weightlessness

Fig. 2 Schematic illustration of the relationship among weightlessness condition, muscular atrophy, and muscle pain. We hypothesize a dynamic feedback model of “weightlessness condition $\Rightarrow$ muscular atrophy $\Leftrightarrow$ muscle pain” entitled “dynamic plastic changes”, during which muscle spindle plays a core/key role. “+” represents induce and increase, and “?” represents uncertainty.

⇒ muscular atrophy (muscle spindle at the core changes) ⇔ muscle pain” as the dynamic feedback model of plastic chain. In zero or nearly zero gravity environment or in a state of muscle pain, muscle spindle afferent impulses may play a significant role in induction and maintenance of muscle pain.

5 Conclusion

So far, series of studies have indirectly revealed the relation among weightlessness, muscular atrophy, and muscle pain. Understanding the role of muscle spindle may be important to researchers and clinicians for the study of muscle atrophy and the follow-up muscle pain. However, we are not yet clear about the muscle pain during special conditions (such as weightless environment or space), or the exact role of supraspinal centers (for example, DSCT neurons) in regulating muscle spindle afferents. Also, it still needs further investigations concerning whether there is a relationship between specific changes and their precise cause and effect? These problems require further studies in aerospace medicine, sports medicine, and clinical science of pain involved in weightlessness-induced muscle atrophy. Exploration for peripheral and central mechanisms of muscle pain is the goal and of great value for theoretical understanding and practical application, especially for the abnormal muscle responses occurring in the mirror of the contralateral leg.

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肌梭在失重性肌萎缩与肌肉痛中的作用

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摘要: 目前, 中、长期航天飞行会对航天员的器官系统造成损害, 如离心性下肢抗重力肌发生明显萎缩, 直接影响宇航员的太空飞行及返回大气层着陆时的准确操纵与应急离舱能力。肌肉萎缩还会严重影响宇航员返回地面后的正常工作和生活。本文将对失重或模拟失重环境下的肌肉结构及功能变化的相关研究给予一定的文献回顾。结合相关肌肉痛研究, 我们提出“肌萎缩(肌梭变化为核心)-肌肉痛”这一动态双向可塑反应模式假设。通过以肌梭为研究核心的肌萎缩/肌肉痛研究, 可能会更好地阐明肌肉萎缩及肌肉痛发生过程中的神经机理, 并为临床提供更好的治疗方案。

关键词: 失重; 肌萎缩; 肌梭; 肌肉痛