

Modulation of Spinal Neural Circuits Induced by Corticospinal Descending and Peripheral Afferent Inputs

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Chapter 1: General introduction

Human movement is controlled by the central nervous system consisting of the brain and spinal cord. Recent evidence suggests that activity-dependent neuroplasticity can occur throughout the central nervous system from the cortex to the spinal cord, and that spinal cord neuroplasticity is likely to contribute to the mastery of motor skills (Wolpaw, 2010; Thompson & Wolpaw, 2014). Moreover, it has been shown that promoting spinal cord neuroplasticity is a useful strategy for inducing motor recovery after spinal cord injury or stroke (Edgerton et al., 2004; Bhagchandani & Schindler-Ivens, 2012; Bunday & Perez, 2012; Ueno et al., 2012; Thompson et al., 2013; McPherson et al., 2015). Therefore, understanding the mechanisms underlying spinal cord neuroplasticity will likely be vital in developing effective rehabilitation approaches for people with central nervous system disorders. Previous studies have shown that motor skill training produces activity changes in spinal neural circuits (Perez et al., 2005; Roche et al., 2011). However, the factors that influence the induction of changes in spinal neural circuits are not clarified. The main goal of this thesis is to elucidate the mechanisms underlying spinal cord neuroplasticity induced by motor training, and to provide useful information about how this plasticity may be used for medical treatment. In general introduction, the function of neural circuits

in the spinal cord involving limb movement and the main experimental techniques used in the present study [i.e., Hoffmann reflex (H-reflex), transcranial magnetic stimulation (TMS)] were described.

This thesis consists of four studies concerning activity-dependent spinal cord neuroplasticity; In chapter 2, the influence of corticospinal descending inputs on spinal reciprocal Ia inhibition was investigated using TMS conditioning of H-reflex. In chapter 3, the neural mechanisms underlying changes in Ia presynaptic inhibition induced by motor skill training were investigated using TMS conditioning of H-reflex. In order to elucidate the factors that induce neuroplasticity in spinal neural circuits, in chapter 4, the effect of the movement speed of the motor task on changes in spinal neural circuits was examined. Moreover, in chapter 5, to reveal the effect of peripheral afferent inputs derived from muscle spindles on neuroplasticity in spinal neural circuits, the effect of sensory inputs induced by electrical stimulation on changes in spinal neural circuits was investigated.

Chapter 2: Effects of corticospinal descending inputs on the activity of reciprocal Ia inhibition

Purpose: The purpose of this study was to investigate the extent to which the corticospinal inputs delivered to Ia inhibitory interneurons

influence the strength of disynaptic reciprocal Ia inhibition.

Methods: Seventeen healthy subjects participated in this study. The amount of reciprocal Ia inhibition was determined via short-latency (condition-test interval:1-3ms) suppression of soleus H-reflex by conditioning stimulation of common peroneal nerve. The effect of corticospinal descending inputs on Ia inhibitory interneurons was assessed by evaluating the conditioning effect of TMS on the soleus H-reflex. Then, we determined the relationship between the amount of reciprocal Ia inhibition and the conditioning effect of TMS on the soleus H-reflex.

Result & Conclusion: The amount of reciprocal Ia inhibition and the extent of change in the amplitude of the TMS-conditioned H-reflex, which was measured from short latency facilitation to inhibition, displayed a strong correlation ($r = 0.76$, $P < 0.01$) in the resting conditions. The degree of reciprocal Ia inhibition is affected by the corticospinal descending inputs delivered to Ia inhibitory interneurons, which might explain the inter-individual variations in reciprocal Ia inhibition.

Chapter 3: The mechanisms of changes in the Ia presynaptic inhibition following skilled motor task

Purpose: Previous studies have shown that activity changes in Ia presynaptic inhibition are induced by motor skill training. However, the mechanisms that influence the activity of Ia presynaptic inhibition are not well understood. The aim of this study was to clarify the mechanisms involved in the modifications of Ia presynaptic inhibition following skilled motor task.

Methods: Sixteen healthy subjects participated in this study. Eight subjects performed a visuomotor task, and the remaining eight subjects performed a non-visuomotor task. The motor training lasted for

20 min. The amounts of Ia presynaptic inhibition (D1 inhibition), the amount of TMS conditioned D1 inhibition, the amplitude of TMS conditioned H-reflex, and Hmax/Mmax were measured before and after the task sessions.

Result & Conclusion: The results showed that Ia presynaptic inhibition was only increased following a visuomotor task, and that the inhibitory effect of Ia presynaptic inhibition induced by TMS was decreased following a visuomotor task, but not following a non-visuomotor task. The increased Ia presynaptic inhibition may be explained by the reduction of inhibitory effects of interneurons activated by the corticospinal tract. These results suggest that modulation of corticospinal descending inhibitory effects on the Ia presynaptic inhibitory pathway may be responsible for the changes in Ia presynaptic inhibition.

Chapter 4: Changes in the spinal neural circuits are dependent on the movement speed of the visuomotor task

Purpose: Previous studies have shown that spinal neural circuits are modulated by motor skill training. However, the effects of task movement speed on changes in spinal neural circuits have not been clarified. The aim of this research was to investigate whether spinal neural circuits were affected by task movement speed.

Methods: Twenty-seven healthy subjects participated in this study. Eighteen subjects performed a visuomotor task involving ankle muscle slow (nine subjects) or fast (nine subjects) movement speed. Another nine subjects performed a non-visuomotor task (controls) in fast movement speed. The motor training lasted for 20 min. The amounts of D1 inhibition and reciprocal Ia inhibition were recorded before, and at 5, 15, and 30 min after the training session.

Result & Conclusion: The amount of D1 inhibition increased after the visuomotor task

irrespective of movement speed. The amount of reciprocal Ia inhibition increased with fast movement speed conditioning, but was unchanged by slow movement speed conditioning. The control task did not induce changes in D1 inhibition and reciprocal Ia inhibition. The results suggest that supraspinal descending inputs for controlling joint movement are responsible for changes in the spinal neural circuits, and that task movement speed is one of the critical factors for inducing plastic changes in reciprocal Ia inhibition.

Chapter 5: Sensory nerve stimulation enhances the reactivity of spinal Ia inhibitory interneurons

Purpose: Peripheral sensory nerve stimulation has been shown to induce plastic changes in the reciprocal Ia inhibitory circuit. However, the mechanisms underlying these changes have not yet been elucidated in detail. The aim of the present study was to determine whether the reactivity of Ia inhibitory interneurons could be altered by peripheral sensory nerve stimulation.

Methods: The amount of reciprocal Ia inhibition, D1 inhibition, the conditioning effects of TMS on the soleus H-reflex, and the Hmax/Mmax were examined in 10 healthy individuals. Electrical nerve stimulation was applied to the common peroneal nerve every 1 s (100 Hz-5train) at the motor threshold intensity of tibialis anterior muscle. Reciprocal Ia inhibition, D1 inhibition, TMS-conditioning H-reflex amplitude, and Hmax/Mmax were recorded before, immediately after, and 15 min after the electrical stimulation.

Result & Conclusion: The electrical nerve stimulation significantly increased the amount of reciprocal Ia inhibition and decreased the amplitude of the TMS-conditioning H-reflex in the short-latency inhibition phase, which was presumably mediated by Ia inhibitory interneurons. However, it had no effect on D1 inhibition and Hmax/Mmax.

The results indicated that sensory nerve stimulation could modulate the activity of Ia inhibitory interneurons, and this change may have been caused by the synaptic modulation of Ia inhibitory interneurons terminals. These results may lead to a clearer understanding of the spinal cord synaptic plasticity produced by sensory inputs.

Chapter 6: General discussion

In summary, the main findings of this thesis are as follows; 1) The activity of Ia inhibitory interneurons is modified by corticospinal descending inputs. 2) Changes in Ia presynaptic inhibition following a skilled motor task are caused by the modulation of corticospinal descending inhibitory effects on the Ia presynaptic inhibitory pathway. 3) Supraspinal descending inputs controlling joint movement are important for producing changes in spinal neural circuits. 4) Task movement speed is a critical factor for inducing changes in reciprocal Ia inhibition, as well as supraspinal descending inputs. 5) Repetitive sensory inputs could modulate the reactivity of Ia inhibitory interneurons. These findings indicate that the changes in spinal neural circuits following motor skill learning result from modulation of interneuron excitability in spinal neural circuits, by corticospinal descending inputs, and that when producing changes in the spinal neural circuits by motor task, it is important to consider what type of motor task to use. Moreover, peripheral sensory nerve stimulation may be useful for improving the abnormal activation of the reciprocal Ia inhibitory circuits. Rehabilitation methods based on the principles of neuroplasticity are likely to be critical for promoting the recovery of motor function in patients with central nervous systems disorders. The findings of this study promote a better understanding of activity-dependent spinal cord neuroplasticity and may lead to the development of effective rehabilitation approaches for improving motor function after trauma or disease.