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Modulation in spinal circuits and corticospinal connections following nerve stimulation and operant conditioning

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Abstract—**Neural plasticity occurs throughout adult life. In healthy individuals, different spinal pathways are differently modulated during different daily activities. Drastic changes to nervous system activity and connections caused by injuries or diseases alter spinal reflexes, and this is often related to disturbed motor functions. In both health and disease, spinal reflexes are subject to substantial modifications. Plasticity in supraspinal descending connections is even more remarkable; corticospinal connectivity has been shown to be extremely plastic.**

In this session, we describe two approaches for possibly improving recovery after central nervous system (CNS) lesions. They are very different, but both involve repetitive nerve stimulation and CNS plasticity. The first approach is functional electrical stimulation (FES) of the common peroneal nerve, which has been used to treat foot drop in patients with CNS lesions. The second approach is operant conditioning of a spinal reflex. Spinal reflex operant conditioning studies in animal models have shown plastic changes in spinal cord neurons associated with this form of learning and improved locomotor function in incomplete spinal cord injured rats. Thus, reflex conditioning might be a robust approach to inducing plasticity at spinal and supraspinal levels. As a first step in establishing this approach and characterizing its effects in the human adult CNS, we are currently investigating the extent and time course of operant conditioning of the soleus H-reflex in healthy subjects. In results to date, all subjects (n=5) have changed reflex size in the correct direction to various degree (16-36%) over 2-3 months of conditioning, indicating possibility that H-reflex conditioning can occur in humans. At the same time, the substantial inter-subject variation in the time course and extent of conditioning suggest that additional data are needed to establish its principal features.

We hope that studying modulation and modification of the CNS by different approaches will help us further understand the plasticity of the human adult nervous system.

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I. Introduction

NEURAL plasticity, or long-term change in CNS structure and function, occurs throughout adult life. In healthy individuals, spinal reflexes are important elements of functional movements, and differently modulated from moment to moment and from task to task [1]-[3]. Damage to the central nervous system (CNS) often changes spinal reflexes, and this is associated with abnormal motor functions [4]. Supraspinal descending connections (e.g., corticospinal connectivity) are also modifiable. Short-term peripheral nerve stimulation in even a single session can change corticospinal excitability [5]-[8].

Here, we discuss two different approaches for inducing plasticity in the CNS and possibly improving functional recovery after CNS lesions. The first approach is functional electrical stimulation (FES) of the common peroneal (CP) nerve, which has been used to treat foot drop in patients with CNS lesions [9],[10]. Effects of FES on the motor evoked potential (MEP) elicited by transcranial magnetic stimulation (TMS) and several different spinal reflexes in the ankle flexor and extensor muscles have been reported. The second approach is operant conditioning of a spinal reflex. The last two decades of studies on spinal reflex operant conditioning in animal models have shown plastic changes in spinal cord neurons associated with this form of learning [11],[12]. Also, recently, Chen, Wolpaw and their colleagues have found that operant conditioning of a spinal cord reflex can lead to improved locomotor function in rats after incomplete spinal cord injury [13]. Reflex conditioning might be a robust approach to inducing plasticity at spinal and supraspinal levels. In order to evaluate this possibility and characterize the effects of reflex conditioning in the human adult CNS, we have started investigating the extent and time course of operant conditioning of the soleus H-reflex in healthy subjects. Early observations from this on-going reflex conditioning study are reported below.

II. Functional Electrical Stimulation of Common Peroneal Nerve

A. Short-term FES studies

Regular use of FES of the CP nerve in hemiplegic patients has been shown to increase walking speed substantially, and after long-term use patients can walk better even without FES [9],[10],[14]. These observations suggest that plastic changes are probably induced in the CNS as a consequence of FES-aided walking, due to the effects of regularly applied

stimulation, increased locomotor activity (i.e., training effect [15],[16]), or the combination of both. In the leg muscles, positive effects of either stimulation or use have been reported repeatedly. Repetitive CP nerve stimulation for a period of time produces short lasting facilitatory effects on the MEP in the tibialis anterior (TA) muscle [8],[17],[18]. Treadmill training with partial body weight support can improve locomotor activity in SCI [19]-[21] or stroke patients [22]. It is not clear whether the nerve stimulation applied during walking at functionally relevant times in the step cycle would be more effective. FES during walking might change corticospinal and spinal excitability more effectively than repetitive nerve stimulation at rest or than walking alone.

Our initial purpose was to investigate the short-term effects of walking with FES on cortical MEPs and inhibitory and excitatory spinal reflexes in healthy subjects. Stimulation was applied to the CP nerve during the swing phase of the step cycle when the ankle flexors are active (i.e., at functionally relevant times, and thus referred to as functional electrical stimulation), using the WalkAide2 foot drop stimulator [23].

In the first experiments, the MEP in the TA was measured using TMS, before, between, and after periods of walking with or without FES, to examine the extent of change in corticospinal excitability. In the second experiments, reciprocal and presynaptic inhibition, and H-reflexes were measured before and after walking with FES. As controls, the effects of FES-like stimulation at rest and of walking without stimulation were tested in separate sessions. Details of these studies have been reported elsewhere [24],[25]. After 30 min of walking with FES, the amplitude of the half-maximum peak-to-peak MEP (MEP_h) in the TA increased. This facilitatory effect lasted for at least 30 min. In contrast, walking without FES had no effects on the MEP_h. The increase in the MEP_h with FES (approximately 40%) was similar to that with repetitive CP nerve stimulation at rest [17].

An increase of corticospinal excitability could be due to changes in spinal and/or cortical excitability. Thus, we examined the short-term effects of FES on excitatory and inhibitory spinal pathways. After 30 min of walking with or without FES, or FES-like repetitive CP nerve stimulation at rest, the TA H-reflex amplitude did not increase, implying that FES did not increase spinal excitability for the TA. The soleus H-reflex decreased slightly (10%) after FES-assisted walking, and remained decreased for at least 30 min. However, the control experiment indicated that this decrease was associated with walking and not with stimulation. After 30 min of FES, there were no significant changes in the inhibitory responses examined in the present study. In summary, the soleus H-reflex showed a small but consistent decrease and no spinal circuits examined showed an increase similar to that observed in the corticospinal excitability [24].

Short-term FES studies in healthy subjects suggest that a single session of FES increases the excitability of the cortex or its connections to the spinal cord more effectively than that of spinal pathways. Similarly, in hemiplegic individuals short-term application of FES or FES-like nerve stimulation has induced an increase of corticospinal excitability for the TA (Stein and Thompson, unpublished data).

B. Long-term effects of FES

The long-term effects of FES on excitatory spinal reflexes have been reported [14],[26]. There has also been some evidence of long-term effects on corticospinal excitability of the TA [27]. Here we introduce some case studies. A 50-year-old male with incomplete SCI at T12-L1 11 years before the study participated in the on-going FES study at the Stein laboratory. By the time of this study he had regained locomotor function, but disturbing foot drop during walking still remained. For several reasons, he chose to use an FES device for therapeutic stimulation; FES-like CP nerve stimulation was used every evening at home for 1 hour at rest. After therapeutic stimulation he often walked around the house with the FES device on. After 1 month of stimulation, he reported his locomotion was clearly improved in balance and effort, and the TA MEP amplitude was increased. However, his TA maximum voluntary contraction (MVC) was also improved, and probably contributed to the MEP increase.

Another participant was a 43-year-old male with incomplete quadriplegia as a result of head injury 19 years before his participation in the study. After the first 6 months of paralysis, he showed gradual motor functional recovery over a few years, and he had lived independently for the last few years. At the first assessment for the FES trial, he could walk with crutches but very slowly, and obvious left toe drag during the swing phase seemed to slow down his walking even more. Over the 7 months of FES trial his walking speed was significantly improved (from 5.6m/min to 8.2m/min with FES). Locomotor improvement was also reflected in a 2.5-3 times increase in the TA MEP amplitude after long-term use of FES [27].

Currently available data indicate that FES/patterned nerve stimulation can produce positive effects on corticospinal excitability. Over a short period of time, changes in corticospinal responses appear to become much stronger and more consistent than those in spinal reflexes. Thus, any (significant or non-significant) changes in spinal reflexes following FES/patterned stimulation may be secondary or compensatory to changes in cortical or corticospinal excitability/connectivity. However, the effects of a persistent, voluntary effort to modify the spinal reflex pathways remain uncertain.

III. Operant Conditioning of the Soleus H-reflex

The last two decades of studies on spinal reflex operant conditioning in animal models have shown that reflex conditioning leads to complex plastic changes in spinal cord neurons and that the corticospinal tract is essential for these changes to occur [11],[12],[28],[29]. Thus, reflex conditioning might be a robust approach to inducing and guiding plasticity at spinal and supraspinal connections [30]-[32]. As an essential step in establishing reflex operant conditioning and characterizing its effects in the human adult nervous system, we are currently investigating the extent and time course of operant conditioning of the soleus H-reflex in healthy subjects.

A. Methods

The protocol consists of 6 baseline, 24-30 conditioning, and 4 follow-up sessions. Sessions, which are always at the same time of day, normally occur 3 times/week for baseline and conditioning and then every 2-8 weeks for follow-up. The soleus H-reflex is measured during standing, and each session has 3 blocks of 75 trials. Subjects maintain a pre-defined level of soleus background EMG for at least 2 s prior to stimulation. The minimum interval between stimuli is 5 s. During baseline, the subject becomes familiar with the daily protocol and the number of reflexes elicited, without paying attention to the size of reflex. After completion of baseline sessions, the subject is randomly assigned to the up-conditioning (HRup) or down-conditioning (HRdown) group. During conditioning sessions the subject receives visual feedback after each trial indicating whether the H-reflex was larger (HRup) or smaller (HRdown) than a pre-set criterion value. Based on the performance, the subject may earn an additional monetary reward. Follow-up sessions are the same as conditioning sessions.

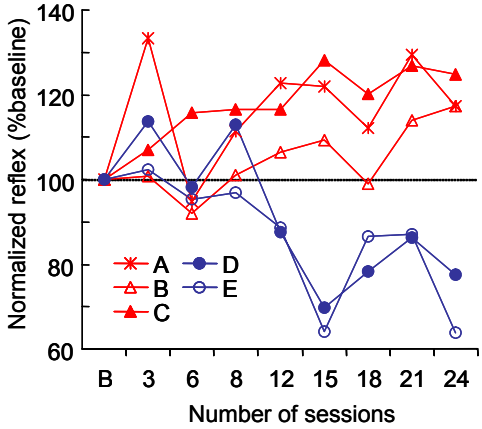

Fig. 1. The time course of the reflex size change. The mean reflex amplitude for each session was normalized by the baseline value, which was calculated from 6 baseline sessions. Different symbols represent different subjects. HRup: subjects A, B, and C. HRdown: subject D and E. Each point represents the average of three conditioning sessions, except for the baseline (B).

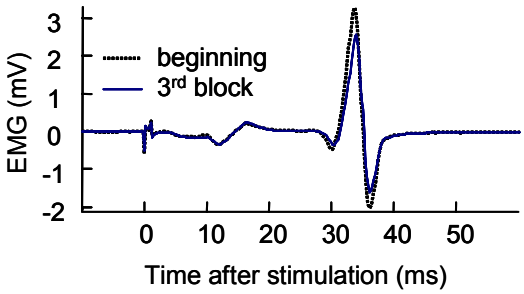

Fig. 2. The within-session training effect seen in the 23rd conditioning session in subject D (HRdown). The dotted line is the average of 20 responses recorded in the beginning of session when the subject was not trying to control the reflex. The solid line is the average of 75 responses (3rd block of conditioning trials). The peak-to-peak reflex amplitude was reduced by 22%. The background EMG level and M-wave amplitude were essentially the same for the two recordings.

B. Results and discussion

In results to date, all subjects (n=5, 3 HRup and 2 HRdown) have changed H-reflex size in the correct direction (Fig. 1). Final change varied from 16% to 36%. Over the first few conditioning sessions, both HRup and HRdown subjects seemed to develop a strategy to control reflex size. This was evident as a within-session training effect. A typical example of within-session change in the reflex is shown in Fig. 2. Development of this strategy preceded the occurrence of persistent H-reflex size change across sessions. After using a developed reflex control strategy for a certain number of conditioning sessions, the reflex seemed to be changed down or up by about 20 % in HRup and HRdown subjects, respectively. Figure 3 shows averaged reflex responses during the baseline session and the 20th conditioning session in an HRup subject (A). In addition to the change in reflex amplitude after successful conditioning, some other changes (i.e., in latency or duration) may possibly occur. Further data are needed to delineate such changes.

These preliminary data indicate that H-reflex conditioning is possible in humans. At the same time, the substantial inter-subject variation in the time course and extent of

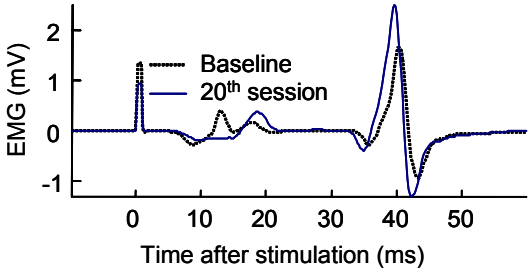

Fig. 3. Effects of HRup conditioning on the size of H-reflex in subject A. The dotted line is the average of 75 responses recorded in the 5th baseline session. The solid line is the average of 75 responses in the 20th conditioning session. The increase in the reflex amplitude was maximum in the 20th session, more than 40% increase from the baseline. The M-wave and background EMG amplitudes were essentially the same between sessions.

conditioning indicate that additional data are needed to delineate its principal features and potential magnitude.

IV. Modulation of Spinal Pathways and Corticospinal Connections

FES, therapeutic, or patterned electrical stimulation can induce plasticity in cortical and/or corticospinal connections significantly [18],[24], and over a long period of time may exert effects at multiple levels of the CNS [9],[10],[14],[27]. Operant conditioning of a spinal reflex, a simple form of learning, also induces plasticity at multiple sites of the CNS. Initial animal studies suggest that reflex operant conditioning could become a new therapeutic technique for restoring more effective motor function after CNS injuries [13]. Future studies will explore in greater detail the effects of reflex conditioning on the excitability of cortical and corticospinal connections, as well as that of other inhibitory and excitatory spinal pathways.

Regaining lost function involves modification of spinal pathways and corticospinal connections. Two very different kinds of nerve stimulation protocols can induce neural plasticity. Studying modulation and modification of the CNS by different methods will help us explore plasticity of the human adult nervous system, and thereby, develop strategies for maximizing functional recovery after CNS lesions.

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