Medical Hypotheses 81 (2013) 784–788

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Neuromuscular electrical stimulation for stroke rehabilitation: Is spinal plasticity a possible mechanism associated with diminished spasticity?

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ARTICLE INFO

Article history:
Received 13 April 2013
Accepted 13 August 2013

ABSTRACT

Although the specific pathophysiological mechanisms underlying the development of spasticity are not fully understood, a large amount of evidence suggests that abnormalities in spinal pathways regulating the stretch reflex may contribute to the hypertonia and hyperreflexia that characterize spasticity. It is quite interesting that neuromuscular electrical stimulation (NMES) has been reported as an efficient treatment for reducing spasticity after stroke while other reports have shown that it promotes neuroplasticity in healthy subjects. The hypothesis addressed in this paper is that plastic effects within some spinal cord pathways may be a possible mechanism associated with the NMES-induced improvements in spasticity. If the hypothesis is proven corrected, the association between plasticity within specific spinal pathways and NMES-induced improvements in spasticity may be used to guide the choice of stimulation parameters to be used in NMES-based stroke rehabilitation protocols.

Introduction

Stroke is the leading cause of long-term adult disability and spasticity is one of the sensorimotor impairments that are often observed in the paretic limbs of patients after stroke [1]. Spasticity may be defined as a motor disorder characterized by a velocity and acceleration-dependent increased resistance to passive muscle stretch and hyperactivity of stretch reflexes [2,3].

Although the exact pathophysiological mechanisms underlying spasticity remain unknown, it is highly likely that it is not caused by a single mechanism, but rather by an intricate chain of alterations in different interdependent networks [4], which may include: (1) spinal mechanism concerning abnormalities in the functioning of the spinal neurons and spinal subsystems; (2) supraspinal and suprasegmental mechanisms; and (3) abnormality in mechanical properties of muscles. Specifically to the interest of this paper, many studies have associated the exaggerated stretch reflex with altered transmission in a variety of spinal cord pathways [5–21]; thereby suggesting that a malfunction in some spinal pathways responsible for controlling the excitability of the stretch reflex might be partially responsible for (or at least correlated with) spasticity [5,11].

Neuromuscular electrical stimulation (NMES) has been shown to be effective in improving function of subjects with central nervous system (CNS) lesions, such as in patients after stroke [22]. Such a stimulation modality may improve neuromuscular functional condition not only by strengthening muscles, decreasing pain and increasing range of motion, but also by reducing spasticity [22–27]. Although some studies have pointed to central neuroplasticity as a potential mechanism of action for the therapeutic effect of electrical stimulation in CNS lesions [24,28–31], most of the experimental researches have focused on supraspinal mechanisms associated with superior brain areas, probably by taking advantage of measurement techniques that allow the evaluation of brain function with a reasonable resolution (e.g., functional magnetic resonance imaging and transcranial magnetic stimulation). However, no direct experimentation has been conducted in order to explore whether neuroplastic effects within specific spinal cord pathways might be associated with NEMS-induced diminished spasticity in patients after stroke (which is likely due to the more challenging task of obtaining objective measures associated with spinal mechanisms).

Given the correlation that has been found between spasticity and altered excitability in some spinal pathways (as commented earlier), the hypothesis addressed in this paper is that plastic effects within specific spinal cord circuitries may be among the possible mechanisms behind the reduced spasticity that has been achieved by NMES-based treatments. The text ahead explores in detail each point involved in the formulation of the hypothesis. Additionally, directions for future research and possible clinical implications are discussed.

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http://dx.doi.org/10.1016/j.mehy.2013.08.013

The association between the excitability of spinal pathways and spasticity

As commented in the Introduction section, it seems highly likely that more than one pathophysiological abnormality contributes to development of spasticity [4], including mechanisms associated with spinal and/or supraspinal dysfunctions as well as changes in the mechanical properties of muscles. In this line of reasoning, the excitability of the stretch reflex is regulated by many spinal cord pathways, and hence a dysfunction in any of these pathways may theoretically be associated with the stretch reflex exaggeration observed in spasticity following stroke [32].

From a methodological standpoint, the excitability of the stretch reflex pathway (or parts of it) can be assessed by means of either electrical stimulation of peripheral nerves (e.g., H-reflexes) or mechanical stimulation of the tendons (T-reflexes) [33]. Specifically, the technique of H-reflex has been widely used to assess the excitability of the stretch reflex pathway and to infer the current state of spinal cord mechanisms associated with different conditions of healthy and disease [33–36]. Besides the primary excitability of the motoneurons due to their membrane properties and the obvious influences from supraspinal centers, there are pre- and post-synaptic influences that affect H-reflex amplitude from a variety of sources [33]. For instance, presynaptic inhibition of Ia afferent terminals, homosynaptic depression (or post-activation depression), disynaptic reciprocal inhibition from Ia afferents of the antagonist muscles, recurrent inhibition via Renshaw cells and short-latency autogenic inhibition (associated with Ib afferents from Golgi tendon organs) are perhaps the most important mechanisms of reflex modulation [33–36]. Fig. 1 illustrates some of these spinal reflex circuits responsible for the stretch reflex modulation that may also be involved in the mechanisms underlying the development of spasticity (see text below for further discussion on this point).

By means of these mechanisms, the CNS can regulate the excitability of the stretch reflex pathway in different conditions. In an attempt to better describe the mechanisms responsible for reflex modulation, protocols based on conditioning stimulation have been developed. For example, it is possible to evaluate the level of presynaptic inhibition or disynaptic reciprocal inhibition under different conditions by means of H-reflex assessments [37,38]. One of the techniques consists in applying a conditioning electrical stimulus (1 ms rectangular pulse) to the nerve of the antagonist muscle and a test stimulus to the nerve of the agonist muscle with a conditioning-to-test interval of appropriate latency, depending on the muscle groups and on the specific spinal mechanism under assessment [35,39]. Due to the inhibitory effect associated with the presynaptic or reciprocal inhibition mechanism, the reflex response conditioned by the antagonist nerve stimulation will have a lower amplitude as compared to the reflex elicited without conditioning. This procedure has been widely used in many research laboratories to investigate changes in the degree of excitability of different spinal pathways among different conditions [33]. Another example of a presynaptic mechanism that affects H-reflex amplitude is post-activation depression (or homosynaptic depression), which consists in a frequency-dependent reduction of reflex amplitude. For instance, when the stimulation is applied with frequencies higher than 0.1 Hz, a depression in H-reflex amplitude is observed, supposedly because repetitive activation would lead to a reduced release of neurotransmitter in the Ia terminals [40,41]. Consequently, assessing the amount of reduction in the H-reflex amplitude after repetitive activation (i.e., at frequencies higher than 0.1 Hz) as compared to a control condition (i.e., H-reflex elicited by a single stimulus) has been used as a means to evaluate the amount of homosynaptic depression during different conditions.

Therefore, thanks to the development of the electrophysiological techniques briefly exemplified above (such as the assessment of H-reflex through a paired-pulse stimulation paradigm, also known as conditioning-test pulse paradigm [33]), several studies could selectively explore the transmission within a variety of human spinal cord pathways so as investigate the possible role of different spinal mechanisms in the pathophysiology of spasticity [5–21]. Although some contradictory results have been reported in the literature [11,42], transmission throughout these spinal reflex circuitries has been found to be modified in spastic patients. For instance, reduced in short-latency autogenic inhibition (Ib inhibition) [12], decreased recurrent inhibition from Renshaw cells [13,14], abnormalities in disynaptic reciprocal Ia inhibition [6–8,15,20], reduced presynaptic inhibition of Ia terminals [5,11,16,21] and decreased post-activation depression [5,11,17–19,43] have been found to be associated with spasticity. Therefore, although the specific pathophysiological mechanisms underlying the development of spasticity are not fully understood, a large amount of evidence suggests that abnormalities in spinal pathways regulating the stretch reflex may contribute to the hypertonia and hyperreflexia that characterize spasticity.

NEMS and neuroplasticity

NMES is a rehabilitation treatment and exercise training modality that consists in delivering electrical pulses through the skin to repeatedly activate muscles [44]. A growing body of evidence suggests that neuroplastic mechanisms may be activated in response to different modalities of electrical stimulation such as NEMS [22,45]. For instance, substantial increases have been described in the myoelectrical activity of various muscles after 4–5 weeks of training by NEMS, a time not sufficient to induce muscle hypertrophy [46,47]. This has led to the suggestion that certain types of NMES may induce adaptations within the neural systems [48], a hypothesis strengthened by the observation that short NMES training programs may cause changes in the motor activity of the non-exercised contralateral limb [49].

In a rehabilitation context, the postulated mechanism underlying the therapeutic effect of electrical stimulation in CNS lesions is through neuroplasticity of the CNS [22]. The premise is that pre-existing functional and non-utilized neuronal connections are activated and/or their inhibition is suspended [28,50]. In this regard, it has been demonstrated that the regular use of a foot-drop stimulator not only increases walking speed in people with CNS disorders but also strengthens activation of motor cortical areas and their residual descending connections, even when the stimulator is off [31]. A treatment of NMES in subjects after stroke showed improvement in the functional use of the hand and changes in cortical activation as measured by functional magnetic resonance imaging [29]. In other study, Shin and colleagues demonstrated that a 10 week use of an electromyography-triggered neuromuscular stimulation led to functional recovery while also changing cortical activation patterns associated with the hemiparetic hand of chronic stroke patients [30]. Similarly, it has also been shown that cutaneous stimulation improves motor performance and limb sensation with concurrent changes in somatosensory evoked potentials of the paretic limb in chronic stroke patients [24].

However, although the effects of NMES in promoting neuroplasticity in superior brain areas have been well established [28], less attention has been given to possible neuroplastic mechanisms within specific spinal cord pathways, such as those responsible for controlling the excitability of the stretch reflex. This is probably linked to the easy of obtaining high-resolution measures associated with brain function by using the various techniques that are currently available to either map regional blood flow and