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Contribution of Corticospinal Modulation and Total Electrical Energy for Peripheral-Nerve-Stimulation-Induced Neuroplasticity as Indexed by Additional Muscular Force

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ABSTRACT

Background: Protocols to induce motor related neuroplasticity are usually directed to central neural structures such as the motor cortex or the spinal cord.
Objective: Herein, we aimed to evaluate the effects of peripheral nerve stimulation using a current intensity (stimulation intensity) approach to understand the contribution of the corticospinal system and total energy to electrically-induced neuroplasticity.
Methods: Electrical stimulation trains of lower intensity, interlaced with 2-s bursts of higher intensity, were applied to anesthetized rabbits. Nerve blocks were applied to the proximal side of the stimulation site with identical stimulation trains in a different session to block the contribution of corticospinal volleys during intensity-modulated electrical stimulation.
Results: Additional force corresponding to additional recruitment of motoneurons was observed when a 2-s burst of high intensity was present (burst/constant: 24.7 ± 3.6%/2.09 ± 4.8%; $p < .001$). Additional force was absent in sessions when the neural pathway to the spinal cord was blocked (unblocked/blocked: 29.3 ± 3.8%/–2.49 ± 4.8%; $p < .001$).
Conclusions: The results suggest that induced neuroplasticity indexed by the additional force is dependent on the total energy applied and connectivity to central structures. These results give additional evidence for the contribution of two factors for induced neuroplasticity: (i) modulation by corticospinal structures and (ii) total energy of stimulation. Further protocols should explore simultaneous peripheral and central stimulation.

Introduction

The rationale underlying the application of electrical stimulation is to improve muscle strength [1,2], delay muscle atrophy [2,3] and induce neuroplasticity to eventually compensate the loss of voluntary and reflexive control. There are different targets used to induce neuroplasticity of the motor system. One of the targets is the peripheral nerve. Hence, the effectiveness of inducing neuroplasticity with peripheral nerve stimulation has been investigated in several studies [4–6].

Various forms of peripheral nerve stimulation have been tested as possible solutions, which, theoretically, should replicate the intrinsic mechanism of a neuromuscular system [7,8]. Nonetheless, limitations exist since externally provided electrical pulses cannot precisely recruit motor units in the normal physiological order [9,10]. Accordingly, studies have focused on methods and procedures to increase spinal circuitry involvement [11,12] with the intention that voluntary contractions will be accurately replicated and motor units may be recruited in the normal physiological order. Frequency modulation approaches for the electrical stimulation were thereby adopted in several non-invasive studies by including a 2-s burst of higher-frequency pulses set in between conventional lower-frequency stimulation pulses in attempt to increase corticospinal contribution [13–18].

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Typically, lower-frequency pulses induce low levels of force while higher-frequency pulses induce high levels of force. However, in some of the studies that adopted the frequency modulation approach [13–15,17,18], higher levels of force than expected were measured despite return to a lower frequency after a temporary burst of higher-frequency pulses (i.e., by comparing the force difference before and after the 2-s burst of higher-frequency pulses). These results thus suggest that this was a sign of corticospinal contribution via the stimulation of afferent pathways since the increased level of force was eliminated when the afferent pathways were blocked in those studies.

To better understand the contribution of two factors that induced neuroplasticity as indexed by additional force, we designed a study to assess: (i) whether the additional energy (or electrical charges) applied during the higher-frequency burst is one of the key factors, thus a higher-intensity burst (as opposed to a higher-frequency burst), specifically designed to inject greater energy without modulating the stimulation frequency, was tested; (ii) whether there is a contribution of the corticospinal system as we tested this protocol in two situations – before nerve blocks and after nerve blocks (to block corticospinal contribution). One of the reasons for utilizing an intensity modulation approach is that higher-frequency stimulation pulses tend to generate fatigue more rapidly [19–22], which poses a major limitation in the development of clinical applications. We wanted to observe whether similar additional forces can be generated reflexively via the afferent pathway by an intensity modulation approach and whether the higher-intensity stimulation burst helped in reducing neuromuscular fatigue. Our goal is to initiate mechanisms that both imitate voluntary contractions and induce desired neuroplasticity, as observed in other non-invasive applications [4,23,24].

Methods

Animal subjects

Ten male New Zealand White rabbits (12–24 months old, weighing 3.2–4.0 kg) were anesthetized with isoflurane (Aerrane, Baxter, Deerfield, IL) at regulated concentrations during the experiments. One of the rabbits underwent more invasive experiment (percutaneous stimulation of the spinal roots with customized cuff electrodes) and was eventually sacrificed for ATPase staining. Preanesthetic agents were not used prior to gas anesthesia to avoid any possible adverse effects of such agents on muscle contraction. The rabbit was selected as the experimental subject because the architecture of its quadriceps muscle is similar to those of humans [25]. In addition, the potential to perform non-invasive in vivo experiments on the rabbit under gaseous anesthesia provided the opportunity to acquire results while excluding unintentional voluntary forces during nociceptive high-intensity stimulations. The animal experiments in this study were conducted in accordance with Institution Guidelines and were approved under the Affidavit of Approval of Animal Use Protocol issued by the Institutional Animal Care and Use Committee.

Experimental setup

The rabbits' knees (flexed at 90° to avoid any antigravity contraction) and hips were restrained to a custom-made base with Velcro straps to prevent knee flexion, hip abduction, and lateral rotation as illustrated in Fig. 1. Force data were acquired using a force transducer (RX-10, AIKOH Engineering, Osaka, Japan) through a sensing shaft that was strapped firmly to the rabbits' shanks. Force readings were recorded with a data-acquisition device (USB-6211, National Instruments, Austin, TX) using LabVIEW (National Instruments).

Electrical stimulation was applied to the skin surface (shaved before each session), immediately over the femoral nerve (1.5 × 1.5-cm self-adhesive electrode), and the quadriceps (3.8 × 5.1-cm self-adhesive electrode) of the left hind limb. The sciatic nerve (corresponding to the antagonist) was avoided to the greatest extent possible. We were unable to rule out the synergistic efforts of the sartorius since we avoided all surgical procedures that may cause inflammations during the course of the experiments. However, we believe that very little extensor force was caused by the sartorius since this small muscle extends concurrently with an adducted and rotated thigh [26], which was restrained from movement once the rabbit was strapped in the upright seated position on the custom-made base. The precise stimulation point was marked with a tattoo to ensure precise placement each time of the self-adhesive electrode on the femoral nerve for pre- and post-nerve-block stimulation

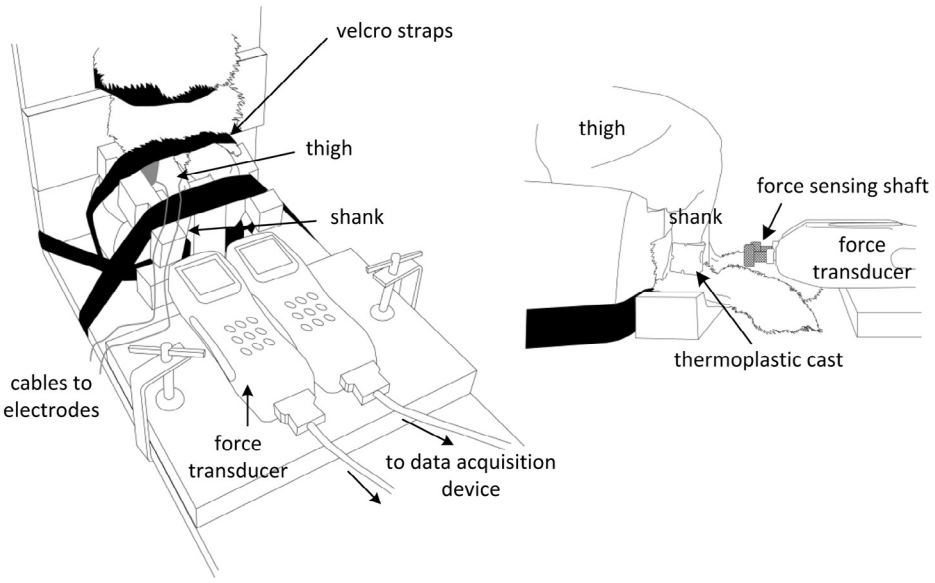

Figure 1. Experimental setup showing the thighs, shanks, force transducers, and cables.