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Neuromuscular electrical stimulation of the median nerve facilitates low motor cortex excitability in patients with spinocerebellar ataxia

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ABSTRACT

The neuromodulation of motor excitability has been shown to improve functional movement in people with central nervous system damage. This study aimed to investigate the mechanism of peripheral neuromuscular electrical stimulation (NMES) in motor excitability and its effects in people with spinocerebellar ataxia (SCA). This single-blind case-control study was conducted on young control ($n = 9$), age-matched control ($n = 9$), and SCA participants ($n = 9$; 7 SCAIII and 2 sporadic). All participants received an accumulated 30 min of NMES (25 Hz, 800 ms on/800 ms off) of the median nerve. The central motor excitability, measured by motor evoked potential (MEP) and silent period, and the peripheral motor excitability, measured by the H-reflex and M-wave, were recorded in flexor carpi radialis (FCR) muscle before, during, and after the NMES was applied. The results showed that NMES significantly enhanced the MEP in all 3 groups. The silent period, H-reflex and maximum M-wave were not changed by NMES. We conclude that NMES enhances low motor excitability in patients with SCA and that the mechanism of the neuromodulation was supra-segmental. These findings are potentially relevant to the utilization of NMES for preparation of motor excitability. The protocol was registered at Clinicaltrials.gov (NCT02103075).

1. Introduction

Spinocerebellar ataxia (SCA) is one of several hereditary neurodegenerative disorders characterized by progressive loss of coordination of gait and poor coordination of speech or eye movements (Ishida et al., 2011; Jayadev and Bird, 2013; Liepert et al., 2000a, 2004; Rossi et al., 2014). To date, no existing treatment can cure this disease. SCA is always observed in atrophy of the cerebellum, and the ataxia arises from damage to the different cerebellar regions (Chen et al., 2004; Ishida et al., 2011; Jayadev and Bird, 2013; Rossi et al., 2014; Soong, 2002, 2004). The primary neurophysiological function of the cerebellum is to maintain the excitability of the motor cortex and its subsequent descending tract for movement control (Di Lazzaro et al., 2002; Klein et al., 2012; Liepert et al., 1998; Meyer et al., 1994; Wessel et al., 1996). Current evidence shows that the cortical facilitation of motor excitability, measured by the size of the motor evoked potential (MEP) in a reaction-time task, is significantly less in SCA patients compared to healthy controls (Liepert et al., 2000b, 1998; Tamburin et al., 2004). An extension of the silent period (SP), thought to reflect the suppression of central excitability, was also demonstrated in some SCA patients (Ganos et al., 2014; Teo et al., 2008; Wessel et al., 1996). These findings suggest that either elevation of the low excitability baseline or restoration of the declined cortical facilitation could benefit the preparation of intentional movement in this disorder.

Adequate central motor excitability is important for movement preparation. Studies showed that, during a reaction-time task in healthy humans, central motor excitability increased progressively as the onset of the movement approached (Klein et al., 2012; Power and Copithorne, 2013). For movement preparation, the low motor excitability in SCA was compensated via an early onset

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with prolonged activation in the motor cortex. This indicates that, in SCA patients, a large proportion of intra-cortical neurons continually struggle to activate movement against the difficulties of initiation and control. Hence, the baseline elevation of central motor excitability, such as movement preparation via neuromodulation, was proposed to help SCA patients with low excitability (Liepert et al., 2000b).

To date, there is no rehabilitation strategy that demonstrably improves central motor excitability in ataxia patients. Neuromuscular electrical stimulation (NMES), a type of non-invasive peripheral electrical stimulation, has been extensively used clinically for health promotion, including incremental gains in muscle strength (Sabut et al., 2010, 2011) and improvement of functional movements in central neurological disorders (Do et al., 2012; Makowski et al., 2012; Westerveld et al., 2012). NMES possesses the feature of easy control of the amplitude of evoked muscle contraction and the sequential induction of movement. Recent studies have reported that NMES could co-modulate the excitability of both primary motor and sensory cortexes in healthy humans (Schabrun et al., 2012). The temporary neuroplasticity induced by NMES for functional reorganization has been observed to occur via motor afferents (Chang et al., 2011). In patients with stroke, the elevation of motor excitability induced by NMES significantly benefit limb function during rehabilitative motor training (Takahashi et al., 2012). These evidences supported the use of NMES on SCA patients since that SCA patients with progressively impaired motor function but preserved sensory function potentially be able to experience improved cortical excitability using NMES before motor performance.

The effects of NMES on central motor excitability are dependent on its electrical characteristics. In previous studies, an increase in MEP in healthy humans was produced by NMES with low pulse frequency (10–25 Hz) and high intensity (up to and above the motor threshold) (Chang et al., 2011; Chipchase et al., 2011; Khaslavskaia et al., 2002; Knash et al., 2003; Ridding et al., 2000). The largest increases in MEP were obtained by treatment durations of up to 30 min (Chang et al., 2011; Chipchase et al., 2011; Khaslavskaia et al., 2002; Knash et al., 2003; Ridding et al., 2000). In contrast, a decline in MEP for a short period in healthy humans was observed at low intensity (below the motor threshold) and high frequency (200 Hz) (Chipchase et al., 2011). Therefore, we proposed that delivery of NMES with low pulse frequency and above motor threshold intensity might promote the low cortical excitability in the patients with SCA.

In summary, this is the first study to explore the central motor excitability modulated by peripheral NMES in patients with SCA. The purpose of this study was to investigate if patients with SCA can regain their central motor excitability by the neuromodulating effect of NMES to the similar extent of healthy non-SCA subjects, and to differentiate whether the motor excitability was coming from the central or peripheral portion of the descending motor pathway. Since SCA is a neurodegenerative disease and the motor symptoms progress with aging, the neuromodulating effect of NMES might be influenced by age. Therefore, the second purpose was to investigate the effects of age on NMES-induced central motor excitability. We hypothesized that a 30-min NMES program would elevate central motor excitability in SCA patients and that the elevation would be similar in younger and age-matched non-SCA subjects.

2. Methods

2.1. Study participants

This study had a single-blind case-control design. Nine people with SCA (5 males and 4 females; mean ± SD age 43.7 ± 7.8 years; 7 SCAIII and 2 sporadic SCA), nine age-matched controls (3 males and 6 females; mean ± SD age 41.3 ± 4.2), and nine young controls (4 males and 5 females; mean ± SD age 24.3 ± 2.3) were recruited from the community. All participants with SCA had been diagnosed by neurologists and showed observable signs including dysmetria, intention tremor, and gait ataxia. All participants had: (a) no history of epilepsy; (b) no other neuromuscular disorder; (c) no fracture within the last 6 months; (d) restricted movement in the upper extremities; and (e) limited trembling of the hand, allowing for the recording of electromyography (EMG). The study protocol was approved by the Institutional Review Board in accordance with the Helsinki Declaration. The protocol was registered at Clinicaltrials.gov (NCT02103075).

2.2. Assessment of central motor excitability

For the assessments, the qualified participants were seated comfortably on a chair with standard back support. No previous studies have reported an influence of hand dominance, so it was assumed that either arm would be acceptable for data collection. However, to avoid the potential influence, the tested upper limb was randomly selected. The upper limb was strapped to a custom-designed hand force plate transducer to determine the maximum voluntary contraction (MVC) of elbow flexion.

Transcranial magnetic stimulation (TMS; Magstim 200, Magstim Company Ltd, UK) was then used to assess central motor excitability. The resting motor threshold (RMT) of the flexor carpi radialis (FCR) was quantified as the minimum intensity of TMS required to evoke the MEP above 50 μV in amplitude in 6 out of 10 stimulations (ICC = 0.97, intra-rater reliability in pilot study). Fifteen MEPs with 10-s intervals were evoked by TMS set to 120% of the RMT. For statistical analysis, the 10 middle MEPs were used after the other 5, the largest 2 and the smallest 3, were discarded. The SP was induced using TMS at 100% of the RMT while the participant held a constant FCR contraction at 10% of the MVC. The SP was defined by measuring the onset time, defined as the beginning of EMG suppression, to the offset time, defined as the earliest re-emergence of background EMG (Garvey et al., 2001; Vry et al., 2008). The onset/offset of the SP was defined as the mean plus 2 times the SD of the flat portion. The SP was measured 5 times, and all 5 recordings were used for statistical analysis.

2.3. Assessment of peripheral motor excitability

Electrical stimulation (Stimulator model DS7A, Digitimer Ltd., England) was applied to the elbow portion of the median nerve for peripheral motor excitability assessment (Lin et al., 2012). For M-waves, the stimulation frequency was 1 Hz, and the intensity was considered supra-maximal at 120% of the intensity required for eliciting maximum M-waves. For H-reflex recording, the stimulating frequency was 0.1 Hz, and the intensity was adjusted to obtain the maximum H-reflex. The detailed protocol has been reported previously (Chang et al., 2011). The MEP, M-waves, and H-reflex were recorded by surface EMG electrodes. The surface electromyography (EMG) of the FCR was recorded by a bipolar surface electrode with a fixed interelectrode distance of 2 cm (B&L Engineering, Canada). The recording electrode was located on the muscle belly of FCR, with the direction parallel to the muscle fiber. A reference electrode was placed on the styloid process (Chang et al., 2011; Wassermann et al., 1992). The EMG activity was on-site pre-amplified by a factor of 350 and was further amplified at the mainframe amplifier (Gould, Inc., Valley View, OH, USA) with an input impedance greater than 10 MΩ, a CMRR equal to 100 dB at 60 Hz, and a gain range from 0.5 to 100,000 times. The signal