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Modulation of temporal summation threshold of the nociceptive withdrawal reflex by transcutaneous spinal direct current stimulation in humans

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HIGHLIGHTS

- Transcutaneous spinal direct currents (tsDCS) modulate the temporal processing of the nociceptive stimuli at spinal level.
- tsDCS could inhibit the transitory frequency-dependent facilitation of the spinal wide dynamic range neurons activity at the basis of temporal summation of pain.
- As future perspective, modulation of temporal processing of nociceptive stimuli by tsDCS could be helpful in pain treatment as well as in preventing pain becoming chronic.

ABSTRACT

Objective: Transcutaneous spinal direct current stimulation (tsDCS) modulates spinal cord pain pathways. The study is aimed to clarify the neurophysiology of the tsDCS-induced modulation of the spinal cord pain processing by evaluating the effect of the tsDCS on temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR).
Methods: In a randomized, double-blind, crossover study the effects of anodal, cathodal and sham tsDCS (2 mA, 15 min) applied on the skin overlying the thoracic spinal cord were investigated in 10 healthy subjects.
Results: Anodal tsDCS induced a long-lasting (up to 60 min) increase in TST of the NWR as well as a parallel decrease in related psychophysical temporal summation of pain, while cathodal and sham tsDCS resulted ineffective.
Conclusions: Anodal tsDCS represents a non-invasive tool able to induce an early and long-lasting depression of the transitory facilitation of the wide dynamic range neurons activity at the basis of both the temporal summation of the NWR and the related temporal summation of pain sensation.
Significance: The modulation of the temporal processing of nociceptive stimuli could be effective in treating clinical pain conditions in which pain is generated by spinal cord structures.

1. Introduction

Transcutaneous direct current stimulation (tDCS) represents a noninvasive, safe, inexpensive method devoted to a long-lasting modulation of the neuronal excitability depending on the current polarity, duration or strength (Priori, 2003).

Applied on the scalp as transcranial direct current stimulation (tcDCS), tcDCS increases or reduces cortical excitability after anodal or cathodal stimulation, respectively (Nitsche and Paulus, 2000), possibly by inducing depolarization or hyperpolarization of the neuronal membrane resting potential (Nitsche and Paulus, 2001; Lang et al., 2005). Depending on duration and strength of the stimulation, tcDCS-induced after effect lasts up to 1 h and

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could be related to a N-methyl-D-aspartate (NMDA) receptors activity modulation (Liebetanz et al., 2002; Nitsche et al., 2003a) as well as to a non-synaptic mechanisms based on changes in neural membrane function (Ardolino et al., 2005). On the basis of these studies, tcDCS has been diffusely tested on the scalp as alternative option to pharmacological and surgical treatment in several neurological diseases, including depression, stroke and central pain, however with conflicting results (Brunoni et al., 2012; Elsner et al., 2013; O'Connell et al., 2014).

Based on the effectiveness of the invasive epidural electrical spinal cord stimulation (SCS) on pain syndromes (Mailis-Gagnon et al., 2004), it is conceivable that the spinal application of the tDCS, defined as transcutaneous spinal DCS (tsDCS), could induce a durable modulation of spinal sensory neurons. tsDCS could represent a noninvasive, safe, non-pharmacological approach to clinical pain condition in which pain is generated or carried by spinal cord structures. In animals, tsDCS modulates the gracile nucleus and somatosensory cortex activity (Aguilar et al., 2011). In humans, a series of studies demonstrated that tsDCS leads to an inhibition of somatosensory (Cogiamanian et al., 2008) and pain-related (Truini et al., 2011) cortical evoked responses after anodal thoracic stimulation, probably as consequence of a segmental modulation of the spinal cord sensory neurons below the stimulating electrode. Similarly, thoracic anodal tsDCS inhibits the nociceptive withdrawal reflex (NWR) of the lower limb (Cogiamanian et al., 2011). The neurophysiological mechanism underlying the tsDCS-induced modulation in somatosensory and pain-related responses is unclear, however has been hypothesized a modulation of the spinal wide dynamic range (WDR) neurons (Cogiamanian et al., 2011). This hypothesis is supported by previous findings of inhibition of WDR neurons activity after SCS (Wallin et al., 2003; Zhang et al., 2014) as well as by indications of involvement of the NMDA receptors in WDR neurons activity (Dickenson and Sullivan, 1987).

Central integration of nociceptive stimuli at spinal as well as at trigeminal level is pivotal in generation and development of physiological and pathological nociception in both humans and animals. In physiological nociception, mechanisms of central plasticity subserve the integration of sensory stimuli, giving rise to a temporary change in sensory neurons excitability, such as WDR neurons, shifting the sensory information from tactile to nociceptive before transmitting the nociceptive information to the higher centres of the brain that, in turn, regulate pain processing by descending brainstem pathways (Dubner and Bennett, 1983; Millan, 2002).

WDR neurons are located within the deep laminae of the spinal dorsal horn and subnucleus oralis of the spinal trigeminal nucleus (Sp5O) (Price et al., 2003) and respond to both subthreshold and threshold C-fiber stimulation in a graded manner, as function of the frequency and intensity stimulation, generating painful sensation via temporal and spatial central integration of non-painful and painful neural responses (Coste et al., 2008). In animals, in physiological condition, this temporary frequency-dependent facilitation of the WDR neurons activity after constant-intensity stimulation of C-fibers has been called "wind-up" phenomenon (Mendell and Wall, 1965). By the wind-up phenomenon characteristics, WDR neurons play a critical role in the sensory discriminative analysis of tactile and nociceptive stimuli (Mendell and Wall, 1965).

In humans, the temporal summation of pain represents the counterpart of the "wind-up" phenomenon observed in animals (Price et al., 1978) and it develops in parallel with the temporal summation of the NWR of the lower limb, represented by an progressive increase in magnitude of the NWR size after a series of constant-intensity electrical stimuli activating A-delta and C fibers (Arendt-Nielsen et al., 1994; You et al., 2003; Sandrini et al., 2005). It is considered an objective representation of temporal processing of nociceptive signals into the spinal cord (Arendt-Nielsen et al., 1994; You et al., 2003; Sandrini et al., 2005).

Interestingly, both wind-up in animals and temporal summation of the NWR in humans are inhibited by NMDA antagonists (Guirimand et al., 2000). Furthermore, a series of studies demonstrated that the evaluation of the temporal summation threshold (TST) of the NWR represents an affordable objective measure of the functional activity of the nociceptive system in humans (Serrao et al., 2004; Perrotta et al., 2010, 2011a,b, 2012, 2013).

The present study is aimed to clarify the neurophysiology of the tsDCS-induced modulation of the pain processing at spinal level by studying the effect of the thoracic anodal, cathodal and sham tsDCS on TST of the NWR in a double-blind, crossover study in healthy human subjects.

2. Materials and methods

The study was approved by the local Ethics Committee and was carried out following the guidelines for proper human research conduct in accordance with the Helsinki Declaration of 1975 as revised in 2000 and all the participants gave their written consent.

2.1. Study population

Ten (5 females; mean age 27.3 ± 5.0) healthy individuals were recruited at Headache and Pain Clinic of the Mediterranean Neurological Institute "Neuromed", Pozzilli, Isernia, Italy.

Exclusion criteria included neurological disorders or clinical history (including family history) of neurological disorders, any serious systemic or psychiatric disorder, Beck Depression Inventory (BDI) scale score higher than 9, current use of anti-depressive and anti-epileptic medications (in the previous 2 months) or analgesics (in the previous 7 days); clinical or instrumental evidence of any central or peripheral disease potentially causing sensory impairment; fibromyalgia, neuropathic pain, complex regional pain syndrome, chronic low back pain and other pain conditions, accordingly with current guidelines.

2.2. Transcutaneous spinal direct current stimulation (tsDCS)

tsDCS was delivered by a constant direct current electrical stimulator (HDCstim, Newronika s.r.l., Milan, Italy) connected to a pair of electrodes respectively placed on the thoracic spinal cord (over the spinal process of the tenth thoracic vertebra) and over the posterior of the right shoulder in the suprascapular region. Type of stimulation (anodal or cathodal) depended on the electrode polarity placed on thoracic vertebra. In sham condition electrodes were placed as for anodal stimulation, but the stimulator automatically turned off after 10 s, as admitted by the sham program of the device.

Electrodes were 1 mm thick, rectangular (7 × 5 cm), rubber membranes, enclosed in saline-soaked sponges. Conducting surface was 35 cm^2 for active and reference electrode. Electrodes were fixed inside by an elastic stripe. We delivered a 2 mA constant, direct current for 15 min in each session with a density of 0.071 mA/cm^2 and delivered a total charge of 63.9 mC/cm^2. These criteria are far below both the threshold for tissue damage and the conscious sensory threshold, apart from transient, and short-lasting tingling sensation below the electrodes at the start of the stimulation (Nitsche et al., 2003a,b; Bikson et al., 2009; Liebetanz et al., 2009).

2.3. Temporal summation of the NWR of the lower limb

The subjects were seated comfortably in a quiet room at constant temperature (23 ± 2 °C). Their lower limbs were positioned to ensure complete muscle relaxation (knee flexed at 130° and