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Neurophysiological Responses for Better Understanding the Antalgic Mechanisms of Spinal Cord Stimulation

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Abstract

Spinal cord stimulation (SCS) is a physical invasive therapy largely used to treat patients with neuropathic pain refractory to pharmacologic treatments. Its mechanisms of action are not completely understood and, so far, patients continue to be enrolled with a trial and error approach. SCS is based on the electrical stimulation of dorsal columns, which evokes a typical electrical paresthesia, similar to that experienced by any person when an electrical stimulation is applied over the skin. This electrical sensation is not physiological because it is the result of an ectopic, direct activation of nerve fibers with a by-pass of the receptor's activation. The electrical stimulation of dorsal columns induces action potentials in the lemniscal pathway, a "system" made by fibers with large diameter and high conduction velocity. As any other electrical stimulation of nerve fibers, SCS creates potentials which travel in opposite direction: cranially and caudally. Afferent, orthodromic propagation of action potentials during SCS is mandatory for any supposed antalgic mechanism occurring in brainstem or brain, while antidromic propagation is considered the basis for the antalgic, segmental effect of SCS. Studies on neurophysiological effects of SCS are rare and further investigations are warranted in order to achieve a better understanding of the antalgic effects of SCS, and consequently improve therapeutic targeting and patient selection.

Keywords: Spinal cord stimulation; Electrical stimulation; Neurophysiological mechanisms; Antalgic mechanisms

Introduction

Spinal cord stimulation (SCS) is a physical invasive therapy largely used to treat patients with neuropathic pain refractory to pharmacologic therapies. In particular, it is frequently used for the treatment of patients with failed back surgery syndrome where it shows the main effect on leg pain, with almost complete ineffectiveness on axial pain. Nevertheless, the antalgic mechanism of SCS remains largely unknown [1,2] and the enrollment of patients to treat with this therapy continues to be related to a trial and error approach which is partially overcome by the efficacy trial performed before the definitive implantation. Despite the possible molecular approach for understanding SCS mechanism, given that SCS is based on the electrical stimulation of dorsal columns, neurophysiological effects can be studied as results of that stimulation.

Electrical Stimulation of Neural Tissues

Any quiescent cell of a human organism has voltage difference between the two sides of the cell membrane. The difference is generated by the unequal distribution of ions across the membrane and is usually called resting membrane potential. It is well known that some tissues are excitable but other not. The first are characterized by the property to generate an action potential when subjected to external stimuli, such as an electrical stimulation. Neural tissues are excitable because the resting membrane potential of the nerve fibers can change during adequate electrical stimulation and create the significant depolarization needed for action potential generation. Importantly, any electrical stimulation leads to an ectopic activation of nerve fibers, because it stimulates directly the nerve fibers and not their receptor.

The main characteristic of neural tissues is the property to transmit electrical signals and the consequence of any ectopic activation is the generation of two action potentials: one travelling orthodromically and one antidromically. It is worth to underline that direction of antidromic/orthodromic potentials depends on the type of fiber: for afferent fibers the orthodromic propagation has a caudo-cranial direction, but for efferent fibers the orthodromic propagation is cranio-caudal. On the contrary, antidromic impulses travel cranio-caudally in afferent fibers and caudo-cranially in efferent ones.

Electrical Stimulation for Clinical Purposes

Electrical stimulation is used in the clinical field for both diagnosis and therapy. Independently from the clinical use, the most important limitation of electrical currents is the evocation of an unpleasant sensation, unbearable for the most part of the patients. For this reason, when performing electrical stimulation for clinical purposes, it is important to remain under the unpleasantness threshold which is usually reached when the stimulation become strong enough to significantly activate the small diameter fibers and the related spino-thalamic pathway. In fact, a basic concept of neurophysiology is that starting from zero the slow increase of the current intensity leads to paresthesias characterized by a typical unnatural (but not unpleasant) "electrical sensation". This sensation is commonly considered the result of large fiber activation and, although unusual, is generally bearable. Interestingly, if the stimulation intensity is maintained at the threshold level, the evoked paresthesia habituates and slowly disappears.

On the other hand, with further increases in stimulation intensity the paresthesia become stronger and stronger, reaching a level in which it changes into unbearable. This change in pleasantness is considered the result of a significant activation of small diameter fibers (low myelinated fibers or A-delta fibers). In other words there is a fixed recruitment order that has to keep in mind when electricity is used in the clinical field (Figure 1).

All that considered, in summary, when electrical stimulation is used for clinical purposes it generally activates almost exclusively the large diameter fibers and this activation undergoes a spontaneous

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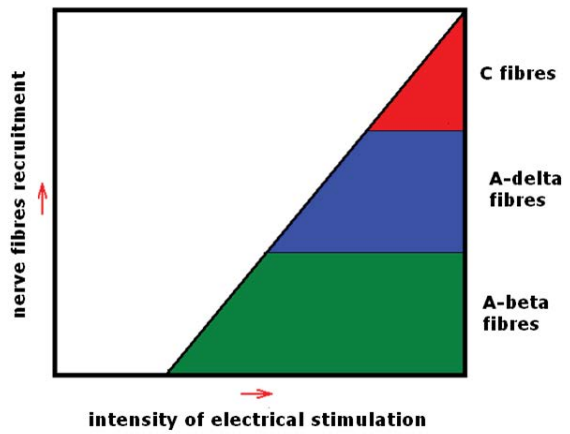

Figure 1: Fixed recruitment of different nerve fibers related to the increase of the electrical stimulation intensity. The passage from A-beta and A-delta fibers is most likely characterized by the change in pleasantness. The stimulation intensity needed for C-fiber activation is practically never reached in the clinical field.

habituation that can lead to the disappearance of the paresthesia felt by the patient.

Clinical Characteristic of Paresthesia Evoked by Electrical Stimulation

Any person experienced the unusual sensation evoked by the application of an electrical stimulation over the skin. This sensation is not physiological because it is the result of an ectopic activation of nerve fibers with a by-pass of the receptor's activity. The typical and universal sensation of an "electrical stimulation" is the result of an activation, for the major part, of the lemniscal system. This seems to be indirectly demonstrated by the different sensation evoked by surgical procedures that selectively stimulate other parts of the nervous system. Important information can be obtained by the selective electrical stimulation of spino-thalamic system usually performed during cordotomy. This is a surgical procedure aimed at selectively create a lesion in the spino-thalamic tract for pain relief in patients with advanced cancer. At the beginning of the procedure, the surgeon has to identify as accurately as possible where is the tip of the needle that will be used to create the selective lesion. To do this an electrical stimulation is induced using the tip of the needle as stimulating electrode and when the tip is in the spino-thalamic tract the surgeon proceeds to the lesion. Interestingly, the recognition of the spino-thalamic tract is the induction of a typical thermal (warm-burning) and not an electrical paresthesia [3]. Similar experiences come from patients who undergone chronic electrical stimulation of the vagus nerve to treat refractory epilepsy. During the electrical stimulation, those patients mainly complain of hoarseness, but not the paresthesia typically associated with an electrical stimulation of a peripheral nerve [4]. The impossibility to evoke the classical "electric" paresthesia during the vagus nerve stimulation can be interpreted as the consequence of the lacking of large diameter fibers in that nerve, as for all the visceral nerves.

In conclusion, there are several clinical and experimental evidences that permit to say that the characteristic paresthesia felt during an electrical stimulation of both a peripheral nerve and dorsal columns is the result of the electrical activation of the lemniscal system.

Electrical Stimulation of Dorsal Columns

The electrical stimulation of dorsal columns induces action potentials in the lemniscal pathway which is composed by a "system" of large diameter fibers with high conduction velocity, classified as A-alpha/A-beta fibers. These fibers transmit several types of sensibility such as proprioception, tactile sensation, position sense, vibratory sensation. Interestingly, the afferent fibers travelling in the dorsal columns are the proximal branch of T cells located in the sensory dorsal ganglia. This means that, although placed in the spinal cord, they are peripheral nerve fibers. This aspect is very important for understanding the propagation of action potentials in consequence of their electrical stimulation.

It is also important to underline that the property of SCS to activate the lemniscal system has gained a new importance in 2008 when the Special Interest Group (SIG) on neuropathic pain of the IASP (International Association for the Study of Pain) introduced the new definition of neuropathic pain: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [5]. In fact, given that the somatosensory system is composed by the dorsal column-lemniscal system and the spino-thalamic tract system [6]. the specification of an involvement of the somatosensory system in neuropathic pain mechanism opened a new scenario. For the first time it was recognized and accepted that neuropathic pain can be generated by a lesion of large diameter (dorsal column-lemniscal) fibers, as already suggested by several authors [7-10]. It is important to specify that involvement of the lemniscal system relates only to neuropathic pain and not to nociceptive pain which, on the basis of the current knowledge, continues to be attributed to the selective activation of small diameter fibers.

Orthodromic Propagation of Action Potentials during SCS

As said before, an adequate, ectopic activation of nerve fibers induces a propagation of action potentials. When the electrical stimulation is applied to dorsal columns it mainly produces action potentials travelling cranially to the brain (afferent fibers stimulation).

Interactions occurring in brainstems have been reported as one of the possible antalgic mechanism of SCS. Considering that SCS activates the dorsal columns in the spinal cord, orthodromic propagation of action potentials during SCS is mandatory for any supposed antalgic mechanism occurring in brainstem or brain.

The diffusion of impulses from the stimulated dorsal columns to the brain is demonstrated by the clinical, neurophysiological recording of cortical responses in the somatosensory brain areas [11]. Given that the electrical currents stimulate first large nerve fibers both in peripheral nerves and dorsal columns, these responses (Figure 2) are equivalent to somatosensory evoked potentials (SEPs) routinely recorded in clinical neurophysiological labs during the stimulation of peripheral nerve trunks [12].

In addition, since in dorsal columns there are also fibers involved in the descending inhibitory control, the electrical stimulation of dorsal columns can also induce an inhibitory effect via an orthodromic (cranio-caudal) activation of those fibers, as demonstrated in animal studies [13].

As far as the "orthodromic effect" of SCS is concerned, in recent years a few studies have been performed using cerebral functional magnetic resonance. In these studies, several cerebral structures have been signaled to be activated or deactivated by SCS. According to one interesting study performed on twenty patients implanted for failed back surgery syndromes, a key role seems to be played by the

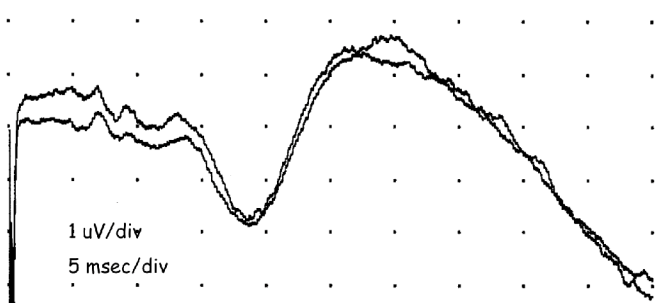

Figure 2: The figure shows an example of cortical responses evoked by SCS. Epidural stimulation leads were at T10-T11 (vertebral level) and the recording electrodes were in Cz-Fpz, the standard placement for routine studies of lower limb somatosensory evoked potentials.

deactivation of the bilateral medial thalamus and by the involvement of cortico-cerebellar networks [14]. Moreover, in a previous study [15] it was demonstrated that the SCS applied to the leg affected by neuropathic pain somatotopically activates the contralateral medial primary sensorimotor cortex, but also the contralateral posterior insula and ipsilateral secondary somatosensory cortex. Future studies using the cerebral functional magnetic resonance will probably add important information on the cerebral effect of SCS.

Antidromic Propagation of Action Potentials during SCS

Adequate electrical stimulations of the nervous system are able to induce an ectopic, bidirectional propagation of action potentials. The property of SCS to antidromically activate afferent fibers to a specific spinal segment, is considered the basis for the antalgic, segmental effect of SCS. This behavior is also the neurophysiological basis for the "gate effect" based on the gate theory [16], which is still considered one of the most important antalgic mechanisms of SCS [2]. Differently from the orthodromic effect which diffusely acts on descending inhibitory systems, the antidromic activation of large diameter fibers conveys "antalgic" impulses only to the spinal segments of the stimulated fibers.

Interestingly, it has been demonstrated that antidromic action potentials activated by SCS do not stop at the correspondent spinal level, but travel to the periphery in peripheral nerves [17,18]. Antidromic evoked responses have been recorded in different nerves of lower limbs being that motor, sensory or mixed [17] and the possibility to record them in pure sensory nerves incontrovertibly demonstrated that those responses were the result of antidromic activation of action potentials during SCS. Moreover, they confirmed that there are not synapses between the stimulating point (dorsal columns) and the registration one (peripheral sensory nerves). Comparing the latencies of antidromic evoked responses [18], lower limb SEPs recorded experimentally from lower thoracic epidural leads [19] and SEPs routinely obtained from lumbar vertebral sites after the stimulation of mixed nerve of lower limbs [12], it is possible to note that latencies are very similar for all the procedures. This similarity means that the different types of recordings assess the conduction properties of the same type of fibers (A-beta), although in opposite directions.

A further demonstration of this concept can be found in the studies that demonstrated how the SCS is able to inhibit the SEPs recorded during the stimulation of lower limb mixed nerves [20-22]. This interference has a neurophysiological basis. It is in fact well known that two impulses travelling on the same fibers but in opposite direction create the neurophysiological phenomenon called collision of impulses [23,24]. The inhibitor effect directly depends on the number of nerve fibers involved in the collision phenomenon: the higher the number of involved fibers, the higher the inhibition. It is worth to underline that this neurophysiological effect is another possible explanation for the well-known clinical necessity to cover the area of pain with paresthesias evoked by the SCS. In fact, the collision only happens if the electrical stimulation antidromically activates the same fibers involved in pain generation.

Moreover, the collision effect permits to explain also a therapeutic limit of SCS. The growing experience on patients with neuropathic pain has demonstrated the necessity to always stimulate the nerve fibers proximally to the nerve lesion. In fact, in case of a stimulation performed distally to the neurological lesion, the collision mechanism blocks the antidromic impulses created by the lesion, which travel to the periphery and not to the brain. Moreover the "distal" stimulation is able to increase the pain because when the impulses generated by the electrical stimulation reach the lesion site they can be amplified according to the mechanism called "impulses multiplication" [8]. It is based on the observation that distal impulses reaching the nerve lesion induce a cross-talk among the fibers with the result of an increase in frequency and irregularity of the nerve fiber discharge.

On a clinical point of view it can be interesting to signal how the neurophysiological collision technique has been recently proposed for a correct placement of leads at cervical and cervico-medullary position [25]. In this study the authors used the principles of impulses collision to correctly localize the leads during the implantation performed in patients who required general anesthesia, suggesting a possible use of intraoperative monitoring and avoiding the collaboration of patients.

Conclusions

Antalgic mechanisms of SCS are far from be completely understood and a neurophysiological approach can add important information to advance upon this field. SCS is physically based on an electrical stimulation of nerve fibers, very similar to that used in clinical neurophysiology for diagnosis of neurological diseases. Nevertheless, neurophysiological tests are rarely performed in patients treated with SCS, both in clinical settings and in research investigations.

This paper was intended to be a short review of the main neurophysiological responses that is possible to record in patients implanted for SCS for refractory neuropathic pain, associated with a discussion on the neurophysiological principles strictly linked to SCS. Further studies are warranted in this field because neurophysiological assessments could help to better understand the antalgic effects of SCS and consequently improve the therapeutic targeting and patient selection.

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