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Spinal Cord Stimulation

Exploration of the Physiological Basis of a Widely Used Therapy

SPINAL cord stimulation (SCS), dating back from the late 1960s, has now become part of the routine pain therapeutic repertoire, and it is estimated that, currently, more than 30,000 SCS systems are implanted every year worldwide. Nonetheless, the mode of action for SCS is still largely unknown, and only during the last 15 yr has more solid evidence for the underlying physiologic mechanisms emerged. Beside the Karolinska group, only a few other groups are presently involved in experimental research on SCS mechanisms (the leading one being that of Nayef Saadé, Ph.D., Professor, American University of Beirut, Beirut, Lebanon, and of Robert Foreman, Ph.D., Professor and Chair, Department of Physiology, Oklahoma Health Sciences Center, Oklahoma, City, Oklahoma).

The study in this issue of ANESTHESIOLOGY by Guan *et al.* with Dr. Srinavasa Raja from the Johns Hopkins University, Baltimore, Maryland, as a senior researcher, represents a reawakening interest in the exploration of the physiologic base for the pain suppressive effects of SCS.[1] In their well-designed and extensive electrophysiological study performed in an animal model of neuropathic pain, they demonstrate that SCS may markedly attenuate neuronal responses in the spinal dorsal horn to both natural innocuous and electrical noxious stimuli applied to a nerve-injured hind paw.

In the 1970s and 1980s, a number of experimental studies with the aim to explore the possible mode of action of SCS appeared.[2] However, these studies were all performed on anesthetized normal healthy animals subjected to acute, noxious stimuli, so their relevance for the alleviating effect of SCS on neuropathic pain was questionable. It was not until 1994 that SCS was experimentally studied in an animal model of neuropathic pain.[3,4] Since then, the Karolinska group has conducted a series of projects to explore the spinal neurobiology of SCS in neuropathic pain.

The hyperexcitability demonstrated by multimodal wide-dynamic range cells in the dorsal horns[5] seems to be related to increased basal release of the excitatory amino acid glutamate and a dysfunction of the local spinal γ-aminobutyric acid (GABA) system.[6,7] It was also shown that SCS may suppress the enhanced responsiveness and pathologic response patterns of wide-dynamic range cells to innocuous peripheral stimuli,[5] and this effect appeared to parallel an SCS-induced release of GABA in the dorsal horn. The GABA release was observed solely in animals responding to SCS with symptom alleviation.[6] Furthermore, SCS was found to produce a decrease in the extracellular dorsal horn glutamate concentration.[7] Activation of the $GABA_B$ receptor appeared to play a pivotal role in this effect.[7,8] This observation was corroborated by the finding that intrathecal injection of the $GABA_B$ receptor agonist baclofen could transform rats not responding to SCS into responders.[9]

Another transmitter system recently found to play a major role in the effects of SCS is the cholinergic. A release of acetylcholine in the dorsal horn with SCS was demonstrated, and later behavioral studies revealed that the effect was associated with activation of the muscarinic M4 receptor.[10] Furthermore, in rats, a subeffective intrathecal dose of a muscarinic receptor agonist could transform nonresponding animals into responders (fig. 1).[11–13]

The experimental SCS study in this issue by Guan *et al.* confirms many of our findings from 1999,[5] although they present a much more advanced analysis of their data and have investigated the effect of SCS on noxiously evoked responses as well. A major methodological advancement is the use of the antidromic sciatic nerve response to ensure that the intensity of dorsal column or dorsal root stimulation does not activate Aδ fibers that would produce painful paresthesiae. This is an elegant method to adapt the stimulation to mimic clinical parameters because in man, SCS is always applied with an intensity that induces only mild to moderate—but never unpleasant or painful—tingling sensations. It could be noted, however, that in 1991, we applied a similar approach in a study on the SCS vasodilatory effect,[14,15] but subsequently we have instead employed the motor threshold as a simple reference for selecting a therapeutic SCS intensity.

The translation of data from bench to bedside should be done with utmost care, and the clinical relevance of experi-

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◆ This Editorial View accompanies the following article: Guan Y, Wacnik PW, Yang F, Carteret AF, Chung C-Y, Meyer RA, Raja SN: Spinal cord stimulation–induced analgesia: Electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. ANESTHESIOLOGY 2010; 113:1392–405.

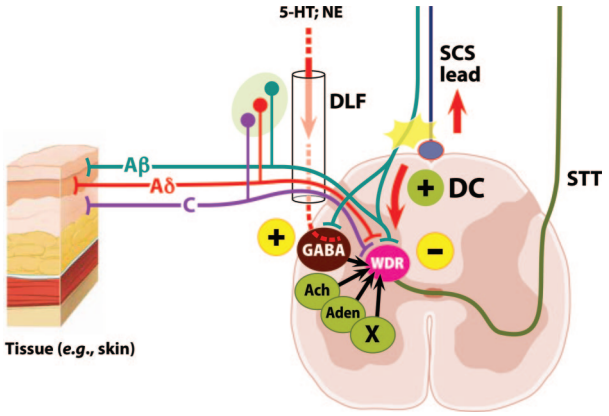

Fig. 1. Schematic representation of spinal transmitters possibly involved in the spinal cord stimulation (SCS) effect in neuropathic pain based on current knowledge derived predominantly from experiments performed on animal (rat) models of mononeuropathy. Antidromic activation of dorsal columns (DC) is, *via* collaterals, destined to the dorsal horns, establishing contact with a multitude of neurons, among them wide-dynamic range neurons and GABAergic interneurons. A stimulation induced release of γ-aminobutyric acid (GABA), binding preferentially to $GABA_B$ receptors, may result in a decreased release of glutamate. Additional effects involve increased release of acetylcholine (Ach) binding to muscarinic M4 receptors and adenosine (Aden) binding to A1 receptors. An important mechanism is activation of descending controls *via* serotonergic and noradrenergic pathways contained in the dorso-lateral funiculus (DLF) originating in supraspinal, brainstem centers. (Many of the mechanisms of action are still unknown [X]). NE = norepinephrine; STT = spinothalamic tract.

mental findings derived from animal models supposedly mimicking pain must always be critically evaluated. In the study of Guan *et al.*, animals presenting with tactile hypersensitivity after a L5 root lesion have been used, but it should be recalled that not more than approximately 20% of patients with neuropathic pain suffer from allodynia. Nevertheless, this phenomenon in the laboratory rat has become the gold standard when evaluating different therapeutic modes for neuropathic pain.

In the Guan *et al.* study, it was reported that dorsal column stimulation did markedly suppress the wide-dynamic range neuronal response to peripheral electrical activation of C-fibers. Moreover, this effect was also current in sham-operated rats. It was also reported that dorsal column stimulation had an attenuating effect on wind-up (tested with electrical C-fiber activation) in both intact and nerve-injured animals. To the best of our knowledge, there is no clear evidence that SCS is effective for acute nociceptive pain, although this appears as a paradox, considering the predictions from Melzack and Wall's 1965 gate control theory,[16] from which SCS emerged. In 1974, it was demonstrated that SCS in patients did not influence the perception of such pain, although it effectively attenuated tactile and pressure allodynia.[17] In our 1995 study, it was shown that in nerve-injured rats, there was no effect of dorsal column stimulation on the C-fiber component of the flexor reflex.[15]

Another puzzling finding in the study of Guan *et al.*[1] is that the Aβ component of the electrically evoked wide-dynamic range response was unaffected by dorsal column stimulation. That finding is difficult to reconcile with the prominent effect on responses to von Frey filament probing, which corresponds to the attenuation of enhanced paw withdrawal responsiveness observed on awake animals.[15] There is much evidence that this form of tactile allodynia is predominantly A β–fiber mediated, and one may ask whether the electrically induced responses represent a physiologic neuronal activation. Are these findings clinically relevant or merely laboratory artifacts?

The current electrophysiological study, like our own from 1999, is focused on the segmental spinal mechanisms that may relate to the pain relieving effect of SCS. However, there is much evidence that the SCS effect is mediated also by the activation of a spinal-brainstem-spinal loop as demonstrated by a series of studies from the Saadé group in Beiruth.[18,19] In line with this idea, we have recently shown that the effect of SCS also depends on the involvement of the descending serotonergic pain-controlling system[20]; there is reason to assume that the descending noradrenergic system takes part as well.

The medical community and the healthcare providers demand that medical therapies are mechanism-oriented and based on solid scientific evidence obtained from well-controlled prospective randomized studies. Thus, research on the physiologic mechanisms underlying the beneficial effects of SCS constitutes a cornerstone in this endeavor, and the article by Guan *et al.* provides important additions to the knowledge approximately SCS mechanisms. SCS is a therapy that is effective in some neuropathic pain conditions otherwise resistant to treatment. The treatment is lenient to patients, minimally invasive, reversible, and possesses few side effects compared with chronic pharmacotherapy. Considering that neuropathic pain is relatively common and that the cost-benefit is balanced after approximately 3 yr, we contend that SCS is presently an underused treatment modality. There has, in recent years, been an impressive advancement of the stimulation device technology, but the understanding of the physiologic mechanisms still lags behind, and more research is urgently needed.

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