Inhibition of Activities of VPL Nociceptive Neurons by Dorsal Column Stimulation

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Abstract

Effects of dorsal column stimulation (DCS) on responses of nociceptive specific (NS) and wide dynamic range (WDR) neurons in the nucleus ventralis posterolateralis (VPL) were studied in urethane-chloralose anesthetized cats. Test stimuli were delivered to the splanchnic nerve (SPL) and to the ventrolateral funiculus (VLF) of the cervical cord. Conditioning DCS suppressed responses of both NS and WDR neurons both to the SPL stimulation and to the VLF stimulation. These results indicate that ascending volleys relayed through the dorsal column nuclei inhibit synaptic transmission of nociceptive impulses in the VPL, a key station in the lateral system of ascending pain pathways, and support the idea that the mechanisms responsible for the clinical effects produced by DCS need not solely be dependent upon interactions in the spinal dorsal horn. It was also found that conditioning stimulation applied to the SI somatosensory cortex suppresses responses of thalamocortical nociceptive VPL neurons, i.e., NS and WDR neurons, to test stimuli delivered to the VLF. Hence, transcortical mechanism of DCS-produced inhibition of nociceptive VPL neurons could not be excluded.

Key words: dorsal column, thalamus, nucleus ventralis posterolateralis, antinociception, analgesia

INTRODUCTION

The concept that large afferent fibers exert an inhibitory action at some places in the central nervous system on the more slowly conducting fibers concerned with nociceptive responses and pain was an idea put forward by Head¹³⁾, by

Foerster⁹⁾, by Noordenbos³⁴⁾ and by other investigators of cutaneous sensibility. The gate control theory of Melzack and Wall²⁶⁾ gave precision to this idea by proposing a mechanism and a location for the inhibition³¹⁾. Unfortunately, the diagram of mechanism they published had disadvantages of excessive clarity with its emphasis

on the substantia gelatinosa and presynaptic mechanisms⁴⁵⁾, and has been challenged in its details. Nevertheless, the basic idea that the interplay between noxious and non-noxious input to the spinal cord may profoundly influence the ascending activity signaling pain, is still valid.

The most obvious prediction of the gate control theory was that stimulation of large diameter peripheral nerve fibers should raise the threshold for detecting injury in the region innervated by the stimulated nerve. Wall and Sweet⁴⁶⁾ immediately proceeded to test this idea, and proved in some patients with chronic intractable pain that the effect of transcutaneous electrical stimulation was sufficiently powerful for therapeutic use.

It is well known that low threshold cutaneous afferents send axons up the dorsal column. Some of these dorsal column axons originate from the dorsal root axons which send collaterals into the dorsal horn of the spinal cord¹⁵⁾. Shealy et al.⁴¹⁾ reasoned that axon collaterals within the dorsal horn may be antidromically activated by stimulating dorsal columns, thus resulting in analgesia. They succeeded in relieving chronic intractable pain by a radiofrequency-induced electrical stimulation of the spinal cord using implanted electrodes over the dorsal columns. Thus the dorsal column stimulation (DCS) evolved as a direct consequence of the introduction of the gate control theory of pain. Since that time many reports have been published on DCS for pain relief^{3,4,6,8,16-25,28,29,32,33,35,39-44)}.

The original notion that DCS predominantly acts via antidromic activation of dorsal column collaterals, which may influence segmental inhibition was first substantiated by Hillman and Wall¹⁴⁾. They recorded activities of wide dynamic range (WDR) neurons in the lamina V of the lumbar cord in decerebrate cats, and examined effects of electrical stimulation of the ipsilateral dorsal column at the level of T10. For every unit

examined, a voltage was reached at which the unit fired. As the intensity of the voltage increased further, the unit responded with brief bursts of repetitive firing followed by prolonged periods of silence. The inhibition as indicated by the silence was powerful and was sufficient to turn off firing of the unit produced by damage to the center of the receptive field. This study was supplemented by other investigators^{7,10,12)}.

Like most new methods of treating chronic pain, DCS was adopted with enthusiasm and often uncritically applied. As a consequence, the often surprisingly high incidence of favorable results obtained during the initial phase was considerably decreased at later follow-ups. Furthermore it became obvious that stimulation applied to the ventral surface of the spinal cord, or from dorsal to ventral surfaces, could also be effective in relieving pain²¹⁾. Hence some investigators^{5,21)} hypothesized that the suppression of pain with DCS is brought about by a direct blockade of the transmission of nociceptive impulses. Despite considerable research, the physiological basis of the clinical effects of DCS, with regard to the site of action, pathways involved and synaptic relays, appears to be still poorly understood.

The pain inhibitory effects of DCS may be exerted at two alternative or complementary levels, segmentally or supraspinally^{1,2,11,27,30,36-38)}. The present study was undertaken to clarify supraspinal mechanisms of antinociception by DCS.

METHODS

Experiments were carried out on adult cats. Anesthesia was induced with ketamine HCl (20 mg/kg, i.m.), and maintained with an i.v. dose (3.5 ml/kg) of urethane and chloralose (urethane 125 mg/ml and chloralose 10 mg/ml). This was supplemented as required. A thermistor probe was placed in the esophagus and the body

temperature was maintained at 37.5 °C by an electric heating pad under the abdomen and by an IR lamp.

The left greater splanchnic nerve (SPL) was exposed retroperitoneally through an incision in the lumbosacral fascia at the lateral edge of the erector spinae muscle mass. The exposed SPL was dissected free from surrounding tissues at the level just proximal to the coeliac ganglion. A pair of stimulating electrodes was applied to the SPL, and sealed in place with a low melting point wax.

After preliminary surgery, the prepared animal was placed in the prone position on a shock-proof table. The head was rigidly fixed in a stereotaxic instrument.

Craniotomies were carried out over the right VPL to allow access for microelectrode exploration. In some experiments, the right somatosensory cortex was also exposed in order to place a platinum stimulating electrode. The dorsal surface of the spinal cord was exposed by a laminectomy at the level of C3–C5. A bipolar concentric electrode was inserted into the right ventrolateral funiculus (VLF). Another bipolar concentric stimulating electrode was more caudally placed in the left dorsal column.

Recordings were made from single units in the VPL using glass capillary microelectrodes filled with a 2% solution of Pontamine sky blue in 0.5 M sodium acetate. During recordings the animals were paralyzed with pancuronium bromide (0.8 mg/kg/h). Endotidal CO₂ was monitored and maintained at 3.5–4.5%. The level of anesthesia was checked intermittently by allowing the animal to recover from the relaxing drug.

The peripheral receptive field properties of neurons in VPL were assessed using a variety of mechanical stimuli: gentle brushing of the skin with a soft brush, pressure applied to a fold of skin using a pair of broad-tipped forceps, and

pinching with a pair of serrated forceps. All units were tested for SPL input.

All nociceptive units with SPL input were tested for effects of conditioning stimulation of the dorsal column. Test stimuli were applied either via SPL or by electrical stimulation of VLF.

The locations of units tested were marked by extruding a small amount of Pontamine sky blue from the microelectrode tip electrophoretically (5 μ A negative DC current passed for 10 min).

At the conclusion of each experiment, the stimulation sites in the VLF and dorsal column were lesioned electrolytically, by passing a current of 100 μ A DC between the poles of the stimulating electrode for 1 min. Animals were then deeply anesthetized, and perfused through the beating heart with 1 l of a solution of 0.5% potassium ferrocyanide in normal saline, followed by 2 l of 10% formalin. Serial sections (50 μ m thick) were cut, stained with Cresyl violet, and the locations of the stimulation and recording sites checked.

RESULTS

Effects of DCS on responses of VPL nociceptive units

A total of 10 nociceptive VPL units receiving SPL input were subjected to the study of effects of DCS on their responses both to the SPL stimulation and to the VLF stimulation. They were recorded from the dorsal or ventral shell region of the VPL^{47,48}. Of these, 5 were nociceptive specific (NS) neurons and the remaining 5 units were wide dynamic range (WDR) neurons. In all the NS and WDR units studied, responses both to the SPL and to the VLF stimulation were inhibited by the conditioning stimulation of the dorsal column with a train of 5 pulses at 400 Hz, 0.1 ms in duration, less than 0.5 mA in intensity.

Fig. 1 illustrates a NS unit. The unit was located in the dorsal shell region of the VPL

Fig. 1 Effects of conditioning dorsal column (DC) stimulation on the responses of a VPL NS unit both to SPL stimulation and to VLF stimulation. **A**: recording site (indicated by an arrow). **B**: cutaneous receptive field (black area). **C**: response of the unit to mechanical stimulation of the skin within the cutaneous receptive field. Upper trace indicates peristimulus time histogram. Bin within is 1 s. Histogram calibration shown in discharges per second. Lower trace shows spike discharges. **D**: dot raster display of the unit response both to SPL stimulation and to VLF stimulation at 1.5 x threshold both with and without conditioning stimulation of the DC with 5 pulses of 11 μ A, 0.1 ms duration at 400 Hz. **E**: time course of inhibition.

Fig. 2 Effects of conditioning dorsal column (DC) stimulation on the responses of a VPL WDR unit both to SPL stimulation and to VLF stimulation. **A**: recording site (indicated by an arrow). **B**: cutaneous receptive field. **C**: response of the unit to mechanical stimulation of the skin within the center of the cutaneous receptive field. **D**: dot raster display of the unit response both to SPL stimulation and to VLF stimulation at 1.5 x threshold both with and without conditioning stimulation of the DC with 5 pulses of 50 μ A, 0.1 ms duration at 400Hz. **E**: time course of inhibition.

(Fig. 1A). This unit had a cutaneous receptive field on the contralateral forearm integument (Fig. 1B). The unit did not respond to brushing and pressure applied to the cutaneous receptive field, but showed a sustained discharge when a noxious pinch with a pair of serrated forceps was applied to the receptive field for 10 s (Fig. 1C). Fig. 1D illustrates dot raster displays of stimulus artifacts and unit discharges. In the record on the left side, a single shock stimulation (test stimulus) was delivered to the SPL at 0.5 Hz. The duration of each SPL stimulation was 0.1 ms and the intensity was 1.5 times threshold for the unit discharges. The stimulation elicited a single or double spike of 11.8–14.0 ms latency from the unit. The first pulse of conditioning stimulation was applied 30 ms prior to the test stimulus. The intensity of the conditioning stimulation was 11 μ A. The responses to the test stimuli were completely suppressed following the conditioning stimulation. In the record on the right side, test stimuli were delivered to the VLF at 1.5 times threshold for the unit discharges. The VLF stimulation elicited 1–3 spikes of 3.6–7.8 ms latency. The same conditioning stimulation as in the left record completely suppressed the responses to the VLF stimulation. The time courses of inhibition of responses both to the SPL stimulation and to the VLF stimulation are plotted in Fig. 1E. The inhibition outlasted 60 ms in both cases.

Results obtained with a WDR unit are illustrated in Fig. 2. The unit was located in the dorsal shell region of the VPL (Fig. 2A). The unit had a cutaneous receptive field on the contralateral thigh integument (Fig. 2B). The unit had a graded response to brushing, pressure and noxious pinch (Fig. 2C) applied to the center of the receptive field (black area in Fig. 2B), responding best to noxious pinch. Outside this zone (cross-hatched area in Fig. 2B), the unit was unresponsive to low-intensity mechanical stimuli, but responded differentially to pres-

Fig. 3 Mean time course of DC stimulation-produced inhibition of responses to SPL stimulation and to VLF stimulation. **A**: mean time courses in 5 NS units. **B**: mean time courses in 5 WDR units.

sure and noxious pinch. Finally, the latter are surrounded by an area in which only noxious pinch resulted in neuronal discharges (shaded area in Fig. 2B). The unit responded to the SPL stimulation with a single or double spike response of 10.9–14.5 ms latency, while to the VLF stimulation with a single or double spike of 3.6–6.2 ms latency. Following conditioning stimulation of the DC at 50 μ A, at a 30 ms conditioning-test interval, the responses to both test stimuli were either completely or almost completely suppressed (Fig. 2D). The time courses of the inhibition are plotted in Fig. 2E. The inhibition outlasted 80 ms in both cases.

The mean time courses of the inhibition of

Fig. 4 Effects of conditioning CX (SI) stimulation on the responses of a VPL WDR unit to CX stimulation. **A**: recording site (indicated by an arrow). **B**: stimulation site of in the SI somatosensory cortex (indicated by arrow). **C**: cutaneous receptive field. **D**: response of the unit to mechanical stimulation of the skin within the center of the cutaneous receptive field. **E**: responses of the unit to 200 Hz stimulation of the SI area shown in **B**. **F**: collision test using the contralateral VLF stimulation and SI area for an antidromic stimulation.

responses both to the SPL stimulation and to the VLF stimulation as observed in 5 NS and 5 WDR units are plotted **Fig. 3**. ANOVA revealed that the inhibition of responses to the SPL stimulation was statistically significant both in the NS units ($F_{8,36}=12.12$, $p<0.001$) and in the WDR units ($F_{8,36}=12.42$, $p<0.001$). The inhibition of responses to the VLF stimulation was also statistically significant both in the NS units ($F_{8,36}=5.33$, $p<0.001$) and in the WDR units ($F_{8,36}=5.34$, $p<0.001$).

Effects of stimulation of somatosensory cortex on responses of nociceptive VPL units

Effects of conditioning stimulation of the SI somatosensory cortex on responses to the VLF stimulation were studied in 2 NS and 2 WDR units.

Results obtained in a WDR unit are illus-

Fig. 5 **A**: dot raster display of the unit response to VLF stimulation at 1.5 x threshold both with and without conditioning stimulation of the CX. **B**: time course of inhibition.

trated in Figs. 4 and 5. The unit was located in the dorsal shell region of the VPL (**Fig. 4A**), and had the center of cutaneous receptive field in the axilla (**Fig. 4C**). The unit followed a 200 Hz stimulation (**Fig. 4E**) delivered to an area in the sigmoid gyrus, which corresponds to the SI somatosensory cortex for the axilla (**Fig. 4B**). The antidromic nature of the unit discharges evoked by the cortical stimulation was further confirmed by a collision test, in which orthodromic stimuli were delivered to the VLF, while antidromic stimuli to the somatosensory cortex (**Fig. 4F**). The unit responded to the VLF stimulation with a single spike of 5.5–7.5 ms latency (**Fig. 5A**). A conditioning stimulation was delivered to the cortical area, stimulation of which evoked antidromic responses from the unit, at an intensity just subthreshold for the antidromic responses. The conditioning stimulation at an 30 ms conditioning–test interval, almost completely suppressed the responses to the test stimuli applied to the VLF (**Fig. 5A**). The time course of inhibition is plotted in **Fig. 5B**. The inhibition outlasted 60 ms. Similar results were also obtained in other units tested.

DISCUSSION

The original notion that DCS predominantly acts via antidromic activation of dorsal column collaterals which may influence segmental inhibitory mechanisms, has been supported by physiological studies^{7,10,12,14}, and no available evidence invalidates this notion. However, it has also been suggested that the mechanisms of action of clinical dorsal column stimulation may depend upon interactions in supraspinal nuclei as well as in the spinal dorsal horn^{1,2,8,11,27,30,35,37,38}. For example, Fields⁸) reported that DCS may effectively produce pain relief in patients who had undergone anterolateral cordotomy. This finding implies that descending, antidromically evoked inhibition of spinotha-

lamic tract neurons in the spinal dorsal horn is not the sole way of producing pain suppression. In rhesus monkey, Bantli et al.²⁾ recorded evoked responses in the nucleus parafascicularis following stimulation of pathways caudal to a lesion transecting the dorsal half of the spinal cord. Conditioning stimuli applied to the dorsal column rostral to the lesion produced a significant reduction in the amplitude of evoked response. The results suggest a supraspinal inhibitory action of DCS in the medial system of ascending pain pathways.

The results of the present experiments demonstrate that DCS may affect neuronal interactions in the VPL, a key station in the lateral system of ascending pain pathways. These findings further support the idea that the mechanisms responsible for the clinical effects produced by DCS need not solely be dependent upon interactions in the spinal dorsal horn, and are consistent with those of Fields⁸), showing that DCS can be effective in patient with anterolateral cordotomy.

The inhibitory effects of DCS on responses of VPL nociceptive neurons as observed in the present experiments may be due to inhibitory action of impulses ascending from the dorsal column nuclei to the VPL where they activate local inhibitory interneurons acting upon nociceptive VPL neurons. Alternatively, DCS may operate via a transcortical loop with an efferent link acting on nociceptive VPL neurons.

In the present experiments, it was found that conditioning stimulation of the SI somatosensory cortex inhibits responses of thalamocortical nociceptive VPL neurons to test stimuli applied to the spinothalamic tract fibers in the VLF. Again there are two possible mechanisms for this inhibition. Firstly, descending impulses from the somatosensory cortex to the VPL may activate thalamic inhibitory interneurons acting upon nociceptive VPL neurons. Secondly, the cortical

stimulation may drive a recurrent inhibitory mechanism within the thalamus via axon collaterals of thalamocortical projection fibers. Hence, transcortical mechanism of DCS-produced inhibition of nociceptive VPL neurons can not be excluded.

By and large, nothing contradicts the possibility of inhibition taking place in the VPL. The present experiments substantiated the thalamic mechanism of DCS-produced antinociception.

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