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Research Report

Direct sensorimotor corticospinal modulation of dorsal horn neuronal C-fiber responses in the rat

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ABSTRACT

Clinically, the stimulation of motor cortical areas has been used to alleviate certain pain conditions. However, the attempts to understand the mechanisms of cortical nociceptive modulation at the spinal cord level have yielded controversial results. The objectives of the present work were to: 1) determine the effects of activating and suppressing the activity of sensorimotor cortical neurons on the nociceptive electrophysiological responses of the segmental C-fibers, and 2) evaluate the contribution of direct and indirect corticospinal projections in segmental nociceptive modulation. By means of a bipolar matrix of stimulation electrodes we mapped the stimulation of cortical areas that modulate C-fiber evoked field potentials in the dorsal horn. In addition, suppressing the cortical activity by means of cortical spreading depression, we observed that the C-fiber evoked field potentials in the dorsal horn are facilitated when cortical activity is suppressed specifically in sensorimotor cortex. Moreover, the C-fiber evoked field potentials were inhibited during spontaneous activation of cortical projecting neurons. Furthermore, after a lesion of the pyramidal tract contralateral to the spinal cord recording sites, the cortical action was suppressed. Our results show that corticospinal tract fibers arising from the sensorimotor cortex modulate directly the nociceptive C-fiber evoked responses of the dorsal horn.

1. Introduction

The group of cortical neurons projecting through the pyramidal system to the spinal cord has been traditionally implicated in motor functions based on the observation that lesions in the sensorimotor cortex produce contralateral motor deficits. However, the pyramidal system is not functionally homogeneous, and it also plays an important role in the selection of ascending sensory information (Canedo 1997). Since the early 1960s it has been reported that motor and somatosensory cortex stimulation produced primary afferent depolarization, leading to presynaptic inhibition in cutaneous and muscular sensory fibers (Carpenter et al., 1963; Andersen et al., 1964; Darian-Smith and Yokota, 1966; Abdelmoumene et al., 1970; Rudomin et al., 1986; Eguibar et al., 1997). This corticospinal control of afferent input is mediated directly by the activation

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Abbreviations: Cx, Cortex; EFPs, Evoked field potentials; FPs, Field potentials; SN, Sciatic nerve; TB, True Blue

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of segmental interneurons (Lundberg and Voorhoeve, 1962; Fetz, 1968; Eguibar et al., 1997), as well as indirectly by extrapyramidal pathways (Hongo and Jankowska, 1967).

Additionally, there is sufficient experimental and clinical evidence showing that sensory and motor cortices modulate the nociceptive information in the dorsal horn (see Brown and Barbaro, 2003 for review). Experimentally, electrical stimulation of the motor and sensory cortices modulates the evoked activity of dorsal horn cells (Coulter et al., 1974; Yezierski et al., 1983; Senapati et al., 2005a,b), as well as the nociceptive behaviors resulting from tissue injury or evoked by painful stimulation. (Kuroda et al., 2000; Kuroda et al., 2001; Fonoff et al., 2009; Wang et al., 2009). Clinically, the stimulation of the motor cortex has been used successfully to manage chronic and drug-resistant peripheral neurophatic pain of various origins (Tsubokawa et al., 1991; Meyerson et al., 1993; Tsubokawa et al., 1993; Nguyen et al., 1997; Katayama et al., 1998; Mertens et al., 1999; Nguyen et al., 1999; Lefaucheur et al., 2001; Brown and Barbaro, 2003; Nuti et al., 2005; Osenbach, 2006). The analgesic effects obtained by motor cortex stimulation apparently involve the modulation of the sensory-discriminative rather than the affective aspects of pain (Lefaucheur et al., 2009), suggesting a top-down regulation of sensory flow. However, since motor cortex stimulation for treatment of pain has been developed empirically, little is known about the mechanisms underlying the modulation of sensory nociceptive information.

Experimental reports analyzing the electrophysiological activity of dorsal horn nociceptive neurons in the monkey indicate that spinothalamic cells are inhibited preferentially by stimulation of the somatosensory cortex, but stimulation of the motor cortex results in both excitation and excitation followed by inhibition of these cells. (Coulter et al., 1974; Yezierski et al., 1983). On the other hand, in the rat the stimulation of sensorimotor cortex produces a significant but transient inhibition in the responses of dorsal horn neurons evoked by higher intensity mechanical stimulation without affecting innocuous stimuli responses (Senapati et al., 2005a,b). Nonetheless, it has not been explored whether the corticospinal projection modulates the activity of nociceptive afferents and how the direct corticospinal pathway and indirect projections contribute to nociceptive modulation (Senapati et al., 2005b).

Most reports have used electrical stimulation of the cortex to analyze the effects on nociceptive responses, but it is difficult to know whether the stimulation parameters used resemble the physiological activation of cortical neurons. In particular, the studies of Senapati et al. argue that the stimulation of both the primary somatosensory cortex (Senapati et al., 2005a) and the primary motor cortex (Senapati et al., 2005b) in the rat inhibits dorsal horn neuronal responses. Since they used strong electrical stimulation (10–30 V) to analyze the effects of cortical electrical stimulation in zones located 0.5 mm apart, they cannot exclude the possibility that the same area was activated in both studies. For this reason it would be more precise to use the term sensorimotor cortex. The purpose of the present study was to evaluate particularly the modulation of nociceptive sensory information carried by C afferents mediated by activation of the sensorimotor cortex. Furthermore, we compared the modulation obtained by cortical electrical stimulation with that resulting from the suppression of ongoing cortical activity or physiological spontaneous activation of cortical neurons. Finally, we tested the contribution of the direct corticospinal projection by means of lesions performed in the pyramidal tract at the medullary level. Preliminary results were reported previously (Rojas-Piloni et al., 2009).

2. Results

The location of sensorimotor cortex neurons stained with the retrograde tracer True Blue placed in the superficial L4 segment dorsal horn was analyzed (Fig. 1). In this way, we positioned the matrix of stimulation electrodes in the region of the cortex where these neurons are located (Fig. 1C).

Evoked field potentials (EFPs) produced by sciatic nerve (SN) stimulation with long latencies (150–200 ms) were analyzed. Based on the latency the conduction velocity estimated was less than 2 m/s, corresponding to the activation of slow C-fibers (Liu and Sandkühler, 1997). Dorsal horn EFPs were produced by SN stimulation, and the stimulation intensity was always adjusted in each experiment to produce long latency responses with amplitudes between 40 and 60% of the maximal response (0.8–1.2 mA). The recording electrodes were positioned at a depth of 150–350 μm from the spinal cord surface where the negative C-fiber EFPs are maximal (Fig. 2).

Cortex stimulation significantly decreases the amplitude of EFP C-fiber responses. To ensure consistency, we analyze the effects in three trials and only consider the experiments in which we observe similar effects. The magnitude of the inhibition depends on which cortical region is stimulated (Fig. 1C) and is maximal in regions located caudal to bregma. The zones in which stimulation produces inhibition correspond to the regions in which the corticospinal projecting neurons are located (Fig. 1C). Since SN stimulation evokes C-fiber responses with a latency that varies among experiments, we analyze the effects produced by cortical stimulation at different time intervals from the onset of cortical stimulation to the beginning of the C-fiber EFP. Thus, the inhibition of C-fiber EFP depends on this time interval; the inhibition is greater at intervals between 20 and 150 ms and gradually decreases with longer intervals (Fig. 3). We found no significant effects on C-fiber EFPs caused by ipsilateral sensorimotor cortex stimulation (data not shown).

In order to analyze if the spontaneous activity of cortical neurons modulates the C-fiber dorsal horn responses, first we produced cortical spreading depression and analyzed the C-fiber responses that occurred when the cortical area projecting to dorsal horn region was depressed. Two recording electrodes were placed in the sensorimotor cortex, one caudal (1 mm caudal to bregma, 2 mm lateral to midline and 1500 μm deep) and one rostral (1 mm rostral to bregma, 2 mm lateral to midline and 1500 μm deep). The cortical spreading depression traveling wave produced by KCl (see the experimental procedure) has a propagation velocity of 4.9±0.4 mm min^{-1} (n=5 experiments). C-fiber EFPs that occurred during the cortical depression were significantly facilitated; however, when depression occurred caudal to bregma, larger responses (57.6±15.6% of control) were observed compared with the EFPs produced when cortical depression reached the region rostral to bregma (33.5±8.1% of control) (Fig. 4).