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Research Report

Upper thoracic postsynaptic dorsal column neurons conduct cardiac mechanoreceptive information, but not cardiac chemical nociception in rats

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ABSTRACT

Postsynaptic dorsal column (PSDC) neurons transmit noxious visceral information from the lower thoracic and lumbosacral spinal cord. Cuneothalamic neurons in the PSDC pathway and upper thoracic (T_3–T_4) spinal neurons ascending through the ventrolateral funiculus (VLF) have been shown to transmit nociceptive cardiac information. Therefore, we hypothesized that upper thoracic PSDC neurons transmit noxious cardiac information. Neuronal responses to intrapericardially injected mechanical (1.0 ml saline) and noxious chemical (0.2 ml algogenic chemicals) stimuli were recorded from antidromically activated PSDC and VLF neurons in the T_3–T_4 spinal cord of anesthetized Sprague–Dawley rats. Of the PSDC neurons, 43% responded to mechanical stimulation, but only one responded to noxious chemical stimuli. Fifty-eight percent of VLF neurons responded to mechanical stimulation and all responded to noxious chemical stimulation. Fluoro-Ruby (FR)-labeled PSDC neurons in the T_3–T_4 spinal cord of Sprague–Dawley rats were processed for c-fos immunohistochemistry following intrapericardial stimulation with mechanical, chemical, or control stimuli. Sections were viewed under epifluorescence and light microscopy to detect FR-labeled neurons containing a c-fos immunoreactive (IR) nucleus. An average of 6 PSDC neurons per rat was found in the T_3 and T_4 spinal segments. The average number of c-fos-IR neurons per segment varied by type of stimulus: 12 (control), 67 (chemical) and 85 (mechanical) for T_3 and 8 (control), 37 (chemical) and 62 (mechanical) for T_4. None of the 200 PSDC neurons examined expressed c-fos-IR regardless of stimulus. Together, these results suggest that thoracic PSDC neurons transmit mechanical cardiac information, but they play a minimal role in cardiac nociception.

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Abbreviations: c-fos-IR, c-fos immunoreactive; CN, cuneate nucleus; CPSA, cardiopulmonary sympathetic afferents; CRD, colorectal distension; DC, dorsal column; DCN, dorsal column nuclei; FE, Fluoro-Emerald; FR, Fluoro-Ruby; GN, gracile nucleus; HT, high threshold; LT, low threshold; PSDC, postsynaptic dorsal column; STT, spinothalamic tract; VLF, ventrolateral funiculus; VPL, ventroposterolateral thalamus; WDR, wide dynamic range

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1. Introduction

Angina pectoris is the chest pain following myocardial ischemia that is typically described as a crushing or burning pain of the left chest that sometimes radiates down the proximal shoulder and left arm and up to the neck and jaw. Approximately 9.8 million Americans suffer from angina pectoris (Lloyd-Jones et al., 2009). Understanding the neural mechanisms and the pathways involved in cardiac nociception can lead to better treatment of this prevalent disease.

Recently, the postsynaptic dorsal column (PSDC) pathway had been described as a major visceral pain pathway (Al-Chaer et al., 1996b, 1998). Cell bodies of PSDC neurons are found in spinal cord laminae III, IV, VII and X with axons projecting through the dorsal columns (DC) to either the gracile (GN) or cuneate (CN) nucleus (Giesler et al., 1984; Hirshberg et al., 1996; Tracey, 1995; Wang et al., 1999). Neurons in these nuclei transmit visceral nociceptive information to the ventroposterolateral thalamus (VPL) (Cliffer and Giesler, 1989; Hirshberg et al., 1996; Al-Chaer et al., 1996b, 1997a).

Since primary afferent neurons in the DC transmit innocuous tactile information, PSDC neurons were first assumed to transmit only innocuous somatic information. However, several clinical and experimental studies indicate that PSDC neurons play a role in transmitting visceral nociceptive information. For example, midline myelotomies transecting the DC have been reported to relieve pain associated with pelvic cancer in terminal patients (Hirshberg et al., 1996; Nauta et al., 1997; Becker et al., 1999). Antidromically activated PSDC neurons in the lumbosacral spinal cord have been shown to respond to colorectal distension (CRD) in rats (Hirshberg et al., 1996; Al-Chaer et al., 1996a, 1997b) and primates (Al-Chaer et al., 1999). Neuronal activity in the GN also increased following noxious stimulation of the uterus, vagina, cervix (Berkley and Hubscher, 1995), colon (Hirshberg et al., 1996; Al-Chaer et al., 1996a, 1997a) and pancreas (Wang and Westlund, 2001). DC lesions significantly abolished or reduced neuronal activity in the VPL responding to CRD in rats (Hirshberg et al., 1996; Al-Chaer et al., 1996b) and primates (Al- Chaer et al., 1998) and to chemical stimulation of the pancreas (Houghton et al., 2001). In addition, severe inflammation of the colon significantly increased responses of PSDC neurons (Al-Chaer et al., 1997b) and electromyography recordings to graded CRDs (Palecek and Willis, 2003).

That PSDC neurons transmit visceral nociceptive information is also indicated by behavioral and immunohistochemical studies. Writhing-like behavior in rats, indicative of duodenal pain, was significantly reduced by DC lesions (Feng et al., 1998). Rats with pancreatitis resumed normal rearing behaviors (Houghton et al., 1997) and rats with severe colonic inflammation resumed normal exploratory activity (Palecek et al., 2002) following DC lesions. In an immunohistochemical study, Palecek et al. (2003) utilized the proto-oncogene c-fos to identify PSDC neurons activated by ureter distension. This study showed a significantly greater number of activated neurons in the PSDC pathway as compared to the spinothalamic (STT) pathway of rats.

Previous studies of the PSDC pathway have focused on the abdominal and pelvic viscera; however, no information is known about the role of PSDC neurons in transmitting nociceptive information from the heart. During cardiac ischemia, the myocardium releases inflammatory mediators that stimulate chemosensitive receptors on cardiac afferent neurons in the epicardium (Baker et al., 1980; Lombardi et al., 1981; Nerdrum et al., 1986). Previous studies have shown that cardiac nociceptive information is transmitted via the STT (Blair et al., 1982; Ammons et al., 1985a,b), as well as other ascending pathways in the ventrolateral funiculus (VLF) of the spinal cord. Only two studies have compared the role of the PSDC pathway with that of the VLF in transmitting information from the heart. Zhang et al. (1997) reported that cardiopulmonary sympathetic afferent (CPSA) information is transmitted bilaterally in the VLF, but not the DC, to the C1–C3 spinal segments from the thoracic spinal cord in rats. Chandler et al. (1998) compared cardiac and somatic information transmitted directly into the VPL from the STT and cuneothalamic pathways and showed that both pathways transmitted cardiac information in the monkey. It has been suggested that the STT and PSDC may play different roles due to the significant differences in neuronal characteristics following electrical stimulation of CPSA and mechanical stimulation of the somatic fields.

Since the PSDC pathway appears to play a major role in abdominal and pelvic visceral pain and that cuneothalamic neurons seem to conduct cardiac information, we hypothesized that upper thoracic PSDC neurons transmit cardiac nociceptive information to the cuneate nucleus. The aim of this study was to determine the electrophysiological and immunohistochemical effects of mechanical and chemical cardiac stimuli on PSDC neurons in the T_3–T_4 spinal segments. Extracellular potentials of neurons from the PSDC pathway were recorded during mechanical and noxious chemical stimulation of the heart and compared to responses of VLF neurons to the same cardiac stimuli. c-fos expression of fluorescent-labeled PSDC neurons was used to determine the activation of PSDC neurons following mechanical and chemical cardiac stimulation. Preliminary results have been published in abstract form (Goodman and Foreman, 2007; Goodman et al., 2009).

2. Results

2.1. *Electrophysiology*

Extracellular responses were recorded to establish the contribution of the PSDC and VLF pathways in transmitting nociceptive cardiac information. Nine PSDC neurons met all three criteria for antidromic activation. The average recording depth of these neurons was 0.28 mm (±0.08 mm) with an average constant latency of 8.3±3.2 ms. Fourteen VLF neurons met all three criteria for antidromic activation. The average depth of recording for these was 0.74 mm (±0.08 mm). The average constant latency for the VLF neuronal responses was 3.4±0.6 ms.

All PSDC and VLF neurons responded similarly to mechanical stimulation of the somatic receptive fields: the left chest or upper left arm and shoulder, where most cardiac pain is