

## The Role of Dorsal Columns Pathway in Visceral Pain

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### Summary

Traditionally, the dorsal column-medial lemniscus system has been viewed as a pathway not involved in pain perception. However, recent clinical and experimental studies have provided compelling evidence that implicates an important role of the dorsal column pathway in relaying visceral nociceptive information. Several clinical studies have shown that a small lesion that interrupts fibers of the dorsal columns (DC) that ascend close to the midline of the spinal cord significantly relieves pain and decreases analgesic requirements in patients suffering from cancer originating in visceral organs. Behavioral, electrophysiological and immunohistochemical methods used under experimental situations in animals showed that DC lesion lead to decreased activation of thalamic and gracile neurons by visceral stimuli, suppressed inhibition of exploratory activity induced by visceral noxious stimulation and prevented potentiation of visceromotor reflex evoked by colorectal distention under inflammatory conditions. Whereas the surgical lesion of the DC tract has proven to be clinically successful, a pharmacological approach would be a better strategy to block this pathway and thus to improve visceral pain conditions under less dramatic circumstances than cancer pain. Our finding that PSDC neurons start to express receptors for substance P after colon inflammation suggests new targets for the development of pharmacological strategies for the control of visceral pain.

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### Key words

Dorsal columns • Myelotomy • Cancer pain

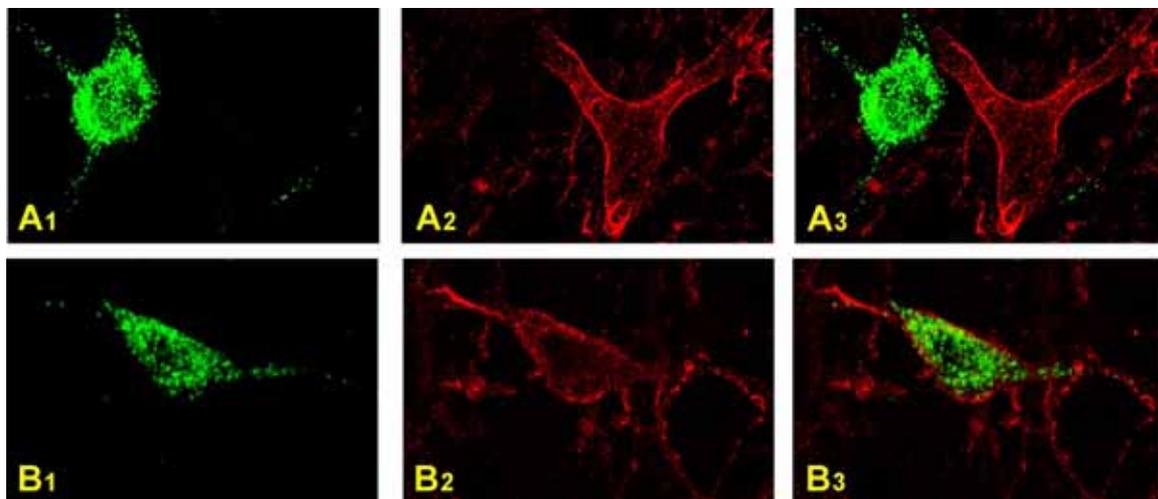
Ascending pathways that convey information about peripheral nociceptive stimuli to higher centers of the CNS have always been in the center of attention of researchers and clinicians as a possible target for pain therapy. The spinothalamic tract (STT) is classically considered to be the major “nociceptive” pathway, while the dorsal column (DC) system is usually thought to be involved just in signaling information about innocuous peripheral stimuli (Willis and Coggeshall 2004). This view on the role of these ascending pathways was considerably disrupted by recent findings that the transection of dorsal columns by limited midline

myelotomy at thoracic level leads to considerable relief of visceral cancer pain in patients (Hirshberg *et al.* 1996, Nauta *et al.* 1997, 2000, Becker *et al.* 1999, Kim and Kwon 2000). The clinical findings were substantiated by initial experimental studies that showed that DC lesion diminished the activation of thalamic neurons by innocuous mechanical stimuli, as expected, and also lead to a significant reduction of the activity evoked in these neurons by visceral stimuli (Al-Chaer *et al.* 1996a, 1998). It was further shown that the positive effect of DC lesion on visceral pain perception is also valid when different organs, such as colon, stomach, pancreas and ureter, were

stimulated (Houghton *et al.* 1997, Feng *et al.* 1998, Paleček *et al.* 2003b).

To examine the role of DC pathway in pain perception in experimental animals, it was important to establish that the changes in activation of thalamic neurons by noxious visceral stimuli also correspond to behavioral signs of pain relief. In our study we have used a decrease in exploratory activity of rats in new environment, as an indicator of perceived pain after noxious stimulus (Paleček *et al.* 2002). In this study, when rats were placed in activity boxes under control conditions, they started to explore the new environment as was registered by changes in their locomotor activity. This pattern of increased exploratory activity was almost

abolished by intradermal injection of capsaicin and significantly reduced by noxious colon stimulation. The reduction of exploratory activity present after the capsaicin injection could be prevented by ipsilateral dorsal rhizotomy or contralateral lesion of the lateral funiculus, but was not affected by DC lesion. In contrast, bilateral DC lesion made prior to the noxious colon stimulation counteracted the decrease of exploratory activity seen in naive animals and this effect was present at least up to 180 days after the DC lesion. These results confirmed the important role of the DC pathway in visceral pain perception and demonstrated that DC lesion leads to visceral pain alleviation in experimental animals similar to the situation in man.



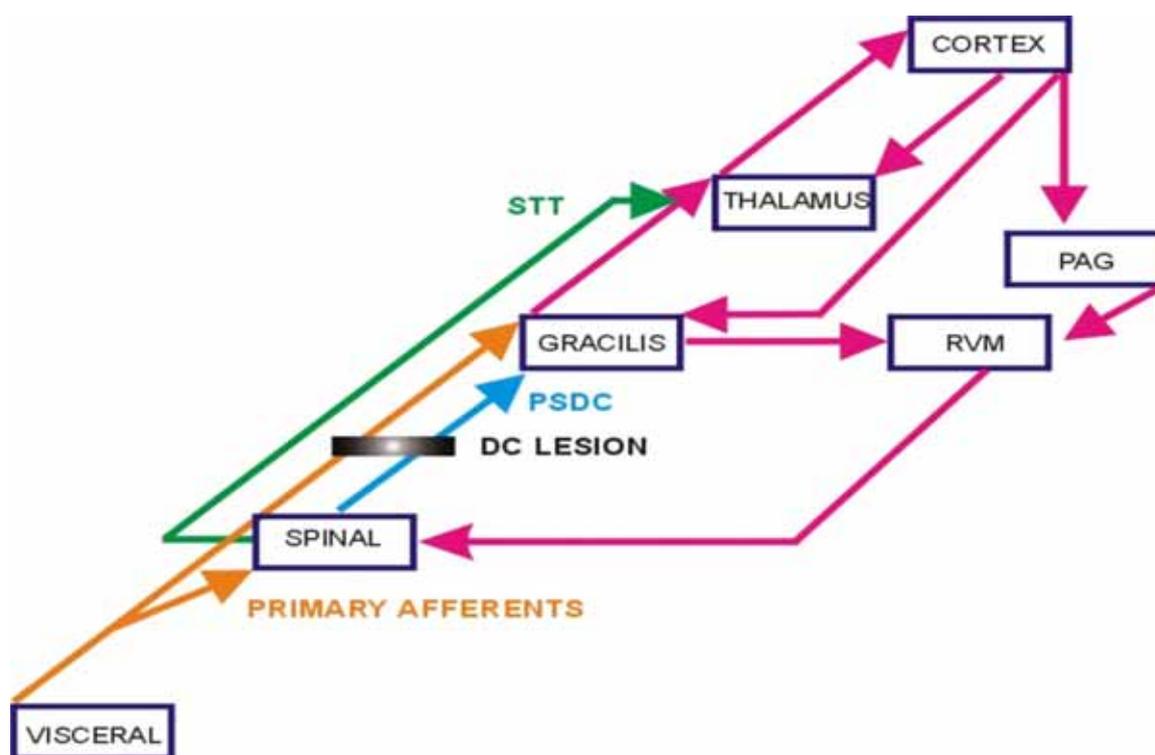
**Fig. 1.** PSDC neurons did not express NK1 receptors under control conditions (A<sub>3</sub>), but NK1 positive PSDC neurons were present after colon inflammation (B<sub>3</sub>). A<sub>1</sub>, B<sub>1</sub> - PSDC neurons were retrogradely labeled from thalamus by dextran conjugated to FITC (green). A<sub>2</sub>, B<sub>2</sub> - NK1 receptors were present prevalently in neuronal membranes (red).

The dorsal column pathway is composed of branches of primary afferent fibers, some of which project directly to the dorsal column nuclei, and of the axons of postsynaptic dorsal column (PSDC) neurons (Willis and Coggeshall 2003). The PSDC neurons are located in the nucleus proprius and in the vicinity of the central canal in the spinal gray matter and project to the gracile and cuneate DC nuclei (Giesler *et al.* 1984, Paleček *et al.* 2003a,b). Intraspinal application of morphine or glutamate receptor antagonist CNQX and thus the attenuation of synaptic transmission at the spinal cord level prevented activation of neurons in the gracile nucleus induced by noxious colonic distention (Al-Chaer *et al.* 1996b). This suggested a major role for the PSDC neurons compared to the branches of primary afferents in transmission of noxious visceral stimuli to the DC nuclei.

The original electrophysiological recordings from PSDC neurons in laminae III-IV have shown that these neurons are mainly responsive to innocuous mechanical stimulation (Giesler and Cliffer 1985). While some of these neurons (30 %) responded to noxious mechanical stimuli, no response could be elicited after cutaneous thermal stimulation. It was therefore suggested that these neurons in rats are not primarily involved in pain transmission. However, activation of PSDC neurons by noxious visceral stimuli in rats was demonstrated in more recent experiments (Al-Chaer *et al.* 1996b, 1997, Paleček and Willis 2004). While electrophysiological experiments can give relatively detailed information on the pattern of neuronal activation, only limited population of neurons can usually be sampled. To further investigate the activation of populations of projecting STT and PSDC

neurons after noxious cutaneous and visceral stimuli we have used immunohistochemical detection of Fos protein in these neurons (Paleček *et al.* 2003b). Fos protein is a nuclear protein product encoded by the immediate early gene *c-fos*, that was shown to be expressed in the spinal dorsal horn after peripheral noxious stimulation (Menétrey *et al.* 1989). Following noxious ureter stimulation, retrogradely labeled PSDC neurons showed the expression of Fos protein in higher percentage than STT neurons, while no significant difference in Fos expression in these two populations of neurons was detected after intradermal capsaicin injection (Paleček *et al.* 2003b). Our data thus further substantiated the role of PSDC neurons in visceral pain perception, but did not explain the substantial effect of the DC lesion on pain of visceral origin as both STT and PSDC ascending systems were activated. Visceral primary afferents are known to be rich in peptides such as substance P (SP) (Perry and

Lawson 1998) and significant deficits in visceral pain perception were shown in studies on SP receptor (NK1) knockout mice (Laird *et al.* 2000). PSDC neurons do not express NK1 receptors under control conditions (Polgar *et al.* 1999, Paleček *et al.* 2003a). However, *de novo* expression of NK1 receptors in the PSDC neurons was demonstrated after visceral inflammation (Fig. 1) (Paleček *et al.* 2003a). This is in good agreement with findings that NK1 receptors are up-regulated in the dorsal horn after bladder irritation (Ishigooka *et al.* 2001) and that intrathecally applied NK1 antagonists reduced significantly abdominal contractions induced by colon distention after colon inflammation (Okano *et al.* 2002). These results suggested the possibility that the PSDC neurons could become sensitized under the conditions of peripheral visceral inflammation and opened the possibility of potential replacement of the neurosurgical approach by pharmacological means.



**Fig. 2.** A simplified schematic drawing suggesting the involvement of DC pathway in the visceral pain transmission. The DC lesion performed as limited midline myelotomy interrupts primary afferents and axons of PSDC neurons ascending in the DC. Our hypothesis suggests that the visceral pain perception is positively modulated by the descending pathways from medulla. The DC lesion blocks this amplification circuit and thus leads to reduction of thalamic activation by visceral stimuli and decreased visceral pain perception. (PAG – periaqueductal gray, RVM – rostro-ventral medulla, PSDC – postsynaptic dorsal column, STT – spinothalamic tract).

The previous experiments clearly demonstrated that the activation of thalamic and dorsal column nuclei neurons by visceral stimuli and the behavioral signs of visceral pain are affected by DC lesion. However, the

study by Ness (2000) showed that visceromotor reflex responses evoked by noxious colorectal distention (CRD) did not change after lesion of the DC pathway. The visceromotor reflex was shown to be mediated by

supraspinal sites, as it was not affected by decerebration but it could not be evoked after spinalization (Ness and Gebhart 1988). It was shown previously that responses of spinal neurons to visceral stimuli are under strong descending facilitatory control (Cervero and Wolstencroft 1984, Tattersall *et al.* 1986, Zhuo and Gebhart 2002). Based on this evidence we have suggested that the DC pathway can be an ascending part of an amplification loop that, when activated, can potentiate responses to noxious visceral stimuli. To test this hypothesis visceromotor reflex EMG activity evoked by CRD was recorded under control conditions and after colon inflammation while the effect of DC and ventrolateral lesions was examined (Paleček and Willis 2003). The colon inflammation robustly increased the visceromotor responses. There was no response to 30 mm Hg CRD under control conditions, while the response evoked at this pressure after colon inflammation was larger than that produced by 80 mm Hg distention before the inflammation. The DC lesion did not change the visceromotor responses under the control conditions, but significantly reduced the highly elevated responses present following colon inflammation. The DC lesion performed before the inflammation prevented the potentiation of these responses. Our results suggested that the role of DC in visceral pain perception may be highly augmented under the conditions of peripheral inflammation, when peripheral nociceptors are sensitized and silent nociceptors are activated. This would correspond to the clinical conditions when symptoms of visceral allodynia and hyperalgesia are present. It also relates to the clinical situation of visceral pain of cancer origin, under which the limited midline myelotomy was tested, where local tissue inflammation of affected visceral organs is likely.

Our results and the evidence from other laboratories suggest that the DC contains an ascending excitatory pathway that plays a crucial role in the

perception of visceral pain, especially under the conditions of peripheral inflammation. Activation of thalamic neurons by the DC pathway, through a relay in the dorsal column nuclei may be an important element in this mechanism. However, there is now increasing evidence that the DC pathway may contain an ascending part of an amplification loop that enhances the responsiveness of spinal cord neurons through a descending facilitatory pathway, possibly originating in the rostroventral medulla (Fig. 2). This amplification circuit could lead to potentiation of the responses of different projection neurons, including viscerosensitive spinothalamic and postsynaptic dorsal column neurons. The effectiveness of the midline myelotomy in visceral pain patients could thus be explained by a direct reduction in the activation of thalamic neurons mediated by postsynaptic dorsal column neurons, as well as by an interruption of the amplification loop, thereby preventing the potentiation of the visceral responses of other projection neurons such as spinothalamic tract cells. While the effect of the DC lesion in patients with cancer pain of visceral origin was clearly demonstrated, new evidence suggests that the DC pathway can also play an important part in other chronic pain states such as peripheral neuropathies (Ossipov *et al.* 2000). This new evidence concerning the role of the DC pathway and the PSDC neurons in pain perception opens new possibilities for the treatment of pain. Further research could suggest a possible pharmacological approach to replace the neurosurgical treatment (limited midline myelotomy) and could be used for pain therapy in wider clinical indications.

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