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Research report

Functional relationship between brainstem putative pain-facilitating neurons and spinal nociceptfive neurons during development of inflammation in rats

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ABSTRACT

The so-called on- and off-cells of the rostral ventromedial medulla (RVM) send their axons to the spinal dorsal horn. Activation of on-cells precedes and coincides with a facilitation, and activation of off-cells coincides with an inhibition, of withdrawal reflexes elicited by noxious agents. Considerable evidence supports the notion that on- and off-cells modulate nocifensive reflexes during opioid and non-opioid action and also during normal circumstances and during peripheral neuropathy and inflammation. Yet it is unclear whether on- and off-cells act upon sensory spinal circuits that might lead to ascending projections and the experience of pain. Here, in deeply anesthetized rats we recorded single unit discharges from pairs of one on-like or off-like cell in RVM and a nociceptive neuron in the spinal dorsal horn with input from a hind paw. Both ongoing activity and responses to a calibrated noxious stimulus applied to the paw were documented during basal conditions and during development of paw inflammation. Probably due to the strong barbiturate anesthesia, off-like cells were depressed and did not yield interpretable results. However, we showed for the first time that during the increase in neuronal activity that results from paw inflammation the activity of spinal nociceptive neurons reflects the activity of their partner on-like cells in a highly correlated manner. This implies a tight relationship between spinal sensory and RVM modulatory functions that may underlie inflammation-induced hyperreflexia and clinically relevant hyperalgesia.

1. Introduction

Experimental evidence indicates that the so-called on- and off-cells of the rostral ventromedial medulla (RVM) participate in a neural circuit that normally modulates nociception (Fields et al., 1983; Fields, 2004; Heinricher et al., 2003; de Novellis et al., 2012; Rossi et al., 2014). In lightly anesthetized rats, activation of on-cells coincides with facilitation of nociceptive withdrawal reflexes, and activation of off-cells coincides with depression of withdrawal reflexes. Experiments in animal models also support the notion that RVM neurons contribute to the hyperalgesia that characterizes clinical syndromes such as inflammation (Carlson et al., 2007; Cleary and Heinricher, 2013; Edelmayer et al., 2009; Goncalves et al., 2007; Khasabov et al., 2012; Pacharinsak et al., 2008; Porreca et al., 2001) and neuropathic pain (Palazzo et al., 2013). Both on- and off-cells project to the spinal cord (Fields et al., 1995; Vanegas et al., 1984) and they are deemed to modulate the excitability of spinal nociceptive neurons involved in local withdrawal reflexes and in the ascending nociceptive information that gives rise to the experience of pain. However, studies on the function of on- and off-cells have generally relied on the coincidence of changes in timing of spinal withdrawal reflexes with changes in timing and firing of RVM neurons, yet changes in spinal reflexes could instead be due to operations in other, e.g., segmental motor, circuits. Research on the direct relationship between RVM and spinal nociceptive neurons is thus necessary. The present study seeks to analyze this functional relationship during the development of peripheral inflammation by means of simultaneous single unit recordings from an RVM neuron and a spinal nociceptive neuron. The present results add support to the notion that

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the facilitatory role that RVM on-cells play upon spinal nociceptive mechanisms is exerted directly upon the spinal nociceptive neurons, both normally and during peripheral inflammation.

2. Results

In 15 rats, data were collected from nine on-like cell/spinal neuron pairs and six off-like cell/spinal neuron pairs. Electrolytic lesions for on-like or off-like cells were found in the RVM, i.e., at the nucleus raphe magnus and adjacent structures dorsal to the medullary pyramids and between the facial nuclei. Lesions for spinal neurons were found in dorsal horn laminae III-V. Sites where all studied neurons were found are shown in Fig. 1.

The single sweep in Fig. 2A shows the occurrence time of action potentials in one RVM and one WDR spinal neuron, recorded simultaneously. Both neurons increase their activity upon the application of a 17 gf clamp to their common receptive field in the hind paw. RVM neurons with this type of behavior are herein called on-like cells. Fig. 2B similarly shows one RVM/spinal neuron pair. The RVM neuron decreases its activity, whereas the spinal neuron is activated, upon the application of a 17 gf clamp to the common receptive field. RVM neurons with this type of behavior are herein called off- like cells.

2.1. On-like cells

2.1.1. Basic characteristics

Nine on-like cell/spinal neuron pairs were studied (Table 1). The on-like cell and the spinal neuron simultaneously increased their firing upon noxious stimulation. Before carrageenan injection, for on-like cells the mean baseline ongoing activity (spikes/s) was 4.84, vs. 10.67, i.e., 120% greater, during application of the 17 gf clamp. For spinal neurons the mean baseline ongoing activity was 5.21, vs. 17.53, i.e., 236.5% greater, during application of the 17 gf clamp.

2.1.2. Inflammation

One hour after induction of inflammation, ongoing activity (Fig. 3A) had increased above pre-carrageenan baseline, 165% for on-like cells and 69.5% for spinal neurons (Table 1). The ongoing activity of on-like cells and of spinal neurons increased in a highly correlated manner (Spearman $r = 0.7$, $p < 0.05$, Table 1, Fig. 3B). One hour post-carrageenan, the responses were 85% greater than

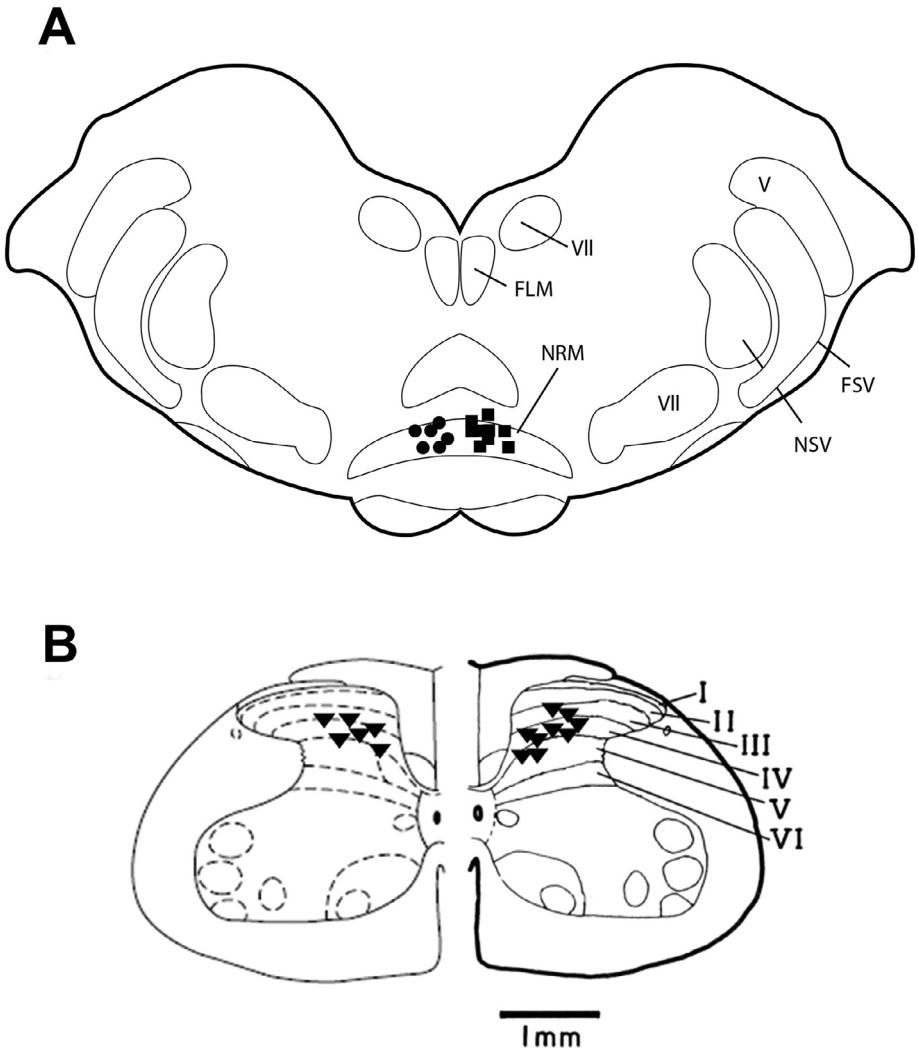

Fig. 1. Locations where all the recording sites were histologically found. Diagrams simplified from Paxinos and Watson (1998). Above: RVM recording sites. Black dots: Off-like cells. Black squares: On-like cells. Below: Neuronal recording sites in the spinal cord. FLM, fasciculus longitudinalis medialis; FSV, fasciculus spinalis trigemini; NRM, nucleus raphe magnus and adjacent structures of the rostral ventromedial medulla (RVM); NSV, nucleus spinalis trigemini; V, trigeminal nerve; VII, facial nerve and nucleus. Only for clarity, off-like cell experiments are represented on the left side and on-like cell experiments on the right side. Rexed's laminae are delineated.