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Research Report

Influence of arthritis on descending modulation of nociception from the paraventricular nucleus of the hypothalamus

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ABSTRACT

We studied the influence of arthritis on descending modulation of nociception from the hypothalamic paraventricular nucleus (PVN) in the rat. Spinal nociception was assessed by the heat-evoked limb withdrawal in awake animals while neuronal responses were recorded in a potential brainstem relay, the rostroventromedial medulla (RVM), under pentobarbitone anesthesia. Following injection into the PVN, glutamate attenuated and lidocaine enhanced nociceptive spinal reflex responses in arthritic and control animals. In controls, PVN-induced antinociception was reversed by spinal administration of a 5-HT_{1A} receptor or an α_2-adrenoceptor antagonist but not by an opioid receptor antagonist. In arthritic animals, PVN-induced antinociception was not reversed by a 5-HT_{1A} receptor antagonist, while the roles of α_2-adrenoceptors or opioid receptors could not be assessed due to significant actions of antagonists alone. The spontaneous activity of presumably pronociceptive ON-cells of the RVM and that of antinociceptive OFF-cells was increased in arthritis. Lidocaine in the PVN increased ON-cell firing in control animals and decreased OFF-cell firing in arthritic animals, while glutamate failed to affect activity of RVM cells. The results indicate that the PVN influences phasic and tonic descending antinociception in arthritic as well as control conditions, and the RVM may contribute to the relay of this influence. In arthritis, the neurochemistry of descending antinociception differs at least partly from that in controls. Arthritis has a dual influence on the PVN-induced drive of relay cells in the RVM which reduces the arthritis-induced net change in the descending antinociceptive influence from the PVN.

1. Introduction

The paraventricular nucleus (PVN) of the hypothalamus is involved in descending modulation of nociception. This is indicated by the finding that electrical or chemical stimulation of the PVN has produced spinal antinociception (Condés-Lara et al., 2006; Miranda-Cardenas et al., 2006; Shiraishi et al., 1995; Wang et al., 1990a; Yang et al., 2006; Yirmiya et al., 1990). In line with this, lesions of the PVN facilitated nociception (Yang et al., 2006) and attenuated stress-induced analgesia (Truesdell and Bodnar, 1987), although not in all experimental conditions (Fuchs and Melzack, 1996; Lariviere et al., 1995). Efferent connections to the spinal dorsal horn directly or indirectly through various relay nuclei in the brainstem, such as the periaqueductal gray and the raphe magnus, provide a potential anatomical substrate for the descending antinociceptive action

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Abbreviations: PVN, paraventricular nucleus of the hypothalamus; RVM, rostroventromedial medulla; WDR, wide-dynamic range

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induced by the PVN (Holstege, 1987; Swanson and Sawchenko, 1983).

The role of various descending pathways and the neurochemistry underlying PVN-induced antinociception is only partly known. Early studies suggested that spinal antinociception induced by PVN stimulation is not dependent on opioid receptors or vasopressin (Shiraishi et al., 1995; Yirmiya et al., 1990). More recent studies, however, suggest that opioid receptors have a minor contribution to the PVN-induced antinociception (Yang et al., 2006; Miranda-Cardenas et al., 2006), while vasopressin (Yang et al., 2006) or oxytocin (Condés-Lara et al., 2006; Miranda-Cardenas et al., 2006) play a major role in mediating the descending antinociceptive action from the PVN. This is in line with a substantial number of hypothalamo-spinal cells that are stained with antisera directed against vasopressin or oxytocin (Cechetto and Saper, 1988; Condés-Lara et al., 2007; Swanson and Sawchenko, 1983). Recent results indicate that activation of GABAergic spinal interneurons by oxytocin may be involved in mediating the PVN-induced antinociception at the spinal cord level (Rojas-Piloni et al., 2007). Although the PVN-induced descending antinociception may be explained by direct hypothalamo-spinal connections, the potential role of various brainstem nuclei in mediating the antinociceptive action from the PVN to the spinal cord still remains to be studied. Concerning potential brainstem relay nuclei and neurotransmitters mediating their action, it is not yet known whether the PVN-induced spinal antinociceptive action involves monoaminergic neurotransmitters, such as serotonin (5-HT) or norepinephrine, that are known to have an important role in descending modulation of nociception (Pertovaara, 2006; Yaksh, 2006).

Pathophysiological conditions may induce significant changes in the function of descending pain-modulatory pathways leading to facilitation or attenuation of nociception (Pertovaara and Almeida, 2006; Vanegas and Schaible, 2004). In experimental arthritis, for example, the descending inhibition of afferent barrage from the inflamed joint was enhanced (Schaible et al., 1991). While it is known that arthritis is associated with changes in the expression of neuropeptides in the PVN (Shanks et al., 1998), it is not known whether the modulation of nociception descending from the PVN is changed in arthritis.

In the present investigation, we studied whether modulation of spinal nociception by the PVN is changed in arthritis. Also, we studied whether neurons in the rostroventromedial medulla (RVM), a final common pathway for many descending pathways (Gebhart, 2004), might have a role in mediating descending modulation of nociception from the PVN of control or arthritic animals. Furthermore, we assessed the roles of spinal noradrenergic α_2, serotoninergic 5-HT_{1A} and opioidergic receptors in mediating the descending modulation of nociception from the PVN by intrathecal microinjections of selective receptor antagonists in control and arthritic animals.

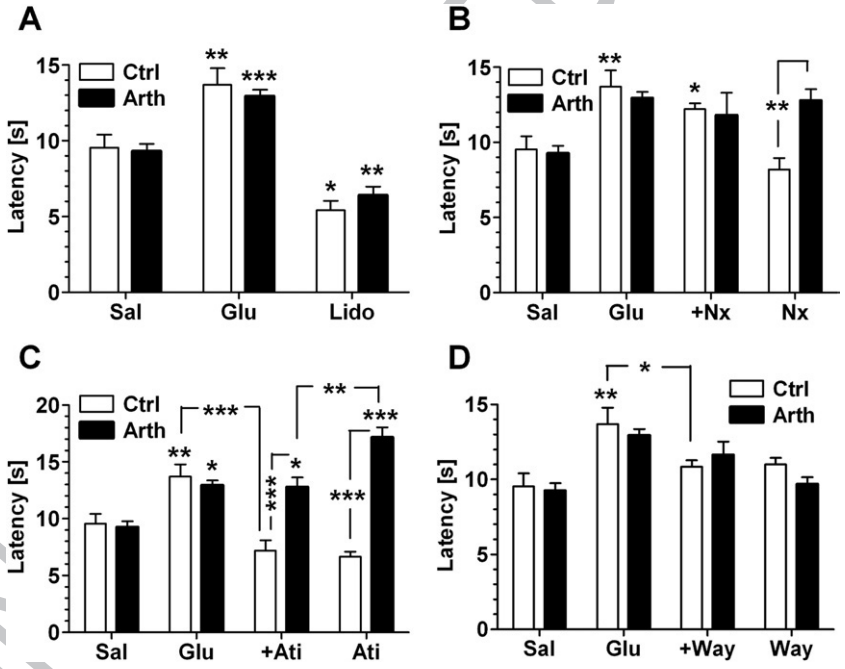

Fig. 1 – Mean latencies of heat-evoked limb withdrawal responses following administration of glutamate (Glu) or lidocaine (Lido) into the hypothalamic paraventricular nucleus (PVN) of control (Ctrl) or arthritic (Arth) animals. The noxious test stimulus was applied to the hind paw that was ipsilateral to the inflamed knee joint in arthritic animals. A) Influence of glutamate or lidocaine alone. B) Attempted reversal of glutamate-induced effect by spinal administration of an opioid receptor antagonist, naloxone (+Nx), and the effect of spinal administration of naloxone alone (Nx). C) Attempted reversal of glutamate-induced effect by spinal administration of an α_2-adrenoceptor antagonist, atipamezole (+Ati), and the effect by spinal administration of atipamezole alone (Ati). D) Attempted reversal of glutamate-induced effect by spinal administration of a 5-HT_{1A} receptor antagonist, WAY-100635 (+Way), and the effect by spinal administration of WAY-100635 alone (Way). The error bars represent S.E.M. (n=5–7). Unless specified otherwise, the asterisks indicate differences within groups (reference: the corresponding saline or Sal-group). *P<0.05, **P<0.01, ***P<0.005 (within groups: Dunnett's test; between groups: t-test).

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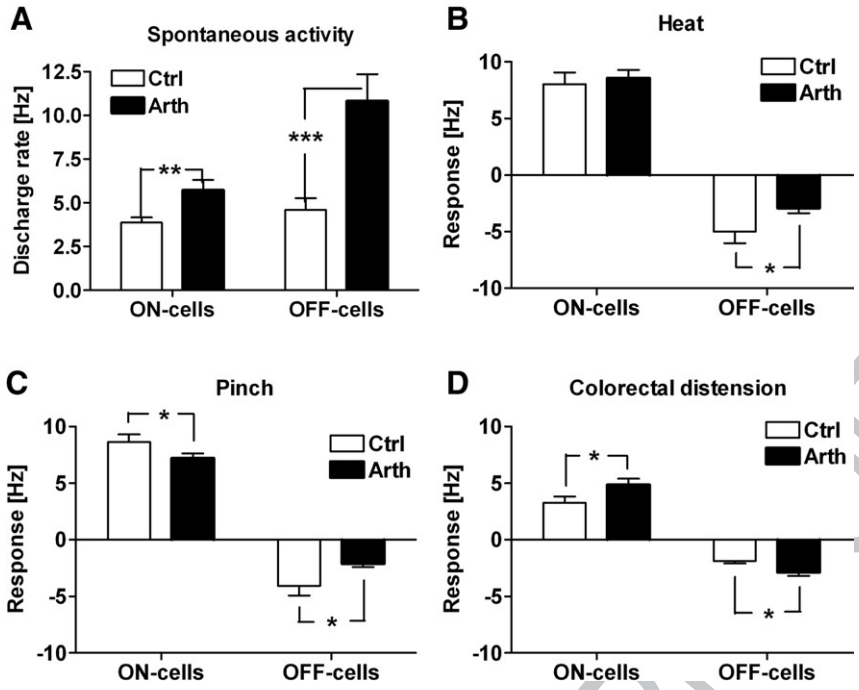

Fig. 2 – Response properties of ON- and OFF-cells of the RVM in control (Ctrl) and arthritic (Arth) animals. A) Spontaneous discharge rate. B) Response to noxious heating of the hind paw skin (ipsilateral to the inflamed knee joint in arthritic animals). C) Response to noxious pinch of the tail. D) Response to noxious visceral stimulation (colorectal distension). The error bars represent S.E.M. (n=14–23 in arthritic groups and n=22–34 in control groups). *P<0.05, **P<0.01, ***P<0.005 (t-test).

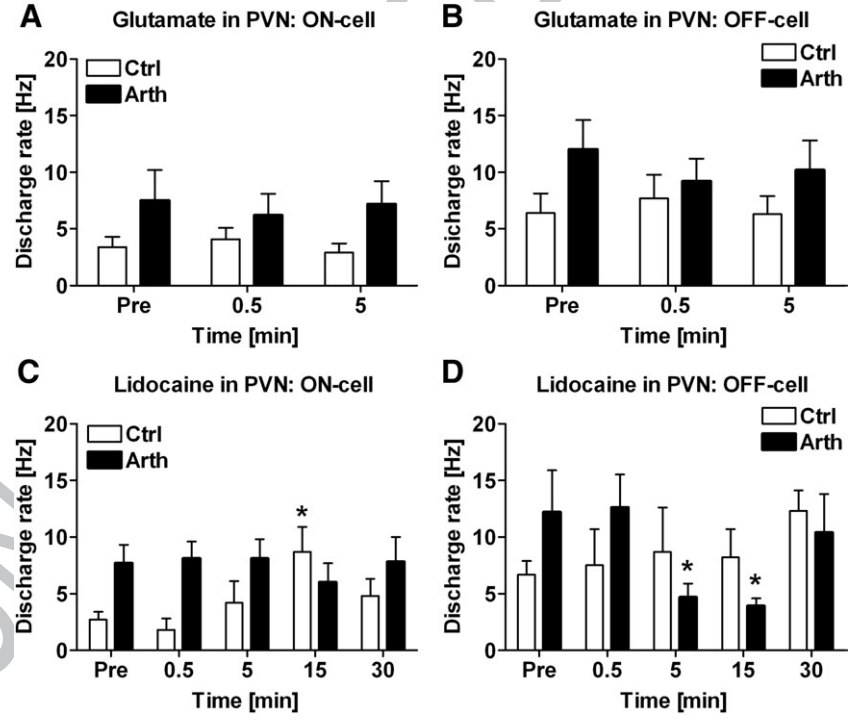

Fig. 3 – Mean spontaneous discharge rates of ON- and OFF-cells of the RVM in control (Ctrl) and arthritic (Arth) animals following microinjection of glutamate or lidocaine into the hypothalamic paraventricular nucleus (PVN). A) Effect of glutamate on discharge rate of ON-cells (n_{Ctrl}=18, n_{Arth}=11). B) Effect of glutamate on discharge rate of OFF-cells (n_{Ctrl}=9, n_{Arth}=6). C) Effect of lidocaine on discharge rate of ON-cells (n_{Ctrl}=8, n_{Arth}=8). D) Effect of lidocaine on discharge rate of OFF-cells (n_{Ctrl}=4, n_{Arth}=5). The error bars represent S.E.M. The Y-axis shows the time elapsed from the microinjection of glutamate or lidocaine. Pre = before injection. *P<0.05 (Dunnett's test; Reference: the corresponding pre-injection rate).

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2. Results

2.1. Behavioral characterization of arthritis

All animals in the arthritic group developed a clear swelling of the treated knee joint and all of them gave a vocalization response to a minor extension and flexion of the affected limb by the experimenter, whereas untreated control animals had no obvious swelling in the knee joint and they did not vocalize when the limb was moved.

2.2. Behavioral assessment of spinal antinociception induced by the PVN

Behaviorally, spinal nociception was assessed by determining the latency of the limb withdrawal response evoked by noxious heating of the hind paw. Saline, glutamate (50 nmol) or lidocaine (4%/0.5 μl) was microinjected into the PVN to study the phasic and tonic regulation of spinal nociception in arthritic animals versus controls. Administration of these compounds in the PVN had a significant effect on the heat-evoked hind-limb withdrawal latency ($F_{2,26}=45.3$, $P<0.0001$): when compared with saline, glutamate induced a significant prolongation (antinociception) and lidocaine a decrease (pronociception) of the withdrawal latency (Fig. 1 A). These modulatory effects by glutamate or lidocaine in the PVN were not significantly different between arthritic and control animals ($F_{1,26}=0.14$).

Naloxone (5.0 μg) was administered intrathecally to study the potential contribution of spinal opioid receptors to the antinociceptive action induced by glutamate in the PVN. Intrathecal administration of naloxone did not attenuate the antinociceptive effect induced by glutamate in the PVN of arthritic or control animals (Fig. 1 B). Intrathecal administration of naloxone alone had no effect in controls but it increased the withdrawal latency in arthritic animals.

Atipamezole, an α_2-adrenoceptor antagonist (5.0 μg), was administered intrathecally to study the involvement of spinal α_2-adrenoceptors in the antinociceptive action induced by administration of glutamate in the PVN. In control animals, atipamezole reversed the antinociceptive action of glutamate in the PVN, while atipamezole alone had no significant effect (Fig. 1 C). In arthritic animals, in contrast, atipamezole did not influence the glutamate-induced antinociception, whereas atipamezole alone induced a significant prolongation of the withdrawal latency (Fig. 1 C).

To study the role of spinal 5-HT_{1A} receptors in antinociception induced by glutamate in the PVN, WAY-100635 (3.0 μg), a 5-HT_{1A} receptor antagonist, was administered intrathecally. In control but not arthritic animals the antinociceptive action induced by glutamate in the PVN was reversed by intrathecal administration of WAY-100635. When administered alone, WAY-100635 had no significant influence on the limb withdrawal latency in arthritic or control animals (Fig. 1 D).

2.3. Response characteristics of ON- and OFF-cells of the RVM

The RVM provides a potential link for mediating the pain-regulatory effect from the PVN to the spinal dorsal horn. In this study, we focused on assessing response properties of the presumably pronociceptive ON-cells and antinociceptive OFF-cells in the RVM. The number of RVM cells tested quantitatively was 49 (23 ON- and 14 OFF-cells) in arthritic animals and 68 (34 ON- and 22 OFF-cells) in controls. The receptive fields of ON- and OFF-cells were typically wide covering all extremities and the whole body. The distribution in the number of ON- and OFF-cells was not significantly different between arthritic and control animals (Fisher's exact test).

2.4. Spontaneous discharge rate of RVM cells

The spontaneous discharge rate of ON- and OFF-cells in the RVM was significantly increased by arthritis ($F_{1,187}=32.6$, $P<0.0001$; Fig. 2 A). The spontaneous discharge rate of OFF-cells was significantly higher than that of ON-cells ($F_{1,187}=17.2$, $P<0.0001$), and this difference was significantly larger in arthritic animals ($F_{1,187}=9.5$, $P<0.003$).

2.5. Peripherally evoked responses of RVM cells

When assessing the peripherally evoked response of ON- and OFF-cells, the noxious stimuli were applied to the non-inflamed area distal to the arthritic knee joint (heat), the tail (pinch) or the viscera. The magnitude of the excitatory ON-cell response evoked by noxious heating of the hind paw skin was not significantly different between arthritic and control animals,

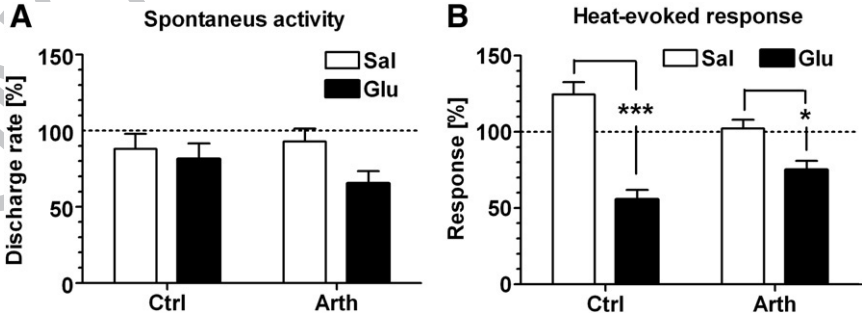

Fig. 4 – Mean changes in spontaneous discharge rates (A) and noxious heat-evoked responses (B) of spinal dorsal horn wide-dynamic range (WDR) neurons following injection of glutamate (Glu) or saline (Sal) into the hypothalamic paraventricular nucleus (PVN) in control (Ctrl) and arthritic (Arth) animals. 100% represents the corresponding pre-injection value. The error bars represent S.E.M. ($n_{Sal}=5$, $n_{Glu}=7$). $^{*}P<0.05$, $^{***}P<0.005$ (t-test).

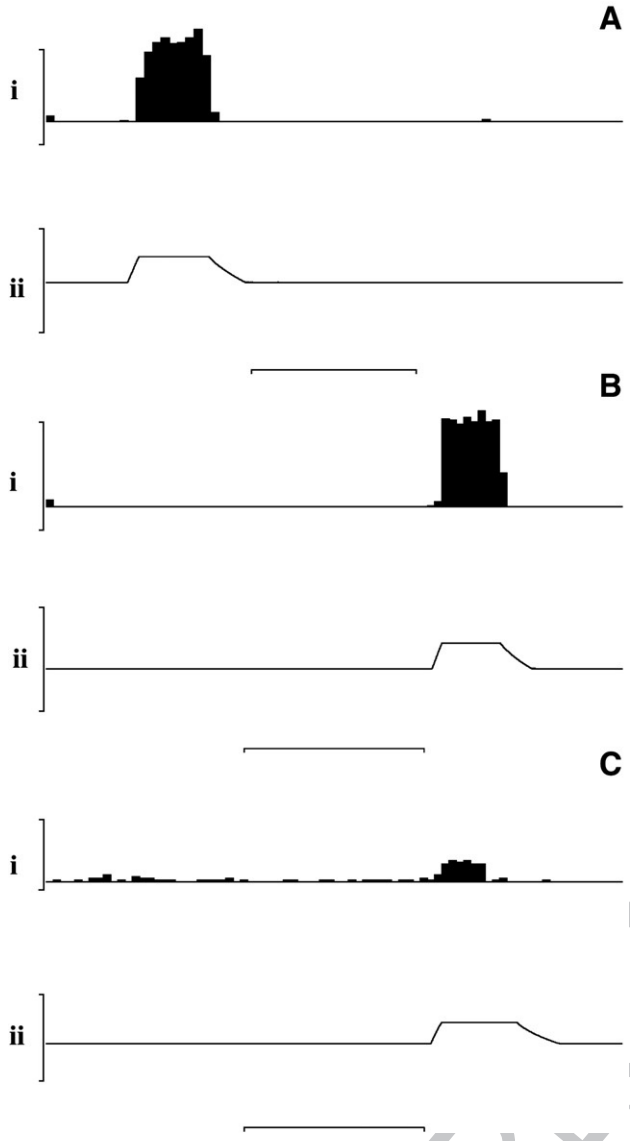

Fig. 5 – Responses of a spinal dorsal horn WDR neuron to noxious heat stimulation of the hind paw in a control animal before PVN injections (A), 30 s after injection of saline in the PVN (B), and 30 s after injection of glutamate in the PVN (C). i: neuronal response, ii: heat stimulus that starts from the baseline temperature of 35 °C and reaches the peak temperature of 54 °C. Vertical calibration bar for i represents 50 Hz and the horizontal one 25 s.

whereas the magnitude of the inhibitory OFF-cell response evoked by noxious heating was reduced in arthritis (Fig. 2 B). The magnitudes of the ON- and OFF-cell responses evoked by noxious tail pinch were reduced in arthritic animals (Fig. 2 C). In contrast, the magnitudes of colorectal distension-induced responses of ON- and OFF-cells were slightly but significantly increased in arthritis (Fig. 2 D).

2.6. *Effects of glutamate or lidocaine administration in the PVN on discharge rates of RVM cells*

The spontaneous discharge rate of ON- and OFF-cells of the RVM was assessed following microinjection of glutamate or lidocaine in the PVN to study arthritis-induced changes in descending modulation of nociception originating in the PVN and relaying through the RVM. Glutamate in the PVN had no significant influence on the discharge rate of ON-cells in arthritic animals ($F_{2,32}=0.5$) or controls ($F_{2,53}=0.6$; Fig. 3 A). Neither did glutamate in the PVN influence the spontaneous discharge rate of OFF-cells in arthritic ($F_{2,26}=0.5$) or control animals ($F_{2,17}=2.1$; Fig. 3 B).

Lidocaine in the RVM had no influence on the discharge rate of ON-cells in arthritic animals ($F_{4,39}=1$), whereas it increased ON-cell activity in controls ($F_{4,39}=3.9$, $P<0.02$; Fig. 3 C). Following lidocaine administration in the PVN, OFF-cell activity was decreased in arthritic animals ($F_{4,24}=5.0$, $P<0.01$), but not changed in controls ($F_{4,19}=1.2$; Fig. 3 C).

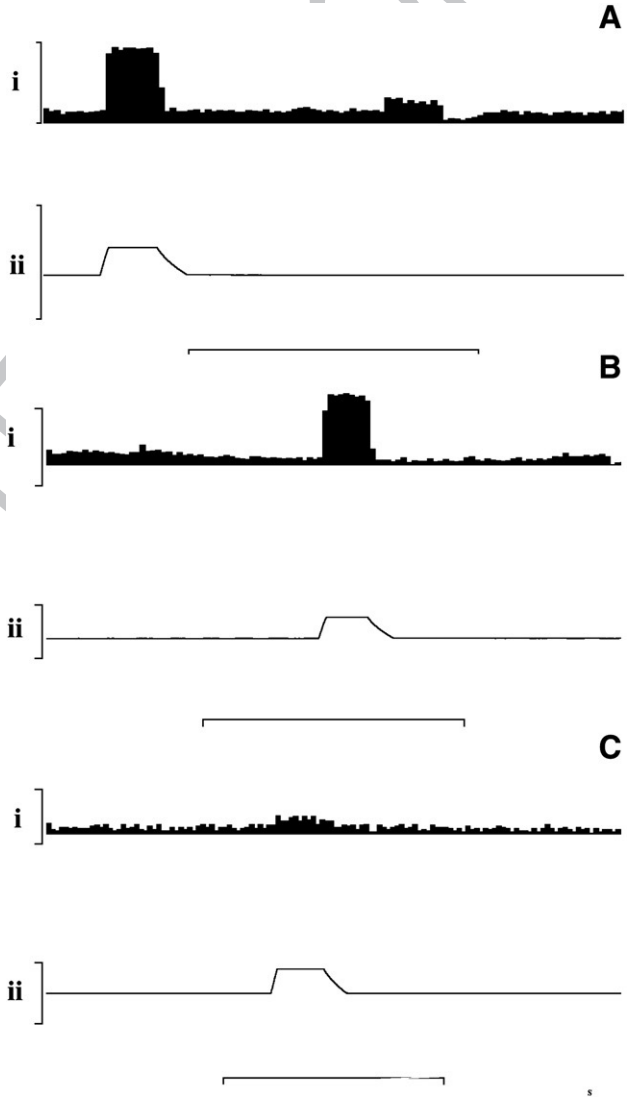

Fig. 6 – Responses of a spinal dorsal horn WDR neuron to noxious heat stimulation of the hind paw in an arthritic animal before PVN injections (A), 30 s after injection of saline in the PVN (B), and 30 s after injection of glutamate in the PVN (C). i: neuronal response, ii: heat stimulus that starts from the baseline temperature of 35 °C and reaches the peak temperature of 54 °C. Vertical calibration bar for the trace i represents 50 Hz, and the horizontal one 25 s.

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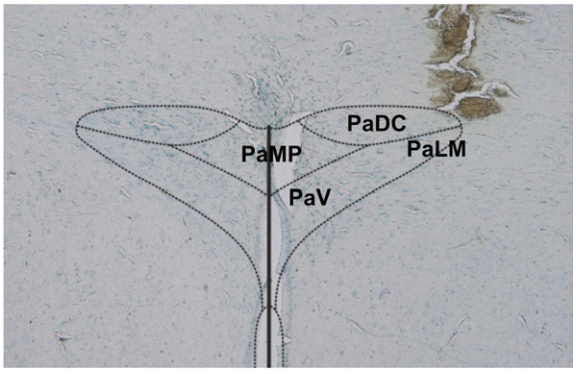

Fig. 7 – A photographic example of a microinjection site in the hypothalamus. Pa: paraventricular nucleus, PaV: ventral part of Pa, PaLM: lateral magnocellular part of Pa, PaDC: dorsal cap of Pa, PaMP: medial parvocellular part of Pa.

2.7. *Spinal dorsal horn WDR neurons*

Effect of glutamate in the PVN on spinal dorsal horn WDR neurons was determined to exclude the possibility that the PVN-induced modulation of spinal nociceptive reflex responses was rather due to suppression of spinal motor than sensory responses. While arthritis produced a significant increase in the baseline spontaneous discharge rate of WDR neurons ($P<0.05$, *t*-test), glutamate in the PVN failed to produce a significant suppression of the spontaneous discharge rate of WDR neurons ($F_{1,20}=2.02$; Fig. 4 A), independent of the experimental group ($F_{1,20}=0.73$). Heat-evoked responses of spinal dorsal horn WDR neurons were significantly decreased by glutamate in the PVN when compared with the effect of saline ($F_{1,20}=9.8$, $P<0.001$; Figs. 4 B, 5 and 6), and this glutamate-induced spinal antinociceptive effect was not significantly different between arthritic and control animals ($F_{1,20}=0.05$).

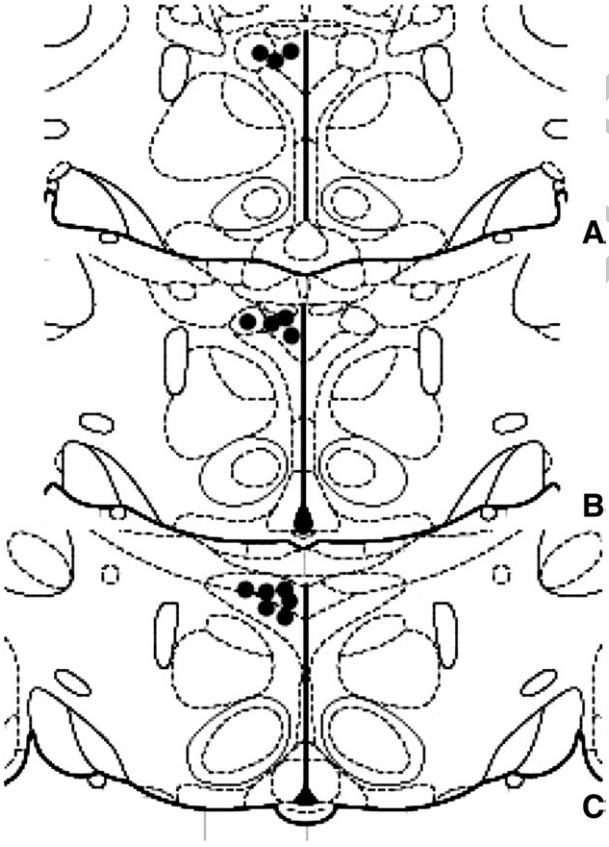

Fig. 8 – Microinjection sites in the PVN. The anteroposterior distance from the interaural line is 7.28 mm for section A, 7.20 mm for section B, and 7.09 mm for section C. Each symbol represents cannula locations in one to four animals.

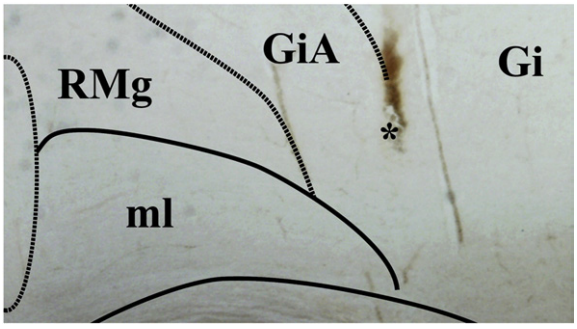

Fig. 9 – A photographic example of a recording site in the medulla (marked with an asterisk). Gi: gigantocellular nucleus, GiA: alpha part of Gi, RMg: raphe magnus nucleus, ml: medial lemniscus.

2.8. *Injection and recording sites*

Figs. 7 and 8 show microinjection sites in the PVN, and Figs. 9 and 10 show recording sites in the RVM. Based on the estimated spread of the currently used injection volume of 0.5 μl (Myers, 1966), the injections spread both to the magno- and parvocellular areas of the PVN and areas immediately adjacent to the PVN. The recording sites in the RVM were in the raphe magnus and the adjacent medial bulboreticular formation. In the spinal dorsal horn, recording sites were in the deep spinal dorsal horn as assessed from the depth of recording sites from the cord surface (400–1000 μm).

3. Discussion

3.1. *Influence of arthritis on the PVN-induced spinal antinociception and a potential relay in the RVM*

Glutamate in the hypothalamic paraventricular nucleus (PVN) suppressed and lidocaine in the PVN facilitated noxious heat-evoked spinal withdrawal responses in arthritic and control animals. This finding indicates that the PVN has a role in phasic and tonic suppression of spinal nociception in arthritic as well as control conditions. It is noteworthy that glutamate in the PVN suppressed not only a spinal withdrawal reflex but also the response of presumed pain-relay neurons in the spinal dorsal horn indicating that the PVN induced rather a true antinociceptive action than only a suppression of the motor expression of nociception. Moreover, the present results indicate that arthritis induces changes in firing rates of presumed pain-modulatory cells in the rostroventromedial medulla (RVM), a structure that

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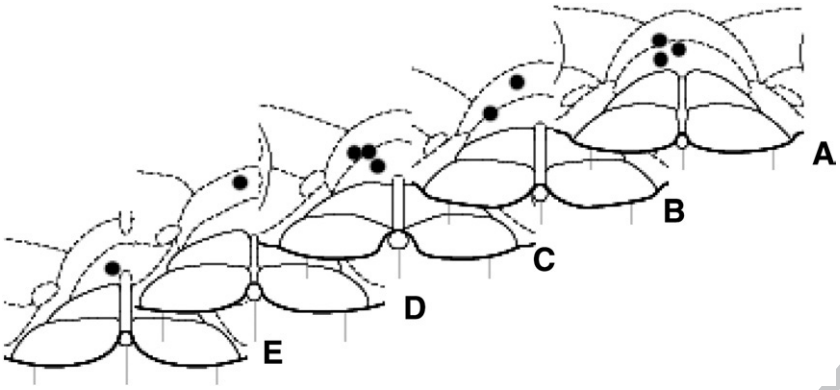

Fig. 10 – Recording sites marked with electrolytic lesions in the RVM. The anteroposterior distance from the interaural line is 1.92 mm for section A, 2.04 mm for section B, 2.16 mm for section C, 2.40 mm for section D and 2.64 mm for section E. Each symbol represents recording sites of one to five neurons.

receives efferent projections from the PVN (Holstege, 1987) and that is known to be an important relay for descending modulation of spinal nociception (Gebhart, 2004). Interestingly, arthritis-induced changes in spontaneous firing rates of pronociceptive ON- and antinociceptive OFF-cells of the RVM were likely to have opposite effects on spinal antinociception. This is indicated by the finding that the spontaneous activity of both pronociceptive ON-cells and antinociceptive OFF-cells was increased in arthritis. The concurrent promotion of descending pro- and antinociceptive influence from the RVM of arthritic animals may contribute to the observations that the baseline nociception of arthritic animals outside of the inflamed region, as indicated by the withdrawal response to heating of the hind paw distal to the inflamed joint, was not significantly different from that in controls. Previous results indicate that during the first hours, inflammation leads to enhanced descending facilitation from the RVM whereas during a later phase the net descending effect from the RVM is inhibition (Terayama et al., 2000). This finding suggests that the pronociceptive influence of arthritis might have been stronger in the present study if the experiments had been performed within the first few hours, instead of several days after induction of arthritis. It should also be noted that the currently used injection volume of 0.5 μl may have spread to areas adjacent to the target area in the PVN and therefore, the present results do not allow excluding the possibility that brain areas adjacent to the PVN contribute to the present findings.

Glutamate in the PVN failed to influence discharge rates of RVM cells in arthritic or control animals. This finding suggests that the RVM may not have a critical role in mediating phasic antinociception induced by PVN-stimulation. On the other hand, lidocaine in the PVN increased firing rates of pronociceptive ON-cells in control animals and decreased firing of antinociceptive OFF-cells in arthritic animals. This finding suggests that the PVN in a tonic and dissociative fashion drives the RVM and that the drive is changed by arthritis. The net descending effect of the PVN-induced tonic drive need not, however, be changed by arthritis, since the PVN-induced tonic suppression of pronociceptive RVM ON-cells in control animals may have an equal effect on spinal nociception as the PVN-induced tonic facilitation of antinociceptive RVM OFF-cells. In line with this proposal, the behavioral results indicated that lidocaine in the PVN had an equal spinal pronociceptive effect in arthritic and control animals. These findings are in line with the hypothesis that the RVM is involved in mediating tonic PVN-induced modulation of spinal nociception.

The magnitudes of pinch- and heat-evoked responses of RVM cells were decreased in arthritis. It should be noted, however, that in this study pinch and heat were applied to the skin area outside of the inflamed joint. Therefore, sustained nociceptive barrage from the inflamed joint may have attenuated concurrent nociceptive signals evoked by pinch and heat stimulation of the healthy skin area. In line with this proposal, this type of a phenomenon that is also called diffuse noxious inhibitory controls (Le Bars et al., 1979) is known to be effective in arthritis (Calvino et al., 1987). Although the RVM is not involved in mediating diffuse noxious inhibitory controls (Bouhassira et al., 1993), the RVM receives ascending nociceptive signals from the spinal dorsal horn, a structure that is influenced by diffuse noxious inhibitory controls (Le Bars et al., 1979). Responses to noxious visceral stimulation, in contrast, were slightly enhanced in arthritis. Possibly the converging cutaneous receptive fields of spinal neurons mediating visceral nociception from the colorectal area are large enough to receive and summate sustained nociceptive signals from the inflamed joint which might explain enhanced visceral responses.

Previous studies have shown that a number of pathophysiological models such as prolonged noxious thermal stimulation, opioid withdrawal, mustard oil-induced neurogenic inflammation and spared nerve injury model of neuropathy produce hypersensitivity that is associated with increased activity of pronociceptive ON-cells in the RVM (Bederson et al., 1990; Gonçalves et al., 2007; Kincaid et al., 2006; Morgan and Fields, 1994; Xu et al., 2007) and that may, in some conditions, be accompanied by a decreased activity of antinociceptive OFF-cells (Gonçalves et al., 2007). In the present study, arthritis increased activity of both pro- and antinociceptive RVM cells. Arthritis failed to produce a significant change in the limb withdrawal evoked by heating the paw distal to the inflamed joint; this was expected based on the arthritis-induced changes in discharge properties of RVM cells. Together, the results are in line with the hypothesis that ON- and OFF-cells of the RVM have a role in modulation of spinal nociception in various

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pathophysiological as well as control conditions (Fields et al., 2006), although the magnitude of contribution and the pattern of firing rate changes may vary depending on the experimental condition.

3.2. *Spinal neurotransmitter receptors involved in the PVN-induced antinociception*

In control animals, antinociception induced by glutamate in the PVN was reversed by spinal administration of a 5-HT_{1A} receptor antagonist and an α_2-adrenoceptor antagonist, whereas the effect of an opioid receptor antagonist on the PVN-induced antinociception was not significant. This finding indicates that under physiological conditions serotoninergic raphe-spinal and descending noradrenergic pathways acting on spinal 5-HT_{1A} and α_2-adrenoceptors, respectively, are involved in mediating the PVN-induced spinal antinociceptive action. This is in line with previous results indicating that the PVN has efferent connections to various pain-modulatory nuclei in the brainstem, including the serotoninergic raphe magnus (Holstege, 1987; Swanson and Sawchenko, 1983) and that electrical or chemical stimulation of the RVM may inhibit nociception due to action on spinal 5-HT_{1A} receptors (el-Yassir and Fleetwood-Walker, 1990; Wei and Pertovaara, 2006). Efferent connections from the PVN directly to the noradrenergic locus coeruleus in the pons (Swanson and Sawchenko, 1983) provide a link for activation of descending noradrenergic pathways that contribute to the PVN-induced antinociception due to action on spinal α_2-adrenoceptors. Additionally, the PVN might recruit descending noradrenergic pathways through the RVM (Nuseir et al., 1999; Sim and Joseph, 1992). In line with earlier findings (Shiraishi et al., 1995; Yirmiya et al., 1990), the present results suggest that spinal opioid receptors do not have a critical role in the PVN-induced antinociception in control animals.

Unlike under control conditions, the contribution of spinal 5-HT_{1A} receptors to the PVN-induced antinociception was not significant in arthritic animals. Thus, arthritis induced a change in the contribution of the serotoninergic system to the PVN-induced antinociception. While spinal administration of an α_2-adrenoceptor or opioid receptor antagonist alone had no significant effect on pain-related behavior in control animals, these compounds produced a significant modulatory action in inflamed animals. Paradoxically, the changes produced by an α_2-adrenoceptor or opioid receptor antagonist alone were prolongations of the limb withdrawal latency. A plausible explanation for the paradoxically increased withdrawal latency by the receptor antagonists alone is removal of arthritis-induced noradrenergic and opioidergic feedback inhibition (Pertovaara, 2006; Yaksh, 2006) and a consequent increase in the sustained nociceptive barrage from the inflamed joint that led to a central suppression of heat-evoked responses from the cutaneous test site in the hind paw; i.e., spinally administered α_2-adrenoceptor and opioid receptor antagonists may have enhanced sustained joint pain and consequently, diffuse noxious inhibitory controls (Calvino et al., 1987) that suppressed concurrent nociception elsewhere. Due to significant actions by the α_2-adrenoceptor and opioid receptor antagonists alone, the present results do not allow concluding whether the contribution of spinal noradrenergic or opioid receptors to the PVN-induced antinociceptive effect is changed in arthritis.

3.3. *Spinal neurotransmitters mediating descending antinociception from the PVN versus other hypothalamic areas*

Interestingly, while the present results indicate that spinal 5-HT_{1A} receptors and α_2-adrenoceptors are involved in mediating the descending antinociceptive effect from the PVN in control conditions, earlier results indicate that these monoaminergic receptors mediate descending antinociception also from the lateral hypothalamus (Holden and Naleway, 2001; Holden et al., 2005). In contrast, while some earlier (Shiraishi et al., 1995; Yirmiya et al., 1990) and the present results indicate that spinal opioid receptors have only a minor, if any, role in the PVN-induced antinociception, the spinal antinociceptive effect induced by stimulation of the hypothalamic arcuate nucleus was reversed by spinal administration of an opioid receptor antagonist (Wang et al., 1990b).

3.4. *Conclusions*

The PVN has a phasic and tonic descending antinociceptive influence in arthritic as well as control animals. The RVM may contribute to the relay of descending influence from the PVN. Arthritis induced a dual change in the baseline activity and the PVN-induced tonic drive of pro- and antinociceptive cells of the RVM. Due to these dual arthritis-induced changes that produced opposite actions, the net effect of RVM cells in the control of baseline nociception or in the relay of tonic inhibitory influence from the PVN may remain the same, although the roles of pro- and antinociceptive cells vary between the arthritic and control conditions. Recent studies indicate that vasopressin (Yang et al., 2006) or oxytocin (e.g., Condés-Lara et al., 2006; Miranda-Cardenas et al., 2006) released from hypothalamo-spinal neurons have an important role in the PVN-induced antinociception. These findings indicate that direct action by descending axons of hypothalamic neurons in the spinal dorsal horn may alone be sufficient to induce antinociception. The present results extend these findings by showing that descending serotoninergic and noradrenergic pathways acting on spinal 5-HT_{1A} receptors and α_2-adrenoceptors, respectively, may also contribute to the PVN-induced inhibition of spinal nociception in control conditions.

4. Experimental procedures

4.1. *Animals, anesthesia and ethical issues*

The experiments were performed in adult male Wistar Han rats with 250–300 g (Harlan Netherlands, Horst, Netherlands). The experimental protocol was approved by the Institutional Ethical Commission and followed the European Community Council Directive 86/609/EEC for the use of experimental animals. All efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

For the experimental surgery and electrophysiological sessions, anesthesia was induced by administering pentobarbitone (50 mg/kg, i.p.) and the anesthesia was maintained by infusing pentobarbitone (15–20 mg/kg/h, i.p.) when necessary. The level of anesthesia was frequently monitored by observing the size of

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the pupils, the general muscle tone and behavioral responses to noxious pinching. Importantly, the anesthesia level was maintained in an identical fashion when studying control and arthritic animals. Therefore, a potential influence of anesthesia level, if any, was identical in control and arthritic groups. A warming blanket was used to maintain the body temperature within physiological range. At the completion of the experiment, animals received a lethal dose of pentobarbitone.

4.2. *Procedures for intrathecal and intracerebral microinjections*

For the insertion of the intrathecal cannula, a thin polyethylene cannula (PE-10, Becton Dickinson & Co., Sparks, MD) was inserted into the lumbar subarachnoid space as described in detail elsewhere (Størkson et al., 1996). The intrathecally inserted catheter was then fixed through a layer of superficial muscles, tunneled rostrally and made to appear through the skin in the occipital region. Upon recovery from anesthesia, 10 μl of 2% lidocaine hydrochloride, followed by 10–15 μl of saline was given through the catheter – with the help of a 50 μl-Hamilton microsyringe (Hamilton Inc., Reno, NV) – to verify if it was indeed spinally located. Only rats that developed reversible symmetrical paralysis of both hind limbs and tail after the injection of lidocaine were used in the experiments. Intrathecal cannula was inserted at least one week before actual experiments. Test-drugs were injected intrathecally at a volume of 5 μl using a 50 μl-Hamilton microsyringe, flushed afterwards with 10–15 μl of saline.

For intracerebral drug administration, the rats were placed in a stereotaxic frame and a stainless steel guide cannula (26 gauge; Plastics One, Roanoke, VA) was implanted in the brain according to the coordinates of the atlas by Paxinos and Watson (1998). The tip of the guide cannula was positioned 1 mm above the desired injection site in the PVN (AP, 7.2 mm; LM, 0.2 mm; DV, 7.9 mm to the interaural line). After the guide cannula was fixed into the skull using a dental screw and dental cement, a dummy cannula was inserted into the guide cannula and the top was closed. Animals were allowed to recover from surgery for one week before testing.

Test-drugs were administered in the PVN through a 33-gauge injection cannula (Plastics One) inserted into and protruding 1 mm beyond the tip of the guide cannula. The microinjection was made using a 1.0-μl-Hamilton syringe connected to the injection cannula by a polyethylene catheter (PE-10). The injection volume was 0.5 μl and therefore, the spread of the injected drugs within the brain was at least 1 mm (Myers, 1966). The efficacy of injection was monitored by watching the movement of a small air bubble through the tubing. The injection lasted 30 s and the injection cannula was left in place for an additional 30 s to minimize the return of drug solution back to the injection cannula. Brain injection sites were histologically verified from post-mortem sections and plotted on standardized sections derived from the stereotaxic atlas of Paxinos and Watson (1998).

4.3. *Induction of arthritis*

The induction of arthritis was performed 7–14 days before the actual experiments as described in detail elsewhere (Ansah and Pertovaara, 2007). Briefly, 3% kaolin and 3% carrageenan (Sigma, St. Louis, MO, USA) were dissolved in distilled water and injected into the synovial cavity of the left knee joint at a volume of 0.1 ml. This model produces mechanical hyperalgesia with the onset of a few hours and a duration of up to 8 weeks (Radhakrishnan et al., 2003). In each animal, development of arthritis was verified 1–2 h prior to each experiment. Only those rats that vocalized every time after five flexion–extension movements of the knee joint were considered to have arthritis, and they were included in the arthritis group. Untreated control animals did not vocalize to any of the five consecutive flexion–extension movements of the knee joint.

4.4. *Behavioral assessment of nociception*

The rats were habituated to the experimental conditions by allowing them to spend 1–2 h daily in the laboratory during two to three days preceding any testing. For assessing nociception in unanesthetized animals, radiant heat-induced latency of paw withdrawal was determined using radiant heat equipment (Plantar Test Device Model 7370, Ugo Basile, Comerio, Italy) as described in detail earlier (Hargreaves et al., 1988). Radiant heat was applied to the plantar skin of the hind limb ipsilateral to the inflamed knee joint and the PVN injection. In each drug treatment session, the withdrawal latency was assessed prior to drug treatment and at various interval following the intracerebral and intrathecal injections. At each time point, the measurement was repeated twice at an interval of 1 min and the mean of these values was used in further calculations. Cut-off time was 20 s. Since spinal transection does not abolish the heat-induced limb withdrawal (e.g., Kauppila et al., 1998), it is a spinally organized nociceptive reflex, although it is modulated by brainstem–spinal pathways in intact animals. Therefore, the heat-induced limb withdrawal provides a method for determining spinal nociception and its supraspinal modulation in behaving animals and also under anesthesia (e.g., Luukko et al., 1994).

4.5. *Recording of neuronal responses in the rostroventromedial medulla (RVM)*

RVM neurons provide a potential relay for descending influence from the RVM. Therefore, we studied the response properties of RVM neurons and the modulation of their activity by the PVN in control and arthritic animals. For electrophysiological recordings of neurons in the RVM, anesthesia was induced and continued as described above, and the animal was placed in a standard stereotaxic frame according to the atlas of Paxinos and Watson (1998). The skull was exposed and a hole was drilled for placement of a recording electrode in the RVM. The desired recording site in the RVM was 1.8–2.3 mm posterior from the ear bar, 0.0–0.5 mm lateral from the midline, and 8.9–10.7 mm ventral from the dura mater. Single neuron activity was recorded extracellularly with lacquer-coated tungsten electrodes (tip impedance 3–10 MΩ at 1 kHz) and then amplified and filtered using standard techniques. Data sampling was performed with a computer connected to a CED Micro 1401 interface and using Spike 2 software (Cambridge Electronic Design, Cambridge, U.K.).

Actual recordings of RVM neurons did not start until the animal was under light anesthesia; i.e., the animals gave a

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brief withdrawal response to noxious pinch, but the pinch did not produce any longer lasting motor activity, nor did the animals have spontaneous limb movements. RVM neurons were classified based on their response to noxious heating (54 °C) of the hind paw with a feedback-controlled Peltier device (LTS-3 Stimulator, Thermal Devices Inc., Golden Valley, MN; Wilcox and Giesler, 1984), as described below. For detection of a heat-evoked limb withdrawal concurrently with the neuronal response, a piezoceramic movement detector (Siemens Elema Ab., Medicinsk Teknik, Solna, Sweden) of low weight (<0.5 g) was taped on the skin overlying the hamstring muscle in the mid thigh level of the stimulated hind limb and the movement of the limb measured with it as described earlier (Hämäläinen et al., 1996). For classification of RVM neurons, the scheme developed earlier (reviewed by Fields et al., 2006) was adapted. Briefly, neurons giving an excitatory heat-evoked response that was associated with a hind-limb withdrawal were considered to be pronociceptive ON-cells, those giving an inhibitory response that was associated with a limb withdrawal were considered to be antinociceptive OFF-cells (Fig. 11). Neurons showing no or only a negligible (<10%) change in their discharge rates as a response to noxious stimulation were considered to be NEUTRAL-cells which were not studied further in this investigation. If a neuron could not be classified it was not included in the study. Classification of RVM neurons was not attempted unless the noxious test stimulus induced a hind-limb withdrawal reflex.

Characterization of the response properties of an RVM cell consisted of the following assessment performed successively: 1. Spontaneous activity. 2. Response to heating of the hind paw ipsilateral to the treated knee with a Peltier device (LTS-3 Stimulator; a heat ramp rising at the rate of 10 °C/s from the baseline temperature of 35 °C to the peak temperature of 54 °C and peak duration of 10 s). 3. Response to pinching of the tail for 5 s by a surgical clamp that produced painful sensation when applied to the hand of the experimenter. 4. Response to colorectal distension (CRD) at a noxious intensity (80 mmHg; Ness et al., 1991) and duration of 10 s. CRD was produced by inflating with air a 7–8 cm flexible latex balloon inserted transanally into the descending colon and rectum. The pressure in the balloon was controlled by an electronic device (Anderson et al., 1987).

When analyzing responses of RVM neurons to peripheral stimulation, the baseline discharge frequency recorded during a corresponding period just before the stimulation was subtracted from the discharge frequencies determined during stimulation; i.e., positive values represent excitatory responses evoked by peripheral stimulation and negative ones inhibitory responses.

The animals used in recordings had a guide cannula for drug administrations into the PVN. Electrophysiological experiments were performed one to two weeks after fixation of the guide cannula to the skull, as described above. After determining the responses of an RVM neuron to peripheral stimulation, the phasic modulation of the discharge rate of RVM neurons by the PVN was assessed by microinjecting glutamate (50 nmol in 0.5 μl) into the PVN using methods described above. The discharge rate of the RVM cells was followed up to 5 min after the injection of glutamate. Thereafter, tonic control of the RVM by the PVN was assessed by microinjecting lidocaine (4% in 0.5 μl) into the PVN and following the discharge rate of RVM neurons up to 30 min.

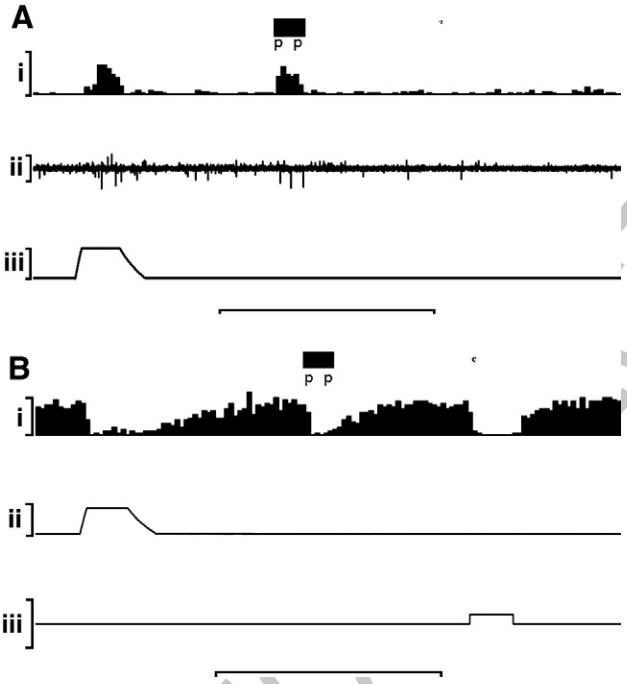

Fig. 11 – Examples of original recordings of RVM cells. A) ON-cell in a control animal. B) OFF-cell in an arthritic animal. In A, i shows the neuronal response, ii the withdrawal response in the hind limb, and iii the noxious heat stimulus applied to the hind paw. In B, i shows the neuronal response, ii the noxious heat stimulus, and iii the noxious visceral stimulus (colorectal distension). In both graphs, P–P indicate the duration of the noxious tail pinch. The vertical calibration bar for neuronal response represents 10 Hz in A and 20 Hz in B. In both graphs, the baseline temperature of the heat stimulus is 35 °C and the peak stimulus temperature 54 °C. In B, colorectal distension is applied at an intensity of 80 mmHg. The horizontal calibration bar represents 50 s in A and 40 s in B.

4.6. *Recording of neuronal responses in the spinal dorsal horn*

To exclude the possibility that the PVN-induced modulation of spinal reflex responses is rather due to action on spinal motor than sensory neurons, we determined the PVN-induced effect on responses of wide-dynamic range (WDR) neurons of the spinal dorsal horn. One to two weeks before the recordings of spinal dorsal horn neurons, a chronic guide cannula was inserted to the PVN as described above. Following induction of anesthesia with pentobarbitone (50 mg/kg i.p. followed by 15–25 mg/kg/h or more, if required according to continuous observation of the anesthesia level), a laminectomy was performed at the level of T12–L2 vertebrae. The dura was removed and the spinal cord was covered with warm mineral oil. Two spinal clamps, one rostral and one distal to the laminectomy, were used to stabilize the preparation. Data sampling methods

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were the same as with the RVM recordings (see above). In the spinal dorsal horn, search and classification of spinal units was performed as described in detail elsewhere (Pertovaara et al., 2001). Only wide-dynamic range (WDR) neurons activated by innocuous stimulation (brush) and giving a differential response to heat stimulation within nociceptive range (46–54 °C) were studied further. All the WDR neurons included in the study had their receptive fields in the plantar skin of the hind paw. The recording depth from the spinal cord surface was 0.4–1.0 mm.

When assessing the PVN-induced modulation of the response of a spinal dorsal horn neuron, the noxious test stimulus was a heat ramp applied from a Peltier device (LTS-3 Stimulator). The stimulus started from the baseline temperature of 35 °C and ascended to the peak temperature of 54 °C at a rate of 10 °C/s. The duration of the peak temperature was 10 s. The response to heat was determined 5 min prior to and 30 s after the injection of saline or glutamate (50 nmol in 0.5 μl) into the PVN. The magnitude of the response before the injection was considered the reference response (100%) for each neuron. The order of testing glutamate or saline was varied between the neurons and the interval between testing the effects of glutamate and saline on the same neuron was at least 5 min. The interval between testing different neurons in the same animal was at least 30 min.

4.7. *Drugs*

The opioid receptor antagonist naloxone hydrochloride and the 5-HT_{1A} receptor antagonist WAY-100635 were purchased from Sigma (St. Louis, MO, USA), while the α_2-adrenoreceptor antagonist atipamezole was obtained from Orion Pharma Inc. (Turku, Finland). The intrathecal doses of naloxone, WAY-100635 and atipamezole were chosen based on our previous investigations showing that at the dose range used these receptor antagonists alone had no significant effects on nociception in control or neuropathic animals (Pertovaara and Wei, 2003, 2007; Wei and Pertovaara, 2006). It should be noted that unlike many other α_2-adrenoreceptor antagonists, atipamezole does not bind to 5-HT_{1A} receptors (Pertovaara et al., 2005). Sodium pentobarbitone, glutamate and physiological saline were obtained from Orion Pharma Inc. (Espoo, Finland), and the local anesthetic, lidocaine, was obtained from Astra (Södertälje, Sweden).

4.8. *Course of the behavioral study*

One to two weeks following induction of the arthritis and at least one week following insertion of the intrathecal catheter and the guide cannula for PVN injections, the efficacy of PVN-induced phasic and tonic modulation of spinal nociception was determined by assessing the effect of glutamate and lidocaine in the PVN on the heat-evoked spinal withdrawal reflex in unanesthetized arthritic and control animals. Physiological saline was used for control injections and untreated animals were used as control animals. In these experiments, the latency of the withdrawal response was assessed 30 s, 5 min, 15 min and 30 min following the injection. The latency measured 30 s after glutamate injection and 15 min after lidocaine injection was used in further calculations, since the maximum effects of the studied compounds are obtained at these time points. The interval between behavioral assessments of glutamate-, lidocaine- or saline-induced effects was at least two days and the order of testing different compounds was varied between the animals.

Assessment of spinal neurotransmitter receptors mediating the descending antinociceptive influence induced by glutamate in the PVN was also assessed one to two weeks following induction of arthritis. In these experiments, one of the three receptor antagonists studied (atipamezole, WAY-100635 or naloxone) was administered intrathecally immediately following the assessment of the pre-drug latency. The effect of the receptor antagonist alone on the withdrawal latency was assessed 10 min following its intrathecal administration. At this time point, all the studied receptor antagonists should have their maximum effects. Glutamate (50 nmol) was microinjected into the PVN about 13 min following the intrathecal injection of the receptor antagonist. To assess possible reversal of the glutamate-induced antinociception by the spinally administered receptor antagonist, the heat-evoked withdrawal latency was again determined 30 s after injection of glutamate into the PVN; i.e., the potential reversal of PVN-induced antinociception was determined about 14–15 min following the intrathecal injection of the receptor antagonist. When testing different receptor antagonists in the same animal, the interval between testing sessions was at least two days. The order of testing different receptor antagonists was varied between the animals. Each animal participated in 1–3 behavioral testing sessions. At the end of the experiment, the animals were given a lethal dose of pentobarbitone and the brains were removed for histological verification of the injections sites.

4.9. *Course of the electrophysiological study*

Electrophysiological recordings of RVM neurons or spinal dorsal horn neurons were performed under pentobarbitone anesthesia in different animals one to two weeks following the induction of arthritis and at least one week following the insertion of the guide cannula for PVN injections. In RVM recordings, the response properties of the neurons were assessed by determining spontaneous activity and response to noxious heating of the skin, tail pinch and CRD. Then, the change in spontaneous activity of RVM neurons following successive microinjections of glutamate and lidocaine at a 15 min interval into the PVN was assessed as described in detail above. Search for the next neuron to be studied started about 30 min after the testing of the previous one was completed. At the end of the recording session, electrolytic lesions were made in the recording sites, the animals were given a lethal dose of pentobarbitone and the brains were removed for histological verification of the recording and injection sites.

In recordings of spinal dorsal horn WDR neurons, the heat-evoked response was determined before and 30 s after injection of glutamate or saline into the PVN; i.e., testing was performed at the time point when glutamate has its maximum effect. The interval between testing the saline and glutamate in the same neurons was at least 5 min, and the interval between testing different neurons in the same animal was at least 15 min. At the end of the recording session, the animals were given a lethal dose of pentobarbitone and the brain removed for histological verification of the injection site.

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4.10. Statistics

Two-way analysis of variance (ANOVA) followed by Dunnett's test (comparisons between three or more groups) or *t*-test (comparisons between two groups) were used in statistical assessment of the data. The differences in the incidence of various types of RVM neurons were analyzed using Fisher's exact test. $P<0.05$ was considered to represent a significant difference.

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