Contralateral but not systemic administration of bupivacaine reduces acute inflammation in the rat hindpaw

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Abstract
The effects of contralateral treatment with local anesthetics following acute hindpaw inflammation were investigated in rats. Inflammation was induced by unilateral injection of either 50 or 100 μl of 1% carrageenan into the right paw. Contralateral injection of either bupivacaine or saline was given immediately before the carrageenan. Hindpaw edema and withdrawal responses to thermal and mechanical stimulation were evaluated after 3, 6 and 24 h. The results showed that the pro-inflammatory effects of carrageenan were strongest at 6 h after the injection of 100 μl carrageenan with bilaterally decreased withdrawal latencies and ipsilateral edema formation. Contralateral treatment with bupivacaine (1.25, 2.5 or 5 mg/ml) dose-dependently reduced nociceptive behavior for 3–24 h. The edema was also reduced at 6 h. No effects on pain-related behavior were observed following systemic administration of bupivacaine. Sciatic nerve ligation on the contralateral side or intrathecal administration of saline significantly reduced the effects of bupivacaine when respectively compared with sham-operation and subcutaneous saline injection. Contralateral treatment with bupivacaine into the knee joint induced the same anti-nociceptive effect as administered into the paw. Our findings indicate that contralateral administration of bupivacaine induces long-lasting anti-nociceptive effects and may serve as a new or complementary treatment approach in acute inflammatory pain conditions.

Key words: bupivacaine, contralateral treatment, nociception, inflammation, rats, nervous system

Introduction
The response of the nervous system to pro-inflammatory challenge involves a local “triple response” which comprises wheal (edema formation), redness (increased blood flow) and flare (spreading of increased blood flow) and is called “neurogenic inflammation”. This response is caused by the axon-reflex mediated by sensory nerves and activation of Aδ- and C-fibers (Jancso et al., 1967; Gamse and Saria, 1985) resulting in the antidromic release of sensory vasodilating neuropeptides. Levine et al. (1985) hypothesized that the nervous system might provide an explanation for the symmetry found in rheumatoid arthritis. This was further elaborated by Kidd et al. (1989, 1995) who suggested that symmetrical neurogenic response is a part of host defense mechanisms. In previous studies we demonstrated a bilateral increase in neuropeptide concentrations in the synovial fluid following experimentally induced acute monoarthritis (Bileviciute et al., 1993). Amann et al. (1996) recently reported that unilateral intra-plantar challenge with nerve growth factor (NGF) resulted in a bilateral increase in the expression and synthesis of CGRP in dorsal root ganglia and nerve afferents, supporting the contribution of neuropeptides to symmetrical responses. The functional implications of the previous studies are that an acute unilateral challenge results in a bilaterally increased neuronal activity contributing to bilateral nociception (Kayser and Guilbaud, 1987; Yu et al., 1996). If so, it might be possible to affect the increased nociception by blocking the nerve activity contralaterally.

The aim of the present study was to elucidate whether a local anesthetic (bupivacaine) administered contralaterally to the site of experimentally induced inflammation affects nociceptive behavior and edema formation. The effects of contralateral treatment were also compared with systemic administration. The contribution of neuronal mechanisms was investigated by ligating the sciatic nerve on the contralateral side or administering saline intrathecally.

Materials and Methods
Experimental Protocol for Animal Studies
Experiments were performed on freely moving male albino Sprague–Dawley rats (B&K Universal AB, Sollentuna, Sweden) weighing 200–250 g and were

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approved by the Karolinska Institutet local ethical committee.

The experiments were preceded by extensive pilot studies aimed at finding the appropriate drugs and doses to be administered.

**Effects of bupivacaine in relation to the dose and the severity of inflammation** Two models of 1% carrageenan inflammation were examined by injecting either 50 or 100 μl intraplantarily and subcutaneously into the right hindpaw. In the model of less severe inflammation (50 μl) the contralateral (left) hindpaw was treated with the highest dose of bupivacaine (5 mg/ml) while in the 100 μl model of carrageenan, three doses of bupivacaine (1.25, 2.5 and 5 mg/ml) were used. Control rats were injected saline into the left paw. All injections into the contralateral hindpaw were given in a volume of 100 μl. To study the effects of local anesthetics on the non-inflamed paw, the left hindpaw of the rat was injected with either bupivacaine (5 mg/ml) or saline while the right was challenged with 100 μl of saline.

**Investigation of neuronal mechanisms behind the contralateral treatment** The model of 100 μl of 1% carrageenan into the right paw was used, while 100 μl of either bupivacaine (5 mg/ml) or saline were administered according to the experimental protocol. To evaluate the effects of systemic administration of bupivacaine vs the contralateral injection, bupivacaine was given either subcutaneously into the back or contralaterally into the paw. The contribution of the nervous system was studied either by dividing the left sciatic nerve or by intrathecal pretreatment with saline before the administration of bupivacaine into the left and carrageenan into the right paw. To study if the effect of contralateral treatment involves several spinal cord segments, 100 μl of bupivacaine (5 mg/ml) was injected into the left knee joint while the right paw was challenged with carrageenan.

Hindpaw withdrawal responses to thermal and mechanical stimulation and degree of edema of both the right and left sides were determined at 3, 6 and 24 h after carrageenan or saline injections. In the case of sham-operation or denervation, only the intact (right) hindpaw was used for measurements.

**Experimental Procedure for Nociceptive Behavioral Tests**

All rats were acclimatized to the testing conditions (determination of withdrawal responses and paw volume) six times daily for 3 days before the experiment was run, using the hot-plate and Randall–Selitto tests and varying the testing 50/50 between the two. Hindpaw volume was measured after the nociceptive tests. The right hindpaw was measured first and then the left, and vice versa during the second measurement with the interval between measurements being approximately 5–7 min. Two measurements were carried out during each test and the average value was used to quantify the percentage changes from the start of the experiment (basal values) for statistical analysis. All assessments were carried out at the same time of day. Drugs were administered in a blind fashion whenever possible.

The withdrawal response to noxious heat was determined using the hot-plate test. The entire ventral surface of the rat’s hindpaw was placed on the hot-plate, which was maintained at a temperature of 50°C (49.7–50.5°C). The time to hindpaw withdrawal was measured in seconds and subsequently referred to as the hindpaw withdrawal latency (HWL) to thermal stimulation. The cut-off time was 20 s.

The Randall–Selitto test (Ugo Basile, Type 7200, Italy) was used to assess withdrawal thresholds to mechanical stimulation. A wedge-shaped pusher with a loading rate of 48 g/s was applied to the dorsal surface of the manually handled hindpaw and the pressure required to initiate the struggle response was assessed and measured in seconds and referred to as the hindpaw withdrawal latency (HWL) to mechanical stimulation. The cut-off time was 15 s.

The hindpaw volume was measured by using a plethysmometer (Ugo Basile, Type 7150, Italy) and expressed in ml.

The basal values of 102 intact rats to thermal stimulation were 6.1 ± 0.3 and 6.1 ± 0.3 s (right and left, respectively); to mechanical stimulation 5.0 ± 0.1 and 5.0 ± 0.1 s (right and left, respectively); hindpaw volumes were 1.49 ± 0.01 and 1.53 ± 0.03 ml (right and left, respectively). Changes in hindpaw withdrawal responses and edema formation are presented as a percentage (%) change from the basal values of each rat.

**Surgical Procedure for Sciatic Nerve Transection**

Rats were anesthetized with intraperitoneal chloralhydrate (350 mg/kg) and the left sciatic nerve was cut. Control rats were sham-operated. Experimentation took place one week after the denervation. Both ligated and sham-operated rats were challenged with bupivacaine into the left and carrageenan into the right hindpaw. To investigate the effects of sciatic nerve ligation on behavioral responses, a group of sciatic nerve ligated rats was given saline into the left and carrageenan into the right paw. The basal values of the right hindpaw of 23 operated rats to thermal stimulation were 5.0 ± 0.3 s and to mechanical stimulation 5.1 ± 0.2 s. Hindpaw volumes were 1.59 ± 0.04 ml.

**Experimental Procedure for Intrathecal Injection**

Intrathecal administration was performed after 3 days of behavioral training. A stainless steel needle, with an outer diameter of 0.5 mm, was directly inserted into the subarachnoid space between the L3 and L4 vertebrae. Ten microliters of saline were infused intrathecally over 1 min. Control rats were injected
Statistical analysis was carried out using the SPSS (Statistical Product and Service Solutions) software (release 6). Each experimental group included 6 ± 10 rats.

### Chemicals
Bupivacaine, 5 mg/ml (Marcain, Astra, Södertälje, Sweden); bupivacaine 2.5 and 1.25 mg/ml were prepared by diluting 5 mg/ml in sterile 0.9% saline; carrageenan (1%) solution (Carrageenan Lambda, Sigma Chemical Co, USA) was prepared in sterile saline.

### Experimental Procedure for Injection into the Knee
Rats were lightly anesthetized with isoflurane. The left hindpaw or knee of the rat was injected with bupivacaine and the right hindpaw was injected with subcutaneous saline at the same site. One hour later the basal values for HWL and paw volumes were measured. Thereafter, bupivacaine was injected into the left paw and carrageenan into the right.

An intrathecal injection of saline was chosen in accordance with our previous studies which showed that such administration abolished the bilateral but not ipsilateral edema formation following unilateral challenge with calcitonin gene-related peptide (Bileviciute et al., 1998).

### Results
Table 1 presents the effects of carrageenan on hindpaw withdrawal latencies and edema formation. Injection of 50 µl of carrageenan induced an ipsilateral reduction in withdrawal latency to thermal stimulation after 3 h and ipsilateral edema at 3, 6 and 24 h. Injection of 100 µl of carrageenan caused an ipsilateral decrease in HWLs both to thermal and mechanical stimulation at 6 h. Ipsilateral hindpaw volume increased at 3, 6 and 24 h after 100 µl of carrageenan injection (Table 1). Both decrease in HWL to thermal stimulation and edema formation were more pronounced following injection of 100 µl of carrageenan than with 50 µl.
Effects of Bupivacaine in Relation to the Dose and the Severity of Inflammation

Inflammation induced by 50 \( \mu l \) of carrageenan

No changes in withdrawal latencies and edema formation were detected following contralateral injection of bupivacaine (5 mg/ml) in rats challenged with saline (Fig. 1). In rats challenged with 50 \( \mu l \) of carrageenan, contralateral injection of bupivacaine (5 mg/ml) increased the withdrawal latency to thermal stimulation at 3 h (Fig. 2). The withdrawal latency to mechanical stimulation remained unaffected. Contralateral injection of bupivacaine did not affect edema at 6 h.

Inflammation induced by 100 \( \mu l \) of carrageenan

In rats challenged with 100 \( \mu l \) of carrageenan, contralateral administration of bupivacaine at strengths 1.25, 2.5 or 5 mg/ml significantly increased HWL to thermal stimulation at 6 and 24 h as compared with saline treatment (Fig. 3). Bupivacaine administered at the highest dose (5 mg/ml) increased HWL to mechanical stimulation at 3 and 6 h (Fig. 3). Bupivacaine at 5 mg/ml was more efficacious in increasing HWL to mechanical stimulation at 3 h as compared to 1.25 mg/ml and at 6 h as compared to both 2.5 and 1.25 mg/ml. Contralateral administration of bupivacaine (5 mg/ml) also decreased edema formation at 6 h (Fig. 3).
Neuronal Mechanisms following Contralateral Treatment with Bupivacaine

Systemic administration of bupivacaine As shown in Figure 4, HWLs to heat and mechanical stimulation significantly decreased for 3–24 h and hindpaw volume increased at 6 h following the systemic injection of bupivacaine in comparison to the contralateral administration.

Sciatic nerve ligation HWLs to heat and mechanical stimulation significantly decreased for 3–24 h and hindpaw volume increased at 3 and 6 h on the inflamed side following sciatic nerve denervation on the contralateral side as compared to sham-operation (Fig. 5). No differences were found in HWL to thermal stimulation and edema formation in sciatic nerve denervated rats treated with bupivacaine as compared to those given saline. However, contralateral injection of bupivacaine in sciatic nerve denervated rats increased HWL to mechanical stimulation at 6 h as compared to saline and had a strong tendency (p < 0.05) to such increase at 24 h (Fig. 5).

Figure 3. Changes in HWL to thermal and mechanical stimulation and volume of the right paw injected with 100 μl of carrageenan. Contralateral hindpaw was administered either saline (●, dashed lines) or bupivacaine 1.25 (○), 2.5 (●), or 5 mg/ml (■). Data are presented as percentage (%) changes and expressed in mean ± SEM (vertical axis). Horizontal axis indicates hours following injection. Significant differences are denoted as ★ bupivacaine 5 mg/ml vs saline; + bupivacaine 2.5 mg/ml vs saline; § bupivacaine 1.25 mg/ml vs saline; ○ bupivacaine 5 vs 2.5 mg/ml and # bupivacaine 5 vs 1.25 mg/ml. p < 0.05, ANOVA test. n = 8–9.

Figure 4. Changes in HWL to thermal and mechanical stimulation and volume of the right paw injected with carrageenan following either contralateral (■) or systemic (□) administration of bupivacaine (5 mg/ml). Data are presented as percentage (%) changes and expressed in mean ± SEM (vertical axis). Horizontal axis indicates hours following injection. ■ denotes significant difference systemic vs contralateral administration. * p < 0.05, ** p < 0.01 and *** p < 0.001, t-test. n = 8.
Intrathecal pretreatment with saline

Saline injected intrathecally abolished the anti-nociceptive effects of contralateral treatment with bupivacaine on carrageenan-induced inflammation in comparison to its administration subcutaneously (Fig. 6).

Contralateral treatment of the knee joint

As shown in Table 2, no differences were found between the anesthetized and non-anesthetized rats injected with carrageenan into the right and bupivacaine into the left hindpaw, except for the HWL to thermal stimulation at 3 h. This indicates that brief anesthesia under isoflurane did not alter the effects of contralateral treatment on nociceptive behavior. No significant differences were found in HWLs to thermal and mechanical stimulation or edema formation whether bupivacaine was injected contralaterally into the knee joint or the paw followed by carrageenan injection into the right paw.
Bilateral Effects of Contralateral Treatment with Bupivacaine (5 mg/ml)

When comparing HWLs between the right and left sides, few irregular differences were found, showing that contralateral administration of bupivacaine induced bilateral changes in HWLs (Table 3). In the case of intrathecal pretreatment with saline, HWLs were increased on the left side at 3–6 h as compared to the right (Table 3).

Discussion

The results of the present study show that unilateral challenge with carrageenan induced a bilateral decrease in hindpaw withdrawal responses and an ipsilateral edema formation. Contralateral administration of a local anesthetic (bupivacaine) attenuated the bilateral decrease in hindpaw withdrawal responses and the ipsilateral edema formation depending on the degree of inflammation. When measuring HWL to mechanical stimulation, the antinociceptive effect of the contralateral treatment was dose related. Systemic administration of bupivacaine did not affect pain-related behavior and edema formation suggesting that the anti-inflammatory effects of bupivacaine are not mediated through the systemic mechanisms.

It has been recently reported that local anesthetics, if administered ipsilaterally prior to carrageenan challenge, may have a short anti-nociceptive effect (Kayser and Guilbaud, 1987; Fletcher et al., 1996). Our findings are that local anesthetics injected contralerally to the inflamed side induced a prolonged anti-inflammatory effect. To elucidate the neuronal contribution to this phenomenon, sciatic nerve ligation or intrathecal pretreatment with saline were performed. In both cases the anti-nociceptive effects of contralateral treatment with bupivacaine were significantly reduced. When comparing the effects of sciatic nerve denervation on the contralateral treatment with either bupivacaine or saline, measuring HWL to mechanical stimulation, the antinociceptive effect of the contralateral treatment was dose related. Systemic administration of bupivacaine did not affect pain-related behavior and edema formation suggesting that the anti-inflammatory effects of bupivacaine are not mediated through the systemic mechanisms.

Table 2. Changes in HWL to thermal and mechanical stimulation and volume of the right paw injected with carrageenan. Bupivacaine (5 mg/ml) was administered into either the left hindpaw or knee joint. Data are presented as percentage changes (%) and expressed in mean ± SEM. Control group represents non-anesthetized rats injected with carrageenan into the right and bupivacaine into the left hindpaw.

<table>
<thead>
<tr>
<th>Injected groups</th>
<th>HWL to thermal stimulation, % changes</th>
<th>HWL to mechanical stimulation, % changes</th>
<th>Hindpaw volume, % changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>Control</td>
<td>43.1 ± 13.2</td>
<td>33.4 ± 12.1</td>
</tr>
<tr>
<td></td>
<td>Paw injection</td>
<td>0.4 ± 12.0*</td>
<td>24.2 ± 12.3</td>
</tr>
<tr>
<td></td>
<td>Knee injection</td>
<td>11.3 ± 15.0</td>
<td>1.8 ± 3.3</td>
</tr>
<tr>
<td>6 h</td>
<td>Control</td>
<td>64.1 ± 20.6</td>
<td>42.5 ± 11.6</td>
</tr>
<tr>
<td></td>
<td>Paw injection</td>
<td>89.3 ± 33.4</td>
<td>12.5 ± 9.9</td>
</tr>
<tr>
<td></td>
<td>Knee injection</td>
<td>43.4 ± 22.2</td>
<td>28.9 ± 11.8</td>
</tr>
<tr>
<td>24 h</td>
<td>Control</td>
<td>34.8 ± 23.2</td>
<td>29.1 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>Paw injection</td>
<td>10.0 ± 18.9</td>
<td>9.5 ± 11.6</td>
</tr>
<tr>
<td></td>
<td>Knee injection</td>
<td>26.6 ± 17.0</td>
<td>12.5 ± 10.5</td>
</tr>
</tbody>
</table>

* denotes significant difference vs control group (non-anesthetized rats). t-test for independent samples. * p < 0.05, n = 6–8.

Table 3. Results represent the differences between the right and left sides in rats treated contralaterally with 100 μl of bupivacaine (5 mg/ml). Differences are presented as mean for each group (percentage changes of the right side minus the left).

<table>
<thead>
<tr>
<th>Injected substance, right paw</th>
<th>Injected substance, left paw</th>
<th>HWL to thermal stimulation</th>
<th>HWL to mechanical stimulation</th>
<th>Hindpaw volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 h 6 h 24 h</td>
<td>3 h 6 h 24 h</td>
<td>3 h 6 h 24 h</td>
</tr>
<tr>
<td>Saline</td>
<td>Bupivacaine, paw</td>
<td>-22.1 -3.9 -11.6</td>
<td>3.9 8.7 -12.3</td>
<td>6.1 1.2 -1.0</td>
</tr>
<tr>
<td>Carrageenan 50 μl</td>
<td>Bupivacaine, paw</td>
<td>15.2 26.2 7.7</td>
<td>-13.0 0.3 2.6</td>
<td>51.5* 35.5* 16.3*</td>
</tr>
<tr>
<td>Carrageenan 100 μl</td>
<td>Bupivacaine, paw</td>
<td>0.67 -10.8 -1.4</td>
<td>11.3 5.6 10.2*</td>
<td>64.7** 45.6** 21.6**</td>
</tr>
<tr>
<td>Carrageenan 100 μl</td>
<td>Bupivacaine, knee</td>
<td>-13.2 12.4 11.6</td>
<td>-2.4 8.1 1.1</td>
<td>78.3* 58.1* 26.9*</td>
</tr>
<tr>
<td>Carrageenan 100 μl</td>
<td>Bupivacaine, paw, saline i.t.</td>
<td>-70.7* -52.7* -16.5</td>
<td>-27.3* -20.3* -19.4</td>
<td>86.6* 73.6* 41.1*</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01. Wilcoxon pairs rank test. n = 6–10.
an increased HWL to mechanical stimulation at 6h and a strong tendency to such increase at 24h were found, indicating that other nerves innervating the paw might mediate the effects of contralateral treatment. The blocking effect of intrathecal saline on bilateral responses, demonstrated in our previous studies (Bileviciute et al., 1998), might be due to the dilution of neuronal substances or the interruption of the nervous system mechanisms involved in bilateral transmission. These findings also indicate that when studying the bilateral transmission, an intrathecal injection of a vehicle should be carefully considered as a control injection vs other substances acting on the spinal cord activity. The neurogenic origin of bilateral responses is also supported by a study showing that a second contralateral injection of formalin into the upper lip of the rat increased the nociceptive behavior, but that this increase was prevented by an ipsilateral anesthetic blockade of the infra-orbital nerve (Cadet et al., 1995). Furthermore, systemic administration of local anesthetics such as lidocain and bupivacaine, in non-toxic doses, did not attenuate nociceptive responses, indicating that neuronal but not systemic mechanisms contribute to local anesthetic-induced anti-nociception (Wiesenfeld-Hallin and Lindblom, 1985; Kaysor and Guilbaud, 1987).

It is possible that these peripheral neurogenic effects on the contralateral side are due to sodium channel blocked on Aδ- and C-fibers (Ritchie, 1994). Local anesthetics are usually tertiary or secondary amines. Reaching the axoplasm and membrane of the nerve, they bind to the sodium channels by blocking them, resulting in a nerve conduction block (Ritchie, 1994). It is possible that injection of 100 μl of carrageenan resulted in the activation of a larger number of silent nociceptors than 50 μl did (Schaible and Schmidt, 1988; Schmidt et al., 1995) and provides a possible explanation of why the same dose of a local anesthetic induced a stronger anti-inflammatory effect in inflammation induced by 100 μl of carrageenan than in that induced by 50 μl.

Sherrington (1898) reported that stimulation of the nerve fibers on one side induces a behavioral phenomenon on the contralateral side, called “crossed extensor reflex”. According to the hypothesis, this suggests an intrinsic spinal reflex. However, Kawasaki et al. (1986) demonstrated that this reflex is under supra-spinal level control, as it was depressed by the central administration of diazepam but not in spinal cord transected rats. Results of our study indicate a possibility of a new crossed spinal reflex, involving nociceptive transmission across the spinal cord and even several segments. This is supported with our present findings showing that, in general, there were no differences in HWL latencies between the right and left sides, except in the case of intrathecal pretreatment with saline, which increased latencies on the non-inflamed side, possibly, due to interruption of the bilateral transmission. Moreover, our results indicate that bupivacaine exerts anti-nociceptive effects when administered contralaterally but not systemically. This indicates different mechanisms involved after contralateral vs systemic administration of a drug acting on the peripheral nerve endings.

One of the most interesting findings of the present study was the long duration (up to 24h) of the anti-nociceptive effects of contralateral local anesthetics. Kayser and Guilbaud (1987) reported that an ipsilateral administration of local anesthetics in unilateral carrageenan-induced inflammation inhibited nociceptive behavior in both fore- and hindpaws for up to 25 min. Ipsilateral administration of local anesthetics prior to challenge with carrageenan has also been reported as reducing edema formation and nociceptive behavior for 2h (Fletcher et al., 1996). A similar injection did not alter the withdrawal latency to mechanical stimulation when carrageenan was injected a second time, either ipsilaterally or contralaterally after 7 days (Fletcher etal., 1997). It may be suggested that the short duration of the ipsilaterally administered local anesthetics, in comparison to the long-lasting effects obtained with contralateral administration, is due to metabolic or dilution effects at the inflammation site. The anti-nociceptive effect of bupivacaine continued even after the expected duration of the pharmacological effect (up to 24h when measuring HWL to thermal stimulation instead of 7–14h). The contribution of the spinal mechanisms to long-lasting effects following unilateral challenge is also supported by our previous study, demonstrating that unilateral injection of calcitonin gene-related peptide (which is effective in a few minutes) induces a bilateral edema formation for 24h (Bileviciute et al., 1998). The long-lasting effects of local anesthetics indicate that a primary peripheral nerve conduction block is followed by other inhibitory mechanisms at the spinal and supraspinal cord levels. Pharmacological intervention during the more severe inflammation, possibly leads to more intensive inhibitory mechanisms at the spinal cord. Mao et al. (1992) obtained similar long-lasting results when NMDA antagonist was given intrathecally to mononeuropathic rats in order to reduce nociceptive behavior. Recently we demonstrated that contralateral treatment with xylocaine reduced pain-related behavior in mononeuropathic rats for several weeks after administration (Bileviciute-Ljungar and Lundeberg, 1999). This suggests a long-lasting inhibition of pain pathways in the central nervous system by contralateral treatment with substances inhibiting peripheral nerve activity. Several mechanisms are reported in the transmission of pain pathways. NMDA, non-NMDA and tachykinin receptors in the spinal cord have been shown to play a major role in the sensitization of pain transmission (Baranauskas and Nistri, 1998). In respect of these findings it is important to further investigate the
mechanisms involved in the effects of contralateral treatment. Altogether, the results of the present study indicate that contralateral administration of bupivacaine attenuated pain-related behavior in rats following acute unilateral inflammation. Our findings support a key role for the nervous system in this phenomenon. The contralateral treatment, inhibiting the neuronal inflammatory mechanisms, might become a new treatment approach during acute inflammatory or pain-related disorders.

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References


