Contribution of Opioid Receptors on Primary Afferent Versus Sympathetic Neurons to Peripheral Opioid Analgesia

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ABSTRACT

Opioid receptors are synthesized in dorsal root ganglia and transported into peripheral terminals of primary afferent neurons. Activation of such receptors results in antinociceptive effects that are most prominent in inflammation. In addition, opioid receptors located on sympathetic postganglionic neurons may be involved in these effects. This study investigates the peripheral analgesic efficacy of the mu, delta and kappa receptor agonists [D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin, [D-Pen2,5]-enkephalin and trans-(-)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide, the effective number of peripheral mu, delta and kappa receptors in relation to the development of inflammation and the contribution of sympathetic vs. sensory neurons by use of capsaicin and 6-hydroxydopamine, respectively. In Wistar rats with Freund’s adjuvant-induced hindpaw inflammation, antinociceptive effects of intraplantar [D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin (1.0–32 μg), [D-Pen2,5]-enkephalin (10–100 μg) and trans-(-)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide (10–100 μg) were evaluated by paw pressure test. These effects increased linearly between 6 and 24 hr, but did not change between 24 and 96 hr of inflammation, whereas the doses of the irreversible antagonists β-funaltrexamine, (D-Ala2,Leu5,Cys6)enkephalin or (±)-(5β,7a,8β)-3,4-dichloro-N-[3-methylene-2-oxo-8-(1-pyrrolidinyl)-1-oxaspir[4,5]dec-7-yl]benzeneacetamide required to abolish the respective agonist effects increased between 12 and 96 hr. Pretreatment with capsaicin (30, 50, 70 mg/kg s.c. over 3 days) but not with 6-hydroxydopamine (75 mg/kg i.p. over 3 days) reversed the hyperalgesia in inflamed paws and almost abolished antinociceptive effects of all three agonists. These results suggest that the increased opioid agonist efficacy is due to an increased number of peripheral opioid receptors at later stages of inflammation and that peripheral opioid antinociceptive effects are primarily mediated by mu, delta and kappa opioid receptors on primary afferent neurons.

Experimental and clinical studies demonstrate that local administration of low doses of opioids elicits potent analgesic effects in inflamed, but not in noninflamed tissue by activation of peripheral opioid receptors (Stein, 1995). Opioid binding studies provide evidence for opioid receptors in dorsal root ganglia and on central terminals of PAN (LaMotte et al., 1976; Fields et al., 1980). More recently, opioid receptors were demonstrated on peripheral sensory nerve terminals in rats and humans (Stein et al., 1990, 1996; Hassan et al., 1993). These receptors are upregulated during inflammation, while mRNA for mu and kappa opioid receptors does not change in DRG (Schäfer et al., 1995, 1997). It has also been suggested that peripheral opioid receptors are located on SPN terminals (Wüster et al., 1981; Berzetei et al., 1987, 1988) and that SPN are involved in the peripheral antinociceptive effects of delta and kappa opioid agonists in a model of BK hyperalgesia (Taiwo and Levine, 1991). However, others have questioned the involvement of SPN in the latter model (Koltzenburg and Reeh, 1992). Moreover, some of the studies attempting the direct demonstration of opioid receptor mRNA in sympathetic ganglia have produced negative results (Schäfer et al., 1994). Thus, there is controversy about the presence of opioid receptors in SPN. Therefore, we set out to examine 1) the peripheral analgesic efficacy of the mu, delta and kappa opioid receptor agonists DAMGO, DPDPE, U50,488H and the effective number of peripheral mu, delta and kappa opioid receptors in relation to the development of CFA inflammation in vivo and 2) the contribution of primary sensory vs. sympathetic postganglionic neurons to the analgesic effects of peripherally administered mu, delta or kappa selective opioid agonists by use of the PAN selective neurotoxin capsaicin and the SPN selective neurotoxin 6-OHDA.

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ABBREVIATIONS: BK, bradykinin; CGRP, calcitonin gene-related peptide; DAMGO, [D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin; DALCE, [D-Ala2-Leu5,Cys6]enkephalin; DPDPE, [D-Pen2,5]-enkephalin; DRG, dorsal root ganglia; CFA, complete Freund’s adjuvant; β-FNA, β-funaltrexamine; i.pl., intraplantar; 6-OHDA, 6-hydroxydopamine; PAN, primary afferent neurons; PPT, paw pressure threshold; SMBU-1, (±)-(5β,7a,8β)-3,4-dichloro-N-[3-methylene-2-oxo-8-(1-pyrrolidinyl)-1-oxaspir[4,5]dec-7-yl]benzeneacetamide; SPN, sympathetic postganglionic neurons; U50,488H, trans-(-)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide; ANOVA, analysis of variance.
Materials and Methods

Subjects. Male wistar rats weighing 200 to 250 g were purchased from Charles River Breeding Laboratories and housed individually in cages lined with ground corn cob bedding. Room temperature was maintained at 22 ± 0.5°C with a relative humidity between 40 and 60%. Standard laboratory rodent food and tap water were available ad libitum. All experiments were conducted in the light phase of a 12 hr/12 hr (7 A.M./7 P.M.) light-dark cycle. Animals were handled three times before any testing was performed. The guidelines on animal care of the American Association for the Study of Pain were followed. Animal facilities were accredited by the American Association of Laboratory Animal Care and experiments were approved by the Institutional Animal Care and Use Committee of the Division of Intramural Research/National Institute on Drug Abuse/National Institutes of Health in accordance with Institute of Laboratory Animal Resources, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985.

Induction of inflammation. Rats received a single i.pl. injection of 0.15 ml of complete Freund’s adjuvant (Calbiochem, La Jolla, CA) into the right hindpaw under brief halothane anesthesia. This model is distinct from polyarthritic rats, in whom signs of disease are generalized and do not appear before 12 days after Freund’s adjuvant inoculation at the tail base. Rats in our model develop only a local inflammation that lasts up to 6 days and remains confined to the inoculated paw (Millan et al., 1988). The advantage of the present model is that the contralateral paw serves as a control and that animals suffer less. As a parameter of inflammation, paw volume was determined by submerging each hindpaw into a water-filled Perspex cell of a plethysmometer (Ugo Basile, Comerio, Italy). The volume of displacement, which is equal to the paw volume, was then read on a digital display. For each animal, measurements were done twice and the average calculated.

Drugs and administration. The following drugs were used: DAMGO (RB1); DPDPE (RB1); U50,488H (RB1); β-FNA (RB1), an irreversible µ-opioid receptor antagonist; DALCE (courtesy of Dr. W. D. Bowen, NIDK, NIH) an irreversible δ-opioid receptor antagonist (Bowen et al., 1987); SMBU-1 (courtesy of Dr. C. Y. Cheng, National Taiwan University), an irreversible kappa opioid receptor antagonist (Cheng et al., 1992); 8-Methyl-N-vanillyl-6-nonenamide (capsaicin) (Sigma Chemical Co., St. Louis, MO); 6-OHDA (RB1); methohexital Na (Eli Lilly, Indianapolis, IN). Routes and volumes of drug administration were i.pl. (100 μl), i.p. (200–300 μl) or s.c. (600–2000 μl). Opioid agonists were given alone or 2 hr before the relative agonist administration in separate groups of animals. PPT were tested 5 min after the agonist injections and dose-response curves were constructed for β-FNA, DALCE and SMBU-1 at 12 and 96 hr of inflammation respectively.

Experiment 1. Dose-response relationships of mu, delta and kappa selective opioid agonists were assessed. After baseline measurements, separate groups of animals received i.pl. injections of the following doses of drugs: DAMGO, 1, 4, 8, 16 and 32 μg; DPDPE, 10, 25, 50 and 100 μg; U-50,488H, 10, 25, 50 and 100 μg. Five min postinjection, when paw pressure thresholds were maximal (Stein et al., 1989), paw pressure thresholds were evaluated. This procedure was carried out in separate groups of animals at different stages (6, 12, 24, 96 hr) of inflammation.

Experiment 2. Whether the antinociceptive effect of the above agonists was brought about by selective activation of mu, delta and kappa opioid receptors was examined. To assess this question, the mu, delta and kappa selective irreversible antagonists β-fumaltrexamine, DALCE and SMBU-1 were i.pl. injected alone or 2 hr before the relative agonist administration in separate groups of animals. PPT were tested 5 min after the agonist injections and dose-response curves were constructed for β-FNA, DALCE and SMBU-1 at 12 and 96 hr of inflammation respectively.

Experiment 3. It was examined whether antinociceptive effects, induced by the above three opioid agonists, are influenced by capsaicin pretreatment. Then 96 hr after Freund’s adjuvant inoculation, dose-response curves of DAMGO, DPDPE and U-50,488H were constructed in both capsaicin and vehicle pretreated groups. In separate groups of animals, the following doses of drugs were used: DAMGO: 2.5, 5, 10 and 20 μg; DPDPE: 25, 50 and 100 μg; U-50,488H: 25, 50 and 100 μg.

Experiment 4. It was examined whether antinociceptive effects, induced by the three opioid agonists, are influenced by 6-OHDA pretreatment. Then 96 hr after Freund’s adjuvant inoculation, dose-response curves of DAMGO, DPDPE and U-50,488H were constructed in both 6-OHDA and vehicle pretreated groups, analogous to the foregoing protocol.

Experiment 5. To assess whether capsaicin or 6-OHDA pretreatment had any effects on the inflammatory signs, baseline PPT and paw volume measurements were carried out both before and after capsaicin or 6-OHDA treatment.

Statistical analysis. Data are presented as means ± S.E.M. For comparison of data between independent groups Mann-Whitney U test was used. Dose-response curves were assessed by an ANOVA and a subsequent linear regression ANOVA to test the zero slope hypothesis. Changes in PPTs and paw volumes in the same animal before and after treatment were analyzed by the Wilcoxon matched pairs test. To assess the difference between dose-response curves, two-way ANOVA was used. Differences were considered significant if P < .05. All calculations were done with the statistics software program StatView Version 4.5 (Abacus Concepts Inc., Berkeley, CA).

Results

Experiment 1. At each stage of the inflammation, i.pl. DAMGO (1–32 μg) increased paw pressure thresholds dose dependently and produced a maximum elevation at 8 μg in paws inoculated with CFA (P < .05, ANOVA), but not in contralateral saline-treated paws (P > .05, ANOVA) (fig. 1A).
The plateau, but not the slope of DAMGO's dose-response curves increased in correlation to the duration of the inflammation. The efficacy of DAMGO, as determined by the area under the dose-response curve, increased linearly until 24 hr after CFA inoculation ($P < .001$, linear regression ANOVA), but did not change significantly between 24 and 96 hr ($P > .05$, unpaired $t$ test) (fig. 1B). After i.pl. DPDPE (10–100 $\mu$g) and U50,488H (10–100 $\mu$g), PPT increased dose-dependently and reached the maximum elevations at 100 $\mu$g in inflamed paws ($P < .05$, ANOVA), but did not change in contralateral noninflamed paws ($P > .05$, ANOVA) (figs. 2A and 3A). The efficacy of DPDPE as determined by the area under the dose-response curve increased linearly until 24 hr after CFA inoculation ($P < .001$, linear regression ANOVA), and that of U50,488H increased linearly until 96 hr after CFA inoculation ($P < .001$, linear regression ANOVA). The efficacy of both DPDPE and U50,488H did not change significantly between 24 and 96 hr ($P > .05$, unpaired $t$ test) (figs. 2B and 3B).

**Experiment 2.**

$\beta$-FNA (0.1–70 $\mu$g), injected into inflamed paws 2 hr before DAMGO (8 $\mu$g), antagonized its effects dose dependently ($P < .001$, linear regression ANOVA) (fig. 1C). At 6, 12 and 24 hr after CFA administration, dose-response curves of $\beta$-FNA were not significantly different ($P > .05$, two-way ANOVA), but significantly higher doses of $\beta$-FNA were required to antagonize DAMGO effects at 96 hr as compared to 12 hr after CFA administration ($P < .001$, two-way ANOVA). $\beta$-FNA given alone did not change paw pressure thresholds until 120 min postinjection ($P > .05$, ANOVA) (fig. 1C).
DALCE (1–50 μg), injected into inflamed paws 2 hr before DPDPE (50 μg), antagonized its effects dose dependently (P < .05, linear regression ANOVA) (fig. 2C). Doses of DALCE required to antagonize DPDPE effects at 96 hr after CFA administration were significantly higher than those at 12 hr (P < .01, two-way ANOVA). The antinociceptive effects of all three opioid agonists in the inflamed paws were almost abolished except for the highest doses (figs. 4A, 5A and 6A).

**Experiment 3.** Capsaicin treatment caused a 28.8% (P < .01, as compared to non-inflamed solvent control, U test) decrease in CGRP-IR in DRG of non-inflamed and inflamed hindlimbs, respectively. This reduction in CGRP-IR staining coincides with a 74% reduction of inflammation-induced c-fos staining in the dorsal spinal cord and indicates a blockade of sensory input to the spinal cord (Zhang et al., 1998).

Intraplantar administration of DAMGO, DPDPE or U50,488H in vehicle pretreated groups produced dose dependent PPT elevations in inflamed but not in noninflamed paws (P < .01, linear regression ANOVA) (figs. 4A, 5A and 6A). After capsaicin pretreatment, the PPT elevations induced by DAMGO, DPDPE and U50,488H in inflamed paws were significantly lower than those of vehicle pretreated groups (P < .001, two-way ANOVA). The antinociceptive effects of all three opioid agonists in the inflamed paws were almost abolished except for the highest doses (figs. 4A, 5A and 6A).

**Experiment 4.** After 6-OHDA treatment, the rats showed typical signs of sympatholysis, i.e., ptosis and slight diarrhoea. However, they were active and showed no other signs of debility. The catecholamine content of the sympathetic plexus around plantar blood vessels and inside the sacral nerve was estimated using glyoxylic acid-induced fluorescence (fig. 8A). In control animals, sympathetic axons could readily be seen in the perivascular plexus as a network surrounding plantar blood vessels (fig. 8B) and inside the sacral nerve (fig. 8C). No differences were observed in catecholamine content of the perivascular plexus and sacral nerve (fig. 8D) between control animals. In animals treated with 6-OHDA, the fluorescence staining in perivascular plexus and sacral nerve almost disappeared.

The antinociceptive effects elicited by i.pl. DAMGO, DPDPE and U50,488H in inflamed paws were not significantly attenuated after 6-OHDA pretreatment compared to the vehicle pretreatment groups (P > .05, two-way ANOVA) (figs. 4B, 5B and 6B). In all groups, PPT in the noninflamed paws remained unchanged after agonist injections.

**Experiment 5.** In vehicle pretreated groups, PPT in the inflamed paws were significantly lower than those in the
noninflamed paws 24 and 96 hr after CFA inoculation (P < .05, Wilcoxon test) (fig. 7). After capsaicin pretreatment, PPT was no longer significantly different between the two sides (P > .05, Wilcoxon test) (fig. 7A). At the same time, PPT in the noninflamed paw remained unchanged. After 6-OHDA treatment, no significant PPT changes occurred on either side (fig. 7B).

After capsaicin or 6-OHDA pretreatment (fig. 8), paw volumes of both sides were not significantly different from those of vehicle pretreated groups (P > .05, Mann-Whitney U test) (table 1). The volume of inflamed paws was significantly higher than that of contralateral noninflamed paws both before and after capsaicin or 6-OHDA treatment (P < .05, Wilcoxon test).

**Discussion**

This study shows that upon i.pl. injection of CFA, the peripheral antinociceptive efficacy of DAMGO, DPDPE and U50,488H increases linearly up to a maximum at 24 hr and remains unchanged between 24 and 96 hr, whereas the doses of β-funaltrexamine, DALCE and SMBU-1 required to abolish the respective opioid receptor agonist effects increases between 12 and 96 hr. During the first 24 hr after inoculation of the paw with CFA, the antinociceptive efficacy of the three opioid receptor agonists increased in parallel with the increase of the paw volume, a typical parameter of inflammation. The early appearance of the opioid effects suggests that mu, delta and kappa opioid receptors are preexistent on peripheral nerves, which is in line with the previous studies showing that axonal transport and density of opioid receptors increased, which is consistent with our previous studies showing that axonal transport and density of opioid receptors in dorsal root ganglia (Maekawa et al., 1994; Schäfer et al., 1995; Buzás and Cox, 1997) and the presence of opioid receptors on subcutaneous nerves in noninflamed paws (Stein et al., 1990; Dado et al., 1993).

To assess the effective number of peripheral opioid receptors in vivo, we used β-funaltrexamine, DALCE and SMBU-1 to selectively and irreversibly inactivate mu, delta and kappa opioid receptors, respectively, thereby decreasing the number of available receptors (Mjanger and Yaksh, 1991; Bowen et al., 1987; Cheng et al., 1992). Significantly higher doses of these antagonists were required to abolish the antinociceptive effects of their respective agonists at 96 hr after inflammation than at 12 hr. This suggests that the effective numbers of peripheral mu, delta and kappa opioid receptors increased, which is consistent with our previous studies showing that axonal transport and density of opioid receptors in peripheral paw tissue begin to increase significantly 2 to 3 days after CFA inoculation (Hassan et al., 1993). However, the early occurrence of antinociceptive effects of the opioid

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Noninflamed Paws</th>
<th>Inflamed Paws</th>
<th>Inflamed/ Noninflamed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>3.35 ± 0.09</td>
<td>5.21 ± 0.16</td>
<td>155.87 ± 4.53</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>3.45 ± 0.11</td>
<td>5.16 ± 0.17</td>
<td>149.00 ± 3.13</td>
</tr>
<tr>
<td>Solvent</td>
<td>3.59 ± 0.08</td>
<td>6.43 ± 0.37</td>
<td>178.83 ± 8.53</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>3.44 ± 0.07</td>
<td>5.74 ± 0.12</td>
<td>167.02 ± 4.22</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± S.E.M.  
* P < .001 indicate significant differences between inflamed and non-inflamed paws (Wilcoxon test).
agonists suggests that preexistent opioid receptors may be activated by other mechanisms during the early phases of inflammation. For instance, a low pH, as a consequence of inflammation, may increase the efficacy of opioid agonists to inhibit adenyl cyclase by decreasing the inactivation rate of receptor-coupled G proteins (Selley et al., 1993), which could play an immediate role in our model of inflamed paw tissue. In addition, opioid agonists have easier access to neuronal opioid receptors because inflammation entails a disruption of the perineurium which is critical for the access of agonists to opioid receptors, particularly in the early phase of inflammation (Antonijevic et al., 1995). The fact that, at later stages (24–96 hr) of inflammation, the efficacy of the three opioid agonists did not increase does not exclude an increased number of receptors at peripheral nerve terminals. One possible reason could be a high intrinsic activity of these opioid agonists, yielding maximal effects at a small fraction of occupied opioid receptors (Mjanger and Yaksh, 1991).

We have previously shown an up-regulation of opioid receptors on peripheral nerve terminals (Hassan et al., 1993) but unchanged levels of mu receptor mRNA in DRG (Schäfer et al., 1995). To evaluate the hypothesis that opioid receptors on SPN are possibly up-regulated and involved in mediating peripheral opioid analgesia in our model, we studied the peripheral analgesic effects of mu, delta and kappa agonists in rats sympathectomized by 6-OHDA. Our results indicate that sympathectomy by 6-OHDA has no significant effects on either of the three opioid agonists' peripheral analgesic effects, the hyperalgesia or the volume of the inflamed paw. The latter is in line with the report showing carrageenan induced inflammation was not influenced by chemical sympathectomy (Donnerer et al., 1991).

It has been reported that nociceptive afferents supplying inflamed tissue (Roberts and Elardo, 1985; Sanjue and Jun, 1989) or in lesioned nerves (Hábler et al., 1987; Sato and Perl, 1991) may be sensitized by sympathetic activity. Furthermore, the behavioral manifestation of hyperalgesia in animal models of inflammatory pain such as the carrageenan edema (Nakamura and Ferreira, 1987), chronic topical chlorof orm treatment, intradermal injection of bradykinin (Levine et al., 1986a) or neuropathy (Kim et al., 1993; Tracey et al., 1995) has been reported to depend critically on the presence of postganglionic sympathetic fibers. However, there are several reports both in vivo (Lam and Ferrell, 1991; Meyer et al., 1992; Schuligoi et al., 1994; Sluka et al., 1994) and in vitro (Koltzenburg and Reeh, 1992; Cesare and McNaughton, 1996) against the hypothesis of sympathetic dependence of inflammatory hyperalgesia, which is consistent with our results. Similarly, Woolf et al. (1996) showed that, after neonatal sympathectomy, the initiation of the inflammation induced hypersensitivity was delayed but the hyperalgesia at 6 to 48 hr after CFA treatment was completely unaffected. Possible explanations for these controversial results may be 1) the time-dependent nature of the involvement of the sympathetic nervous system in inflammatory hyperalgesia, 2) different animal models used and 3) different agents and routes of administration used to introduce inflammation.

Levine and Taiwo (1989, 1991) observed that PGE$_2$ induced hyperalgesia can be blocked by mu but not by delta and kappa opioids injected i.d., and that mechanical hyperalgesia induced by i.d. injection of BK can be blocked by kappa, delta, as well as mu opioid agonists. They suggested that an SPN site of action is involved in the peripheral antinociception of kappa and delta opioid agonists, based on the assumption that BK-induced hyperalgesia is produced by a release of PGE$_2$ from SPN terminals. In our study, the antinociceptive effects of neither of the three opioid receptor agonists were significantly attenuated after chemical sympathectomy with 6-OHDA. This indicates that the peripheral opioid antinociceptive effects in our model are not mediated by opioid receptors on SPN terminals.

In contrast, the antinociceptive effects of all three agonists were almost abolished after capsaicin treatment. This is in line with the demonstration of decreased antinociceptive effects of morphine in inflamed tissue after capsaicin treatment (Barthó et al., 1990) and indicates that mu, delta and kappa opioid receptors are located on capsaicin-sensitive C-fibers, in agreement with morphological studies showing opioid receptors on peripheral sensory nerve terminals (Stein et al., 1990, 1996; Hassan et al., 1993; Coggeshall et al., 1997).

We have previously shown that basal nociceptive pressure thresholds decreased and paw volume, as a parameter of inflammation, increases in inflamed paws, although these parameters do not change in the contralateral noninflamed paw (Schäfer et al., 1995). Our results, in keeping with our previous observations (Barthó et al., 1990), indicate that capsaicin-sensitive C-fibers play an essential role in the decrease of nociceptive pressure thresholds in the inflamed paw, but have no influence on either volume or nociceptive thresholds in the contralateral noninflamed paw. This is in contrast to neonatal capsaicin treatment, where mechanical hyperalgesia can still be induced (Ren et al., 1994; Shir and Seltzer, 1990), which could be the result of ongoing reorganization in the spinal cord with possible compensation by large primary afferents (Marlier et al., 1992; Hammond and

![Image](https://example.com/image1.png)

**Fig. 8.** Dark-field photomicrographs showing the fluorescence staining of sympathetic nerve fibers innervating blood vessels in rat subcutaneous tissue (a) and inside the sciatic nerve (c) before 6-OHDA treatment. After 6-OHDA treatment, this fluorescence staining almost disappears both around the blood vessels (b) and inside the sciatic nerve (d).
mediated by opioid receptors on primary afferent neurons. 

(delta) 6-OHDA reverses the development of hyperalgesia in inflammation. 2) Pretreatment with capsaicin but not may enhance the efficacy of opioid agonists at later stages of kappa

Ren et al., affected by capsaicin treatment (also see Cervero and 1986b). By contrast, paw inflammation in our study was not

Antonijevic I, Mousa SA, Schafer M and Stein C (1995) Perineurial defect and long-term effects. 3-day capsaicin treatment is not long enough to induce such such effects on paw inflammation. These results suggest that peripheral mu, delta and kappa opioid antinociceptive effects are primarily mediated by opioid receptors on primary afferent neurons.

Acknowledgements

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References