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Differential Behavioral Effects of Peripheral and Systemic Morphine and Naloxone in a Rat Model of Repeated Acute Inflammation

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Background: **It has been reported that opioid antinociceptive effects are enhanced in animal models of inflammation, but it remains unclear whether this sensitization to morphine is related to predominant central or peripheral increased effects.**

Methods: **The authors compared the behavioral effects of intraplantar and intravenous morphine and naloxone in a rat model of repeated acute carrageenan-induced inflammation in which enhanced responses to noxious stimuli result from sensitization in peripheral tissues or central sensitization. The antinociceptive effects of intraplantar morphine (50, 75, 100, 150, and 200 μg), intravenous morphine (0.3, 0.6, and 1 mg/kg), and the pronociceptive effects of intraplantar naloxone methiodide (150 μg) and intravenous naloxone (1 mg/kg) against noxious pressure (vocalization thresholds to paw pressure) in rats were assessed 3 h after one or two carrageenan plantar injections performed 7 days apart.**

Results: **After the first carrageenan injection, intraplantar and intravenous morphine produced significant increase of vocalization thresholds to paw pressure in inflamed but not in noninflamed paws. After the second carrageenan injection, the antinociceptive effects of intraplantar morphine were significantly reduced compared with those obtained after the first carrageenan injection, whereas effects of intravenous morphine were significantly enhanced and present in both hind paws. Intravenous naloxone demonstrated similar pronociceptive patterns after the first and second carrageenan injection. Intraplantar naloxone methiodide produced pronociceptive effects in inflamed hind paw that were significantly enhanced after the second carrageenan injection.**

Conclusions: **When inflammation is enhanced by recurrent stimulations, the antinociceptive effects of systemic morphine are enhanced. This increase is more likely related to central than peripheral sites of action, beyond endogenous opioid system activation.**

NUMEROUS studies have demonstrated that morphine injected by systemic and intrathecal routes has enhanced antinociceptive effects in inflammatory conditions.[1–5] However, a large body of recent work has suggested that locally administrated opioid agonists elicit antinociceptive effects through peripheral opioid receptors that become functional within inflamed tissue.[6–16] Numerous reports indicate that primary afferent neurons contain opioid receptors.[17–23] It remains unclear whether the greater opioid antinociceptive potency in inflamed tissue is related to predominant central or peripheral opioid sensitization or a combination of both.

A rat model of repeated acute inflammation induced by two hind-paw injections of carrageenan performed 7 days apart has been developed in our group. The first injection of carrageenan induces a significant reduction of the vocalization thresholds to paw pressure (VTPP) of all four paws.[24] When carrageenan is injected for the second time, the amplitude of the inflammatory response of both hind paws increases not only in the previously inflamed hind paw but also in the contralateral hind paw,[16,25,26] suggesting that sensitization of the nervous system has occurred. This model, at least in part, mimics some recurrent inflammatory pain states encountered in clinical situations. To investigate the target of morphine antinociceptive effects in inflammatory states, this study compared the antinociceptive effects of intraplantar and intravenous morphine in rats 3 h after acute inflammation induced by one or two carrageenan plantar injections. To investigate activation of endogenous opioid system in recurrent inflammation, behavioral effects of intravenous naloxone and intraplantar naloxone methiodide were also determined.

Material and Methods

All experiments were conducted in accordance with the European Communities Council Directive (86/6609/EEC; Brussels, Belgium) as well as with the Ministry of Agriculture (Brussels, Belgium) regulations. In addition, we adhered to the recommendations of the Committee for Research and Ethical Issues of the International Association for the Study of Pain (IASP) Ethical Guidelines.[27] In particular, the duration of the experiments was as short as possible, and the number of animals used was kept to a minimum.

Animals

Male Sprague-Dawley rats [n = 185, strain designation = Crl:CD(SD)BR; Charles River, Saint-Aubin-les-Elbeuf, France] that weighed 175–200 g on arrival were used. The animals were housed seven per cage in the experimental facilities for a week before the experiments. The ambient temperature was kept at 22°C. They were maintained on a 12-h light–dark cycle and had free access to standard rat chow and tap water. Each animal was used in only one experiment.

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Inflammation

Inflammation was induced by 0.2 ml of 1% solution of lambda carrageenan in saline (Satia Laboratory, Paris, France) injected into the plantar surface of the right hind paw. Carrageenan was prepared 24 h before each experiment.

Drugs and Doses

Intravenous and intraplantar injections were performed on nonanesthetized rats. The intraplantar morphine injection was performed in the same way as carrageenan plantar injection. Briefly, rats were placed in a cylinder with only the hind paw free for injection: the intraplantar injections were given rapidly (5 s), and rats were allowed to recover in their cages for 10 min before nociceptive testing.

The following substances were used: morphine hydrochloride (Meram, Paris, France), naloxone hydrochloride (DuPont Pharma, Paris, France), naloxone methiodide (Research Biomedical International, Natick, MA), and saline (0.9% NaCl). The doses of morphine (50–200 μg intraplantar, 0.3–1 mg/kg intravenous), naloxone (1 mg/kg intravenous), and naloxone methiodide (150 μg intraplantar) used were based on our previous studies in this model of inflammatory pain.[4,16,28]

Behavioral Testing

Experiments were conducted in a quiet room beginning at 9:30 AM. On the testing day, the rats were brought into the behavior room 1 h before the test session to habituate them to the environment. The antinociceptive action was determined by measuring VTPP using the Ugo Basile analgesymeter (Comerio, Italy). The animals were gently restrained under a soft towel, and steadily increasing pressure was applied to the dorsal surface of a hind paw *via* a dome-shaped plastic tip (diameter = 1 mm). The pressure required to elicit VTPP was determined. Two measurements were taken, and the mean was calculated. This centrally integrated response is especially sensitive to analgesic compounds, particularly in this model of inflammation.[1,4,16] The order of inflamed (right) versus noninflamed (left) paw testing was alternated between successive rats to avoid any possible order effects. By use of coded syringes, the experimenter was blind to the drug dose tested.

Experimental Designs

We investigated the behavioral effects of intraplantar and intravenous morphine and naloxone in rats after a first or a second carrageenan injection, with all injections performed in the same hind paw. The time of 3 h after carrageenan injection was chosen because maximal edema and mechanical abnormalities has been observed at this time point.[4,24–26] After baseline measurements of VTPP, saline, morphine (50–200 μg injected into the inflamed paw), intravenous morphine (0.3, 0.6, and 1 mg/kg), intravenous naloxone (1 mg/kg), or naloxone methiodide (150 μg injected into the inflamed paw) were administered. We determined the VTPP of both inflamed and noninflamed paws every 10 min after morphine or saline intraplantar or intravenous injection and every 5 min after naloxone intravenous or naloxone methiodide intraplantar injection.

Statistical Analysis

Data are expressed as mean ± SD. The overall effects of various treatments (areas under the curves) were calculated by the use of the trapezoidal rule. The Student *t* test was used to determine the difference between two means. With three or more means, analysis of variance was used. The observed significance was then confirmed with Tukey test. Simple regressions (linear model) were performed to establish dose-dependent effects. The statistical procedures were performed with a statistical computer program (Statgraphics Plus; Manugistics, Rockville, MD). The observed differences were regarded as significant when *P* values were less than 0.05.

Results

Vocalization Threshold to Paw Pressure after One and Two Carrageenan Injections

Three hours after carrageenan injection, in agreement with previous studies,[16] baseline VTPP of the inflamed paw was significantly decreased by 42% after a single carrageenan injection and was further decreased by 57% after the second carrageenan injection (table 1). Baseline VTPP of the noninflamed paw was not significantly reduced after the first carrageenan injection, whereas baseline VTPP of the noninflamed paw was significantly reduced ($P < 0.01$) after the second carrageenan injection.

Antinociceptive Effects of Intraplantar Morphine

Morphine injected into the inflamed paw produced an increase of the VTPP (table 1), but not in the noninflamed paw, either after one or two carrageenan injections. After the first carrageenan injection, the effects were dose-dependent ($r = 0.51$, $P < 0.05$) and lasted for 40 (75 μg) to 70 min (150 μg), with a plateau at the highest dose of 200 μg (fig. 1A).

As previously observed,[16] after the second carrageenan injection, the intensity and the duration of the effects of morphine were strongly reduced (fig. 1B) compared with the first carrageenan injection. The effects were dose-dependent ($r = 0.77$, $P < 0.05$), lasted for 40 (75 μg) to 50 min (150 μg), and plateaued beyond the 100-μg dose of morphine (fig. 1B). At doses between 100 and 200 μg, antinociceptive effects were significantly lower after the second than after the first carrageenan

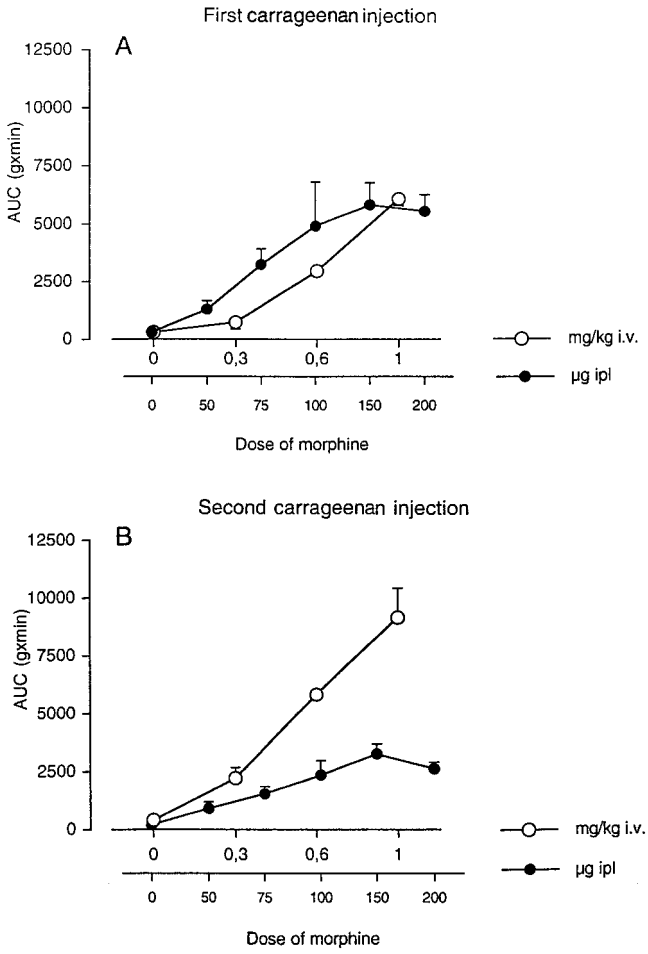

Fig. 1. Comparative antinociceptive effects of intraplantar (ipl; solid circles) and intravenous (i.v.; open circles) morphine on vocalization thresholds to paw pressure of the inflamed paw after a first (*A*) and a second (*B*) carrageenan plantar injection performed in the same hind paw 7 days apart. Data (mean ± SD, n = 7) are given as areas under the curve (AUC; g × min) of the respective time curves.

injection ($P < 0.05$ for 100, 150, and 200 μg of intraplantar morphine; fig. 1B).

Antinociceptive Effects of Intravenous Morphine

After the first carrageenan injection, morphine injected intravenously produced significant increases of the VTPP in inflamed paws (fig. 1A and table 1), but in noninflamed paws only for the highest dose (1 mg/kg). Antinociceptive effects were dose-dependent ($r = 0.94$, $P < 0.05$; fig. 1A) in inflamed paws and lasted for up to 60 min.

After the second carrageenan injection, the duration of the antinociceptive effects of intravenous morphine was enhanced compared with the first carrageenan injection. Morphine injected intravenously produced significant increases of the VTPP in reinflamed paws (table 1) and noninflamed paws. The antinociceptive effect on the inflamed paw was significant for all the doses tested and lasted for 60 (0.3 mg/kg) to 80 min (1 mg/kg). The effects were dose-dependent ($r = 0.88$, $P < 0.05$; fig. 1B).

Comparison of Intravenous and Intraplantar Morphine

Antinociceptive effects of intraplantar and intravenous morphine after the first carrageenan injection showed relatively equivalent patterns (fig. 1A). Intravenous administration of 1 mg/kg morphine produced antinociceptive effects (maximal VTPP increase of 170%; table1) that were similar in magnitude to the effects of 150 μg intraplantar morphine.

Antinociceptive effects of intraplantar and intravenous morphine after the second carrageenan injection showed very different patterns (fig 1B). Intraplantar morphine showed mild antinociceptive effects (maximal VTPP increase of 37% for the 150-μg dose; table 1). By contrast, intravenous morphine dramatically increased at 1 mg/kg with a maximal VTPP increase of 192%. The duration of the effect was different in the two sets of experiments: 40–50 min for intraplantar morphine and 60–80 min for intravenous morphine, respectively.

Effects of Intravenous Naloxone

Naloxone injected intravenously 3 h after carrageenan plantar injection showed pronociceptive effects, as described previously.[28] The effects in the inflamed paw were similar in magnitude after the first and the second inflammation ($P = 0.05$; fig. 2A). After the first carrageenan injection, intravenous naloxone produced significant decreases of the VTPP by 34% in the inflamed paw and by 35% in the noninflamed paw (maximum at 20 min). After the second carrageenan injection, intravenous naloxone showed significant decreases of the VTPP by 37% in the inflamed paw and by 25% in the noninflamed paw (maximum at 20 min).

Effects of Intraplantar Naloxone Methiodide

Naloxone methiodide injected into the inflamed paw 3 h after carrageenan injection produced a decrease of the VTPP in the inflamed paw but not in the noninflamed paw, either after one or two carrageenan injections (fig. 2B). After the first carrageenan injection, the effect lasted for 15 min, with a maximal VTPP decrease by 30% at 10 min. After the second carrageenan injection, the intensity and duration of the effect of naloxone methiodide was enhanced compared with the first carrageenan injection ($P < 0.001$). The effects lasted for 20 min with a maximal VTPP decrease by 46% at 10 min.

Discussion

In agreement with our previous studies,[16,26] the first carrageenan injection induced a significant reduction of the thresholds to mechanical stimulation of the inflamed paw. The established sensitization of the nervous system in inflammatory situations could be related either to

Table 1. Maximal Mean Vocalization Thresholds from the Inflamed Hind Paw in the Paw Pressure Test before and after Injection of Saline and Morphine

	Baseline Values	3 h after First Carrageenan Injection		3 h after Second Carrageenan Injection	
Treatment	Before Carrageenan	Before Treatment	After Treatment*	Before Treatment	After Treatment*
Intraplantar saline	426 ± 18	220 ± 16	244 ± 18	148 ± 15	166 ± 17
Intraplantar morphine (μg)					
50	457 ± 15	205 ± 7	244 ± 7†	152 ± 14	178 ± 14
75	402 ± 18	235 ± 4	315 ± 17‡	167 ± 6	206 ± 15†
100	441 ± 13	240 ± 9	386 ± 28‡	162 ± 12	203 ± 17‡
150	456 ± 24	222 ± 8	391 ± 15‡	172 ± 11	237 ± 24‡
200	435 ± 15	240 ± 9	376 ± 28‡	152 ± 22	202 ± 34‡
Intravenous saline	402 ± 19	225 ± 14	228 ± 12	194 ± 15	193 ± 18
Intravenous morphine (mg/kg)					
0.3	459 ± 21	245 ± 7	262 ± 8	150 ± 0	198 ± 15†
0.6	463 ± 24	257 ± 12	370 ± 25‡	156 ± 13	272 ± 8‡
1	456 ± 21	252 ± 14	430 ± 30†	156 ± 15	342 ± 21‡

Results are expressed in grams, as mean ± SEM. N = 7 rats in each group.

* After treatment, values expressed are those recorded at the time of the peak effect. † $P < 0.05$ *versus* before treatment. ‡ $P < 0.01$ *versus* before treatment.

peripheral and/or central mechanisms, and it is not known which one is predominant.

Antinociceptive Effects of Systemic Morphine Are Increased by Repeated Inflammation

Numerous studies have demonstrated that opioid agonists, including morphine, show a greater antinociceptive potency during experimentally produced inflammation. This has been described in different situations such as localized inflammation (carrageenan plantar injection),[2,29] Freund adjuvant–induced monoarthritis,[3,30,31] or diffuse Freund adjuvant–induced polyarthritis.[32] Opioid receptors are widely distributed throughout the central[30,32] and to a lesser extent the peripheral nervous system.[18,23,33] Data from several studies suggest that central and peripheral effects may be relevant in increasing opioid effectiveness during inflammation. Hurley and Hammond[30] demonstrated that the antinociceptive potency of DAMGO, a μ-opioid receptor agonist, microinjected in the rostral ventromedial medulla of rats, was progressively enhanced 4 days and 2 weeks after peripheral inflammatory injury in the ipsilateral and the contralateral hind paw. This study suggests that peripheral inflammatory injury enhances the effects of opioid agonists in the rostral ventromedial medulla region. Our study demonstrates that in rats in which inflammation has faded out and is reinduced and therefore enhanced, the antinociceptive potency of intravenous morphine is further increased. This increase in antinociceptive potency can be observed both in the inflamed and the noninflamed paw for doses of 0.6 and 1 mg/kg.

Antinociceptive Effects of Peripheral Morphine Are Reduced in Recurrent Inflammation

Once inflammation induced by the first carrageenan injection has fully developed, intraplantar morphine exerts pronounced and long-lasting effects. These results

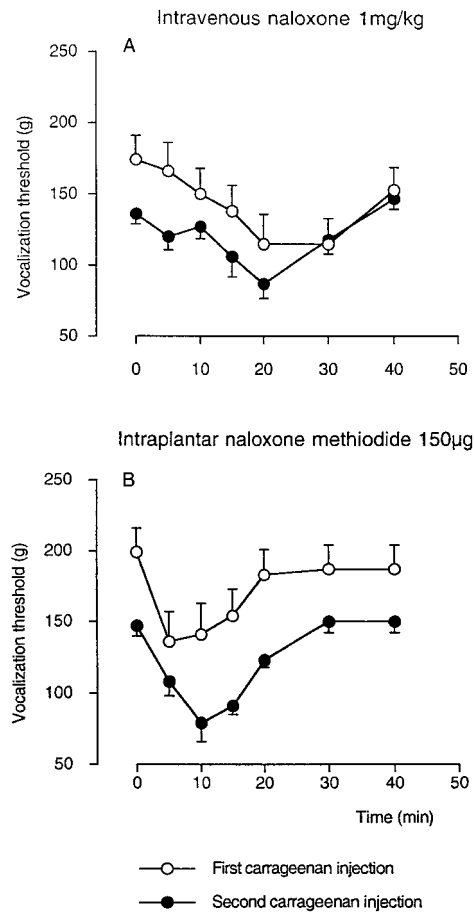

Fig. 2. Comparative pronociceptive effects of intravenous naloxone (*A*) and intraplantar naloxone methiodide (*B*) on vocalization thresholds to paw pressure (VTPP) of the inflamed paw after the first (open circles) and a second (solid circles) carrageenan plantar injection performed in the same hind paws 7 days apart. Data (mean ± SD, n = 5) are given as grams.

are in accordance with previous studies, showing that peripheral opioids produce dose-dependent antinociceptive effects in inflamed tissues.[16] There is abundant evidence indicating that peripheral opioid antinociceptive effects are mediated by opioid receptors located on primary afferent neurons.[15,20,23,33–38] As reported previously,[16] the peripheral morphine antinociceptive effects were weaker after the second carrageenan injection. Because the second injection of carrageenan increased the extent of paw edema, it might be that the different volume of the paw at the time of morphine injection induces a difference in the distribution of intraplantar morphine and therefore a different effect. However, we noted that the magnitude of the effects of the lower doses (50–75 μg) of morphine after the first and second inflammation was similar, likely reflecting adequate diffusion of the drug.

The decrease in intraplantar morphine antinociceptive potency observed after second inflammation could be related to further modifications at the peripheral level: enhancement of immune response involving different cytokines, possible mechanisms of nerve repair, or activation of anti-opioid systems caused by the increase of inflammatory response. Because morphine is a weak base with limited lipid solubility, with acid environment caused by increased inflammation, a greater proportion of morphine can exist in the ionized form. This might be a factor in the changes of the distribution of morphine after intraplantar injections. It is also possible that some antiinflammatory properties of high doses of opioids[39–41] that may play a role in the antinociceptive action could be overtaken when inflammation is enhanced, thus limiting the antinociceptive effects.

Differential Antinociceptive Effects of Intraplantar and Intravenous Morphine

During the initial inflammatory process, intravenous and intraplantar morphine showed similar antinociceptive effects for the doses tested. Three hours after the second induction of inflammation, once sensitization of the nervous system was fully established, the patterns are completely different: intravenous morphine has enhanced action, whereas intraplantar morphine has a reduced effectiveness.

The increased antinociceptive potency of intravenous morphine has been mainly attributed to central sensitization to opioids during inflammation, and numerous studies have demonstrated that morphine injected by systemic and central routes has enhanced antinociceptive effects in inflammatory conditions.[1–5,30,31] It is generally acknowledged that opioids produce their antinociceptive effects *via* actions within the central nervous system[42]; however, there is some question regarding the pain modulatory function of both peripheral and central opioid receptors during inflammation.

Endogenous opioid system activation could be involved in the nociceptive behavioral modifications observed in inflammatory conditions.[28] After the second inflammation, intraplantar naloxone methiodide showed increased pronociceptive effect, whereas intraplantar morphine demonstrated reduced antinociceptive effects. This may suggest an increased peripheral endogenous opioid system activation that could interfere with peripheral exogenous (intraplantar) morphine. Surprisingly, intravenous naloxone did not show an increase of pronociceptive effect after recurrent inflammation in both hind paws, suggesting that central endogenous opioid system activation does not interfere with exogenous systemic morphine.

Our experimental model of repeated acute inflammation may be a suitable model of human painful joint disorders (*e.g.*, osteoarthritis or rheumatoid arthritis) where there are recurrent flares. Aley *et al.*[43] used a model of recurrent inflammation close to our model and investigated pronociceptive peripheral mechanisms, most likely in nociceptors, that may have a role in such chronic inflammatory pain states. Three weeks after a first carrageenan intraplantar injection, injection of inflammatory mediators such as prostaglandin E_2 or 5-hydroxytryptamine or of an adenosine A_2 agonist at the same site produced increased prolonged hyperalgesia (up to 24 h compared with $\leq$ 5 h in control rats not pretreated with carrageenan). Although intraarticular morphine produces analgesia in chronic arthritis,[44] it has not yet been demonstrated if systemic morphine shows greater analgesic effects in inflammatory rheumatic diseases (*e.g.*, rheumatoid arthritis) than in other painful situations.

In conclusion, our study demonstrates that morphine antinociceptive effects are dependent on the conditions of inflammatory pain. In acute inflammation, peripheral and central effects both play a role, whereas, when inflammation is reinduced and enhanced, central effects become predominant with a reduction of peripheral effects. Although the current findings cannot be extrapolated directly to the clinical management of pain,[32,45,46] the results suggest that peripheral administration of morphine does not carry significant advantage with respect to suppression of pain in recurrent inflammation.

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