Intracisternal and Intraperitoneal Administration of Morphine Attenuates Mechanical Allodynia Following Compression of the Trigeminal Ganglion in Rats

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Aims: *To investigate the effects of morphine on mechanical allodynia following compression of the trigeminal ganglion in the rat.* ***Methods:*** *Experiments were carried out on male Sprague-Dawley rats weighing between 250 and 260 g. For compression, a 4% agar solution (8 µL) was injected into the trigeminal ganglion. In the control group, rats were sham operated without agar injections. The authors evaluated the effects of intraperitoneal or intracisternal administration of morphine on mechanical allodynia evoked by air-puff stimulation of the vibrissa pad area 14 days following compression of the trigeminal ganglion.* ***Results:*** *Mechanical allodynia was established within 3 days and lasted beyond postoperative day 24. Intraperitoneal administration of morphine (2 or 5 mg/kg) significantly blocked mechanical allodynia ipsilateral to the compression of the trigeminal ganglion. Intraperitoneal administration of morphine also inhibited mechanical allodynia on the contralateral side. Moreover, intracisternal administration of morphine (5 µg) strongly suppressed both ipsilateral and contralateral mechanical allodynia. The antiallodynic effects of morphine were blocked by pretreatment with naloxone, an opioid receptor antagonist.* ***Conclusion:*** *These results suggest that the application of a high dose of morphine may be of great benefit in treating trigeminal neuralgia-like nociception.* J OROFAC PAIN 2010;24:113–121

Key words: allodynia, animal model, morphine, trigeminal ganglion, trigeminal neuralgia

It has been well established that opioids produce analgesic effects through the stimulation of central opioid receptors.[1] In addition, several studies have inducted that morphine may modulate orofacial pain. Morphine administered systemically reduced in a dose-dependent fashion the face grooming provoked by subcutaneous capsaicin,[2] and systemic injection of morphine attenuated nociceptive behavior as well as the c-*fos* expression levels produced by the intra-articular injection of mustard oil into the temporomandibular joint and these antinociceptive effects were reversed by naltrexone, a µ opioid receptor antagonist.[3] Furthermore, submucous injections of morphine in conjunction with a standard local anesthetic during dental surgery significantly improved postoperative analgesia.[4]

Opiates are generally considered to be poor analgesics for neuropathic pain. Neither a single pre-injury injection nor chronic post-injury administration of morphine affected mechanical and cold allodynia in rats with unilateral peripheral neuropathy due to tight ligation of the L5 and L6 spinal nerves.[5] Moreover, a previous clinical investigation has demonstrated that treatment with morphine does not affect the neuropathic pain profile.[6] Although several studies demonstrated that opiates did not produce analgesic effects in neuropathic pain, opiates may recover some efficacy, either by dramatically increasing the doses,[7] by using the intrathecal route,[8–10] or by adding coanalgesics such as gabapentin.[11,12] It is also apparent that opiates can reduce some of the symptoms of neuropathy, such as mechanical or thermal allodynia,[8,13] while clinical effects on spontaneous pain are poor in humans. However, the underlying mechanisms of analgesic effects of morphine on neuropathic pain are unclear.

A previous study from the authors' laboratory was the first to show that compression of the trigeminal ganglion produces trigeminal neuralgia-like nociceptive behavior in rats.[14] Compression of the trigeminal ganglion in this animal model produced prolonged mechanical allodynia and hyperalgesia. Although treatment of morphine reduces some of the symptoms of neuropathy, limited data are available concerning the antinociceptive effects of morphine on trigeminal neuralgia-like nociceptive behavior. This current study investigated the effects of morphine upon mechanical allodynia in rats with compression of the trigeminal ganglion by examining changes in facial air-puff thresholds after intraperitoneal or intracisternal injection of morphine.

Materials and Methods

All procedures involving the use of animals were approved by the Institutional Care and Use Committee of the School of Dentistry, Kyungpook National University, and were carried out in accordance with the ethical guidelines for the investigation of experimental pain in conscious animals of the International Association for the Study of Pain.

Animals

Experiments were carried out on male Sprague-Dawley rats weighing between 250 and 260 g. Animals were housed one per cage ($26 \times 50 \times 18$ cm) and maintained under constant temperature and lighting conditions with a 12-hour light/dark cycle. Food and water were freely available. All behavioral responses were measured in a blind fashion.

Compression of the Trigeminal Ganglion

Surgical procedures were performed under a 0.5 cc/kg (im) mixture of equal volumes of ketamine (100 mg/ml) and xylazine (20 mg/ml) anesthesia. Anesthetized rats were mounted onto a stereotaxic frame (Model 1404, David Kopf Instruments) and a guide cannula (21-gauge) was implanted into the left trigeminal ganglion (3.4 mm posterior to the bregma, 3.5 mm lateral from the midline, and 6.0 mm ventral from the surface of the skull). Compression of the trigeminal ganglion was induced as described in a previous study.[14] Briefly, a 4% agar solution was injected into the left trigeminal ganglion through a stainless-steel injector (24 gauge), which extended 2 mm beyond the end of a guide cannula. The injector was connected to a 100 µl Hamilton syringe with a polyethylene tube (PE 50, Clay Adams) and was preheated in a water bath at 38°C. The agar solution (8 µl) was injected slowly over 5 seconds and the injector was left in place for 10 minutes before withdrawal. After the removal of the injector and guide cannula, a topical anesthetic gel (Hurricaine) was applied to the sutured wounds. Only data from rats with injection sites clearly within the trigeminal ganglion were used in the final analysis.

Evaluation of Orofacial Mechanical Allodynia

The extent of mechanical allodynia in each rat was examined 3 days before and at 3, 7, 10, 14, 17, 21, 24, 30, and 40 days after surgery. Rats were randomly assigned to one of three groups. In the compression of the trigeminal ganglion group (n = 10), the left trigeminal ganglion was compressed. In the sham group (n = 10), rats received a sham procedure. Behavioral responses in the naïve group (n = 10) that did not receive any surgery were also examined. For behavioral observations, each animal in the three groups was placed in a customized restraining cage with holes in the top so that air-puffs could be administered to the head.[15] Each cage was placed in a darkened and noise-free room and the animals were habituated for at least 30 minutes. Also examined were the withdrawal behavioral responses, such as escape from air-puff stimulation or aggressive behavior including biting after the application of 10 successive trials of constant air-puff pressure (4-second duration, 10-second intervals) to the vibrissa pad area. The intensity and

interval of the air-puff pressure were controlled by a pneumatic pump module (BH2 system, Harvard Apparatus). The air puffs were applied through a 26-gauge metal tube (length, 10 cm) located 1 cm from the skin at a 90° angle. The air-puff thresholds were determined as the air-puff pressure at which each rat responded in 50% of the trials.[16] The cutoff pressure for the air puffs was 40 psi.

Experimental Protocol

The aim of the first set of experiments was to examine the effect of intraperitoneal injection of morphine on mechanical allodynia in rats with compression of the trigeminal ganglion. Rats were randomly assigned to one of three groups (n = 6 in each group). Morphine (2 mg or 5 mg/kg) was injected intraperitoneally in two groups and vehicle (saline) was injected in the control group.

A second set of experiments was performed to investigate the effects of pretreatment with naloxone on antinociceptive effects by intraperitoneal administration of morphine. Rats were randomly assigned to one of two groups (n = 6 in each group). The opioid receptor antagonist naloxone (1 mg/kg) or vehicle was administered intraperitoneally 10 minutes prior to the injection of morphine (5 mg/kg) in rats with compression of the trigeminal ganglion.

A third set of experiments was performed to investigate the effect of intracisternal injection of morphine on mechanical allodynia in rats with compression of the trigeminal ganglion. Rats were randomly assigned to one of three groups (n = 6 in each group). Morphine (1 or 5 μg/10 μL) or vehicle was injected intracisternally.

A fourth set of experiments was performed to investigate the effects of pretreatment with naloxone on antinociceptive effects by intracisternal administration of morphine. Rats were randomly assigned to one of two groups (n = 6 in each group). Naloxone (10 μg/10 μL) or vehicle was administered intracisternally 10 minutes prior to the injection of morphine (5 μg) in rats with compression of the trigeminal ganglion.

Effects of Morphine on Mechanical Allodynia

All morphine tests were conducted on postoperative day 14. Morphine was administered intraperitoneally in rats with compression of the trigeminal ganglion. The rats were examined for the withdrawal behavior produced by 10 successive trials of constant air-puff pressure (4-second duration, 10-second intervals), which were applied to the ipsilateral or contralateral side to the trigeminal territory, after intraperitoneal administration of morphine.

For intracisternal injection, a polyethylene tube (PE10) was implanted in anesthetized rats 3 days before conducting the morphine tests, as described previously.[17] A limited skin incision was made and part of the atlanto-occipital membrane was exposed by deflecting a part of the muscle from the occipital bone. A tiny opening was made with a 27-gauge needle in the dura and the tip of the cannula was inserted through the opening and secured in place with glue. The polyethylene tube was subcutaneously led to the top of the skull and secured in place by a stainless-steel screw and dental acrylic resin. Each tube was stopped by a steel wire in order to prevent leakage of cerebrospinal fluid. Morphine was administered intracisternally on postoperative day 14. Withdrawal behavior produced by 10 successive trials of constant air-puff pressure was examined in the ipsilateral or contralateral side after intracisternal administration of morphine. In some experiments, after pretreatment with naloxone intraperitoneally or intracisternally 10 minutes prior to the injection of morphine, withdrawal behavior was examined in the ipsilateral or contralateral side.

Rotarod Test

To investigate the effects of morphine treatments on motor function, changes in motor performance in the rats were measured using a rotarod (Ugo Basil, Comerio), as described previously.[18] The rotarod speed was set at 18 rpm with a maximum time spent with the rod set at 180 seconds. Rats with compression of the trigeminal ganglion received two or three training trials on two separate days prior to testing for acclimatization. On postoperative day 14, the basal response was examined. After intraperitoneal (5 mg/kg) or intracisternal (5 μg) administration of morphine or vehicle (n = 5 in each group), the time course of motor performance was examined.

Statistical Analyses

Statistical analyses of the behavioral data sets were carried out using a repeated measures ANOVA followed by multiple group comparisons using a Bonferroni post-hoc analysis ($P < .05$). To compare the effects between the groups treated with morphine, a one-way ANOVA with a Bonferroni post-hoc analysis ($P < .05$) was used. Comparisons between the two means (naloxone data) were

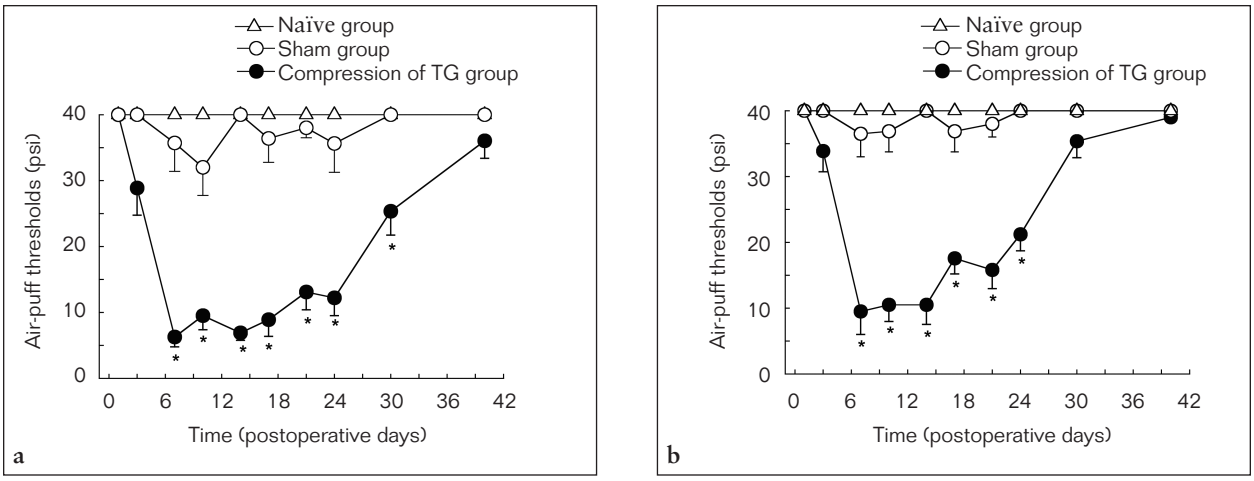

Fig 1 Time course of the changes in ipsilateral *(a)* and contralateral *(b)* air-puff thresholds following compression of the trigeminal ganglion. Sham (n = 10) and naïve (n = 10) animals did not produce any significant responses to air-puff stimulation. Ipsilateral air-puff thresholds were significantly lower in the animals with trigeminal ganglion compression (n = 10) than in the sham-operated group. Compression of the trigeminal ganglion produced mechanical allodynia within 3 days following surgery, persisted until postoperative day 24, and then recovered to the preoperative levels at 40 days following the induction of compression. Decreased air-puff thresholds contralateral to the compression of the trigeminal ganglion were also observed. *$P < .05$, sham versus animals with the trigeminal ganglion compression.

performed by a Wilcoxon signed ranks test. In all statistical comparisons, $P < .05$ was used as the criteria for statistical significance. All data are presented as mean ± standard error (SEM).

Results

Compression of the trigeminal ganglion produced a dramatic increase in responses to the mechanical stimulation of the face. Figure 1 illustrates changes in air-puff thresholds following compression of the trigeminal ganglion. Naïve rats did not respond to a pressure of less than 40 psi. Sham-treated rats did not show significant changes in air-puff threshold, compared with the naïve group. However, the ipsilateral air-puff thresholds were significantly lower in the animals with compression of the trigeminal ganglion ($F_{(2, 24)} = 42.478$, $P < .0001$, Fig 1a) than in the sham-treated rats. The mean air-puff threshold decreased to 6.2 ± 1.5 psi 7 days after compression of the trigeminal ganglion and this decrease persisted significantly until postoperative day 24. Air-puff thresholds recovered to the preoperative levels 40 days after compression of the trigeminal ganglion. Compression of the trigeminal ganglion also significantly decreased contralateral air-puff thresholds compared with the sham-treated group ($F_{(2, 24)} = 18.113$, $P < .0001$, Fig 1b). Air-puff thresholds decreased to 9.5 ± 3.5 psi at postoperative day 7 and remained at low levels until postoperative day 24.

Figure 2 illustrates the effects of intraperitoneal administration of morphine on mechanical allodynia in rats 14 days following compression of the trigeminal ganglion. Treatment with vehicle did not affect air-puff thresholds. However, intraperitoneal administration of 2 mg or 5 mg/kg of morphine significantly reduced the suppression of ipsilateral air-puff thresholds compared with the vehicle-treated group ($F_{(2, 15)} = 6.037$, $P < .05$, Fig 2a). The intraperitoneal administration of morphine also blocked mechanical allodynia contralateral to the compression of the trigeminal ganglion ($F_{(2, 15)} = 3.735$, $P < .05$, Fig 2b). The antiallodynic effects of intraperitoneal administration of 5 mg/kg of morphine were blocked by intraperitoneal pretreatment with 1 mg/kg of naloxone ($P < .05$, Figs 2c and 2d).

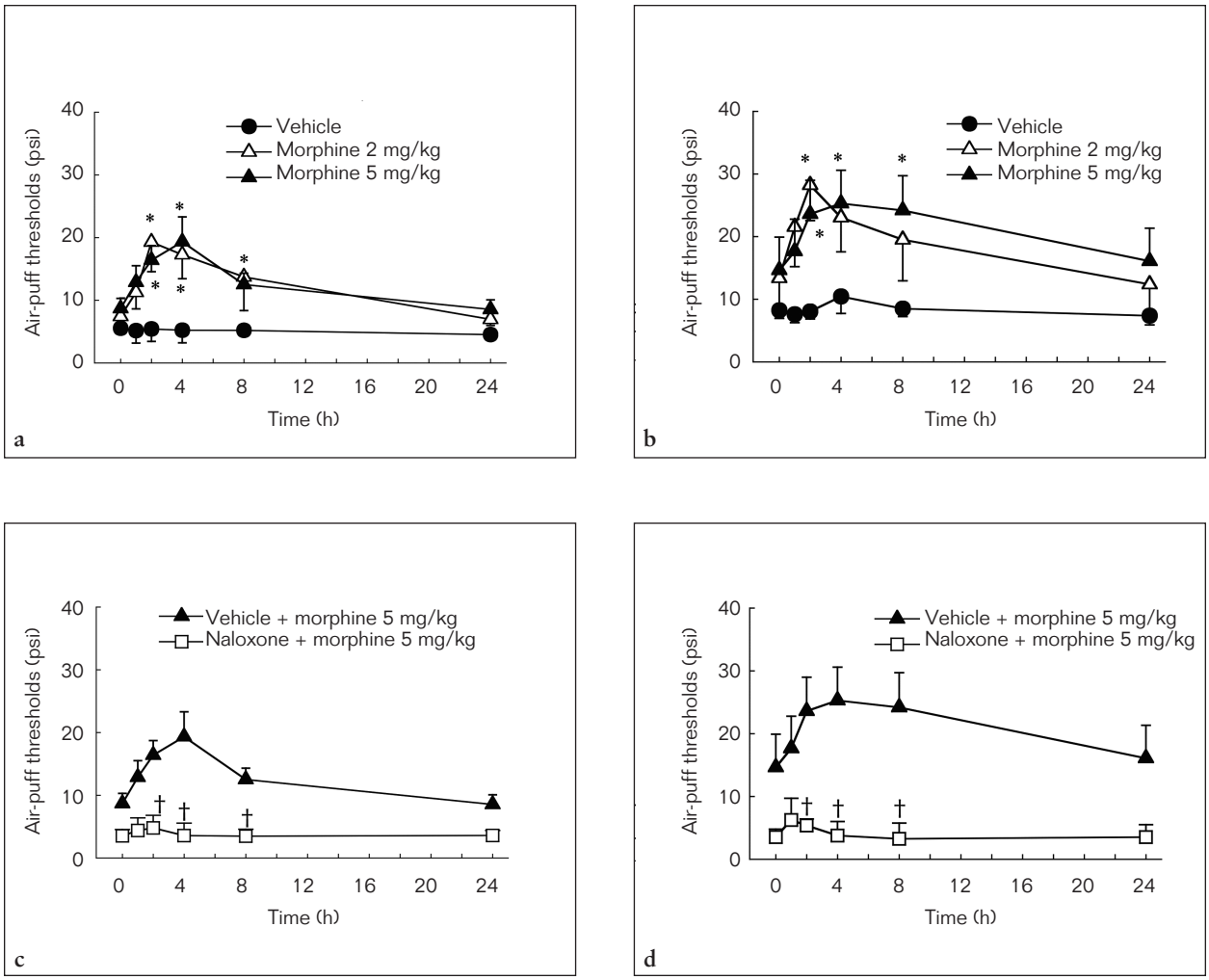

Fig 2 Effects of the intraperitoneal administration of morphine on ipsilateral *(a and c)* and contralateral *(b and d)* mechanical allodynia in rats with compression of the trigeminal ganglion. Intraperitoneal administration of morphine (2 or 5 mg/kg) 14 days following compression produced prolonged anti-allodynic effects compared with vehicle treatment. The anti-allodynic effects of the intraperitoneal administration of 5 mg/kg of morphine were blocked by intraperitoneal pretreatment with 1 mg/kg of naloxone. There were six animals in each group. **P* < .05, vehicle- versus morphine-treated groups. †*P* < .05, vehicle- versus naloxone-treated groups.

Figure 3 illustrates the effects of intracisternal administration of morphine on mechanical allodynia on postoperative day 14. Neither vehicle nor 1 µg of morphine affected the air-puff threshold. However, intracisternal administration of 5 µg of morphine significantly inhibited mechanical allodynia both ipsilateral ($F_{(2, 15)} = 11.754$, $P < .01$, Fig 3a) and contralateral ($F_{(2, 15)} = 3.725$, $P < .05$, Fig 3b) to the compression of the trigeminal ganglion compared with the vehicle-treated group. The antiallodynic effects of the intracisternal administration of 5 µg of morphine were blocked by intracisternal pretreatment with 10 µg of naloxone ($P < .05$, Figs 3c and 3d).

To evaluate whether an antinociceptive dose of morphine was associated with motor dysfunction, a rotarod test was performed after the drugs were administered. Naïve rats showed 180 seconds of rotarod performance time. Neither intraperitoneal (5 mg/kg, 176 ± 5 seconds) nor intracisternal (5 µg, 177 ± 7 seconds) administration of morphine affected rotarod performance time ($P = .629$).

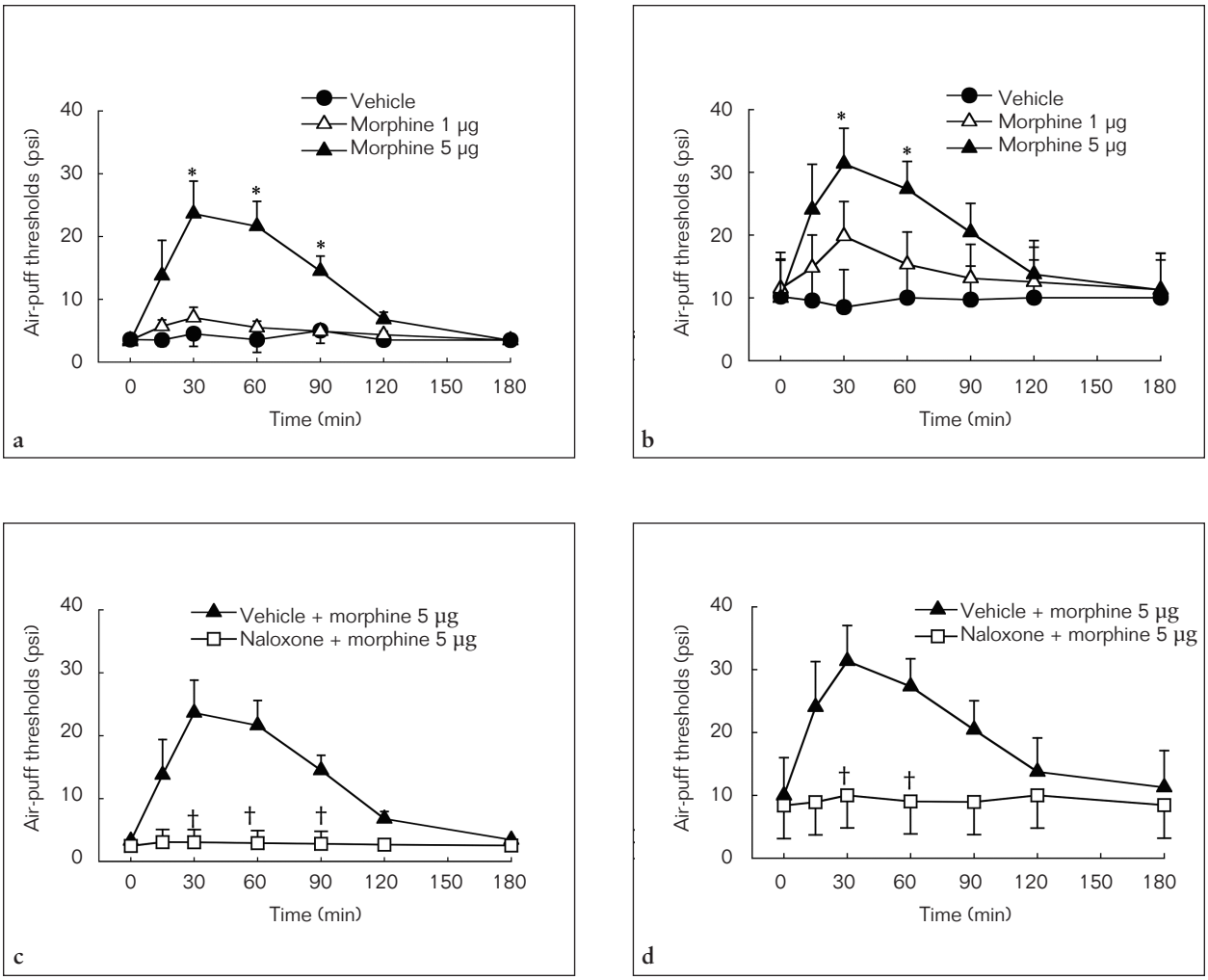

Fig 3 Effects of the intracisternal administration of morphine on ipsilateral *(a and c)* and contralateral *(b and d)* mechanical allodynia in rats with compression of the trigeminal ganglion. The intracisternal administration of morphine (5 μg) 14 days following compression produced prolonged anti-allodynic effects compared with vehicle treatment. The anti-allodynic effects of the intracisternal administration of 5 μg of morphine were blocked by intracisternal pretreatment with 10 μg of naloxone. There were six animals in each group. $^{*}P < .05$, vehicle- versus morphine-treated groups. $^{\dagger}P < .05$, vehicle- versus naloxone-treated groups.

Discussion

The results of the present study demonstrate that mechanical allodynia is sensitive to treatment with morphine in rats with compression of the trigeminal ganglion. It has been demonstrated in a previous study that prolonged nociceptive behavior occurs in the trigeminal region following compression of the trigeminal ganglion in rats.[14] The most obvious behavioral change following this compression was a dramatic increase in the responses to mechanical stimulation of the face. This mechanical allodynia was blocked by either the intraperitoneal or intracisternal administration of morphine.

Trigeminal neuralgia (tic douloureux) is a severe chronic pain syndrome characterized by brief but intense stabbing or electrical shock-like paroxysmal pain. Paroxysmal pain usually occurs unilaterally and it is triggered by gentle tactile stimulation of the trigger zone on the face or in the oral cavity. Since microvascular compression of the trigeminal root was first reported to be a cause of trigeminal neuralgia,[19] this etiological factor has been supported by further clinical observations.[20,21] Adjacent arterial loops, tumors, or arteriovenous malformations have been shown to compress the trigeminal root[19,22] and produce focal demyelination[23] in patients with trigeminal neuralgia.

However, recent clinical studies have demonstrated that some trigeminal neuralgia patients lacking or with minimal trigeminal root pathology show a primary disorder in or near the trigeminal ganglion.[24] Evidence from electron microscopic studies in trigeminal neuralgia patients has also demonstrated that proliferative and degenerative changes occur in the myelin sheaths of fibers in the trigeminal ganglion.[25,26] Compression of the trigeminal ganglion in rats has been reported to mimic trigeminal neuralgia-like nociceptive behavior.[14] These observations suggest that the trigeminal ganglion also plays an important role in the pathological processes in some trigeminal neuralgia patients.

The results of the present study demonstrate that compression of the trigeminal ganglion in a rat model produces prolonged mechanical allodynia which is sensitive to treatment with the systemic or central administration of morphine. Although morphine can produce antinociceptive effects, it can also produce impairments of motor function. However, neither the intraperitoneal nor intracisternal administration of antinociceptive doses of morphine produced any motor dysfunction in rats. These results suggest that the long-lasting antiallodynic effects of morphine are not mediated by motor impairment.

The analgesic efficacy of opioids has been well established for acute pain conditions. Opioids are routinely used to manage postoperative pain, including short-term painful conditions, as an analgesic. However, the sensitivity to opioids depends on pain conditions. Inflammatory pain is effectively suppressed by these compounds, whereas mixed results are obtained for opioid treatment of neuropathic pain. Some studies have shown that systemically or intrathecally administered morphine blocks mechanical allodynia in rats with central neuropathic pain.[13,27] Moreover, the systemic administration of morphine has been observed to produce powerful antinociception effects in a tail flick test in rats with central and peripheral neuropathic pain.[13] However, a previous clinical investigation has demonstrated that treatment with morphine does not affect the neuropathic pain profile.[6] These inconsistent results for opioids may be explained partly in the dose and levels of efficacy of morphine or the nature of the stimulus that evoked nociception. Treatment with 120 mg of codeine did not produce analgesic effects in patients with postherpetic neuralgia.[28] However, these results might have been simply due to an insufficient dose.[29] Intrathecal injections of morphine did not alleviate tactile allodynia in rats with L5/6 spinal nerve ligation,[30,31] whereas the intrathecal injection of morphine reversed thermal hyperalgesia in both chronic constriction injury[32] and in an L5/6 spinal nerve ligation model[8] of neuropathic pain. Although it remains unclear whether opioids are effective in neuropathic pain conditions,[33] better understanding of opioid systems may well facilitate the development of novel therapeutic strategies to alleviate neuropathic pain including trigeminal neuralgia.[34]

It has been well established that the activation of opioid receptors, located on the presynaptic terminals of unmyelinated nociceptor C fibers, prevents the levels of calcium influx necessary for synaptic transmission.[35] Opioid receptors are also located postsynaptically on the cell bodies of projection neurons. Opioid receptor binding sites are found predominantly in the superficial layers of the dorsal horn, including the medullary dorsal horn.[36] Dorsal rhizotomy produces a 60% loss of μ-opioid receptors in the superficial layers of the cervical dorsal horn.[37] These results suggest that postsynaptic opioid receptors can lead to the hyperpolarization of the second-order neurons and inhibit the ascending transmission of nociceptive input to supraspinal centers. These data also suggest that mechanical allodynia following compression of the trigeminal ganglion, mediated by large-diameter afferents, was suppressed through postsynaptic opioid receptors.

In the present study, air-puff stimulation was used to evaluate mechanical allodynia because this stimulation easily allows the evaluation of mechanical allodynia in the orofacial area. Compression of the trigeminal ganglion significantly decreased air-puff thresholds, while the animals in the naïve group did not respond to a pressure of less than 40 psi. These results indicate that the air-puff test is a convenient method for evaluation of orofacial mechanical allodynia in conscious rats.

Mirror-image allodynia has been demonstrated after chronic constriction of the spinal nerve[38] or infraorbital nerve[39,40] in several previous studies. The present study also demonstrated contralateral mechanical allodynia following compression of the trigeminal ganglion. This mirror-image mechanical allodynia is apparently not caused by the sham surgery, because the sham-treated group did not show mechanical allodynia after surgery. The participation of spinal glia in mirror-image neuropathic pain was first demonstrated in rats with induced sciatic inflammatory neuropathy.[41] Moreover, mirror-image neuropathic pain following infraorbital nerve ligation was significantly blocked by intracisternal pretreatment with MAPK inhibitors.[40] These results suggest that central

MAPK pathways may contribute to possible mechanisms of mirror-image mechanical allodynia following compression of the trigeminal ganglion.

Neuropathic pain behaviors produced by tight ligation of the left L5 and L6 spinal nerves were significantly reduced after intrathecal administration of ketamine prior to undergoing surgery.[42] These results suggest that ketamine has some protective effects against neuropathic pain by preventing spinal cord sensitization. In the present study, although animals were anesthetized by ketamine for surgical procedures, compression of the trigeminal ganglion significantly produced mechanical allodynia.

Although the present study has reported data from a rodent trigeminal neuralgia model following compression of the trigeminal ganglion, this model has several limitations. The nociceptive symptoms did not follow the typical clinical trigeminal neuralgia case. Generally, a trigeminal neuralgia case shows a unilateral tactile trigger, not a bilateral trigger as shown in the present study. Moreover, the trigeminal ganglion was compressed instead of the trigeminal root in the present study. Vascular compression of the trigeminal root is one of the reported etiologies of trigeminal neuralgia. Therefore, the role of trigeminal root compression in the development of trigeminal neuralgia should be examined in further studies.

Intracisternal administration of SB203580, a p38 MAPK inhibitor, or minocycline, a selective inhibitor of microglial cell activation, attenuated mechanical allodynia in the trigeminal ganglion compression–treated animals (unpublished data). Moreover, the blockade of central COX-1 or -2 pathways may produce antiallodynic effects in rats with compression of the trigeminal ganglion.[43] These results suggest glia or central MAPK pathways may be involved in the mechanical allodynia following compression of the trigeminal ganglion. Therefore, they should be studied in future correlative experiments.

In conclusion, compression of the trigeminal ganglion produces mechanical allodynia in rats but this is reversed by intraperitoneal or intracisternal administration of morphine. The use of morphine may therefore be appropriate in treating trigeminal neuralgia-like nociception.

Acknowledgments

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (No. R13-2008-009-01001-0).

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