Analgesic Effects of Intranasal Ketamine in Rat Models of Facial Pain

Rafaela Claudino, PhD
Postdoctoral Fellow
Pharmacology Postgraduate Program
Department of Pharmacology
Federal University of Paraná
Curitiba, Paraná, Brazil

Carina Nones, PhD
Pharmacology Postgraduate Program
Department of Pharmacology
Federal University of Paraná
Curitiba, Paraná, Brazil

Erika Araya, MSc
PhD Student
Pharmacology Postgraduate Program
Department of Pharmacology
Federal University of Paraná
Curitiba, Paraná, Brazil

Juliana Chichorro, PhD
Assistant Professor
Pharmacology Postgraduate Program
Department of Pharmacology
Federal University of Paraná
Curitiba, Paraná, Brazil

Correspondence to:
Dr Juliana Geremias Chichorro
Biological Sciences
Department of Pharmacology
Federal University of Paraná
Curitiba, PR 81540970, Brazil
Fax: +55 41 3266- 2042
Email: juliana.chichorro@ufpr.br

Aims: To assess the analgesic effect of intranasal administration of S-ketamine in different rat models of facial pain. **Methods:** Nociceptive responses induced by formalin injected into the upper lip and facial hyperalgesia induced by capsaicin or carrageenan injected into the upper lip were used to evaluate the analgesic effect of intranasal ketamine in acute facial pain models in rats (n = 173). The effect of intranasal ketamine on heat and mechanical hyperalgesia induced by constriction of the infraorbital nerve (CION) was also evaluated. In addition, locomotor activity in the open field test was assessed after intranasal ketamine administration. Two-way repeated measures analysis of variance followed by Bonferroni post hoc correction were used to analyze all data. **Results:** Intranasal ketamine (0.5 mg/kg) failed to modify the first phase of the orofacial formalin test, but reduced the second phase by about 40%. Intranasal ketamine also reduced the facial heat hyperalgesia induced by capsaicin and carrageenan. In the CION model, intranasal ketamine at 0.5 mg/kg reversed the heat hyperalgesia and at 1 mg/kg attenuated the mechanical hyperalgesia 4 and 14 days after the surgery, respectively. The open field test did not reveal locomotor deficits in rats treated with intranasal ketamine. **Conclusion:** This study has demonstrated that intranasal ketamine produces analgesic effects in inflammatory and neuropathic facial pain models and may represent an adjuvant in the treatment of such conditions, especially when rapid pain relief is needed.
J Oral Facial Pain Headache 2018;32:238–246. doi: 10.11607/ofph.1973

Keywords: *formalin test, heat hyperalgesia, inflammatory pain, ketamine, mechanical hyperalgesia, NMDA receptors, trigeminal neuropathic pain*

Ketamine was introduced into clinical medicine during the late 1960s as an anesthetic agent capable of inducing dissociative anesthesia, and about 20 years later it was demonstrated to act as an antagonist of N-methyl-D-aspartate (NMDA) receptors.[1] As NMDA receptors emerged as crucial contributors to central sensitization in acute and chronic pain states, many clinical studies have addressed the analgesic potential of ketamine in different pain conditions.[2–6]

Most of these studies have assessed the effects of parenteral administration (ie, mainly boluses or infusions) or oral administration, and some of them have shown promising results.[3] However, the poor bioavailability of ketamine limits its oral use in the clinical setting, and systemic administration of ketamine in pain treatment raises safety concerns about recreational use in addition to its well-known psychotomimetic and cognitive adverse effects.[7,8]

Some clinical studies have reported that intrasanal administration of ketamine is able to induce analgesia in patients with chronic pain and that it promotes rapid pain relief with a small number of side effects.[9–11] It has been described that the bioavailability of the ketamine nasal spray is approximately 45%, which is slightly greater in comparison with sublingual administration, rectal administration, and especially oral administration.[12,13] It is also noteworthy that the intranasal route provides a noninvasive method of bypassing the blood-brain barrier to rapidly deliver therapeutic agents to the brain, spinal cord, and other

cerebral structures, and it also allows drug delivery to orofacial structures innervated by the trigeminal nerve.[14] Thus, the intranasal route may represent a safe and noninvasive method to explore the analgesic potential of ketamine that may result in more favorable outcomes, especially in orofacial pain conditions.

Ketamine is available for oral use in humans as a racemate or S-isomer. S-ketamine has been described as being four times more potent an analgesic than the racemate and the R-isomer and has been demonstrated to have a higher affinity for the NMDA receptor than the racemic compound.[8,15–17]

There is some clinical evidence that ketamine treatment may also be beneficial for the treatment of some painful orofacial conditions. Local or systemic administration of ketamine has been shown to reduce orofacial postoperative pain, including ameliorating some inflammatory parameters and patients' anxiety levels in some studies.[16,18–22] In chronic orofacial pain conditions, studies have reported that a variable proportion of the patients presented significant pain relief with use of systemic ketamine, but the data are very limited and the populations studied have been too heterogenous to draw a conclusion.[16,23] In light of these considerations, the aim of this study was to assess the analgesic effect of intranasal administration of S-ketamine in different rat models of facial pain.

Material and Methods

Animals

Experiments were performed on a total of 173 adult male Wistar rats (Rattus norvegicus) weighing 200 to 220 g. The rats were housed five per cage on wood shaver bedding in a climate-controlled room at 22 ± 2°C on a 12-hour light/dark cycle (lights on at 7:00 am) with laboratory chow and tap water ad libitum. Experiments were conducted during the light phase of the cycle, and the animals were acclimatized to the laboratory for at least 48 hours before testing. Animals were provided by the animal care facility of Universidade Federal do Parana (UFPR) with all procedures previously approved by UFPR's Institutional Committee on the Ethical Use of Animals (authorization #980) and performed in accordance with ethical guidelines, including the policies and recommendations of the International Association for the Study of Pain and Brazilian regulations on animal welfare. The experiments were always performed by two experimenters, one responsible for treatment and one for testing; thus, the experimenter responsible for animal testing was always blind to the animal treatment. All efforts were made to provide the animals comfortable housing with conspecifics and good care and handling in the research facilities according to the recommendations of the Brazilian Agency National Council of Control of Experimental Animals (CONCEA) and to minimize the number of animals used.

Drugs and Reagents

The following drugs were used: carrageenan (Sigma), formalin (Vetec), capsaicin (Sigma), thiopental (Cristália), and ketamine (Ketamin-S, Cristália). Carrageenan and formalin were dissolved in isotonic saline just before use. Capsaicin was prepared in a stock solution containing 10% Tween 80 and 10% ethanol in phosphate-buffered saline (PBS; pH 7.4), maintained at –18°C and dissolved in isotonic saline just before use. The concentration of ethanol in the final solution never exceeded 0.5%, as this concentration has been reported not to cause any hyperalgesic effect.[24]

Intranasal Administration of Ketamine

Ketamine is a racemic mixture containing equal parts R-ketamine and S-ketamine. In this study, the effects of S-ketamine were examined, since it has approximately four-fold greater affinity for the NMDA receptor than the R-isomer, is about four times more potent an anesthetic and analgesic than the R-enantiomer, and is approximately two times more effective than the racemic mixture of ketamine.[1,8] The choice of ketamine doses (0.5 and 1.0 mg/kg) was based on previous studies that have demonstrated its analgesic efficacy by the intranasal route.[10,25,26] In addition, it has been described that the maximum plasma concentration and antinociceptive effects of ketamine have been observed within 30 minutes after its intranasal administration.[9,10,12] Based on this information, the treatments performed in this study were always initiated 15 minutes prior to the behavioral tests. For intranasal administration of ketamine, rats were initially lightly anesthetized with halothane in a supine position and received ketamine into the nostrils (20 µL/kg in each nostril) with the help of a micropipette.

Facial Formalin Test

This test was conducted as previously described.[27] Each animal was left individually in acrylic cages to adapt for at least 30 minutes. Next, each animal received a subcutaneous injection into the right upper lip of 2.5% formalin or vehicle (50 µL isotonic saline) and was placed immediately in the observation cage. The facial grooming time was registered in 3-minute intervals for a total period of 30 minutes. The formalin test consisted of the first phase (0 to 3 minutes), the quiescent phase (3 to 12 minutes), and the second phase (12 to 30 minutes). To assess the effect of intranasal ketamine, rats received intranasal ketamine (0.5 mg/kg) or isotonic saline equivolume (20 µL/kg) 15 minutes before the formalin injection and were

returned immediately to the observation cage (n = 7 to 9 in each group).

Constriction of the Infraorbital Nerve

Constriction of the infraorbital nerve (CION) was performed as described by Vos et al[28] with some modifications.[29] In brief, rats were anesthetized by an intraperitoneal injection of thiopental (50 mg/kg). Under the right eye, the skin of the snout was incised unilaterally about 3 mm caudal to the mystacial pads. The infraorbital nerve was exposed by dissection of the adjacent tissues in the vicinity of the infraorbital fissure. As branches of the facial nerve are close to this region, care was taken not to damage them. Two silk 4-0 ligatures were tied loosely around the infraorbital nerve 2 mm apart, and the wound was closed with additional silk sutures. Sham-operated rats were treated identically, but no ligatures were applied to the infraorbital nerve. At the end of the surgery, rats were kept in a warm room until complete recovery from anesthesia. Independent groups of sham and CION rats were used for each behavioral test.

Evaluation of Heat Hyperalgesia

Facial Heat Hyperalgesia. Thermal sensory threshold was evaluated based on the original protocol[30] with some minor modifications and as already extensively detailed.[31–35] Briefly, the rat was individually and gently restrained by the experimenter to allow the placement of a radiant heat source (about 50°C) exactly 1.1 cm from the surface of the right vibrissal pad. The intensity of the thermal stimulus was adjusted so that it raised the vibrissal pad skin temperature to 50°C within 15 seconds. This equipment allows for adjustment of the temperature, and by the time the protocol was set, the heat intensity was adjusted to result in a baseline for the nocifensive response time of around 10 seconds[35]; this time was used in the present study. The time (in seconds) required for the rat to show either withdrawal of the head or vigorous flicking of the snout was recorded using a stopwatch. A cutoff time of 20 seconds was established to prevent tissue damage. Heat hyperalgesia was considered as a significant reduction in the time to exhibit the nociceptive responses following the radiant heat application.

Capsaicin-Induced Facial Heat Hyperalgesia. Facial heat hyperalgesia induced by upper lip injection of capsaicin was evaluated as previously described.[33] Following the evaluation of the basal thermal sensory threshold, the animals received a subcutaneous injection of vehicle (isotonic saline, 50 µL) or capsaicin (3 µg/50 µL) into the upper lip, and response latencies to the thermal stimulus were assessed 0.5, 1, 2, 3, and 4 hours postinjection. To examine the effect of intranasal ketamine on capsaicin-induced facial heat hyperalgesia, rats received ketamine (0.5 mg/kg) or isotonic saline equivolume (20 µL/kg, by intranasal injection) at 15 minutes before capsaicin or vehicle (isotonic saline) injection (n = 7 to 10 in each group).

Carrageenan-Induced Facial Heat Hyperalgesia. Following the evaluation of the basal thermal sensory threshold, the animals received a subcutaneous injection of vehicle (50 µL isotonic saline) or carrageenan (100 µg/50 µL) into the upper lip, and the heat stimulation was repeated every hour up to 6 hours.[34] To evaluate the effect of intranasal ketamine (0.5 mg/kg) pretreatment in carrageenan-induced facial heat hyperalgesia, animals were treated with ketamine 15 minutes before carrageenan injection. In another set of experiments, to assess the effect of posttreatment with ketamine on carrageenan-induced heat hyperalgesia, the animals received ketamine 2.5 hours after the carrageenan injection, when the heat hyperalgesia was already established. Control animals received an intranasal injection of isotonic saline (20 µL/kg) followed by a local injection of vehicle (n = 7 to 9 in each group).

Heat Hyperalgesia Associated with Infraorbital Nerve Injury. Heat sensory thresholds were measured before surgery and 4 days after surgery as previously described. To examine the effect of ketamine on CION-induced thermal heat hyperalgesia, rats received ketamine (0.5 mg/kg) or isotonic saline equivolume, and response latencies to the thermal stimulus were assessed at 0.5, 1, 2, 3, and 4 hours postinjection (n = 6 to 9 each group). Only the operated side of the face was tested since the development of heat hyperalgesia following CION is unilateral (at least when performed by the surgical method described above[31–33,35]).

Mechanical Hyperalgesia Associated with Infraorbital Nerve Injury

Facial mechanical hypersensitivity was assessed before surgery and 14 days after surgery. During each testing session, animals were habituated to individual cages (30 × 30 × 30 cm) for a minimum of 2 hours as described.[36,37] Mechanical thresholds were measured using calibrated von Frey filaments ranging from 0.04 to 8 g. The filaments were applied in ascending order three times near the center of the right vibrissal pad, beginning with the 0.04-g filament, until the filament was able to evoke one of the following nociceptive behaviors twice: brisk head withdrawal; escape or attack reactions; or short-lasting facial grooming. Only rats that did not react to application of the 8-g filament at presurgery testing were used for subsequent testing. To examine the effects of intranasal ketamine on mechanical hypersensitivity, rats received ketamine (0.5 mg/kg or 1 mg/kg) or isotonic saline equivolume, and mechanical thresholds were

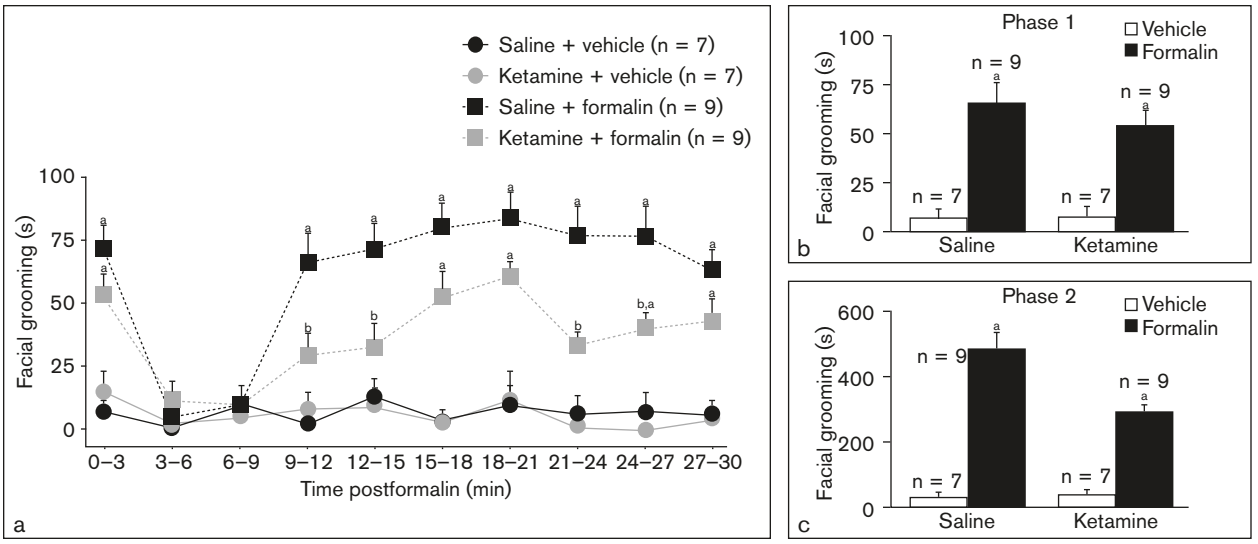

Fig 1 Effect of intrasanal ketamine on facial nociception induced by formalin. **(a)** Time course of formalin-induced nociceptive behavior compared to vehicle (isotonic saline) and the effect of ketamine throughout the observation period. The cumulative grooming response **(b)** in the first 3 minutes after injection (first phase) and **(c)** from 12 to 30 minutes after the injection (second phase). Values represent mean ± SEM of 7 to 9 rats per group.

[a]*P* < .05 compared to corresponding value of isotonic saline + vehicle group.

[b]*P* < .05 compared to corresponding value of isotonic saline + formalin group. Two-way repeated measures ANOVA followed by Bonferroni poct hoc test were used.

assessed at 0.5, 1, 2, 3, and 4 hours posttreament (n = 6 to 8 in each group). Although the development of mechanical hyperalgesia is bilateral after CION,[37] only the ipsilateral side of the face was tested to avoid overstimulation of the animal during assessment of the time course of ketamine effects.

Open Field Test

The open field test was used to evaluate the locomotor activity of rats, as previously described.[38] Animals were placed individually in the lower right corner of a square wood arena (30 × 60 × 60 cm), the floor of which was divided by lines into six small squares. Briefly, the crossings between the squares were counted manually for 5 minutes and used as a primary index of locomotor activity. Only when the rat placed its two forepaws in the next square and moved forward was the square considered to be crossed. The open field test was performed 45 minutes after intranasal ketamine or isotonic saline administration (n = 9 in each group), the time interval in which the drug presents consistent anti-hyperalgesic effects.

Statistical Analyses

All data are presented as mean ± standard error of the mean (SEM). Two-way repeated measures analysis of variance (ANOVA) was used to analyze all data, with drug treatment as the independent factor and the different time points of evaluation of nociceptive behavior as the repeated measure. In cases of significant differences with the independent factor or with the interaction between the independent and repeated factors, one-way ANOVA followed by the Bonferroni post hoc test was performed. In all statistical analyses, *P* values < .05 were considered significant.

Results

Effect of Intrasanal Ketamine on Facial Nociception Induced by Formalin

Injection of formalin (2.5%) in the upper lip compared to vehicle induced two phases of significant increase in facial grooming time. Pretreament with intranasal ketamine (0.5 mg/kg; 15 minutes beforehand) failed to modify the first phase of the formalin response (Figs 1a and 1b). However, ketamine administration, but not isotonic saline, caused a significant reduction (ie, by about 40%) in the second phase of the formalin response (Figs 1a and 1c). The formalin vehicle used did not induce significant increases in the facial grooming time in either phase (Figs 1b and 1c).

Effect of Intrasanal Ketamine on Heat Hyperalgesia Induced by Capsaicin or Carrageenan

Injection of capsaicin into the upper lip induced heat hyperalgesia that lasted for 2 hours. Pretreatment with intranasal ketamine (0.5 mg/kg; 15 minutes beforehand), but not isotonic saline, was able to prevent the development of heat hyperalgesia induced by capsaicin, causing an anti-hyperalgesic effect that

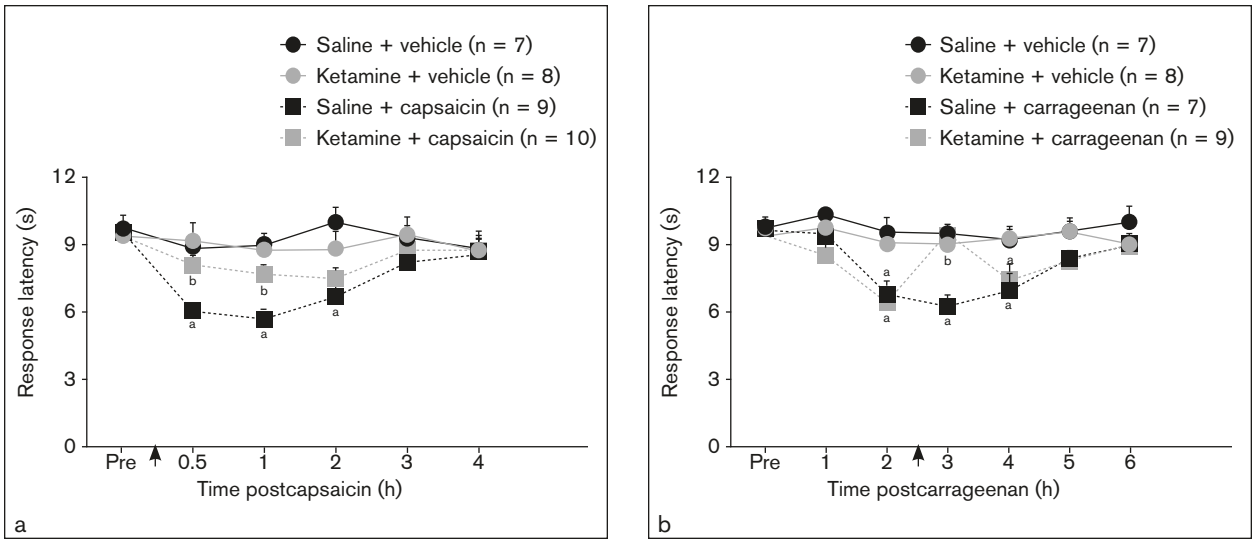

Fig 2 Effect of intranasal ketamine on heat hyperalgesia induced by **(a)** capsaicin or **(b)** carrageenan. **(a)** Heat hyperalgesia was assessed before the ketamine or isotonic saline intranasal treatments (Pre) and at 30 minutes after capsaicin or vehicle (isotonic saline) injection to 4 hours at 1-hour intervals. **(b)** Heat hyperalgesia was assessed before local treatment with vehicle or carrageenan (Pre) and at 1-hour intervals to 6 hours after intranasal isotonic saline or ketamine administration. Values represent mean ± SEM of 7 to 10 rats per group. The arrow indicates administration of ketamine.
[a]$P < .05$ compared to corresponding value of isotonic saline + vehicle group.
[b]$P < .05$ compared to corresponding value of isotonic saline + capsaicin or isotonic saline + carrageenan group. Two-way repeated measures ANOVA followed by Bonferroni poct hoc were was used.

was detected 30 minutes up to 1 hour after capsaicin injection. The local administration of vehicle or the intranasal administration of ketamine in the isotonic saline–treated rats did not modify the thermal threshold of these animals during the testing period (Fig 2a).

Injection of carrageenan into the upper lip produced a significant reduction in the latency to display head withdrawal or vigorous snout flicking compared to the vehicle group between 2 and 4 hours postinjection. However, the posttreatment with ketamine (2.5 hours after carrageenan injection) caused a marked but short-lasting (30 minutes) reduction in inflammatory heat hyperalgesia. Animals treated with vehicle in the upper lip and that received intranasal administration of isotonic saline or ketamine did not show any significant change in the response latency to the heat stimulus during the testing period (Fig 2b).

Effect of Intranasal Ketamine on Heat and Mechanical Hyperalgesia Induced by CION

The effect of intranasal administration of ketamine was next evaluated in the model of orofacial neuropathic pain. At the 4-day time point, CION reduced the latency of the animals' responsiveness to facial heat stimulants compared to sham-operated animals, indicating the development of heat hyperalgesia. Intranasal administration of ketamine (0.5 mg/kg) reversed the CION-induced heat hyperalgesia, with an effect observed at 30 to 60 minutes after administration (Fig 3a). CION also produced a significant reduction in the facial mechanical threshold, detected on day 14. The same dose of ketamine (0.5 mg/kg) that reversed heat hyperalgesia failed to change the mechanical threshold in sham and CION rats; however, CION-induced mechanical hyperalgesia was reduced by the intranasal administration of ketamine at 1 mg/kg, with significantly higher withdrawal thresholds at 30 minutes postinjection (Fig 3b).

The influence of ketamine treatment was also evaluated in the open field test. There was no significant difference in the number of crossed squares between rats that received intranasal ketamine or isotonic saline (55.2 ± 3.7 and 58.4 ± 2.6, respectively, $P = .48$; data not shown), suggesting that intranasal ketamine treatment did not cause a locomotor deficit in the animals.

Discussion

Current evidence suggests that ketamine administered intranasally is very useful for reducing pain associated with several distinct conditions in hospital emergencies,[25,26,39–41] including burn dressing,[11] pediatric laceration repair,[41] and control of postoperative pain,[42,43] as well as in prehospital settings (eg, in cases of accidents or disasters).[44] The present results provide preclinical evidence that intranasal ketamine promotes rapid relief of orofacial pain of inflammatory and neuropathic origin, suggesting that its use by the intranasal route deserves further clinical investigation in orofacial pain conditions.

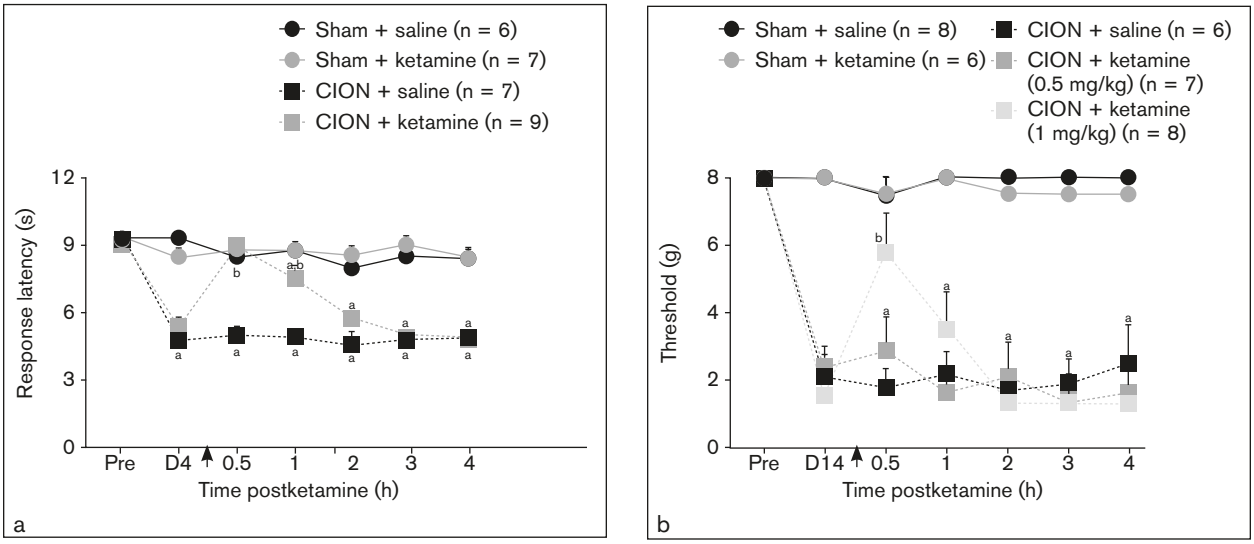

Fig 3 Effect of intranasal ketamine on heat and mechanical hyperalgesia induced by constriction of the infraorbital nerve (CION). **(a)** Heat responsiveness of all rats was evaluated before CION or sham surgery (Pre). **(a)** On day 4 (D4) after surgery, response latency was measured before intranasal ketamine (0.5 mg/kg) or isotonic saline (equivolume) and at 30 minutes postinjection to 4 hours postinjection at 1-hour intervals. **(b)** On day 14 (D14) after surgery, mechanical thresholds were measured before intranasal ketamine (0.5 or 1 mg/kg) or isotonic saline (equivolume) and at 30 minutes postinjection to 4 hours at 1-hour intervals. Values represent mean ± SEM of rats. The arrow indicates administration of ketamine.

[a]$P < .05$ compared to corresponding value of sham-operated rats treated with vehicle.

[b]$P < .05$ compared to corresponding value of CION rats treated with vehicle. Two-way repeated measures ANOVA followed by Bonferroni poct hoc test were used.

The present study has demonstrated that intranasal ketamine was able to reduce the inflammatory phase of the formalin test without causing any change in the first (neurogenic) phase. Several mechanisms have been considered to contribute to the analgesic actions of the systemic administration of ketamine, such as binding to opioid receptors, binding to muscarinic and nicotinic cholinergic receptors, inhibition of monoamine reuptake, and blockade of sodium channels, among others.[45] In addition, anti-inflammatory actions of ketamine have been reported in clinical studies.[18,21,22] However, the analgesic action of ketamine in humans has been associated with plasma concentrations in a very low micromolar range, which is consistent with the blockade of NMDA receptors.[46,47] In line with this idea, the second (tonic) phase of the formalin response is considered a model of central sensitization, in which NMDA glutamate receptors play a crucial role.[48] Indeed, antagonists of NMDA receptors markedly inhibit the second phase of formalin-induced nociception.[49,50] Thus, it is possible to suggest that the analgesic effect of ketamine in the second phase of the facial formalin test is due to the blockade of glutamate receptors that participate in the nociceptive transmission in the trigeminal subnucleus caudalis. This hypothesis is consistent with several observations, including the use in the present study of the S-isomer of ketamine, which has a higher affinity for the NMDA receptor than the racemic compound.[8] Activation of NMDA receptors, both in the trigeminal subnucleus caudalis and the subnucleus oralis, have been demonstrated to result in a facilitatory effect on orofacial nociceptive transmission.[51,52] In addition, Otahara et al[53] have demonstrated that MK801, an NMDA receptor antagonist, reduced c-fos expression in the trigeminal subnucleus caudalis induced by formalin injection into the whisker pad. It is also important to point out that peripheral NMDA receptors may contribute to the analgesic effect of ketamine, as it has been demonstrated that peripheral administration of NMDA receptor antagonists were able to reduce orofacial nociceptive responses.[54–57]

The present study also demonstrated that intranasal administration of ketamine caused a significant reduction in heat hyperalgesia induced by capsaicin and by carrageenan. It is widely accepted that intradermal injection of capsaicin induces central sensitization by activating nociceptive C fibers.[58,59] Likewise, the carrageenan model is a well-established rat model of inflammatory pain and manifests hyperalgesia peaking after 1 to 4 hours (acute pain) and a longer-lasting hyperalgesia (24 to 96 hours) that, in rodents, may be comparable to the time course of postoperative pain.[60–62] Interestingly, systemic treatment with ketamine totally prevented long-lasting carrageenan-induced hyperalgesia.[62] This is the first study that has examined the antihyperalgesic effect of ketamine by the intranasal route in

preclinical models, but the present findings are consistent with some clinical studies. Administration of intranasal ketamine to patients with acute moderate to severe pain related to several causes, including fracture, burn, and dislocation, resulted in an 80% reduction in pain at 15 minutes and in a 100% reduction at 30 minutes.[41] In postoperative pain patients following wisdom tooth removal, intranasal administration of ketamine (50 mg) resulted in significant pain relief within 14 minutes in 70% of the treated patients, with the peak analgesic effect occurring around 30 minutes after administration.[43] Moreover, local administration of ketamine in combination with local anesthetics in patients undergoing surgical removal of impacted mandibular third molars provided a significantly higher degree of analgesia with less swelling and minimal side effects.[22] In line with this observation, submucosal infiltration of 0.5 mg/kg of ketamine around the impacted mandibular third molar 10 minutes before the incision has been reported to produce significant reduction of postoperative pain within the first 24 hours.[19] Taken together, these results point to an important potential application for ketamine as a preemptive analgesic or as an adjuvant in the control of orofacial inflammatory and postsurgical pain, especially when used by a route of administration that limits its side effects.

Clinical studies have also pointed out a role for ketamine in the control of chronic pain. Regarding studies that used ketamine by the intranasal route, Huge et al[10] demonstrated that in patients with different types of chronic pain, intranasal ketamine reduced pain by 70% at 60 minutes postadministration. Likewise, Carr et al[9] found that ketamine doses of up to 50 mg were effective in a significant proportion of patients with breakthrough pain, with pain relief within 10 minutes of dosing and lasting for up to 60 minutes. The results of the present study are consistent with this clinical evidence: Intranasal ketamine produced a short but significant reduction of heat and mechanical hyperalgesia associated with CION, which is a model of trigeminal neuropathic pain. The crucial role of NMDA receptors in the maintenance of central sensitization has been demonstrated in several models of neuropathic pain, including of trigeminal neuropathic pain. Several of these studies have also reported the potential utility of ketamine in reducing several nocifensive behaviors related to the nerve injury, but in most cases the side effects of ketamine would be the major limitation to its clinical application.[36,48,63–65] Thus, the use of ketamine by the intranasal route may represent a safer alternative to achieving rapid onset of analgesia with few side effects.

After intranasal administration, ketamine can be rapidly delivered to central nervous system structures, but it has also been reported to achieve about 45% bioavailability in humans (for review see Peltoniemi et al[8]). There is also evidence that both the onset and the time course of ketamine-induced analgesia correlated well with plasma concentrations of ketamine and in active metabolite norketamine in humans.[9,10] This aspect has not yet been evaluated in rodents, and so further studies are needed to establish the contribution of peripheral and central NMDA receptors to the analgesic effect of ketamine. It is also noteworthy that one limitation of the present study was that female rats were not used in spite of growing clinical evidence indicating that some orofacial pain conditions are more prevalent in women than in men.[66–70] There are several reasons that justify the preference for using male rats (for review see Fillingim and Maixner[70] and Dao and LeResche[71]), and one of them is the necessity to determine the estrous cycle when females are used in pain studies since the nociceptive behavior and the regulation of NMDA receptor expression of females may be influenced, at least in part, by estrous cycles.[72–74]

Conclusions

The present study has demonstrated that intranasal ketamine produces analgesic effects in models of inflammatory and neuropathic facial pain conditions and may represent an adjuvant in the treatment of such conditions, especially when rapid pain relief is needed. This aspect may be of special importance for providing pain relief in orofacial pain–related emergencies, as well as in orofacial pain conditions that involve pain attacks, such as trigeminal neuralgia.

Acknowledgments

All authors approved the final version of the manuscript and agree with all aspects of the work. The authors declare that there are no conflicts of interest.

References

1. Domino EF. Taming the ketamine tiger. 1965. Anesthesiology 2010;113:678–684.
2. Bell RF. Ketamine for chronic non-cancer pain. Pain 2009; 141:210–214.
3. Sin B, Tatunchak T, Paryavi M, et al. The use of ketamine for acute treatment of pain: A randomized, double-blind, placebo-controlled trial. J Emerg Med 2017;52:601–608.
4. Allen CA, Ivester JR Jr. Ketamine for pain management—Side effects & potential adverse events. Pain Manag Nurs 2017;18:372–377.

5. Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. Eur J Pain 2015;19:984–993.
6. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009;145:304–311.
7. Bell RF. Ketamine for chronic noncancer pain: Concerns regarding toxicity. Curr Opin Support Palliat Care 2012;6:183–187.
8. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet 2016; 55:1059–1077.
9. Carr DB, Goudas LC, Denman WT, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: A randomized, double-blind, placebo-controlled, crossover study. Pain 2004;108:17–27.
10. Huge V, Lauchart M, Magerl W et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. Eur J Pain 2010;14:387–394.
11. Kulbe J. The use of ketamine nasal spray for short-term analgesia. Home Healthc Nurse 1998;16:367–370.
12. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 1996;77: 203–207.
13. Yanagihara Y, Ohtani M, Kariya S, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Dispos 2003;24:37–43.
14. Johnson NJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. Mol Pharm 2010;7:884–893.
15. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM. Effect of racemic mixture and the (S+)-isomer of ketamine on temporal and spatial summation of pain. Br J Anaesth 1996;77:625–631.
16. Mathisen LC, Skjelbred P, Skoglund LA, Oye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. Pain 1995;61:215–220.
17. Mion G, Villevieille T. Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 2013;19:370–380.
18. Gupta R, Sharma K, Dhiman UK. Effect of a combination of oral midazolam and low-dose ketamine on anxiety, pain, swelling, and comfort during and after surgical extractions of mandibular third molars. Indian J Dent Res 2012;23:295–296.
19. Hadhimane A, Shankariah M, Neswi KV. Pre-emptive analgesia with ketamine for relief of postoperative pain after surgical removal of impacted mandibular third molars. J Maxillofac Oral Surg 2016;15:156–163.
20. Kaviani N, Khademi A, Ebtehaj I, Mohammadi Z. The effect of orally administered ketamine on requirement for anesthetics and postoperative pain in mandibular molar teeth with irreversible pulpitis. J Oral Sci 2011;53:461–465.
21. Satilmiş T, Garip H, Arpaci E, Sener C, Göker K. Assessment of combined local anesthesia and ketamine for pain, swelling, and trismus after surgical extraction of third molars. J Oral Maxillofac Surg 2009;67:1206–1210.
22. Shah A, Halli R, Merchant Y, Kshirsagar R, Khurana J. Efficacy of ketamine as an adjunct to local anesthesia in the surgical removal of impacted mandibular third molars—A split mouth prospective controlled clinical study. J Clin Diagn Res 2016; 10:ZC29–ZC33.
23. Rabben T, Øye I. Interindividual differences in the analgesic response to ketamine in chronic orofacial pain. Eur J Pain 2001;5:233–240.
24. Motta EM, Chichorro JG, Rae GA. Role of ET(A) and ET(B) endothelin receptors on endothelin-1-induced potentiation of nociceptive and thermal hyperalgesic responses evoked by capsaicin in rats. Neurosci Lett 2009;457:146–150.
25. Andolfatto G, Willman E, Joo D, et al. Intranasal ketamine for analgesia in the emergency department: A prospective observational series. Acad Emerg Med 2013;20:1050–1054.
26. Yeaman F, Meek R, Egerton-Warburton D, Rosengarten P, Graudins A. Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. Emerg Med Australas 2014;26:237–242.
27. Chichorro JG, Lorenzetti BB, Zampronio AR. Involvement of bradykinin, cytokines, sympathetic amines and prostaglandins in formalin-induced orofacial nociception in rats. Br J Pharmacol 2004;141:1175–1184.
28. Vos BP, Strassman AM, Maciewicz RJ. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. J Neurosci 1994;14:2708–2723.
29. Chichorro JG, Zampronio AR, Souza GE, Rae GA. Orofacial cold hyperalgesia due to infraorbital nerve constriction injury in rats: Reversal by endothelin receptor antagonists but not non-steroidal anti-inflammatory drugs. Pain 2006;123:64–74.
30. Almeida RT, Duarte ID. Nitric oxide/cGMP pathway mediates orofacial antinociception induced by electroacupuncture at the St36 acupoint. Brain Res 2008;1188:54–60.
31. Luiz AP, Schroeder SD, Chichorro JG, Calixto JB, Zampronio AR, Rae GA. Kinin B(1) and B(2) receptors contribute to orofacial heat hyperalgesia induced by infraorbital nerve constriction injury in mice and rats. Neuropeptides 2010;44:87–92.
32. Kopruszinski CM, Reis RC, Chichorro JG. B vitamins relieve neuropathic pain behaviors induced by infraorbital nerve constriction in rats. Life Sci 2012;91:1187–1195.
33. Kopruszinski CM, Reis RC, Bressan E, Reeh PW, Chichorro JG. Vitamin B complex attenuated heat hyperalgesia following infraorbital nerve constriction in rats and reduced capsaicin in vivo and in vitro effects. Eur J Pharmacol 2015;762:326–332.
34. Hummig W, Kopruszinski CM, Chichorro JG. Pregabalin reduces acute inflammatory and persistent pain associated with nerve injury and cancer in rat models of orofacial pain. J Oral Facial Pain Headache 2014;28:350–359.
35. Chichorro JG, Zampronio AR, Cabrini DA, Franco CR, Rae GA. Mechanisms operated by endothelin ETA and ETB receptors in the trigeminal ganglion contribute to orofacial thermal hyperalgesia induced by infraorbital nerve constriction in rats. Neuropeptides 2009;43:133–142.
36. Christensen D, Gautron M, Guilbaud G, Kayser V. Combined systemic administration of the glycine/NMDA receptor antagonist, (+)-HA966 and morphine attenuates pain-related behaviour in a rat model of trigeminal neuropathic pain. Pain 1999; 83:433–440.
37. Chichorro JG, Zampronio AR, Rae GA. Endothelin ET(B) receptor antagonist reduces mechanical allodynia in rats with trigeminal neuropathic pain. Exp Biol Med (Maywood) 2006; 231:1136–1140.
38. Chioca LR, Raupp IM, Da Cunha C, Losso EM, Andreatini R. Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats. Eur J Pharmacol 2008; 579:196–201.
39. Farnia MR, Jalali A, Vahidi E, Momeni M, Seyedhosseini J, Saeedi M. Comparison of intranasal ketamine versus IV morphine in reducing pain in patients with renal colic. Am J Emerg Med 2017;35:434–437.
40. Shimonovich S, Gigi R, Shapira A, et al. Intranasal ketamine for acute traumatic pain in the emergency department: A prospective, randomized clinical trial of efficacy and safety. BMC Emerg Med 2016;16:43.

41. Shrestha R, Pant S, Shrestha A, Batajoo KH, Thapa R, Vaidya S. Intranasal ketamine for the treatment of patients with acute pain in the emergency department. World J Emerg Med 2016;7:19–24.
42. Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: A narrative review. Biomed Res Int 2015;2015:749837.
43. Christensen K, Rogers E, Green GA, et al. Safety and efficacy of intranasal ketamine for acute postoperative pain. Acute Pain 2007;9:183–192.
44. Johansson J, Sjöberg J, Nordgren M, Sandström E, Sjöberg F, Zetterström H. Prehospital analgesia using nasal administration of S-ketamine—A case series. Scand J Trauma Resusc Emerg Med 2013;21:38.
45. Persson J. Ketamine in pain management. CNS Neurosci Ther 2013;19:396–402.
46. Eide PK, Stubhaug A. Relief of glossopharyngeal neuralgia by ketamine-induced N-methyl-aspartate receptor blockade. Neurosurgery 1997;41:505–508.
47. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology 1997;86:903–917.
48. Chaplan SR, Malmberg AB, Yaksh TL. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. J Pharmacol Exp Ther 1997; 280:829–838.
49. Yamamoto T, Yaksh TL. Comparison of the antinociceptive effects of pre- and posttreatment with intrathecal morphine and MK801, an NMDA antagonist, on the formalin test in the rat. Anesthesiology 1992;77:757–763.
50. Yang Y, Guo QL, Zou WY, Wang E, Yan JQ. Effect of intrathecal ketamine injection on protein kinase C expression in the spinal dorsal horn of rats with formalin-induced pain [in Chinese]. Nan Fang Yi Ke Da Xue Xue Bao 2011;31:461–464.
51. Luccarini P, Sessle BJ, Woda A. Superficial and deep convergent nociceptive neurons are differentially affected by N-methyl-D-aspartate applied on the brainstem surface of the rat medullary dorsal horn. Neuroscience 2001;107:311–316.
52. Parada CA, Luccarini P, Woda A. Effect of an NMDA receptor antagonist on the wind-up of neurons in the trigeminal oralis subnucleus. Brain Res 1997;761:313–320.
53. Otahara N, Ikeda T, Sakoda S, Shiba R, Nishimori T. Involvement of NMDA receptors in Zif/268 expression in the trigeminal nucleus caudalis following formalin injection into the rat whisker pad. Brain Res Bull 2003;62:63–70.
54. Yu XM, Sessle BJ, Haas DA, Izzo A, Vernon H, Hu JW. Involvement of NMDA receptor mechanisms in jaw electromyographic activity and plasma extravasation induced by inflammatory irritant application to temporomandibular joint region of rats. Pain 1996;68:169–178.
55. Dong XD, Mann MK, Sessle BJ, Arendt-Nielsen L, Svensson P, Cairns BE. Sensitivity of rat temporalis muscle afferent fibers to peripheral N-methyl-D-aspartate receptor activation. Neuroscience 2006;141:939–945.
56. Ro JY, Capra NF, Lee JS, Masri R, Chun YH. Hypertonic saline-induced muscle nociception and c-fos activation are partially mediated by peripheral NMDA receptors. Eur J Pain 2007;11:398–405.
57. Wong H, Kang I, Dong XD, et al. NGF-induced mechanical sensitization of the masseter muscle is mediated through peripheral NMDA receptors. Neuroscience 2014;269:232–244.
58. Weng HR, Dougherty PM. Response properties of dorsal root reflexes in cutaneous C fibers before and after intradermal capsaicin injection in rats. Neuroscience 2005;132:823–831.
59. Wu J, Fang L, Lin Q, Willis WD. Nitric oxide synthase in spinal cord central sensitization following intradermal injection of capsaicin. Pain 2001;94:47–58.
60. Fletcher D, Le Corre P, Guilbaud G, LeVerge R. Antinociceptive effect of bupivacaine encapsulated in poly(D,L)-lactide-co-glycolide microspheres in the acute inflammatory pain model of carrageenin-injected rats. Anesth Analg 1997;84:90–94.
61. Kayser V, Guilbaud G. Local and remote modifications of nociceptive sensitivity during carrageenin-induced inflammation in the rat. Pain 1987;28:99–107.
62. Rivat C, Laulin JP, Corcuff JB, Célèrier E, Pain L, Simonnet G. Fentanyl enhancement of carrageenan-induced long-lasting hyperalgesia in rats: Prevention by the N-methyl-D-aspartate receptor antagonist ketamine. Anesthesiology 2002;96:381–391.
63. Burton AW, Lee DH, Saab C, Chung JM. Preemptive intrathecal ketamine injection produces a long-lasting decrease in neuropathic pain behaviors in a rat model. Reg Anesth Pain Med 1999;24:208–213.
64. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ, Frenk H. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. Brain Res 1993;605:164–168.
65. Qian J, Brown SD, Carlton SM. Systemic ketamine attenuates nociceptive behaviors in a rat model of peripheral neuropathy. Brain Res 1996;715:51–62.
66. Rozen TD. Trigeminal neuralgia and glossopharyngeal neuralgia. Neurol Clin 2004;22:185–206.
67. van Kleef M, van Genderen WE, Narouze S, et al. 1. Trigeminal neuralgia. Pain Pract 2009;9:252–259.
68. De Toledo IP, Conti Réus J, Fernandes M, et al. Prevalence of trigeminal neuralgia: A systematic review. J Am Dent Assoc 2016;147:570–576.
69. Younis S, Maarbjerg S, Reimer M, et al. Quantitative sensory testing in classical trigeminal neuralgia—A blinded study in patients with and without concomitant persistent pain. Pain 2016;157:1407–1414.
70. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum 1995;4:209–221.
71. Dao TT, LeResche L. Gender differences in pain. J Orofac Pain 2000;14:169–184.
72. Dong XD, Mann MK, Kumar U, et al. Sex-related differences in NMDA-evoked rat masseter muscle afferent discharge result from estrogen-mediated modulation of peripheral NMDA receptor activity. Neuroscience 2007;146:822–832.
73. Fischer L, Torres-Chávez KE, Clemente-Napimoga JT, et al. The influence of sex and ovarian hormones on temporomandibular joint nociception in rats. J Pain 2008;9:630–638.
74. Wong H, Dong XD, Cairns BE. Nerve growth factor alters the sensitivity of rat masseter muscle mechanoreceptors to NMDA receptor activation. J Neurophysiol 2014;112:2275–2282.