

Intrathecal Lidocaine Reverses Tactile Allodynia Caused by Nerve Injuries and Potentiates the Antiallodynic Effect of the COX Inhibitor Ketorolac

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Background: **Systemic lidocaine and other local anesthetics reduce hypersensitivity states induced by both acute inflammation and peripheral nerve injury in animals and produce analgesia in some patients with chronic pain. The mechanisms underlying the antiallodynic effect of systemic lidocaine are unclear, although most focus is on peripheral mechanisms. Central mechanisms, particularly at the spinal dorsal horn level, are less known. In this study, the authors aimed to determine whether intrathecal lidocaine has an antiallodynic effect on established mechanical allodynia in two well-characterized neuropathic pain rat models: partial sciatic nerve ligation (PSNL) and spinal nerve ligation (SNL).**

Methods: **Lidocaine (100–300 μg) was intrathecally injected in PSNL and SNL rats. The withdrawal threshold of both hind paws in response to mechanical stimulation was measured using a series of calibrated von Frey filaments.**

Results: **This single injection reduced ongoing tactile allodynia in PSNL and SNL rats. The antiallodynic effect of intrathecal lidocaine lasted longer in PSNL (> 3 days) than in SNL rats (< 3 days). Intraperitoneal lidocaine (300 μg) had no effect on tactile allodynia in PSNL rats. In SNL rats, prior intrathecal lidocaine (200 and 300 μg) potentiated the antiallodynic effect of intrathecal ketorolac, a nonselective cyclooxygenase inhibitor. Intrathecal ketorolac alone had no antiallodynic effect on SNL rats. However, prior intrathecal lidocaine (100 μg) failed to potentiate the antiallodynic effect of intrathecal ketorolac.**

Conclusion: **The authors' data suggest that intrathecal lidocaine possibly suppressed the hyperexcitability of the dorsal horn neurons and likely interacted with eicosanoid systems in the spinal dorsal horn.**

PREVIOUS isolated trials examined the analgesic effect of intravenous lidocaine to treat postoperative pain[1] and deafferentation pain.[2] More recently, the analgesic effect of systemic lidocaine has received more attention due to accumulating evidence for its efficacy to treat neuropathic pain in animal models and in patients.[3] In nerve-injured rats, intravenous lidocaine silences ectopic discharge of injured afferent fibers or dorsal root ganglion cells,[4] alleviates mechanical allodynia,[5,6] and reduces ongoing pain in some patients suffering from neuropathic pain.[3] There is a plasma concentration-dependent relationship between lidocaine and reduction in allodynia in patients with complex regional pain syndromes,[7] suggesting a peripheral mechanism of action. All these lines of evidence have led to a research focus on peripheral mechanisms of systemic lidocaine action.[3] A spinal component of systemic lidocaine has been questioned by the observation that intrathecal lidocaine failed to attenuate neuropathic pain following spinal nerve ligation (SNL).[5]

It is a common practice to test the correct placement of an intrathecal catheter in rats by injection of a small dose (200–300 μg) of lidocaine. Transient (10–20 min) bilateral hind limb motor weakness or paralysis is considered indicative of correct catheter tip location in the lumbar intrathecal space. In studies using rats with partial sciatic nerve ligation (PSNL), a widely used rat model for neuropathic pain,[8] we noticed that 300 μg intrathecal lidocaine had a long-lasting antiallodynic effect in addition to causing transient paralysis of both hind limbs. This observation was unexpected since others had reported no antiallodynic effect of intrathecal lidocaine (500 μg) in SNL rats.[5] Inspired by the unexpected finding, the first purpose of this study was to further explore whether intrathecal lidocaine was able to reverse established tactile allodynia induced by both PSNL and SNL.

By chance, we observed that intrathecal injection of lidocaine 1 week earlier potentiated the antiallodynic effect of intrathecal ketorolac, a cyclooxygenase (COX) inhibitor, on SNL rats. Intrathecal ketorolac was ineffective when administered alone as previously reported.[9,10] These additional preliminary observations indicated that intrathecal lidocaine interacted with eicosanoid systems at the spinal cord level. Therefore, the second purpose of the current study was to determine the dose range in which intrathecal lidocaine potentiates the antiallodynic effect of intrathecal ketorolac.

Materials and Methods

Intrathecal Catheter Implantation and Lidocaine Injection

A total of 26 male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN), weighing 200–250 g, were used in this study. The number of all rats used in different treatments is summarized in table 1. All surgical procedures were in conformity with the Wake Forest University (Winston-Salem, North Carolina) guidelines on the ethical use of animals, and studies were approved by the

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Table 1. Number of Rats Used in Each Treatment

Injury	IT Saline	IT LDC	IP LDC	IT KET	IT LDC + IT KET
PSNL	5	5 (300 μg)	4 (300 μg)		
SNL		4 (100 μg)		5 (50 μg)	4 (LDC 100 μg + KET 50 μg)
		5 (200 μg)			5 (LDC 200 μg + KET 50 μg)
		5 (300 μg)			5 (LDC 300 μg + KET 50 μg)

IP = intraperitoneal injection; IT = intrathecal injection; KET = ketorolac; LDC = lidocaine; PSNL, partial sciatic nerve ligation; SNL, spinal nerve ligation.

Animal Care and Use Committee. Animals were implanted with intrathecal catheters according to the method described previously.[11] Under halothane anesthesia (2–4% in oxygen–air), a polyethylene catheter (PE-10, 7.5 cm) was inserted intrathecally through a small puncture made in the atlanto-occipital membrane of the cisterna magna to reach the lumbar enlargement of the spinal cord. Animals were allowed 4 to 5 days to recover from the surgery, and those displaying signs of motor dysfunction (forelimb or hind limb paralysis) were excluded from the study. Lidocaine (100, 200, or 300 μg; Abbott Laboratories, Chicago, IL) was injected through the exteriorized portion of the catheter in 15 μl volume followed by a flush with 10 μl saline, 0.9%. Control rats were only injected with the same volume of saline. To determine whether systemically administered lidocaine is able to reverse established tactile allodynia, lidocaine (300 μg dissolved in 150 μl saline) was injected intraperitoneally in four PSNL rats 3 weeks following PSNL. To determine the effect of prior intrathecal lidocaine injection on the antiallodynic effect of the COX inhibitor ketorolac, 1 week following intrathecal lidocaine injection (100–300 μg), 10 μl ketorolac (0.5%, 50 μg; Allergan, Irvine, CA) was intrathecally injected in these SNL rats.

Partial Sciatic Nerve Ligation, L5 and L6 Spinal Nerve Ligation, and Behavioral Tests

Rats were anesthetized with 2–4% halothane in oxygen–air. For PSNL, the left sciatic nerve was exposed at the high thigh level, and one third to one half of the nerve was ligated with 6-0 silk suture as previously described.[8] For SNL, the left L5 and L6 spinal nerves were exposed and ligated with 6-0 silk suture as described before.[12] Before and after surgery, all rats were behaviorally tested to determine the paw withdrawal threshold of both hind paws to mechanical stimuli. Animals were placed in a plastic cage with a wire mesh floor and allowed to explore and groom until they settled. A set of von Frey filaments with bending forces ranging from 1.25 to 30 g was applied, in ascending order, to both plantar hind paws ("up-and-down" method[13]). A transient (10–20 min) weakness or paralysis of both hind limbs was seen in almost all rats with 300 μg intrathecal lidocaine injection but only in one third of rats with 200 μg intrathecal lidocaine and was completely absent in rats treated with 100 μg intrathecal lidocaine. Rats receiving either intrathecal saline or intraperitoneal lidocaine exhibited no abnormal behavior. Only after complete recovery from this paralysis were these rats tested behaviorally (2 h after intrathecal lidocaine). Each hind paw was measured three times, and the average values were obtained. Two independent individuals who were blinded to the study groups did the behavioral test. Similar results were obtained from the two examiners.

Statistical Analysis

The mean ± SEM values from both hind paws were determined for each group. The mean values after nerve injury or after injection were compared with prelesion baseline values statistically using a one-way repeated measures analysis of variance with Dunnett multiple comparisons (SigmaStat, v. 2.03; Jandel Scientific Inc., San Rafael, CA). The significance level was set at $P < 0.05$.

Results

Intrathecal Injection of Lidocaine Reverses Established Tactile Allodynia Caused by Partial Sciatic Nerve Ligation and Spinal Nerve Ligation

Two weeks after PSNL, the withdrawal threshold of both hind paws of all rats was significantly lower than the baseline value (fig. 1, $P < 0.05$), indicating that tactile allodynia had developed. Then, 15 μl lidocaine (2%, 300 μg) was intrathecally injected in five rats, while saline in the same volume was injected in another five rats that served as controls. Another four rats received 300 μg intraperitoneal lidocaine. Two hours following intrathecal lidocaine, the tactile allodynia in both hind paws of intrathecal lidocaine–injected rats was significantly reversed (fig. 1). This reversal was also observed 3 days after intrathecal lidocaine. By then, intrathecal lidocaine also had an antinociceptive effect on the ipsilateral hind paw (fig. 1, $P < 0.05$). However, 1 week after injection, the antiallodynic effect disappeared, and tactile allodynia was restored to preinjection level. At all time points following intrathecal saline injection, tactile allodynia was persistent in all rats (fig. 1, $P < 0.05$). In four PSNL rats with intraperitoneal lidocaine, no attenuation or reversal of tactile allodynia was observed (data not shown).

Four weeks following SNL, all rats exhibited a significant reduction in the withdrawal threshold of the ipsi-

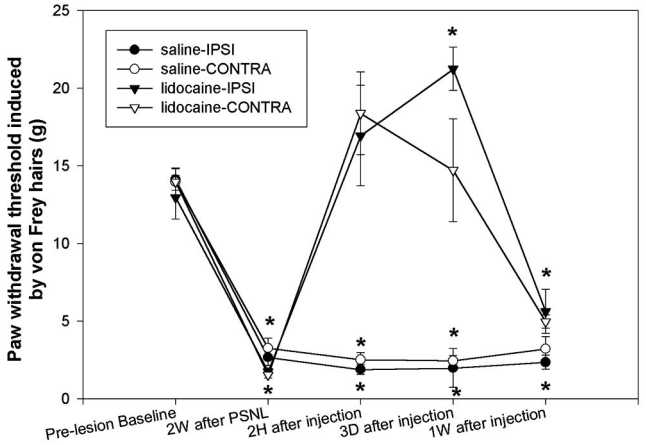

Fig. 1. Intrathecal lidocaine reversed well-developed tactile allodynia caused by partial sciatic nerve ligation (PSNL). Two weeks after PSNL, the withdrawal threshold of both hind paws was significantly lower than the prelesion baseline (*$P < 0.05$). Two hours and 3 days after intrathecal lidocaine (300 μg), the withdrawal threshold in both hind paws was reversed to the prelesion level. Three days after injection, the value in the ipsilateral (IPSI) hind paw was significantly higher than prelesion baseline (*$P < 0.05$), indicating antinociceptive effect. One week after injection, the values from both hind paws returned to the preinjection level, *i.e.*, significantly lower than the prelesion baseline (*$P < 0.05$). At all time points after intrathecal saline injection, the withdrawal threshold in both hind paws was always significantly decreased compared to the prelesion baseline value. Mean ± SEM, n = 5 in each group. CONTRA = contralateral.

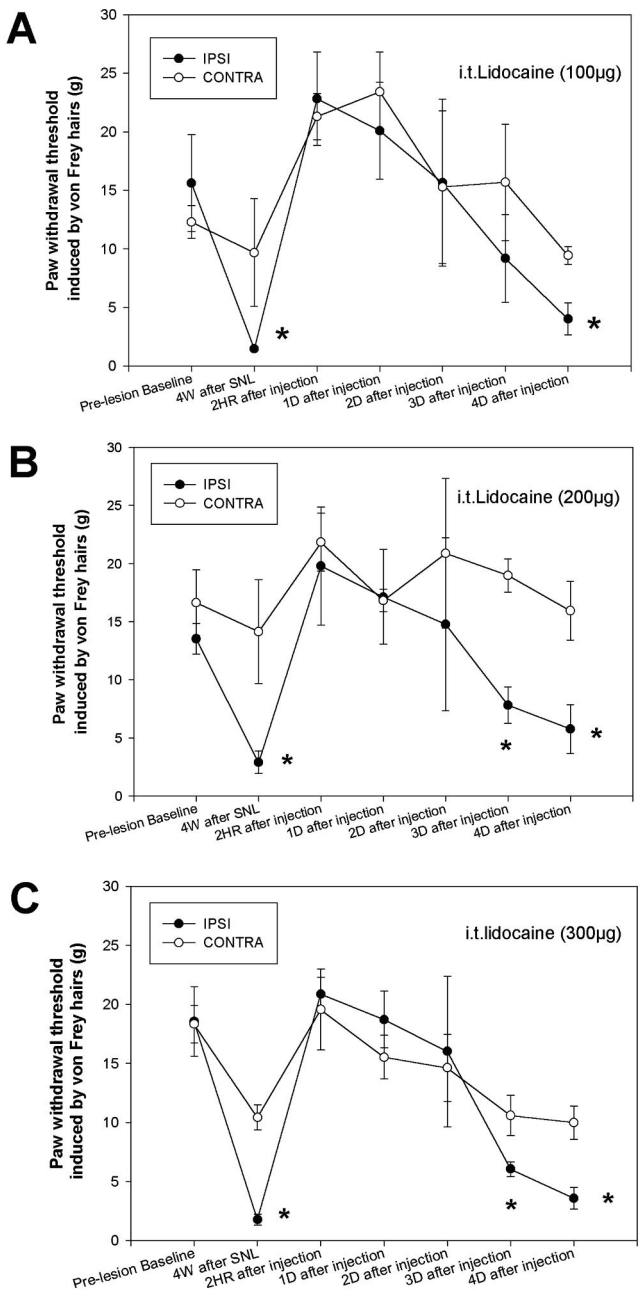

Fig. 2. Intrathecal lidocaine injection reversed well-established tactile allodynia caused by sciatic nerve ligation (SNL). Four weeks after SNL, the withdrawal threshold of the ipsilateral (IPSI) hind paw was significantly decreased compared with the prelesion baseline (*A–C*, *$P < 0.05$). The value in the contralateral (CONTRA) hind paw was not significantly different from the prelesion baseline at all time points tested. Two hours, 1 and 2 days after 100 (*A*), 200 (*B*), and 300 μg (*C*) intrathecal lidocaine injection, the withdrawal threshold in the ipsilateral hind paw was reversed to the prelesion level. Three days after injection, the value in the ipsilateral hind paw in SNL rats receiving 200 (*B*) and 300 μg (*C*) lidocaine returned to a level that was significantly lower than the prelesion baseline (*$P < 0.05$). However, the value in the contralateral hind paw of SNL rats intrathecally injected with 100 μg lidocaine still remained elevated (*A*). Four days after injection, the withdrawal threshold in the ipsilateral hind paw of all lidocaine-injected rats was significantly lower than the prelesion baseline (*A–C*, *$P < 0.05$). Mean ± SEM, n = 4–5 in each group.

lateral hind paw when compared to the prelesion baseline (figs. 2A–C, $P < 0.05$). Two hours and 2 days following 100, 200, and 300 μg intrathecal lidocaine injection, tactile allodynia was markedly reversed to the prelesion level. Three days after injection, tactile allodynia reappeared in the ipsilateral hind paw of 200 and 300 μg intrathecal lidocaine–injected SNL rats (figs. 2B and C, $P < 0.05$). Although the withdrawal threshold in the hind paw of the 100 μg intrathecal lidocaine–injected SNL rats also declined, it was not significantly lower than the prelesion baseline value (fig. 2A). The withdrawal threshold in the contralateral hind paw of all SNL rats was not significantly different from the prelesion level after either SNL or intrathecal lidocaine injection.

Intrathecal Lidocaine Potentiates the Antiallodynic Effect of Intrathecal Ketorolac in Spinal Nerve Ligation Rats

Consistent with a previous report,[9] intrathecal ketorolac (50 μg) failed to attenuate the tactile allodynia caused by SNL (fig. 3A). Interestingly, 1 week after intrathecal lidocaine, when tactile allodynia reappeared, intrathecal ketorolac reversed tactile allodynia for 4 h in SNL rats that had previously received 200 (fig. 3B) and 300 μg (not shown) lidocaine. One day after intrathecal ketorolac, its antiallodynic effect disappeared. However, intrathecal ketorolac failed to exert any antiallodynic effect on SNL rats that had received 100 μg intrathecal lido-

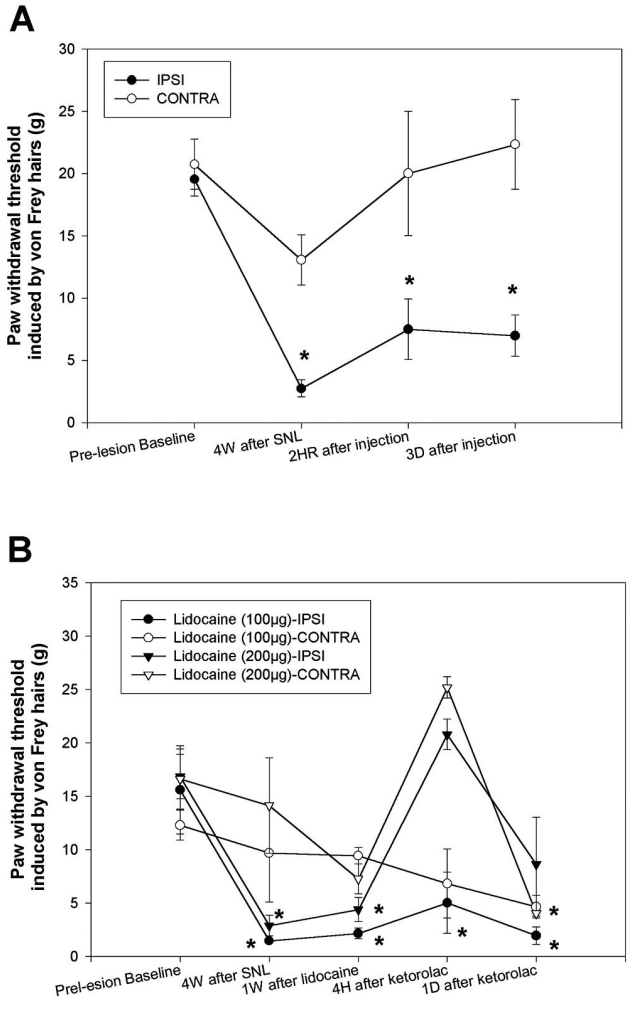

Fig. 3. (*A*) Intrathecal ketorolac (50 μg) failed to attenuate tactile allodynia caused by sciatic nerve ligation (SNL). Four weeks after SNL, the withdrawal threshold of the ipsilateral (IPSI) hind paw was significantly decreased compared to the prelesion baseline (P* < 0.05). Two hours and 3 days after intrathecal ketorolac injection, the value remained significantly lower than the prelesion level (**P* < 0.05). The value in the contralateral (CONTRA) hind paw was not significantly different from the prelesion baseline at all time points tested. Mean ± SEM, n = 5. (*B*) Lidocaine (200 μg) potentiated the antiallodynic effect induced by intrathecal ketorolac (50 μg). Four weeks after SNL, the withdrawal threshold of the ipsilateral hind paw was significantly decreased compared to the prelesion baseline (**P* < 0.05). One week after intrathecal lidocaine injection, the withdrawal threshold in the ipsilateral hind paw remained at a significantly lower level than prelesion baseline (**P* < 0.05). However, 4 h after intrathecal ketorolac injection, the withdrawal threshold from both hind paws of SNL rats receiving 200 μg intrathecal lidocaine was significantly reversed to the prelesion level. One day after injection, the value returned to a significantly lower level than prelesion baseline (**P* < 0.05). However, in SNL rats receiving 100 μg intrathecal lidocaine, intrathecal ketorolac injection failed to reverse the withdrawal threshold to the prelesion level 4 h and 1 day after injection (**P* < 0.05). Mean ± SEM, n = 4–5 in each group.**

caine previously (fig. 3B). Intrathecal ketorolac (100 μg) alone also failed to alleviate SNL-induced tactile allodynia but also exhibited the antiallodynic effect 1 week after intrathecal lidocaine (data not shown). The magnitude of the antiallodynic effect exerted by 100 μg intrathecal ketorolac was similar to that induced by 50 μg intrathecal ketorolac 1 week after prior intrathecal lidocaine injection (data not shown). Either intrathecal saline injection 1 week following prior lidocaine injection or intrathecal ketorolac (50 μg) injection 1 week following prior intrathecal ketorolac (50 μg) injection failed to alleviate SNL-induced tactile allodynia (data not shown).

Discussion

Intrathecal Lidocaine Injection Reverses Tactile Allodynia following Partial Sciatic Nerve Ligation and Spinal Nerve Ligation

The long-lasting effects of intrathecal lidocaine observed in this study were unexpected and carry important fundamental and methodological considerations for the laboratory study of neuropathic pain states as well as potential clinical implications. Although the mechanisms underlying the antiallodynic effects of lidocaine on animals and patients are unknown, a peripheral mechanism has been proposed. Expression of sodium channel subtypes in afferents is altered following nerve injury,[14,15] and ectopic discharges are noted from neuroma sites, afferent fibers, and dorsal root ganglion cells.[4,16,17] Lidocaine reduces ectopic discharge after systemic administration at concentrations that fail to block nerve conduction,[3] perhaps by acting on unique or up-regulated sodium channel subtypes induced by nerve injury. A noncentral site of lidocaine action is further supported by failure of intrathecal lidocaine to reverse mechanical allodynia in SNL rats.[5] In the current study, we observed that 100 μg intrathecal lidocaine, which failed to block motor nerve conduction (signs including any weakness or paralysis of the hind limb), also effectively reversed tactile allodynia for more than 3 days in PSNL rats and less than 3 days in SNL rats. Higher doses of intrathecal lidocaine, 200 and 300 μg, triggered a transient paralysis of both hind limbs in both PSNL and SNL rats. Reversal of tactile allodynia persisted long after paralysis of both hind limbs disappeared, indicating that the blockade of nerve impulse conduction in thick myelinated Aβ axons in the lumbar dorsal root is not likely involved. A previous study showed that local infusion of lidocaine onto injured sciatic nerve failed to relieve thermal hyperalgesia in PSNL rats,[18] suggesting that the antiallodynic effect induced by intrathecal lidocaine in PSNL rats is not mediated through blocking conductance of the small-diameter Aδ and C axons in the dorsal roots. Therefore, it is more likely that intrathecal lidocaine has a central suppressing effect at the dorsal horn level. Several lines of evidence also support this assumption. Previous *in vivo*[19] and *in vitro*[20,21] studies showed that lidocaine inhibits spinal neuron activity, likely by blocking sodium and potassium currents evoked in dorsal horn neurons.[21] PSNL[22] and SNL[23,24] induces hyperexcitability in the

ipsilateral dorsal horn neurons in rats exhibiting tactile allodynia. Thus, intrathecal lidocaine may suppress this hyperexcitability of the dorsal horn neurons, thus achieving its antiallodynic effect.

We also noticed that the antiallodynic effect induced by intrathecal lidocaine lasted longer and was more effective in the PSNL model than in the SNL model since the antinociceptive effect in the ipsilateral hind paw was also observed by day 3 after injection. These observations suggest that the sensitivity to intrathecal lidocaine depends on the injury model. The reasons for the variability of sensitivity in different injury models are currently unknown. This difference may contribute to the different effects of intrathecal ketorolac on the two models (see the section below entitled Prior Intrathecal Lidocaine Potentiates the Antiallodynic Effect of Intrathecal Ketorolac on Spinal Nerve Ligation Rats).

The etiology of the long duration of intrathecal lidocaine in alleviating tactile allodynia following PSNL and SNL is uncertain but is reminiscent of long-lasting effects observed after intravenous lidocaine administration in animal models[5] and in some patients with chronic neuropathic pain.[3] It is unlikely that lidocaine remains in spinal tissue for more than a few hours after intrathecal injection.[25] Although some have speculated that longer-lasting lidocaine metabolites may be responsible for long-lasting effects,[5] the current study is not consistent with this interpretation since lidocaine is metabolized in the liver, and lidocaine metabolites would thus occur only after systemic absorption. However, systemic (intraperitoneal) lidocaine in the current study, which would also be metabolized in the liver, had no effect on tactile allodynia at this dose. Since we observed that intrathecal lidocaine likely interacts with eicosanoid systems in the spinal dorsal horn (see the section below entitled Prior Intrathecal Lidocaine Potentiates the Antiallodynic Effect of Intrathecal Ketorolac on Spinal Nerve Ligation Rats), lidocaine's interaction with other pain-related systems could possibly underlie its prolonged antiallodynic effects. Further study is required to test this hypothesis.

Prior Intrathecal Lidocaine Potentiates the Antiallodynic Effect of Intrathecal Ketorolac on Spinal Nerve Ligation Rats

It has been shown previously that COX inhibitors, including ketorolac, when intrathecal injected alone, fail to attenuate SNL-induced neuropathic pain but potentiate morphine.[9,10] Consistent with these studies, we confirmed here that intrathecal ketorolac alone had no antiallodynic effect on SNL-induced tactile allodynia. Although we observed that intrathecal ketorolac alleviated PSNL-induced tactile allodynia,[26] its antiallodynic effect in SNL rats was observed only following prior intrathecal lidocaine. The potentiating effect was only seen following 200 and 300 μg but not 100 μg intrathecal lidocaine, indicating that the potentiation is dose dependent. However, 50 and 100 μg intrathecal ketorolac exerted the same magnitude of antiallodynia following prior intrathecal lidocaine. Intrathecal saline did not display any antiallodynic effect on SNL rats 1 week after intrathecal lidocaine. Our data strongly suggest that intrathecal lidocaine interacts with eicosanoid systems in the spinal cord following nerve injury. In the spinal cord, both neurons and glia produce prostaglandins (PG).[27] The production is enhanced by peripheral inflammation.[28] *In vitro* studies show that high-dose lidocaine reduces the production of PGE2 in human gastric mucosa.[29] Local lidocaine inhibits the eicosanoid formation in burned skin.[30] *In vitro* administration of the local anesthetic ropivacaine dose-dependently inhibits zymosan-induced release of eicosanoid from human granulocytes and endothelial cells,[31] and bupivacaine inhibits the EP1 receptor at high concentrations.[32] Based on these findings, we speculate that intrathecal lidocaine may either inhibit the production and release of PGs or inhibit EP1 receptors in the spinal dorsal horn, thus down-regulating PG systems. This down-regulation of PG systems may persist following high doses of lidocaine (200–300 μg), even after their antiallodynic effect disappears, hence potentiating the antiallodynic effect of intrathecal ketorolac. However, following prior intrathecal injection of ketorolac, the second intrathecal injection of ketorolac did not alleviate the tactile allodynia. This result indicates that the potentiation of ketorolac's antiallodynic effect by prior intrathecal lidocaine may be mediated through mechanisms other than the inhibition of PG production in the spinal cord. Further studies are certainly warranted to address this issue.

Concluding Remarks

Single intrathecal lidocaine alleviates established tactile allodynia for up to 3 days in PSNL rats and less than 3 days in SNL rats. The alleviation is likely mediated through a central mechanism. Our data also suggest that nerve injury models differ in their sensitivity to intrathecal lidocaine. The use of a test dose of lidocaine to confirm intrathecal catheter location can have long-lasting effects in some models of nerve injury. Thus, the test should be done only at the end of the experiments. The analgesic property of systemic lidocaine in chronic pain states involving nerve damage has made it useful in treating neuropathic pain patients.[3] However, its side effects, including dizziness, tinnitus, tremor, and paresthesias, may limit its systemic application. Local anesthetics are the class of drugs most commonly administered with opioids by chronic intrathecal infusion in chronic pain patients.[33,34] Intrathecal injection of 100 μg lidocaine, which failed to block motor nerve conduction, yet reversed neuropathic pain as reported in the present study, may provide another approach to alleviate chronic pain in some patients. The dose-dependent potentiation of intrathecal ke-

torolac by intrathecal lidocaine also provides a new avenue in the future treatment of neuropathic pain.

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