Prolonged Suppression of Postincisional Pain by a Slow-release Formulation of Lidocaine

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ABSTRACT

Background: Postoperative pain can occur despite nerve blocks during the surgical period. Here we tested Xybrex (Orthocon, Inc., Irvington, NY), a slow-release formulation of lidocaine that blocks rat sciatic nerve for 1–2 days, for its ability to suppress postincisional pain.

Methods: A plantar paw incision was made in rats, either along the midline (Brennan model) or at the lateral edge, 30 min after different treatment groups received either lidocaine (0.2 ml, 2%) or Xybrex implant at the ipsilateral sciatic nerve or Xybrex at the contralateral sciatic nerve. Behavioral testing by von Frey filaments occurred at 2 and 6 h postoperatively and for the next 10 postoperative days. The fractional response (paw withdrawal responses per 10 pokes) was scored at each time.

Results: Mechanosensitivity from the Brennan paw incision was reduced throughout the postoperative period by ipsilateral Xybrex, although lidocaine injection almost had no effect. Contralateral Xybrex had a weaker but still significant antihyperalgesic effect, converging to that from ipsilateral Xybrex at postoperative day 2. Xybrex at the nuchal midline reduced allodynia for only postoperative days 1–3, whereas hyperalgesia was reduced continuously after postoperative day 2. Hyperalgesia from the lateral incision was also reduced by ipsilateral Xybrex but not by contralateral Xybrex.

Conclusions: Implants of slow-release lidocaine formulations are most effective against postincisional pain when placed at the

What We Already Know about This Topic

- Nerve block with currently available local anesthetics usually produces analgesia for 12–18 h
- Sustained release local anesthetics used for nerve block could improve the duration of analgesia for postoperative patients

What This Article Tells Us That Is New

- Using animal models for postoperative pain, a sustained release lidocaine formulation, applied to nerves innervating incised tissue, reduced hypersensitivity for 2–3 days; such a formulation could be useful for nerve blockade in postoperative patients

ipsilateral nerve innervating the area of incision. Contralateral nerve implants are somewhat less effective, probably acting by releasing lidocaine into the systemic circulation. There appears to be a differential role of central sensitization between postincisional allodynia and hyperalgesia.

LONG-TERM postoperative pain follows many common surgical procedures, including thoracotomies, breast surgery, cholecystectomy, and herniorrhaphy.[1–3] It is characterized by both resting and incident-related pain contributing to morbidity and delaying or preventing a return to a full and active life. The single factor that seems to be predictive of the duration and degree of prolonged (several months) or long-term (more than 6 months) postoperative pain is the intensity of the long-term postoperative pain.[4] This long-term pain results from either the previous responses to a high degree of tissue/nerve injury or inflammation[5–7] or is an indication of the individual patient's response to an unexceptional surgical procedure. It is probable, therefore, that treatments that reduce long-term postoperative pain also will reduce long-term pain in intensity or duration. The object of this study was to investigate one such treatment, prolonged blockade of the peripheral nerve innervating the surgical field, on long-term pain after paw incision.

Both the initial injury discharge in local nerves caused directly by the incision[6,7] and the later, delayed activation of impulses from peripheral nerve that may be conducted by injured or uninjured fibers[6,8,9] probably contribute to the establishment of longer lasting hyperalgesia. In addition, there is little doubt that changes in the central nervous system, at least at the spinal cord (and probably also in the brain), are essential for long-term pain management.[10,11] Although the results of many preemptive efforts to prevent or

suppress clinical long-term postoperative pain have been equivocal,[12,13] the strong success of this strategy using animal models[14,15] encourages a mechanistically designed approach to understanding the causes and developing effective therapeutics for postoperative pain.

Incision of the plantar paw skin, sometimes with damage of the underlying muscle,[16–18] and incision of the hairy skin on the back[14] both result in localized mechanical hypersensitivity that lasts 3–5 days. Such hypersensitivity has been separated into those pain responses to stimuli that are normally not noxious, or allodynia, and the heightened responses to noxious stimuli, or hyperalgesia. Punctate tactile cutaneous stimulation reveals pain hypersensitivity at both the primary (1°) area, very near the incision, and the secondary (2°) regions farther away.[14,16] Primary hyperesthesia involves the release and actions of local factors at the incision site[17–20] and the sensitization of nerves that innervate that site,[21] as well as changes in the spinal cord and brain, or central sensitization, whereas secondary hyperesthesia appears to result from central sensitization alone.[10,11,22] In both cases, however, changes in the central nervous system are driven by the intense, prolonged discharge from afferent nerve fibers, either fibers directly injured by the incision or uninjured fibers modified by chemicals (*e.g.*, inflammatory mediators) that are released around the injury site.[20] In principle, such peripheral nerve impulses can be prevented by some form of local anesthesia.

Peripheral nerve blockade during surgery almost always is accomplished with local anesthetics (LA). These drugs can be used safely and effectively to abolish sensation, producing a somewhat selective block of small myelinated (*e.g.*, A-δ) fibers with a significantly less potent block of C-fibers.[23,24] Infiltration of a surgical area before an incision[25–27] or of the wound after an incision[28,29] both can effectively suppress long-term clinical postoperative pain. Evidence from other studies indicates that afferent discharge is critical for establishing neuropathic pain after nerve injury,[30] and on the basis of clinical data, it has been hypothesized that it is also critical for postoperative pain.[12] But what is the critical postoperative period for pain sensitization from afferent discharge, during which impulse blockade is an effective treatment? Here, we examine this question with nerve blocks of typically short (less than 2 h) and unusually long (more than 12 h) duration, the latter using a new, slow-release formulation of lidocaine.[31]

Materials and Methods

Drugs

Xybrex anesthetic matrix, a suspension of a water-insoluble particulate and a hydrophobic carrier containing 16% lidocaine (w/w),[31] was obtained from Orthocon, Inc., (Irvington, NY). Lidocaine HCl was purchased from Sigma Chemical Co., St. Louis, MO, and freshly prepared at a concentration of 1% or 2% (w/v) by dissolving it in 0.9% unbuffered NaCl (pH of the final solution was 6.6–6.7).

Sciatic Nerve Implantations/Injections

The procedures in this study were approved by the Harvard Medical Area Standing Committee on Animals (Boston, MA) and are consistent with the published guidelines for the humane use of laboratory animals. Male Sprague–Dawley rats were purchased from Charles River Laboratory (Wilmington, MA) and kept in the animal housing facilities at Brigham and Women's Hospital, with controlled humidity (20–30% relative humidity), room temperature (24°C), and a 12-h (6:00 AM to 6:00 PM) light–dark cycle. For 5–7 days before the experiments, the animals were handled to familiarize them with the behavioral investigator, experimental environment, and specific experimental procedures.[32] At the time of implantation or injection, the rats weighed approximately 300 g. For all surgical procedures and implants or injections, the rats were anesthetized by sevoflurane (Ultane; Abbott Laboratories, Abbott Park, IL) through uncontrolled inhalation (preliminary assays of the mixed inspired/expired vapors during this brief anesthetizing period showed a range of 2–6% sevoflurane).

Each experimental group contained six rats. For subfascial nerve implantation of Xybrex, rats were anesthetized with sevoflurane, and the sciatic nerve was exposed by lateral incision of the thigh and blunt division of the superficial fascia and muscle; the saphenous nerve was similarly exposed by lateral incision next to the vessel-nerve protrusion more than the medial side of the thigh. Xybrex, which was hand-molded into a cylindrical shape measuring approximately $1–1.5 \times 0.125–0.25$ cm, was placed next to the sciatic or saphenous nerve after dissecting the epineurial fascia at 200 mg total mass (corresponding to 32 mg lidocaine) per rat. An inactive control group (matrix only) received lidocaine-free matrix at 200 mg per rat. For dual subfascial implantation/injection at sciatic and saphenous nerves, half the dose of the above implant (*e.g.*, 100 mg Xybrex) was applied to each nerve.

After implantation of the Xybrex or matrix or injection of a lidocaine solution, the superficial muscle layer was closed with 4-0 Vicryl sutures, placed approximately 3 mm apart to minimize displacement of Xybrex, and the skin incision was closed with 4-0 Prolene sutures.

Lidocaine is released from Xybrex *in vitro* with a half-time of approximately 6–8 h and provides complete functional motor block of the rat sciatic nerve *in vivo* for 18 h and complete nociceptive block for approximately 7 h.[31] The sciatic block by either lidocaine or Xybrex did not affect the rat's ability to execute a nocifensive withdrawal from a paw prick or a toe pinch.

In experimental contralateral groups, 200 mg Xybrex was implanted at the contralateral sciatic or the sciatic and saphenous nerve (100 mg at each) 30 min before incision of the paw. In another subcutaneous group used to determine the effects of systemically accumulated lidocaine, 200 mg Xybrex was implanted under the skin at the nuchal midline at a distance of 7–8 or 11–12 cm, respectively, from the site for

injection/implantation on the leg or the plantar hind paw incision site.

For rats injected with 2% lidocaine solution (containing 4 mg drug), the same general anesthesia was performed, and a 0.2-ml volume was injected with a 30-gauge needle attached to a tuberculin syringe directly beneath the clear epineurial fascia that surrounds the nerve but outside the perineurium at the same site used for Xybrex implants in other animals.

For some rats, the cutaneous distribution of functional analgesia was determined by injection of 0.2 ml lidocaine 2% next to the saphenous nerve. To test these animals' responses to the stimulation (pin prick or skin pinch) of the dorsum, it was necessary to use a light general anesthetic, with 0.3% halothane (measured as the inspired gas). Under this halothane concentration, rats that received no LA still were able to maintain an upright position and to respond to a pinch of their plantar hind paw with that paw's withdrawal and arching of the spine, showing that nocifensive reflexes still were present.

Surgery: Brennan and Lateral Paw Incision

Two locations for incision on the plantar paw were used, one at the midline of the heel, the classic Brennan paw incision (BPI) model,[16] and one that we initiated for these experiments, with an incision of the same length but located at the most lateral plantar aspect, the lateral paw incision (LPI). This second location was chosen because this area of the paw is completely insensate by lidocaine blockade of the sciatic nerve, whereas the midline area of the BPI is sometimes not insensate by this procedure (see Results below).

Rats were anesthetized with nose-inhaled sevoflurane: a 1-cm longitudinal incision was made with a No. 11 blade through the skin and fascia of the median (BPI) plantar surface of the hind paw beginning 0.5 cm distal from the end of the heel (fig. 1). The underlying flexor muscle was increased, and a longitudinal incision to both ends was made. The skin was closed with 5-0 nylon sutures, and topical antibiotics were administered. For the LPI model, a 1-cm longitudinal incision was made along the hairs bordering the lateral plantar surface of the hind paw beginning 0.5 cm distal from the end of the heel (fig. 1). The underlying flexor muscle was longitudinally sectioned, as far along its length as possible. Animals were allowed to recover in their cages, and sutures were removed on the third postoperative day (POD).

Neurobehavioral Examination

Individual rats were placed on an increased wire mesh floor and confined underneath individual overturned plastic boxes. Mechanical allodynia and hyperalgesia were assessed using von Frey filaments with bending forces of 4 or 15 g (Touch-Test Sensory Evaluators; Stoelting Co., Wood Dale, IL), respectively. In the initial tests, both forces were applied, but in later experiments, only responses to the 15 g force are reported because these demonstrated the general effectiveness of nerve block on postincisional pain hypersensitivity.

Each filament was applied 10 times to highly localized medial, lateral, and central test areas of the plantar surface of the incised (left) hind paw (fig. 1 inset).[33] Care was taken to avoid stimulating the same exact spot repeatedly within these regions or the tori/footpads themselves to minimize sensitization from the test *per se*. Nocifensive withdrawal responses to each of the von Frey filaments were counted and recorded as a fraction per 10 stimuli. Before the incision, two baseline measurements of mechanical sensitivity were taken for each test area on separate days and then averaged to provide the presurgery baseline response, graphically denoted as the response on day 0. Neurobehavioral responses were evaluated at 2 and 6 h postsurgery and then daily until POD 10.

Data Treatment and Statistical Analysis

The primary results are expressed as the normalized response (number of responses per 10 stimuli) to punctate stimulation, and these are graphed in the figures and collected as mean $\pm$ SD for the same PODs among the treatment groups. Comparisons were made using multigroup, two-way ANOVA to test for the significance of changes in time and among the different treatment groups, followed by the Tukey *post hoc* test to compare the differences among pairs of treatments (tables 1–3). In addition, the integrated hypersensitivity was calculated as the area-under-curve (AUC) for the normalized response minus the baseline normalized response subtracted at each POD time point. These AUCs (which have units of days) were collected and compared among treatments and the incisional controls (tables 4–6). Results in these tables, presented as mean $\pm$ SD, were compared by one-way, repeated measures, ANOVA followed by Tukey *post hoc* pair-wise test. Statistical analyses were conducted using SAS software (Cary, NC). A *P* value of less than 0.05 was considered statistically significant.

Results

Anatomy of Hind Paw Innervation

The objective of this study was to determine whether a prolonged block of the nerves innervating the skin at an incision could prevent postincisional pain. Initially, the rat hind paw plantar incision model of Brennan was adopted because the course of pain after that procedure is well replicated and the LA block of the rat sciatic nerve equally well characterized. One early concern, however, questioned the plantar area that was effectively anesthetized from a sciatic nerve block because previous studies demonstrated that the lateral (fourth and fifth) digits of the hind paw were insensate during sciatic nerve block, whereas the medial-most (first) toe remained unanesthetized. Because the BPI model requires an incision at the midline of the distal paw (fig. 1), it is important to know whether this area is fully anesthetized during sciatic block. The shaded areas of the plantar surface in figure 1 show those places on the feet of six rats, tested at 10 min after injection of 0.2 ml lidocaine 2% (4 mg), that were unrespon-

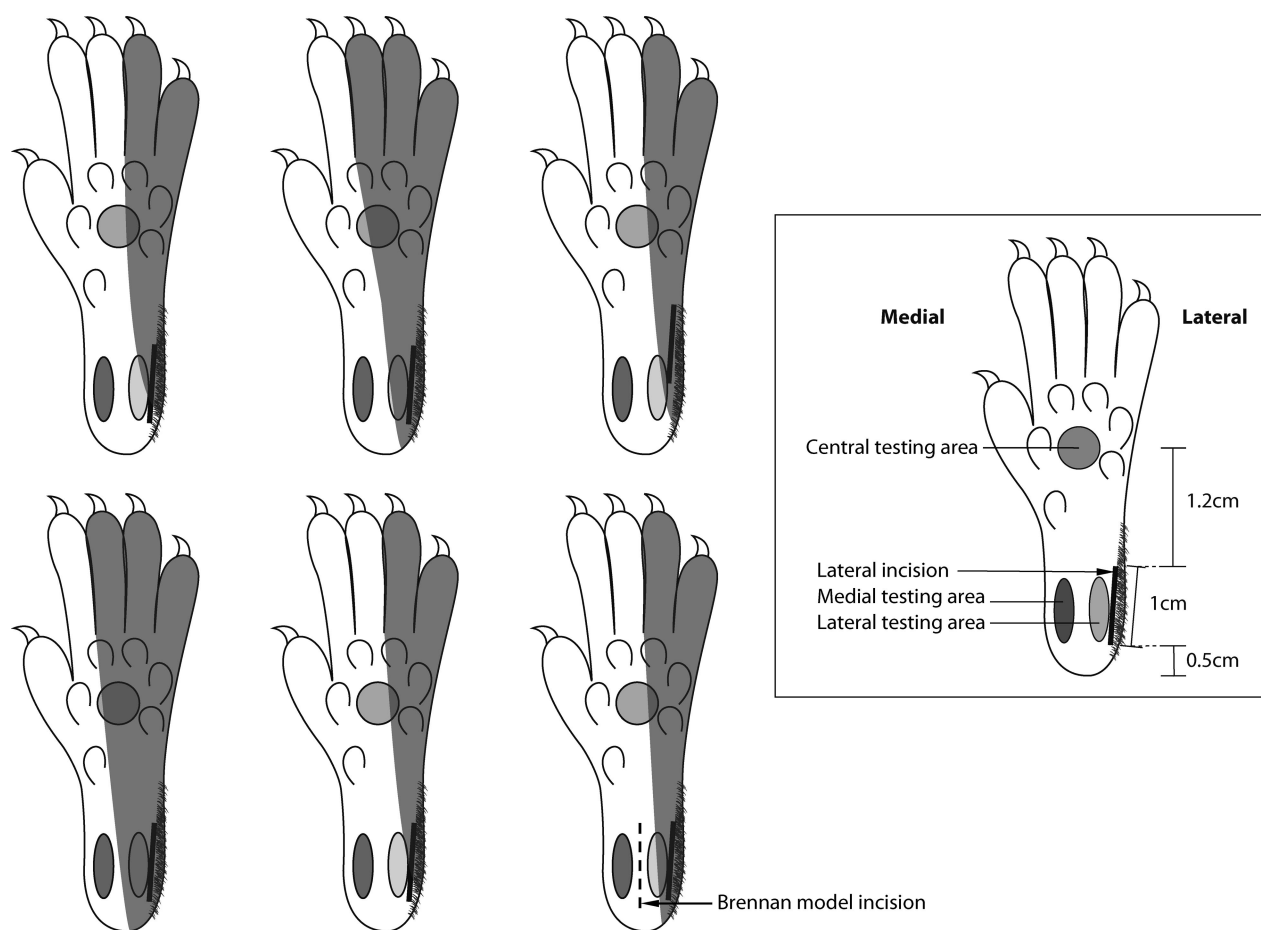Analgesia to pinprick by perisciatic injection of 2% Lidocaine (0.2ml) ▢

Fig. 1. Areas of anesthesia to pin prick on the plantar surface of six rats injected with 2% lidocaine (0.2 ml) at the ipsilateral sciatic nerve. Rats were placed on a wire grid and the skin of the paw probed with a sharp but nonpenetrating pin throughout the entire plantar surface. Probed areas that induced a brisk withdrawal of the leg are shown in *white*, and those for which no withdrawal occurred are *shaded*. The webs of skin between the toes were not probed. In five of six rats, the plantar region where the skin incision was made in the Brennan paw incision model was not anesthetized (see *lower right paw diagram*). (*Inset*) The locations of the test areas (medial, lateral, and central) and that of the incision in the lateral paw incision model are shown on this diagram of the plantar paw surface.

sive to punctate stimulation with a stiff pin prick, a stimulus that always results in paw withdrawal in unanesthetized animals. The incision locus for the BPI model is excluded from this zone of anesthesia in five of six rats, all of which were unresponsive at this time to a deep pinch to the bone of the fifth toe.

Injection of the same LA dose, 0.2 ml lidocaine 2%, at the saphenous nerve did not change the response to pin prick throughout the entire central and lateral plantar surface, except for the most medial edge. For comparison, 0.1 ml lidocaine 1% (1 mg) (0.25 of the previous dose) at the saphenous nerve completely anesthetized the dorsum of the hind paw to pin prick, revealing the efficacy of the block and the apparently sharp anatomic distribution of the saphenous innervation.[34,35]

However, when both sciatic and saphenous nerves were blocked by lidocaine (0.1 ml lidocaine 1% at each nerve),

the entire plantar surface of the paw was unresponsive to pin prick or pinch stimulation (a similar effect was observed on the medial-dorsal surface, where saphenous injection of lidocaine could prevent nocifensive withdrawal responses to pin prick but not to pinch, but where coinjection of lidocaine at saphenous and sciatic nerves produced complete anesthesia). In response to the possibility of inadequate local anesthesia of the BPI site during sciatic nerve block, we made two experimental adjustments. First, we blocked both sciatic and saphenous nerves, maintaining the original BPI location. Second, in different experiments, we shifted the location for incision to the most lateral glabrous skin, adjacent to the hairy skin at the edge of the foot (fig. 1 inset). The region of this LPI was always completely within the area insensate by sciatic nerve block. Furthermore, to define better the primary hypersensitivity from the incision from any secondary

Table 1. Sciatic Nerve Xybrex/Lidocaine on Hyperalgesia from Brennan Paw Incision

	0	2 h	6 h	1 d	2 d	3 d	4 d	5 d	6 d	7 d	8 d	9 d	10 d
Medial area													
IX *vs.* BPI	—	***	***	***	**	***	***	**	**	***	—	—	—
CX *vs.* BPI	—	*	*	*	**	**	**	**	**	***	—	—	—
IL *vs.* BPI	—	—	—	—	—	—	—	—	*	***	—	—	—
IX *vs.* CX	—	###	#	—	—	—	—	—	—	—	—	—	—
IX *vs.* IL	—	+++	+++	+++	++	++	+++	—	—	—	—	—	—
Lateral area													
IX *vs.* BPI	—	***	***	***	***	***	***	***	*	—	—	—	—
CX *vs.* BPI	—	***	***	***	***	***	***	**	*	—	—	—	—
IL *vs.* BPI	—	—	—	—	—	—	—	—	—	—	—	—	—
IX *vs.* CX	—	###	###	###	—	—	—	—	—	—	—	—	—
IX *vs.* IL	—	+++	+++	+++	+++	+++	+++	+++	—	—	—	—	—
Central area													
IX *vs.* BPI	—	***	***	***	***	***	***	***	***	***	—	*	—
CX *vs.* BPI	—	***	***	***	***	***	***	**	***	***	—	*	—
IL *vs.* BPI	—	—	—	—	—	—	—	—	***	***	—	—	—
IX *vs.* CX	—	##	##	###	—	—	—	—	—	—	—	—	—
IX *vs.* IL	—	+++	+++	+++	+++	+++	+++	++	—	—	—	—	—

Statistical significance: Two-way ANOVA plus *post hoc* Tukey pair-wise tests. For all three test areas, this analysis resulted in $P < 0.0001$ for time, group, and time × group comparisons.
From the *post hoc* analysis, the statistical values shown in the table correspond to the following values: *#+ $P < 0.05$; **##++ $P < 0.01$; ***###+++ $P < 0.001$. — identifies values of $P > 0.05$.
BPI = Brennan paw incision; CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex.

changes that might affect the ipsilateral paw, we tested the plantar surface of the hind paw at three locations: a lateral site, directly adjacent to the LPI; a medial site, innervated exclusively by the saphenous nerve, at the other edge of the heel; and a central site (fig. 1 inset).[33] All three test locations were routinely tested after a BPI or a LPI.

Characteristics of Hypersensitivity after BPI

Mechanical stimulation of the plantar region confirmed that BPI causes both tactile allodynia (fig. 2A) and hyperalgesia (fig. 2B). Allodynia, tested by a 4-g von Frey hair, was maximal (approximately 9 responses per 10 stimuli) at 2 and 6 h after incision, changed little through POD 2, and declined progres-

Table 2. Both Sciatic and Saphenous Xybrex/Lidocaine on Hyperalgesia from Brennan Paw Incision

	0	2 h	6 h	1 d	2 d	3 d	4 d	5 d	6 d	7 d	8 d	9 d	10 d
Medial area													
IX *vs.* BPI	—	***	—	—	**	*	—	—	—	—	—	—	—
CX *vs.* BPI	—	***	***	***	***	***	***	***	**	***	—	—	—
IL *vs.* BPI	—	—	—	—	—	—	—	**	**	***	—	—	—
IX *vs.* CX	—	—	###	###	—	#	##	###	#	##	—	—	—
IX *vs.* IL	+	+++	—	—	+	—	—	—	—	+	—	—	—
Lateral area													
IX *vs.* BPI	—	***	***	—	***	***	***	—	—	—	—	*	—
CX *vs.* BPI	—	***	***	***	***	***	***	***	—	—	—	—	—
IL *vs.* BPI	—	—	—	—	—	—	—	—	—	—	—	—	—
IX *vs.* CX	—	###	###	—	#	—	—	—	—	—	—	—	—
IX *vs.* IL	—	+++	+++	—	+++	+	+	—	—	—	—	—	—
Central area													
IX *vs.* BPI	—	***	***	*	—	—	***	*	***	***	—	**	***
CX *vs.* BPI	—	***	***	***	***	***	***	**	***	***	*	**	**
IL *vs.* BPI	—	—	—	—	*	—	—	—	***	***	—	—	—
IX *vs.* CX	—	—	#	###	##	###	##	—	—	#	—	—	—
IX *vs.* IL	—	+++	++	—	—	—	+++	—	—	—	—	—	++

Statistical significance: Two-way ANOVA plus *post hoc* Tukey pair-wise tests. For all three test areas, this analysis resulted in $P < 0.0001$ for time, group, and time × group comparisons.
From the *post hoc* analysis, the statistical values shown in the table correspond to the following values: *#+ $P < 0.05$; **##++ $P < 0.01$; ***###+++ $P < 0.001$. — identifies values of $P > 0.05$.
BPI = Brennan paw incision; CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex.

Table 3. Sciatic Nerve Xybrex/Lidocaine on Hyperalgesia from Lateral Paw Incision

	0	2 h	6 h	1 d	2 d	3 d	4 d	5 d	6 d	7 d	8 d	9 d	10 d
Medial area													
IX *vs.* LPI	—	—	—	—	—	—	—	**	—	—	—	—	—
CX *vs.* LPI	—	—	—	—	—	—	—	—	—	—	—	—	—
IL *vs.* LPI	—	—	*	—	—	—	*	**	—	—	—	—	—
IX *vs.* CX	—	—	##	#	—	#	#	###	#	—	—	#	—
IX *vs.* IL	—	—	+++	+++	—	—	—	—	—	—	—	—	—
Lateral area													
IX *vs.* LPI	—	***	***	***	***	*	—	—	—	—	—	—	—
CX *vs.* LPI	—	—	—	—	—	—	—	—	***	—	—	—	—
IL *vs.* LPI	—	—	—	—	—	—	*	*	—	—	—	—	—
IX *vs.* CX	—	###	###	###	##	##	#	—	###	#	—	—	—
IX *vs.* IL	—	+++	+++	++	++	+	—	—	—	—	—	—	—
Central area													
IX *vs.* LPI	—	***	***	***	*	—	—	—	—	—	—	—	—
CX *vs.* LPI	—	—	—	—	—	—	—	—	—	—	—	—	—
IL *vs.* LPI	—	**	—	—	*	—	—	—	—	—	—	—	—
IX *vs.* CX	—	###	###	###	—	—	—	—	—	—	—	—	—
IX *vs.* IL	—	+++	+++	+++	—	—	—	—	—	—	—	—	—

Statistical significance: Two-way ANOVA plus *post hoc* Tukey pair-wise tests. For all three test areas, this analysis resulted in $P < 0.0001$ for time, group, and time $\times$ group comparisons.

From the *post hoc* analysis, the statistical values shown in the table correspond to the following values: $*\#+ P < 0.05$; $**\#\#++ P < 0.01$; $***\#\#\#+++ P < 0.001$. — identifies values of $P > 0.05$.

CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex; LPI = lateral paw incision.

sively during the next several days, with the response returning at PODs 4 and 5 to the preoperatively determined baseline concentrations (fig. 2A). Hyperalgesia, tested by the more forceful 15-g von Frey hair, was longer lasting, maintaining a maximal value (10 responses per 10 stimuli) for 3–4 PODs and then slowly declining, with a return to baseline at 8–9 days (fig. 2B). This general pattern occurred in all three test areas after BPI, although when hyperalgesia was examined over time, its duration appeared to be longer for the medial and the central test areas than for the lateral test area (compare POD 7 responses in

fig. 2B). Correspondingly, the values for AUC of responses more than baseline in the lateral test area (49 days) were approximately 20% smaller than those in the medial (59 days) or the central test areas (63 days) (table 4).

Xybrex Implant at the Sciatic Nerve Reduces Hypersensitivity from BPI

When Xybrex slow-release material (200 mg containing 32 mg lidocaine) was implanted at the ipsilateral sciatic nerve 30 min before the incision, postoperative hypersensitivity was

Table 4. Quantitated Postincisional Hyperalgesia: Sciatic Nerve Xybrex or Lidocaine on Brennan Paw Incision

	AUC (Mean ± SD)/% Reduction of AUC from Control (BPI)			
15 g VFH	Control (Paw Incision) (BPI)	Ipsilateral Xybrex 200 mg (IX)	Contralateral Xybrex 200 mg (CX)	Ipsilateral Lidocaine 4 mg (IL)
Medial area	59.2 ± 8.4	34.5 ± 8.7/41.7	37.2 ± 10.4/37.2	57.6 ± 6.4/2.7
Lateral area	49.4 ± 6.8	13.9 ± 9.7/71.9	22.4 ± 10.7/54.7	51.5 ± 10.5/−4.3
Central area	63.2 ± 7.5	15.7 ± 6.2/75.2	22.1 ± 8.1/65.0	54.4 ± 16.6/13.9

		P Value of ANOVA *post hoc* Tukey Pair-wise Tests				
	ANOVA $F_{3,20}$			*P* Value of Pair-wise Test		
15 g VFH	*P* Value	IX *vs.* BPI	CX *vs.* BPI	IL *vs.* BPI	IX *vs.* CX	IX *vs.* IL
Medial area	13.969 <0.001	<0.001	0.001	0.987	0.951	0.001
Lateral area	23.605 <0.001	<0.001	<0.001	0.979	0.430	<0.001
Central area	30.271 <0.001	<0.001	<0.001	0.482	0.710	<0.001

AUC = area under the curve; BPI = Brenner paw incision; CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex; VFH = von Frey hair.

Table 5. Quantitated Postincisional Hyperalgesia: Both Sciatic and Saphenous Xybrex or Lidocaine on Brennan Paw Incision

	AUC (Mean ± SD)/% Reduction of AUC from Control (BPI)			
15 g VFH	Control (Paw Incision) (BPI)	Ipsilateral Xybrex 200 mg (IX)	Contralateral Xybrex 200 mg (CX)	Ipsilateral Lidocaine 4 mg (IL)
Medial area	59.2 ± 8.4	45.4 ± 13.0/23.3	28.9 ± 4.0/51.2	51.6 ± 9.6/12.8
Lateral area	49.4 ± 6.8	28.7 ± 9.0/41.9	24.6 ± 6.8/50.2	48.5 ± 12.2/2.0
Central area	63.2 ± 7.5	33.3 ± 7.1/47.4	17.2 ± 4.1/72.8	49.6 ± 16.9/21.5

	P Value of ANOVA post hoc Tukey Pair-wise Tests				
		P Value of Pair-wise Test			
15 g VFH	ANOVA $F_{3,20}$ P Value	IX vs. BPI	CX vs. BPI	IL vs. BPI	IX vs. CX	IX vs. IL
Medial area	11.488 <0.001	0.080	<0.001	0.504	0.028	0.666
Lateral area	12.538 <0.001	0.004	0.001	0.999	0.860	0.005
Central area	23.271 <0.001	<0.001	<0.001	0.125	0.054	0.051

AUC = area under the curve; BPI = Brenner paw incision; CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex; VFH = von Frey hair.

reduced. Hypersensitivity reached decreased peak values and was slower to develop (figs. 2A and B) partly because the nerve was completely or partially blocked for much of the first POD (see profile in Medial test panel of fig. 2A).[31]

Allodynia was generally reduced more than hyperalgesia (compare AUC between figs. 2A and B). Injections of 4 mg lidocaine in solution, which produce functional analgesia of the more lateral aspects of the plantar paw surface (compare responses in fig. 1) for approximately 2 h, had no effect on allodynia after BPI (fig. 2A).

Most of the remaining tests in this report used 15-g von Frey hair and thus only assessed hyperalgesia after incisions. Xybrex, implanted at the ipsilateral sciatic nerve, resulted in nearly zero response in the lateral and the central test areas up to POD 1 and then led to responses lower than the BPI controls up to POD 6–7 (fig. 2B, table 1). Tests in the medial area showed rises in response within 6 h after surgery, albeit lower than the controls (fig. 2B) and responses reduced in comparison with BPI control for the first 7 PODs (table 1). This smaller antihyperalgesic effect is apparent in the comparative AUCs, where ipsilateral

Table 6. Quantitated Postincisional Hyperalgesia: Sciatic Nerve Xybrex or Lidocaine on Lateral Paw Incision

	Area Under the Curve (Mean ± SD)/% Reduction of AUC from Control (LPI)				
15 g VFH	Control (Paw Incision) (LPI)	Ipsilateral Xybrex 200 mg (IX)	Contralateral Xybrex 200 mg (CX)	Ipsilateral Lidocaine 4 mg (IL)	Ipsilateral Matrix 200 mg
Medial area	6.1 ± 2.3	3.0 ± 2.8	8.7 ± 5.5	3.9 ± 1.2	4.1 ± 3.3
Lateral area	23.9 ± 9.7	6.5 ± 2.5/72.8	24.9 ± 2.9/−4.2	19.3 ± 7.2/19.2	22.6 ± 9.3/5.4
Central area	17.1 ± 4.0	7.5 ± 3.1/56.1	9.4 ± 3.0/45.0	15.2 ± 6.0/11.1	12.5 ± 6.6/26.9

	P Value of ANOVA post Hoc Tukey Pair-wise Tests				
		P Value of Pair-wise Test			
15 g VFH	ANOVA $F_{3,20}$ P Value	IX vs. LPI	CX vs. LPI	IL vs. LPI	IX vs. CX	IX vs. IL
Medial area	3.441 0.036	0.397	0.562	0.652	0.038	0.971
Lateral area	10.675 <0.001	0.001	0.993	0.594	<0.001	0.011
Central area	7.106 0.002	0.004	0.023	0.857	0.855	0.023

AUC = area under the curve; CX = contralateral Xybrex; IL = ipsilateral lidocaine; IX = ipsilateral Xybrex; LPI, lateral paw incision; VFH = von Frey hair.
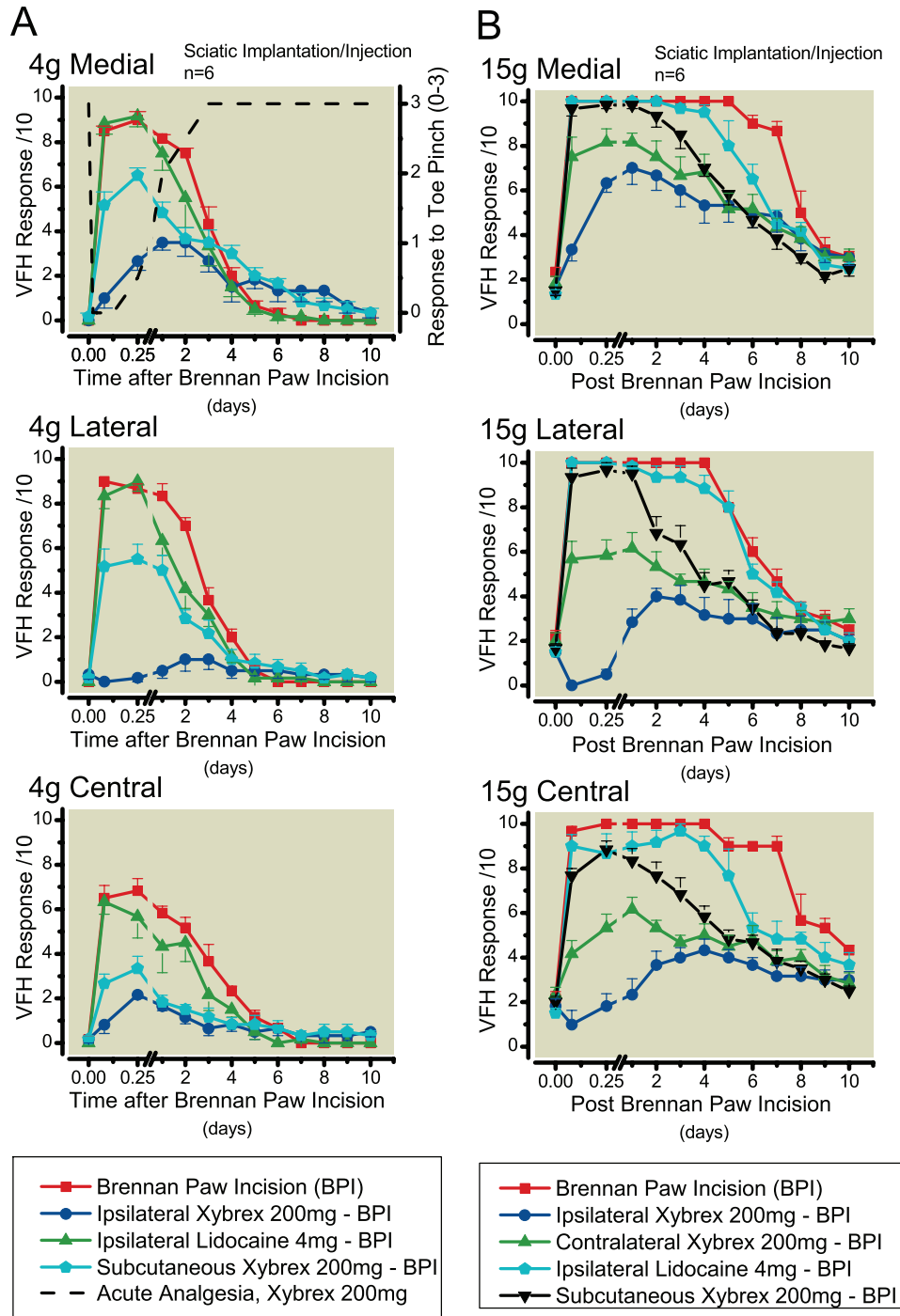
Fig. 2. (*A*) Allodynia after Brennan paw incision (BPI) is indicated by responses to plantar probing with a 4-g von Frey filament. Responses to probing in the medial, lateral, and central test areas (see fig. 1 inset) are shown *top* to *bottom*. Baseline responses, tested during three preoperative days, are averaged, and this value, always approximately 0, is graphed on day 0. Responses (mean ± SE) are measured at 2 and 6 h after the incision (shown in an expanded time scale) and then daily for 10 days (see Methods for test details). The *broken line* shows the time course of the nocifensive withdrawal response to a pinch of the lateral-most toe after implanting 200 mg Xybrex at the sciatic nerve in an intact rat.[31] (*B*) Hyperalgesia after BPI is indicated by the increased response to probing with a 15-g von Frey filament (details as in *A*). Responses briefly decreased less than baseline in the lateral and the central test areas as a result of sciatic nerve block by Xybrex (see tables 1 and 4 for significance data). VFH = von Frey hair.

Xybrex causes 70–75% reductions in increased responses in central and lateral test areas but only a 40% reduction in the medial test area, all significant reductions (table 2).

Implanting the matrix for Xybrex, free of any lidocaine, at the ipsilateral sciatic nerve before the incision had no effect on hyperalgesia in the medial or the lateral test areas, but it did reduce the increased response by a small (20%), yet significant, amount in the central area.

Lidocaine solution injected preoperatively at the ipsilateral sciatic nerve has no effect on hyperalgesia at the medial and the central test areas for the first 5 PODs, but reduces the responses at PODs 6 and 7 (fig. 2B, table 1). In the lateral test area, where hyperalgesia is briefest (table 4), there is no effect at any of the measured postoperative times of the preoperative ipsilateral lidocaine block (fig. 2B, table 1).

Contralateral Nerve Xybrex Implants Reduce BPI-induced Hyperalgesia

Because BPI-induced hyperalgesia and allodynia in the medial test area were affected by an ipsilateral sciatic implant of Xybrex, although this medial test area was not anesthetized by such Xybrex (nor by lidocaine block of the sciatic nerve), we wondered whether the effect resulted from systemically distributed lidocaine, which might be taken up from Xybrex by the local vasculature. This question was addressed by analyzing hyperalgesia from a contralateral sciatic implant of Xybrex, with identical surrounding anatomical structures, or from a subcutaneous implant at the nuchal midline, far removed from the surgical site or the sciatic block locations.

Contralateral Xybrex implants slowed the appearance and reduced the maximum hyperalgesia after BPI (fig. 2B), although no block of contralateral paw functions occurs after Xybrex implant. The duration of antihyperalgesia from contralateral Xybrex was the same as from the ipsilateral implant, with effects that converged after POD 1 (table 1). The effectiveness in reducing the AUC also was the same for these two implant locations, with a likewise smaller reduction at the medial test area (37 and 41%, respectively, for contralateral and ipsilateral implants) than at the lateral (55 and 72%, respectively) and the central (65 and 75%, respectively) test areas (table 4).

Systemic Lidocaine Released by Distant Xybrex Also Is Antihyperalgesic

Xybrex was implanted subcutaneously at the nuchal midline to effect a systemic concentration similar to that resulting from nerve implants. Here, it reduced allodynia, but only for the first 2–3 PODs (fig. 2A). In an almost mirror image effect, no reduction in hyperalgesia from systemic lidocaine from this Xybrex implant occurred until POD 2 and later (fig. 2B). By PODs 4 and 5, these implants had reduced responsiveness to the concentrations caused by the contralateral implant. Calculated AUCs for hyperalgesia were reduced from the BPI control concentrations by subcutaneous Xybrex by $24 \pm 2.4\%$, $38 \pm 5.1\%$, and $46 \pm 5.1\%$,

compared with BPI, in the medial, the lateral, and the central test areas, respectively. Because these results from systemic lidocaine show the same anatomically selective effect as the ipsilateral and the contralateral implants, they therefore cannot be a result of a differential distribution of LA within the sciatic nerve.

Dual Block of Sciatic and Saphenous Nerves on Hyperalgesia from BPI

In an attempt to provide a more uniform block of the entire plantar paw, and thus more effectively reduce postincisional pain, we blocked both sciatic and saphenous nerves. To have approximately the same systemic lidocaine concentrations that occurred with a single nerve implant or injection (see above Results [*e.g.*, Xybrex Implant at the Sciatic Nerve Reduces Hypersensitivity from BPI]), we used the same total dose, placing half at each nerve (*i.e.*, 100 mg Xybrex at both sciatic and saphenous nerves or 2 mg [0.1 ml lidocaine 2%] lidocaine at each nerve).

This dual nerve ipsilateral implant also slowed the rise of hyperalgesia, but not as much as the single implant at the higher dose (fig. 3; compare with fig. 2B). Peak hyperalgesia was reduced less by the dual ipsilateral than the single implant (fig. 3), and the AUC was reduced only by approximately half as much: 23% *versus* 41%, 42% *versus* 72%, and 47% *versus* 75% for dual *versus* single nerve implants tested at medial, lateral, and central test areas, respectively (compare tables 4 and 5). Durations of the antihyperalgesic effect were slightly shorter than those from the single ipsilateral implant for the lateral test area (4 days *vs.* 6 days), slightly longer in the central test area (10 days *vs.* 8–9 days), and much shorter in the medial test area (3 days *vs.* 7 days) (for all comparisons see tables 1 and 2).

In contrast, dual Xybrex implants at the contralateral nerves were about as effective as the single contralateral implants. Although contralateral implants did not numb the incised paw, the initial rise in hyperalgesia still was somewhat reduced and the peak hyperalgesia markedly lower than the BPI control (fig. 3). Duration of antihyperalgesic effect was as long for contralateral as ipsilateral dual implants in the lateral and the central test areas and far longer (7 days *vs.* 2–3 days) in the medial test area (table 2). In a comparison between single and dual implants on the contralateral nerves, antihyperalgesia lasted approximately as long in all of the test areas for both contralateral treatments (tables 1 and 2). With regard to the integrated actions, the AUC from the dual contralateral implants was reduced equally to the single contralateral implant at the central test area (72% *vs.* 65%) and the lateral test area (50% *vs.* 55%), but was reduced more at the medial test area (51% *vs.* 37%) (see tables 4 and 5 for comparisons).

The dual injection of lidocaine at the ipsilateral sciatic and saphenous nerves (2 mg at each) suppressed hyperalgesia at later times (PODs 5–7) in the medial and the central test areas (table 2), but was ineffective in the lateral test area, the
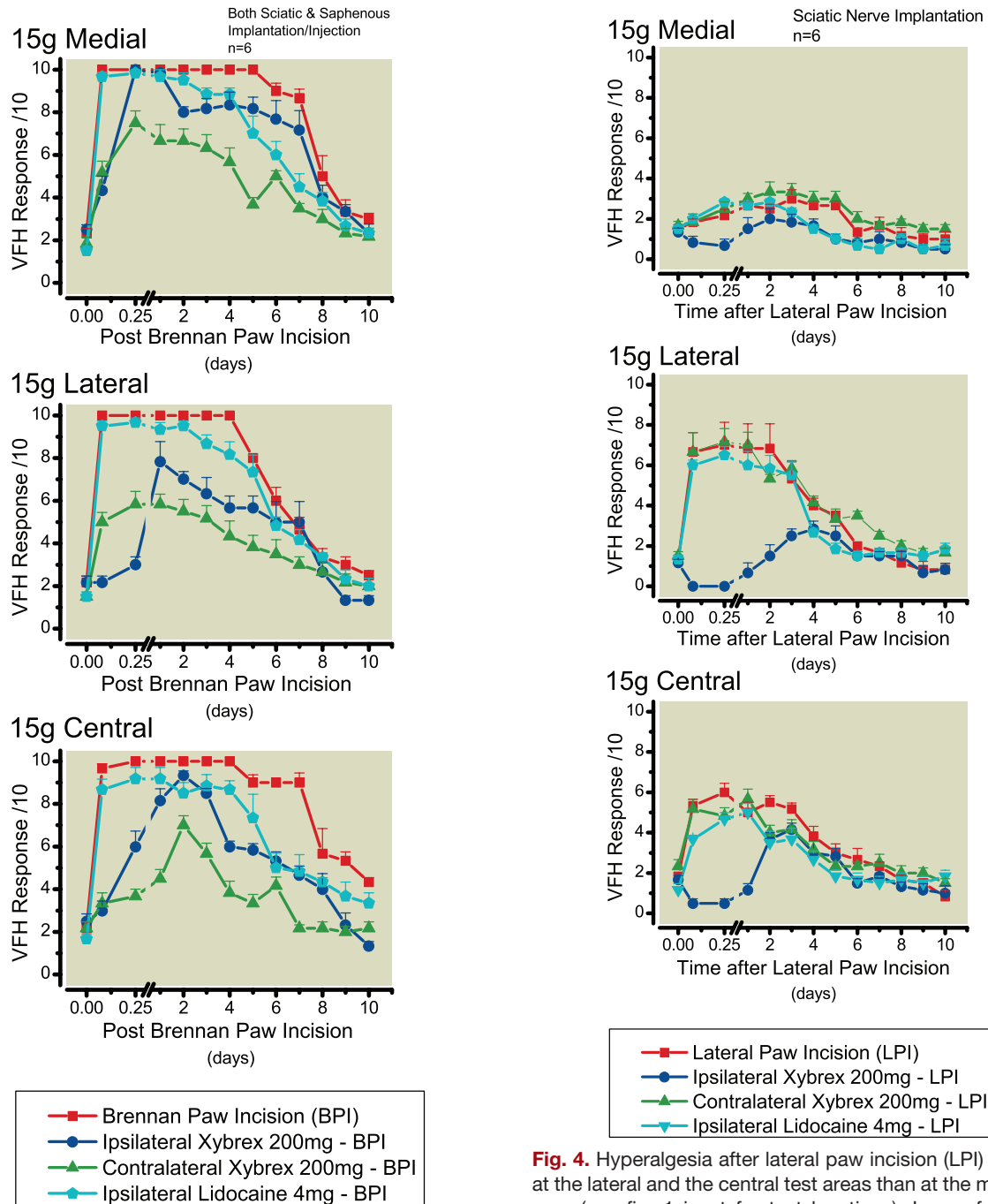
Fig. 3. Hyperalgesia after Brennan paw incision (BPI) is suppressed by Xybrex divided evenly between the sciatic and the saphenous nerves (details as in fig. 2 legend). Compare these results with those in figure 2B, when the same total dose is implanted only at the sciatic nerve (see tables 2 and 5 for significance data). VFH = von Frey hair.

same pattern as for the single injection (4 mg) (table 1). In none of these three test areas was the AUC significantly reduced by dual nerve injections of lidocaine (table 5).

Characteristics of Hyperalgesia from LPI

Incision at the lateral edge of the paw produced a pronounced hyperalgesia in that location (lateral test area), a

Fig. 4. Hyperalgesia after lateral paw incision (LPI) is greater at the lateral and the central test areas than at the medial test area (see fig. 1 inset for test locations). Loss of response during the first 6 h postincision is because of Xybrex blockade of the ipsilateral sciatic nerve (see tables 3 and 6 for significance data). VFH = von Frey hair.

smaller response in the central test area, and very little change in the medial test area (fig. 4). Comparison of AUCs in these three areas between the BPI and the LPI shows the latter with 50% of the former's response in the lateral test area, 27% in the central test area, and only 10% in the medial test area (tables 4 and 6). The durations of hyperalgesia also were shorter for the LPI; half of the maximum response is reached at PODs 4 and 5 in the lateral test area after LPI compared with POD 7 for BPI.

In the central test area, these conditions were reached at PODs 4 and 5 for LPI and POD 8 for BPI (figs. 2B and 4). Despite having the same length and depth, the incision at the lateral paw edge caused a weaker and briefer hyperalgesia than that in the center of the paw. Its selective expression in the lateral and the central test area aspects of the paw fulfills the intent to have a wound at a site innervated by one nerve, the sciatic.

Xybrex Effects on Pain from LPI

An implant of Xybrex (200 mg) at the ipsilateral sciatic nerve suppressed hyperalgesia from LPI. The lateral test area was anesthetized for the first 6 h after the implant, most probably as a result of nerve block,[31] and then showed a slow rise in response to control LPI concentrations by POD 4. The central test area was similarly anesthetized and remained less responsive than the LPI control through POD 2 (fig. 4, table 3). The response in the medial test area was so small that treatment effects could not be analyzed statistically (although the modest AUC was halved); there was a significant reduction of response after LPI at POD 5 (table 3).

An implant of Xybrex at the contralateral sciatic nerve had no effect on the AUC of hyperalgesia in the lateral test area but did reduce it by approximately 45% in the central test area (table 6), an effect that still was less than the 65% reduction from contralateral Xybrex in the BPI model (table 4). When investigated at each individual test time, contralateral Xybrex caused no reduction in LPI-induced hyperalgesia, except for POD 6 in the lateral test area (table 3).

Sciatic nerve block by injected lidocaine (0.2 ml, 2%) reduced the responses at the lateral and the medial test areas at PODs 4 and 5 and in the central test area at POD 2 (table 3). These effects of 1–2 day duration did not amount to any significant reduction in the AUCs for any of the test areas (table 6).

Finally, implanting the lidocaine-free matrix at the ipsilateral sciatic nerve had no effect on hyperalgesia in the lateral test area, although it did reduce it in the central test area by approximately 25% ($P < 0.01$, by paired t test).

Discussion

By using slowly delivered lidocaine (*via* Xybrex) from sources implanted at different locations, we have been able to identify the different effects of nerve block *versus* systemic actions in the preventive analgesia from perioperative lidocaine. In addition, by testing mechanosensitivity in different areas after incision of the plantar paw, either along the midline or at the lateral edge, we have been able to examine the effects of these anesthetic treatments on primary *versus* secondary responses to surgery.

In this discussion, we will consider the characteristics of the postincisional pain models used here in light of the known peripheral and central mechanisms for increased pain, analyze the effects of the Xybrex treatment to under-

stand its mode and locus of action, and compare the antihyperalgesic actions for Xybrex reported here with the literature on LAs and postoperative pain.

Primary and Secondary Responses to Incision

Postincisional pain results from a combination of primary and secondary mechanisms.[5,22,36] In primary hypersensitivity, direct injury or inflammation changes the properties of the nerves in the region of incision,[21] including those areas of the skin that are reached by locally diffusing cytokines, interleukins, or nerve growth factors,[18,19,37,38] because it is known that nerve fibers need not be injured to be sensitized by an adjacent tissue injury.[8,39] The resulting increase of impulse activity, which can drive peripheral and central contributions to hypersensitivity, can be blocked by locally delivered LAs.

Secondary hypersensitivity results from alterations in the processing of afferent impulses in the central nervous system by central sensitization.[36] This is a complex, heterogeneous process that involves both presynaptic and postsynaptic changes underlying long-term and, sometimes, more persistent synaptic facilitation and depression.[40] Central nervous system pain responses also are modulated by descending activity from the brainstem and other more rostral loci,[41,42] which can alter both acute responses and long-term plasticity.

In the current study, we found that BPIs in the midline region of the paw resulted in increased responses in the medial test area, a region innervated by the saphenous nerve, as indicated by nerve transection studies[34,35,43,44] and by specific LA block effects (fig. 1). This result suggests that central sensitization, resulting in physiologic coupling of the inputs from saphenous and sciatic nerves, occurs after BPI, a possibility that is consistent with the adjacent projections of these nerves in the spinal cord[34,35] and with the observation that blockade of sciatic impulses by a Xybrex implant reduces the hyperalgesia in the medial test area after BPI, despite the absence of effect of such an implant on normal nocifensive responses to noxious pinch of this medial test region in the intact rat.

One source of potential confounding effects in this study is the interaction between the incision on the leg, required to deposit Xybrex, and the incisions on the paw. Both operations involve areas served by the sciatic nerve and both have inputs into L4–L5 segments of spinal cord, allowing opportunities for localized central sensitization. Incision of the skin on the medial aspect of the thigh causes a tactile hyperalgesic response a day or two later on the ipsilateral hind paw,[45] which might well portend increased sensitivity to subsequent incision. Although implantation of the lidocaine-free matrix for Xybrex caused minor changes in resting paw sensitivity,[31] hyperalgesic responses to subsequent insults still could be increased, such as has been shown to occur weeks after the resolution of inflammatory pain.[46]

Effects of LAs on Postincisional Pain

In this study, prolonged blockade of the innervating nerve by Xybrex implants strongly suppressed postincisional allodynia and hyperalgesia in the region of the incision and, to a lesser degree, in adjacent regions innervated by other nerves but where postincisional hypersensitivity still was detected. Brief blockade at the same nerve site by lidocaine solution was essentially ineffective in reducing postincisional hypersensitivity, confirming that the time period when afferent transmission was critical for establishing postoperative sensitivity extended beyond 2 h.

More specifically, we found that BPI led to hypersensitivity in all three test areas of the paw, and an ipsilateral sciatic implant of Xybrex suppressed the hyperalgesia in all three regions. A very similar antihyperalgesic effect resulted from a contralateral sciatic Xybrex implant, albeit slightly less in the lateral test area than in the other two. Identical Xybrex implants located at a distant site under the skin of the nuchal midline also suppressed hyperalgesia after BPI at all three test locations and slightly less (approximately 70%) than that from the contralateral implants. Such results are much more consistent with actions from a systemically distributed drug that reaches the peripheral and central nervous system locations than with direct conduction blockade of the nerve innervating the wound site. This conclusion agrees with previous findings on secondary allodynia and hyperalgesia after back incision, which, like the primary responses, can be prevented by perioperative LAs (see Mechanisms of Antihyperalgesia from LAs).[14] Although there appear to be different mechanisms for the development of tactile allodynia and hyperalgesia after incision,[15] each is equally suppressed by systemic LA, whose presence in the perioperative or immediate postoperative period causes a profound suppression of prolonged postoperative pain.[14,47]

When incising only the lateral edge of the hind paw, we injured a cutaneous area exclusively innervated by the sciatic nerve, resulting in tactile allodynia and hyperalgesia focused in the lateral and the central paw areas, with minimal effects on the medial paw area innervated by the saphenous nerve. This lateral area's postincisional hyperalgesia, an index of primary hypersensitivity, was strongly suppressed by Xybrex implants at the ipsilateral sciatic nerve. Postincisional hyperalgesia at the ipsilateral paw central area also was suppressed by the ipsilateral sciatic implant, but an almost identical suppression resulted from an implant at the contralateral sciatic nerve, a location that gave no relief of postincisional hyperalgesia in the lateral area. Because there is no contralateral tactile hypersensitivity after paw incision, and because only the central area and not the lateral area hyperalgesia is suppressed by the contralateral implant, the effect of this implant is unlikely to arise from blocked conduction of contralateral impulses. Therefore, Xybrex effects on pain from LPI are a result of both direct conduction block for impulses originating at the incision site and systemic effects, modifying pain processes at central locations.

Mechanisms of Antihyperalgesia from LAs

How do perioperative LAs suppress postoperative pain? Both local peripheral actions and systemic central actions seem to be involved. The traditional actions of Na^+ channel blockade acting on axonal excitability will prevent afferent impulses from being generated[48] and from being conducted to the spinal cord, and also will suppress local neurogenic inflammation, actions that are known to reduce hypersensitivity after incisions.[49,50] LAs not only block Na^+ channels (and Ca^{2+} and K^+ channels,[51,52] as well as transient receptor potential vanniloid-1 receptors[53] and other ligand-gated receptors,[54,55]) but they also disrupt the coupling between certain G proteins and their associated receptors.[56–58] Through this action, LAs exert potent antiinflammatory effects, particularly on neutrophil priming reactions.[49,58,59] There are, in addition, a variety of other antithrombotic and neuroprotective actions of intravenous LAs[58] that are independent of Na^+ channel blockade but may account for many of the improvements in pain after surgery.[60,61]

Central sensitization can be suppressed by many of the same mechanisms, including the blockade of presynaptic and postsynaptic receptors and ion channels of central synapses, although these typically require LA concentrations at least 10 times higher than those that occur systemically during perioperative procedures (see Antihyperalgesic Actions of Perioperative Intravenous Lidocaine). Acute effects of LAs on existing targets, such as receptors or channels, can prevent impulses or synaptic activity that is critical for the formation of more slowly reversing or irreversible changes that underlie central neuroplasticity. In addition, these drugs also can directly suppress cellular responses that develop slowly and are persistent, such as neurite outgrowth and glial activation.[62–64]

Most studies of central sensitization underlying postinjury hyperalgesia have examined changes in the spinal cord, but more rostral sites also are involved.[65,66] For example, glial activation occurs in the rostroventromedial medulla of the brainstem after inflammation, and microinjections of glial mitogen-activated protein kinase inhibitors[67] and of LAs[68] into the rostroventromedial medulla are known to strongly reduce this sensitization. It is possible that systemic LAs, with their ability to penetrate all tissues, also could act in this inhibitory manner at the rostroventromedial medulla and may affect other sites of brain activity that underlie long-term postoperative pain.

Antihyperalgesic Actions of Perioperative Intravenous Lidocaine

Xybrex implants at sciatic nerves and elsewhere might slowly release lidocaine that is taken up systemically and distributed into the central nervous system, where it is able to suppress central sensitization. Indeed, preliminary data from our laboratory show that plasma lidocaine concentrations after the sciatic implants of Xybrex may reach a peak value of 3–4 μg lidocaine base/ml plasma and be detectable at therapeutic concentrations, 1.0 μg/ml, for up to 12 h

(unpublished observations, April-May, 2008; Gary Strichartz, Ph.D., and Chi-Fei Wang, M.D., Pain Research Center, Harvard Medical School, Boston, Massachusetts). These values are at or above the lidocaine concentrations that occur during intentional intravenous administration for relieving preexisting pain and that have been used in animal experimental studies.[69,70]

The effects of perioperative systemic lidocaine may occur through actions like those that reduce existing neuropathic pain when lidocaine is delivered intravenously. This has been an effective method for reducing long-term postoperative pain[71] and also for treating, with some success, existing neuropathic pain arising from various causes.[72] Perioperative infusions of lidocaine, starting shortly before abdominal surgery, cholecystectomy, or prostatectomy and extending to 1–3 h after surgery, have decreased self-reported pain scores (usually as visual-analog scales), reduced the consumption of postoperative analgesics (opioid), accelerated return of function, and shortened hospital stays.[60,61,73,74]

LA conduction block (*e.g.*, by neuraxial administration) may appear equally effective as intravenous lidocaine in providing preemptive relief of postoperative pain.[12,75] For epidural blocks, however, systemic redistribution may result in plasma LA concentrations that are therapeutically effective. Although such concentrations (*e.g.*, of lidocaine) are inadequate to block conduction of normal nerve impulses,[23] abnormal impulses, such as those that arise ectopically at sites of injury or inflammation or at other locations of affected neurons, almost are fully suppressed by such low concentrations.[76,77] Similar effects occur on abnormal repetitive impulses that result from an increased expression of atypically gating Na^+ channels on peripheral nerve fibers, such as what may occur after injury or incision.[78,79]

The effect of intravenous lidocaine on experimental pain in humans has been studied using infusion protocols like those for perioperative administration. In a human model of skin incision at the volar forearm, Kawamata *et al.*[80] found that systemic lidocaine (delivered over 45 min in preincisional and postincisional periods) transiently suppressed 1° allodynia but persistently suppressed 2° allodynia. In the same study, intravenous lidocaine given 30 min after the incision was effective only during the drug administration period, with allodynia returning quickly after that. Using an almost identical dosing endpoint (to give up to 3 μg lidocaine/ml plasma), Koppert *et al.*[81] found that the increased pain that occurred during the repeated presentation of a skin pinch was prevented from developing by intravenous lidocaine restricted to the test arm's circulation, whereas the pain threshold for heat stimulation was unaffected. These changes did not occur when the same dose of lidocaine was allowed to distribute within the entire circulation, showing that the site of action was peripheral and not central.

Animal studies confirm the preemptive actions of intravenous LAs. Although systemic bupivacaine has little effect on the initial postincisional primary mechanical allodynia and hyperalgesia at the incision site on the hairy skin of the rat, it can suppress the later components of this pain and virtually abolish secondary allodynia and hyperalgesia.[14] This antihyperalgesic effect suppresses postoperative pain that would otherwise last for 4–5 days, although bupivacaine's half-life in blood is less than 3 h, showing that the systemic drug is interfering with a key process early in the induction stage of postoperative pain. Identical delivery of bupivacaine 4–6 h after the back incision, when the hypersensitivity had reached a constant value and the maintenance stage of postoperative pain had been reached and had less than 0.5 the effectiveness in reversing both 1° and 2° responses, showed that the mechanisms and pathways for developing pain after surgery are different from those for maintaining it.[14] These results mirror the findings of Kawamata *et al.*,[80] who applied local lidocaine before or after experimental skin incision in humans. In that study, preincisional block prevented the development of 2° allodynia, but postincisional block had no effect, implying that the initial afferent impulse activity was essential for causing the central sensitization that underlies 2° hyperesthesia but was unnecessary for maintaining that sensitization.

A very similar result occurred when bupivacaine was delivered systemically around the time of experimental thoracotomy, such that 3 weeks after the procedure those rats that received the LA were 70% less likely to show mechano-allodynia as those that received no bupivacaine.[53] Changes in the activity of spinal wide dynamic range neurons after skin incision are transiently suppressed by systemic lidocaine and by its quaternary homolog, QX-314, which does not pass through the blood–brain barrier and so is restricted to peripheral sites.[11,82] This suggests that some peripheral activity, perhaps other than impulse inhibition, is a factor in central neuron changes, although the role of wide dynamic ranges in ongoing pain has not been established.

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