Different Mechanisms of Development and Maintenance of Experimental Incision-induced Hyperalgesia in Human Skin

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Background: To determine the mechanisms of postoperative pain, the effects of local anesthesia on development and maintenance of surgical incision-induced hyperalgesia were evaluated in a crossover, double-blinded, placebo-controlled human study using 17 subjects.

Methods: An experimental 4-mm-long incision through skin, fascia, and muscle was made in the volar forearm of each subject. In experiment 1, 1% lidocaine or saline in a volume of 0.2 ml was subcutaneously injected into the incision site pretraumatically and posttraumatically. In experiment 2, a 5-cm-long strip of skin was subcutaneously injected with 0.2 ml of 1% lidocaine near the incision site pretraumatically and posttraumatically. Flare, spontaneous pain, and primary and secondary hyperalgesia to punctate mechanical stimuli were assessed after the incision had been made.

Results: Pretraumatic lidocaine injection prevented the occurrence of spontaneous pain and development of flare formation that was found surrounding the incision site immediately (1 min) after the incision had been made. The lidocaine suppressed primary hyperalgesia more effectively than did posttraumatic block, but only for the first 4 h after the incision. The preincision block prevented development of secondary hyperalgesia, whereas posttraumatic block did not significantly affect the fully developed secondary hyperalgesia. The area of flare formation and the area of secondary hyperalgesia did not extend over the strip of the skin that had been pretraumatically anesthetized, whereas the posttraumatic block did not significantly reduce the area of fully developed secondary hyperalgesia.

Conclusions: Pretraumatic injection of lidocaine reduces primary hyperalgesia more effectively than does posttraumatic injection, but only for a short period after incision. The spread of secondary hyperalgesia is mediated via peripheral nerve fibers, but when secondary hyperalgesia has fully developed, it becomes less dependent on or even independent of peripheral neural activity originating from the injured site.

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healthy human volunteers (12 men and 5 women) aged 26–40 yr (mean age, 31.4 yr) participated in two experiments, which are described later. Informed consent was obtained from all of the subjects, and the experimental protocol, which was in accordance with the IASP ethical guidelines for pain research in humans,10 was approved by the Committee of Medical Ethics of Sapporo Medical University School of Medicine, Sapporo, Japan. All experiments started with the subjects sitting semirecumbent at a room temperature of 23°C.

Skin Incision
In each subject, a small surgical incision was made through the skin, fascia, and muscle of the anterior aspect of the forearm, midway between the elbow and the wrist, with a 4-mm-long blade attached to a small rod used for skin cutting for implantation of an intravenous catheter (Top Inc., Tokyo, Japan). The blade was pushed into the skin, and a resistance was felt when the blade penetrated the fascia. The blade was advanced 5–7 mm from the fascia into the muscle and then pulled up from the skin. Gauze was gently pressed onto the site of incision for 30 s to stop bleeding.

Assessment of Vasoactive Reflexes
Dynamic changes in blood flow in the forearm were monitored by means of laser doppler imaging (LDI; Moor Instruments Ltd., Devon, United Kingdom) in experiment 1 and in trials in which pretraumatic treatment with lidocaine was used in experiment 2. The scanning imager was centered on the site of the incision, at 30 cm from the skin surface. An area of 12 × 12 cm, which included the surrounding area of the injury, was scanned at a resolution of 16,384 pixels. A small piece of black adhesive tape was placed at each end of the imaged area to act as landmarks and to improve alignment in subsequent scans. Each scan lasted 2.5 min. Two scans were performed before making the incision to establish a stable baseline. The scanning images were recorded and processed in a personal computer. Flare profile and mean flux in the flare area were determined using dedicated software (MoorLDI version 3.0; Moor Instruments Ltd.) in offline analysis according to a method described in a previous report.11

Assessment of Pain and Hyperalgesia
Spontaneous Pain. The time required to make the incision was 5–10 s. The pain induced by the incision was rated using the visual analog scale (VAS; 0–100 mm: 0 mm = no pain, 100 mm = intolerable pain) just after the incision had been made. Spontaneous pain from the incisional injury was rated using the VAS at 15, 30, 60, 120, 180, 240, and 360 min after the incision had been made. Verbal descriptors (weak pain, 2%; mild pain, 8%; moderate pain, 18%; strong pain, 39%; and very intense pain, 74%) along a 10-cm line between anchor points, which had been used in a previous study,12 were added to make the VAS more comprehensive.

Mechanical Hyperalgesia. Primary hyperalgesia was quantified by determining mechanical pain thresholds within the injured site. The mechanical pain threshold was determined by pinprick with nine progressively rigid von Frey hairs, ranging from 7 to 151 mN (Stoelting, Wood Dale, IL). Each von Frey filament (7, 12, 15, 20, 36, 55, 85, 117, and 151 mN) was applied once to an area adjacent to the incision (3 mm from the incision site) starting with 7 mN at a rate of approximately one per second. The force of the hair producing pain or discomfort was defined as the mechanical pain threshold. The lowest force that evoked pain sensation in at least three of five attempts was defined as the mechanical pain threshold. For this study, 288 mN was recorded as the withdrawal threshold if there was no withdrawal response to stimulation by the 151-mN von Frey filament. Primary hyperalgesia was assessed before the incision was made and at 30 min and 1, 2, 3, 4, 6, and 12 h after the incision had been made and then daily for the next 4 days.

Secondary hyperalgesia was quantified as follows. The 151-mN von Frey hair, which causes a sensation of slight discomfort in normal skin, was applied along at least 12 radial linear paths beginning outside the area of secondary hyperalgesia and moving centripetally toward the incision site in steps of 5 mm at a rate of 5 mm per second until the subject reported that the sensation became increasingly painful. The particular points were marked with a felt-tip pen. Later, the dots that enclosed the hyperalgesic area were connected together to make a continuous border and traced onto a clear acetate paper. This enclosed area was calculated by the use of a digitizing pad connected to a personal computer according to a method described in a previous report.13 Secondary hyperalgesia was determined before the incision was made and at 15, 30, 60, 120, 180, 240, and 360 min after the incision had been made.

Experimental Protocol
Twelve subjects (9 men and 3 women; mean age, 29.9 yr) participated in experiment 1, and seven subjects (5 men and 2 women; mean age, 34.6 yr) participated in experiment 2. Two subjects participated both in experiment 1 and experiment 2. Each experiment was divided into two trials, one in which lidocaine was administered and a control trial in which normal saline (0.9% NaCl) was administered, and the order of administration was randomized. Each participant participated in all trials with a period of at least 4 weeks between trials.

Experiment 1
The purpose of this experiment was to determine whether development and maintenance of mechanical...
hyperalgesia are mediated by peripheral neural activity within or close to the injection site. On one experimental day, the subjects (n = 6) randomly received subcutaneous injection of 0.2 ml normal saline or 1% lidocaine via a 1-ml volume tuberculin syringe with a 28-gauge needle at the site on the right or left forearm where the surgical incision was to be made. On another day, the subjects received subcutaneous injection with another agent, saline, or 1% lidocaine, in the other forearm in which subcutaneous saline or lidocaine was not injected in the first trial. The surgical incision was made in the center of the injected site in each subject 10 min after each injection had been performed. The vasoactive reactions determined using LDI, spontaneous pain, and primary and secondary hyperalgesia were then assessed.

On one experimental day, another 6 subjects randomly received subcutaneous injection of 0.2 ml saline or 1% lidocaine as closely as possible to the incised site of the right or left forearm 30 min after the surgical incision had been made. On another day, the subjects received subcutaneous injection of another agent in the same manner as that described above. Care was taken to prevent leakage of lidocaine and normal saline. The vasoactive reactions were monitored as "controls" using LDI until 30 min after the incision had been made (just before posttraumatic injection was performed). Primary hyperalgesia and secondary hyperalgesia were determined before and after the incision had been made and after the injection had been performed.

Experiment 2

To determine whether the development of flare formation and the development of hyperalgesia depend on cutaneous nerve fibers that transmit neural activity from the injured site to remote surrounding skin, a strip of skin of 5 cm in length was subcutaneously injected with 0.2 ml of 1% lidocaine (a linear series of 3–4 injections of ~0.05 ml each) in six subjects as described previously. Ten minutes later, an incision was made on one side 1 cm from the anesthetized strip. Development of flare was monitored using LDI, and incision-evoked pain and spontaneous pain following the incision were determined using the VAS. The areas of secondary hyperalgesia and mechanical pain thresholds in the injured area were assessed in the same manner as that described in the Mechanical Hyperalgesia section of Assessment of Pain and Hyperalgesia. On another day, in the same six subjects, a 5-cm-long strip of skin was injected with 1% lidocaine 30 min after the incision had been made. The pain induced by the incision was assessed using the VAS, and pain detection thresholds in the injured area and area of secondary hyperalgesia were determined. In some subjects, a 5-cm-long strip of skin was subcutaneously injected with saline pretraumatically (n = 2) or posttraumatically (n = 3) in the same manner as that used in the lidocaine trial to exclude the effect of needle insertion for a linear series of 3–4 injections on development of flare formation and primary and secondary hyperalgesia.

Plasma Lidocaine Concentrations

Blood samples were taken from a left dorsal foot vein in some trials of experiment 1 and experiment 2 at the beginning of each experiment (baseline) and at 15 min after the lidocaine injection, and plasma was separated from the blood samples by centrifugation (×3,000, 10 min). The plasma lidocaine concentration was determined using a Dinabot TDX system (Dinabot Laboratories, Irving, TX) by a modified enzymatic fluorescence-photometric method.

Statistical Analysis

Sizes of flare formation, flux of blood flow in the flare areas, VAS values, and areas of secondary hyperalgesia were presented as mean ± SEM. These data were evaluated using multifactorial analysis of variance for repeated measurements. Planned comparison and Bonferroni post hoc tests were performed when appropriate. Primary mechanical pain thresholds are presented as medians with 1st and 3rd quartiles and 10th and 90th percentiles. The Friedman test was used for within-group comparisons, and the Kruskal-Wallis and Wilcoxon-Mann-Whitney tests were used for between-group comparisons. Multiple comparisons following the Friedman and Kruskal-Wallis tests were performed using the Dunnett test. A P value < 0.05 was considered significant.

Results

In all experimental trials, bleeding was stopped by gentle pressure on the incised site for 30 s using gauze. No infection was observed in the injured site in any of the experiments. The incised site was clearly repaired within 1 week and replaced by a small scar within 2 weeks. None of the subjects subsequently experienced sensory abnormality such as loss of tactile sensation or hyperalgesia. This allowed us to perform several experimental trials at intervals of 4 weeks for each subject enrolled in the current study.

Plasma lidocaine was not detected (< 0.1 μg/ml) in experiment 1 (n = 8) or experiment 2 (n = 6). The only side effect observed was slight nausea in one subject just after the injection of saline in one trial.

Experiment 1: Pretraumatic and Posttraumatic Infiltration with Lidocaine in the Site of Incision

The VAS values were 12 ± 4 and 8 ± 5 mm, respectively, and decreased to zero within 5 min after lidocaine and saline had been pretraumatically injected. In the trials of pretraumatic injection with saline, the subjects experienced a sharp pricking pain when the blade was
blade had been pulled out from the skin, and spontaneous pain, also determined by the VAS, rapidly decreased within a period of 1 h after the incision had been made (fig. 1). In contrast, when the blade penetrated the skin, none of the subjects experienced pain after lidocaine had been pretraumatically injected at the site where the incision was to be made. When the blade penetrated into the muscle, some of the subjects complained of dull pain or discomfort (VAS, 3 ± 2 mm). Following the incision, spontaneous pain determined by the VAS was significantly lower in the lidocaine trials than in the saline trials (P < 0.001).

In the second session of experiment 1, VAS values were 52 ± 13 and 41 ± 10 mm when the incision was made in the trials of posttraumatic injection of saline and lidocaine, respectively, and rapidly decreased to 4 ± 3 and 8 ± 5 mm over a period of 30 min after the incision had been made. When lidocaine and saline were then posttraumatically injected in the injured site, the VAS values slightly increased to 16 ± 4 and 12 ± 2 mm, respectively, but then decreased to 3 ± 1 and 0 ± 0 mm, respectively, at 1 h after the incision had been made. There was no significant difference between VAS values in the trials of pretraumatic and posttraumatic injection of saline (P = 0.72).

Pretraumatic injection of saline produced a relatively large area of increased blood flow immediately (1 min) after the incision had been made (table 1 and fig. 2A). The increased area of blood flow began to rapidly shrink at 15 min and was finally limited to the injured site at 30 min after the incision had been made. Pretraumatic lidocaine injection resulted in a small area of increased blood flow at the injection site, but development of flare for-

![Figure 1](image.png)

**Fig. 1.** Time courses of experimental incision-evoked pain and subsequent spontaneous pain determined by the visual analog scale (VAS) in trials of pretraumatic injection of saline (open circles) and lidocaine (filled circles). Pretraumatic injection of lidocaine almost completely suppressed the incision-evoked pain and subsequent spontaneous pain. *P < 0.001 versus the saline injection trials. Data are shown as mean ± SEM.

Table 1. Size of Flare Area and Blood Perfusion within the Area after Incision

<table>
<thead>
<tr>
<th>Size of area (cm²)</th>
<th>Control (n = 12)</th>
<th>Presaline (n = 6)</th>
<th>Prelidocaine (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Postinfiltration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td></td>
<td>0.3 ± 0.1*</td>
<td>0.5 ± 0.3*†</td>
</tr>
<tr>
<td>Postincision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>5.6 ± 2.1*</td>
<td>6.0 ± 2.9*</td>
<td>1.2 ± 0.7*†</td>
</tr>
<tr>
<td>15 min</td>
<td>2.7 ± 1.5*</td>
<td>2.9 ± 1.8*</td>
<td>0.9 ± 0.3*†</td>
</tr>
<tr>
<td>30 min</td>
<td>1.0 ± 0.5*</td>
<td>1.1 ± 0.6*</td>
<td>0.8 ± 0.3*†</td>
</tr>
<tr>
<td>Flux (RU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>98 ± 48</td>
<td>110 ± 56</td>
<td>103 ± 45</td>
</tr>
<tr>
<td>Postinfiltration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td></td>
<td>142 ± 41*</td>
<td>176 ± 50*</td>
</tr>
<tr>
<td>Postincision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>388 ± 155*</td>
<td>403 ± 185*</td>
<td>216 ± 96*†</td>
</tr>
<tr>
<td>15 min</td>
<td>310 ± 116*</td>
<td>342 ± 103*</td>
<td>208 ± 86*†</td>
</tr>
<tr>
<td>30 min</td>
<td>208 ± 71*</td>
<td>231 ± 94*</td>
<td>182 ± 54*</td>
</tr>
</tbody>
</table>

* P < 0.01 versus pre (intragroups). † P < 0.01 between groups.

Control = blood flow monitored before and until 30 min after the incision had been made in the subjects receiving posttraumatic infiltration with saline or lidocaine; Presaline = pretraumatic injection of 0.2 ml saline; Prelidocaine = pretraumatic subcutaneous injection of 0.2 ml lidocaine, 1%; Pre = basal level; Postinfiltration = data obtained at 10 min after subcutaneous injection of saline or lidocaine; Postincision = data obtained at 1, 15, and 30 min after the incision had been made; Flux = blood flow; RU = relative units.

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mation was significantly suppressed after the incision had been made ($P < 0.01$; table 1 and fig. 2B).

In the trials of pretraumatic injection of saline, mechanical pain thresholds to von Frey hairs in the injured area ("primary area") rapidly and significantly decreased over a period of 30 min after the incision had been made, and the significant decrease lasted for 2 days ($P < 0.05$; fig. 3A). Pretraumatic injection of lidocaine resulted in analgesia to mechanical stimuli used in this study 10 min after the injection. The threshold was significantly higher than that in the control trial until 4 h after the incision had been made ($P < 0.05$).

In the second session of experiment 1, injection of saline or 1% lidocaine in a volume of 0.2 ml was performed 30 min after the incision had been made, when primary and secondary hyperalgesia had fully developed. The lidocaine injection rendered the injected skin analgesic to mechanical stimulation 5 min after the injection (fig. 3B). The thresholds at 1 and 2 h after the incision had been made were significantly higher than the threshold at 30 min after the incision had been made and the thresholds following posttraumatic injection of saline. The thresholds in the trials of pretraumatic injection of lidocaine in the first session of experiment 1 at 3 and 4 h after the incision had been made were significantly higher than those in the second session of experiment 1, in which lidocaine was posttraumatically injected ($P < 0.05$; figs. 3A and B).

The area of secondary hyperalgesia to punctate mechanical stimuli was apparent in the trials of pretraumatic and posttraumatic injection of saline 30 min after the incision had been made (fig. 4). The area of secondary hyperalgesia tended to gradually shrink, and it had decreased to a limited area just around the incision site at 6 h after the incision had been made. Pretraumatic injection of lidocaine almost completely suppressed the development of secondary hyperalgesia ($P < 0.001$; fig. 4A), whereas the area of secondary hyperalgesia that had fully developed was not significantly reduced by the posttraumatic injection of lidocaine ($P = 0.48$; fig. 4B).
Experiment 2: Preinjection and Postinjection of Lidocaine into a Strip of Skin Near the Incision

Pretraumatic anesthetization of a 5-cm-long strip of skin with lidocaine resulted in sensory loss in the skin, but the subjects experienced unpleasant sensation to mechanical stimuli using a 151-mN von Frey hair in areas 5 mm or more from the injected skin on both sides, indicating that local anesthesia was restricted to the strip of the skin. Increased blood flow was still observed in the strip of the skin anesthetized 10 min after the incision had been made, probably because of lidocaine-induced vasodilatation (fig. 5). Development of flare response was arrested beyond the strip of lidocaine-anesthetized skin when the incision was made on one side of the strip of skin. The changes in incision-evoked pain and subsequent spontaneous pain determined by the VAS and pain detection thresholds to von Frey hair stimulation in the injured site were similar, and there were no significant differences between these results in experiment 2 and those of the saline trials in experiment 1 (P = 0.54–0.84; fig. 6).

The area of secondary hyperalgesia did not extend over the strip of skin that was anesthetized by lidocaine (fig. 7A). The size of the area of secondary hyperalgesia on the side opposite the injury was significantly reduced by the pretraumatic injection of lidocaine (P < 0.001; fig. 7B). However, posttraumatic injection did not significantly decrease the size of secondary hyperalgesia that had fully developed 30 min after the incision had been made (P = 0.31; figs. 7C and D).

In some subjects who received pretraumatic (n = 2) or posttraumatic (n = 3) injection of saline into the strip of skin, the time courses of changes in the mechanical pain detection thresholds in the “primary area” or in the size of secondary hyperalgesia area were similar to those in the trials of pretraumatic and posttraumatic injection of saline in experiment 1 (data not shown).

Discussion

Incision-evoked Pain and Spontaneous Pain following the Incision

In this study, the small surgical incision induced a maximum VAS value, as determined by the subjects, when the blade penetrated the skin, and then VAS values rapidly decreased and disappeared within 1 h after the incision had been made. Incision-induced pain and subsequent spontaneous pain may reflect the temporal and spatial summation of “injury discharge” and subsequent spontaneous firing in primary afferent fibers in the injured site and areas surrounding the injured site and hence spinal neurons of the dorsal horn. Thus, it is possible that incision-evoked “injury discharge” showed a maximal rate when the incision was made and that subsequent spontaneous firing then rapidly decreased. It has been reported that incisions made within receptive

Fig. 4. Time courses of secondary hyperalgesia (area determined by a 151-mN von Frey hair) in trials of pretraumatic injection (A) and posttraumatic injection (B) of saline (open circles) and lidocaine (filled circles). *P < 0.001 versus the saline trials. Data are shown as mean ± SEM.
fields of glabrous and hairy skin of rats produced a burst of activity in spinal dorsal horn neurons that persisted throughout the duration of surgery but then decreased to the control level or to a level only slightly above the control level within 1 h. These results seem to agree with the results of changes in VAS values in the current study, despite the fact that different species were used.

In the current study, flare was observed in a relative large area immediately (1 min) after the incision had been made, and this area then rapidly shank to the injured site within a period of 30 min after the incision had been made. The time courses of the incision-evoked pain and subsequent spontaneous pain thus coincided with that of the flare formation in our study. When the strip of the skin near the site to be incised was pretraumatically anesthetized in experiment 2, the changes and time courses of incision-evoked pain and subsequent spontaneous pain were not significantly different from those in the trials of pretraumatic and posttraumatic injection of saline in experiment 1, despite the fact that the size of the secondary hyperalgesia area was suppressed to about half of those in the saline trials of experiment 1 (figs. 4 and 7). On the other hand, in experiment 1, pretraumatic injection of lidocaine at the site to be incised almost completely abolished incision-induced pain and subsequent spontaneous pain. It is thus likely that spontaneous pain following an incision is mainly caused by neural excitation in primary afferent fibers originating from the injured site, not from the area surrounding the injured site (“secondary area”).

**Effects of Pretraumatic and Posttraumatic Injection of Lidocaine on Primary Hyperalgesia and Blood Flow in the Incision Site**

Pretraumatic injection of lidocaine delayed development of primary hyperalgesia up to 4 h, but there was no significant difference between the mechanical thresholds in the pretraumatic lidocaine and saline trials from 6 h after the incision had been made and thereafter. Posttraumatic injection of lidocaine reversed primary...
hyperalgesia that had fully developed, but only for 1.5 h after lidocaine had been injected. These results suggest that pretraumatic injection of lidocaine reduces primary hyperalgesia more effectively than does posttraumatic injection, but only for a short period after incisional injury, consistent with the results in other types of tissue injury.17

Inflammatory mediators (prostaglandin E2, 5-HT, bradykinin, epinephrine, adenosine) and neurotrophic factors (NGFs) released during tissue injury and subsequent inflammation sensitize peripheral nociceptors, and this sensitization of peripheral nociceptors contributes to the development of primary hyperalgesia. Pretraumatic injection of lidocaine suppressed the incision-induced increase in blood flow in the injured site compared with that in the case of pretraumatic saline injection. However, a significant increase compared with the preinjection value was seen at 30 min after the incision had been made (table 1 and fig. 2), suggesting the existence of inflammation in the injured skin, since an increase in blood flow detected by LDI depends on superficial vasodilation.18 On the other hand, it has been shown that small unmyelinated and myelinated nociceptors, which innervate into muscle, can be sensitized by bradykinin, prostaglandin E2, and neuropeptides,19 and the deep tissue including muscle would not have been affected by subcutaneous injection of lidocaine in this study. Thus, tissue injury and inflammation must have existed in the injured skin and deep tissue for a long time following the incision, and the existence of inflammation might have sensitized peripheral nerves after the inhibitory effects of pretraumatic and posttraumatic injection of lidocaine had disappeared. This may explain why pretraumatic and posttraumatic injection with lidocaine had only temporary effects on primary hyperalgesia in the current study.

Effects of Pretraumatic and Posttraumatic Infiltration of Lidocaine on Secondary Hyperalgesia and Flare Formation Outside the Incision Site

In our study, secondary hyperalgesia developed maximally within 30 min and persisted for 3 h after the incision, and the area of hyperalgesia did not extend over the strip of skin that had been pretraumatically anesthetized (hatch marks) before the incision was made (A and B). After secondary hyperalgesia had fully developed, posttraumatic injection of lidocaine in a strip of skin did not affect the area of secondary hyperalgesia (C and D). The areas of secondary hyperalgesia are shown in (A) and (C) by a gray line (30 min after incision) and black line (1 h after incision), *P < 0.01 versus size of secondary hyperalgesia medial to the strip of skin injected with lidocaine. Data are shown as mean ± SEM.
incision had been made and then gradually disappeared. On the other hand, flare formation surrounding the injury site was found immediately after the injury and then rapidly decreased and was restricted to the injured site within 30 min. The time courses of development of flare formation and secondary hyperalgesia were different, and the maximal area of flare was less than that of secondary hyperalgesia to punctate mechanical stimuli in the current study (table 1 and fig. 4). Pretraumatic injection of lidocaine at the site to be incised prevented development of flare formation and secondary hyperalgesia induced by the incision in our study. Flare spreads and develops via cutaneous axon reflexes and hence by release of neuropeptides such as substance P and calcitonin gene–related peptide from the axons.18 A large flare response has been suggested to be triggered by “injury discharges” of and depend on excitation of small peripheral nerves, particularly C-mechanoreceptors sensitive fibers, resulting in axon reflexes in the surrounding area as well as the injured site.20 This speculation is supported by the results of experiment 2, showing that a thin strip of skin infiltrated with lidocaine acted as a barrier to the development of flare on the medial side to the strip of skin infiltrated with lidocaine. Although the area of secondary hyperalgesia did not completely coincide with the area of flare formation, these results suggest that development of flare and the development of secondary hyperalgesia are not caused by the same mechanisms, but that both are mediated by neural factors that operate peripherally. On the other hand, secondary hyperalgesia is believed to be maintained by central facilitation with or without mechano receptive inputs from the periphery.1 In our study, posttraumatic block at the incision site and also in a strip of skin did not significantly reduce the area of secondary hyperalgesia that had fully developed. When secondary hyperalgesia has fully developed by establishment of central sensitization, it would become less dependent on or even independent of such peripheral neural activity.

Another possible explanation is that secondary hyperalgesia is also maintained by peripheral mechanisms, but that different mechanisms are involved in the development and maintenance of secondary hyperalgesia. There is growing evidence from both psychophysical and electrophysiological studies that chemosensitive, previously mechanoreceptive nociceptors become mechanosensitive in the wake of inflammation or injury and then contribute to the development of primary hyperalgesia.21–23 A change in these neurons has been reported, and it is thought that these fibers extend over a relatively large area of a few centimeters, including the “secondary area,” through discrete long axons.1,20 Thus, awakening of so-called “silent” or “sleeping” nociceptors may be responsible for the development of secondary hyperalgesia as well as primary hyperalgesia following surgical injury. However, the finding that posttraumatic injection of lidocaine did not affect secondary hyperalgesia in the current study suggests that peripheral neural activity originating from the injured site does not necessarily contribute to maintenance of secondary hyperalgesia. Thus, even if peripheral mechanisms are greatly involved in both development and maintenance of secondary hyperalgesia following a surgical incision, it still remains to be established how secondary hyperalgesia is maintained in the periphery, independent of the activity originating from the injured site.

Another possible explanation is that development of secondary hyperalgesia is mediated by peripheral mechanisms and that maintenance of secondary hyperalgesia is mediated by both peripheral and central mechanisms; that is, after development of secondary hyperalgesia, peripheral sensitization of nociceptors in the “secondary area” and responses to mechanical stimuli that could be amplified by central sensitization might be maintained, independent of neural activity of nociceptors sensitized in the “primary area.”

There are two types of secondary hyperalgesia to mechanical stimuli, that is, punctate stimulation-evoked secondary hyperalgesia and “touch-evoked” low-threshold mechanical hyperalgesia or allodynia,1,13 a phenomenon we did not deal with in the current study. In our preliminary study, the experimental incision did not produce secondary hyperalgesia to stroking using a paintbrush in most subjects, and this is why the latter type of secondary hyperalgesia was not qualified in the current study. It has been shown that fully developed secondary hyperalgesia to stroking but not to punctate stimuli was reduced or eliminated by postinjury as well as preinjury injection of lidocaine at the injured site, and anesthetization of a strip of skin 1 cm from the injured site also reduced the area of secondary hyperalgesia to stroking after intradermal injection of capsaicin.12 Thus, in contrast to secondary hyperalgesia to punctate mechanical stimuli, secondary hyperalgesia to stroking may continue to be maintained by peripheral activity both at the site of injury and through radial transmission of neural activity to areas remote to the injury site even after the hyperalgesia to stroking has fully developed.

Possible Relation between the Results of this Study and Postoperative Pain in a Clinical Setting
Previous clinical studies have shown that primary hyperalgesia to mechanical stimuli persist for at least 4 days after abdominal surgery and correlates with pain at rest and with movement.24–26 Time to first request for an analgesic was longer in patients receiving preoperative local anesthesia,27 whereas no significant differences in analgesic requirements or pain scores were observed for a period of 7 days after the operation.28 If spontaneous postoperative pain and surgical injury-induced primary hyperalgesia are closely related to each other in a clinical setting, the results of these clinical studies would be in
agreement with the results for primary hyperalgesia in the current study. On the other hand, it has been shown that secondary hyperalgesia persists for at least 24 h after abdominal hysterectomy and nephrectomy. However, secondary hyperalgesia was observed for a period of only 3 h in the current study. In clinical situations, the area of surgical injury is larger than that in this experimental model. Furthermore, injuries are repeatedly added to the surgical area during surgery, and the injured area is regularly stimulated by respiratory movements, especially after thoracic and abdominal surgery. Such larger injuries and repetitive stimulation in the injured area may produce excessive inputs from the injured site to the “secondary area,” and temporal and spatial summation of the inputs may result in repeated “refreshing” of the sensitization in the peripheral and central nervous system neurons. These events during and after surgery may produce long-lasting spontaneous pain with or without inputs from the periphery and also result in long-lasting secondary hyperalgesia.

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References