Central Origin of Secondary Mechanical Hyperalgesia

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Klede, Monika, Hermann O. Handwerker, and Martin Schmelz. Central origin of secondary mechanical hyperalgesia. J Neurophysiol 90: 353–359, 2003; 10.1152/jn.01136.2002. The contribution for the development of secondary mechanical hyperalgesia by peripheral mechanisms has not been fully elucidated. We have reevaluated the effects of local anesthetics on electrically evoked flares and mechanical hyperalgesia in human skin. We applied 2% lidocaine via intradermal microdialysis fibers at a length of 10 cm for 110 min to the volar forearm to establish a narrow and stable “anesthetic strip.” After 60 min of lidocaine perfusion, transdermal electrical stimulation (1 Hz, 50 mA) was applied at a distance of 1 cm from the microdialysis fibers for 30 min. The areas of allodynia and punctate hyperalgesia were marked at the end of the stimulation period. The flare reaction was assessed by laser Doppler scanner and infrared thermography. Total protein content of the dialysate collected at the stimulating electrode was measured photometrically. We found no increase in protein content during electrical stimulation. Flare area (12.4 ± 2.3 vs. 3.5 ± 1.2 cm²) and intensity (426 ± 24 vs. 257 ± 21 PU) were significantly reduced beyond the lidocaine strip. The mean temperature increase in the area beyond the lidocaine strip was significantly reduced (1.1 ± 0.1 vs. 0.2 ± 0.1°C) and did not differ from control areas. In contrast, allodynia (7.4 ± 0.7 and 8.6 ± 0.9 cm) and punctate hyperalgesia (7.6 ± 0.7 and 8.6 ± 0.9 cm) developed symmetrically on both sides of the anesthetic strip. Allodynia subsided 4 min after the end of the electrical stimulation. We conclude that the development of allodynia and punctate hyperalgesia in human skin is centrally mediated, whereas the axon reflex vasodilation is of peripheral origin.

INTRODUCTION

In the beginning of the last century, Thomas Lewis described that a local trauma provokes an erythema that extends into the uninjured vicinity (Lewis et al. 1927). This “flare response” is dependent on the integrity of primary afferent nerves but not on their central nervous connections. In addition, mechanical hyperalgesia develops in the uninjured skin surrounding the injury. Two types of mechanical hyperalgesia have been differentiated in neuropathic pain patients: dynamic and static (Ochoa and Yarnitsky 1993). Dynamic hyperalgesia denotes pain induced by gentle stroking, while static hyperalgesia denotes hypersensitivity from constant pressure. Both types of mechanical hyperalgesia can also be evoked in healthy volunteers using topical application of alogogens, such as mustard oil or capsaicin (Koltzenburg et al. 1992). The development of experimental models for the induction of secondary hyperalgesia in human subjects and animals has provided the basis to further explore the mechanisms of secondary hyperalgesia (Simone et al. 1989a,b). Measurements of spatial extension and time course are different between allodynia and punctate hyperalgesia. These differences suggest different mechanisms (Baumann et al. 1991; Cervero et al. 1994; LaMotte et al. 1991; Simone et al. 1989a). Whereas Aβ-fibers have been suggested to mediate allodynia (Torebjörk et al. 1992a), punctate hyperalgesia has recently been linked to excitation of capsaicin-insensitive Aδ-fibers (Fuchs et al. 2000; Magerl et al. 2001; Ziegler et al. 1999). Although it is widely accepted that secondary mechanical hyperalgesia is due to sensitization of spinal nociceptive neurons (Koltzenburg 2000; LaMotte et al. 1991; Torebjörk et al. 1992b), there are also reports suggesting that peripheral mechanisms are involved. Axon reflex erythema and mechanical hyperalgesia have been identified to have similar borders surrounding the injured tissue; this has led to the hypothesis that the axon reflex mechanism may be linked to secondary hyperalgesia (Serra et al. 1998). Moreover, multiple intracutaneous injections of lidocaine, forming an “anesthetic strip,” after a nearby capsaicin injection, have not only been shown to block the spreading of the axon reflex erythema but also the development of punctate hyperalgesia (LaMotte et al. 1991; Serra et al. 1998).

In this study, we used a newly developed model of electrically induced secondary mechanical hyperalgesia (Koppert et al. 2001) in which large and stable areas of allodynia and punctate hyperalgesia are provoked for prolonged periods and are accompanied by a large axon reflex erythema. Intradermal microdialysis was employed to continuously deliver lidocaine in a narrow strip a length of 10 cm, thereby providing a stable and narrow anesthetic strip. This experimental setup enabled us to investigate the effects of the anesthetic strip on the development of secondary mechanical hyperalgesia and the axon reflex vasodilation (infrared thermography and laser Doppler scanning).

METHODS

Subjects

In this study, 12 healthy volunteers (8 male, 4 female; mean age 26.7 ± 1 yr) participated after having given their informed consent. All subjects were informed about the general intention of the study but

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Microdialysis

Three single plasmapheresis hollow fibers (0.4 mm in diameter, cutoff: 3,000 kDa; Asashi) were inserted intracutaneously (Fig. 1A). All microdialysis membranes were oriented transversally to the axis of the volar forearm and were perfused at a constant flow rate of 5 μl/min via a Tygon tubing (Novodirect) by a microdialysis pump (Pump 22, Harvard Apparatus). The stimulation membrane was inserted over a length of 1.5 cm in the center of the left volar forearm using a 25 G canula. No local anesthesia was required during the insertion of the small-diameter canula. The remaining two membranes were inserted a length of 0.8 cm each a distance of 1 cm from the stimulation site. These two membranes formed a line an average of 0.66 mm (0.5–0.9 mm, minimum-maximum, n = 11). After the membranes were passed through the skin, the membranes were inserted into glass capillaries (150 μl, 1.0 mm ID; Servoprax, GLW) for the collection of the dialysate. The capillaries were tilted at an angle of 5° to minimize the outflow resistance. The length of the microdialysis fibers that was exposed to air was <3 mm at both the inflow and outflow sites. The dialysate was taken from the stimulation membrane every 15 min for a total duration of 75 min. The samples were then stored in polyethylene cups. The experimental protocol is depicted schematically in Fig. 1B.

Electrical stimulation

After waiting a period of 60 min to establish a baseline, sensitivity of the skin above the lidocaine membranes was tested with light strokes and with pinpricks. After complete anesthesia was confirmed for the entire length of the two lidocaine catheters, transcutaneous electrical stimulation was applied between a stainless steel wire of 0.1 mm diam, inserted in the stimulation membrane (cathode), and a 1 cm² TENS electrode attached epicutaneously above the membrane. Electrical stimulation was applied at a frequency of 1 Hz and with a pulse duration of 0.5 ms via a constant current stimulator (DS7A, Digitimer). Subjects were asked to numerically rate the electrically induced pain sensation on a scale from 0 to 10 (no pain to worst pain imaginable). Current was increased in 5-mA steps until the subject rated the electrically induced pain 5 of 10. During the first 15 min of stimulation, current intensity was increased at intervals of 2 min to maintain the same pain rating. The stimulus intensity was kept constant at this level for 15 min, and then the electrical stimulation was stopped.

Protein analysis

The dialysate samples were analyzed for total protein. Total protein content was measured photometrically (MRX reader, Dynatech) according to Bradford (Bradford 1976) using Coomassie blue dye for the analysis and bovine serum albumin as normal curve.

FIG. 1. A: a schematic of the experimental setting. One centimeter next to the electrical stimulation 2% lidocaine was delivered intradermally via 2 serial microdialysis membranes. The extent of allodynia and hyperalgesia was tested along 6 paths (dotted lines). Allodynia was tested by consecutive gentle strokes with a cotton swap perpendicular to the paths; hyperalgesia was tested by punctate stimuli with a 250 mN von Frey hair along the paths toward the electrical stimulation. Subjects indicated when allodynia or punctate hyperalgesia was evoked. The sites A–D indicate the 4 areas that were included in the analysis of laser Doppler scanner (LDI) measurements and sites C and D served as reference areas in the thermography analysis. The 2 polygons indicate the approximate locations that were analysed for the flare area, flare intensity, and temperature increase by thermography. B: the time line shows the chronology of measurements assessed during the experiments.

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Vasodilation

Using a laser Doppler scanner (LDI, Moor instruments, Devon, UK), superficial blood flow was assessed at 5-min intervals, beginning at the lidocaine perfusion until the maximum current was reached (60-min baseline and 15 min during electrical stimulation), in an area of 20 * 15 cm around the stimulation site (Fig. 1). Another single LDI scan was taken at the end of the electrical stimulation. The neurogenic flare was analyzed in the last scan of the series taken. The blood flux was evaluated in two rectangular areas (1 * 1.5 cm), which were positioned 2.5 cm distal and proximal from the stimulation site. One was positioned on the same side of the anesthetic strip as the stimulation (site A), and the other was positioned on the side of the anesthetic strip that was not stimulated (site B). Two additional sites on each side of the anesthetic strip were analyzed as controls for systemic responses (sites C and D; Fig. 1). Superficial blood flux (perfusion units, PU) in these areas was assessed after 30 min of electrical stimulation by dedicated software (MLDI, Moor instruments).

For the analysis of the flare size on either side of the anesthetic strip, the mean flux in perfusion units and its standard deviation were calculated for the baseline scan. Mean flux plus twice the standard deviation was used as the threshold for the flare reaction. Pixels exceeding the threshold were defined as flare and their areas were assessed on both sides of the anesthetic strip after 30 min of electrical stimulation. To enable in this analysis, a comparison of corresponding skin areas on either side of the anesthetic strip, only pixels at a distance of >1.5 cm from the stimulation site were included (Fig. 1). The mean flux of the pixels exceeding the flare threshold also were calculated.

Thermography

The skin temperature was assessed using an infrared thermocamera (AGEMA Thermovision Scanner 900 SW/TE). The temperature resolution of the device was 0.1°C, spatial resolution was 1.5 mm (248 * 108 pixel), and individual scans were taken at a frequency of 3 Hz. Averages of 32 successive scans were stored on a hard disk at 15-s intervals for offline analysis. Skin temperature was scanned for 15 min from the start of electrical stimulation. In an offline analysis (Greiner et al. 1995), the “thermographic flare” reaction was assessed. An increase in skin temperature of ≥0.6°C was set as the threshold for detecting the thermographic axon reflex by computer assisted analysis (Greiner et al. 1995). Only pixels a distance of >1.5 cm from the stimulation site were included to enable comparison of the corresponding skin areas (see Fig. 1). Time course of the temperature increase was measured after a 15-min stimulation within the area of the largest flare on the stimulation side of the anesthetic strip and its mirror image opposite of the anesthetic strip (Fig. 1A). In addition, control areas (2 * 2 cm) on each side of the anesthetic strip, chosen outside the flare area (sites C and D), were analyzed for temperature changes.

Psychophysics

The allodynic area was delineated by light strokes with a cotton swab. The strokes were applied perpendicular to the direction from either the wrist or the cubital fossa towards the stimulation site. These strokes were applied in 0.5-cm steps at a frequency of 1 Hz in three lines on either side of the anesthetic strip. The subjects were instructed to indicate when the evoked sensation changed from touch to pain or to the sensation of soreness. The borders of the allodynic areas were marked on the skin.

After the current was switched off, the time course of the decline of allodynia was measured. The extension of allodynia along the central trajectory was tested and marked at 30-s intervals on either side of the anesthetic strip until there was no longer a feeling of allodynia. The measurements on the side treated with lidocaine were stopped 3 mm from the lidocaine membrane as touch was not felt in the region above the membrane.

When allodynia was no longer detectable, the area of punctate hyperalgesia using a von Frey filament (bending force 250 mN, Stoelting) was assessed analogous to the allodynia test. Subjects were instructed to indicate when the painful stimulus became notably more painful. The borders of the punctate hyperalgesia were marked on the skin. All marks on the skin were transferred to a transparency at the end of the experiment, which was digitized and analyzed off line.

Statistics

For statistical evaluation, an ANOVA for repeated measures was calculated using protein concentration, superficial blood flow, or temperature as dependent variables. Normalized data were used if not indicated otherwise. Scheffe’s post hoc test was employed to identify significant differences. Paired t-tests were used to compare hyperalgesic areas and vasodilation on both sides of the anesthetic strip. P values <5% were considered significant. All values are given as means ± SE.

RESULTS

Electrical stimulation

The mean maximum current during stimulation was 49.6 ± 2.3 mA. Maximum pain rating was 5.3 ± 0.3 on a scale from 0 to 10. The current needed to induce a pain rating of 5 was independent of the side of the lidocaine strip (t-test, n.s.). The quality of the electrically evoked pain was reported as burning and stinging.

Protein extravasation

After insertion of the canula, we detected protein concentrations in the dialysate of the stimulation membrane of 0.89 ± 0.06 mg/ml, which exponentially declined after 60 min to a stable baseline of 0.43 ± 0.04 mg/ml. Electrical stimulation did not result in any increase in protein concentration (0.40 ± 0.03 mg/ml after 75 min).

Vasodilation

Insertion flare declined to baseline blood flow during the 1 h of baseline perfusion with Ringer solution. Vasodilation of ~3 mm in width was observed above the lidocaine membranes. This area of vasodilation did not subside during the 60-min baseline. A flare reaction developed on the control side during the electrical stimulation, but this did not extend beyond the anesthetic strip (Fig. 2). When electrical stimulation had reached the final current, a flare reaction was detected which differed significantly in size and intensity on both sides of the anesthetic strip (Fig. 3).

The size of the flare on the control side was 12.4 ± 2.3 cm², whereas beyond the lidocaine strip the flare was 3.5 ± 1.2 cm² (t-test, P < 0.001, n = 12). The superficial blood flows inside the flare on the control side and in the area beyond the anesthetic strip (mean flux in entire flare area) were 426 ± 24 and 257 ± 21 PU, respectively (t-test, P < 0.001, n = 12). The radius of the flare erythema was 4.6 ± 0.3 cm on the control side. In five of the subjects, the block of the flare erythema beyond the anesthetic strip was not complete. Elevated superficial blood flow was detected in this area beyond the anesthetic
In these five subjects, the area of this erythema was 6.0 ± 1.9 cm² and its intensity was 299 ± 31 PU. Even in these cases, the reduction of flare size and intensity was significant (t-test, \( P < 0.05; n = 5 \)). In those seven subjects in which no visible erythema developed beyond the area treated with lidocaine, the flare area, as assessed by the laser Doppler, was 1.1 ± 0.3 cm² with a mean intensity of 214 ± 18 PU (data not shown). When comparing superficial blood flow in the two 1.5 cm² areas on each side of the lidocaine strip, the highest flux was found within the flare on the control side (511 ± 66 PU, site A; Fig. 3). The flare in site A was significantly higher as compared to control areas (111 ± 13 PU, site C) and the areas beyond the anesthetic strip (184 ± 24 PU in the hypothetical flare; site B vs. 99 ± 10 PU in the 2nd control area; site D, ANOVA, Scheffe’s post hoc test). No significant differences in flux were observed between the control areas (sites C and D) and the area inside the hypothetical flare beyond the anesthetic strip (site B).

Infrared thermography

Before stimulation, we observed a baseline skin temperature of 32.0 ± 0.1°C without significant differences between the

FIG. 2. Specimen of transcutaneous electrical stimulation [1 Hz, 50 mA, 0.5 ms; stimulation site (“stim”) is marked by a rectangle] provoking an area of increased superficial blood flow as assessed with LDI (top) and with an infrared thermocamera (bottom). An anesthetic strip was induced by perfusing 2 intradermal microdialysis membranes (vertical white lines) with 2% lidocaine. The borders of hyperalgesia to punctate stimuli (grey lines) and to light stroking (dotted lines) are shown in the LDI and the thermogram.

FIG. 3. Mean superficial blood flow measured after 30 min of electrical stimulation on both sides of the anesthetic strip (sites A and B) by a LDI are shown (mean ± SE, \( n = 12 \)). The blood flow in the reference areas outside the neurogenic inflammation are also shown (sites C and D). Even though the subjects in which the flare erythema was not completely blocked were included, the blood flow in site B was not significantly different from the reference areas. Inset: the product of the area and the intensity of the flare erythema on each side of the anesthetic strip symmetrical to the stimulation site. (**P < 0.001, ANOVA)
four analyzed areas. Electrical stimulation provoked a significant increase of skin temperature of \(1.1 \pm 0.1^\circ\text{C}\) only on the stimulation side of the anesthetic strip \((P < 0.05, \text{ANOVA, Scheffe’s post hoc tests; } n = 12; \text{Figs. 2 and 4})\). No major changes in temperature were observed in the corresponding area outside the anesthetic strip or in the two remote control areas \((\text{sites } C \text{ and } D; \text{Fig. 4})\). There was no significant difference whether the lidocaine strip was distal or proximal of the stimulation membrane in this temperature increase (data not shown).

**Psychophysics**

The integrity of the anesthetic strip was tested several times prior to electrical stimulation by applying punctate stimuli above and in the vicinity of the lidocaine membranes. The anesthetized area covered the length of the lidocaine membranes and extended 2 mm on each side of the membranes. This anesthetized area was stable during the 30-min lidocaine perfusion. Areas of allodynia and hyperalgesia were assessed at the end of the electrical stimulation \((\text{Fig. 5})\). Subjects reported a clear difference between normal skin and allodynic or hyperalgesic areas. Alloodynia was described as a slightly burning, unpleasant, or sore sensation evoked by brushing. Hyperalgesia was described as a heightened pain response to a pricking with a von Frey hair. The maximum extent of the allodynic and hyperalgesic areas was slightly smaller beyond the anesthetic strip, but these differences were not significant. The mean maximum radius of the area of alloodynia was \(7.4 \pm 0.7\) and \(8.6 \pm 0.9\) cm, and the area of hyperalgesia was \(7.6 \pm 0.7\) and \(8.7 \pm 0.9\) cm. There was no significant difference between the sides of the lidocaine strip \((t\text{-test, } n.s.)\). The areas of alloodynia and hyperalgesia were significantly larger than the area of erythema on either side of the anesthetic strip \((\text{ANOVA, } P < 0.001)\).

In the five subjects whose flare reaction was not completely blocked beyond the lidocaine strip, we compared the maximum radius of areas of alloodynia and hyperalgesia. In the seven subjects whose flare reaction was completely blocked by the lidocaine strip, there was no significant difference between the extent of alloodynia \((9.86 \pm 1.18\) vs. \(8.06 \pm 0.96\) cm mean maximum radius) and the area of punctate hyperalgesia \((9.51 \pm 1.21\) vs. \(8.13 \pm 0.89\) cm mean maximum radius) on either side of the anesthetic strip \((t\text{-test, } n.s.)\). We did not attempt to quantify the intensity of the secondary mechanical hyperalgesia.

After the end of the electrical stimulation, we assessed the time course of allodynia on each side of the anesthetic strip separately. The decrease of allodynic areas was rapid and occurred symmetrically \((\text{Fig. 5})\). The allodynia beyond the anesthetic strip had subsided after \(157 \pm 18\) s and on the control side after \(172 \pm 15\) s \((\text{ANOVA, } n.s.)\).

**DISCUSSION**

This study provides evidence, that spreading of the electrically evoked flare reaction can be interrupted by a dermal anesthetic strip of lidocaine and is therefore peripherally mediated via dermal nerve fibers. However, mechanical hyperalgesia \((\text{punctate hyperalgesia and allodynia})\) develops on both sides of the anesthetic strip and is therefore centrally mediated. Our results do not confirm a link between axon reflex erythema and mechanical hyperalgesia as alloodynia and punctate hyperalgesia developed without axon reflex erythema beyond the anesthetic strip. Even on the non-blocked side, the areas of axon reflex erythema and mechanical hyperalgesia had different spatial extensions.

High intensity transcutaneous electrical stimulation was used for the induction of the axon reflex flare reaction. The short distance of \(<1\) mm between the stimulation electrodes provided a high current density, which is necessary to excite mechano-insensitive \("silent\) C nociceptors. This class of nociceptors is characterized by very high electrical excitation thresholds \((\text{Weidner et al. 1999})\) and large innervation territories \((\text{Schmidt et al. 2002})\). This nociceptor class has also been shown to mediate the visible axon reflex erythema \((\text{Schmelz et al. 2000a})\). Anesthetic strips achieved by multiple small injections of a local anesthetic have been used before to block the development of the neurogenic axon flare reaction \((\text{LaMotte et al. 1991; Serra et al. 1998})\). In this study, intradermal microdialysis was used to deliver lidocaine. Due to the limited diffusion, the anesthetic strip achieved by microdialysis is very

**FIG. 4.** The increase in temperature inside the thermographically assessed flare area on both sides of the anesthetic strip. A significant increase in skin temperature develops on the stimulation side but not beyond the anesthetic strip \((\text{mean } \pm \text{ SE, } n = 12)\). The temperature changes beyond the anesthetic strip are not significantly different from those observed in the 2 reference areas outside the flare erythema \((\text{sites } C \text{ and } D)\).

**FIG. 5.** Time course of allodynic areas after termination of electrical stimulation is shown. The radius of alloodynia on the stimulation side; the area beyond the anesthetic strip \((\text{mean } \pm \text{ SE, } n = 12)\). The radius of the punctate hyperalgesia \((\text{bars on the right})\) was tested after alloodynia had ceased, \(<4\) min after termination of the electrical stimulation.
narrow (<5 mm), which can be maintained over a prolonged period. In 7 of 12 experiments, the block of the axon reflex was complete, i.e., even with the very sensitive methods of LDI and infrared thermography no increase in temperature or superficial blood flow was detectable. In those cases in which we were not able to block the development of the flare completely, the anesthetic strip might not have been evenly distributed over the entire length of the microdialysis catheter, although the mechanical testing prior to electrical stimulation indicated complete anesthesia. As the remaining flare beyond the strip developed close to the overlap of the two membranes delivering lidocaine, some collaterals might have remained unaffected by the lidocaine. This result confirms the concept that the axon reflex is the underlying mechanism for neurogenic erythema. An alternative explanation for the incomplete blockade could be arborizations of C fibers, which separate from the parent axon proximally and reach their innervation territory in the skin by a different path. Proximal branching in nociceptors has been shown previously in monkey skin (Peng et al. 1999). Also, in human skin, there is evidence for extensive branching of cutaneous C fibers; however, it is unclear how proximal these arborizations occur (Weidner et al. 2000b). In most of the subjects, the blockade of the flare was complete, suggesting there are too few of these proximally branching units to produce a neurogenic vasodilation beyond the anesthetic strip.

Excitation of mechano-insensitive C nociceptors has been linked to induction of central sensitization (LaMotte et al. 1991; Schmelz et al. 2000b). Taking into account the high electrical thresholds of these fibers, high-intensity electrical stimulation has been successfully used to provoke stable areas of secondary mechanical hyperalgesia (punctate hyperalgesia and allodynia) (Koppert et al. 2001). The spatial extent of this hyperalgesia is comparable to the one observed after the injection of 100 µg capsaicin (Simone et al. 1989b). In our study, areas of allodynia and punctate hyperalgesia developed symmetrically on both sides of the stimulation electrode and were not blocked by the anesthetic strip. Even under the condition of a complete block of the axon reflex flare, we did observe symmetrical development of punctate hyperalgesia and allodynia beyond the anesthetic strip. This indicates that no peripheral coupling is needed to provoke secondary mechanical hyperalgesia. This result is at variance with previous reports of capsaicin-induced mechanical hyperalgesia (LaMotte et al. 1991; Serra et al. 1998). In these studies, punctate hyperalgesia was not observed beyond the anesthetic strip. The contradictory results might be explained by either the differences between capsaicin and electrically induced hyperalgesia or between the application techniques of the block. The spatial extent of the electrically induced hyperalgesia and allodynia is equivalent to the one induced by injection of 100 µg capsaicin and therefore cannot account for the variant results. However, the two models differ in the time course of allodynic areas: in the electrical model, allodynic areas are constant, whereas in the capsaicin model, allodynia follows a similar time course as the capsaicin-induced pain (Koltzenburg et al. 1994; LaMotte et al. 1991). The extent of allodynic areas might therefore be more problematic to assess in the capsaicin model. However, capsaicin-induced punctate hyperalgesia has a prolonged time course and can be measured several hours after the injection.

Electrical current and capsaicin may also activate different sets of nociceptors. It has been shown that especially high-threshold mechanoreceptors are nonresponsive to capsaicin in rat skin (Seno and Dray 1993). However, capsaicin-induced punctate hyperalgesia has been shown to cross an anesthetic strip, which was applied by dermal microdialysis (Schmelz et al. 1999). Thus the controversial results might be attributed to the mode of application of the lidocaine strip (injection vs. microdialysis). Although the spread of substances applied via intradermal microdialysis is restricted to the immediate vicinity of the probe (Weidner et al. 2000a), repeated intracutaneous injections might cause some uncontrolled spread of the anesthetic and thereby interfere with the psychophysical test for mechanical hyperalgesia.

The areas of punctate hyperalgesia and allodynia were slightly smaller beyond the anesthetic strip. We did not test for the intensity of the hyperalgesia, thus we cannot exclude a reduction by the anesthetic strip. Our data are therefore not at variance with a block of some widely branched chemonociceptors, which pass the anesthetic strip before heading centrally. As proposed by LaMotte, this mechanism would result in less noxious inputs to the spinal cord from the skin area beyond the anesthetic strip; this could lead to less pronounced hyperalgesia in this area as proposed before (LaMotte et al. 1991). However, the arborization of the unblocked chemonociceptors is wide enough to compensate for the decreased input, at least as far as the spatial extent of the hyperalgesia and allodynia is concerned.

Although we could not confirm the hypothesis that widely branched chemonociceptors would not only initiate neurogenic inflammation but also be sensitized in this process (Serra et al. 1998), our results substantiate the crucial role of this class of nociceptors in both processes: the induction of neurogenic inflammation in the periphery and in the induction of hyperalgesia in the spinal cord. Our data therefore add to the prevailing view of a central mechanism of secondary mechanical hyperalgesia (Koltzenburg 2000).

In this study, we observed a rapid decrease in allodynia after electrical stimulation was switched off. After ~4 min, allodynia was not detected on either side of the lidocaine strip, whereas punctate hyperalgesia had a more prolonged time course. The maintenance of allodynia requires ongoing noxious input to the spinal cord (Koltzenburg et al. 1992, 1994; LaMotte et al. 1991). The magnitude, duration, and area of allodynia are closely related to the magnitude and duration of ongoing pain after capsaicin injection (Simone et al. 1989b), although allodynia can be observed for some time after the spontaneous pain has subsided. Ongoing activity in mechano-insensitive C nociceptors after capsaicin injection has been proposed to generate this noxious input (Schmelz et al. 2000b). The capsaicin-induced allodynia has been reported to last for 2 h (LaMotte et al. 1991) after capsaicin injection with the area decreasing rapidly after the capsaicin-induced pain has subsided. Capsaicin-induced activity in mechano-insensitive chemonociceptors can be recorded for prolonged periods after the injection (Ringkamp et al. 2001; Schmelz et al. 2000b), exceeding the period in which pain is perceived. Thus the time course of nociceptor activity rather than the time course of pain sensation matches the time course of allodynia. In our model of electrically evoked allodynia and hyperalgesia, termination of the electrical stimulation will instantaneously stop the noxious input to the spinal cord and thereby facilitate the studies of the time course for resolving hyperalgesia. The rapid decline in
alldynia and the prolonged time course of punctate hyperalgesia observed in this study confirm the view that ongoing input from nociceptors is required to maintain alldynia, whereas punctate hyperalgesia does not depend on it.

In conclusion, this study confirms the peripheral origin of the axon reflex and provides strong evidence to the central origin of secondary mechanical hyperalgesia without peripheral coupling.

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REFERENCES


Lewis T, Harris KE, and Grant RT. Observations relating to the influence of the cutaneous nerves on various reactions of the cutaneous vessels. Heart 14: 1–17, 1927.


