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Low-dose Lidocaine Suppresses Experimentally Induced Hyperalgesia in Humans

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Background: **The antinociceptive effects of systemically administered local anesthetics have been shown in various conditions, such as neuralgia, polyneuropathy, fibromyalgia, and postoperative pain. The objective of the study was to identify the peripheral mechanisms of action of low-dose local anesthetics in a model of experimental pain.**

Methods: **In a first experimental trial, participants (n = 12) received lidocaine systemically (a bolus injection of 2 mg/kg in 10 min followed by an intravenous infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ for another 50 min). In a second trial, modified intravenous regional anesthesia was administered to exclude possible central analgesic effects. In one arm, patients received an infusion of 40 ml lidocaine, 0.05%; in their other arm, 40 ml NaCl, 0.9%, served as a control. In both trials, calibrated tonic and phasic mechanical and chemical (histamine) stimuli were applied to determine differentially the impairment of tactile and nociceptive perception.**

Results: **Mechanical sensitivity to touch, phasic mechanical stimuli of noxious intensity, and heat pain thresholds remained unchanged after systemic and regional application of the anesthetic. In contrast, histamine-induced itch (intravenous regional anesthesia), axon reflex flare (systemic treatment), and development of acute mechanical hyperalgesia during tonic pressure (12 N; 2 min) of an interdigital web was significantly suppressed after both treatments.**

Conclusions: **Increasing painfulness during sustained pinching has been attributed to excitation and simultaneous sensitization of particular Aδ- and C-nociceptors. This hyperalgesic mechanism seems to be particularly sensitive to low concentrations of lidocaine. These findings confirm clinical experience with lidocaine in pain states dominated by hyperalgesia. (Key words: Bier block; histamine; itch; wind up.)**

SYSTEMICALLY administered local anesthetics have been shown to alleviate chronic pain states such as neuralgia, polyneuropathy, fibromyalgia, and postoperative pain in most[1–8] but not all studies.[9–11] In contrast, in acute experimental pain models such as a tourniquet, heat and cold pain thresholds were unchanged after low-dose lidocaine.[12,13] Interestingly, systemic lidocaine also decreased capsaicin-induced axon reflex flare without a change in sensory thresholds.[14] In the current study, we tried to locate the site of action of a low concentration of lidocaine by comparing the antihyperalgesic effects of intravenous administration and administration in a modified intravenous regional anesthesia (IVRA, Bier block) with placebo treatment (saline). The effectiveness of lidocaine was tested in two models of mechanical hyperalgesia. In addition, touch sensitivity, thermal pain thresholds, and neurogenic inflammation induced by histamine iontophoresis were evaluated. As a central model of mechanical hyperalgesia, the "wind-up" phenomenon was induced by applying trains of impact stimuli that are perceived as increasingly painful by the participants.[15] As a peripheral model of hyperalgesia, tonic pinching of skin folds over periods of 2 min was performed. This stimulus is experienced as increasingly painful by the participants and also sensitizes the pinched skin site to subsequent tonic pressure stimuli.[16,17]

According to clinical observations that low-dose lidocaine preferentially alleviates pain states dominated by hyperalgesia, we wanted to evaluate the effectiveness of low concentrations of lidocaine in acute experimental models of hyperalgesia. In addition, use of an IVRA that prevents systemic spread of the lidocaine should allow the peripheral effects of the anesthetic to be studied.

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Materials and Methods

The study was designed to be randomized and double blinded. Twelve healthy, right-handed subjects (6 women, 6 men; mean age, 33.4 yr; age range, 27–48 yr) participated in two experimental trials 1 month apart. Each volunteer gave informed consent to take part in the study; the experimental protocol was approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nuremberg.

Stimulation Procedures

Touch Perception. Calibrated von Frey filaments (Stoelting, Chicago, IL) were used to determine detection thresholds at the medial aspect of the central volar forearm. Participants were instructed to close their eyes and report when they felt a touch sensation. Filaments exerting increasing bending forces were applied five times each for 1 s until the participant correctly sensed at least three of five trials.

Heat Stimulus. Heat stimuli were delivered from a halogen lamp (beam diameter, 1 cm) controlled by feedback from a thermocouple attached to the skin.[18] A skin site 5 cm proximal to the wrist on the central volar forearm was marked, and temperature was increased from 32°C at a rate of 0.66°C/s until the participants stopped the stimulus at the pain threshold. The values of each two stimulus repetitions were averaged.

Pinch Stimulus. The mechanical stimulator for pinching has been described previously.[16] The interdigital webs between the second and third fingers were squeezed at a force of 12 N for periods of 2 min (probe diameter, 6 mm). This stimulus is experienced as increasingly painful and also sensitizes the pinched skin site to subsequent tonic pressure stimuli.[16,17] Because conventional mechanoheat-sensitive C fibers adapt to this kind of stimulus, the origin of the hyperalgesia remained unclear.[19] In recent microneurography studies, mechanoinsensitive "silent" C-nociceptors were found to be recruited during the tonic pressure stimulus[20] and thus could account, at least in part, for increasing painfulness of this stimulus.

During each stimulus, the volunteers were asked to rate the painfulness at 15-s intervals. A rating of 100 should be assigned to stimuli of pain threshold intensity. Volunteers were instructed to rate the perceived intensity of the sensation to other stimuli in proportion to this modulus, whereby 200 would indicate an intensity of sensation that was twice as intense as a pain threshold stimulus. They were asked to estimate the intensity of nonpainful or "prepain" sensations by giving proportionate values less than 100.[21,22]

Mechanical Impact Stimulus. Impact stimuli were delivered by perpendicularly shooting a small plastic cylinder (0.5 g, 4-mm diameter) against the skin of the central volar forearm 10 cm proximal from the wrist using a pressurized air-driven stimulator.[23] A rapid sequence of three subsequent impact stimuli (1 Hz) was applied at a velocity of 14 m/s, and participants were asked to give pain ratings for each stimulus (using the same rating scale as described before). The trains of impact stimuli are perceived as increasingly painful. The origin of this type of mechanical hyperalgesia has been located in the spinal cord, and it is responsive to the N-methyl-D-aspartate receptor channel blocker ketamine.[15,24] Nociceptors readily discharge at stimulus intensities of less than one half the impact velocity used in this study, and pain thresholds were expected at the speed of the bullet of about 10 m/s.[22]

Histamine Iontophoresis. Histamine iontophoresis was used to evaluate itch ratings and neurogenic inflammation on the volar side of the central forearm. Histamine dihydrochloride (Sigma Chemical, Deisenhofen, Germany) was dissolved in distilled water to a 1% (wt/vol) solution. A piece of cotton wool, soaked in the histamine solution, was placed in an acrylic applicator with a diameter of 1.5 mm and a volume of 20 μl. A positive current of 1 mA (A 360 R-B; WPI, New Haven, CT) was applied for 20 s *via* a silver-silver chloride electrode in this applicator with the indifferent electrode (3 × 3 cm) attached 10 cm distal to the stimulus site, as described previously.[25]

Itch ratings were given at 15-s intervals following acoustic signals by moving a lever controlling a display of a visual analog scale. The end points of the scale were defined as "no itch" (0) and "maximum itch" (10). Visual analog scale values were recorded on-line using a personal computer *via* an interface card (DAP; Microstar Bellevue, WA) for 10 min after the end of iontophoresis and were stored for further analysis.

Video Flare Analysis. Images of the respective skin areas were recorded using an RGB camera (Cohu 8312; Cohu, San Diego, CA). The three-color frames (red, green, and blue) of a 10- × 10-cm skin area were digitized in true color by a framegrabber (Oculus TCX2; Coreco, St. Laurent, Canada) every 15 s.

Off-line analysis was performed to detect the border of the reddening, and thus to determine the size of the flare reaction. This analysis was performed for each image of a sequence by using dedicated computer software. De-

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tails of data acquisition and analysis are described in another publication.[26]

Thermography. An AGEMA (Danderyd, Sweden) camera system was used for thermography. The thermograms of the stimulated sites of the forearm were scanned and processed by an OS9 computer every 15 s using GESOTEK software (Darmstadt, Germany). The raw data were stored on a hard disk. The thermographic flare size, mean temperature increase, and time course of warming were analyzed off-line using dedicated software.[27]

Experimental Protocol

All participants were familiar with the stimulation procedures to be used in the study.

Systemic Lidocaine. The participants received an intravenous bolus injection of lidocaine (2 mg/kg in 10 min) followed by an intravenous infusion at 2 $mg \cdot kg^{-1} \cdot h^{-1}$ for another 50 min. As a placebo, the participants received an infusion of saline in an equal manner. Both randomized sessions were performed within a 1-week interval. The volunteers were monitored by electrocardiography, pulse oximetry, and noninvasive blood pressure recordings during and for as long as 2 h after the experiment.

Heat pain thresholds and pain ratings to impact stimuli were measured at the predefined skin sites before infusion of lidocaine or saline at baseline. Test sites were spaced by at least 5 cm to avoid sensitization. The first pinch stimulus was delivered immediately after completing the bolus injection of lidocaine (t = 10 min), followed by two subsequent pinch stimuli at intervals of 20 min. After each pinch stimulus, heat and impact stimuli were applied. Between the second (t = 30 min) and third pinch stimuli (t = 50 min), histamine iontophoresis was performed on the central volar forearm.

Thermographic images of the forearm were recorded before infusion, immediately after infusion and, as described already, for a period of 10 min after histamine iontophoresis. Venous blood samples were taken from a vein of the noninfused arm after completing the protocol (t = 58–60 min). Plasma was stored at −72°C for later analysis. Lidocaine levels were analyzed with a validated high-pressure liquid chromatography method using a C 18 reversed-phase column (Machery Nagel, Düren, Germany). The mobile phase was 30% methanol and 70% water, containing 2 g sodium acetate (pH 3). Detection was performed at 220 nm with a Waters 484 ultraviolet detector (Waters, Milford, MA). Plasma samples were extracted with C 18 solid-phase extraction columns (ict, Bad Homburg, Germany) using etidocaine as the internal standard. The columns were rinsed twice with methanol and buffer (20 ml of 1 M Na_2CO_3 in 200 ml water). One milliliter of plasma, together with the internal standard, was added to the column and rinsed twice with buffer. Elution of lidocaine was performed with 200 μl methanol. The method was linear up to 10,000 ng/ml with a recovery rate more than 90%.

Regional Lidocaine. To exclude possible central effects of lidocaine, a second trial was performed using intravenous regional anesthesia (IVRA, Bier block). Double-cuff tourniquets were placed around both upper arms. Intravenous cannulae (22 gauge) were placed in a vein of the dorsum of the hand. The arms were elevated and Esmarch bandages were applied to exsanguinate the arms. The cuffs were then inflated to 250 mmHg and kept at that pressure while the Esmarch bandages were unwound. In a randomized manner, either 40 ml lidocaine, 0.05%, or saline were injected. Ten minutes later, pinch stimuli were applied on both sides, followed by determination of heat pain thresholds and application of impact stimuli, as described before. Histamine iontophoresis was performed at the end of this protocol (20–22 min after inflating the tourniquets) at both central volar forearms. Because of absent blood circulation in this trial, no thermographic images and flare areas were evaluated. Ten minutes after termination of iontophoresis, the experimenter was unblinded and opened the tourniquet of the arm that received vehicle infusion. Venous blood samples were taken from this arm 2 min after the tourniquet was opened to determine systemic lidocaine levels. Ischemia lasted 28–30 min.

After ischemia of approximately 30 min Aβ and Aδ fibers are blocked, which can be verified by absent electrically evoked sensory potentials[28] or psychophysically by absent touch and cold sensation,[29] whereas the functions of unmyelinated fibers remain unaffected (acoustically evoked sympathetic skin response,[28] warmth, and second pain[29]). In pilot experiments (n = 3), touch-evoked sensation and subjective muscle function began to deteriorate after 20–25 min of ischemia, whereas heat pain thresholds were unchanged for more than 30 min. Paralysis and increasing discomfort, which could influence psychophysic measurements, led us to limit the duration of ischemia to 30 min.

Statistical Analysis

Pain and itch ratings and videographic flare sizes were evaluated using analysis of variance (ANOVA) in a two-way within-subjects (subsequent measures) model.

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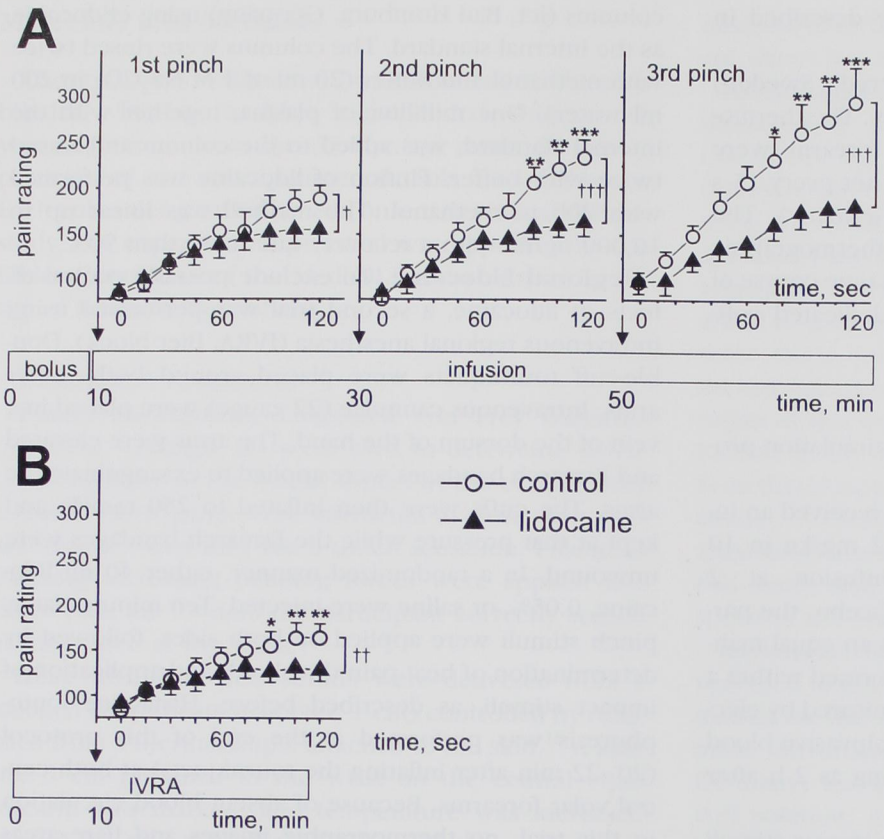

Fig. 1. (*A*) During control conditions, pinch stimuli led to increasing pain ratings during one stimulus (by analysis of variance [ANOVA]; $P < 0.001$) and increasing pain rating with repetitions (ANOVA; $P < 0.001$). Systemic administration of lidocaine significantly attenuates inflammatory hyperalgesia during each single pinching stimulus when compared with placebo (†$P < 0.05$, ††$P < 0.001$, †††$P <$ 0. 001 for the first, second, and third stimulation, respectively; treatment × time effect; by ANOVA). Scheffé's *post hoc* tests revealed significant differences in pain ratings during the last 30 s of the second stimulus and during the last 45 s of the third stimulus (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; by ANOVA and Scheffé's *post hoc* tests). (*B*) Administration of lidocaine in the intravenous regional anesthesia (IVRA) setting significantly attenuated mechanical hyperalgesia during the first pinch stimulus (‡$P < 0.01$, for the first stimulation; treatment × time effect; by ANOVA). Scheffé's *post hoc* tests revealed significant differences between pain ratings in the last 30 s of the stimulus (*$P < 0.05$, **$P < 0.01$; by ANOVA and Scheffé's *post hoc* tests). Because of the limited time of ischemia, only one pinching stimulus could be applied in the IVRA setting.

Planned comparison and Scheffé's *post hoc* tests were performed when suitable. The data of thermographic evaluation were analyzed using the Student's paired *t* test.

Significance levels throughout this study were $P < 0.05$; all data were expressed as the mean ± SD, except the pain ratings, which are presented, nonnormalized, as the mean ± SEM. The STATISTICA software package (Statsoft, Tulsa, OK) was used for statistical analyses.

Results

Systemic Lidocaine

During bolus injection (10 min), nine volunteers reported light-headedness, drowsiness, tinnitus, or all of these, especially after lidocaine treatment, but in three instances also after the placebo. During infusion of lidocaine, five volunteers felt tired. After finishing the study, they were asked to identify the session in which they received the drug. Six volunteers gave a correct answer, three gave an incorrect answer, and four could not make a decision.

Mean plasma levels of lidocaine were 3,468 ± 983 ng/ml. No significant correlations were found between lidocaine plasma levels and gender, age, weight, or pain ratings. In addition, no significant gender differences were found in pain ratings, pain thresholds, or antihyperalgesic effects. Touch perception as measured by von Frey filament detection threshold remained unchanged after infusion of either saline or lidocaine.

Pinch Stimulus. Tonic pinch stimuli of interdigital webs were described as being "increasingly painful" during control conditions. Pain ratings increased during each stimulus and with subsequent repetitions, reflecting the development of hyperalgesia (fig. 1A). After administration of lidocaine, however, the increase of pain ratings during each stimulus ($P < 0.05$, $P < 0.001$, $P <$ 0.001 for the first, second, and third stimuli, respectively; treatment × time effect; by ANOVA) and the development of hyperalgesia with subsequent stimuli ($P < 0.001$; by ANOVA, treatment × repetition effect) was significantly reduced (fig. 1A).

Heat Pain Thresholds. Heat pain thresholds were 44.4 ± 2.7°C and 45.5 ± 3.8°C (control and lidocaine)

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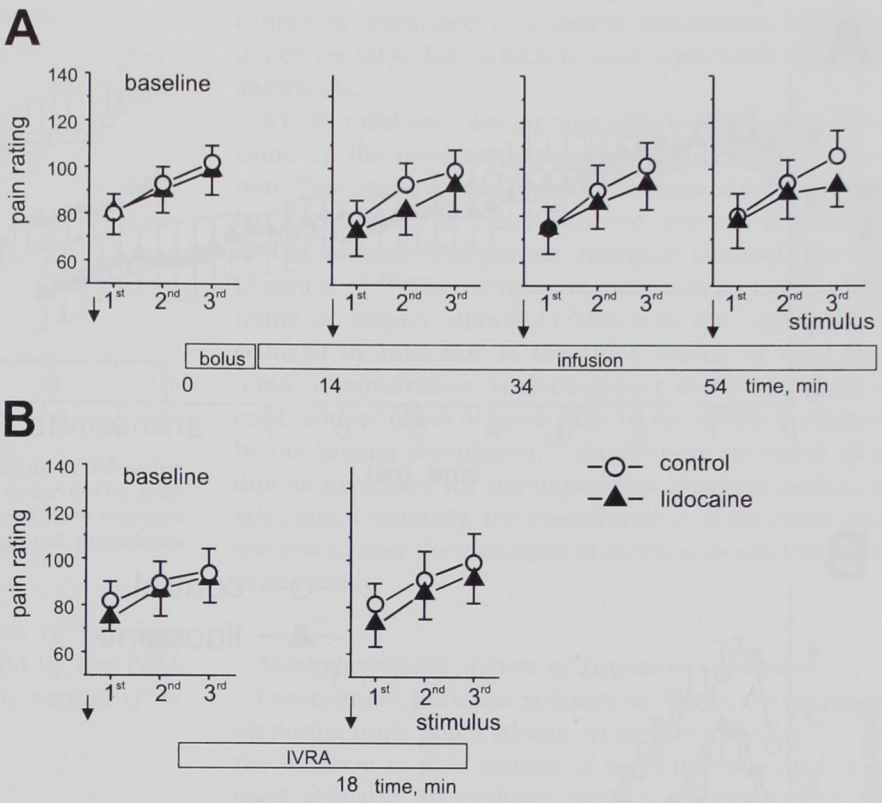

Fig. 2. (*A*) Pain ratings induced by trains of three subsequent-impact stimuli (1 Hz) are shown for systemic lidocaine (triangles) and placebo treatment (circles). The trains were applied at baseline (*left*) and 14, 34, and 54 min (arrows) after the start of systemic lidocaine treatment. Pain ratings were not affected by sytemic administration of lidocaine (by analysis of variance; differences not significant). (*B*) Pain ratings induced by trains of three subsequent-impact stimuli (1 Hz) are shown for lidocaine treatment in the intravenous regional anesthesia setting with lidocaine (triangles) or saline (circles). The trains were applied at baseline and 18 min after inflating the tourniquets (arrows on time scale).

during baseline conditions. After intravenous infusion of saline (44.6 ± 1.7°C, 44.1 ± 2.1°C, and 44.3 ± 2.7°C; at t = 14, 24, and 34 min, respectively) or low-dose lidocaine (45.4 ± 3.1°C, 46.1 ± 2.4°C, and 45.6 ± 3.1°C; at t = 14, 24, and 34 min, respectively), the thresholds did not change significantly.

Impact Stimuli. The participants reported that the trains of three phasic mechanical stimuli (14 m/s; 1 Hz) were increasingly painful (80 ± 8, 93 ± 7, and 102 ± 7 for the first, second, and third stimuli, respectively (fig. 2A). Pain ratings remained nearly unchanged after intravenous infusion of saline (80 ± 10, 94 ± 10, and 105 ± 11 at 54 min) or lidocaine (78 ±11 , 90 ± 11, and 93 ± 9 at 54 min).

Histamine Iontophoresis. Iontophoretic application of histamine induced the well-known wheal-and-flare reaction and concomitant itch sensations.

The levels and time courses of itch ratings in both treatment groups showed no significant differences (fig. 3A). Itching started within 30 s after discontinuation of the iontophoresis, reaching peak ratings after approximately 1 min, followed by a slow decrease during the remaining observation period.

The increment of the visible flare was significantly slower during lidocaine treatment (fig. 4). The final flare size, determined 10 min after histamine iontophoresis, was significantly smaller in lidocaine-treated participants compared with saline treatment (6.75 ± 5.7 cm^2 *vs.* 10.74 ± 6.7 cm^2; $P < 0.05$; by ANOVA, planned comparison).

In contrast, the maximum temperature and maximum temperature increase, time course of temperature increase, and size of thermographic flare were not affected by the medication (by Student's *t* test; difference not significant).

Regional Lidocaine

Ten minutes after inflation of the tourniquets and administration of saline or lidocaine, pinch stimulation was performed, followed by measurements of heat pain thresholds (t = 15 min), impact stimulation (t = 18 min), and histamine iontophoresis (t = 20 min). Blood samples were taken from the saline-treated arm 2 min after the tourniquet on the control arm only was deflated (t = 28–30 min). No detectable lidocaine levels were found in these samples, indicating that the tourniquet on the lidocaine-treated arm was effective to prevent systemic spread. None of the participants reported any side effects after the tourniquet on the lidocaine-treated arm was released.

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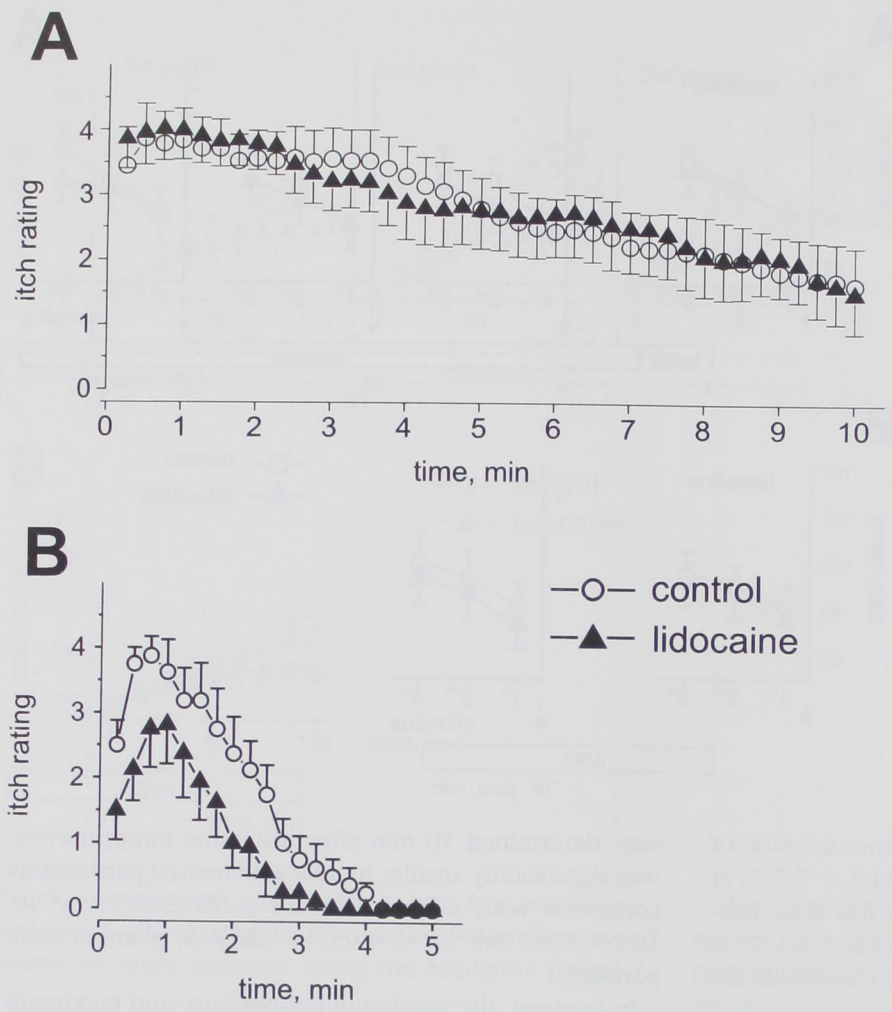

Fig. 3. (*A*) Itch ratings (visual analog scale from 0 = "no itch" to 10 = "maximum itch") induced by iontophoretic application of histamine (20 s, 1 mA) were not affected by systemic lidocaine treatment (by analysis of variance [ANOVA]; differences not significant). (*B*) Regional lidocaine significantly decreased the histamine-induced itch ($P < 0.05$; treatment × time effect; by ANOVA). However, regardless of the lidocaine treatment, itch ratings were also reduced by the intravenous regional anesthesia itself when compared with the systemic setting ($P < 0.001$; by ANOVA).

Pinch Stimuli. Pain ratings during IVRA were significantly reduced during the first pinch stimulus ($P \times 0.01$, for the first stimulation; treatment × time effect; by ANOVA). Scheffé *post hoc* tests revealed significant differences between pain ratings in the last 30 s of the stimulus ($P < 0.05$; by ANOVA, Scheffé *post hoc* tests; fig. 1B). No significant differences in pain ratings were observed between the IVRA setting and systemic application (by ANOVA; differences not significant). In the IVRA setting, only one pinch stimulus could be applied because of the limited time of ischemia.

Heat Stimuli. The heat pain threshold decreased slightly from a baseline value of 44.8 ± 4.5°C to 44.7 ± 4.5°C in the saline-treated arm and to 43.7 ± 5.5°C in the lidocaine-treated arm 16 min after the onset of IVRA. No significant difference was observed between the saline- and lidocaine-treated arm (by ANOVA; differences not significant).

Impact Stimuli. Trains of three phasic mechanical stimuli (14 m/s; 1 Hz) induced increasing pain ratings during control conditions (81 ± 9, 89 ± 9, and 93 ± 10 for the first, second, and third stimuli, respectively) and with lidocaine (76 ± 7, 87 ± 12, and 92 ± 11 for the first, second, and third stimuli, respectively). Pain ratings remained nearly unchanged after intravenous administration of saline (81 ± 9, 92 ± 11, and 99 ± 12; t = 18 min) or lidocaine (74 ± 11, 87 ± 12, and 92 ± 11; t = 18 min; fig. 2B).

Histamine Iontophoresis. Histamine-induced itch was short lasting during IVRA conditions (fig. 3B). Approximately 4 min after iontophoresis, no detectable itch sensations were observed. Peak itch ratings were significantly lower after regional administration of lidocaine (2.8 ± 1.7 *vs.* 3.9 ± 0.8, $P < 0.05$; by ANOVA, planned comparison), and the time course of itch sensations differed significantly ($P < 0.05$; treatment × time

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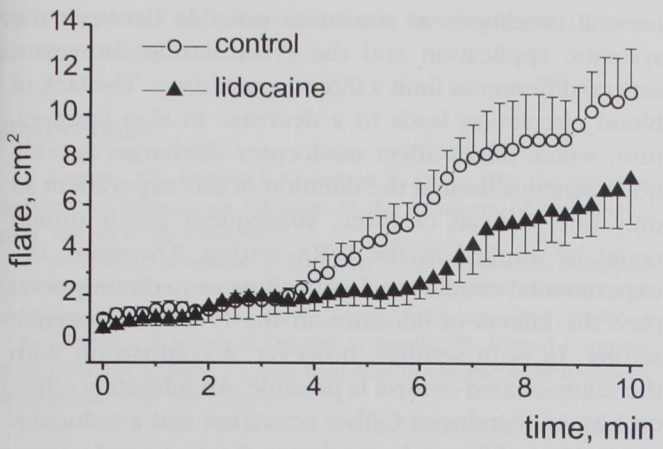

Fig. 4. Flare sizes after systemic administration of lidocaine were significantly diminished compared with controls (by analysis of variance; $P < 0.001$). Histamine-induced flare reaction could not be studied in the intravenous regional anesthesia setting because there was no perfusion.

effect; by ANOVA). However, regardless of lidocaine treatment, itch ratings were also reduced by the IVRA itself when compared with the systemic setting ($P < 0.001$; by ANOVA).

Discussion

Analgesic versus *Antihyperalgesic Effects of Low-dose Lidocaine*

In accordance with previous studies,[14] lidocaine in a low concentration of 2 or 3 μg/ml (serum concentration) did not alter touch sensitivity, thermal pain thresholds, or mechanically evoked pain sensations. Lidocaine levels in our studies corresponded to those found during clinical administration. Levels between 1 and 5 μg/ml were described, and severe neurotoxicity (convulsion, unconsciousness) can be assumed above a level of 10 to 15 μg/ml. Sedative effects cannot be ruled out completely in a concentration range of approximately 3 μg/ml; however, unchanged heat pain thresholds and ratings of mechanical impact do not confirm a relevant effect in the systemic setting. A reliable estimate of lidocaine concentration during IVRA could not be given because of absent blood circulation after exsanguination. Considering the distribution volume of the exsanguinated arm, we chose the greater amount of 20 mg lidocaine in 40 ml saline, in accordance with the amount used for systemic administration. No impairment of perception to touch and temperature was observed because of low-dose lidocaine. Therefore, the results of the study cannot be attributed to a simple conduction block induced by lidocaine, which is used commonly for local anesthesia.

We also did not observe any effect of low-dose lidocaine on the mechanically induced wind-up phenomenon. The origin of this type of mechanical hyperalgesia has been located in the spinal cord, and it is responsive to the N-methyl-D-aspartate receptor channel blocker ketamine.[15,24] The increase in pain ratings induced by trains of impact stimuli (1 Hz) was not significantly reduced by lidocaine in the IVRA setting or after systemic administration. High-frequency discharge of afferent C and Aδ fibers of more than 10 Hz, which is elicited by our impact stimulation,[22] should have provided conditions necessary for use-dependent blocking action of lidocaine. Obviously, the concentration of lidocaine was too low to alter the measures of mechanosensitivity used in our study.

Antihyperalgesic Action of Low-dose Lidocaine

Interestingly, lidocaine reduced mechanical hyperalgesia during tonic pinch stimuli. In previous studies,[16,17,30] the increase in pain ratings of repetitive pinching was used primarily to evaluate antihyperalgesic effects of antiinflammatory analgesics. In our study, the pressure was increased from 8 to 12 N, which resulted in a more pronounced increase in pain ratings also during one stimulus. This was of particular importance in the IVRA setting in which only one pinch stimulus could be applied. During a tonic pinch stimulus, mechanosensitive afferent fibers adapt to the stimulus.[19] Conversely, mechano*in*sensitive C-fibers in humans, which do not respond to short-lasting mechanical stimuli, were found to be recruited and increasingly activated during the pinch stimulus.[20] The discharge in these mechanoinsensitive C-nociceptors paralleled the pain ratings of the participants. A characteristic property of the mechanoinsensitive fibers in addition to low conduction velocity is pronounced activity-induced hyperpolarization,[31] which could make them more susceptible to the lidocaine effect. Interestingly, lidocaine also has inhibited capsaicin-induced flare and secondary hyperalgesia.[14] Again, mechano*in*sensitive C-[20] and Aδ-nociceptors[32] provide ongoing discharge after capsaicin injection, which could explain the lasting pain sensation that our participants felt. Mechanosensitive "polymodal" units, however, only respond with a "shriek" of activation lasting for a few seconds after the injection and remain desensitized at the injection site thereafter.[33]

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Antipruritic Effects of Low-dose Lidocaine

Lidocaine inhibited itch sensations in the IVRA setting and reduced histamine-induced flare size after systemic application. These observations correspond with the antipruritic effect of low-dose lidocaine reported in patients with the acquired immunodeficiency syndrome who had intractable itching.[34] In a recent article,[35] the "itch receptor" was reported to be found among the mechano*in*sensitive C-nociceptors. A subgroup of mechanoinsensitive C-nociceptors gave a sustained response to histamine application that paralleled the itch sensation of humans.[35] Again, this subgroup was characterized by extremely low conduction velocities of approximately 0.5 m/s, which would confirm the hypothesis that low-dose lidocaine preferentially suppresses activity in mechanoinsensitive C-nociceptors.

In contrast to observations during the flare response, no effects on itch sensations were observed during systemic lidocaine treatment. This could be explained by different lidocaine concentrations at the nociceptor. In the IVRA setting, shorter-lasting itch sensations were observed. Because of absent perfusion, temperature in the exsanguinated arm decreases. Lower temperatures, however, counteract itch and flare reactions to histamine[36] and thus could explain the difference in itch rating between the intravenous regional anesthesia setting and systemic treatment. In addition, painful stimuli were reported to decrease the intensity and duration of histamine-induced itch, whereas injection of histamine in an anesthetic bleb resulted in more intense and prolonged itch sensation.§‖ In this respect, the pain arising from the tourniquet could counteract itch sensation and contribute to a shorter duration in the IVRA setting.

Systemic versus *Peripheral Effects of Low-dose Lidocaine*

In this study, we administered lidocaine either systemically or in a modified IVRA model, which excludes central mechanisms of action. In accordance with the findings of Heavner *et al.*,[37] touch sensitivity and thermal and mechanical pain sensations were unchanged for at least 20 min of ischemia. Care was taken to keep experimental conditions as similar as possible between the systemic application and the IVRA setting. However, several differences limit a direct comparison. The lack of blood circulation leads to a decrease in skin temperature, which might affect nociceptor discharge; in addition, ischemia limited the duration of this experiment so only one, instead of three, subsequent pinch stimuli could be applied in the IVRA setting. Therefore, the experimental conditions do not allow us to directly compare the effects of lidocaine in the IVRA and systemic setting. In both settings, however, a comparison with the saline-treated control is possible. An inhibiting effect on histamine-induced C-fiber activation and a reduction of mechanical hyperalgesia during the first pinch stimulus could be shown in the IVRA setting. Thus, we conclude that there is a peripheral antihyperalgesic and antipruritic effect of a low concentration of lidocaine. The reduction of pinch-induced hyperalgesia was more obvious after systemic application, presumably because three repetitions could be performed.

A spinal action of low-dose lidocaine has been proposed for decreasing pain in patients with fibromyalgia.[38] But the mechanisms of peripheral and spinal action do not necessarily have to be different. Assuming that the spinal ramifications of primary afferents have similar properties as their peripheral counterparts, an axonal mode of action could also affect the spinal terminals. The problem of conduction blockade at spinal branching points has been discussed by Wall[39] for long-range myelinated afferents in the rat. It is at least conceivable that low concentrations of lidocaine similarly affect mechanoinsensitive nociceptors at their peripheral and spinal arborization.

Our study provided indirect evidence that low-dose lidocaine also acts peripherally on the mechano*in*sensitive C-nociceptors and thus decreases mechanical hyperalgesia and histamine-induced itch. Conventional "polymodal" mechanoheat-sensitive nociceptors remain unaffected, and therefore heat pain thresholds and mechanical pain sensations are unchanged. However, this hypothesis needs further confirmation from electrophysiologic studies. Pilot microneurography experiments in collaboration with Torebjörk's group in Uppsala gave promising results, showing that low-dose lidocaine increases the drop-out rate to electrical stimulation only in mechano*in*sensitive units (Schmelz M, Schmidt R, Koppert W, Handwerker HO, Torebjörk HE, unpublished results). The differential sensitivity of mechanosensitive and mechnoinsensitive C-nociceptors thus could pro-

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vide the basis for pharmacologic development of new antihyperalgesic drugs.

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