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On the Mechanism by Which Epinephrine Potentiates Lidocaine's Peripheral Nerve Block

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Background: **Adding epinephrine to lidocaine solutions for peripheral nerve block potentiates and prolongs the action, but by incompletely understood mechanisms. In an effort to discriminate the pharmacokinetic from the pharmacodynamic effects of epinephrine, the authors measured the lidocaine content of peripheral nerve over the course of block produced by 0.5% lidocaine, with and without epinephrine, and correlated it with the degree of analgesia.**

Methods: **Percutaneous sciatic nerve blocks were performed in 18 groups of rats (10 in each) with 0.1 ml of either 0.5% lidocaine or 0.5% lidocaine with epinephrine (1:100,000). Over the full course of nerve block, the authors regularly measured analgesia to toe pinch and then rapidly removed nerves to assay intraneural lidocaine content at 2–120 min after injection.**

Results: **The kinetics of lidocaine's clearance from nerve was composed of a fast-decaying transient superimposed on a very slowly decaying component. The effect of epinephrine on the intraneural lidocaine content was to increase the amount of lidocaine in the slow-decaying component by threefold to fourfold, although the total neural content was not altered by epinephrine for the first 10 min after injection. Epinephrine prolonged blockade by almost fourfold and enhanced the intensity of peak analgesia, as well as the fraction of rats with complete block, almost throughout the 2–120-min period of behavioral observation.**

Conclusions: **Adding epinephrine to lidocaine solutions increases the intensity and duration of sciatic nerve block in the rat. The early increase in intensity is not matched with an increase in intraneural lidocaine content at these early times, although the prolonged duration of block by epinephrine appears to correspond to an enlarged lidocaine content in nerve at later times, as if a very slowly emptying "effector compartment" received a larger share of the dose. The increase in early analgesia without increased lidocaine content may be explained by a pharmacodynamic action of epinephrine that transiently enhances lidocaine's potency, but also by a pharmacokinetic effect that alters the distribution of the same net content of lidocaine within the nerve.**

DURING peripheral nerve block with lidocaine, vasomotor effects often result in diverse changes in local blood flow.[1] The actions of lidocaine on sciatic nerve blood flow are primarily vasoconstrictive but are concentration-dependent. Little reduction in nerve blood flow occurs when 0.5% of this local anesthetic (LA) is dripped directly onto the nerve,[2] but reductions are apparent when 1% or 2% are thus applied.[2,3] In contrast to nerve, the isolated surrounding muscle has a biphasic vascular (arteriole) response to lidocaine, with vasoconstriction occurring in 0.1% drug and vasodilation at 1%.[4] When LA is injected percutaneously for nerve block, the diverse actions on the muscle and nerve vascular beds surrounding and within the nerve, respectively, may result in a net decrease or increase in the local circulation that removes drug from the neural site of action. Furthermore, the initial blood flow change may itself be reversed over time as the effective LA concentration naturally decreases as a result of the local redistribution into the different tissues and removal by the circulation.[5]

Anesthesiologists often add epinephrine to lidocaine during peripheral nerve block procedures.[6,7] The advantage of this practice is twofold. First, it reduces the LA plasma concentration and thus minimizes the possibility of systemic toxicity,[8] and second, it improves the quality and prolongs the duration of peripheral nerve block.[7,9,10] Most anesthesiologists accept the idea that epinephrine mediates this prolongation of LA action by its vasoconstrictive actions.[5] By stimulating α-adrenergic receptors on the neural vasculature,[11] epinephrine mediates contraction of the vascular smooth muscle,[12,13] reduces local blood flow, and thereby slows clearance of lidocaine from the nerve. It appears that epinephrine binds to those adrenergic receptors located on the extrinsic plexus of vessels in the epineural space.[11] These vessels then cross the perineurium and anastomose with the intrinsic circulation in the peripheral nerves,[3] which is responsible for the direct clearance of the LA from within the nerve, the "effector compartment" for neural blockade.

An increase in the duration of LA block by epinephrine is accompanied by a potentiation of effect at submaximal LA doses.[14] This could result from pharmacokinetic factors that ultimately increase the intraneural LA concentration in the effector compartment and thus effectively potentiate impulse blockade. However, such potentiation may also occur by pharmacodynamic actions of epinephrine on nerve membranes. Adrenoreceptor activation may affect various factors that regulate excitability, such as K^+ channels,[15] Cl^- channels, or the Na^+–K^+ pump.[16] The selective α_2-agonist clonidine alters clinical peripheral nerve block by lidocaine differently than epinephrine does, suggesting that more than a single type of receptor is being modulated by these agents.[17,18]

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To discriminate between these two mechanisms, we correlated measures of intraneural lidocaine with assays of analgesia. To do this, we performed percutaneous sciatic nerve blocks in rats with 0.5% lidocaine HCl, radiolabeled with [^{14}C], with and without epinephrine (1:100,000). We chose this relatively low concentration of lidocaine, which alone does not produce complete impairment of nociception, to resolve differences in the intensity as well as the duration of block and so that any vasoactive effects of lidocaine would be small and not obscure those of epinephrine. For similar reasons, we chose 1:100,000 epinephrine, twice the usual concentration coinjected with LA, to produce a greater vasoconstriction and to overcome any vasodilator actions of lidocaine.[1,4] Sciatic nerves were excised from early (2 min) to late (2 h) times after injection to monitor the full kinetics of lidocaine's onset and recovery (uptake and washout). Just before nerves were dissected, the intensity of sensory block was assessed by the withdrawal response to a strong forceps pinch to the fifth metatarsal. The general objective was to compare and correlate intraneural lidocaine content with the intensity of block and to determine if epinephrine modified that relation.

Materials and Methods

Animals

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY) weighing 250–350 g were housed in the Brigham and Women's Hospital animal facilities under a 12-h light–dark cycle. All behavioral testing and surgical procedures were approved by the Harvard Medical Area Committee on Animals.

Preparation of [^{14}C] Radiolabeled 0.5% Lidocaine Solutions

Two solutions of [^{14}C] radiolabeled lidocaine, both at 0.5% and pH = 7.8, were prepared from crystalline lidocaine HCl: (1) 0.5% lidocaine HCl alkalinized with NaOH (pH = 7.8). Fifty milligrams of lidocaine HCl powder (Sigma Chemical, St. Louis, MO) was dissolved in 10 ml sterile water; [^{14}C] lidocaine HCl (0.1 mCi/ml ethanol; New England Nuclear, Boston, MA) was added to the solution at a 1:100 dilution to achieve a final radioactivity of 5×10^{-3} mCi/ml; (2) 0.5% lidocaine HCl with epinephrine (1:100,000). Ten milliliters of 0.5% lidocaine HCl was prepared by dissolving 50 mg lidocaine HCl powder in sterile water. Epinephrine HCl solution (1:100), prepared by dissolving epinephrine HCl crystal (Sigma Chemical) in sterile water, was further diluted in the lidocaine solutions to a final epinephrine concentration of 1:100,000. The pH of all lidocaine solutions was adjusted to pH 7.8 ($\pm$ 0.05) with 30 μl (1:333) of 2N NaOH (Fisher Scientific, Pittsburgh, PA) at room temperature in a slowly stirred solution to minimize vortex-induced dissolution of carbon dioxide. These solutions were made slightly alkaline (pH 7.8) so that the results could ultimately be compared with previously published data on the actions of bicarbonate buffer on lidocaine's block,[19] wherein the pH reached 7.8 after bicarbonate was added to commercial lidocaine (1:10, vol:vol). Lidocaine is stable for several hours at pH 7.8 and 22°C, as judged by spectrophotometry.

Since the objective of this investigation was to correlate the degree of analgesia with intraneural lidocaine content using solutions of lidocaine alone and lidocaine containing epinephrine (LE), it is important to mention the results of a previous study performed in our laboratory. The injection of epinephrine alone at a concentration of 1:100,000 in the rat sciatic nerve produced no impairment of nocifensive function for 60 min.[19]

Preparation of Nonradiolabeled 0.5% Lidocaine Solutions

Two solutions of 0.5% lidocaine HCl, one with epinephrine (1:100,000) and one without, were prepared according to the same method as that described above for [^{14}C] radiolabeled solutions except that nonradiolabeled crystalline lidocaine HCl (Sigma Chemical) was used. These two solutions were injected into two cohorts of rats (n = 10 in each) to determine the effect of epinephrine on the duration of lidocaine's peripheral nerve block.

Injection of [^{14}C] Radiolabeled and Nonradiolabeled 0.5% Lidocaine Solutions

The injection technique used in this study was the same used previously to produce motor and sensory block of the sciatic nerve in the rat.[19–21] Brief general anesthesia was induced by placing the rat's muzzle in a beaker containing a cotton ball saturated with Ultane® sevoflurane (Abbott Laboratories, North Chicago, IL) until the corneal reflex disappeared (15–20 s), at which time the general anesthetic was removed. At this point, 100 μl of one of the two radiolabeled lidocaine solutions was injected at the sciatic notch with a 27-gauge needle; 16 groups of rats, each with n = 10, received a percutaneous injection of either the lidocaine-alone or the LE radiolabeled solution, described above. Full recovery of behavior occurred within 90–120 s after removal of sevoflurane anesthesia in rats receiving no LA.

Evaluation of Intensity and Duration of Nerve Block

Before the nerves were excised for analysis of neural content, the lateral toe of the hind limb on the injected side was pinched strongly (until bone resistance was felt) with serrated forceps (#11003–12; Fine Science Tools, Foster City, CA). This was done to directly correlate the intensity of nerve block with intraneural lido-

caine content in individual animals used for the uptake studies. In separate experiments conducted to account for any general anesthetic effects on the subsequent analgesia, we periodically monitored the course of functional deficits in rats from which no nerves were removed. These animals, handled and familiarized according to our standard procedures,[20] were never anesthetized by sevoflurane.

To assess the intensity of nerve block, we used a modification of the neurologic evaluation described by Thalhammer *et al.*[20] Nociception was scored by grading the rat's withdrawal response to a "deep pinch" (see above) on an ordinal scale of 0 to 4. A score of 4 was assigned for a "normal" reaction characterized by a (1) brisk, strong paw withdrawal, (2) vocalization, and (3) an attempt to bite the forceps; a score of 3 for (1) a slower, weaker withdrawal response, (2) vocalization, and (3) no attempt to bite forceps; a score of 2 for (1) an even slower withdrawal response, (2) no vocalization, and (3) no biting of forceps; a score of 1 for a very weak attempt to withdraw; and, finally, a score of 0 was given when the rat showed none of these responses. Previous reports showed that motor block of the sciatic nerve could not account for withdrawal response deficits, proving that true nociceptive loss was being tested.[20] The degree of analgesia was expressed as the mean value for the deep pinch response ± SD, but these scores were compared between groups using nonparametric statistics on the total population response (see below). In addition, the percent of animals in each group that were fully blocked (score of 0) was assessed, and differences between this parameter in epinephrine-containing and epinephrine-free groups were compared for identical times after injection

The duration of block, which was assessed using the two groups of rats receiving injection of the nonradiolabeled lidocaine solution, was defined as the time until the response returned to a value of 3 (75% of normal) after injection.

Nerve Dissection and Measurement of Lidocaine Uptake

After injection of a radiolabeled lidocaine solution, the sciatic nerve was excised at one of eight time points: 2, 4, 7, 10, 15, 30, 60, and 120 min. Animals were killed by deep inhalation anesthesia with a cotton ball saturated with sevoflurane. The sciatic nerve was then dissected in less than 3 min in a modification of the technique described by Popitz *et al.*[21] The portion of the sciatic nerve removed was located between the region 10 mm proximal to the sciatic notch and the popliteal fossa. The excised portion of the sciatic nerve was frozen in less than 5 s on a flat surface of dry ice and cut into six segments, 5 mm long. Each segment of nerve was weighed on an analytical balance (± 0.5 mg; Mettler AE 100; Highstown, NJ) and digested at 50°C for 2 h in a mixture of 0.5 ml of tissue solubilizer (Solvable®; Packard Chemical Operations, The Netherlands) and 0.1 ml distilled water. Five milliliters of Aquasol®-2 (Du Pont New England Nuclear, Boston, MA) scintillation cocktail was added, and the radioactivity was determined by liquid scintillation counting. The specific radioactivity was determined by dividing the counts per minute for each injectate by the moles of lidocaine in the solution. Background was subtracted using the counts per minute from a mixture of 500 μl of tissue solubilizer, 100 μl distilled water, and 5 ml scintillation cocktail. The measured radioactivity represented the amount of intraneural lidocaine, expressed as nanomoles of lidocaine per milligram wet weight of nerve. The total lidocaine content in the nerve was determined by summing the lidocaine content of each of the six segments of nerve; minimal radioactivity in the proximal and distal segments confirmed that 90% or greater of the intraneural lidocaine was counted.

Pharmacokinetic Analysis

We used a decaying exponential function to describe the clearance of lidocaine from peripheral nerve, both with and without epinephrine. Because the large coefficient of variation of experimental data would accommodate fits of other mathematical functions, we chose the simplest one on the principle of parsimony. The kinetics of intraneural lidocaine content (L) beginning at the time of peak content (t = 4 min) and ending at t = 60 min were fit using Origin® software (version 5.1; Origin Inc., Northhampton, MA) to the following exponential:

$$L = L_f \times \exp(-k \times (t - 4)) + L_s$$

Parameter L_f describes the amplitude of the fast-decaying component, k represents a transport rate coefficient for the rapid removal phase (washout from nerve), and L_s represents the amplitude of the steady state (plateau) component, which eventually decays to the baseline value; t is the time after the injection. By fitting this equation to the intraneural lidocaine content data points, we were able to determine how epinephrine affected the three parameters, L_f, k, and L_s.

Statistical Analysis

Intensity and duration of block were reported as the mean withdrawal response score and the mean time (± SD), respectively, while intraneural lidocaine content was reported as the mean content value (± SD), in nanomoles per milligram wet weight of nerve. Standard deviations were only reported as an indication of the spread of observations but were not used in the statistical analysis. Intensity and duration of block and intraneural LA content with plain lidocaine *versus* LE were compared using the nonparametric Mann–Whitney U rank sum test (SPSS® Software; SPSS Inc., Chicago, IL), and the criterion for significance was $P < 0.05$. The

percentage of animals fully blocked was compared between groups at each time point using the Fisher exact test (Statview® Software; SAS Institute Inc., Cary, NC). All behavioral data for each condition were collected from one group for each time point (taken for neural content just before animals were killed), so no adjustment was necessary for repeated measures. The parameters of the function used to fit a curve to the intraneural lidocaine data points, k, L_s, and L_f are given by the curve-fitting software (Origin® v. 5.1) as means ± SE and tested for significance using the Student paired *t* test.

Results

Analgesia

Addition of epinephrine enhanced sciatic nerve blockade by lidocaine. The degree of analgesia obtained with epinephrine was significantly greater than that without epinephrine throughout almost the entire procedure (fig. 1A). The percent of animals fully blocked by lidocaine was almost always greater in the LE group, the single exception occurring at 7 min after injection, the time of maximum block for rats without epinephrine (fig. 1B). Indeed, at 4 min after the LA injection, all the rats receiving LE were completely blocked, whereas none of the rats receiving lidocaine alone were completely blocked. Complete block by LE (occurring in all rats) lasted for 1 h, and complete recovery was achieved after 2 h, whereas, in the fewer rats that were completely blocked by lidocaine alone, that block lasted for about 10 min and fully recovered by 30 min (fig. 1B).

Total Intraneural Lidocaine Content

Injection of the LE solution produced generally higher total intraneural drug content compared with the solution without epinephrine (fig. 2). For the first 10 min after injection, this difference did not reach significance (because of, at least in part, the large variances), but at 15, 30, and 60 min, differences in intraneural lidocaine content were significant. At 15 min, the intraneural lidocaine content was 3.1 ± 1.4 nmol/mg(wet) without epinephrine *versus* 7.4 ± 1.2 nmol/mg(wet) with epinephrine ($P = 0.0003$); at 30 min, it was 2.2 ± 0.9 *versus* 6.5 ± 2.7 nmol/mg(wet) ($P = 0.0037$); at 60 min, values were 1.7 ± 0.6 *versus* 6.4 ± 2.4 nmol/mg(wet) ($P = 0.0002$); and at 120 min, values were 0.4 ± 0.2 *versus* 2.0 ± 3.3 nmol/mg(wet) ($P = 0.069$). The ratio of mean lidocaine content for injections of LE to that of lidocaine alone was 1.3–1.6 for the early times (2–10 min) after injection ($P > 0.05$), but then grew progressively from 2.4 to 5.2 for nerves taken from 15 to 120 min, respectively, after injection. Therefore, the effect of epinephrine on content grew stronger at longer times after injection, primarily because of the decay in lidocaine content in epinephrine-free nerves over this period.

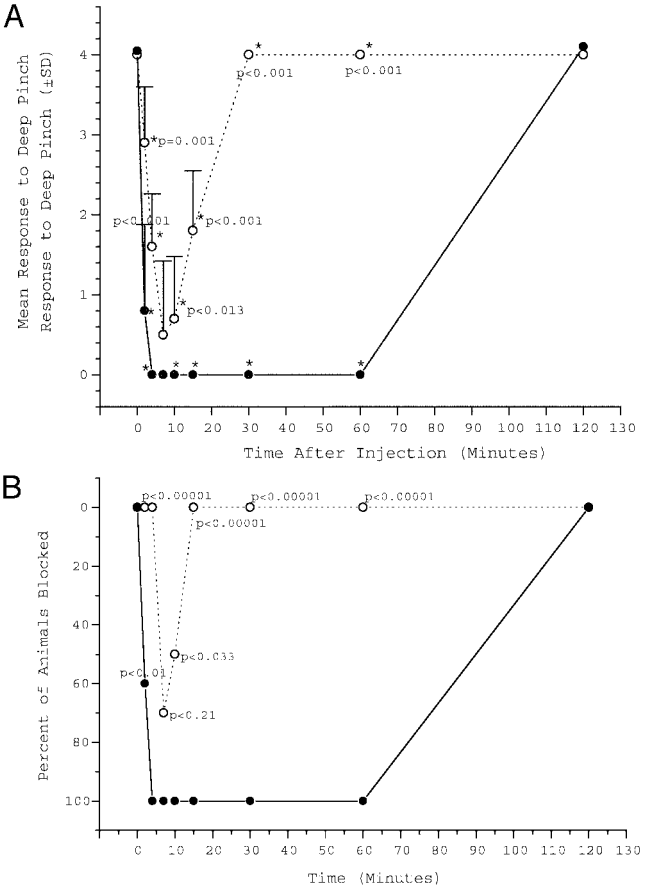

Fig. 1. (*A*) Time course of analgesia (measured by the response to a deep forceps pinch of the fifth metatarsal) after injection of 0.5% plain lidocaine (open circles) or 0.5% lidocaine with epinephrine (1:100,000; filled circles). n = 10 at each time point. (*B*) Time course of percent animals completely blocked (measured by response to deep pinch of fifth metatarsal) after injection of 0.5% plain lidocaine (open circles) or 0.5% lidocaine with epinephrine (1:100,000; filled circles). n = 10 at each time point.

Pharmacokinetic Analysis

The intraneural content of lidocaine over time can be described by an early, transient washout phase whose rapid disappearance is followed by a constant plateau phase, which eventually decreases to zero over 1–2 h (fig. 2). These kinetics can be fit from 4 to 60 min by a fast exponentially decaying function, with rate constant k, superimposed on a constant level, with respective amplitudes L_f and L_s (see Methods). Fits of this function to the data show that the transient decay rate constant, k, was almost twofold greater with epinephrine than without (0.30 ± 0.04 min^{-1} *vs.* 0.15 ± 0.02 min^{-1}; $P < 0.025$), although the choice of an exponential fitting function was arbitrary, and the "rate constants" are unlikely to differ importantly. The amplitude of the fast transient, L_f, *i.e.*, the intraneural lidocaine content that was rapidly cleared (assuming a constant plateau starting at 4 min), was not altered by epinephrine (7.86 ± 0.47 *vs.* 8.68 ± 0.54; $P > 0.05$), whereas the amplitude of the plateau, L_s, was about fourfold greater with epinephrine

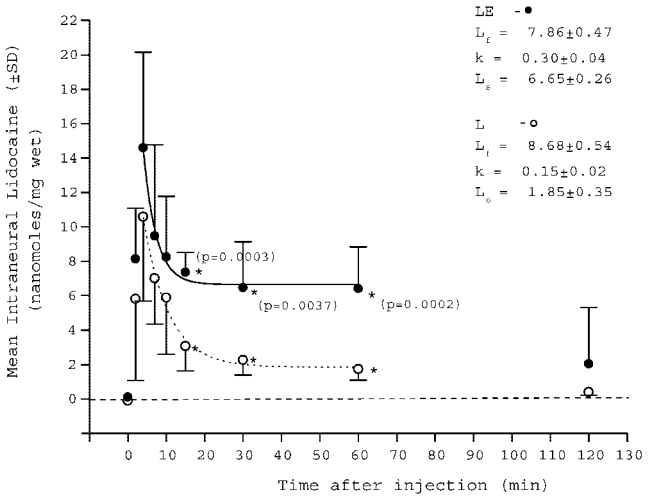

Fig. 2. Time course of total intraneural lidocaine content (nanomoles per milligram wet weight of nerve) after injection of 0.5% plain lidocaine (L; open circles) or 0.5% lidocaine with epinephrine (LE; 1:100,000; filled circles); n = 10 at each time point. The solid and dashed lines are fits to the separate data sets from 4 to 60 min using the equation, $L = L_f \times \exp(-k\,(t - 4)) + L_s$. Parameters of the fit are shown on the figure. k = transport rate coefficient for the rapid removal phase (washout from nerve); L_f = amplitude of the fast-decaying component; L_s = amplitude of the steady state (plateau) component, which eventually decays to the baseline value.

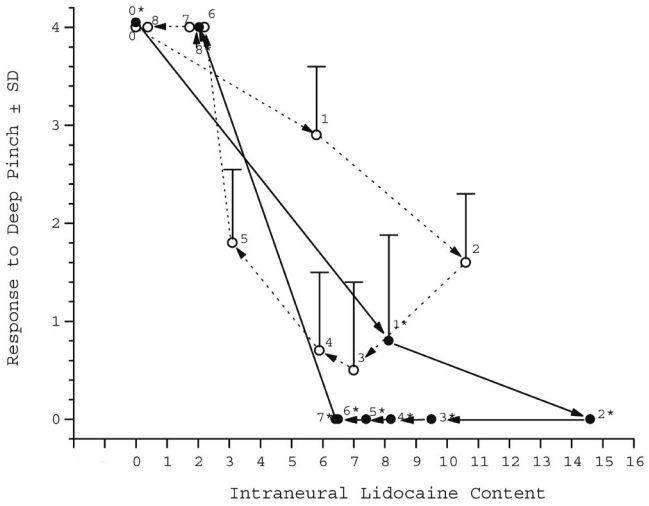

Fig. 3. Intensity of analgesia (measured by the response to deep pinch) *versus* intraneural lidocaine content after injection of 0.5% plain lidocaine (open circles) and 0.5% lidocaine with epinephrine (1:100,000). Data replotted from figures 1A and 2.

than without (6.65 ± 0.26 *vs.* 1.85 ± 0.35; $P < 0.005$). We emphasize the empirical basis for this fitting and the arbitrary assumption of a constant content for the plateau from 4 min onward.

Analgesia as a Function of Intraneural Lidocaine Content

The relation between the degree of analgesia and the intraneural content for different conditions is illustrated in figure 3. The points are numbered in their temporal order during the block, *i.e.*, data points 1, 2, and 3 correspond, respectively, to times 2, 4, and 7 min after injection, with data for block by lidocaine alone connected by the dashed line and those for LE connected by the solid line. Two conclusions are apparent: (1) different degrees of analgesia result from the same intraneural lidocaine content for each condition. For example, with lidocaine alone, a content of about 6 ng/mg(wet) is reached during both onset (point 1, 2 min) and regression (point 4, 10 min), but analgesia is not the same at these times, whether scored by graded responses (fig. 1A) or as percent of animals fully blocked (0 and 50%, respectively; fig. 1B); (2) different degrees of analgesia accompany the same intraneural lidocaine content when comparing blocks from lidocaine alone with those from LE. For example, point 2 for lidocaine alone (4 min) and point 3 for LE (7 min) both correspond to intraneural lidocaine of 9–10 ng/mg(wet), but analgesia with lidocaine alone at 4 min scores 1.5 (with 0% of animals fully blocked), while that from LE at 7 min scores 0 (with 100% of animals fully blocked). Clearly, there is no strict dependence of block on neural lidocaine content under varying conditions of time or adjuvant agent.

The threshold content for complete recovery from functional deficit (score > 3) occurs at 2 or 3 nmol/mg (wet) of nerve for block by lidocaine alone (points #5 and #6) and probably occurs at about the same level for block by LE, although the recovery course from the latter solution was far more variable, and only the final recovery at 120 min is known (points #7 and #8).

Effect of Sevoflurane on Behavior and Content

Comparison of functional nerve block in naive rats injected with lidocaine (during sevoflurane anesthesia), as in the above Results, with nerve block in handled rats (injected without general anesthesia, see Methods) showed no behavioral difference. The maximum degree of analgesia, the duration of analgesia, and the onset of regression times were not affected by general anesthesia for block by lidocaine alone or by LE.

Discussion

The results of this investigation in the rat are consistent with clinical anesthesiology; epinephrine enhances the degree and extends the duration of lidocaine's peripheral nerve block.[6,9,10] In addition, the findings reveal several aspects of the temporal changes in distribution of intraneural lidocaine. First, adding epinephrine to lidocaine solutions does not significantly increase the amount of intraneural lidocaine at the time of peak content (4 min after injection), corresponding to the onset of analgesia. Second, the lidocaine content at later times is relatively constant (10–60 min) and is four times

greater with epinephrine than without. In addition, we found that equal intraneural lidocaine concentrations—obtained at different times with both LA solutions—are associated with unequal degrees of analgesia.

These results can be explained by a consideration of the cross-sectional anatomy of the peripheral nerve and the different responses to epinephrine of vascular beds in and around the nerve. We propose a simplified two-compartment model to explain epinephrine's effect on intraneural lidocaine distribution during peripheral nerve block in the rat. The first compartment is composed of the combined superficial tissues of the nerve, the fat, the epineurial connective tissue, and the blood vessels surrounding the sciatic nerve, taken along with the nerve during our dissection procedure. The second compartment is the perineurial space containing the endoneurium, the connective tissue, and the nerve fibers,[22,23] the "effector compartment" wherein LAs produce impulse blockade and analgesia.

The response of vascular beds to epinephrine differs in different regions inside and outside the nerve. Vascular smooth muscle contains three adrenoreceptor types: α_1, α_2, and β_2 receptors.[24] Epinephrine binding to α_1 and α_2 receptors causes vessel constriction, whereas epinephrine binding to β_2 receptors causes vasodilatation.[12] Both lidocaine and epinephrine cause vasodilation of the skeletal muscle vasculature, the latter through β_2 receptors. The dynamic changes in blood flow after nerve block result from the combination of the kinetics of drug diffusion and the differential vascular responses. Specifically, percutaneously injected epinephrine will reach and vasoconstrict the vessels in the superficial epineurial space first, and then penetrate into the nerve and the muscle. We hypothesize that the initial vasoconstriction of epineurial compartment vessels retards the rapid removal of lidocaine and allows more LA to enter the deeper perineurial compartment early in the block. Simultaneous redistribution of the injected bolus into the surrounding skeletal muscle accounts for rapid removal of lidocaine from the superficial epineurial compartment and the fast-decaying transient. The lidocaine that enters the perineurial compartment is removed very slowly, however, primarily because of its lipophilic adsorption to the membrane-dense myelin, but also because this compartment's blood flow is reduced through its anastomoses with the endoneurial vessel, which are directly constricted by epinephrine. Accordingly, we equate the intraneural lidocaine content of the plateau phase to LA in the perineurial effector compartment. Epinephrine is cleared from the nerve in 1–2 h (see below), vascular flow returns to normal (or greater, in response to local reactive hyperemia), and lidocaine removal from the perineurial compartment is accelerated (fig. 2).

Similar general findings on lidocaine were reported by Fink *et al.*,[25] who injected 0.2 ml of a 1% lidocaine solution into the more distal extremity of the rat infraorbital nerve. They found that lidocaine content peaked at 1–10 min after injection but decayed more slowly, decreasing by half after 30 min and requiring 1–2 h to disappear completely. The infraorbital nerve tunnels through the bony canal of the maxilla rather than being surrounded by a large mass of muscle, as is the sciatic nerve, so the slower clearance is not unexpected. Epinephrine (1:200,000) extended the block in this model such that at 2 h after injection, 6 of 10 rats injected with lidocaine alone responded to pinch, whereas all 10 rats injected with LE remained unresponsive. At this time, the corresponding lidocaine concentrations in the nerve were increased 5–10-fold by epinephrine.

Previous publications report the vasoconstrictive actions of epinephrine and of lidocaine in peripheral nerve. Partridge[2] measured the effects of direct neural application of lidocaine and epinephrine on nerve blood flow in rat sciatic nerve using laser Doppler flowmetry. Epinephrine 1:100,000 reduced nerve blood flow by 35% from the control, while changes in nerve blood flow with 0.5% lidocaine produced no change in nerve blood flow. Myers and Heckman,[3] also using the laser Doppler technique, showed that epinephrine at 1:200,000 by itself significantly reduced rat sciatic nerve blood flow and reduced nerve blood flow even more when added to a 1% lidocaine solution that was itself vasoconstrictive. In a microdialysis study in humans, Bernards and Kopacz[7] showed that epinephrine 1:400,000 prolonged the action of 1% lidocaine during superficial peroneal nerve block, apparently by decreasing local blood flow (again assessed by laser Doppler). Thus, both lidocaine and epinephrine lower the blood flow around peripheral nerve.

One difficulty in analyzing the complex actions of LAs plus epinephrine on block dynamics is the interactive relations among the components. Through vasoconstriction, lidocaine limits its own as well as epinephrine's removal, and *vice versa*. While the acute vasoconstrictive action of epinephrine has been measured, its prolonged effects are not known. Partridge[2] detected a dose-dependent reduction in sciatic nerve blood flow for up to 60 min after application of epinephrine or lidocaine, but his measurements stopped there. Fink *et al.*[16] measured the ^{3}H content, which they equated with radio-labeled epinephrine, of the infraorbital nerve during block by lidocaine plus this vasoconstrictor (1:200,000) and found the same kinetics for the two drugs. One interpretation of this result is that both compounds are slowly cleared (2 h half-time) from this bony compartment, although the local biotransformation of epinephrine by tissue enzymes will not be detected by this radioassay, and the lifetime of the true drug is not known. However, the extension of infraorbital lidocaine block by epinephrine could be obtunded by phentolamine, an antagonist of α_1 and α_2 adrenoreceptors, whether coinjected with the vasoconstrictor and LA or

administered at the same locus 1 h later. This result proves that the reversible actions from agonist binding to the receptor are necessary for the continued enhancement as late as 1 h after the infraorbital block. What vasoconstrictive actions persist in sciatic nerve during the regression of epinephrine-extended lidocaine block remain to be demonstrated.

Our investigation also showed that equivalent intraneural lidocaine content achieved with epinephrine-containing and epinephrine-free solutions did not produce similar degrees of analgesia. This discrepancy was particularly apparent during the onset of nerve block (0–10 min), when the LA concentration gradient in the nerve is greatest. We believe that it is most likely the result of a difference in the cross-sectional (radial) distribution of lidocaine in peripheral nerve resulting from vasoconstriction. Our explanation posits that adding epinephrine to lidocaine solutions slows early clearance from the superficial compartment and allows more anesthetic to reach the deeper perineurial, axon-containing compartment. We also postulate that the drug's spatial distribution becomes more uniform with time. Just as the longitudinal gradient becomes more shallow as the block regresses,[21] the radial distribution will also become more uniform, whether the injectate contained epinephrine or not. At the time of "full recovery" from analgesia, the neural content of lidocaine is about the same (2–3 nmol/mg [wet]) in nerves with lidocaine alone or with LE (fig. 3). Interestingly, a similar content of 1–2 nmol/mg (wet) was also measured by Fink *et al.*[26] at the time of recovery of infraorbital nerve block, regardless of the presence or absence of epinephrine.

We cannot, however, rule out a pharmacodynamic action for epinephrine, acting through sensory axons *per se*, particularly at the early stages of neural blockade. Impulse blockade by lidocaine, resulting directly from the blockade of Na^+ channels, has a potency that can be modified by the state (conformation) of those Na^+ channels as well as by changes in other neuronal ion channels, such at K^+ channels.[27] Certain K^+ channels are modified through adrenoreceptors,[15] and these changes could reduce the margin of safety for impulse transmission and potentiate the impulse-blocking actions of any Na^+ channel inhibitor. Changes in local metabolism secondary to vasoconstriction can also potentiate blockade. Hypoxia from reduced blood flow increases local carbon dioxide, bicarbonate, and H^+. Lidocaine is a more potent impulse blocker when carbon dioxide and bicarbonate are elevated,[28] and an increase in extracellular H^+ potentiates the use-dependent actions of LAs[29,30] that are particularly relevant in blocking high-frequency trains of impulses[31] that signal intense stimuli (such as toe pinch). Any one of these mechanisms could contribute to the potentiation of lidocaine's analgesic actions. Bicarbonate buffer enhances the inactivated state of neuronal Na^+ channels in resting membranes (Kin Wong, D.M.D., Anesthesia Research Laboratories, Brigham and Women's Hospital, Boston, MA, and Gary Strichartz, Ph.D., unpublished observation), and lidocaine binds with higher affinity to this inactivated state.[32]

In previous experiments that examined the degree of impulse blockade and the lidocaine content in rat nerves continuously superfused *in vivo* by low concentrations of drug, Huang *et al.*[32] showed that blockade of all nociceptive C-fibers required 1.0–1.4 mM lidocaine, a concentration that yielded an intraneural content of 2.5–3.5 nmol/mg (wet) after equilibration with drug in the superfusion chamber. This result is remarkably consistent with the intraneural lidocaine content we and other investigators measured at recovery after percutaneous delivery of much higher concentrations of drug (0.5% equals 18.5 mM) and suggests that the injected anesthetic has also achieved some uniform distribution within the nerve at this time. Together, these results provide a figure for the minimal blocking concentration of lidocaine in rat sciatic nerves: about 1–1.5 mM of free drug corresponding to a tissue content of 2.5–3.5 nmol/mg (wet). In addition, the approximately equal intraneural content of lidocaine at recovery from block, with epinephrine-containing and epinephrine-free solutions, implies that epinephrine has no sustained pharmacodynamic effect in this assay. This result could occur either because adrenoreceptors in nerve do not produce analgesia (as shown previously)[19] or alter LA block, or because the injected epinephrine has been removed or transformed by the time the block has regressed.

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