

# Preferential Block of Small Myelinated Sensory and Motor Fibers by Lidocaine

## In Vivo Electrophysiology in the Rat Sciatic Nerve

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**Background:** Controversy still surrounds the differential susceptibility of nerve fibers to local anesthetics and its relation to selective functional deficits. In the current study we report features of conduction blockade in different classes of rat sciatic nerve fibers after injection of lidocaine by a percutaneous procedure that closely resembles clinical applications.

**Methods:** In 30 adult male Sprague-Dawley rats (weight, 300–400 g) during general anesthesia, impulses were recorded in different classes of sensory axons (large, A $\alpha$  and  $\beta$  fibers; small, A $\delta$  myelinated fibers and unmyelinated C fibers) and motor axons (large, A $\alpha$  fibers; small, A $\gamma$  myelinated fibers) classified by conduction velocity. The sciatic nerve was stimulated distally, and impulses were recorded from small filaments teased from L4–L5 dorsal (sensory) and ventral (motor) roots sectioned acutely from the spinal cord. Lidocaine at concentration of 0.05–1% was injected percutaneously in 0.1-ml solutions at the sciatic notch. Both tonic (stimulated at 0.5 Hz) and use-dependent (stimulated at 40 Hz for A $\delta$  and A $\gamma$  fibers and at 5 Hz for C fibers) impulse inhibitions by lidocaine were assayed.

**Results:** Minimal effective (threshold) lidocaine concentrations (*i.e.*, to block conduction in 10% of fibers) were, for sensory, 0.03% for A $\delta$ , 0.07% for A $\alpha\beta$ , and 0.09–0.1% for C fibers, and for motor, 0.03% for A $\gamma$  and 0.05% for A $\alpha$  fibers. The order of fiber susceptibility, ranked by concentrations that gave peak tonic fiber blockade of 50% (IC<sub>50s</sub>), was A $\gamma$  > A $\delta$  = A $\alpha$  > A $\alpha\beta$  > C. Faster-conducting C fibers (conduction velocity > 1 m/s) were more susceptible (IC<sub>50</sub> = 0.13%) than slower ones (conduction velocity < 1 m/s; IC<sub>50</sub> = 0.30%). At 1% lidocaine, all fibers were tonically blocked. Use-dependent effects accounted for only a modest potentiation of block (at a lidocaine concentration of 0.25%) in A $\delta$  and A $\gamma$  fibers, and in C fibers phasic stimulation had even smaller effects and sometimes relieved tonic block.

**Conclusions:** Susceptibility to lidocaine does not strictly follow the “size principle” that smaller (slower) axons are always blocked first. This order of fiber blockade is qualitatively consistent with previous reports of the order of functional deficits in the rat after percutaneous lidocaine, that is, motor = proprioception > nociception, if we assume that motor deficits first

arise from conduction failure in A $\gamma$  fibers and that nociception relies on C fiber conduction.

THE differential blockade of conduction by local anesthetics in nerve fibers of different diameter was first described by Gasser and Erlanger.<sup>1</sup> They found that within the myelinated (A-group) fibers of the dog and frog, cocaine reduced the compound action potential components from slower-conducting (smaller-diameter) fibers more rapidly than those from faster-conducting (larger) fibers. This original observation has been reexamined and generally confirmed by many studies on different peripheral nerves and spinal root fibers. In different animals and for different local anesthetics, small myelinated (*e.g.*, A $\delta$ ) fibers have been found to be more susceptible to local anesthetic (LA) block than larger myelinated (A $\alpha$ , A $\beta$ ) fibers.<sup>2–7</sup> These findings led to formulation of the “size principle” of differential block, which states that susceptibility to LA depends inversely on fiber diameter. However, this size principle is not universally true. For instance, it was found that the smaller, preganglionic, myelinated B fibers in rabbit vagus nerve were less susceptible than the larger A $\beta$  fibers to local anesthetic block. Nor was this principle applicable to the whole continuum of myelinated and unmyelinated fibers.<sup>8–11</sup> Earlier reports clearly noted that the LA susceptibility of many C fibers (*e.g.*, in dorsal roots or saphenous nerve of the cat assayed *in vivo*) was comparable to or even less than that of the faster A $\delta$  fibers.<sup>5,6</sup> Recently Huang et al.<sup>12</sup>, using a perfusion cell to achieve equilibrium block by lidocaine of rat sciatic nerve *in vivo*, showed that C-fiber nociceptors were three or four times less susceptible to block than A $\delta$  nociceptors or A $\beta$  mechanoreceptors.

The characteristics of differential impulse block may vary among different peripheral nerves, among different local anesthetics, and even among different animal species (*e.g.*, frog, rat, cat, and human) (see review by Raymond and Gissen<sup>13</sup>). Differential block cannot be predicted *a priori*, certainly not on the basis of the classic size principle. Nevertheless, physiologic observations and clinical experience provide evidence that differential block of impulses in nerve fibers exists, depending on anatomic features, critical duration of drug exposure, or some other, function-related property. This belief is the basis for exploring principles and mechanisms of LA action to understand and, eventually, to produce functionally selective nerve blocks.

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Nerve block by local anesthetics presents two closely related "research" questions. One is fundamentally physiologic: What are the dynamic characteristics and mechanisms of differential impulse block *per se*? The other is more clinically relevant: How is differential inhibition of impulses related to the functional impairments that constitute an LA block in humans? *In vivo* studies are relevant for investigating both of these questions, in particular, to directly correlate the changes in electrophysiologic activity in peripheral nerve fibers with modifications of functions.

The aim of the present study was to examine the effect of different doses of lidocaine on the impulse activity of various classes of sciatic sensory and motor nerve fibers during both "tonic" and "phasic" nerve activity, using an *in vivo* model of local anesthesia with injection of LA at the "sciatic notch." This survey should provide detailed information on conduction failure in different fibers during percutaneous injection of lidocaine, the most experimentally well studied and clinically used LA and one for which there are published neurobehavioral data using the same mode of administration in rats.<sup>14</sup>

## Materials and Methods

Animal treatment and all procedures for these experiments were approved by Harvard Medical Area Standing Committee on Animals.

### Animal Preparation

Experiments were conducted on 30 adult, male Sprague-Dawley rats weighing 300–400 g (Taconic Farms, Germantown, NY). Rats were initially anesthetized with either urethane (Sigma Chemical Company, St. Louis, MO) or pentobarbital (Abbott Laboratories, North Chicago, IL) *via* intraperitoneal injection of 1.3 g/kg or 50 mg/kg, respectively. (Pentobarbital was used in earlier experiments but was supplanted by urethane, which gave a more consistent anesthetic state and produced no spontaneous firing of single units). The jugular vein was cannulated for supplemental intravenous bolus administration of general anesthetic, provided throughout the experiment using both the absence of the corneal reflex and the increase of heart rate on noxious stimulation as end points for adequate anesthesia. The heart rate was monitored with a Tektronix Model 498 EKG Monitor (Tektronix, Beaverton, OR). Core body temperature was monitored by a rectal thermometer and maintained at 35.5–37°C with a water-circulated heating pad placed under the rat. At the end of each experiment, rats were euthanized by an overdose of 100 mg/kg intravenous sodium pentobarbital.

A longitudinal skin incision was made at the posterior right hind leg, and the skin and muscle freed to expose the distal part of the sciatic nerve and its main branches:

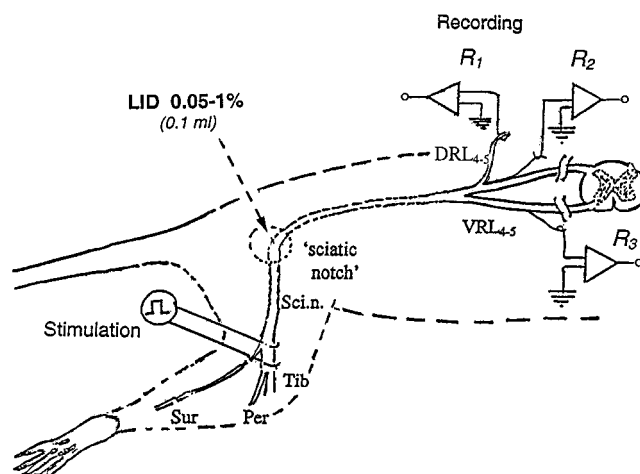


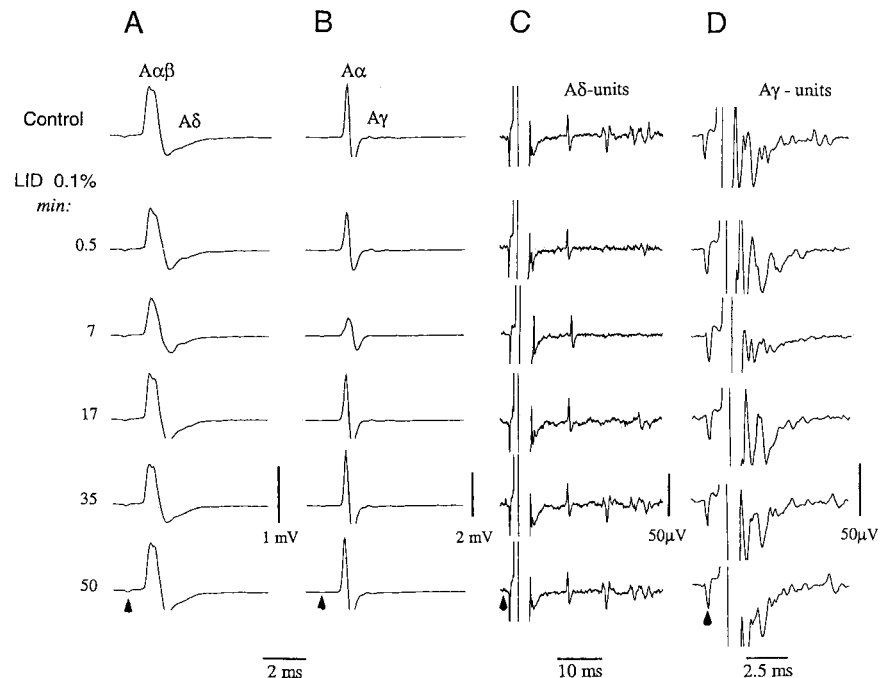
Fig. 1. Diagram of the experimental arrangement. R = recording electrodes at the fourth to fifth dorsal (DRL4–DRL5) and ventral lumbar (VRL4–VRL5) spinal root fascicles and filaments. Arrow indicates the location of percutaneous injection at "sciatic notch" area. Stimulating electrodes on sciatic nerve, tibial (Tib), sural (Sur), and common peroneal (Per) nerves. Spinal roots are transected between recording sites and their entry to the spinal cord.

posterior tibial, common peroneal, and sural nerves (fig. 1). All these nerves were transected distally and placed on stimulating electrodes. The skin at the incision was then sewn to a metal ring, which thus formed a pool to hold mineral oil covering the peripheral nerves. This right leg was fixed to a Plexiglas holder with the plantum of the foot facing upward. Laminectomy was performed between T13 and L5–L6 vertebrae to expose the caudal spinal cord with lumbar spinal roots. After putting the rats in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) to immobilize the lower spine and pelvis, a second electrode pool was similarly arranged from skin at the area of the exposed cord and spinal roots and also filled with warm mineral oil maintained at  $35.0 \pm 0.5^\circ\text{C}$  by radiant heat. During recording sessions rats were immobilized with  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  intravenous pancuronium bromide (Sigma), and the lungs were artificially ventilated at 60 respirations/min *via* a pressure-controlled respirator (Model RSP1002; Kent Scientific Corporation, Litchfield, CT). In the final five experiments, end-tidal carbon dioxide was continuously monitored (by a just-acquired CAPSTAR-100 End Tidal  $\text{CO}_2$  Analyser; IITC Inc., Woodland Hills, CA) and maintained at 4–4.5%; results from these experiments were the same as in those without carbon dioxide monitoring.

### Recording Procedures

Spinal root filaments were teased from the larger root stems and wrapped around bare silver wire electrodes. Simultaneous, unipolar recordings were made from three separate filaments, with reference electrodes placed on the surrounding tissues (*e.g.*, dorsal spine muscles). One input channel (R1) (fig. 1) recorded summary sensory activity

**Fig. 2.** Examples of impulse activity and lidocaine action after injection of 0.1% solution. (A) Block of sensory myelinated fibers. Two elevations ( $A\alpha\beta$  and  $A\delta$  waves) of the compound action potential (CAP) recorded from DRL5 during sciatic nerve stimulation (0.2 ms, 8V) before (upper trace) and during different times (listed at left) after injection of lidocaine, 0.1%. Arrowheads show stimulus artifacts. (B) CAP showing  $A\alpha$  and  $A\gamma$  elevations recorded from VRL4 filament at the same time and conditions as in A. Microfilament recordings show impulses from (C) individual  $A\delta$  fibers in DRL5 and (D) individual  $A\gamma$  fibers in VRL4 taken at the same time and conditions as in A and B. Note the differences in time scales and amplifications among the different columns. Each trace was obtained as result of waveform averaging of five to eight single successive sweeps.



(compound action potentials [CAPs]) from thick filaments of L4–L5 dorsal root (comprising one fourth to one fifth of the whole root), monitoring large myelinated fibers. A second channel (R2) recorded the activity of single sensory fibers (unitary recording) from thin filaments of the same dorsal root, and the third channel (R3) was used to record activity from moderate-sized “microfilaments” teased from the (L4–L5) ventral root. Channels R1 and R2 used model ISO-DAM8 amplifiers (WPI Company, Sarasota, FL) with low- and high-frequency cut-off filters usually set at 300 Hz and 3 kHz, respectively, whereas R3 used a differential electrometer preamplifier (Model AK47uu; MetaMetrics, Cambridge, MA) with filter corner frequency of 1–5 kHz.

Filtered signals were visualized on an oscilloscope (Tektronix) with parallel audio monitoring and recorded and stored on computer disk using the CED1401 Plus interface (Cambridge Electronics Design, Cambridge, UK) coupled to a Pentium processor-based PC. Signals were analyzed with Spike-2 software (Cambridge Electronics Design). The waveform averaging mode was used for processing small unitary signals, particularly, spikes in single C fibers whose amplitudes were often only tens of microvolts. Waveform averaging (5–10 successive traces) was also applied to CAP records to obtain faithfully the mean value of these responses and thus to increase the significance of any drug-induced changes. (Most of the records presented in this study were obtained by digital averaging of 3–10 successive waveform sweeps, the number determined by the criterion of a 5–10 signal-to-noise ratio.)

#### Stimulation

Impulses were elicited by electrical stimulation of the distal sciatic nerve or its branches at sites distal to the

injection (fig. 1). Rectangular pulses were generated by a Grass S44 stimulator (Grass Instrument Co., Braintree, MA) and delivered through bipolar silver wire electrodes, with amplitudes usually 1.5 times the threshold: 5–10 V at 0.2-ms duration for A fibers and 20–50 V at 0.5–0.75 ms for C fibers. When studying the tonic effect of lidocaine, the stimulus frequency was 0.5 Hz; during phasic assays the frequencies were increased to 5 Hz for C fibers and 40 Hz for  $A\delta$  and  $A\gamma$  fibers. The typical stimulation protocol was as follows: an initial train of 8–10 impulses at 0.5 Hz, to explore the tonic effect of lidocaine, was followed immediately by one high-frequency tetanic episode (30–40 stimuli) to evaluate phasic effects. For  $A\delta$  and  $A\gamma$  fibers we applied a different protocol: first, 4-Hz stimulation, followed by one 40-Hz tetanic train (40–50 impulses) and an immediate return to 4 Hz. These frequencies were selected from published firing rates recorded in various fibers during “natural” activation, in particular, noxious activation of C- and  $A\delta$ -fiber nociceptors.<sup>15–20</sup>

#### Stability of Preparation

Control recordings (from experiments without lidocaine application, data not shown) indicated that the magnitude of CAPs and the latency (and incidence) of spikes in single units remained stable over the span of recording sessions, 3–4 h: Changes in these response parameters did not exceed 5–8% of initial values for up to 3 h of continuous monitoring. Baseline control recordings during at least 0.5 h (5 or 6 stimulation sessions over intervals of 5 min) preceded each drug injection episode and served to verify the stability of the recording and as the normalizing control (denominator) for quantitative evaluation of the action of lidocaine.

**Table 1. Maximum Inhibition by Lidocaine in Different Fiber Classes**

Lidocaine	Large Myelinated Fibers		Sensory A $\delta$ Fibers	Motor A $\gamma$ Fibers	Sensory C Fibers
	Sensory A $\alpha$ , $\beta$ -fiber CAP (% inhibition, mean $\pm$ SD)	Motor A $\alpha$ fiber CAP (% inhibition, mean $\pm$ SD)	Percent of units blocked (blocked/total)	Percent of units blocked (blocked/total)	Percent of units blocked (blocked/total)
0.05%	-3.7 $\pm$ 4.5* (n = 3)	4.3 $\pm$ 0.7* (n = 3)	25   (6/24)	33.311 (7/21)	0   (0/13)
0.075%	ND	31 (n = 2)	ND	63.6 (14/22)	0 (0/4)
0.1%	18.0 $\pm$ 8.0† (n = 4)	38.8 $\pm$ 12.8† (n = 3)	44.4 (12/27)	68   (21/31)	14.3   (3/21)
0.175%	56.7 $\pm$ 27.5‡ (n = 3)	80.0 $\pm$ 2.8‡ (n = 2)	63.6 (7/11)	92.3   (12/13)	36.4   (4/11)
0.25%	58.9 $\pm$ 7.8§ (n = 5)	79.1 $\pm$ 17.9§ (n = 5)	74 (20/27)	95.2 (20/21)	68.2 (15/22)

Values in parentheses are number of compound action potentials (CAPs) or units recorded.

\* Not significantly different from control (experiments with PIPES buffer injections) or each other ( $P = 0.153$ , one-way analysis of variance.) † Significantly different ( $P = 0.044$ , one-way analysis of variance). ‡ Insignificantly different ( $P = 0.339$ , one-way analysis of variance.) § Significantly different ( $P = 0.049$ , one-way analysis of variance.) || Significantly different between fiber classes at the given concentration ( $P < 0.05$ , chi square from  $2 \times 2$  contingency tables): between C fibers and A $\delta$ , A $\gamma$  fibers at 0.05%; and between C fibers and A $\gamma$  fibers at 0.1% and 0.175%.

ND = not done.

### Isolation, Identification, and Classification of Fibers

The resting conduction velocity of fibers was calculated by measuring the distance from the cathodal stimulation pole to the recording electrode site on the spinal roots (varying between 68 and 85 mm) and dividing it by the resting response latency, measured as the time from stimulus artifact onset to the initial rise of the spike or CAP. Classification followed established categories from previous studies on rats.<sup>12,16-19</sup> Dorsal root fibers with conduction velocities (measured values in parentheses) greater than 20 m/s were classified as sensory A $\alpha$  and A $\beta$  fibers (maximum conduction velocity = 80 m/s); units with conduction velocities of 2.2-20 m/s (2.18-19.7 m/s) classified as A $\delta$  fibers, and fibers with conduction velocities below 2 m/s (0.64-1.97 m/s) as sensory C fibers. Compound action potentials included impulses from all the large myelinated afferent fibers, A $\beta$  mechanoreceptors, Ia muscle spindle afferents, and Ib Golgi tendon afferents, which are referred to in the present study as "A $\alpha$  $\beta$  fibers." Ventral root fibers with conduction velocities less than 32 m/s (9.4-32 m/s) were classified as A $\gamma$  motor fibers, and those with conduction velocities greater than 32 m/s as A $\alpha$  motor fibers. As mentioned previously, dorsal and ventral roots were transected between spinal cord and recording sites so that all measured impulses were conducted from the distal stimulation sites and did not originate in or pass through the spinal cord (fig. 1).

### Lidocaine Application

The experimental protocol usually included three to five successive injections of lidocaine during a single recording session lasting 3 or 4 h. Lidocaine (0.1 ml of 0.05-1% solutions at pH 6.8) was percutaneously injected at an anatomically defined region known as the

sciatic notch, with the needle's tip located 1 mm dorsal and rostral to the nerve. This location (between the greater trochanter and ischial tuberosity) has been used routinely in our laboratory for neurobehavioral and drug uptake experiments.<sup>14,21</sup> The lidocaine solutions were made *ex tempore* by adding lidocaine HCl powder (Sigma) to saline containing 150 mM NaCl with 5 mM PIPES buffer and adjusting it to a final pH of 6.8 with 0.1 N NaOH.

### Measurement of Fiber Response during Tonic and Phasic Block

In general, lidocaine-induced conduction slowing and failure was most easily and accurately determined from unit activity recordings. The tonic block of impulse conduction was assayed by the percentage of failures in fiber responses (during 0.5-Hz stimulation), starting at the first minute after injection and extending through recovery to predrug control values. The minimal interval between test stimuli was 20 s after injection, then every minute for the first 10-min period, every 2 min for the next 20-min period, and then each 2.5 or 5 min, as noted, until full recovery (50 min-2 h). As a result, the interval between two successive injections varied from approximately 60 to 90 min, thus allowing us to construct detailed time courses of the action of lidocaine action at different doses. The degree and duration of inhibition produced by a single injection of moderate or high concentrations of lidocaine, when given first, were the same as those that occurred from the same dose after previous, lower doses, showing that there was no residual action between sequential dosing.

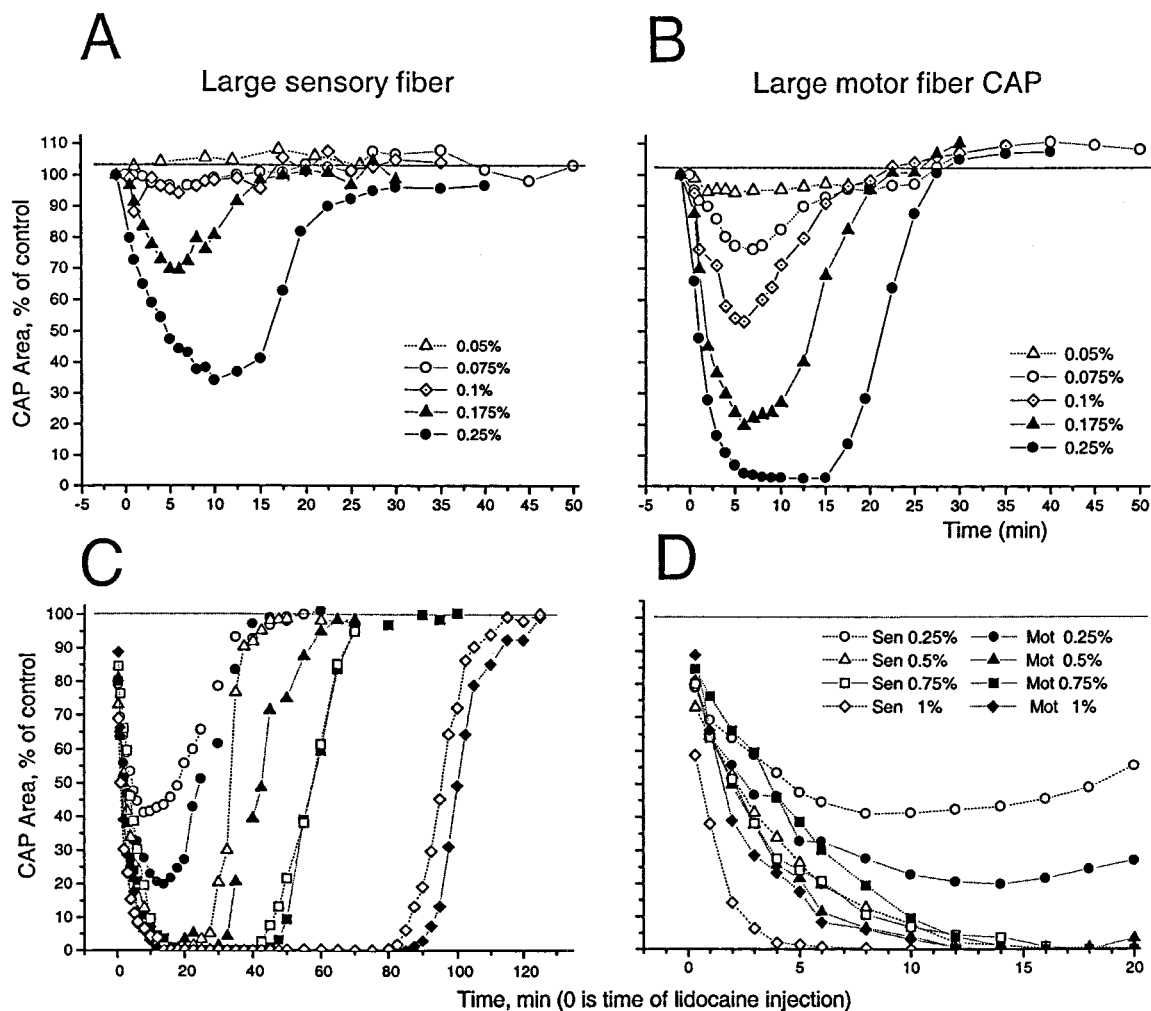


Fig. 3. Examples of the dose-dependent action of low to moderate (A and B) and moderate to high (C and D) concentrations of lidocaine on compound action potential (CAP) of large sensory and motor fibers. Time course of effects of five successive low-concentration lidocaine injections (at  $t = 0$ ) at increasing concentrations (0.05, 0.075, 0.1, 0.175, and 0.25%) on (A) the large myelinated sensory fiber CAP and (B) the large motor fiber CAP. Recordings from the several different experiments show the time course of effects of successive injections of moderate to high-concentration lidocaine (0.25, 0.5%, 0.75, and 1.0%) on sensory A $\alpha\beta$  (open symbols) and motor A $\alpha$  (closed symbols) CAPs at (C) a slow time scale to show complete recovery and (D) an expanded time scale to show the onset of block.

Blockade of large myelinated motor (A $\alpha$ ) fibers was estimated by measuring the area of under the initial, "positive" deviation of the CAP, using a special program ("Area evaluation") created in Spike-2 software script (courtesy of Daniel L. Young, M.S., Harvard-Massachusetts Institute of Technology, Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA). This area evaluation is a more accurate measurement of impulse failure than the more traditional measurement of peak amplitude of the CAP because it accounts for the dispersion of fiber activity attributable to intrinsically different conduction velocities and to differential slowing of conduction.<sup>12</sup> Blockade of large myelinated sensory (A $\alpha\beta$ ) fibers was evaluated by CAP area as well as by single-unit analysis. Means for quantifying and normalizing data are presented at the appropriate passages in the Results section.

### Statistics

The results are reported as means  $\pm$  SD, along with the number of independent observations. One-way analysis of variance was used to evaluate the difference of means of continuous variables, and chi-square values from  $2 \times 2$  contingency tables (followed by *post hoc* cell contribution evaluation) were used for the statistical analysis of the differences in the fraction of single units blocked among different groups of fibers. Both tests were conducted using StatView software (SAS Institute, Inc., Cary, NC). Statistical significance was set at  $P < 0.05$ .

## Results

### General Nature of Experiments

The dorsal root CAPs typically consisted of two main waves propagating with mean maximum conduction

**Table 2. The Course of Action of Moderate to High Lidocaine on Compound Action Potential of Large Myelinated Fibers**

Lidocaine	Sensory Fiber CAP				Motor Fiber CAP			
	Max Depression (%) <sup>*</sup>	Onset t <sub>50</sub> <sup>+</sup> (min)	Recovery t <sub>50</sub> <sup>+</sup> (min)	Total Duration of Block (min)	Max Depression (%) <sup>†</sup>	Onset t <sub>50</sub> <sup>+</sup> (min)	Recovery t <sub>50</sub> <sup>+</sup> (min)	Total Duration of Block (min)
0.25% (n = 5)	58.9 ± 3.5 <sup>†</sup>	1.7 ± 0.8	25.5 ± 2.8	35 ± 2.3	80.1 ± 8.5 <sup>†</sup>	2.5 ± 0.6	29.4 ± 3.0	39.1 ± 3.7
0.5% (n = 5)	100	2.7 ± 0.8	29.1 ± 3.7 <sup>†</sup>	45.5 ± 2.0 <sup>‡</sup>	100	2.3 ± 0.5	42.1 ± 2.6 <sup>†</sup>	54.5 ± 1.8 <sup>‡</sup>
0.75% (n = 2)	100	2.2 ± 1.3	58.1 ± 4.6	70.3 ± 5.8	100	3.6 ± 0.9	56.9 ± 5.8	68 ± 7.0
1% (n = 3)	100	1.6 ± 0.9	96 ± 3.0	106 ± 4.7	100	2.0 ± 0.6	100 ± 2.8	117 ± 4.0

<sup>\*</sup> Mean ± SD (data at 0.25% are the same as those in table 1). <sup>†</sup> and <sup>‡</sup> denote significantly different values ( $P < 0.05$ ; one-way analysis of variance) between sensory and motor compound action potentials (CAPs) at the same lidocaine concentration.

velocities of  $78.1 \pm 5.1$  m/s (large, fast wave; fig. 2A) and  $22.6 \pm 3.5$  m/s (much smaller, slower wave), the first wave reflecting activity in fast-conducting, large myelinated ( $A\alpha\beta$ ) sensory fibers and the second, activity in small myelinated sensory  $A\delta$  fibers. The ventral root CAP also consisted of two waves; the first, propagating at  $75.4 \pm 4.8$  m/s, represented activity in large myelinated,  $A\alpha$ -motor fibers, and the second, at  $25.5 \pm 3.47$  m/s, corresponded to volleys in small myelinated  $A\gamma$  motor fibers (fig. 2B). Unitary activity was studied in all classes of sensory fibers (e.g.,  $A\delta$ , shown in fig. 2C) and in  $A\gamma$  motor fibers (fig. 2D). C fibers, detectable as single units in microfilament recordings, were labeled as "fast" when conduction velocity was greater than 1 m/s and as "slow" when conduction velocity was less than 1 m/s.

Lidocaine was injected at concentrations of 0.05–1%. Data were collected in three series of experiments with one set of rats being given a sequence of lidocaine injections at "very low" (0.05–0.175%) concentrations, a second set being given a "low" (0.25%) concentration, and a third set being given a "moderate" (0.5%) concentration, wherein 63 sensory and 51 motor fibers, 68 sensory and 21 motor fibers, and 95 sensory and 15 motor fibers, respectively, were analyzed. Fewer experiments were performed to assess near-complete and total block at 0.75 and 1% lidocaine.

#### Tonic Blockade of Large Fibers

At the lowest concentration studied, 1.85 mM lidocaine, 0.05%, did not affect CAPs of large myelinated motor or sensory fibers, whereas impulses failed transiently (at 12 and 20 min) in 7 of 21  $A\gamma$  motor fibers studied. Failure was also detected in 6 of 24  $A\delta$  fibers but not in any of 13 C fibers (table 1). Injections of lidocaine, 0.075%, suppressed large motor fiber CAPs (by approximately 30%) and blocked more than half (14 of 22) of  $A\gamma$  motor fibers. The slightly more concentrated lidocaine, 0.1%, affected conduction in all classes of myelinated fibers (fig. 2 and table 1), with the CAP of large motor  $A\alpha$  fibers being blocked significantly more (39%) than that

of large sensory  $A\alpha\beta$  fibers (18%;  $P < 0.02$ ) (figs. 2A and B). The majority of  $A\gamma$ -motor fibers (21 of 31) and almost half (12 of 27) of  $A\delta$  sensory fibers (all slower units: mean conduction velocity = 7.2 m/s) were blocked at this concentration. However, only 3 of 21 C fibers (with conduction velocity = 1.61 m/s; faster group) failed to conduct at a lidocaine concentration of 0.1%, and impulses in the remaining 18 units were slowed by less than 10%.

A typical example of the time course and differential actions of lidocaine, 0.05–0.25%, on large-fiber CAPs from one experiment is presented in figures 3A and B. For these recordings, taken simultaneously from dorsal (fig. 3A) and ventral (fig. 3B) roots during the same injection, the "threshold" concentration for block (defined by the dose for inhibition  $\geq 10\%$ ) is lower for the motor than for the sensory CAP (0.075 vs. 0.175%), and the maximum degree of blockade of motor fibers exceeds that of sensory fibers, significantly at 0.1 and 0.25% concentrations (table 1). Paralleling this order, impulses in almost all (12 of 13)  $A\gamma$  fibers but only two thirds (7 of 11) of  $A\delta$  units failed at lidocaine, 0.175% (table 1).

The effects of more concentrated (0.25–1%) lidocaine on CAPs of large sensory and motor fibers are presented in figures 3C and D, and their characteristics collected in table 2. Injections of lidocaine, 0.25%, reduced the CAPs by more than 25% within the first minute (fig. 3D), with the  $A\alpha\beta$  sensory CAP being reduced less and beginning recovery sooner than the  $A\alpha$  motor CAP. Despite a significant difference in maximum block ( $P = 0.039$ , one-way analysis of variance) no kinetic parameters differed significantly between block of motor and sensory CAPs at this concentration (table 2).

Large-fiber CAPs were more profoundly depressed by higher lidocaine concentrations, which effected complete block for 15–20 min at 0.5%, for 45 min at 0.75%, and 90 min at 1% (fig. 3C and table 2). Inhibition grew to 50% by 2–4 min after injection and was 100% within 15 min for the three highest concentrations (fig. 3D and

table 2). Kinetic parameters for block were comparable between motor and sensory CAPs, except at a lidocaine concentration of 0.5%, when the motor block lasted longer than the sensory. It is important that the differences between the large fiber responses apparent at the lower lidocaine concentrations (table 1) were not detected when the "clinical" concentrations were injected (table 2).

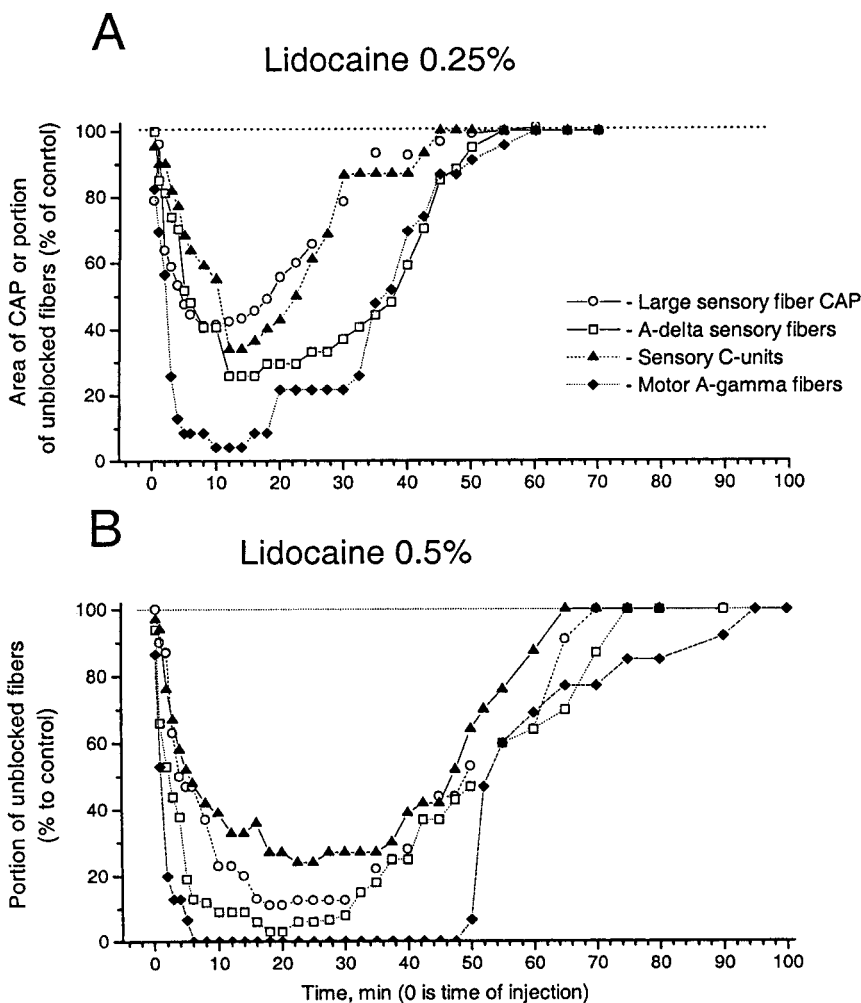
#### Differences in Tonic Blockade between Large and Small Myelinated Fibers

At concentrations of 0.05–0.25%, lidocaine differentially inhibited impulses in large and small myelinated fibers (fig. 4 and table 1). Large sensory fiber CAPs were maximally depressed by only 18% at 0.1% concentration of lidocaine, whereas 44% of the small ( $A\delta$ ) sensory units were blocked; the large  $A\alpha$  motor CAP was similarly less depressed (39%) than the blockade of small ( $A\gamma$ ) motor fibers (68%). Such differential blockade was also observed at lidocaine concentrations of 0.25 and 0.5% (figs. 4A and B and table 3). (Depression of the CAP for large myelinated sensory ( $A\alpha\beta$ ) fibers may overestimate the degree of failure; e.g., at a lidocaine concentration of

0.25%, the CAP area is reduced by 60%, whereas only 37% (4 of 11) of single units show conduction failure. The discrepancy may arise from a slowing of unblocked impulses that puts them beyond the positive phase of the CAP and thus excludes them from the integration procedure. A similar difference would also be expected for large  $A\alpha$  motor fibers.) Even accounting for this factor, the order of maximum block was  $A\gamma \geq A\delta > A\alpha\beta$ . Thus, it is generally true that impulses in small myelinated axons are more susceptible to lidocaine block than those in large myelinated axons.

Interestingly, at lidocaine concentrations of 0.25% and 0.5%,  $A\gamma$  fibers (conduction velocity = 9.4–32 m/s; mean =  $18.8 \pm 1.6$  m/s) were blocked more often and for a longer time than  $A\delta$  fibers (table 3), even though the average impulse velocity of  $A\delta$  fibers was slower (4.2–20 m/s; mean =  $11.4 \pm 1.0$  m/s). Thus, even within one anatomic category of fiber, the size principle does not apply. Still, as with the large myelinated axons, motor fibers were blocked more than sensory fibers. Function, rather than impulse velocity, appears to predict relative fiber susceptibility.

Fig 4. Averaged actions of lidocaine (0.25 and 0.5% concentrations) on activity in four main classes of sensory and motor fibers. (A) Time course of lidocaine, 0.25%, effects on "population" conduction in large sensory fibers ( $A\alpha\beta$ , CAP data), small single sensory ( $A\delta$ ) myelinated fibers ( $n = 27$ ), C fibers ( $n = 22$ ), and  $A\gamma$  motor units ( $n = 23$ ). Y-axis is the normalized area of CAP (for  $A\alpha\beta$  fibers) or the percentage of unblocked fibers (relative to total number of fibers) against time after injection ( $t = 0$ ). (B) Time course of effects of lidocaine, 0.5%, on activity in large sensory fibers ( $A\alpha\beta$ ;  $n = 30$ ), small sensory myelinated fibers ( $n = 32$ ), C fibers ( $n = 33$ ), and  $\gamma$  motor units ( $n = 15$ ).



**Table 3. The Course of Tonic Blockade of Single Fibers at 0.25% and 0.5% Lidocaine**

Fiber Class	0.25%			0.5%		
	Max % of Units Blocked	Mean Duration of Block* (min)	Time for Complete Recovery† (min)	Max % of Units Blocked	Mean Duration of Block* (min)	Time for Complete Recovery† (min)
A $\alpha$ $\beta$ Sensory	57.9 (11/19)	18.2 $\pm$ 3.79	50	89 (27/30)	46.5 $\pm$ 4.3	70
A $\delta$ Sensory	74 (20/27)	28.4 $\pm$ 2.38	56	97 (31/32)	38.5 $\pm$ 5.11	75
C (all units) Sensory	63.6 (14/22)	14.4 $\pm$ 2.70	45	78 (26/34)	35.8 $\pm$ 4.3	65
C > 1 m/s Sensory	90 (9/10)	19.3 $\pm$ 3.86	42	92 (11/12)	49.8 $\pm$ 5.86	65
C < 1 m/s Sensory	42 (5/12)	8.3 $\pm$ 2.56	30	68.2 (15/22)	27.7 $\pm$ 4.66	60
A $\gamma$ Motor	96 (20/21)	34.0 $\pm$ 2.99	60	100 (15/15)	57.7 $\pm$ 4.25	95

Values in parentheses are number of units blocked/total units recorded.

For 0.25% lidocaine, the difference was significant for mean duration of block: A $\alpha$  $\beta$  versus A $\delta$  ( $P = 0.024$ ), A $\alpha$  $\beta$  versus A $\gamma$  ( $P = 0.002$ ), and A $\delta$  versus C ( $P = 0.001$ ), but not for A $\alpha$  $\beta$  versus C ( $P = 0.52$ ) and A $\delta$  versus A $\gamma$  ( $P = 0.135$ ), all by one-way analysis of variance.

For 0.5% lidocaine, the difference was significant for mean duration of block between both A $\delta$  and C versus A $\gamma$  ( $P = 0.001$  and  $0.003$ ) and between "faster" versus "slower" C fibers ( $P = 0.01$ ).

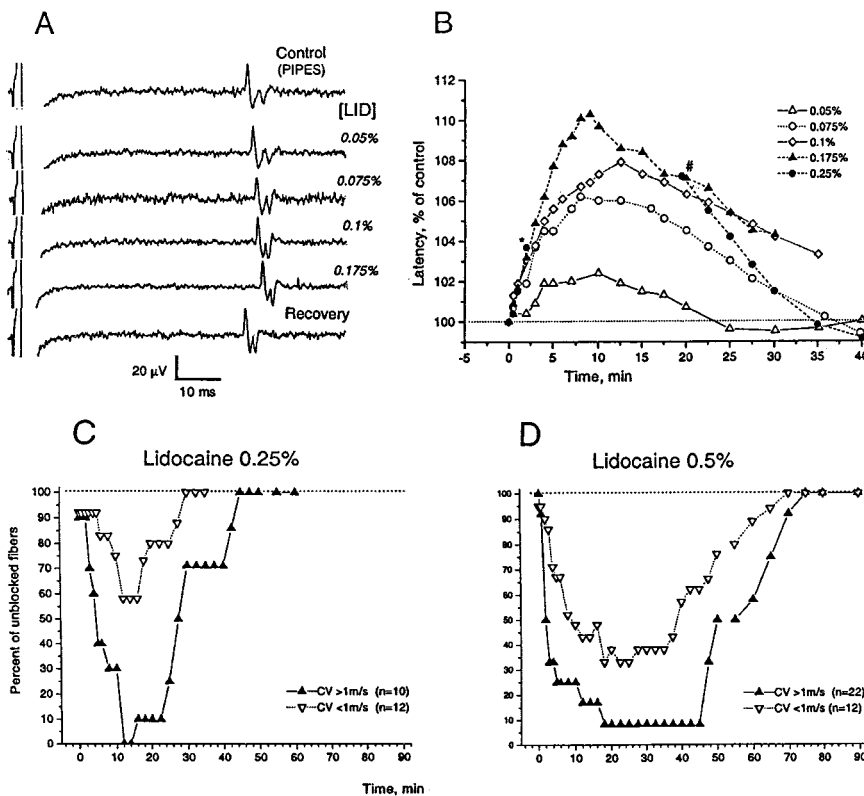
\* Average time from first impulse failure to first recovered impulse. † Determined as the time after injection until slowing was reversed for all units tested, using data like those in figure 4.

### Relative Insensitivity to Lidocaine of Nonmyelinated Axons

Nonmyelinated sensory C fibers were the least susceptible among small fibers to block by lidocaine. One C fiber's response to lidocaine is shown in figures 5A and B; for concentrations of 0.05–0.175%, modest, reversible slowing occurred but failure was absent. On average, little block occurred at lidocaine concentrations below 0.175% (table 1), and the failure rate for all C fibers at lidocaine concentrations of 0.25–0.5% was less than that for all other fiber classes (table 3), although there were significant differences in block susceptibility between

different classes of C fibers (figs. 5C and D; see also the following text).

Relative resistance to blockade of nonmyelinated fibers over myelinated fibers is exemplified by traces in figure 6, showing sequential recordings of unitary responses of one A $\delta$  and five C fibers at different times after injection of lidocaine, 0.25%. Impulses in the A $\delta$  fiber disappeared during the first 3 min after lidocaine application when all C fibers were still conducting. From 3 to 10 min, separate C fibers were blocked, starting with the faster-conducting ones (conduction velocity = 1.7 m/s, then 1.3 m/s, and finally, 1.2 m/s). Slower-conducting units



**Fig. 5. Relative resistance of C fibers to block by lidocaine.** (A) Example of unitary activity in one C fiber (conduction velocity = 1.46 m/s). Upper trace is control (10 min after control buffer [PIPES] injection); second to fifth traces were recorded at 10-min intervals after injections of lidocaine, 0.05, 0.075, 0.1, and 0.175%, respectively; and the lowest trace is a record made 40 min after the last lidocaine injection. (B) Changes in conduction velocity (latency, as percentage of control value) for the same C fiber shown in A. Conduction after lidocaine, 0.25%, failed at (\*) and was regained at (#). (C) The time course of tonic impulse failure after lidocaine, 0.25%, in "fast" (closed triangles) and "slow" (open triangles) C fibers. (D) The time course of tonic failure of impulses in fast and slow C fibers after lidocaine, 0.5%, injection.



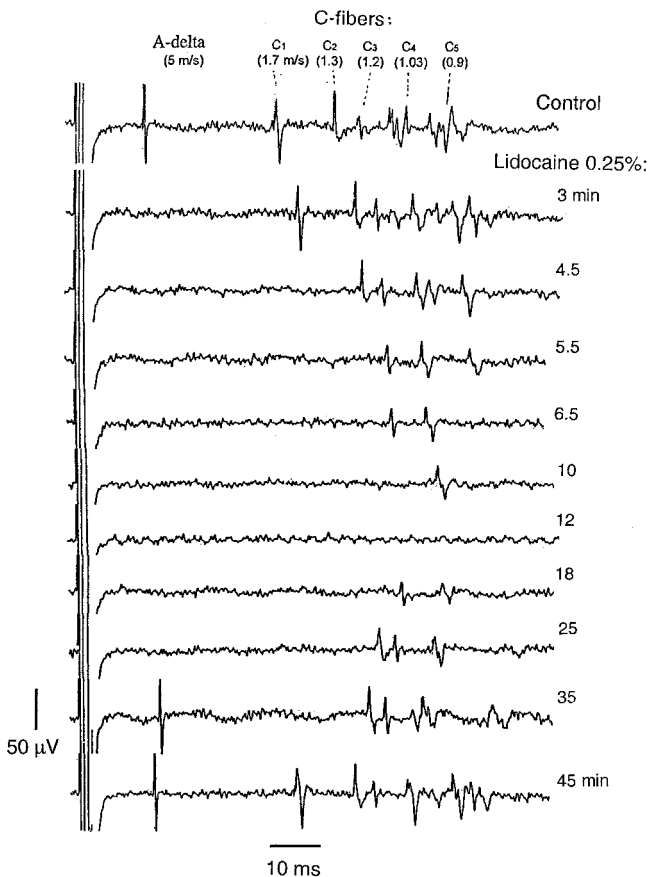


Fig. 6. One example of differential block of small myelinated and nonmyelinated fibers. Unitary responses of one A $\delta$  fiber (conduction velocity = 5 m/s) and five C fibers (with conduction velocity ranging from 1.7 to 0.9 m/s) recorded from a microfilament of DRL5 before (control, upper trace) and at different times (shown at right of traces) after injection of lidocaine, 0.25%. Each trace is the average of three to five single successive records.

also recovered sooner, being blocked for less than 8 min, whereas the fastest C fiber and the A $\delta$  fiber were blocked for approximately 40 min. This preferential block behavior is a general feature seen among all C fibers, as shown by the group's block profile after injection of lidocaine at concentrations of 0.25% and 0.5% (figs. 5C and D).

Propensity to fail depended on C-fiber conduction velocity. All of the C fibers that were blocked at 0.175% concentration of lidocaine (4 of 11) were from the faster group (mean conduction velocity =  $1.13 \pm 0.11$  m/s;  $n = 6$ ), whereas those that were only slowed but not blocked were all from the slower group (mean conduction velocity =  $0.77 \pm 0.06$  m/s;  $n = 4$ ) (table 1). A parallel difference occurred in 0.25 and 0.5% concentrations of lidocaine (table 3). Thus, as occurred in the small myelinated axons, within nonmyelinated fibers an "inverse size principle" also describes the order of block.

#### Summary Dose-response Data for All Fiber Types

The concentration-dependence of maximum tonic blockade by lidocaine in different fiber classes is sum-

marized in figure 7. Differential block is apparent both in the order of threshold concentrations to produce significant block (*i.e.*, 10% failure),  $A\gamma \approx A\delta < A\alpha$  (motor)  $\approx A\alpha\beta$  (sensory)  $< C$  fast  $< C$  slow, and in the order of concentrations to effect 50% inhibition,  $IC_{50s}$ ,  $A\gamma < A\alpha$  (motor)  $\approx A\delta < C$  fast  $< A\alpha\beta$  (sensory)  $< C$  slow. Although it is not possible to calculate the variance for these estimated parameters, and thus to establish their significance, the absolute sensitivities of different fiber types at single lidocaine doses listed in tables 1-3 and the foregoing text are fully consistent with the rank order of concentration dependences derived from the curves in figure 7.

#### Slowing of Conduction

Conduction slowing was observed in all fibers and at all doses of lidocaine. It was often detectable at the first minute after injection (fig. 5B) and reached a maximum just before failure of conduction (*e.g.*, as shown in fig. 6). At the moment of impulse reappearance (recovery from block) the latency was usually approximately the same as at failure, and it followed a slow recovery to control values.

Tonic slowing, measured during both onset and recovery phases of lidocaine action, differed among different classes of fibers (table 4). For example, at a concentration of 0.25% lidocaine, maximum slowing just before failure in large sensory (A $\alpha\beta$ ) myelinated fibers was significantly larger than that in A $\delta$  fibers, in C fibers, and in A $\gamma$  fibers. A similar pattern was found for conduction slowing of the first impulses detectable during recovery (table 4). The longest mean duration of detectable slowing (from a concentration of 0.25% lidocaine) was found for A $\gamma$  motor fibers, longer than that measured for A $\beta$  but not for C fibers or A $\delta$  units.

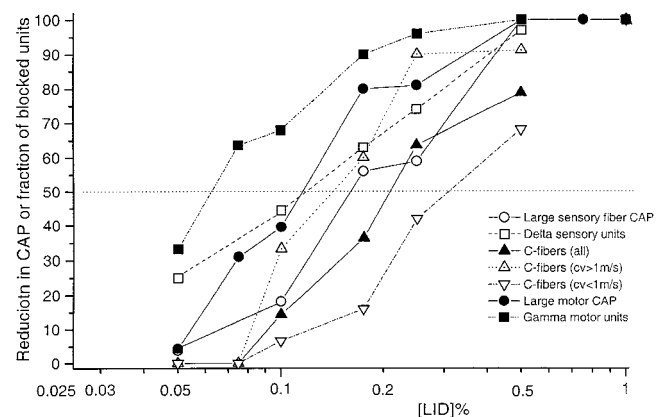


Fig. 7. Concentration dependence of lidocaine action on conduction in all main classes of sciatic nerve. Averaged maximum depression of conduction in five classes of fibers, calculated from compound action potential (CAP) (sensory A $\alpha\beta$  and motor A $\alpha$ ) or from unitary recordings (sensory A $\delta$  and C fibers and motor A $\gamma$  fibers), are plotted against lidocaine concentration. For purposes of clarity, SD values have been omitted from graph.

**Table 4. Characteristics of Tonic Conduction Slowing in Different Classes of Fibers at 0.25% Lidocaine\***

Fiber Class	First Minute Slowing	Maximum Slowing in Units without Failure	Maximum Slowing at Onset of Block	Maximum Slowing at Recovery of Block	Duration of Slowing
Sensory A $\alpha,\beta$	3.7 $\pm$ 2.4 (13)	18.5 $\pm$ 11.1 (8)	20.0 $\pm$ 11.7 (11)	22.7 $\pm$ 10.1 (11)	56.7 $\pm$ 18.3 (19)
Sensory A $\delta$	0.99 $\pm$ 0.82 (14)	13.8 $\pm$ 3.2 (7)	10.9 $\pm$ 5.7 (20)	13.8 $\pm$ 0.8 (20)	63.0 $\pm$ 16.4 (20)
Sensory C	1.98 $\pm$ 1.6 (21)	17.3 $\pm$ 5.2 (8)	12.3 $\pm$ 5.8 (17)	12.6 $\pm$ 1.2 (14)	59.6 $\pm$ 14.4 (14)
Motor A $\gamma$	2.8 $\pm$ 2.7 (18)	Only one unit without failure	10.5 $\pm$ 9.4 (19)	14.3 $\pm$ 2.5 (20)	71.5 $\pm$ 12.3 (17)

For first minute slowing, significant difference were found between A $\alpha,\beta$  versus A $\gamma$  ( $P < 0.0005$ ), A $\alpha,\beta$  versus C ( $P = 0.016$ ), A $\delta$  versus C ( $P = 0.043$ ), and A $\delta$  versus A $\gamma$  ( $P = 0.02$ ).

For maximum slowing without failure, no significant differences between fiber groups.

For maximum slowing at block onset, significant differences between A $\alpha,\beta$  vs A $\delta$  ( $P = 0.009$ ), A $\alpha,\beta$  versus C ( $P = 0.033$ ), and A $\alpha,\beta$  versus A $\delta$  ( $P = 0.013$ ).

For duration of slowing, significant differences between A $\alpha,\beta$  versus A $\delta$  ( $P < 0.02$ ), and C versus A $\gamma$  ( $P = 0.019$ ).

\* Percent decrease of c.v.s from control values. Number of units in parentheses.

Lidocaine-induced slowing showed a selectivity among fibers that somewhat paralleled lidocaine-induced failure (compare table 4 and fig. 4A). The fast-conducting A $\beta$  (sensory) fibers and the slow-conducting C fibers, both relatively resistant to block, were also the populations that sustained the greatest impulse slowing (approximately 20%), consistent with a higher margin of safety for impulse propagation and, possibly, a generally greater resilience to metabolic or toxic challenges.

#### *Effects of Repetitive Stimulation on the Actions of Lidocaine*

The inhibition of conduction by local anesthetics measured *in vitro* depends strongly on impulse frequency. Fiber block that is absent or initially just detectable at very low frequencies (0.1- to 0.5-Hz tonic block) increases at higher frequencies (5- 40 Hz), a phenomenon called phasic or use-dependent block.<sup>22</sup> Because high-frequency firing is a normal occurrence *in vivo* through intense activation of sensory receptors or the strong excitation of spinal motor neurons, we examined whether such trains of impulses, driven electrically at "physiologic" frequencies,<sup>15-20</sup> would modify the impulse blocking actions of lidocaine *in vivo*.

Repetitive nerve stimulation provokes changes in spike conduction even in the absence of local anesthetics, a phenomenon referred to as "activity dependence."<sup>23</sup> These physiologic changes are characterized by a slowing of impulse propagation along axons and even selective failure of conduction.<sup>19,24</sup> However, in the presence of local anesthetics, these changes become more prominent as they are dominated by the use-dependent actions of LA, mentioned previously. Thus, overall, LA block *in vivo* is composed of both endogenous activity dependence and tonic block, as well as phasic actions of local anesthetics that modify conduction during trains of impulses.

Use-dependent effects of lidocaine were examined in small myelinated (A $\delta$  and A $\gamma$ ) and nonmyelinated (C) fibers. During the repetitive stimulation used in these experiments (see Materials and Methods section: a

30-pulse train at 40 Hz for small myelinated fibers or at 5 Hz for C units), endogenous, activity-dependent conduction failure rarely occurred, although activity-dependent conduction slowing was regularly observed at maximum levels of 4.6 + 0.63% in A $\delta$  fibers and 7.9 + 0.64% in C fibers. In experiments with lidocaine, 0.25%, use-dependent effects were studied in the 4 (of 13 total) A $\delta$  units, which did not fail tonically. These fibers experienced moderate use-dependent block, characterized by a relatively short-lasting failure of impulses (total duration, 10.5 + 2.6 min) that was preceded by additional (to tonic) use-dependent slowing of conduction (maximum, 10.8 + 3.31%). The mean onset time after injection to reach use-dependent failure was 7.3 + 2.46 min.

The remaining nine A $\delta$  units were eventually blocked at the tonic stimulation frequency, but before that, they also showed use-dependent effects. These consisted of additional slowing of conduction (maximum, 14.1 + 5.2% during onset of block and 6.7 + 0.7% at recovery), with earlier (by 1.33 + 0.33 min) onset of failure and later recovery (2.72 + 1.03 min) than measured under tonic conditions. The net result was a modest phasic increase of mean duration of block of 4.05 min (17.5%) compared with tonic block duration.

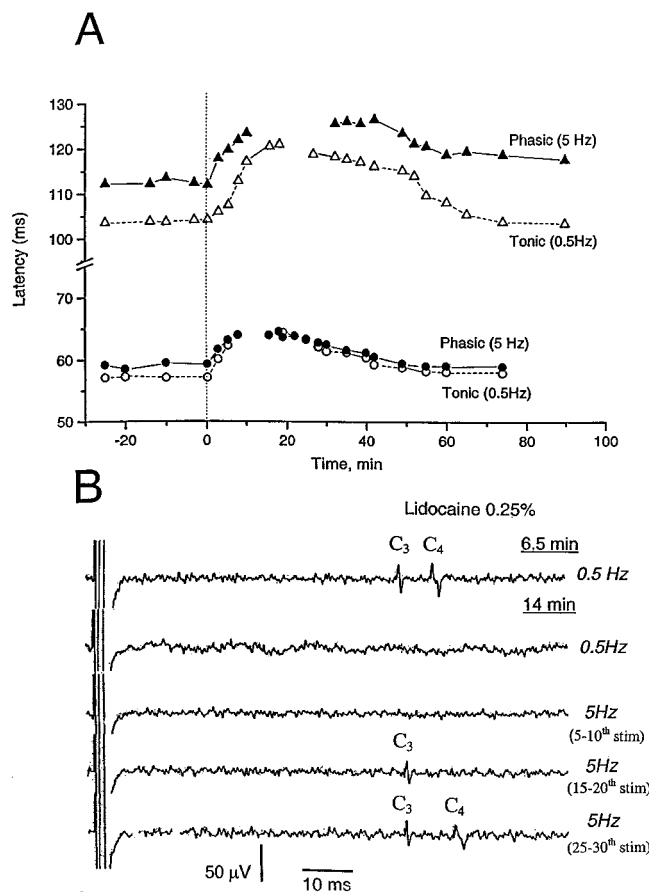
As mentioned previously, all A $\gamma$  motor units were blocked by lidocaine, 0.25%, during their tonic activation. Before this failure they revealed additional slowing and failure at both phasic frequencies of sustained nerve stimulation: 4 and 40 Hz. Seven of nine units tested failed in the first 1 or 2 min under tonic conditions and were unavailable to test for use-dependent failure. Additional phasic slowing during block onset in them was just 3.7 + 0.94%. Phasic effects during the recovery period for these fibers were also found to be small: 2.7 + 0.52% of additional slowing and 2.7 + 1.2 min "prolongation" of blockade. Use-dependent changes differed insignificantly between A $\delta$  and A $\gamma$  fibers, except for the levels of use-dependent slowing during block onset: 6.7 + 0.7% (A $\delta$  fibers) and 3.66 + 0.94% (A $\gamma$  fibers;  $P < 0.05$ ).

Use-dependent actions among C fibers were more varied than those in small myelinated fibers, as determined

in an additional 44 C units examined for these phenomena. Use-dependence also differed dramatically between subpopulations of C fibers: (1) In "slower" C fibers (conduction velocity = 0.62–0.88 m/s;  $n = 5$ ), which were not tonically blocked at lidocaine, 0.25%, no use-dependent failure occurred, but only moderate additional slowing of conduction ( $8.9 \pm 3.4\%$ ), in addition to tonic slowing (11.6%), was found. (2) Among "faster" C units (conduction velocity = 0.90–1.96 m/s;  $n = 17$ ), showing tonic failure at a 0.25% concentration of lidocaine, two opposite types of use-dependent behavior were observed. In nine of these units either an additional slowing of conduction and "moderate" phasic block was found ( $n = 5$ ; fig. 8A) or no use-dependent failure ( $n = 4$ ) occurred. However, for the remaining eight faster C fibers with tonic failure, an anomalous response was revealed, one that was totally absent in the behavior of small myelinated fibers. In these C units, exemplified by the records in figure 8B, repetitive stimulation (5 Hz) caused a reappearance of spikes that had been blocked in the tonic condition, a use-dependent recovery of conduction. Among individual fibers this restitution needed different duration of phasic stimulation to appear. Slowing of conduction in such recovered units during repetitive stimulation was typically very small (1–3%; fig. 8A). Moreover, in three of these cases we measured a further decrease in the latency of "relieved" spikes during subsequent phasic stimulation, indicating an acceleration of conduction.

## Discussion

We have observed a differential block by lidocaine of different sciatic nerve fibers. Impulse conduction in small, slowly conducting myelinated sensory and motor fibers failed faster, more frequently, and for longer times, than those in large, fast-conducting sensory and motor fibers. Such differential block probably does not arise from pharmacokinetic factors associated with percutaneous injection (e.g., slow drug penetration into the nerve) because the same order of failure among sensory fibers was found in *in vivo* studies in cats with direct application (*via* superfusion chambers) of local anesthetics to dorsal roots<sup>5</sup> or to saphenous nerve,<sup>6</sup> as well as when equilibrium block was verified in rat sciatic nerve.<sup>12</sup> Although the smaller-diameter myelinated fibers were blocked more than the larger ones, disagreements with the classic size principle were found: (1) The fibers of smallest diameter, unmyelinated sensory C fibers, were least susceptible to block and (2) within the subclasses of small and large myelinated axons the relatively faster-conducting motor fibers ( $A\gamma$  and  $A\alpha$  fibers) were blocked more than the anatomically corresponding but slower-conducting sensory fibers ( $A\delta$ - and  $A\alpha\beta$  fibers, respectively). In this discussion these results are com-



**Fig. 8.** Tonic and phasic (use-dependent) effects of lidocaine, 0.25%, on latency and incidence of spikes in C fibers. (A) Time course of lidocaine action in two C fibers: one "slow" unit (upper traces, triangles; resting conduction velocity = 0.72 m/s) and one "fast" unit (lower traces, circles; conduction velocity = 1.19 m/s). Activity was measured under "tonic" (0.5 Hz, open symbols) and "phasic" (5 Hz, filled symbols) modes of stimulation. The spaces of unconnected symbols indicate the times of spike failure. (B) Lidocaine induced a use-dependent relief of block at higher-frequency (5-Hz) phasic stimulation in two C fibers (C fiber 3, conduction velocity = 1.19 m/s; C fiber 4, conduction velocity = 1.04 m/s) that were blocked at low-frequency (tonic, 0.5-Hz) stimulation. The topmost trace shows the tonic responses at 6.5 min after lidocaine injection. Both units experienced tonic block of conduction by 14 min after injection (second trace), but block was relieved during one train of phasic stimulation (5 Hz), the activity of C fiber 3 returning earlier than that of C fiber 4. Recovery from tonic block was detected 4 min after phasic stimulation episode (trace not shown).

pared with previous neurophysiologic reports and correlated with known functional changes that accompany peripheral nerve block.

### Comparative Neurophysiology

A differential block of myelinated fibers, similar to that described in the current study, was reported for *in vivo* CAP recordings.<sup>4–6</sup> For example, procaine applied to cat peripheral muscle nerves at a concentration of 0.2% completely blocked the  $A\gamma$  wave before significant reduction of the  $A\alpha$  component.<sup>4</sup> In clinical observations of

human radial nerve afferent fiber activity, percutaneous lidocaine, 0.25%, blocked all A $\delta$  fibers, whereas A $\beta$  fibers were only partially blocked.<sup>25,26</sup>

#### *Myelinated versus Nonmyelinated Fibers*

Preferential block of A $\delta$  over C fibers is consistent with previous *in vivo* observations in cats<sup>5,6</sup> and with results of recent *in vivo* studies in rat,<sup>12</sup> as well as older reports of C fiber susceptibility *in vitro*.<sup>27-30</sup> The first two studies, with "low" concentrations of procaine (0.03–0.2%),<sup>5,6</sup> found that about half of the C fibers were still conducting when the majority of A $\delta$  and some A $\alpha$  fibers had been blocked. Human studies<sup>25,26</sup> also have shown that a low concentration of lidocaine (0.25%) can block all A $\delta$  fibers and many of the A $\beta$  fibers while blocking only a few C fibers. In *in vitro* studies with a 0.05% concentration of procaine bathing vagus nerves from different animal species (rabbits, guinea pigs, and frogs), total block of the fast "A-wave" preceded total block of the C elevation.<sup>27</sup> A similar order was found in frog sciatic nerves using anesthetics or reduced Na<sup>+</sup>; procaine blocked A $\delta$  fibers first, then large A fibers, then a faster C component, and finally, the slowest-conducting C component.<sup>28-30</sup> Consistent with these reports, unmyelinated fibers of rat dorsal root *in vitro* were significantly less sensitive to the conduction-slowing effect of lidocaine, 0.61%, than their myelinated counterparts.<sup>31</sup>

#### *Comparison of Effective Doses with Absolute Blocking Concentrations*

The lidocaine concentrations effective for impulse blockade by percutaneous injection are much higher than those required to inhibit Na<sup>+</sup> channels or to abolish impulses in isolated fibers. The IC<sub>50</sub> of lidocaine for neuronal Na<sup>+</sup> channel inhibition in voltage clamp studies is approximately 0.2 mM<sup>32-35</sup> and for blockade of impulses, 0.3–1.0 mM.<sup>10-12,36-40</sup> When single sensory units were studied in nerves equilibrated with lidocaine solutions *in vivo*, the median blocking concentration for nociceptive A $\delta$  fibers was 0.32 mM, compared with 0.41 mM for low-threshold mechanoreceptive A $\beta$  fibers and 0.80 mM for nociceptive C fibers.<sup>12</sup> Contrast those values to the lidocaine concentrations reported in the present study that blocked half of the impulses (or CAP area) when injected percutaneously in 0.1-ml boluses: 4 mM for A $\delta$ , 6 mM for A $\alpha\beta$ , and 5 mM (0.13%) and 12 mM (0.32%) for faster and slower C fibers, respectively. The requirement for a concentration of lidocaine 10-to-15-fold higher than equilibrium to accomplish the same degree of transient block when percutaneous injection was used is not surprising because it has been shown that less than 10% of percutaneously injected lidocaine molecules actually enter the sciatic nerve during the same blocking procedure.<sup>21</sup>

#### *Phasic, Use-dependent Effect of Low-Concentration Lidocaine In Vivo*

In addition to tonic blockade, local anesthetics have a well described use-dependent or phasic action, which is clearly present in *in vitro* studies during high-frequency trains of stimuli.<sup>22,36-41</sup> The present study showed phasic changes in conduction that were relatively uniform in small myelinated A $\delta$  sensory and A $\gamma$  motor fibers, resulting in moderate enhancement of tonic block. The few A $\delta$  units that remained unblocked during tonic stimulation (0.5 Hz, with 0.25% concentration of lidocaine) experienced moderate block during sustained high-frequency (40-Hz) stimulation. These enhancements effectively increased the mean duration of block in these fibers by approximately 20%.

Similar use-dependence also contributed to block of A $\gamma$  motor units. However, because practically all A $\gamma$  fibers were tonically blocked at lidocaine concentrations of 0.175% and higher, we can only report qualitatively that the additional slowing at onset of phasic block found in A $\gamma$  units was smaller than that seen in A $\delta$  fibers.

More diverse phasic changes were found in C fibers. The C units that were not blocked tonically (at 0.25% concentration of lidocaine) also did not fail during phasic (5-Hz) stimulation. Use-dependent changes in one population of tonically blocked C units were similar to those found for A $\gamma$  and A $\delta$  units (*i.e.*, additional conduction slowing and moderate prolongation of tonic blockade); a second population of tonically blocked units did not demonstrate use-dependent conduction failure. Remarkably, a new behavior occurred in one third of the tonically blocked C fibers (more often encountered among faster C units) that was never observed in small myelinated fibers: a use-dependent "facilitation." The main sign of facilitation was a restoration of tonically blocked impulses, usually with stable latency. In some cases a small (1–3%) but consistent increase in conduction velocity of such "relieved" spikes with successive phasic stimulation occurred.

A similar decrease in latency of approximately 4% was also recorded *in vitro* in 4 of 11 unmyelinated vagus nerve fibers stimulated at 10 Hz in 0.6 mM lidocaine, 0.0016%.<sup>36</sup> These phenomena are reminiscent of an earlier observation *in vivo* of the phasic restoration of tonically blocked C fiber CAPs in the saphenous nerve of cat, where it was shown that these signals could be abolished tonically by 0.4 mM lidocaine, but reappeared during phasic nerve stimulation at 5 or 10 Hz (unpublished observation, G. R. Strichartz and M. Zimmermann, Dr. Med., University of Heidelberg, Heidelberg, Germany; recordings of impulses in cat sural nerve, 1984).

A likely mechanism for use-dependent relief of tonic block combines the voltage-dependent aspect of the use-dependent potency of lidocaine for blocking Na<sup>+</sup> channels with the occurrence of posttetanic hyperpolarization in C fibers. The well-documented state-depen-

dent affinity of lidocaine shows that inactivated  $\text{Na}^+$  channels bind the drug and are inhibited more than resting, closed channels. This difference manifests as an inhibition that is potentiated in depolarized membranes and lessened in hyperpolarized ones.<sup>22,34,41-43</sup> Repetitive stimulation of C fibers often leads to an accumulating "posttetanic" hyperpolarization, mediated by stimulus- and  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels and by the electrogenic  $\text{Na}^+/\text{K}^+$  pump.<sup>44,45</sup> Thus, such a hyperpolarization, generated in active regions of fibers proximal to a blocked zone and spreading electrotonically into that zone, could reverse  $\text{Na}^+$  channel inactivation and thus reduce the effective affinity for lidocaine, leading to anesthetic unbinding and the restoration of conduction.

#### *Neurophysiological Changes and Functional Local Anesthesia*

In previous neurobehavioral studies from this laboratory<sup>14</sup> using 1% percutaneous lidocaine application, different rates of impairment of various neurologic functions were demonstrated. In particular, proprioception and motor activity were depressed earlier, more completely, and for a longer time than nociception. Today we have neurophysiologic evidence for the cause of these neurobehavioral differences.

The correlation between the order and degree of neurophysiologic effects and those of neurobehavioral deficits supports two causal linkages: (1) that early and strong motor or proprioceptive changes are due to impulse blockade in  $\text{A}\gamma$  motoneurons and (2) that the later, weaker decrease in nocifensive withdrawal from mechanical noxious stimulation is due to impulse blockade in C fibers. Preferential blockade by lidocaine of  $\text{A}\gamma$  fibers over the larger, faster-conducting  $\text{A}\alpha$  motor axons results in inhibition of  $\text{A}\gamma$  tonic activity, intrafusal muscle fiber relaxation, and a resulting attenuation or absence of Ia afferents (activity in muscle spindle). The accompanying flaccid paralysis is as profound as that accomplished by direct blockade of  $\text{A}\alpha$  motoneuron.

Although first (fast) pain and the directed withdrawal response from sharp mechanical stimuli are often equated with  $\text{A}\delta$  nociceptor activity (see next paragraph), both the late onset of this behavioral loss and its weak susceptibility to lidocaine in rats correlate more strongly with C fiber blockade than with the earlier, stronger depression of  $\text{A}\delta$  fibers. However, caution is required in interpreting pain perception by nocifensive response because the two events are not identical.

The differential sensitivity to *in vivo* lidocaine between small ( $\text{A}\delta$  and C) sensory fibers may make an important difference in the physiologic consequences of local anesthetics on the two different pain "modalities" and on clinical judgments made therefrom. "Fast," "sharp," or "pricking" pain is generally believed to be conducted by nociceptive  $\text{A}\delta$  fibers, whereas "slow," "burning" pain is thought to be mediated through nociceptive C fi-

bers.<sup>13,15,46,47</sup> Preoperative tests for local anesthesia using brief, sharp but mild stimuli, characterized as "pinprick," could indicate an adequacy of analgesia based on  $\text{A}\delta$ -fiber blockade under conditions in which many nociceptive C fibers still conduct impulses. This situation may be particularly true at the anatomic margins of blocked regions, corresponding to more lightly anesthetized nerves, and is important for both the evaluation of blockade preoperative blockade and the development of postoperative pain, for the following reasons. Nociceptive C fibers in monkey and human, involved in the "slow" pain,<sup>46-48</sup> have been implicated in "spinal sensitization" and are related to stimulus-dependent hyperalgesia. (By comparison, nociceptive  $\text{A}\delta$  fibers, similar to the type I nociceptive A fibers found in human and monkey, are responsible for the primary hyperalgesia after injury to glabrous skin.<sup>48</sup>) Blockade of the acute nociception mediated by  $\text{A}\delta$  fibers could coexist with conduction in C fibers, whose ongoing activity would sensitize the central nervous system, facilitating nociceptive transmission and leading to postoperative hyperalgesia.<sup>47,48</sup> Thus, the traditional (*i.e.*, pinprick) tests for acute nociception might misinform us about the presence of conduction in C nociceptors that mediate other functions and result in a block that was less than adequate to minimize perioperative pain.

#### *Blockade of Sensory versus Motor Fibers*

Earlier reports suggested an intrinsic difference in the LA sensitivity of sensory *versus* motor fibers; for example, Macintosh<sup>49</sup> declared, "It is well known that in local and spinal analgesia, sensory nerve fibers are affected before motor." During *in vivo* recording of CAPs of spinal roots while applying procaine, 0.2%, on hindlimb muscle nerve(s) in cats, Matthews and Rushworth<sup>4</sup> did not find a significant difference between large sensory and large motor fibers; both were blocked at approximately the same rate.

In the present study, CAPs recorded simultaneously from both large myelinated sensory and motor sciatic nerve fibers showed no difference in the degree and rate of tonic block at relatively high lidocaine concentrations (0.25-1%; fig. 3). However, at lower concentrations (0.1-0.175%) large motor fibers were suppressed significantly more than large sensory fibers. We propose that this difference represents a different susceptibility to lidocaine of these classes of fibers, rather than arising from pharmacokinetic factors, as would occur if motor fibers were located closer to the outer edge of the nerve and thus exposed to a higher effective lidocaine concentration, because the onset of block is generally faster for large sensory than large motor axons (table 3), despite their lower failure tendency. It remains to be shown how this differential blockade of rat sciatic fibers translates to differential functional blockade in those animals, or to the blockade of nerve impulses and function in *Homo sapiens*, the substance of clinical anesthesia.

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