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Differential Sensitivities of Mammalian Nerve Fibers to Local Anesthetic Agents

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The differential sensitivities of mammalian nerve fibers to various local anesthetic agents were investigated. Lidocaine, tetracaine, etidocaine, and bupivacaine demonstrated a consistent pattern of conduction blockade in which the large fast-conducting A fibers were blocked at the lowest drug concentration, the intermediate B fibers were blocked at a higher drug concentration, and the smallest, slowest-conducting C fibers required the highest drug concentration for conduction blockade. A comparison of procaine, chloroprocaine, cocaine, tetrodotoxin and saxitoxin on B and C fibers showed similar effects. These findings indicate that local anesthetic agents are similar to other biological stress modalities in terms of their differential effects on nerve fibers of various sizes and conduction velocities, *i.e.*, the large fast-conducting fibers are more susceptible to conduction blockade than are the smaller, slower-conducting fibers. Discrepancies between results of this study and previous reports in the literature are discussed. (Key words: Anesthetics, local: bupivacaine; etidocaine; lidocaine; tetracaine. Nerve: block; conduction.)

THE RELATIONSHIP between sizes of nerve fibers and differential sensitivities to conduction blockade by local anesthetic agents is based on the classic studies of Gasser and Erlanger in 1929.[1] They reported that small slow-conducting fibers were blocked at a lower concentration of cocaine than fast-conducting large fibers. The explanation proposed was that small fibers were more accessible to applied drug than large fibers because "[the ratio of] the surface [area] per unit volume increases directly as the diameter decreases, the smaller the fibers the greater the accessibility."

Present teaching in physiology and anesthesiology still states that small nerve fibers are more susceptible than large fibers to conduction blockade. Also, the statement is frequently made that pain is abolished at concentrations of nerve-blocking drugs lower than those needed to block the motor function. Other studies frequently quoted in support of the work of Gasser and Erlanger include those of Nathan and Sears[2] and Franz and Perry.[3] However, all of these investigators clearly indicate that the relationship between nerve fiber size and rate of conduction blockade is not absolute. Several more recent studies suggest that this traditional concept may be inaccurate. Heavner and de Jong[4] demonstrated that the preganglionic B fibers of the rabbit cervical sympathetic trunk were more susceptible to conduction block with lidocaine than were the smaller unmyelinated postganglionic C fibers. More recently, Condouris *et al.*[5] employed a computer-simulated model of conduction blockade in nerve fibers of various sizes and concluded that large myelinated fibers are blocked at lower concentrations of local anesthetic agents than are smaller unmyelinated nerve fibers. Finally, the introduction into clinical practice of the newer longer-acting local anesthetics, bupivacaine and etidocaine, has led to the clinical impression that these drugs have differential nerve blocking effects (for instance, bupivacaine at low concentration will block pain sensation while leaving motor function relatively unimpaired).

The present investigation was directed towards identifying the differential blocking effects of local anesthetic drugs. We did an *in vitro* study of mammalian nerve (rabbit vagus or sciatic nerve), and assumed that motor function was served by fast-conducting fibers, while pain and some sensation involved slow-conducting fibers. We hoped that the evaluation of such differential effects would be relevant to the motor and sensory effects of the local anesthetic drugs seen clinically, and particularly to the differential blocking effect of bupivacaine referred to above.

Materials and Methods

Adult albino rabbits were sacrificed by air embolus and the vagus or sciatic nerve removed in less than 15 minutes. Excised nerves were temporarily stored at room temperature (22 C) in a beaker containing modified Liley solution stirred constantly by O_2 aeration. The modified Liley solution (used for the bath and subsequent drug perfusion) consisted of: NaCl, 136.8 mM; KCl, 5.0 mM; $CaCl_2$, 2.0 mM; $MgCl_2$, 1.0 mM; dextrose, 11.0 mM; Hepes buffer [4-(2 hydroxyethyl)-1-piperazine-ethane sulfonic acid], 2.53 mM. The *p*H was adjusted to 7.4 by addition of 15.0 ml of 0.1 N NaOH.

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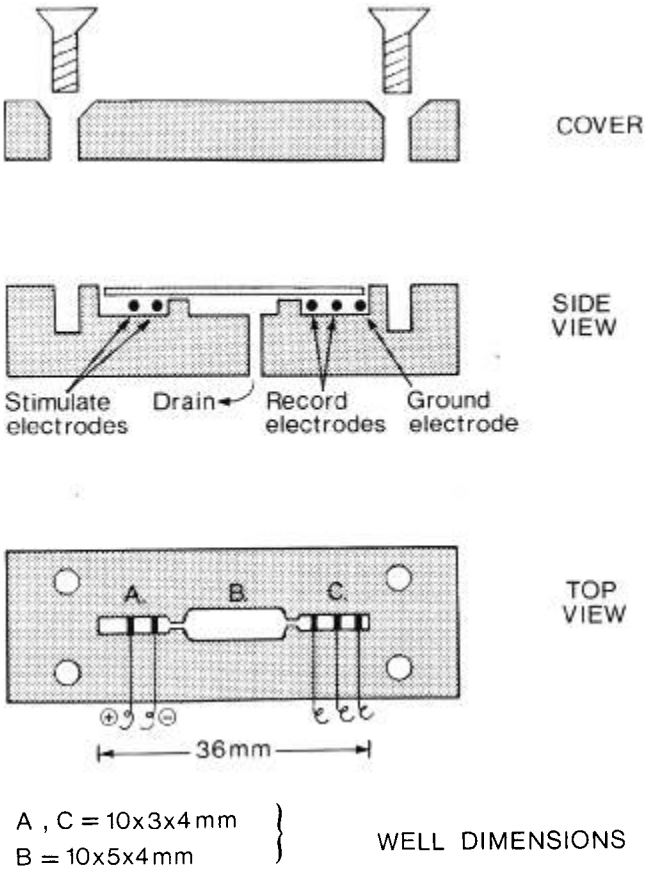

FIG. 1. Design of plastic nerve chamber. Platinum electrodes were .015 inch in diameter, soldered to coaxial output leads. Dimensions as indicated. The groove between wells was 3 mm long, filled with Vaseline® following placement of nerve.

The nerve chamber was made of plastic with three connecting wells (fig. 1). Stimulating and recording electrodes were bare platinum wire. In each group of electrodes wires were 3 mm apart. The two lateral wells (stimulating and recording) were 10 mm long × 3 mm wide × 4 mm deep. The central drug well was 10 × 5 × 4 mm and had two perfusion ports. The three wells were connected by short passages (3 mm long) used as Vaseline® seals to isolate each compartment. In the dish, the nerve length from the cathode stimulating electrode to the nearest recording electrode was 20 mm. Of this length of nerve, 10 mm (desheathed) was exposed to the drug in the central well. The entire assembly could be sealed airtight by the plastic cover.

The nerve (either vagus or sciatic) was desheathed under the dissecting microscope and laid across the three wells. The passages were sealed with Vaseline. The two lateral wells were moistened (but not filled) with Liley solution. The middle well was filled with Liley solution during the control period (at least 30 minutes), then was drained and refilled with Liley solution plus drug for the test period. Drainage and refill of the central well was done every 10 minutes. The dish was made airtight with the screw-on cover following nerve placement. The stimulus was repeated once per minute. Temperature throughout the experiment was 22 C.

The stimulus duration was set at 0.05 msec for A fibers (which are here classified solely by conduction velocity as fibers whose compound action potential travels down the nerve at 30–60 meters per second), at 0.1 msec for B fibers (conducting at 5–15 m/sec) and at 1.0 msec for C fibers (1 m/sec or less).

Stimulus intensities (from Grass S48 stimulators) for A, B and C fibers were adjusted separately for maximum amplitude of the action potential (AP) as displayed on a Tektronix 5103 storage oscilloscope (fig. 2). The electrical signal from the stimulated nerve was led into a Tektronix differential amplifier AM502 by coaxial cable and capacitive coupling. After 500× amplification, the signal was fed into the oscilloscope amplifiers (SA22N Differential Amplifiers). The measurements of AP were made from photographs of the face of the storage oscilloscope (fig. 2).

A control period of 30 minutes was employed to ensure AP stability; then drug dissolved in Liley solution at various concentrations was applied. After 30 minutes of exposure to the drug, the AP amplitude was compared with the control AP amplitude. Washout of drug always returned AP amplitudes to 90 per cent of control values. Separate individual nerves were used for each drug at each concentration. Only occasionally was a second, higher, concentration of drug applied to a previously used nerve after an adequate washout period. Experimental responses less than 5 per cent or more than 95 per cent were excluded from the calculations, since we were primarily interested in the 50 per cent point and the adjacent linear portion of the dose–response curve.

The effects of lidocaine, tetracaine, etidocaine, and bupivacaine on the rabbit sciatic and cervical vagus nerves were studied. Experiments using procaine, chloroprocaine, cocaine, tetrodotoxin (TTX), and saxitoxin (STX) were done on the rabbit vagus only. Finally, to evaluate the effect of the nerve sheath, experiments with lidocaine and tetracaine were done using the vagus nerve with its sheath intact.

For each agent, linear regression curves were derived relating drug concentration to percentage decrease in AP amplitude. These linear regression equations were solved for the drug concentration at the 50 per cent point of depression of the AP response (ED_{50}). Conversion of percentage response to probit computed the standard error of the estimate for ED_{50} by a graphic method.[6] The standard error of the estimate (SEE) is equivalent to standard deviation.

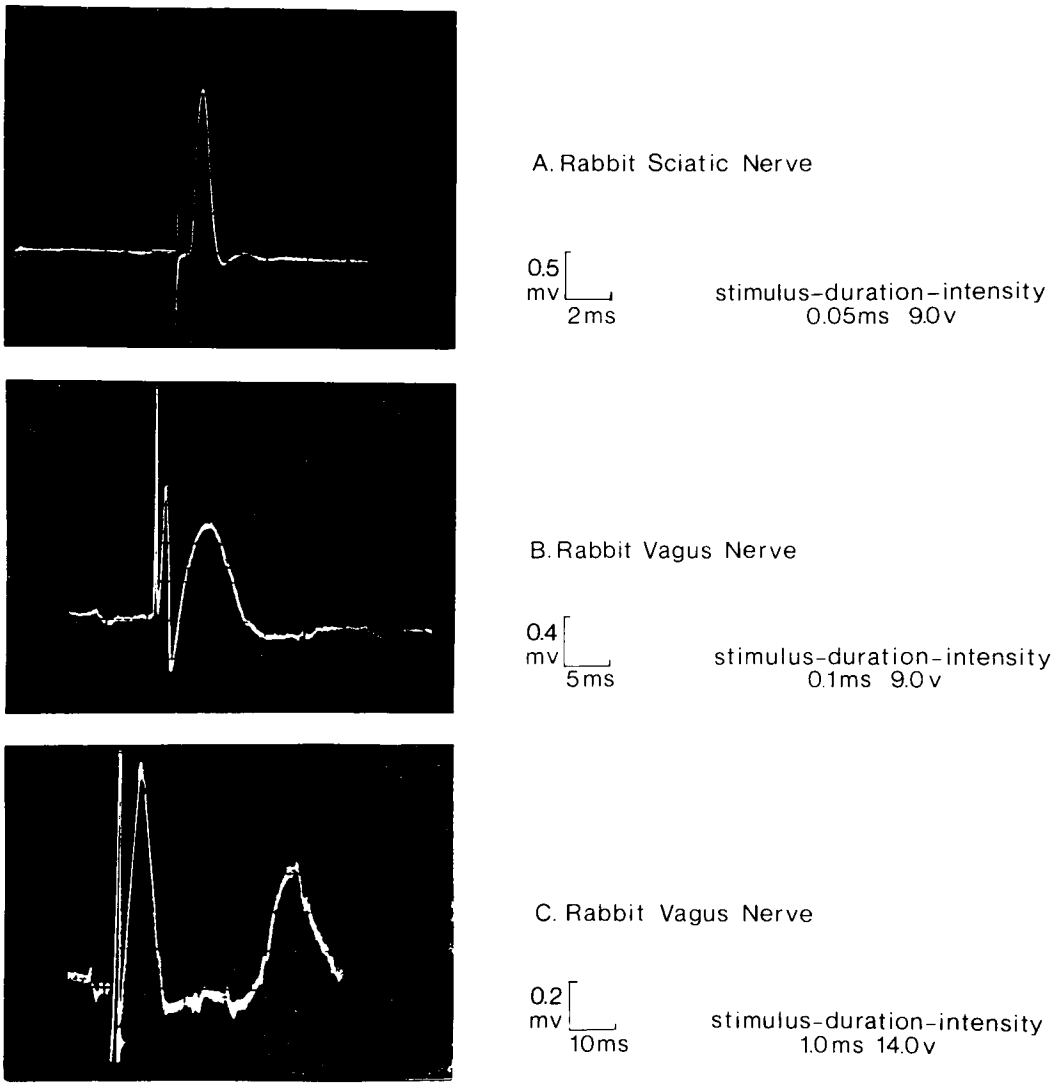

FIG. 2. Oscilloscope traces, showing nerve action potential (AP) from desheathed rabbit sciatic nerve (A fibers) or desheathed vagus nerve (B and C fibers) at indicated stimulus durations and intensities. Temperature 22 C in Hepes–Liley solution. Preamplifier gain = 500×.

Finally, by standard statistical methods, the 95 per cent confidence range for y (the percentage response of the AP) at ED_{50} drug concentration was calculated (table 1).

Results

The relative susceptibilities of A fibers (30–60 m/sec), B fibers (5–15 m/sec), and C fibers (<1 m/sec) to lidocaine, tetracaine, etidocaine, and bupivacaine are shown in figure 3 and table 1. All of the drugs caused significant conduction blockade, expressed as reduction of action potential amplitude. The fast-conducting A fibers were inhibited at a lower concentration of drug than that needed for comparable blocks in the slower-conducting B and C fibers. The smallest and slowest-conducting C fibers were most resistant to conduction blockade. Table 2,I shows the concentrations of lidocaine, tetracaine, etidocaine, and bupivacaine (ED_{50} ± standard error) needed to cause 50 per cent reduction in AP amplitude in each type of nerve fiber.

Lidocaine had the greatest differential effect on fibers of different conduction velocities. A 50 per cent reduction of AP amplitude of the A fibers occurred at a lidocaine concentration of 0.085 ± 0.044 mM. A 50 per cent reduction of AP amplitude of C fibers was seen at 0.724 ± 0.169 mM of lidocaine. Tetracaine, the most potent anesthetic agent tested, had the least differential effect between A fibers (0.009 ± 0.003 mM) and C fibers (0.025 ± 0.007 mM).

The effects of procaine, chloroprocaine, cocaine, and the biotoxins, TTX and STX, on B and C fibers in the desheathed vagus nerve are shown in table 2,II. All of these substances caused conduction blockade

in the faster-conducting B fibers at concentrations lower than those necessary for equivalent inhibition in the slower-conducting C fibers. A 50 per cent reduction in the AP amplitude of B fibers occurred at a chloroprocaine concentration of 0.42 mM, compared with 0.45 mM necessary for 50 per cent inhibition of C fiber AP amplitude. As expected, the biotoxins were the most potent conduction blockers: TTX reduced the AP amplitudes of B and C fibers by 50 per cent at concentrations of 0.46 μM and 0.64 μM, respectively; STX produced similar reductions in AP amplitudes of B and C fibers at 0.29 μM and 0.50 μM.

The possible role of drug diffusion across the intact nerve sheath was investigated in a separate series of experiments utilizing lidocaine and tetracaine. Again, the faster-conducting nerve fibers were blocked at lower concentrations of lidocaine and tetracaine than were the slower-conducting fibers. Predictably, a higher concentration of local anesthetic agent was needed to achieve a 50 per cent reduction in AP amplitude in the sheathed nerve as compared with the desheathed preparations (table 2,I and II).

Discussion

The classic teaching that small, nonmyelinated, slow-conducting nerve fibers are more susceptible to blockade by local anesthetic drugs than are large, myelinated, fast-conducting fibers was not substantiated by the results obtained in the present study.

The evidence that slow-conducting fibers fail before fast-conducting fibers is based primarily on the results of the studies of Gasser and Erlanger with cocaine.[1] Reports by Nathan and Sears[2] and Franz and Perry[3] are frequently quoted to support this premise. However, the findings in the latter studies are not consistent. For example, Nathan and Sears state at one point that the concentration necessary to block small fibers was found to be lower than that necessary to block large fibers, while also pointing out that the lower concentrations of anesthetic blocked the very smallest myelinated fibers without blocking the group of nonmyelinated fibers, which are still smaller. In fact, Gasser and Erlanger themselves clearly stated that the apparent relationship between fiber size and local anesthetic-induced blockade does not rigidly hold.[1] Unfortunately, these statements expressing their lack of certainty have been largely ignored. More recently, studies by Heavner and de Jong[4] and Condouris *et al.*[5] failed to corroborate the original findings of Gasser and Erlanger. Both Heavner and de Jong and Condouris *et al.* presented evidence that slow-conducting fibers are less susceptible to the blocking action of local anesthetic agents than are faster-conducting nerve fibers.

TABLE 1. Calculated Values of Results of Applications of Lidocaine, Tetracaine, Etidocaine and Bupivacaine to Nerve Fibers Conducting at 30–60 m/sec (A fibers), 5–15 m/sec (B fibers), and less than 1 m/sec (C fibers)*

	Number of Experiments	$\bar{x}$	SD_x	$\bar{y}$	SD_y	$ED_{50} \pm SEE_x$	Y = A + BX	r	95 Per Cent Confidence Range of y Response at $x = ED_{50}$
Lidocaine									
A fibers	12	0.12	0.065	58.42	18.54	0.085 ± 0.044	Y = 30.83 + 224.47x	0.79	±11.00
B fibers	28	0.44	0.250	56.57	25.55	0.335 ± 0.078	= 29.58 + 61.20x	0.60	±9.06
C fibers	28	0.55	0.244	41.64	19.41	0.724 ± 0.169	= 14.85 + 48.56x	0.61	±5.41
Tetracaine									
A fibers	7	0.009	0.002	53.14	12.74	0.009 ± 0.003	Y = 13.28 ± 4133.99x	0.62	±19.75
B fibers	20	0.014	0.006	53.00	34.88	0.013 ± 0.003	= 7.86 + 3236.18x	0.77	±6.25
C fibers	13	0.024	0.012	44.38	22.61	0.028 ± 0.007	= 8.17 + 1490.03x	0.77	±13.14
Etidocaine									
A fibers	7	0.047	0.019	53.71	17.45	0.042 ± 0.021	Y = 21.68 + 679.64x	0.75	±28.10
B fibers	36	0.073	0.031	47.11	27.83	0.084 ± 0.009	= 28.04 + 260.02x	0.29	±7.99
C fibers	17	0.145	0.055	36.14	19.04	0.201 ± 0.005	= 9.59 + 243.45x	0.70	±9.31
Bupivacaine									
A fibers	9	0.083	0.039	62.44	22.08	0.048 ± 0.023	Y = 33.45 + 347.94x	0.62	±64.39
B fibers	27	0.126	0.034	47.67	28.75	0.134 ± 0.009	= 12.12 + 282.29x	0.33	±12.37
C fibers	19	0.159	0.061	41.26	21.94	0.201 ± 0.041	= 7.82 ± 209.71x	0.58	±13.67

Key:
x = concentration of drug in mM (independent variable); $\bar{x}$ = mean of independent variable
y = per cent response of action potential (dependent variable); $\bar{y}$ = mean of dependent variable
SD_x = standard deviation of x; SD_y = standard deviation of y
SEE_x = standard error of estimate of x
r = correlation coefficient
ED_{50} = drug concentration at 50 per cent response (mM)

* ED_{50}, SEE_x, r, 95 per cent confidence limits based on linear regression calculations. y = A + Bx. Calculated by least-squares analysis. All other values derived directly from the experimental results.

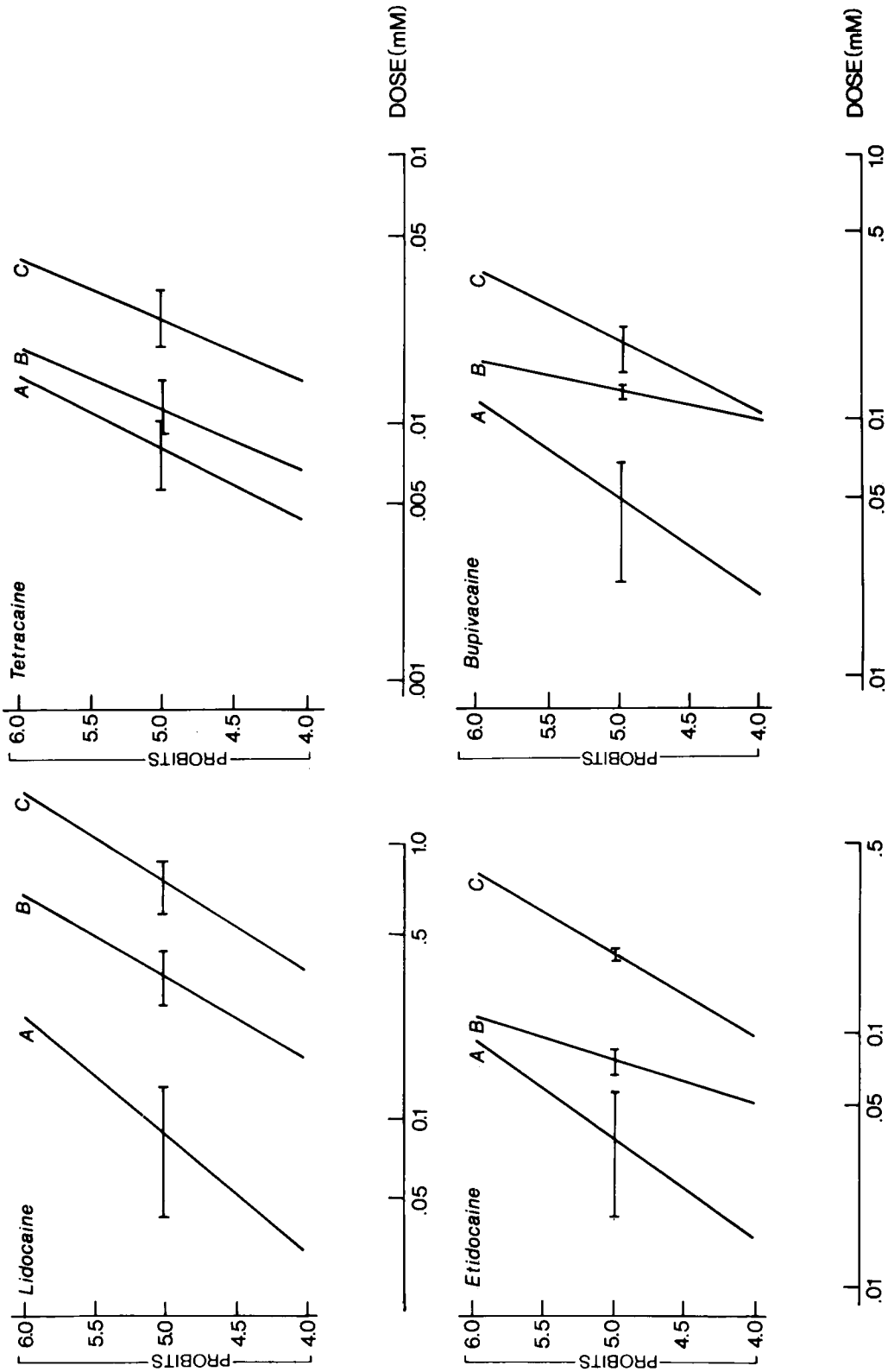

FIG. 3. Linear regression curves from vagus (B and C fibers) and sciatic nerves (A fibers) of action potential amplitudes with increasing concentrations of local anesthetic agents. Nerves were exposed at 22 C to lidocaine, tetracaine, etidocaine, and bupivacaine dissolved in Hepes–Liley solution. Drug doses are plotted in millimolar concentrations in logarithmic units. Responses as percentage decreases in AP amplitude are plotted as probits. Standard error of the estimate (SEE_x) at ED_{50}. Scale at the top relates percentages to probits.

It should be noted that in various biological stress situations fast-conducting fibers are more liable to conduction failure than are slow-conducting fibers. Fast-conducting fibers fail before slow-conducting fibers when the nerve bundle is compressed.[1,7] As bath temperature is reduced, fast-conducting fiber conduction fails, in general, at a higher temperature than does slow-conducting fiber conduction.[7] Hyperpolarization of the membrane by anodal block suppresses fast-conducting fibers before slow-conducting fibers.[7,8] Decrease in oxygen partial pressure of the perfusing medium causes large-diameter fibers to fail before small-diameter fibers.[9]

It is of interest here that clinical findings also indicate that large-diameter fibers are more liable to damage than are small-diameter fibers. In a recent revision of *Physiology and Biophysics, The Brain and Neural Function,* Ruch states that "fiber dissociation also occurs in . . . hyperpathias, nutritional or alcoholic polyneuritis, tabes dorsalis and postherpetic neuralgia, with the damage falling heaviest on the fibers of large diameter."[10]

It is possible to reconcile all of these findings if one interprets the conduction process as a bioelectrical signal traveling down an elongated conductor (the nerve fiber) (fig. 4). Conduction in an excitable membrane is a process of sequential activation in which one activated membrane area depolarizes the nearby section of membrane to threshold level by local sodium currents. In myelinated nerves the sites of membrane activation, the nodes of Ranvier, are separated by internodal areas covered with an insulating myelin sheath. However, even nonmyelinated nerves can be expected to show discontinuity between adjacent activated and nonactivated areas, and even in a nonmyelinated nerve membrane conduction should proceed in a stepwise fashion. The longer the space of interruption in sites of activation the faster the speed of conduction, but this interruption does not affect the basic physiology of excitable membrane or the process of membrane activation. Conduction velocity is thus directly proportional to the distance between activation sites (nodes of Ranvier). The largest-diameter fibers with the fastest conduction velocity always show the greatest distance between nodes (L in fig. 4).

Activation of an excitable membrane is marked by a large, rapid increase in sodium ion diffusion into the cell.[11] This occurs when the transmembrane potential reaches a critical threshold level. If this critical level is not reached, a propagated action potential does not appear and the nerve shows conduction block or failure. During sodium influx, inward current flowing at one section of the membrane cause a decrease in the magnitude of the negative transmembrane potential at the adjacent site. When the transmembrane potential at this site reaches threshold level, it too becomes highly sodium-permeable and generates current flow for the next adjacent area. Measurement of transmembrane potentials at various distances from the first activated membrane reveals that the potential shows decrement in exponential fashion with distance. This is typical of a capacity–resistance electrical circuit. If the magnitude of the

TABLE 2. Concentration ± SEE_x of Local Anesthetic Agents Required for 50 Per Cent Reduction of Nerve Action Potential Amplitudes* in Nerve Fibers of Different Conduction Velocities

	Concentrations in Nerves Classified by Conduction Velocity (mM except for TTX and STX)		
	30–60 m/sec (A fibers)	5–15 m/sec (B fibers)	Less than 1 m/sec (C fibers)
I, vagus/sciatic nerve, desheathed, 22 C			
Lidocaine	(12†) 0.085 ± 0.044	(28) 0.335 ± 0.078	(28) 0.724 ± 0.169
Tetracaine	(7) 0.009 ± 0.003	(20) 0.013 ± 0.003	(13) 0.028 ± 0.007
Etidocaine	(7) 0.042 ± 0.021	(36) 0.084 ± 0.009	(17) 0.201 ± 0.005
Bupivacaine	(9) 0.048 ± 0.023	(27) 0.134 ± 0.009	(19) 0.201 ± 0.041
II, vagus nerve, desheathed, 22 C			
Chloroprocaine		(14) 0.42 ± 0.043	(8) 0.45 ± 0.078
Procaine		(4) 0.91 ± 0.249	(3) 1.56 ± 0.305
Cocaine		(9) 0.57 ± 0.057	(4) 0.85 ± 0.306
Tetrodotoxin (TTX)		(19) 0.40 ± 0.108 μM	(12) 0.64 ± 0.294 μM
Saxitoxin (STX)		(4) 0.29 ± 0.037 μM	(11) 0.50 ± 0.145 μM
III, vagus nerve, sheath intact, 22 C			
Lidocaine		(6) 1.30 ± 0.289	(10) 2.83 ± 0.215
Tetracaine		(12) 0.03 ± 0.008	(13) 0.08 ± 0.045

* ED_{50} ± SEE_x[8].

† Numbers of experiments are given in parentheses.

potential change due to sodium influx at the first activation site is reduced, as by a local anesthetic drug, transmembrane potential is least affected at long distances from the initial activation site, while shorter distances will still be depolarized sufficiently to reach threshold conditions and activate the membrane. Therefore, conduction block should occur in the largest fibers with the longest internodal distances before the smaller fibers are similarly affected (fig. 4). This implies that the margin of safety for successful neural transmission is less in large-diameter, fast-conducting fibers than in small-diameter, slow-conducting fibers. Large-diameter fibers with longer internodal distances should be blocked at lower concentrations of local anesthetic than should small-diameter fibers.

It should be emphasized that the results obtained here apply to conduction in a peripheral mixed nerve stimulated at a frequency of one impulse per minute at room temperature. Neural communication in the intact organism is associated with repetitive stimulation at varying rates. Future studies using repetitive stimulation of varying rates on fast- and slow-conducting fibers certainly are warranted, and are now in progress in our laboratories. The use of room temperature rather than body temperature probably cannot account for these results, since Heavner and de Jong observed the same qualitative findings with lidocaine in a study of rabbit cervical sympathetic B and C nerve fibers (at 38 C, nerves not desheathed). Their report showed a 50 per cent block of B fibers at 100 μM lidocaine; similar blocks of C fibers occurred at 300 μM lidocaine.[4]

The clinical observation that pain sensation may be inhibited without motor blockade, as in differential spinal or epidural blocks, may not be contradictory to our findings. Our studies have involved peripheral mixed nerve, whereas differential spinal or epidural blockade for relief of pain sensation involves drug-induced blockade in the spinal canal.[12] The anatomy of the dorsal root entry into the spinal cord brings small-diameter nerve fibers close to the nerve root surface, thereby shortening the diffusion path of a drug instilled into the spinal subarachnoid space. The diffusion path to large-diameter fibers, which are situated deep in the nerve bundle, is longer. This would make it appear that small-diameter fibers are more susceptible to drug action than are large-diameter fibers.[13] In peripheral mixed nerve small- and large-diameter fibers are scattered at random throughout the nerve bundle, so that on the average the diffusion paths to different types of nerve are similar.[14]

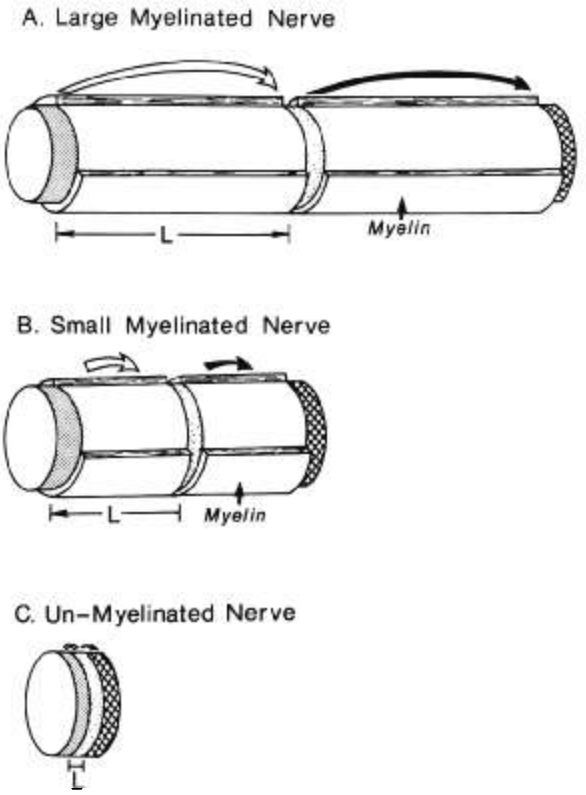

FIG. 4. The arrows represent the progression of membrane excitation in different sizes of nerve fibers at different velocities. Activation progresses from the previously activated area (heavily stippled axon segment) to an activated and sodium ion-permeable area (lightly stippled segment) to an area (crosshatched segment) not yet permeable, but being depolarized to critical threshold level. The light arrow represents decreasing current flow, the dark arrow increasing current flow. L = fiber distance between sequentially activated membrane areas.

With regard to the comparative conduction blocking potencies of the various agents evaluated, our results are similar to those obtained in the clinical situation. The biotoxins, TTX and STX, were the most potent conduction blockers. For example, the ED_{50} for inhibition of C fibers by STX was 0.50 μM, compared with an ED_{50} of 1.56 mM for procaine. Comparison in our study of the three most potent long-acting local anesthetics employed clinically, *i.e.*, tetracaine, bupivacaine, and etidocaine, revealed that tetracaine was significantly more potent than were bupivacaine and etidocaine.

The clinical impression that differential effects on sensory and motor modalities exist between bupivacaine and etidocaine could not be substantiated under the experimental conditions in this study. The ED_{50}s for conduction blockades of A and C fibers were found to be almost identical for bupivacaine and etidocaine.

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