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Lidocaine Blocking Concentrations for B- and C-Nerve Fibers

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Rabbit cervical sympathetic trunk contains myelinated preganglionic axons (B-fibers) and unmyelinated postganglionic axons (C-fibers). Using this nerve, we found B-fibers to be three times more sensitive than C-fibers to lidocaine blockade. At 38 C and pH 7.5, 100 μM (~0.003 per cent) lidocaine depresses the B-fiber compound action potential by 50 per cent. In contrast, 300 μM (~0.009 per cent) lidocaine is necessary to halve the C-fiber potential amplitude. These *in vitro* findings support clinical evidence that sympathetic block is more extensive than sensory block during spinal anesthesia. (Key words: Sympathetic nervous system: lidocaine; Anesthetics, local: lidocaine; Nerve: sympathetic blockade.)

NEARLY 50 YEARS AGO, Gasser and Erlanger[1] demonstrated that less cocaine is needed to stop conduction in thin myelinated A nerve fibers than in thicker ones. Subsequent experiments have shown, however, that this relationship between axon size and local anesthetic sensitivity does not hold when different fiber groups are compared. The smallest Aδ-fibers (1–4 μ in diameter) in spinal roots, for instance, are blocked with lower concentrations of local anesthetic than are tinier C-fibers (unmyelinated, 0.5–1 μ in diameter).[2]

While the local anesthetic susceptibility of A- and C-fibers has been well documented, that of B-fibers (1–3 μ diameter myelinated preganglionic autonomic axons) has not. Yet B-fibers are particularly important to anesthesiologists, for none of the effects of spinal anesthesia is more critical from a physiologic standpoint than profound hypotension produced by extensive preganglionic sympathetic paralysis.

Though concrete evidence is lacking, clinical observations suggest that of all nerve fibers, the preganglionic autonomic fibers are the most readily blocked. Signs of autonomic deprivation such as peripheral vasodilation and warming of the extremities often herald the onset of spinal anesthesia and commonly precede tingling and analgesia.[3] Greene[4] noted that at a time when complete preganglionic block has been achieved during spinal anesthesia, sensory anesthesia usually extends only to the second or third thoracic segment and somatic motor nerves are blocked only to the fourth or fifth thoracic level.

We present laboratory evidence to support the clinical impression that B-fibers are more readily blocked by local anesthetics than are other nerve fibers.

Methods

Small myelinated preganglionic (B-) fibers and unmyelinated postganglionic (C-) fibers predominate in the rabbit cervical sympathetic trunk.[5] When the trunk is given an adequate electrical stimulus, two discrete action potentials are recorded—an initial short latency potential arising from the B-fibers, and a later-arriving, broader-based one from the C-fibers. We used decrement in amplitude of these potentials induced by lidocaine as an index for comparing the sensitivities of B- and C-fibers to local anesthetics.[6]

Adult rabbits were killed by injecting air into an ear vein and the left and right cervical sympathetic trunks—from thoracic inlet to superior cervical sympathetic ganglion—were removed rapidly. Excess connective tissue was dissected from one trunk under a stereo microscope and the trunk placed in a nerve chamber. The other trunk was refrigerated in modified Krebs-Henseleit solution as a back-up.

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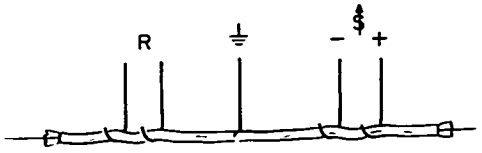

FIG. 1. Electrode array. Hooked stimulating (⏚) and recording (R) electrodes supported the nerve trunk; the grounding (⏚) electrode kept the nerve submerged in the bath. Stimulating cathode was always closest to recording electrodes.

NERVE CHAMBER

A covered nerve chamber (150 ml capacity) containing electrodes and ports for introducing fluids and gases was built for these experiments. Warm water flowing through a surrounding jacket maintained the chamber at 38 C. An assembly of two stimulating, one grounding, and two recording electrodes (platinum), as well as two plastic posts—all of which could be raised and lowered simultaneously—passed through the chamber's lid. Distance between the stimulating and recording electrodes was about 25 mm. To record from a nerve, it was loosely draped over the electrodes and each end fixed to a post with fine silk.

During an experiment, 25 to 35 ml of fresh bathing solution (modified Krebs-Henseleit continuously bubbled with 95 per cent O_2–5 per cent CO_2; see below) were placed in the chamber and the nerve immersed by lowering the electrode assembly (fig. 1). Each time records were made, the nerve was lifted out of the electrolyte solution into the chamber's moist, warm carbogen atmosphere.

A square-wave stimulator delivered pulses to the nerve (stimulating cathode closest to recording electrode) via a capacity-coupled stimulus-isolation unit. Action potentials recorded at the other end of the nerve were amplified 1000-fold (bandpass 1.5 Hz to 10 KHz), displayed on an oscilloscope, and photographed on 35-mm film.

PROCEDURE

The nerve was given 30 minutes to adapt to its new environment, then a control sequence of three B- and three C-fiber action potentials was obtained. B-fiber potentials were elicited by maximal pulses (1.5–10 V) of 0.15 msec duration. C-fiber potentials were similarly obtained with maximal (4–30 V), 0.5-msec pulses.

Next the bathing solution was replaced with fresh warmed solution equilibrated with 95 per cent O_2–5 per cent CO_2 ($pH = 7.5$) containing 25, 50, 100, 200, 300, 400, or 500 μM lidocaine (kindly supplied by Dr. Benjamin Covino of Astra Pharmaceutical Products, Inc.). Subsequently, the sympathetic trunk was lifted from the solution at set intervals (2.5, 5, 7.5, 10, 15, 20, and 30 minutes) and three B- and three C-fiber action potentials photographed. After 30 minutes, the chamber was drained, flushed twice with lidocaine-free solution, and the nerve given 60 minutes to recover.

At 60 minutes, when the action potentials' amplitudes and latencies were back to 90 per cent of control level or better, the sequence was repeated with another concentration of

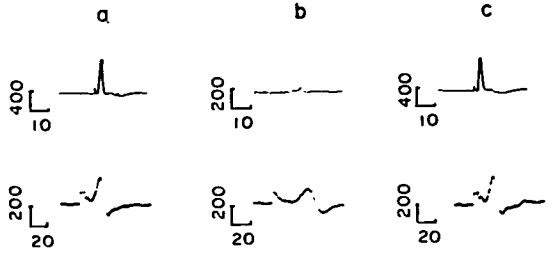

FIG. 2. B- and C-fiber potentials (upper and lower traces, respectively). In traces showing C-fiber potentials, a stimulus artifact and B-fiber potential form the first peak. *a*, control; *b*, after 10 minutes in 200 μM lidocaine; *c*, 15-minute recovery. Vertical scale = μV; horizontal scale = msec.

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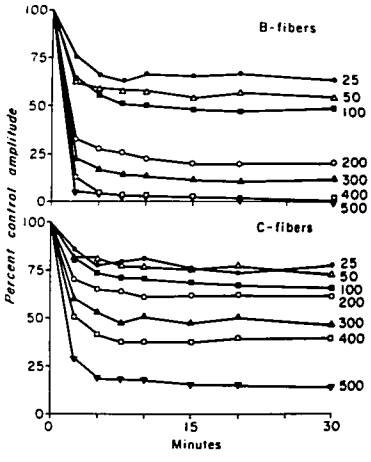

FIG. 3. Average courses of B- and C-fiber action potential changes induced by lidocaine. Lidocaine concentrations (μM) shown at the end of each trace.

lidocaine. Two or three strengths of lidocaine solution were applied, in random order, to each nerve.

Film images were enlarged and B- and C-fiber potentials identified by their characteristic propagation velocities‡ (3–15 and 0.7–2.3 m/sec, respectively[7]). Then amplitudes of the evoked potentials were measured, each set of three averaged, and the averages expressed as per cent of control amplitude.

‡ Determined by dividing distance between stimulating cathode and proximal recording electrode by period between stimulus artifact and appearance of action potential.

BATHING SOLUTION

The composition of the modified Krebs-Henseleit[8] solution was: NaCl, 109.6 mM; KCl, 6.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 27.2 mM; $CaCl_2$, 2.7 mM; NaH_2PO_4, 1.2 mM; glucose, 9.9 mM. The solution's *p*H (at 38 C) was 7.5 when bubbled with 95 per cent O_2–5 per cent CO_2.

Results

Average B- and C-fiber conduction velocities (14.8 and 1.8 m/sec, respectively; table 1) were in the normal range, and action potential waveforms were similar in all 21 nerves studied. Further, the three control B- and C-fiber action potential amplitudes for each nerve were remarkably stable, varying less than 10 per cent.

With the administration of lidocaine, action potential amplitudes and conduction velocities of both B- and C-fibers began to fall (fig. 2). The average course of amplitude changes for each fiber group is shown in figure 3. Observe the fast initial fall of spike height and rapid equilibration to a new level—maximum depression was usually reached in less than 10 minutes. In every case, the time courses of B- and C-fiber depression were the same, but the B-fiber potential always fell much farther.

Dose-response curves relating mean depression of B- and C-fiber spike heights at 10 minutes to lidocaine concentration are shown in figure 4. These curves make it apparent that B-fibers are about three times more sensitive to lidocaine than are the C-fibers. On the average,

TABLE 1. Electrical Characteristics of B- and C-fibers in Rabbit Cervical Sympathetic Trunk* (Means ± SD)

	Action Potential Amplitude (μV)	Conduction Velocity (m/sec)	Maximal Stimulus Strength (V)
B-fibers	355 ± 142.4	14.8 ± 3.1	4.5 ± 2.0 (0.15-msec pulse)
C-fibers	280 ± 139.2	1.8 ± 0.4	11.6 ± 5.4 (0.5-msec pulse)

* Trunk diameter = 315 ± 62.7 μ, measured directly with a calibrated ocular micrometer in a light microscope.

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100 μM (~0.003 per cent) lidocaine depressed the B-fiber potential by 50 per cent, whereas 300 μM (~0.009 per cent) lidocaine was needed to produce equal depression of the C-fiber potential.

The marked sensitivity of B-fibers to depression by lidocaine is further highlighted in figure 5, where amplitude changes caused by 100 and 300 μM lidocaine are compared. After 10 minutes' exposure to 100 μM lidocaine, the B-fiber potentials were half control height, whereas the C-fiber potentials remained at three fourths of control level. The lidocaine concentration (300 μM) which decreased the C-fiber response to 50 per cent of control reduced the B-fiber response to a mere 19 per cent of pre-drug level.

Discussion

Few direct measurements of B-fiber sensitivity to local anesthetics have been made. In an abstract, Everett and Toman[9] reported that

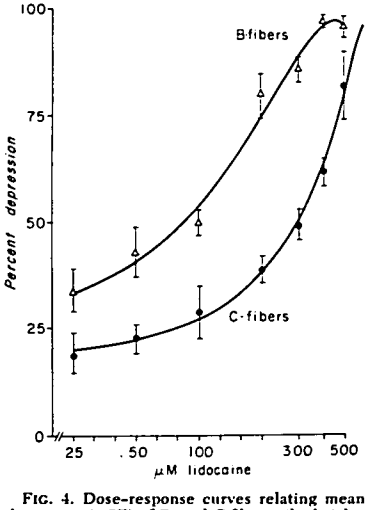

FIG. 4. Dose-response curves relating mean depression (± SE) of B- and C-fiber spike heights after 10 minutes' exposure to various lidocaine concentrations (log scale). Lines represent computed best-fitting curves.

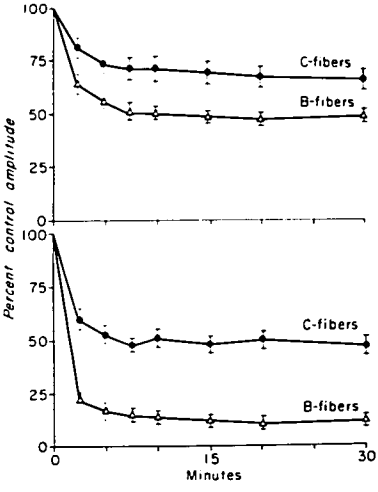

FIG. 5. Courses of B- and C-fiber action potential changes induced by 100 μM lidocaine (upper graph) and by 300 μM lidocaine (lower graph) (mean ± SE).

of the fibers in vagus, phrenic, and sciatic nerves (from rabbits, cats, guinea pigs and frogs), the B's were most sensitive to procaine. Crescitelli[10] concluded from studies on desheathed sciatic–peroneal nerves of bullfrogs that B-fibers are blocked by local anesthetics before the majority of A-fibers and before many of the C-fibers. Similarly, Ritchie and co-workers[11] showed that the onset of B-fiber block with lidocaine was faster than onset of either A- or C-fiber block in intact rabbit vagus trunks.

But the above results are not as straightforward as would appear. Vagus nerves, and probably phrenic nerves too, contain many small myelinated axons[12] which fit into the Aγ- and Aδ-fiber groups of Erlanger and Gasser.[13] These axons may contribute to "B-fiber" potentials, as some of them conduct impulses at the same rate as B-fibers do.[7] A fall in "B-fiber" potential amplitude in vagus and phrenic nerves, therefore, might just as well indicate block of small A-fibers or both small A- and B-fibers, as block of B-fibers alone.

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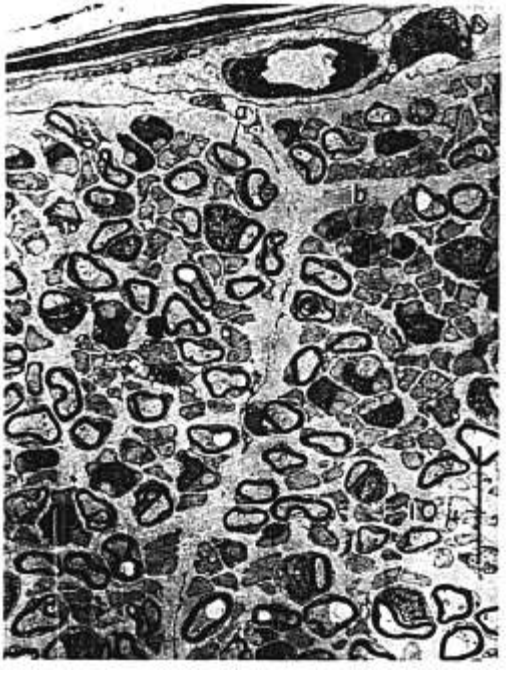

FIG. 6. Electronmicrograph showing cross-sectional portion of cervical sympathetic trunk. *a*, B-fiber; *b*, Remak bundle (several C-fibers surrounded by one Schwann cell). Note the heterogeneous dispersion of the B- and C-fibers. (Courtesy Dr. Margaret Byers, Research Associate, Department of Anesthesiology, University of Washington.)

Along the same line, conclusions drawn from sciatic nerves are questionable, as preganglionic autonomic axons probably do not course through this fiber bundle.[13] In contrast, the rabbit cervical sympathetic trunk, used in the present study, contains predominately B- and C-fibers with few, if any, A's.[14] Our data from this nerve with "pure" B- and C-fiber potentials show that B-fibers are indeed more sensitive to a representative local anesthetic than are C-fibers.

The differential sensitivities of these two fiber groups do not occur because B-fibers form the nerve's mantle layers and protect C-fibers, for B- and C-fibers are randomly dispersed in the sympathetic trunk (fig. 6). Nor is the sensitivity of the fibers a direct function of their surface area/volume ratio (which is inversely proportional to diameter), as previously suggested, for C-fibers have a higher ratio than B-fibers (0.5 μ *vs.* 1–3 μ diameter).

Local anesthetics apparently stop axonal conduction by blocking sodium channels[15] —perhaps fewer sodium channels must be "closed" or "clogged"[16] to stop impulse transmission in B-fibers. If so, the difference between the "factors of safety" of B- and C-fibers may arise because, as a result of their dissimilar relations to Schwann cells, they conduct action potentials differently. Unlike B-fibers (and A-fibers), individual C-fibers lack separate myelin sheaths.[7] Instead, a single Schwann cell forms the sheath of several C-fibers, which lie in grooves formed by the

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invagination of the outer surface of Schwann cells. A space approximately 100 Å wide between C-fibers and the invaginated Schwann cell membrane permits action potentials to flow uninterrupted along the entrapped axon. But there is no space between the nonconductive myelin sheath and membrane of B-fibers. Hence, in these nerves impulses spread by jumping from one unsheathed portion of the axon (node of Ranvier) to the next.

Another possible reason why the local anesthetic sensitivities of B- and C-fibers differ is that B-fibers, with their separate myelin sheaths, attract local anesthetics more readily than do C-fibers. (Recall that there is a high affinity between myelin and local anesthetics.) However, this does not explain our results as well as the "factor of safety" hypothesis indicated above, for when equilibration is achieved, as it evidently was in our preparation, anesthetic concentrations at the conductive areas of B- and C-fibers—*i.e.*, nodal membrane and total membrane, respectively—would be equal.

Strictly speaking, our results apply to lidocaine only. Conceivably, local anesthetics that differ physicochemically from lidocaine may block C-fibers more readily than B's. Based on clinical impression, this seems unlikely.

While B-fibers clearly are more readily blocked than are C-fibers, their comparative sensitivity with A-fibers remains to be worked out. From the known relation between A- and C-fibers—Aδ- and C-fibers being approximately equally sensitive to local anesthetics[2]—we would predict that B-fibers are the most sensitive to local anesthetics of all mammalian nerve axons. It seems reasonable to assume this, especially in view of the earlier-mentioned clinical evidence that during spinal anesthesia the level of sympathetic block extends several segments cephalad to the dermatomal level of cutaneous sensory block.

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