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Differential Effect of Nerve Fiber Structure on Block by Local Anesthetic

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The incidence of conduction block by lidocaine 0.3 mmol/l (8.1 mg/dl) in several successive lengths of individual afferent axons of rabbit was compared. The conduction velocity of the axons was either "slow," "intermediate" (1.3–4 m/s), or "fast." The "intermediate" group showed a higher incidence of proximal acceleration of conduction ($P < 0.001$) and a greater incidence of block ($P < 0.001$) than the "slow" and "fast" fiber groups. The results were interpreted as indicating that the fibers of the "intermediate" group had an unmyelinated peripheral and a myelinated proximal length, with a junctional heminodal region that was the seat of the high sensitivity to block. The potential clinical significance of the observation is discussed in terms of the known distribution of heminodes in the peripheral nervous system. (Key words: Anesthetics, local: lidocaine. Nerve: axons; conduction. Potency, anesthetic: MAC; lidocaine in vitro.

RECENT STUDIES[1–3] called in question the long-accepted doctrine that axonal size is a determinant of the blocking concentration of a local anesthetic.[4–7] They indicated that the critical concentration in individual afferent fibers depended simply on nonmyelination or myelination and recognized three pharmacologic groups, having mean blocking concentrations approximately in the ratios 3:2:1, the mean blocking concentrations for lidocaine were 0.61, 0.41, and 0.19 mmol/l (16, 11, and 5 mg/dl). The fiber groups consisted, respectively, of unmyelinated "slow" units, myelinated "fast" units of diverse sizes, and high-sensitivity units. The high sensitivity fibers had overall conduction velocities in the range 1.2–3 m/s, intermediate between that of unmyelinated and myelinated axons and were tentatively identifiable as so-called BC myelinated axons[8] with very long dendrites, such that the tested length was probably partly unmyelinated and partly myelinated, and unusually susceptible to block in the transitional region. In this paper we document the presence of increase in conduction velocity (CV) proximally in fibers of the "intermediate" group and an association with high sensitivity to block by lidocaine.

Methods

A measured length of excised vagus nerve and the inferior (nodose) ganglion from rabbit were installed in a chamber comprising two independently perfused compartments (fig. 1). Conduction in individual cervical afferent axons was detected with an extracellular recording tungsten microelectrode in the ganglion at G. Stimulation was performed in the other compartment, with one of four bare-tipped insulated platinum wire cathodes, A, B, C, D, in contact with the nerve at intervals of 10 mm. The partition between the compartments was sealed with petroleum jelly. Each compartment held about 1 ml of solution and was perfused at a rate of 5–10 ml/min with Ringer–bicarbonate–glucose solution[2] at *p*H 7.35 ± 0.05 and 37–38° C, equilibrated with 5–95% CO_2–O_2 gas mixture. The control CV (reciprocal of conduction time, CT) between A and G, termed the overall CV, as well as the CV in segments AB, BC, CD, and DG of the specimen, were determined from the CTs to G, using twice-threshold strength stimuli lasting either 100 μs, or 200 μs in the case of some unmyelinated units, applied at the various cathodes. The interval between successive stimuli was 10 s. To study the effect of lidocaine HCl on threshold and CT and the incidence of block, lidocaine 0.3 or 0.6 mmol/l (8.1 or 16.2 mg/dl) was added to the perfusate of the stimulating compartment. Exposures that did not result in block were maintained for at least 25 min, a period previously shown to suffice for approximate diffusional equilibrium of the drug.[2]

The conducted impulses were recorded with a digital oscilloscope (Nicolet 4094®) and the incidence of block during a 25–30 min exposure to lidocaine determined. The statistical significance of differences was evaluated by *t* test or contingency analysis ($P < 0.01$ being considered significant).

Results

SERIES 1

A survey of conduction velocities in different parts of the same axon was performed on 114 units, in seven preparations (41 units in two preparations in which the perineurial sheath was retained, 73 units in five preparations from which the perineurial sheath had been removed). None of these preparations subsequently was exposed to lidocaine. The ratio of the CVs in lengths BG, CG, and DG, to the overall CV in length AG is shown in figure 2, plotted as a function of the overall CV; a ratio exceeding 1.0 indicated that conduction

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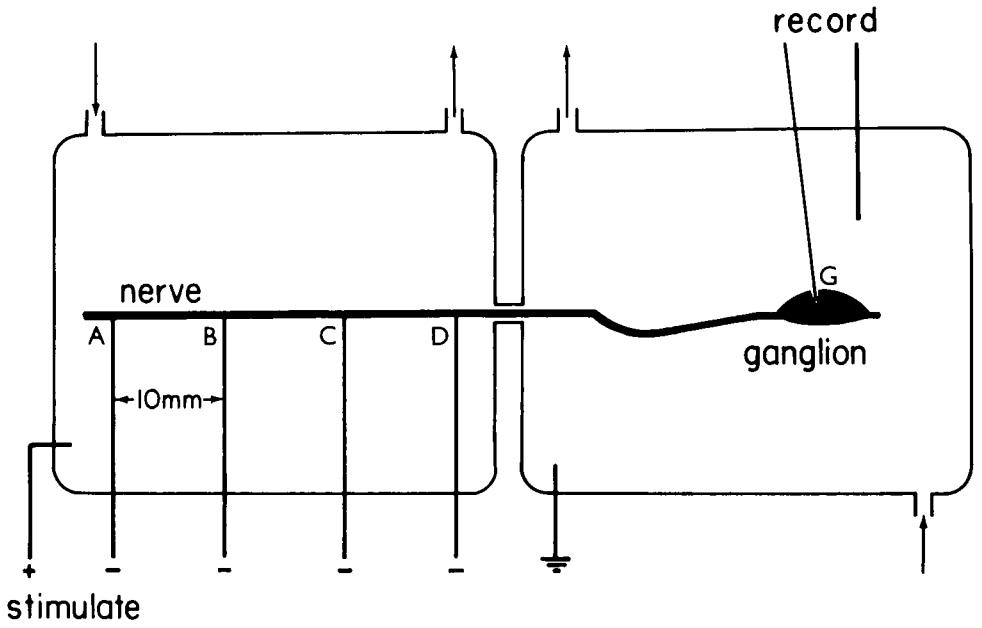

FIG. 1. Diagram of vagus nerve and inferior (nodose) ganglion in separately perfused compartments of the exposure chamber. The tungsten microelectrode G recorded extracellularly; the nerve was in contact with the bare end of four insulated platinum wire stimulating cathodes A, B, C, D, at intervals of 10 mm. The drawing is schematic and not to scale.

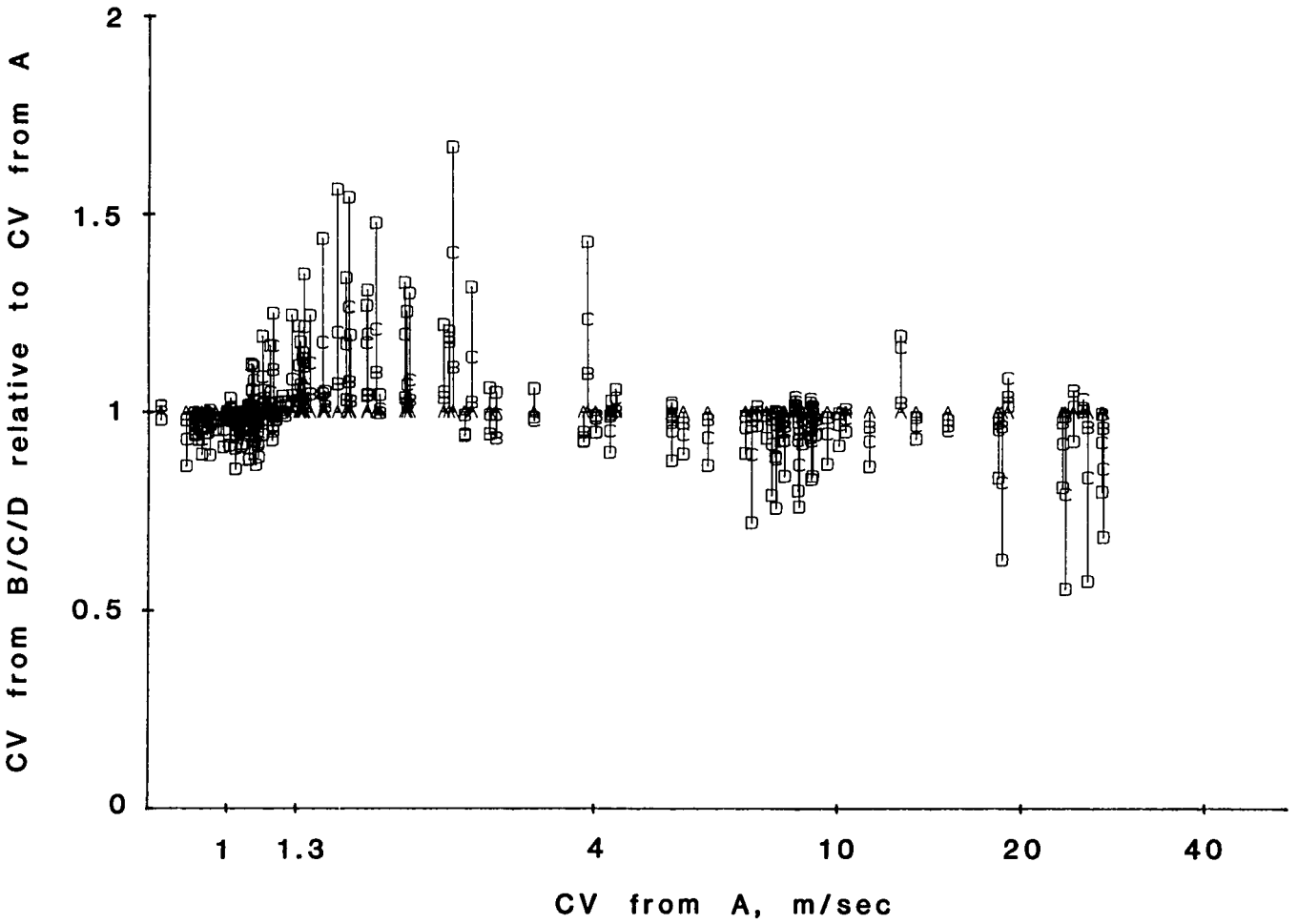

FIG. 2. Proximal-to-overall CV ratio in 114 units. Overall CV (plotted on the abscissa) was calculated from the conduction time (CT) between cathode A and the recording microelectrode in the ganglion. Proximal CV was measured from cathodes B, C, and D. A ratio exceeding 1.0 indicates impulse acceleration in the proximal length of nerve. The ratios exceeding 1.0, indicating proximal acceleration, occurred mainly in axons whose overall CV was in the intermediate range, 1.3–4.0 m/s.

accelerated somewhere between cathodes B, C, or D, and G. Acceleration appeared to be independent of the presence or absence of the perineurium. The data in figure 2 demonstrate that fibers in which ratios exceeded 1.0 belonged preponderantly to the "intermediate" velocity groups:‡ 21 of 22 fibers in which the ratio DG/AG exceeded 1.2 were in the "intermediate" group.

SERIES 2

A further 34 units in 16 preparations (perineurium retained in 1, removed in 15) underwent similar measurements and were then tested with lidocaine 0.3 mM. Of these units, 11 were "slow," 12 were "intermediate," and 11 were "fast," (table 1), intermediate here comprising units with overall conduction velocities from 1.3 to 4 m/s. Column 2 of table 1 lists the control overall conduction velocity in length AG of each fiber; columns 3 and 4, the ratio of the CV in the length DG to the CV in length AB, or DG/AB ratio, and to the overall CV in length AG or DG/AG ratio. If acceleration of conduction occurred proximal to B, one would expect to find DG/AG > 1.0 and DG/AB > DG/AG. Most of the fibers in the intermediate group conformed to this pattern; many of the fibers in the other two groups did not.

Column 5 of table 1 lists the stimulus cathodes from which stimulus conduction was blocked by lidocaine 0.3 mM. Block from all four cathodes was observed in nine units, and eight of these units belonged to the "intermediate" CV group. Contingency analysis of the grouped results (table 2) yielded chi-squared = 15.6286, $P = 0.0004$, from which we conclude that the probability of block with 0.3 mM lidocaine was significantly greater in the intermediate units than in either the slow or the fast units, *i.e.*, they were high-sensitivity units. From column 3 it is apparent that proximal acceleration of conduction was also a characteristic of these fibers.

TABLE 1. Control Overall Conduction Velocities and Proximal Acceleration of Conduction and Development of Block with Lidocaine 0.3 mM, in Fast, Intermediate, and Slow Units*

Unit No.	Conduction Velocity AG m/s	DG/AB	DG/AG	Ineffective Cathode (in lidocaine)
1	21.3	1.03	0.82	None
2	19.9	0.80	0.95	A, B, C
3†	11.4	0.54	0.62	None
4	10.6	1.05	0.97	None
5	9.14	0.73	0.76	None
6	9.12	0.98	0.95	A
7	8.25	0.76	0.80	A
8	8.17	0.66	0.77	None
9	8.13	0.93	0.93	A, B
10	7.22	0.88	0.94	None
11	5.70	1.07	1.04	None
12	3.58	1.11	1.02	None
13	3.18	1.48	0.96	All
14	2.33	1.31	1.22	All
15	2.19	1.33	1.12	All
16	2.08	1.03	1.23	All
17	2.02	1.04	1.12	All
18	1.84	2.51	1.92	A, B, C
19	1.64	1.56	1.24	A
20	1.56	2.12	1.51	All
21†	1.38	1.96	1.64	All
22	1.37	1.32	1.23	None
23	1.35	1.42	1.19	All
24	1.28	1.48	1.30	A, B, C
25	1.23	0.99	0.99	A, B, C
26	1.13	0.99	0.98	A
27	1.08	0.93	0.96	None
28	1.06	0.99	0.96	All
29	1.05	0.94	0.95	None
30	1.02	0.91	0.97	None
31	1.01	0.98	0.95	None
32	0.99	1.00	0.99	A, B
33	0.91	0.87	0.73	None
34†	0.86	1.00	0.92	None

* The units are arranged in sequence according to the control overall conduction velocity in length AG. Proximal acceleration was estimated from the ratio of conduction velocity in length DG to the conduction velocity in length AB and AG. Lidocaine 0.3 mM was perfused through the nerve compartment for 25 min. Block was monitored at the ganglion and tested every 5–10 min from stimulus cathodes A, B, C, and D. All blocks recovered with washing.

† Units in a preparation with perineurium retained.

Discussion

The data in figure 2 and table 1 demonstrate that both in series 1 and series 2 the fibers in which conduction accelerated toward the ganglion usually belonged to the high-sensitivity intermediate group. Acceleration proximally in relatively slow-conducting fibers has been noted previously in the vagus by Iggo[9] as well as by Duclaux *et al.*[8] and also in saphenous nerve.[10] Our study, however, is the first to examine the incidence of rostral acceleration of conduction in relation to overall velocity of conduction. By chi-squared test the DG/AG ratios of the high-sensitivity intermediate fibers were significantly greater than those of both the slow and fast fibers ($P = 0.001$).

Distal–proximal acceleration of unmyelinated axonal impulse conduction could be explained, in principle, by

TABLE 2. Contingency of Block in the AG Length of Vagal Afferents by Lidocaine 0.3 mmol/l

Velocity Group	Block	No Block
Fast	0	11
Intermediate	8	4
Slow	1	10

‡ In Fink and Cairns[1] the equivalent group was termed the "lidocaine high sensitivity" group and was assigned a lower conduction velocity limit of 1.2 m/s; no fibers of conduction velocities between 1.2 and 1.4 m/s were encountered. The conduction velocity limits of unmyelinated and myelinated fiber groups are not precise.

a simple increase in diameter of axon, but in the case of a DG/AB ratio of 1.96, for example (fiber 21), this would theoretically require an almost fourfold increase in diameter,[11] which seems implausibly high. It seems more likely that the acceleration was associated with the presence of a myelinated portion; in that case there would be a half node of Ranvier or heminode at the transition between the unmyelinated and myelinated portions, somewhere in the tested length of fiber. At a heminode, a relatively high probability of block by local anesthetic might be expected.[12] Such heminodes do occur in the cervical vagus of rabbit[1] and are estimated to be present in 10% of the afferents.[8]

The incidence of block by lidocaine 0.3 mM from all four cathodes in eight of the 12 intermediate units tested with this concentration (table 1) is comparable to our earlier finding,[2] where six of the group of seven intermediate units were blocked by lidocaine concentrations 0.3 mM or less. The results summarized in table 2 thus confirm the relatively high sensitivity of units in the intermediate group to block by lidocaine.

The clinical impact of the above arises out of the presence of two heminodes, one at the periphery, the other at the ganglion, in all afferent myelinated axons; on the basis of our results, each heminode could constitute a potential site for early conduction block by a local anesthetic.

In regional intravenous anesthesia the balance of evidence indicates that conduction block initially takes effect at sensory nerve endings[13–17] or small nerve branches[18] and only several minutes later at the nerve trunks.[16,19] In the light of our *in vitro* findings, this may be interpreted as early block at axonal or dendritic branch points[20] or at the peripheral heminodes of sensory fibers. Block at the neuromuscular junction during intravenous regional anesthesia,[15] which has been attributed to inhibition of the production of acetylcholine,[21,15] may also be attributable in part to early block of conduction at the terminal motor heminode.

Rostrally, a heminodal transition to nonmyelination and a "branching" occur at the approach of the bipolar afferent myelinated axon to the soma in the ganglion; these sites may be, at least in part, the seat of the reported high sensitivity of spinal ganglia to block by local anesthetic.§

Some myelinated axons may have additional heminodes at stretches of nonmyelination intercalated between myelinated segments, such as have been found in the myocardium of the dog.[22] It is tempting to ask whether the vulnerability of such sites to lidocaine plays any part in the antiarrhythmic action of this drug.[23]

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