Differential Use-dependent (Frequency-dependent) Effects in Single Mammalian Axons: Data and Clinical Considerations

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The potential clinical scope of use-dependent block of conduction (UDB) was assessed by studying characteristics of UDB in vitro in individual mammalian axons. Single and repetitive stimulation was applied to rabbit cervical sympathetic and vagus nerves exposed to solutions containing lidocaine 0.3, or 0.6 mM (9.1 or 18.2 mg/dl) at 37° C. Unit responses were recorded in dissected filaments or extracellularly in the vagus nodose ganglion. With lidocaine 0.3 mM, equilibrium conduction block, tested by single shocks, was rare. 40-Hz trains produced a significantly greater increase in latency (slowing of conduction) and a much greater incidence of UDB in the sympathetic units than in myelinated vagus axons of equivalent control conduction velocities or in unmyelinated axons. 10-Hz stimulation did not produce UDB. With lidocaine 0.6 mM, the incidence of equilibrium block was too high among sympathetic axons to assess UDB, and significantly higher than among nonsympathetic myelinated and unmyelinated units. The observations support the hypothesis that the differential block of sympathetics observed clinically with spinal anesthesia may be, at least in part, a use-dependent (frequency-dependent) effect. UDB seems unlikely to contribute to local anesthetic block of pain impulses. (Key words: Anesthetics, local; lidocaine. Anesthetic techniques: spinal. Nerve, axon; differential nerve block. Nerve: electrophysiology; frequency-dependent block; use-dependent block.)

IN SPINAL ANESTHESIA, sympathetic block extends several segments higher than somatic sensory or motor block. This differential block was previously ascribed to high sensitivity of small-diameter axons (such as preganglionic sympathetic axons) to conduction block by local anesthetics. However, this explanation seemed undermined by reports that mammalian axons in vivo and in vitro all require about the same blocking concentration, whatever their diameter (as inferred from conduction velocity). A suggested alternative explanation is use-dependent block (UDB), also known as frequency-dependent block. Hitherto, UDB has been studied only in amphibian nerve. The conditions necessary for UDB include a weak concentration of local anesthetic and a train of repetitive stimuli. Both conditions are present clinically in the zone cephaled to somatic block in spinal anesthesia, where the cerebrospinal fluid concentration of local anesthetic is too low to block somatic axons and the preganglionic sympathetic fibers carry a normal tonic flow of vasoconstrictor impulses whose effect, in cat, is maximal at a repetition rate of about 12 per second. However, the UDB diagnosed in amphibian nerve presented as depression of the amplitude of compound action potentials, and the inference of use-dependent conduction block was strictly unjustified because the depression could have been due entirely to slowing of conduction (temporal dispersion). To evaluate the true scope of use-dependent conduction block in the clinical setting it is first necessary to observe its occurrence in individual axons, notably in individual mammalian preganglionic sympathetic axons equilibrated at 37° C with known low concentrations of local anesthetic, and compare this with use-dependent behavior in individual mammalian non-sympathetic axons, myelinated and unmyelinated. The first data for such an evaluation are presented in this paper.

Materials and Methods

The required material was obtained from 66 3–5 kg white New Zealand rabbits, one nerve per rabbit. The myelinated axons in the cervical sympathetic trunk are preganglionic, conduction velocity (CV) generally 3–13 m/s, and of convenient length (4–5 cm). Action potentials in individual fibers were identified in dissected filaments of the excised trunk (fig. 1, system 1). Comparison was made with dissected filaments of cervical vagus nerve, which, in practice, yielded data for approximately equal numbers of myelinated axons of CV in and above the CV range of the sympathetic fibers (CV range of the observed sympathetic fibers was 242 m/s, of the observed myelinated vagus filament fibers 862 m/s). The faster vagal fibers were probably somatic motor axons going to the laryngeal muscles. The useful life of such preparations was relatively brief, about 2–3 h. The cervical vagus was chosen for comparison, in preference to a somatic nerve, because it is an unbranched single fascicle, suitably long (4–5 cm) and thin (0.8×0.4 mm cross section, including perineurium) for perifusional maintenance in vitro; most importantly, this nerve has received much other single fiber study and the lidocaine concentrations required for equilibrium block of conduction of individual axons, myelinated and unmyelinated, are already known. There are no grounds for supposing that the data from vagus nerve would not

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477
System 1

System 2

System 3

Fig. 1. Diagrams of exposure chambers. Partitions between compartments were sealed with vaseline. System 1, was used with sympathetic and some vagus nerves. B and A, monopolar stimulating electrodes 10 mm apart in distal, perfused compartment. Single shocks were delivered from these electrodes, to determine the conduction velocity between B and A of the unit recorded in the dissected filament in the proximal compartment. All trains of impulses were delivered from B. Systems 2 and 3 were used for vagus nerves with nodose ganglion attached. X, bipolar electrode in recording compartment, employed to search for units recorded by extracellular microelectrode in the ganglion and to verify integrity of the unit during block. In system 2 both compartments were perfused continuously but separately, and only the distal compartment received local anesthetic. In system 3, the distal and proximal compartments were perfused in tandem, and were drug-free throughout; local anesthetic was applied only to the 5 mm of nerve in the separately perfused middle compartment.

also apply to somatic nerve; data submitted for publication elsewhere do not detect any difference in sensitivity to equilibrium block between recurrent laryngeal nerve axons and small myelinated axons of cervical vagus nerve.

Additional study in individual units of cervical vagus nerve was made on undissected axons whose activity was monitored extracellularly by a microelectrode in the attached nodose ganglion (fig. 1, system 2) as previously described; these were afferent unmyelinated and small myelinated axons (CV respectively about 1 m/s and 3–25 m/s). System 2 preparations were more

convenient and sturdier than those of system 1, and allowed observation for 6 h with less than 3% increase in control latency per hour; system 2 was necessary for study of unmyelinated axons, which run in bundles and are too fine to endure protracted recording sessions after dissection.

System 3 (fig. 1) was employed because, in systems 1 and 2, the monopolar electrodes applied stimulation to a stretch of axon that was exposed to drug in the course of use-dependence tests. This did not affect responses to a supra-threshold electric stimulus, as in this investigation. However, in the clinical setting, an action potential is usually generated in a drug-free region of axon before it encounters an area containing local anesthetic. Further tests were, therefore, performed in a corresponding arrangement in vitro, system 3. This used the same type of vagus preparation as system 2, but a different length and arrangement of perfused compartments.

The design of the study thus involved several systems of exposure, which differed in the method of obtaining records from individual axons and also in the length of anesthetized and unanesthetized segments of nerve. Statistical tests described below suggested that the results in different exposure systems were at least broadly comparable.

EXPOSURE SYSTEMS

System 1, used with dissected filaments of sympathetic or vagus. The peripheral end of the excised nerve was teased into filaments under a dissecting microscope (magnifying power 10–30X); the perineurial sheath otherwise remained intact. The nerve was then installed in a Plexiglas trough comprising two compartments (fig. 1). In the distal, perfused, stimulating compartment (30 × 10 mm × 0.5 cm deep) the nerve rested on the bare tips of two insulated 0.15 mm diameter platinum wires 20 mm apart, A and B, either of which served as monopolar cathodal stimulating electrode, enabling determination of the CV of the portion of axon between the wires. The distant monopolar wire, B, was the one used for stimulation in the use-dependence tests; the total distance from this wire to the recording site was approximately 28 mm, with 1–2 mm uncertainty regarding the length of the filament in the recording compartment. The stimulating circuit was completed through a bare Pt wire projecting into the perfusate.

The teased end of the nerve lay in the unperfused, about 3 mm long, proximal compartment, in a pool of oxygenated glucose-containing Ringer's solution covered by a thin layer of mineral oil. This compartment was made as short as possible to minimize the length of unperfused nerve. One of the filaments, fine enough
to demonstrate spikes of individual fibers, was lifted on a bare 0.6 mm-diameter Pt wire into the mineral oil. This wire served as the recording electrode; an inverting electrode in the underlying solution completed the recording circuit. The potentials recorded by this technique were stable for the 30–60 min needed to complete the tests of use-dependent behavior described below. With some nerves, a second filament was studied after completing the protocol on the first.

System 2, used with ganglionated vagus nerve. This system has been described in detail elsewhere. In brief, the chamber (fig. 1) consisted of two compartments independently perfused, the distal one for stimulating, the proximal one for recording, and separated by a narrow gap through which the nerve was passed; the gap was then gently plugged with vaseline petroleum jelly. The distal compartment contained a 25-mm length of the nerve lying on two monopolar stimulating electrodes, A and B, 10 mm apart. The distal monopolar electrode, B, was used for delivering trains of shocks during tests of use-dependent behavior. The distance from this electrode to the seal between the two compartments was 15 mm. Beyond the seal, the proximal compartment contained a further 20-mm length of the nerve and the nodose ganglion. A bipolar stimulating electrode, X, was placed against this part of the nerve, approximately 10 mm from the ganglion, and was used to apply one shock every 3 s while probing the ganglion with a tungsten microelectrode in search of unitary potentials. When the axon stemming from a cell was stimulated, the conducted axonal potential invaded the parent cell body and a large action current was produced, easily distinguishable from background noise (fig. 2).

After solution containing lidocaine had been introduced into the distal compartment, the bipolar electrode could still be used to search for units. A response from this site when there was none from either A or B in the drug-perfused compartment was taken as evidence of conduction block produced by lidocaine. In the absence of drug, whenever responses were elicited from the bipolar electrode in the proximal compartment, responses could also be elicited from the two monopolar electrodes in the distal compartment, suggesting that block observed in the presence of drug was due to lidocaine and not to the condition of the nerve in the gap between the two compartments.

System 3, used with ganglionated vagus nerve. The chamber built for this purpose (fig. 1) had three compartments. The distal compartment, for stimulation and the proximal compartment, for recording, were similar in design to the two compartments of system 2. They were perfused in tandem, throughout with drug-free solution. The middle compartment, separated from the other two by vaseline-sealed partitions, was separately perfused, enabling exposure to drug to be restricted to the intervening 5 mm length of nerve. Drug equilibration times, judged by time to 95% maximal increase in latency in unblocked axons, were 20 min or less in all three systems. As discussed below, system 3 was used only with the vagus nerve and lidocaine 0.6 mM, and gave results for UDB that did not differ statistically from those on vagus in system 2 (table 1).

**Test Protocols**

The control perfusate contained (mmol/liter) NaCl 120, CaCl₂ 2.2, MgCl₂ 0.8, NaHCO₃ 16, glucose 20, equilibrated with 5% CO₂ = 95% O₂, pH 7.35–7.40, at 37–38°C. For tests of equilibrium block and UDB, made with single shocks, the perfusate contained in addition lidocaine hydrochloride 0.3 or 0.6 mM. These concentrations, known to be respectively above and below the ED₅₀ concentrations for equilibrium conduction block of individual myelinated and unmyelinated

**Fig. 2.** Responses of two individual units. Left panel, vagus myelinated axon in system 2; CV: control 9.85 m/s, in drug 3.65 m/s. Right panel, sympathetic axon in system 1; CV: control 8.85 m/s, in drug 4.89 m/s. Calibration bars: vertical, 150 µV; horizontal, 2 msec. Within each panel, the traces on the left are drug-free, the traces on the right are after equilibration with lidocaine; lidocaine concentration was 0.6 mM for vagus, 0.3 mM for sympathetic. Upper traces: responses to single shocks applied at monopolar stimulating electrodes B and A, and at bipolar electrode X in system 2. Note the increased latency (slower conduction velocity) in lidocaine from stimuli at electrodes A and B but not from X. Lower 20 traces: responses to 20 shock 40-Hz train applied at B. In control solution, both axons responded to every shock of the train; with drug, only four shocks in the train elicited responses after the first. The difference in drug concentrations is intended to exemplify the high sensitivity of sympathetic preganglionic axons to use-dependent block. The first deflection in each trace is the stimulus artifact.
TABLE 1. Use-dependent Block in Sympathetic and Vagus Units Exposed to Lidocaine 0.3 or 0.6 mM and Stimulated by a 40-Hz Train of 20 Shocks

<table>
<thead>
<tr>
<th>Nerves and (Filaments)</th>
<th>Units Tested</th>
<th>Units Blocked</th>
<th>Responses (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 0.3 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 (43) Sympathetic</td>
<td>56</td>
<td>35</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>9 (44) Vagus myelinated</td>
<td>69</td>
<td>4</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lidocaine 0.6 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagus myelinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (2)</td>
<td>11</td>
<td>5</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>6 (5)</td>
<td>10</td>
<td>3</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Vagus unmyelinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (2)</td>
<td>11</td>
<td>8</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>6 (3)</td>
<td>11</td>
<td>9</td>
<td>16 ± 3</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate system used.

axons of rabbit vagus nerve, were used to compare the incidence of equilibrium block in sympathetic and vagus units and, in unextinguished units, to produce the partial drug effect necessary for study of use-dependent block of conduction.

Stimulation was provided by a HP 85 computer interfaced to a stimulus isolation unit (model 305-2, WPI, New Haven, CT). Single electric shocks of amplitude 20% above the threshold of the studied unit were used to measure conduction times from the two monopolar stimulating electrodes and derive the CV in the intervening length of axon. Shock duration was 0.1–1.0 ms, shock amplitude 500–5000 μA. In shock trains testing use-dependence, the amplitude was set at twice the threshold of the unit and stimulation was applied at the distal electrode (monopolar electrode B). Trains consisted of eight or 20 shocks, usually at frequencies of 10 and 40 Hz. On some units, tests were made with a range of frequencies up to 160 Hz. The repetitive stimuli produced an increase in latency, most of which occurred in the first two or three responses of a train. Recovery after a train was tested with four single shocks delivered 5 s after the end of a train, and was then always more than 95% complete; however, a 5-min interval was allowed to elapse between successive presentations of shock trains. Responses were amplified by a WPI DAM-5A differential amplifier, gain 1000, bandpass 300–3000 Hz, and recorded on magnetic disk via a digital storage oscilloscope (Model 4027, Nicolet, Madison, WI).

Each study began by observing the spike of a single unit under control conditions, followed by observation of the unit during 20 min exposure of the nerve to 0.3 or 0.6 mM lidocaine. This period was more than long enough for a spike to reach equilibrium increase in latency or to be extinguished, i.e., to manifest equilibrium block. If the unit spike was not extinguished, UDB was studied in this unit both before exposure and at equilibrium during exposure to anesthetic. UDB was usually also tested in one to three other units which had remained unextinguished by the anesthetic. One of these unextinguished units was selected for observation of latency decrease during 20-min washout, and for repeat testing of UDB after washout was complete. This protocol design meant that more fibers were tested for UDB in presence of drug than were tested for UDB both in presence and absence of drug. UDB was never observed at any stimulation frequency in any axon before drug or after washout; observations after washout were, therefore, considered equivalent to observations before exposure to anesthetic, thus adding to the number of individual units studied both in the presence and absence of exposure to drug. Failures of response during trains administered to units studied only in the presence of drug were held to reflect UDB and not deterioration of the unit. The amplitude of a unit spike was stable throughout an experiment and in unblocked responses of a train, and no block was ever seen in the absence of drug, indicating that the preparation was in good condition. Therefore, when response failures occurred in the presence of lidocaine, they could be considered a drug effect, and not artificial.

STATISTICS

The $x^2$ test was used to evaluate the difference between incidences of resting block by lidocaine in sympathetic and vagus axons, and the difference between incidences of UDB in different sympathetic and vagus axon groups. The unpaired t-test was used to evaluate the difference between mean latency changes. $P < 0.05$ was considered to be statistically significant.

RESULTS

EQUILIBRIUM BLOCK

The incidence of equilibrium block of conduction in the various fiber groups and systems is summarized in table 2. The results show that, in lidocaine 0.3 mM in systems 1 and 2, the incidence of equilibrium block was approximately the same for all types of units. In lidocaine 0.6 mM, the incidence of equilibrium block did not differ significantly between systems 2 and 3 either in vagus myelinated axons ($x^2, P = 0.46$) or in unmyelinated vagus axons ($x^2, P = 0.31$), nor between pooled system 2 and pooled system 3 data ($P = 0.09$). The incidence of equilibrium block in 0.6 mM lidocaine was higher in myelinated than in unmyelinated vagus axons both in system 2 and system 3. This reached statistical
significance in system 2 (P = 0.04), but not in system 3 (P = 0.7) or the pooled data (P = 0.09). The incidence of block in sympathetic axons with lidocaine 0.6 mM was significantly higher than in vagus myelinated axons in either system 2 or 3 (P = 0.02, and 0.001, unpoled data; P < 0.001, vagus data pooled), and also higher than in unmymelanated axons (at similar levels of confidence). Equilibrium block in lidocaine 0.5 mM occurred significantly more often in vagus myelinated axons than in vagus unmymelanated axons in system 2 (χ², P < 0.05), but not in system 3 (P > 0.70).

The equilibrium decrease of conduction velocity (increase in latency) occasioned by lidocaine was determined in those units not extinguished by the anesthetic and for which comparison observations in control solution also were available (table 3). Lidocaine 0.3 mM slowed conduction in sympathetic units to about the same extent as in vagus myelinated units, but more than in unmymelanated units (P < 0.02). Lidocaine 0.6 mM extinguished so many units in a sympathetic multi-axon filament that it became difficult to identify the control of the others; it slowed conduction significantly more in vagus myelinated than in unmymelanated axons (P < 0.02), consistent with previous observations.

**USE-DEPENDENT BLOCK**

Before or after UDB test in the presence of drug, 31 sympathetic units and 22 myelinated vagus units were tested for UDB in control solution, either before exposure to anesthetic or after washout; no failure of conduction was observed during trains of impulses in any of these units at any stimulus frequency. These units are included in table 1, lidocaine 0.3 mM, where units tested only in drug are also included.

With lidocaine 0.3 mM, in system 1, UDB was tested with trains of eight 10-Hz shocks and 20 40-Hz shocks in a total of 56 sympathetic and 69 myelinated vagus units. No UDB occurred with 10-Hz stimulation. With 40 Hz stimulation (table 1), only four of the vagus axons (6%) showed any use-dependent failure of response, whereas 35 sympathetic units (62%) showed one or more response failures during a train (mean number of response failures = 12 ± 6 SD).

With lidocaine 0.6 mM, as already indicated, it was not practical to test UDB in sympathetic axons because too many were extinguished, reversibly, by this concentration. In vagus axons exposed to lidocaine 0.6 mM, 10-Hz trains failed to elicit any UDB. In system 2, 40-Hz trains of 20 shocks elicited UDB in five of 11 unmyelinated myelinated axons (mean number of response failures 9 ± 6) and eight of 11 unmyelinated myelinated axons (mean number of response failures 16 ± 3, significantly more than in the myelinated axons, t test, P < 0.05).

The high sensitivity of preganglionic sympathetic units to UDB as compared to nonsympathetic myelinated units is exemplified in fig. 2, which is representa-

<p>| Table 3. Equilibrium Slowing of Conduction by Lidocaine in Unextinguished Resting Units (Mean ± SD) |</p>
<table>
<thead>
<tr>
<th>Nerves and (Filaments)</th>
<th>No. of Axons</th>
<th>Conduction Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control m/s</td>
</tr>
<tr>
<td><strong>Lidocaine 0.3 mM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 (25) Sympathetic</td>
<td>(1)</td>
<td>33</td>
</tr>
<tr>
<td>8 (8) Vagus myelinated</td>
<td>(1)</td>
<td>14</td>
</tr>
<tr>
<td>7 Vagus myelinated</td>
<td>(2)</td>
<td>10</td>
</tr>
<tr>
<td>7 Vagus unmymelanated</td>
<td>(2)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Lidocaine 0.6 mM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Vagus myelinated</td>
<td>(2)</td>
<td>5</td>
</tr>
<tr>
<td>8 Vagus unmymelanated</td>
<td>(2)</td>
<td>8</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate system used.

* Significantly different from vagus unmymelanated axons (P < 0.02).
Table 4. Effect of Stimulation Frequency on Percentage of Units Responding to Every Stimulus of a Shock Train

<table>
<thead>
<tr>
<th>Stimulus Frequency</th>
<th>Lidocaine 0.5 mM</th>
<th>Lidocaine 0.5 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sympathetic N = 19</td>
<td>Vagus Myelinated N = 21</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>30</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>40</td>
<td>26</td>
<td>95</td>
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<tr>
<td>60</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>80</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>160</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N states number of nerves (filaments); units.

The frequency dependence of UDB was further examined using trains of shocks delivered at frequencies of 10–160 Hz (table 4). At least 5 min elapsed between successive shock trains. Nineteen sympathetic and 21 vagus myelinated axons were tested in system 1, with lidocaine 0.3 mM. Ten other vagus myelinated and 10 vagus unmyelinated axons were tested in system 3, with lidocaine 0.6 mM. Table 4 presents the percentages of these axons which responded to every shock at the various frequencies. The highest frequency at which 100% of the fibers responded to every shock is the point of particular interest. In 0.3 mM lidocaine, this was 15 Hz in sympathetic as compared to 30 Hz for vagus myelinated axons in 0.5 mM lidocaine. At frequencies greater than 40 Hz, all of the sympathetic fibers showed UDB of one or more responses, whereas about 40% of the vagus units still showed no UDB with 160-Hz stimulation. In 0.6 mM lidocaine, all vagus myelinated axons still responded to every shock of a 20-Hz train; the threshold frequency for UDB in these axons was higher than in unmyelinated axons, and 20% of them still showed no UDB with 160-Hz trains.

**Latency Increase During Shock Train**

This was studied in units which showed no block of conduction during a 10- or 40-Hz train. In lidocaine 0.3 mM, 10-Hz stimulation increased the latency in unex- tinguished cervical sympathetic axons by 7.3 ± 3.0%; 40-Hz stimulation (figs. 3, 4) increased it by 45 ± 17%; in both cases, the increase was significantly greater than in myelinated vagus axons of similar conduction velocity (t test, P < 0.02). The behavior of myelinated vagus axons was similar in system 1 and system 2 (fig. 4). In slow myelinated vagus units, the fractional latency increase during a 40-Hz train tended to vary inversely with the control conduction velocity (fig. 4, lower panel). Four of 11 unmyelinated units tested showed decrease in latency (increase in conduction velocity) during 10-Hz shock trains in lidocaine 0.6 mM (fig. 3, inset); such behavior was never seen in lidocaine 0.3 mM.

**Discussion**

This investigation has produced at least two new items of information relevant to the clinical problem and mechanism of differential spinal sympathetic block. One concerns differential sensitivity to equilibrium block; the other, differential sensitivity to use-dependent block.

Previous data on the selective sensitivity of sympathetic preganglionic axons to equilibrium block in vitro were obtained by Heavner and de Jong. They showed...
that, in weak lidocaine solutions (0.025–0.5 mM), the
compound potential of preganglionic myelinated axons
(B fibers) in rabbit cervical sympathetic trunk was more
depressed than that of unmyelinated axons in the same
trunk (C fibers). Their inference that sympathetic axons
are more sensitive to block than unmyelinated axons,
thought not strictly warranted by that evidence, as it
failed to allow for the effect of temporal dispersion, is
now confirmed and extended by the data on equilib-
rium conduction block in individual axons in the
present study (table 2). These suggest that the absolute
sensitivity of sympathetic preganglionic axons to
conduction block by lidocaine is greater than that of
non-sympathetic axons, both myelinated and unmye-
linated. However, the data indicate that this difference
amounts to a few tenths of millimol/l, which, it should
be noted, is only a small fraction of the concentration
injected by the clinician performing spinal anesthesia.
For example, 100 mg of lidocaine or equivalent drug in
2 ml of solvent is present in approximately 200 milli-
molar concentration in the injectate. Thus, the dif-
ference in absolute sensitivity may not suffice to ac-
count for the pronounced differential spinal sympa-
thetic block observed clinically.

The experimental 10- and 40-Hz trains in this study
bracketed the probable maximal physiological fre-
quency of impulses in sympathetic vasoconstrictor
fibers of cat.7 While 10-Hz stimulation did not produce
UBD in rabbit sympathetic trunk axons in 0.3 mM lidoi-
caine, it did cause significant slowing of conduction, and
might tend to decrease the preganglionic release of
vasoconstrictor in vivo.

40-Hz stimulation in the presence of lidocaine 0.3
mM elicited considerable in-tra-train increase in latency
in sympathetic axons (fig. 3), significantly more than in
vagus myelinated axons (fig. 4, bottom); intra-train
slowing of conduction seemed to be inversely related to
the conduction velocity of the axon. Also, the propor-
tion of sympathetic axons evidencing UDB with 40-Hz
was higher than in vagus myelinated axons (table 4), as
was the mean number of failures of conduction during a
train (P < 0.001). Although data on the concentra-
tion-dependence of these effects was not obtained, the
findings suffice to demonstrate that sympathetic pregan-
glionic fibers have an unusually high sensitivity to UDB.

The intermittency of UDB in many of the fibers, here
demonstrated for the first time (fig. 2), was often irreg-
ular and is readily explained. When no response was
recorded, the probability of reopening of blocked so-
dium channels increased and, eventually, enough
channels recovered to sustain a regenerative conducted
response. It should be noted that UDB of sodium chan-
nels was originally deduced from study of voltage-
clamped amphibian node of Ranvier,10,11 a preparation
that, by definition, excludes impulse conduction. UDB
of conduction was an interpretation of changes in the
amplitude of conducted amphibian compound poten-
tials, and was investigated only in myelinated axons of
undetermined conduction velocity.5,6 This is mentioned
here to point out that the magnitude of the effect in
amphibian nerve varied with the drug and happened to
be particularly rapid in onset and recovery with lidoi-
caine. In mammalian units, the onset and disappearance
of use-dependent effect of lidocaine were completed in
a few seconds (fig. 3). The differential effects of repeti-
tive stimulation in vitro, if transferable to the clinical
setting, indicate that UDB is likely to enhance the ten-
dency to selective block of sympathetic preganglionic
fibers cranial to the somatic block of spinal anesthesia.

Comparisons between vagus myelinated axons across
systems yielded similar results, and this was also true of
unmyelinated axons, both as regards equilibrium block
(tables 2, 3) and UDB (table 1). However, the increase in
conduction velocity observed in four of 11 unmye-
linated axons during 10-Hz stimulation applied to lidoi-
caine 0.6 mM was quite unusual. Such behavior was
never seen in myelinated axons of either the vagus or the
cervical sympathetic at any tested frequency of stim-
ulation, whether in lidocaine 0.3 or 0.6 mM. Nor was it seen in any unmyelinated axons in lidocaine 0.3 mM. The finding is reminiscent of the behavior of C-fiber compound potential of cat saphenous nerve discussed by Raymond and Gissen, where the potential suppressed by lidocaine 0.4 mM reappeared during 5- or 10-Hz stimulation. It is quite possible that reappearance of the C-potential was, at least in part, due to a decrease in temporal dispersion, occasioned by increased conduction velocity such as seen here in a number of individual unmyelinated units (fig. 4, inset). In nociceptive fibers, it has been suggested that this phenomenon might play a role in the perception of tourniquet pain. In general, in unmyelinated pain fibers, where physiological impulse traffic is often of less than 10 per second, useful enhancement of analgesia by UDB is unlikely to occur.

In conclusion, the relatively high incidence of UDB in vivo in preganglionic sympathetic units supports the idea the UDB occasioned by tonic physiological impulse traffic probably does contribute to differential sympathetic block during spinal anesthesia. Such UDB would be expected to develop in the zone where the anesthetic in cerebrospinal fluid is present in concentrations too low to block the somatic fibers, a zone which is well known to migrate up and down the cord in association with clinical onset and recovery.

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References