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The Long and Short of Differential Block

THE ABILITY OF LOCAL anesthetics to block impulse conduction in certain nerve fibers while sparing conduction in others has historically generated much attention. Textbooks present, as if a tested fact, the maxim that impulses in fibers of small diameter are blocked by lower concentrations of drug than those required to block impulses in larger diameter fibers.[1] This "size principle" grew from the early studies of the effects of cocaine on myelinated nerve fibers by Gasser and Erlanger.[2] By the end of the 1930s, the size principle had come to link fiber function, fiber susceptibility to anesthetics, and fiber diameter in an explanatory paradigm of such power that it continues to persist in the face of direct evidence contradicting its original premise.

Dr. Fink, whose contribution to this issue of ANESTHESIOLOGY[3] prompts this editorial, has been a significant figure among the small group of investigators who have challenged the size principle by showing that in a population of individual fibers *exposed over a sufficient length* the susceptibility to conduction block by local anesthetics (LA) is not correlated with fiber size.[4] His present paper suggests a novel anatomical basis for two types of differential block that occur clinically, integrating old concepts with more recent observations concerning the *length* of nerve exposed to LA. Our editorial goal here is to set these observations in an historical and conceptual frame and to amplify the possible mechanisms for both differential impulse blockade and differential loss of sensory and motor functions.

Impulses fail to propagate through a segment of an axon exposed to LA ("exposed segment") when the local ionic current falls below the level required to depolarize to threshold an as yet unexcited region. This apparently simple statement embraces a complex relationship between local current and impulse threshold. Even in the absence of any drug, endogenous processes modulate both the time-course of membrane current and the value of the threshold as a result of normal nerve activity. Specifically, during repetitive firing of a nerve, ions accumulate inside and outside of the axolemma, ion pumps are activated, the "resting" membrane potential changes, and metabolic activities lead to alterations of pH, CO_2, ATP, etc., which in turn alter the ionic permeabilities. The charge provided by an impulse as well as its distribution in time and over the adjacent length of nerve "cable" are correspondingly altered. As a result of all these processes, the impulse threshold is strongly shifted by repetitive impulse activity.[5]

The introduction of LA imposes a new set of processes in addition to modifying the endogenous ones. Impulses are slowed and eventually halted by LA, as the drug binds to and inhibits the voltage-gated Na^+ channels essential for membrane depolarization. (Potassium channels are also sensitive to LA, however, an effect which reduces the impulse blocking action of LAs.[6]) There are also the important "use-dependent" actions of LA, which arise from binding of drug to "activated" channels, adding to the binding to the "resting" conformations.[7] Use-dependence provides a dynamic modulation of impulse conduction (see below) that overlays the drug effects at low firing frequency and shapes the pattern of action potentials that encode sensation and motor output. The integrated phenomena are complex, yet they provide a vivid image for intuiting LA action under clinical conditions where impulse activity is present, and where the length of the exposed segment and the concentration of LA are continually changing.

Aspects of this image are illustrated in figure 1, where propagation of a train of impulses through a single myelinated axon is simulated during exposure of a 2.25-cm

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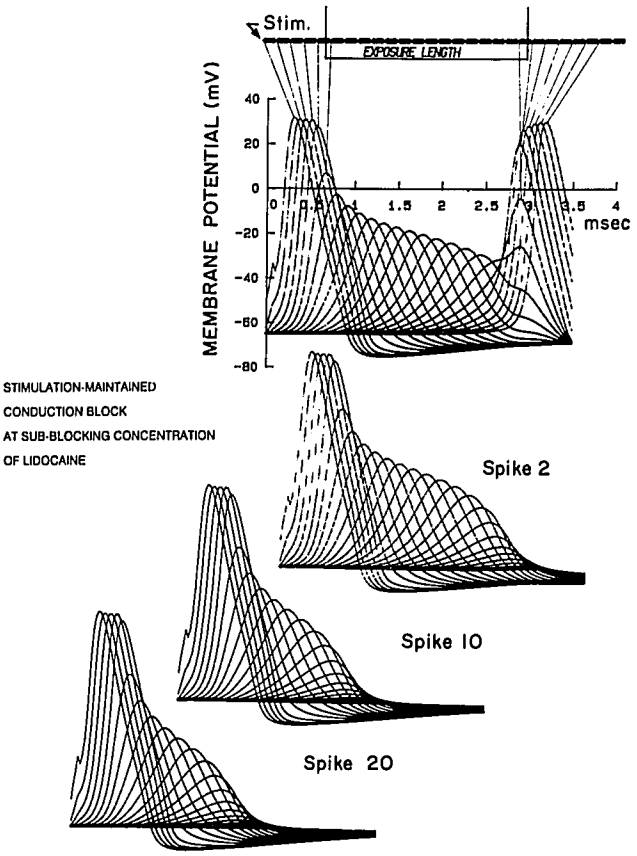

FIG. 1. Mathematical model of myelinated axon showing use-dependent conduction failure during a train of 20 impulses at 50 Hz. The first impulse, plotted *versus* time (top) at each successive node, declines in amplitude and slows as it propagates through the 15-node segment exposed to lidocaine. The second (and later) impulses diminish so extensively in the exposed segment that they do not have enough local current to depolarize the first unexposed node past its threshold, and the impulse dies. We incorporated the binding affinities of lidocaine to Na^+ and K^+ channels under resting conditions and to Na^+ channels during depolarizations into a simulation of the conducting spike using the "CABLE" program supplied by Drs. Hines and Moore at Duke University. Reprinted from Raymond SA, Thalhammer JG, Strichartz GR: Axonal excitability: Endogenous and exogenous modulation, Restorative Neurology: Altered Sensation and Pain. Edited by Dimitrievic MR. Basel, Karger, 1989, in press, with permission of the publisher.

segment to a sub-blocking dose of LA. At the chosen frequency of incoming pulses (50 Hz), [LA] (.29 mM) and length of the exposed segment (15 nodes), only the first impulse in the train avoids annihilation. The others fail within the exposed region, but each impulse partially invades and depolarizes this zone, thereby maintaining the use-dependent block for all subsequent impulses in the train.[9] Imagine now that any one of the parameters critical for propagation failure in this one axon is changed; impulses may now succeed because of decreases in either drug concentration, length of the exposed segment, or frequency of incoming impulses.

In the present article, Dr. Fink focuses on the role of the length of the exposed segment. After Tasaki demonstrated in 1939 that the impulse in a myelinated nerve could usually jump one, occasionally two, but never three, completely blocked nodes,[10] the importance of exposure length was widely accepted.[11] It was also commonly assumed, however, that exposure lengths of 1 cm (approximately twice the length occupied by three internodal segments in the largest diameter myelinated fibers[12]) were more than sufficient to equalize LA actions on fibers of all diameters.[13] However, decremental conduction had been demonstrated in axons exposed to LA concentrations just sufficient to block impulse conduction.[14] These concentrations do not block all voltage-gated current, so the exposed nodes give a sub-maximal depolarization that will not propagate indefinitely but will "decrementally" extend the reach of a dying impulse along the axon.

Recent studies of single fibers, exposed to drug over 3–6 cm, do not support the size principle.[4,15] Furthermore, review of decremental conduction in the context of experimental studies of differential block suggests that exposure length could be an important factor determining the blocking concentration of LA over distances greater than three internodal lengths.[13,16] This suggestion anticipated Dr. Fink's retrospective survey of his and Dr. Cairns' previously published results from single vagal fibers studied at several different set lengths.[15] They reported a tendency for any given LA concentration to block more fibers when the exposure length was longer (25–40 mm) than when it was relatively shorter (5–15 mm). Concurrently, the original suggestion was confirmed by direct tests where the exposure length was varied systematically (with LA concentration constant) from 7 to 33 mm.[17] It now appears that length of nerve exposed is an important determinant of the blocking LA concentration, particularly for exposure lengths up to 3 cm, and declining progressively at greater distances.

Dr. Fink's present paper uses this relation to reinterpret the *differential* block of pain during epidural block where motor function is spared. He points out that the length-dependence of sensitivity to LA, together with the previously established relationships between fiber diameter, internodal distance, and conduction velocity, as well as the relationship of conduction velocity to fiber modality or function, can account for *differential* block of motor function and pain sensation. In contrast to prior explanations based on an absolutely higher susceptibility to block of small fibers, his hypothesis requires only that the local anatomy provide diffusion constraints to limit the length of axons exposed to a blocking concentration of LA. Given this, a differential block of small fibers follows even if the susceptibility of small and large fibers (exposed over long distances) is the same.

He also interprets the dermatomal distribution of loss

of pain sensation *versus* touch or motor function during axial blockade—the well-known feature that the pain sensation will not be present several dermatomes rostral to the dermatome where sensation to light touch of the skin is blocked.[18] Here, he recognizes that the effective bathed length (equivalent, he claims, to the length of the dorsal roots themselves) decreases progressively along the cord from sacral to thoracic segments. Thus, in the thoracic region, where root lengths are in the range where exposure length is an important determinant of blocking concentration, the larger fibers will have fewer nodes exposed to LA and might therefore preserve conduction longer than small fibers where more nodes would be exposed.

These suggestions are innovative. They link clinical observations to anatomical findings in both human and animals and to measurements made *in vitro* on isolated nerves, thereby generating interesting predictions and possibilities. They lead the discussion of differential block away from a broad susceptibility to LA according to fiber size to focus on the number of nodes per unit length, which is correlated with fiber size. Clinically, this permits retention of familiar interpretations (based on the size principle) of phenomena consistently seen during epidural and spinal anesthesia, and it does not deny the single fiber data showing similar LA susceptibility across the fiber spectrum (for long exposed segments). The ideas are, in this sense, an extension of the size principle, not a renunciation of it.

The position of nonmyelinated fibers in the order of LA susceptibility is not easily specified according to exposure length, for the extent of decremental conduction has not been measured in these small fibers. Second pain and the sensation of warmth, both mediated by C-fibers, are typically lost early during the onset of regional blocks, and the reduction of the C-fiber component of compound action potentials measured *in vitro* occurs earlier than that of myelinated fiber elevations, although the A-fiber component eventually falls proportionately more than that of C-fibers.[19]

To date, there have been no direct tests of the central tenet required for Dr. Fink's explanations to hold true, that small fibers will, in fact, fail as a group to conduct under conditions of LA concentration/exposure length where large fibers will conduct successfully. Existing direct data show only that wide individual variation exists among fibers, and that exposure length is a factor for both large and small fibers even above 20 mm.[17]

Implicit in all these arguments is an assumed proportionality between perceived intensity, and the relative firing frequencies in modality-specific peripheral afferents. During partial LA blockade, the most profound change in peripheral nerve conduction is the altered pattern of impulses arriving at the spinal cord (fig. 1), but the consequences of this modification for postsynaptic integration and for qualities of sensation are unknown.

At present, the field is at a cusp. It may be that size-based distinctions among fibers regarding both physiological function and susceptibility to LA will be shown to be the most appropriate explanations of differential block; or it may be that other distinctions among fibers are the essential ones. What other dimensions of conduction success might be discerned in differences among fibers? Fibers may vary in the relative densities of Na^+ and K^+ channels, in the incremental changes in ion concentration following impulses, in the degree of metabolic activity (ion pumps) required to restore the ionic gradients, and even in the type and LA sensitivity and binding kinetics of the different ion channels. Present research on the relation of these fiber differences to LA susceptibility holds the promise of testing Dr. Fink's novel ideas concerning the importance of exposure length in differential block.

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References

1. Miller RD: Anesthesia. New York, Churchill Livingstone, 1981, p 575
2. Gasser HS, Erlanger J: Role of fiber size in establishment of nerve block by pressure or cocaine. Am J Physiol 88:581–591, 1929
3. Fink BR: Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. ANESTHESIOLOGY 70:851–858, 1989
4. Fink BR, Cairns AM: Differential peripheral axon block with lidocaine: Unit studies in the cervical vagus nerve. ANESTHESIOLOGY 59:182–186, 1983
5. Raymond SA: Effects of nerve impulses on threshold of frog sciatic nerve fibres. J Physiol (Lond) 290:273–303, 1979
6. Strichartz G: Interactions of local anesthetics with neuronal sodium channels, Effects of Anesthesia. Edited by Covino BG, Fozzard HA, Rehder K, Strichartz GR. Bethesda, American Physiological Society, 1985, pp 39–52
7. Strichartz GR, Ritchie JM: The action of local anesthetics on ion channels of excitable tissues, Local Anesthetics, Handbook of Experimental Pharmacology, volume 81. Edited by Strichartz GR. New York, Springer-Verlag, 1987, pp 21–52
8. Courtney KR, Kendig JJ, Cohen EN: Frequency-dependent conduction block: The role of nerve impulse pattern in local anesthetic potency. ANESTHESIOLOGY 48:111–117, 1978
9. Raymond SA, Thalhammer JG, Strichartz GR: Axonal excitability: Endogenous and exogenous modulation, Restorative Neurology: Altered Sensation and Pain. Edited by Dimitrievic MR. Basel, Karger, 1989, in press

10. Tasaki I: Nervous Transmission. Springfield, Thomas, 1953, p 164
11. Franz DN, Perry RS: Mechanisms for differential block among single myelinated and non-myelinated axons by procaine. J Physiol (Lond) 236:193–210, 1974
12. Arbuthnott R, Boyd IA, Kalu KU: Ultrastructural dimensions of myelinated peripheral nerve fibers in the cat and their relation to conduction velocity. J Physiol (Lond) 308:125–157, 1980
13. Raymond SA, Gissen AJ: Mechanisms of differential nerve block, Local Anesthetics, Handbook of Experimental Pharmacology, Vol. 81. Edited by Strichartz GR. New York, Springer-Verlag, 1987, pp 95–164
14. Lorente de Nó R, Condouris GA: Decremental conduction in peripheral nerve: Integration of stimuli in the neuron. Proc Natl Acad Sci USA 45:592–617, 1959
15. Fink BR, Cairns AM: Lack of size-related differential sensitivity to equilibrium conduction block among mammalian myelinated axons exposed to lidocaine. Anesth Analg 66:948–953, 1987
16. Condouris GA, Goebel RH, Brady T: Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. J Pharmacol Exp Ther 196:737–745, 1976
17. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR: The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 1989, in press
18. Rocco AG, Raymond SA, Murray E, Dhingra U, Freiberger D: Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. Anesth Analg 64:917–923, 1985
19. Gissen AJ, Covino BG, Gergus J: Differential sensitivity of fast and slow fibers in mammalian nerve. II. Margin of safety for nerve transmission. Anesth Analg 61:561–569, 1982