New Modes of Nerve Block

In 1966, Bertil Hille showed that lidocaine and procaine selectively depress sodium currents in large-diameter myelinated nerve axons. Since that demonstration, clinically useful local anesthetics have been assumed to block nerve conduction by directly blocking sodium channels. The paper by Schneider et al. in this issue of ANESTHESIOLOGY breaks new ground by showing a different mechanism for nerve conduction block, and moreover a mechanism that apparently has the useful property of selectively blocking small-diameter unmyelinated C-fibers.

The steroidal alkaloid veratridine holds sodium channels open rather than blocking them. The resulting high permeability to sodium leads to membrane depolarization and to sodium ion accumulation inside the axon. Because veratridine preferentially binds to open channels, the membrane potential further decreases every time a passing impulse opens the remaining drug-free channels and more drug binds. The cumulative activity-dependent depolarization results in conduction block because of the way transmembrane voltage regulates sodium channels; they become inactivated when exposed to prolonged depolarization. Sodium channels are exquisitely sensitive even to small changes in membrane potential, so that a 4–5-mV decrease in resting potential can reduce channel availability by 25%. Selectivity for sensory versus motor and for nociceptive versus nonnociceptive sensory afferent fibers is a highly desirable and long-sought property for local anesthetics. Veratridine appears to preferentially block unmyelinated C-fibers, a population which includes some nociceptive afferent fibers, for reasons probably including those suggested in the paper by Schneider et al. The large surface-to-volume ratio of small-diameter fibers permits more sodium accumulation in them than in large-diameter fibers. Differences in sodium and potassium ion channel distribution between myelinated and unmyelinated fibers may also play a part in selective block.

There may be more than one way to achieve conduction block with such selectivity. Veratridine produces its indirect effects on sodium channel availability probably by a direct action on sodium channels. However, any drug action that prolongs depolarization after an impulse passage may exert some of these same effects, either by blocking conduction itself or possibly by serving as an adjuvant to more traditional local anesthetics, themselves voltage-dependent. Among promising additional possibilities are agents that block potassium channels and thereby delay repolarization in some nerves. Differences in potassium channel populations may offer an additional avenue for selective actions on sensory nerves of different modalities. Indeed, local anesthetics themselves block certain potassium channels and thus potentially modify their own conduction blocking properties. It is desirable, therefore, that design of useful new local anesthetics or anesthetic adjuvants focus on agents which foster activity-dependent depolarization.

Clinical application of veratridine or other novel agents for local anesthesia probably lies some distance in the future. Currently, the paper by Schneider et al. is important because it may change the way one thinks about local anesthesia. Wherever the search for new strategies may

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turn, it is time to expand the idea that local anesthetics act only by directly blocking sodium channels. Local anesthetics block conduction by definition, but there are more than one means to that end.

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