EFFECTS OF TERTIARY LOCAL ANESTHETICS AND THEIR QUATERNARY DERIVATIVES ON SODIUM CHANNELS OF NERVE MEMBRANES

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Local anesthetics selectively block sodium channels in excitable membranes. Several mechanisms for blocking action have been hypothesized, including membrane distortion due to volume expansion and changes of the intramembrane electric field due to surface charge alterations, but the evidence from most electrophysiological experiments supports the concept of a specific interaction between a local anesthetic molecule and the sodium channel itself. Since local anesthetics are usually tertiary amines, existing as neutral base and cationic forms in equilibrium at physiological pH, questions arise about the relative efficacy of the two forms as well as the site of action and the mechanism of the block. The experimental results summarized here suggest that (*a*) both forms of the drug are effective as inhibitors; (*b*) receptor "sites" exist both within the aqueous pore of the sodium channel and in the hydrophobic region adjacent to the channel, and (*c*) there may be more than one mechanism of action. For example, one anesthetic type may plug the aqueous pore, and another type interfere with the normal opening and closing (gating) function, and some may act both ways. To determine the site of local anesthetic action, tertiary anesthetics have been applied inside and outside axons at different internal and external pH values. Faster, larger blocks of sodium permeability (P_{Na}) occur under conditions which favor the presence of cationic anesthetic inside the axons, a conclusion supported by the observation that cationic quaternary derivatives of anesthetics (QX), which are relatively membrane-impermeant, block sodium channels only from the inside.

A remarkable feature of the block by both QX and tertiary anesthetics is its "use-dependence;" rapid stimulation of action potentials or depolarization under voltage clamp enhances the P_{Na} inhibition beyond its value at rest. Use-dependence is readily reversible and the electrical conditions that promote its onset and its reversal show that it requires an opening of the sodium channels. In particular, the inactivation parameter of sodium permeability (*h*) must be removed for use-dependent block. Pronase-treated squid axons that have no inactivation show no use-dependence. The pronased axon acquires an "inactivation" in the presence of certain QX molecules; apparently the channels open during a depolarization and are then continuously occluded by QX molecules throughout the depolarization.

Modulation of anesthetic block by inactivation is reciprocated; the inactivation

parameter itself is modified by local anesthetics when they block. Voltage-dependence of h is shifted to hyperpolarizing potentials and the time-constant is lengthened, and use-enhanced block of P_{Na} corresponds to an increased shift. The shift may be reversed by changing external Ca^{2+} concentrations; this may be the basis for reports of the antagonism between calcium and local anesthetics. The shift in the voltage-dependence of h cannot be due simply to a local charge (cationic anesthetic) binding near the channel gates, because the neutral anesthetic benzocaine also produces these shifts.

Certain tertiary anesthetics produce a very slow inhibition of P_{Na} during a long, continuous membrane depolarization. This depression has the same dependence on the voltage of the long depolarization as normal sodium inactivation and is believed to represent a population of inactivated sodium channels that subsequently bind tertiary anesthetics, producing so-called slow inactivation. Since the conditions for slow inactivation are very different for use-dependent block, Khodorov et al. have proposed several different "receptors" for tertiary local anesthetics and QX compounds (3).

Very recent experiments by Almers and Cahalan have shown that QX molecules can interfere with sodium gating currents (I_g) (4). In normal squid axons the establishment of a use-dependent block is paralled by a depression of gating current. Such a depression is absent in pronase-treated (inactivation-free) axons, which show no use-dependence. If tetrodotoxin is blocking the sodium channels from the external opening, then the reduction of I_g by QX is greater than normal and becomes independent of use. Perhaps the sodium ions that normally pass through the channel pore compete with the charged QX molecules for some binding site.

A model to explain the several mechanisms of anesthetic block has been proposed by Hille (5). This scheme includes only one anesthetic receptor in the sodium channel, accessible to hydrophobic molecules via the membrane phase and to hydrophilic molecules via the aqueous pore from the axoplasmic opening. Hydrophobic molecules can reach the receptor at any time whereas the hydrophilic drugs can only enter open sodium channels. However, both types of anesthetic promote sodium inactivation upon binding to the receptor; thus the block by either type depends on the state of the inactivation parameter. Depression of P_{Na} also occurs because of blocking of the channel pore by the anesthetics at their binding site.

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