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LOCAL ANESTHETIC MOLECULES TRANSIENTLY BLOCK CURRENTS THROUGH INDIVIDUAL OPEN ACETYLCHOLINE RECEPTOR CHANNELS

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Local anesthetics modify the time-course of end plate currents (EPCs) and miniature (M) EPC's and alter the spectra of acetylcholine (ACh)-induced EPC's, but the mechanism of local anesthetic action is not known. After studies of MEPC's and spectra of ACh noise, Ruff (1976) found that a sequential kinetic scheme described the effect of QX-222: $(nA + R \rightleftharpoons AnR) \overset{}{\underset{\alpha}{\rightleftharpoons}} AnR^* \overset{Q\overset{G}{}}{\underset{F}{\rightleftharpoons}} A_n R' Q$ where R is a receptor, R^* is an open receptor, R' is an open receptor with a greatly reduced conductance, A is an agonist molecule, and Q is a local anesthetic molecule. Erwin Neher and I have used the extracellular patch clamp (Neher and Sakmann, 1976) to examine the effect of QX-222 on currents through single, open ACh receptor channels in the extrajunctional regions of denervated frog cutaneous pectoris muscles. Receptors were activated by suberyldicholine in the absence or presence of QX-222 (5-50 μM). Typical records are shown below:
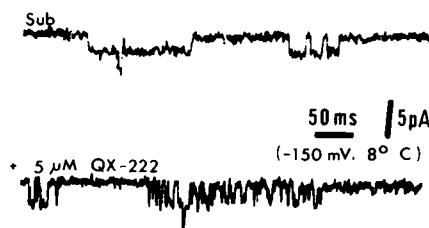
Qualitatively, the effect of QX-222 is consistent with the sequential scheme. Quantitative analysis of the data confirmed this impression, and allowed us to extract the fol-

lowing rate constants for QX-222 at 8–9°C: α = 120 exp $(V/76)$ s^{-1} (Voltage in milli-volts), F = 1.85 · 10^3 exp $(V/92)$ s^{-1}, and G = 1.80 · 10^6 exp $(-V/62)$ M^{-1} s^{-1}.

All of the data conformed to the predictions of the sequential scheme. In particular, the derived rate constants could be used to predict the average burst duration at various membrane potentials and QX-222 concentrations and also the spectrum of intracellularly recorded membrane current fluctuations produced by suberyldicholine application in the presence of QX-222.

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A UNITARY THEORY OF ANESTHESIA
BASED ON LATERAL PHASE SEPARATIONS
IN NERVE MEMBRANES

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A theory of anesthesia has been presented that suggests that the primary effect of anesthetic agents is an alteration of the lateral phase separation behavior of nerve membranes (1). Anesthetics may produce this effect by interacting with the fatty acid chains of the membranes (2–5), with the polar head groups of phospholipids (6, 7), as well as by modifying or competing with the effect of di- or monovalent ions (8). Changes in temperature or pressure will produce the expected thermodynamic response in the phase separation temperature. The sum of all the effects of an anesthetic molecule due to its charge, steric bulk, polarizability, hydrophobicity, and ability to affect van der Waals interactions leads to a modification in the phase separation behavior in a membrane of a particular composition. Membranes of different composition will respond differently: hence the selective effect of certain drugs with regard to inside versus outside of a nerve as well as axonal versus synaptic function. A modification of phase separations in a membrane will affect many of the properties of the nerve (1, 9). Some of these effects may be irrelevant to anesthesia but nevertheless depend on anesthetics concentration.

It is suggested that local anesthetics act by the same mechanism as inhalation anesthetics: changes in ion concentration, pH, temperature, and pressure, to modify the lateral phase separation properties of a particular membrane. This modification re-