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

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.

## REFERENCES


RUFF, R. L. 1976. Local anesthetic alteration of miniature endplate currents and endplate current fluctuations. *Biophys. J.* **16**:433–440.

NEHER, E., and B. SAKMANN. 1976. Single-channel currents recorded from membrane of denervated frog muscle fibres. *Nature (Lond.).* **260**:779–802.


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


JAMES R. TRUDELL, *Department of Anesthesiology, Stanford Medical School, Stanford, California 94305*


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-

sults in a loss of lateral compressibility in the plane of the membrane (9) with a resulting inability of membrane proteins to change conformation or undergo insertion. Examples of the many membrane functions which may be altered by this unitary mechanism are: inability of a sodium pore to change conformation during the gating process, inability of sodium pore subunits to self-assemble in the plane of the membrane to form an ion channel, and the reduced rate of synaptic vesicle fusion when lateral phase separations are destroyed by anesthetic molecules.

## REFERENCES


1. TRUDELL, J. R. 1977. A unitary theory of anesthesia based on lateral phase separations in nerve membranes. *Anesthesiology.* **46**:5–10.
2. TRUDELL, J. R., D. G. PAYAN, J. H. CHIN, and E. N. COHEN. 1975. The antagonistic effect of an inhalation anesthetic and high pressure on the phase diagram of mixed dipalmitoyl-dimyristoylphosphatidylcholine bilayers. *Proc. Natl. Acad. Sci. U.S.A.* **72**:210–213.
3. JAIN, M. K., T. W. NORA, and L. V. WRAY 1975. Drug-induced change in bilayer as possible mode of action of membrane expanding drugs. *Nature (Lond.).* **255**:494–495.
4. VANDERKOOI, W. M., R. LANDESBERG, H. SELCK, II, and G. G. MCDONALD. 1977. Interaction of general anesthetics with phospholipid vesicles and biological membranes. *Biochim. Biophys. Acta.* **464**: 1–16.
5. HILL, M. W. 1974. The effect of anesthetic-like molecules on the phase transition in smectic mesophases of dipalmitoyllecithin. I. The normal alcohol up to C = 9 and three inhalation anaesthetics. *Biochim. Biophys. Acta.* **356**:117–124.
6. SHIEH, D. D., I. VEDA, H. C. LIN, and H. EYRING. 1976. Nuclear magnetic resonance studies of the interaction of general anesthetics with 1,2-dihexadecyl-*SN*-glycero-3-phosphorylcholine bilayer. *Proc. Natl. Acad. Sci. U.S.A.* **13**:3999–4002.
7. LEE, A. G. 1976. A model for action of local anesthetics. *Nature (Lond.).* **262**:545–548.
8. STRICHARTZ, G. 1976. Molecular mechanisms of nerve block by local anesthetics. *Anesthesiology.* **54**: 421–441.
9. SHIMSHICK, E. J., and H. M. MCCONNELL. 1973. Lateral phase separation in phospholipid membranes. *Biochemistry.* **12**:2351–2360.