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Editorial Views

The Applicability of Membrane Models to Studies of the Mechanism of Anesthetic Action

DESPITE nearly a century of effort, the molecular basis of anesthesia remains an unsolved problem. Its solution is made difficult by the lack of a generally accepted molecular mechanism of nerve action. Thus a study of anesthetic action cannot proceed until the primary site of action of drugs within the nerve is known. The paper by Ueda, Shieh, and Eyring, "Anesthetic Interaction with a Model Cell Membrane: Expansion, Phase Transition and Melting of the Lecithin Monolayer," describes how inhalation anesthetics may affect a model membrane system. It is valuable to consider their results in the context of other research into the mechanisms of anesthesia.

Numerous difficulties are present when one attempts to isolate a single function within a system as complex and relatively unknown as a nerve. Therefore, investigations of anesthetic effects are often performed on nerve membrane models. Appropriate choice of the model system allows precise measurement of a particular variable. It remains, of course, for the investigator to prove that that which was measured in the model is relevant to the *in-vivo* function of actual nerves.

A currently accepted description of a nerve cell membrane (Singer and Nicholson[1]) is that of a phospholipid bilayer with functional proteins solvated within, as well as bound to, the inside and outside of the bilayer. The phospholipid bilayer is two phospholipid molecules thick, the polar phosphate head groups of the phospholipids forming the inner and outer membrane walls, while the hydrocarbon chains of the phospholipid form the hydrophobic center of the membrane. If one were to split this phospholipid bilayer membrane in the plane of the hydrophobic core, it would yield two identical monolayers.

Ueda *et al.* have prepared such monolayers by spreading phospholipid molecules onto a water surface until a film exactly one molecule thick is formed. The monolayer then self-assembles such that the very polar hydrophilic phosphate head group of each phospholipid is in contact with water at a water–air interface, while the hydrophobic, hydrocarbon "tails" of the associated fatty acid chains are perpendicular to the water–air interface and extend into the air. The lipid–water interface in a monolayer model is similar to the environment of the surface of a nerve membrane. The surface tension at this interface is measured by a sensitive balance. Expansion of the monolayer in a plane parallel to the lipid–water interface is reflected as a change in surface tension. The ease of this measurement provides an important reason for use of a monolayer model in surface expansion studies. The model mimics a characteristic of the nerve cell membrane, and effects of anesthetics on this model may predict their effects on the phospholipid components of real cells.

In these studies, Ueda, Shieh, and Eyring have added some important data to the body

of knowledge relating the effects of anesthetics on model membrane structure. Translation of their monolayer model results to the properties of a nerve membrane would suggest that anesthetics make the interior of the membrane more fluid, expand the membrane surface area, make it more compressible, decrease the work required to expand or contract it, and cause the membrane to function as though it were at a higher temperature. These results are in good agreement with the previous work of Dean,[2] Clements and Wilson,[3] and others.[4,5,6] These anesthetic-induced changes in membrane properties may be important to understanding how anesthetics act.

Johnson and Eyring[7] previously suggested that anesthesia is a result of a direct protein–anesthetic interaction which causes a conformation change in a protein. A small conformation change in a protein essential to nerve function is likely to inhibit that function; a larger change may stop the function altogether. The present authors suggest that the anesthetic-induced changes in the lipid matrix of a nerve membrane allow the direct anesthetic effect on proteins to proceed more easily. Their data, presented here, do not necessarily support their further suggestion that anesthetics also act by changing the hydration and ionization at the membrane surface.

In fact, their data may be interpreted in several ways. For example, it has recently been suggested[6] that rather than a direct lipid–protein interaction, the membrane-solvated proteins respond to the altered fluidity and compressibility of the lipid membrane. In a membrane with altered characteristics, these proteins would change their conformation in order to establish a new thermodynamic equilibrium with their surroundings. The altered conformation, as well as the potentially different molecular motion in the more fluid surroundings, would thereby cause a change in the function of a protein important to nerve action. This conformational change would be analogous to that of a water-soluble protein in response to a change in *p*H or ionic strength.

Both these concepts of anesthesia, anesthetics acting directly on protein or indirectly through the effects on surrounding lipids, are consistent with the present findings of Ueda *et al.* Certainly their results tend to underscore the importance of lipid mobility in the phenomenon of anesthesia. Further experiments will have to be designed and performed in order to define the primary site of anesthesia. When sufficient model-system data are accumulated, it will become possible to elucidate the molecular details of anesthetic action. Ultimately, such knowledge will lead towards this goal of improving the design and administration of anesthetics.

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