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Editorial Views

Closer Still to a Mechanism of Anesthesia

RECENT CAREFUL COMPARISONS of anesthetic thresholds for a variety of unconventional compounds have served to show the clear superiority of oil/gas partition coefficients over Pauling-Miller hydrate dissociation pressures,[1] providing strong support for the Meyer-Overton concept as a correlation between anesthetic potency and the physical properties of a compound. However, neither hydrate dissociation pressures nor oil partition correlations deal with a mechanism for anesthesia in the sense that would explain just what an anesthetic does at the molecular level to render a neuron inexcitable. The paper by Trudell, Hubbell, Cohen, and Kendig in this issue is a major advance in the experimental study of the mechanism of anesthesia and will undoubtedly contribute greatly to our ability to develop a theory for the mechanism of anesthesia.

Although reversal of anesthesia by pressure has been known for some time, an explanation for the effect has not been verified experimentally. An early explanation offered was that anesthetics brought about protein denaturation and an accompanying increase in volume of the protein which pressure would be expected to reverse.[2] Alternately, it seemed possible that pressure might simply squeeze the anesthetic molecules out of the lipid phase of the membrane. In their present work, however, Trudell *et al.* have shown that there is only a trivial change in anesthetic concentration in the lipid phase when pressure is applied, and while they do not have information about the possible interaction of anesthetics with protein, the information they do have makes such a postulate unnecessary.

The search for practical, clinically useful anesthetics has been a continuing activity for many individuals. The number of chemical compounds that fit this definition is measured in tens, while the number of compounds tested is in the tens of thousands. A look at the general scheme for bringing about anesthesia may provide clues to the solution of this problem.

A good deal of information presently available regarding the origin of excitability in neurons can be summarized by saying that the membrane of these cells is a phospholipid bilayer with a very small number of protein units (which one may call "receptors") embedded in it. These receptors may respond to acetylcholine, to a change in membrane potential, or to other transmitter substances, by opening a channel through their central core, thus allowing ions to flow across the membrane. This ionic current then generates a postsynaptic potential or an action potential, depending on whether a "chemical" or an "electrical" receptor is involved. It would appear, however, that when the structure of the lipid bilayer is disorganized by lipid-soluble molecules, pressure is then exerted on the receptors, thus preventing them from carrying an ionic current in response to a stimulus.[3] Thus, the seemingly exotic finding by Trudell *et al.* that foreign lipid molecules can disorder a lipid bilayer, and that pressure can reverse this disorder, is of great importance to our quest for new and better anesthetics.

A further problem with current theories of anesthesia revolves around the relative importance of molecular size and/or number of molecules in the process of anesthesia, and it is likely that the technique of Trudell *et al.*

will be useful in solving this problem. There is good evidence that it is not the number of anesthetic molecules in the membrane but rather their number multiplied by their molecular volume which produces the effect observed.[3, 4] Yet, very large ($>C_{10}$) molecules are not anesthetics. It should follow, therefore, that large lipid-soluble molecules produce less disorder in the membrane than do smaller molecules. This appears reasonable because the more a molecule looks like a phospholipid, the more it may be expected to fit into the membrane by substitution rather than by disorganizing the structure.

A few concluding remarks on why some substances are practical anesthetics. One wishes for substances that have negligible interaction with the cell membrane of, for example, cardiac cells, while having a maximum effect on certain neurons of the cerebral cortex. We may expect that the phospholipids of these cells are different in composition and that their disorganization by anesthetic molecules will be different. Additionally, it may well be that the "receptors" in the two types of membranes have differing sensitivities to a given amount of disruption of the lipid bilayer structures that surround them. On straightforward physicochemical grounds, one might expect CF_3–$CHClBr$ and CF_3–CCl_3 to have similar abilities to produce anesthesia, yet the latter substance requires four times the concentration of the former. An explanation for this difference may well lie in the differential structure-breaking abilities of the two compounds when they are introduced into lipid bilayers.

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