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Molecular Models of Anesthetic Drug Action—Variations on a Theme

To the Editor:—The article by Trudell[1] on the molecular actions of anesthetic drugs presents interesting concepts, but I believe that it does not indicate the conceptual similarities between the proposed model and the ideas advanced by Seeman in 1972.[2] Neurophysiologic studies of isolated nerve preparations have shown that anesthetic drugs inhibit sodium conductance associated with excitation, but do not appreciably affect resting membrane potential.[2,3] The inhibition of sodium conductance is considered to be directly responsible for nerve impulse conduction block by anesthetic drugs.[3,4] Therefore, it has been stated that "for any particular hypothesis to be termed a 'theory of anesthesia,' it is necessary for that hypothesis to explain the manner in which the sodium conductance channel is inhibited or the manner in which synaptic transmission is modified."[2] Accordingly, in 1972, Seeman suggested the following model for the molecular events that result in the inhibition of sodium conductance[2]: The drug molecules interact with both the sodium conductance channel (hypothesized to be a protein; briefly named "sodium channel") and the lipids around it. As a result of these interactions, the lipids are fluidized and the conformation of the sodium channel changes, resulting in inhibition of sodium conductance in response to depolarizing influences. In this model the relative roles of the drug interactions with lipids versus the sodium channel in bringing about the conformational change was not stated.

In Trudell's model the basic principle is that anesthetic drugs fluidize membrane lipids. Fluidization of certain lipids near the sodium channel that are hypothesized to be solid in the resting state, then, affects the ability of the sodium channel to undergo conformational changes necessary for sodium conductance.

Anesthetic drugs, at concentrations required for general or local anesthesia, may effect a change in the sodium channel by several means (table 1). Seeman's model in 1972 included a combination of I and II, whereas Trudell's model is based on II. Thus, this model is essentially based on only one aspect of Seeman's model.

In Trudell's article the basic idea presented by II (table 1) is applied to three different hypothetical models of the sodium channel, one proposed by Trudell and the other two by others. Currently, our knowledge of the molecular structure and function of the sodium channel is very meager. Trudell's ideas, as well as Lee's,[5] about the sodium channel structure and function are novel, and can help increase our understanding of the sodium channel. Furthermore, these ideas demonstrate beautifully that the knowledge of anesthetic action can be used towards an understanding of normal biologic and physiologic phenomena. However, each application of concept II to a newly hypothesized sodium channel cannot be considered a new "unitary theory of anesthesia." A model that is very similar to that of Lee and Trudell's has been also advanced by Browning,[6] and has been more aptly named a "model for electrical excitability."

Table 1. Some Possible Interactions by Which Anesthetic Drugs May Cause a Conformational Change in the Sodium Channel (Read Arrow as "Causes a Change in")

I.	Drug → sodium channel
II.	Drug → lipids around sodium channel → sodium channel
III.	Drug → another entity or relation → sodium channel
IV.	Any combination of I, II, III

Additionally, the idea that increased membrane lipid fluidization may affect the fusion of intracellular vesicles with cell membranes, and thus exocytosis, proposed by Trudell,[1] has also been presented previously (ref. 2, p. 633). Trudell suggests that the increased fluidization would result in an inhibition of fusion and thus a decrease in the amount of vesicle content released. The evidence, however, indicates that increased fluidity may result in an enhancement of exocytosis rather than inhibition.[2] The final effect would probably depend on the balance between the lipid fluidizing and Ca^{++} flux inhibiting effects of the specific anesthetic drug.[2]

Finally, Trudell indicates that anesthetics fluidize lipids "at concentrations in the order of magnitude of those used clinically." However, the findings of others who could not detect fluidity changes at general and local anesthetic concentrations of halothane, chloroform, ether, and benzyl alcohol[7] are not cited. It is on the basis of these findings that membrane protein has been suggested as the primary site of anesthetic action.[7]

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In reply:—Molecular models of anesthetic drug action: Read the music before playing the song.

The statement of Dr. Hanukoglu that "In Trudell's model the basic principle is that anesthetic drugs fluidize membrane lipids" betrays a complete misunderstanding of the concepts I have described in diagrams and text.[1] A lateral phase separation in a biological membrane conveys to integral membrane proteins properties that are entirely different from those resulting from membrane fluidity. In fact, in my model the suggestion that anesthetic agents destroy lateral phase separations in membranes means that the environment of the protein becomes *more rigid* with respect to lateral expansion.

Historically, around 1970 a number of workers, including Seeman, Bangham, Hubbell, Metcalfe, Burgen, Smith, and myself, observed that various anesthetic agents increase the internal fluidity of membranes in several model systems. In general, neither the investigators mentioned nor other researchers were able to relate the small anesthetic-induced increase in membrane fluidity to a molecular mechanism of anesthesia. That is, we could not explain how a slight change in membrane fluidity would affect the sodium channel or the components of synaptic transmission. This frustration led others to study the direct interaction of anesthetic agents with protein, and Hill, Jain, and myself, and several others to study the effects of anesthetic agents on the phase behavior of synthetic membranes.

The direct binding of anesthetic agents to proteins, as well as modification of protein function, has been well documented. The possibility remains that this direct drug–protein association is the primary effect of anesthetic agents. On the other hand, I have shown that an anesthetic agent produces more than a one-hundred fold greater effect in a part of a membrane containing a lateral phase separation than in a homogenous membrane. I have used this amplification effect of phase separations to suggest molecular details for the mechanism of action of anesthetic agents. Careful reading will demonstrate that my model is very different from that of Lee, which suggests that local anesthetics may fluidize the phospholipids that form the immobilized halo around membrane proteins.[2] My model is somewhat like that proposed in the Ph.D. Thesis of Browning,[3] although he focuses on membrane asymmetry produced by local anesthetics, rather like that suggested by Sheetz and Singer in 1974.[4]

Through a misinterpretation of my model, Dr. Hanukoglu stated: "Trudell suggests that the increased fluidization would result in an inhibition of fusion . . ." and went on to say that this conflicts with experimental evidence. In fact, I presented the evidence of others that the existence of lateral phase separations are important for vesicle fusion. I then reasoned that since anesthetic agents destroy lateral phase separations, the exocytosis process may be modified. Indeed, it is likely that calcium acts as a trigger for exocytosis by means of lateral phase separations.

Finally, the ability of various investigators to detect positive,[5] biphasic,[6] or no[7] effect of anesthetic agents on membrane fluidity depends on: 1) their estimation of drug concentration in a membrane exposed to a clinically-used concentration of a particular anesthetic; 2) the model system they investigate; 3) the ability of their measurement technique to detect small changes. The sum of these effects has been reviewed recently by Miller.[8] I know of no investigator who has failed to detect a change in lateral phase separation properties with a low concentration of an anesthetic agent.

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