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# A MODEL FOR THE INTERACTION OF ANESTHETICS WITH THE PHOSPHOLIPID MEMBRANE HEADGROUP-INTERFACE REGION

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**A previous model for lipid-anesthetic interaction is modified to account for anesthetics which bind to the headgroup-interface region of the bilayer rather than the acyl chain region. The new models account for anesthetic-induced changes in membrane phase transition temperature and permeability as well as the previous model, while still accounting for pressure reversal of anesthesia. In addition, the new models account for a 'saturation' of the effect of increasing concentrations of anesthetic on the membrane phase transition temperature, in agreement with experiment and in contrast to our previous model.**

## Introduction

Although many experiments have been done to elucidate the nature of anesthetic-membrane interactions [1], only a few theoretical models have been developed which unify these observations [2–6]. Most of the models [2–4] fall into a group, often referred to as Marcelja-type models, in which excluded volume interactions between different lipid acyl chains are accounted for in a mean-field way and the details of chain packing are ignored. Anesthetics have been assumed to occupy either the acyl chain region [2] or the headgroup region [3,4] of the bilayer. Another model of lipid-anesthetic effects is a Nagle-type model in which the excluded volume interactions between acyl chains are accounted for exactly, and the long-range van der Waals interactions are treated as mean-field. In this model, anesthetics are assumed to interact with the acyl chain region of the bilayer. While the Marcelja-type models may give a somewhat more realistic picture of the lipid bilayer above the phase transition temperature, $T_m$, the latter appears to better describe the phase transition itself [7] and is the only type which gives a qualitatively correct description of membrane compressibility below, at, and above the phase transition [8]. This is particularly important since anesthetic-induced changes in membrane compressibility have been implicated by some authors [6,9] as the most likely mechanism for the anesthetics' functional effects on membranes. In addition, only the Nagle-type models can account for membrane changes due to changes in the bulk pressure. This is important since an understanding of the pressure reversal of anesthesia [10] would seem to be a crucial ingredient in any theory of anesthetic effects.

The Nagle-type theory which we have previously proposed for the lipid-anesthetic interaction assumes that anesthetic molecules interact primarily with the acyl chain region of the lipid bilayer. Several studies have suggested that the major effects of anesthetics is in the headgroup-interface region (Craig, N., Bryant, G. and Levin, I.W., unpublished data; and Ref. 11). For this reason we developed a model for the anesthetic-lipid interaction which places the anesthetic in the headgroup-

interface region of the membrane. We then examined the thermodynamics of anesthetic-membrane interactions using this model, and compared the results both with experiments and with other theoretical results.

## The Membrane Model

We assume that the acyl chain region of the lipid bilayer is adequately described by the Nagle model [12] and that the details of the headgroup-interface structure may be ignored. We further assume that anesthetic molecules may adsorb to the membrane surface at sites which are of uniform size and affinity. Adsorption to these sites is assumed to be independent of the occupation state of other sites. These are the basic criteria of Langmuir-type adsorption. We consider two specific adsorption models.

Model 1: Adsorption sites have a constant affinity, but the number of sites increases linearly with area/lipid.

Model 2: The number of adsorption sites is constant, but the anesthetic-binding site interaction energy increases linearly with the area/lipid.

For both models

$$Z_{\text{mem}} = Z_{\text{Nagle}} \cdot Z_{\text{ads}} \tag{1}$$

where
$Z_{\text{mem}}$ = the membrane partition function
$Z_{\text{Nagle}}$ = partition function for the membrane without anesthetics, computed as in Ref. 12
$Z_{\text{ads}}$ = partition function for anesthetic adsorption.

The adsorption partition function is simply a Langmuir type, modified for differences in the anesthetic-lipid interaction.

For model 1

$$Z_{\text{ads}} = (1 + z\eta)^N = (1 + z\eta)^{[\alpha(A - A_0) + N_0]} \tag{2}$$

where
$\eta = e^{-\epsilon^*/kT}$
$\epsilon^*$ = anesthetic-adsorption site interaction energy
$k$ = Boltzmann's constant
$T$ = temperature (K)
$z$ = dimensionless activity = $(2\pi mkT\, A_S/\hbar^2)e^{\mu/kT}$
$\mu$ = chemical potential of anesthetic
$\alpha$ = proportionality constant relating the area/lipid to the number of anesthetic binding sites
$A$ = area/lipid
$A_0$ = area/lipid of the fully condensed membrane
$A_s$ = area of an anesthetic binding site (constant)
$N$ = number of anesthetic binding sites
$N_0$ = number of binding sites in the fully condensed membrane
$m$ = molecular weight of anesthetic.

Hence

$$\ln Z_{\text{mem}}^{\text{model 1}} = \ln Z_{\text{Nagle}} + N_0 \ln(1 + z\eta) + \alpha(A - A_0)\ln(1 + z\eta) \tag{3}$$

$$P_{\text{model 1}} = P_{\text{Nagle}}$$

$$\Pi_{\text{model 1}} = \Pi_{\text{Nagle}} + \alpha \ln(1 + z\eta) \tag{4}$$

For model 2

$$Z_{\text{ads}} = (1 + z\eta)^N = (1 + ze^{[-\epsilon_0 + \gamma(A - A_0)]/kT})^N \tag{5}$$

where
$\epsilon_0$ = binding energy for anesthetics with a completely condensed membrane
$\gamma$ = proportionality constant relating the change in the anesthetic binding energy to the membrane area,
and all the other symbols have their previous meanings.

$$\ln Z_{\text{mem}}^{\text{model 2}} = \ln Z_{\text{Nagle}} + N \ln(1 + z\eta) \tag{6}$$

$$P_{\text{model 2}} = P_{\text{Nagle}}$$

$$\Pi_{\text{model 2}} = \Pi_{\text{Nagle}} + (Nz\eta\gamma A)/[(1 + z\eta)kT] \tag{7}$$

The effect on the phase transition temperature of changing the membrane surface pressure has been examined by Nagle [12], who shows that

$$\Delta T_{\text{m}} = \beta\, \Delta\Pi_{\text{Nagle}} \tag{8}$$

where $\beta$ is a proportionality constant. Hence

$$\Delta T_{\text{m}} = -\beta\, \Pi_{\text{ads}} \tag{9}$$

for a system held at constant surface pressure $P$.

For low anesthetic activities $z\eta \ll 1$ we have

$$\Pi_{\text{model 1}} = \Pi_{\text{Nagle}} + \alpha z\eta \tag{10}$$

and

$$\Pi_{\text{model 2}} = \Pi_{\text{Nagle}} + z\eta N_0 \gamma A/kT \tag{11}$$

Thus, the change in phase transition temperature is linear with activity in the range of low anesthetic activities. In the range of high activities we have

$$\Pi_{\text{model 1}} = \Pi_{\text{Nagle}} + \alpha \ln(z\eta) \tag{12}$$

and

$$\Pi_{\text{model 2}} = \Pi_{\text{Nagle}} + N_0 \gamma A/kT \tag{13}$$

Hence model 2, which has a fixed number of adsorption sites, shows evidence of saturation. Even in model 1 $dT_m/dz < 1$ in contrast with previous models [5,6] in which the $dT_m/dz \geq 1$. As in the case of previous models it is possible for changes in the anesthetic concentration to cause a change in the number of phases present in the membrane. Similar effects of anesthetic on membrane compressibility occur, and increases in the hydrostatic pressure may cause condensation of the membrane and reversal of anesthetic-induced decreases in the phase transition temperature.

## Discussion

Recent experimental evidence suggests that many general anesthetics exert their effects as a result of penetration into the headgroup and interface region of the lipid membrane, rather than into the acyl chain region assumed by some models to be the site of action. The models presented here take this localization into account, but still predict a partial (in some cases complete) reversal of anesthetic effect upon application of hydrostatic pressure. Thus, the present models account for all the experimental data accounted for by our earlier model. In addition, one of the models (model 2) predicts a 'saturation' of the headgroup/interface region and of anesthetic effect on the membrane phase transition temperature when the concentration becomes large. This effect has been seen experimentally in dipalmitoylphosphatidylcholine liposomes perturbed by halothane (Craig, N., Bryant, G. and Levin, I.W., unpublished data). In addition, saturation of the headgroup/interface region of the bilayer has been reported with methoxyfluorane, chloroform, halothane and enfluorane [11]. Comparison of these calculations with those in Ref. 5 suggests that anesthetics which interact with the headgroup interface region should be significantly more potent in their effects on the phase transition than those which interact only with the acyl chains.

While these models are more consistent than our earlier model with locations of some anesthetics, such as halothane, in the bilayer, this success should not be taken as evidence that absorption into the acyl chain region is an unimportant lipid-anesthetic interaction. It is possible that with some anesthetics bulk absorption dominates, that in others the headgroup effects are most important, and that in yet others both play a role. It is also possible that the evidence of localization in the headgroup region is misleading, since one may readily construct models in which anesthetics bind strongly in this region without changing either the bulk or the surface pressure of the membrane, and thus have no effect on the phase transition.

While these models postulate an anesthetic-membrane interaction which is similar to that proposed in Refs. 3 and 4, the phase diagrams expected for our models are much simpler. This results from allowing no anesthetic-anesthetic interaction in the current models, and from differences in the underlying membrane models. This is not a drawback, as there is no experimental evidence suggesting such complicated phase behavior for most anesthetics.

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