Effect of Anesthetics on a Planar to Curved Lipid Bilayer Transition

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It was recently proposed that infinite periodic two-dimensional minimal surfaces can occur in membranes. Hypothetical phase transitions of the lipid bilayer of membranes, involving intrinsic curvature, could provide a mechanism for cooperative action in membrane functions. The effect of general anesthetics on the lipid bilayer of the membranes, which leads to blocking of the sodium channels, has been related to the proposed curvature transition hypothesis by an investigation of the effect of anesthetics on the corresponding phase transitions in a lipid-water system. It was found that as little as 0.5 % (w/w) of chloroform, calculated on the amount of lipid, was able to completely eliminate the existence of the planar bilayer (L_α) phase in favor of the curved minimal surface phase (C) in excess of water. Comparative studies of the effect of ethyl ether gave results consistent with its relative anesthetic potency.

It is well known that the effect of general anesthetics, like chloroform, ethyl ether or halothane, is due to blocking of the transmission of electric signals along the neurons, and it is generally accepted that the site of action is the lipid bilayer of the neuronal membranes.[1] The influx of sodium ions associated with the action potential does not occur when an anesthetic agent is present, and this is considered to be a secondary effect on the sodium channels due to some effect on the lipid bilayer. The structural effects on the lipids and the mechanism behind the anesthetic effect are not known. The possibility of phase transitions in biomembranes involving intrinsic curvature has recently been proposed[2,3] on the basis of the existence of lipid-water phases, where the lipid bilayers form infinite periodic minimal surfaces.[4] The transition between a planar and minimal surface curved lipid bilayer of a membrane would thus correspond to a phase transition in the corresponding lipid-water system between the lamellar liquid-crystalline phase (L_α) and a cubic phase (C) of the infinite periodic minimal surface type.

A lipid which gives a $L_\alpha \rightleftharpoons C$ transition in excess of water is a suitable model system for evaluating the structural properties of the hypothetical two-dimensional phase transition planar $\rightleftharpoons$ minimal surface curved bilayer in a membrane. There is, however, no well defined membrane lipid which exhibits this phase transition in excess of water. The 1-monoacylglycerides of saturated chains above C_{14} give this transition,[5] and 1-monopalmitoylglycerol[6] was chosen in this work in order to study the $L_\alpha \rightleftharpoons C$ transition. This work was undertaken to test the proposed phase transition model; as the effect of anesthetic agents, discussed above, seemed to be a case where transition between a planar and curved bilayer might be involved.

Experimental

1-Monopalmitoylglycerol synthesised according to the standard method[6] was used. The lipid was melted and chloroform (pro analysi) was added by an Agla microsyringe. Double distilled water was then added to a lipid:water weight ratio of 3:7. Most samples contained as much as 1 g lipid in a order to obtain as accurate a lipid-chloroform ratio as possible. Phase equilibria were then followed in a thermocontrolled water bath

Dedicated to Professor Per Ekwall on his 90th birthday.

(±0.5 °C) and the phases were identified by their anisotropy/isotropy using crossed polarizers. Phase transitions were also followed in a polarizing microscope equipped with a heated stage.

Results and discussion

The drastic effect of chloroform on the $L_\alpha \rightleftharpoons C$ transition is shown in Fig. 1. The presence of more than 0.5 % (w/w) of chloroform in the lipid bilayer meant that the planar bilayer structure (L_α) did not even exist. Above 2 % (w/w) of chloroform, an L_2 phase was formed all the way down to the chain crystallization temperature. No two-phase region between the L_α and C phases could be observed with the experimental technique used.

The transition $L_\alpha \rightarrow C$ and further to L_2 is a consequence of increased wedge-shape of the average hydrocarbon region per lipid molecules (cf. Ref. 7). The accommodation of the chloroform molecules probably induces increased mobility and hence more disorder or a higher degree of *gauche* conformations towards the methyl end groups.

A remarkable effect on potency of anesthetics is the pressure antagonism;[1] an increase in pressure leads to a linear reduction of the anesthetic effect. No study of the effect of pressure on the $L_\alpha \rightleftharpoons C$ transition has been reported. The general features of increased pressure on pressure-temperature phase diagrams, however, is well-known. A transition from one phase to a phase with more disorder, as in the $L_\alpha \rightarrow C$ transition, should thus take place at a higher temperature when the pressure is increased. If this relationship is applied in Fig. 1, it can be seen that the effect is consistent with the antagonism of pressure against anesthetic activity. Many studies have also been reported on the pressure effects on the lipid structure of membranes, confirming the same direction of phase transitions (chain crystallization has been observed at about 2000 bar).

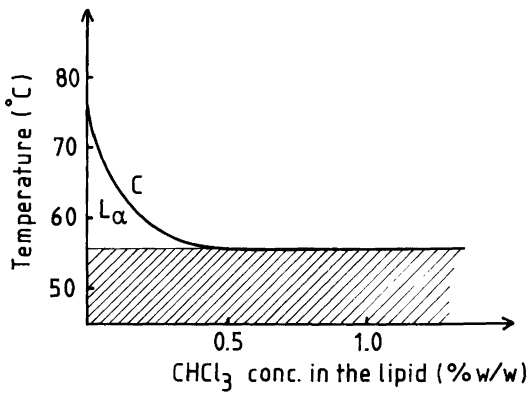

Fig. 1. Effect of chloroform on the phase transition $L_\alpha \rightleftharpoons C$ of monopalmitoylglycerol in excess of water. The shaded area corresponds to the formation of crystalline lipids.

The potency of anesthetics is expressed as the minimum concentration abolishing movement in response to stimulus. If ethyl ether is compared with chloroform, a higher concentration (expressed as partial pressure of the inhalation gas mixture) is needed in order to reach the minimum anesthetic concentration and the relative lipid solubility of chloroform compared to ethyl ether shows a similar relation. When ethyl ether was added to the aqueous monopalmitoylglycerol system, it reduced the transition temperature $L_\alpha \rightarrow C$. The effect of the same concentration was smaller than that of chloroform, although an accurate comparison was not possible due to the high vapour pressure of ethyl ether at the actual transition temperatures.

On the basis of the present results, it is proposed that the $L_\alpha \rightarrow C$ transition of the model system corresponds to the transition from a planar bilayer of the membrane to a lipid bilayer curved as a two-dimensional minimal surface. It is not surprising that such a transition can influence the structure of the membrane proteins so that the sodium channels are blocked. The structure of the myelin sheath can be described as an L_2 phase, and the possibility that anesthetics induce an $L_\alpha \rightarrow C$ transition of the myelin layer with its adjacent neuron membrane should be considered. Direct studies of phase behaviour of the myelin system are therefore planned as a continuation of the present study.

References

1. Winter, P. M. and Miller, J. N. *Scientific American 252* (1985) 94.
2. Hyde, S. T., Andersson, S. and Larsson, K. *Z. Kristallogr. In press.*
4. Hyde, S. T., Andersson, S., Ericsson, B. and Larsson, K. *Z. Kristallogr. 168* (1984) 213.
5. Lutton, E. S. *J. Am. Oil Chemists Soc. 42* (1965) 1068.
6. Larsson, K. *Z. Phys. Chem. 56* (1967) 173.
7. Israelachvili, J. N., Mitchell, D. J. and Ninham, B. W. *J. Chem. Soc. Faraday Trans.* II *72* (1976) 1525.

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