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Liquid membrane phenomena in antiarrhythmic action

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Summary

Antiarrhythmic drugs have been shown to generate liquid membranes in series with a supporting membrane. Transport of sodium ions across the liquid membrane generated by these drugs has be n studied. The data indicate that the transport of sodium ions is impeded in presence of the liquid membranes. Relevance of this observation to antiarrhythmic action has been discussed. Four structurally dissimilar antiarrhythmic drugs, namely quinidine, disopyramide, procainamide and propranolol, have been investigated.

Introduction

Recent studies (Bhise et al., 1982, 1983a, b and c, 1984a and b, 1985; Srivastava et al., 1982, 1983a and b, 1984) on a wide variety of surface-active drugs indicated that the liquid membranes (Kesting et al., 1968) generated by them modify the transport of relevant permeants across the interface. The data have indicated that the formation of liquid membranes at the site of action may be an important step common to the mechanism of action of all surface-active drugs (Srivastava et al., 1984). In the present communication, the studies have been extended to include antiarrhythmic drugs. Antiarrhythmic drugs are known to contain both hydrophobic and hydrophilic moieties in their structure (Thomas, 1981) and hence are expected to be surface-active in nature. These drugs are known to cause increase in membrane surface pressure and stabilization of membranes (Thomas, 1981).

The antiarrhythmic action is known to be (Bowman and Rand, 1980) mainly on account of modification in the permeability of biomembranes to sodium ions. Since antiarrhythmic drugs are expected to be surface-active and hence capable of generating liquid membranes at the interface (Kesting et al., 1968), it is logical to suspect that modification in the permeability of sodium ions may be on account of the liquid membranes generated by them at the respective sites of action. It is of interest to mention that many local anesthetics also show antiarrhythmic action (Marshall and Wollman, 1980). Since, in local anesthetics, the liquid membranes generated by them have been shown to contribute to the modification in cation permeability (Srivastava et al., 1983b), it appears likely that the phenomenon of liquid membrane formation may also be important in the mode of action of antiarrhythmic drugs. This precisely is the point of investigation in this communication.

Four structurally dissimilar drugs, viz. quinidine hydrochloride, disopyramide phosphate, procainamide hydrochloride and propranolol hydrochloride, were chosen for the present study. The first three drugs belong to the class I and propranolol to the class II in Vaughan William classification (Bowman and Rand, 1980). Existence of liquid membranes generated by each of these drugs at the interface has been demonstrated. Data on the permeability of sodium ions in presence of the liquid membranes have been obtained to gain information on the role of the liquid membranes in antiarrhythmic action. A Sartorius cellulose nitrate/aqueous solution interface was deliberately chosen as site for the formation of liquid membranes, so that the active interaction of the drugs with the constituents of biomembranes as a cause for the modification of solute permeability is totally ruled out and the role of passive transport through the drug liquid membranes is highlighted.

Materials and Methods

Materials

Quinidine hydrochloride (Sigma, U.S.A.), disopyramide phosphate (Searle, India), procainamide hydrochloride (Sigma, U.S.A.), propranolol hydrochloride (Sigma, U.S.A.), sodium chloride (BDH, Analar grade) and triple-distilled water, distilled in an all-pyrex glass still was used.

Methods

The critical micelle concentrations (CMC) of aqueous solutions of the drugs were determined from the variation of surface tension with concentrations. These are recorded in Table 1. The surface tensions were measured using a surface tensiomat (Fisher Tensiomat model 21).

TABLE 1

CRITICAL MICELLE CONCENTRATIONS OF ANTIARRHYTHMIC DRUGS IN WATER

Drugs	CMC (M)
Quinidine hydrochloride	3.96×10^{-7}
Disopyramide phosphate	4.00×10^{-7}
Procainamide hydrochloride	4.00×10^{-3}
Propranolol hydrochloride	4.75×10^{-5}

The all-glass cell described earlier (Bhise et al., 1982, 1983c) was used for the transport studies. A Sartorius cellulose nitrate microfiltration membrane (Cat. No. 11307; average pore size 0.2 μm) of thickness 1×10^{-4} m and area 5.373×10^{-5} m^2 which acted as a support for liquid membranes, separated the transport cell into two compartments C and D (Fig. 1 of Bhise et al., 1982, 1983c). The hydraulic permeability data at various concentrations of antiarrhythmic drugs, which were utilized to demonstrate the existence of liquid membrane on the supporting membrane, were obtained using the method described earlier (Bhise et al., 1982, 1983c). The concentration ranges selected were such that data are obtained above and below the CMC of the drugs.

For the measurement of solute permeability (ω) of sodium (Na^+), two sets of experiments were performed. In the first set of experiments, a mixture of the aqueous solution of sodium chloride and one of the drugs under investigation was filled in compartment C and compartment D (Fig. 1 of Bhise et al., 1982, 1983c) was filled with distilled water. In the second set of experiments, an aqueous solution of sodium chloride was kept in compartment C and compartment D was filled with aqueous solution of one of the drugs. However, in control experiments, no drug was used. The concentration of the drugs taken were always higher than their CMCs, because according to liquid membrane hypothesis (Kesting et al., 1968) at concentrations equal to or higher than the critical micelle concentration the supporting membrane gets completely covered with the liquid membrane generated by the surface-active substances (drugs).

The values of solute permeability (ω) were obtained using the definition (Katchalsky and Curran, 1967; Katchalsky and Kedem, 1962)

$$\left(\frac{J_s}{\Delta\pi}\right)_{J_v=0} = \omega \qquad (1)$$

where $\Delta\pi$ is the osmotic pressure difference and J_s and J_v, respectively, are the solute flux and volume flux per unit area of the membrane. The details of the method of the measurement have been des-

cribed earlier (Bhise et al., 1982, 1983c).

All measurements including the CMC determination were carried out at $37 \pm 0.1°C$. The amount of sodium (Na^+) transported to the compartment D were estimated using a flame photometer (Elico (India), Model CL 22).

Results and Discussion

The hydraulic permeability data at various concentrations of the drugs, in case of all the four antiarrhythmic drugs, were found to obey the linear relationship,

$$J_v = L \cdot \Delta P \qquad (2)$$

where J_v represents the volume flux per unit area of the membrane, ΔP is the applied pressure difference and L is the hydraulic conductivity coefficient. The normalized values of the hydraulic conductivity coefficient, the values of (L/L^0) where L^0 is the value of L when no drug was used—estimated from the J_v versus ΔP plots—are plotted against the concentrations of the drugs in Fig. 1. The values of (L/L^0) in case of all the four drugs show a progressive decrease with increase in concentration of the drugs up to their CMC beyond which either they become more or less constant or decrease only marginally (Fig. 1). This trend is in accordance with the liquid membrane hypothesis (Kesting et al., 1968) according to which as concentration of the surfactant is increased, the supporting membrane gets progressively covered with the surfactant layer liquid membrane until it is completely covered at the CMC. The marginal decrease in the value of (L/L^0) beyond the CMCs, particularly in the case of quinidine, procainamide and propranolol may be due to increase in density of liquid membranes (Kesting et al., 1968).

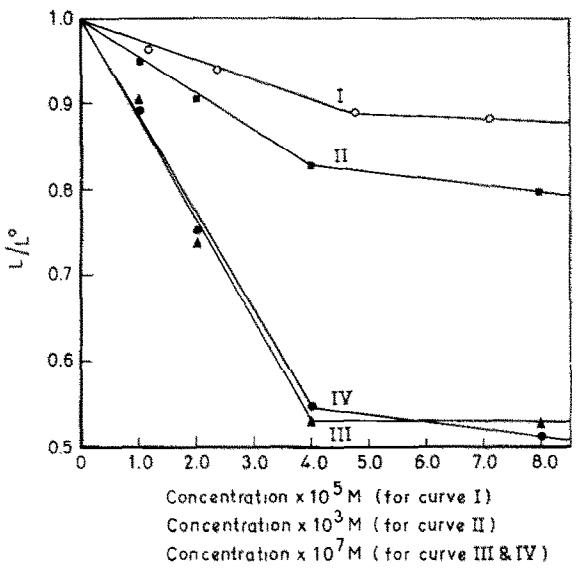

Fig. 1. Variation of (L/L^0) with concentration of the drugs. Curves I, II, III and IV represents data for propranolol hydrochloride, procainamide hydrochloride, disopyramide phosphate and quinidine hydrochloride, respectively.

Analysis of the flow data in the light of mosaic membrane model (Spiegler and Kedem, 1966; Sherwood et al., 1967; Harris et al., 1976) further corroborates the existence of liquid membrane in series with the supporting membrane. Following the arguments given earlier (Bhise et al., 1982, 1983c) it is possible to compute the values of L below its CMC from the experimentally determined values of L at 0 and CMC of the surfactant. It has been shown that if the concentration of the surfactant is n times its CMC, $n \leqslant 1$, the value of L would be equal to $[L^0(1-n) + nL^c]$ where L^0 and L^c, respectively, stand for the values of L at 0 and the CMC of the surfactant. The values of L thus computed at $0.25 \cdot CMC$ and $0.5 \cdot CMC$ in case of quinidine are in agreement with the experimentally determined values (Table 2). Similar results were found in the case of other three drugs also, viz. disopyramide phosphate, procainamide hydrochloride and propranolol hydrochloride, confirming the formation of liquid membranes in series with the supporting membrane.

Since the antiarrhythmic drugs have both hydrophilic and hydrophobic moieties in their structure (Thomas, 1981), it is expected that orientation of the drug molecules in the liquid membrane would be different in the two sets of experiments for ω measurements. In the first set of experiments, where both drug and the permeant (Na^+) were present in the same compartment C of the transport cell (Fig. 1 of Bhise et al., 1982, 1983c), the hydrophobic moieties of the drug molecules would be preferentially oriented towards the hy-

TABLE 2

VALUES OF L AT VARIOUS CONCENTRATIONS OF QUINIDINE HYDROCHLORIDE

	Quinidine hydrochloride concentration $\times 10^7$ M				
	0	0.989 (0.25 · CMC)	1.978 (0.50 · CMC)	3.956 (CMC)	7.912
$L^a \times 10^8$ ($m^3 \cdot s^{-1} \cdot N^{-1}$)	2.9647 ± 0.0902	2.6516 ± 0.0648	2.2359 ± 0.0250	1.6253 ± 0.0337	1.5239 ± 0.0311
$L^b \times 10^8$ ($m^3 \cdot s^{-1} \cdot N^{-1}$)	–	2.6299 ± 0.0761	2.2950 ± 0.0680	–	–

[a] Experimental values.
[b] Calculated values on the basis of mosaic model.

drophobic supporting membrane and therefore, the permeant would face the hydrophilic surface of the drug liquid membrane. Similarly, in the second set of experiments, where the permeant was present in compartment C and the drug in compartment D, the permeant would face the hydrophobic surface of the drug liquid membrane. The values of ω for sodium (Na^+) in presence of the antiarrhythmic drugs obtained in the two sets of experiments are recorded in Table 3.

A perusal of Table 3 indicates that the liquid membranes generated by the antiarrhythmic drugs, in both the orientations—hydrophilic ends facing the permeant and hydrophobic ends facing the permeant—impede the transport of sodium ions. Antiarrhythmic drugs are known (Bowman and Rand, 1980) to stabilize cardiac membrane by a non-specific mechanism. The present study indicates that the liquid membranes generated by antiarrhythmic drugs in series with the cardiac membrane impeding the transport of sodium ions may be such a mechanism. A persual of Table 3 further reveals that impediment in the transport of sodium ions is not significantly different in the two orientations of the liquid membranes generated by the drugs which implies that both hydrophilic and hydrophobic moieties in the structure of these drugs may be necessary for antiarrhythmic action. This conjecture is consistent with the literature report (Thomas, 1981) that non-specific antiarrhythmic agents interact with both hydrophilic and hydrophobic regions of the biomembrane. Propranolol which is primarily a β-blocker drug is also known (Thomas, 1981) to exert a non-specific membrane-stabilizing action similar to that of quinidine at concentrations higher than those needed for β-blocking action. It is for this reason, that the transport of sodium ions in presence of

TABLE 3

PERMEABILITY OF SODIUM [a] (Na^+), (ω) [b], IN PRESENCE OF ANTIARRHYTHMIC DRUGS [c]

Drug	$\omega_1 \times 10^{10}$ (mol · $s^{-1} \cdot N^{-1}$)	$\omega_2 \times 10^{10}$ (mol · $s^{-1} \cdot N^{-1}$)	$\omega_3 \times 10^{10}$ (mol · $s^{-1} \cdot N^{-1}$)
Quinidine hydrochloride	5.3255 ± 0.3521	2.8934 ± 0.1710	2.8757 ± 0.1405
Disopyramide phosphate	5.3255 ± 0.3521	3.0709 ± 0.1731	3.3823 ± 0.1540
Procainamide hydrochloride	5.3255 ± 0.3521	3.1132 ± 0.2108	3.1778 ± 0.2475
Propranolol hydrochloride	5.3255 ± 0.3521	2.5844 ± 0.1293	2.5885 ± 0.1542

ω_1 = control value—when no drug was used. ω_2 = drug and sodium ion in compartment C and water in the compartment D. ω_3 = drug in compartment D and sodium ion in the compartment C.

[a] Initial concentration of sodium ion 2117.2 ppm.
[b] Values of ω are reported as arithmetic mean of 10 repeats ± S.D.
[c] The concentrations of quinidine hydrochloride, disopyramide phosphate, procainamide hydrochloride and propranolol hydrochloride used were: 1.6×10^{-6} M, 1.6×10^{-6} M, 8.0×10^{-3} M and 7.315×10^{-5} M, respectively.

propranolol was studied. The data on the inhibition of sodium ion transport in presence of propranolol (Table 3) is consistent with its reported antiarrhythmic action.

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