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# Liquid membrane phenomena in cimetidine, ranitidine and disodium cromoglycate

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## Summary

The phenomenon of liquid membrane formation has been investigated in two $H_2$-antagonists, namely cimetidine and ranitidine, and one histamine release blocker, disodium cromoglycate. All three drugs have been shown to generate liquid membranes in series with a supporting membrane and modify the permeability of histamine. The data on the modification in the permeability of histamine indicate that the formation of liquid membranes, at the respective sites of action impeding the transport of histamine, may be an important step common to the mechanism of action of the $H_2$-receptor antagonists and the histamine release blocker.

## Introduction

The role of surface activity in the biological action of several categories of drugs has had enough attention in the literature (Florence, 1968; Felmeister, 1972). In several cases excellent correlations between surface activity and biological effects have been demonstrated (Seeman, 1972). Since the structural requirements for surface activity are often similar to those for interaction of drugs with receptor sites (Attwood et al., 1974), the correlations between surface activity and biological effects appear to indicate that there might exist at least one crucial step common to the mechanism of action of all surface-active drugs. In view of the liquid membrane hypothesis (Kesting et al., 1968), it was suspected that the liquid membranes generated at the site of action of the respective drugs, modifying the transport of the

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relevant permeants, might be an important step common to the mechanism of action of all surface-active drugs. Recent studies on several drugs belonging to different pharmacological categories have strongly indicated in favour of such a possibility (Bhise et al., 1982, 1983a, b and c; Srivastava et al., 1982, 1983a and b, 1984).

In a recent study (Bhise et al., 1983c) three structurally dissimilar antihistamines, namely chlorpheniramine, diphenhydramine and tripelennamine (all $H_1$-antagonists), have been investigated for the role of liquid membrane phenomenon in the mechanism of their action. All three antihistamine drugs were shown to generate liquid membranes at the interface and modify the permeability of histamine. The trends in the data on the modification in the permeability of histamine have strongly indicated in favour of the role played by the liquid membranes generated by the antihistamines in the mechanism of their action.

The present paper contains an extension of the earlier study (Bhise et al., 1983c). In this communication are reported studies on cimetidine, ranitidine and disodium cromoglycate. The first two drugs, viz. cimetidine and ranitidine, are histamine $H_2$-receptor antagonists (Domschke et al., 1979) while disodium cromoglycate is known (Witiak and Cavestri, 1981) to act by inhibiting release of histamine from mast cells. All three drugs have been shown to generate liquid membranes in series with a supporting membrane in accordance with liquid membrane hypothesis (Kesting et al., 1968). Data on the transport of histamine in presence of the drugs have been obtained to gain information on the role of the liquid membranes generated by the drugs in the mechanism of their action. In these studies a cellulose acetate microfiltration membrane/aqueous interface has been deliberately chosen as site for the formation of liquid membranes so that active interaction of the drugs with the constituents of biological membranes is ruled out and the role of passive transport through liquid membranes is highlighted.

## Materials and Methods

Cimetidine (CIPLA, India), ranitidine (GLAXO, U.K.) disodium cromoglycate (Unique Pharmaceuticals, India), histamine acid phosphate (BDH), *o*-phthalaldehyde (Sigma, U.S.A.) and distilled water, distilled once over potassium permanganate in an all-pyrex glass still were used for the present study.

The critical micelle concentrations (CMCs) of aqueous solutions of the drugs were determined from the variation of surface tension with concentration and are recorded in Table 1. Surface tensions were measured using a Fisher Tensiomat (Model 21).

The all-glass cell described earlier (Bhise et al., 1982, 1983c) was used for the transport studies. A Sartorious cellulose acetate microfiltration membrane (Cat. No. 11107, average pore size 0.2 $\mu$m) of thickness $1 \times 10^{-4}$ m and area $5.373 \times 10^{-5}$ m$^2$ acted as a support for the liquid membrane and separated the transport cell into two compartments C and D (Fig. 1; Bhise et al., 1982).

The hydraulic permeability data at various concentrations of the drugs, which were utilized to demonstrate the existence of the liquid membrane in series with the

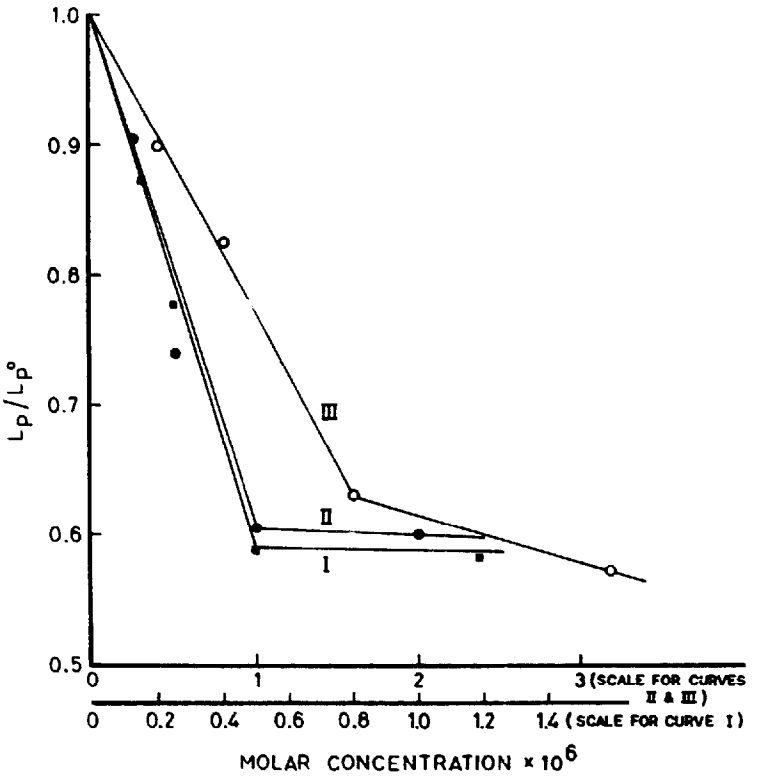


Fig. 1. Variation of $L_p/L_{p^o}$ with concentration of the drugs. Curves I, II and III represent the data for cimetidine, ranitidine and disodium cromoglycate, respectively.

supporting membrane, were obtained using the method described earlier (Bhise et al., 1982). The concentration ranges, selected for hydraulic permeability measurements, were such that the data are obtained both below and above the CMCs of the drugs.

The solute permeability ($\omega$) of histamine was measured in the presence of each of the three drugs individually. For this two sets of experiments were performed. In the first set of experiments aqueous solutions of known concentration of the drugs and histamine were kept in the same compartment—compartment C of the transport cell and distilled water was filled in the other compartment—compartment D (Fig. 1; Bhise et al., 1982). In the second set of experiments aqueous solution of histamine was kept in the compartment C and the compartment D contained aqueous solution

TABLE 1

CRITICAL MICELLE CONCENTRATIONS

| Drug | CMC |
|---|---|
| Cimetidine | $5.1024 \times 10^{-6}$ M |
| Ranitidine | $1.0188 \times 10^{-6}$ M |
| Cromoglycate disodium | $1.5925 \times 10^{-6}$ M |

of the drug. Concentration of the drugs in these experiments were always higher than their CMC to ensure complete coverage of the supporting membrane with the liquid membrane generated by the drug. According to the liquid membrane hypothesis (Kesting et al., 1968), complete liquid membranes are generated at concentrations equal to or higher than CMC. In control experiments no drug was used. Because of their surface-active nature, the hydrophobic moieties of the drug molecules will be preferentially oriented towards the hydrophobic supporting membrane and the hydrophilic portion will face outwards away from it. In the first set of experiments, therefore, the permeant, histamine, would face the hydrophilic surface of the liquid membrane generated by the drug while in the second set of experiments the permeant would face the hydrophobic surface of the drug liquid membrane. The values of the solute permeability ($\omega$) of histamine were estimated using the definition (Katchalsky and Kedem, 1962; Katchalsky and Curran, 1967).

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

where $J_s$ is the solute flux per unit area of the membrane, $\Delta\pi$ is the osmotic pressure difference and $J_v$ is the volume flux. The details of the method of measurement of $\omega$ are described in earlier publication (Bhise et al., 1982). Fifteen repeats were taken for each value of $\omega$.

All measurements including CMC determination were carried out at constant temperature, using a thermostat set at $37 \pm 0.1°C$.

*Estimations*

The amount of histamine transported to compartment D was estimated by fluorimetric measurement of the fluorophor derivative obtained from its reaction with *o*-phthalaldehyde (Redlich and Glick, 1965). A Photovolt fluorescence meter (model 540) was used for the estimation.

## Results and Discussion

The hydraulic permeability data at various concentrations of the drugs in the case of all the three drugs were found to be in accordance with the linear relationship:

$$J_v = L_p \cdot \Delta P \tag{2}$$

where $J_v$ is the volume flux per unit area of the membrane, $\Delta P$ is the applied pressure difference and $L_p$ is the hydraulic conductivity coefficient. The normalized values of the hydraulic conductivity coefficients, i.e. the values of $L_p/L_{p^0}$ where $L_{p^0}$ is the value when drug concentration was zero, computed from the $J_v$ vs $\Delta P$ plots, show a progressive decrease (Fig. 1) with increase in the concentration of the drugs up to their CMCs beyond which they become more or less constant. This trend is in accordance with liquid membrane hypothesis (Kesting et al., 1968) according to

TABLE 2

SOLUTE PERMEABILITY ($\omega$)[a] OF HISTAMINE[b] IN PRESENCE OF DRUGS

| Drug | $\omega_1 \times 10^{10}$ (mol·s$^{-1}$·N$^{-1}$) | $\omega_2 \times 10^{10}$ (mol·s$^{-1}$·N$^{-1}$) | $\omega_3 \times 10^{10}$ (mol·s$^{-1}$·N$^{-1}$) |
|---|---|---|---|
| Cimetidine | 5.1855 ± 0.6379 | 3.0379 ± 0.3531 | 3.6516 ± 0.2716 |
| Ranitidine | 5.1855 ± 0.6379 | 1.6630 ± 0.3205 | 2.6741 ± 0.4347 |
| Cromoglycate disodium | 5.1855 ± 0.6379 | 1.3139 ± 0.1952 | 4207 ± 0.2631 |

$\omega_1$ = Control value—when no drug was used.

$\omega_2$ = Drug and histamine in compartment C and water in compartment D.

$\omega_3$ = Drug in compartment D and histamine in compartment C.

[a] The values of $\omega$ expressed as arithmetic mean ± standard deviation.

[b] Initial concentration of histamine 10 $\mu$g/ml.

[c] The concentrations of cimetidine, ranitidine and cromoglycate disodium were $2.0410 \times 10^{-5}$ M, $4.0756 \times 10^{-6}$ M and $6.3700 \times 10^{-6}$ M, respectively.

which as concentration of the surfactant is increased, the supporting membrane gets progressively covered with the surfactant layer liquid membrane and at the CMC it is completely covered. The slight decrease in the values of $L_P/L_{P^0}$ beyond the CMC particularly in the case of disodium cromoglycate is most probably, as postulated by Kesting (1968), due to an increase in density of the liquid membrane, which is fully developed at the CMC and completely covers the supporting membrane.

Both cimetidine and ranitidine are known to be $H_2$-antagonists. The data on histamine permeability ($\omega$) in presence of these drugs (Table 2) indicate that the liquid membranes which are likely to be formed at the site of action of the respective drugs may contribute to their biological action. A perusal of Table 2 reveals that the permeability of histamine is reduced to a greater extent in the first set of experiments in which the permeant, histamine, faces the hydrophilic surface of the drug liquid membrane. This trend appears to indicate that the $H_2$-receptors are oriented in such a manner that their hydrophobic moieties are available to get attached with the hydrophobic moieties of the $H_2$-antagonists—cimetidine and ranitidine, leaving hydrophilic moieties of the drugs to face histamine molecules. This is in contrast to our earlier observation (Bhise et al., 1983c) in the case of $H_1$-antagonists, where the transport of histamine was impeded more when histamine faces hydrophobic surface of the liquid membrane generated by the antagonists. These observations, therefore, appear to indicate that orientation of $H_1$- and $H_2$-receptors for histamine may be opposite to each other. Similar opposing orientations of $H_1$- and $H_2$-receptors are already indicated in literature (Ganellin and Durant, 1981).

Ranitidine is known to be a more potent $H_2$-antagonist than cimetidine (Domschke et al., 1979). This fact can be rationalized on the basis of CMC values (Table 1) of the two drugs. Since the CMC of ranitidine is less than that of cimetidine, the former would form the complete liquid membrane offering maximum resistance to the transport of histamine, at a lower concentration than cimetidine would require, thus making ranitidine more potent than cimetidine.

In the case of disodium cromoglycate also, which is a histamine release blocker, the transport of histamine is impeded most when the drug liquid membrane presents

its hydrophilic surface to the permeant (Table 2). It appears, therefore, that a similar orientation of the liquid membrane with hydrophilic moieties of disodium cromoglycate molecules facing histamine molecules may be necessary even on mast cells. However, more information on the nature and orientation of the actual site of action on mast cells is called for.

Thus the present study indicates that the formation of liquid membrane at the respective sites of action, impeding the transport of histamine, may be an important step common to the mechanism of action of $H_2$-antagonists, viz. cimetidine and ranitidine, and histamine release blocker like disodium cromoglycate.

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