EFFECT OF SEROTONIN AND PROSTAGLANDINS ON PERMEABILITY OF MODEL LIPID MEMBRANES

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More and more attention continues to be paid to the use of biological and model membranes in order to study the effects of various pharmacological and biologically active substances on ion transport [2, 4].

An important role in these investigations is played by model lipid membranes, with properties similar to those of biological membranes: They are convenient for the quantitative study of transport processes, and they contain molecules of known structure as the component responsible for permeability.

In the investigation described below the effect of serotonin (5-HT) and prostaglandins (PG) on permeability of model membranes made from lecithin, cardiolipin, gangliosides, and a mixture of lecithin with gangliosides, was studied.

EXPERIMENTAL METHOD

Bilayer membranes were formed from lecithin and cardiolipin by Mueller's method [6] and membranes from gangliosides, alone or mixed with lecithin, by the method described in [5]. Electrical measurements were made by means of a high-ohmic electrometer, using a pair of chlorided silver electrodes [1], in 0.1 M solutions of KCl and $CaCl_2$ at 26°C. All points used to plot graphs were obtained as the mean values of at least six measurements on two or three different films.

The lecithin and cardiolipin used in the experiments were from the Khar'kov Bacterial Preparations Factory, the PG E_2 and $F_{2\alpha}$ were from the Upjohn Company (USA), and 5-HT was from Sigma (USA).

EXPERIMENTAL RESULTS

The results of experiments to measure permeability of model membranes from lecithin, cardiolipin, gangliosides, and a mixture of lecithin with gangliosides for potassium and calcium ions, without modifiers and in the presence of 5-HT, PG, and 5-HT with PG are given in Tables 1 and 2. They show that the permeability of bilayer membranes from phospholipid fractions (lecithin, cardiolipin) is low, and that of membranes from gangliosides, with or without lecithin, is an order of magnitude higher. The permeability of phospholipid bilayers was unchanged in the presence of serotonin, whereas that of membranes made from gangliosides, alone or mixed with lecithin, was increased by 0.5 to 1 order of magnitude. Consequently, ganglioside molecules, by interacting with 5-HT, increase the permeability of the membranes to cations.

It will be clear from Figs. 1 and 2 that the permeability of lecithin membranes was independent of the serotonin concentration, the permeability of ganglioside membranes changed only in the presence of high 5-HT concentrations (10^{-4}-10^{-6} M), but that of membranes made from a mixture of gangliosides and lecithin changed only a little (by 2-3 times) under the influence of 5-HT in concentrations of 10^{-4}-10^{-5} M.

The permeability of the model membranes tested is considerably increased in the presence of PG E_2 and $F_{2\alpha}$. These substances increase membrane permeability for cations in both high and low concentrations. The maximal increase in permeability (by 3 or 4 orders of magnitude) was observed on phospholipid bilayers to cations in concentrations of 10^{-6}-10^{-8} M. The increase in permeability on ganglioside membranes was rather less. Permeability for cations of mixed membranes from lecithin and gangliosides differed from that of phospholipid and ganglioside membranes alone. The permeability of mixed membranes was increased by up to 3 orders of magnitude in concentrations of 10^{-8}-10^{-9} M for potassium ions and 10^{-4}-10^{-5} M for calcium ions.

The results of the experiments with simultaneous addition of 5-HT and PG showed that this combination affects

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TABLE 1. Permeability of Phospholipid Bilayers (in $\Omega^{-1} \cdot cm^{-2}$) in the Presence of Modifiers in a Concentration of 10^{-5} M (M ± m)

Experimental conditions (modifiers)	Lecithin bilayer		Cardiolipin bilayer	
	K^+	Ca^{2+}	K^+	Ca^{+2}
Without modifiers	$(2,3\pm0,3)\cdot10^{-8}$	$(5,5\pm0,2)\cdot10^{-8}$	$(3,5\pm0,2)\cdot10^{-8}$	$(3,7\pm0,2)\cdot10^{-8}$
5-HT	$(2,1\pm0,2)\cdot10^{-8}$	$(3,2\pm0,3)\cdot10^{-8}$	$(3,1\pm0,3)\cdot10^{-8}$	$(2,1\pm0,2)\cdot10^{-8}$
PGE_2	$(6,2\pm0,2)\cdot10^{-5}$	$(6,1\pm02,)\cdot10^{-7}$	$(8,2\pm0,2)\cdot10^{-6}$	$(7,1\pm0,2)\cdot10^{-6}$
$PGF_{2\alpha}$	$(7,6\pm0,2)\cdot10^{-6}$	$(3,3\pm0,2)\cdot10^{-6}$	$(7,1\pm0,3)\cdot10^{-6}$	$(3,1\pm0,3)\cdot10^{-6}$
5-HT + PG E_2	$(3,2\pm0,2)\cdot10^{-6}$	$(1,2\pm0,3)\cdot10^{-6}$	$(3,1\pm0,3)\cdot10^{-6}$	$(2,1\pm0,2)\cdot10^{-6}$
5-HT + PG $F_{2\alpha}$	$(2,1\pm0,2)\cdot10^{-6}$	$(5,2\pm0,2)\cdot10^{-7}$	$(2,5\pm0,3)\cdot10^{-6}$	$(1,2\pm0,3)\cdot10^{-6}$

TABLE 2. Permeability of Model Membranes (in $\Omega^{-1} \cdot cm^{-2}$) Made from Gangliosides and a Mixture of Gangliosides with Lecithin in the Presence of Modifiers in a Concentration of 10^{-5} M (M ± m)

Experimental conditions (modifiers)	Ganglioside membrane		Membrane made from mix. of lecithin & gangliosides	
	K^+	Ca^{2+}	K^+	Ca^{2+}
Without modifiers	$(3,2\pm0,2)\cdot10^{-8}$	$(7,2\pm0,2)\cdot10^{-6}$	$(5,2\pm0,3)\cdot10^{-8}$	$(6,8\pm0,3)\cdot10^{-7}$
5-HT	$(7,2\pm0,3)\cdot10^{-7}$	$(2,1\pm0,3)\cdot10^{-5}$	$(1,2\pm0,2)\cdot10^{-6}$	$(2,1\pm0,2)\cdot10^{-6}$
PG E_2	$(7,8\pm0,2)\cdot10^{-5}$	$(3,2\pm0,3)\cdot10^{-5}$	$(8,5\pm0,3)\cdot10^{-6}$	$(3,8\pm0,2)\cdot10^{-4}$
PG $F_{2\alpha}$	$(5,2\pm0,3)\cdot10^{-5}$	$(2,8\pm0,2)\cdot10^{-5}$	$(7,8\pm0,2)\cdot10^{-6}$	$(4,5\pm0,3)\cdot10^{-6}$
5-HT + PG E_2	$(4,2\pm0,3)\cdot10^{-5}$	$(3,8\pm0,2)\cdot10^{-6}$	$(1,2\pm0,2)\cdot10^{-6}$	$(3,1\pm0,2)\cdot10^{-5}$
5-HT + PG $F_{2\alpha}$	$(6,1\pm0,2)\cdot10^{-5}$	$(4,1\pm0,2)\cdot10^{-6}$	$(1,5\pm0,3)\cdot10^{-6}$	$(1,2\pm0,3)\cdot10^{-6}$

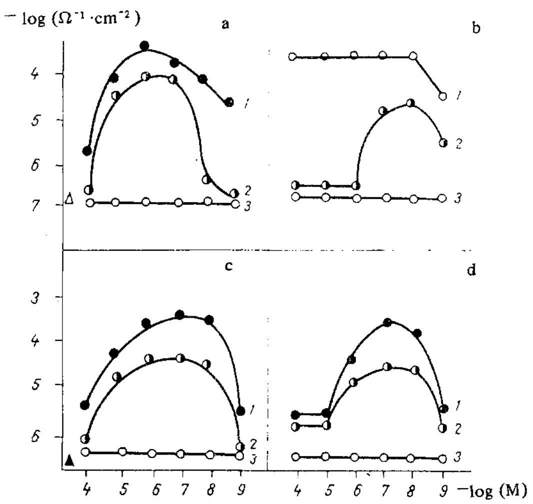

Fig. 1

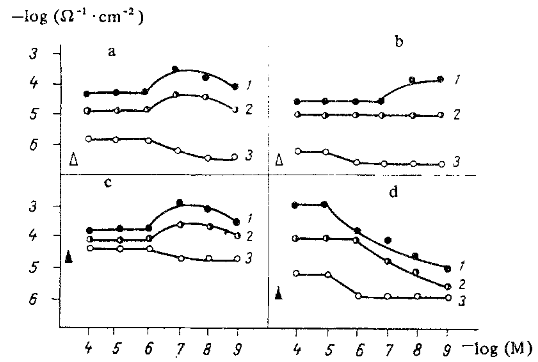

Fig. 2

Fig. 1. Effect of concentration of PG, PG + 5-HT, and 5-HT on permeability of model lecithin membranes in 0.1M KCl solution (a, b) and in 0.1 M $CaCl_2$ solution (c, d). a, c) Permeability of membrane as a function of concentration of PG $F_{2\alpha}$ (1), PG $F_{2\alpha}$ + 5-HT (2), and 5-HT (3); b, d) the same for PG E_2 (1), PG E_2 + 5-HT (2), and 5-HT (3). Here and in Fig. 2, empty triangle represents permeability of unmodified membranes for potassium ions, filled triangle the same for calcium ions.

Fig. 2. Effect of PG $F_{2\alpha}$ (1), PG $F_{2\alpha}$ + 5-HT (2), and 5-HT (3) concentrations on permeability of model membranes made from 0.1M gangliosides (a, c) and lecithin and gangliosides (b, d) in KCl solution (a, b) and 0.1 M $CaCl_2$ solution (c, d).

lipid membranes differently.

The permeability of lecithin bilayers under the influence of PG and 5-HT was much higher than that of membranes modified by serotonin, but lower than the permeability of membranes modified by PG (Figs. 1 and 2). Thus, 5-HT apparently blocks the effect of PG. Permeability on model membranes made from gangliosides alone or mixed with lecithin, created by 5-HT with PG, is similar to the permeability of lecithin membranes. The mechanism of interaction of 5-HT with PG is not clear, but the two substances, both separately and in combination, increase the permeability of model membranes for cations. It is difficult as yet to postulate a mechanism for. the transfer of cations through membranes in general and lipid fractions in particular: whether these modifiers create conduction channels or whether they are themselves ionophores.

It is a particularly interesting fact that the degree of the influence of the above-mentioned substances on permeability of model membranes depends on changes in the lipid composition of those membranes. This phenomenon was described by the writers previously [3]. However, the results of the present investigations show that this change also affects the sensitivity of the bilayer to the action of different effectors.

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