CORRELATION BETWEEN ANTIARRHYTHMIC ACTIVITY OF ACYL DERIVATIVES OF PHENOTHIAZINE AND THEIR AFFINITY FOR PHOSPHOLIPID MEMBRANES

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Binding constants for thirteen 10-acylaminopropionyl derivatives of phenothiazine possessing antiarrhythmic activity with model phospholipid membranes were determined by the fluorescent probe method. For ten of these substances significant correlation was observed between the binding constant and antiarrhythmic activity: Activity increased with an increase in the constant; three substances, those with the highest binding constants, however, possess low activity. The results are evidence that interaction between antiarrhythmic drugs and lipids of target membranes in vivo may be an important element in the molecular mechanism of their action. Meanwhile, very high affinity for lipids may evidently lead to delocalization of the drug in the body and to a reduction in its antiarrhythmic activity.

KEY WORDS: *acyl derivatives of phenothiazine; antiarrhythmic activity; phospholipid membranes.*

It is now known that the action of many pharmacological agents is directed toward biological membranes. Meanwhile, in most cases the structure of the membrane receptors with which these compounds interact is unknown. It is suggested that phenothiazine derivatives can interact in membranes not only with proteins, but also with lipids [7, 8]. Definite correlation has been found between the affinity of phenothiazine compounds for membranes and their pharmacological activity [6]. In the investigation described below binding constants were determined for a series of 10-acylaminopropionyl derivatives of phenothiazine with model

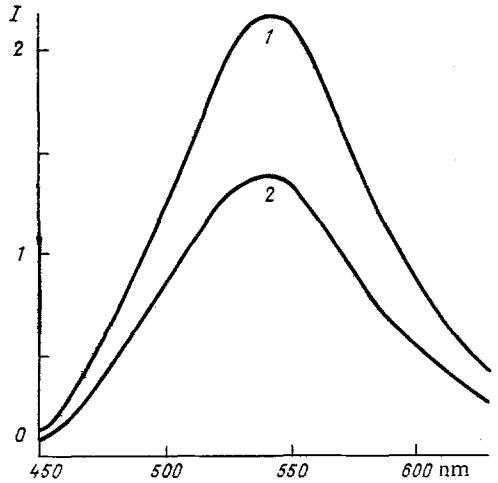

Fig. 1. Effect of ethmozine on fluorescent spectrum of MBA (5 μM) in suspensions of phospholipid liposomes (0.3 mg/ml): 1) before addition, 2) after addition of 0.5 mM ethmozine.

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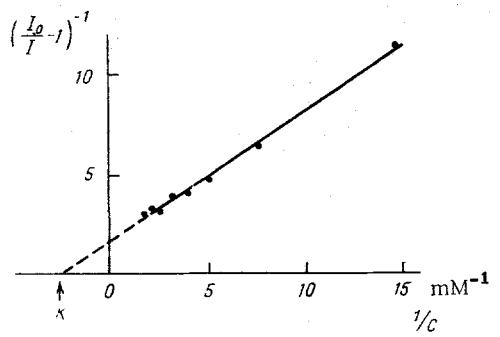

Fig. 2. Determination of binding constant (K) of ethmozine with phospholipid liposomes. C) Concentration of ethmozine; I_0 and I) intensity of fluorescence of MBA in liposome suspension in absence and presence of ethmozine respectively. Remainder of legend as in Fig. 1.

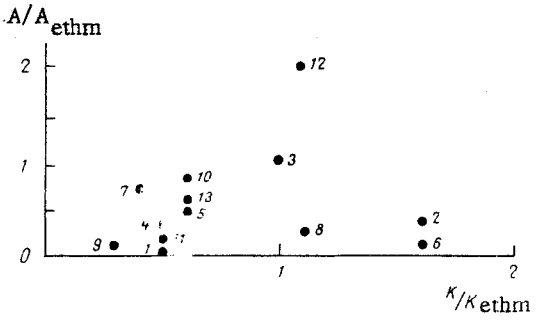

Fig. 3. Correlation between antiarrhythmic activity (A) and binding constant (K) with liposomes of 10-acylaminopropionyl derivatives of phenothiazine: 1) G-291; 2) G-349; 3) G-214 (ethmozine); 4) G-410; 5) G-246; 6) G-364; 7) G-413; 8) G-366; 9) G-264; 10) G-351; 11) EZ-54; 12) EZ-55; 13) G-2365. All values of A and K expressed relative to values for ethmozine.

phospholipid membranes. These values were compared with the antiarrhythmic activity of the compound in order to discover if correlation exists between the activity of the preparation and its affinity for lipid membranes.

EXPERIMENTAL METHOD

The structural formulas of the compounds and the method of determination and the values of the antiarrhythmic activity (aconitine arrhythmia) were described previously [4]. Model phospholipid membrane vesicles (liposomes) [5] were obtained from egg phosphatidylcholine (Olaine Chemical Reagents Factory). The properties of the fluorescent probe 3-methoxybenzanthrone (MBA) [2, 3] and the method of determination of the binding constant of the compound with liposomes with the aid of the fluorescent MBA probe [1] also were described previously. All experiments with liposomes were carried out in a solution of 0.01 M Tris-HCl, pH 7.5.

EXPERIMENTAL RESULTS AND DISCUSSION

All the phenothiazine derivatives investigated caused extinction of fluorescence of molecules of the fluorescent MBA probe present in the liposome membrane (Fig. 1). Consequently, they were able to interact with the phospholipid membrane. The quenching effect can be used to determine the value of the binding constant of the compound with these membranes [1]. For this purpose, increasing quantities of the compound were added to a suspension of liposomes containing MBA, and the binding constants were determined by the double-reciprocal coordinates method (Fig. 2). The results of determination of the constant for the whole group of preparations and also data on their antiarrhythmic activity are given in Fig. 3.

To determine whether there is any correlation between the activity of the compound and their affinity for membranes the coefficient of correlation (r) was calculated. For all 13 compounds r = 0.13, i.e., there is virtually no correlation. Meanwhile, it will be clear from Fig. 3 that for 10 compounds there was a tendency for activity to increase with an increase in the value of the constant. In the group of these 10 substances r = 0.86, i.e., significant correlation (P = 0.05) is present. The remaining three substances (G-349, G-364, and G-366) had the highest binding constant but, at the same time, very low antiarrhythmic activity. The substances with the highest binding constant thus did not follow the general tendency for activity to rise with an increase in the binding constant.

On the basis of the results obtained the 13 substances tested can be divided into two groups. For most of them significant correlation exists between their behavior in vivo and the character of their interaction with model lipid membranes. These results confirm the view that this class of pharmacological compounds interacts in vivo with certain membrane systems; binding of the compound with the lipid phase of the target membranes may play an im-

portant role in these interactions. The greater the affinity of the compound for the lipids of the target membranes, the higher its antiarrhythmic activity.

Meanwhile, the other group of compounds consists of three preparations did not obey this rule. Possibly their very high affinity for lipids may have caused these substances to interact in the body not only with target membranes, but also with other lipid systems. As a result, the substance is delocalized in the body, its effective concentration in the target organ falls, and its aniarrhythmic activity is reduced correspondingly.

These results indicate that model phospholipid membranes can be used for the screening of pharmacological activity of heterocyclic compounds.

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POSSIBILITY OF PHARMACOLOGICAL REGULATION OF GASTROINTESTINAL MOTOR ACTIVITY

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The results of a pharmacological study of the effect of the gallate of the alkaloid cynoglossophine-heliosupine (cyngal), isolated from *Cynoglossum officinale*, on motor activity of the gastrointestinal tract are described. The substance was found to have high stimulating activity in both acute and chronic experiments on dogs, using balloon and electrographic recording methods. The stimulating action of cyngal on gastrointestinal motor activity can evidently be explained by the ability of the preparation to liberate serotonin from the bound state.

KEY WORDS: *motor activity of the gastrointestinal tract; pharmacology; serotonin; cyngal.*

Various methods can be used to influence the motor activity of the gastrointestinal tract when it is weakened: first, by the use of direct muscarinic (m) cholinomimetics, which excite peristalsis and increase smooth muscle tone through their direct effect on m-cholinergic systems of the digestive tract; second, by the use of anticholinesterase drugs, which facilitate the accumulation of endogenous acetylcholine and thereby maintain the level of nervous regulation. Third, the least studied method of influencing motor activity of the gastrointestinal tract is by the use of substances promoting the liberation of physiologically active substances from the bound, inactive state, e.g., certain sympatholytics [4] and liberators [1, 10].

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