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Surface Activity and Mechanism of Action of Antiarrhythmic Drugs*

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Surface active substances are widely used in medicine, among them the drugs capable of adsorption in efficient concentrations at various interface points. The relationship between the pharmacological action of antiarrhythmic drugs and their surface activity and influence on the lipid-containing interfaces (bimolecular layers of phosphatidylcholine) have been studied. It has been revealed that diphisopronyle (diethylaminopropyl ether α-isopropyloxydiphenylacetic acid, hydrochloride), fubromegane (1-methyl-3-diethylaminopropyl ether 5-bromofurane-2-carboxylic acid, iodomethylate), methamicile (β-diethylaminopropyl ether benzyl acid, hydrochloride), propranolole (1-isopropylamino-3 (oxynaphtyl-1)-propanol-2, hydrochloride), chinidine (chinidine sulphate), novocainamide (β-diethylaminoethyl-amid *p*-aminobenzoic acid, hydrochloride), novocaine (β-diethylaminoethyl ether *p*-aminobenzoic acid, hydrochloride), xylocaine (*N,N*-diethylamino-2,6-dimethylacethanilide, hydrochloride), trimecaine (*N,N*-diethylamino-2,4,6-trimethylacethanilide, hydrochloride) possess surface activity. Parallelism between the physiological action and interfacial activity of antiarrhythmic drugs has been established. Antiarrhythmics increase the electric conductance of lecithine bilayers. There exists a symbate dependence between the effect of drugs on the permeability of a bimolecular lecithin membrane and their pharmacological activity. These results are essential a) for understanding the mode of action of antiarrhythmic agents and b) discovering new drugs which possess the required properties.

INTRODUCTION

The progress of modern molecular pharmacology and surface chemistry makes it necessary to interpret in a new way many problems related to the investigation of the interaction of drugs and receptors. Physico-chemical and biological processes at the interfaces of the cellular structures and liquid disperse systems of the organism, which are determined by the surface active properties of drug molecules and the macromolecules of a living substrate referred to as receptor, may be considered as surface phenomena in the organism.

Many drugs possess the adsorption ability on the interfaces in certain concentrations necessary for pharmacological action. The mechanism of action

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of physiologically active substances is characterized by the intrinsic unity of two factors which, as it was stressed by P. A. Rehbinder, directly denote the nature of surface activity and form the basis for the use of surface active substances. These are: a) adsorption of surface active substances, i. e. the ability of the given molecules to concentrate at a certain interface in amounts, which are by far greater than their bulk concentrations; b) spontaneity of the adsorption process which is predetermined thermodynamically by the excess of free energy at the initial interface. However, the extent to which the adsorption takes place may be limited by kinetic factors (mass transfer, diffusion)[1,2].

The significance of the surface phenomena of the physiological active agents was first stated as early as 1927—1929[1] by P. A. Rehbinder. At present these investigations are still of essential importance since it is impossible to represent the interaction of a comparatively small molecule of a drug with a macromolecule of an organism if the phenomena which occur in the interfaces are not characterized.

Formerly it was revealed that physical colloidal and chemical properties are of great importance for the mechanism of action of neurotropic drugs (anaesthetics, analgesics, antihistamines and curare-like agents)[3–15]. Special attention was paid to the elucidation of the role of surface phenomena.[3,8,11,13,15]

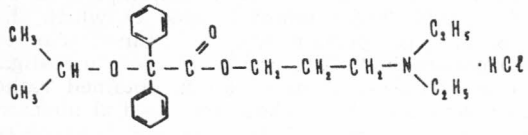
In earlier studies[16–18], a supposition was voiced that the interaction of drugs with the membranes is of great importance for the realization of the antiarrhythmic effect. For example it is known that antiarrhythmic action of β-blocking agents is connected with the »membrane-depressant« effect. There is even evidence of a correlation between the »membrane-depressant« influence of β-blockers and their effective antiarrhythmic doses (observed in patients)[18]. At the same time, the role of surface phenomena in the mechanism of antiarrhythmic action is not clear yet. We thought it reasonable to study the role of surface phenomena in the mode of action of antiarrhythmic drugs. For this purpose the relationship between the pharmacological effect of various antiarrhythmic drugs and their surface activity and influence on the lipid-containing interfaces: bimolecular layers of phosphatidylcholine, has been studied.

MATERIALS AND METHODS

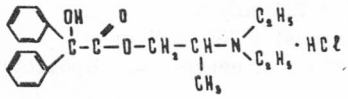
The chemical structure of the antiarrhythmic drugs is given in Figure 1. The following compounds have been used: diphisoprohyle (diethylaminopropyl ether α-isopropyloxydiphenylacetic acid, hydrochloride)[21], fubromegane (1-methyl-3-diethylaminopropyl ether 5-bromofuran-2-carboxylic acid, iodomethylate)[25], methamicile (β-diethylaminopropyl ether benzylic acid, hydrochloride)[25], propranolole (1-isopropylamino-3 (oxynaphthyl-1)-propanol-2, hydrochloride)[25], chinidine (chinidine sulfate)[25], novocainamide (β-diethylaminoethylamide *p*-aminobenzoic acid, hydrochloride)[25] novocaine (β-diethylaminoethyl ether *p*-aminobenzoic acid, hydrochloride)[25], xylocaine (*N*,*N*-diethylamino-2,6-dimethylacetanilide, hydrochloride)[25], trimecaine (*N*,*N*-diethylamino-2,4,6-trimethylacetanilide, hydrochloride)[25].

Investigations of surface active properties of antiarrhythmic drugs have been carried out in accordance with the method described previously in detail[1,3].

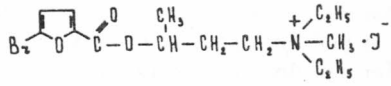
Surface activity of aqueous solutions of drugs has been studied at the air interface, interfaces of benzene and benzene solutions of nerve-tissue lipoproteins. Surface tension, σ has, been measured by the method of maximum bubble (or drop) pressure using the P. A. Rehbinder apparatus. The measurements of σ as a function of the concentration of each compound were always carried out at $(20 \pm 0.1)\,^{\circ}C$, in the equilibrium state, with pH being 7.0. Selection of the time interval required for the formation of an equilibrium adsorption layer was essential. Two series of



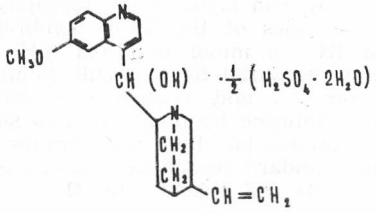
Diphisopronyl



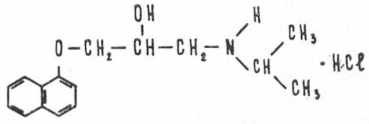
Methamicil



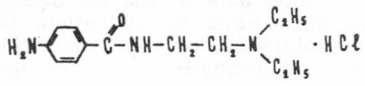
Fubromegan



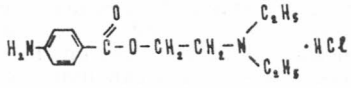
Chinidin



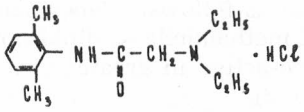
Propranolol



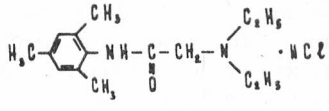
Novocainamid



Novocain



Xylocain



Trimecain

Figure 1. Antiarrhythmics formulae

determinations were carried out; during the first series of measurements the surface tension was determined immediately after the formation of the interface and during the second series — the surface tension was measured 30 min, 1 hour and 2 hours after the interface had been formed. The minimum speed at which the value of surface tension (σ) remains practically constant was determined with the help of $\sigma - \tau$ plot (τ is the bubble formation time). The results of these investigations have shown that the constant value of surface tension (σ) is obtained rather rapidly. Therefore, σ at the interface air-aqueous phase was determined at novel surfaces; at the interface formed by the aqueous phase with benzene and benzene solutions of nerve-tissue lipoproteins surface tension was measured after 2 hours. During all the experiments the maximum time of bubble formation was assumed equal to 4 to 5 minutes.

Preliminary measurements have shown that:

σ {(1/15) mol dm^{-3} phosphate-buffer / air at 20 °C} = 72.7 mN m^{-1}

σ {(1/15) mol dm^{-3} phosphate-buffer / benzene solutions} = 35.0 mN m^{-1}

σ {(1/15) mol dm^{-3} phosphate-buffer / benzene solutions of nerve-tissue lipoproteins} = 21.14 mN m^{-1}

Each drug was investigated in eight concentrations. The mean value out of ten σ measurements was assumed to be valid. The accuracy of σ measurements is 0.1 mN m^{-1}.

The bilayer phosphatidylcholine membrane was used as a model of a biological membrane. It was formed by P. Mueller et al. method[19]. 2% Solution of egg lecithin in *n*-heptane was used to form the bilayer. The identification of egg lecithin with the sample of synthetic lecithin[20] was carried out by thin layer chromatography, IK spectra and optical rotation dispersion. On both sides of the lipid membrane a solution containing 0.25 mol sucrose, 5 mmol KCl, 5 mmol tris HCl (pH = 7.0; t = 30 °C) was present. Membrane resistance was measured by a circuit comprised of voltage supply, calibrated resistors, electrometer, and recording instrument КСП-4. Voltage of 50 mV was supplied to the membrane by means of two silver--chloride electrodes. Electric conductance of bimolecular lipid membranes was measured by comparison of voltage drop at the standard resistance and the membrane resistance. Resistance of the membranes was $(0.8 \pm 0.02) \times 10^7$ Ω [3].

In the experiments on urethane chloralose, anaesthetized cats experimental arrhythmia was evoked by threshold electric stimulation of heart auricles and ventricles for 10 s (1.5 v, 1 ms, 1 imps/s, continuous series). Mean effective dose (ED_{50}) of drugs, preventing arrhythmia was determined. The ability of compounds to induce conduction anaesthesia was investigated on frogs by the Turke method. The concentration of a compound at which the reflex of jerking balk of the leg disappeared for 5 min was assumed to be the minimum anaesthetic concentration. Surface anaesthesia was investigated on the cornea of a rabbit's eye by the Rengier method. The Rengier index was calculated to determine the anaesthetic activity of the drug.

RESULTS

It has been demonstrated that the antiarrhythmic compounds are surface active in concentrations from $2 \cdot 10^{-3}$ mmol kg^{-1} to $1 \cdot 10^{-2}$ mol kg^{-1} at all studied interfaces. With regard to their increasing surface activity at the air/solution interface the drugs may be arranged as follows: novocainamide $<$ $<$ chinidine $<$ fubromegane $<$ propranolole $<$ methamicile $<$ diphisopronyle. Novocaine, xylocaine and trimecaine are surface-active in greater concentrations ranging from $2 \cdot 10^{-2}$ to $1 \cdot 10^{-1}$ mol (Figure 2).

P. A. Rehbinder showed that the compounds, which are surface inactive under the conditions of normal measurements at the air — aqueous solution interface, may appear to be capable of considerable adsorption at the interfaces of organism or of water-lipophile medium type models. These investigations brought about correct conceptions on the significance of surface activity in biological systems. In the course of the discussion with I. Traube following

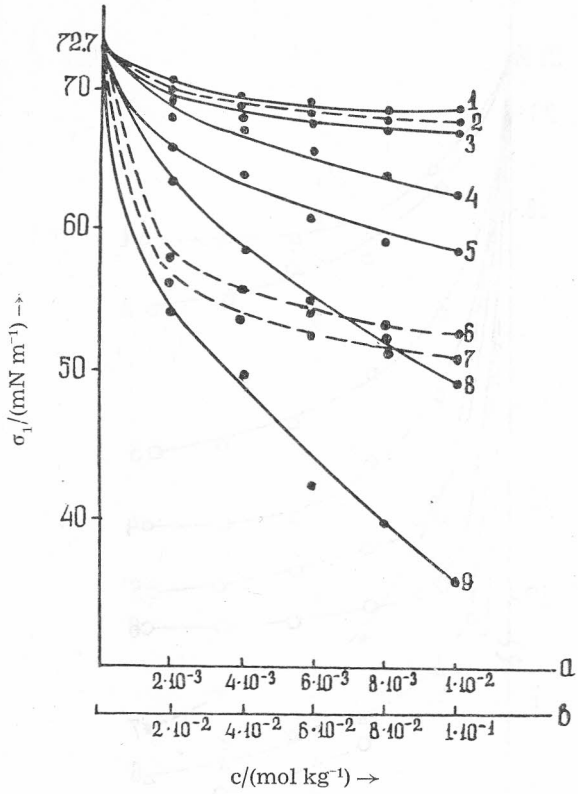


Figure 2. Surface tension of antiarrhythmic solutions in 1/15 molar phosphate buffer, σ, as a function of molal concentration, c; (pH = 7.0; $t = (20 \pm 0.1^0)$ C).

a — for novocainamide (1), chinidine (3), fubromegane (4), propranolole (5), methamicile (8), diphisopronyle (9);

b — for novocaine (2), xylocaine (6) and trimecaine (7).

Each curve point is a result of ten measurements of surface tension.

the publication of these papers, a number of propositions of I. Traube himself and his followers[22,23] as well as the significance of the specificity of phases which form the interface were determined. This specificity is important for the determination of the relationship between the pharmacological action and interfacial activity of drugs.

Thus, it is impossible to limit modern studies on surface activity of physiologically active compounds by mere measurements at the air/solution interface. Surface-active properties should be determined on models which are as close to physiological conditions as possible.

As a model we used the determination of interfacial activity of antiarrhythmic drugs at the antiarrhythmic solutions/benzene solutions of nerve-tissue lipoproteins interface.

It has been shown that antiarrhythmics possess high interfacial activity (Figure 3). The order of antiarrhythmic drugs at the interface of benzene

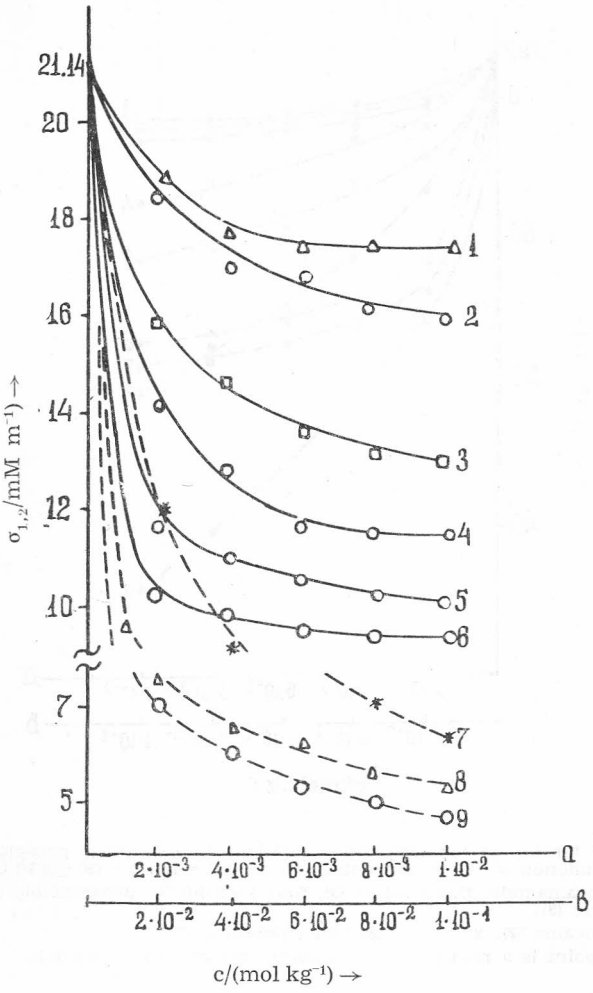


Figure 3. Interfacial tension of antiarrhythmic solutions in 1/15 molar phosphate buffer at the boundary with benzene solutions of nerve-tissue lipoproteins $\sigma_{1,2}$ as a function of molal concentration, c; pH = 7.0; $t = (20 \pm 0.1^0)$ C).

a — for novocainamide (1), propanolole (2), chinidine (3), fubromegane (4), methamicile (5), diphisopronyle (6);

b — for novocaine (7), xylocaine (8) and trimecaine (9).

Each curve point is a result of ten measurements of interfacial tension.

solutions of nerve-tissue lipoproteins is as follows: novocainamide < propranolole < chinidine < fubromegane < methamicile < diphisopronyle. This succession does not completely correspond to the one at the air-solution interface, which confirms the above-mentioned conception on the significance of the specificity of phases. Absolute surface activity of antiarrhythmic drugs at the air/solution interface, interfaces of benzene and benzene solutions of nerve-tissue lipoproteins is different and this is quite natural. The influence of chemical structure of substances at the interface between lipid and water phases is less

evident as compared to the air-solution interface. This is seemingly connected with the identical conformational transformation (within the given range of concentrations) during the formation of the complicated adsorption layer which is formed by a lipoproteid complex together with the substance being studied. Comparison of the antiarrhythmic effect of the drugs to their surface and interfacial activity showed that there exists an interrelationship between these properties (Figure 4). The revealed interrelationship is more pronounced when comparing the antiarrhythmic action to the interfacial activity, than when comparing the pharmacological effect to the surface activity, which is quite normal as the first model is closer to physiological conditions. Comparing of surface and interfacial activity of antiarrhythmic drugs and their local anaesthetic action (conduction anaesthesia) has shown that these characteristics are also interrelated: highly active antiarrhythmic drugs have pronounced surface-active properties and induce conduction anaesthesia in lowest concentrations (Figure 4). These results correlate well with the data presented

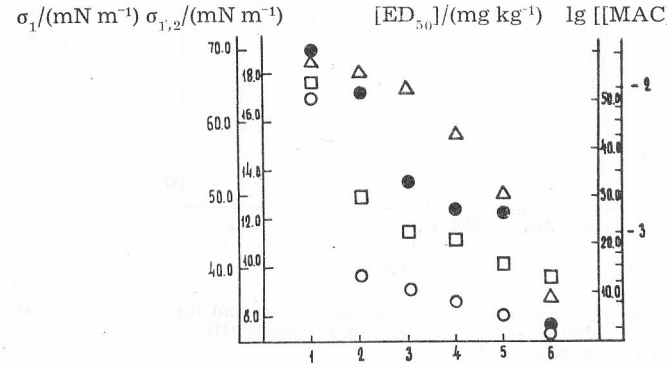


Figure 4. Surface tension (σ_1), interfacial tension ($\sigma_{1,2}$) [at the concentration $1 \cdot 10^{-2}$ mmol kg^{-1}; pH = 7.0; t= 20 °C], antiarrhythmic (ED_{50} and anaesthetic activity (MAC) of novocainamide (1), chinidine (2), fubromegane (3), propranolole (4), methamicile (5), diphisopronyle (6). △ — σ_1: □ — $\sigma_{1,2}$; ○ — ED_{50}; ● — MAC.

above as to the relationship between the local anaesthetic effect of drugs belonging to different chemical classes and their surface and especially interfacial activity (Figure 5).

It is known that the influence of substances on monomolecular and bimolecular layers is closely connected with their surface activity. For example, it has been revealed that the monolayer of nerve-tissue lipids can serve as a model for the nerve axonal membrane during the investigation of local anaesthetics mode of action[11]. These open up broad possibilities in the organism for the formation of extremely thin adsorption layers of surface active substances both on the surface of living cells and on the various interior surfaces of cells. The living cells display spontaneous properties of surface-active lipids, specifically phospholipids, directed as bimolecular layers or membranes. The role of lipid component of the membrane in the mechanism of drug action may be estimated during the investigation of conductivity of artificial lipid membranes at various concentrations of the drugs[24].

For this purpose the influence of compounds, which have antiarrhythmic activity (diphisopronyle, trimecaine, novocainamid) on the properties of the

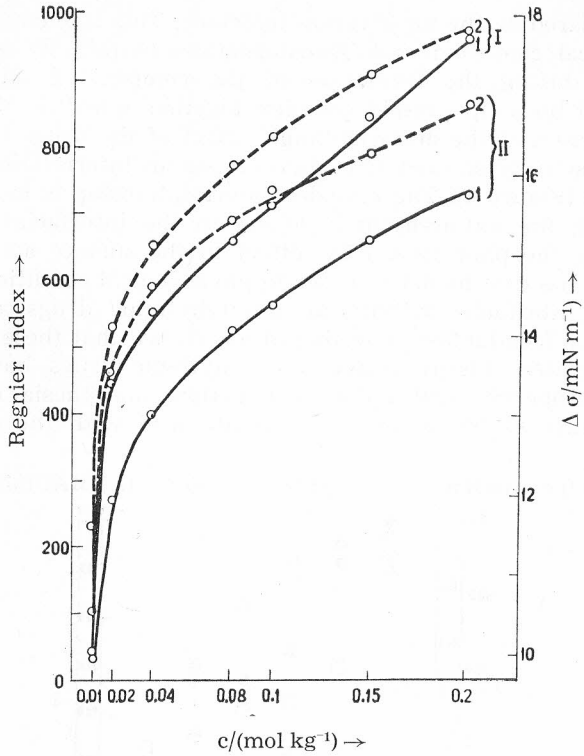


Figure 5. Correlation of local anaesthetic effect (unbroken line) and the surface activity (dashed line) of trimecaine (I) and xylocaine (II)

1 — anaesthetic effect (Régnier index)

2 — surface activity of aqueous solutions drugs at the interfaces of benzene solutions of nerve tissue lipoproteins (pH = 7.0; t = 20 °C).

bilayer phospholipid membrane, has been investigated. The measurements of surface activity at different interface have been taken into consideration when selecting the agent concentrations. Diphisopronyle has been studied in the following concentrations: 0.05 mmol kg^{-1}; 0.1 mmol kg^{-1}; 0.2 mmol kg^{-1}; 0.3 mmol kg^{-1}; 0.4 mmol kg^{-1}; 0.5 mmol kg^{-1}. Trimecaine and novocainamid has been studied in the following concentrations: 0.25 mmol kg^{-1}; 0.5 mmol kg^{-1}; 0.75 mmol kg^{-1}; 1.0 mmol kg^{-1}; 1.25 mmol kg^{-1}; 1.5 mmol kg^{-1}. Two series of experiments were carried out. In the first series of tests, an attempt was made to investigate the influence of antiarrhythmic drugs on the electric conductivity and stability of the membrane under the conditions of introducing the drugs in the buffer solution from one side of the membrane. In the second series of tests the drugs were introduced from both sides of the membrane. The membrane becomes highly unstable if antiarrhythmic drugs are introduced into the buffer solution from one side of the membrane. It is supposed that antiarrhythmics by interacting with the lecithin membrane upset the symmetry of its layers, which leads to the alteration of resistance and upsets the integrity of the membrane. The introduction of drugs from both sides of the membrane ensures its

stability. All further investigations were carried out under conditions of introducing antiarrhythmic drugs from both sides of the lecithin membrane.

It has been demonstrated that diphisopronyle, trimecaine and novocainamid change the electric conductivity of the membrane. The reduction of membrane electric resistance depends directly on the concentration of agents.

Diphisopronyle in the concentration from 0.05 mmol kg^{-1} up to 0.5 mmol kg^{-1} concentrations (pH = 7.0; t = 30 °C) causes considerable, by a factor of 10^2, reduction of bimolecular membrane resistance. The influence of trimecaine on the permeability of the bilayer lipid membrane is less pronounced. The reduction of the mebrane resistance is observed at higher 0.5 to 10.0 mmol kg^{-1}) concentrations of the drug. Novocainamid in higher concentrations up to 1 to 1.5 mmol kg^{-1}, reduces the membrane resistance insignificantly, only by 2 to 3 times (Figure 6). In the course of the investigation of the kinetics of change,

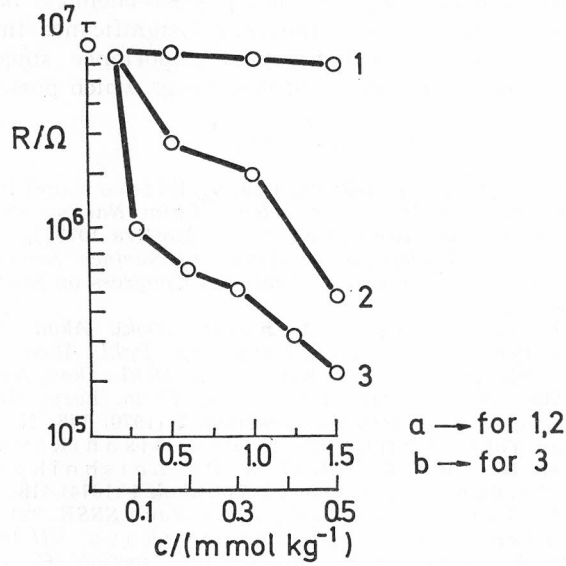


Figure 6. Effect of antiarrhythmic drugs (in various concentrations, c) on the electric resistance (*R*) of bimolecular lecithin membrane; pH = 7.0; t = 30 °C.
a — for novocainamide (1) and trimecaine (2);
b — for diphisopronyle (3).

the membrane electric resistance revealed the following. Once the antiarrhythmic drugs (Diphisopronyl in dose 0.2 mmol kg^{-1}, trimecaine and novocainamide in dose 1 mmol kg^{-1}) are introduced into the buffer solution which surrounds the membrane, the resistance remains unchanged; in 10 to 12 minutes the resistance changes abruptly. It is supposed that prior to the registration of the influence of the molecules on the electric conductivity of the membrane, a certain critical number of molecules should be adsorbed at the surface of the membrane and penetrate into it.

The influence of the studied drugs on the permeability of the membrane is correlated with their antiarrhythmic activity: ED_{50} diphisopronyle = $3 \cdot 10^{-3}$ mol kg^{-1}, trimecaine = $12 \cdot 10^{-3}$ mol kg^{-1}, novocainamide = $2 \cdot 10^{-2}$ mol kg^{-1}. This comparison may lead to the conclusion on the interrelationship between

the antiarrhythmic effect of drugs and their influence on the bilayer lecithin membrane. The most active antiarrhythmic drugs have considerable affinity for the molecules of lecithin. This may be explained by their pronounced surface-active and lipophilic properties, as well as by the role of the chosen phospholipid in the formation of the antiarrhythmics receptor. Apparently the bilayers of phosphatidylcholine may serve as a model of receptors during the investigation of action of antiarrhythmic drugs. These results are essential for understanding the mode of action of antiarrhythmics on the receptor.

Thus, the investigation of surface phenomena gives the information on the interaction of drug molecules (specifically antiarrhythmics) with macromolecules of receptors, i. e. on the primary pharmacological reaction. In addition to that the behaviour of the antiarrhythmics at the interfaces, which depends on their structure and on their colloido-chemical properties, makes it possible to pass a judgment on the probable structure and physico-chemical basis of receptor functions. Besides being of obvious theoretical significance this field of molecular pharmacology is of great practical importance since the revealed patterns can be used in the discovery of new drugs which possess the required properties.

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SAŽETAK

Površinska aktivnost i mehanizam djelovanja antiaritmikâ

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Istraživana je uloga površinskih efekata na djelovanje antiaritmikâ: novokainamida, kinidina, fubromegana, propranolola, metamicila, difizopronila, novokaina, ksilokaina i trimekaina, odnosno veza između farmakoloških efekata tih spojeva i njihove površinske aktivnosti te utjecaja na međufaze koje sadržavaju lipide (bimolekularne slojeve fosfatidilkolina). Usporedba antiaritmičkog efekta kao i lokalnoga anestetskog djelovanja s površinskom i međufaznom aktivnosti ovih lijekova pokazala je da postoji međuodnos ovih svojstava. Utjecaj spojeva na dvoslojnu fosfolipidsku membranu tj. površinsku aktivnost, električnu vodljivost (otpor) i propusnost membrane, upućuje na zaključak o međuodnosu antiaritmičkog efekta ljekova i njihovog utjecaja na dvoslojnu lecitinsku membranu i ulozi korištenog fosfolipida u sastavu antiaritmičkog receptora.

Ističe se značenje ovih rezultata za razumijevanje djelovanja antiaritmika na receptoru, tj. primarne farmakološke reakcije.

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