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ROLE OF SURFACE PHENOMENA IN THE MECHANISM OF ACTION OF ANTIARRHYTHMIC DRUGS

N. T. Pryanishnikova, V. M. Samvelyan, and Zh. A. Dyadyura

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Surface activity of antiarrhythmic drugs and their effect on lipid-containing interphases were studied. Compound No. 7351 (diethylaminopropyl ester of diphenylisopropylacetic acid), Fubromegan, methyldiazine, propranolol, quinidine, novocainamide, xylocaine, and trimecaine were shown to be surface active. The curves of surface activity and, in particular, of interphase activity and those of antiarrhythmic action follow parallel courses. The most active antiarrhythmic compound (No. 7351) increased the electrical conductivity of a lecithin bilayer membrane much more strongly than novocainamide.

KEY WORDS: physicochemical properties; surface activity; artificial bilayer lipid membrane; antiarrhythmic drugs.

The physicochemical and colloid-chemical properties of neurotropic drugs (local anesthetics, narcotic analgesics, etc.) are known to play an important role in the mechanism of their action [2-9]. At the same time it has been suggested that interaction with the membrane is of great importance in the mechanism of action of antiarrhythmic drugs [1, 14, 15].

It was accordingly decided to study the role of surface phenomena in the action of antiarrhythmic drugs. The connection between the pharmacological action of antiarrhythmic drugs and their surface activity and their effect on lipid-containing interphases (a lecithin bilayer) was investigated.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Laboratory of Pharmacology, Institute of Cardiology, Ministry of Health of the Armenian SSR, Erevan.

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EXPERIMENTAL METHOD

The antiarrhythmic drugs tested included compound No. 7351 [11] (the diethylaminopropyl ester of diphenylisopropylacetic acid), Fubromegan [10], methyldiazine, propranolol, quinidine, and novocainamide; the local anesthetics xylocaine, trimecaine, and procaine also were studied because they are sometimes used in medical practice as antiarrhythmic agents.

In experiments on cats anesthetized with urethane and chloralose (1 g/kg and 50 mg/kg, respectively) and artificially ventilated, experimental arrhythmia was induced by threshold electrical stimulation of the atria and ventricles for 10 sec (1.5 V, 1 msec, 1 pulse/sec, continuous series). The mean effective dose (ED_{50}) of the substance abolishing the arrhythmia was determined. The ability of the drugs to cause conduction anesthesia was tested on frogs by Turk's method. The minimal anesthetic concentration (MAC) was taken to be that concentration of the drugs with which the limb withdrawal reflex disappeared in the course of 5 min.

The surface-active properties of the antiarrhythmic drugs were investigated by the method fully described previously [6, 6]; isotherms of surface tension of aqueous solutions of the antiarrhythmic drugs in different concentrations at the boundary with air, benzene, and solutions of nerve tissue lipoproteins in benzene were obtained. Surface tension (σ) was measured by a semistatic method of maximal pressure of the bubble (or drop) on Rebinder's instrument, always under strictly maintained conditions: at 20 ± 0.1°C, after establishment of equilibrium, at pH 7.0; the maximal time of bubble formation was 5 min. Each drug was studied in eight concentrations. The mean of ten measurements of σ was taken as a reliable result. The accuracy of measurement of σ was ± 0.1 dyne · cm^{-1}.

A bilayer lecithin membrane formed by the method of Müeller et al. [13] on a hole (1 mm in diameter), in a Teflon container placed in a quartz cuvette, was used as the model of an artificial lipid membrane. Identification of egg lecithin with the sample of synthetic lecithin [12] was carried out by thin-layer chromatography, the IR spectra, and optical rotatory dispersion. A solution containing 0.25 M sucrose, 5 mM KCl, and 5 mM Tris-HCl, pH 7.0, at 30°C was present on both sides of the membrane. The membrane resistance was measured by means of a circuit including a voltage source, calibrated resistors, an electrometer, and a KSP-4 automatic writer. A potential of 50 mV was applied to the membrane by means of two Ag–AgCl electrodes. The resistance of the membranes was $(0.8 \pm 0.02) \cdot 10^7$ $\Omega \cdot cm^{-2}$ [9].

EXPERIMENTAL RESULTS

The antiarrhythmic drugs were shown to be surface active in concentrations of between $2 \cdot 10^{-3}$ and $1 \cdot 10^{-2}$ M on all studied interfaces (Fig. 1). In order of increasing surface activity at the boundary with air they were arranged as follows: novocainamide < quinidine < Fubromegan < propranolol < methyldiazine < No. 7351. Procaine, xylocaine, and trimecaine were surface active in higher concentrations, namely from $2 \cdot 10^{-2}$ to $1 \cdot 10^{-1}$ M. The absolute activity of the antiarrhythmic drugs on boundaries with air, benzene, and solutions of nerve tissue lipoproteins in benzene differed, as is perfectly logical. The order of arrangement of the compounds by increasing interphase activity was as follows: novocainamide < propranolol < quinidine < Fubromegan < methyldiazine < No. 7351. The influence of the chemical nature of the drugs on the interphase boundary was less marked, evidently, just as with the action of narcotic analgesics [4], because of identical conformational changes (over a given range of concentrations) during the formation of the complex adsorption layer formed by the lipoprotein complex together with the drug tested.

Comparison of the antiarrhythmic activity of the drugs with their surface and interphase activity showed that the two properties are interconnected (Fig. 2). The connection was more marked when antiarrhythmic action and interphase activity were compared than when the pharmacological effect and surface activity were compared, which again is perfectly logical. When surface and interphase activities of the antiarrhythmic drugs were compared with their local anesthetic action in the production of conduction anesthesia, these characteristics also were found to be interdependent: Highly active antiarrhythmic drugs possessed well-marked surface-active properties and produced conduction anesthesia in the lowest concentrations (Fig. 2). These results correlate closely with previous findings indicating a parallel relationship between the anesthetic effect of drugs belonging to different chemical classes and their surfaces and, in particular, their interphase activity, on the one hand, and their effect on monomolecular layers of lipids, on the other hand [2, 3, 6, 8].

The effect of the new antiarrhythmic preparation No. 7351 and of novocainamide, taken for comparison, on the properties of the artificial bilayer phospholipid membrane was next studied. The results showed that compound No. 7351 and novocainamide both altered the electrical conductivity of the membrane: The fall in electrical resistance of the membrane was found to depend directly on the concentration of the drug. Solutions

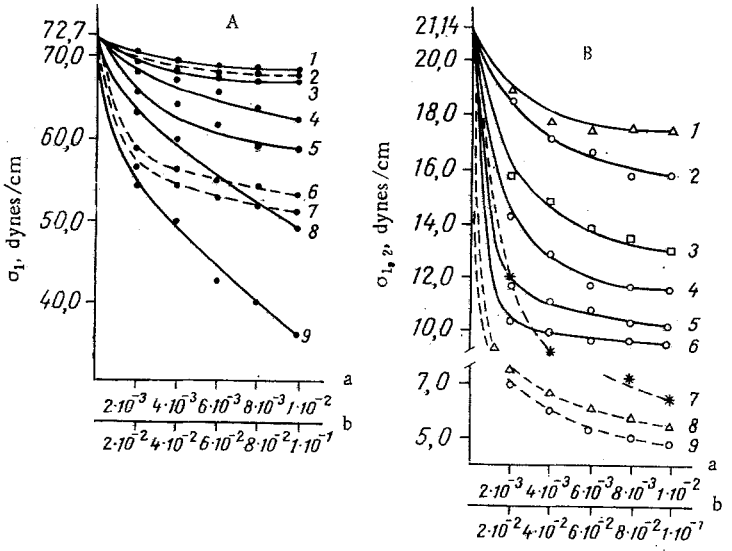

Fig. 1. Surface and interphase tension of solutions of antiarrhythmic drugs in water at boundary with air (A) and with solutions of nerve tissue lipoproteins in benzene (B) at 20 ± 0.1°C. Ordinate, surface (σ_1) and interphase ($\sigma_{1,2}$) tension (in dynes/cm); abscissa, concentration of drugs (in M). Each point on curve plotted on basis of 10 measurements of surface tension. A: a) For novocainamide (1), quinidine (3), Fubromegan (4), propranolol (5), methyldiazine (8), and compound No. 7351 (9); b) for procaine (2), xylocaine (6), and trimecaine (7). B: a) For novocainamide (1), propranolol (2), quinidine (3), Fubromegan (4), methyldiazine (5), and compound No. 7351 (6); b) for procaine (7), xylocaine (8), and trimecaine (9).

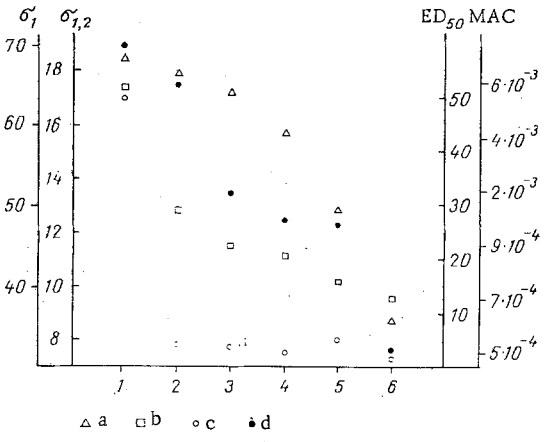

Fig. 2

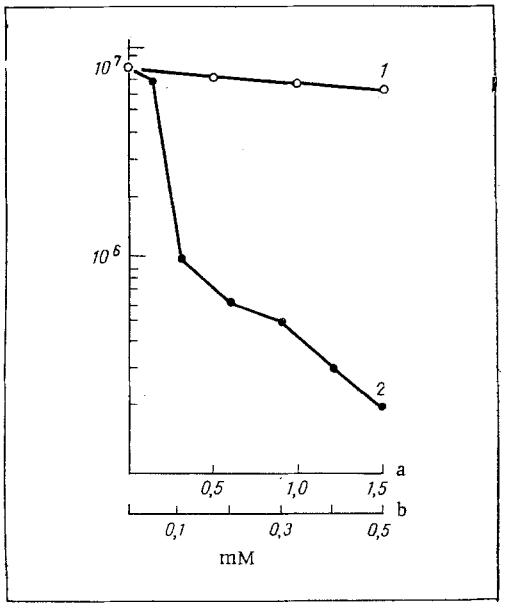

Fig. 3

Fig. 2. Surface (σ_1), interphase ($\sigma_{1,2}$), antiarrhythmic (ED_{50}, mg/kg), and anesthetic (MAC, M) activity of novocainamide (1), quinidine (2), Fubromegan (3), propranolol (4), methyldiazine (5), and compound No. 7351 (6). Concentration of drugs 10^{-2} M. a) Surface, b) interphase, c) antiarrhythmic, and d) anesthetic activity.

Fig. 3. Resistance of bimolecular lecithin membrane as a function of concentration of antiarrhythmic drugs (pH 7.0; 30°C). a) For novocainamide 1); b) for compound No. 7351 (2). Ordinate, resistance (in $\Omega \cdot cm^{-2}$); abscissa, concentration (in mM).

of No. 7351 in buffer (pH 7.0) in 0.05-0.5 mM concentrations caused a marked decrease (by two orders of magnitude) in the electrical resistance of the artificial bilayer lecithin membrane. Novocainamide, in high concentrations (0.5-1.5 mM) reduced the membrane resistance only a little, by 50-67% (Fig. 3). Compound No. 7351 thus exhibited greater affinity for lecithin molecules, a result attributable to its stronger surface-active and lipophilic properties. The effect of the drugs on the electrical conductivity of the membrane correlated with their antiarrhythmic activity: ED_{50} for compound No. 7351 was $3 \cdot 10^{-3}$ M and for novocainamide $2 \cdot 10^{-2}$ M.

It can be concluded from these relationships that characteristic physicochemical properties, namely surface and interphase activity and binding with phosphatidylcholine molecules, play an important role in the interaction between antiarrhythmic drugs and the receptor.

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