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CORRELATION BETWEEN ANESTHETIC AND ANTIARRHYTHMIC ACTIVITY OF α-AZACYCLOALKANECARBOXYLIC ACIDS AND THEIR EFFECT ON PERMEABILITY OF BILAYER PHOSPHOLIPID MEMBRANES

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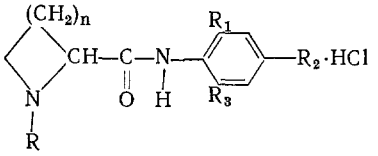
UDC 615.211:547.46].017:615.22

KEY WORDS: physicochemical properties; surface activity; artificial bilayer phospholipid membrane; anesthetic activity; antiarrhythmic activity.

In the search for new anesthetics, a number of aromatic amides of N-substituted α-azacycloalkanecarboxylic acids (AACACA) with the general formula



were synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR.

Meanwhile, the importance of physicochemical properties in the action of neurotropic drugs has been demonstrated [2, 4]. Correlation has been found between the anesthetic effect of compounds of various derivatives of the AACACA and their surface and interphase activity on different partition boundaries.

It was decided to study the effect of the most strongly surface-active substances on electrical conductance of bilayer phospholipid membranes, and the investigation described below was carried out for this purpose.

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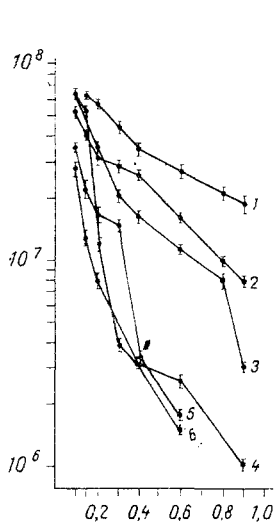

Fig. 1

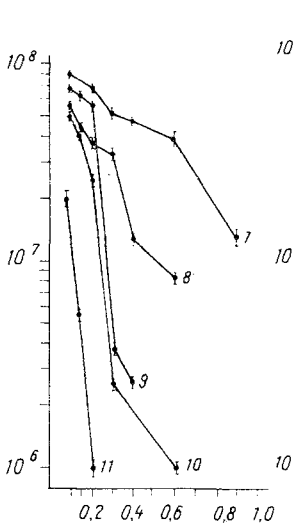

Fig. 2

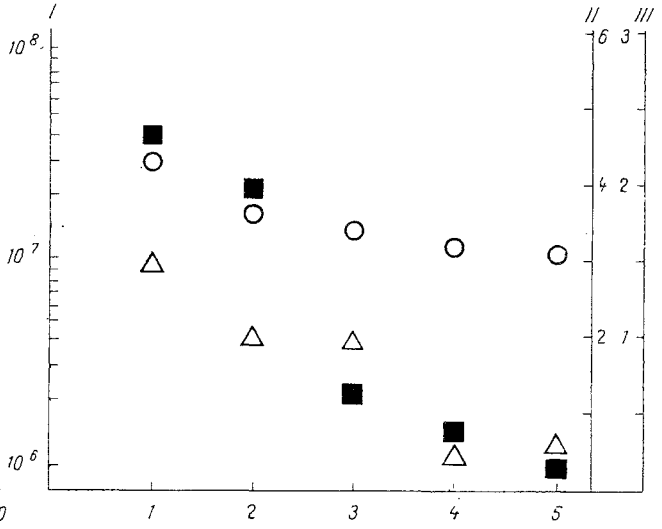

Fig. 3

Fig. 1. Effect of derivatives of AACACA on electrical resistance of bimolecular phosphatidylcholine membrane. Abscissa, concentration of compounds (in mmoles/kg); ordinate, membrane resistance (in ohm) at pH 7.4 and 20°C. Compounds: 1) C-1, 2) C-2, 3) C-3, 4) C-4, 5) C-5, 6) C-6.

Fig. 2. Effect of derivatives of AACACA on electrical resistance of bimolecular phosphatidylcholine membrane. Compounds: 7) C-7, 8) C-8, 9) C-9, 10) C-10, 11) C-11. Remainder of legend as to Fig. 1.

Fig. 3. Resistance of bimolecular phosphatidylcholine membrane (I) in the presence of a concentration of 0.5 mmole/kg, anesthetic activity MAC (II), and antiarrhythmic activity ED_{50} (III) of derivatives of AACACA during electrical stimulation of cat atrium. Compounds: 1) C-2, 2) C-3, 3) C-5, 4) C-10, 5) C-11. Black squares denote R (in ohm), circles denote MAC (in moles/kg), triangles ED_{50} (in mg/kg).

EXPERIMENTAL METHOD

The method in [6] was used. The scheme of the investigation was described previously [3]. The compounds were tested in five concentrations: 0.2, 0.4, 0.5, 0.8, and 1.0 mmole/kg at 20°C and pH 7.4. The mean value (of five experiments) of the membrane resistance (R) was adopted as a reliable result. A potential of 50 mV was applied to the membrane. The resistance of the membrane was $(0.8 \pm 0.02) \times 10^7$ $\Omega \cdot cm^2$. Surface anesthesia was studied in rabbits by Regnier's method, conduction anesthesia in frogs by Turck's method. Antiarrhythmic activity was investigated on models of arrhythmias induced by electrical stimulation of the cat atrium [7] and by aconitine [9].

EXPERIMENTAL RESULTS

Derivatives of the series of aromatic amides of AACACA were shown to reduce the electrical resistance of the bilayer phospholipid membrane. The degree of reduction of membrane resistance increased proportionally to an increase in the concentration of the substances. Compounds with low anesthetic activity were found to have a moderate effect on membrane permeability: C-1($R_1=R_2=R_3=CH_3$; $R(=CH_2)_2 \cdot NH_2$; n=2), C-2($R_1=R_2=R_3=CH_3$; $R=(CH_2)_2 \cdot OH$; n=2) substances inducing a marked anesthetic effect — C-3($R_1=R_2=R_3=CH_3$; $R=IC_4H_9$; n=2) and C-9($R_1=R_3=CH_3$; $R_2=H$; $R=C_4H_9$; n=3) — changed membrane resistance by 1.5 orders of magnitude. The most active anesthetics were compounds C-6($R_1=R_2=R_3=CH_3$; $R=CH_3$; n=4); C-10($R_1=R_3=CH_3$; $R_2=H$; $R=C_6H_{11}$; n=3) and C-11($R_1=R_2=R_3=CH_3$; $R=C_6H_{11}$; n=3), and they lowered the electrical resistance of the membrane by almost two orders of magnitude: from 0.8×10^7 to 10^5 $\Omega \cdot cm^2$ (Figs. 1 and 2). These same substances had the smallest ED_{50} for conduction anesthesia (Fig. 3). Consequently, correlation exists between the anesthetic effect of the new compounds and changes produced by them in bilayer phospholipid membranes.

Among antiarrhythmic agents, there is a group of compounds with affinity for membranes [8, 9]. It has been shown that correlation exists between the antiarrhythmic activity of substances belonging to different chemical classes and their colloid-chemical properties. Accord-

ingly, compounds with highest membrane activity in the series of aromatic amides of AACACA were chosen for a study of the antiarrhythmic effect. The action of the compounds was assessed on the basis of their ability to prevent the development of aconitine arrhythmia in waking rats and to raise the threshold of electrical atrial fibrillation in cats. The membrane-active substances of the class of aromatic amides of AACACA were found to possess marked antiarrhthmic activity (Fig. 3): these were compounds C-6 (ED_{50} = 2 mg/kg), C-3 (ED_{50} = 1 mg/kg), C-10, and C-11 (ED_{50} = 0.3 mg/kg).

It can thus be concluded that compounds of a series of aromatic amides of AACACA possess surface-active and lipophilic properties. They increase the permeability of artificial bilayer phosphatidylcholine membranes. The physicochemical characteristics and anesthetic and antiarrhythmic activity of the compounds are interrelated. The results are important for the search for new drugs with anesthetic and antiarrhythmic action.

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