havioral effect of THC it accumulates rapidly to a high level in the thalamohypothalamic region [11].

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EFFECT OF ETHMOZINE AND ITS DIETHYLAMINO ANALOG ON THE SLOW INWARD AND OUTWARD CURRENTS OF FROG ATRIAL FIBERS

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KEY WORDS: ethmozine; diethylamino analog of ethmozine; slow inward current; outward current.

The new antiarrhythmic drug ethmozine and its diethylamino analog (DAA-ethmozine) abolish arrhythmias arising experimentally 24 h after occlusion of the coronary artery [1, 2, 4, 7, 9]. These drugs inhibit the fast inward sodium current and reduce the rate of rise of the leading edge of the transmembrane action potential [3, 5, 8]. DAA-ethmozine differs from ethmozine in causing longer inhibition of the fast inward sodium current and in the longer duration of its antiarrhythmic action in the late stage of experimental myocardial infarction [3]. The antiarrhythmic action of ethmozine and of DAA-ethmozine in the late stage of myocardial infarction can thus be linked with the effect of these drugs on the fast inward sodium current. However, this hypothesis has not yet been adequately verified, for the action of these drugs on other ionic currents of heart muscle cells has not been studied.

The object of this investigation was to study the action of ethmozine and DAA-ethmozine on the slow inward and outward currents of myocardial cells.

EXPERIMENTAL METHOD

The voltage clamp method under double sucrose gap conditions was used to record the ionic currents. Experiments were carried out on isolated atrial trabeculae of *Rana ridibunda*

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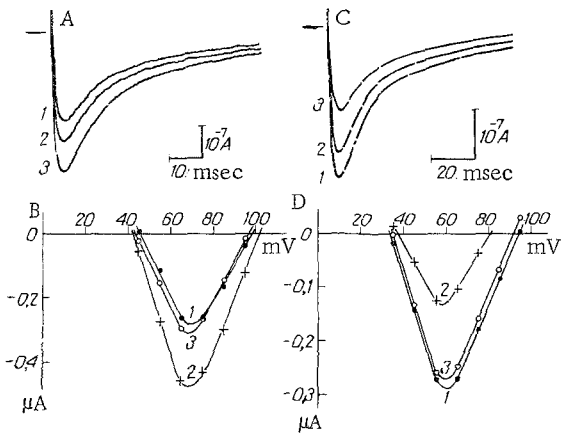

Fig. 1

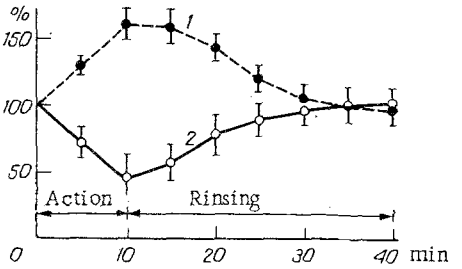

Fig. 2

Fig. 1. Action of ethmozine (A and B) and of DAA-ethmozine (C and D) in a concentration of 2×10^{-5} g/ml on the slow inward current of frog atrial cells. A and C) Measurement of peak value of slow inward current: 1) control, 2 and 3) after action of drug for 5 and 10 min, respectively. Currents recorded in presence of tetrodotoxin (2×10^{-7} M). Amplitude of depolarizing stimulus 70 mV in A and 60 mV in C. B and D) Change in current–voltage curves of slow inward current under the influence of ethmozine and DAA-ethmozine respectively: 1) control, 2) after action of drug for 10 min, 3) after rinsing out for 30 min with normal Ringer's solution. Calibration: 20 msec, 10^{-7} A. Abscissa, membrane potential (in mV); ordinate, slow inward current (in μA).

Fig. 2. Changes in peak value of slow inward current with time during action of ethmozine (2×10^{-5} g/ml) (1) and of DAA-ethmozine (2), and also in period of rinsing with normal Ringer's solution. Each curve plotted from data for five experiments: M ± m. Abscissa, time (in min); ordinate, ratio of slow inward current during action of drug to corresponding current in control (in %).

and *Rana catesbiana*, with a diameter of 100-200 μ and a length of 3-4 mm. The trabeculae were perfused with Ringer's solution of the following composition (in mM): NaCl — 114, KCl — 2.7, $CaCl_2$ — 1.8; $MgCl_2$ — 1.2, $NaHPO_4$ — 0.5, $NaHCO_3$ — 5; pH 7.5-7.6. The slow inward current was recorded in the presence of tetrodotoxin, which blocks the fast inward current, in a concentration of 2×10^{-7} M. The outward current was recorded in the presence of tetrodotoxin (2×10^{-7} M) and also of izoptin (verapamil) (5×10^{-6} g/ml), which blocks the slow inward current. The frequency of stimulation in all the experiments was 0.1 Hz. The amplitude of the outward current was measured at the end of a depolarizing stimulus 0.5 sec in duration. The experimental results were recorded on magnetic tape (Hewlett-Packard 3964A tape recorder) and subsequently displayed on the screen of a storage oscilloscope (Tektronix 5113N).

EXPERIMENTAL RESULTS

During perfusion of an atrial trabecula with Ringer's solution containing ethmozine in a concentration of 2×10^{-5} g/ml a considerable increase in amplitude of the slow inward current was observed (Fig. 1A), and it occurred at all values of membrane potential (Fig. 1B, 2). The initial amplitude of the slow inward current was practically completely restored after rinsing out the ethmozine with normal Ringer's solution for 30 min (Fib. 1B, 3).

DAA-ethmozine in a concentration of 2×10^{-5} g/ml caused a decrease in the amplitude of the slow inward current (Fig. 1C), which took place at all values of membrane potential (Fig. 1D, 2). During rinsing with normal Ringer's solution for 30 min the initial value of the slow inward current was practically completely restored (Fig. 1D, 3). Under the influence of ethmozine (Fig. 1B) and of DAA-ethmozine (Fig. 1D) changes were observed in the reversal potentials, and these were attributable to a change in the relative contribution of the outward current to the measured resultant current.

The dynamics of changes in the peak value of the slow inward current in the presence of ethmozine and of DAA-ethmozine and also during the period of rinsing with normal Ringer's

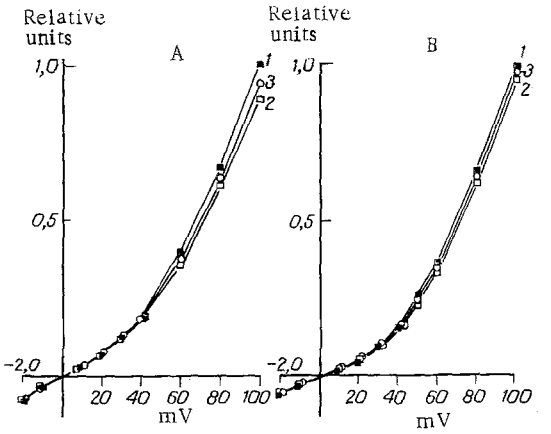

Fig. 3. Action of ethmozine (A) and of DAA-ethmozine (B) on steady-state value of outward current recorded in the presence of tetrodotoxin (2×10^{-7} M) and izoptin (5×10^{-6} g/ml). In A and B: 1) current–voltage curves in control; 2) after action of drug for 10 min; 3) after rinsing for 30 min with normal Ringer's solution. Value of outward current during depolarization of membrane by 100 mV from resting potential level taken as the unit. Abscissa, membrane potential (in mV); ordinate, value of outward current (in relative units).

solution is shown in Fig. 2. After the action of ethmozine for 10 min the amplitude of the peak value of the slow inward current was increased on average by 62 ± 11%, whereas DAA-ethmozine in the same period inhibited the slow inward current by 54 ± 17%. Rinsing with normal Ringer's solution led to restoration of the initial values of the currents after 20-30 min.

Ethmozine and DAA-ethmozine in a concentration of 2×10^{-5} g/ml had no significant effect on the steady-state value of the outward current within the range of potentials from −20 to +100 mV from the resting potential level (Fig. 3). Similar results were obtained in four other experiments.

Experiments also were carried out in which the action of ethmozine and of DAA-ethmozine was studied on the slow inward and outward currents in lower concentrations, namely 5×10^{-6} and 1×10^{-6} g/ml. The effect of these drugs in these lower concentrations was weaker, but the character remained the same.

The results obtained in this investigation for the increase in slow inward current supply an explanation of the positive inotropic action of ethmozine, for the slow inward current is mainly determined by the inward flow of calcium ions into the cell. It was shown previously that ethmozine increases the force of contraction of the frog myocardium [8] and of the false tendon of the dog's heart [5]. These data are evidence that ethmozine has a similar effect on the myocardium of warm-blooded and cold-blooded animals.

The opposite action of the two phenothiazine drugs on the slow inward current and their weak effect on the outward current lead to the conclusion that the cause of the antiarrhythmic action of these drugs is their ability to influence the fast inward sodium current. This conclusion is supported by data indicating that the duration of the antiarrhythmic action of ethmozine and of DAA-ethmozine in the late stage of myocardial infarction correlates with the duration of action of these drugs on the fast inward sodium current [3].

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EFFECT OF DIAZEPAM AND PHENAZEPAM ON NERVOUS REGULATION OF THE CEREBRAL CIRCULATION

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KEY WORDS: diazepam; phenazepam; cerebral circulation; cerebrovascular reflexes.

According to data in the literature, diazepam reduces the cerebral blood flow [11-13]. Chai and Wang [10] found that diazepam inhibits pressor responses of the arterial blood pressure (BP) to stimulation of the carotid sinus, medulla, and hypothalamus. It also has an antihypertensive effect during emotional stress [4]. However, reports have been published that diazepam may increase the intensity of pressor vasomotor reflexes in animals under general anesthesia and in unanesthetized, curarized cats [3, 8, 9]. As regards phenazepam, there is no information in the literature on its effect on the cerebral hemodynamics.

The object of the present investigation was to study the effect of diazepam and phenazepam on nervous regulation of the cerebral blood supply.

EXPERIMENTAL METHOD

Experiments were carried out on 63 cats under general anesthesia (urethane and chloralose) with artificial ventilation of the lungs and on seven waking cats.

The cerebral blood flow was determined by the ^{133}Xe method on the VAV-100 apparatus. The results were subjected to statistical analysis on the Minsk-22 computer. The value of the blood flow was determined by successive derivation of exponential functions [6]. The state of the cerebral circulation also was judged from the inflow of blood into the cat's brain through the internal maxillary artery, which was recorded by means of an electromagnetic measuring device in acute and chronic experiments. The EEG was recorded in the parietal region, the ECG in lead II, and BP in the femoral artery. The vascular component of the action of the drugs on the cerebral hemodynamics was differentiated by separate perfusion of the carotid and vertebral arteries on the two sides [5]. The acid–base balance and partial pressure of oxygen was determined in samples of arterial blood and CSF by the ABC-1 apparatus. Tonic and reflex activity were recorded in the sympathetic nerves with differentiation of responses to impulses from afferent fibers of groups A and C, and postactivation inhibition and inhibition of somatosympathetic responses evoked by excitation of low-threshold spinal afferents also were estimated [1]. Diazepam and phenazepam were injected intravenously in doses of 0.05 and 0.5 mg/kg.

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