observed a significant decrease in the number of ulcers in the gastric mucosa from 4.4 ± 1.0 to 2.5 ± 1.1 ($P_U < 0.05$).

Comparison of the total number of points on the integral evaluation of stress scale in the stress control and in the group of mice receiving enkephalin analog also confirmed the antistressor action of D-Ala^2-Leu^5-Arg^6-enkephalin. In this case the difference between the total number of points was 2.

The results are thus evidence that enkephalins may have a marked antistressor action. This suggests that activation of the system of opioid neuropeptides in stress [6, 7] may be adaptive in character and aimed at natural prevention of injuries caused by excessive response to the action of extremal factors.

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EFFECT OF PENTOBARBITAL ON SODIUM PERMEABILITY OF HEART MUSCLE CELLS

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KEY WORDS: pentobarbital, myocardium, sodium permeability.

Barbituric acid derivatives are known to influence the sodium permeability of cell membranes [6, 11], and according to some workers, changes in that permeability are linked with the basic mechanism of action of general anesthetics [1, 12]. No such data are available for the myocardium, although barbiturates have been found to have a cardiodepressive effect [8].

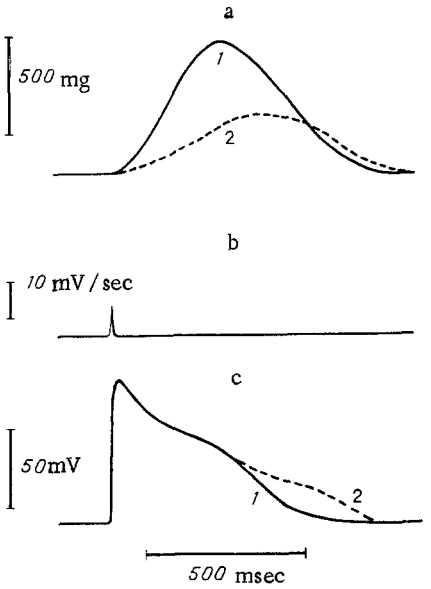

Fig. 1. Action of pentobarbital ($5 \cdot 10^{-4}$ M) on contractile (a) and electrical (b) activity of frog myocardial strip; 1) control; 2) pentobarbital.

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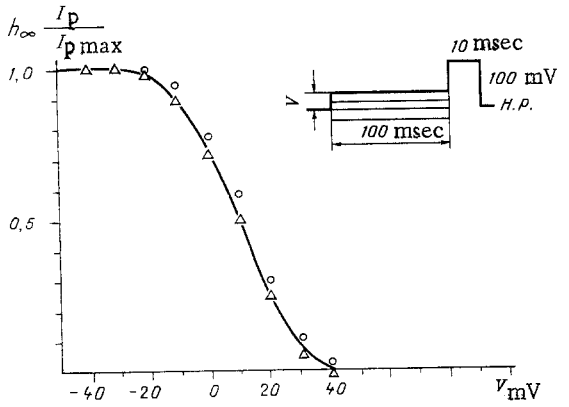

Fig. 2

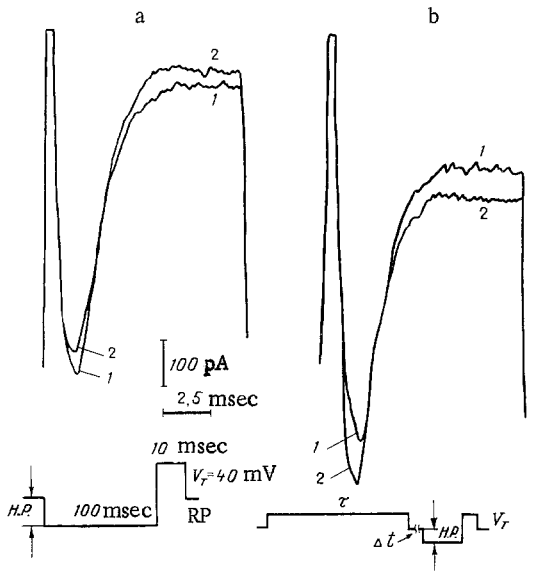

Fig. 3

Fig. 2. Steady-state inactivation of sodium current (h_∞) of isolated rat heart cell as a function of potential. I_p) Peak values of currents at different potentials; $I_{p\ max}$)maximal peak value of current. Triangles denote control, circles — after exposure to pentobarbital ($5 \cdot 10^{-4}$ M) for 15 min. Pulse program indicated above; V) amplitude of conditioning pulse; 100 mV) amplitude of test pulse. Zero marker corresponds to holding potential (H.P.) = —65 mV.

Fig. 3. Traces of sodium currents of isolated rat heart cell under the influence of pentobarbital ($5 \cdot 10^{-4}$ M): a) stimulation at frequencies of: 0.5 (1) and 5 Hz (2); b) prolonged depolarization; 1) control; 2) after prolonged depolarization. Pulse program indicated below: V_T) amplitude of test pulse; τ = 3 min, $\Delta t \sim 1$ sec ΔE = 20 mV. Holding potential (H.P.) = —65 mV. (All potentials counted from resting potential — RP.)

The aim of this investigation was to study the effect of pentobarbital, in concentrations close to those inducing general anesthesia [10], on the action potential (AP) and its first derivative in the ventricles of the frog's heart, the sodium current in the trabecula of the frog atrium, and the sodium current of the rat myocardiocyte.

EXPERIMENTAL METHOD

The contractile response, AP, and its first derivative were recorded in tissue strips from the ventricles of the frog *Rana temporaria*, perfused with Ringer's solution with the following composition; 110 mM NaCl, 2.5 mM KCl, 0.08 mM K_2HPO_4, 2.4 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 5.5 mM glucose (pH 7.2-7.4). Contractile activity was recorded with the 6MKh2B mechanotron under close to isometric conditions, during stimulation of the strip of heart muscle by square pulses with a frequency of 0.5 Hz, duration 5 msec, and amplitude twice the threshold of stimulation, from an ÉSL-2 stimulator through silver electrodes. Membrane potentials were recorded by "floating" glass microelectrodes, an S1-18 oscilloscope, and FOR-2 recording camera. The first derivative of AP was recorded with a time constant of 10 msec. The sodium current of the atrial trabeculae was recorded in the frog *Rana ridibunda*. A strip 0.1-0.2 mm in diameter and 3-5 mm long was placed in the working chamber 10-30 min after isolation. Ionic currents were measured by the double sucrose gap method, using a four-electrode recording circuit, differential preamplifier, main amplifier, and current amplifier, designed by the Institute of Biological Physics, Academy of Sciences of the USSR. The membrane current was recorded by FOR-1 camera for S1-18 oscilloscope. Fast inward currents were measured by the standard method in response to a square pulse 0-100 mV in amplitude and 30-50 msec in duration. The current—voltage characteristic curve was plotted at peak values of the fast sodium current. The sodium current on the membrane of single heart cells was measured by a "microderivation" method. Single heart cells were isolated from the rat heart by a modified method [14]. Sodium currents through the membrane of single heart cells were measured by means of a high-precision ammeter. The measured currents were recorded on a VC-9 oscillograph (Nihon Kohden,

Japan) and then on a tape recorder (Teac, Japan) and automatic writer (Honeywell, USA). Details of the technique were described previously [2-4].

EXPERIMENTAL RESULTS

Exposure of the isolated strip of myocardial tissue from the frog heart ventricle to pentobarbital in a wide range of concentrations ($5 \cdot 10^{-6}$-$5 \cdot 10^{-4}$ M) led to suppression of the contractile response and lengthening of the duration of AP in the repolarization phase depending on concentration (by 14 ± 4 to 31 ± 8%). Typical changes in AP and contractile response of the frog myocardial strip under the influence of the highest concentration of pentobarbital, namely $5 \cdot 10^{-4}$ M, are illustrated in Fig. 1. The results of measurement of the amplitude of AP and its first derivative during exposure to pentobarbital were different in value, thus questioning the hypothesis that pentobarbital affects the rate of depolarization of myocardial cells, although a decrease in the first derivative of AP occurred in only 30% of cases and it did not exceed 5-7%, even under the influence of high concentrations of the anesthetic. These doubts were strengthened by data in the literature on a decrease in the rate of depolarization of the cell membranes [9] in experiments on the rabbit atrial septum under the influence of thiopental. Since this method is not sufficiently reliable to enable the dynamics of sodium permeability to be judged, it was decided to undertake investigations by the voltage clamp method in experiments on frog trabeculae. However, the results of this series of experiments also were inconsistent. In only one of four experiments was a change in the inward sodium current observed during the action of low pentobarbital concentrations ($5 \cdot 10^{-5}$ M), and in the other experiments the sodium current was unchanged. Only with an increase in concentration of the anesthetic to $5 \cdot 10^{-3}$ M, at which contraction almost completely disappeared, was a decrease in the sodium current observed.

Zero and negative results were thus obtained during the action of pentobarbital in both low ($5 \cdot 10^{-5}$ M) and high ($5 \cdot 10^{-3}$ M) concentrations, evidence that qualitative evaluation of the change in sodium permeability under these conditions is inadequate voltage clamping on multicellular objects [3].

Advantages of the "microderivation" method, permitting more reliable voltage clamping on the membrane of a s-ngle heart cell [3], led us to carry out a series of experiments to study the action of pentobarbital on the sodium current by means of this method. The current–voltage characteristic curves of the sodium current during exposure to pentobarbital over the whole range of concentrations tested ($5 \cdot 10^{-6}$-$5 \cdot 10^{-4}$ M) were found virtually to coincide with the control curves. No appreciable deviations of dependence of the steady-state inactivation of the sodium current on potential likewise were observed in this case (Fig. 2), evidence that pentobarbital does not affect the sodium current. To detect any possible interaction between pentobarbital and activated sodium channels, a series of experiments was carried out at a higher frequency of stimulation [7, 13]. Original traces of currents in response to the last pulse in series with different frequencies of stimulation are illustrated in Fig. 3. They show that the values of the currents were virtually the same. Hence it can be concluded that, in the concentrations tested, pentobarbital does not interact with activated sodium channels. The possibility that pentobarbital may interact with inactivated sodium channels [5] was tested after prolonged (3 min) preliminary depolarization. In this case also, the currents in response to the same test pulse were virtually identical before and after depolarization (Fig. 3).

It can accordingly be concluded that pentobarbital does not affect the fast sodium current of heart muscle cells and that the mechanism of depression of contractile activity of the myocardium during anesthesia with pentobarbital and, perhaps, with other barbituric acid derivatives, is unconnected with sodium permeability.

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MULTIFACTORIAL ANALYSIS OF THE EFFECT OF FENTANYL ON NOCICEPTIVE HEMODYNAMIC RESPONSES

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KEY WORDS: dental pulp; hemodynamic responses; fentanyl; multifactorial analysis.

Abolition of responses of the cardiovascular system to nociceptive stimuli is one indicator of adequate pharmacologic analgesia [1, 5, 7]. However, existing data on the ability of specific pain-relieving drugs (narcotic analgesics) to stabilize the hemodynamics during nociceptive stimulation are highly contradictory [6, 8, 9], due to differences in the conditions of the experimental and clincial investigations and the absence of analysis of the action of the drugs depending on the initial state of the recipient. In turn, objective analysis of the influence of the original state on the effect of the drug calls for a study of relations between background values of the whole range of parameters recorded and their changes after administration of the drug [4]. It is virtually impossible to discover complex relationships of this kind by traditional analysis of data based on average tendencies.

In the investigations described below the effect of fentanyl on nociceptive hemodynamic responses was studied depending on the initial state of the animals, and a comparative evaluation of the data was made by determination of average tendencies and by the multiple step-by-step bilinear regression methods.

EXPERIMENTAL METHOD

The pulp of the upper canine teeth was stimulated in 14 experiments on eight cats thorough chronically implanted electrodes. The emotional reactivity of the animals was assessed virtually in accordance with special scales [3], the arterial blood pressure (BP) and intersystolic intervals (ISI) were recorded, and the values of the cardioinhibitory baroreflex [2] were calculated. Fentanyl (solution in ampules) was injected intravenously in doses of 1 to 30 μg/kg body weight.

Multifactorial analysis of the data was carried out on the SM-3 computer, using a multiple step-by-step regression program. Regression equations were constructed [4] to estimate dependence of changes in hemodynamic responses not only on dose and time after injection of fentanyl, but also on the initial state of the animals. Parameters (14) of emotional reactivity, reflex mechanisms of regulation of the hemodynamics — intrinsic (baroreflex) and coupled (responses of BP and ISI to stimulation of the dental pulp) were analyzed as factors reflecting intial state (Table 1). At the first and each subsequent step of its program, the factor correlating most strongly with the effect of the drug was introduced into the equation from the number of factors not taken into account by the program previously. Ultimately factors with a level of significance not below 0.01 were included in the final form of the equations.

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