It can be postulated on the basis of the facts described above and data in the literature indicating a rise in the endorphin level in the body in response to such procedures as physical training [11], acupuncture [1, 12], hypnosis [10], and so on, that the system of endogenous opioid neuropeptides is a universal mechanism involved in the action of antistressor factors of varied nature, and which may increase the resistance of the body to stress.

Determination of plasma levels of β-endorphin and other opioids could evidently be an important method of assessing the state of resistance of the organism to stress.

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EFFECT OF LIGANDS OF OPIATE RECEPTORS ON EMOTIOGENIC CARDIOVASCULAR RESPONSES IN LOWER PRIMATES

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KEY WORDS: endogenous opioid system; opiate receptors; lower primates.

Numerous investigations have shown that the endogenous opioid system (EOS) participates directly in the regulation of many physiological processes taking place in the body, including regulation of activity of the cardiovascular system (CVS) [1, 2]. However, the facts confirm that the EOS has only a weak tonic effect directly on the blood pressure (BP) level and cardiac activity. The question accordingly arises of its role in the phasic regulation of responses of the CVS, including those to emotionally meaningful stimuli.

The aim of this investigation was to analyze the role of the EOS in the course of such responses in lower primates.

EXPERIMENTAL METHOD

Experiments were carried out on nine male baboons (*Papio hamadryas*) weighing 8-10 kg. Conditioned-reflex fear [5] was chosen as the model of the emotionally meaningful situation: for 1 min a conditioned acoustic stimulus (CS; 1000 Hz, 60 dB) was presented to the animal and was followed by an unconditioned stimulus (US), namely electrodermal stimulation of the anterior abdominal wall, with a burst of pulses, each with a duration of 1 msec, frequency 50 Hz, 5 mA, total duration 1 sec). After preliminary adaptation of the animals for 2 weeks

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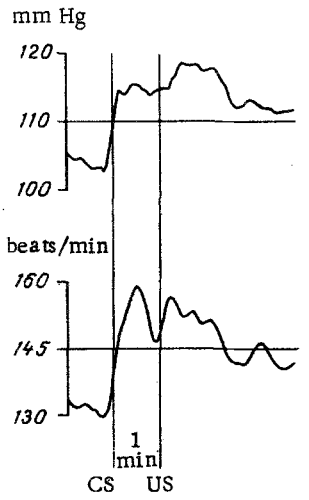

Fig. 1

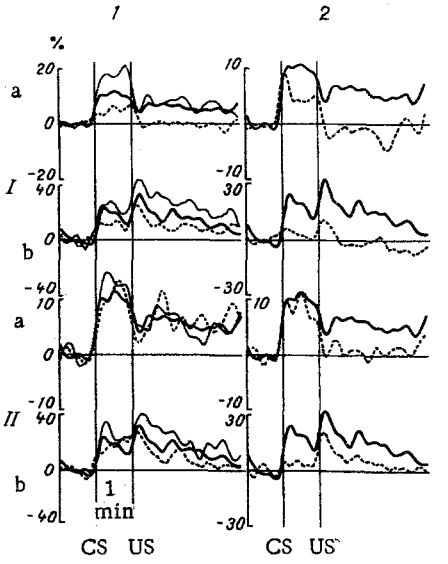

Fig. 2

Fig. 1. Changes in BP (a) and HR (b) in response to presentation of CS and US to baboons. Vertical axes: a) mm Hg, b) number of beats per minute.

Fig. 2. Changes in response of BP (a) and HR (b) to CS and US 5 min (I) and 40 min (II) after intravenous injection of naloxone (1) in doses of 0.1 mg/kg (short dashes) and 1 mg/kg (long dashes), and morphine (2) in a dose of 1 mg/kg (dashes). Continuous line indicates response before injection of drugs.

to the conditions of confinement in an armchair, they were trained in an isolated chamber until a reproducible response of an increase in heart rate (HR) was formed, as monitored from the ECG, in response to CG. During the training period the animals received not more than two or three combinations of CS and US in the course of 2-3 h, with an interval of 1 day between procedures. After training, the animals were anesthetized with ketamine (5 mg/kg) and metal cannulas 0.5 mm in diameter were inserted stereotaxially into structures of the medulla and diencephalon bilaterally, in accordance with coordinates taken from [7]. Simultaneously arterial and venous catheters were inserted into the axillary artery and vein, and brought out subcutaneously on the animal's back. The experiments began 7-10 days after the operation. In the course of the experiments after 30-40 min of adaptation in the experimental chamber, CS and US were presented to the conscious animals, after which drugs were injected either into the venous catheter (1 ml followed by rinsing the catheter with 2 ml of physiological saline), or bilaterally into brain structures (naloxone and morphine, in a volume of 2 µl, in the course of 2 min. The CS and US were next presented 5-10 and 40-50 min after the injection. The ECG and BP were recorded by the direct method. The experiments were repeated after 2-3 days. The position of the tip of the cannula was verified roentgenologically and histologically. The animal was killed by injection of a large dose of pentobarbital. The data were analyzed by computer by averaging values of BP and HR during 4 sec time intervals. The values obtained for individual responses were then averaged and statistical analysis carried out. The significance of differences was determined by Student's paired T test.

EXPERIMENTAL RESULTS

Averaged values of responses of BP and HR to presentation of CS and US are shown in Fig. 1. After intravenous injection of naloxone (0.1 and 1 mg/kg) or morphine (1 mg/kg) no significant changes in the mean BP and HR levels were observed compared with the background values.

It will be clear from Fig. 2 that in response to injection of naloxone in a dose of 0.1 mg/kg the animals showed significant ($p < 0.5$) facilitation of the response of elevation of BP to presentation of CS, whereas naloxone in a dose of 1 mg/kg, elicited, on the contrary, a significant fall in magnitude of the response to presentation of both CS and US ($p < 0.05$). Differences in responses of HR did not reach the level of significance ($p > 0.1$). When the stimuli were presented 40 min after injection of naloxone in both doses, the responses were virtually indistinguishable from those in the background.

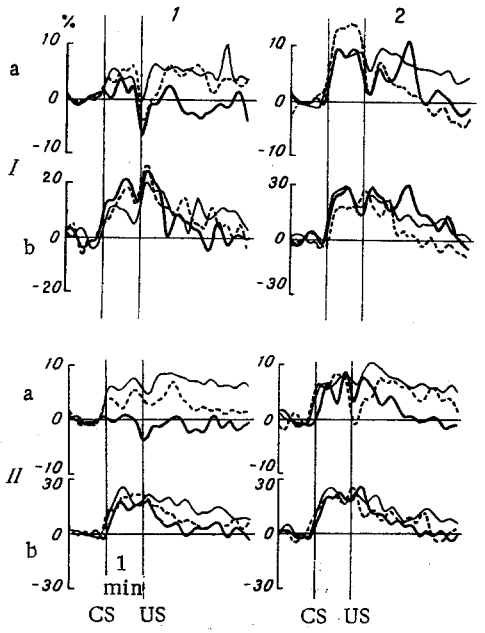

Fig. 3. Changes in response of BP (a) and HR (b) to presentation of CS and US after microinjections of naloxone (1) and morphine (2) into PVH (I) and NTS (II) Thin line — before injection of drugs, bold line — 5 min after injection, broken line — 40 min after injection. PVH) Paraventricular region of hypothalamus; NTS) nucleus of tractus solitarius.

After intravenous injection of morphine the values of the response of BP fell ($p < 0.01$) to both CS and US; in addition, there was a significant fall ($p < 0.05$) in the degree of increase of HR. The response of changes in BP and HR was restored 40 min after injection of morphine, although not fully to its initial level.

After injection of naloxone into the periventricular region of the hypothalamus (PVH, the region of the paraventricular and dorsomedial nuclei) an increase in average HR by 11 ± 3 beats/min ($p < 0.05$) was observed 40 min after the injection. In two animals, after injection of naloxone into the ventromedial region of the hypothalamus, HR fell after 5 min by 26.7 beats/min ($p < 0.05$).

It will be clear from Fig. 3 that as a result of injection of naloxone into PVH there was a significant ($p < 0.05$) decrease in the degree of rise of BP in response to presentation of US and a reduction in the amplitude of rise of HR by the 2nd and 3rd minutes after US ($p < 0.05$). The differences mentioned had virtually disappeared completely 40 min after injection. When naloxone was injected into the ventromedial hypothalamus no signficiant changes were observed in response to CS and US.

The tachycardic response to US was considerably facilitated 5 min after injection of morphine into PVH ($p < 0.05$, Fig. 3), whereas after 40 min the hypertensive response to CS was facilitated, although the difference was below the level of significance ($p > 0.1$).

When naloxone was injected into the nuclei of the tractus solitarius (NTS) no changes were observed in the initial level of BP and HR. The hypertensive response to CS and US was virtually completely suppressed 5 min after the injection, and the response of an increase in HR to US was weakened. These values were indistinguishable from the background values 40 min after the injection.

Five minutes after injection of morphine into NTS, BP and HR were significantly increased on average by 14 ± 2 mm Hg ($p < 0.025$) and 9 ± 2 beats/min ($p < 0.05$), respectively. At the same time changes in the response to CS and US were not significant (Fig. 3).

Injection of naloxone and morphine into the regions of the medulla lying 3 mm dorsally to NTS, and also injection of physiological saline into NTS evoked no significant changes in responses.

The results show that EOS plays a direct part in the formation of the response of changes in BP and HR to presentation of emotionally meaningful stimuli to lower primates. Nalaxone, when injected intravenously, depending on its dose may have opposite actions on the intensity of the responses of changes in BP, for it acts primarily on changes in BP developing in response to CS. This is evidently connected with its interaction, in a dose of 0.1 mg/kg, predominantly with μ-opiate receptors, and only if the dose is increased does it block δ-receptors, with which the hypertensive action of opioids is associated [1]. Attention must also be drawn to the similarity of action of morphine and naloxone in a dose of 1 mg/kg. In the writers' opinion, the reason for this is that morphine, which is an agonist of μ-receptors, may behave as an antagonist relative to endogenous substances that interact with δ-receptors.

The investigation also showed that injection of naloxone into PVH considerably facilitates the response of the CVS to emotiogenic stimuli, whereas its injection into NTS completely blocks the rise of BP in this situation. We know that PVH, which is rich in opiatergic structures [3, 4], is a key region in the formation of the autonomic response of lower primates to emotionally meaningful stimuli [5]. It can thus be concluded that the opiatergic structures of PVH and NTS participate actively in the formation of the response of BP to emotionally meaningful stimuli. Incidentally, if the effects of suppression of the responses of BP and HR to CS and US can be completely transmitted through PVH and NTS, the points of application of the effect of naloxone in doses acting chiefly on μ-receptors, and also probably of morphine, may be other brain structures or structures of the autonomic nervous system.

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EFFECT OF RATIBOL, RETABOLIL, AND SOLASODIN ON THE BLOOD CLOTTING SYSTEM

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KEY WORDS: ratibol; blood coagulation; hemostasis.

This paper describes a study of the effect of three preparations, retabolil, ratibol, and solasodin, on the blood clotting system and on fibrinolysis; the first of the three is widely used in clinical practice in various diseases, and the last two have been approved by the Pharmacological Committee of the USSR for clinical trials.

Since one side effect of retabolil is its damaging action on the liver, especially if used over a long period of time, a closer study of the behavior and interconnection between blood coagulation factors, synthesized in the liver in response to repeated injections of retabolil, would appear to be an urgent task.

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