CHANGES IN BLOOD PRESSURE AND SENSOMOTOR CORTICAL EVOKED POTENTIALS AFTER INTRAHYPOTHALAMIC INJECTION OF NALORPHINE IN RABBITS SUBJECTED TO NOCICEPTIVE ELECTRODERMAL STIMULATION

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Specific antagonists of opioid peptides, administered systemically, have been shown to improve the state of animals with endotoxic [10] and hypovolemic [9] shock and with shock due to painful electrical stimulation [2]. In burn shock the opioid peptide levels in the blood plasma and brain structures are raised [6]. These facts suggest that the endogenous opioid system participates in the genesis of these shock states. It is also known that an important role in the regulation of the cardiovascular response to nociceptive stimulation is played by the region of the periventricular nuclei of the hypothalamus [1], which contains a high concentration of endorphins and enkephalins [8]. Destruction of the hypothalamic dorsomedial nuclei leads to an improvement in the state of animals with shock due to painful electrical stimulation [3]. It has accordingly been suggested that an important role in the genesis of pain-induced shock is played by the hypothalamic opioid system.

The object of this investigation was to study the role of the endogenous opioid system of the hypothalamus and the central gray matter of the mesencephalon, which are the principal structures of the antinociceptive opioid system [4], in the genesis of shock induced by painful electrical stimulation. For this purpose the effect of injection of nalorphine into the hypothalamus and central gray matter of the mesencephalon on changes in blood pressure, as the principal parameter of the state of shock [5], and in the sensomotor cortical evoked potential (EP) in response to nociceptive electrical stimulation, giving rise to shock in rabbits, was studied.

EXPERIMENTAL METHOD

The mean blood pressure (BP) was recorded in 22 waking rabbits by the direct method in the femoral artery. Sensomotor cortical EPs in response to nociceptive electrodermal stimulation (EDS) of the contralateral hind limb were recorded by a monopolar method and analyzed on the NTA-1024 amplitude-phase analyzer (Orion) for 10 realizations. Parameters of EDS were a single square pulse with duration 1 msec and strength 3-10 mA.

For the intracerebral injections, 3-5 days before the beginning of the experiment, guide cannulas were implanted in the cranial bones in accordance with coordinates [11], in the region of the hypothalamic periventricular nuclei and central gray matter of the mesencephalon. Nalorphine (5 μg) was injected in a dose of 1 μl bilaterally by means of a microsyringe in the course of 90 sec. Animals of the control group received the same volume of physiological saline. The region of injection of the drugs was subsequently verified histologically. Shock due to nociceptive electrical stimulation (NES) was produced by the method described previously [2, 3].

EXPERIMENTAL RESULTS

As the experiments of Golanov et al. [2, 3] showed, in this model of NES a definite time course of changes is observed in the autonomic parameters of the rabbits: ECG, respiration rate, BP, rectal temperature, corneal reflex – characteristic of the development of the shock process [5], and for that reason in the present experiments only the dynamics of changes in BP and EP were investigated.

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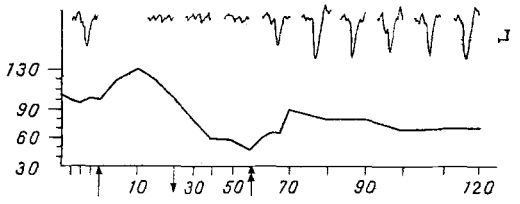

Fig. 1

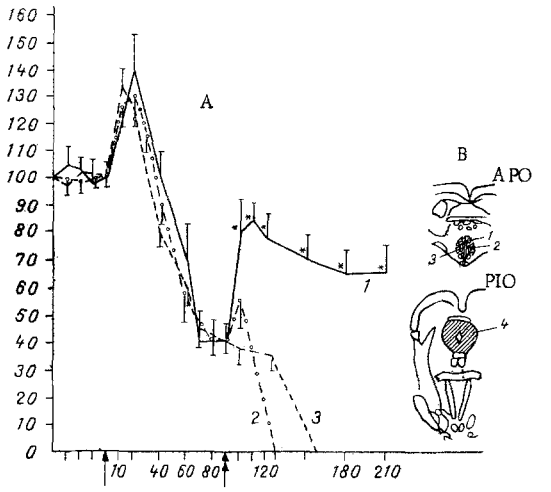

Fig. 2

Fig. 1. Changes in BP and sensomotor cortical EP of rabbit in response to EDS after intrahypothalamic injection of nalorphine against the background of development of shock. Top trace – EP, bottom trace – BP (in mm Hg). Abscissa, time (in min).

Fig. 2. Changes in BP in rabbits after intracerebral injection of nalorphine against the background of shock development. A) Injection of nalorphine: 1) into hypothalamus, 2) into central gray matter of mesencephalon; 3) injection of physiological saline into hypothalamus. * $P < 0.05$ relative to other groups. Arrow–shock-inducing procedure. Double arrow indicates injection of nalorphine. Abscissa, time (in min); ordinate, BP (in % of initial level). B) Regions of injection of nalorphine (shaded): 1) hypothalamic paraventricular nucleus; 2) fornix; 3) hypothalamic dorsomedial nucleus; 4) central gray matter of mesencephalon.

The initial mean BP of the experimental rabbits was 103 ± 14.1 mm Hg. Sensomotor cortical EPs in response to nociceptive EDS were characterized by a primary response with latent period of 10-12 msec and an amplitude of 22 ± 7.0 μV, and a secondary positive wave with latent period of 20-40 msec and amplitude 85.5 ± 15.0 μV. Periodic electrical stimulation of the sciatic nerve in the control series of experiments in five intact rabbits caused initially a transient rise of BP, on average by 35.3% of the initial level (Fig. 1). The amplitude of the secondary positive component of EP in this case fell to 34 ± 6 μV. The dynamics of subsequent changes in the BP level in different animals showed individual differences, but in all animals as a rule a marked hypotensive reaction was observed toward 60-90 min after the beginning of stimulation and BP fell by 51.9-63% of the initial level (Fig. 1). By this time no EP was recorded in 100% of cases. The general state of the animals under these circumstances was characterized by depression of general muscle tone, absence of a vocal response and absence of reflex withdrawal of the limb in response to EDS. In 80% of cases the animals died in the course of 2.5 h after exposure to the shock-inducing stimulus.

In the next series of experiments, against the background of a developed hypotensive reaction, at the 90th minute after application of the shock-inducing stimulus, nalorphine was injected into the region of the hypothalamic periventricular nuclei. In five animals immediately after injection of the drug BP rose and the amplitude of EP increased (Fig. 2). Ten minutes after injection of nalorphine BP was 40.3% higher than the level before injection of the drug, by contrast ($P < 0.05$) with BP in animals of the control group (Fig. 1). The amplitude of the secondary positive component of EP as a rule increased to its initial background level during the first 5 min after injection of nalorphine, to reach a maximum (106 ± 10 μV) after 10-15 min (Fig. 2). During the next 3 h of observation the amplitude of EP remained visibly unchanged, but BP fell and remained during this period at the level of 72.9 ± 5.5 mm Hg. In two animals of this group, by the time of injection of the drug, 90 min after application of EDS, BP had fallen to 37.5 ± 1.5 mm Hg. Nalorphine, injected into these animals, caused no change in BP and did not restore EP. Both animals died, with a progressive fall of BP, during 15 min after the microinjection.

Against the background of developed hypotension five animals were given an injection of physiological saline into the periventricular region of the hypothalamus. No significant differences were found in the time course of BP and EP compared with animals with NES untreated with any drugs (Fig. 1). All animals of this group died within 65 ± 10 min after injection.

Finally, in the last series of experiments, against the background of a developed hypotensive reaction, five animals were given an injection of nalorphine into the central gray matter of the mesencephalon. In the first 5-10 min after microinjection BP rose by 15.2% relative to the level preceding injection of the drug (Fig. 2). However, this effect was of short duration, and by the 12th-18th minute after injection of nalorphine, BP had already begun to fall, and this progressed rapidly. All animals of this group died in the course of 40 ± 10.5 min after microinjection.

Nalorphine, injected into the central gray matter of the mesencephalon, thus did not cause any lasting rise of BP in the torpid hypotensive phase of NES. Meanwhile microinjections of nalorphine into the region of the periventricular hypothalamic nuclei, one of the main levels of integration of somatic and autonomic responses to pain [1], caused BP to rise and completely restored the sensomotor cortical EP. This positive effect of intrahypothalamic injection of the antagonist of the narcotic analgesics evidently depends on the animal's state when the drug was injected. In the present experiments nalorphine, injected into animals with BP lowered to 36% of its initial level, was ineffective.

Since the hypothalamus possesses many opiate receptors [7] and has a high concentration of their endogenous ligands [8], the results of the present experiments can be attributed to effects produced on the opioid system of the hypothalamus. This suggests that the endogenous opioid system of the hypothalamus plays a definite role in the genesis of hypotension and depression of the sensomotor cortical EP in shock induced by nociceptive electrodermal stimulation.

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