EFFECT OF NALORPHINE AND NALOXONE ON THE COURSE OF ELECTRONOCICEPTIVE SHOCK IN RABBITS

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KEY WORDS: electronociceptive shock; endogenous opioid peptides; nalorphine; naloxone; morphine

Administration of naloxone, a specific antagonist of the narcotic analgesics, leads to a marked improvement in the state of animals with shock due to massive blood loss or injection of interspinal endotoxin [3]. It can be postulated that the endogenous opioid system participates in the genesis of other shock states also, and that, consequently, antagonists of narcotic analgesics can be used to arrest the development of shock.

On the basis of these arguments it was decided to study the effect of nalorphine and naloxone, antagonists of narcotic analgesics, on the course of electronociceptive shock in rabbits.

EXPERIMENTAL METHOD

The electroencephalogram (EEG) in the sensomotor cortex, ECG in standard lead II, respiration rate (RR), arterial pressure (BP), rectal temperature (RT), and corneal reflex (CR) were recorded by standard methods in 34 waking rabbits.

Electronociceptive shock was induced by electrical stimulation (square pulses 1 msec in duration, frequency 50 Hz, amplitude 110 V), which were applied through two electrodes, one located directly on the sciatic nerve, the other inserted subcutaneously in the region of the lumbar spine. The duration of stimulation was 15 min. The substances were injected intravenously.

EXPERIMENTAL RESULTS

In the experiments of series I changes in the EEG, ECG, BP, HR, RT, and CR were studied after electric shock in seven animals into which physiological saline (2.0 ml) was injected after development of the state of shock. Data showing the time course of development of the shock reaction are given in Fig. 1.

Before electric shock the EEG consisted of high-amplitude waves with a frequency of 3.1 ± 0.3 Hz, on which were superposed low-amplitude waves with a frequency of 9.8 ± 0.8 Hz. The heart rate (HR) was 272.2 ± 14.9 beats/min, BP 104.0 ± 11.7/77.7 ± 7.3 mm Hg, RR was regular at 47.5 ± 2.5 cycles/min, RT 38.3 ± 0.1°C, and the CR was brisk.

The frequency of the high-amplitude component of the EEG 60 min after electrical stimulation was 1.5 ± 0.2 Hz and that of the low-amplitude component 10.0 ± 0.9 Hz. HR was increased to 282.2 ± 18.1 beats/min. The appearance of arrhythmias was noted on the ECG and the S-T interval was raised above the isoelectric line. BP became unstable and fell to 72.5 ± 11.1/61.3 ± 8.3 mm Hg. Respiration became irregular in character in both frequency and amplitude. RR was 77.5 ± 7.5 cycles/min, RT fell to 37.1 ± 0.3°C, and CR was absent. The frequency of the high-amplitude component of the EEG 90 min after electric shock was 1.5 ± 0.2 Hz and that of the low-amplitude component 9.8 ± 1.0 Hz. HR was 256.3 ± 22.5 beats/min, the rhythm was often disturbed, and the S-T segment was raised higher above the isoelectric line and the P

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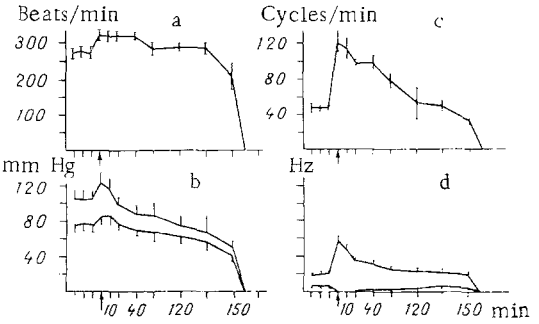

Fig. 1. Changes in HR (a), BP (b), RR (c), and high-amplitude (bottom curve) and low-amplitude (top curve) components of EEG (d) in rabbits after electric shock (period of stimulation indicated by arrow and not shown on graph).

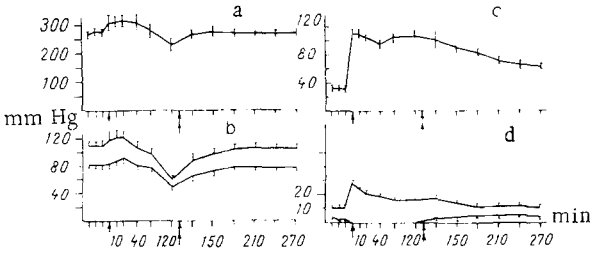

Fig. 2. Changes in autonomic parameters and EEG of animals receiving injection of nalorphine after development of shock. Legend as to Fig. 1. Arrow indicates time of electric shock; double arrow indicates injection of nalorphine.

wave inverted. RR was 52.5 ± 12.4 beats/min and respiration became arrhythmic in character. RT fell to 36.8 ± 0.2°C and CR was completely absent in all the animals. After 60-90 min the animals were given an injection of physiological saline. This was followed by progressive flattening of the EEG and slowing of the rhythm, HR continued to fall, the S-T fragment became dome-shaped, and arrhythmia was observed, changing into ventricular fibrillation in the terminal state. BP fell, and the systolic-diastolic difference fell particular sharply. Respiration became paroxysmal. RT fell by more than 1.5°C and CR was completely absent. All the animals of this group died on average after 163.9 ± 28.1 min.

In nine experiments 60-90 min after electric shock, against the background of the changes described above the animals were given morphine in a dose of 2 mg/kg. Some increase in frequency of the EEG rhythm and an increase in HR and RR were observed immediately after the injection of morphine, but after 5-10 min the values of these parameters returned to those corresponding to the period of the control experiments. The animals died after 132.9 ± 25.4 min (difference not significant).

In the experiments of series III, against the background of development of marked shock, 60-90 min after electric shock the animals were given an injection of nalorphine in a dose of 0.4 mg/kg. During the first 10 min after injection of nalorphine an increase in the frequency of the high-amplitude EEG rhythm to 1.9 ± 0.6 Hz and of the low-amplitude rhythm to 17.0 ± 1.9 Hz was observed. HR rose to 277.8 ± 16.4 beats/min, the arrhythmias disappeared, the inverted P wave was smoothed, and the S-T interval depressed a little; BP was increased to 90.2 ± 8.9/68.3 ± 7.4 mm Hg. The normal rhythm of respiration was restored and its rate increased to 101.4 ± 12.9 cycles/min. RT was raised to 37.3 ± 0.3°C. A weakened CR appeared (Fig. 2). Later all the parameters tested gradually returned to their normal values, and by 90-120 min after injection of nalorphine they had returned to their initial values.

No animal died in this experimental group and 2-3 h after injection of the drug all the principal parameters had returned to normal, evidence that the animal has recovered from the state of shock. Two rabbits of this group were kept under observation for 2 days and their state remained satisfactory; four other animals, against the background of the development of shock, were given an injection of naloxone, 0.1 mg/kg. The effect of naloxone was completely identical.

In the experiments of series IV the effect of naloxone in a dose of 0.1 mg/kg on BP was studied in four reserpinized rabbits. The initial BP in the femoral artery was 72.4 ± 5.6/67.7 ± 5.2 mm Hg. BP fell 2-3 h after injection of reserpine in a dose of 2.5 mg/kg to 35.4 ± 4.4/30.2 ± 3.9 mm Hg. During this period the animals were given naloxone in a dose of 1.1 mg/kg. No changes in BP were observed in response to injection of naloxone.

It has been shown that under the influence of stressors, including nociceptive stimuli, an increase in the concentration of endogenous opioid peptides, especially β-endorphin, is observed in the blood of animals (rats [3], rabbits [5]). These substances are known to be capable of inhibiting various autonomic systems of the body, including the cardiovascular and respiratory systems [2]. These facts suggest that endogenous opioid peptides may play an important role in the formation of disturbances of activity of autonomic systems under the influence of shock-producing factors. This is shown by blocking of the development of electronociceptive shock observed in rabbits in the present experiments, and also by results indicating an improvement in the state of rats during hypovolemic and endotoxic shock, and in dogs with hypovolemic shock after administration of antagonists of endogenous opioid peptides [1, 4]. Injection of naloxone into animals with marked hypotension, due not to the shock-producing factor but to injection of reserpine, was ineffective.

LITERATURE CITED

1. J. Faden and J. Holaday, J. Pharmacol. Exp. Ther., 212, 441 (1980).
2. J. Florez and A. V. Mediavilla, Brain Res., 199, 197 (1980).
3. R. Guillemin, T. Vargo, J. Rossier, et al., Science, 194, 1367 (1977).
4. J. W. Holaday, G. L. Belenky, A. J. Faden, et al., in: Neuropsychopharmacology, Vienna (1978), p. 503.
5. T. Orlowski, J. Lapinski, A. Lypka, et al., Pol. Tyg. Lek., 34, 1945 (1979).

THE USE OF DISPERSION ANALYSIS TO ESTIMATE THE ANTICONVULSANT ACTIVITY OF 1,4-BENZODIAZEPINES IN MICE

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The object of this investigation was to study the time course of changes in the convulsant action of metrazol following injection of 1,4-benzodiazepine derivatives, with different chemical structure, into mice. To assess the significance of the effect of the time factor and the structure of the compounds used on the effect formed by them, the experimental results were subjected to dispersion analysis [2, 4].

EXPERIMENTAL METHOD

Experiments were carried out on 213 male CBA mice weighing 18-24 g. The animals were given 1,4-benzodiazepines (phenazepam and its 3-hydroxy derivative, demethyldiazepam, demethylsulazepam) in a dose of 5 mg/kg in Tween emulsion. Control animals (25 mice) received an aqueous solution of Tween-80. Minimal doses of metrazol which, when injected into the caudal vein of mice 5, 15, 30, and 120 min after injection of the test compounds, caused pseudoclonic twitches (DPCT), clonicotonic convulsions (DCTC), and tonic extension (DTE) were established; a 1% solution of metrazol was injected at the rate of 0.01 ml/sec [1].

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