completely abolishes the effects of EA, i.e., it acts similarly to naloxone in doses of 0.05-0.1 mg/kg. Consequently, motropine, as an antagonist of the narcotic analgesics, when tested on electroacupuncture analgesia, is about 100-200 times weaker than naloxone, the classical opiate antagonist. It must be remembered, however, that the toxicity of naloxone is much greater that of motropine, and this is undoubtedly a favorable property of the new drug.

The experimental data given in this paper are evidence that motropine can antagonize endogenous opioid peptides which are secreted during electroacupuncture analgesia. Considering this fact, and also previous data on antagonism of motropine and exogenous opiates, as shown by analgesia tests [1], it can be tentatively suggested that motropine is the first preparation of the tropane class which possesses marked affinity for opiate receptors, interaction of endogenous and exogenous opiates with which is accompanied by the development of an analgesic effect.

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COMPARATIVE CHARACTERISTICS OF SELF-STIMULATION REACTION IN RABBITS RECEIVING ANGIOTENSIN II BY THE INTRAVENTRICULAR ROUTE AND BY APPLICATION TO THE CONJUNCTIVA

V. I. Badikov, E. A. Lomakina, and K. V. Sudakov

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KEY WORDS: self-stimulation; angiotensin II; intraventricular injection; application to the conjuctiva.

Recent experimental studies have shown conclusively that endogenous neuropeptides play an active part in the formation of learning and memory processes, motivations, and sleep [1, 3, 12]. However, the role of oligopeptides in the mechanisms of formation of emotional behavior has so far received little study.

The object of the investigation described below was accordingly to study the effect of angiotensin II on the self-stimulation reaction in rabbits, regarded by some workers as an adequate model of a positive emotional behavioral reaction. In view of indications in the literature that certain substances, when applied to peripheral receptors, can penetrate directly into the CNS, by-passing the blood stream [2, 5, 10], it was decided to compare the action of angiotensin II on self-stimulation when injected into the cerebral ventricles and when applied to the conjunctiva.

EXPERIMENTAL METHOD

Experiments were carried out on 28 adult male waking rabbits weighing 2.5-3 kg. Bipolar electrodes were implanted into the lateral region of the hypothalamus of each animal. Freely behaving rabbits were tested for the self-stimulation reaction. The parameters of the stimulating current were: frequency 100 Hz, pulse duration 1.4 msec, duration of series of pulses 0.3 sec, voltage 2-5 V. The self-stimulation reaction was evaluated on the basis of changes in the frequency with which the animal closed the electric circuit in each 32-sec interval.

P. K. Anokhin Research Institute of Normal Physiology, Academy of Medical Sciences of the USSR. I. M. Sechenov First Moscow Medical Institute.

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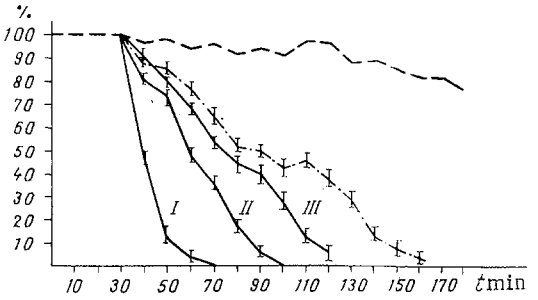

Fig. 1. Dynamics of changes in self-stimulation reaction on injection of angiotensin II into cerebral ventricles and after its local application to the conjunctiva. Abscissa, time (in min); ordinate, changes in frequency of self-stimulation (in %). Broken line indicates background frequency of self-stimulation; continuous line shows self-stimulation following intraventricular injection of angiotensin II in doses of 150 ng (I), 50 ng (II), and 5 ng (III); line of dots and dashes denotes self-stimulation following application of angiotensin II to the conjunctiva in a dose of 500 ng.

After spontaneous stimulation had been recorded for 30 min, angiotensin II (Serva, West Germany) was injected by means of a microinjector into the lateral cerebral ventricles of the animals of one group through metal cannulas in doses of 5, 50, and 150 ng in 3 µl of distilled water. An aqueous solution of angiotensin II in doses of 150 and 500 ng in 2 drops was applied to the conjunctiva of rabbits of the other group. Animals receiving distilled water and physiological saline served as the controls to the two groups.

To study the effect of angiotensin II on autonomic indices, in a special series of experiments on rabbits lightly fixed in a frame, the arterial blood pressure, the ECG in standard lead II, and respiration were recorded during intraventricular and intravenous injection of angiotensin II and its local application to the conjunctiva in the above doses.

The total duration of recording of self-stimulation was 2.5-3 h. Background values of the frequency of self-stimulation in the course of 30 min were taken as 100%. All changes in the frequency characteristics of the reaction were expressed as percentages of the background value. The number of drinking reactions of the animals during the period of the experiment also was recorded.

EXPERIMENTAL RESULTS

Observations on the self-stimulation reaction in 10 rabbits showed that by the end of the second hour there was a certain tendency for the mean frequency of closure of the electric circuit by the animals to decrease, and after 3 h the mean frequency of self-stimulation was 78.7% of its initial level.

The dynamics of changes in self-stimulation during the 2.5 h after administration of angiotensin II by the different methods is illustrated in Fig. 1. The effect was found to depend on dose.

Intraventricular injection of angiotensin II in a dose of 5 ng caused depression of self-stimulation after 40 min in four of the six rabbits, in a dose of 50 ng it depressed self-stimulation in all six rabbits of this group after an interval of 20-70 min; when given in a dose of 150 ng, total cessation of self-stimulation was observed in all 12 rabbits after 40 min.

Angiotensin II was applied in doses of 150 and 500 ng to the conjunctiva of nine rabbits. Changes in the self-stimulation reaction in response to a dose of 150 ng were not significant. Application of the peptide in a dose of 500 ng caused changes in the character of self-stimulation of the rabbits, reflected in shortening of individual self-stimulation cycles, and lengthening of the time intervals between them. Practically all the rabbits of

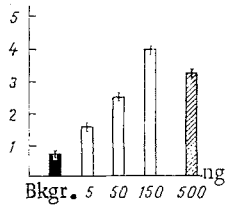

Fig. 2. Increase in number of drinking reactions in rabbits depending on method of administration of angiotensin II and its dose (mean values for each group of animals).

this group ceased self-stimulation after different time intervals during the first 3 h of the experiment, which was never observed in the background period.

Besides depression of the self-stimulation reaction a significant increase in the number of drinking reactions also was observed under the influence of angiotensin II in the rabbits, depending on the dose and method of administration of the peptide (Fig. 2).

To test the possibility of inhibition of the self-stimulation reaction of animals under the influence of angiotensin II as a result of primary changes in blood pressure when administered by different routes, a series of experiments was carried out in which the arterial blood pressure, respiration, and the ECG were recorded. The results of these experiments showed that only intravenous injection of angiotensin II in a dose of 500 ng caused a temporary rise of blood pressure, marked bradycardia, and changes in respiration. These observations, like the results of special experiments [4, 6], are evidence that angiotensin II has a central inhibiting action on the self-stimulation reaction. The central action of angiotensin II may be both direct, on the neuronal mechanisms responsible for this type of behavior, and indirect, through the liberation of catecholamines [8] or an increase in vasopressin secretion [7]. Vasopressin is known to inhibit the self-stimulation reaction [11].

The experiments described above indicate that application of oligopeptides to the conjunctiva can be used as a means of influencing behavioral reactions of animals.

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