EFFECT OF MORPHINE AND NALOXONE ON ACUPUNCTURE ANALGESIA IN UNRESTRAINED RATS

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Experiments on unrestrained rats showed that electroacupuncture of an acupuncture point distinctly reduces the nociceptive response to electrical stimulation of the base of the tail. Morphine, in a subanalgesic dose (5 mg/kg), potentiated the analgesic effect of acupuncture. Naloxone, in a dose of 5 mg/kg, completely abolished acupuncture analgesia. The possible mechanisms of analgesia production by electroacupuncture are discussed.

KEY WORDS: acupuncture; analgesia; morphine; naloxone.

There is much recent clinical evidence that reflex therapy is an effective means of minimizing pain syndromes of different genesis [4, 5, 7]. Meanwhile, neurophysiological mechanisms of the analgesic effect, and in particular their pharmacological modulation, have received very inadequate study. This is largely because the analgesic action of acupuncture has been the subject of little experimental research, and the few investigations which have been undertaken to study electrophysiological manifestations of acupuncture were undertaken on anesthetized animals [11]. There have been only a few studies of acupuncture analgesia on unanesthetized but immobilized animals [8, 10]. The analgesic effect of acupuncture has virtually never been studied in chronic experiments, nor have the individual manifestations of the pain response, integrated at different levels of the CNS, been analyzed [1, 2].

The objects of the present investigation were accordingly to design an experimental model with which to obtain acupuncture analgesia and to study the dynamics of its development and its changes under the influence of morphine and naloxone.

METHODS

Altogether 60 experiments were carried out on 20 male albino rats weighing 250-300 g. Nociceptive stimulation of the base of the tail was carried out through special bipolar electrodes with short series of pulses (100 Hz, 0.5 msec, 1 sec). The intensity of stimulation was gradually increased from 30 to 100 V. The total duration of nociceptive stimulation for each rat did not exceed 10 sec in one experiment.

Electroacupuncture (EA) was carried out with No. 1 acupuncture needles, connected to an ESU-1 stimulator. The reference electrode was fixed to the tip of the tail. The analog of the Yao-Yang-Kuan acupuncture point (AP), in the midline between the spinous processes of the 4th and 5th lumbar vertebrae, was chosen for EA. This AP was chosen because of clinical evidence that a good analgesic effect is obtained from this AP in lumbosacral radiculitis [4]. EA was induced with square pulses (0.5 to 100 Hz, 0.5 msec). The amplitude of stimulation was chosen individually in each case — until small fibrillations of the muscles in the region of the needle appeared. The total duration of EA stimulation was 20 min. The effect of EA was analyzed from changes in individual manifestations of the nociceptive response, by means of a special five-point scale, in unrestrained animals. Morphine was injected subcutaneously and intramuscularly in doses of 5 and 10 mg/kg and naloxone in a dose of 5 mg/kg. Van der Waerden's criterion of signs was used for the statistical analysis.

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TABLE 1. Responses to Gradually Increasing Stimulation of Rat Tail with Rating in Points

Points	Character of response	Intensity of stimulation	
		V	thresholds
1	Twitching, stretching tail	32,8±3,6	1
2	Turning head, tapping with paws, single rotations	41,0±3,4	1,3
3	Squeaking, single rotations	56,0±5,6	1,7
4	Loud and repeated cries	62,2±8,3	1,9
5	Running with a cry, repeated rotations while crying, aggressiveness	69,5±6,2	2,2

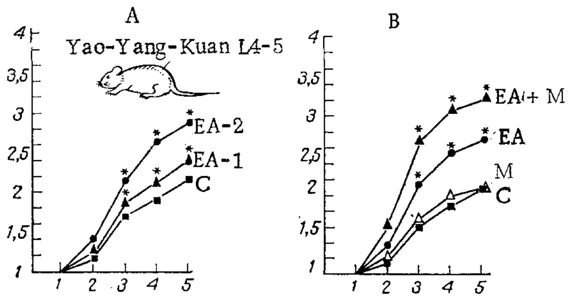

Fig. 1. Changes in structure of nociceptive response in rats during EA (A) and during EA after receiving morphine in a subanalgesic dose (B). A: Abscissa, individual components of nociceptive response (as indicated in Table 1); ordinate, intensity of stimulation (in thresholds) required to cause appearance of corresponding components of nociceptive response during stimulation of base of rat's tail. C) Control (original structure of nociceptive response); EA-1) structure of nociceptive response during EA with frequency of stimulation 1-2 Hz; EA-2) structure of nociceptive response during EA with frequency of stimulation 5-10 Hz. B: C) Control; EA) structure of nociceptive response during EA with frequency of stimulation 1 Hz; M) structure of nociceptive response after morphine in a dose of 5 mg/kg; EA + M) nociceptive response during EA after morphine in a dose of 5 mg/kg. *) Difference from control significant ($P < 0.05$).

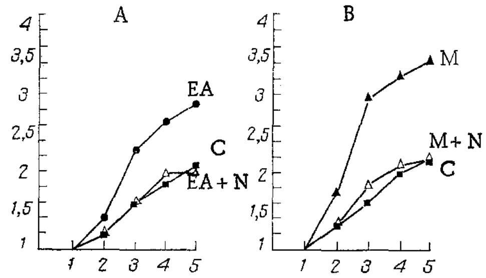

Fig. 2. Effect of naloxone on analgesia induced by EA (A) and morphine in a dose of 10 mg/kg (B). A: C) Control; EA) structure of nociceptive response during EA with a frequency of stimulation of 1 Hz; EA + N) the same, after naloxone in a dose of 5 mg/kg; B: C) control; M) structure of nociceptive response after morphine in a dose of 10 mg/kg; M + N) the same after naloxone in a dose of 5 mg/kg. Remainder of legend as in Fig. 1.

RESULTS

Stimulation of the base of the tail with gradually increasing intensity was accompanied by the successive appearance of individual features of the response, ranging from an orienting reaction, evidence of perception of stimuli with aversive properties, to a generalized response to intolerable nociceptive stimulation (Table 1).

Insertion of the acupuncture needle into AP was accompanied by twitching movements of the animal, sometimes with a squeak. Immediately after the beginning of electrical stimulation of AP a characteristic response occurred, consisting of rapid turning of the head, sniffing, alternating with periods of stillness. Most animals exhibited grooming of the upper part of the body.

Between 3 and 5 min after the beginning of stimulation, the rats as a rule lay in the prone position with their eyes closed and they did not move during subsequent stimulation. However, the animals responded adequately to touch and to stimuli provoking aggressiveness, evidence of the absence of any sensory or motor deficit. The behavioral changes observed during EA can be regarded as analogs of the sedative and hypnotic effect of reflex therapy in man [4]. In control animals, into which acupuncture needles were inserted not at AP, no behavioral changes were found.

Electroacupuncture of AP was accompanied by definite changes in the response of the rats to stimulation of the tail by stimuli of increasing intensity. Whereas normally during stimulation of the base of the tail with a strength of 60-70 V, the rats developed a generalized response, consisting of repeated cries, running, rotation, increased motor activity, followed by aggressiveness, stimulation of the same intensity against the background of EA was accompanied by features indicating perception of nociceptive, but "tolerable" stimulation. It will be clear from Fig. 1, illustrating the combined results of all experiments, that EA led to a marked and statistically significant increase in the threshold of appearance of crying and running. EA caused virtually no change in the threshold of appearance of the orienting reaction or of reactions characteristic of perception of stimuli with aversive properties. The analgesic effect of EA varied with the frequency of stimulation of AP. The optimal frequency for its appearance was 1-10 Hz.

The analgesic effect of EA was sharply potentiated by previous administration of subanalgesic doses of membrane. As Fig. 1B shows, EA in rats receiving morphine beforehand in a dose of 5 mg/kg, which did not change the thresholds of appearance of individual components of the combined nociceptive response, was accompanied by definite analgesia, which corresponded in the dynamics of its development and intensity to the analgesia produced by morphine in a dose of 5 mg/kg completely abolished the changes in the structure of the nociceptive response arising during EA or under the influence of morphine in a dose of 10 mg/kg (Fig. 2). Under the influence of naloxone in this dose the analgesia induced by a combination of EA and morphine also disappeared.

The experimental results thus show that EA of AP in unrestrained rats has an analgesic effect. The possibility of obtaining acupuncture analgesia in animals is evidence that the analgesic effect of acupuncture is due to definite neurophysiological mechanisms and cannot be explained purely on the basis of suggestion or hypnosis. The similarity between the changes in the dynamics of development of individual features of the composite nociceptive response under the influence of EA and morphine, separately and together, manifested primarily as inhibition of the most highly integrated affective components of the nociceptive response, suggests that an important role inthe development of both acupuncture and morphine analgesia is played by influences oriented toward the limbic system and fronto-orbital brain structures responsible for the formation of generalized emotional—behavioral nociceptive responses [1].

Characteristically the development of the analgesic effect of EA has a definite similarity with the analgesia arising during stimulation of antinociceptive areas of the brain [3, 6]. Very probably acupuncture analgesia may arise through inhibition of the ascending nociceptive flow. The validity of this hypothesis is confirmed by existing data showing that acupuncture inhibits the transmission of nociceptive impulses in the thalamus, reticular formation, and spinal cord.

Potentiation of EA analgesia by morphine in subanalgesic doses and its abolition by naloxone suggest that the analgesic effect of acupuncture may be associated with liberation of endogenous morphine-like substances (enkephalins), which interact with opiate receptors. The suggestion that enkephalins play a part in the mechanism of the antinociceptive effect arising during stimulation of certain brain structures in noteworthy [9].

The model of acupuncture analgesia described above enables this phenomenon to be investigated in the course of its modulation by drugs and by stimulation of antinociceptive areas of the brain.

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