MECHANISM OF THE PAIN-RELIEVING ACTION OF NARCOTIC ANALGESICS

S. A. Borisenko

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The effect of the analgesics morphine, trimeperidine, fentanyl, and pentazocine and of the psychostimulant amphetamine on the threshold of pain sensation and on autostimulation of the hypothalamus and septum was studied in rats. Electrical stimulation of positive reinforcement systems of the hypothalamus and septum, and also administration of the analgesics increased the threshold of pain sensation, but amphetamine had no effect on the pain threshold. Amphetamine and morphine facilitated, trimeperidine did not affect, fentanyl weakened, and pentazocine completely suppressed hypothalamic autostimulation. Autostimulation of the septum was unchanged by morphine, trimeperidine, and fentanyl but was weakened by pentazocine and potentiated by amphetamine. It is concluded that the analgesic action and the activating action on the system of positive emotions are independent effects of psychotropic drugs.

KEY WORDS: autostimulation; analgesics; analgesic effect.

Changes in the emotional state caused by electrical stimulation of the system of positive emotions has been shown to abolish or reduce the sensation of pain in man and to raise the threshold of pain sensation in animals [6, 11, 15]. Among the narcotic analgesics morphine has the strongest action on the emotional manifestations of the pain response [2]. It also facilitates the autostimulation response at the hypothalamic level [12], i.e., it activates the system of positive emotions. Meanwhile amphetamine, which activates autostimulation considerably [3, 9], has the property of potentiating the analgesic effect of morphine [10].

With these facts in mind, some connection can be postulated between the analgesic effect of psychotropic drugs and their activating effect on the system of positive emotions. The investigation described below was carried out to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats by a method of recording the animals' squeaking in response to electrical stimulation of the paws through electrodes incorporated into the floor. The ED_{50} values required to increase the threshold of pain sensation were calculated by Litchfield's method [1].

Twenty-two rats with monopolar nichrome electrodes 250 μ in diameter implanted bilaterally in accordance with the coordinates of De Groot's atlas of the brain [8] into the lateral hypothalamus (A 4.4 mm, L 1.5 mm, H 9.0 mm) and septum (A 8.5 mm, L 0.7 mm, H 8.0 mm) were trained 7 days after the operation in self-stimulation with sinusoidal pulses 0.02 sec in duration and with a frequency of 50 Hz. The following two parameters were determined: 1) the effect of fentanyl (40 and 60 μg/kg), morphine (3.6 and 10 mg/kg), trimeperidine (4.5 and 8 mg/kg), pentazocine (20 mg/kg), and amphetamine (0.5, 1, and 2 mg/kg) on the threshold of autostimulation and the frequency of atuostimulation with a current of threshold strength, and 2) the threshold of pain sensation in animals and its changes during imposed stimulation (the same parameters as for autostimulation) of the positive reinforcement systems of the hypothalamus and septum during

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stimulation with a current of threshold and optimal (the strength of current at which the frequency of autostimulation was greatest), and 12-40 μA above optimal strength of current. These doses of the analgesics were close to ED_{50} for raising the level of pain sensation. The drugs were injected intraperitoneally 30-40 min before the experiment, except fentanyl, which was injected 15 min before the experiment. In the statistical analysis the mean values of the frequency of autostimulation were determined and the significance of their differences was calculated by Fisher's criterion [5].

EXPERIMENTAL RESULTS

For fentanyl the ED_{50} for raising the threshold of pain sensation was 42 μg/kg, for morphine 2.9 mg/kg, for trimeperidine 4.6 mg/kg, and for pentazocine 18 mg/kg. The greatest increase in the threshold of pain sensation (26-32 V in the control) was observed under the influence of morphine (mean increase 8-12 V), the smallest with pentazocine (increase 2-4 V). Fentanyl and trimeperidine increased the pain threshold by 6-10 V. Amphetamine did not affect the pain threshold except in some cases (in a dose of 1 and 2 mg/kg), when it reduced it.

Amphetamine (0.5 and 1 mg/kg) and morphine (3 mg/kg) lowered the threshold of autostimulation of the hypothalamus and increased the number of autostimulations in response to a current of threshold strength. Under the influence of trimeperidine (4.5 mg/kg) a tendency was found for the frequency of autostimulation to increase, but the threshold of the response was unchanged. Fentanyl (40 μg/kg) raised the threshold and reduced the frequency of autostimulation. Pentazocine (20 mg/kg) completely suppressed hypothalamic autostimulation.

Autostimulation of the septum was facilitated only by amphetamine, which lowered the threshold of the response and increased the number of autostimulations in response to a current of threshold strength. Morphine, trimeperidine, and fentanyl in the doses mentioned above had no significant action on septal autostimulation indices. Pentazocine (20 mg/kg) increased the threshold and lowered the intensity of septal autostimulation. Under the influence of larger doses of the drugs – morphine (10 mg/kg), trimeperidine (8 mg/kg), and fentanyl (60 μg/kg) – the analgesic effect was potentiated and autostimulation of both hypothalamus and septum was weakened. The stronger inhibitory effect of the analgesics was observed against the hypothalamic autostimulation response.

Imposed stimulation of the system of positive emotions of the hypothalamus by a current of threshold strength, which varied for individual animals between 5 and 15 μA, raised the threshold of pain sensation by 2-6 V. During stimulation with a current of optimal strength (30-40 μA) the threshold of pain sensation rose by 8-12 V. If the intensity of imposed hypothalamic stimulation exceeded optimal by 20-30 μA, the threshold of the pain response was reduced by comparison with its value during imposed stimulation by a current of optimal strength. Under these circumstances, however, the threshold was 4-6 V higher than in the control.

Septal stimulation also evoked an increase in the threshold of the pain response of 6-10 V, but in this case (by contrast with hypothalamic stimulation) in most animals no appreciable variations in the pain threshold were observed with a change in the intensity of imposed stimulation.

Elevation of the threshold of pain sensation during hypothalamic and septal stimulation confirms the observations made by workers cited above of a decrease in emotional-behavioral manifestations of the pain response during activation of the systems of positive emotions.

The analgesics differed in their effects on the emotional component of the pain response. According to Zhukova [2], trimeperidine and fentanyl are much weaker than morphine in this respect. Considering the results of the present investigation, this suggests that the effectiveness of morphine in reducing the emotional component of the pain response may depend on its activating effect on the hypothalamic system of positive emotions, whereas the septal system of positive reinforcement is evidently not concerned in this action of morphine. However, potentiation of the analgesic effect of morphine and the weakening of hypothalamic autostimulation with an increase in the dose indicate that on the whole its analgesic action is not the result of activation of this particular system, but it is brought about through different neurophysiological mechanisms. The absence of any regular relationship between the effect of the drugs on the autostimulation indices and on the threshold of the pain response lead to the conclusion that activation of the system of positive emotions, or its inhibition, and the analgesic action are independent effects of psychotropic drugs.

The observations showing the opposite effects of morphine and pentazocine on the hypothalamic system of positive emotions go some way toward explaining clinical observations [14] according to which, unlike to morphine, habituation practically never develops to pentazocine, which does not induce euphoria [7]. These observations also indicate that one cause of the development of habituation to psychotropic drugs and, in particular, to morphine may be their ability to activate mechanisms of positive reinforcement, and thereby to induce positive emotions.

The effectiveness of electrical stimulation of the hypothalamus and septum as a means of raising the pain threshold could serve as confirmation of the hypothesis, put forward by several workers [4, 13], of the nonspecific function of the system of positive emotions, as a special mechanism which counteracts the influence of "negative" factors.

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