CHANGES IN THE ANTINOCICEPTIVE EFFECT OF MESENCEPHALIC STIMULATION PRODUCED BY ANALGESICS AND TRANQUILIZERS

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Chronic experiments on cats showed that analgesics, in subanalgesic doses, not only exhibit an antinociceptive effect when accompanied by subthreshold stimulation of the mesencephalon, but also potentiate the analgesic action of central stimulation. Tranquilizers only facilitate the development of an analgesic effect during subthreshold mesencephalic stimulation. The possible reasons for differences in the action of these substances are discussed.

KEY WORDS: pain; analgesia; mesencephalon; emotional behavior; analgesics; tranquilizers.

Electrical stimulation of certain brain structures is accompanied by an antinociceptive effect, i.e., by the reduction or total suppression of the responses of animals to nociceptive stimulation [5, 7, 9, 10]. As a result of the study of this effect and of neurophysiological ways of its elicitation [2, 9], the foundations have been laid for a fresh approach to the investigation and explanation of the mechanisms of the analgesic action of neurotropic drugs from the standpoint of their effect on the antinociceptive systems.

However, this problem has been inadequately studied. Only isolated fragments of information showing that morphine, in subanalgesic doses, potentiates analgesia during mesencephalic stimulation in rats have so far been obtained [11].

The object of this investigation was to make a more detailed study of the potentiating action of analgesics and tranquilizers on the antinociceptive effect of central stimulation, assessed, unlike in earlier investigations, on the basis of changes in individual components of the complex nociceptive response in cats to stimulation of the dental pulp.

EXPERIMENTAL METHOD

Under free behavior conditions 45 experiments were carried out on five cats with electrodes implanted into the central gray matter and into the dental pulp by the methods described previously [3, 5]. The dental pulp was stimulated with square pulses (6-10 Hz, 0.5-1.0 msec, 0.1-10.0 mA). The parameters of stimulation of the central gray matter varied between 30 and 100 Hz, 0.5 and 1.0 msec, and 0.2 and 0.7 mA. The minimal strength of current causing a change in the initial structure of the nociceptive response, on account of a reduction in the emotional behavioral manifestations of pain, was taken as the threshold intensity of stimulation. During the investigation of the dynamics of the nociceptive response and for assessment of the analgesic effect of central stimulation, a conventional scale worked out by the writers previously [5] was used.

The analgesics (morphine, fentanyl, trimeperidine) and the tranquilizers (diazepam, nitrazepam, phenazepam) were injected in doses not evoking a response to nociceptive stimulation in the animal. For the statistical analysis of the results the Van der Waerden criterion was used [6].

EXPERIMENTAL RESULTS AND DISCUSSION

Morphine (1 mg/kg) and fentanyl (20-30 μg/kg) had a similar action, namely potentiation of the analgesic effect of central stimulation and prolongation of after-analgesia. For instance, whereas under normal conditions mesencephalic stimulation merely reduced the manifestations of the generalized nociceptive response (Fig. 1A: 3), when accompanied by the action of analgesics, stimulation of the same intensity led to complete disappearance of the manifestations of emotional-behavioral response to pain and to marked depression of the

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TABLE 1. Effect of Analgesics and Tranquilizers on Antinociceptive Effect of Mesencephalic Stimulation in Cats

Drug	Number of experiments	Intensity of nociceptive response, conventional, points			Duration of after-analgesia (in sec) following brain stimulation fall	
		before brain stimulation	during brain stimulation			
			of below threshold intensity	of threshold intensity	30 sec	5 min
Control	22	15—17	15—17	12—14	19.8	38.4
Morphine	12	15—17	12—14*	7—9*	36.8*	70.6*
Fentanyl	7	15—16	13—14*	8—9*	35.0*	67.0*
Trimeperidine	5	15—17	15—16	12—13	20.0	45.0*
Diazepam	10	15—16	13—14*	11—13	22.5	63.7*
Nitrazepam	6	15—17	13—14*	12—14	21.0	58.0*
Phenazepam	5	15—17	15—16	12—14	22.0	39.0

*$P \leq 0.01$ compared with control.

Legend. Intensity of nociceptive response assessed by total number of points scored by individual manifestations, using scale worked out in [5].

autonomic motor manifestations of pain (piloerection, changes in respiration, contraction of muscles, and so on). Threshold mesencephalic stimulation after injection of the analgesics was accompanied by an even greater (by 3-3.5 times) increase in the threshold of the reflex of opening the mouth and licking. The results showing changes in the antinociceptive effect under the influence of analgesics are summarized in Table 1.

Morphine and fentanyl increased the duration of after-analgesia particularly clearly (Fig. 1B, C). In the control after-analgesia appeared after mesencephalic stimulation which completely abolished the generalized response to pain, and its duration after stimulation lasting 30 sec and 5 min was 20-30 and 40-50 sec respectively. When the analgesics were given the duration of after-analgesia was increased by 50 sec and by 75-80 sec following preceding stimulation for 30 sec and for 5 min respectively. The increase in the duration of after-analgesia was due not only to inhibition of the components of the generalized response, but also to a sharp decrease in the autonomic motor manifestations of the response to pain. However, restoration of the manifestations of pain perception (reflex opening of the mouth and licking) took place within the same time interval as in the control.

Morphine and fentanyl, in subanalgesic doses, facilitated the manifestation of the analgesic effect during subthreshold mesencephalic stimulation. As Fig. 1A shows, stimulation of the central gray matter with a strength of 0.2 mA under normal conditions did not change the structure of the nociceptive response. However, brain stimulation of equal intensity, if applied during the action of analgesics, was accompanied by a sharp decrease in the intensity of emotional and behavioral manifestations of the nociceptive response: running away, vocal responses, and scratching all disappeared and the intensity of the defensive movements was reduced.

Trimeperidine had a weaker action than morphine and fentanyl. Under its influence no significant change took place in the analgesic effect of threshold mesencephalic stimulation, but only a small increase in the duration of after-analgesia was observed during mesencephalic stimulation for 5 min. This analgesic did not disturb the structure of the nociceptive response during subthreshold brain stimulation either.

Diazepam in a dose of 0.25 mg/kg and nitrazepam in a dose of 1 mg/kg, like the narcotic analgesics, led to the appearance of an analgesic effect during subthreshold stimulation of the central gray matter (Table 1). As Fig. 2A shows, brain stimulation caused no changes in the structure of the original nociceptive response. However, analogous stimulation, against the background of the action of the tranquilizers, led to a distinct decrease in the intensity of the emotional-behavioral manifestations of the response to the same nociceptive stimulation.

Diazepam and nitrazepam, unlike the narcotic analgesics, did not change the effects of threshold stimulation of the "antinociceptive points" (Fig. 2A: 3), i.e., did not potentiate the analgesia when the manifestations of the generalized response had already been abolished by mesencephalic stimulation. However, after preliminary administration of these tranquilizers, the duration of after-analgesia was increased (Fig. 2B, C). The dynamics of recovery of the combined nociceptive response in the period after stimulation shows that prolongation of after-analgesia was due to preferential inhibition of development of the emotional-behavioral manifestations of pain. Unlike with morphine and fentanyl, prolongation of the period of analgesia was observed only

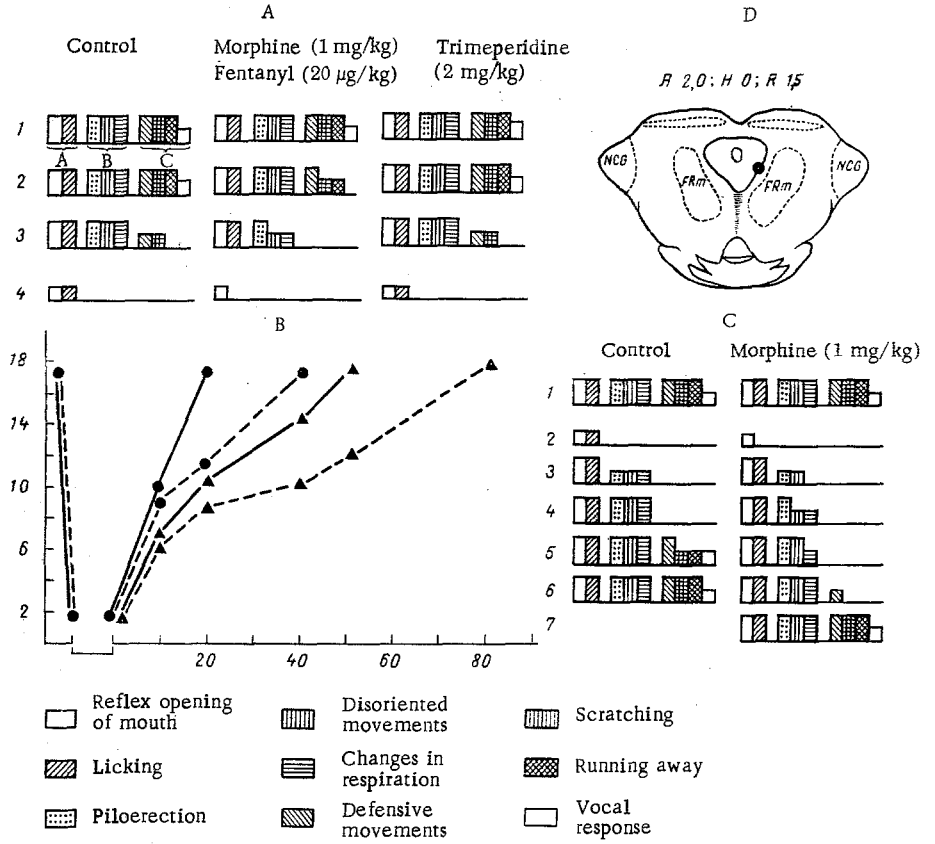

Fig. 1. Effect of analgesics on development and intensity of antinociceptive effect following mesencephalic stimulation in cats. A) Change in individual manifestations of combined nociceptive response during mesencephalic stimulation in normal animals and after injection of analgesics: 1) initial structure of nociceptive response to stimulation of dental pulp with an intensity of 8 thresholds; 2, 3, 4) in response to mesencephalic stimulation with intensity of 0.2, 0.25, and 0.35 mA respectively; a, b, c) 1st, 2nd, and 3rd levels of nociceptive response distinguished previously [5]; B) summarized data (12 experiments) showing changes in intensity and dynamics of recovery of nociceptive response during brain stimulation for 30 sec (circles) and 5 min (triangles) under normal conditions (continuous line) and after injection of morphine (broken line). Here and in Fig. 2: abscissa, time (in sec), numbers below abscissa denote time after ending of brain stimulation (in sec); ordinate, amplitude of response (in conventional points) [5]; C) dynamics of recovery of individual manifestations of combined nociceptive response after brain stimulation for 5 min. 1) Structure of nociceptive response under normal conditions; 2) during stimulation; 3-7) 10, 20, 40, 50, and 80 sec after stimulation; D) scheme of frontal section through mesencephalon showing location of stimulating electrode (black dot) and stereotaxic coordinates of stimulation taken from Snider and Niemer's atlas [13].

after long (5 min) preliminary mesencephalic stimulation, whereas the analgesics prolonged after-analgesia in the case of stimulation for 30 sec also.

It will be clear from Table 1 that phenazepam, in doses higher than 0.1 mg/kg, evoking marked ataxia, had no appreciable effect on the intensity of the analgesic effect or on the duration of after-analgesia.

The results thus indicate distinct differentiation, qualitative as well as quantitative, of the modulating effect of analgesics and tranquilizers on the antinociceptive effect.

Tranquilizers manifested this effect only in conjunction with subthreshold mesencephalic stimulation, as was shown by disappearance of the emotional-behavioral response to pain. No action of the tranquilizers was observed against the background of the initial and marked antinociceptive effect produced by threshold brain stimulation and manifested as a decrease in the intensity of the generalized nociceptive response.

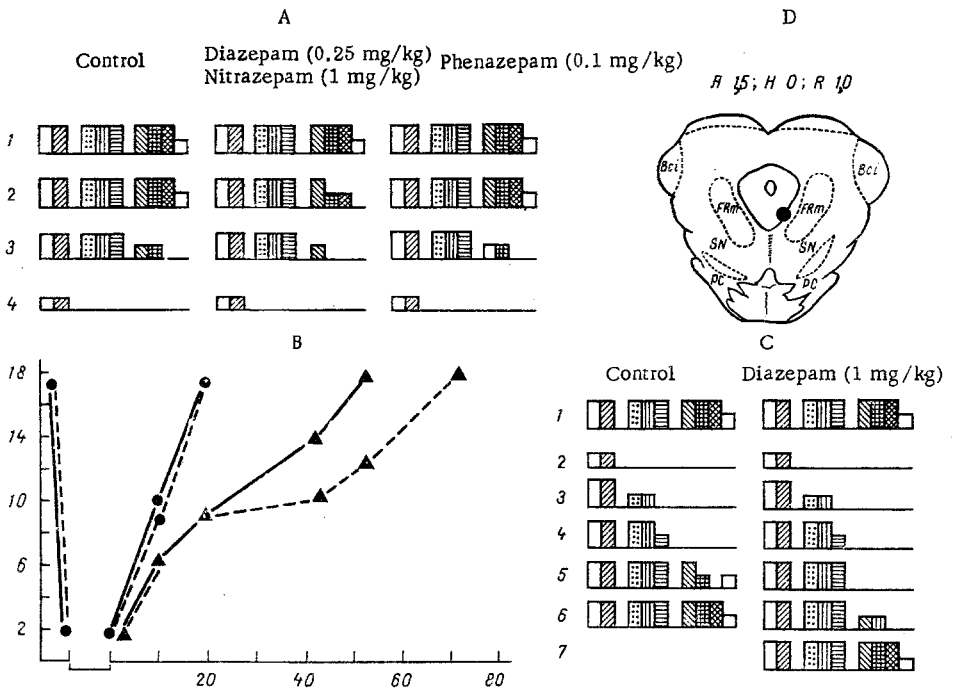

Fig. 2. Effect of tranquilizers on development and intensity of antinociceptive effect following mesencephalic stimulation. A) Change in individual manifestations of combined nociceptive response during mesencephalic stimulation under normal conditions and after injection of tranquilizers; B) summarized data (10 experiments) showing changes in intensity and dynamics of recovery of nociceptive response during brain stimulation for 30 sec (circles) and 5 min (triangles) under normal conditions (continuous line) and after injection of diazepam 0.25 mg/kg. Remainder of legend as in Fig. 1.

Analgesics, injected in subanalgesic doses, not only exhibited an antinociceptive effect in conjunction with subthreshold brain stimulation but, unlike tranquilizers, they also potentiated the initial analgesic action of central stimulation and they caused definite prolongation of after-analgesia; the potentiation of the antinociceptive effect and the prolongation of after-analgesia, moreover, were accompanied by inhibition of autonomic motor manifestations of pain and even by elevation of the pain threshold.

The differences between the modulating effect of analgesics and tranquilizers on the antinociceptive effect of central stimulation can be explained from the standpoint of the possible mechanisms of appearance of this effect. It is suggested that, as a phenomenon controlling sensitivity to pain, this effect may arise through primary inhibition of the high-threshold flow of impulses arising from the relay neurons which receive "pain" afferentation, and through disturbance of the mechanisms forming the emotional response to pain [2, 9].

Since analgesics, in subanalgesic doses, facilitate both potentiation of the existing antinociceptive effect and the appearance of that effect in response to subthreshold stimulation, they presumably not only act on processes inhibiting the formation of the ascending high-threshold flow of impulses [2], but also modify the antinociceptive influences reducing the emotional behavioral manifestations of pain. Tranquilizers which, in the doses used, merely make manifest antinociceptive effect on account of selective inhibition of the generalized response to pain, in all probability do not act on processes of descending regulation, but cause significant changes in influences from antinociceptive zones oriented toward the structures of hypothalamic-limbic system, which is responsible for the formation of emotional-behavioral manifestations of pain [1].

It is also known that analgesics, in subanalgesic doses, and tranquilizers, within the range of doses studied, possess psychodepressive activity and change the animal's psychological attitude toward pain through their influence at the hypothalamic-limbic level [1, 4, 8]. Consequently, the ability of these drugs to manifest the antinociceptive influences during subthreshold mesencephalic stimulation, discovered in the present experiments, can also be attributed to summation of the effects of their direct action on substrates integrating the emotional-behavioral components of the pain response with changes arising in these substrates on stimulation of antinociceptive brain structures.

The reasons for the difference in the action of individual drugs belonging to the analgesic group and the benzodiazepine derivatives are not absolutely clear and are difficult to explain at the present time. The possibility cannot be ruled out that the differences are connected with their influence on different mediator mechanisms of the antinociceptive effect [12].

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EFFECT OF INTRAVENOUS DIAZEPAM ON CORTICAL UNIT ACTIVITY IN RABBITS

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Changes in single unit activity were studied by a microelectrode technique in the sensomotor cortex of rabbits at different times after a single intravenous injection of diazepam (1-5 mg/kg). A few seconds after the injection of diazepam marked depression of spontaneous activity and of activity evoked by sciatic nerve stimulation was observed, together with an increase in the duration of the inhibitory pause in responses of the neurons to afferent stimulation and to direct stimulation of the cortical surface. These changes were considerably reduced 15-60 min after injection of diazepam. The results were compared with those of other workers who studied the clinical and pharmacokinetic effects of the benzodiazepines. It is concluded that the depressant effect of diazepam on cortical activity is connected with its sedative, amnesic, and anticonvulsant effect, and also that GABA plays an important role in the mechanism of these effects.

KEY WORDS: diazepam; sensomotor cortex; dynamics of depression of unit activity.

In a series of articles devoted to the benzodiazepines the effect of these drugs on electrical activity of nerve cells in different parts of the CNS is described [2, 6, 7, 11, 14]. The data given are not only episodic, but also sometimes contradictory in character. As yet no systematic study has been made of changes in the activity of brain neurons in the course of time after injection of benzodiazepines.

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