PSYCHOTROPIC EFFECT OF ANALGESICS AND NEUROLEPTICS ON MODELS OF INVESTIGATIVE BEHAVIOR MODIFIED BY PAIN

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The effect of analgesics (fentanyl, morphine) and neuroleptics (droperidol, chlorpromazine) on the investigative behavior and the dynamics of affective manifestations of the response to pain was studied in experiments on albino mice exposed to a combination of nociceptive stimulation with a novel experimental situation. The action of small doses of the drugs was found to be directed toward the affective manifestations of pain, including the most highly integrated components of behavior. This effect was observed to coincide with their effect on the most complex manifestations of investigative activity.

When the psychotropic action of drugs on intact animals is studied during direct application of a nociceptive stimulus, it is very difficult to differentiate between pain as the perceptive phenomenon and as a phenomenon of the distressing experience of this perception. A psychological model using pain as an indirect factor of the inhibition or activation of behavior is more adequate for such investigations.

The object of the present investigation was to study the effect of analgesics (fentanyl, morphine) and neuroleptics (droperidol, chlorpromazine) on the behavior of animals in a novel experimental situation, modified by nociceptive stimulation, and to examine the dynamics of the affective manifestations of the behavioral response to a nociceptive stimulus.

EXPERIMENTAL METHOD

Experiments were carried out on 180 male albino mice weighing 18-25 g which were used once only. The experimental apparatus was similar to an "open field apparatus" and consisted of a chamber with a floor area of 3600 cm square, divided into squares. On the first day the animal was placed in the central square of the chamber (exposure 1) and the horizontal (number of times the squares were crossed) and vertical (number of times the animal stood on its hind limbs) movements were recorded for 2 min. After 10 min the mouse was again placed in the chamber (exposure 2); a calibrated clamp (800 g, duration of application 15 sec) was applied to the base of the tail. The response to compression was assessed in points using a conventional scale. The scale of assessment was obtained in a series of experiments using clamps with gradually increasing strength of compression: 0) absence of visible response, 1) jumping or turning, 2) turning and touching the clamp, 3) single bites at the clamp, crying, 4) struggling with the clamp, 5) a generalized response with running, jumping, and struggling; the number of cries and bites was recorded separately. After nociceptive stimulation the investigative activity (horizontal and vertical movements) was recorded for 4 min, and any distinguishing features of behavior were noted.

On the second day two exposures (3 and 4) also were given at the same time. Droperidol (in doses of 0.06, 0.125, and 1.25 mg/kg), chlorpromazine (1.0, 2.0, and 10.0 mg/kg), and morphine (1.0, 1.5, 10.0, and 15.0 mg/kg) were injected intraperitoneally 30 min before exposure 3, or fentanyl (0.0025, 0.005, 0.01, and

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TABLE 1. Investigative Activity of Animals during Exposures 1 and 3 (M±m)

	No. of crossings of squares		No. of times standing on hind limbs	
	1st exposure	3rd exposure	1st exposure	3rd exposure
A. Control – intact animals. . . .	21,2±4,8	25,8±4,8	7,0±2,7	10,0±2,5
B. Control – with nociceptive stimulation	26,7±7,56	11,6±3,59	12,0±3,0	5,4±4,3

TABLE 2. Comparison of Effects of Analgesics and Neuroleptics on Investigative Behavior and Some Parameters of Response to Nociceptive Stimulation (change of indices relative to control with nociceptive stimulation)

Drug	Dose (in mg/kg)	Activity before nociceptive stimulation		Activating effect after stimulation		Parameters of response to nociceptive stimulus (with assessment according to scale)		
		vertical	horizontal	vertical	horizontal	cries	bites (3 points)	struggle (4 points)
Chlorpromazine	1,0—2,0 10,0	▼ ▼▼▼	▼ ▼▼▼	▼▼ ▼▼▼	▼ ▼▼▼	○ ▼	▼ ▼▼▼	▼ ▼▼▼
Droperidol	0,06 0,125 1,25	▲ ▼ ▼▼	▲ ▼ ▼▼	▼ ▼▼ ▼▼	▼ ▼ ▼	○ ○ ▼	▼ ▼ ▼	○ ▼ ▼▼
Fentanyl	0,0025 0,005—0,01 0,15	▲ ▼ ▼▼	▲ ▼ ▼	○ ▼▼ ▼▼	▼ ▼ ▼▼	○ ○ ▼▼	▼ ▼ ▼▼▼	○ ▼ ▼▼▼
Morphine	1,0—1,5 10,0—15,0	▼ ▼▼▼	▼ ●	▼ ▼▼▼	▼ ●	○ ▼▼▼	▼ ▼▼▼	▼ ▼▼▼

Legend: ▼▼▼) complete inhibition, ▼▼) incomplete, ▼) partial inhibition, ○) no effect, ▲) increase, ●) locomotor excitation.

0.15 mg/kg) was injected 15 min beforehand. Control experiments (without or with nociceptive stimulation) were carried out in which physiological saline was injected.

EXPERIMENTAL RESULTS

Preliminary determination of the investigative activity of intact animals exposed to a novel experimental situation showed that on the second day the animals demonstrated only a very small increase in vertical and horizontal activity compared with the first day (Table 1A), and this can be interpreted as an element of their identification of the surrounding situation [5].

The introduction of additional factors (photic, nociceptive, acoustic stimulation) into the situation could either strengthen or inhibit the natural motivations lying at the basis of this activity (investigative drive, a tendency to revert to the habitual situation, anxiety) and modify the animals' behavior, and it has frequently been used as an experimental method to evaluate the psychotropic properties of drugs [1-4].

In the control series of experiments in which a nociceptive stimulus was used the investigative activity in exposure 3 was reduced compared with exposure 1 (Table 1B). This may reflect an increase in anxiety when confronted with a situation in which the animal received a painful stimulus. Depending on the character of the response to nociceptive stimulation and of the investigative activity after its removal, all the animals studied could be divided into two groups: 1) intensive but not maximal response to nociceptive stimulation (3 and 4 points), initial inhibition of investigative activity (1-2 min) followed by its recovery

and enhancement (activation phenomenon); 2) generalized response to a nociceptive stimulus of the same intensity (5 points) and inhibition of investigative activity. Behavioral group 1 was used for analysis.

The direction of the effect of these drugs, in principle, is shown in Table 2. The change in the response to nociceptive stimulation in mice receiving droperidol in a dose of 0.06 mg/kg and fentanyl in a dose of 0.0025 mg/kg, as Table 2 shows, was slight whereas the more sensitive indices changed substantially: investigative activity before nociceptive stimulation was increased, and the activating effect after stimulation reduced. Presumably the first effect was due to reduction of anxiety before the nociceptive stimulation while the second was due to inhibition of the tendency to run away from the painful situation by the drugs.

An increase in the dose of the neuroleptics (droperidol 0.125 mg/kg, chlorpromazine 1.0-2.0 mg/kg) did not block the affective manifestations of pain (crying, biting) but reduced their intensity and also reduced the coordinated complex manifestations (struggling) and the investigative activity before and after nociceptive stimulation. An increase in the dose of analgesic (fentanyl 0.005-0.001 mg/kg, morphine 1.0-1.5 mg/kg) reduced investigative activity, especially vertical. The main features of the response to nociceptive stimulation were a change in the frequency of biting and a decrease in the intensity of struggling. Doses of the drugs not producing complete analgesia affected mainly the most complex act of investigative behavior (the one requiring considerable expenditure of energy), namely, the vertical activity of the animals and coordinated complex manifestations of the response to nociceptive stimulation.

It will be clear from Table 2 that a further increase in the dose of the neuroleptics (chlorpromazine 10.0 mg/kg, droperidol 1.25 mg/kg) sharply inhibited but did not completely suppress the affective manifestations of pain and activity of the animals. High doses of the analgesics (morphine 10.0-15.0 mg/kg, fentanyl 0.15 mg/kg) completely blocked the specific manifestations of pain, and a characteristic feature of morphine was the increase in the animals' activity which was characterized by chaotic and purposeless movements.

The results show that the action of small doses of the drugs was directed chiefly toward the affective manifestations of pain, including the most highly integrated components of behavior. This effect was parallel to the effect on the most complex manifestations of investigative activity, reflecting the animals' psychological relations with the external environment, coupled with interaction between several emotionally motivated processes. The change in this behavioral complex can be considered to be a reflection of the psychotropic effect of the drug.

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