ROLE OF TRICYCLIC ANTIDEPRESSANTS IN CENTRAL CONTROL OF HYPERALGESIA AND STRESS ANALGESIA

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The pituitary occupies a leading position in the realization of functions of antinociceptive systems of the brain. An important role also has been ascribed to pituitary β-endorphins in the development of acupuncture analgesia [6]. Pituitary factors, it is emphaized, participate in the mechanism of stress analgesia [14, 17]. In hypophysectomized (HE) rats stress analgesia induced by electrical stimulation of the tail [18] or electroshock [14] has been shown to be reduced, but after electrodermal stimulation no such changes were observed [11].

During recent years the writers have studied the effect of psychotropic drugs on activity on brain systems, using neurophysiological and neurochemical methods for this purpose [3, 4]. The possibility of using these psychotropic drugs to potentiate, first, the action of narcotic analgesics and, second, states of the body, in animals and man, in which what is called stress-induced analgesia develops, also has been investigated. Elucidation of the predominantly suprahypophyseal or hypophyseal level of application of psychotropic drugs is of great practical importance, especially in patients with diencephalic pathology. Tricyclic antidepressants, which hitherto have been used traditionally only in psychiatric practice, are particularily interesting in this connection. Reports have recently been published of their successful use in protracted pain syndromes [12] and also in the treatment of ischemic heart disease [2]. The writers have shown [4] that imipramine (melipramine), a tricyclic antidepressant, potentiates poststress autoanalgesia considerably.

The aim of this investigation was to study the influence of the suprahypophyseal level of application of psychotropic drugs on the duration and intensity of analgesia induced by analgesics and painful stress. To analyze the mechanisms of a phenomenon such as hyperalgesia, the effect of droperidol, which induces this state [7], and of amitriptyline on thresholds of the pain response in intact and HE animals also was investigated.

EXPERIMENTAL METHOD

Analgesimetric tests were conducted on noninbred female albino rats weighing 130-180 g by the tail-flick method [13]. The animals's tail was immersed to a depth of 5 cm in water heated to a temperature of 55±0.5°C. When the latent period of the response to pain was estimated, the time obtained in rats in the initial state, before administration of the drugs or exposure to stress, was taken as 100%. In some experiments the prolonged vocalization response, corresponding to level 3 of pain integration in the CNS [1, 18], was estimated. The duration of this response was estimated to be not less than 4-5 sec. To rule out the effect of immobilization stress on thresholds of nociception the rats were adapted to the conditions of keeping in standard cages in which the experiments were carried out [10]. The effect of hunger [15] also was excluded for the same purpose. Painful stress was induced by application of "crocodile" forceps to the animal's right forelimb for 30 min.

The pituitary was removed from sexually mature rats by the transauricular method [8]. Postoperative care followed the usual rules, but no antibiotics were given. The quality of the operation was subsequently verified after decapitation by direct examination of the region of the sella turcica. The animals were used in the experiments on the 3rd day after the operation.

There were five series of experiments. Thresholds of the pain response were determined: in series I) in HE rats from the 1st through the 6th days after the operation, in series II) in HE rats during painful stress lasting 30 min and after stress, in series III) in HE rats receiving fentanyl (25 μg/kg, intraperitonally) after painful stress for 30 min, in series IV) in HE rats receiving fentanyl in the same dose simultaneously with imipramine (5 mg/kg, intraperitoneally) after painful stress for 30 min, and in series V) in He rats receiving

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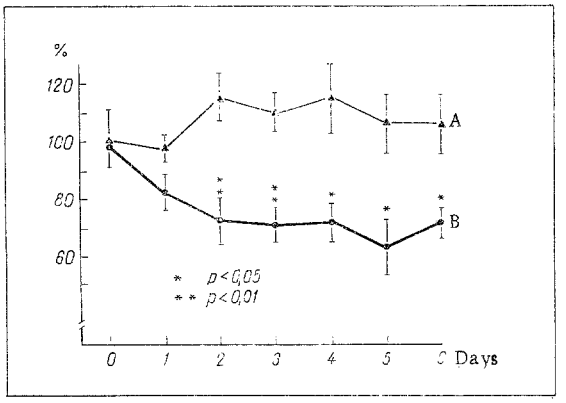

Fig. 1. Thresholds of pain response in HE rats. Abscissa, time (in days); ordinate, pain threshold (in %). 100% Corresponds to 4.7 sec. A) MOR (n = 4); B) HE rats (n = 5). *P < 0.05, **P < 0.01 compared with MOR.

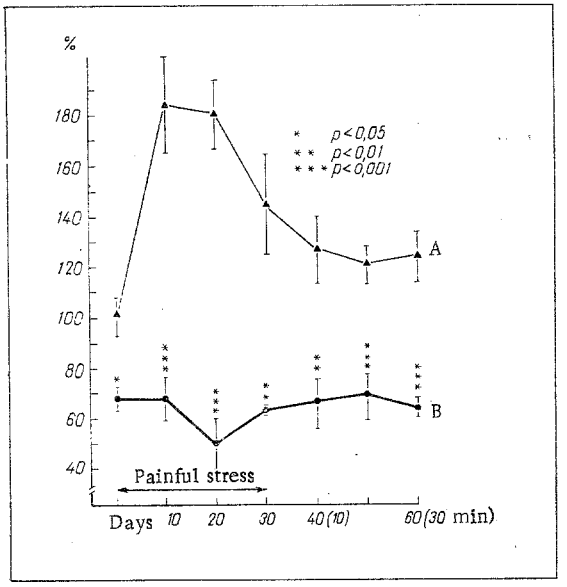

Fig. 2. Thresholds of nociceptive response in rats during painful stress and poststress period. Abscissa, time (in min); ordinate, pain thresholds (in %). 100% corresponds to 5.0 sec. A) MOR (n = 5); B) HE rats (n = 5). *P < 0.05, **P < 0.01, ***P < 0.001 compared with A. Arrow indicates painful stress.

droperidol (1 mg/kg, intraperitoneally) or amitriptyline (5 mg/kg, intraperitoneally). The control to each series of experiments consisted of rats undergoing a mock operation (MOR). The animals were used only once in the experiments with painful stress.

EXPERIMENTAL RESULTS

In HE rats thresholds of the pain response were lowered on the 1st day after the operation to 82.9±6.2%. The vocalization threshold changed from 97.9±5.5 to 53.2±15.5% compared with 100.0±9.6 and 97.4±4.0% in MOR. The rats were inert, did not rush to obtain food, and when the tail was dried after the tail-flick test, they gave a prolonged squeak. On the 2nd day thresholds were reduced to 72.3±7.7%, the rats remained apathetic, but the squeak response to drying of the tail was reduced. On the 3rd day the pain threshold was lowered to 70.2±6.0% and the vocalization response to 57.4±12.6% compared with 108.5±7.4% in MOR. Low thresholds of

TABLE 1. Effect of Hypophysectomy on Thresholds of Nociceptive Response in Rats Receiving Fentanyl or a Combination of Fentanyl and Imipramine after Painful Stress for 30 min (M±m)

Experimental conditions	Background	Time, min							
		5	10	15	20	25	30	40	60
Fentanyl, intact rats, without painful stress (19)	100±5,5	119,5±7,4	138,1±6,2	159,5±9,0	135,7±7,6	126,2±6,4	123,8±3,8	104,8±2,4	95,2±3,8
Fentanyl after painful stress for 30 min.									
MOR (5)	100±4,7	224,4±27,8**	248,9±28,0*	248,9±28,9*	184,4±14,7	158,3±12,4	157,3±12,9	142,2±23,6	124,4±10,9
HE rats (5)	100±4,0	111,4±7,7	162,9±12,9	162,9±7,4	154,3±10,0	120,0±12,9	125,7±6,0	114,3±4,9	100,0±7,7
Fentanyl and imipramine, intact rats without painful stress	100±22,4	151,2±13,4	165,9±10,2	182,9±9,0	182,9±11,2	168,3±9,8	182,9±10,7	168,3±13,7	141,5±11,5
Fentanyl and imipramine, after painful stress for 30 min:									
MOR (6)	100±5,3	192,9±27,9	310,7±26,8	346,4±63,2	414,3±35,0**		378,6±75,0*	346,4±39,3**	232,1±9,3**
HE rats (5)	100±4,1	220,6±15,3	288,2±16,5	305,9±26,2	258,8±26,5		182,2±19,4	179,4±18,2	138,2±20,9

Legend. Here and in Table 2: * $P < 0.05$, ** $P < 0.01$ compared with HE rats. Number of animals given in parenthesis.

TABLE 2. Effect of Hypophysectomy on Thresholds of Nociceptive Response in Rats Receiving Amitriptyline and Droperidol (M±m)

Experimental conditions	Background	Time, min					
		10	20	30	40	60	90
Isotonic sodium chloride solution, intact rats (21)	100±9,8	107,5±8,8	102,5±6,0	112,5±6,3	102,5±6,0	92,5±8,5	92,5±8,5
Amitriptyline							
MOR (6)	100±10,2	75,0±7,3	65,0±4,8**	57,5±2,5	70,0±10,8	75,0±11,3	105,0±13,5*
HE rats (4)	100±4,5	67,5±12,0	40,0±5,3	45,0±5,5	47,5±5,5	50,0±3,3	57,5±4,8
Droperidol							
MOR (8)	100±5,8	77,8±8,2	64,4±6,2	68,9±6,4	75,6±6,7*	68,9±5,6	82,2±6,7
HE rats (3)	100±13,7	76,7±9,7	56,7±2,3	50,0±11,7	56,0±6,0	66,7±13,3	86,7±7,7

the pain response and vocalization response were recorded on the 4th-6th day of observation also, when they fluctuated from 72.3 to 59.6% (Fig. 1).

In HE rats taken on the 3rd day after the operation no rise in the level of pain thresholds was recorded during pain stress for 30 min, as in MOR. A hyperalgesic phase was observed at the 20th min, when the pain threshold was 50.0 ± 9.4%, compared with 181.8 ± 12.4% in MOR. The maximal rise was observed in MOR at the 10th min of painful stimulation, namely to 184.8 ±18.2%. In the poststress period autoanalgesia was absent in the HE rats, the level of the pain thresholds remained low, varying between 60 and 70%, but in MOR a moderate degree of stress analgesia was observed, on average 122.5-127.5%, and this lasted more than 30 min (Fig. 2).

In HE rats receiving fentanyl after painful stress for 30 min potentiation of analgesia was not observed, as in MOR. Thresholds of the nociceptive response were virtually equal to those observed when the same dose of the analgesic was given to intact rats, not exposed to painful stimulation. Simultaneous injection of imipramine and fentanyl into HE rats after nociceptive stimulation caused marked potentiation of the analgesic effect at the 15th min, but the effect was less than in MOR. The duration of the analgesic action of this mixture also was shorted in HE rats (Table 1).

Droperidol and amitriptyline, in the doses mentioned above, induced hyperalgesia in MOR, and this response was intensified a little in the HE rats. The difference in the hyperalgesic effect of droperidol was less marked (Table 2).

Hypophysectomy thus facilitates the development of hyperalgesia in rats. Painful stress causes elevation of pain thresholds both during stress itself and in the poststress period, in agreement with clinical data obtained in patients with acute myocardial infarction [9]. Elevation of the pain thresholds in the stress period was not observed in HE rats and poststress autoanalgesia did not develop. Absence of the potentiating effect of painful stress on the analgesic effect of fentanyl in HE animals must be noted. The tricyclic antidepressant imipramine facilitated potentiation of the analgesic action of fentanyl when injected after nociceptive stimulation, even in HE rats, although this effect was rather weaker than in MOR.

The use of the traditional neuroleptanalgesic drug droperidol considerably weakened stress-induced analgesia and the analgesic effect of fentanyl in the poststress period [7]. The use of imipramine thus provides an opportunity for reducing the dose of narcotic analgesics in patients with a pain syndrome, as was confirmed by abolition of a resistant pain syndrome in acute myocardial infarction [5]. When dopamine receptors are blocked by droperidol, dopamine, which is a hypothalamic regulator of release of hormones from the pituitary gland and also, evidently, of pituitary endorphins [16], cannot promote their release. As a result, it can be tentatively suggested that the balance between endogenous analgesia and hyperalgesia is disturbed, in favor of the latter. However, the present experiments showed that droperidol not only induces hyperalgesia in HE rats, but the hyperalgesia is even stronger. This phenomenon is evidently made up of at least two components: hypophyseal and, to a greater degree, suprahypophyseal mechanisms. As regards hyperalgesia induced by amitriptyline, this fact requires further analysis and it emphasizes one again the neurochemical polymorphism of this phenomenon.

The following conclusions can be drawn from these experiments. First, hyperalgesia and stress-induced autoanalgesia are manifestations of systemic integrative activity of the whole brain, of its most complex intracentral neurochemical and neurophysiological processes. Second, in some types of pathology (diencephalic syndromes), with changes in the structural and functional integrity of the pituitary gland, the use of amitriptyline

or imipramine to potentiate the analgesic action of narcotic analgesics will evidently components for disturbances of systemic regulation arising during the development of pain or of anesthesia. Third, the operation of hypophysectomy, and also administration of the tricyclic antidepressant amitriptyline or the neuroleptic droperidol, which are representatives of different chemical and pharmacological groups, cause hyperalgesia, proof of the neurochemical and morphological polymorphism of this phenomenon and of its predominantly suprahypophyseal etiology.

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ISOLATION FROM BOVINE BRAIN OF SUBSTANCES INHIBITING SPECIFIC BINDING OF IMIPRAMINE AND SEROTONIN UPTAKE

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The discovery of specific binding sites for various psychotropic drugs, including benzodiazepines, neuroleptics, and tricyclic antidepressants, in mammalian brain tissue has raised the question of the possible existence of endogenous ligands for these binding sites. Research in this field has been conducted very intensively [3, 4, 6, 8], due in particular to the role which their detection could play in the task of synthesizing new drugs and in the development of our ideas on brain function under normal and pathological conditions.

The investigation described below is one step in the search for endogenous ligands of the "imipramine receptor" in brain tissue. Since the endogenous ligand interacts in vivo with the same binding sites as the drug, and since one of the important properties of imipramine, on which its pharmacological action is based, is its ability to inhibit serotonin reuptake by nerve endings, in the present investigation an attempt was made to isolate substances from bovine brain tissue capable of inhibiting specific binding of ^{3}H-imipramine and reuptake of ^{3}H-serotonin simultaneously.

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