be ruled out. It can be tentatively suggested that during the action of LE, like that of morphine, their effects are brought about through the liberation of endorphins [13], which have a high euphorigenic potential [14].

Enkephalins inhibit activity of the negative reinforcement system by their action on its perceptual and emotional components [1]. The inhibiting effect of LE is stronger than that of ME, evidently due to its stimulating action on the "reward" system, which reciprocally depresses the activity of the negative reinforcement system [2]. Information in the literature on the modulating action of enkephalins on serotoninergic brain mechanisms [6], which play a direct part in the functioning of reinforcement system [2], suggest an important role for this substrate in the mechanism of the effect of these peptides on "reward" and "punishment" systems.

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INFLUENCE OF THE STATE OF BRAIN CATECHOLAMINERGIC SYSTEMS ON PSYCHOTROPIC EFFECTS ON EMOTIONAL REACTIVITY AND BEHAVIOR UNDER STRESS

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UDC 612.821.3-06:613.863].014.46:615.214

KEY WORDS: stress situation; psychotropic effect; emotional reactivity.

Variations in reactivity of certain animals to stress [10] and differences in the effects of psychotropic drugs depending on the type of emotional reaction of different individuals [3] are associated with individual variations in concentration and turnover of brain catecholamines (CA) [14].

In the investigation described below particular features of the action of some psychotropic drugs on behavioral manifestations in an acute stress situation were studied in animals after preliminary destruction of catecholaminergic terminals and also in intact animals, allowing for their original type of emotional-behavioral reactivity. The functional level of the catecholaminergic system of the brain was judged from activity of tyrosine hydroxylase (TH), the key enzyme of CA biosynthesis.

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 92, No. 7, pp. 35-38, July, 1981. Original article submitted February 13, 1981.

TABLE 1. Behavioral Indices in Emotional (1) and Unemotional (2) Rats of Control and Experimental Groups (M ± m)

Drug administered	Group of animals	Subgroup of animals	Open field			Reactions to unfamiliar moving objects	
			vertical activity, number of rearings up	horizontal activity, number of squares crossed	number of acts of grooming	level of affective manifestations, conventional units	investigative activity, number of approaches
Physiological saline	Control	1	1,6±0,4	80,2±10,3	4,8±1,7	13,8±3,0	None
		2	12,7±3,8	64,0±5,4	1,8±0,6	6,7±1,4	3,1±0,4
	Experimental	1	3,1±0,7*	96,5±11,4*	6,7±1,8*	18,4±2,7*	None
		2	7,4±1,3*	69,0±5,0	2,1±0,3	9,3±1,6*	None†
Clonidine (0.05 mg/kg)	Control	1	2,9±0,8	48,0±11,7†	3,2±0,5	10,2±3,0	None
		2	9,3±0,4	38,0±9,0 †	None	5,6±2,3	1,6±0,3
	Experimental	1	4,8±0,5	79,0±9,7	2,1±0,8 †	6,3±1,2†	2,7±0,4†
		2	5,6±0,7	55,4±5,9*	1,8±0,6	4,1±0,8†	5,3±1.2†
Amphetamine (0.25 mg/kg)	Control	1	0,9±0,2	92,1±11,3	5,0±1,8	17,1±4,7	None
		2	13,1±5,1	70,2±6,3	2,8±0,9*	7,9±2,3	None
	Experimental	1	None	122,7±12,4*	4,1±0,8	12,3±3,8*	0,8±0,6†
		2	2,6±0,7†	79,3±6,0*	2,8±0,6	7,1±2,0	2,3±0,3†
Haloperidol (0.015 mg/kg)	Control	1	1,1±0,2	54,0±6,7†	2,9±0,4*	7,2±2,1†	None
		2	4,2±2,1 †	49,6±4,0*	2,1±0,7	4,0±1,2*	2,8±0,2
	Experimental	1	None	28,6±5,7†	None	11,5±2,9†	None
		2	None	17,0±3,1†	None	6,2±1,2*	None
Phenazepam (0.25 mg/kg)	Control	1	3,9±0,8*	68,2±7,0*	1,6±0,3 †	4,6±1,5*	2,5±0,8†
		2	10,1±3,2*	43,0±8,3*	None	2,0±0,5*	3,7±1,1
	Experimental	1	3,1±0,6	101,3±11,2	3,2±0,8†	5,4±1,6†	3,2±0,3†
		2	5,0±1,9*	71,0±10,1	1,9±0,2	3,0±0,4†	4,0±0,6†

Legend. Here and in Table 2 differences significant between groups for each subgroup in control test and also between control test and experimental test; *P < 0.05, †P < 0.01.

TABLE 2. Effect of Psychotropic Drugs on Behavior Aimed at Avoiding Acute Stress-Inducing Situation in Emotional (1) and Unemotional (2) Rats of Control and Experimental Groups (M ± m)

Drug administered	Group of animals	Subgroup of animals	Latent period of appearance of motor responses, sec	Number of unsuccessful attempts to escape	Level of affective manifestations, conventional units	Latent period of avoidance, sec
Physiological saline	Control	1	6,7±2,6	28,3±4,2	9,4±3,7	∞
		2	15,2±6,3	None	None	26,5±8.4
	Experimental	1	2,3±0,8 †	42,3±8,4†	18,2±4,8 †	∞
		2	4,2±1,9 †	8,7±1,8†	7,4±2,6 †	43,6±5,9†
Clonidine (0.05 mg/kg)	Control	1	8,3±3,5	17,6±3,7	7,6±2,0	∞
		2	18,4±4,2	None	None	24,6±3,7
	Experimental	1	4,5±0,9*	6,2±2,5†	3,0±0,9 †	15,2±4,1†
		2	2,1±0,4*	Her	None	6,5±2,6†
Amphetamine (0.25 mg/kg)	Control	1	4,0±1,9	31,9±4,3	13,2±3,8*	∞
		2	13,3±5,1	None	None	28,7±7,4
	Experimental	1	2,1±0,8	29,4±5,1*	19,4±6,2	28,1±6,2 †
		2	3,2±1,3	7,6±2,0	6,6±2,4	21,1±4,9†
Haloperidol (0.015 mg/kg)	Control	1	9,2±3,0*	21,4±5,7	5,1±1,7*	23,2±6,1†
		2	15,4±4,2	4,3±1,2*	None	28,4±6,8
	Experimental	1	11,3±4,8 †	15,2±2,7*	11,7±6,0	21,7±4,3 †
		2	8,7±3,4*	2,1±0,8*	7,3±2,5	19,4±5,2 †
Phenazepam (0.25 mg/kg)	Control	1	12,5±2,9 †	6,8±1,9 †	None	18,1±3,3†
		2	8,2±3,1 †	None	None	19,6±5,2
	Experimental	1	6,7±2,1*	13,9±3,8 †	4,2±1.0 †	17,3±3,6†
		2	5,0±1,0	3,6±0,4*	None	10,2±4,7†

EXPERIMENTAL METHOD

Degeneration of catecholamine terminals was produced by the method in [9]. Wistar rats during the first 3 days after birth were given a subcutaneous injection of 100 mg/kg of 6-hydroxydopamine (6-OHDA; from Sigma, USA) in a volume of 0.1 ml. The animals, weighing 220-270 g, were used in the experiments 14-16 weeks later. Emotional-behavioral reactivity to an unfamiliar moving object, to being picked up by the hand in an "open field," and ability

to solve an extrapolation problem involving escape from an acute stress-inducing situation, in a modified Henderson's apparatus (to escape the animal had to extrapolate the parameters of an obstacle, to overcome fear, and to dive beneath the wall of the cylinder and to get out of the experimental chamber, using a grid lowered into water) was assessed. The testing procedure was fully described previously [1]. The control group consisted of male Wistar rats of the same body weight. TH activity in structures of the corpus striatum and hypothalamus was determined fluorometrically [15] from the rate of formation of the reaction product, namely dopa. Each animal took part in the experiment 2 weeks after previous testing. Drugs — clonidine, haloperidol, amphetamine, and phenazepam — were injected intraperitoneally 15-20 min before the experiment. Behavioral manifestations were assessed quantitatively or by means of a point system. The significance of differences was determined by the nonparametric U test [2].

EXPERIMENTAL RESULTS

The emotional-behavioral reactivity of animals receiving 6-OHDA in the neonatal period was higher on the whole than in the control. This fact has been noted previously [7]. By contrast with investigations in which mean statistical data for all animals were evaluated, in the present case it was shown that the group of rats receiving 6-OHDA was heterogeneous in its emotional-behavioral reactivity, and that, just as in the control group, subgroups of emotional and unemotional animals, differing significantly with respect to all indices tested, had to be distinguished (Tables 1 and 2).

Differences in the behavior of animals of the two subgroups correlated with the unequal functional activity of the brain catecholaminergic systems, reflected in TH activity. For instance, in emotional animals receiving 6-OHDA, TH activity in the corpus striatum was 0.144 ± 0.02 nmoles dopa/mg protein in 15 min, compared with 0.324 ± 0.03 nmole dopa/mg protein in 15 min in the emotional control rats.

TH activity in the corpus striatum of unemotional control rats also was higher than in the same part of the brain of unemotional animals treated with 6-OHDA (0.261 ± 0.02 and 0.214 ± 0.02 units respectively; $P < 0.01$). No significant differences were found between these indices in the hypothalamus of the experimental and control animals (between the corresponding groups). After administration of 6-OHDA in the neonatal period, a significant decrease in the CA level was found in the forebrain and diencephalon, as a result of destruction of catecholamine terminals in the adult rats, whereas its concentration in the cerebellum was increased (on average to 200%) [9]. The ratio of injury to noradrenalin (NA) and dopamine (DA) terminals varies considerably between individual animals [11]. A fall in the NA level only is not accompanied by any significant change in behavior, whereas a fall in the DA level is a dominant factor in the development of a behavioral deficit [8]. The different levels of emotional-behavioral reactivity in the group of rats receiving 6-OHDA could be attributable to precisely this factor.

Clonidine (0.05 mg/kg) completely abolished affective manifestations in unemotional rats in this group and sharply depressed them in emotional rats, with the result that in an acute stress situation the number of unsuccessful attempts was reduced and avoidance behavior took place. In emotional control animals the effect of clonidine was limited to the sedative component, so that manifestation of avoidance behavior was not facilitated. The sedative action of clonidine is due to activation of presynaptic α-adrenoreceptors and inhibition of NA liberation [6]. Destruction of catecholamine terminals leads to the development of postsynaptic hypersensitivity of those neurons which remain intact [13]. Under these conditions, when the presynaptic and the enhanced postsynaptic action of clonidine is depressed, excessive emotional reactivity is abolished without detriment to adaptive forms of response (the animals exhibit activity necessary for avoiding the stress situation).

Haloperidol (0.015 mg/kg), which blocks postsynaptic DA receptors, led to more marked inhibition of motor and investigative activity in animals receiving 6-OHDA. In the control group haloperidol, modulating reactivity of the emotional animals, led to more successful behavior for avoiding the acute stress situation. In emotional rats receiving 6-OHDA haloperidol inhibited behavioral manifestations as reflected in all indices. The change in the character of the psychotropic effect of haloperidol in rats of the experimental group compared with the control animals may be due to differences in the total content and the turnover rate of CA in structures of the diencephalon and mesencephalon, and also to the appearance of hypersensitivity of postsynaptic DA receptors. Under these circumstances an increase in binding of ^{3}H-haloperidol with DA receptors has been observed [5].

Amphetamine (0.25 mg/kg) caused even greater hyperreactivity and an increase in motor activity in the experimental animals receiving 6-OHDA, but in an acute stress situation the level of effective manifestations remained the same as in the control test, and the number of mistakes made by the emotional rats was reduced. The action of stress on the control animals sharply lowered the level of investigative activity in an open field, and also when brought near to an unfamiliar object. By contrast with the emotional experimental rats, the emotional control animals did not avoid the stress-inducing situation, for the number of their affective manifestations increased sharply. Amphetamine is known to increase mediator liberation by terminals and to block reassimilation of CA [4]. The different effect of amphetamine in the two groups of animals may be due to the development of postsynaptic hypersensitivity of striatal CA neurons in rats receiving 6-OHDA.

Phenazepam (0.25 mg/kg) lowered the intensity of emotional-behavioral reactivity in both control and experimental rats, as a result of which the emotional animals of both groups acquired the ability to solve the extrapolation problem involved in avoiding the acute stress situation. Tranquilizers react with "benzodiazepine" brain receptors and indirectly modify activity of GABA-ergic mechanisms [12], and their action is unconnected with the catecholamine component. For this reason no difference can be observed in the effect of phenazepam in animals of different groups.

Disturbance of the balance of functional activity of catecholaminergic systems at the diencephalic and mesencephalic levels following degeneration of catecholamine terminals as a result of administration of 6-OHDA thus causes a sharp rise in the level of emotional-behavioral reactivity, makes it more difficult for the animals to escape from an acute stress situation, and creates significant differences in the action of psychotropic drugs whose effect is mediated through the catecholamine neuromediator system. The behavior of animals with partial destruction of catecholamine terminals can be regarded as a model of a pathological affective state, which can be used to study mechanisms of action of psychotropic drugs depending on intensity of original emotional-behavioral reactivity.

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