Modulatory Effect of 8-OH-DPAT on Behavior of Ovariectomized Female Rats

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Behavior of ovariectomized rats was studied after chronic administration of serotonin 1A receptor agonist 8-OH-DPAT alone or in combination with 17β-estradiol for 14 days. The effect of 8-OH-DPAT on learning was evaluated in the conditioned passive avoidance task. Behavioral activity in elevated plus-maze and open field was recorded. Administration of 8-OH-DPAT to ovariectomized female rats increased the number of entries into open arms of the maze and the time spent there. Combination treatment of ovariectomized animals with 8-OH-DPAT and 17β-estradiol decreased total locomotor and emotional activity in the open field. Administration of 8-OH-DPAT alone or in combination with 17β-estradiol improved performance of the conditioned passive avoidance response.

Key Words: *8-OH-DPAT; passive avoidance; plus-maze; behavior; estrogens; pharmacotherapy*

Psychoneuroendocrinologists developed a new approach to the search for pharmacological preparations that directly or indirectly modulate functional activity of the neuromediator or hormonal system and improve or normalize disturbances in higher nervous activity [8,10]. The best plan to be followed is to synthesize pharmaceutics possessing hormonal and neurotropic properties. These preparations hold promise to treat endocrine and neuromediator dysfunction and break a vicious circle. The effects of chronic treatment with L-tryptophan, *p*-chlorophenylalanine, and Cipramil on behavior of ovariectomized (OE) female rats were studied in our previous experiments. Specific features of the conditioned response in rats with estrogen deficiency were evaluated after administration of the test compounds [4,5]. Here we studied the effect of a highly selective serotonin 1A receptor agonist on behavioral activity of OE rats.

MATERIALS AND METHODS

Experiments were performed on 160 adult female outbred albino rats weighing 200-220 and obtained from the Rappolovo nursery. The animals were kept under the natural light/dark regimen, standard temperature and feeding conditions, and *ad libitum* water and food supply. The study was conducted at 9.00-12.00. The rats were divided into groups (8-10 rats per group): intact females, physiological saline (group 1, control I); intact females, 8-OH-DPAT subcutaneously (0.05 mg/kg, Sigma), 14 days (group 2); OE females, oil solution intramuscularly (group 3, control II); OE females, 17β-estradiol intramuscularly, daily dose 5.0 μg per 0.5 ml oil solution, 14 days starting from the 3rd week after ovariectomy (group 4); OE females, 8-OH-DPAT subcutaneously (Sigma), daily dose 0.05 mg/kg, 14 days starting from the 3rd week after castration (group 5); OE females, 8-OH-DPAT subcutaneously (daily dose 0.05 mg/kg, Sigma) and 17β-estradiol intramuscularly (5.0 μg per 0.5 ml oil solution), 14 days starting from the 3rd week after castration (group 6).

Ovariectomy was performed routinely [2]. The effects of exogenous estradiol in OE females and phases of the estrous cycle in intact rats were evaluated by examining vaginal smears.

Learning capacity was determined by the conditioned passive avoidance response (CPAR) [1]. Animal behavior of was assessed using the open-field and elevated plus-maze tests [3,11].

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The results were analyzed by ANOVA and *t* test (SPSS software).

RESULTS

Control diestrous and metestrous females demonstrated good performance of CPAR ($p<0.001$) 24 h after training. By contrast, proestrous and estrous rats demonstrated amnesia. In intact animals receiving 8-OH-DPAT, CPAR performance was observed during the same phases of the estrous cycle (metestrus and diestrus, Fig. 1, *a*). Control OE rats did not perform CPAR after 24 h. However, CPAR was incompletely preserved in OE females treated with estradiol. CPAR performance was not disturbed in OE rats receiving 8-OH-DPAT alone or in combination with estradiol ($p<0.001$, Fig. 1, *b*).

Chronic administration of 8-OH-DPAT to intact females during various phases of the estrous cycle had no effect on the time spent in open arms of the elevated plus-maze, but markedly increased the number of entries into these compartments ($p<0.05$, Fig. 2, *a*, *b*). Ovariectomy decreased the time spent in open arms and number of entries into these compartments. Injection of estradiol to OE rats slightly increased the time spent in the open arms. Administration of 8-OH-DPAT to OE animals increased the number of entries into open arms and the time spent there ($p<0.05$). However, combination treatment of OE females with 8-OH-DPAT and estradiol had no effect on these indexes (compared to control and estradiol-treated OE animals, Fig. 3, *a*, *b*).

Administration of 8-OH-DPAT to intact proestrous and estrous rats increased horizontal and vertical activity and the time of grooming in the open field ($p<0.05$, Table 1). 8-OH-DPAT increased exploratory activity, but decreased emotionality of intact rats in various phases of the estrous cycle. Ovariectomy did not modulate behavioral activity of animals (except the increase in emotionality). Injection of estradiol to OE females decreased horizontal activity (by 1.8 times, $p<0.05$) and time of grooming ($p<0.05$) compared to intact and control OE rats (Table 1). Moreover, the emotional component of behavior was absent in these animals. Chronic administration of 8-OH-DPAT practically did not change horizontal activity, emotionality, and time of grooming, but stimulated exploratory behavior of OE rats ($p<0.05$). Combination treatment of OE animals with 8-OH-DPAT and estradiol decreased total locomotor and emotional activity, but had no effect on exploratory behavior and time of grooming (compared to control and estradiol-receiving OE females, Table 1).

Our results suggest that serotonin 1A receptor agonist produces different and inverse effects on behavior of intact and OE females. 8-OH-DPAT did not improve passive learning and had no effect on the degree of anxiety in intact proestrous and estrous rats. However, 8-OH-DPAT completely normalized passive learning and reduced anxiety in OE animals. Therefore, the serotonin 1A receptor agonist possesses anxiolytic activity. 8-OH-DPAT stimulated behavioral reactions of intact rats in the open-field test, which was especially pronounced during proestrous and estrus. 8-OH-DPAT increased exploratory activity of OE females, but had no effect on other behavioral characteristics. Combination treatment with 8-OH-DPAT and estradiol improved only passive learning. How-

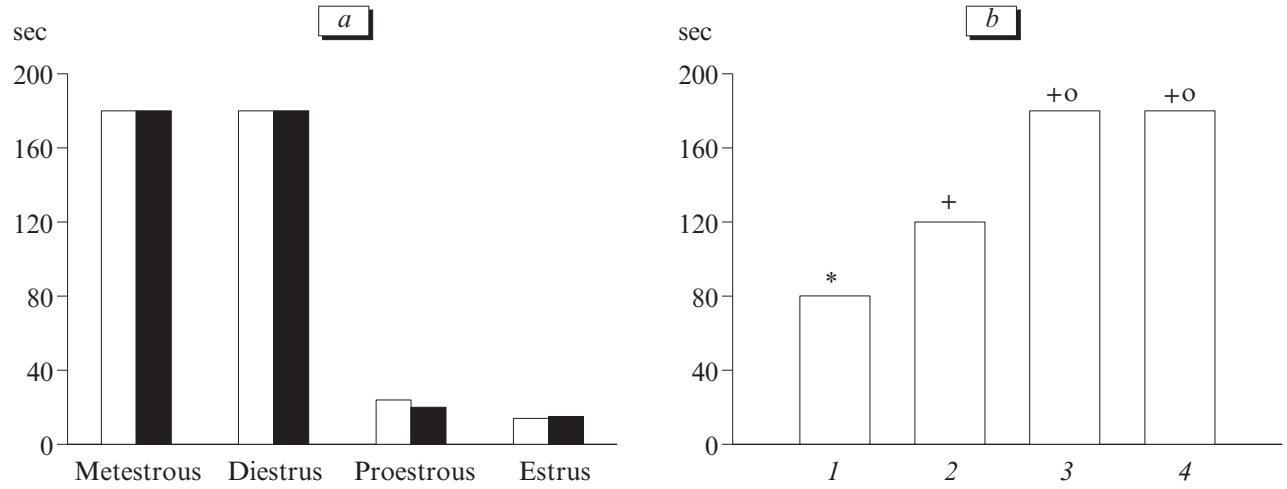

Fig. 1. Performance of conditioned passive avoidance response after chronic treatment of intact and ovariectomized (OE) female rats with 8-OH-DPAT. Ordinate: latency of entry into dark compartment, testing of the conditioned passive avoidance response after 24 h. Light bars: control I. Dark bars: intact females receiving 8-OH-DPAT (*1*, *a*; *2*, *a*; *3*, *a*). Control II (*1*); OE females, 17β-estradiol (*2*); OE females, 8-OH-DPAT (*3*); OE females, 8-OH-DPAT and 17β-estradiol (*1*, *b*; *2*, *b*; *3*, *b*). Here and in Figs. 2 and 3: $p<0.05$: *compared to control I; +compared to control II; °compared to OE rats receiving 17β-estradiol.

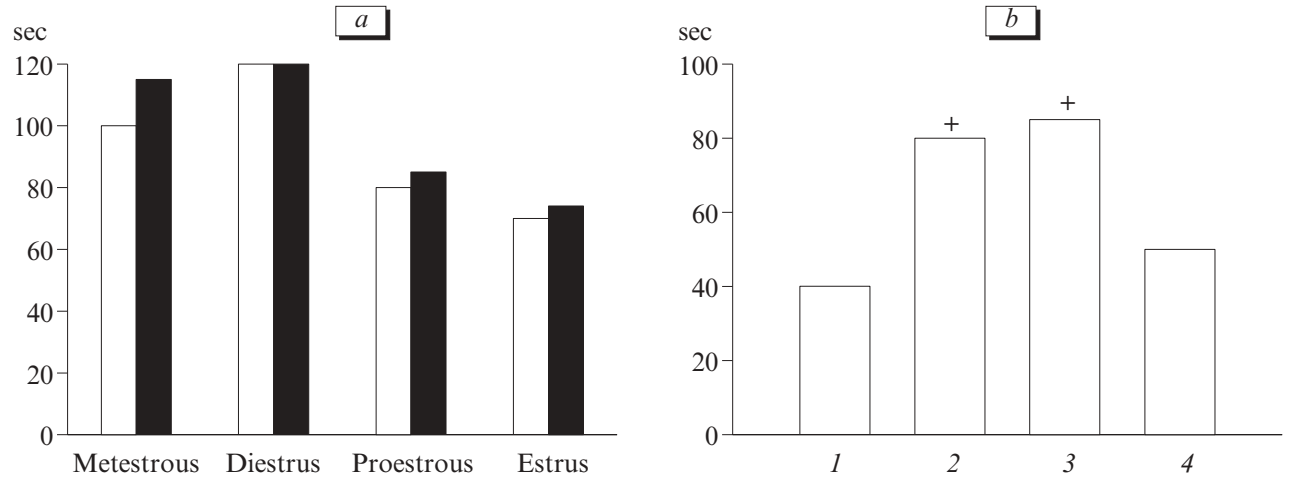

Fig. 2. Time spent in open arms of elevated-plus maze after chronic treatment of intact and OE female rats with 8-OH-DPAT. Ordinate: time spent in open arms.

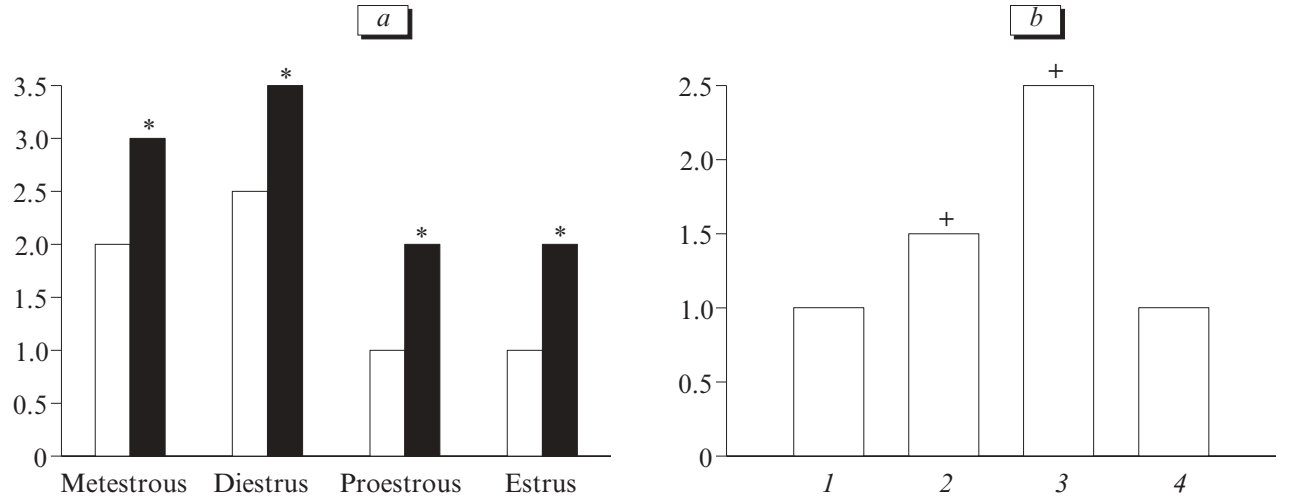

Fig. 3. Number of entries into the open arms of the elevated-plus maze after chronic treatment of intact and OE female rats with 8-OH-DPAT. Ordinate: number of entries into open arms.

TABLE 1. Effect of Chronic Treatment with 8-OH-DPAT on Open Field Behavior in Intact and OE Females ($M \pm m$, n=8-10)

Group		Locomotor activity		Exploratory activity	Emotionality	
		ambulation	rearing postures		grooming	defecation
Control I	metestrous	56.3±4.5	12.4±0.3	7.4±0.8	3.8±0.3	0.50±0.01
	diestrus	50.7±1.6	12.0±0.4	1.9±2.7	2.5±0.4	2.1±0.2
	proestrous	34.8±1.6	4.6±0.2	3.7±0.3	3.0±0.3	2.5±0.3
	estrus	78.3±2.6	15.6±0.4	4.2±0.3	3.3±0.3	2.0±0.3
Intact, 8-OH-DPAT	metestrous	47.8±2.6	12.6±0.4	12.7±0.3*	3.0±0.3	0.10±0.01*
	diestrus	54.8±2.3	14.1±0.2	6.5±0.3*	2.8±0.2	0.8±0.3*
	proestrous	56.3±2.4	10.8±0.2*	1.7±0.3*	6.3±0.3*	0.50±0.01*
	estrus	74.8±1.5	20.6±0.4*	13.4±0.2*	6.0±0.4*	0.60±0.01*
OE (control II)		60.0±2.6	11.6±0.4	4.6±0.6	2.8±0.3	0.10±0.01*
OE, 17β-estradiol		35.4±1.4*+	12.4±0.2	3.7±0.3	0.8±0.3*+	0
OE, 8-OH-DPAT		64.7±1.6	13.1±0.4	10.2±1.2*	2.4±0.2	0.40±0.02*
OE, 8-OH-DPAT and 17β-estradiol		24.8±2.6+o	2.3±0.2+o	4.0±0.2	2.2±0.3	0

Note. $p<0.05$: *compared to control I; +compared to control II; ocompared to OE rats receiving 17β-estradiol.

ever, these compounds decreased total locomotor and exploratory activity of rats in the open field. Changes in the behavior of OE females observed after combination treatment with 8-OH-DPAT and 17β-estradiol were similar to those produced by 17β-estradiol.

Serotonin is involved in a variety of vitally important processes and plays an important role in the regulation of behavior [7,9,10]. The existence of a close relationship between sex hormones and serotoninergic system is beyond doubt. The negative inverse effects of estrogens and androgens are realized via the serotoninergic system [10]. Several agonists of serotonin 1A receptors produce anxiolytic and antidepressant effects in intact male rats [7,9]. However, little is known about the influence of serotonin 1A receptor agonists on behavioral reactions of intact and OE females. The opposite effects of 8-OH-DPAT in intact and OE rats can be related to differences in expression of serotonin 1A receptors, expression of estrogen β-receptors, and their binding activity in brain structures responsible for cognitive function [6,10]. Further studies will elucidate the mechanisms underlying the influence of 8-OH-DPAT. It is important to evaluate the effects of serotoninergic substances used for pharmacotherapy of brain dysfunction during estrogen deficiency.

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