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Blockade of the Anxiolytic Action of 8-OH-DPAT in Lactating Rats

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FERNÁNDEZ-GUASTI, A. O. PICAZO AND A. FERREIRA. *Blockade of the anxiolytic action of 8-OH-DPAT in lactating rats*. PHARMACOL BIOCHEM BEHAV **59**(1) 45–50, 1998.—The anxiolytic action of 8-OH-DPAT (0.125, 0.5, and 0.75 mg/kg, IP, −15 min) was evaluated in ovariectomized and 7-day lactating mother rats. This serotonergic anxiolytic produces a clear reduction in cumulative burying behavior and in freezing time (parameters denoting a reduction in anxiety levels) in ovariectomized subjects. However, in 7-day lactating mother rats, 8-OH-DPAT lacked its antianxiety effects. Additionally, as an extra parameter of the animal's emotionality the number of defecation bolus was registered. A reduction in this parameter in ovariectomized animals after 8-OH-DPAT (0.5 mg/kg) injection was found. This effect was also blocked in 7-day lactating rats. None of the doses of the compound tested altered the burying behavior latency (a parameter inversely representing the animal's reactivity). The general ambulatory behavior of ovariectomized subjects was significantly impaired at the highest dose (0.75 mg/kg) of 8-OH-DPAT. Lower doses did not alter this parameter or the number of times lines are crossed (a parameter denoting exploratory activity). Discussion is focused on the relationship between the activity of the serotonergic system and the secretion of prolactin in this period. © 1998 Elsevier Science Inc.

8-OH-DPAT Lactation Burying behavior Freezing behavior Anxiety

IT has been demonstrated that the serotonergic agonists 8-hydroxy-2 (di-n-propylamino)tetralin (8-OH-DPAT) (3,10,26), ipsapirone (6,37), buspirone (9,15,49), gepirone (9), and indorenate (12,14) possess anxiolytic activity in various animal models and in some cases in clinical trials (5,20,40,45).

We and others have reported on the anxiety levels during various endocrine stages of females (1,17,21,41). Thus, we have observed a reduction in burying behavior during the late (but not early) proestrus (17), at the 14th day of pregnancy and immediately after delivery (35). Such observations have been interpreted on the light of the different steroid hormonal milieu that characterizes each of these stages. Interestingly, no changes in experimental anxiety were found at other periods of gestation, estrous cycle, and active lactation (35).

Various evidences reveal that the serotonergic anxiolytics produce differential effects under various physiological conditions including gender (16,48), age (31), species (13), and different phases of the rat estrous cycle (16). However, there are no reports concerning the effect of these drugs during lactation.

The main purpose of this study was to assess the anxiolytic effect of 8-OH-DPAT under two endocrine stages: ovariectomized and mother rats in the seventh day of lactation. This day was selected on the bases that lactation, at this moment, is a completely installed process (4).

Experimental anxiety was established by using the defensive burying behavior and the freezing tests, both reported to be sensitive and useful methods for testing physiological (17,22,31) and pharmacological (23,36,38,46,47) changes in anxiety. Defecation and exploratory activity have been also suggested as indicators of emotionality (1,46). Therefore, together with the freezing test, these parameters were also registered.

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METHOD

General

Animals. Female Wistar rats weighing 250–300 g b wt were used in this study. All animals were individually housed in a room under inverted light:dark cycle conditions (lights on at 2200 h) with ad lib access to water and Purina Rat Chow all over the experiments. Female rats were divided in two main groups: ovariectomized and lactating females. Ovariectomy was performed through a ventral incision under pentobarbital (35 mg/kg, IP) anesthesia. Animals were tested for anxiety 15 days after ovariectomy. Females were mated with sexual active studs and individually caged when pregnant. These animals were daily checked for delivery and that day numbered as day 0. Thereafter, the animals were maintained with their pups until day seventh of lactation. On that day the mothers were separated from their litter, at least 3 h before the observation. All animals were tested between 1 and 3 h after lights off.

The treatments, common to both conditions, were: saline (2.0 ml/kg, IP, $^{-}$20 min) or 8-OH-DPAT (Biochemical Research, Natick, USA, 0.125, 0.5, and 0.75 mg/kg, IP, $^{-}$20 min). The drug was dissolved in physiological saline. Doses, route of administration, and latency were established according to previous data (37).

Anxiety Tests

Burying behavior. The burying behavior test consists of a cage measuring 27 × 16 × 23 cm (identical to the animal home cage) with an electrified prod (7 cm long) emerging from one of its walls 2 cm above the bedding material (consisting of fine sawdust). Thus, when the rat touches the prod it receives an electric shock of 0.3 mA (the electric source was a constant current shocker, model 5806, LaFayette Instruments, Inc.). After the placement of the animal in the test cage its behavior was observed for 10 min. Once the animal receives a shock it displays a phylogenetic learned behavior characterized by pushing the sawdust ahead with rapid alternating movements of the forepaws oriented to cover the electrified prod. The parameters registered in this test were: burying behavior latency, i.e., time from the first shock to the burying behavior display and cumulative burying behavior, i.e., cumulative time that the rat spends burying the prod during a 10-min period. The cumulative burying behavior has been directly related with the experimental anxiety levels, while the burying behavior latency inversely reflects the animal's reactivity (38,46). Data were statistically compared using two-way ANOVA (44) followed by Duncan test as post hoc analysis (43).

Freezing behavior. This paradigm includes a circular Plexiglas arena (39 cm diameter), the floor of which is covered by a filter paper divided by two lines to form four 90° sectors. This floor covering was changed after testing the rat. The cage is enclosed in a soundproof chamber 70 × 41 × 40 cm, which is illuminated by a 15 W white light bulb suspended together with a door bell (95 dB) on the ceiling of the test chamber. The behavior of the rat was registered through a Plexiglas window on the front wall. The animals were allowed a 5-min adaptation period to the novel observation cage. During this period the number of the following behaviors were registered: crossing over lines and defecations. The door bell was then activated for 6 s, during the sound the rat typically rushed around in the cage and eventually immobilized either concurrently with, or slightly before, the end of the signal. In both cases, freezing was defined as the lack of all observable movements of any parts of the body and vibrissae, except for those movements related to respiration (22,23). All other behaviors were scored as active. In general it is considered that defecation represents a measure of the general emotionality of the rat (1). The number of line crossing times reflects changes in exploratory activity. The Mann–Whitney *U*-test was made to compare these results (43).

Activity Test

For controlling changes in the anxiety tests due to alterations in motor activity, ovariectomized and 7-day lactating rats were evaluated for general activity in a cage measuring 43 × 36 × 19 cm that was placed over a sensitive plaque 38 × 40 cm connected to a counter (Stoelting Co., Chicago, IL). The number of counts over a 10-min session were recorded and the cage carefully cleaned with tap water after each test. These data were statistically compared using ANOVA (44) followed by the Duncan test (43).

RESULTS

The results obtained in the burying behavior test are shown in Figs. 1 and 2 and those of freezing behavior in Fig. 3.

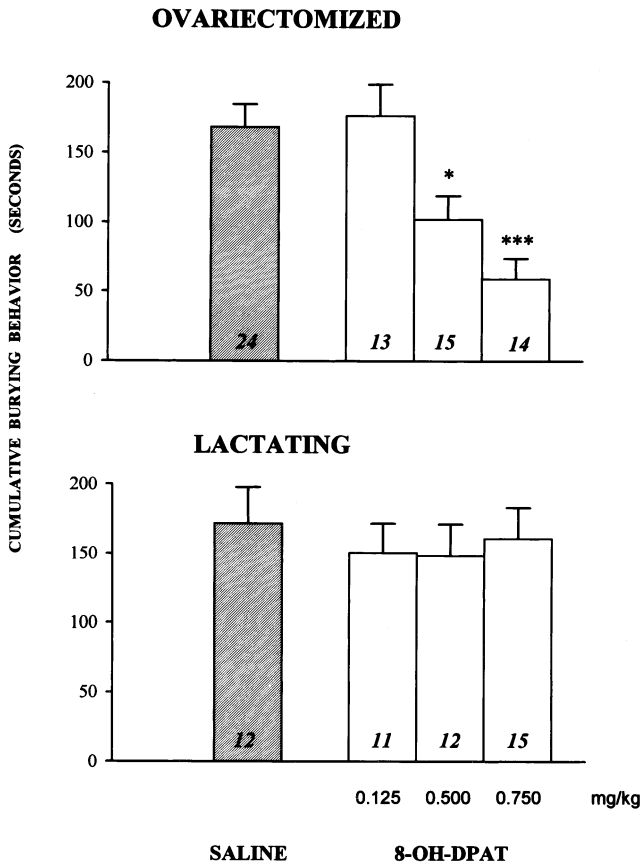

FIG. 1. Cumulative burying behavior (mean ± SE) after the administration of 8-OH-DPAT (0.125, 0.5, and 0.75 mg/kg) in ovariectomized and 7-day lactating mother rats. Numbers within columns represent the *n* of each experiment. Asterisks over columns show comparisons between the experimental (open bars) and the control (dashed bars) groups. Duncan's test, $*p < 0.05$, $***p < 0.01$.

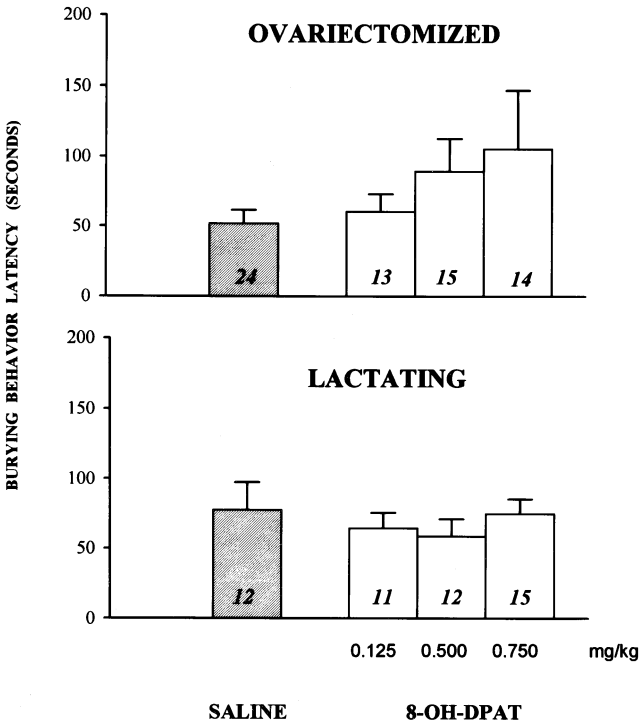

FIG. 2. Burying behavior latency (mean ± SE) after the administration of 8-OH-DPAT in ovariectomized and 7-day lactating mother rats. Numbers within columns represent the *n* of each experiment. After two-way ANOVA, any significant difference was found.

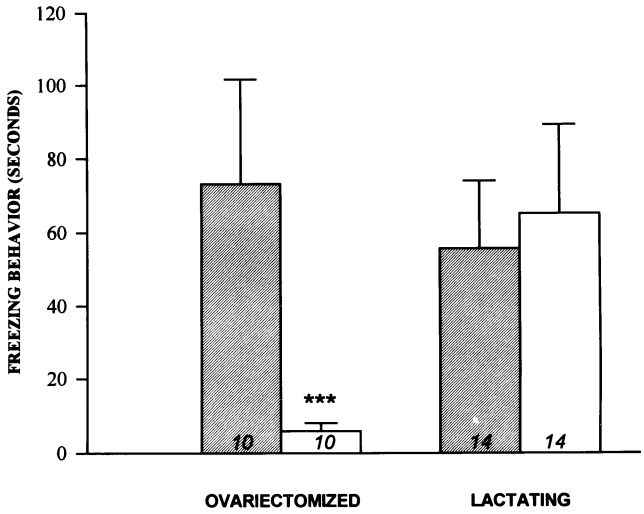

FIG. 3. Time spent freezing (mean ± SE) after injection of 0.5 mg/kg of 8-OH-DPAT to ovariectomized and 7-day lactating mother rats. Numbers within columns represent the *n* of each experiment. Dashed bars: vehicle control; open bars: 8-OH-DPAT treated groups. Paired comparisons were made using the Mann–Whitney *U*-test, $***p < 0.01$.

Figure 1 shows the cumulative burying behavior of ovariectomized and 7-day lactating mother rats. The results from the two-way analysis of variance for the main effect of hormonal condition (ovariectomized or 7-day lactating) and drug action (doses) were as follows: for hormonal condition, $F = 3.90$, $p = 0.048$; for drug, $F = 3.58$, $p = 0.016$, and for condition × drug interaction, $F = 3.93$, $p = 0.011$. These data indicate that the effect of 8-OH-DPAT is different between ovariectomized and 7-day lactating mother rats.

Clearly, the administration of the low dose of the serotonergic anxiolytic 8-OH-DPAT produced no effects neither in ovariectomized nor in 7-day lactating mother rats compared with their respective saline control group (dashed bar). However, in ovariectomized rats, the median and large doses of this antianxiety agent (0.5 and 0.75 mg/kg) produced a robust reduction in burying behavior, as evidenced by the paired comparison using the Duncan's test. Interestingly, in 7-day lactating mother rats no effect on the cumulative burying behavior was found after any dose assayed.

Figure 2 summarizes the burying behavior latencies after the administration of the same treatments showed in Fig. 1. Neither in ovariectomized nor in 7-day lactating mother rats, 8-OH-DPAT produced an effect on this parameter. Thus, the two-way analyses of variance revealed no statistical significant differences; $F = 0.26$, $p = 0.617$ for hormonal condition; $F = 0.68$, $p = 0.569$ for drug; and $F = 1.09$, $p = 0.356$ for condition × drug interaction.

The freezing behavior data are shown in Fig. 3. Clearly, in ovariectomized rats, 8-OH-DPAT (0.5 mg/kg) reduced the immobility time while in lactating rats this serotonergic drug at this dose produced no effect. Additionally, this compound also reduced the number of fecal bolus registered during the test in ovariectomized rats. Such drug effect was also absent in lactating animals (Table 1).

The effect of 8-OH-DPAT (0.5 mg/kg) on the exploratory activity is also shown in Table 1. In ovariectomized rats 8-OH-DPAT significantly increased the line's crossing times, which was not evident in lactating animals.

The results obtained from the activity test are expressed as the number of counts in a 10-min session (Table 2). The two-way analysis of variance did not reflect statistical differences: $F = 0.02$, $p = 0.887$ for hormonal condition; $F = 4.23$, $p = 0.008$ for drug, and $F = 1.52$, $p = 0.212$ for condition × drug interaction. However, a clear reduction in the number of

TABLE 1

EFFECT OF 8-OH-DPAT (0.5 mg/kg) ON SOME BEHAVIORAL PARAMETERS REGISTERED 5 MIN BEFORE FREEZING DISPLAY BY OVARIECTOMIZED OR 7-DAY LACTATING MOTHER RATS

Treatment		Crossing	Defecation
Ovariectomized	$n = 10$		
Saline		18.1 ± 1.90	2.7 ± 0.68
8-OH-DPAT		34.1 ± 4.50	0.3 ± 0.20
p		NS	<0.05
7-day Lactating Mother Rats	$n = 14$		
Saline		16.71 ± 2.13	3.8 ± 0.53
8-OH-DPAT		18.57 ± 3.00	4.6 ± 0.78
p		NS	NS

Data are expressed as mean frequency ± SE. Statistical comparisons were made using the Mann–Whitney *U*-test.

TABLE 2

GENERAL AMBULATORY BEHAVIOR, EXPRESSED AS NUMBER OF COUNTS PER 10 MIN TEST, AFTER THE ADMINISTRATION OF 8-OH-DPAT (0.125, 0.5, AND 0.75 mg/kg) TO OVARIECTOMIZED OR 7-DAY LACTATING MOTHER RATS

Treatment		n	Mean Counts ± SE
	Ovariectomized		
Saline		22	509 ± 31
8-OH-DPAT	0.125	8	479 ± 36
(mg/kg)	0.5	15	561 ± 23
	0.75	14	349 ± 22*
		ANOVA, $F = 8.630, p < 0.001$	
	7-Day Lactating Mother Rats		
Saline		9	491 ± 61
8-OH-DPAT	0.125	11	466 ± 45
(mg/kg)	0.5	12	506 ± 42
	0.75	14	451 ± 38
		ANOVA, $F = 0.310, p > 0.05$	

All experimental groups of ovariectomized rats were statistically compared with their respective saline control group using the Duncan's test (45). *$p < 0.05$.

counts was found after the highest dose particularly in ovariectomized rats. On this basis, a one-way analysis of variance was performed for each endocrine condition. These analyses are shown in Table 2. Clearly, in ovariectomized rats was the highest dose-impaired motor activity.

DISCUSSION

This report shows that the actions here registered of 8-OH-DPAT in ovariectomized rats were blocked in lactating animals. Thus, the antianxiety effects of this serotonergic compound, in ovariectomized rats, evidenced by three different parameters: cumulative burying behavior, time spent freezing, and the number of times the lines were crossed, were completely absent in 7-day lactating rats. Additionally, the number of fecal bolus registered during the test was diminished only in ovariectomized animals. Furthermore, even the unspecific motor drug effects were blocked in lactating rats because the reduction in ambulatory behavior produced by the highest dose of 8-OH-DPAT (0.75 mg/kg) was exclusive of ovariectomized subjects.

In the present and in a previous report (35) it was demonstrated that anxiety, as tested in the burying behavior test, does not vary along active lactation. These results differ from those obtained by other authors (18,19,23). These discrepancies could rely upon several factors, including the time of testing during lactation and the presence of the litter. Regarding the former, it is worth mentioning that we (35) and others (22) found a reduction in anxiety the day after delivery that apparently did not last for 1 week. In relation to the latter, it should be noted that in all our experiments, the litter was separated approximately 3 h before exposing the mother rat to the anxiety tests used. Hard and Hansen in 1985 (23) demonstrated that the litter withdrawal increases drastically the freezing behavior, while setting of the young produces the opposite effect. In the same line, Ferreira et al. (18) showed a reduced anxiety in lactating rats using conflict tests; in these experiments, the released behavior was drastically potentiated by the presence of the offspring. One hypothesis proposed to understand the mechanism through which the litter reduces anxiety in lactating rats is via the stimulation of the gamma-aminobutyric acid (GABA) system. In this respect, Qureshi and Sodersten (39) have demonstrated that the presence of the progeny augments the GABA levels in the cerebrospinal fluid; conversely, a reduction in GABA is observed after the litter separation. Needless to mention, the complete analysis of the experimental anxiety levels along all the lactation period in the presence or absence of the offspring should be made.

Of special interest arises the finding showing that the anxiolytic actions of 8-OH-DPAT were completely absent in lactating females. Lactation is endocrinologically characterized by a rise in prolactin and oxytocin, accompanied by a very low secretion of steroid hormones (4). Although the influence of serotonin on prolactin release is well known (7,29,33), the effects of lactation on the serotonergic transmission has been poorly investigated. Regarding the last, some biochemical data indicate (32,34) that the suckling-induced prolactin release is accompanied by a rapid fall in hypothalamic 5-HT levels and a corresponding increase in its major metabolite 5-hydroxyindolacetic acid (5-HIAA). Additionally, it is important to consider that behavioral reports reveal that in this (15) and other animal models of anxiety (10,25,37), 8-OH-DPAT induces an anxiolytic response after the stimulation of presynaptic receptors located at the dorsal raphe nucleus, which is sequentially followed by a reduction in the release of 5-HT (8,24,27). These two lines, taken together, could explain the lack of effect of 8-OH-DPAT in lactating animals by assuming that in these rats the levels of 5-HT are already diminished by the action of prolactin; thus, it seems unlikely that the 5-HT_1A compound modifies the release of a depleted neurotransmitter. It is worth mentioning that up to date the possible role of prolactin in blocking some actions of 8-OH-DPAT remains only as a matter of speculation. Further experiments should be made to investigate whether the increase in peripheral prolactin levels and/or changes in the prolactinergic neurotransmission in brain areas related with anxiety could modify the effect of anxiolytic drugs.

The modulation of the action of 5-HT_1A compounds by hormones is a recent field of research; for example, it has been found that estradiol injection modifies the serotonin receptor density in the female brain (2), and more recently it was reported that estradiol, but not progesterone, reduces the sensitivity of 5-HT_1A receptors in the dorsal raphe nucleus (30). Additionally, the hyperphagic and inhibitory effect on lordosis by 5-HT_1A agents, acting at presynaptic level, appear to be strongly influenced by estrogens. Thus, estrogen is reported to diminish the hyperphagia and the potency in inhibiting lordosis behavior induced by 8-OH-DPAT (11,28,42). For explaining the present results the interaction between estrogens and the serotonergic system does not seems plausible because during lactation there is a tonic and very low secretion of steroid hormones (4). Lactation is characterized by a complex endocrine profile; therefore, the role of other hormones on anxiety modulation should not be disregarded.

From present results it could be proposed that higher doses of 8-OH-DPAT should be required in lactating rats to produce similar anxiolytic responses than those observed in ovariectomized subjects. This, however, does not appear to be the case because the highest dose of this serotonergic agonist (0.75 mg/kg) produced in ovariectomized rats a clear reduction in burying behavior, accompanied by a decreased ambulation. Both effects of this dose were absent in lactating animals. Additionally, the clear effects of 0.5 mg/kg of 8-OH-DPAT on defecation and exploratory activity—also suggesting an anxiolytic effect—were only found in ovariectomized rats. All

these data, taken together, indicate that lactation blocks the effects of 8-OH-DPAT on the expression of various behaviors.

Present results showing that 8-OH-DPAT vary in their anxiolytic action depending upon lactation further supports the idea that the physiological conditions may affect the behavior after the drugs administration.

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