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Inhibitory Effect of Buspirone and Diazepam, but not of 8-OH-DPAT, on Maternal Behavior and Aggression

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FERREIRA, A., O. PICAZO, N. URIARTE, M. PEREIRA AND A. FERNÁNDEZ-GUASTI. *Inhibitory effect of buspirone and diazepam, but not of 8-OH-DPAT, on maternal behavior and aggression.* PHARMACOL BIOCHEM BEHAV **66**(2) 389–396, 2000.—The action of diazepam (0.0, 1.0, and 2.0 mg/kg) and the serotonergic compounds buspirone (0.0, 2.5, and 5.0 mg/kg) and 8-OH-DPAT (0.0, 0.1, and 1.0 mg/kg) on maternal behavior and aggression were studied. An activity test was made after these treatments to control for unspecific actions due to motor impairment. Diazepam and buspirone dose-dependently inhibited the expression of maternal aggression and the active components of maternal behavior such as retrieving and nest building. 8-OH-DPAT did not affect these behaviors. 8-OH-DPAT (1.0 mg/kg) provoked the serotonergic syndrome and hypothermia; however, ovariectomized animals showed more signs of the syndrome and a decrease in body temperature after 8-OH-DPAT than lactating rats. Buspirone, but not the other anxiolytics, reduced motor activity. The role of drugs acting at the serotonergic, dopaminergic, and GABA-benzodiazepine systems in the control of maternal behavior and aggression is discussed. © 2000 Elsevier Science Inc.

Diazepam Buspirone 8-OH-DPAT Maternal behavior Maternal aggression

IMMEDIATELY after parturition the mother rat develops a series of responses characterized by retrieving, licking, sniffing, and nursing of the newborn accompanied by nest building (39). In addition to these behaviors, dams show less fear and reduced anxiety (17,18,27) as well as an increased aggression towards intruders (11,12,23,35). The triggering clue in the display of these behaviors includes the hormonal changes during parturition followed by sensory stimuli produced by the litter (39).

In the neural control of maternal behavior and aggression, several neurotransmitters, including the GABA-benzodiazepine and serotonergic systems, have been implicated. Thus Qureshi et al. (38) reported an elevation in GABA levels in cerebrospinal fluid of rats during lactation that depends on the presence of the offspring. This neurotransmitter system dissimilarly regulates maternal aggression because at low doses some benzodiazepines enhance this behavior whereas at higher concentrations these compounds consistently inhibit this form of aggression (8,33). In the serotonergic control of maternal behavior controversial results were obtained by Barofsky and coworkers (1,2). Thus electrolytic lesions of the median raphé nucleus, performed before parturition, did not affect maternal behavior (1), whereas neurotoxic lesions (with 5,7 dihydroxytryptamine) of this brain area drastically impaired this behavior (2). Additionally, it is generally accepted that the expression of maternal aggression is inversely related to the activation of the serotonergic system (32). Consequently, the 5-HT_{1A} agonists 8-hydroxy-2(di-*n*-propylamino) tetralin (8-OH-DPAT), buspirone, and ipsapirone reduce maternal aggression (32).

Most of the data indicate that the stimulation of either 5-HT_{1A} and GABA-benzodiazepine-receptors produce clear anxiolytic-like responses (10,20,21). However, variations in such responses depend on the endocrine status of the female (3,4,15,44). Thus recently we demonstrated that the systemic injection of diazepam to lactating female rats reduced experi-

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mental anxiety (13), whereas administration of the serotonergic full agonist 8-OH-DPAT completely lacked anxiolytic-like effects (16). Furthermore, buspirone, a partial $5HT_{1A}$ agonist, reduced anxiety but also general ambulation (13). In conclusion, these data suggest that some behavioral effects of 8-OH-DPAT, but not those of diazepam and buspirone, are absent in lactating rats.

The purpose of the present study was to analyze if the anxiolytics with different chemical structure and profile: buspirone, 8-OH-DPAT, and diazepam differentially affect the maternal behavior and aggression of lactating rats. To control for behavioral effects due to motor impairment in an independent group of rats the general activity was analyzed after these treatments.

On the basis that 8-OH-DPAT completely lacked an effect on maternal behavior and aggression, we analyzed if other well-established effects of this drug were also absent in lactating rats. A series of specific behavioral features, named the serotonergic syndrome, and the reduction in core body temperature or hypothermia are general effects induced by a variety of 5-HT agonists that increase serotonergic activity, including 8-OH-DPAT (36). Therefore, in another series of experiments, it was studied whether 8-OH-DPAT produces differential effects—between ovariectomized and lactating rats—on the serotonergic syndrome and hypothermia.

METHOD

Animals

Female and male Wistar rats 250–350 g body weight were used in this study. All animals were housed in a room under inverted 12 h light-dark cycle conditions (lights on at 2200 h) with ad libitum access to water and Purina Rat Chow all over the experiments. Females were mated with sexually active studs and individually caged when pregnant. These animals were daily checked for delivery, and that day was numbered as day 1. Thereafter the animals were maintained with their pups (adjusted to six on the delivery day) until day 8th of lactation. Throughout the sawdust was not changed.

For the control groups studying a possible differential effect of serotonergic compounds on the serotonergic syndrome and hypothermia, virgin female rats were ovariectomized through a ventral incision under anesthesia (pentobarbital, 35 mg/kg intraperitoneally [IP]). Animals were tested 10 days after the ovariectomy.

Procedure

Two to three hours after lights off, dams were injected with either diazepam (0.0, 1.0, and 2.0 mg/kg, Hoffman La-Roche, Basel, Switzerland), buspirone (0.0, 2.5, and 5.0 mg/kg, Sigma Chemicals, St. Louis, MO, USA), or 8-OH-DPAT (0.0, 0.1, and 1.0 mg/kg, Biochemical Research, Natick, MA, USA). All drugs were IP injected in a volume of 2.0 ml/kg. Buspirone and 8-OH-DPAT were dissolved in physiologic saline and administered 20 min before the tests. Diazepam was dissolved in propylene glycol (40%) and tests made 30 min after its injection. All groups consisted of 8 to 10 animals.

Maternal Behavior Test

This test lasted 5 min and was carried out in the home cage under dim red light. The observation began by removing the pups from the cage. Thereafter three pups were dispersed in the area opposite to the nest side. The time (in seconds) taken for the mother to retrieve the first pup to the nest was measure and termed retrieving latency. The number of retrievings, lickings, sniffings, and suckling postures or crouchings over the 5 min test were also counted. When the mother remained in crouching posture continuously, a positive score for this behavior was registered every 10 sec. The presence or absence of nest building was also recorded (39).

Maternal Aggression Test

Immediately after the maternal behavior test, the animal aggressiveness towards conspecifics was assessed using a procedure similar to that described by Erskine et al. (11,12). The observation (5 min) was carried out under dim red light. A male rat (350 g) was placed in the female's cage, in the presence of all six pups, and the frequencies of the following behavior patterns recorded: attack (female lunges towards the male, sometimes followed by rolling and scuffing for a brief period); bite (female mouth in contact with the intruder body and the male vocalizes); lateral posture (female approaches male sideways, but presenting the lateral aspect of her body

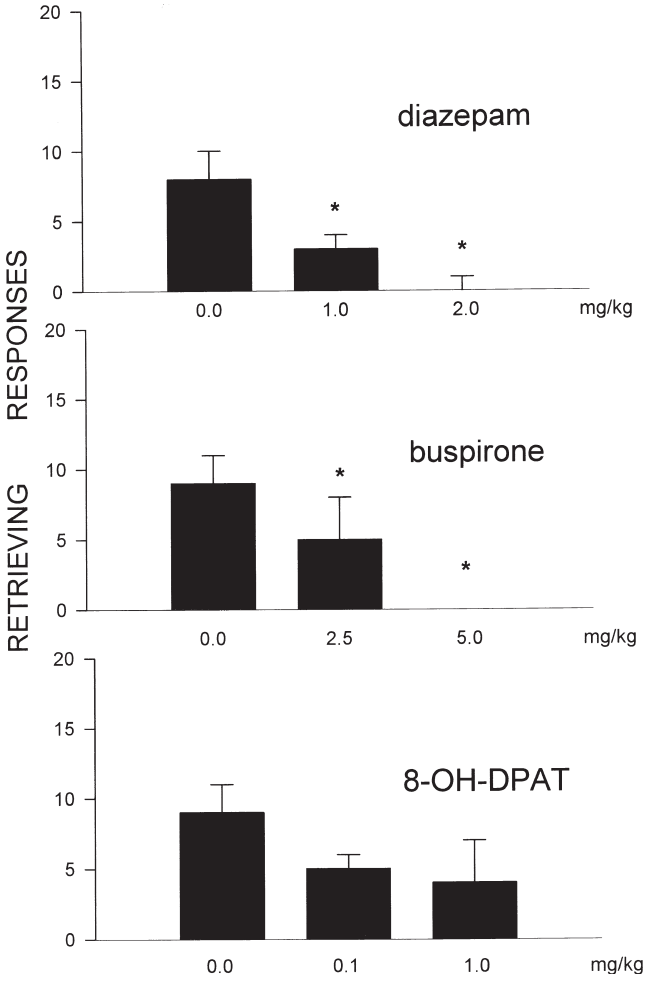

FIG. 1. Maternal behavior (total number of retrievings in a 5–min test) in lactating rats that received several doses of diazepam, buspirone, or 8–OH-DPAT. The figure shows the median ± semi-interquartile range of 8–10 values. Data were statistically analyzed by the Kruskal Wallis analysis of variance followed by the Mann Whitney *U* test, $*p < 0.05$.

TABLE 1

SOME COMPONENTS OF RAT'S MATERNAL BEHAVIOR FOLLOWING DIAZEPAM, BUSPIRONE, OR 8-OH-DPAT

	Retrieving Latency	Licking	Sniffing	Suckling	Nest Building
Diazepam (mg/kg)					
0.0	5.0 ± 4.0	1.0 ± 1.0	1.0 ± 1.0	2.0 ± 1.0	7/10
1.0	16.0 ± 10.0*	1.0 ± 1.0	1.1 ± 1.0	2.0 ± 2.0	2/10*
2.0	300.0 ± 124*	0.0 ± 1.0	2.0 ± 1.0	1.1 ± 1.1	1/10*
H	11.3	0.6	3.4	1.3	
p<	0.01	NS	NS	NS	0.01
Buspirone (mg/kg)					
0.0	7.0 ± 4.0	1.0 ± 1.0	1.0 ± 1.0	1.0 ± 1.0	8/8
2.5	20.0 ± 31.0*	1.0 ± 1.0	2.0 ± 1.0	1.0 ± 0.0	3/8*
5.0	300.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0*	3/7*
H	15.1	8.4	6.9	1.1	
p<	0.001	0.001	0.05	NS	0.01
8-OH-DPAT					
0.0	7.0 ± 6.0	4.1 ± 1.0	2.0 ± 0.0	3.0 ± 1.0	8/9
1.0	20.0 ± 6.0	3.0 ± 3.0	1.0 ± 1.0	4.0 ± 1.0	5/9
1.0	4.0 ± 1.0	4.0 ± 2.0	1.0 ± 0.0	1.0 ± 1.0	8/9
H	5.8	0.2	4.0	5.9	
p=	NS	NS	NS	NS	NS

Table shows the medians ± semi-interquartile ranges of 8-10 rats. Data were analyzed by the Kruskal-Wallis analysis of variance (H) and the Mann-Whitney U-test. Nest building was analyzed by the chi square test.

towards him); kick (with rear leg); and boxing (both rats facing one another while standing upright on rear legs; typically accompanied by the female striking with forepaws at the male's face). The number of times the intruder male adopted an upright subordinate posture (sitting on haunches, curved back, forepaws at the female's face) was also recorded. The stimulus males were never used more than once on a particular testing day (35).

Activity Test

For controlling changes in maternal behavior or aggression due to alterations in motor activity, the rats were evaluated for ambulation 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, USA). The number of counts over a 10 min session were recorded and the cage carefully cleaned with tap water after each test. To prevent effects of one paradigm on another, independent groups of animals were used for this test.

Serotonergic Syndrome

Five minutes before an IP injection of 8-OH-DPAT (0.0, 0.1, and 1.0 mg/kg), rats were placed in individual clear Plexiglas cages with a layer of sawdust covering the bottom. Immediately after observation periods of 45 sec per rat were initiated. Observations were repeated every 5 min for 40 min post-injection. The following components were registered: forepaw treading, flattened body posture, hind limb abduction, straub tail, and tremor. A 4-point ranked intensity scale was used (0=absent, 1=equivocal, 2=definite and 3= intensive) (41).

Body Temperature

Core temperature was measured by inserting the probe of a digital thermometer approximately 2.5 cm into the rectum, immediately before, and then 20 and 40 min after the IP injection of 8-OH-DPAT (0.0, 0.1, and 1.0 mg/kg) (5).

Statistical Analysis

Most of the data were statistically analyzed by the Kruskal Wallis analysis of variance followed by the Mann Whitney *U* test. The presence or absence of nest building was analyzed by means of the chi square test (42). The serotonergic syndrome and the body temperature were statistically analyzed using a two way ANOVA considering: 1) condition: ovariectomized or lactating, 2) drug-dose-treatment and time, and 3) the possible interactions between these factors. Post hoc comparisons were made by the Newman-Keuls test for a $p < 0.05$ (43).

RESULTS

The results of diazepam, buspirone, and 8-OH-DPAT on maternal behavior are shown in Fig. 1 and Table 1. Diazepam produced a dose-dependent increase in retrieving latency and a drastic decrease in the number of retrievings ($H = 17$, $p < 0.001$) (Fig. 1) and nest building (Table 1). Other components of maternal behavior (lickings, sniffings, and suckling postures) were unmodified after diazepam injection. Similar results were obtained after buspirone administration (Table 1). This drug treatment significantly reduced the number of retrievings ($H = 16.8$, $p < 0.001$) (Fig. 1) and nest building (Table 1) and increased the retrieving latency. Crouching was unaffected by this drug. By contrast with diazepam, buspirone, at the highest dose (5.0 mg/kg), inhibited the licking behavior. Interestingly, 8-OH-DPAT did not modify any parameter of maternal behavior (Fig. 1 and Table 1).

Fig. 2 shows that maternal aggression (sum of attacks, lateral postures, and bites) was significantly decreased after treatment with diazepam ($H = 14.2$, $p < 0.001$). The latency to the first aggressive behavior was significantly increased af-

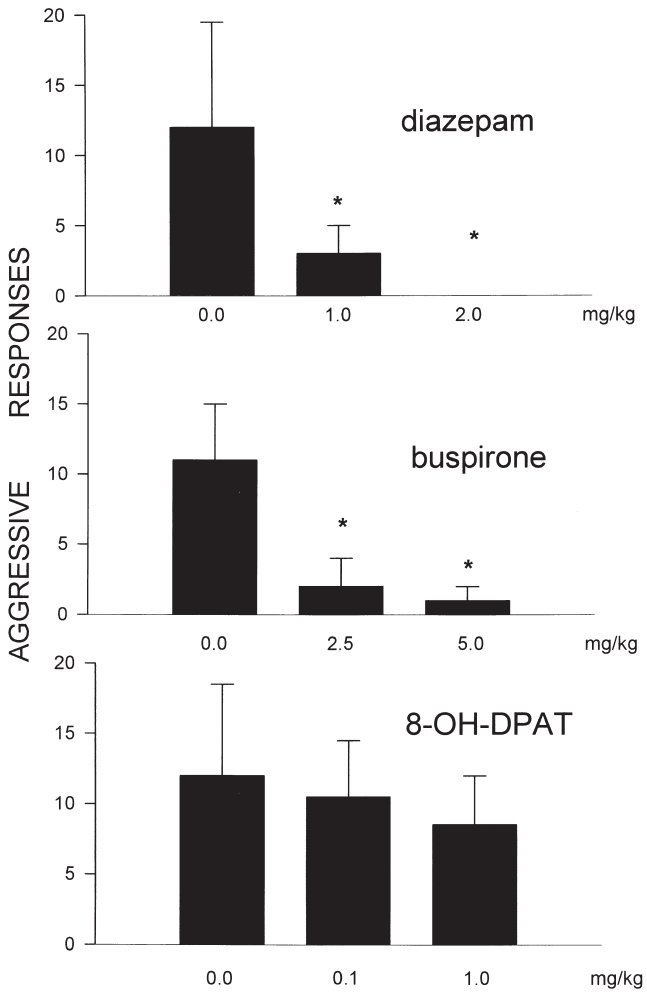

FIG. 2. Effect of various doses of diazepam, buspirone, or 8-OH-DPAT on the number of aggressive responses (sum of attacks, bites, and lateral postures, for detailed description see text) displayed by lactating females. The figure shows the median ± semi-interquartile range of 8–10 values. Data were statistically analyzed by the Kruskal Wallis analysis of variance followed by the Mann Whitney U test, * $p < 0.05$.

ter this treatment. The male submissive behavior consequently decreased and the latency to the first submission posture increased due to the low female aggressiveness (Table 2). Buspirone, at both doses, significantly reduced maternal aggression ($H = 14.0$, $p < 0.001$) (Fig. 2) and most of the female aggressive behaviors (Table 2). The latency to the first aggressive female attack was significantly increased with both doses of buspirone (2.5 and 5.0 mg/kg). The male submission postures were also significantly reduced, and the latency to this behavior increased after buspirone treatment to the lactating female. As occurred for maternal behavior, 8-OH-DPAT (0.1 and 1.0 mg/kg) administration did not affect aggressive female responses (Fig. 2 and Table 2) or the male submission postures (Table 2).

Fig. 3 shows the effect of buspirone, diazepam, and 8-OH-DPAT on ambulatory behavior. Buspirone dose-dependently reduced motor activity ($H = 17.3$, $p < 0.001$) in lactating rats. A lower dose of buspirone (1.25 mg/kg) also reduced the ambulatory activity of lactating rats (data not shown). Diazepam and 8-OH-DPAT, at these doses, did not affect the number of counts.

Table 3 shows the effect of 8-OH-DPAT on individual components of the 5-HT syndrome. The ANOVA revealed statistical significant differences for hind limb abduction (condition: $F(1, 25) = 12.69$, $p < 0.05$; doses: $F(2, 25) = 54.65$, $p < 0.05$; interaction: $F(2, 25) = 7.38$, $p < 0.05$), flattened body posture (condition: $F(1, 25) = 27.89$, $p < 0.05$; doses: $F(2, 25) = 30.84$, $p < 0.05$; interaction: $F(2, 25) = 10.62$, $p < 0.05$), straub tail (condition: $F(1, 25) = 12.06$, $p < 0.05$; doses: $F(2, 25) = 7.53$, $p < 0.05$; interaction: $F(2, 25) = 8.29$, $p < 0.05$) and tremor (condition: $F(1, 25) = 256.0$, $p < 0.05$; doses: $F(2, 25) = 170.19$, $p < 0.05$; interaction: $F(2, 25) = 190.19$, $p < 0.05$). Clearly, 8-OH-DPAT produced a clear dose-dependent induction of these behavior that was much more intense in ovariectomized than in lactating female rats (as revealed by the interaction values of the ANOVA).

The differential effects of 8-OH-DPAT on body temperature in ovariectomized and lactating rats are shown in Table 4. This drug produced a clear dose-dependent hypothermia in ovariectomized rats that was absent in lactating rats. Thus the ANOVA revealed statistical significant differences in core temperature (condition: $F(1, 60) = 40.86$, $p < 0.05$; dose: $F(1, 60) = 227.73$, $p < 0.05$; interaction: $F(1, 60) = 210.84$, $p < 0.05$).

DISCUSSION

The present results summarized that diazepam and buspirone disrupted the active components of maternal behavior (retrieving and nest building) and maternal aggression. Buspirone, but not diazepam, inhibited motor activity. By contrast with these anxiolytics, 8-OH-DPAT did not affect any of these parameters. Additionally, this drug induced an intense 5-HT syndrome and hypothermia in ovariectomized rats but not in lactating animals.

The observed data showed that diazepam impairs some components of maternal behavior. This finding, together with those of D'Amarato et al. (6) indicate that benzodiazepines inhibit maternal behavior. Hansen et al. (24) firstly proposed that some behavioral changes that characterize the lactating female such as the increased aggression, the reduced fearfulness and anxiety, hyperphagia, and maternal behavior, could be underlyed by an increase in the GABA-benzodiazepine neurotransmission. In addition, elevated GABA levels (38) accompanied by higher receptor sensitivity (30) during post partum has been reported. After several experiments (23,31), however, it is clear that the augmented GABAergic neurotransmission during this period does not participate in the control of maternal behavior itself but rather seems to regulate other behaviors characteristic of puerperium such as the reduced anxiety and the increased aggression. Indeed, the repeated administration of diazepam does not accelerate the onset of maternal behavior in virgin female rats constantly exposed to pups (sensitization procedure) (Ferreira and Hansen, unpublished observations). The inhibition of some components of the maternal behavior after benzodiazepines cannot be explained on the basis of motor impairments because clear maternal inhibitory effects were found without actions on general activity. All these data, taken together, support a differential regulation of this neurotransmitter system during lactation.

Present results show that diazepam dose-dependently reduced maternal aggression. This finding is in line with data illustrating antiaggressive actions of benzodiazepines administered to lactating rats (31,33). These authors, however,

TABLE 2

EFFECT OF DIAZEPAM, BUSPIRONE AND 8-OH-DPAT ON THE FREQUENCY AND LATENCY TO SOME AGGRESSIVE RESPONSES DISPLAYED BY LACTATING RATS AS WELL AS THE NUMBER AND LATENCY OF SUBORDINATE POSTURES OF THE MALE INTRUDERS

	Aggresive Latency	Attack	Lateral Posture	Bite	Boxing	Submission Latency	Submission
DIAZEPAM (mg/kg)							
0.0	40.5 ± 10.9	7.0 ± 4.0	1 ± 1.5	3.0 ± 2.0	4.0 ± 2.0	60.0 ± 14.0	9.0 ± 4.5
1.0	72.0 ± 50.0	1.0 ± 1.5*	0.0 ± 1.0	1.0 ± 1.0	1.0 ± 1.0	60.0 ± 8.0	3.0 ± 0.0
2.0	300.0 ± 119.5*	0.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0*	300.0 ± 0.0	0.0 ± 0.5*
H	8.4	13.4	7	13.4	13.6	4.8	13.8
p <	0.05	0.001	0.001	0.001	0.01	NS	0.001
BUSPIRONE (mg/kg)							
0	40.5 ± 10.9	7.0 ± 2.5	2.0 ± 1.0	3.0 ± 1.5	0.0 ± 0.0	40.5 ± 8.7	11.5 ± 2.7
2.5	80.0 ± 134.5*	1.0 ± 1.0*	1.0 ± 0.5*	0.0 ± 0.5*	0.0 ± 2.0	56.0 ± 98.5	4.0 ± 2.0*
5.0	212.0 ± 79.0*	0.0 ± 0.5*	1 ± 0.5*	0.0 ± 0.0*	0.0 ± 0.0	300.0 ± 0.0*	0.0 ± 0.0*
H	9.9	1.4	5.96	15.4	3.3	12.0	16.0
p <	0.01	0.01	0.01	0.001	NS	0.001	0.001
8-OH-DPAT (mg/kg)							
0	46.0 ± 27.7	8.5 ± 4.1	2.0 ± 1.2	2.0 ± 2.0	0.0 ± 0.5	46.0 ± 21.0	9.0 ± 4.0
0.1	48.5 ± 16.4	5.0 ± 1.7	4.0 ± 1.7	2.5 ± 1.2	0.0 ± 2.1	71.0 ± 35.0	1.5 ± 3.6
1.0	42.0 ± 17.0	3.0 ± 0.7	1.0 ± 1.0	3.0 ± 2.5	0.5 ± 1.0	27.0 ± 19.0	5.5 ± 1.6
H	0.2	2.8	8.14	1.47	0.8199	1.0	3.14
p =	NS	NS	NS	NS	NS	NS	NS

Data are expresed as medians ± semi-interquartile ranges of 8–10 rats. Data were compared by the Kruskal-Wallis analysis of variance and the Mann-Whitney *U*-test.

suggested a biphasic role of benzodiazepines on maternal aggression (33) by showing that low doses of chlordiazepoxide increased aggression by provoking a desinhibition in the female's behavior towards an aversive intruder, whereas high doses directly inhibit the expression of this behavior. The present results demonstrating inhibitory actions of diazepam could be explained on the use of two relatively high doses that, however, lacked motor actions.

Buspirone has been pharmacologically characterized as a partial 5-HT_{1A} agonist with dopaminergic antagonistic properties (9,28). The inhibitory actions of buspirone on the active components of maternal behavior such as retrieving, nest building, and licking, could be interpreted on its dopaminergic antagonistic activity since full 5-HT agonists most likely lack an action (*vide infra*). It has been suggested that the mesolimbic dopaminergic system is involved in the activational impact of pups' stimuli by facilitating locomotor excitement, as well as more specific appetitive behaviors such as retrieving (22). In addition, several reports indicate that lactating rats treated with the dopaminergic antagonists, haloperidol (19), or with dopaminergic neurotoxins (22,25,26) inhibit the active components of maternal behavior similarly as buspirone. All these results, together with the finding that apomorphine reverses the inhibition in care activities provoked by haloperidol (19,29), indicate that specifically the dopamine antagonism inhibits the active components of the maternal behavior. Further experiments designed to counteract the inhibitory action of buspirone with apomorphine or other dopaminergic agents should be undertaken to experimentally confirm the idea of this drug acting via this neurotransmitter system.

In line with others results (32), treatment with buspirone reduced maternal aggression and decreased ambulatory activity. As previously mentioned, most studies suggested that 5-HT is inhibitory for aggression. Thus decreasing the serotonergic neurotransmission by lesions of specific brain areas, dietary manipulations, or administration of 5-HT antagonists enhance aggression (32). Buspirone is a partial agonist of $5HT_{1A}$ with primarily postsynaptic actions (14). Thus the observed inhibitory effect of buspirone on aggression may be explained by an enhanced serotonergic transmission.

The effect of buspirone on motor activity (32, present data) suggest that its inhibitory actions on maternal aggression, and probably maternal behavior, may be unspecific. In this line, we recently reported on a higher sensitivity of lactating females to the motor actions of buspirone (13). Thus even lower doses of buspirone (1.25 mg/kg) than those here used reduced ambulation in lactating rats without affecting other behavioral effects such as burying behavior. A nonexclusive interpretation to the antiaggressive action and the impaired motor activity of buspirone could include a similar hypothesis to that stated for its maternal behavior effects: the antagonism of the dopaminergic transmission. In agreement, Oliver et al. (33) reported that haloperidol has antiaggressive actions on maternal rats.

The present result showing that the 5-HT_{1A} full agonist 8-OH-DPAT completely lacked an action on maternal behavior confirm the observations of De Almeida and Lucion (7) and suggests that serotonin, at least via this receptor subtype, is not involved in the control of this behavior. Other authors, by contrast with present observations, found that 8-OH-DPAT may reduce maternal aggression and general motor activity (32). Such effects are indicative of a nonspecific antiaggressive drug profile. Albeit 8-OH-DPAT induces some behavioral actions in maternal rats, it is interesting to note that in the mentioned report, the motor activity of maternal females is much less affected when compared with that observed in males after a similar treatment. This finding further indicates a differential drug effect depending on the sex and endocrine condition of the female.

Interestingly, present and previous (16) data show that 8-OH-DPAT produces a clear effect on anxiety (as tested in two paradigms), motor activity, hypothermia, and the sero-

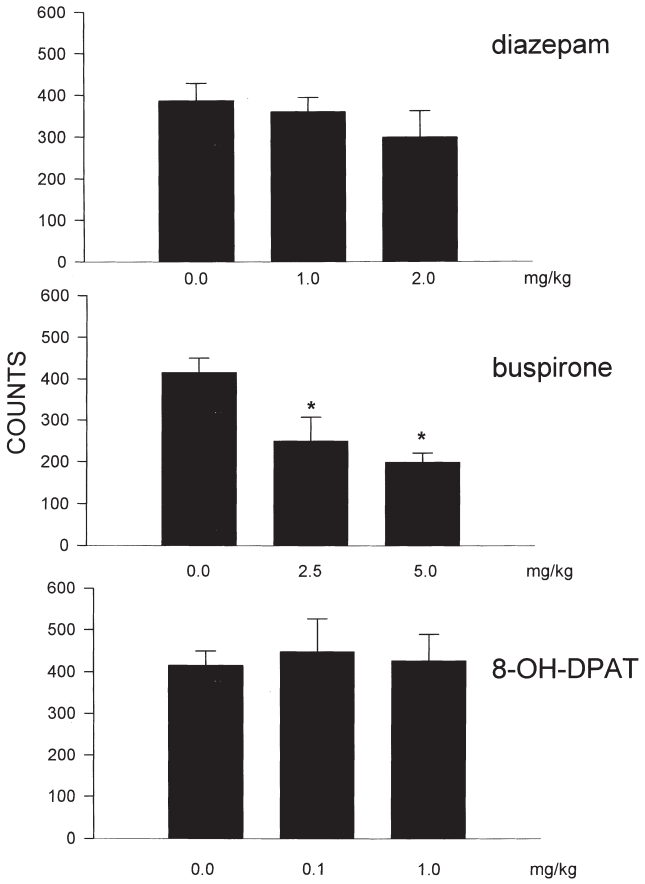

FIG. 3. Effect of various doses of diazepam, buspirone or 8-OH-DPAT on the ambulatory behavior (expressed as number of counts in a 10-min test) of lactating rats. The figure shows the median ± semi-interquartile range of 8–10 values. Data were statistically analyzed by the Kruskal Wallis analysis of variance followed by the Mann Whitney *U* test, * $p < 0.05$.

tonergic syndrome in ovariectomized but not in lactating females. In addition, the lactating female is also insensitive to the actions of 8-OH-DPAT on maternal behavior and aggression. The mechanisms underlying the lack of effects of 8-OH-DPAT during postpartum are unknown. However, some hypotheses might be suggested: 8-OH-DPAT is a full agonist and may activate both pre- and post-synaptic receptors. The effect of a $5HT_{1A}$ agonist on somatodendritic autoreceptors would inhibit the discharge of the serotonergic neurons, whereas the stimulation of postsynaptic $5HT_{1A}$ receptors would mimic the endogenous effects of 5-HT on target neurons. These neuropharmacologic actions—possibly of similar intensity in lactating rats—result in opposite effects that may cancel each other (34,40). Another possibility includes that either the number or the sensitivity of the serotonergic receptors affected by 8-OH-DPAT are diminished in lactating animals. In support of this idea is the finding that ovariectomized rats showed a more pronounced 5-HT syndrome and hypothermia than lactating females after 8-OH-DPAT injection. However, in order to fully sustain this idea, the $5HT_{1A}$ receptors should be directly evaluated in lactating females. A third possibility, posed previously (16), is that the levels of serotonin are reduced by a putative long lasting effect of prolactin, seeming unlikely that 8-OH-DPAT modify the release of an already depleted neurotransmitter. To confirm this hypothesis we aim to measure the levels of serotonin in mother and ovariectomized animals.

Recently, we found that the expression of maternal behavior does not interfere with the drug action because clear anxiolytic behavioral effects of 8-OH-DPAT were observed in rats rendered maternal by the sensitization procedure (37). Additionally, it has also been demonstrated that neither the endocrine process that accompany lactation nor the sensory clues produced by the young are the causes for the lack of effect of 8-OH-DPAT. Thus mother rats separated from their offspring for long periods remain insensitive to the antianxiety actions of this drug (37).

The present series of results show that lactating females are in-

TABLE 4

EFFECT OF THE ADMINISTRATION OF 8-OH-DPAT ON BODY TEMPERATURE (°C) IN OVARIECTOMIZED AND LACTATING RATS 20 MIN POST-INJECTION

Doses	0.0 mg/kg	0.1 mg/kg	1.0 mg/kg
Ovariectomized	39.3 ± 0.4	38.9 ± 0.1	34.8 ± 0.6*#
Lactating	38.2 ± 0.1	38.0 ± 0.3	37.9 ± 0.3#

Data are expressed as means ± SE of 6 rats per condition.
*$p < 0.05$ between different doses under the same condition.
#$p < 0.05$ between different conditions at the same dose.

TABLE 3

SEROTONERGIC SYNDROME COMPONENTS INDUCED BY 8-OH-DPAT IN OVARIECTOMIZED AND LACTATING RATS

	Forepaw Treading	Hindlimb Abduction	Flattened Body	Straub Tail	Tremor
Ovariectomized (mg/kg)					
0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
0.1	0.0 ± 0.0	1.0 ± 1.0	5.0 ± 2.1*	1.0 ± 0.5	0.6 ± 0.1
1.0	0.5 ± 0.5	8.0 ± 2.9*	14.7 ± 2.0*#	5.2 ± 1.7*#	10.5 ± 3.2*#
Lactating (mg/kg)					
0.0	0.0 ± 0.0	0.0 ± 0 .0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
0.1	0.3 ± 0.3	0.6 ± 0.3	2.3 ± 0.9	1.0 ± 0.0	0.0 ± 0.0
1.0	0.0 ± 0.0	5.3 ± 0.3*	3.6 ± 0.3#	1.0 ± 1.0#	0.0 ± 0.0#

Data are expressed as mean ± SE of a ranked intensity scale (see Method).
*$p < 0.05$ between different doses under the same condition.
#$p < 0.05$ between different conditions at the same dose.

sensitive to the actions of 8-OH-DPAT on maternal behavior and aggression, the serotonin syndrome, and hypothermia. Conversely, buspirone and diazepam produce clear inhibitory actions on maternal behavior and aggression. These drug differences seem to be underlyed by their pharmacologic characteristics.

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