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Effects of dopamine receptor antagonists on ongoing maternal behavior in rats

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Abstract

The effects of different peripheral doses of four dopamine (DA) receptor antagonists on general activity and maternal behavior were examined in lactating female rats. Administration of the classic D1-like and D2-like DA receptor blocker haloperidol (0.1 and 0.05 mg/kg) disrupted pup retrieval and nest-building behaviors and reduced motor activity. Pimozide (0.5 and 0.2 mg/kg), which has more affinity for DA D2-like receptors, mildly disrupted pup retrieval while showing no significant influence on open-field behaviors. The putative DA D_4 receptor blocker, clozapine (1.5 and 1.0 mg/kg) reduced motor activity significantly, while only 1.0 mg/kg dose significantly decreased percent of rats displaying nest building. The DA D1-like receptor blocker SKF-83566 (0.2 and 0.1 mg/kg) significantly reduced pup retrieval, nest building and motor activity. These results suggest a role for DA receptors in ongoing maternal behavior that correlates directly with general activity.

Keywords: Neuroleptic; Antipsychotic; Haloperidol; Pimozide; SKF-83566; Clozapine

1. Introduction

The regulation of maternal behavior in rat occurs in two phases (Numan, 1994). The natural onset of maternal behavior occurs at parturition, and is controlled by several pregnancy-related hormones (estrogen, progesterone, prolactin and oxytocin). The maintenance phase of maternal behavior occurs during the postpartum period, and is controlled primarily by nonhormonal factors (i.e., the multisensory stimuli provided by pups).

Researchers have shown that dopamine (DA) is involved in both the onset and maintenance of maternal care (Bridges, 1996; Bridges et al., 1985; Bridges et al., 1990; Broadhurst, 1957; Castner et al., 1993; Clarke-Hall et al., 1995; Hansen, 1994; Hansen et al., 1991a,b; Hecht et al., 1999; Levy et al., 1999; Lonstein et al., 1998; Stern and Taylor, 1991). Lesion studies suggest that DA neurons innervating the nucleus accumbens may be particularly important for locomotor aspects of maternal behavior, for example, the pup retrieval response (Hansen et al., 1991a,b). On the other hand, lesions in caudate–putamen (dorsal striatum) were without effect on both the onset and maintenance of maternal behavior (Hansen et al., 1991a). The mesolimbic dopaminergic system is involved in motivational processes, such as reward and reinforcement (Keer and Stern, 1999a; McCullough et al., 1993). Reinforcing stimuli, such as exposing maternal dams to pups, induce DA release in the nucleus accumbens and dorsal striatum (Fleming et al., 1994; Hansen et al., 1993).

There are two pharmacologically distinct DA receptor families, D1-like and D2-like (Seeman, 1980). Those receptors are at least five different proteins: D_1 and D_5 are subtypes of the D1, while D_2, D_3 and D_4 are subtypes of D2 receptors (Sokoloff and Schwartz, 1995). While it is possible to differentiate between the two subfamilies of DA receptors, the different members within each subfamily cannot be distinguished by pharmaceutical means. Subcutaneous injections of haloperidol, a D2-like and D1-like DA receptor antagonist, into lactating female abolishes licking, nest building and pup retrieval (Giordano et al., 1990; Stern and Taylor, 1991).

Several lines of evidence indicate that hormones prominent during pregnancy, such as prolactin, cholecystokinin and estrogen, have influence on the dopaminergic system (Bazzett

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and Becker, 1994; Castner et al., 1993; Tieppo et al., 2000). Acute central prolactin injections increase, while chronic treatments with this hormone inhibit dopaminergic activity in rats (Cruz-Casallas et al., 1999). Cholecystokinin facilitates or inhibits dopaminergic transmission according to the brain region. In most situations, this peptide has a neuroleptic-like effect (Tieppo et al., 1995, 1997, 2000; Van Ree et al., 1983; Crawley, 1991). Antidopaminergic actions of estradiol have been reported in both clinical and experimental studies (Bedard et al., 1977; Ben-Jonathan, 1985; Dorce and Palermo-Neto, 1992). Since elevated prolactin levels decrease pup retrieval latencies (Bridges et al., 1990), it is possible that the endocrine actions of prolactin in the maternal virgin may be mediated through the stimulation of DA release (Bridges, 1996). In addition, since both estrogen and cholecystokinin are involved with induction and maintenance of maternal behavior, respectively, their behavioral action may be related to dopaminergic transmission (Felicio et al., 1991; Mann et al., 1995). On the other hand, locomotor activity requires synergistic activation of D1-like and D2-like DA receptors (Braun and Chase, 1986), therefore, it is possible that some motor components of maternal behavior might be mediated by concurrent stimulation of both families of DA receptors.

In this study, various doses of DA receptor antagonists with different affinity and specificity for DA receptor subtypes were used to assess their effects on ongoing maternal behavior in the rat. The drugs used were haloperidol, a mixed D1-like and D2-like DA receptor antagonist; pimozide, a D2-like receptor blocker; clozapine, an atypical D2-like antagonist, which displays greater affinity for the D_4 DA receptor over D_2 or D_3 (Baldessarini and Frankenburg, 1991) with effects on serotonin receptor (5HT1), and SKF-83566, a D1-like receptor antagonist. The comparative in vivo selectivity for these drugs for D1-like and D2-like receptors is as follows, D1-like: SKF-83566 > haloperidol>-clozapine>pimozide; D2-like: haloperidol>clozapine>pimozide>SKF-83566 (Schwartz et al., 1998). Since haloperidol (0.1 mg/kg) and pimozide (0.2 mg/kg) are considered clinically equivalent, this range of doses was used to compare the behavioral effects of the drugs. The experiments were designed to verify the effects of the drugs on motivational and motoric parameters, such as retrieval and nest-building behavior. The hypothesis that the drug effects on maternal behavior might occur simultaneously with an inhibitory effect on locomotion was tested in experiments where possible effects of these drugs on general activity in open field were also examined.

2. Methods

2.1. Subjects

The subjects were (232) nulliparous female rats from our own colony (Wistar origin, 200–250 g). At 90–100 days of age, they were bred by placing two females with a male of the same strain for 4 days.

2.2. Housing and maintenance

All animals were housed in polypropylene cage measuring $32 \times 40 \times 18$ cm, which contained wood shavings as bedding material. Food and water were available ad lib, and the animals were maintained under 12:12 h day/night cycle (lights on 06:00 AM) and under controlled temperature of $22 \pm 3°C$. At the end of pregnancy, the females were individually housed and allowed to give birth. Their neonates were culled to six pups the day after parturition. On the day before testing, each female was removed from her cage and weighed. No animal was submitted to more than one dose, drug treatment or behavioral test. Animals used in this study were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.3. Drugs

The following drugs were used: clozapine (1.0 and 1.5 mg/kg; RBI) and pimozide (0.1, 0.2 and 0.5 mg/kg; JANSSEN) dissolved in 0.5% lactic acid and in warmed 1% tartaric acid, respectively, and saline solutions of haloperidol (0.05 and 0.1 mg/kg; JANSSEN) and SKF-83566 (0.1 and 0.2 mg/kg; RBI). Drugs were administered 1.0 ml/kg s.c.

Table 1
Effects of haloperidol (0.05 and 0.1 mg/kg) or vehicle administration on LF and RF, and on ID in seconds, observed in the open field

	Parameters		
Groups	LF	RF	ID
30 min after injection			
Vehicle	104 (84–133)	17 (7–30)	2 (0–12)
Haloperidol (0.05 mg/kg)	51 (32–70)*	12 (4–21)*	43 (10–101)*
Haloperidol (0.1 mg/kg)	29 (19–37)*	5 (2–8)*	94 (54–114)*
60 min after injection			
Vehicle	84 (58–188)	16 (11–23)	11 (0–25)
Haloperidol (0.05 mg/kg)	40 (21–54)*	13 (6–23)	33 (6–78)*
Haloperidol (0.1 mg/kg)	20 (10–32)*	3 (0–12)*	87 (35–140)*
90 min after injection			
Vehicle	77 (39–98)	19 (6–29)	14 (2–63)
Haloperidol (0.05 mg/kg)	31 (16–43)*	14 (5–19)	46 (11–88)*
Haloperidol (0.1 mg/kg)	16 (4–36)*	3 (1–10)*	90 (54–165)*

Behavior was evaluated in the 5- to 7-day postpartum lactating female rats. Data are reported as medians and respective ranges. $N = 10$ for haloperidol (0.05 mg/kg) group and $N = 9$ for vehicle and haloperidol (0.1 mg/kg) groups.

* Significantly different compared to the vehicle group ($P < .05$). Kruskal–Wallis followed by Mann–Whitney U test.

Table 2
Effects of pimozide (0.2 and 0.5 mg/kg) or vehicle administration on LF and RF, and on ID in seconds, observed in the open field

Groups	Parameters		
	LF	RF	ID
30 min after injection			
Vehicle	104 (84–133)	17 (7–30)	2 (0–12)
Pimozide (0.2 mg/kg)	124 (87–140)	15 (9–31)	0 (0–18)
Pimozide (0.5 mg/kg)	110 (77–121)	20 (13–26)	12 (0–30)
60 min after injection			
Vehicle	84 (58–188)	16 (11–23)	11 (0–25)
Pimozide (0.2 mg/kg)	72 (60–133)	17 (7–29)	14 (0–45)
Pimozide (0.5 mg/kg)	62 (27–108)	16 (4–21)	24 (0–90)
90 min after injection			
Vehicle	77 (39–98)	19 (6–29)	14 (2–63)
Pimozide (0.2 mg/kg)	52 (28–73)	14 (9–26)	22 (4–64)
Pimozide (0.5 mg/kg)	48 (21–86)	14 (7–25)	26 (7–76)

Behavior was evaluated in the 5- to 7-day postpartum lactating female rats. Data are reported as medians and respective ranges. $N=9$ for all groups.

2.4. Measurements and observations

Activity measures were taken on animals whose maternal behavior was not examined. On the day of testing (days 5, 6 or 7 of lactation), general activity was observed in an open-field arena. This arena was as described previously (Bernardi and Palermo-Neto, 1979; Felicio et al., 1987). Briefly, the open field used was 80 cm in diameter and 30 cm in height. This arena was washed with a water–alcohol (5%) solution before behavioral testing to eliminate possible bias due to odors left by previous subjects. To minimize possible circadian influences on rat open-field behavior, experimental and control observations were alternated. Between 14:00

Table 3
Effects of clozapine (1.0 and 1.5 mg/kg) or vehicle administration on LF and RF, and ID in seconds, observed in the open field

Groups	Parameters		
	LF	RF	ID
30 min after injection			
Vehicle	93 (75–130)	17 (10–27)	3 (0–16)
Clozapine (1.0 mg/kg)	93 (83–136)	21 (10–29)	1 (0–14)
Clozapine (1.5 mg/kg)	72 (61–95)*	14 (8–24)	7 (0–20)
60 min after injection			
Vehicle	61 (45–85)	14 (7–22)	11 (0–28)
Clozapine (1.0 mg/kg)	58 (31–114)	13 (4–23)	7 (0–93)
Clozapine (1.5 mg/kg)	62 (33–86)	10 (6–21)	25 (6–80)*
90 min after injection			
Vehicle	60 (21–79)	16 (6–22)	18 (2–49)
Clozapine (1.0 mg/kg)	56 (37–75)	13 (4–20)	15 (0–106)
Clozapine (1.5 mg/kg)	51 (25–59)	11 (4–23)	26 (5–68)

Behavior was evaluated in the 5- to 7-day postpartum lactating female rats. Data are reported as medians and respective ranges. $N=9$ for clozapine (1.5 mg/kg) group and $N=10$ for vehicle and clozapine (1.0 mg/kg) groups.

* Significant differences in comparison to the vehicle group ($P<.05$). Kruskal–Wallis followed by Mann–Whitney U test.

Table 4
Effects of SKF-83566 (0.1 and 0.2 mg/kg) or vehicle administration on LF and RF, and on ID in seconds, observed in the open field

Groups	Parameters		
	LF	RF	ID
30 min after injection			
Vehicle	94 (69–176)	20 (8–26)	0 (0–13)
SKF-83566 (0.1 mg/kg)	45 (30–76)*	7 (5–15)*	38 (10–82)*
SKF-83566 (0.2 mg/kg)	28 (15–38)*	6 (3–11)*	51 (2–98)*
60 min after injection			
Vehicle	72 (35–109)	17 (3–31)	15 (4–99)
SKF-83566 (0.1 mg/kg)	43 (37–62)	8 (6–16)	40 (23–57)
SKF-83566 (0.2 mg/kg)	31 (28–45)*	7 (1–12)*	49 (30–103)*
90 min after injection			
Vehicle	65 (30–122)	21 (3–35)	11 (0–92)
SKF-83566 (0.1 mg/kg)	47 (33–83)	11 (5–19)	45 (10–68)
SKF-83566 (0.2 mg/kg)	23 (17–37)*	4 (1–11)*	75 (55–125)*

Behavior was evaluated in the 5- to 7-day postpartum lactating female rats. Data are reported as medians and respective ranges. $N=8$ for each SKF-83566 group and $N=10$ for vehicle group.

* Significantly different compared to the vehicle group ($P<.05$). Kruskal–Wallis followed by Mann–Whitney U test.

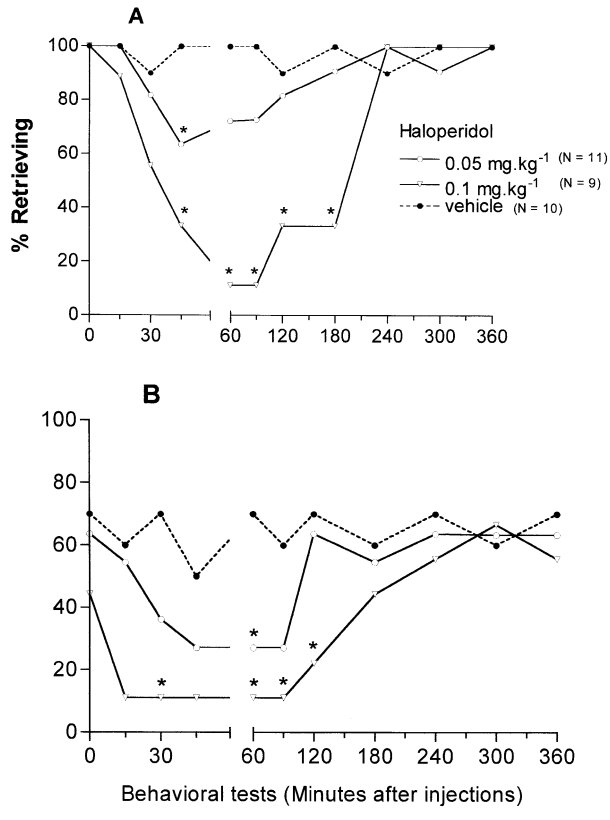

Fig. 1. Percentages of animals (5- to 7-day lactating rats) displaying pup retrieval behavior (A) and nest-building behavior (B) after two dosages of haloperidol or vehicle administration. Asterisks indicate significant differences ($P<.05$, Fisher exact probability) between vehicle and haloperidol groups.

Table 5
Effects of DA receptor antagonists on pup retrieving

		Time (min)										
Drug	Dose (mg/kg)	0	15	30	45	60	90	120	180	240	300	360
Haloperidol	vehicle	6 (6–6)[a]	6 (6–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (6–6)	6 (3–6)	6 (6–6)	6 (6–6)	6 (5–6)	6 (6–6)
	0.05	6 (6–6)	6 (4–6)	6 (0–6)	6 (0–6)	6 (5–6)	6 (0–6)	6 (0–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (6–6)
	0.1	6 (6–6)	6 (1–6)	6 (0–6)	4 (0–6)*	3 (0–6)*·**	0 (0–6)*·**	2 (0–6)*	4 (0–6)*·**	6 (6–6)	6 (6–6)	6 (6–6)
Pimozide	vehicle	6 (6–6)	6 (4–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (5–6)	6 (3–6)	6 (5–6)	6 (6–6)	6 (5–6)	6 (6–6)
	0.1	6 (6–6)	6 (6–6)	6 (3–6)	6 (0–6)	6 (6–6)	6 (3–6)	6 (3–6)	6 (2–6)	6 (6–6)	6 (5–6)	6 (6–6)
	0.2	6 (6–6)	6 (3–6)	6 (0–6)	5.5 (0–6)	6 (0–6)	5.5 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (6–6)
	0.5	6 (6–6)	4 (0–6)*	6 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (5–6)	6 (5–6)	6 (0–6)
Clozapine	vehicle	6 (6–6)	6 (4–6)	6 (5–6)	6 (5–6)	6 (5–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (5–6)
	1.0	6 (6–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (0–6)	6 (5–6)	6 (5–6)	6 (5–6)	6 (5–6)	6 (5–6)	6 (6–6)
	1.5	6 (6–6)	6 (6–6)	6 (0–6)	6 (4–6)	6 (6–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (6–6)	6 (6–6)
SKF-83566	vehicle	6 (6–6)	6 (6–6)	6 (4–6)	6 (5–6)	6 (5–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (6–6)
	0.1	6 (6–6)	6 (4–6)	5 (0–6)	6 (0–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (6–6)	6 (5–6)	6 (6–6)	6 (6–6)
	0.2	6 (6–6)	4.5 (0–6)*	0 (0–5)*	0 (0–3)*·***	0 (0–5)*·***	0 (0–6)*·***	6 (0–6)*	6 (5–6)	6 (5–6)	6 (6–6)	6 (6–6)

[a] Data are medians (ranges) of number of pups retrieved.
* $P<.05$ from 0.0 mg/kg (Kruskal–Wallis and Mann–Whitney U tests).
** $P<.05$ from 0.5 mg/kg haloperidol (Kruskal–Wallis and Mann–Whitney U tests).
*** $P<.05$ from 0.1 mg/kg SKF-83566 (Kruskal–Wallis and Mann–Whitney U tests).

and 18:00 h locomotion frequency (LF; number of floor units entered), rearing frequency (RF; number of times the animal stood on its hind legs) and immobility duration (ID; total seconds without movement) were counted for 3 min at 30, 60 and 90 min after drug injection. Between each open-field observation, animals were returned to their pups. Within a given dose treatment, repeated measures were taken on the same animals.

On the day of testing (days 5, 6 or 7 of lactation), a home-cage maternal behavior pretest was performed. The pretest consisted of removing the female's pups, disorganizing the nest and returning the pups immediately, placing them in the quadrants, which did not contain the nest. If all the pups were retrieved to the nest area within 5 min, the female remained in the experiment. After drug administration, pups were again removed, nest disorganized and pups returned at 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after drug administration. Retrieval behavior and nest building were observed for 5 and 15 min, respectively, each time the pups were returned. Within a given dose treatment, repeated measures were taken on the same animals. Retrieval was rated for each female in the following way: *yes* = all pups retrieved to nest area within 5 min and *no* = when at least one pup was left outside nest area within the same period of time. In addition, the number of pups retrieved was recorded each time they were returned into the cage. Nest building was rated as *yes* when female displayed nest building within 15 min and *no* when no nest building was observed in this period.

2.5. Statistical analysis

For open field, as well as number of pups retrieved data, Kruskal–Wallis analysis of variance followed by the Mann–Whitney U tests were applied since Bartlett's test showed no existence of homogeneity among data. One-tailed Fisher's test was used to compare other maternal behavior data. A probability of $P<.05$ was considered significant for all comparisons made.

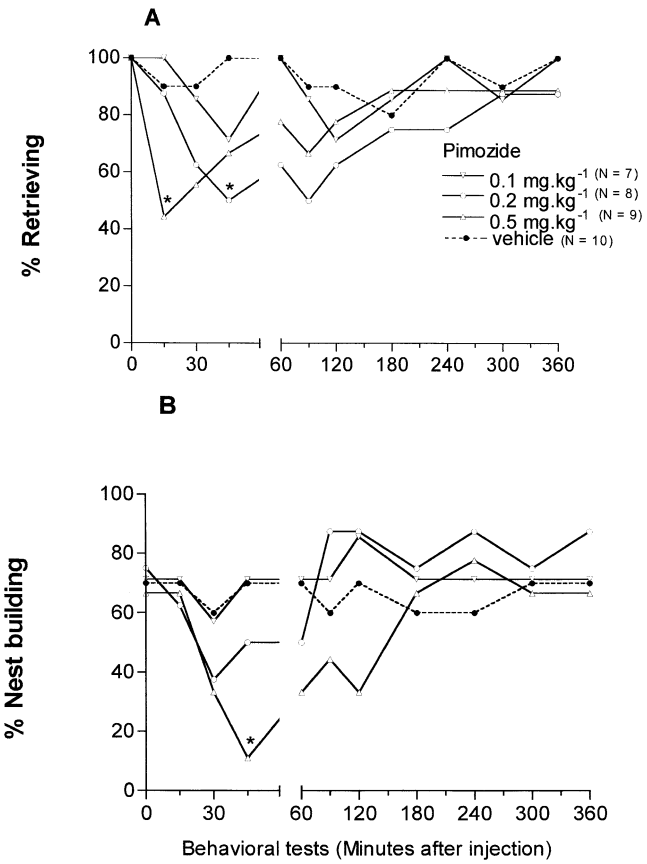

Fig. 2. Percentages of animals (5- to 7-day lactating rats) displaying pup retrieval behavior (A) and nest-building behavior (B) after various dosages of pimozide or vehicle administration. Asterisks indicate significant differences ($P<.05$, Fisher exact probability) between vehicle and pimozide groups.

3. Results

3.1. General activity

General activity data of lactating rats treated with haloperidol, pimozide, clozapine and SKF-83566 were analyzed. Haloperidol (0.1 mg/kg) significantly reduced locomotion and rearing, and increased ID at 30, 60 and 90 min after injection ($P<.05$). While 0.05 mg/kg haloperidol reduced locomotion and increased ID in all observation periods, it reduced rearing only at 30 min ($P<.05$; Table 1). Neither the 0.2 nor 0.5 mg/kg doses of pimozide induced any significant change in the behavioral parameters observed in the open field (Table 2). Clozapine (1.5 mg/kg) significantly reduced locomotion at 30 min and increased ID at 60 min. The lower clozapine dose (1.0 mg/kg) did not induce any significant change in open-field behavior (Table 3). Animals treated with SKF-83566 (0.2 mg/kg) showed a significant decrease in LF and RF, and an increase in ID at all time periods studied. While a 0.1 mg/kg SKF-83566 dose induced those behavioral changes only at 30 min (Table 4).

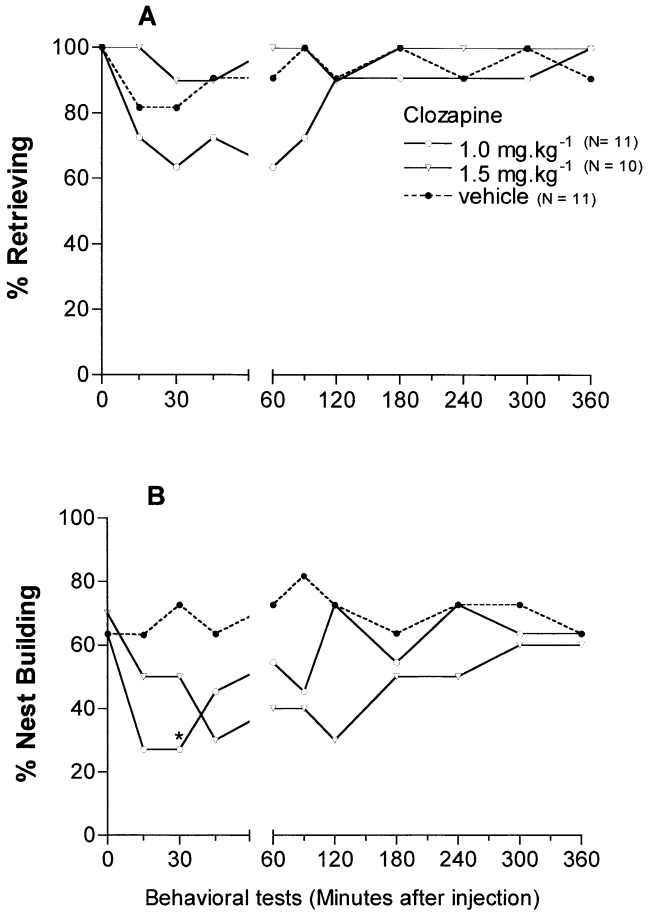

Fig. 3. Percentages of animals (5- to 7-day lactating rats) displaying pup retrieval behavior (A) and nest-building behavior (B) after two dosages of clozapine or vehicle administration.

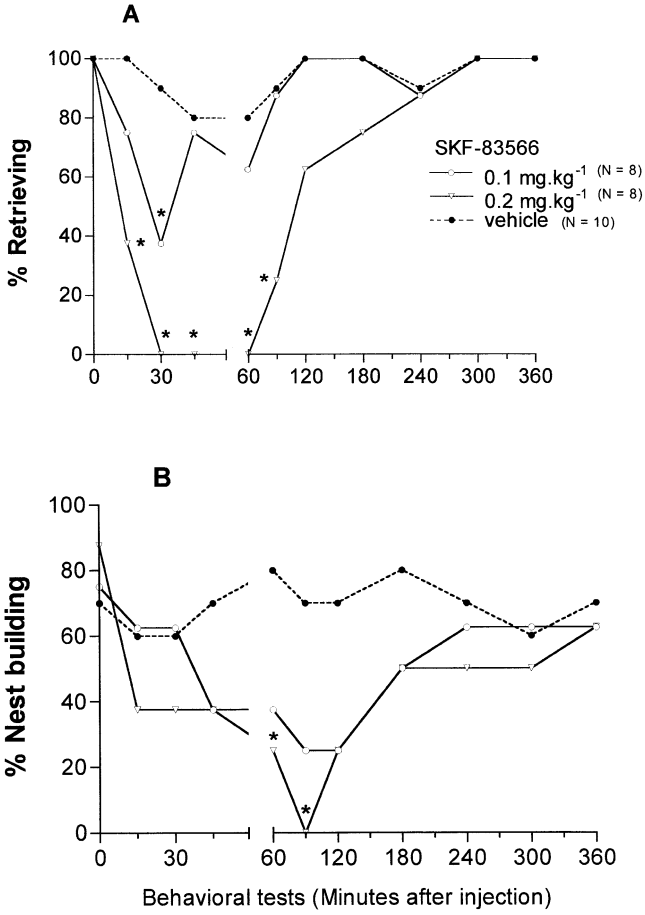

Fig. 4. Percentages of animals (5- to 7-day lactating rats) displaying pup retrieval behavior (A) and nest-building behavior (B) after two dosages of SKF-83566 or vehicle administration. Asterisks indicate significant differences ($P<.05$, Fisher exact probability) between vehicle and SKF-83566 groups.

3.2. Maternal behavior

The high dose of haloperidol (0.1 mg/kg) significantly reduced the percent of rats retrieving and grouping pups, as well as the number of pups retrieved at 45, 60, 90, 120 and 180 min after drug injection, and reduced the percent of animals that built nests at 30, 60, 90 and 120 min, while a 0.05 mg/kg haloperidol dose significantly reduced the percent of rats displaying retrieval at 45 min and nest building at 60 min (Fig. 1; Table 5). The high dose of pimozide (0.5 mg/kg) significantly reduced the percentage of rats retrieving and grouping pups, as well as the number of pups retrieved at the 15-min time point. A significant reduction in the percent of rats showing nest building was also observed at 45 min (Fig. 2; Table 5). Pimozide at 0.2 mg/kg reduced the percent of mothers retrieving and grouping their pups at 45 min after drug injection. Although clozapine treatment at a dose of 1.5 mg/kg did not induce any significant change in any of the maternal behavior parameters analyzed 30 min after the 1.0 mg/kg clozapine

injection, a significant reduction in the percentage of dams showing nest building was observed (Fig. 3; Table 5). SKF-83566 (0.2 mg/kg) significantly reduced the percent of mothers retrieving and grouping the pups at 15, 30, 45, 60 and 90 min time points. This dose reduced significantly the number of pups retrieved at 15, 30, 45, 90 and 120 min as well (Table 5). While a 0.1 mg/kg dose significantly reduced this percent only at 30 min. Nest building was reduced significantly at 60 and 90 min in rats treated with 0.2 mg/kg SKF-83566 (Fig. 4).

4. Discussion

The present results are consistent with the hypothesis that central DA receptors play a key role in the control and maintenance of ongoing maternal behavior. This fact has been suggested previously since both pharmacological blockade of DA receptors (Giordano et al., 1990; Keer and Stern, 1999a,b) or knocking out the gene encoding for the subtype D_2 of the DA D2 receptors (Clarke-Hall et al., 1995) have been reported as having inhibitory effects on maternal behavior. Our results confirm and expand on results of previous papers, which describe the inhibition of maternal behavior by the classical DA receptor blocker, haloperidol (Giordano et al., 1990). The main goal of this work was to study the effects of different DA receptor antagonists on maternal behavior. Since each of the drugs used in this study has a unique pharmacodynamic profile, this study provides information on the role of DA receptor subtypes in this behavior. In addition, since DA blockade can have motor effects, activity in an open field was also observed.

Haloperidol (0.1 mg/kg) induced a reduction in percent of rats retrieving the pups to the nest and grouping them from 45 to 180 min and reduced nest building at 30, 60, 90 and 120 min observation times as well. These results are similar to those of Giordano et al. (1990). Since laboratory conditions and animal strains may influence experimental results (Crabbe et al., 1999; Miranda-Paiva and Felicio, 1999; Spearow et al., 1999), particularly for behavioral studies, the confirmation of the effects of haloperidol on maternal behavior with this dose within different laboratories using diverse rat strains was a necessary starting point for this study. Haloperidol (0.1 mg/kg)-induced reduction in the number of pups retrieved by the dams from 45 to 180 min suggests that this is a sensitive parameter to detect drug influences on maternal behavior. In addition, the haloperidol-induced decrease in motor activity in an open field agrees with previous results from our laboratory, obtained from adult male rats (Bernardi and Palermo-Neto, 1979).

The lower behaviorally active dose of pimozide (0.2 mg/kg) induced a decrease in the percent of animals retrieving and grouping the pups at 45 min after drug injection. While in animals treated with 0.5 mg/kg, the same effect, i.e., reduced percent of mothers retrieving and grouping, was observed 30 min earlier. This finding may be due to the kinetic profile of pimozide. In other words, the highest pimozide dose may have taken less time to reach the sufficient number of receptors to cause an inhibitory influence on this behavior. The reduction in the number of pups retrieved at 15 min agrees with this hypothesis. Both haloperidol and pimozide bind DA D2-like receptors. Pimozide is more specific and induces less extrapyramidal effects than haloperidol (McCullough et al., 1993). Since extrapyramidal effects are mainly due to a blockade of DA striatal receptors, pimozide striatal effects are considered less intense than those of haloperidol. The haloperidol (0.1 mg/kg) and pimozide (0.2 mg/kg) doses, while being considered clinically equivalent, produced distinct effects on rat maternal behavior. Haloperidol (0.1 mg/kg) inhibitory effects on this behavior were far more intense than those observed for pimozide (0.2 mg/kg). Haloperidol inhibited both locomotion and maternal behavior, while an equivalent dose of pimozide showed only a mild inhibitory influence on maternal behavior and no significant effects on the activity in an open field. Since both haloperidol and pimozide block the DA D2-like receptor subtype, the behavioral differences may be due to the kinetic differences among the drugs, such as different drug distribution in the brain and differences in drug affinity for its receptor according to the brain region. Responses displayed after pimozide treatment suggest that it is possible to block maternal behavior with no simultaneous significant effect on exploratory open-field behavior.

Clozapine inhibited the general activity in the open field, while its lowest dose induced a decrease in nest building. This suggests that this parameter may not be dose-dependent, and that nest building may be more sensitive to clozapine-induced blockade of dopaminergic transmission than retrieving. This drug has a unique clinical profile (Baldessarini, 1996; Baldessarini and Frankenburg, 1991; Bartholini et al., 1972; Pickar, 1995), which is due to its affinity for DA D_4 receptor or due to its low ability to compete for DA D2-like receptors allowing clozapine binding to DA D2-like receptors only in brain regions with low concentrations of this neurotransmitter in the synaptic cleft, such as the cortex (Lidow et al., 1998). The behavioral results observed with clozapine treatment suggest that the DA D_4 receptors may play a role on the control of the ongoing maternal behavior. Alternatively, since clozapine weakly binds the DA D2-like receptors and is not able to bind DA receptors in regions with high concentrations of this neurotransmitter such as striatum, this would imply that dopaminergic neurotransmission in regions such as the striatum is important for maternal behavior.

The blockade of the DA D1-like receptors with SKF-83566 inhibited both maternal behavior and the activity in an open field. Although the highest doses of SKF-83566 and haloperidol similarly influenced open-field behavior, their effects on maternal behavior were distinct. SKF-83566 disrupted retrieving earlier than haloperidol. While its

inhibitory effect on nest building occurred only in two time points, compared to the four time points observed in haloperidol-treated animals. This may be due to the different kinetic profile of these drugs. Alternatively, since each of these drugs bind different DA receptors, these results may suggest a different role for D1-like and D2-like DA receptor families in the control of ongoing maternal behavior.

DA has inhibitory effects on prolactin synthesis and secretion acting mainly through pituitary DA D2-like receptors (Ben-Jonathan, 1985), and DA receptor blockers can reverse DA inhibition of prolactin secretion (Felicio and Bridges, 1992). Prolactin crosses the blood–brain barrier, and may influence the activity of dopaminergic terminals (Cruz-Casallas et al., 1999; Felicio and Bridges, 1992). This hormone has a facilitatory role on maternal behavior (Bridges et al., 1985; Felicio and Bridges, 1992). Since prolactin, once accessing the brain, may influence maternal behavior through stimulation of dopaminergic transmission, the blockage of DA receptors could inhibit the very same pathway by which this hormone would stimulate this behavior. In addition, prolactin is thought to be involved mainly in the induction, instead of maintenance, of maternal behavior (Bridges, 1996; Bridges et al., 1990; Kinsley et al., 1994). Previous results have shown that acute hyperprolactinemia, by itself, does not influence significantly general activity in an open field (Nasello et al., 1991; Vanzeler et al., 1990) and that acute treatments with other central DA receptor blockers, such as bromopride (Nasello and Felicio, 1988), metoclopramide (Frussa-Filho and Palermo-Neto, 1988) and droperidol (Frussa-Filho and Palermo-Neto, 1991), induce a decrease in general activity in an open field. The data in the literature support the hypothesis that acute behavioral effects on general activity reported here are due to central DA receptors blockade instead of a hyperprolactinemia central effect.

The results suggest that dopaminergic pathways play a role in ongoing maternal behavior. In addition, the various dopaminergic systems and receptor subtypes seem to play unique roles in this important behavior as well. Specific studies determining the role of each of these receptors in brain regions important for this behavior, such as nucleus accumbens and medial preoptic area, may lead to a better knowledge of the role of dopaminergic systems in ongoing maternal behavior.

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