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Dopamine antagonists during parturition disrupt maternal care and the retention of maternal behavior in rats

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Abstract

Brief contact with pups at parturition enables the female rat to establish and retain the full repertoire of maternal behaviors, allowing her to respond rapidly to pups in the future. To determine whether the dopamine system is involved in the retention of maternal behavior, females were continuously infused with dopamine antagonists during the periparturitional period and then allowed either a brief interaction period with pups (3 h) or no interaction with pups (pups removed as they were born). Females were exposed to either the D1-like antagonist SCH 23390 (0.1 or 1.0 mg/kg/day) or the D2-like antagonist clebopride (0.5 or 1.0 mg/kg/day). The high dose of either DA antagonist resulted in significant attenuation of maternal care immediately postpartum. When tested for the retention of maternal behavior 7 days later, however, only the females exposed to the D2 antagonist displayed a delayed response to shown full maternal behavior (FMB) towards donor pups. Thus, while both dopamine receptor subtypes appear necessary for the full and rapid expression of maternal behavior during the early postpartum period, only the D2 receptor subtype appears to be involved in the retention of this behavior.

Keywords: Maternal behavior; Parturition; Dopamine antagonist; Maternal retention

1. Introduction

In primiparous rats, a relatively brief exposure to pups (1–2 h) around the time of parturition results in the rapid retention of maternal behavior several days to weeks later. If, however, pups are removed immediately after delivery or are delivered by cesarean section, then the retention of maternal behavior is diminished (Bridges, 1975; Bridges, 1977; Orpen and Fleming, 1987; Orpen et al., 1987). The neural systems underlying the retention of maternal behavior are not fully understood, although several recent studies have implicated limbic structures, specifically the nucleus accumbens, in the acquisition and/or consolidation of this memory (Fleming and Korsmit, 1996; Fleming et al., 1994a,b; Lee et al., 1999). When the nucleus accumbens is lesioned prior to parturition, the retention of maternal behavior tested 10 days later is significantly delayed. Lesioning the nucleus accumbens after postpartum interaction with pups, however, does not diminish retention of maternal behavior (Lee et al., 1999). Recently, we demonstrated that opioids also influence the long-term retention of maternal behavior (Byrnes and Bridges, 2000). Administration of the opioid antagonist, β-funaltrexamine (βFNA), around the time of parturition, attenuates the retention of maternal behavior in females tested 7 days later. Interestingly, decreased opioid activity is often associated with enhanced performance on learning and memory tasks (Flood et al., 1987; Gallagher, 1982, 1985; Gallagher et al., 1983). One exception, however, is the formation of conditioned place/cue preference (CPP). In CPP, a neutral stimulus or location is paired with a reinforcer such that upon subsequent testing, the previously neutral cue or place becomes preferred. Numerous studies have shown that pairing a neutral location with morphine administration results in CPP (Andrews et al., 2001; Manzanedo et al., 2001; Mucha and Iversen, 1984; Olmstead and Franklin, 1997; Nieto et al., 2002; Randall et al., 1998; Tolliver et al., 2000). Moreover, the nucleus accumbens is necessary for this association (Andrews et al., 2001; Kelsey et al., 1989; Olmstead and Franklin, 1997; Tolliver et al., 2000). Thus, both the retention of maternal behavior and the formation of CPP involve increased opioid activity and an intact nucleus accumbens.

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Based upon these similarities, it is possible that the retention of maternal behavior is mediated by processes similar to those underlying CPP. Additional support for this hypothesis comes from studies that demonstrate that pups can serve as reinforcers to primiparous females and further, that the reinforcing property of pups can be blocked by the dopamine antagonist *cis*-flupentixol (Fleming et al., 1994a,b; Lee et al., 2000). These findings are of interest as dopamine antagonists can also block the formation of CPP (Bardo et al., 1999; Manzanedo et al., 2001; Pruitt et al., 1995). The purpose of the present set of studies was to determine whether administration of dopamine antagonists throughout parturition attenuates the retention of maternal behavior tested 7 days later. To determine the possible roles of different dopamine receptor subtypes in this process, both a selective D1-like antagonist (SCH 23390) and a selective D2-like antagonist (clebopride) were utilized.

2. Materials and methods

2.1. Animals

Female Sprague–Dawley rats (Crl:CD[SD]BR) were purchased from Charles River Laboratories (Kingston, NY, USA). The animals used in these experiments were maintained in accordance with the guidelines of the Committee of Care and Use of Laboratory Animal Resources, National Research Council. Subjects were housed in polypropylene cages ($45 \times 25 \times 20$ cm) with food and water available ad libitum in light (on 0500–1900 h)- and temperature (21–25 °C)-controlled rooms. Females were group housed until day 21 of gestation at which time they were housed individually.

2.2. Procedures

Virgin female Sprague–Dawley rats (175–200 g) were housed with males from our colony. The presence of sperm in vaginal lavage was designated as gestation day 1. On gestation day 21, females were lightly anesthetized with isoflurane and implanted subcutaneously with an Alzet mini-osmotic pump (model 2001: − 1.9 μl/h, 7 days; Palo Alto, CA) containing one of the following: SCH 23390 (0.1 or 1.0 mg/kg/day) or its vehicle (30% DMSO in sterile water); clebopride (0.5 or 1.0 mg/kg/day) or its vehicle (physiological saline). Pumps were removed 1 day after parturition again under isoflurane anesthesia.

Beginning on gestation day 22, females were monitored every 15 min for the initiation of parturition. Females were allowed 3 h to interact with pups beginning after the delivery of the first pup. At the end of this period, all pups were removed. Fifteen minutes later, six of the females own pups were returned to the dam and the following behaviors were monitored over the next 15 min: latency to retrieve the first and sixth pup, latency to group pups and latency to crouch over pups. If females failed to retrieve, group or crouch over pups a maximum score of 900 s was assigned. Following behavioral testing, all pups were removed.

To verify that experience with pups is necessary for retention of maternal behavior when testing is conducted 7 days after parturition, two groups of nonexperienced females were also generated. One group received pumps containing physiological saline, while the other group received pumps containing the D2 antagonist clebopride (1.0 mg/kg/day). Females in these nonexperienced groups were monitored continuously throughout parturition with each pup removed after delivery.

Seven days later, all females were tested for their retention of maternal behavior using three pups (ages 3–8 days) obtained from donor mothers. Behaviors were continuously monitored for 15 min (pup retrieval, grouping and crouching); following this initial period females were spot checked every 15 min for a total of 60 min to determine their proximity to pups and the presence or absence of crouching behavior. Pups remained with females until the next day when donor pups were removed (between 0800 and 1000 h) and 1 h later maternal behavior testing commenced using three recently fed donor pups. Females were considered fully maternal if they retrieved, grouped and crouched over all three pups during the 1-h test session for 2 consecutive test days. Maternal behavior was evaluated for 1 h every day beginning on postpartum day 7. Females were tested for a maximum of 8 days or until they were fully maternal. Latency scores were based on the test day that the animal responded, i.e., test day 1 = latency of zero.

2.3. Statistical analysis

Maternal behavior testing was analyzed using nonparametric analyses. Group differences were analyzed using the Kruskal–Wallis one-way analysis of variance on ranks. Subsequent post-hoc analyses between groups utilized the Mann–Whitney rank sum test. Percent responding data was analyzed using a Fisher's exact test on each test day.

3. Results

3.1. Maternal behavior 3-h postpartum

Continuous antagonism of the D1-like dopamine receptors significantly disrupted some aspects of maternal behavior during the initial 3-h postpartum interaction period. Although the duration of delivery was unaffected, and all of the dams were observed crouching over some or all of their pups, SCH 23390-treatment did affect grooming behavior. As illustrated in Fig. 1, females treated with the D1 antagonist SCH 23390 at the higher dose (1 mg/kg/day) had a significant number of ungroomed offspring with their

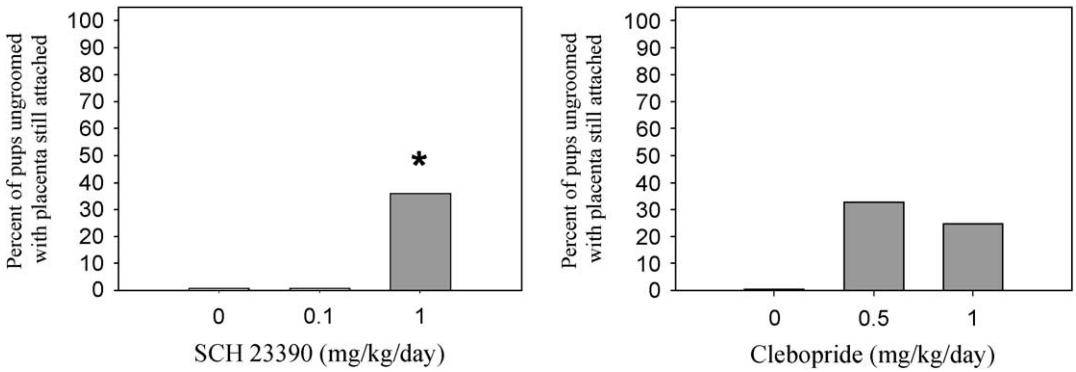

Fig. 1. Percentage of pups who were not cleaned or who still had their placenta attached after either SCH 23390 (D1) or clebopride (D2) receptor antagonist treatments. * $P<.05$ as compared to vehicle-treated controls, n's = 9–11.

placenta still attached at the end of the 3-h postpartum interaction period ($P<.05$). Pups were considered ungroomed if blood or amniotic fluid remained on their skin, which often caused the bedding to stick to them. Grooming and placentophagia were not significantly affected in females exposed to clebopride. Again, all females were observed crouching over all or some of their pups and while some females also had a number of ungroomed pups with placentas still attached, these numbers failed to reach significance ($P<.07$).

Maternal behavior deficits were observed in both SCH 23390- and clebopride-treated dams during postpartum testing. As shown in Fig. 2 (top panel), during the 15-min postpartum test, the highest dose of the D1-like antagonist SCH 23390 (1.0 mg/kg/day) increased the median latency to retrieve the first pup ($H_{[2]}=8.891$, $P=.012$), to retrieve all six pups ($H_{[2]}=10.8$, $P=.005$) and to crouch over all six pups ($H_{[2]}=11.51$, $P=.003$). Interestingly, this was not simply a retrieval deficit as 8 out of the 11 high dose SCH 23390-treated females retrieved at least 4 of the 6 test pups. Rather, these females often failed to group all of the pups in their nest and then crouch over them. The high dose SCH 23390 dams would often leave some pups scattered throughout the cage, crouching over only a few pups or they would retrieve pups and then leave the nest and settle elsewhere in the cage.

Significant deficits were also observed following infusion of the D2-like antagonist clebopride. Females treated with the higher dose of clebopride demonstrated significant delays in the latency to retrieve all six test pups ($H_{[2]}=9.97$, $P=.007$) as well as delays in crouching over all six test pups ($H_{[2]}=8.8$, $P=.01$) when tested after a brief separation (see Fig. 2; bottom panel). Overall, 4 out of the 10 high-dose-treated females failed to display full maternal behavior (FMB) during the postpartum test. Once again, this was not due to a general deficit in retrieval as 8 out of the 10 high-dose-treated females retrieved all 6 test pups. However, in addition to being slow to retrieve the pups, these females did not group pups together in a nest, often crouching over only two or three pups, or crouching next to the pups. Thus, antagonism of either the D1- or D2-like dopamine receptor delayed retrieval and disrupted the coordinated grouping and crouching over pups in the postpartum testing period.

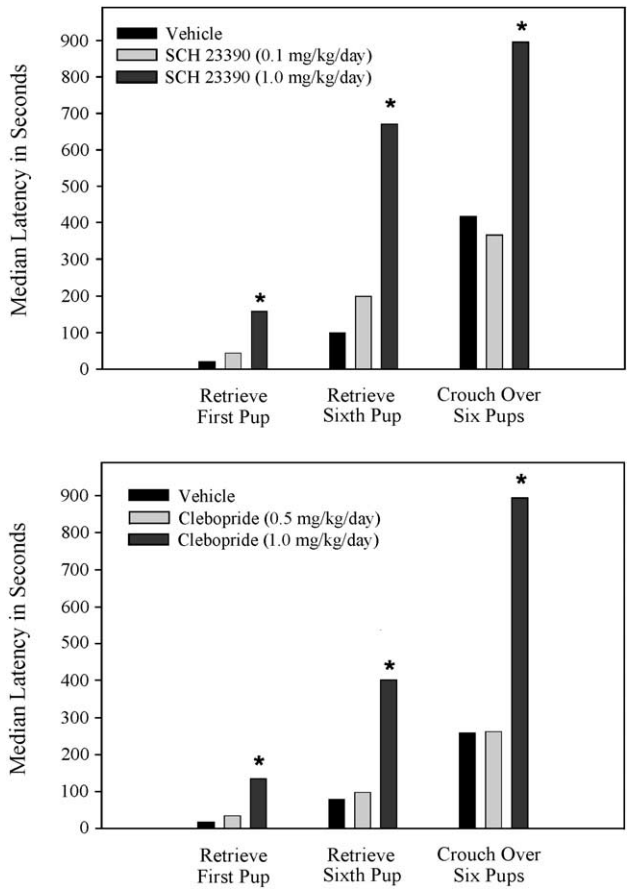

Fig. 2. Maternal behavior in females tested 3 h after the birth of the first pup and following a 15-min separation. Top panel: the median latency to retrieve the first of six test pups, retrieve all six test pups and crouch over all six test pups in females treated with SCH 23390 (0.1 or 1.0 mg/kg/day) or vehicle (30% DMSO). * $P<.05$ as compared to vehicle, n's = 10–11. Bottom panel: the median latency to retrieve the first of six test pups, retrieve all six test pups and crouch over all six test pups in females treated with clebopride (0.5 or 1.0 mg/kg/day) or vehicle (saline). * $P<.05$ as compared to vehicle, n's = 9–10.

3.2. Retention of maternal behavior tested 7 days postpartum

When tested for the retention of maternal behavior 7 days postpartum females treated with the D1-like dopamine antagonist SCH 23390 throughout parturition did not demonstrate any significant deficits. Thus, while the high dose of the D1-like antagonist SCH 23390 significantly disrupted maternal behavior postpartum, the majority of females reinitiated the behavior within 24 h of exposure to three donor pups 7 days later. As shown in Fig. 3A and B, there were no differences in either the median number of days to display maternal behavior or in the percent of females displaying FMB towards the donor pups during testing for the retention of the behavior.

Exposure to the higher dose of the D2-like antagonist clebopride during parturition significantly effected maternal retention, increasing the median number of days necessary to elicit FMB in females tested 7 days after parturition ($H_{[4]} = 12.2$, $P = .02$). As shown in Fig. 3D, the median latency to display FMB was significantly delayed in experienced females treated with the high dose of clebopride as compared to saline-treated females. Indeed, these experienced females had median response latencies similar to nonexperienced females whose pups were removed immediately after delivery. Thus, females treated with the high dose of clebopride, and then either allowed 3-h interaction with pups or no interaction with pups, did not differ in response latencies. Similar results were observed with regard to the percentage of females displaying maternal behavior during testing (Fig. 3C) with the experienced high dose clebopride group, as well as both nonexperienced groups, having significantly fewer females displaying FMB during the first 2 days of testing when compared to saline-treated controls. These data demonstrate that while both D1- and D2-like dopamine antagonists disrupt the

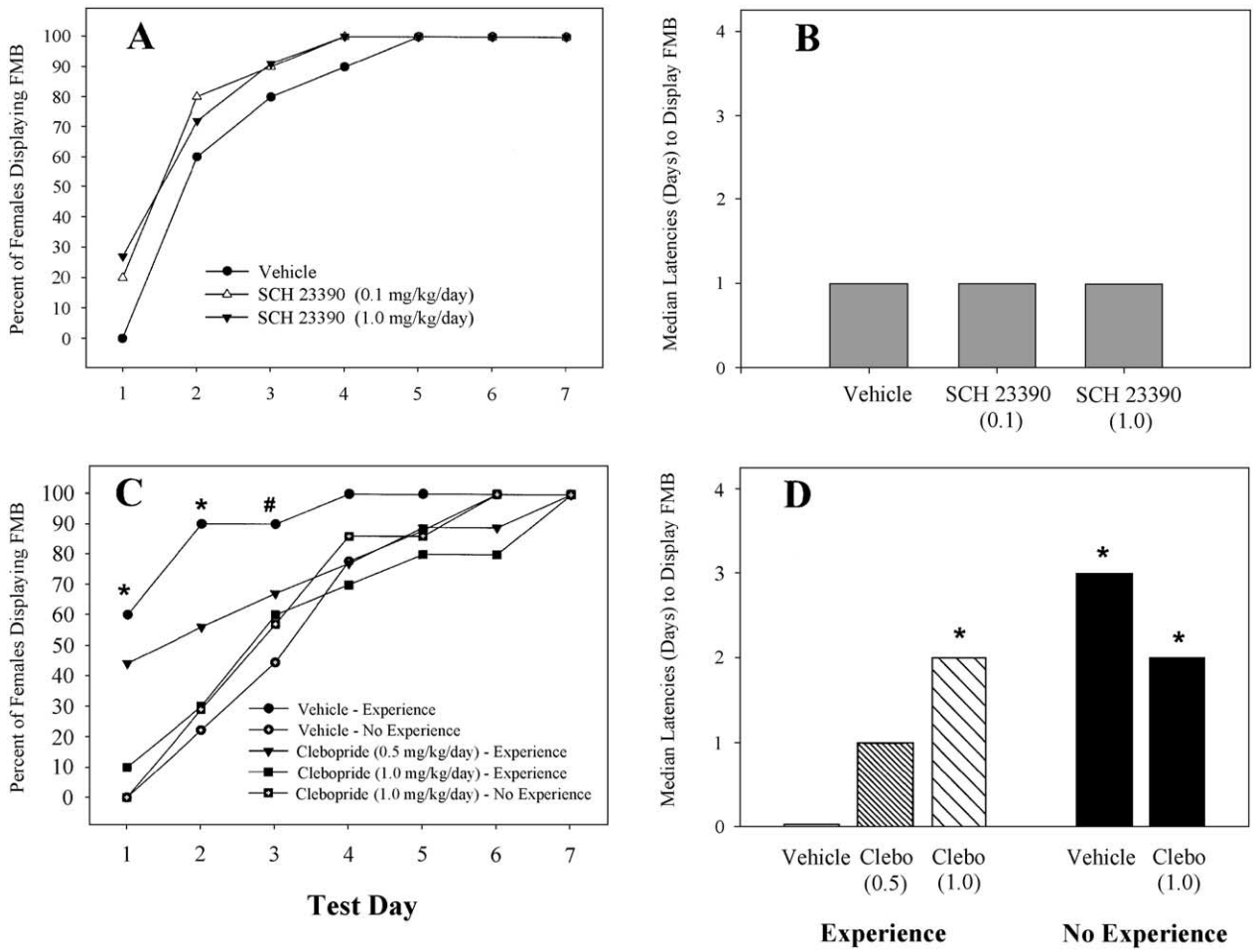

Fig. 3. Retention of maternal behavior tested 7 days postpartum. All females were tested for the display of FMB (retrieving, grouping and crouching over three donor test pups) during a 1-h test period. (A) The percentage of SCH 23390-treated females displaying FMB on each test day. (B) Latencies (median number of days) to display FMB in females treated with SCH 23390 during parturition. (C) The percentage of clebopride- or vehicle-treated females, with and without maternal experience, displaying FMB on each test day. * $P < .05$ vehicle- and clebopride-nonexperienced groups as well as clebopride- vs. vehicle-experienced group. # $P < .05$ vehicle-nonexperienced vs. vehicle-experienced group. (D) Latencies (in days) to display FMB in clebopride- or vehicle-treated females, with and without maternal experience. * $P < .05$ as compared to the vehicle-experienced group, n's = 9–11.

expression of maternal behavior postpartum, only the D2-like antagonist impairs the retention of maternal behavior.

4. Discussion

The present work investigated the role of the dopamine system around the time of parturition in the retention of maternal behavior 7 days postpartum. Previous studies have shown that either lesions of the nucleus accumbens (Lee et al., 1999) or infusion of opioid antagonists into the ventricles (Byrnes and Bridges, 2000) prior to the mothers interaction with her newborn pups can delay the reestablishment of maternal responding when the females are tested at least 1-week postpartum. The present findings indicate that pharmacological disruption of D2-like, but not D1-like dopamine receptors, around the time of parturition interferes with the retention of maternal behavior 7 days postpartum.

During testing immediately postpartum, both the D1-like antagonist SCH 23390 and the D2-like antagonist clebopride significantly disrupted maternal behavior. Females treated with the high dose of either of these antagonists retrieved pups more slowly, retrieved pups to more than one nest site or retrieved to the nest, but then failed to group pups together. Other dams would crouch over only one or two pups leaving the other pups scattered throughout the home cage, while some antagonist-treated females placed pups in the nest and then crouched next to their litter. These data confirm several studies that have reported deficits in maternal behavior during the postpartum period after administration of dopamine antagonists (Giordano et al., 1990; Keer and Stern, 1999) or after lesions of the limbic dopamine system (Gaffori and Le Moal, 1979; Hansen, 1994).

It is likely that treatment with either of these dopamine antagonists resulted in motor deficits, however, it is unclear to what extent such deficits interfered with postpartum maternal behavior. Indeed, the majority of females were able to retrieve all their pups during the postpartum test, and yet still did not display full coordinated maternal behavior. It is possible that these drugs decreased the motivation to perform some aspects of maternal behavior. In fact, studies have demonstrated that retrieval deficits following dopamine depletion can be overcome by increasing the amount of time the dam is separated from her pups (Hansen, 1994), ostensibly due to the female's increased motivation to retrieve. Moreover, Giordano et al. (1990) demonstrated that doses of haloperidol that disrupted pup retrieval did not disrupt food retrieval, again dissociating deficits in maternal responses from general motor deficits.

In our studies, females were only separated from their pups for a brief 15-min period. Perhaps, a longer separation would have decreased the deficits observed in the high dose antagonist-treated dams. However, it is interesting to note that even during the 3-h interaction period, females treated with high doses of either SCH 23390 or clebopride were often observed crouching over only some of their pups with others either in another nest or scattered throughout the cage. This is in contrast to vehicle-treated females who typically grouped all of their pups into a single nest and crouched over the entire litter. Thus, in addition to slowing retrieval times, it is the failure to group their pups prior to initiating the crouching posture that appears to be deficient in females treated with dopamine receptor antagonists.

Despite these postpartum deficits, however, the retention of maternal behavior was not affected 7 days later in females treated with the D1-like antagonist SCH 23390. It is possible that at 7 days postpartum these females are still in a period of increased responsiveness to pups and that a longer separation between parturition and testing for the retention of the behavior may be necessary to observe a disruption in the retention of the behavior. Indeed, some studies have observed a rapid induction of maternal behavior in females not allowed any access to pups (cesarean sectioned) and then tested 7 days postpartum (Orpen and Fleming, 1987). In the present studies nonexperienced females did respond to pups more quickly than virgin females (3 vs. 6–8 days) and the possibility remains that a longer interval between parturition and testing for the retention of the behavior may have yielded longer delays in the retention of the behavior. However, significant delays in the median latency to display maternal behavior were observed in both nonexperienced females and experienced females administered clebopride. Thus, it seems unlikely that the failure to observe a deficit in SCH 23390-treated females was due to the duration of separation between parturition and testing. Moreover, the rapid response of the high dose SCH 23390-treated females upon reintroduction to pups 7 days postpartum, demonstrates a disparity between the quality of the maternal interaction postpartum (which in these females was markedly disordered) and the ability to rapidly respond to pups in the future.

The question that arises from these data then is what are the females acquiring from their postpartum interaction with pups, which we know from many previous studies are absolutely necessary for the retention of the behavior (Bridges, 1975, 1977; Cohen and Bridges, 1981; Orpen and Fleming, 1987; Orpen et al., 1987). One possibility is that the retention is due to the reinforcing properties of pups. Previous studies have shown that primiparous females will bar press for pups, an effect that is antagonized by the mixed dopamine D1/D2 antagonist cis-flupentixol (Fleming et al., 1994a,b; Lee et al., 2000). One could speculate that it was the D2 component of the drug that blocked the reinforcing properties of the pups. Interestingly, while in many instances blocking either the D1 or the D2 receptor is sufficient to block CPP, there are some specific instances during which only the D2 receptor blockade is sufficient.

Recently, work in prairie voles (*Microtus ochrogaster*) has demonstrated that the formation of partner preference following mating can be blocked by treatment with the D2 antagonist sulpiride, but not the D1 antagonist SCH 23390, when given prior to mating (Wang et al., 1999). Moreover,

this effect is mediated by D2 receptors within the nucleus accumbens (Gingrich et al., 2000). Several authors have speculated that partner preference and other forms of social attachment rely on the same limbic systems that underlie both reward and addiction (Panksepp et al., 1997; Panksepp et al., 1994; Pitkow et al., 2001; Wang et al., 1999). It is possible that the retention of maternal behavior in rodents functions similarly to other forms of social attachment. In line with this reasoning, studies examining infant–parent bonding in other species have also indicated a role for both limbic structures and opioids, similar to the findings on maternal retention (Keverne and Kendrick, 1994; Martel et al., 1995; Panksepp et al., 1994; Schino and Troisi, 1992). Thus, the formation and consolidation of maternal memory may be quite similar to CPP, with the hormones of pregnancy perhaps priming the D2 dopamine receptor, such that responses to pups are intensified. Indeed, an examination of the expression of the D2 receptor on gestation day 21 demonstrates a significant decrease in the number of D2 receptors expressed in the nucleus accumbens when compared to the expression in virgin rats or rats on gestation day 2 (Bakowska and Morrell, 1995). These decreased receptor numbers could indicate increased dopamine release in this region as dopamine receptors have been shown to down-regulate in the presence of ligand (Chen et al., 1993; Zhou et al., 1992). Whether our findings with regard to antagonism of the D2 receptor are due to decreased receptor activation in the nucleus accumbens remains to be determined.

In summary, the present findings have demonstrated that (1) both D1- and D2-like receptor activation is necessary for the coordinated expression of maternal behavior immediately postpartum; (2) disruption of maternal behavior during the initial postpartum interaction with pups does not result in delayed responding to pups when tested 7 days later; and (3) antagonism of D2-like, but not D1-like, dopamine receptors around the time of parturition disrupts the retention of maternal behavior when tested 7 days later. These findings support the hypothesis that the retention of maternal behavior may utilize neural systems similar to those mediating CPP and may indeed be similar to processes involved in other forms of social attachment.

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