Pharmacology Biochemistry and Behavior, Vol. 66, No. 2, pp. 353–359, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00180-5

Effects of Low Dosages of Apomorphine on Maternal Responsiveness in Lactating Rats

JUDITH M. STERN AND MARIA PROTOMASTRO

Department of Psychology, Rutgers–The State University of New Jersey, New Brunswick, NJ 08903

Received 5 March 1999; Revised 6 October 1999; Accepted 28 October 1999

STERN, J. M. AND M. PROTOMASTRO. *Effects of low dosages of apomorphine on maternal responsiveness in lactating rats.* PHARMACOL BIOCHEM BEHAV **66**(2) 353–359, 2000.—Lactating rats (day 7 ± 1 postpartum) were observed during a 1-h reunion with their pups 4 h after separation from them and 10 min after subcutaneous injection of saline (SAL; 0.1 ml) or low dosages of the dopamine agonist, apomorphine (APO; 0.1 or 0.25 mg/kg). Although APO did not affect latency to sniff pups or retrieve the first pup, there were dosage-dependent delays in onset of licking and nursing pups, and decreases in retrieval and grouping of pups, nursing duration, and litter weight gain. The alterations in maternal responsiveness among APO-treated dams were related to increased carrying and mouthing of pups and markedly increased sniffing of pups, bedding, and cage. Duration of time spent licking pups, exploring, and self-grooming did not differ between groups. Thus, certain APO-induced stereotypic behaviors interfered with the normal sequence of maternal behavior by exaggerating some components and delaying others. These results are relevant to disturbances in maternal behavior caused by hyperreactivity or by other drugs that increase dopaminergic activity, such as cocaine. © 2000 Elsevier Science Inc.

Maternal behavior Nursing behavior Dopamine Cocaine Hyperactivity Stereotypy

IN common with other motorically active motivated behaviors, maternal retrieval and grouping of pups at the nest site in rats are dependent upon adequate levels of dopamine (DA) (39). This has been shown with systemic administration of the D_2 DA receptor antagonists, haloperidol (13,44) or raclopride (15), 6-OHDA neurotoxic lesions of DA source neurons in the ventral tegmental area (15), or of target neurons in the ventral striatum (16), and microinfusion of the D_1-D_2 DA receptor antagonist *cis*-flupenthixol into the nucleus accumbens (23). Nest building (13) and pup licking (23,44) are also inhibited by effective antagonism of DA. Further, active interaction with pups increases release of DA in the ventral striatum of lactating rats (14), which is consonant with the findings that systemic administration of low dosages of haloperidol (0.05 or 0.10 mg/kg) reduce maternal motivation to make snout contact with pups, but do not interfere with retrieval and licking of pups when such contact is unimpeded (41). Thus, baseline levels of DA are needed to ensure maternal contact with pups despite an obstacle; this contact then increases mesostriatal DA levels, an increase necessary for the normal display of active maternal behaviors, such as the efficient and complete execution of retrieval and grouping of pups. In contrast, suckling-induced quiescent nursing behavior (40,45) is facilitated by systemic (38,44) or intra-accumbens (23) DA receptor blockade, suggesting that suckling inhibits extrahypothalamic DA (38,44).

The exquisite sensitivity of distinct components of maternal behavior (MB) to variations in levels of DA, and in interaction with variations in the dam's level of motivation as well (41), raise the question of whether mild increases in DA activity would interfere with maternal responsiveness; this may occur after stressful arousal that leads to the dam's delay in settling down to nurse due to increased exploratory sniffing, prolonged carrying of pups, or both. There is suggestive evidence for such interference from several studies on the acute effects on MB in rats of cocaine, a psychomotor stimulant that blocks the reuptake of DA, norepinephrine, and serotonin transporters (33); these studies were carried out because of reports that cocaine abuse by women increases the likelihood of maternal neglect (3) and child abuse (28). The consensus of these studies is that one or more component of MB is disrupted when circulating cocaine levels are high (18,21,22,24, 49,50,54), but not once it is no longer present (49). Such disruption is evident not only after a series of daily administrations beginning either prepartum (18,49) or postpartum (21,54), but also after a single acute injection of cocaine at the

Requests for reprints should be addressed to Judith M. Stern, Rutgers–The State University of NJ, Department of Psychology, 152 Frelinghuysen Road, Piscataway, NJ 08854.

onset of MB just after parturition (22) or during established MB (24), and with dosages as low as 5–15 mg/kg (21,24,54). Several studies also quantified large increases in locomotor activity (21,48–50) and stereotypy (21,50) with these treatments.

The purpose of the present study was to assess the acute effects of a low dosage of a mixed D_1-D_2 DA receptor agonist, apomorphine (APO), on established MB. In male rats, low dosages of APO (0.125, 0.25, and 0.5 mg/kg) elicited dosage-dependent increases in the low intensity components of stereotypy, sniffing, and repetitive head movements, whereas high dosages (1–4 mg/kg) elicited the high intensity components of licking, biting, and gnawing (6); also, treatment with 0.25, but not 0.1, mg/kg APO increased stereotypy scores at 30-min postinjection (27). In lactating rats, 0.1 mg/kg APO did not significantly alter maternal retrieval in a 5-min test (13). Therefore, we hypothesized that initial maternal responsiveness would not be altered by low dosages of APO, but that the normal maternal sequence would then be disrupted due to the induction of stereotyped behaviors. We observed dams one at a time and continuously for 1 h after a 4-h dam–litter separation and 10 min after injection of 0, 0.1, and 0.25 mg/kg APO SC, a procedure that ensures the full repertoire of pup-directed MBs in controls (39) and the provision of quantitative data on competitive behaviors that may account for any observed alterations in the MB sequence.

METHOD

Animals

The subjects were primiparous Long–Evans rats, *Rattus norvegicus*, raised and bred in our laboratory. They were housed three to four per suspension cage in a colony maintained at 22°C, on a 12 L:12 D cycle, with lights on at 0800 h. Food (Purina Rat Chow) and water were available ad lib. Females, 65–90 days-old, were mated with a Long–Evans male on a night of proestrus; pregnancy was confirmed by the presence of a copulatory plug and sperm in vaginal smears the next day (gestation day 1). At least 3 days prior to parturition, pregnant females were transferred to clear, polypropylene cages (42 × 22 × 20 cm), with wood shavings for bedding. By day 1, postpartum litters were culled to eight pups each. Four hours before the start of behavioral testing, pups were removed from their dams and placed in a moist incubator at nest temperature (~34°C). Pups were manually expressed of urine and feces shortly before reunion and weighed before and after the observation.

Observations

Maternal behaviors were assessed with a minicomputer-based event recorder (S & K Computer Products, Toronto, Canada). We recorded behaviors directed toward the pups including sniffing, retrieval (in which the dam picks up a pup by the mouth and carries it to the nest), mouthing (repositioning), licking, hovering over (while motorically active), and nursing in an upright-crouched, dorsally-arched, or kyphotic (39) posture (while immobile), as well as nest building (nosing or paw manipulation of bedding near the nest site), self-grooming, feeding, and immobility away from the nest. We also recorded pup stretch responses (PSRs), indicative of a milk ejection (11).

Procedure

Testing took place on day 7 ± 1 postpartum. Ten minutes before the start of the test, dams (n = 8/group) were injected subcutaneously (in the neck) with apomorphine (APO; Sigma Chemicals), 0.1 or 0.25 mg/kg/ml, or the saline vehicle (SAL). At the start of the 60-min observation, pups were scattered in the dam's cage opposite the nest site.

Statistical Analyses

Statistical differences between groups were assessed with one-way analysis of variance (ANOVA) using SigmaStat. If either normality or equal variance were violated using the parametric F-test, then the Kruskal–Wallis nonparametric ANOVA was carried out and the H-value reported instead. Latencies included responders only, whereas other measures also included nonresponders. Proportion positive for a given measure was assessed with the Fisher Exact Probability Test. The relative litter weight gain (RLWG; g) was calculated as: [gain/weight before] × 100.

RESULTS

All dams sniffed pups and within the first 5 min, and all but one APO 0.25 dam retrieved ⩾1 pup; the groups did not differ significantly in the latency to sniff pups, $H(2) = 4.45$, $p > 0.1$, or to retrieve the first pup, $H(2) = 1.41$, $p > 0.4$ (responders only) (Fig. 1A). The groups did not differ significantly in number of pups retrieved within the first 5 min, $H(2) = 4.39$, $p > 0.1$ (Fig. 1B, left), although it was lowest in group APO 0.25. The percentage of dams retrieving ⩾5 pups within 5 min, however, was

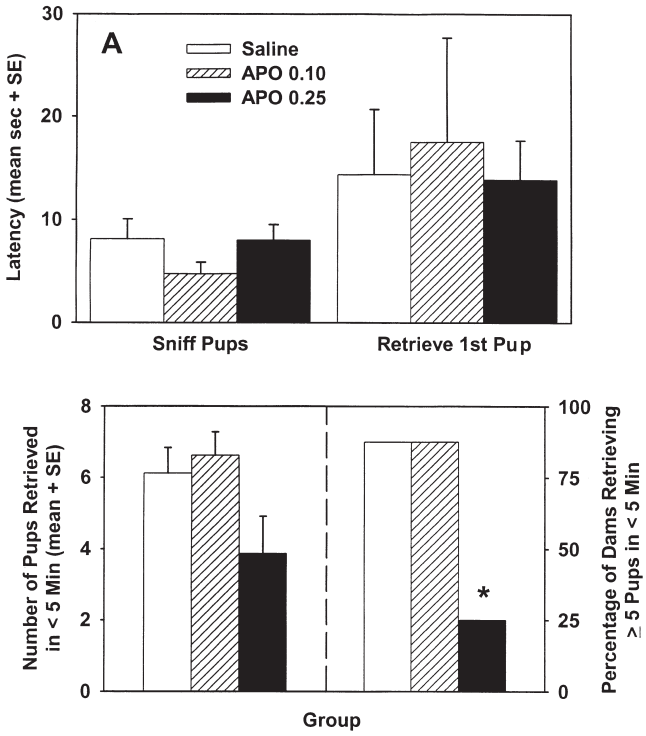

FIG. 1. Effects on day 7 ± 1 postpartum dams of treatment with 0 (saline), 0.10, or 0.25 mg/kg apomorphine (APO) on maternal behavior during the first 5 min after reunion with their litter following a 4-h separation. (A) Latency (mean second + SE) to sniff pups and to retrieve the first pup. (B) Left: number of pups retrieved (mean + SE); right: percentage of dams that retrieved ⩾5 pups in <5 min. *$p < 0.05$.

significantly lower in group APO 0.25 (Fig. 1B, right). When retrieval was not completed by 5 min, either the remaining pups grouped themselves or retrieval began or resumed later.

APO-treated dams displayed a 7–13-fold increase in time spent carrying pups in the entire observation, both during retrieval while the dam roamed about the cage and when repositioning them within the nest by mouthing, $H(2) = 6.20$, $p < 0.05$ (Fig. 2A). APO dams often grasped a pup in abnormal areas, such as near the head or by the leg, rather than by the back, and each pup-carrying episode was very prolonged, sometimes for ⩾1 min continuously. Similarly, APO-treated dams displayed a 10–15-fold increase in sniffing pups, $H(2) = 15.80$, $p < 0.001$ (Fig. 2B), a five- to sevenfold increase in sniffing the cage, $H(2) = 6.08$, $p < 0.05$ (Fig. 2C), and a 14–46-fold increase in sniffing the bedding, $H(2) = 17.83$, $p < 0.001$ (Fig. 2D). The pup sniffing that occurred in the APO animals seemed not to be directed specifically at the pups, but rather was a consequence of the pups being on the bedding; indeed, often an APO-treated dam would push away a pup to continue sniffing the bedding. The differences between the two dosages of APO are not significant for these behaviors, except for "sniff bedding," in which case the effects of only the higher dosage is significantly different from that of the saline control condition. Whereas the total duration of all sniffing (Table 1) constituted less than 2% of the observation time among control dams, it was 16% and 32% in APO 0.10 and 0.25 dams, respectively, a significant dosage-dependent effect. In contrast to these pronounced effects of APO treatment, there were no group differences in durations of nesting or self-grooming (Table 1), or in feeding (data not shown), which was displayed by only a few dams. Unlike a report on male rats treated with 0.03 or 0.3 mg/kg APO (1), we observed little or no immobility and no vacuous mouth movements. Although exploration (data not shown), including rearing and walking about the cage, was highest in the APO 0.25 group, the group differences are not significant, the variance is high, and this measure, regrettably, was contaminated with that of sniffing, whether displayed in one location for prolonged periods or while moving.

The long time spent carrying and sniffing pups and sniffing the cage and its bedding interfered with the normal progress of maternal activities among APO-treated dams. Thus, there were dosage-dependent increases in the latency to lick the pups, $H(2) = 18.68$, $p < 0.001$ (Fig. 3A), and to nurse them in a sustained kyphotic posture, $F(2,21) = 28.00$ $p < 0.001$ (Fig. 3B). The duration of pup licking once begun did not differ significantly between groups, $H(2) = 4.96$, $p = 0.084$ (Fig. 3C), but among the dams treated with 0.25 mg/kg APO there was a significant decrease in the duration of total kyphotic nursing, $F(2,21) = 10.90$, $p < 0.001$ (Fig. 3D), as well as in kyphotic nursing with either a low or high dorsal arch (Table 1). Nursing in other postures, such as supine (lying on side), was not seen. The group differences in latency and duration of kyphotic nursing are consonant with those in latency to first PSR from time of reunion, number of PSRs, and RLWG (Table 1). In contrast, there are no significant group differences in duration of hovering over the pups, total time over the pups (hovering over while active plus quiescent nursing), or latency to first PSR from onset of sustained kyphosis (Table 1).

DISCUSSION

Treatment of lactating rats with low dosages of apomorphine did not interfere with initial maternal responsiveness,

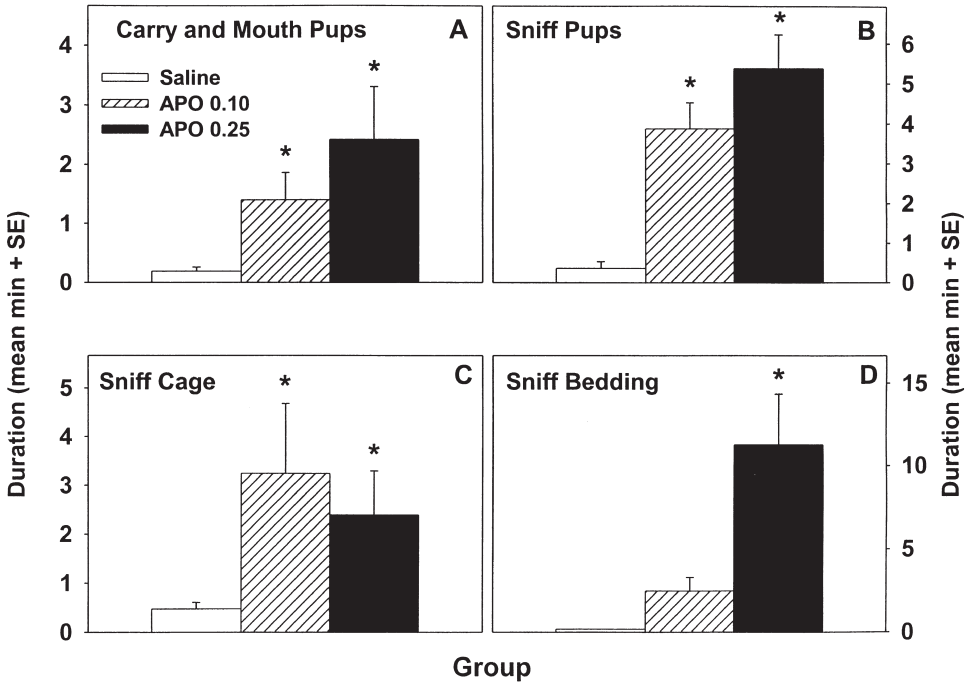

FIG. 2. Effects on day 7 ± 1 postpartum dams of treatment with 0 (saline), 0.10, or 0.25 mg/kg apomorphine (APO) on duration of various behaviors (mean minute + SE) of day 7 ± 1 postpartum dams during 1 h with their litter following a 4-h separation. (A) Carry and mouth pups; (B) sniff pups; (C) sniff the cage, other than bedding; and (D) sniff bedding. *$p < 0.05$ vs. saline control group.

TABLE 1

EFFECTS OF APOMORPHINE (0, 0.10, OR 0.25 mg/kg SC; n = 8 PER GROUP) ON MEAN ± SEM VALUES OF DAM BEHAVIORS AND OFFSPRING WEIGHT GAINS

Measure	SAL	APO 0.10	APO 0.25	$F(2, 21)$ or $H(2)$	$p \leq$
Duration (s)					
Total sniffing	61 ± 16*	573 ± 93†	1142 ± 199‡	**17.36**	0.001
Hovering over	1113 ± 77	1250 ± 128	1449 ± 276	0.87	NS
Low kyphotic crouch	1299 ± 176*	1332 ± 101*	830 ± 112†	4.41	0.025
High kyphotic crouch	581 ± 105*	276 ± 56†	169 ± 37†	**9.38**	0.01
Total time over pups	2992 ± 155	2858 ± 104	2447 ± 263	**2.80**	NS
Nesting	98 ± 11	105 ± 37	105 ± 24	0.25	NS
Self-grooming	196 ± 35	251 ± 34	296 ± 75	0.95	NS
Latency (s)					
PSR	1203 ± 177*	1865 ± 249†	2884 ± 162‡	16.82	0.0001
PSR from bout kyphosis	474 ± 50	514 ± 105	512 ± 63	0.09	NS
Number of PSRs	5.5 ± 0.6*	4.6 ± 1.0*†	2.5 ± 0.5†	4.45	0.03
RLWG (g)	4.5 ± 0.4*	4.0 ± 0.6*	1.8 ± 0.4†	8.28	0.002

PSR (pup stretch response) from bout kyphosis = the latency to first PSR from the onset of kyphotic nursing within that bout; thus, two instances of ⩾2 min of kyphosis followed by prolonged interruption of that nursing bout were excluded for this analysis. RLWG = relative weight gain. Different symbols indicate significant mean differences, $p \leq 0.05$.

as revealed by latency to sniff and to retrieve pups and retrieval frequency within the first 5 min after reunion. Subsequently, however, APO disrupted the maternal sequence in various ways, effects that were more pronounced with 0.25 than with 0.1 mg/kg. APO treatment resulted in a delayed onset of licking pups, of nursing them, and, therefore, of milk ejections. These delays were preceded by prolonged oral carrying of pups and stereotyped sniffing of pups, bedding, and other parts of the cage. Once the effects of APO—which has a half-life of about 10 min (1)—wore off, the normal sequence

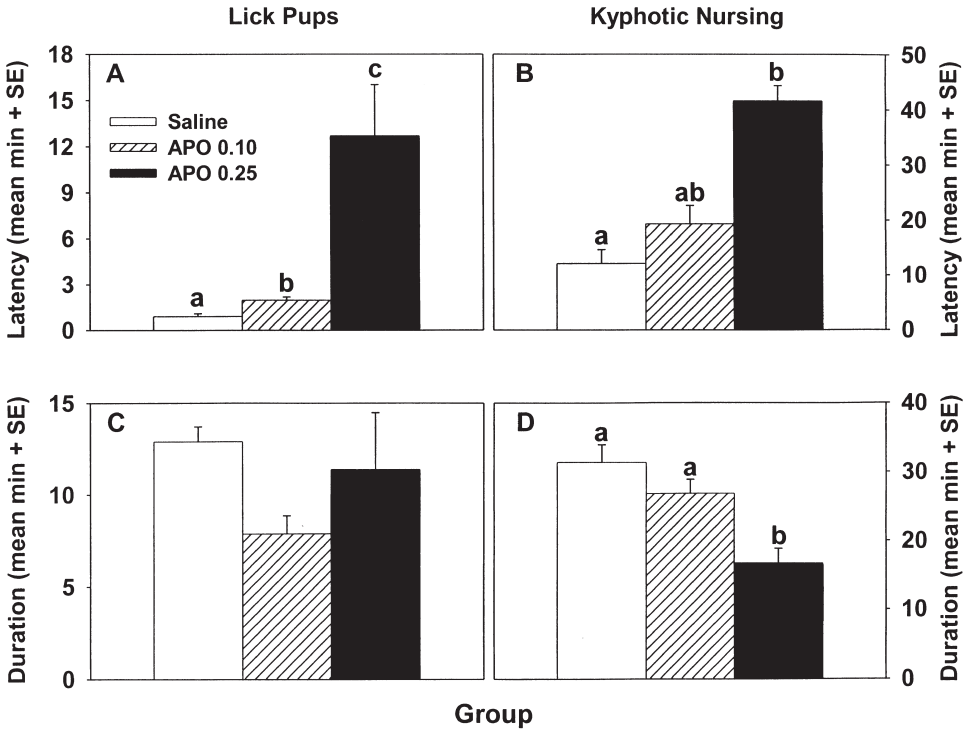

FIG. 3. Effects on day 7 ± 1 postpartum dams of treatment with 0 (saline), 0.10, or 0.25 mg/kg apomorphine (APO) on latency (top) and duration (bottom) of licking pups (left) and kyphotic nursing (right) (mean minute + SE) during 1 h with their litter following a 4-h separation. Latency (A) to lick pups and (B) to display the kyphotic nursing posture for ⩾2 min continuously; duration of (C) pup licking and (D) kyphotic nursing. Means with different letters are significantly different, $p \leq 0.05$.

of MB resumed. These results are the first to show the disruptive effects on MB of a DA receptor agonist; thus, the expression of normal MB is impaired by either too little dopaminergic activity (13,15,16,23,38,44) or too much.

Our finding that initial maternal responsiveness is not prevented by a low intensity of DA agonism is supported by other reports. While 0.1 mg/kg APO in lactating rats injected immediately before 5-min tests (with no prior dam–litter separation) counteracted the retrieval-disrupting effect of treatment with 0.2 mg/kg haloperidol 2–2.5 h earlier (86 vs. 0–14% retrieved and grouped all six pups), this dosage of APO alone decreased the percentage retrieving slightly but not significantly (57 vs. 100% pretest), a decrease that may have been due to the transient display of stereotypical behaviors (13). Similarly, daily retrieval frequency of lactating rats during 5-min tests in the home cage was not impaired after injection of a low dosage of cocaine (5 mg/kg) (54) and retrieval latency was not impaired after a single injection of 5, 10 (24), or 15 (22) mg/kg cocaine. Indeed, low dosages of APO (e.g., 0.2 mg/kg) have been used to reactive the sexual arousal of male rats thought to have a blockade of DA transmission due to sexual satiety (26); perhaps waning maternal responsiveness—due, for example, to prolonged separation from pups (35)—may be similarly reactivated.

Apomorphine, by binding to DA receptors of both the D_1 and D_2 families, induces a variety of stereotypies; as the dosage of APO increases, the stereotypy progressively intensifies (17,29). DA agonism, induced in this study with low dosages of APO, may have been heightened by the dam's physical contact with pups, which induces release of DA from the ventral striatum, including the nucleus accumbens (Acb) (14), probably via stimulation of the trigeminal nerve during sniffing and carrying pups (20,36,39,42,43). Stereotypical behaviors interfered with normal responsiveness to stimuli from pups until the APO wore off (12,46). When the dam directed her sniffing toward pups, it was abnormally prolonged [vs. $<$0.5 s normally before each retrieval: (42)], and she was likely to push the pup away to sniff the bedding instead, which has been termed "head down" (5). Similarly, during APO treatment male rats paired with another male in an open field are asocial, but increase their activity level in response to the other rat (5). Although licking is another type of oral stereotypy, licking of pups was delayed until the APO wore off. Stereotypical licking requires a higher level of DA agonism than that administered in the present study (6,17), and may not be expressed in a social context (12,46). Because quiescent nursing necessarily requires inhibition of motoric activity (39,40,45), and is enhanced by DA receptor antagonism (23,38,44), it is understandable that it was delayed while motorically active stereotypical behaviors were displayed. These effects on nursing behavior were reflected as well by prolonged latency to the first milk ejection and reduced litter weight gains, the latter being due to the limited time available in the 60-min observation once sustained nursing finally began.

Because no research group that has reported on the effects of cocaine on MB in animals has yet to assess the neurochemical basis of their positive findings—for example, by comparisons with amphetamine or by coadministration of a DA or serotonin receptor antagonist—the present findings on the effects of APO on MB in rats provide an initial perspective on the extent to which these effects of cocaine may be due to its heightened dopaminergic activity. As indicated above, low dosages of cocaine (5–15 mg/kg), administered acutely shortly before a test, like low dosages of APO in the present study, did not interfere with initial maternal responsiveness. Subsequently, the responsiveness to pups by cocaine-treated dams resembles that seen herein after APO, including roaming about the cage with a pup in the mouth (54), delayed or decreased licking of pups (24,54), and decreased nursing behavior (18,21,22,24,48,49). These comparisons lend strong support to an interpretation of disruptions in MB while APO or cocaine are circulating as due largely to display of competitive behaviors elicited by heightened dopaminergic activity in mesotelencephalic pathways. Indeed, acute, systemic administration of 15, 20, or 40 mg/kg cocaine in lactating rats caused substantial increases in stereotypical behaviors (21,49,50), locomotor activity (48–50), or both. Further, the various behavioral effects of cocaine in rats—including hyperactivity, sniffing, and oral stereotypies—are dependent upon heightened mesolimbic dopaminergic activity [see (51)], including activation of both the D_1 and D_2 DA receptors (47), while a drug substitution test revealed comparable effects of apomorphine and cocaine (4). It is not surprising, therefore, that all papers on effects of cocaine on MB acknowledge that heightened dopaminergic transmission is the most likely mediating factor. Until the appropriate experiments are carried out, however, interaction with other neurotransmitters or interference with neuroendocrine regulation cannot be ruled out for at least a partial explanation of the effects on MB of cocaine [see (21) and (24)] or APO, although these are unlikely when a low dosage is administered acutely.

Systemically administered APO and cocaine have widespread actions on the brain. Infusion of a D_2 receptor antisense oligonucleotide was used recently to show that stereotypic sniffing induced by low dosages of APO are mediated by presynaptic D_2 autoreceptors in the striatum (34). Microinfusion of various dopaminergic drugs revealed that both D_1 and D_2 receptor subtypes are involved in the expression of oral stereotypies, including head-down sniffing and mouth movements, and that the ventrolateral striatum is the major site for the elicitation of these behaviors (7). In contrast, locomotor activation is elicited by cocaine microinfusions into the Acb (8). These findings shed light on the site-specific effects of cocaine (50 μg/0.5 μl/side) on MB that were demonstrated recently. Following microinfusions into the medial preoptic area (MPOA) or Acb in lactating rats, but not into the dorsal striatum or dorsomedial hippocampus, both hyperactivity and impairments in all aspects of pup-oriented MB were found, but no stereotypy (51). Thus, cocaine infused specifically into two regions known to be important for the expression of MB, but not into sites known not to be so involved (16,23,30,37), essentially duplicated findings with systemic administration. The authors argue persuasively that the effects of acutely administered cocaine on MB are due to its stimulant and not its anesthetic properties because cocaine, but not the local anesthetics, procaine or lidocaine, elicited hyperactivity when infused into the Acb (8). The further argument that because of differences in their temporal pattern the disruptions in MB are not due to hyperactivity—measured in a special apparatus away from the home cage— is less persuasive. What is needed are measures of activity and other nonmaternal behaviors during the interactions with pups to provide a behavioral explanation of the dysfunctions, and because the temporal pattern of hyperactivity induced by cocaine may be altered by pup-elicited DA release from the ventral striatum (14).

Whether or not the effects of site-specific microinfusions of cocaine are all due to specific "alterations in the neural circuit that supports MB" (51) remains to be determined. Infusions of cocaine in the core of the Acb were as effective as those in the shell of the Acb in interfering with retrieval of

pups (51), findings at variance with results from our laboratory showing that microinfusions of the DA receptor antagonist, *cis*-flupenthixol, in the Acb that included the shell, but not those confined to the core, prevented retrieval of pups (23). This shell-core difference is supported by a wealth of data on their distinctions, such as mesolimbic vs. nigrostriatal characteristics (2,10,19,53); in particular, the shell, but not the core, of Acb is connected with regions known to be important for retrieval of pups, such as the lateral hypothalamus and preoptic area (30), bed nucleus of the stria terminalis (31), ventral tegmental area (32), and periaqueductal gray (25). Thus, it is likely that hyperactivity induced by microinfusions of cocaine into either the core or the shell of Acb, or the MPOA, largely contributes to impairments in MB.

In conclusion, elucidating the basis for the disruptions in maternal behavior following acute administration of apomorphine revealed that they are not specific to maternal motivation, but rather to induction of competitive responses; this view may be applicable as well to the effects of cocaine on MB. In support of the present interpretation, operant responding for food reinforcement was dose dependently decreased by low dosages of APO, with cessation of responding after 0.3 mg/kg (9), similar to the higher dosage used herein to assess spontaneous maternal behavior. Appropriate site- and neurochemical-specific manipulations, however, can reveal the precise role of a given neurotransmitter, such as dopamine, with respect to each component of a complex motivated behavior (23,52).

ACKNOWLEDGEMENTS

The authors thank Anthony Azzara and Joseph Lonstein for assistance with collection of data. This work was supported by NIMH Grant MH40459 (J.M.S.) and a Busch Bequest Grant. The present study was part of the thesis work of Maria Protomastro, submitted in partial fulfillment of the Master's degree at Rutgers University (1994), and was presented at the first meeting of the Society for Behavioral Neuroendocrinology, Baltimore, MD, May 28–31, 1997.

REFERENCES

1. Bianchi, G.; Landi, M.; Garattini, S.: Disposition of apomorphine in rat brain areas: Relationship to stereotypy. Eur. J. Pharmacol. 131:229–236; 1986.
2. Brog, J. S.; Salyapongse, A.; Deutch, A. Y.; Zahm, D. S.: The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: Immunohistochemical detection of retrogradely transported fluro-gold. J. Comp. Neurol. 338:255–278; 1993.
3. Burns, K.; Chethik, L.; Burns, W. J.; Clark, R.: Dyadic disturbances in cocaine-abusing mothers and their infants. J. Clin. Psychol. 313:666–669; 1991.
4. Carey, R. J.; Damianopoulos, E. N.: Activation of an apomorphine behavior pattern by cocaine: A new behavioral test for drug substitution. J. Neurosci. Methods 46:1–10; 1993.
5. Chow, H. L.; Beck, H. M.: The effect of apomorphine on the open-field behavior of rats: Alone and in pairs. Pharmacol. Biochem. Behav. 21:85–88; 1984.
6. Costall, B.; Naylor, B. J.; Neumeyer, J. L.: Differences in the nature of stereotyped behaviour induced by apomorphine derivatives in the rat and in their actions in extrapyramidal and mesolimbic brain areas. Eur. J. Pharmacol. 31:1–16; 1975.
7. Delfs, J. M.; Kelley, A. E.: The role of D1 and D2 dopamine receptors in oral stereotypy induced by dopaminergic stimulation of the ventrolateral striatum. Neuroscience 39:59–67; 1990.
8. Delfs, J. M.; Schreiber, L.; Kelley, A. E.: Microinjection of cocaine into the nucleus accumbens elicits locomotor activation in the rat. J. Neurosci. 10:303–310; 1990.
9. Depoortere, R.; Perrault, G.; Sanger, D. J.: Behavioural effects in the rat of the putative dopamine D3 receptor agonist 7-OH-DPAT: Comparison with quinpirole and apomorphine. Psychopharmacology (Berlin) 124:231–240; 1996.
10. Deutch, A. Y.; Cameron, D. S.: Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. Neuroscience 46:49–56; 1992.
11. Drewett, R. F.; Trew, A. M.: The milk ejection of the rat, as a stimulus and a response to the litter. Anim. Behav. 26:982–987; 1978.
12. Geyer, M. A.; Russo, P. V.; Segal, D. S.; Kuczenski, R.: Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behavior in rats. Pharmacol. Bichem. Behav. 28:393–399; 1987.
13. Giordano, A. L.; Johnson, A. E.; Rosenblatt, J. S.: Haloperidol-induced disruption of retrieval behavior and reversal with apomorphine in lactating rats. Physiol. Behav. 48:211–214; 1990.
14. Hansen, S.; Bergvall, A. H.; Nyiredi, S.: Interaction with pups enhances dopamine release in the ventral striatum of maternal rats: A microdialysis study. Pharmacol. Biochem. Behav. 45:673–676; 1993.
15. Hansen, S.; Harthon, C.; Wallin, E.; Lofberg, L.; Svennson, K.: Mesotelencephalic dopamine system and reproductive behavior in the female rat: Effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. Behav. Neurosci. 105:588–598; 1991.
16. Hansen, S.; Harthon, C.; Wallin, E.; Lofberg, L.; Svennson, K.: The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat. Pharmacol. Biochem. Behav. 39:71–77; 1991.
17. Havemann, U.; Magnus, B.; Möller, H. G.; Kuschinsky, K.: Individual and morphological differences in the behavioural response to apomorphine in rats. Psychopharmacology (Berlin) 90:40–48; 1986.
18. Hecht, G. S.; Spear, N. E.; Spear, L. P.: Changes in progressive ratio responding for intravenous cocaine throughout the reproductive process in female rats. Dev. Psychobiol. 35:136–145; 1999.
19. Heimer, L.; Zahm, D. S.; Churchill, L.; Kalivas, P. W.; Wohltmann, C.: Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41:89–125; 1991.
20. Huston, J. P.; Steiner, H.; Schwarting, R. K.; Morgan, S.: Parallels in behavioral and neural plasticity induced by unilateral vibrissae removal and unilateral lesion of the substantia nigra. In: Flohr, H., ed. Postlesion neural plasticity. Berlin: Springer Verlag; 1988:537–551.
21. Johns, J. M.; Nelson, C. J.; Meter, K. E.; Lubin, D. A.; Couch, C. D.; Ayers, A.; Walker, C. H.: Dose-dependent effects of multiple acute cocaine injections on maternal behavior and aggression in Sprague–Dawley rats. Dev. Neurosci. 20:525–532; 1998.
22. Johns, J. M.; Noonan, L. R.; Zimmerman, L. I.; Pedersen, C. A.: Effects of chronic and acute cocaine treatment on the onset of maternal behavior and aggression in Sprague–Dawley rats. Behav. Neurosci. 108:107–112; 1994.
23. Keer, S. E.; Stern, J. M.: Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieval and licking, but enhances nursing behavior in lactating rats. Physiol. Behav. 67:659–669; 1999.
24. Kinsley, C. H.; Turco, D.; Bauer, A.; Beverley, M.; Wellman, J.; Graham, A. L.: Cocaine alters the onset and maintenance of maternal behavior in lactating rats. Pharmacol. Biochem. Behav. 47:857–864; 1994.
25. Lonstein, J. S.; Stern, J. M.: Site and behavioral specificity of periaqueductal gray lesions on postpartum sexual, maternal, and aggressive behaviors in rats. Brain Res. 804:21–35; 1998.
26. Mas, M.; Fumero, B.; Perez-Rodriguez, I.: Induction of mating behavior by apomorphine in sexually sated rats. Eur. J. Pharmacol. 280:331–334; 1995.

27. Mittleman, G.; LeDuc, P. A.; Whishaw, I. Q.: The role of D1 and D2 receptors in the heightened locomotion induced by direct and indirect dopamine agonists in rats with hippocampal damage: An animal analogue of schizophrenia. Behav. Brain Res. 55:253–267; 1993.
28. Murphy, J. M.; Jellinik, M.; Quinn, D.; Smith, G.; Poitrast, F. G.; Goshko, M.: Substance abuse and serious child mistreatment: Prevalence, risk and outcome in a court sample. Child Abuse Neglect 15:197–211; 1991.
29. Murray, A.; Waddington, J. L.: The interaction of clozapine with dopamine D1 versus dopamine D2 receptor-mediated function: Behavioral indices. Eur. J. Pharmacol. 186:79–86; 1990.
30. Numan, M.: Maternal behavior. In: Knobil, E.; Neill, J. D., eds. The physiology of reproduction, 2nd ed. New York: Raven; 1994:221–302.
31. Numan, M.; Numan, M. J.: A lesion and neuroanatomical tract-tracing analysis of the role of the bed nucleus of the stria terminalis in retrieval behavior and other aspects of maternal responsiveness in rats. Dev. Psychobiol. 29:23–52; 1996.
32. Numan, M.; Smith, H. G.: Maternal behavior in rats: Evidence for the involvement of preoptic projections to the ventral tegmental area. Behav. Neurosci. 98:712–727; 1984.
33. Pitts, D. K.; Marwah, J.: Neuropharmacology of cocaine: Role of monoaminergic systems. Mongr. Neural Sci. 13:34–54; 1987.
34. Rajakumar, N.; Laurier, L.; Niznik, H. B.; Stoessl, A. J.: Effects of intrastriatal infusion of D2 receptor antisense oligonucleotide on apomorphine-induced behaviors in the rats. Synapse 26:199–208; 1997.
35. Rosenblatt, J. S.; Lehrman, D. S.: Maternal behavior of the laboratory rat. In: Rheingold, H., ed. Maternal behavior in mammals. New York: Wiley; 1963:8–57.
36. Steiner, H.; Huston, J. P.; Morgan, S.: Apomorphine reverses direction of asymmetry in facial scanning after 10 days of unilateral vibrissae removal in rat: Vibrissotomy-induced denervation supersensitivity? Behav. Brain Res. 22:283–287; 1986.
37. Stern, J. M.: Maternal behavior: Sensory, hormonal, and neural determinants. In: Brush, F. R.; Levine, S., eds. Psychoendocrinology. New York: Academic Press; 1989:105–226.
38. Stern, J. M.: Nursing posture is elicited rapidly in maternally naive, haloperidol-treated female and male rats in response to ventral trunk stimulation from active pups. Horm. Behav. 25:504–517; 1991.
39. Stern, J. M.: Somatosensation and maternal care in Norway rats. In: Rosenblatt, J. S.; Snowden, C. T., eds. Parental care: Evolution, mechanisms, and adaptive significance. Advances in the study of behavior, vol. 25. New York: Academic Press; 1996:243–294.
40. Stern, J. M.; Johnson, S. K.: Ventral somatosensory determinants of nursing behavior in Norway rats. I. Effects of variations in the quality and quantity of pup stimuli. Physiol. Behav. 47:993–1011; 1990.
41. Stern, J. M.; Keer, S. E.: Maternal motivation of lactating rats is disrupted by low dosages of haloperidol. Behav. Brain Res. 99:231–239; 1999.
42. Stern, J. M.; Kolunie, J. M.: Perioral anesthesia disrupts maternal behavior during early lactation in Long–Evans Rats. Behav. Neural Biol. 52:20–38; 1989.
43. Stern, J. M.; Kolunie, J. M.: Trigeminal lesions and maternal behavior in rats. I. Effects of cutaneous rostral snout denervation on maintenance of nurturance and maternal aggression. Behav. Neurosci. 105:984–997; 1991.
44. Stern, J. M.; Taylor, L.: Haloperidol inhibits maternal retrieval and licking, but enhances nursing behavior and litter weight gains in lactating rats. J. Neuroendocrinol. 3:591–596; 1991.
45. Stern, J. M.; Dix, L.; Bellomo, C.; Thramann, C.: Ventral trunk somatosensory determinants of nursing in Norway rats. 2. Role of nipple and surrounding sensations. Psychobiology 20:71–80; 1992.
46. Szechtman, H.: Behavior performed at onset of drug action and apomorphine stereotypy. Eur. J. Pharmacol. 121:49–56; 1986.
47. Ushijima, I.; Carion, M. A.; Horita, A.: Involvement of D1 and D2 dopamine systems in the behavioral effects of cocaine in rats. Pharmacol. Biochem. Behav. 52:737–741; 1995.
48. Vernotica, E. M.; Morrell, J. I.: Plasma cocaine levels and locomotor activity after systemic injection in virgin and in lactating female rats. Physiol. Behav. 64:399–407; 1998.
49. Vernotica, E. M.; Lisciotto, C. A.; Rosenblatt, J. S.; Morrell, J. I.: Cocaine transiently impairs maternal behavior in the rat. Behav. Neurosci. 110:315–323; 1996.
50. Vernotica, E. M.; Rosenblatt, J. S.; Morrell, J. I.: Acute cocaine disrupts all components of established maternal behavior in the rat. Soc. Neurosci. Abstr. 26:1884; 1996.
51. Vernotica, E. M.; Rosenblatt, J. S.; Morrell, J. I.: Microinfusion of cocaine into the medial preoptic area or nucleus accumbens transiently impairs maternal behavior in the rat. Behav. Neurosci. 113:377–390; 1999.
52. Warner, R. K.; Thompson, J. T.; Markowski, V. P.; Loucks, J. A.; Bazzett, T. J.; Eaton, R. C.; Hull, E. M.: Microinjection of the dopamine antagonist cis-flupenthixol into the MPOA impairs copulation, penile reflexes and sexual motivation in male rats. Brain Res. 540:177–182; 1991.
53. Zahm, D. S.; Heimer, L.: Specificity in the efferent projections of the nucleus accumbens in the rat: Comparison of the rostral pole projection patterns with those of the core and shell. J. Comp. Neurol. 327:220–232; 1993.
54. Zimmerberg, B.; Gray, M. S.: The effects of cocaine on maternal behavior in the rat. Physiol. Behav. 52:379–384; 1992.