Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 4, pp. 857-864, 1994

0091-3057/94 $6.00 + .00

Cocaine Alters the Onset and Maintenance of Maternal Behavior in Lactating Rats

CRAIG HOWARD KINSLEY,[1] DIANE TURCO, ANGELA BAUER, MICHAEL BEVERLY, JACQUELINE WELLMAN AND AMANDA L. GRAHAM

Department of Psychology, 116 Richmond Hall, University of Richmond, VA 23173

Received 15 June 1993

KINSLEY, C. H., D. TURCO, A. BAUER, M. BEVERLY, J. WELLMAN AND A. L. GRAHAM. *Cocaine alters the onset and maintenance of maternal behavior in lactating rats.* PHARMACOL BIOCHEM BEHAV 47(4) 857-864, 1994.—Though much attention has been devoted to the behavioral and physiological consequences of cocaine abuse in offspring, little is known regarding the effects on the maternal behavior of the cocaine-exposed dam. We examined whether cocaine affects the initiation (late pregnancy) and/or maintenance (postpartum [PP]) phases of full maternal behavior (FMB; retrieving, grouping, and crouching over six pups) in Sprague-Dawley female rats. In Experiment 1, cocaine (5.0 or 10.0 mg/kg) or saline was administered on PP day 5 or 6 and FMB scored. Both dosages significantly disrupted FMB, particularly crouching, though 10.0 mg/kg had a greater effect on FMB. Experiment 2 (using 10.0 mg/kg cocaine) examined specific elements of the disruption and found significant reductions in proportion of females engaging in FMB, as well as increases in the latencies to contact, retrieve, lick, group, and crouch over pups. In Experiment 3 osmotic pumps containing 20 mg cocaine/kg/day or saline were implanted SC in day 14 pregnant rats. FMB testing was performed on days 1-2 postpartum together with a T-maze pup-retrieval test on postpartum days 3-5. Cocaine disrupted FMB in the homecage, in general, rendering the females less attentive to young, but was without effect in the T-maze tests. Cocaine—perhaps owing to its purported dopaminergic activity—may operate through motivational mechanisms to disrupt FMB in the postpartum maintenance phase; and through effects on late pregnancy levels of prolactin (a hormone which stimulates FMB), to disrupt maternal behavior during the initiation phase.

Dopamine Drug abuse Hormones Lactation Maternal behavior Neonates Pregnancy Prolactin

COCAINE consumption is a major public health concern; attention, however, has primarily focused on the myriad ways cocaine may reduce the viability of a fetus or neonate [and, hence, the adult; (1,10,21,36)]. Relative to what we know about the teratological consequences of cocaine-exposure, little is known regarding cocaine's effects on the mother's maternal behavior. Cocaine modifies endocrine profiles and development in the mother as well as her fetus (19,45). Maternal behavior—that which is stimulated during pregnancy in the female—relies primarily on the interaction among ovarian hormones such as estradiol and progesterone, and the pituitary hormone prolactin (4). Cocaine, therefore, may interfere with this endocrine stimulation of maternal behavior.

Though there is a dearth of information regarding cocaine's effects on the mother's maternal behavior [cf., (28, 56)], Zimmerberg and Gray reported that cocaine exposure reduced parental care across sex and parity. Therefore, given the resilience of maternal responsiveness, and given that cocaine targets so-called motivational mechanisms (33,50), we wished to determine if and to what extent cocaine exposure could affect both the initiation and maintenance of maternal behavior, herein defined as retrieving, grouping, and crouching over, six pups. Further, we examined another facet of the maternal motivation of cocaine-exposed females by having them venture into a T-maze to retrieve pups [cf., (9)].

GENERAL METHOD

Animals

Female nulliparous Sprague-Dawley rats [Crl : CD(SD)BR] purchased from Charles River Laboratories, Inc. (Wilmington, MA) were timed mated. The day that sperm was observed in the vaginal lavage was designated day 0 of pregnancy, at which time the females were isolated in 20 × 45 × 25 cm polypropylene cages whose floors were covered with pine shavings. Food (Purina rat chow) and water were available ad

[1] To whom requests for reprints should be addressed.

lib and all animals were housed in light (on from 0500–1900 h) and temperature (21–24°C)-controlled testing rooms for the duration of the present work. Animals used in this study were maintained in accordance with the guidelines of the Institutional Animal Care and Use Committee of the University of Richmond and those prepared by the Committee on Care and Use of Laboratory Animal Resources, National Research Council (DHHS publication No. (NIH) 85-23, Revised, 1985).

Statistics

Proportions were analyzed with the Fisher's exact probability (FEP) test because of the presence of zeros in some of the cells. The latency data in Experiment 2 were analyzed with a one-tailed within-groups *t*-test. In Experiment 3, a repeated-measures analysis of variance (ANOVA) was used to test for overall latency effects. Significance in all cases was considered to be $p < 0.05$.

EXPERIMENT 1

Procedure

On the day of parturition (day 0), two separate groups of females had their litters culled to six pups. On day 5 of lactation, the females' pups were removed and one group of females ($n = 20$) was then administered 5.0 mg/kg cocaine (COC) or saline. The second group of females ($n = 20$) was administered 10.0 mg/kg cocaine or saline. Thirty minutes later the six pups were returned to the homecage and scattered about opposite the mother's location, and the females' homecage maternal behavior toward the pups was observed. The behaviors we examined [and hereafter refer to as full maternal behavior (FMB)] consisted of retrieving and grouping, and crouching over the pups during a 1-h test session. The females were scored as fully maternal if they retrieved, grouped, and crouched within 60 min of exposure to the young, following which, the pups remained in the homecage until testing the next and final day (day 6). All testing took place between 1000 and 1300 h. On day 6 of lactation, the complementary treatment (COC or saline) was administered. Thus, each female served as her own control.

Results

Figure 1 depicts the results for the first study showing the 5.0 mg/kg dosage of COC. Whereas when treated with saline 100% of the mothers responded with FMB, these same females' maternal behavior was marginally (though significantly) disrupted with 5.0 mg/kg of COC. The proportion of COC- vs. saline-treated females responding with FMB was 70% vs. 100%, respectively (FEP = $p < 0.01$). Furthermore, significantly fewer COC-treated females retrieved ($p < 0.024$), grouped ($p < 0.024$), and crouched ($p < 0.01$), compared to their saline-treated behavior.

Figure 2 depicts the results for a second study using the 10.0 mg/kg dosage of COC. Treatment with this dosage had a much greater effect on the maternal behavior of postpartum females. The proportion of 10.0 mg/kg COC- vs. saline-treated females responding with FMB was 10% vs. 100%, respectively (FEP = $p < 0.00001$). And, significantly fewer 10.0 mg/kg COC-treated females retrieved ($p < 0.00001$), grouped ($p < 0.00001$), and crouched ($p < 0.00001$), when compared to their own saline-treated control condition. In no case were there differences owing to order of cocaine exposure, either day 5 or day 6.

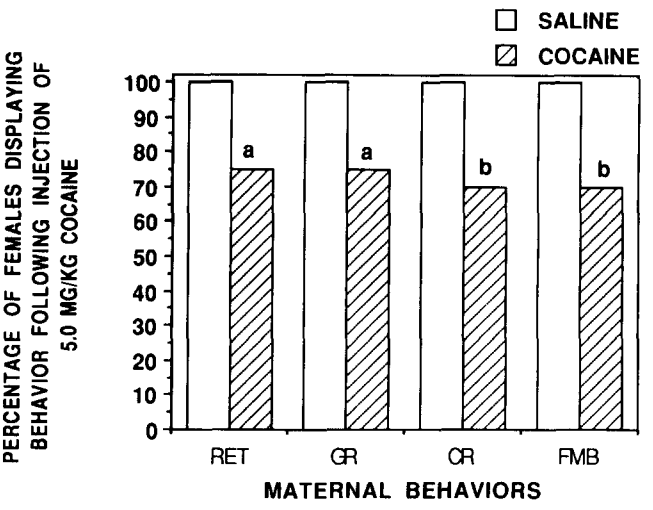

FIG. 1. Proportion (percentage) of cocaine-exposed and control (saline) females displaying maternal behaviors in Experiment 1, using 5.0 mg/kg cocaine. On days 5 and 6 of lactation, the females' pups were removed and the females were then injected (SC) with 5.0 mg/kg cocaine or saline. Thirty minutes later the six pups were returned to the homecage and scattered around opposite the mother's location, and the females' homecage maternal behavior toward the pups was observed. The behaviors we examined [referred to as full maternal behavior (FMB)] consisted of retrieving and grouping and crouching over the pups during the 1 h test session. The females were scored as fully maternal if they retrieved all pups, grouped and crouched over them within 60 min of exposure to the young ($n = 20$). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

EXPERIMENT 2

Procedure

Because the aim in Experiment 1 was to establish a dose of cocaine that was effective in disrupting FMB, we did not examine the finer and more subtle aspects of the behavioral disruption. Experiment 2, then, sought to establish how, and the degree to which, individual components of maternal behavior were affected using the most effective dosage from Experiment 1, 10.0 mg/kg (see the Results section). A separate group of nulliparous females ($n = 11$) was timed mated and treated identically to those in Experiment 1, using the single dosage of 10.0 mg/kg COC. On days 5 and 6, though, in addition to the measures recorded in Experiment 1 for determining homecage FMB, we examined: the exhibition of FMB 1 and 2 h after exposure to COC; the proportion and latencies of animals exhibiting initial contact; retrieving the first through sixth pups; grouping, crouching over, and licking the pups. Lastly, we recorded total time spent on the nest in contact with the pups.

Results

Figure 3 depicts the results for the second experiment, wherein postpartum females were treated with 10.0 mg/kg COC. Whereas when treated with saline, all the females responded with full maternal behavior; in contrast, 10.0 mg/kg was again disruptive of FMB, during both the first hour (FEP = $p < 0.0001$) and second hour, ($p < 0.0005$). And, COC exposure significantly disrupted the proportion of females

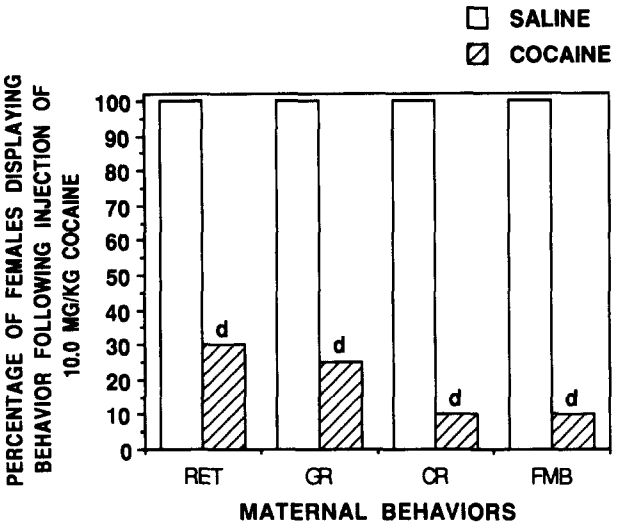

FIG. 2. Proportion (percentage) of cocaine-exposed and control (saline) females displaying maternal behaviors in Experiment 1, using 10.0 mg/kg cocaine. On days 5 and 6 of lactation, the females' pups were removed and the females were then injected (SC) with 10.0 mg/kg cocaine or saline. Thirty minutes later the six pups were returned to the homecage and scattered around opposite the mother's location, and the females' homecage maternal behavior toward the pups was observed. The behaviors examined (referred to as FMB) consisted of retrieving and grouping and crouching over the pups during the 1 h test session. The females were scored as fully maternal if they retrieved all pups, grouped and crouched over them within 60 min of exposure to the young (n = 20). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

grouping, crouching over, and licking pups, each at $p < 0.018$. Cocaine had no effect on the proportion of females retrieving the first or sixth pup (both at $p < 0.50$, NS) (see Fig. 3.)

There may not be significant differences in the proportion of animals displaying a certain behavior, owing to the range (and hence, the inherent imprecision) of times during which an animal can be considered a responder in our maternal behavior testing paradigm. Thus, we also recorded the latencies to respond with the components of maternal behavior (see Fig. 4). There were no significant effects on latencies to contact or retrieve the first through the fifth pup, though these latencies did approach significance with COC-treated females taking longer (range of $p < 0.08$ to $p < 0.06$). There was a significant increase in the latency to retrieve the sixth pup, $t(10) = 2.04$, $p < 0.034$; to group all six pups, $t(10) = 3.63$, $p < 0.0025$; to begin licking the pups, $t(10) = 3.61$, $p < 0.0025$; and to crouch over the pups, $t(10) = 3.93$, $p < 0.0015$. Lastly, once the pups had been retrieved and grouped, and the female had begun to crouch over the pups, COC-treated females spent significantly less time on the nest and in contact with the pups, $t(10) = 10.08$, $p < 0.00001$. Again, as in Experiment 1, no day-of-injection order effects were observed.

EXPERIMENT 3

Procedure

Experiments 1 and 2 demonstrated that COC administration, given acutely on days 5 or 6 postpartum, could disrupt established maternal behavior. The third experiment was designed to examine the effects of chronic COC-exposure during

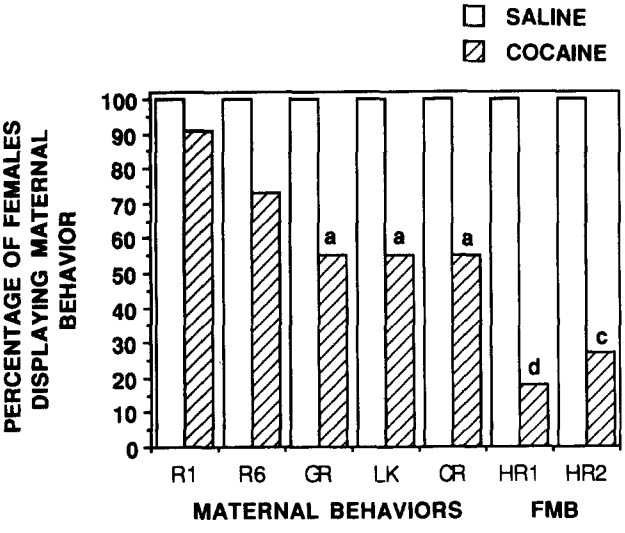

FIG. 3. Proportion (percentage) of a separate group of cocaine-exposed and control (saline) females displaying maternal behaviors in Experiment 2, using 10.0 mg/kg cocaine. On days 5 and 6 of lactation, the females' pups were removed and the females were then administered (SC injection) the cocaine or saline. Thirty minutes later the six pups were returned to the homecage and scattered around opposite the mother's location, and the females' homecage maternal behavior (retrieving, grouping, and crouching within both 60 min and 120 min) toward the pups was observed (n = 11). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

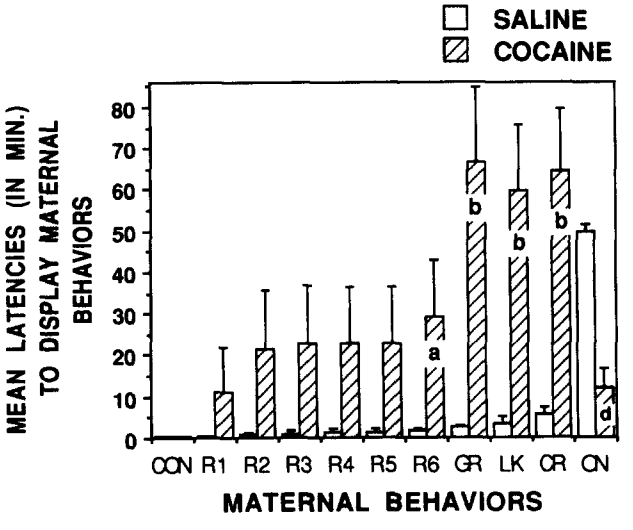

FIG. 4. Latencies (in minutes ± SEM) of cocaine-exposed and control (saline) females to display various components of maternal behavior in Experiment 2. On days 5 and 6 of lactation, the females' pups were removed and the females were then administered 10.0 mg/kg cocaine or saline. Thirty minutes later the six pups were returned to the homecage and scattered around opposite the mother's location, and we recorded the latencies of animals to exhibit initial contact; retrieve the first through sixth pups; group, crouch over, and lick the pups. Lastly, we recorded total time spent on the nest in contact with the pups (n = 11). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

pregnancy on maternal behavior, as opposed to acutely, during the postpartum period. Therefore, on day 14 of pregnancy, females were implanted under ether anesthesia with Alzet osmotic pumps (model #2ML2; Alza Corporation, Palo Alto, CA) containing 2 ml of solution. The pumps were calibrated to secrete saline or a chronic dose of COC equal to 20 mg/kg/day, double the acute higher dosage from the previous experiments (viz., 0.833 mg/kg/h) for 14 days. Thus, the females were under the influence of COC prior to and after the pups were present. Females were monitored, but remained undisturbed (save for routine maintenance) for the duration of pregnancy. At parturition (day 0), litters were checked for any anomalies (dead or deformed pups, low body weights, etc.) and culled to six pups, and initial behavioral interactions between mother and pups were observed informally. On days 1 and 2 of lactation, the females were examined for homecage maternal behavior. The pups were removed for a period of 1 h, and then scattered about the cage with the female. The incidence of and latencies to retrieve and lick, group and crouch over the six pups were recorded. On days 3, 4, and 5, we examined the females' maternal behavior in the face of a challenge, that of having to retrieve their pups from the arms of a T-maze. The pups were removed from the females and 1 h later, one pup was placed in each arm of a T-maze (tunnel = 10.5 × 10.5 cm, arms = 60 cm and 90 cm). The female's cage was attached to the opening to the long arm of the T-maze through a fitted aperture in the female's cage. A guillotine door was raised and the female was, thus, introduced to the entrance of the maze and the following behaviors scored for up to 30 min: latencies to enter the maze and to retrieve the first and second pups; and time spent on the nest (i.e., out of the T-maze). This test is a measure of the females' willingness to endure novelty to retrieve pups and, hence, examines another facet of her maternal behavioral repertoire (9).

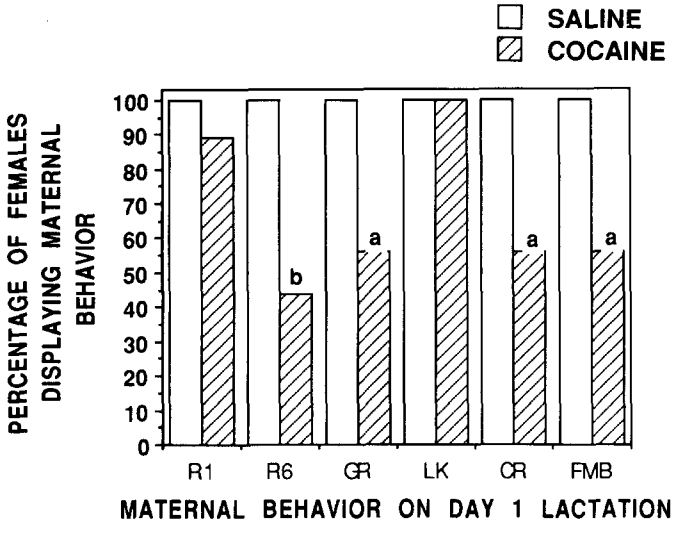

FIG. 5. Proportion (percentage) of cocaine-exposed and control (saline) females displaying maternal behaviors in Experiment 3, day 1. Each female was implanted with an osmotic pump containing cocaine (20 mg/kg/day) or saline on day 14 of pregnancy and maternal behavior testing—display of full maternal behavior; retrieving one or six pups; grouping, crouching over, and licking the pups—was conducted on both days 1 and 2 of lactation (n = 9). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

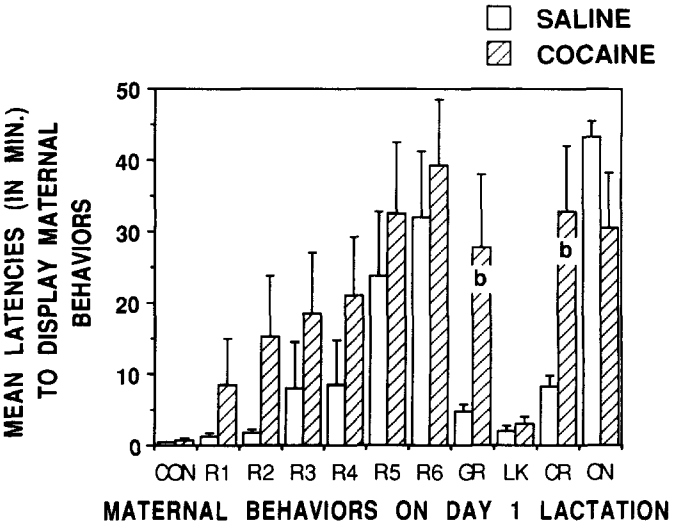

FIG. 6. Latencies (in minutes ± SEM) of cocaine-exposed and control (saline) females to display various components of maternal behavior testing—display of full maternal behavior; retrieving one or six pups; grouping, crouching over, and licking the pups—was conducted on both days 1 and 2 of lactation (n = 9). (a) $p < 0.05$; (b) $p < 0.01$; (c) $p < 0.001$; (d) $p < 0.0001$, cocaine-treated vs. saline-treated.

Results

Figure 5 depicts the proportion of females implanted with COC-containing pumps to display maternal behavior on day 1 postpartum. Significantly fewer COC-implanted females responded with FMB relative to saline-implanted females, 55%

TABLE 1

PROPORTION (PERCENTAGE) OF COCAINE-EXPOSED AND CONTROL (SALINE) FEMALES DISPLAYING MATERNAL BEHAVIORS IN EXPERIMENT 3, DAY 2*

	Cocaine Implanted	Saline Implanted
FMB	6/9 (67)	9/9 (100)
Retrieve 1 pup	9/9 (100)	9/9 (100)
Retrieve 6 pups	8/9 (89)	9/9 (100)
Group all pups	7/9 (78)	9/9 (100)
Crouch on at least 1 pup	6/9 (67)	9/9 (100)
Lick pups	9/9 (100)	9/9 (100)
ns	9	9

Each female was implanted with an osmotic pump on day 14 of pregnancy and maternal behavior testing was conducted on days 1 and 2 of lactation.

*Overall data were analyzed with the Fishers exact probability (FEP) test. See the Results section for details.

TABLE 2

LATENCIES (IN MINUTES ± SEM) OF COCAINE-EXPOSED AND CONTROL (SALINE) FEMALES TO DISPLAY VARIOUS COMPONENTS OF MATERNAL BEHAVIOR IN EXPERIMENT 3, DAY 2*

	Cocaine Implanted	Saline Implanted
Contact pups	0.37 (0.12)	0.51 (0.10)
Retrieve 1 pup	0.90 (0.12)	1.22 (0.62)
Retrieve 2 pups	1.28 (0.41)	1.87 (0.68)
Retrieve 3 pups	1.67 (0.40)	2.93 (1.00)
Retrieve 4 pups	2.60 (0.72)	3.23 (1.05)
Retrieve 5 pups	18.32 (8.15)	5.10 (1.25)
Retrieve 6 pups	17.10 (8.30)	16.85 (8.23)
Group all pups	16.90 (8.22)	11.38 (3.15)
Crouch on at least 1 pup	17.60 (6.10)	13.10 (3.05)
Lick pups	6.48 (2.25)	6.43 (1.27)
Time spent on the nest	28.48 (5.95)†	40.58 (3.33)
ns	9	9

Each female was implanted with an osmotic pump on day 14 of pregnancy and maternal behavior testing was conducted on days 1 and 2 of lactation.

*Overall data were analyzed with the Fishers exact probability (FEP) test. See the Results section for details.

†Significantly different, $p < 0.05$.

vs. 100%, FEP = $p < 0.04$. Also, significantly fewer COC females retrieved six pups, $p < 0.014$; and significantly fewer grouped ($p < 0.04$) and crouched over ($p < 0.04$) young.

We also examined the latencies with which the COC-and saline implant females displayed the various subcomponents of maternal behavior (see Fig. 6). There were neither differences in latencies to contact pups, retrieving one through six pups, licking the pups, nor in total time on nest. COC females, however, took significantly longer to group the six pups, $t(16) = 2.26$, $p < 0.02$. Also, the COC females took significantly longer to crouch over the pups, $t(16) = 2.57$, $p < 0.01$.

On day 2 postpartum, there were improvements in the display of maternal behavior by the COC-exposed females, owing possibly to having the previous 24 h maternal experience. There were no differences in the proportions of COC-exposed females vs. controls to display maternal behavior (see Table 1). And, there were no differences in the latencies to contact pups, retrieve one through six pups, group, or crouch over pups. There was, however, a significant difference in the amount of time the COC-exposed females spent on the nest compared with the controls, $t(16) = 1.77$, $p < 0.05$ (see Table 2).

As for the females' performance in the T-maze, we observed very few, if any, effects on their behavior during this maternal behavioral challenge (Table 3), and no significant between-group (i.e., COC vs. saline) differences in latencies to enter the maze, to retrieve the first or second pup, or the amount of time spent on the nest. Lastly, we observed no evidence of litter anomalies following the pregnancy cocaine exposure.

GENERAL DISCUSSION

The present work demonstrates that cocaine administration reduces maternal responsiveness. Whether administered acutely during the postpartum, maintenance phase (at which time maternal behavior has been established and is maintained primarily by pup cues), or chronically during the initiation phase [wherein the cascade of hormonal and neurochemical factors are prevalent and serve to stimulate the behavior;(4)], cocaine reduces the smooth integration of the maternal behavior of lactating females toward young. As discussed below, cocaine may modify motivational and/or hormonal mechanisms. These findings, together with those reported by Zimmerberg and Gray (56), suggest that cocaine should be considered doubly threatening to the offspring because of: a) the marked debilitation in the pups' biological development; coupled to b) the complete nutritional dependence of these altricial pups on their mother, not to mention the sensory and excretory stimulation provided by her (24). (Though one may

TABLE 3

LATENCIES (IN MINUTES ± SEM) OF COCAINE-EXPOSED AND CONTROL (SALINE) FEMALES TO DISPLAY MATERNAL BEHAVIOR FOLLOWING A BEHAVIORAL CHALLENGE IN A T-MAZE IN EXPERIMENT 3, LACTATION DAYS 3–5*

	Lactation Day					
	3		4		5	
	COC	SAL	COC	SAL	COC	SAL
Latency to enter maze	3.98	5.73	2.58	1.83	0.43	0.45
	(1.35)	(1.45)	(1.22)	(0.73)	(0.13)	(0.15)
Retrieve 1st pup	6.43	6.62	3.05	2.55	1.72	0.73
	(1.27)	(1.37)	(1.22)	(0.83)	(1.18)	(0.20)
Retrieve 2nd pup	6.68	6.83	3.68	3.02	2.13	0.98
	(1.30)	(1.28)	(1.25)	(0.95)	(1.13)	(0.20)
Time spent on the nest	9.28	9.73	9.87	9.68	5.50	6.18
	(0.57)	(0.27)	(0.14)	(0.32)	(1.37)	(1.47)

Each female was implanted with an osmotic pump on day 14 of pregnancy and homecage maternal behavior testing was conducted on days 1 and 2 of lactation (n = 9/group).

*Overall data were analyzed with a repeated measures ANOVA. No between-group (Cocaine vs. Saline) differences were observed. See the Results section for details.

argue that cocaine merely increases locomotor activity—thereby indirectly reducing maternal behavior—casual observations of locomotor activity revealed little to account for the marked inattention to pups; the females simply failed to behave maternally as defined by our criteria.) Cocaine-treated females preferred to investigate the cage, to rear and climb along the top, and to eat and drink, all of which increased the latency to approach and carry/retrieve pups. These observations are in accord with those of Zimmerberg and Gray (56), who reported that cocaine-treated mothers would retrieve pups, but would not attend to them thereafter.

Where there were increases in the latencies to engage in maternal behavior, the effects took the form of less time spent with the offspring. For example, in Experiment 2, which used injections of 10.0 mg/kg, FMB was reduced, and this reduction was due in large part to poor crouching responses by the females. In Experiment 3, in which cocaine-containing pumps were implanted, similar effects of the cocaine were observed on day 1 of lactation (and, in part, on day 2). In general, then, cocaine appears to reduce, not eliminate, maternal responsiveness. In contrast, the opiate morphine, in dosages ranging from 2.5 mg/kg to 10 mg/kg, affected maternal behavior much differently, rendering the female averse to pups and thereby abolishing her maternal behavior [with the higher doses (6,29,30)].

That cocaine hindered the females' maternal responsiveness during the observation period, or extended latencies to retrieve or crouch over pups, points to a different mechanism of effect relative to morphine's—in which case the females generally failed to display any behavior toward pups whatsoever. Though there were slight effects on retrieving and grouping the pups in cocaine-treated females, the latter generally failed to spend much time in the nest with the pups (Experiments 1 and 2; and Experiment 3, day 2); in fact, once the pups were retrieved, the cocaine-treated mothers virtually ignored them. It seems apparent, then, that cocaine prevents the full integration of the maternal response, that it affects how the components of maternal behavior mesh together. Whereas morphine may affect the olfactory perception and consequent interest in pups—rendering the odors of the pups aversive to the mother (30)—cocaine may alter individual motivational mechanisms, per se, independent of olfactory mediation [cf., (33,50)].

As with other varieties of pharmacological research, questions of route and manner of drug administration must be addressed. In Experiments 1 and 2, SC injections of 5.0 or 10.0 mg/kg cocaine were given, whereas in Experiment 3, an implanted osmotic pump was used that secreted 20 mg cocaine/kg/day. Without clearance rates and other pharmacodynamic data then, comparing across experiments is problematical. This latter route was chosen for two main reasons: first, to obviate the rarely reported findings of tissue damage, necrosis, and accompanying discomfort at the site of the injection; and to eliminate the repeated stress of daily injections of the pregnant female. This cocaine regimen allowed us to examine pregnancy exposure, whereas Experiments 1 and 2 investigated postpartum, lactational cocaine exposure.

Though there were effects on maternal behavior in Experiment 3 using the osmotic pumps, the reader should keep in mind several points: First, neither the brain levels, nor temporal pattern, of cocaine induced by the two methods (injection and pumps) may be comparable (nor was this our aim). Second, there are obvious differences between the endocrinologic states of a pregnant female and a lactating one that could affect the pharmacokinetics of cocaine exposure. Third, there may be differences in the onset rates of tolerance vs. sensitization between the two routes of administration. Together, though, the two time points (lactation and pregnancy) and the three experiments demonstrate a significant effect of cocaine on overall maternal responsiveness.

Cocaine is a central nervous system sympathomimetic. Its many effects, both acute and chronic (and especially those involving its reinforcing properties of cocaine), are mediated through monoaminergic mechanisms such as dopamine (DA) (14,12,21,25,27,43,44,50,52–54). Cocaine also affects reproductive functions (13,15–18,22,35,47,48). The data, however, on cocaine's effects on endocrine levels/dynamics are less clear and consistent, particularly regarding a likely hormonal factor, prolactin (Prl), in a variety of species (3,32,34,41,49).

Direct involvement of cocaine on DA systems and maternal behavior is likely as well, as shown by Numan and Smith (39). Bilateral lesions of the ventral tegmental area (VTA), an area rich in DA-ergic fibers, in particular, ascending mesolimbic-mesocortical projections, disrupt maternal behavior in lactating rats. Numan (37) speculates that such lesions may affect maternal behavior through a DA sensory–motor interaction involving motor output relevant to care of the young, together with olfactory input from the young. In other words, such lesions may disrupt the integration of maternal responsiveness. Further, there is other evidence of DA involvement in maternal behavior [cf., (23,51)]. Also, both Prl and estradiol administration affect DA-ergic neural activity in VTA and nucleus accumbens (20,26); and, fiber projections, transmitting the suckling stimulation received by a lactating female, course through afferents that project to and through the medial forebrain bundle (55)—an area rich in DA and involved in self-stimulation (50). Too little has been done investigating direct DA involvement in maternal behavior. Nevertheless, what data there are suggest a role for this neurotransmitter in the exhibition of the behavior. As summarized in (37), " . . . estrogen, and perhaps prolactin, via actions on the MPOA [medial preoptic area, a site of maternal mediation; see (38)], stimulate maternal behavior via preoptic activation of VTA dopaminergic input to the ventral striatum (p. 1620)."

There are interactions among opioids, maternal behavior, and DA. For instance, morphine and other opioids can decrease DA synthesis and turnover in the median eminence and DA concentrations in pituitary portal circulation (2,42), and opioids can reverse DA inhibition of Prl secretion (11) and increase Prl secretion in the presence of dopamine infusions (2). Thus, an examination of such complex interactions may prove fruitful [cf., (46)].

As discussed above, cocaine may work via a DA mechanism (44,52,54); given DA's generally inhibitory effects on Prl secretion (outlined above), cocaine may suppress Prl in both the pregnant and the lactating female. Prolactin is under tonic DA inhibition (save for the disinihibition that occurs during proestrus and early and late pregnancy and lactation [when there are elevated levels of Prl; (3)]. Because of the pervasive role of Prl in the display of maternal behavior (5,7,8,31) perhaps cocaine reduces maternal behavior (particularly that established during pregnancy) by inhibiting adequate secretion of Prl during critical periods in the pregnant and the lactating female—to date, stages in the reproductive life of the female yet to be examined adequately for cocaine effects on behavior.

In conclusion, cocaine prevents the full display of maternal behavior in lactating rats. Hurt [cited in (40)] reported that maternal caring for newborns was significantly impaired in cocaine-abusing human mothers. For instance, measures such as hospital visitations of babies in neonatal intensive care units by their mothers, quality of interactions with young, and num-

bers of babies put up for adoption, were telling for cocaine moms: in each case—fewer maternal visits, stilted and averse reactions to young, and greater numbers put up for adoption—the offspring of cocaine moms were at a severe disadvantage. In short, cocaine abuse/addiction significantly reduced maternal behavior. Because the primary care for the neonates is provided by the postpartum mother, maternal behavior compromised through pharmacological means may imperil the offspring. Thus, in combination with, and in addition to, the teratological effects of gestational cocaine exposure, the offspring may face the double jeopardy of poor maternal care.

ACKNOWLEDGEMENTS

A portion of this work was presented at the annual meeting for the Society for Neuroscience, New Orleans, LA, November, 1991.

The experiments reported here were conducted with support from the University of Richmond Faculty Research, Graduate Research, and Undergraduate Research Committees, for which the authors are grateful.

REFERENCES

1. Abelson, H. I.; Miller, J. D. A decade of trends in cocaine use in the household population. Natl. Inst. Drug Abuse Res. Monogr. 61:35–49; 1985.
2. Arita, J.; Porter, J. C. Relationship between dopamine release into hypophysial portal blood and prolactin release after morphine treatment in rats. Neuroendocrinology 38:62–67; 1984.
3. Ben-Jonathan, N. Dopamine: A prolactin-inhibiting hormone. Endocr. Rev. 6:564–589; 1985.
4. Bridges, R. S. Endocrine regulation of parental behavior in rodents. In: Krasnegor, N. A.; Bridges, R. S., eds. Mammalian parenting: Biochemical, neurobiological and behavioral determinants. New York: Oxford University Press; 1990:93–117.
5. Bridges, R. S.; DiBiase, R.; Loundes, D. D.; Doherty, P. C. Prolactin stimulation of maternal behavior in female rats. Science 227:782–784; 1985.
6. Bridges, R. S.; Grimm, C. T. Reversal of morphine disruption of maternal behavior by concurrent treatment with the opiate antagonist naloxone. Science 218:166–168; 1982.
7. Bridges, R. S.; Numan, M.; Ronsheim, P. M.; Mann, P.E.; Lupini, C. E. Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. Proc. Natl. Acad. Sci. USA 87:8003–8007; 1990.
8. Bridges, R. S.; Ronsheim, P. M. Prolactin (PRL) regulation of maternal behavior in rats: Bromocriptine treatment delays and PRL promotes the rapid onset of behavior. Endocrinology 126: 837–848; 1986.
9. Bridges, R. S.; Zarrow, M. X.; Denenberg, V. H. The role of neonatal androgen in the expression of hormonally induced maternal responsiveness. Horm. Behav. 4:315–322; 1973.
10. Chasnoff, I. J.; Burns, W. J.; Schnoll, S. H.; Burns, K. A. Cocaine use in pregnancy. N. Engl. J. Med. 313:666–669; 1985.
11. Cheung, C. Y. Does β-endorphin modulate basal and dopamine-inhibited prolactin release by an action at the anterior pituitary? Neuroendocrinology 39:489–495; 1984.
12. Chieuh, C.; Kopin, I. Centrally mediated release by cocaine of endogenous epinepherine and norepinepherine from the sympathoadrenal medullary system of unanesthetized rats. J. Pharmacol. Exp. Ther. 205:148–154; 1978.
13. Cocores, J. A.; Dackis, C. A.; Gold, M. S. Sexual dysfunction secondary to cocaine abuse in two patients. J. Clin. Psychiatry 47:384–385; 1986.
14. Covino, B. Toxicity and systemic effects of local anesthetic agents. In: Strichartz, G., ed. Local anesthetics. Berlin: Springer Verlag; 1987:187–212.
15. Cregler, L. L.; Mark, H. Medical complications of cocaine abuse. N. Engl. J. Med. 315:1495–1500; 1986.
16. Dackis, C. A.; Gold, M. S. New concepts in cocaine addiction. Neurosci. Biobehav. Rev. 9:469–477; 1985.
17. Dackis, C. A.; Gold, M. S. Pharmacological approaches to cocaine addiction. J. Subst. Abuse Treatment 2:139–145; 1985.
18. Dackis, C. A.; Gold, M. S.; Estroff, T. W.; Sweeney, D. R. Hyperprolactinemia in cocaine abuse. Soc. Neurosci. Abstr. 10: 1099; 1984.
19. Fantel, A. G.; McPhail, B. J. The teratogenicity of cocaine. Teratology 26:17–19; 1982.
20. Fuxe, K.; Eneroth, P.; Gustafsson, J.-A.; Lofstrom, A.; Skett, P. Dopamine in the nucleus accumbens: Preferential increase of DA turnover by rat prolactin. Brain Res. 122:177–182; 1977.
21. Gawin, F. H. Cocaine addiction: Psychology and neurophysiology. Science 251:1580–1586; 1991.
22. Gawin, F. H.; Kleber, H. D. Neuroendocrine findings in chronioc cocaine abusers: A preliminary report. Br. J. Psychiatry 247:569–573; 1985.
23. 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.
24. Hofer, M. A. Parental contributions to development of offspring. In: Gubernick, D. J.; Klopfer, P. H., eds. Parental care in mammals. New York: Plenum Press; 1981:77–115.
25. Jaffe, J. H. Drug addiction and drug abuse. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murid, F., eds. Goodman and Gilman's the pharmacological basis of therapeutics. New York: Macmillan; 1985:532–581.
26. Joyce, J. N.; Montero, E.; Van Hartesveldt, C. Dopamine-mediated behaviors: Characteristics of modulation by estrogen. Pharmacol. Biochem. Behav. 21:791–800; 1984.
27. Julien, R. M. A primer of drug action. New York: W. H. Freeman and Company; 1988.
28. Kinsley, C. H.; Bauer, A.; Beverly, M.; Turco, D.; Wellman, J. Cocaine disrupts maternal behavior in lactating rats. Soc. Neurosci. Abstr. 17:1412; 1991.
29. Kinsley, C. H.; Bridges, R. S. Parity-associated reductions in behavioral sensitivity to morphine. Biol. Reprod. 39:270–278; 1988.
30. Kinsley, C. H.; Bridges, R. S. Morphine treatment and reproductive condition alter olfactory preferences for pup and adult male odors in female rats. Dev. Psychobiol. 23:331–347; 1990.
31. Loundes, D. D.; Bridges, R. S. Length of prolactin priming differentially affects maternal behavior in female rats. Biol. Reprod. 34:495–501; 1986.
32. Mello, N. K.; Mendelson, J. H.; Bree, M. P.; Kelly, M.; Drieze, J. Cocaine stimulates LH and reduces PRL in female rhesus monkeys. In: Harris, L. S., ed. Problems of drug dependence 1989. Washington, DC: National Instit. Drug Abuse Res. Monogr. No. 95; 1989:337–338.
33. Mello, N. K.; Mendelson, J. H.; Bree, M. P.; Lukas, S. E. Buprenorphine and naltrexone effects on cocaine self-administration by rhesus monkeys. J. Pharmacol. Exp. Ther. 254:926–939; 1990.
34. Mello, N. K.; Mendelson, J. H.; Drieze, J.; Kelly, M. Acute effects of cocaine on prolactin and gonadotropins in female rhesus monkey during the follicular phase of the menstrual cycle. J. Pharmacol. Exp. Ther. 254:815–823; 1990.
35. Mendelson, J. H.; Teoh, S. K.; Lange, U.; Mello, N. K.; Weiss, R.; Skupny, A. S. T. Hyperprolactinemia during cocaine withdrawal. In: Harris, L. S., ed. Problems of drug dependence 1987. Washington, DC: US Government Printing Office; 1988: 67–73.
36. Mofenson, H. C; Caraccio, T. R. Maternal cocaine abuse and effects on the newborn. Pediatrics 77:209–211; 1987.
37. Numan, M. Maternal behavior. In: Knobil, E.; Neill, J.; Ewing, L. L.; Greenwald, G. S.; Markert, C. L.; Pfaff, D. W., eds. The

physiology of reproduction. New York: Raven Press; 1988:1569–1645.
38. Numan, M. Neural control of maternal behavior. In: Krasnegor, N. A.; Bridges, R. S., eds. Mammalian parenting: Biochemical, neurobiological and behavioral determinants. New York: Oxford University Press; 1990:69–85.
39. Numan, M.; Smith, H. G. Maternal behavior in rats: Evidence for the involvement of preoptic projections to ventral tegmental area. Behav. Neurosci. 98:712–727; 1984.
40. Orndorff, B. Cocaine impairs maternal instinct, study shows. Richmond Times-Dispatch 1990 March 3:1–8.
41. Ravitz, A. J.; Moore, K. E. Effects of amphetamine, methylphenidate and cocaine on serum prolactin concentrations in the male rat. Life Sci. 21:167–272; 1977.
42. Reymond, M. J.; Kaur, C.; Porter, J. C. An inhibitory role for morphine on the release of dopamine into hypophysial portal blood and on the synthesis of dopamine in tuberinfundibular neurons. Brain Res. 262:253–258; 1983.
43. Ritchie, J. M.; Greene, N. M. Local anesthetics. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murid, F., eds. Goodman and Gilman's the pharmacological basis of therapeutics. New York: Macmillan; 1985:302–321.
44. Ritz, M. C.; Lamb, R. J.; Golberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
45. Ross, B.; Liang, K.; Rajguru, S.; Clark, J. F. J.; Ahluwalia, B. Evidence that cocaine use during pregnancy effects endocrine secretions and causes chromosomal abbreations [*sic*] in human fetus. Endocrine Soc. Abstr. 101:56; 1991.
46. Selmanoff, M.; Gregerson, K. A. Suckling-induced prolactin release is suppressed by naloxone and stimulated by *b*-endorphin. Neuroendocrinology 45:255–259; 1986.
47. Siegel, R. K. Cocaine sexual dysfunction: The curse of mama coca. J. Psychoactive Drugs 14:71–74; 1982.
48. Smith, D. E.; Wesson, D. R.; Apter-Marsh, M. Cocaine- and alcohol-induced sexual dysfunction in patients with addictive disease. J. Psychoactive Drugs 16:359–361; 1984.
49. Steger, R. W.; Silverman, A. Y.; Johns, A.; Asch, R. H. Interactions of cocaine and delta-9-tetrahydrocannabinol with the hypothalamic-hypophysial axis of the female rat. Fertility Sterility 35: 567–572; 1981.
50. Stellar, J. R.; Stellar, E. The neurobiology of motivation and reward. New York: Springer-Verlag; 1985.
51. Szechtman, H.; Siegel, H. I.; Rosenblatt, J. S.; Komisaruk, B. R. Tail-pinch facilitates onset of maternal behavior in rats. Physiol. Behav. 19:807–809; 1977.
52. Taylor, D. L.; Ho, D. T.; Fagin, J. D. Increased dopamine receptor binding in rat brain by repeated cocaine injection. Commun. Psychopharmacol. 3:137–142; 1979.
53. Trendlenburg, U. The supersensitivity caused by cocaine. J. Pharmacol. Exp. Ther. 125:55–65; 1959.
54. Trulson, M. E.; Ulissey, M. J. Chronic cocaine administration decreases dopamine synthesis rate and increases [^{3}H]spiroperidol binding in rat brain. Brain Res. Bull. 19:35–38; 1987.
55. Wakerley, J. B.; Clarke, G.; Summerlee, A. J. S. Milk ejection and its control. In: Knobil, E.; Neill, J.; Ewing, L. L.; Greenwald, G. S.; Markert, C. L.; Pfaff, D. W., eds. The physiology of reproduction. New York: Raven Press; 1988:2283–2321.
56. Zimmerberg, B.; Gray, M. S. The effects of cocaine on maternal behaviors in the rat. Physiol. Behav. 52:379–384; 1992.