Gerald S. Hecht
Norman E. Spear
Linda P. Spear
Department of Psychology and Center for Developmental Psychobiology
Binghamton University
Binghamton, NY 13902–6000

Changes in Progressive Ratio Responding for Intravenous Cocaine throughout the Reproductive Process in Female Rats

Received 26 December 1998; accepted 4 February 1999

ABSTRACT: *Operant responding on a progressive ratio (PR) schedule for intravenous cocaine as well as sucrose reinforcement was examined in female rats throughout the reproductive process. Self-administration sessions began before mating, and continued throughout pregnancy and until lactational Day 8; following parturition, litters were present with dams during operant sessions. Physiological changes associated with the reproductive process dramatically altered PR responding for cocaine, while PR responding for sucrose was relatively stable throughout pregnancy and lactation. Female animals exhibited the highest number of responses/session for cocaine during estrus and the 1st trimester of pregnancy and the lowest responding near parturition, with levels only partially recovering during lactation. Dams self-administering cocaine exhibited notably different patterns of maternal behavior in the operant chambers than dams responding for sucrose. Thus, cocaine's reinforcing efficacy may be influenced by (a) the changing physiological profile associated with the reproductive process and (b) competition from the reinforcing properties of offspring during lactation.* © *1999 John Wiley & Sons, Inc.* Dev Psychobiol 35: 136–145, 1999

Keywords: *cocaine; self-administration; female; estrous cycle; progressive ratio; pregnancy; lactation; Sprague-Dawley; maternal behavior*

Epidemiologic data indicate a high frequency of cocaine use in some populations of pregnant women, with estimates that 18–20% (Zuckerman et al., 1989) to 31% (Ostrea, Brady, Gause, Raymundo, & Stevens, 1992) of infants born in some inner-city hospitals have been exposed gestationally to cocaine. The few studies examining temporal use patterns have generally reported a decrease in cocaine use during pregnancy (Cornelius et al., 1994; Richardson & Day, 1991), although MacGregor and colleagues (1987) reported that only 33% of cocaine users in their prenatal care program were found to eliminate cocaine use during pregnancy. Mechanisms underlying this possible pregnancy-related decrease in cocaine use are unknown but may include social pressure to abstain from drug use

Correspondence to: L. P. Spear, Department of Psychology and Center for Developmental Psychobiology, Binghamton University, Box 6000, State University of New York, Binghamton, NY 13902–6000.
Contract grant sponsor: NIDA
Contract grant numbers: R01 DA04478 and K02 DA00140

© 1999 John Wiley & Sons, Inc. CCC 1012-1630/99/020136-10

rather than physiological changes in the neural processing of drug reinforcement.

Maternal cocaine use can affect offspring not only because of direct fetal-exposure effects, but also because of cocaine's potential consequences on maternal behavior. For example, Hurt (cited in Orndoff, 1990) reported that cocaine-abusing mothers showed stilted and averse reactions to children, visited their babies less often, and were more likely to give up their babies for adoption than non-drug-using mothers. Cocaine-related disruptions of maternal behavior have also been reported in studies with lactating rats (Vernotica, Lisciotto, Rosenblatt, & Morell, 1996).

A variety of animal models have been developed to examine offspring exposed gestationally to cocaine (see Spear, 1995 for a review), and the impact of cocaine administration on maternal behavior (Heyser, Molina, & Spear, 1992; Johns, Noonan, Zimmerman, Li, & Pedersen, 1994; Kinsley et al., 1994; Vernotica et al., 1996). Most of these studies have used cocaine administration routes (e.g., subcutaneous and intragastric) that differ substantially from the pharmacokinetic profile associated with human intravenous (IV) and inhalation use patterns, although an IV model of gestational cocaine exposure has been developed (Mactutus, Herman, & Booze, 1994). Using animal models involving predetermined, fixed levels of cocaine exposure does not, of course, provide information regarding how the reinforcement value of cocaine may vary as a consequence of the physiological changes associated with the reproductive process. Yet, pregnancy alters the pharmacokinetic and pharmacodynamic profiles of cocaine (Plessinger & Woods, 1990; Woods & Plessinger, 1990), with pregnant females showing progressively lower serum/brain cocaine levels than nonpregnant females (Dwivedi, Engineer, & Vaughan, 1993). The neuroendocrine changes associated with pregnancy may also modulate responsivity to cocaine.

It is well documented that gender and hormonal status influence many of the responses to psychomotor stimulants. Female rats often exhibit greater behavioral reactivity to psychomotor stimulants than males (Brass & Glick, 1981; Robinson, Becker, & Presty, 1982), with the sensitivity of females being higher during estrus than at other stages of the estrus cycle (Diaz-Veliz, Baeza, Benavente, Dussaubat, & Mora, 1994). Amphetamine-stimulated dopamine (DA) release in striatum of females is likewise greatest during estrus (Becker & Cha, 1989). Estrogen administered to ovariectomized rats enhances amphetamine-stimulated DA release in striatum (Castner, Xiao, & Becker, 1993), and increases DA turnover both in striatum (Di Paolo et al., 1985) and nucleus accumbens (Shimizu & Bray, 1993).

Roberts, Bennett, and Vickers (1989a) showed gender differences in cocaine self-administration on an operant progressive ratio (PR) reinforcement schedule. Under this schedule, the requirements to obtain each successive reinforcer become increasingly more demanding in terms of the number of bar presses required. The point in the escalating series at which responding ceases is termed the breakpoint and is used to estimate the reinforcing efficacy of the drug for the animal on that day (Hodos, 1961; Richardson & Roberts, 1995). Roberts et al. (1989a) observed that, while there were no gender- or cyclicity-specific differences in cocaine self-administration when traditional fixed ratio (FR) schedules were used, female rats displayed much higher PR breakpoints than male rats, with the highest breakpoints observed during estrus.

Little is known, however, regarding sensitivity to cocaine during pregnancy and lactation, despite the potential significance of this information. The present study was designed to examine PR responding for cocaine, as well as another reinforcer (sucrose), in female rats throughout the reproductive process. Rats began bar pressing for intravenous cocaine or sucrose pellets under a PR schedule before conception and continued to do so through pregnancy and into the post-postpartum period in the presence of their offspring.

METHODS

Subjects

Charles-River-derived female Sprague-Dawley rats born and reared at Binghamton University were used as subjects. Animals were group-housed under a 16:8 hr light:dark cycle (lights on at 6:00 a.m.) until the start of the experimental procedures at postnatal Days 55–60. At this time the dams were housed individually in breeding cages where they received ad-libitum food and water throughout the remainder of the study except as noted. Dams were randomly assigned to one of two groups: a cocaine self-administration group (CA) and a surgical control group allowed to bar-press for sucrose (SX).

Following initial operant training, surgery, recovery, and acquisition of stable PR responding (as described below), each dam was placed individually in a hanging cage with an adult male rat at 5:00 p.m. daily and removed the following morning at approximately 9:00 a.m. Detection of a copulatory plug was defined as Day 1 of gestation. Body weights of the

dams were recorded daily during gestation. On Day 1, the number of pups of each sex was recorded and each litter was culled to 10 pups, with 5 pups of each gender retained whenever possible. Pups were examined for the presence of milk lines daily and were weighed on postnatal Days 1 and 7.

Due to the inherent difficulty in maintaining patent catheters given the unusual strains of mating, pregnancy, and offspring contact, a total of 38 dams was needed to generate the final sample size of 12 dams (6/group). Only data from animals that completed all phases of the study were analyzed.

Apparatus

Standard operant chambers (Med-Associates Inc., East Fairfield, VT) located inside sound-attenuating chambers were used; each contained two operant levers mounted on either side of a food cup that could be used to deliver 45-mg sweetened food pellets (Formula F, Fruit Punch Flavor, P. J. Noyes Co. Inc., NH). A motorized infusion pump (Razel, Model A) located outside each chamber was used to deliver the cocaine infusions. All operations were computer-controlled with Med-Associates Inc. (East Fairfield, VT) software and additional programming conducted using Turbo Pascal.

Procedure

All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University's Institutional Animal Care and Use Committee.

Initial Operant Training. Each rat was food deprived to 85% of its initial body weight, acclimated to the chamber, magazine-trained, and shaped to bar-press for sucrose pellets. Initial training during daily 1-hr sessions was conducted on an FR1 schedule (one response on the active lever yielding one sucrose pellet). Over days, this schedule was increased until responding on an FR10 was constant, as defined by the emitting of 200 responses during 1 hr for three consecutive sessions. Animals were then food-deprived for 24 hr and trained for 7 days under a PR schedule, in which a progressively greater number of lever presses had to be emitted for each successive sucrose pellet according to the exponential equation used by Richardson and Roberts (1995):

$$\text{Response ratio} = [5e^{(\text{injection number} \times 0.2)}] - 5$$

Each PR session ended when a rat failed to complete the next scheduled ratio within 20 min after delivery of a reinforcer. After the first PR session, the animals were returned to ad lib feeding for the remainder of the study.

Surgery. Surgeries were performed 2 to 3 days after the last of these PR sessions. Dams in the CA group were implanted with chronic Silastic (0.12 i.d./0.25 o.d.) catheters in the external jugular vein. Surgeries were conducted aseptically under ketamine/xylazine anesthesia using standard IV catheterization procedures and a skull-mounted external injection cannula. Each cannula was composed of a 22-ga stainless-steel guide cannula (Plastics 1 Inc.) bent to a curved 90-degree angle and attached to the Silastic implant tubing; the cannula was secured to the skull and four self-tapping bone screws with dental acrylic. Animals in the SX group underwent a similar surgical procedure; however, the venotomy itself was not performed and the distal end of the catheter was sutured to the exterior of the intact jugular vein. The catheters in the CA animals were flushed with 0.1 ml of a solution consisting of 1.0-mg streptokinase (Sigma Co.), and 100-mg Timentin (Smith Kline Beckman) dissolved in 1.5 ml of heparinized saline immediately following implantation and once daily thereafter for 3 days. Beginning on the 4th postoperative day, the catheters were flushed once daily with a similar solution which did not contain streptokinase. Animals were allowed to recover for at least 5 days before resumption of the operant sessions. At that time, CA animals began training on the cocaine self-administration task while SX animals were similarly tethered to the IV lines but resumed daily PR sessions for sucrose.

Self-Administration Training. The training procedure for cocaine self-administration was similar to that used for sucrose, although a priming infusion of cocaine was given at the start of each session. Subjects were first shaped on an FR1 schedule with 15 self-infusions per session and no time limit. Each 0.1-ml infusion was given over 5 s and consisted of 0.25 mg of cocaine HCl (NIDA, Research Triangle Park, NC) prepared immediately before the operant session in a saline vehicle (1.0 U/ml heparinized 0.9% saline). This dose is lower than that used previously to explore estrus-cycle effects on PR performance (i.e., 0.50 mg/infusion—Roberts et al., 1989a) and was chosen to represent a low-to-moderate dose sufficient to support self-administration (e.g., Roberts, Loh, & Vickers, 1989b). Each cocaine infusion was accompanied by illumination of a jeweled stimulus light above the cor-

rect lever. This light stayed illuminated during a subsequent 25-s time-out period during which bar presses had no consequences. Once self-administration rates were stable (i.e., the IRI did not vary by more than 20% between two consecutive sessions), an FR2 schedule was initiated, with each session being limited to 15 self-injections of cocaine, again with no time limit. The same criterion used for the FR1 schedule was applied before switching dams to the PR schedule. This schedule was the same as used for sucrose PR except that a priming infusion of cocaine was administered at the start of each session and a 1-hr time limit was given to obtain each reinforcer. Responses on the active and incorrect levers were separately recorded during each of the daily postsurgical self-administration sessions for each animal. Data were also collected for the number of earned reinforcements and the highest ratio completed (breakpoint) prior to terminating responding.

Data Collection During Estrus Cycle, Gestation, and Lactation. Rats were allowed to self-administer the training dose of cocaine or sucrose for 10 PR sessions prior to mating to permit data collection during two full estrus cycles. Vaginal lavage followed by examination of the vaginal epithelium was used to index stage of the estrus cycle (e.g., Baker, Lindsey, & Weisbroth, 1980); these determinations were not verified hormonally. Sessions continued daily throughout gestation, although dams were not placed in the operant chambers on the day of parturition (postnatal Day 0). Beginning on postnatal Day 1 and continuing until Day 8, pups from each litter were placed in the operant chamber with their dam. For these sessions a sheet of clear Plexiglas was placed over the grid bottom of the operant chamber to create a solid floor. The pups were placed in a Tupperware nest, which was lined with shavings from the home cage and located at the rear of the operant chamber.

Maternal Behavior Assessments. Three of the postpartum sessions (Days 1, 4, and 8) were videotaped for scoring of maternal behaviors. For videotaping, the door of the exterior sound-attenuating chamber was left ajar, and lights and ambient noise minimized in the testing room. The proportion of the total session length that each dam spent attending to pups (AP) and exhibiting a full maternal crouch (FMC) was quantified from the videotapes. AP was defined as any combination of the following behaviors: gathering pups to a centralized location, retrieving stray pups, licking of pups, and hovering over them (see Stern & Taylor, 1991; Vernotica et al., 1996 for details). FMC was defined as crouching over the pups in a full kyphotic pose while remaining motionless for at least 1 min (e.g., see Stern & Taylor, 1991; Vernotica et al., 1996).

Data Analysis

Analyses of variance (ANOVAs) were used to analyze maternal weight gain during pregnancy, the number of male and female pups in each litter, and litter means of male and female body weights at postnatal Days 1 and 7. Operant data from the CA and SX groups were analyzed via separate ANOVAs to avoid homogeneity violations associated with the use of different breakpoint criteria for the two groups. Each of the operant measures was examined using Cochran tests (Winer, 1962) to assess potential violations of homogeneity of variance, which have been noted previously in data from PR experiments (Depoortere, Li, Lane, & Emmett-Oglesby, 1993). In no case did the dependent measure of responses/session violate the assumption of homogeneity of variance, hence this dependent measure was used as an index of breakpoints in the analysis of the operant data. The premating PR operant data were grouped according to phase of the estrus cycle and analyzed via ANOVA for cycle effects. ANOVAs were also used to compare responses/session during estrus with comparable data at the onset of pregnancy. For analysis of the PR data throughout pregnancy, the data were grouped into 3-day blocks for the entire pregnancy (except for the final period, which was 3–4 days in length, depending on the time of parturition for each animal). Tukey's post-hoc tests were used to determine the locus of significant main effects or interactions. The maternal behavior data were analyzed via ANOVAs or, in the case of significant nonhomogeneity of variance, using nonparametric statistics as detailed later.

RESULTS

Maternal/Litter Data

The CA and SX dams did not differ in body weights on the 1st day of gestation. There was no indication of anorexia in the cocaine-exposed dams, with no significant differences in percent weight gain during pregnancy between the groups. Indeed, if anything there was a trend for the dams self-administering cocaine to gain more weight during pregnancy than SX control dams who self-administered sucrose during each daily session (see Table 1). There were also no differences between the CA and SX groups with re-

Table 1. Maternal/Litter Data

	CA		SX	
Body weights—gestational Day 1	278.5	(13.0)*	273.4	(11.3)
Percent gestational weight gain	50.8	(2.8)	41.8	(3.8)
Numbers of live pups/litter	12.5	(0.8)	12.0	(0.4)
males	6.5	(0.8)	6.2	(0.4)
females	6.0	(0.7)	5.8	(0.5)
Offspring body weights				
P1 male	7.20	(0.23)	7.29	(0.20)
female	6.77	(0.27)	7.10	(0.26)
P7 male	15.35	(0.60)	15.28	(0.56)
female	15.27	(0.64)	15.31	(0.57)

*SEMs are presented in parentheses.

spect to litter sizes, number of male and female offspring delivered in each litter, or offspring body weights on postnatal Days 1 or 7 (Table 1).

Self-Administration Data

PR Responding Across the Estrus Cycle. Estrus cycle significantly influenced breakpoints (as indexed by the number of responses/session) for cocaine self-administration in the CA group, $F(2, 10) = 124.54$, $p < .001$, an effect that was not evident in the SX group. Tukey's post-hoc tests revealed a marked increase in responses/session for cocaine during estrus relative to metestrus/diestrus and proestrus (see Figure 1).

To compare how the onset of pregnancy influenced breakpoints for cocaine or sucrose, separate analyses were conducted for each reinforcer comparing responses/session during estrus with comparable data derived from the 1st trimester of pregnancy. Only breakpoints for sucrose self-administration varied significantly, $F(1, 5) = 97.01$, $p < .001$, with responses/session for sucrose being significantly higher during estrus than during the 1st trimester (see Figure 1).

PR Responding During Gestation. The repeated measure ANOVAs of the responses/session data during gestation revealed a significant influence of gestational block for the CA dams, $F(6, 30) = 23.81$, $p < .001$, but not the SX dams. Subsequent Tukey's post-hoc tests showed that in the CA animals, the responses/session measure for cocaine showed an initial increase from the first to the second 3-day block of pregnancy followed by a progressive decrease as the pregnancy progressed to term (see middle portion of Figure 1). Gestational Blocks 6 and 7 were significantly lower than all earlier blocks, while responding during Block 5 was significantly suppressed relative to Blocks 1–3.

When interpreting these data, it should be considered that the dams gained over 100 g in weight during gestation while the amount of cocaine per infusion remained constant. To examine the impact of this weight gain on self-administered dose, the entire gestational period was blocked into 3 trimesters, and the average

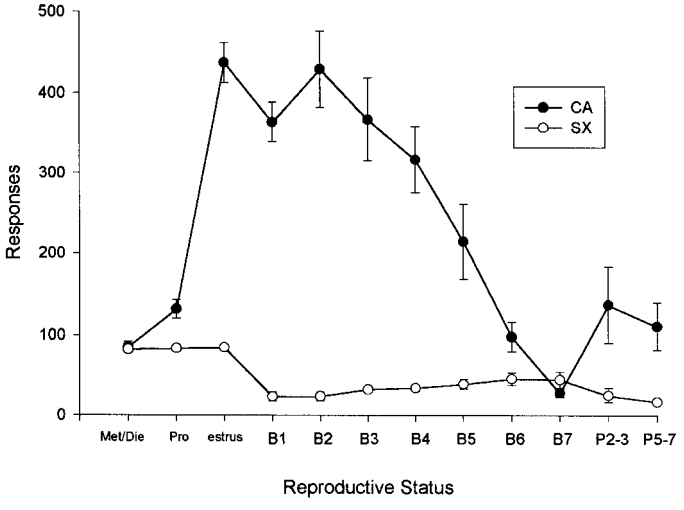

FIGURE 1 Changes in breakpoints for cocaine and sucrose throughout the entire study. The points along the *x* axis labeled B1–B7 represent the average daily breakpoints during each of the seven 3-day gestational periods (See Methods for details). The points labeled P2–3 and P5–7 represent similar averages for successive postnatal blocks; the mean number of responses for postnatal Days 2 and 3 were combined into an average score as were postnatal Days 5–7. Vertical bars, 1 *SEM*.

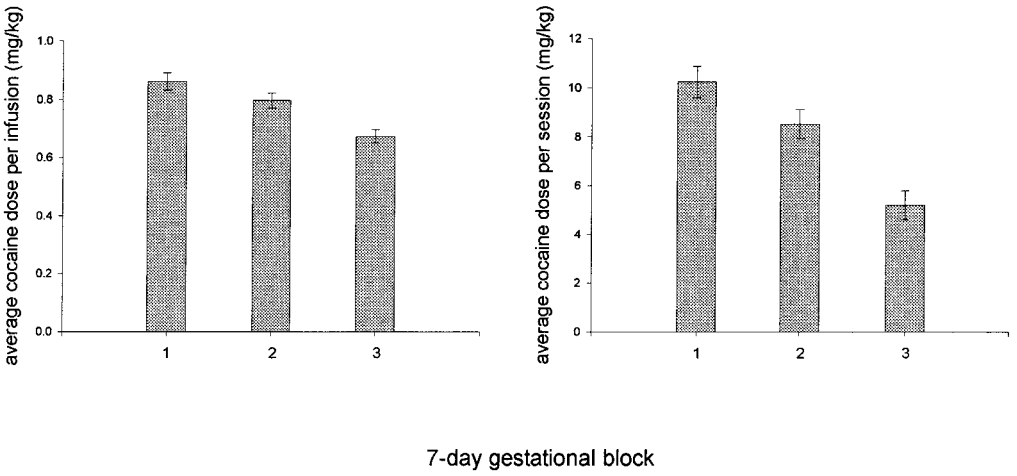

FIGURE 2a, b Effects of maternal weight gain on received doses of cocaine during gestation. The gestational period was divided into three 7-day blocks. Figure 2a shows the effect of maternal weight gain on the dose of each cocaine infusion. Figure 2b shows the effect of maternal weight gain on the total per session dose of cocaine. Vertical bars, 1 *SEM*.

dose of cocaine per infusion and per session (in mg/kg of body weight) was calculated for each animal during each trimester. Repeated measure ANOVAs revealed a significant effect of trimester for both measures, dose per infusion: $F(2, 10) = 410.86$, $p < .001$; dose per session: $F(2, 10) = 28.40$, $p < .001$. Tukey's post-hoc tests revealed that the average infusion dose in mg/kg progressively decreased during pregnancy as the dams gained weight (Figure 2a) while the average total session dose was significantly lower during the 3rd than the earlier trimesters (which did not differ significantly from each other) (see Figure 2b).

A significant correlation between the per-infusion cocaine dose and number of responses/session was found only during the 1st trimester, $r = .849$, $p < .05$, with the heaviest animals (animals receiving the lowest per-infusion cocaine doses) having the lowest number of responses/session. This typical relationship between cocaine dose and PR performance (Depoortere et al., 1993) was disrupted and no longer significant later in pregnancy (2nd trimester: $r = .321$, $p > .05$; 3rd trimester: $r = .089$, $p > .05$.

PR Responding During Lactation. Repeated measure ANOVAs of the PR data collected from postnatal Days 1–8 revealed a significant effect of postnatal day only for the CA group, $F(7, 35) = 4.05$, $p < .001$. As can be seen in Table 2, breakpoints for cocaine (as indexed by the responses/session measure) were significantly lower on postnatal Days 1, 4, and 8, days during which the test sessions were videotaped. The reasons for this apparent group difference in reactivity to the disruptive effects of videotaping are unclear, but could potentially be related to a cocaine-induced increase in arousal and vigilance. PR responding for those sessions during lactation that were not videotaped are presented in Figure 1.

Inactive Lever Responses. As can be seen in Table 3, animals clearly did not direct responding toward the inactive lever, data suggesting that the PR performance of the CA group was not merely a function of the motor-activating effects of cocaine.

Table 2. Breakpoints for Cocaine (CA) and Sucrose (SX) From Postnatal Days 1–8 (P1–8)*

	P1	P2	P3	P4	P5	P6	P7	P8
CA	17.5	143.0	130.7	30.2	131.8	102.3	97.7	16.8
	(3.8)**	(53.8)	(39.7)	(12.8)	(45.6)	(28.9)	(24.9)	(3.0)
SX	21.3	29.3	20.7	13.3	23.5	15.0	12.0	30.8
	(3.6)	(13.4)	(10.1)	(4.7)	(5.2)	(3.5)	(1.9)	(12.0)

*Litters were present with the dam in the operant chamber during these sessions. Sessions on Days 1, 4, and 8 were videotaped.
***SEM*s are presented in parentheses.

Table 3. Number of Responses on Inactive Lever Throughout the Experiment

Experimental Phase	Group	
	CA	SX
Met/Diestrus	1.8*	1.4
Proestrus	2.5	1.2
Estrus	5.7	1.1
Trimester 1	2.6	1.4
Trimester 2	2.4	1.5
Trimester 3	2.3	1.5
P2–3	2.3	1.5
P5–7	4.5	1.1

*Each score represents the mean of 6 animals for each phase of the experiment.

Maternal Behavior During Operant Sessions

Attending to Pups (AP). A 2 × 3 (Group × Postnatal Day) ANOVA on the percentage of each videotaped session during which dams were observed attending to pups revealed a main effect of group (CA vs. SX), $F(1, 30) = 12.70$, $p < .01$. Animals in the CA group spent a significantly greater proportion of each session exhibiting AP behaviors than animals in the SX group. Although it appears from Figure 3a that this effect was most evident during the later postnatal sessions, the Group × Day interaction approached but did not reach significance, $p < .06$.

Full Maternal Crouch (FMC). These data were found to violate assumptions of homogeneity of variance, so the data were analyzed using nonparametric Mann-Whitney *U*-tests. As can be seen in Figure 3b, on all test days cocaine self-administration severely disrupted expression of the rigid, kyphotic crouch in the dams which is normally associated with the suckling of offspring, p's $< .001$.

Location of Pups. Every CA dam, in each of the videotaped postnatal sessions, moved the pups out of the nest at the rear of the chamber and located them underneath the levers, where they remained for the rest of the session. In contrast, all of the SX dams left their litters in the nest throughout the session.

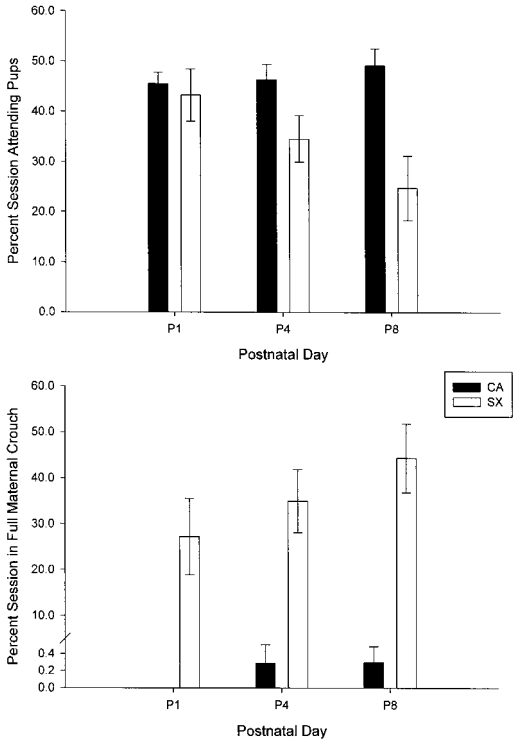

FIGURE 3 Percentage of PR sessions spent engaging in AP behaviors (Figure 3a) and FMC (Figure 3b) on postnatal Days 1, 4, and 8. During these sessions female animals had their litters present in the operant chamber while the session was videotaped for analysis of maternal behaviors. Each column represents the mean percentage score for 6 animals. Vertical bars, 1 *SEM*.

DISCUSSION

Patterns of cocaine self-administration were found to vary substantially during the reproductive process, while few changes were evident in dams responding for sucrose pellets. Number of responses/session for cocaine were markedly increased during estrus, and exhibited a progressive decrease during pregnancy, reaching a nadir just before term. During lactation, dams never regained the peak levels of sensitivity to cocaine reinforcement seen during estrus and early gestation, and exhibited atypical patterns of maternal behavior while in the operant chambers.

The marked increase in per session responding for cocaine during estrus confirms previous findings of Roberts et al. (1989a). Although the mechanisms underlying an estrus-related enhancement in stimulated DA release remain to be determined (Castner et al., 1993), resulting increases in extracellular DA would be expected to be accentuated following reuptake inhibition by cocaine, thereby prolonging DA availability at postsynaptic sites involved in modulating drug reinforcing effects (Bozarth, 1983).

A number of factors may contribute to the gradual attenuation in PR performance during pregnancy. One consideration is the pregnancy-related weight gains that functionally decreased infusion dose on a mg/kg basis as the pregnancy progressed. Decreases in per-

infusion dose typically result in related decreases in PR responding (Depoortere et al., 1993). However, while per-infusion dose in mg/kg and number of responses/session were highly correlated during the 1st trimester (before the pregnant animals exhibited any measurable pregnancy-related weight gain), these correlations were not significant during later trimesters. Thus, the physiological processes associated with pregnancy eventually disrupt the normal relationship between cocaine dose and PR performance during latter stages of pregnancy, suggesting that other factors may be involved in the marked pregnancy-associated decline in PR responding.

Hormonal changes associated with the reproductive process may contribute to these reductions in PR responding. The hormonal profile late in pregnancy, when responses/session were lowest, is characterized in Sprague-Dawley rats by decreased plasma levels of progesterone and corticosterone, and elevated levels of estradiol and prolactin relative to levels seen in early stages of gestation (Clark & Roy, 1985; Garland, Atherton, Baylis, Morgan, & Milne, 1987). Following parturition, when PR responses/session increased slightly to approximate the still relatively low levels seen during metestrus/diestrus and proestrus, lactating Sprague-Dawley dams are characterized hormonally by an increase in prolactin levels, an insensitivity to the effects of progesterone, and a blunting of the ACTH and corticosterone response to stress (Clark & Roy, 1985; Lightman, 1992). While the effects of these hormones on brain reinforcement mechanisms are incompletely understood and undoubtedly complex, the reinforcing properties of cocaine have been reported to be attenuated at lower corticosterone levels (Goeders & Guerin, 1996), an association that could contribute to the relatively low PR responses/session seen late in gestation and during lactation. PR responding during lactation also may have been relatively modest due to the presence of offspring in the operant chamber; pups are positive reinforcers for lactating rats (Stern, 1989) and competition from alternate reinforcers can influence drug taking behavior (Katz & Goldberg, 1987).

While cocaine self-administration markedly lowered the incidence of one measure of maternal behavior—full maternal crouch (FMC), other aspects of maternal behavior were not disrupted. Indeed, the CA dams spent proportionally more time attending to their pups than SX controls, perhaps because they expended considerable effort transporting their litter (and retrieving straying pups) to a location near the cocaine contingent lever, a relocation strategy never seen in SX dams. Moreover, although rarely exhibiting the FMC thought to be necessary for offspring to suckle (Stern, 1989), CA dams apparently exhibited somewhat normal lactation in the intervals between sessions. The weights of CA and SX derived pups did not differ on either postnatal Days 1 or 7 and all pups had visible milk bands when examined prior to testing on each day. These findings are reminiscent of those of Vernotica et al. (1996) who reported that cocaine-induced disruptions in maternal behavior are transient and only evident when cocaine levels are detectable in plasma. In rodents, DA agonists such as cocaine transiently lower levels of prolactin (Levy, Baumann, & Van de Kar, 1994), a critical hormone for lactation (Ben-Jonathan, 1985). Acute cocaine administration could also disrupt ongoing maternal behavior through altering activity in mesolimbic DA regions seemingly involved in the regulation of maternal behaviors (e.g., Numan & Smith, 1984; Wakerley, Clarke, & Summerlee, 1988), perhaps by modulating the reinforcing value of pup stimuli (Fahrbach & Pfaff, 1982; Stern, 1989).

In contrast to the considerable alterations in PR responding for cocaine seen during the reproductive cycle, the number of responses/session for sucrose in the SX control animals, though declining at the onset of pregnancy, remained fairly constant throughout pregnancy and lactation. Preference for sodium-saccharin in rat dams has likewise been reported to decrease rapidly at the onset of pregnancy and to remain suppressed throughout gestation and lactation (Wade & Zucker, 1969). In humans as well, preference for sweets has been shown to be lower in pregnant than nonpregnant women, with no significant differences in sweetness preferences across trimesters (Dippel & Elias, 1980).

The different pattern of breakpoints seen during pregnancy when dams are responding for sucrose versus cocaine could be interpreted to suggest the existence of at least partially separable reinforcement mechanisms in the rodent brain that are differentially influenced by the physiological processes of reproduction. However, inferences about differential effects of cocaine and conventional nutrients as reinforcers must be drawn with great caution. Magnitude and rate of reinforcement and response–reinforcer delay are among the potentially confounding factors inherent when comparing IV-delivered drugs with other positive reinforcers. There appear to be no data that address these issues with clarity. Thus, it cannot be concluded that the dissimilar PR response patterns obtained with cocaine and sucrose necessarily represent categorical differences in the processing of these reinforcers. Further work will be necessary to determine if the decrease in cocaine self-administration seen during later stages of gestation generalizes to other types of positive reinforcers as well as to other drugs of abuse.

There is some evidence that pregnancy may be associated with a decrease in the reinforcement value of other abused drugs, with a marked decrease in voluntary consumption of ethanol reported in pregnant mice relative to their levels of consumption prior to pregnancy (Becker, Randall, & Anton, 1986). Taken together with initial clinical reports of pregnancy-related attenuations in cocaine use (Cornelius et al., 1994; Richardson & Day, 1991; but see MacGregor et al., 1987), these results support the intriguing hypothesis that the progressive physiological changes associated with pregnancy may attenuate the rewarding properties of a variety of reinforcing drugs. However, given that moderate attenuations in reward value are often associated with increases in self-administration when drugs are freely available (e.g., Koob, Vaccarino, Amalric, & Bloom, 1987), the ultimate consequence of a pregnancy-associated attenuation in drug reward efficacy for drug-seeking behavior may vary dramatically as a function of the drug's availability and its perceived behavioral, social, and economic cost.

NOTES

The authors gratefully acknowledge the technical and administrative assistance of Yolanda Pinzas and Pat Heebner.

REFERENCES

Baker, H. J., Lindsey, J. R., & Weisbroth, S. H. (1980). The laboratory rat: Vol. II. Research applications. New York: Academic Press.

Becker, H. C., Randall, C. L., & Anton, R. F. (1986). Prepregnancy alcohol experience attenuates typical decrease in gestational alcohol consumption in mice. Alcohol, 3, 19–22.

Becker, J. B., & Cha, J. (1989). Estrous cycle-dependent variation in amphetamine-induced behaviors and striatal dopamine release assessed with microdialysis. Behavioural Brain Research, 35, 117–125.

Ben-Jonathan, N. (1985). Dopamine: A prolactin-inhibiting hormone. Endocrine Reviews, 6, 564–589.

Bozarth, M. A. (1983). Opiate reward mechanisms mapped by intracranial stimulation. In J. E. Smith & J. D. Lane (Eds.), The neurobiology of opiate reward processes (pp. 313–359). Amsterdam: Elsevier Biomedical.

Brass, C. A., & Glick, S. D. (1981). Sex differences in drug-induced rotation in two strains of rats. Brain Research, 223, 229–234.

Castner, S. A., Xiao, L., & Becker, J. B. (1993). Sex differences in striatal dopamine: In vivo microdialysis and behavioral studies. Brain Research, 610, 127–134.

Clark, A. S., & Roy, E. J. (1985). Behavioral insensitivity to progesterone during lactation in female rats. Physiology & Behavior, 34, 677–682.

Cornelius, M. D., Richardson, G. A., Day, N. L., Cornelius, J. R., Geva, D., & Taylor, P. M. (1994). A comparison of prenatal drinking in two recent samples of adolescents and adults. Journal of Studies on Alcohol, 55, 412–419.

Depoortere, R. Y., Li, D. H., Lane, J. D., & Emmett-Oglesby, M.W. (1993). Parameters of self-administration of cocaine in rats under a progressive-ratio schedule. Pharmacology Biochemistry and Behavior, 45, 539–548.

Diaz-Veliz, G., Baeza, R., Benavente, F., Dussaubat, N., & Mora, S. (1994). Influence of the estrus cycle and estradiol on the behavioral effects of amphetamine and apomorphine in rats. Pharmacology Biochemistry and Behavior, 49, 819–825.

DiPaolo, T., Rouillard, C., & Bedard, P. (1985). 17β-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Eur. J. Pharmacol., 117, 197–203.

Dippel, R. L., & Elias, J. W. (1980). Preferences for sweet in relationship to use of oral contraceptives and pregnancy. Hormones and Behavior, 14, 1–6.

Dwivedi, C., Engineer, F. N., & Vaughan, S. L. (1993). Alterations in biodistribution of cocaine may explain differential toxicity in pregnant and postpartum rats. Toxicology and Applied Pharmacology, 118, 131–134.

Fahrbach, S. E., & Pfaff, D. W. (1982). Hormonal and neural mechanisms underlying maternal behavior in the rat. In D. W. Pfaff (Ed.), The physiological mechanism of motivation (pp. 253–283). New York: Springer-Verlag.

Garland, H. O., Atherton, J. C., Baylis, C., Morgan, M. R. A., & Milne, C. M. (1987). Hormone profiles for progesterone, oestradiol, prolactin, plasma renin activity, aldosterone, and corticosterone during pregnancy and pseudopregnancy in two strains of rat: Correlation with renal studies. Journal of Endocrinology, 113, 435–444.

Goeders, N. E., & Guerin, G. F. (1996). Role of corticosterone in intravenous cocaine self-administration in rats. Neuroendocrinology, 64, 337–348.

Heyser, C. J., Molina, V. A., & Spear, L. P. (1992). A fostering study of the effects of prenatal cocaine exposure: I. Maternal behaviors. Neurotoxicology and Teratology, 14, 415–421.

Hodos, W. (1961). Progressive-ratio as a measure of reward strength. Science, 134, 943–944.

Johns, J. M., Noonan, L. R., Zimmerman, L. I., Li, L., & Pedersen, C. A. (1994). Effects of chronic and acute cocaine treatment on the onset of maternal behavior and aggression in Sprague-Dawley rats. Behavioral Neuroscience, 108, 107–112.

Katz, J. L., & Goldberg, S. R. (1987). Second-order schedules of drug injection. In M. A. Bozarth (Ed.), Methods of assessing the reinforcing properties of abused drugs (pp. 105–116). New York: Springer-Verlag.

Kinsley, C. H., Turco, D., Bauer, A., Beverly, M., Wellman, J., & Graham, A. (1994). Cocaine alters the onset and maintenance of maternal behavior in lactating rats. Pharmacology Biochemistry and Behavior, 47, 857–864.

Koob, G. F., Vaccarino, F. J., Amalric, M., & Bloom, F. (1987). Positive reinforcement properties of drugs: Search for neural substrates. In J. Engel & L. Oreland (Eds.),

Brain reward systems and abuse (pp. 35–50). New York: Raven Press.

Levy, A. D., Baumann, M. H., & Van de Kar, L. D. (1994). Monoaminergic regulation of neuroendocrine function and its modification by cocaine. Frontiers in Neuroendocrinology, 15, 85–156.

Lightman, S. L. (1992). Alterations in hypothalamic–pituitary responsiveness during lactation. Annals of the New York Academy of Sciences, 652, 340–346.

MacGregor, S. N., Keith, L. G., Chasnoff, I. J., Rosner, M. A., Chisum, G. M., Shaw, P., & Minogue, J. P. (1987). Cocaine use during pregnancy: Adverse perinatal outcome. American Journal of Obstetrics and Gynecology, 157, 686–690.

Mactutus, C. F., Herman, A. S., & Booze, R. M. (1994). Chronic intravenous model for studies of drug abuse in the pregnant and/or group-housed rat: An initial study with cocaine. Neurotoxicology and Teratology, 16, 183–191.

Numan, M., & Smith, H. G. (1984). Maternal behavior in rats: Evidence for the involvement of preoptic projections to the ventral tegmental area. Behavioral Neuroscience, 98, 712–719.

Orndoff, B. (1990, March 3). Cocaine impairs maternal instinct, study shows. Richmond Times-Dispatch, pp. 1–8.

Ostrea, E. M., Jr., Brady, M., Gause, S., Raymundo, A. L., & Stevens, M. (1992). Drug screening of newborns by meconium analysis: A large-scale, prospective, epidemiologic study. Pediatrics, 89, 107–113.

Plessinger, M. A., & Woods, J. R., Jr. (1990). Progesterone increases cardiovascular toxicity to cocaine in nonpregnant ewes. American Journal of Obstetrics and Gynecology, 163, 1659–1664.

Richardson, G. A., & Day, N. L. (1991). Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicology and Teratology, 13, 455–460.

Richardson, N. R., & Roberts, D. C. S. (1995). Progressive ratio schedules in drug self-administration studies in rats: A method to evaluate reinforcing efficacy. Journal of Neuroscience Methods, 66, 1–11.

Roberts, D. C. S., Bennett, S. A. L., & Vickers, G. J. (1989a). The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology, 98, 408–411.

Roberts, D. C. S., Loh, E. A., & Vickers, G. J. (1989b). Self-administration of cocaine on a progressive ratio schedule in rats: Dose–response relationship and effect of haloperidol pretreatment. Psychopharmacology, 97, 535–538.

Robinson, T. E., Becker, J. B., & Presty, S. K. (1982). Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: Sex differences. Brain Research, 253, 231–241.

Shimizu, H., & Bray, G. A. (1993). Effects of castration, estrogen replacement, and estrous cycle on monoamine metabolism in the nucleus accumbens, measured by microdialysis. Brain Research, 621, 200–206.

Spear, L. P. (1995). Neurobehavioral consequences of gestational cocaine exposure: A comparative analysis. In C. Rovee-Collier & L. P. Lipsitt (Eds.), Advances in infancy research (pp. 55–105). Norwood, NJ: Ablex.

Stern, J. M. (1989). Maternal behavior: Sensory, hormonal, and neural determinants. In F. R. Rush & S. Levine (Eds.), Psychoendocrinology (pp. 105–226). New York: Academic Press.

Stern, J. M., & Taylor, L. A. (1991). Haloperidol inhibits maternal retrieval and licking, but enhances nursing behavior and litter weight gain in lactating rats. Journal of Neuroendocrinology, 3, 591–596.

Vernotica, E. M., Lisciotto, C. A., Rosenblatt, J. S., & Morell, J. I. (1996). Cocaine transiently impairs maternal behavior in the rat. Behavioral Neuroscience, 110, 315–323.

Wade G. N., & Zucker, I. (1969). Hormonal and developmental influences on rat saccharin preferences. Journal of Comparative and Physiological Psychology, 69, 291–300.

Wakerly, J. B., Clarke, G., & Summerlee, A. J. S. (1988). Milk ejection and its control. In: E. Knobil, J. Neill, L. L. Ewing, G. S. Greenwald, C. L. Markert, & D. W. Pfaff (Eds.), The physiology of reproduction (pp. 2283–2321). New York: Raven Press.

Winer, B. J. (1962). Statistical principles in experimental design. New York: McGraw-Hill.

Woods, J. R., Jr., & Plessinger, M. A. (1990). Pregnancy increases cardiovascular toxicity to cocaine. American Journal of Obstetrics and Gynecology, 162, 529–533.

Zuckerman, B., Frank, D. A., Hingson, R., Amaro, H., Levenson, S., Kayne, H., Parker, S., Vinci, R., Aboagye, K., Fried, L., Cabral, H., Timperi, R., & Bauchner, H. (1989). Effects of maternal marijuana and cocaine use on fetal growth. New England Journal of Medicine, 320, 762–768.