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Cocaine Exposure Prebreeding to Weaning: Maternal and Offspring Effects

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PEEKE, H. V. S., K. A. DARK, A. SALAMY, M. SALFI AND S. N. SHAH. *Cocaine exposure prebreeding to weaning: Maternal and offspring effects.* PHARMACOL BIOCHEM BEHAV **48**(2) 403–410, 1994. — In a model emphasizing prebreeding cocaine administration, rats exposed to cocaine (50 mg/kg) daily were compared to saline-injected and noninjected controls with respect to weight changes, food and water intake, maternal behavior, offspring weight, and activity. During the first 21 days cocaine-treated dams lost weight, while the control dams gained. Throughout gestation and the first 14 days of lactation all groups gained weight, but the cocaine-exposed dams never completely recovered from the initial anorectic effect. Except during the first week of exposure, cocaine dams ate and drank more than the normal controls and drank more than the saline group. During gestation there was no difference in food intake, although the cocaine dams continued to drink more than controls. During lactation there were no differences in food and water consumption across groups. However, the cocaine dams exhibited more nursing behavior. From birth to day 21, the offspring of cocaine-treated dams were smaller than those of either control group. By 51 days of age, group differences had disappeared. Cocaine-exposed pups and saline offspring tested at days 28 and 85 were more active than those of noninjected controls. The results indicate that administration of cocaine for a period prior to breeding and during gestation and lactation, a protocol which closely resembles human drug abuse patterns, is more devastating than the administration during gestation.

Cocaine Development Animal model

THE illicit use of cocaine continues to pose a public health problem of epidemic proportions. Its widespread use by pregnant women raises concern regarding possible teratologic consequences for their children (1,2,18). To date, evidence derived from both human and animal cocaine studies reveal only "minor teratologic abnormalities" (8). While mild effects have been reported at moderate doses, more deleterious outcomes have resulted from higher dosages (4,25).

In view of the multiple confounding variables encountered in human drug abuse research (e.g., poverty, disease, polydrug use, etc.), animal models have been advanced in order to examine the exclusive influence of cocaine on development. A number of investigators have demonstrated the utility of controlled drug regimens during the course of pregnancy in delineating growth and neurobiologic outcome in fetuses and exposed progeny (3–6,11,21–25). In these studies, drug administration and control procedures are confined to a period commencing several days after impregnation and continuing until parturition. Typically, the offspring are then fostered to normal (non-cocaine-treated) dams for lactation. While this procedure may help isolate temporal drug effects during gestation, it fails to reflect the pattern of cocaine use in pregnant women, thereby diminishing the generality of the animal model to the human condition. Moreover, starting cocaine administration during pregnancy confounds early intrapartum events with the drug effects as would occur in the experienced user who becomes pregnant.

The purpose of this research was to further our understanding of the influence of cocaine on maternal and offspring variables following drug treatment in a manner that more closely resembles human drug abuse practices. We accomplished this objective by pre-exposing female rats to daily cocaine administration for three weeks prior to breeding and continuing through gestation and lactation. In addition, we included both saline-injected and noninjected controls to assess injection stress effects.

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METHODS

Fifty-two female and 40 male Long-Evans rats purchased from a commercial vendor were used in this study. The females were housed singly in plastic tub cages with hardwood shavings for bedding material. The animals were maintained on a 14 : 10 reversed light-dark cycle, and all were fed and watered ad lib throughout the experiment. Water and food were replenished daily, and consumption was monitored between days by weight decrements. Food was supplied in pellet form. We observed negligible spillage, but retrievable crumbs found upon daily inspection were included in the calculations of the weight of the remaining food.

The females were randomly divided into three groups. One group (cocaine) received 50 mg/kg/4 cc of cocaine hydrochloride (n = 28) by SC injection via a 26-gauge needle in the upper back. Normal tonicity of the cocaine solution was maintained by decreasing the sodium chloride concentration to account for the ionic components introduced by the cocaine hydrochloride. Injections of cocaine sometimes cause minor local necrosis [see Church et al. (4)]. Routinely moving the site of the injection significantly reduces the severity of the problem. There was no evidence that the small scabs caused any discomfort to the animals. A second group (saline) received the same volume of the saline vehicle injected into the same area (n = 16). The third group (normal controls) was neither injected nor handled other than during routine cage and laboratory maintenance (n = 8). The male rats were used only as breeders and were pharmacologically untreated.

This protocol began one week after the animals arrived in the laboratory. Each day food and water was weighed and replenished, and the animals were weighed, experimentally treated, and returned to their cage at 0900. After 21 days a male was introduced into the female's cage. Nine days later the male was removed. If it was determined that the female was not pregnant, a new male was provided for an additional 9 days. Food and water intake data was not collected during the breeding period because it would reflect consumption by both male and female. During gestation and throughout lactation the female was maintained according to the original 21-day regimen.

At birth the litter was counted, weighed, sexed, and culled to four female and four male pups, or as near to that ratio as possible. In addition, each dam's nursing behavior was observed morning (0900) and evening (1630). A rating of the dam's nursing behavior was made every 15 s for 10 min (40 observations) during both sessions for a total of 80 observations per day per dam. Following the morning session the pups were weighed. On day 21 the pups were taken from the dams and housed together until approximately day 30 when the vaginal openings began to occur. Thereafter the pups were housed by sex within litters four to a cage except in several instances when the males grew too large and had to be housed two to a cage.

A version of the Dashiell Maze was employed to quantify locomotor exploration (7). This apparatus is ideal for the study of locomotion in that rats do not show habituation of exploratory behavior for over 30 min repeated daily for up to 10 days (Peeke & Petrinovich, unpublished). The maze consisted of a plywood box 121 cm^2 with 20-cm-high walls and 16 plywood boxes arranged in four equally spaced rows of four. A start box with a guillotine door was placed in the center of one wall (Fig. 1). The entire maze was painted dark gray.

Trials were carried out during the dark phase of the light cycle under red illumination from a 25-W bulb in a reflector suspended six feet above the center of the maze. Each pup was placed in the start box, and after 15 s the door was opened and the animal was allowed to enter the maze for 6 min. During this time the path the animal traversed was traced on a map of the maze from direct observation. The number of alleys and culls entered represented the measure of exploratory activity.

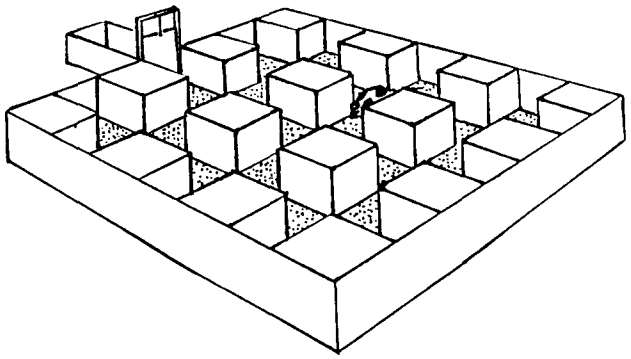

FIG. 1. Modified Dashiell maze.

A series of analyses of variance (ANOVAS, Group × Days) followed by post hoc (t test) comparisons were used to assess the various sets of the data.

RESULTS

Fifty-two females were placed with males. Seven of 8 non-injected control females conceived, and all 7 bore litters which reached weaning age (Fig. 2). Of the saline group, all 16 conceived, 14 bore litters, and only 12 reached weaning. Twenty-two of 28 cocaine-treated females became pregnant, 17 bore litters, but only 7 litters reached weaning age. A chi-square test was used to compare the frequency of success and failure of dams to become pregnant and carry their litter to weaning. There was a significant difference among the groups, χ^2 = 15.5(2), p = .001. Fisher exact probability tests were employed in cases where group differences occurred. The cocaine dams differed from the saline-injected animals (p = .002) and the normal controls (p = .003). There was no difference between the normal and saline-injected groups.

All of the data on weight, food, and water intake were based on the dams that brought their litters to weaning age. The elimination of the unsuccessful dams did not bias the initial weights of the groups as there were no differences on the first day among the females that were successful, $F(2, 23)$ = 1.14, NS. An ANOVA on the initial weights of all the females also disclosed no group differences, $F(2, 49)$ = 0.15, NS.

Maternal Effects

Prepregnancy effects of cocaine. A two-way ANOVA (Group × Days) on the weight of the dams revealed no main effect for group; a significant days effect, $F(20, 460)$ = 10.19, $p < .001$; and a Group × Days interaction, $F(40, 460)$ = 6.31, $p < .001$. During the first 21 days of daily cocaine exposure the drug-treated females did not gain weight, whereas both control groups did (Fig. 3, prepregnancy).

For food intake, which reflects the weight change data, a significant group effect (ANOVA) was found, $F(2, 23)$ = 5.08, $p < .015$, with specific contrasts showing a difference

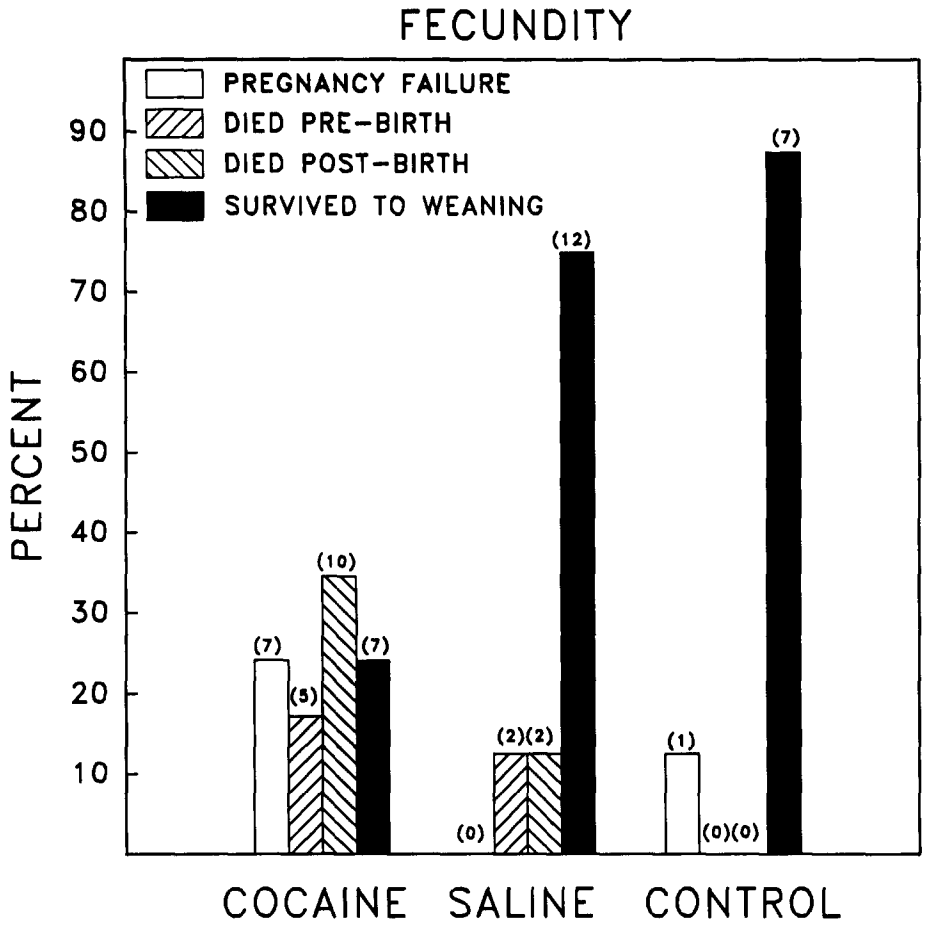

FIG. 2. Reproductive capacity limitations of cocaine- and saline-treated rat dams and untreated dams. Percentage of females becoming pregnant, retaining litters, and maintaining them until weaning. Numbers in parentheses are number of litters.

between the cocaine- and noninjected subjects ($p < .004$). The saline group did not differ from the other groups. There was also a days effect, $F(20, 460) = 4.96$, $p < .001$, and a Group × Days interaction, $F(40, 460) = 2.54$, $p < .001$, indicating that the experimental animals (cocaine) increased their food intake at a greater rate than the control groups (Fig. 3).

A parallel analysis of daily water intake revealed a reliable group effect, $F(2, 23) = 5.89$, $p < .009$. Post hoc t tests indicated that the cocaine group drank more than the noninjected group ($p < .003$) and more than the saline group ($p < .02$). The increase in water intake over the 21 days was also significant, $F(20, 460) = 3.49$, $p < .001$. There was no interaction between group and days (Fig. 3).

The three-week prepregnancy period (Fig. 3) reflects a change within this phase of the study. To carefully quantify weight, food, and water intake during this time, we analyzed each week independently. During the first week there was a days effect, $F(6, 138) = 2.57$, $p < .022$, and a significant Group × Days interaction for weight, $F(12, 138) = 5.77$, $p < .001$. There was a group effect for food intake, $F(2, 23) = 13.98$, $p < .001$, with the cocaine females consuming less than either control group ($p < .001$ in both cases). There were no differences in water intake.

With regard to weight changes during the second prepregnancy week, there was a days effect, $F(6, 138) = 9.05$, $p < .001$, and a Group × Days interaction, $F(12, 138) = 2.119$, $p < .015$. There were no significant effects for group or days nor any interaction with food intake. For water consumption there was a group effect, $F(2, 26) = 6.37$ $p < .001$, with the cocaine females drinking more than either control group ($p < .003$, cocaine vs. normal controls; $p < .014$, cocaine vs. saline controls).

By the third prepregnancy week there were no group or interaction effects for weight, but there continued to be a days effect, $F(6, 138) = 11.24$, $p < .001$. Food intake showed a reliable group effect, $F(2, 23) = 3.94$, $p < .034$; the normal group consumed more food than either of the injected groups. Water intake also differed among groups, $F(2, 26) = 4.43$, $p < .022$. The cocaine females drank more than the saline ($p < .008$) and normal controls ($p < .049$). Again there was the ongoing days effect, $F(6, 138) = 5.77$, $p < .001$.

Effects of cocaine during gestation. Just the last 10 days of gestation, counting backward from the day of birth rather than the entire period, were analyzed. This is the only time that all of the females were separated from the males. Conventional methods of determining pregnancy such as finding a copulatory plug were undependable under dim red illumina-

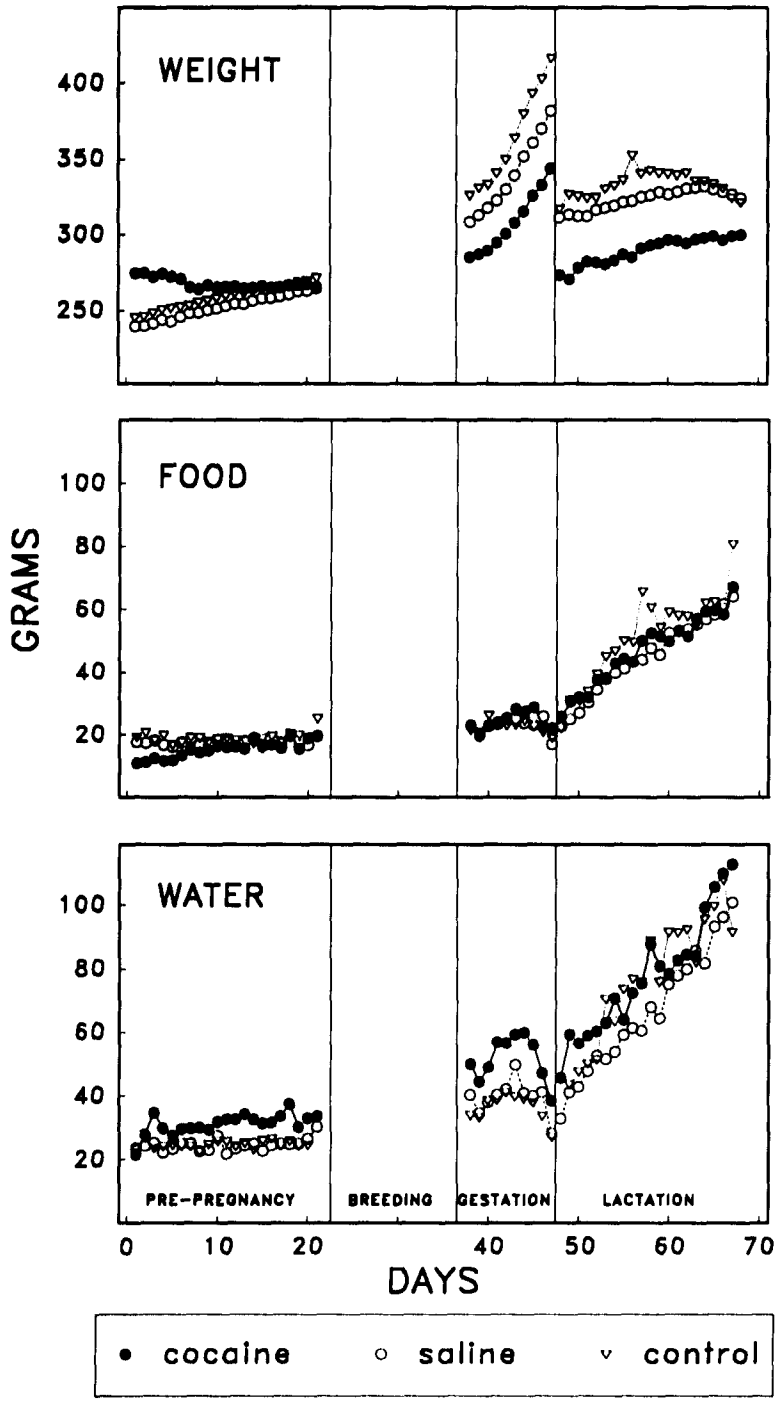

FIG. 3. Weight change and food and water intake of cocaine- and saline-treated rat dams and untreated dams.

tion (our reversed day-night cycle) and with the use of tub cages with hardwood shavings. The assessment of vaginal smears was rejected as too invasive and stressful for this study. We are not aware of any evidence that cocaine affects the length of pregnancy in rats.

An ANOVA revealed a significant group effect, $F(2, 23) = 4.44, p < .023$), with the cocaine dams being smaller than the noninjected animals ($p < .007$), while the saline group did not differ from the other groups. A days effect, $F(9, 207) = 218.6, p < .001$, and a Group × Days interaction, $F(18, 207) = 3.60, p < .001$, were also identified. Cocaine females were lighter, and while all groups gained weight, the cocaine

group did so at a slower rate (Fig. 3, gestation). Food intake during the last 10 days of gestation revealed only a days effect, $F(9, 207) = 2.41, p < .013$.

Statistical analysis of water intake showed a significant group effect, $F(2, 23) = 7.66$, $p < .003$, with the cocaine dams drinking more than both the saline ($p < .003$) and noninjected ($p < .001$) controls. The ANOVA also showed a reliable days effect, $F(9, 207) = 8.75, p < .001$, but no interaction between group and days.

Effects of cocaine during lactation. The offspring were weaned at 21 days of age; however, by day 15 the pups began to eat and drink from the mother's food and water, thus contaminating the data in terms of consumption. To avoid this source of error we analyzed only the first 14 days of lactation (Fig. 3, lactation).

Analysis of maternal weight revealed a significant group effect, $F(2, 23) = 5.20, p < .014$. Cocaine females weighed less than both noninjected ($p < .005$) and saline ($p < .021$) females. All groups gained weight over the 14-day period, $F(13, 299) = 16.10, p < .001$.

Food intake by the lactating dams was also assessed. There was a significant group effect, $F(2, 23) = 4.12, p < .03$, with the control groups differing from each other ($p < .009$). The noninjected controls drank more than saline-injected animals. Again, a reliable days effect, $F(13, 299) = 39.54, p < .001$, but no interaction was observed (Fig. 3).

Analysis of the water intake failed to distinguish the groups. As expected, a significant days effect was noted, $F(13, 299) = 32.89, p < .001$, with no interaction (Fig. 3).

Although no meaningful assessment of food and water intake during the last seven days of lactation could be performed (see above), analysis of the maternal weight during this period revealed a significant group effect, $F(2, 23) = 3.43, p < .05$, with the cocaine animals being lighter than either saline ($p < .031$) or noninjected ($p < .029$) controls. There was also a significant days effect, $F(6, 138) = 4.93, p < .001$, and a Group × Days interaction, $F(12, 13) = 3.43, p < .001$. The cocaine dams, unlike either control group, continued to gain weight.

Nursing behavior. Evaluation of the time spent nursing during lactation revealed a significant group effect, $F(2, 22) = 28.30, p < .001$, and a reliable days effect, $F(19, 418) = 2127.4, p < .001$, with the cocaine group nursing more frequently than the other groups (Fig. 4).

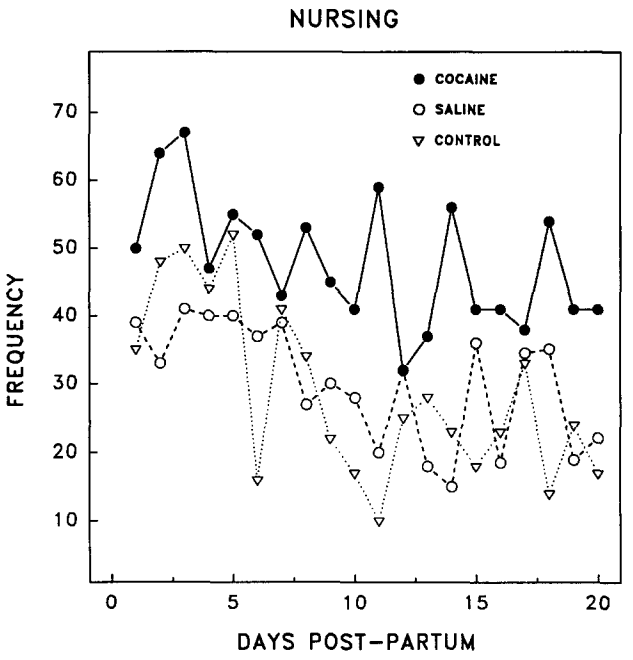

FIG. 4. Nursing behavior of cocaine- and saline-treated rat dams and untreated dams.

Offspring Effects

Analysis of pup weight and activity level was based upon the means of the female and male pups in each litter. It is the convention in behavioral teratologic research that the litter constitutes the unit of measurement (or each sex of a litter) rather than the individual pups (15). The underlying assumption is that shared variance within a litter (a litter effect) would result in an overestimation of the effect, thereby increasing the risk of a Type I error. (Intuitively, the within-litter common variance should result in an overestimation of experimental effects. However, we were unable to find any clear documentation in the literature on this drug in rats. To convince ourselves that, in fact, only the means of each sex rather than all of the littermates within each litter should be used, we tested the variance obtained from using all of the offspring's weights vs. artificial "litters" created by randomly selecting four males and four females from the pool of subjects but with the stipulation that none of the eight in any of the 27 artificial "litters" could come from the same litter. This was compared to the variance from the 27 actual litters. We arbitrarily selected pup weights on day 10 as the period that we compared the real and "created" litters. The mean standard deviation from the real 27 litters was 1.068 and from the created 27 litters, 3.640. This difference is highly significant, $p < .001$.)

Pup weights: days 1–14. During the first 14 days a Group × Days × Sex ANOVA revealed a significant main effect for group, $F(2, 40) = 4.15, p < .023$, and days, $F(13, 520) = 1138.48, p < .001$, as well as the respective interaction term, $F(26, 520) = 11.79, p < .001$. The normal controls were distinguished from the cocaine pups ($p < .01$), with the offspring of the saline-injected dams falling midway between the two. There was no sex effect (Fig. 5).

Pup weights: days 15–21. Prior to removing the dams, the group effect, $F(2, 40) = 3.370, p < .044$, and days effect, $F(6, 240) = 672.01, p < .001$, persisted, but there were no interactions or sex effect at this time.

Pup weights: days 22–28. During this period only a days effect reached significance, $F(6, 240) = 963.0, p < .001$ (Fig. 5).

Pup weights: days 24–51. In this time frame there was no group effect, but a significant sex effect emerged, $F(1, 40) = 33.51, p < .001$. There was also a reliable days effect, $F(9, 360) = 3511.93, p < .001$, and a Sex × Days interaction, $F(9, 360) = 174.79, p < .001$ (Fig. 5).

Pup weights: days 54–84. This final phase mirrored the results of the previous period. There was a significant days effect, $F(10, 400) = 1963.87, p < .001$; sex effect, $F(1, 40) = 211.89, p < .001$; and Days × Sex interaction, $F(10, 400) = 205.69, p < .001$ (Fig. 5).

Activity: days 28 and 85. The ANOVA based on the number of lines crossed in the maze by the mean of the males and the mean of females of each litter disclosed a significant

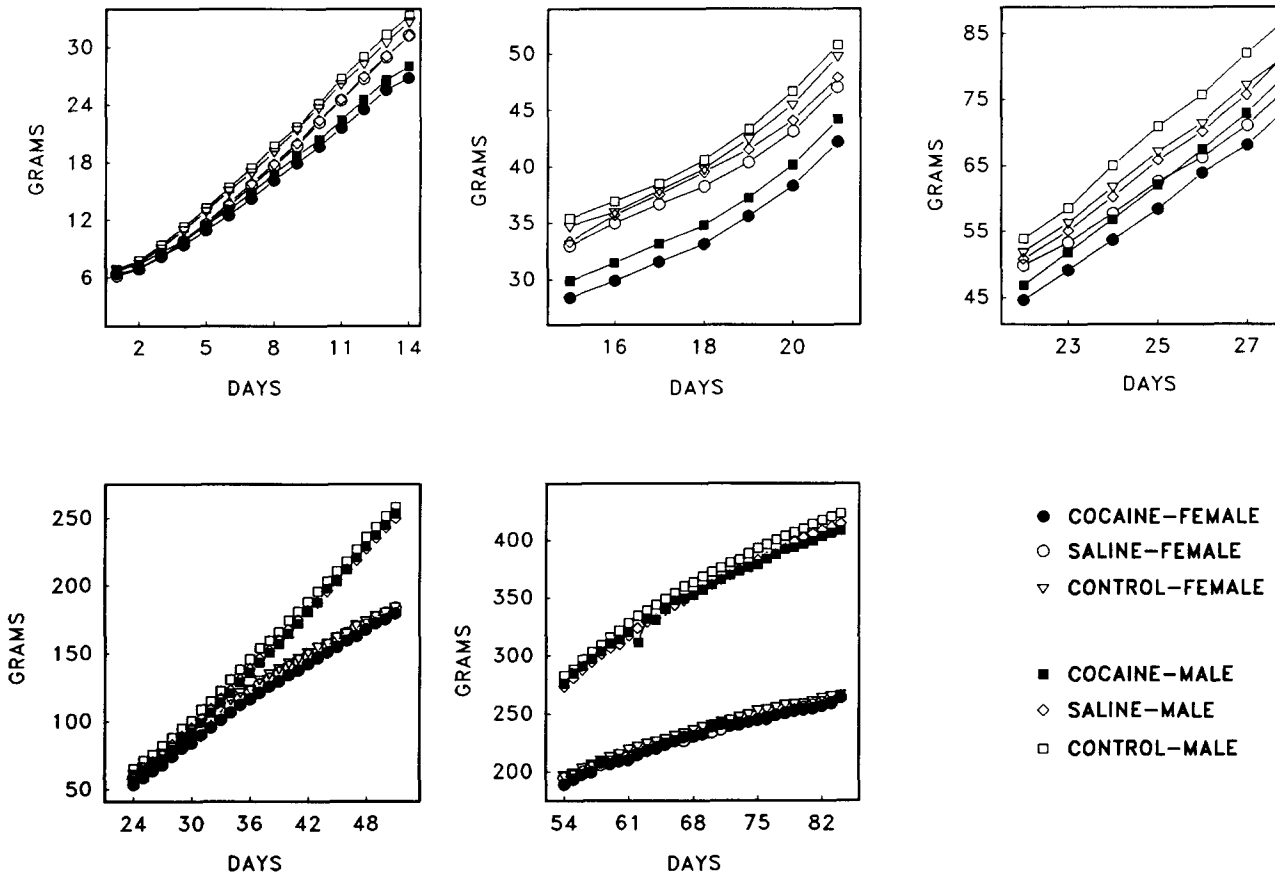

FIG. 5. Weight changes of the offspring of cocaine- and saline-treated rat dams and of untreated dams.

groups effect, $F(2, 38) = 3.67$, $p < .035$, with the normal control group differing from both injected groups (cocaine and saline groups were more active than the noninjected group, $p < .03$). There was also a significant days effect, $F(1, 38) = 38.62$, $p < .001$, with activity across groups greater on day 85 than on day 28 (Fig. 6).

DISCUSSION

The role of animal models in elucidating the effects of cocaine on maternal status and offspring development, neurobiology, and behavior as well as providing relevant information toward the understanding of the clinical effects of cocaine on pregnancy and outcome has been amply documented in the literature (5,22). In a recent review, Spear et al. (23) summarized the findings to date, emphasizing that gestational cocaine exposure does, in fact, result in neurochemical and behavioral alterations that persist into adulthood. To our knowledge, the present work is the first controlled animal study in which rat dams were exposed to cocaine for some time prior to mating and through gestation and lactation, and fecundity was evaluated.

Maternal Effects

Daily exposure to cocaine resulted in a sharp decline in fecundity. Only 30% of the cocaine-treated females who conceived were able to produce litters and maintain them to 21 days of age. Litter size was only slightly (nonsignificantly) smaller among the cocaine animals. The noninjected control females carried 100% of their litters (7 of 7) to weaning, and the saline controls carried 71% (12 of 16) to weaning (see Fig. 2), intimating a nonspecific effect (i.e., injection-induced stress) on fecundity.

During the three-week prebreeding period the cocaine females failed to gain weight despite significant increases in both food and water intake. The initial insult of cocaine, particularly during the first few days, resulted in a pronounced anorectic effect. Females from both control groups gained weight during this time (see Fig. 3). A closer examination of the prepregnancy period showed that the anorectic effect was confined to the first week. During this time the cocaine-exposed dams ate less than their control counterparts. By the second week, food intake was not different between groups, and the weight difference was reduced. By the third week the cocaine group was consuming slightly more food than the saline-injected controls but significantly less than the normal controls. Water consumption was greater for the cocaine group than the controls in both the second and third weeks of the prepregnancy period. Retardation of weight gain despite equal food intake during week 2 may be indicative of a defect in food utilization. Fortunately, this period did not correlate with the onset or continuation of pregnancy, thereby avoiding the potential confounding of these two important events.

During gestation the cocaine dams also gained weight, but at a slower rate than the controls. This is consistent with the general findings of Spear et al. (23) that cocaine at a dose

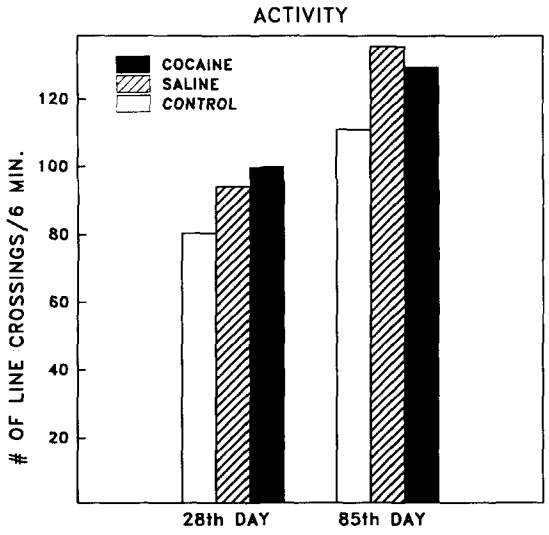

FIG. 6. Locomotor activity of the offspring of cocaine- and saline-treated rat dams and of untreated dams at 28 and 85 days postpartum.

slightly lower than ours (40 mg/kg) may or may not attenuate weight gain. Throughout pregnancy the cocaine dams drank more water then the controls, as also reported by Church et al. (3).

During lactation there were no group differences in terms of food or water intake, but the cocaine dams continued to weigh less, as they had throughout the postbreeding stage. Church et al. (4) have interpreted similar findings as evidence for nutritional protection of the fetus. This view receives some support from the significantly higher incidence of nursing behavior exhibited by our cocaine group (see Fig. 4) and may reflect a compensatory mechanism for nutritional sparing of the offspring. Our data show enhancement of maternal conduct in cocaine-treated dams.

Offspring Effects

The cocaine-exposed offspring were smaller during the period they were with the dam. For the first two weeks of life the pups received virtually all of their nutrition from the mother. During the last week prior to weaning a significant amount was still furnished from the dam. At the time of weaning the pups were readily eating and drinking from the mother's supply. From one week postweaning until the end of the experiment (day 85) there was no longer any cocaine effect on pup weight (see Fig. 5). This implies that reduced pup growth during lactation may be due to nutritional deficiency associated with the quality or quantity of milk. Apparently the dams treated with cocaine were malnourished, equivalent or greater food and water intake notwithstanding. Their pups were also exposed to cocaine suckled daily from mother's milk (24). Perhaps the anorectic effect on the pups is due to some direct action of cocaine rather than, or in addition to, a residual effect of the dam's inability to provide sufficient nourishment.

Alternatively, another maternal factor, injection stress, may influence the behavior and growth of the pups. This is suggested in the weights of the saline-injected offspring, which fell between the noninjected control and the cocaine groups during lactation. This indicates that the injections, per se, may account for some of the effect seen in the cocaine-exposed pups. Additional evidence for a similar and more developmentally persistent effect of injection-related stress was observed in locomotor activity. The offspring of both the saline-injected dams and the cocaine-injected dams were more active than the normal, noninjected controls. These differences continued into adulthood (see Fig. 6). Studies that employ both saline injection and normal controls ordinarily do not report differences in gestational effects of drugs on either the dams or the offspring. However, in the present study daily injections (vs. no injections) were conducted over a longer period. Characteristically, other studies administer injections only during some interval in gestation. Thus dams might experience "injection stress" for a range of 13–19 days. In contrast, our treatment procedures were maintained for a minimum of 42 days prior to birth. If injection stress is a cumulative process, differences not seen in reports of shorter treatment duration might eventually emerge.

Smith et al. (20), using a very low dose of cocaine (10 mg/kg), found only scant evidence for the reverse effect (i.e., cocaine lowering activity level). They did not have a noninjected control, and hence the possibility of injection stress could not be appraised. Hutchings et al. (11), using a dose of 60 mg/kg IG, found heightened activity at a postnatal period similar to our first locomotion measure. They used both vehicle and nontreated control groups, but the use of intubation as a route of administration circumvented the possibility of injection effects but might have precipitated stress of a different nature. Their study did not measure activity after day 32; thus, our finding of differences enduring into adulthood could not be confirmed. A similar study (13) using open-field activity and neophobia was unique in that they used continuous and periodic schedules of drug administration but they failed to use both injected and noninjected controls, making interpretation difficult.

Church and Overbeck (6), using doses similar to ours but measuring activity via an automated monitor, reported hypoactivity in cocaine-exposed offspring. This finding was present at 20 days of age but not at 80. Perhaps the two very different methods of measuring "activity" reflect distinct processes.

Animal Models of the Human Condition

"In general, the model systems of clinically oriented researchers represent a compromise between the advantages of experimental simplicity and those of similarity (or homology) of model functions to functions manifest in human behavior" (12). Previous work (e.g., 3–6,11,20–25) has contributed detailed information on the effects of cocaine on development during carefully demarcated maturational periods. In these studies the dam may be viewed primarily as a vehicle for transporting cocaine to the fetus. It is imperative that the dam remain healthy to deliver offspring that are then typically cross-fostered to normal (cocaine-free) dams until weaning.

The model we are advancing views the physiology and behavior of the offspring as the sequela of dams that have been affected by cocaine administered in a fashion more analogous to the human situation assuming, in this first approximation, a single dose per day. Inherent in this approach is the assumption that females preexposed to cocaine prior to breeding are fundamentally different from normal females as a result of physiological changes brought about by protracted drug administration. It is clear that human users undergo a series of psychological and neurophysiological changes with repeated cocaine use. Animal models that more closely approximate human use and abuse patterns will better contribute to our knowledge of this drug in man (9).

In this regard, the low fecundity rate found here may indeed be reflective of the human condition. Significant infertility due to tubal abnormality has been linked to cocaine use in humans (17). Increased rates of in utero deaths associated with cocaine use have been revealed through meta-analysis of nondrug and cocaine users. However, differences are greatly reduced when the comparison is made between polydrug users who do or do not also abuse cocaine (14). One interpretation of this finding is that cocaine and other illicit drugs, particularly stimulants, may have a common mode of action thereby decreasing differences between groups of polydrug abusers. In 103 cases of fetal death studied by the medical examiners of New York City, over 62% contained either cocaine or a cocaine metabolite (16). In another study of the New York data, death rates for infants born of cocaine- or opiate-abusing mothers were almost two and one half times that of unaffected infants (10). Although investigators have consistently tied placental abruption to cocaine use, many confounding factors in the classification of drug histories are often not taken into account (17). Despite this cautionary note, there appears to be evidence that cocaine has a negative impact on fertility, fetal health, and infant survival consistent with impaired fecundity found in our animal model.

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