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Prenatal Buprenorphine Exposure and Sexually Dimorphic Nonreproductive Behaviors in Rats

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BARRON, S. AND V. M. CHUNG. *Prenatal buprenorphine exposure and sexually dimorphic nonreproductive behaviors in rats.* PHARMACOL BIOCHEM BEHAV **58**(2) 337–343, 1997.—This set of experiments examined the effects of prenatal buprenorphine (BUP) exposure on three measures of sexual differentiation in rats. Pregnant female rats were divided into four treatment groups: 0.6 mg/kg BUP, 0.3 mg/kg BUP, a pair-fed control (PFC), and an untreated control (UTC). Drugs were injected starting on gestation day (GD) 6 and continuing through GD 20 with a 48-h interval between drug administrations. Three variables were examined in the offspring: anogenital (AG) distance on postnatal day (PND) 1, spontaneous parental behavior on PNDs 23–28, and saccharin consumption on PNDs 42–55. Whereas prenatal BUP exposure had no effect on AG distance, spontaneous parental behavior was impaired in the 0.6-mg/kg-exposed offspring on two measures: pup-retrieval latencies and pup-directed behaviors. Furthermore, although both control groups and the 0.3-mg/kg-exposed offspring showed the expected sex difference in consumption of a 0.25% saccharin solution, this difference was not displayed by the 0.6-mg/kg-exposed offspring. These findings suggest that exposure to relatively high doses of buprenorphine during development may have long-term effects on behavior. © 1997 Elsevier Science Inc.

Prenatal buprenorphine exposure Opiates Sexually dimorphic nonreproductive behaviors

BUPRENORPHINE (BUP) is a mixed opiate μ agonist and κ antagonist currently approved in the United States for use as an analgesic. Its primary actions appear to be mediated at the μ receptor, resulting in morphinelike effects; however, BUP is 25–40 times more potent than morphine as an analgesic (29). Because of its partial agonist effects at the μ receptor, it is considered to be relatively safe and unlikely to produce the respiratory depression and other adverse effects associated with opiate overdose.

These partial agonist actions of BUP also result in a lower abuse liability, a milder withdrawal syndrome after discontinuation (12,29,30), and relatively low levels of physical dependence (35) compared with other opiates. This has sparked considerable interest in the use of BUP as a potential treatment for opiate addiction. In clinical trials, BUP and methadone were found to be equally effective in sustaining retention in treatment programs and compliance with medication and counseling regimens (55). An additional advantage of BUP is that it has a longer duration of action than most of the more traditional opiates used for maintenance treatment (2), thus reducing the need for daily administration.

Additional therapeutic uses have also been suggested for BUP. It reduces cocaine self-administration in a number of species, including rats (16), rhesus monkeys (45), and possibly humans (34,53). There are also a limited number of studies suggesting that BUP is an effective treatment for clinical depression (13,23). Although there have been occasional reports of illicit use/abuse of BUP, these seemed to be primarily instances in which heroin was unavailable and BUP served to help prevent withdrawal symptoms (49). Still, BUP is not widely available on the street in the United States, and further work is needed to determine its abuse liability. With the increased interest in the use of this drug as a pharmacological treatment and the possibility of illicit use, it is surprising how few data there are on the possible consequences of prenatal BUP exposure.

Although early studies suggested that prenatal BUP exposure did not alter met- or leu-enkephalin levels in rodents (46,47,57), Coscia and colleagues have since reported a transient downregulation of μ receptor binding in postnatal day (PND) 1 rat brain following prenatal exposure (7,9). Neonatal BUP exposure also resulted in a marked downregulation of

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μ receptor sites, whereas δ and κ sites were upregulated (7,9). Interestingly, prenatal exposure to other opiates (i.e., methadone and morphine) produces a similar temporary change in opioid receptor densities but also produces long-term behavioral effects (56).

Pregnancy outcome measures have been examined in rats following BUP exposure. BUP produced a dose-dependent reduction in maternal water consumption but no differences in maternal food consumption, frequency of resorptions, or birth weights. BUP also had no effect on perinatal mortality, although there were some mixed effects on postnatal growth (28), and there are some contradictory findings within this limited literature (57). The data on possible behavioral effects associated with prenatal BUP exposure are also extremely limited, with no change in activity or developmental milestones (46,47) reported, although there is one conflicting report (50). To the best of our knowledge, no other published reports have examined the effects of prenatal BUP on behavioral outcome.

One method of predicting the types of behaviors that might be affected by prenatal BUP exposure is to examine the effects of exposure to other opiates on behavior. Both prenatal and postnatal exposure to opiates can alter endocrine and sexual function in humans and nonhumans. For example, changes in prolactin, luteinizing hormone, and testosterone levels as well as reduced structural and functional integrity of sex organs have been reported in adults following morphine and methadone exposure (15,17,18,40,48). Similarly, prenatal exposure to various opiate drugs can alter steroid levels and the development of sexually dimorphic behaviors in rats (54,58–60), golden hamsters (31,32), and possibly humans (52).

Consequently, this set of experiments was designed to examine the effects of prenatal BUP exposure on three sexually dimorphic nonreproductive measures: anogenital (AG) distance, spontaneous parental behavior, and saccharin consumption. These measures are all sensitive to pre and/or perinatal hormonal manipulations (6). Males have a markedly larger AG distance than females at birth. Spontaneous maternal or parental behavior can be elicited in virgin rats with repeated exposure to young pups [e.g., (25)], and the phenomenon can be manipulated by hormones. The behaviors displayed include pup retrieval, grooming, and hovering or crouching over the pups in a nursing posture. Both adult male and female rats can be sensitized to show these behaviors with repeated pup exposure, although intact males take longer than females to become sensitized. These parental behaviors are also displayed by prepubertal rats, although there are some distinct differences relative to adults. Prepubertal rats show these retrieval and maternal behaviors much more rapidly than adults, with maternal behaviors emerging within 1–2 days of pup exposure. In addition, the sex difference observed in adults is reversed: prepubertal males display the behavior more rapidly than prepubertal females (26). Saccharin consumption also shows specific sex differences: females consume more saccharin (when corrected for body weight) than males and, again, prenatal and/or neonatal hormonal manipulations can reverse this sex difference (6).

MATERIALS AND METHODS

Parent Subjects and Prenatal Treatment

Sprague–Dawley virgin female rats obtained from Harlan Labs were individually housed with males nightly until a seminal plug was found, marking day 1 of gestation (GD 1). Pregnant females were then weighed and individually housed in plastic cages (25.4 × 47 × 19 cm) with ad lib chow and water in a temperature-controlled (20–21°C) nursery with a 14 L:10 D cycle. These dams were randomly assigned to one of four treatment groups: high-dose buprenorphine hydrochloride (BUP) (0.6 mg/kg), low-dose BUP (0.3 mg/kg), pair-fed saline control (PFC), and untreated control (UTC).

Beginning on GD 6 and continuing through GD 20, subjects in both BUP groups were weighed and injected subcutaneously (SC) with BUP on alternate days (i.e., GD 6, 8, 10, 12, etc.) in a 1-ml/kg injection volume. This 48-h interval between drug administrations was based on both preclinical and clinical data. In rats, cocaine self-administration returned to baseline levels by the third day after BUP treatment, suggesting a 2-day time course for at least some of BUP actions (19). Similar alternate-day administration regimes have been reported effective in maintenance drug programs for opiate addicts (2).

The PFC group received a saline injection according to the same schedule. On the intervening days, subjects were weighed, but no injection was given. Food and water consumption were recorded daily. Subjects from all of the treatment groups except the PFC group were given ad lib access to water and chow. Each PFC subject received the same amount of rat chow on a grams/kilogram body weight basis as consumed by a matched 0.6-mg/kg BUP partner for each given day of pregnancy. This PFC group controlled for possible reduction in food consumption following BUP administration. Subjects in the UTC group were also weighed daily, and food and water consumption were recorded. The UTC group served as a control for the injection procedure and for possible food restriction.

After the final injection (GD 20), dams from all four prenatal treatment groups were given free access to chow and water. The dams were observed periodically throughout the day for evidence of withdrawal signs and/or parturition; otherwise, they were undisturbed until 24 h after parturition.

Postnatal Assessment

Experiment 1: Anogenital distance. Approximately 24 h after parturition, the AG distance of the pups was measured using a vernier caliper. AG distance was defined as the distance between the anus and the genital papilla (24,39). Body weights were also recorded at this time and pups were examined for evidence of obvious abnormalities. To avoid possible litter bias, the average AG distance and body weight for each sex within a given litter was calculated and used as a single data point (1).

Litters were culled to 10, maintaining 5 males and 5 females per litter when possible, and all litters were maintained by their natural dam. For Experiments 2 and 3, one subject per sex per litter was included in each cell of the experimental design. The number of subjects included in each experiment is presented in Table 1. Experimenters were blind to treatment condition until the conclusion of the study.

Experiment 2: Pup-induced parental behavior. Spontaneous parental behavior was examined in 23-day-old offspring from the prenatal treatment groups for five consecutive days. On postnatal day (PND) 21, one male and one female juvenile were randomly selected from each litter and individually housed in large plastic cages (25.4 × 47 × 19 cm) with food and water provided ad lib. Starting on PND 23, two pups (1–5 days of age) were placed in the opposite corner of the cage from where the juvenile was located. The behavior of the juvenile toward the surrogate pups was observed for 10 min and pup-retrieval latencies were recorded. The latency to retrieve a pup

was defined as the amount of time from the start of the test session until the subject carried or dragged the pup to its nest. If the juvenile did not retrieve either pup by the end of the 10-min test session, a ceiling retrieval score of 601 s was recorded.

Pup-directed behaviors were also recorded during this retrieval session by using a time sampling method. The behavior of the juvenile in relation to the pups was recorded at 30-s intervals. These observations were tallied as an indicator of pup-oriented behaviors during the retrieval session. If the juvenile showed pup-directed behavior at all time points assessed, it received a perfect score of 20. Pup-oriented behaviors included pup grooming, pup sniffing, and/or hovering over the pups. Retrieval behavior was examined between 1000 h and 1130 h each day.

As an additional measure of parental behavior, the juvenile's behavior toward the two pups was recorded at three additional single time points throughout the day (1200, 1400, and 1600 h). These data were again tallied to provide an added measure of pup-oriented behaviors. This paradigm is similar to that previously used in this laboratory (4).

After the last daily observation, the surrogate pups were removed from the juvenile's cage and returned to a lactating dam overnight. These surrogate pups were generated by untreated female rats whose sole purpose was to provide the surrogate pups. Care was taken to ensure that the surrogate pups were not used on two consecutive days.

On PND 28, experimental subjects were earmarked for later identification, weighed, and randomly housed with same sex conspecifics in groups of two or three.

Experiment 3: Saccharin consumption. On PND 42, subjects were singly housed in plastic cages with chow and water provided ad lib. Beginning on PND 46, subjects were given access to two graduated cylinders of water with sipper tubes so that the amount of fluid consumed daily could be easily measured. Daily water consumption of each subject was recorded for 4 days to obtain a baseline water consumption measure and to familiarize the subjects with the test procedure. Subjects were then given access to the two cylinders with one containing water and the other containing a sodium saccharin solution. Four concentrations, 0.25%, 0.50%, 0.75%, and 1.0% sodium saccharin (by volume), were provided to the subjects in ascending order of concentration. Each concentration was provided for two consecutive days, and the position of the graduated tubes was counterbalanced for each concentration to avoid side preference. On each day, the amount of fluid consumed from each cylinder was recorded. Cages were also checked in the unlikely event of spillage. Body weights were recorded on PNDs 46 and 50. Testing was conducted between 0830 and 1030 h.

TABLE 1

EFFECT OF PRENATAL BUPRENORPHINE EXPOSURE ON BODY WEIGHT OF RAT OFFSPRING

Prenatal Treatment	PND 1: Experiment 1	PND 28: Experiment 2	PND 50: Experiment 3
0.6 mg/kg BUP			
Male	6.67 ± 0.1 (6)	88.8 ± 2 (8)	229 ± 6 (8)
Female	6.37 ± 0.2 (6)	78.2 ± 3 (8)	167 ± 4 (7)
0.3 mg/kg BUP			
Male	7.06 ± 0.2 (9)	89.4 ± 1 (8)	231 ± 4 (8)
Female	6.57 ± 0.2 (9)	78.5 ± 3 (8)	169 ± 3 (8)
PFC			
Male	7.0 ± 0.1 (6)	86.5 ± 2 (7)	223 ± 4 (6)
Female	6.8 ± 0.2 (6)	78.5 ± 2 (7)	168 ± 3 (7)
UTC			
Male	7.6 ± 0.2* (9)	90.9 ± 3 (8)	233 ± 5 (8)
Female	7.1 ± 0.5* (9)	79.7 ± 2 (8)	171 ± 3 (8)

Values are mean body weight (in g) ± SEM. Numbers in parentheses indicate number of litters represented per group. PND, postnatal day; BUP, buprenorphine; PFC, pair-fed controls; UTC, untreated controls.

*$p < 0.05$ vs. all other same-age groups.

General Statistical Issues

Data were examined with analysis of variance (ANOVA) with repeated measures when needed. Significant interactions and main effects were broken down with simple main effect analyses or Newman–Keuls multiple-range test. The accepted statistical probability level was 0.05 unless otherwise stated.

RESULTS

Maternal Data

Weight gain during pregnancy was affected by BUP treatment. Both BUP-exposed groups and the PFC group gained significantly less weight during pregnancy than did the UTC control group (21%, 24%, 27%, and 36% for the 0.6 mg/kg BUP, 0.3 mg/kg BUP, PFC, and UTC groups, respectively) [$F(3, 31) = 14.32, p < 0.001$].

Some unusual behaviors were displayed by the pregnant females following BUP injections. A reduction in movement and an increase of chewing and stereotypical jaw movements were displayed by both BUP groups after the first BUP injection. Subsequent BUP injections resulted in marked locomotor activation. One consequence of this marked activation was that a number of BUP dams repeatedly drained the water from their water bottles. The bottles were refilled, but this proved somewhat problematic for the assessment of food and water consumption during drug administration. Subjects that repeatedly spilled water (two or more days) from their bottles were eliminated from the analysis of food and water consumption. This resulted in inclusion of 5/9 and 8/10 rats in the 0.3 mg/kg and 0.6 mg/kg BUP groups, respectively.

For the remaining subjects, both the 0.6 mg/kg and 0.3 mg/kg BUP groups consumed significantly less food did than the UTC group when corrected for body weight. Because food availability for the PFC group was controlled by the amount of food consumed by the 0.6 mg/kg BUP group, it was not surprising that the PFC closely resembled the 0.6 mg/kg BUP group. The greatest reduction in food consumption by the BUP females was early in the drug treatment regimen, as can be seen in Fig. 1A (drug administration days marked "b"). The ANOVA on food consumption revealed a significant main effect of treatment [$F(3, 25) = 19.41, p < 0.01$]. There was also a significant day × treatment interaction. An unusual pattern of increased food consumption on the days of BUP injection began to emerge toward the end of gestation. This pattern is more dramatically depicted by the water consumption data (see Fig. 1B; drug administration days marked "b"). Although there was not a significant overall main effect of treatment on water consumption ($p < 0.08$), there was a significant day × treatment interaction [$F(18, 150) = 3.21, p < 0.01$] due to the dramatically different pattern of water consumption

displayed by both the 0.6 mg/kg and 0.3 mg/kg BUP groups relative to the two control groups. Although not systematically examined, there were no visible withdrawal symptoms displayed by the BUP-treated dams.

Offspring Data

There were no differences across prenatal treatment groups in sex ratio or litter size (9.9, 12.0, 11.9, and 12.1 pups for 0.6 mg/kg BUP, 0.3 mg/kg BUP, PFC, and UTC, respectively). Body weights on PND 1 are presented in Table 1. Pups from both BUP groups and the PFC group weighed significantly less than pups from the UTC group on PND 1. The ANOVA revealed a significant main effect of prenatal treatment and a main effect of sex [$F(3, 52) = 7.00$, $p < 0.01$ and $F(1, 52) = 7.41$ for treatment and sex, respectively]. Males weighed significantly more than females.

Body weight differences were no longer apparent on PND 28 or PND 50 (see Table 1). As predicted, males weighed more than females at both of these older ages.

Experiment 1: AG Distance

As expected, males had significantly larger AG distances than did females. The ANOVA revealed a main effect of sex [$F(1, 52) = 985.39$, $p < 0.001$]; however, this did not interact with prenatal treatment. Because there were body weight differences across the prenatal treatment groups, an analysis of covariance (ANCOVA) was also conducted using body weight as a covariant; however, this did not alter the overall findings. The adjusted AG distance means from the ANCOVA are presented in Table 2.

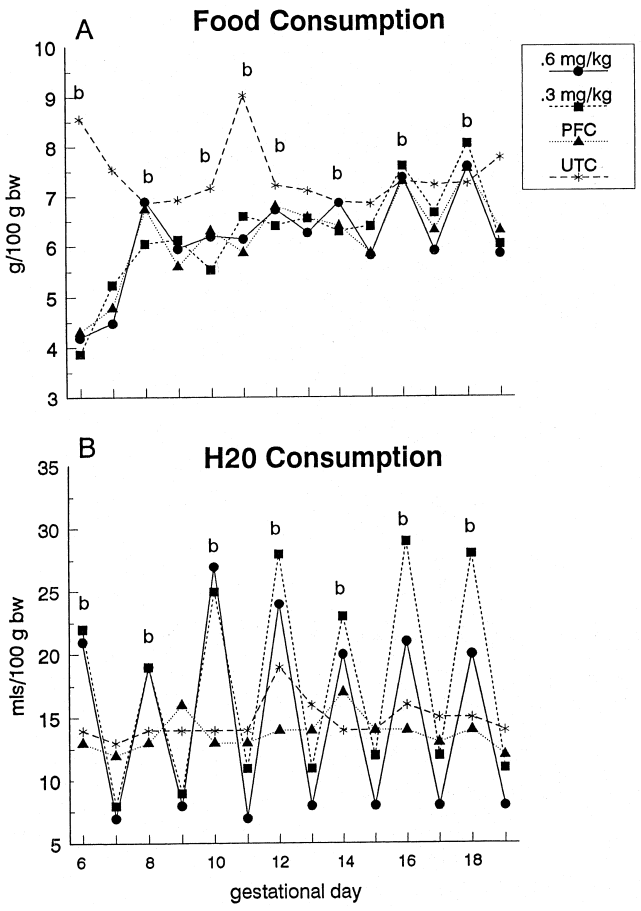

FIG. 1. Average maternal food (A) and water (B) consumption (corrected for body weight) during pregnancy as a function of treatment [0.6 mg/kg BUP, 0.3 mg/kg BUP, pair-fed control (PFC), and untreated control (UTC)]. Days of BUP injection are marked with "b".

Experiment 2: Juvenile Spontaneous Parental Behavior

Exposure to the higher dose of BUP (0.6 mg/kg) resulted in longer pup-retrieval latencies than were seen in controls (see Fig. 2A). The ANOVA on the latency to retrieve both pups across the five test days revealed an effect of treatment [$F(3, 54) = 2.76$, $p = 0.0507$] and a main effect of sex [$F(1, 54) = 5.07$, $p < 0.01$]. Subsequent Newman–Keuls tests revealed that the group exposed to 0.6 mg/kg BUP showed longer pup-retrieval latencies than did the two control groups. Juvenile males retrieved pups more quickly than did females; however, this did not interact with prenatal treatment. Although retrieval latencies decreased over the five test days (as indicated by a significant main effect of day), this also did not interact with prenatal treatment.

Pup-oriented behaviors during the retrieval test were also impaired in the 0.6 mg/kg BUP group. An ANOVA revealed a significant main effect of treatment [$F(3, 58) = 6.88$, $p < 0.001$] and a main effect of day. There was no main effect of sex. Subsequent Newman–Keuls tests again showed that the 0.6 mg/kg group showed fewer pup-oriented behaviors than all other treatment groups, which did not differ from each other (see Fig. 2B). In contrast, there were no differences across prenatal treatment groups in pup-oriented behaviors observed later each day (data not shown).

Experiment 3: Saccharin Study

Baseline water consumption was unaffected by prenatal treatment. Saccharin consumption (ml/100 g body weight) at each of the four concentrations is presented in Fig. 3. The ANOVA revealed a significant saccharin concentration $\times$ sex interaction [$F(3, 156) = 4.5$]. The only saccharin concentration in which a sex difference was observed was at 0.25%, the most preferred concentration [$F(1, 156) = 26.90$]. The 0.3 mg/kg BUP and both control groups showed the expected sex difference in saccharin consumption at 0.25% ($ps > 0.01$); however, there was no sex difference displayed by the 0.6 mg/kg BUP group.

DISCUSSION

These findings suggest that prenatal buprenorphine exposure impaired spontaneous parental behavior and eliminated

TABLE 2

EFFECT OF PRENATAL BUPRENORPHINE EXPOSURE ON ANOGENITAL DISTANCE IN RAT OFFSPRING

Prenatal Treatment	Males	Females
0.6 mg/kg BUP	4.32 ± 0.05	2.42 ± 0.07
0.3 mg/kg BUP	4.30 ± 0.09	2.54 ± 0.06
PFC	4.38 ± 0.15	2.47 ± 0.10
UTC	4.26 ± 0.09	2.44 ± 0.08

Values are mean anogenital distance (in mm) on postnatal day 1 ± SEM. BUP, buprenorphine; PFC, pair-fed controls; UTC, untreated controls.

the normal sexual dimorphism in saccharin consumption by offspring exposed to 0.6 mg/kg BUP in utero. These effects were apparent only with the higher dose of BUP and were not displayed by offspring exposed to the 0.3 mg/kg dose of BUP. In contrast, prenatal BUP exposure had no effect on AG distance, a physiological measure of sexual differentiation.

Previous data have shown that prenatal methadone or morphine exposure altered reproductive behavior in rats (54,58–60). Our study suggests that prenatal BUP exposure may have long-term effects on sexually dimorphic nonreproductive behaviors. Of note, the behavioral effects associated with BUP exposure were not simply an alteration in sexual differentiation, that is, we did not see a consistent pattern of masculinization or feminization displayed by the BUP-exposed offspring across these experiments. Therefore, we cannot say if the effects observed in this study are due to an alteration in sexual differentiation or to some other underlying effect of prenatal buprenorphine exposure on development.

Buprenorphine injections also had an effect on the dam's behavior. These females displayed altered food and water consumption, unusual mouthing movements, and initial immobility followed by later hyperactivity immediately following BUP injection. Similar behaviors have previously been reported in nonpregnant rats (20,36). Although one study did not find BUP-related altered food consumption in pregnant rats, BUP administration was via an osmotic minipump, which probably resulted in lower peaks and more constant BUP levels (28) than the SC method used for drug administration in this study.

It was surprising that we did not see a more robust sex difference in saccharin consumption. The only consistent sex difference in saccharin consumption displayed by the controls and the 0.3 mg/kg BUP group was at the most preferred saccharin concentration (0.25%). We have previously shown sex differences in saccharin consumption at all four of the concentrations used in this study (3). However, subjects in the current study were tested at a younger age relative to our previous work (PND 45 vs. PND 110). The age chosen for the current study was based on recent pilot data collected in our laboratory that showed clear sex differences in saccharin consumption at this age. Of note, in our pilot study, we looked at only the 0.25% concentration, suggesting that maturational factors may play a differential role in this sex difference, depending on saccharin concentration. Therefore, the absence of a sex difference in the 0.6 mg/kg BUP offspring at the 0.25% concentration could be some form of developmental delay for the emergence of this sex difference in saccharin consumption.

A number of mechanisms could explain how BUP exerted these effects. It is well known that manipulations of the perinatal steroid environment can affect all of the dependent variables examined in this set of experiments. Because opiates can produce a variety of changes in the steroid environment, it is possible that prenatal BUP exposure altered the prenatal steroid environment, resulting in long-term effects on these sexually dimorphic behaviors. However, prenatal BUP did not alter AG distance, the only physiological measure, suggesting that BUP's effects may be mediated more by the central nervous system. In other words, rather than gross morphological alterations, BUP may have more subtle effects on central nervous system circuitry, which resulted in the observed behavioral alterations.

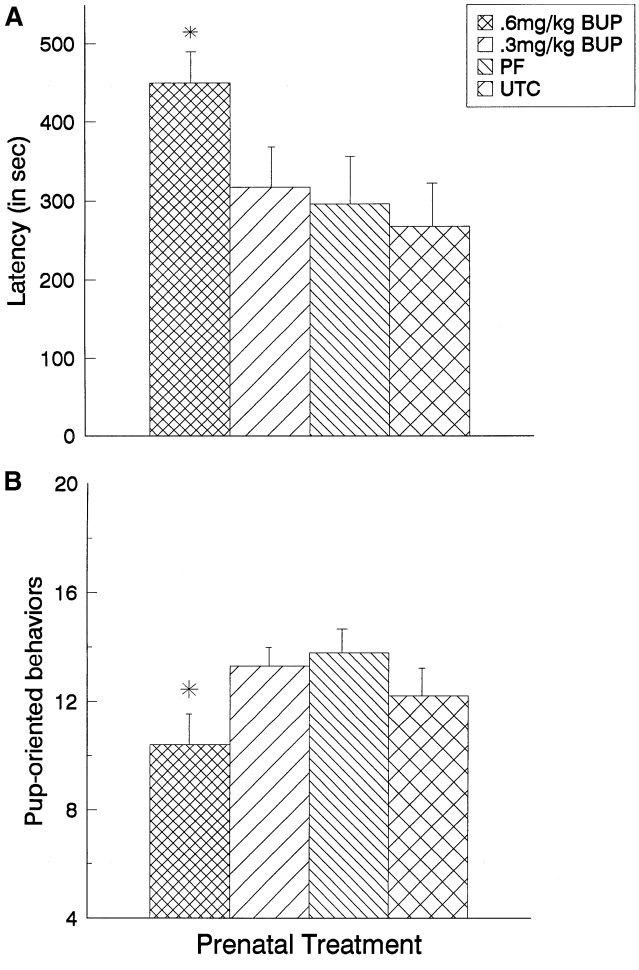

FIG. 2A. Latency of pup-retrieval behavior displayed by juveniles as a function of prenatal treatment [0.6 mg/kg BUP, 0.3 mg/kg BUP, pair-fed control (PFC), and untreated control (UTC)]. B. Frequency of pup-oriented behaviors during the 10-min daily observation as a function of prenatal treatment. *$p < 0.05$ vs. all other groups.

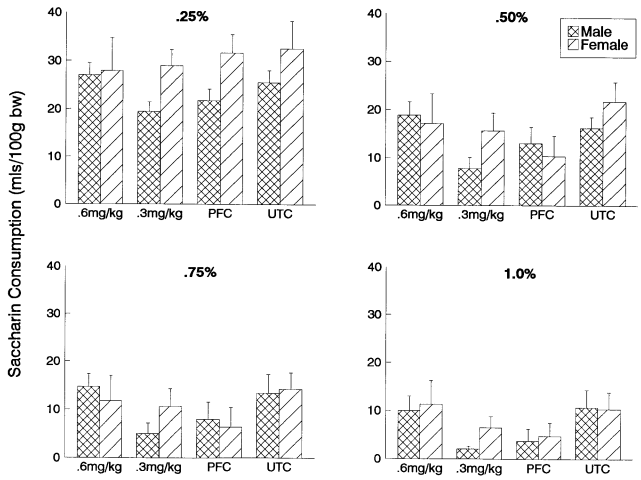

FIG. 3. Saccharin consumption corrected for body weight as a function of prenatal treatment group [0.6 mg/kg BUP, 0.3 mg/kg BUP, pair-fed control (PFC), and untreated control (UTC)] and sex.

Opiates also play a direct role in the regulation of parental behavior in juvenile rats (33) and in saccharin consumption (10,27). Data from a recent collaborative project with Coscia and colleagues suggest that our 0.6 mg/kg BUP exposure regime does result in a downregulation of μ receptors in PND 1 offspring (8). Therefore, it is also possible that BUP's effects on these behaviors may be mediated by its effects on the endogenous opioid system.

To the best of our knowledge, this is one of the first studies using this exposure model to look at the effects of prenatal BUP exposure on behavioral outcome. The doses used in this study stemmed from earlier work by Coscia and colleagues, who did not see BUP-related changes in μ receptor density of offspring at doses lower than 0.5 mg/kg (7,9). Similarly, the findings from this set of studies revealed behavioral effects following exposure to the higher dose of BUP. These doses are well within the effective range typically employed in animal studies. For example, data from a number of rodent studies show that BUP doses ranging between 0 and 1 mg/kg are effective in disrupting scheduled controlled behaviors (11,14), producing analgesia (22), and influencing conditioned place preference (51). Of particular relevance for the current findings, this same dose range is also effective for reduce reducing opiate, cocaine, and/or alcohol self-administration in both rats and monkeys (16,38,41–44). It should be noted that BUP shows similar distributions in pregnant and nonpregnant rats, and it readily crosses both the blood–brain barrier and the placental barrier [see (37,61)].

One potential concern with the results from our study was that the offspring were reared by their natural dams. Although we did not observe any obvious withdrawal syndrome in either the dam or the newborn pups, it is possible that BUP exposure during pregnancy had subtle effects on maternal and pup interactions. A cross-fostering procedure should probably be included in future studies to eliminate this potential confound.

Currently, methadone is the only drug approved for treatment of opiate addiction during pregnancy. However, prenatal methadone exposure is not without inherent risks, and adverse outcomes following prenatal methadone exposure in both clinical and preclinical populations have been reported [see (62) for review]. Bauman and Levine suggested that the presence of a withdrawal syndrome by infants is a key risk factor for impaired developmental outcome after prenatal methadone exposure (5). One major potential advantage of buprenorphine is that the severe signs of withdrawal frequently seen after long-term methadone exposure do not occur after long-term intake of buprenorphine in monkeys, rats, mice, or humans (21,22,29,37). Further work with preclinical models is clearly needed to assess the relative safety and/or risk of prenatal buprenorphine exposure and to evaluate its effects relative to prenatal methadone exposure.

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