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Pharmacology, Biochemistry and Behavior 80 (2005) 445–451

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Chronic morphine exposure during puberty decreases postpartum prolactin secretion in adult female rats

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Received 7 October 2004; received in revised form 10 December 2004; accepted 30 December 2004

Abstract

Opiate use in teenage populations has been increasing in recent years. The potential impact of exposure to high levels of opiates at a time when reproductive systems are maturing has not been well studied, especially in females. The present study used an animal model of adolescent opiate abuse in females to examine the potential impact of high levels of opiates during puberty on several reproductive parameters, including suckling-induced prolactin secretion. Two groups of juvenile female rats were administered increasing doses of morphine sulfate or saline (s.c.) from age 30–50 days, beginning with a dose of 2.5 mg/kg and achieving a maximal dose of 50 mg/kg. As adults, these females were mated and reared either their own or foster pups. On either postpartum day 5 or 10, following a 4 h separation, suckling-induced prolactin secretion was measured. In addition, on postpartum day 5 maternal behavior latencies were determined. The results demonstrate reduced suckling-induced prolactin secretion on postpartum day 5 in females previously exposed to morphine during pubertal development. These effects were observed in females rearing either their own or fostered pups. These effects were not due to any differences in maternal behavior latencies, as retrieval or crouching latencies were unaffected. In summary, chronic morphine exposure during puberty results in changes in the regulation of prolactin secretion during early lactation, which are observed several weeks after cessation of drug treatment. These data suggest that prior opiate use during puberty can continue to affect the regulation of prolactin secretion into adulthood.

Keywords: Lactation; Chronic morphine; Maternal behavior

1. Introduction

Within the past decade, the use of opiates in adolescent populations has been rising (Johnson and Gerstein, 1998, Johnston et al., 2000/2001), with the opiates of choice including heroin, oxycontin and vicodin. Moreover, while historically substance abuse disorders have been more prevalent in males than females, recent epidemiological data have observed a trend toward similar rates of use for opiates in boys and girls between the ages 12 and 17 (Greenfield and O'leary, 1999, Greenfield et al., 2003). Thus, there is an emergence of a new population of users at risk for the sequela of consequences associated with opiate abuse. These users are increasingly female and are initiating drug use at earlier ages. Unfortunately, little is known about the potential risks of opiate abuse that may be unique to this segment of the population.

One of the well documented, although often overlooked effects of opiate use, is an opiate-mediated elevation in the secretion of the hormone prolactin (Afrasiabi et al., 1979; Brambilla et al., 1977; Celani et al., 1984; Spagnolli et al., 1987; Vescovi et al., 1990). This elevation in prolactin is particularly resistant to tolerance and continues to occur even in chronic abusers. In fact, patients maintained on methadone therapy still demonstrate increased levels of prolactin after several years of treatment (Willenbring et al., 1989). In addition, in recovering heroin addicts, alterations in prolactin secretion have been shown to persist even after

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doi:10.1016/j.pbb.2004.12.011

periods of abstinence, with blunted D-fenfluramine-stimulated prolactin secretion still observed up to 8 weeks after detoxification (Gerra et al., 2000). Other studies have observed both elevated levels of basal prolactin following opiate withdrawal as well as decreased prolactin secretion in response to thyrotropin releasing hormone (Spagnolli et al., 1987). Thus, chronic opiate use results in a profound and persistent change in the regulation of prolactin secretion. It is unknown whether similar changes in prolactin secretion would occur in younger populations, especially those in which opiate use is initiated at a time when the endogenous opioid regulation of prolactin secretion is just emerging, namely puberty.

Puberty is the developmental stage during which children are transitioning into adulthood. Part of this transition involves the emergence of adult patterns of hormone secretion. In females, endogenous opioids play a significant role in this transition (Ojeda and Urbanski, 1998). Believed to be influential with regard to the onset of puberty, endogenous opioids become increasingly involved in the regulation of hormone secretion as puberty progresses; including the regulation of the hormone prolactin (Shieh and Pan, 1998). Thus, it is possible that the presence of high levels of opiates during this period could alter the manner in which endogenous opioids regulate prolactin secretion. Moreover, such an alteration could persist into adulthood, even in subjects no longer exposed to opiates.

In addition to its role in reproduction and lactation, prolactin also effects immune function (Reber, 1993; Reichlin, 1993), stress responsiveness (Rossier et al., 1979; Turner and Neumann, 2002), as well as fetal and neonatal growth and development (Nusser and Frawley, 1997; Phelps and Hurley, 1999; Phelps et al., 2003; Stoker et al., 1999). Thus, the effects of opiate abuse on prolactin secretion could have significant health consequences for the abuser, which may be even more profound in reproductively active women. Given the evidence that changes in prolactin secretion can persist following prolonged abstinence, women with a history of opiate abuse may continue to have altered prolactin regulation as a consequence of their prior use. These changes may be even more marked when the abuse occurs during puberty. The present study was designed to examine the impact of opiate exposure during puberty using an escalating dose model of opiate abuse. Specifically, these studies examined the impact of chronic morphine exposure during puberty on subsequent prolactin secretion during lactation in adult female rats.

2. Methods

2.1. Subjects

Ninety-six 20-day-old female Sprague–Dawley rats [Crl:CD(SD)BR] were purchased from Charles River Breeding Laboratories. The animals used in these experiments were maintained in accordance with the guidelines of the Committee of Care and Use of Laboratory Animal Resources, National Research Council. All animals were housed 3–4 per cage in light- (on 0700–1900 h) and temperature- (21–24 °C) controlled rooms and provided food (Purina Rat Chow) and water ad libitum.

2.2. Peripubertal morphine exposure

Beginning at 30 days of age half of the subjects (n=48) began treatment with morphine sulfate (MS) using an increasing dose regimen for a total of 20 days. On day 1 of morphine treatment rats received 2.5 mg/kg MS subcutaneously (sc) twice a day. Each subsequent day the dose of MS was increased by 2.5 mg/kg such that by the final day of treatment subjects received two 50 mg/kg injections. This regimen was designed to model escalating opiate use throughout the peripubertal period, which is the time during which opioid-mediated control of prolactin secretion develops (Shieh and Pan, 1998). The other 48 females served as age-matched controls receiving saline injections (sc) twice a day with volumes adjusted to match those of drug-treated females. Females were weighed and examined for vaginal opening at the time of each injection. Body weight gain was calculated as body weight on the final day of treatment minus body weight on the first day of treatment.

Following the final drug treatment (50 days of age) females were observed for behavioral signs of withdrawal (i.e. wet dog shakes, burrowing, rearing). Subjects were observed hourly between 0800 and 1600 h beginning the day after the final drug exposure. Observations continued the following day as well, again between 0800 and 1600 h. Behaviors were scored as either present or absent during a 5-min observation period. All subjects were then undisturbed until they reached 60 days of age.

2.3. Mating and postpartum assessment

At 60 days of age all females were housed with males from our colony. Of the original 96 subjects, 42 morphine-treated and 42 saline-treated subjects became pregnant. On postpartum day 1 (parturition = postpartum day 0), all litters were weighed and culled to 4 males and 4 females. To examine the potential impact of the offspring on maternal behavior and prolactin release, half of the litters were cross-fostered. Thus, four groups were created, females treated with morphine during puberty raising their own pups (morphine dam × morphine offspring), females treated with morphine during puberty raising the offspring of females treated with saline during puberty (morphine dam × saline offspring), females treated with saline during puberty raising their own pups (saline dam × saline offspring), and females treated with saline during puberty raising the offspring of females treated with morphine during puberty (saline dam × morphine offspring). All pups were weighed daily from

postpartum day 1 until weaning on postpartum day 21. In addition, pups were examined for tooth eruption and eye opening.

2.4. Intraatrial catheterization and blood sampling

On either postpartum day 2 or 7, subjects were anesthetized with ketamine/xylazine (100 μl/100 g) and catheters (35 mm) were inserted into the atrium and flushed with heparinized saline. Females were then immediately returned to their litters to minimize maternal separation. Three days later, either on postpartum day 5 or 10, between 0900 and 1100 h litters were separated from their mothers for 4 h. Prior to reintroduction of the pups two blood samples (400 μl/sample) were taken to measure baseline prolactin levels (−10 and 0 min). Upon return of the pups to the home cage maternal behavior latencies were monitored until all pups were retrieved, grouped in the nest and the female was crouching over the litter. Additional blood samples were taken (10, 30, 60 and 120 min), while the mother interacted with her litter. All samples were collected into heparinized tubes using a catheter extension. Samples were centrifuged and plasma was stored at −20 °C until assayed.

2.5. Radioimmunoassay

Plasma concentrations of prolactin were measured using the NIDDK rat PRL kit which was supplied by Dr. A.F. Parlow at the National Hormone Pituitary Program. This kit included reference preparation NIDDK-rPRL-RP-3 and anti-rat prolactin S-9. All plasma samples were assayed in duplicate. Assay sensitivity averaged 0.5 ng/ml, interassay and intraassay coefficients of variation were 9% and 5%, respectively.

2.6. Statistical analysis

Body weight gain and vaginal opening data collected during the injection regimen were analyzed using a *t*-test. Postpartum litter weight and litter number were also analyzed using a *t*-test, while gender ratio was examined using a chi-square. Age at tooth eruption, eye opening, bodyweight gain (postpartum day 21 − postpartum day 1) and maternal behavior latencies were analyzed using a Two-Way ANOVA with drug treatment during puberty (morphine or saline) and rearing condition (cross-fostered or non-cross-fostered) as the between subject factors. Plasma prolactin secretion was analyzed using a Three-Way Repeated Measures ANOVA with time (−10, 0, 10, 30, 60, and 120 min) as the repeated measure and drug treatment and rearing condition as the between subjects factors. Of the 84 subjects that gave birth, 5 had to be excluded due to catheter problems. Thus, the final number of subjects that completed all aspects of the experiment were as follows: Day 5 sampling–morphine-treated (n=20), saline-treated (n=18); Day 10 sampling–morphine-treated (n=18), saline-treated (n=21).

3. Results

Chronic morphine exposure around the time of puberty resulted in diminished body weight gain ($t_{[94]}$=−7.75, p<0.001; Fig. 1a) and delayed vaginal opening ($t_{[94]}$=2.18, p<0.03; Fig. 1b). These results confirm previous findings that have demonstrated a significant effect of opioids on sexual maturation in female rats (Macdonald and Wilkinson, 1991). The impact of morphine on bodyweight was not permanent, as bodyweights between the two groups were no longer different on the first day of mating (10 days after the end of treatment). Finally, few withdrawal signs were observed in morphine-treated females. The most prevalent withdrawal sign was an increased occurrence of headshakes, which was most pronounced on the second day of observations. At this time 80% of morphine-treated females displayed headshakes during at least one of the nine observation periods, as compared to vehicle-treated females in whom this behavior was never observed (Fisher's p<0.01).

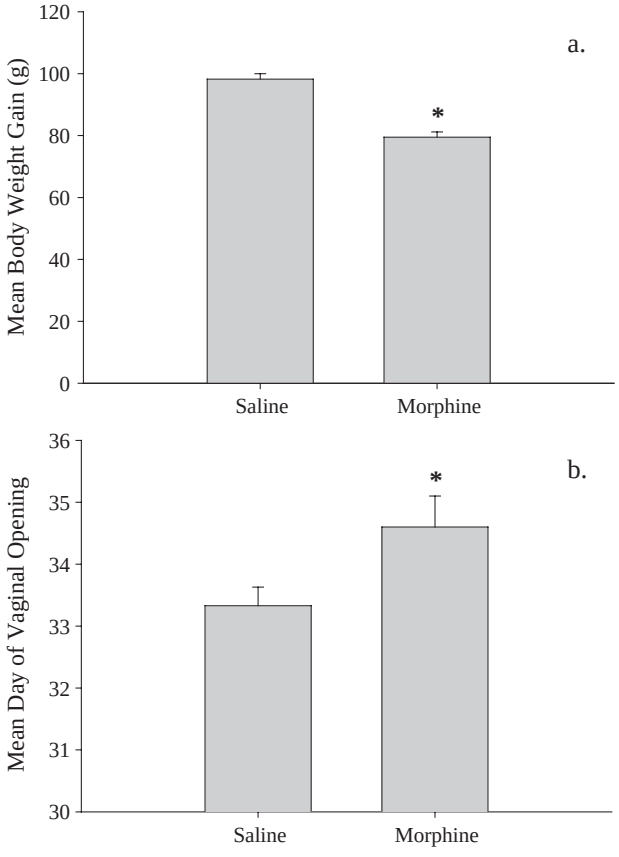

Fig. 1. Panel a: Mean (±SEM) body weight gain during the 20 days of morphine administration. Panel b: Mean (±SEM) day that vaginal opening was first observed. *p<0.05 as compared to saline-treated females.

Table 1
Summary of offspring data (mean±SEM) during the postpartum period

Treatment of rearing dam	Litter weight (g)	Litter no.	No. of males	No. of females	Age at tooth eruption (days)	Age at eye opening	Body weight gain
Saline-treated (*N*=39)	97.5±2.5	13.6±0.4	7.0±0.4	6.7±0.3	10.7±0.1	14.3±0.1	382.8±9.9
Morphine-treated (*N*=38)	98.3±2.2	13.5±0.3	6.7±0.3	6.8±0.3	10.8±0.2	14.4±0.2	379.1±11.1

Body weights were measured daily with no significant differences observed at any point during postnatal development. Body weight gain represents the increase in body weight (in grams) between postpartum day 1 and weaning on postpartum day 21.

Morphine exposure during puberty had no significant effect on the physical development of offspring. All females gave birth on either gestation day 22 or 23 and no differences in litter size, weight or sex ratios were observed. In addition, there were no differences in tooth eruption, eye-opening or bodyweight gain during the postnatal period, either as a function of drug treatment during puberty or cross-fostering. These data are shown in Table 1. As cross-fostering had no effect on any of these measures, the data have been collapsed across rearing condition and are presented as offspring reared by morphine-treated dams or offspring reared by saline-treated dams.

3.1. Postpartum day 5

As shown in Fig. 2, exposure to morphine during puberty had no affect on postpartum maternal behavior latencies. Following a 4 h separation on postpartum day 5, the latencies to retrieve the first pup, the eighth pup, group all eight pups and crouch over all eight pups were measured. There were no significant effects of either drug treatment during puberty or cross-fostering on any of these measures.

Exposure to morphine during puberty, however, did significantly effect suckling-induced prolactin secretion during early lactation. A three-way repeated measures analysis revealed significant main effects for time ($F_{[5,170]}$=24.84, p<0.001) and drug treatment ($F_{[1,34]}$=8.41, p<0.006) as well as a time × drug treatment interaction ($F_{[5,170]}$=2.79, p<0.02). Rearing condition had no significant effect on suckling-induced prolactin; therefore, posthoc analyses were performed on data collapsed across rearing condition. These data are presented in Fig. 3. There were no significant differences in basal prolactin concentrations on postpartum day 5 between females treated with either saline or morphine during puberty. Moreover, the initial response to the suckling stimulus was similar in both groups with significant increases in plasma prolactin concentrations observed 30 min after reunion with pups (all ps<0.01 as compared to basal levels). However, while elevated prolactin concentrations were observed at the 60- and 120-min collection times in females treated with saline during puberty, prolactin concentrations in females treated with morphine during puberty were significantly lower when compared to the saline-treated controls (p<0.003 between groups at both the 60 and 120 min time points).

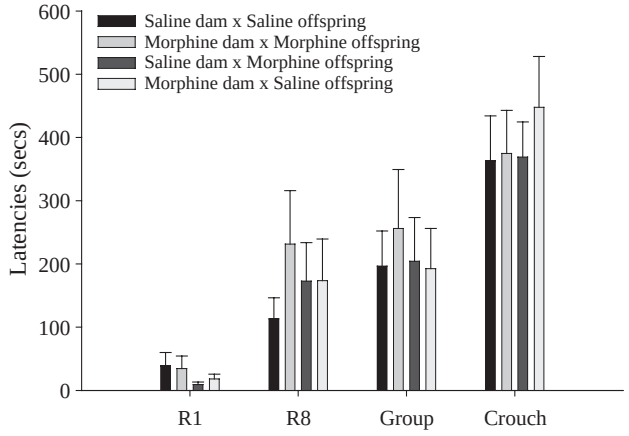

Fig. 2. Mean (±SEM) latencies in seconds to retrieve the first pup (R1), the eighth pup (R8), to group all eight pups (Group), and to crouch over all eight pups (Crouch). Saline dam × Saline offspring: Pubertal saline-treated females rearing their own pups; Morphine dam × Morphine offspring: Pubertal morphine-treated females rearing their own pups; Saline dam × Morphine offspring: Pubertal saline-treated females rearing pups cross-fostered from morphine-treated females; Morphine dam × Saline offspring: Pubertal morphine-treated females rearing pups cross-fostered from saline-treated females.

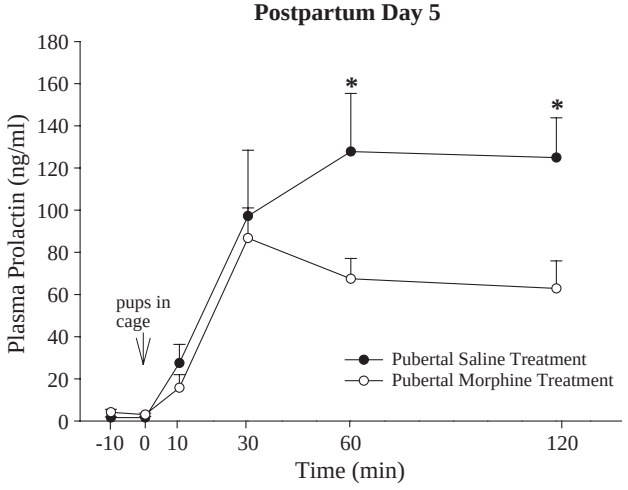

Fig. 3. Mean (±SEM) plasma prolactin concentrations (ng/ml) on postpartum day 5. Females were separated from pups for 4 h prior to baseline samples (−10, 0 min) after which pups were placed back in the home cage opposite the nest site. Blood sampling (400 μl) commenced 10 min later. Saline-treated dams—females treated with saline during puberty rearing their own pups or pups cross-fostered from morphine-treated females; Morphine-treated dams—females treated with morphine during puberty rearing their own pups or pups cross-fostered from saline-treated females. *p<0.05 between treatment groups.

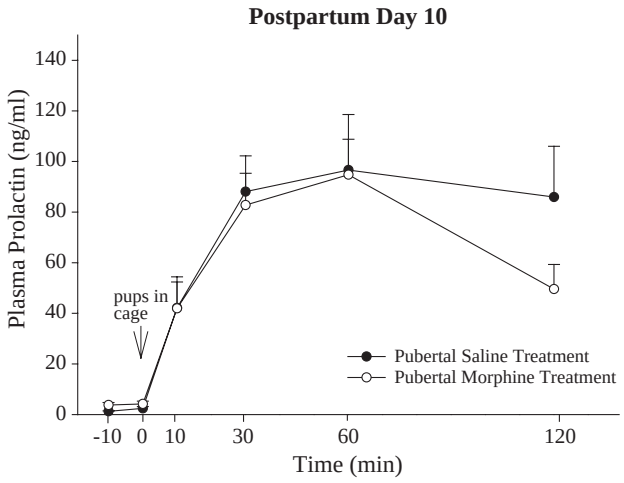

Fig. 4. Mean (±SEM) plasma prolactin concentrations (ng/ml) on postpartum day 10. Females were separated from pups for h prior to baseline samples (−10, 0 min) after which pups were placed back in the home cage opposite the nest site. Blood sampling (400 μl) commenced 10 min later. Saline-treated dams—females treated with saline during puberty rearing their own pups or pups cross-fostered from morphine-treated females; Morphine-treated dams—females treated with morphine during puberty rearing their own pups or pups cross-fostered from saline-treated females.

3.2. Postpartum day 10

Similar findings were not observed on postpartum day 10. As shown in Fig. 4, on postpartum day 10 all groups displayed a significant increase in plasma prolactin concentrations following the reintroduction of the pups into the home cage. A three way repeated measures ANOVA revealed a significant effect of time ($F_{[5,175]}$=23.87, p<0.001) with increased prolactin concentrations observed at all time points as compared to baseline (all ps<0.01). There was, however, no significant main effect of drug treatment ($F_{[1,35]}$=0.22, p=0.64), nor a significant time × drug treatment interaction ($F_{[5,175]}$=.627, p=0.63). As observed on postpartum day 5, there were no significant effects of cross fostering (all ps>0.6); therefore data are presented collapsed across rearing treatment.

4. Discussion

The present findings indicate that chronic morphine exposure during puberty can significantly alter suckling-induced prolactin secretion during early lactation. This effect was not due to a change in maternal behavior latencies, as no differences in the amount of time necessary to retrieve, group and crouch over pups were observed. Indeed, all females were observed to be in the characteristic nursing posture (kyphosis) prior to the 10 min sampling period. In addition, reduced suckling-induced prolactin secretion was not due to any change in the suckling abilities of offspring born to pubertal morphine-treated mothers, as cross-fostering did not alter the effect of pubertal morphine treatment on suckling-induced prolactin secretion.

The impact of prior morphine exposure on suckling-induced prolactin secretion was not revealed during the initial elevation of prolactin concentrations, but rather appeared to reflect a diminished capacity to maintain high levels of secretion. Thus, it is possible that dams previously exposed to morphine during puberty may be limited in terms of their capacity to sustain prolonged production and/or release of high levels of prolactin. The failure to observe an effect on day 10 of lactation may suggest that some compensatory mechanism occurs as lactation progresses, resulting in the normalization of prolactin secretion in pubertal morphine-treated females. It is interesting to note, however, that while there were no significant differences between the treatment groups on day 10 of lactation, there was a trend (p=0.12) at the final time-point (120 min) for the morphine-treated females to have lower prolactin levels. This may suggest that even during mid-lactation, morphine-treated females may not be capable of sustaining high levels of prolactin release over time.

In the rat, the regulation of prolactin secretion via endogenous opioid peptides emerges during puberty (Shieh and Pan, 1998). The impact of high doses of opiates during this developmental period may, therefore, alter the normal interaction between endogenous opioid peptides and prolactin secretory responses. Endogenous opioid peptides play an important role in the regulation of prolactin secretion during lactation. Several studies have demonstrated that β-endorphin is a potent stimulator of prolactin secretion during lactation (Kehoe et al., 1993; Janik et al., 1992). The effect of β-endorphin on prolactin secretion appears to be mediated by activation of not only the μ-receptor subtype but the δ- and κ-subtypes as well (Kehoe et al., 1993). In fact, antagonizing any one of these subtypes can block β-endorphin-stimulated prolactin secretion (Kehoe et al., 1993). Furthermore, while morphine normally stimulates prolactin secretion (Deyo et al., 1979; Gudelsky and Porter, 1979; Shieh and Pan, 1998), this effect is not observed in lactating females (Callahan et al., 1988a,b). As morphine has a high affinity for the μ-receptor subtype, but far less affinity for the δ- and κ-subtypes, it is possible that a minimal threshold of activity at all three receptor subtypes is necessary to stimulate prolactin secretion during lactation. Thus, in the normal lactating rat, the suckling stimulus increases prolactin secretion via endogenous opioid peptide activation of δ-, κ- and μ-receptor subtypes. (Andrews and Grattan, 2003; Baumann and Rabii, 1990; Callahan et al., 1996; Selmanoff and Gregerson, 1986).

Several studies have demonstrated that the effects of endogenous opioid peptides on prolactin secretion are mediated by the inhibition of tuberoinfundibular dopamine (TIDA) neurons (Andrews and Grattan, 2003; Arbogast and Voogt, 1998; Callahan et al., 2000). Suckling increases endogenous opioid peptides, which then decrease TIDA activation, resulting in decreased dopamine release into the

median eminance and subsequently, increased prolactin release (Andrews and Grattan, 2003; Arbogast and Voogt, 1998; Callahan et al., 2000). Chronic morphine exposure during puberty could potentially alter the amount of endogenous opioids released in response to suckling, the sensitivities of the δ-, κ-, and/or μ-receptor subtypes to endogenous opioids, or the ability of opioid receptor activity to influence the TIDA system. Any of these changes could result in a system that responds differently during lactation. In addition, as morphine administration significantly increases prolactin secretion in non-lactating females, chronic morphine exposure during puberty could functionally alter prolactin synthesis or feedback systems, resulting in a long-term reduction in prolactin stores following withdrawal.

It is possible, however, that the interaction between the mother and pups may have mediated the blunted prolactin secretion during early lactation. While all of the females were observed to be crouching over their litters during sampling, it is still conceivable that some subtle behavioral change in the female, for example increased pup grooming or litter rearranging, may have prevented a number of pups from maintaining prolonged contact with the nipple. As the number of pups suckling can significantly affect the amount of prolactin released (Mattheij et al., 1979, 1984; Grosvenor et al., 1986), such a behavioral change could result in lower levels of prolactin. Such an explanation might also account for the lack of an effect observed on day 10 of lactation, as grooming behavior declines during lactation, with peak frequencies observed during the first week postpartum (Champagne et al., 2003). Moreover, older pups are better able to maintain nipple contact when the female readjusts her position on the nest. Thus, a change in maternal behavior, which could alter prolactin secretion early in lactation, may be less influential during later lactation. Interestingly, recent data examining feeding behavior in 1-month old infants of opiate-dependent mothers, demonstrated significant feeding problems, which were due primarily to maternal behavior during the feeding session (LaGasse et al, 2003).

In the present study, considering the decline in sustained prolactin release observed during early lactation, it is of interest that the offspring still demonstrate physical development similar to the offspring of saline-treated females. No differences in body weight were observed on any day postpartum, nor were delays in eye opening or tooth eruption observed. Further examination of these offspring, however, revealed alterations in sexual maturation and stress responsiveness in adulthood (Byrnes et al., 2003). Several studies have demonstrated that reducing prolactin levels during the neonatal period can significantly impact adult reproductive parameters (Nusser and Frawley, 1997; Stoker et al., 1999) as well as the maturation of the TIDA system (Phelps and Hurley, 1999; Phelps et al., 2003). Thus, subtle changes in neuroendocrine function observed in the offspring of pubertal morphine-treated mothers may indeed be related to the blunted prolactin secretion observed during the neonatal period.

A number of studies use animal models to detail the impact of prenatal morphine exposure on maternal behavior and offspring development (Rimanoczy at al., 2003; Slamberova et al., 2001a,b, 2003; Vathy, 2002). Indeed, morphine administered during early pregnancy has been shown to result in attenuated suckling-induced prolactin secretion (Litto et al., 1983). To our knowledge, however, the present study is the first to examine the impact of prior morphine exposure during puberty on these parameters. The effects on suckling-induced prolactin appear relatively long-lasting, as the final drug exposure was at least 5 weeks prior to prolactin sampling. Future studies will attempt to elucidate the mechanisms involved in the observed changes in suckling-induced prolactin secretion and determine whether other prolactin-mediated functions, such as immune responses, are also affected.

Acknowledgements

I would like to thank Dr. Robert Bridges for generously allowing the use of his laboratory facilities and Ms. Beth A. Rigero for her excellent technical assistance. This work was supported by the National Institute on Drug Abuse, grant R03 DA14613, awarded to E.M. Byrnes.

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