

DEVELOPMENT OF COCAINE SENSITIZATION BEFORE PREGNANCY AFFECTS SUBSEQUENT MATERNAL RETRIEVAL OF PUPS AND PREFRONTAL CORTICAL ACTIVITY DURING NURSING

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Abstract—Pups are a highly rewarding stimulus for early postpartum rats. Our previous work supports this notion by showing that suckling activates the mesocorticolimbic system in mothers. In the present study, we tested whether development of behavioral sensitization to cocaine before pregnancy affects the neural response to pups during the early postpartum days (PD). Virgin rats were repeatedly administered cocaine for 14 days (15 mg kg^{-1}) and withdrawn from treatment during breeding and pregnancy. The neural response to suckling was measured at PD 4–8 using blood-oxygen-level-dependent (BOLD) MRI or microdialysis. Our results show that BOLD activation in the medial prefrontal cortex (PFC), septum and auditory cortex was curtailed in cocaine-sensitized dams. No differences between cocaine sensitized and saline control dams were observed in the nucleus accumbens, olfactory structures, or in 48 additional major brain regions that were analyzed. Baseline, but not pup-stimulated, dopamine (DA) levels in the medial PFC were lower in cocaine-sensitized dams than in controls. When tested for maternal behaviors, cocaine-sensitized dams showed significantly faster retrieval of pups without changes in other maternal behaviors such as grouping, crouching and defending the nest. Taken together, the present findings suggest that maternal motivation to retrieve pups was enhanced by repeated cocaine exposure and withdrawal, a result reminiscent of ‘cross-sensitization’ between the drug and a natural reward. Changes in retrieval behavior in cocaine-sensitized mothers might be associated with a hypo-responsive medial PFC. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: maternal behavior, dopamine, cocaine sensitization, medial prefrontal cortex, suckling, functional MRI.

Mothers recovering from cocaine addiction experience difficulties in their maternal roles as care givers (Coyer, 2001, 2003). Evidence for this comes from studies reporting reduced mother–child play interactions, low self-esteem, emotional neglect, lack of maternal identity, increased hostility toward own child and inability to cope with stressful

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Abbreviations: BOLD, blood-oxygen-level-dependent; DA, dopamine; DOPAC, dihydrophenylacetic acid; NAC, nucleus accumbens; PFC, prefrontal cortex; TE_{eff} , effective echo time; VTA, ventral tegmental area.

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doi:10.1016/j.neuroscience.2007.05.026

situations (Amir and Donath, 2002; Coyer, 2001; Harmer et al., 1999; Johnson et al., 2002; Nair et al., 1997). Although socioeconomic factors affect mothers recovering from cocaine addiction, neurobiological changes resulting from chronic cocaine abuse may also have lasting effects on the maternal brain.

Studies in rats have examined the effects of acute and chronic cocaine administration in gestation and after parturition on the expression of maternal behaviors. Acute cocaine administration during early postpartum causes a dose-dependent disruption in maternal behaviors (Kinsley et al., 1994), that returns to normal once plasma cocaine levels drop, suggesting that the acute effects of cocaine are reversible (Vernotica et al., 1996). Virgin rats trained to self-administer cocaine were reported to escalate their intake dramatically during pregnancy, but showed a decline during early postpartum days that may have been associated with the attendance of their newborn pups (Hecht et al., 1999). Interestingly, Hecht et al. (1999) reported that mothers attend pups by placing them near the active cocaine lever, suggesting that the reinforcing properties of pups compete with those of cocaine. This is supported by Morell and colleagues (Mattson et al., 2001) who reported data suggesting that the motivation for pups during this reproductive stage is greater than the motivation to seek cocaine. Newborn pups are so reinforcing that lactating rats will incessantly attempt to make snout contact with pups, even if prevented to do so by muzzling (Stern and Keer, 1999), and will also lever-press to gain access to them (Lee et al., 1999). Will the intense motivation to seek, attend and protect pups be modified by chronic cocaine exposure early in life, before pregnancy? The present study tested whether development of behavioral sensitization to cocaine in virgin rats affects subsequent maternal behaviors. We hypothesized that repeated cocaine administration before pregnancy would have long-term behavioral and neurobiological outcomes that might contribute to changes in maternal motivation.

Maternal retrieval, nursing and aggression is under the control of several areas of the brain. A core neural circuitry includes the medial preoptic area, paraventricular nucleus of the hypothalamus, ventral pallidum, ventral tegmental area (VTA), bed nucleus of the stria terminalis, nucleus accumbens (NAC), periaqueductal gray, portions of the amygdala, and the olfactory system (Bosch et al., 2004, 2005; Fleming et al., 1979; Lee et al., 1999; Lonstein and Stern, 1997; Numan, 2007; Numan et al., 2005b; Numan and Smith, 1984). Although several of these areas share connectivity with midbrain dopamine (DA) neurons, the

release of this neurotransmitter in the NAC plays an important part in modulating retrieval behavior and nursing of newborn pups (Keer and Stern, 1999). The recent use of blood-oxygen-level-dependent (BOLD) fMRI in lactating dams has allowed a detailed analysis of neural processing of an important sensory stimulus for the maternal brain, the suckling stimulus (Ferris et al., 2005). Increasing amounts of data show that the BOLD signal originates from underlying hemodynamic alterations in relation to increases in neuronal activity (Devor et al., 2007; Shmuel et al., 2006), specifically with changes in local field potentials (Logothetis et al., 2001). We previously reported that suckling stimulation robustly activates brain areas of the mesocorticolimbic DA system (Ferris et al., 2005). In the present work we observed that females that were sensitized to cocaine before pregnancy showed lower BOLD activation in the prefrontal cortex (PFC), with no changes in the NAC or VTA during the postpartum period. Diminished basal levels of extracellular DA in the medial PFC were also observed with cocaine pre-exposure. Interestingly, cocaine-sensitized females showed quicker retrieval of pups than cocaine-naïve dams, a result reminiscent of behavioral 'cross-sensitization' between pup retrieval and cocaine. The enhanced maternal retrieval was not accompanied by differences in other measures of maternal behavior between control and cocaine-pretreated dams, a result that does not support the notion that full maternal responding is affected with cocaine pretreatment and withdrawal. Instead, the overall findings support the idea that maternal motivation to retrieve her pups is increased despite the low neural response during mother–pup interactions.

EXPERIMENTAL PROCEDURES

Animals

Adult Sprague–Dawley females were purchased from Charles River Laboratories (Charles River, MA, USA). Virgin rats were bred in the animal resource facilities of the University of Massachusetts Medical School. Dams were housed with their litters in a temperature- and humidity-controlled room, under a 12-h light/dark cycle with lights off at 18:00 h. Water and Purina rat chow (Harlan, Boston, MA, USA) were provided *ad libitum*. Animals were acquired and cared for in accordance with the guidelines published in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publications No. 85-23, revised 1985) and adhere to the National Institutes of Health and the American Association for Laboratory Animal Science guidelines. The protocols used in this study were in compliance with the regulations of the Institutional Animal Care and Use Committee at the University of Massachusetts Medical School. The study design used the minimum number of animals to achieve statistically valid data, and all efforts were made to minimize pain and discomfort.

Cocaine administration and behavioral testing

Cocaine administration and behavioral assessments were conducted during the light phase of the light/dark cycle (09:00–11:00 h). Female rats were given a daily injection of cocaine (15 mg kg⁻¹, i.p.) for 14 consecutive days (Fig. 1A). Control animals received an injection of 0.9% sterile saline vehicle (0.1 ml 100 g⁻¹, i.p.). The initial number of animals included in the study was 24 cocaine-pretreated females and 21 controls, which were later divided between microdialysis and fMRI experiments. The behavioral re-

sponse to cocaine was assessed using a nine-point behavioral rating scale developed by Ellinwood and Balster (1974). Briefly, scores were assigned as follows: 1, lying down, eyes closed; 2, lying down, eyes open; 3, normal grooming or chewing cage litter; 4, moving about cage, sniffing and rearing; 5, running movements characterized by rapid changes in position; 6, repetitive exploration of the cage at normal level of activity; 7, repetitive exploration of the cage with hyperactivity; 8, remaining in the same place in cage with fast repetitive head and/or foreleg movement (includes licking, chewing, and gnawing stereotypies); and 9, backing up, jumping, seizures, abnormally maintained postures, dyskinetic movements.

Following 60 min of habituation to the testing cages, a behavioral score was assigned to each rat every 5 min for 30 min. Testing began 5 min prior to cocaine administration and lasted up to 25 min following injections. During testing, one rat was observed for 10 s and a score assigned within 10 s before passing to the next (Ellinwood and Balster, 1974). Behavioral scoring was done for 14 consecutive days. The day after the final saline or cocaine injection, nulliparous control and drug-treated rats were housed for 5 days with sexually experienced males. Pregnancy was verified by the presence of a sperm plug in the cage bedding or vaginal canal. In many cases, vaginal smears were observed under a light microscope to confirm the presence of sperm. Females remained undisturbed throughout breeding, pregnancy, and postpartum days 1–2, until maternal behavior testing, functional imaging and *in vivo* microdialysis (Fig. 1A).

Maternal behavior testing

The average litter sizes did not vary between the control and cocaine-pretreated rats (control litter size was 11.6±1.5 and cocaine-sensitized litter size was 12.7±2.4). Group sizes were not standardized and mothers were allowed to freely interact with their pups before the day of testing. Maternal behaviors were assessed on postpartum days 3–4 according to work published by Bridges (1984), with minor modifications. Behavioral measurements were done during the light phase of the light/dark cycle (08:00–11:00 h). Dams and pups were removed from their home cage and placed into two separate cages. The nest area was located within the home cage and six pups were placed opposite to the nest, three pups in each corner. After a short 15-min separation from the pups, dams were returned to their cages for testing. The time taken to retrieve six pups, group and crouch over them was registered during a 15 min testing session. Afterward, the number of pups in nest was verified at 30, 45 and 60 min after the start of maternal testing. At the end of the study, all pups were returned to their respective mothers. Once all pups were grouped in the nest, a male intruder equal in size to the dam was placed inside the home cage and the latency to attack was also noted.

Functional MRI of pup suckling stimulation

Studies were performed using a multi-concentric dual-coil small animal restrainer (Insight NeuroImaging Systems, Worcester, MA, USA). Prior to breeding, females were acclimated to the restrainer and the imaging protocol as described previously (King et al., 2005). To reduce discomfort from ear and nose bars during acclimation and experiments, a topical anesthetic (2.5% lidocaine/2.5% prilocaine EMLA™ cream; Webster Veterinary, Sterling, MA, USA) was applied to skin and soft tissue in the ear canal and over the bridge of the nose. Details of the setup for suckling stimulation are provided in Ferris et al. (2005). Briefly, four pups (4–8 days of age) were placed in a weigh boat cradle padded with a double-layer of gauze sheets. The pup cradle was positioned under a ventral opening in the body tube that allowed immediate access to two pairs of teats on each side of the dams' abdomen (for a total of four teats accessible to pups). Gliding a thin plastic sheet over the ventral opening of the body tube controlled access to teats.

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