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Effects of chronic cocaine on monoamine levels in discrete brain structures of lactating rat dams

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Abstract

Chronic gestational cocaine administration has been correlated with high levels of postpartum maternal aggression towards intruders and altered levels of oxytocin in the amygdala. Cocaine may alter both oxytocin and maternal aggression either directly or indirectly through changes in monoamine levels in relevant brain regions. In this study, pregnant female rats were randomly assigned to one of four groups; three cocaine dose groups (7.5, 15 or 30 mg/kg), or a saline-treated group (0.9% normal saline) and given subcutaneous injections twice daily (total volume 2 ml/kg) throughout gestation. Behavioral responses to an inanimate object placed in the homecage were assessed on Postpartum Day (PPD) 6. Immediately following testing, animals were sacrificed and four brain regions implicated in maternal/aggressive behavior (medial preoptic area [MPOA], ventral tegmental area [VTA], hippocampus, and amygdala) were removed for monoamine level analyses using high-performance liquid chromatography. Dams given 30 mg/kg cocaine throughout gestation had significantly higher levels of dopamine (DA) and nonsignificantly elevated serotonin (5-HT) levels relative to saline-treated controls. These dams also exhibited higher frequencies of defensive behavior toward an inanimate object compared to saline-treated controls. Potential mechanisms mediating cocaine-induced increases in responding are proposed.

Keywords: Dopamine; Serotonin; Cocaine; Maternal aggression

1. Introduction

Chronic gestational cocaine administration has been associated with increases in maternal aggressive behavior towards male and female homecage intruders on Postpartum Days (PPDs) 6 and 10 (Heyser et al., 1992; Johns et al., 1994, 1995, 1997b), but not earlier in the postpartum period (Lubin et al., 2001). This potentiated aggressive response is apparent regardless of whether cocaine administration ceased on the last day of pregnancy or continued into the postpartum period (Johns et al., 1997b). Cocaine-induced increases in maternal aggressive behavior have consistently been associated with decreased levels of the neuropeptide oxytocin (OT) in the amygdala on PPD 6 (Johns et al., 1995). Cocaine-induced decreases in OT levels in other brain structures implicated in maternal behavior (in the early postpartum period) such as the ventral tegmental area (VTA) (Gaffori and Le Moal, 1979; Numan and Smith, 1984), the medial preoptic area (MPOA) (Numan, 1986, 1994), and the hippocampus (Kimble et al., 1967) are no longer present by PPD 6 (Johns et al., 1997a). Therefore, Johns et al. (1995) have proposed that heightened maternal aggressive behavior may be mediated by cocaine's interaction with and reduction of OT levels, specifically in the amygdala on PPD 6.

It is unclear whether chronic cocaine decreases OT levels directly, via an intermediary process, or through one of its primary pharmacodynamic activities (inhibition of dopamine [DA], serotonin [5-HT], and norepinephrine [NE] uptake (Koe, 1976; Ritz et al., 1987)). The extant literature describing chronic cocaine's effects on central concentrations of monoamine and metabolite levels varies widely depending on the duration of cocaine exposure, the brain region examined, and the length of abstinence prior to assay. Some studies report increases (Johnson et al., 1993; Pettit and Justice, 1989), and some report decreases (Karoum et al., 1990), while others reported no change (Alburges and

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Wamsley, 1993; Alburges et al., 1993; Kleven et al., 1988; Yeh and DeSouza, 1991) in monoamine levels following chronic cocaine administration.

We are unaware of any other investigations that have examined catecholamine levels in brain regions implicated in maternal aggression on PPD 6 following chronic cocaine exposure in lactating rats. Furthermore, we have not found any other explorations of the potential link between cocaine-induced alterations in monoamine and metabolite levels and decreases in OT levels in brain areas putatively mediating maternal aggressive behavior. Therefore, the current investigation was conducted to determine the effects of gestational cocaine or saline administration on monoamine and metabolite levels in specific brain regions of lactating rats where cocaine-induced decreases in OT levels have previously been found on PPD 6.

2. Methods

2.1. Subjects

Virgin, female, Sprague–Dawley rats (Charles River, Raleigh, NC) were habituated to a colony room for 1 week prior to breeding. Each female was then singly housed with a male until conception was noted by the presence of a sperm plug. Upon conception, females were randomly assigned to one of four groups (10 per group; 3 cocaine-treated, 1 saline-treated) and singly housed in a colony room maintained on a reverse 12:12 light cycle, with the lights off at 0900 for 1 week. Females were then transferred to a room on a standard light cycle for the remainder of the experiment, resulting in the majority of dams delivering their litters during daylight hours (Mayer and Rosenblatt, 1998). Gestational weight gain was recorded daily for all groups.

2.2. Treatment

Cocaine- and saline-treated dams were injected subcutaneously twice daily, throughout gestation, with either 3.75, 7.5, or 15 mg/kg of cocaine HCl dissolved in 0.9% normal saline (dose calculated as the free base; Sigma, St. Louis, MO) or 0.9% normal saline, in a volume of 1 ml/kg. Injections were given at 0800 and 1600 on gestation days 1–20. As skin lesions are prone to develop following repeated subcutaneous administration of cocaine solution, injection sites on the flanks were varied. Also, skin lesions that developed were cleaned with a betadine wash and a topical antibacterial ointment (Polymycin–Bacitracin–Neomycin, Burroughs Wellcome, Raleigh, NC) was applied as soon as they were discovered. All procedures were conducted under federal and University Institutional Animal Care and Use Committee (IACUC) guidelines for humane treatment of laboratory subjects.

Saline-treated animals were pair-fed with cocaine-treated dams to control for the anorectic effects of cocaine on weight gain. In the pair-feeding paradigm, each saline-treated female was offered only the amount of food that was consumed by her respective cocaine-matched dam on the corresponding gestation day.

Upon parturition, dam weight, litter weight, and the number of male and female pups were recorded. Litters were then culled to four male and four female pups and the culled litter weight was recorded.

2.3. Procedure

On PPD 6 an inanimate, hard, plastic, elephant toy was placed in each dam's cage, opposite the dam and her litter. This task was chosen so that monoamine levels could be assessed following a behavioral challenge with a homecage "intruder" providing consistency with the protocol typically employed in our laboratory. While any behavior-induced alterations in monoamine or metabolite levels would likely be undetectable immediately after a very brief test session, our research to date using this paradigm has revealed treatment-related differences in OT levels on PPD 6. Therefore, in this experiment, the constitutive levels of monoamines and metabolites following chronic cocaine or saline administration were of primary interest.

The dam's behavior toward the "intruder" was assessed by observing whether or not dams performed any of the following seven behaviors over a 3-min period. The behaviors recorded included:

Approach dam moves across the cage from the litter to elephant toy;
Sniff dam sniffs the toy;
Touch dam physically contacts the toy using her snout or forepaws;
Bury/Make Barrier dam either covers the toy in bedding or constructs a barrier of bedding between the toy and the litter;
Attack/Push dam attacks, bites, or pushes the toy with her body;
Move/Lick Pup dam licks or picks up at least one pup and moves it to an alternate location in the homecage;
Locomotion dam runs rapidly around the cage (often back and forth between her litter to the toy).

Immediately following the behavioral session, the animals were killed by decapitation, and the whole MPOA, amygdala, VTA, and hippocampus were dissected and frozen at −70 °C for later monoamine and metabolite assay.

2.4. Brain dissection

To define the preoptic–anterior hypothalamic area, the cerebrum was coronally sectioned from the ventral side,

Table 1
Gestational variables

Treatment (mg/kg)	Gestation length (days)	Weight gain (g)	Number of pups	Litter weight (g)
30	21.18 ± 0.14	128.36 ± 5.35	15.27 ± 0.67	91.64 ± 4.12
15	21.38 ± 0.17	146.38 ± 6.27	16.13 ± 0.79	99.75 ± 4.83
7.5	21.00 ± 0.15	143.80 ± 5.61	15.70 ± 0.70	93.30 ± 4.32
Saline	21.00 ± 0.16	158.44 ± 5.91[a]	14.11 ± 0.74	88.44 ± 4.56

[a] Saline-treated, pair-fed dams gained more weight across gestation than dams given 30 mg/kg cocaine, $P < .01$.

rostral to the optic chiasm (approximately A 7100 μm), and just caudal to the optic chiasm (approximately A 5800 μm). Vertical cuts, ventral from the lines of the lateral ventricles, and a horizontal slice below the anterior commissure were made to produce a block section of the MPOA. Brains were sectioned once again just caudal to the tuber cinereum (approximately A 3800 μm) and slightly above the cerebellum, and the amygdala was removed in this section. The whole hippocampus was then removed from the caudal remainder of the brain, and the VTA was dissected from this portion by making dorsoventral cuts medial to the optic tracts with a dorsal cut at the ventral extent of the central gray. The brain areas were then individually weighed and stored at −70 °C.

2.5. Monoamine and metabolite level determination

Levels of DA, 5-HT, and their metabolites were determined using reverse-phase high-performance liquid chromatography (NE and metabolite levels were not able to be determined using these samples and available equipment). Brain areas were homogenized and centrifuged for 20 min at 14,000 rpm (Eppendorf centrifuge 5415C). Following centrifugation, 150 μl of the supernatant was loaded into a 150-μl loop and the sample was injected onto a C18 reverse-phase column (Alltech, Adsorosphere; 7 μm, 250 × 4.6 mm i.d.). The mobile phase consisted of 0.1 M sodium phosphate dibasic, 1 mM heptane sulfonic acid, and 15% methanol, adjusted to a pH of 4.5 with 0.06 M citric acid. The mobile phase was pumped in at a flow rate of 1.5 ml/min using an LDC Constametric pump. The samples were oxidized with a +0.75 V potential and were detected with a BAS LC4B amperometric detector. Peaks were measured by hand and compared to internal standards to determine levels of DA and its metabolites; dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), as well as 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA).

2.6. Statistics

Group differences in monoamine and metabolite levels were assessed for each brain area using a one-way analysis of variance (ANOVA) followed by Tukey's HSD for post hoc comparisons of significant main effects. The minimal subject size necessary for assessment of monoamine levels was set at six per group. Data from the behavioral task were analyzed using a Fisher's Exact Probability test for nominal data. A probability level of $P \leq .05$ was established as the significance level for rejection of the null hypothesis.

3. Results

3.1. Gestational variables

There were no significant differences in gestation length, number of live pups per litter, or litter birthweight among groups. However, as shown in Table 1, females that received 30 mg/kg cocaine throughout gestation gained less weight than saline-treated, pair-fed controls [$F(3,34) = 4.87$, $P < .01$].

3.2. Behavior

The only significant difference in the behavior displayed towards the inanimate object was in the frequency of "bury/make barrier" that was seen in 9/10 of the 30 mg/kg cocaine-treated group compared to only 3/10 of the saline-treated group ($P < .05$, Fisher's Exact Test).

3.3. DA, DOPAC, and HVA levels

There was a significant main effect of treatment on DA [$F(3,34) = 5.002$, $P < .01$] and DOPAC [$F(3,37) = 3.183$, $P < .04$, Fig. 1] levels in the amygdala. Post hoc analyses indicated animals given 30 mg/kg cocaine throughout gestation had significantly higher amgdalar levels of DA compared to saline-treated controls ($P < .01$), whereas animals given 7.5 mg/kg cocaine had higher levels of DOPAC than saline-treated controls ($P < .05$). There was also a main effect of treatment on DOPAC levels in the MPOA [$F(3,32) = 3.490$, $P < .05$]. However, in this brain area,

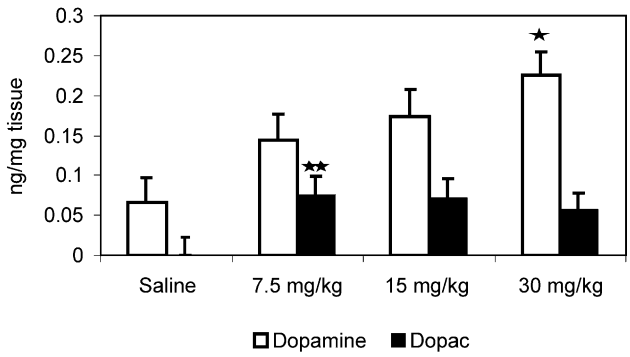

Fig. 1. DA and DOPAC levels in the amygdala. Mean (± S.E.M.) amygdala levels of DA and DOPAC in lactating rats treated with daily injections of saline, 7.5, 15, or 30 mg/kg cocaine throughout gestation. DA was significantly increased in the 30-mg/kg cocaine group ($P < .01$) compared to saline-treated controls. Likewise, the 7.5-mg/kg cocaine group ($P < .05$) showed higher levels of DOPAC than saline-treated controls.

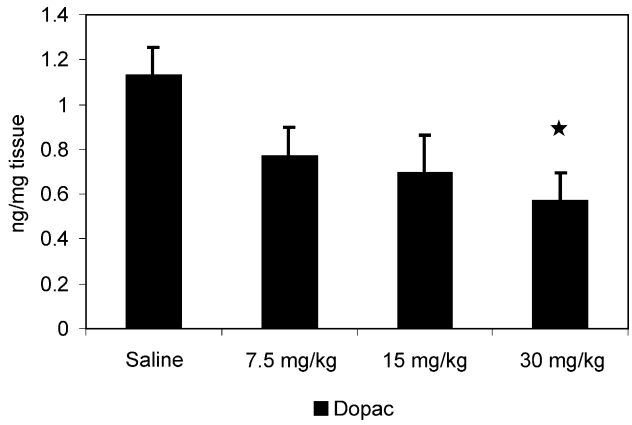

Fig. 2. DOPAC levels in the MPOA. Mean (±S.E.M.) MPOA levels of DOPAC in lactating rats given daily injections of saline, 7.5, 15, or 30 mg/kg cocaine throughout gestation. Saline-treated dams had significantly higher MPOA levels of DOPAC ($P<.02$) than dams that received 30 mg/kg cocaine.

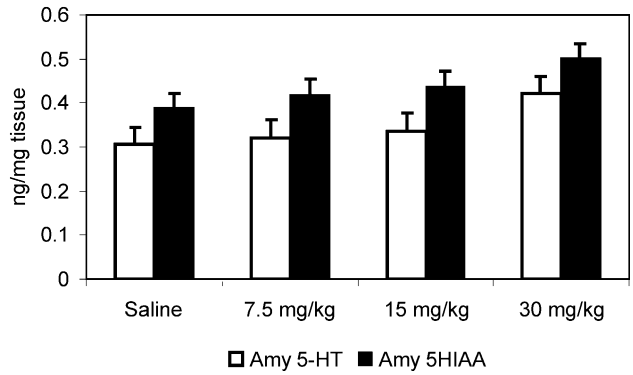

Fig. 4. 5-HT and 5-HIAA levels in the amygdala. Mean (±S.E.M.) levels of 5-HT and 5-HIAA in the amygdala of lactating rats given daily injections of saline, 7.5, 15, or 30 mg/kg cocaine throughout gestation. There were no statistically significant differences in monoamine or metabolite levels among groups, but there was a trend toward increased levels of 5-HT and 5-HIAA in 30 mg/kg cocaine-treated dams compared to saline-treated controls.

saline-treated dams had higher levels of DOPAC ($P<.02$) than the 30-mg/kg cocaine treatment group (Fig. 2). There were no significant differences in DA or DOPAC levels in the VTA or in the hippocampus and there were no group-dependent differences in levels of HVA on PPD 6 in any brain region assayed.

3.4. 5-HT and 5-HIAA levels

The only statistically significant treatment-dependent difference in 5-HT or 5-HIAA levels was found in the VTA [$F(3,36)=5.107$, $P<.05$]. Post hoc comparisons revealed that the saline-treated dams had higher 5-HT levels than dams that received 30 mg/kg cocaine ($P<.01$) (Fig. 3). There were no group differences in 5-HIAA levels among groups. While there were no statistically significant differences in amygdala levels of 5-HT or 5-HIAA among groups, there was a trend towards higher levels of this monoamine and its metabolite in the 30-mg/kg cocaine-treated females compared to saline-treated females ($P<.16$ and $P<.12$, respectively, Fig. 4). There were no significant group differences in 5-HT or 5-HIAA levels in the MPOA or the hippocampus.

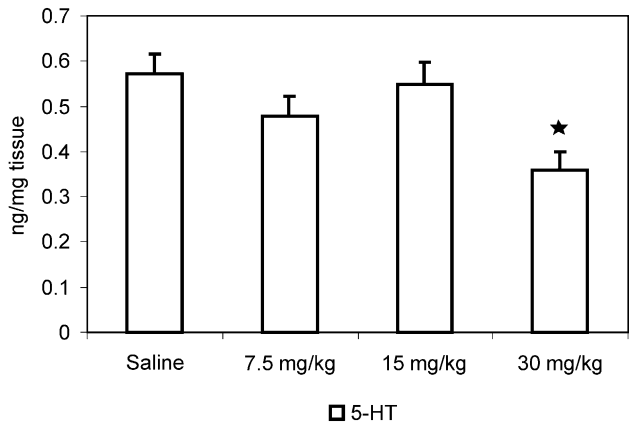

Fig. 3. 5-HT levels in the VTA. Mean (±S.E.M.) levels of 5-HT within the VTA of lactating rats given daily injections of saline, 7.5, 15, or 30 mg/kg cocaine throughout gestation. Saline-treated dams had significantly higher serotonin levels ($P<.01$) than dams in the 30-mg/kg cocaine-treated group.

4. Discussion

The bury/make barrier behavior has been characterized as a defensive response to a perceived threat or an anxiety reaction in the presence of a stressor (Pinel and Treit, 1978). Using a variety of paradigms, investigators have demonstrated heightened anxiety as evidenced by increased burying behavior following cessation of chronic cocaine administration (Basso et al., 1999; Harris and Aston-Jones, 1993). Similarly, in the current experiment, females that received 30 mg/kg cocaine daily throughout gestation engaged in more burying behavior than saline-treated controls. While the interaction between the cocaine-treated dams and the inanimate object (toy) was not as dramatic as that seen in previous studies using live intruders (Johns et al., 1994, 1997b), the 30-mg/kg cocaine-treated group did react more strongly to the inanimate object than saline-treated controls. This may provide further evidence that cocaine-treated animals may have an altered perception or assessment of threat.

Threat assessment, fear processing, and aggression have all been localized to the amygdala, among other brain areas. This experiment suggests that following chronic gestational cocaine administration, there are concurrent increases in DA levels and trends towards increases in 5-HT levels in the amygdala, as well as potentiated responding to a stressor in lactating rat dams. Historically, however, increases in serotonergic activation have been considered anti-aggressive, even in the context of maternal aggressive behavior (De

Almeida and Lucion, 1994; Olivier and Mos, 1992; Olivier et al., 1985, 1995). The effect of dopaminergic activity on maternal aggressive behavior is much less clear. For example, preliminary data from this lab suggest that dopaminergic activation reduces aggressive behavior in lactating rat dams (Johns et al., 1996). That is, rats that received chronic treatment with the selective DA reuptake inhibitor amfonelic acid throughout gestation were less aggressive towards a homecage intruder than chronic cocaine or saline-treated control dams. However, other investigators have reported that acute antagonism of DA activity (with haloperidol) reduced maternal aggressive behavior, although it was conceded that the sedative effects of this drug may have contributed to decreased responsiveness (Olivier et al., 1985). Still other groups have determined that dams whose mesolimbic dopaminergic pathways were destroyed during lactation showed no alteration in maternal aggressive behavior (Hansen et al., 1991).

While increased amygdala DA levels and trends toward increased 5-HT levels in this study have been correlated with increased responding to an inanimate object, previous investigations found that decreased OT levels in the amygdala (Johns et al., 1995; Lubin et al., in press) were associated with heightened maternal aggressive behavior. The dynamic among cocaine, monoamines, and OT levels in the amygdala is currently unknown. Clearly, assessment of monoamine and metabolite levels from a single timepoint is of limited use in beginning to discern this relationship. However, this method was employed in order to maintain some consistency with previous investigations from our laboratory in which neuropeptide levels were assayed in whole brain structures following chronic gestational cocaine administration (Johns et al., 1995, 1997a). While conclusions based on independent investigations using parallel study designs are unfounded, hypotheses regarding possible mechanisms by which these systems interact may begin to be generated.

Cocaine may directly reduce OT levels in the amygdala or alter monoamine levels that ultimately act to lower OT levels in relevant brain regions. Another equally plausible mechanism of action is that cocaine independently alters both OT and monoamine levels, which act in parallel to increase maternal aggressive behavior towards stressors/intruders. Cocaine may also impact some third variable that moderates both neurochemistry and behavioral outcomes. For example, the potential confound of the development of skin lesions in pregnant rats receiving subcutaneous cocaine injections is often discussed in the extant literature. However, it has been concluded that these lesions have no statistically significant effect on behavioral outcomes (NIDA Research Monographs, 1993). In the current experiment, however, not all females in each cocaine-treated group developed skin lesions. Therefore, only a fraction of the animals received topical antibiotic treatment, and it is possible, although unlikely, that this short-term antibiotic treatment during gestation indirectly affected monoamine levels in discrete brain structures and behavioral responses on PPD 6, although no gestational variables were affected. Also, pair-fed, saline-treated groups are often used in these experiments in an attempt to control for both known anorectic effects of chronic cocaine administration as well as for injection stress. Although we have found no behavioral or OT level differences between saline-treated, pair-fed, and non-pair-fed groups (Lubin et al., 2001), it is possible that separate control groups accounting for single variables might have allowed for a more discerning interpretation of specific drug-related effects.

It is unknown whether DA and/or 5-HT regulate release of OT in the amygdala as the monoaminergic control of central OT release is, in general, poorly defined. However, Honda et al. (1985) determined that OT neurons in the paraventricular nucleus of the hypothalamus (the main site of central OT projections and synthesis) receive inhibitory serotonergic and dopaminergic inputs. Yet, various serotonergic agonists stimulate peripheral OT release (Bagdy, 1996; Saydoff et al., 1991; Uvnas-Moberg et al., 1996), while D1 receptor agonists stimulate and D2 receptor agonists inhibit OT release (Crowley et al., 1991). Interestingly, chronic cocaine administration decreases 5-HT's regulation of neuroendocrine responses, including the release of OT (Levy et al., 1992), while administration of OT has also been shown to alter monoamine concentrations in various brain regions (Pfister and Muir, 1989). Therefore, it is possible that increased DA levels and the trends toward increased 5-HT levels in the amygdala are sufficient to potentiate responses to a stressor in lactating rat dams. It is also possible that chronic cocaine dysregulates monoaminergic control of OT release in the amygdala, such that even though greater amine levels are present in dams that received 30 mg/kg cocaine throughout gestation, OT levels are reduced leading to increases in aggressive behavior.

Experiments are currently being conducted in our lab to examine the role of discrete monoamines in the release of OT and their direct effects on maternal aggressive behavior. It would also prove valuable to study whether monoamine synthesis, release, turnover (or some combination) are significantly affected by chronic gestational cocaine administration. Whether increases in amygdalar DA and 5-HT levels in 30 mg/kg cocaine-treated dams are directly related to more robust responding to homecage intruders (Johns et al., 1994, 1995, 1997b) is unknown. Therefore, it will be important to assess monoamine levels in relevant brain regions in the presence of a live intruder and in the absence of a homecage stressor to allow more direct correlation between putative differences in monoamine levels and previously determined decreases in amygdala OT levels.

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