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EFFECTS OF CHRONIC COCAINE ADMINISTRATION ON AGGRESSIVE BEHAVIOR IN VIRGIN RATS

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Abstract

1. Virgin Sprague-Dawley rats received subcutaneous injections of saline, 3.5, 7.5 or 15 mg/kg of cocaine, twice daily, for 20 consecutive days.
2. Females were videotaped for 10 minutes in the presence of a male rat for assessment of aggression towards the intruder 2, 3, and 5 days following cessation of cocaine or saline administration. Oxytocin levels in discrete brain areas were assayed following behavioral testing, 5 days following cessation of cocaine or saline administration.
3. The 30 mg/kg-dose group tended to have a lower frequency of fight attacks and aggressive postures compared to saline-treated controls across sessions.
4. The frequency of most of the behaviors analyzed were represented by quadratic functions across time, such that the highest frequency of behavior occurred 2 days following the final injection with relatively less activity 3 and 5 days following cessation of saline or cocaine administration.
5. The 30 mg/kg cocaine-treated group had significantly lower hippocampal OT levels than the 15 mg/kg group 5 days following cessation of cocaine or saline administration.

Keywords

amygdala; cocaine; maternal aggression; oxytocin

Introduction

The public perception of violence associated with cocaine abuse is typified in anecdotal reports of crime related to the procurement of the abused substance. However, increases in aggressive behavior in chronic users (Miller et al 1991;Moeller et al 1994;Yudofsky et al 1993) as well as in non-users following acute administration of cocaine (Licata et al 1993) have been reported, independent of drug acquisition. Most of the literature examining cocaine-induced alterations of aggressive behavior in humans reflects only male participants. Yet recent investigations have linked gestational cocaine use with increased levels of child abuse and neglect (Tyler et al 1997;Wasserman and Leventhal 1993). Also,

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Goldstein et al (1991) found differences in the types of violent behaviors associated with cocaine use between men and women, but data collected on violence towards children was only obtained for the female sample and thus was excluded from further analysis.

In order to avoid the many confounds associated with studies of substance abuse in humans, various animal models have been employed to study the relationship between cocaine administration and aggressive behavior. In rats, chronic gestational cocaine exposure has been correlated with subsequent increased levels of maternal aggressive behavior towards a home cage intruder (Heyser et al 1992;Johns et al 1994;Johns et al 1995;Johns et al 1997;Johns et al 1998b) and decreased levels of oxytocin (a nonapeptide critical to the initiation of maternal behavior in rats) in the amygdala (Johns et al 1995;Johns et al 1997). While several experiments have demonstrated heightened levels of maternal aggression in rats given moderately high doses of cocaine (15 mg/kg or 20 mg/kg, twice daily) throughout gestation, we are unaware of any investigations examining whether cocaine similarly increases aggressive behavior toward an intruder male, in virgin females.

Mayer et al, (1987) reported that singly housed, untreated virgin female rats were much less likely to attack a home cage intruder than lactating females. Erskine et al (1978) also reported relatively low levels of aggressive behavior toward an intruder regardless of whether the virgin females were housed in isolation for as little as 4 days or as long as 20 days. In addition, Erskine et al (1978) found no differences in the frequency of attacks relative to phase of the estrous cycle, with 89% of their virgin subjects attacking a male intruder at least once during a 10 minute testing session (Erskine et al 1978).

Ovariectomized females tested for aggressive behavior twice weekly for 7 weeks; treated in the 8 week with estrogen alone (inducing proestrus); and in the 9^{th} week with estrogen and progesterone (inducing behavioral estrus) maintained virtually the same levels of aggressive behavior toward a male intruder across sessions (DeBold and Miczek 1981). In the absence of ovarian steroids, non-lactating females maintained consistent levels of aggressive behavior toward an intruder before and up to 7 weeks following ovariectomy (DeBold and Miczek 1984). However, several investigators have determined that untreated lactating females are much more aggressive towards a home cage intruder than virgin females (Erskine et al 1978;Mayer et al 1987;Mayer and Rosenblatt 1993). It has been suggested that the onset of maternal aggression is under hormonal control as ovariectomized virgin females become more aggressive toward an intruder when treated with estrogen and progesterone, in a regimen paralleling late pregnancy (Mayer et al 1990). Therefore, it seems that the heightened aggressive activity displayed by lactating dams may be at least partially driven by the unique hormonal environment surrounding parturition, while aggressive behavior in virgin females may be more independent of normally cycling ovarian steroids.

The current study was conducted to determine whether chronic cocaine administration would produce similar increases in aggressive behavior (towards an intruder male) in virgin rats as previously found in lactating rats (Heyser et al 1992;Johns et al 1994;Johns et al 1997;Johns et al 1998b;Lubin et al 1998). The dynamic of behavior across test sessions was also explored. Finally, whether cocaine-induced alterations in aggressive behavior were correlated with changes in amygdaloid OT levels in virgin females was investigated.

Methods

Animals

Female Sprague-Dawley rats (200–225g) were group housed in temperature and humidity controlled rooms for a one week habituation period prior to random assignment to one of four treatment groups (see treatment). Upon assignment to a treatment group, the virgins

were singly housed and maintained on a reversed 12hr:12hr light cycle (with lights out at 0900) for 8 days, then transferred to a room with a regular light cycle (lights on at 0700) for the remainder of the experiment - consistent with the housing conditions for pregnant animals housed in the same animal quarters. All females were allowed ad libitum access to food and water except those in the saline control group which were “yoke-fed” to females in the 30 mg/kg cocaine treatment group. Yoke-fed females were offered only the amount of food eaten by a female in the high dose cocaine group on the corresponding treatment day. This procedure was employed to control for the potential anorectic effects of cocaine treatment on weight gain.

Treatment

Virgin females were assigned to one of three cocaine hydrochloride dose groups or a yoke-fed saline control (10 females per group). Cocaine-treated females were injected subcutaneously, on alternating flanks, twice daily (bid), with either 15, 7 5, or 3.75 mg/kg of cocaine dissolved in 0.9% normal saline for a total volume of 1 ml/kg. Saline-treated females received 1 ml//kg 0.9% normal saline, bid. Injections were given at 0800 and 1600 for 20 consecutive days. Subcutaneous injections of 30 mg/kg cocaine caused some skin lesions after about 15 days of injections but did not appear to cause the rats notable distress. As skin lesions are prone to develop following repeated subcutaneous administration of cocaine solution, injection sites were varied. Also, skin lesions that developed were cleaned with a betadine wash and a topical antibacterial ointment (Polymycin-Bacitracin-Neomycin, Burroughs Wellcome, Raleigh, N.C.) was applied as soon as they were discovered.

Drug

Cocaine was dissolved in normal (0.9%) saline. The solutions were stored in amber bottles and maintained in a standard refrigerator when not in use. New solutions were prepared approximately every three days.

Aggression Testing

Two days following the final injection of saline or cocaine, each female was brought to the observation room in her home cage. Her weight was recorded and she was allowed to habituate to the room for 5 minutes. A smaller (175–200g) intruder male was then introduced into the home cage. The interaction between male and female was videotaped for a ten-minute period beginning as soon as the male was placed in the cage, and later scored by two independent observers, blind to treatment conditions, for 11 behaviors exhibited by the female, including:

Push/Box/Kick—Female pushes or kicks the intruder away from her body with her paws or whole body.

Receptive Behavior—Female displays ear wiggling, hop darting and/or lordosis.

Aggressive Posture—Female stands over the intruder, which is usually lying on it’s back, and tries to force it into a full submissive posture by pushing with front paws.

Fight Attack—A quick lunge by the female usually followed by rolling, biting and fur pulling directed towards the neck and back regions.

Selfgroom—Female grooms herself with her tongue or forepaws.

Lateral/Front Threat—Female turns her flank towards intruder with her back arched and legs extended, moving laterally and usually pushing against intruder. Front threat involves dam extending her nose and neck stiffly towards the intruder sometimes with teeth chattering. Intruder responds by freezing or escaping.

Defensive/Submissive Posture—Female lies on her side or back with her ventral surface exposed, usually immobile with legs extended.

Rough Groom/Nip—Female nips or grooms intruder male roughly.

Locomotion—Female is ambulatory and moves all four paws in one direction.

Rear/Sniff—Female rears on hind legs and sniffs the top or sides or rear of cage.

Other—Any other behavior other than those included in the categories above.

Test sessions were immediately discontinued if the female mortally wounded the intruder, and data from that session were not included in the statistical analysis. Behavior was independently scored by two individuals for frequency, duration and latency using a computer program specifically designed for that purpose. Inter-rater agreement was within 90% (or better) for frequency and latency and within 80% (or better) for duration of behavior. Following the testing procedures, the animals were returned to the colony room. Identical procedures were followed 3 days and 5 days following the cessation of cocaine or saline administration.

Brain Dissections

Immediately following the final aggression testing session (5 days following the last injection), females were decapitated and the whole hippocampus, amygdala, and ventral tegmental area (VTA), of their brains were dissected on ice, weighed, and rapidly frozen and stored at −70C for subsequent oxytocin radioimmunoassay. Briefly, brains were coronally sectioned from the ventral side rostral to the optic chiasm [approximately A7100 according to Konig and Klippel (1963)] and just caudal to the optic chiasm (approximately A5800) to define the preoptic-anterior hypothalamic area. The brains were sectioned once again just caudal to the tuber cinereum (approximately A3800) to define the medial basal hypothalamus. The amygdala was removed from these two sections. The whole hippocampus was then removed from the caudal remainder of the brain, and the ventral tegmental area dissected from this portion by making dorso-ventral cuts medial to the optic tracts with a dorsal cut at the ventral extent of the central gray.

Oxytocin (OXY) Radioimmunoassay

Brain tissue samples from the hippocampus, amygdala and VTA were homogenized in 1.5, 0.6, or 0.5 ml, respectively, of cold buffer (19mM monobasic sodium phosphate, 81mM dibasic sodium phosphate, 0.05M sodium chloride, 0.1% Bovine albumin serum, 0.1% triton X-100, and 0.01% sodium azide at a pH of 7.4). Samples were then centrifuged at 3000 x g for 30 min. The subsequent supernatants were assayed for oxytocin immunoreactive content using a protocol and reagents from Peninsula Laboratories Inc. (Belmont, California). Briefly, oxytocin-like immunoreactivity was assayed by incubating samples and standards (0.5 – 500pg) in duplicate, at 0C, for 16–24 hours with rabbit anti-oxytocin serum. The tracer, ^{125}I-Oxytocin (specific activity = 1286 Ci/mmol), was incubated with samples and standards for 16–24 hours at 0C. Then, the ^{125}I-Oxytocin bound to the antibody was separated from free by adding 0.1 ml normal rabbit serum and 0.1 ml goat anti-rabbit IgG and incubating for 2 hours, at room temperature. Then 500 ml of buffer were added and the

tubes were centrifuged at 2500 × g for 40 minutes. Radioactivity in the pellet was measured by an LKB Clinigamma counter which estimates B/B_0 from the standard curve and estimates pg amounts from that determination for each sample. Brain concentrations were expressed as pg OXY/mg tissue Cross-reactivity with arginine vasopressin and somatostatin was undetectable. The sensitivity of the assay was 0.5 pg oxytocin/tube and the intra-assay coefficient of variance of <5% and an interassay coefficient of <14% at approximately 50% binding.

Statistical Analysis

Behavioral differences were examined using a 2-way (group by test session) Analysis of Variance (ANOVA) using a general linear models approach to repeated measures analysis allowing for inclusion of individuals with missing data (e.g data from an animal 2 and 3 days following the final injection was included in the analyses whether or not the data from the 5th day following the last injection was missing). Follow-up contrasts were conducted for significance. Oxytocin levels (pg/mg wet brain tissue weight) were statistically analyzed by ANOVA followed by Tukey's HSD post hoc analysis.

Results

Food Consumption

The 30 mg/kg cocaine-treated group consumed significantly more rat chow on average than the yoke-fed saline-treated controls, $F(1, 18) = 8.16$, $p<.01$, although the yoke-fed females tended to gain slightly more weight over the 20 day interval (non-significant).

Behavior

There were very few dose-dependent differences in aggressive behavior among virgin females toward an intruder male. While there was a significant main effect of group in the frequency of fight attacks $F(3, 36)=3.89$, $p<.02$, and aggressive postures, $F(3, 36)=4.16$, $p<.01$, follow-up contrasts reveal group differences that were not statistically significant (except a single group difference in aggressive posture) (Fig. 1).

A repeated measures ANOVA indicated that there was a systematic variation in behavior within groups, and in some cases between groups, across time. That is, in each of the metrics recorded (frequency, duration, latency), 8 behaviors were represented by quadratic functions The highest frequencies of receptive behavior, rough groom/nip, selfgroom, fight attack, defensive behavior, and aggressive posture were observed 2 days after the final injection of saline or cocaine and were generally followed by a precipitous drop 3 and 5 days following the final injection. Alternatively, there was a lower frequency of rear/sniff and "other" behaviors 2 days following chronic injections with an increase in these behaviors on the 3rd and 5th day following the final injection. These asymptotic functions were typified by significant rates of change of behavior in each of the groups with few significant differences in slope among groups (Table 1).

There were also significant interactions of group and session in terms of duration and latency of the behaviors examined. The 30 mg/kg group consistently had a significantly smaller rate of change (in duration of fight attack, rear/sniff and "other" behavior, and in latency to push/box/kick, exhibit receptive behavior, and rear/sniff) across the testing period relative to the other groups (data not shown).

Oxytocin Levels

Five days following cessation of cocaine or saline administration, there were no significant differences in OT levels in the amygdalas or VTAs of the virgin females. There was a

significant group difference in OT levels in the hippocampus, $F(3,36)=4.07$, $p<.01$. The 30 mg/kg cocaine-treated dams had significantly lower hippocampal OT levels compared to the 15 mg/kg cocaine-treated group, $p<.02$.

Discussion

Relationship To Previous Investigations

Based on cocaine-induced increases in maternal aggressive behavior in lactating dams (Heyser et al 1992;Johns et al 1994;Johns et al 1997;Johns et al 1998b), and studies of aggression in virgin rats (DeBold and Miczek 1981; DeBold and Miczek 1984; Erskine et al 1978; Mayer and Rosenblatt 1993), it was hypothesized that chronic cocaine administrations would either produce dose-related increases in aggression or negligible behavioral effects in virgin females. Therefore, the dose dependent trend toward decreased frequencies of fight attack and aggressive postures in the 30 mg/kg virgin group was unanticipated. The relatively low levels of aggressive behavior in this group were not attributable to increases in stereotypical, hyperactive behaviors. Whether withdrawal from cocaine played a role in altered aggressive behavior is unknown, however no animal exhibited overt signs of withdrawal or appeared ill. Previous investigations have documented that lactating dams either withdrawn from cocaine or maintained on a twice daily regimen during the postpartum period exhibited equivalent increases in aggressive behavior (Johns et al 1997) Further experiments are required to determine the potential role of withdrawal on aggressive behavior in virgin females.

Two important observations distinguish the behavior of the virgins in this investigation from that of parturient dams in previous work. First, in chronically treated parturient dams, the 30–40 mg/kg group typically exhibited the highest levels of aggressive behavior (Heyser et al 1992;Johns et al 1994;Johns et al 1997;Johns et al 1998b). In virgin rats, the 30 mg/kg group tended to exhibit the lowest frequencies of aggressive behavior. The virgin pattern of behavior more closely parallels that of untreated, parturient dams given acute cocaine injections during the postpartum period (Johns et al 1998a). Perhaps the sharp increase in oxytocinergic activity in the peripartum period (Insel 1986) and its modification by chronic cocaine administration is necessary for the induction of increases in aggressive behavior.

Second, parturient dams given cocaine or saline throughout gestation (20 days) and tested for maternal aggression on postpartum days 2, 3 and 5, maintained relatively consistent frequencies of 11 behaviors across test sessions (Lubin et al 1998). The virgin females, on the other hand, had a much higher frequency of almost all evaluated behaviors 2 days relative to 3 and 5 day following cessation of cocaine or saline administration (although the 30 mg/kg treated group tended to have more consistent levels of aggressive behavior across sessions compared to saline-treated virgins). As increased activity on the 2nd injection free day was reflected in both cocaine and saline-treated animals, attributing this phenomenon to some type of withdrawal syndrome is premature. Further investigations including evaluations of behavior 1 day following the final cocaine or saline injection should be conducted.

Possible Mechanisms

Disparate levels of cocaine-induced aggression between virgins and lactating animals may be attributed to many factors including differential pharmacokinetic profiles of cocaine in pregnant versus non-pregnant females. While Duhart et al (1993) demonstrated that the pharmacokinetics of cocaine and benzoylecgonine (a cocaine metabolite) were very similar between chronically treated pregnant versus acutely treated non-pregnant Rhesus Monkeys, Church and Subramanian (1997) demonstrated increased benzoylecgonine levels and

increased mortality in rats during late versus mid gestation. Also, Vernotica and Morrell (1998) found that while acute injections of cocaine did not yield statistically significantly different plasma cocaine levels, the lactating females consistently had higher mean plasma cocaine levels than virgins (Vernotica and Morrell 1998). Therefore, differential levels of absorption, distribution as well as altered levels of active and inactive metabolites may have affected behavioral outcomes (Morishima and Whittington 1995). Finally, in this investigation, normally cycling virgin rats were used. We did not allow sensitization to pups, which has been shown to increase maternal aggressive behavior (Mayer and Rosenblatt 1993). Instead, the interest was in determining whether chronic cocaine-induced enhancement of aggressive behavior and correlated decreases in OT levels were unique to the lactating female or might also be manifest in virgin females

Perhaps importantly, the 30 mg/kg-treated virgin group had significantly less OT in their hippocampi, relative to the other virgin groups. Unlike the relationship of decreased OT levels in the amygdala to increases in aggressive behavior in lactating dams, the role of decreased OT levels in the hippocampus has not been established in lactating or virgin rats Further investigation is required to determine whether altered OT system dynamics facilitate alterations in aggressive behavior in cocaine-treated virgins.

Conclusion

The hormonal milieu of pregnancy and lactation seems to produce more robust increases in aggressive behavior than normally cycling ovarian steroids, and chronic cocaine administration may exaggerate that disparity. Minimal alterations in aggression were apparent in virgin rats 2 3, and 5 days following the cessation of cocaine or saline administration. Therefore, future investigations will explore potential behavioral and biochemical differences between withdrawn and non-withdrawn virgin groups (1 day following cessation of chronic cocaine administrations) and include evaluations of aggressive behavior corresponding to a time when significant increases in maternal aggression have been found in lactating animals (6 days following final injections). Also parallel investigations of the effects of chronic cocaine administration on aggressive behavior in castrated versus intact male rats would be an important addition to the literature.

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Abbreviations

AMY	amygdala
PPD	postpartum day
OT	oxytocin
VTA	ventral tegmental area

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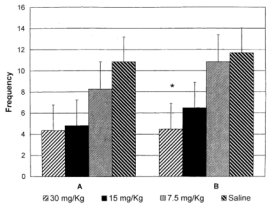

Fig 1.

Frequency of Fight Attack and Aggressive Posture. A. The saline-treated group had non-significantly higher rates of fighting compared to each of the cocaine-treated groups. B. Saline-treated controls pinned intruders using an aggressive posture more often than the 30 mg/kg cocaine-treated group (*p<.04).

Table 1

Effects of Chronic Cocaine or Saline Administration on the Rate of Change of the Frequency of Several Behaviors Across Time

	30 mg/kg	15 mg/kg	7.5 mg/kg	Saline	Session F statistic	Group × Session F statistic
	Slope Estimates ± SE					
Receptive Behavior	−27.6±6.3	−29.3±6.3	−35.3±6.3	−28.6±6.3	*24.3	a4.6
Rough Groom/Nip	−11.6±5.8	−12.2±5.8	−15.3±5.8	−14.6±5.8	+5.6	1.5
Selfgroom	−16.1±6.1	−19.0±6.1	−20.8±6.2	−19.5±6.1	*9.9	1.6
Fight Attack	−21.4±5.6	−22.8+5.6	−25.2±5.6	−26.0±5.6	*19.1	2.4
Defensive Behavior	−31.3±5.9	−33.5±5.9	−37.2±6.0	−35.6±6.0	*35.0	b2.9
Aggressive Posture	−24.2±6.3	−26.7±6.3	−29.5±6.3	−29.0±6.3	*19.7	2.4
Rear/Sniff	27.6±6.3	33.6±6.3	33.3±6.4	35.4±6.4	*27.5	c4.7
Other	74.8±9.7	79.7±9.7	80.6±9.8	79.4±9.8	*68.0	1.1

*Each group had a significant rate of change across sessions, p<.01

+Each group had a significant rate of change across sessions: 30 mg/kg, p<.05; 15 mg/kg, p< 04; 7.5 mg/kg and saline, p<.01.

*a*The rate of change of the 7.5 mg/kg group was greater than all other groups, p<.01.

*b*The rate of change of the 30 mg/kg group was significantly less than that of the 7.5 mg/kg group, p<.01, and the saline-treated group, p<.04.

*c*The rate of change of the 30 mg/kg group was significantly less than that of all other groups p<.01.

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