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Effects of prenatal cocaine exposure on latent inhibition in 1-year-old female rats

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Abstract

Prenatal cocaine exposure has been shown to produce attentional changes in human infants and children, as well as in preweanling and young adult animals. The aim of the current study was to determine whether attentional effects of in utero cocaine exposure persist into middle adulthood. Sprague–Dawley dams received twice-daily subcutaneous (sc) administration of either 20 mg/kg cocaine HCl or 0.9% saline vehicle from Gestational Day 8 to 20. Saline-injected dams were pair-fed to cocaine-injected subjects during prenatal treatment. A second control group received no treatment and had ad lib access to food. One-year-old female offspring were tested for latent inhibition (LI) of a context conditioning task, using freezing and vertical nose crossing (VNC) as behavioral measures of fear. Although freezing did not reveal any differences between prenatal treatment groups, a cocaine-dependent reduction in baseline VNC indicated that cocaine-exposed adult offspring were less explorative than controls. In addition, cocaine-exposed animals showed enhanced LI as measured by greater levels of VNC than controls in the context preexposed condition of the task. These results provide insight into the nature of attentional contributions to prenatal cocaine effects on learning and indicate that such effects persist well into adulthood.

Keywords: Attention; Context conditioning; Freezing; Learning; Long-term effects

1. Introduction

Numerous clinical studies have shown that prenatal cocaine exposure leads to changes in infant arousal (Alessandri et al., 1993; Coles et al., 1999; Karmel and Gardner, 1996; Mayes et al., 1995; Singer et al., 2000) that might be indicative of later learning and attention deficits. In fact, longitudinal studies have reported an increased incidence of impulsivity (Mayes et al., 1998) and inattention (Leech et al., 1999) in cocaine-exposed 4–6-year-olds. It is not yet known, however, whether these abnormalities persist into adulthood.

Animal studies can be useful for examining behavioral outcomes of prenatal drug exposure because they provide greater control over treatment parameters (e.g., polydrug use and anorectic effects of cocaine), as well as over prenatal and postnatal environments. For rodents in particular, the relatively short life span permits investigation of possible long-term effects that persist into middle and late adulthood. A number of research groups have previously shown cocaine-dependent changes in arousal and attention in preweanling, adolescent and young adult animals (Garavan et al., 2000; Mactutus, 1999; Overstreet et al., 2000; Romano and Harvey, 1996; Vorhees et al., 2000). The aim of the present study was to determine whether prenatal cocaine exposure alters latent inhibition (LI) performance of rats in middle adulthood.

LI is a Pavlovian learning task and an animal model of attention in which preexposure to a stimulus results in an attenuation of subsequent conditioning to that stimulus (Lubow and Josman, 1993). Processing of the conditioned stimulus (CS) is thought to be inhibited by nonreinforced stimulus preexposure, thereby impairing CS/unconditioned stimulus (US) associations (Hall and Pearce, 1979; Lubow, 1973, 1997). In animals preexposed to either a CS tone or context prior to fear conditioning, c-*fos* expression was reduced in both learning-related areas (i.e., hippocampus and amygdala) and sensory processing areas of the brain (Radulovic et al., 1998; Sotty et al.,

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1996). These results are consistent with an attentional explanation of LI and may provide insight into the neural mechanisms that underlie possible prenatal cocaine-dependent alterations in LI. In the current study, 1-year-old female offspring of cocaine-treated dams were tested in a LI contextual fear conditioning paradigm to determine if attentional changes associated with prenatal cocaine exposure endure into middle adulthood.

2. Methods

2.1. Subjects, breeding and prenatal treatment

Nulliparous Sprague–Dawley rats were bred in our laboratory. Prior to breeding, females were handled for at least 5 days and group-housed in a temperature-controlled colony room on a 14:10-h light–dark cycle (lights on at 07:00 h), with ad lib access to Lab Diet 5001 rodent chow and water. Each dam was placed in a double-sized, hanging metal cage with an adult male stud. Detection of a copulatory plug defined Gestational Day 1. Gravid dams were housed separately in hanging cages and switched to powdered chow to facilitate subsequent pair-feeding.

Dams were randomly assigned to one of three treatment groups: cocaine-injected (COC), vehicle-injected and pair-fed to COC (SAL) and untreated (UT). COC animals received twice-daily (morning and afternoon) subcutaneous (sc) injections of 20 mg/kg cocaine HCl at a concentration of 1.5 mg/ml from Gestational Day 8 to 20. Under this dilute dosing regimen, we and others see virtually none of the skin necrosis that is otherwise observed with more concentrated subcutaneous cocaine injections (Durazzo et al., 1994). The first dose was administered between 10:00 and 12:00 h, and the second was given 5 h later, a time point at which we have previously shown a large decline in plasma cocaine levels following the initial treatment (Collins et al., 1999). SAL dams were injected subcutaneously with vehicle (0.9% saline) twice daily at the same interval. UT animals received daily handling and weighing but no injections. COC and UT animals continued to have ad lib access to food and water throughout gestation. Pair-feeding of the SAL group controlled for the anorectic effect of cocaine by limiting daily food availability to the quantity ingested by COC animals for the 13 days of drug administration. To minimize the stress of food deprivation, pair-fed SAL animals were matched by weight to the COC animals, and they received the majority of their food rations following the afternoon injection, which is closer to their natural feeding time. Litters were culled to eight pups each (four males and four females) on Postnatal Day (PD) 1, after which all the pups were fostered to untreated dams that had given birth within the previous 72 h. Animals were weaned at PD 25 and housed socially with same-gender littermates.

Two male and two female rats from each litter were tested between PD 96 and PD 136 on a multiple-trial context conditioning task. Those results are reported elsewhere (Brunzell et al., in press). The remaining animals were maintained in pairs with same-gender littermates for use at approximately 1 year of age in the present study. Unfortunately, there was a significant mortality among the males prior to the beginning of the study, probably as a consequence of the obesity that occurs in older Sprague–Dawley male rats under free-feeding conditions (Hubert et al., 2000; Keenan et al., 1996). Because the experimental design necessitated having both littermates of a given gender, the loss of males precluded their use in the present study.

The subjects were experimentally naive female littermate pairs that were between PD 345 and PD 360 at the beginning of the study. Animals from nine COC litters, six SAL litters and eight UT litters were available for testing. Two weeks prior to the beginning of the experiment, rats were transferred from the initial colony room to an animal room in a different building where testing would take place. Littermates were housed in pairs in hanging wire cages, maintained on a 16:8 light/dark cycle (lights on at 06:00 h) and given ad lib access to Lab Diet 5001 rodent chow and water. All subjects were handled for approximately 1 min/day for 5 days prior to the experiment. All animal procedures were carried out in accordance with the PHS Guide for the Care and Use of Laboratory Animals and were approved by the University of Massachusetts Institutional Animal Care and Use Committee.

2.2. Apparatus

Two modified Plexiglas Skinner boxes ($21.5 \times 20.5 \times 19.2$ cm internal dimensions) served as the preexposure, context conditioning and test chambers. A stainless-steel insert prevented access to the lever and hopper in each box. A high-voltage, high-resistance shock source provided a 1-mA, 2-s footshock that was scrambled through a Hoffman & Fleshler relay scrambler and delivered through a stainless steel floor grid. Each Skinner box was placed within a $55.5 \times 59.0 \times 54.5$-cm sound-attenuating plywood chamber lined with acoustic tiles. The front wall of this chamber remained open during conditioning for videotaping purposes.

Toshiba and RCA video cameras were used to record behavior during conditioning and testing. A Grason-Stadler Model 901B noise generator piped 82 dB of white masking noise through a speaker mounted in the lid of each box. The overhead lights of the experimental room were turned off, and each chamber was lit by a 40-W, 120-V, white lightbulb positioned approximately 21 cm from the lid of the Skinner box. For the purpose of measuring vertical nose crossing (VNC) during conditioning and testing (see below), a strip of electrician's tape was placed on the outside of each chamber at a position 14 cm above and parallel to the floor grid. A small red lightbulb was placed out of view of the rat but within the field of view of the video camera. This light, which pulsed on at 2-s intervals, was used to score the presence or absence of freezing at each interval.

In another room, the overhead fluorescent lights were left on and two rectangular 16-l plastic buckets (20.5 × 20.5 × 36.0 cm internal dimensions) served as holding cages for nonpreexposed animals. Buckets were lined with Carefresh bedding (Absorption).

2.3. Procedure

The two littermates were randomly assigned to either the preexposure (PE) or nonpreexposure (NPE) condition, so that there were a total of six groups: COC-PE, $n = 9$; COC-NPE, $n = 9$; SAL-PE, $n = 6$; SAL-NPE, $n = 6$; UT-PE, $n = 8$; and UT-NPE, $n = 8$. For each of 3 days prior to conditioning, pairs of PE animals were transported via a cart to the experimental room. PE subjects received 12 min of preexposure to the conditioning/test chamber. Each chamber was wiped with a 5% vinegar solution and the cardboard in each dropping tray was replaced between subjects. NPE subjects, also run in pairs, were carried by the experimenter to a separate room where they spent three daily 12-min sessions in the plastic bucket holding cages. The bedding lining the bottom of each NPE chamber was replaced between subjects. The two PE and NPE chambers were counterbalanced across prenatal treatment groups, but individual animals were consistently placed in the same chamber during each of the 3 days prior to conditioning, and then again during conditioning and testing.

All animals (PE and NPE) received conditioning to the context on Day 4. Except for the fact that PE animals were run with another PE subject during preexposure and with their NPE littermate during conditioning and testing, the experimental cues and context were kept constant throughout all experimental procedures. Following a 555-s baseline observation period, animals received three 1-mA, 1-s footshocks with a 72-s intershock interval. Subjects remained in the conditioning chamber for 212 s following the last shock, after which they were returned to their home cages. On Day 5, all animals were placed back in the box for a period of 5 min to determine retention of conditioned fear. No shock was administered on this day.

It has long been known that animals in fear paradigms show increases in various defensive behaviors such as freezing or fleeing, and suppression of nondefensive behaviors such as rearing and exploration (Blanchard and Blanchard, 1969a). To optimize detection of possible prenatal treatment effects, videotapes were scored for two measures of fear: defensive freezing and VNC. Freezing was defined as absence of movement except for that associated with respiration. VNC was scored to assess suppression of activity. Rearing is typically regarded as an exploratory posture that is inconsistent with fearful behaviors. However, animals are known to sometimes take their forepaws off the grid in a freezing posture following footshock. To differentiate this defensive crouched type of rearing from the more elongated rearing associated with exploration, we established a criterion of vertical extension that we termed VNC. VNC was operationally defined as nose crossing above a strip of electrician's tape placed horizontally 14 cm above the floor of the chamber. This criterion required animals to stand in an upright position with their bodies extended. A primary observer scored 100% of the subjects for freezing and VNC behaviors. For the purpose of assessing interobserver reliability, three secondary observers each scored freezing behavior in one-third of the subjects, and two secondary observers each scored VNC activity in one-half of the subjects.

2.4. Data analysis

Behavioral data were analyzed using analysis of variance (ANOVA) with prenatal treatment (COC, SAL and UT) as a between-litters factor and experimental condition (PE vs. NPE) as a within-litters factor. Baseline freezing and VNC activity of all animals were measured during the preshock period. Activity during the interval following each shock served as an acquisition measure and was treated as a repeated measure of contextual fear. According to the principles of LI, it was predicted that PE subjects would show lower freezing levels and higher VNC scores than NPE littermates. Overall conditioning should accumulate with repeated US-shock presentations, i.e., freezing levels should increase and VNC levels should decrease over shocks. Therefore, planned contrasts compared conditioning trends between PE and NPE subjects across postshock intervals. Interobserver reliability was assessed using Pearson product–moment correlation.

3. Results

3.1. Maternal and litter data

Maternal and litter data are presented elsewhere (Brunzell et al., in press). Briefly, there was a significant treatment effect on maternal weight gain and food intake, with UT subjects showing greater food intake than both COC and SAL pair-fed animals but only averaging significantly more weight gain than the SAL controls ($P < .05$). There was no effect of prenatal treatment on litter size and composition, or on the weight of the pups (F's < 1.0). Regardless of prenatal treatment, male offspring weighed more than their female littermates ($P < .001$). There was no interaction of treatment with gender on any of the litter measures. We did not record body weights of the animals at the time of testing in the present study. However, earlier measurements at PD 25 and PD 90 found no effects of prenatal treatment on offspring weight at those ages.

3.2. Freezing data

Both PE and NPE subjects showed virtually no preshock freezing (PE = 0.022 ± 0.007, NPE = 0.018 ± 0.007; mean ±

S.E.M.) [$F(2,20) = 1.56$, $P > .05$]. The postshock freezing results, however, demonstrated the presence of a LI effect. As expected, PE subjects showed a lower percentage of freezing than NPE subjects following each of the three shocks (Fig. 1A). There were main effects of condition [$F(1,20) = 18.58$, $P < .001$] and shock number [$F(2,40) = 134.59$, $P < .001$] on acquisition freezing behavior, but no interaction between these variables ($F < 1.0$). A post hoc contrast of the shock main effect revealed a positive linear trend for freezing over shocks [$F(1,20) = 193.28$, $P < .001$]. This change was similar for both PE and NPE animals as reflected by the absence of a significant interaction between condition and linear trend ($F < 1.0$). LI was still apparent 24 h later as measured by an attenuation of PE subject freezing during the no-shock test period [$F(1,20) = 6.51$, $P = .019$] (Fig. 1B).

Freezing behavior failed to show a LI difference between cocaine-exposed and control subjects (Fig. 2). There were no effects of prenatal drug treatment on baseline freezing [$F(2,20) = 1.56$, $P > .05$], overall postshock freezing ($F < 1.0$), intershock freezing ($F < 1.0$) or freezing during testing [$F(2,20) = 1.04$, $P > .05$]. Interobserver reliability for the freezing measure was $r \geq .93$ for all scorers.

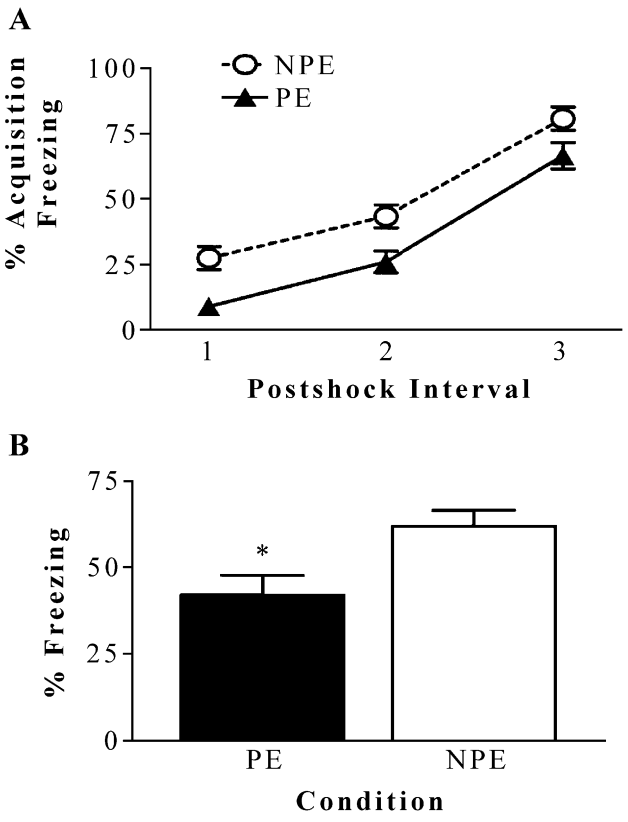

Fig. 1. LI of acquisition and retention of fear as measured by freezing. LI was evident in context preexposed (PE) animals whose freezing scores were lower than nonpreexposed (NPE) animals during (A) acquisition of contextual fear conditioning ($P < .001$) and (B) the no-shock 24-h retention test ($P < .05$). Data are shown as the percentage of time spent freezing (mean ± S.E.M.) and are collapsed across prenatal treatment groups.

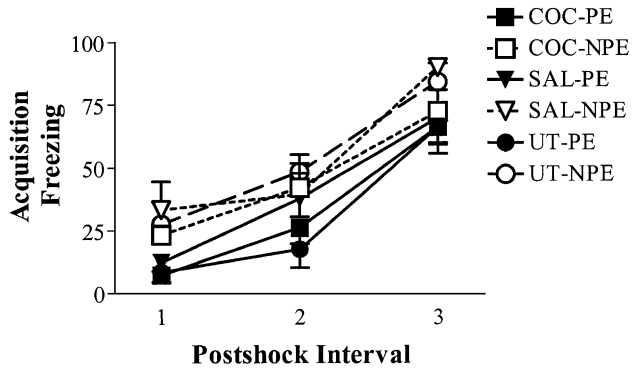

Fig. 2. Acquisition freezing across prenatal treatment groups and experimental conditions. Data are shown as percent freezing (mean ± S.E.M.) for cocaine-exposed (COC), saline-exposed/pair-fed (SAL) and untreated (UT) adult offspring in the context preexposed (PE) and nonpreexposed (NPE) conditions.

3.3. VNC data

Unlike freezing, the VNC measure detected a preexposure difference in baseline activity as indicated by a main effect of experimental condition [$F(1,20) = 6.86$, $P = .016$]. NPE subjects showed slightly more exploration of the chamber, displaying higher preshock VNC scores (23.32 ± 1.15) than littermates who received preexposure to the context (20.24 ± 1.29). There was also a prenatal treatment main effect for baseline VNC [$F(2,20) = 3.60$, $P = .046$], but no Treatment × Condition interaction ($F < 1.0$). Post hoc contrasts of the treatment main effect revealed that COC offspring had lower overall VNC scores than SAL or UT control subjects [$F(1,20) = 7.06$, $P = .015$], which did not differ from each other ($F < 1.0$) (Fig. 3).

VNC was also a reliable indicator of LI. There was a significantly higher level of VNC per minute for PE subjects

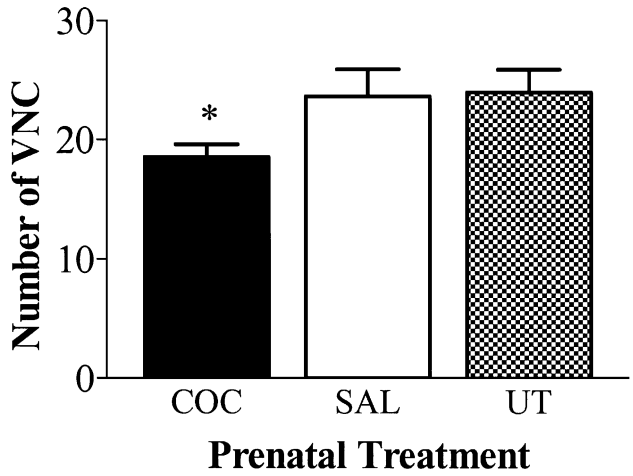

Fig. 3. Baseline exploratory behavior as measured by the amount of VNC. Animals prenatally exposed to cocaine (COC) exhibited less exploratory behavior than offspring of saline-injected/pair-fed (SAL), and untreated (UT) dams ($P < .05$). Data are presented as mean ± S.E.M.

(2.47 ± 0.23) than for NPE subjects (1.05 ± 0.15) collapsed across all postshock intervals [$F(2,40) = 37.33$, $P < .001$]. There was also a main effect of shock interval [$F(2,40) = 9.21$, $P = .001$] and a Condition × Shock interaction [$F(2,40) = 6.62$, $P = .004$]. Post hoc analyses indicated that overall VNC activity declined over shocks [$F(1,20) = 12.51$, $P = .002$]. However, linear contrast analysis demonstrated that this pattern was mainly due to changes in PE subject behavior [$F(1,20) = 15.42$, $P = .001$]. NPE animals responded strongly to the first shock, showing a low level of VNC activity that remained relatively constant across subsequent shocks (Fig. 4). PE subjects, however, required multiple shocks to show a decline in VNC that matched NPE levels. Following the third shock, there was no longer an apparent difference between PE and NPE littermate VNC behavior.

Despite lower baseline VNC activity, COC subjects within the PE condition showed greater initial postshock VNC activity than control animals. ANOVA of VNC during acquisition showed no treatment main effect ($F < 1.0$), however, there was a three-way Treatment × Condition × Shock Number interaction [$F(4,40) = 2.94$, $P = .036$]. This was further demonstrated by a linear trend analysis that yielded a significant interaction of prenatal treatment with adult experimental condition for VNC scores [$F(2,20) = 5.23$, $P = .015$]. Post hoc contrasts showed that these interactions reflected an exaggeration of the condition effect for COC-PE subjects. Within the PE condition, but not the NPE condition, COC subjects showed higher levels of VNC during the first postshock interval than the control groups [$F(2,20) = 3.59$, $P = .05$], which did not differ from each other. There were no treatment effects at any other postshock interval. Within the NPE conditions, all animals showed low levels of VNC across each shock interval that did not differ according to prenatal treatment (overall NPE VNC scores: COC = 0.958 ± 0.235, SAL = 1.185 ± 0.269, UT = 1.042 ± 0.297; mean ± S.E.M.). The enhanced LI effect for the COC group is clearly illustrated by difference scores between PE and NPE subjects within each treatment group (Fig. 5).

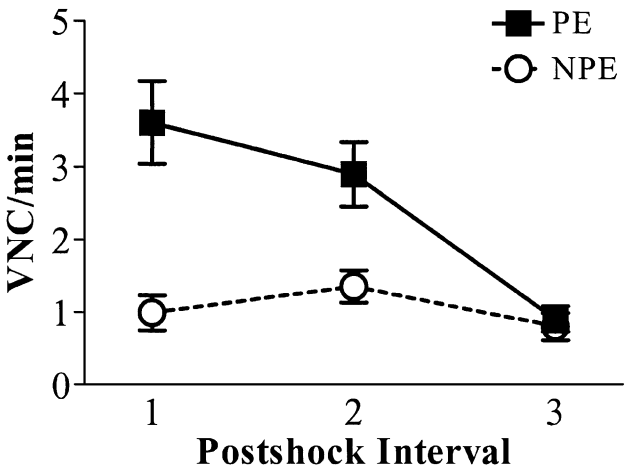

Fig. 4. LI of fear acquisition as measured by VNC. LI was evidenced by initially higher VNC scores of preexposed (PE) than nonpreexposed (NPE) animals during contextual fear conditioning ($P = .001$). Data are collapsed across prenatal treatment groups and presented as mean ± S.E.M.

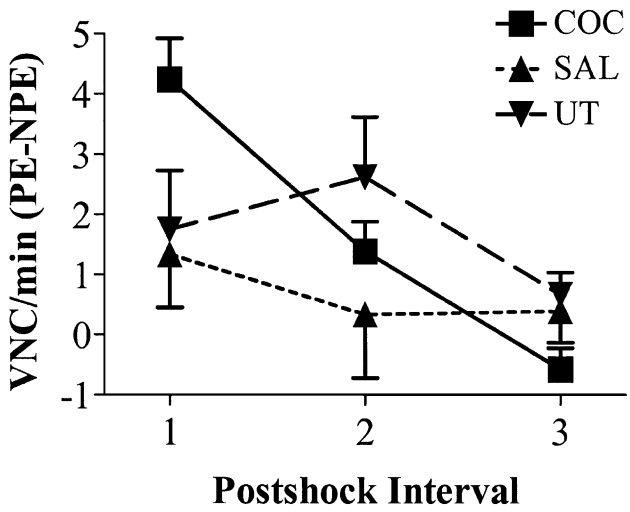

Fig. 5. Effects of prenatal treatment on LI during acquisition of conditioned fear. VNC data are presented as mean difference scores ± S.E.M. between preexposed (PE) and nonpreexposed (NPE) subjects within each prenatal treatment group. Prenatal cocaine-exposed (COC) subjects showed exaggerated LI as indicated by initially higher VNC difference scores compared to offspring of saline-injected/pair-fed (SAL) and untreated (UT) dams ($P = .001$).

Unlike freezing, VNC activity did not show a LI effect on the no-shock test day. Both PE (1.44 ± 0.26) and NPE (0.887 ± 0.17) littermates showed low levels of VNC per minute on this day [$F(1,20) = 2.41$, $P > .05$]. There was also no treatment main effect [$F(2,20) = 1.073$, $P > .05$] and no Condition × Treatment interaction ($F < 1.0$) on Day 5 VNC scores. Interobserver reliability for VNC was $r \geq .94$ for all scorers.

4. Discussion

The current study provides evidence for altered attentional processing in 1-year-old female rats exposed to cocaine prenatally. As predicted, animals in the present experiment showed increases in freezing and decreases in VNC following pairing of footshock with the context CS. Preexposure to the context, however, resulted in a LI of contextual fear conditioning as measured by overall lower levels of freezing and higher levels of VNC in PE versus NPE subjects. Compared to SAL-PE and UT-PE controls, COC-PE subjects exhibited exaggerated LI as indicated by significantly higher VNC scores during the first postshock interval. Seemingly contrary to the VNC results, there was no effect of prenatal treatment on LI as measured by freezing. As mentioned earlier, a variety of responses may occur under fear-provoking conditions. The expression of these behaviors is highly dependent upon experimental parameters such as shock intensity, number of trials, experi-

mental apparatus and the discrete or diffuse nature of the CS. It is therefore not uncommon for one but not another behavioral measure to reveal differences between treatment groups (Blanchard and Blanchard, 1969a,b; Blanchard et al., 2000; Kim et al., 1996; Bevins et al., 1997; Brunzell et al., in press). In the current experiment, the VNC measure was more sensitive to the detection of prenatal treatment differences.

The increased postshock VNC behavior of COC-PE subjects is particularly convincing as an exaggerated LI effect given that baseline VNC during the preshock period revealed COC subjects to be generally less active and exploratory than controls. Consequently, the prenatal treatment effect observed during conditioning cannot be attributed to differences in overall activity. Because animals showed virtually no preshock freezing, this behavior was not a reliable measure of baseline activity. A greater number of shock presentations might have revealed a treatment effect on postshock freezing, but an enhancement of freezing would have been confounded by the lower overall baseline activity of cocaine-exposed subjects.

An alternative explanation for the higher levels of VNC during the first postshock interval in the COC group is that these animals exhibited greater risk assessment (of the context) or more escape attempts than the control groups. In environments that enable escape, flight is typically the immediate response of rodents to a discrete fearful stimulus such as a cat or shock-delivering prod. Interestingly, this is often followed by cautious approach and orienting towards the stimulus, i.e., risk assessment (Blanchard and Blanchard, 1969b; Blanchard et al., 2000). Risk assessment is uncommon in response to a diffuse stimulus such as a context, however, and COC-NPE animals did not show footshock-dependent increases in VNC as one would expect if the prenatal cocaine exposure were altering this type of behavior.

Another possibility is that changes in VNC reflect an exaggerated stress response by the COC group. Prenatal cocaine exposure influences pituitary–adrenocortical activity in both adult rats (Cabrera et al., 1994) and human infants (Scafidi et al., 1996), and it also alters behavioral stress responses in rats (Molina et al., 1994). It could be argued that the reduced baseline VNC scores in the COC group result from heightened stress reactivity. However, this explanation does not account for the increased postshock VNC behavior specifically found in the preexposed COC animals. Furthermore, if the prenatal cocaine effects were mediated by increased stress, one might expect to find a concomitant enhancement of contextual fear conditioning. Yet, this did not occur either in the present study (no difference between NPE-COC and either NPE-SAL or NPE-UT animals) or in our previous research (Brunzell et al., in press).

Although rearing is typically considered an exploratory posture, it is uncertain whether the lower baseline VNC scores of the COC group in the current experiment indicate differences in exploration, motor activity or both. Other studies using a similar dosing regimen, period of gestational exposure and method of administration have reported decreased exploration and hypoactivity in cocaine-exposed offspring (Johns et al., 1992a,b; Riley and Foss, 1991). Such findings are consistent with clinical reports that children prenatally exposed to cocaine are also less likely to spend time in exploration (Mayes et al., 1998). The present study suggests that this behavioral change may persist well into adulthood.

Animal studies have generally shown that cocaine-exposed offspring learn simple associative tasks without difficulty but have problems performing increasingly complex tasks such as discrimination reversal and higher-order conditioning (Garavan et al., 2000; Heyser et al., 1990, 1992). The present results and other recent studies suggest that such impairments might be partly due to altered attentional processing (Garavan et al., 2000; Romano and Harvey, 1996). In a discrimination paradigm utilizing various CS cues, prenatal cocaine-exposed rabbits showed an impaired ability to ignore irrelevant, but salient stimuli, as well as greater difficulty in learning to respond to less salient but relevant cues (Romano and Harvey, 1996). A similar finding was reported in rats. Although cocaine-exposed offspring displayed no difficulty in a two-choice serial discrimination task with alternating olfactory cues, extradimensional shifts from olfactory to spatial cues (but not spatial to olfactory) showed these animals to be distracted by the more salient olfactory cues in later blocks of trials (Garavan et al., 2000). The sustained attention of these animals was impaired in the more challenging task. The LI task in the present study measured animals' responsiveness to a change in the predictive quality of a context cue. Prenatal cocaine-exposed subjects were particularly delayed in their recognition of this switch, i.e. they did not appear to attend as well to the new relevance of the CS. This augmentation of LI suggests decreased flexibility in attentional shift that may have contributed to previously reported impairments in discrimination reversal and sensory preconditioning following gestational exposure to cocaine (Garavan et al., 2000; Heyser et al., 1990, 1992). Animals exposed to cocaine in utero appear to have a greater propensity for perseveration.

Further research is necessary to explore the neural mechanisms underlying behavioral changes resulting from prenatal cocaine exposure. The LI paradigm is a well-studied model of attention that should prove useful in this endeavor. Growing evidence suggests that alterations in monoamine systems might contribute to the prenatal cocaine-dependent enhancement of LI and other changes in attentional function. Several studies have shown that systemic administration of amphetamine blocked the LI effect in both rats (Gray et al., 1997; Killcross et al., 1994; Young et al., 1993) and humans (Thornton et al., 1996), and that the amphetamine reversal was abolished by local infusion of the D_2 receptor antagonist haloperidol into the nucleus accumbens (Gray et al., 1997). Further work by Joseph et al. (2000) found a potentiation of LI following

either microinjection of haloperidol into the accumbens or 6-hydroxydopamine lesions of accumbens DA terminals. It is possible that gestational exposure to cocaine might cause permanent alterations in dopaminergic development that are behaviorally manifested as disruptions in arousal and attention (for review, see Mayes, 1999). Supporting this hypothesis, systemic administration of the D_1 agonist SKF 81297 led to a specific impairment of sustained attention in cocaine offspring but not in controls (Bayer et al., 2000). Although less attention has been given to the role of serotonin (5-HT) in LI, administration of a selective 5-$HT1_A$ receptor antagonist resulted in an exaggeration of LI like that observed for COC subjects in the current study (Killcross et al., 1997). The demonstrated involvement of monoamines in LI and sustained attention warrants further investigation of these systems as potential factors mediating some of the behavioral changes observed in cocaine-exposed offspring.

The results of the current study support a case for lasting teratogenic effects of prenatal cocaine exposure on the developing brain. One-year-old female cocaine-exposed offspring showed a decrease in baseline exploratory activity and enhanced LI compared to controls. These results are consistent with reports of inattention and blunted exploration in prenatal cocaine-exposed children, and they add insights into the nature of possible attentional contributions of cocaine's effects on learned behaviors. Although the neural mechanisms underlying such changes need further study, it is evident that gestational exposure to cocaine has behavioral consequences in rats that persist well into adulthood.

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