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Early developmental lead exposure increases sensitivity to cocaine in a self-administration paradigm

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Abstract

The purpose of this investigation was to determine if lead exposure during pregnancy and nursing alters cocaine sensitivity later in the adult cycle, although lead exposure had been discontinued following early development. Female rats were exposed via gavage to 0 or 16 mg/kg lead daily for 30 days prior to breeding with nonexposed males. The respective daily exposure regimens continued throughout gestation and lactation (perinatal lead exposure). Lead exposure was discontinued on the day of weaning (postnatal day [PND] 21). Beginning on PND 70, male offspring were trained to self-administer cocaine HCl intravenously. Examination of a range of cocaine doses (0.030, 0.060, 0.125, 0.250, and 0.500 mg/kg/infusion) revealed that, as adults, animals exposed to lead during early development self-administered cocaine at significantly greater rates at a low dose of the drug. In addition, self-administration rates were lower among lead-exposed animals at higher doses of cocaine. These findings were observed in metal-exposed animals where blood and brain tissue levels had returned to the levels of controls. Collectively, these data suggest that early developmental lead exposure may increase sensitivity to cocaine later in the life cycle.

Keywords: Addiction; Cocaine; Developmental; Lead; Self-administration

1. Introduction

Although the interactive effects associated with multiple drug applications have long been a focus of pharmacologic research, the potential synergism/antagonism among xenobiotic contaminants and drugs possessing abuse liability only recently has attracted the attention of the scientific community. Moreover, minimal information is available regarding environmental dispositional factors that may promote the transition from casual drug use to an addictive profile.

Environmental lead exposure remains the number one pollution problem in North America, and health risks are especially of concern for inner-city populations (Pirkle et al., 1998). The urban subpopulation also is presented with increased challenges associated with drug use/abuse, where cocaine ranks among the greater threats to a drug-free status (Ensminger et al., 1997). Preliminary investigations have shown that adult lead exposure decreases behavioral sensitivity to cocaine (Burkey et al., 1997; Nation et al., 1996). Developmental lead exposure increases the stimulatory properties of repeated cocaine administration (Nation et al., 2000), but attenuates the impact of cocaine on a variety of behavioral endpoints when the drug is presented acutely (Miller et al., 2000, 2001). What remains undetermined is the effect of chronic low-level lead exposure on cocaine self-administration. That is, it is unknown whether lead toxicity increases or decreases sensitivity to cocaine and therein via some biologic imperative alters patterns of drug use/abuse.

The possibility that lead body burdens may contribute to the selection for and actual use of psychoactive drugs is a particularly noteworthy public health concern when the toxicant is distributed to the developing organism. It is established that the nervous system during early development is more vulnerable to toxic lead exposure than the morphologically intact adult nervous system (cf. Moreira et al., 2001). Given that the aforementioned health threats associated with lead contamination in the inner-city regions

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of large population sectors are amplified among the very young (Mielke, 1999), it would be especially worthwhile to investigate potential biobehavioral interactions between developmental lead exposure and the intake of a commonly abused stimulant such as cocaine. Should linkages between chemical pollution and cocaine sensitivity endure, a better understanding of the motivation for drug use in high-risk adolescent and adult populations may be realized. To determine the relation between developmental lead exposure and the reinforcing effects of cocaine later in the life cycle, we employed an animal model that tested adult male rats for cocaine self-administration long after the metal-exposure regimen had been discontinued.

2. Methods

2.1. Animals

All aspects of the research reported here were approved by the Texas A&M University Laboratory Animal Care Committee. For the initial phase of the investigation, for 30 days adult female Sprague–Dawley rats (Harlan, Houston, TX) were exposed to 0 (sodium acetate) or 16 mg lead (as lead acetate) daily using a 16-gauge gavage needle to administer the respective solutions in a volume of 1.0 ml deionized water. Following this 30-day toxicant exposure period, females were bred with nonexposed males. Males were removed from the home cage once females tested positive for copulatory plugs. Females continued to receive their daily doses of the control solution or lead acetate throughout the gestational and lactation periods. The resulting procedure permitted perinatal lead exposure within an experimental framework where pups were unable to gain access to lead postnatally via routes other than the maternal milk supply. Standard rat chow and tap water were available ad libitum in the home cage.

Litters were culled to eight pups on postnatal day (PND) 1, and only one pup from each litter was used in the experiment to avoid confounds that are sometimes evident in studies involving toxic exposure (Holson and Pearce, 1992). That is, because alteration in maternal care resulting from lead-based changes in dam/pup interactions or idiosyncratic early experiences, such as differential anal licking of control/lead neonates (Cuomo et al., 1996), may later have an impact on behavioral endpoints, such as drug self-administration, this manipulation is essential.

For the dams, 100–150 μl of tail blood was drawn at breeding, 10 days of gestation, parturition (PND 1), and weaning (PND 21). Littermates were sacrificed on PND 1 and 21, and blood samples were collected for subsequent analysis. On PND 21, pups used for testing were weaned, and for the remainder of the study, the pups were placed on ad libitum standard rat chow diets and with continuous access to a tap water supply that contained no added lead. All animals were maintained on a 12-h light/dark cycle and individually housed from PND 21 until the study was completed.

2.2. Procedure

Animals born to dams exposed to 0 or 16 mg lead daily prior to breeding, and throughout gestation and lactation, were tested in a cocaine self-administration preparation beginning on PND 70. As indicated, no test animals were exposed to lead after weaning. The range of cocaine doses (0.030–0.500 mg/kg/intravenous infusion) was sufficient to characterize the complete dose–effect curve for both control and lead-exposed animals, i.e., animals responded at low rates at low doses, responded more frequently as the cocaine dose was increased, and decreased responding at the highest doses of the drug.

On PND 70, under aseptic conditions, chronic indwelling jugular catheters were implanted in 12 control and 12 lead-exposed male offspring. Rats were anesthetized with separate injections of 50 mg/kg ketamine and 50 mg/kg sodium pentobarbital. A catheter consisting of 0.25-mm ID Silastic tubing (Dow Corning, Midland, MI) was inserted into the right jugular vein and sutured to muscle tissue in the area of the vein. Using an 11-gauge stainless steel tube as a guide, the catheter was passed subcutaneously through the body of the animal and exited the back between the scapulae. A backplate consisting of two stainless steel ovals separated by polypropylene mesh (Ethicon, Somerville, NJ) was sutured to muscle tissue below the skin. The backplate accommodated a spring leash, through which the catheter was threaded. Connecting to the backplate at one end, the other end of the leash was connected to a single fluid channel swivel. The swivel design permitted an interlock with separate connecting arms located in the home cage and operant test chambers (see below). The movable arm allowed for free movement and delivery of appropriate solutions in either the home cage or test chamber. A 0.51-mm ID catheter continued from the top of the swivel to an infusion pump that controlled solution delivery. The rats were allowed 7 days to recover from surgery before commencing cocaine self-administration testing. During this recovery period, each rat received in the home cage automated hourly intravenous infusions (200 μl) of a sterile saline solution containing heparin (1.25 U/ml), penicillin G potassium (250,000 U/ml), and streptokinase (8000 U/ml). On self-administration test days, the cannulae were flushed with this solution daily following the test, and this solution was cleared with a subsequent application of 500 μl heparinized saline. Once cocaine self-administration testing began, each animal continued to receive hourly infusions in the home cage, but the solution was changed to heparinized saline. Catheter patency was checked an equal number of times for each animal during testing, and at the completion of the study, by administering an intravenous infusion of 7.5 mg/kg sodium pentobarbital. One animal from the control condition and

one animal from the lead-exposed condition failed to lose consciousness at different points in the self-administration test, and their data were excluded from all analyses reported here.

Twelve operant chambers (Model E10-10, Coulbourn, Allentown, PA) in sound-attenuating cubicles served as the test apparatus. Each chamber had two levers and a stimulus light located above each lever. Infusion pumps (Razel Scientific Instruments, Stamford, CT) controlled drug delivery to each of the boxes. A 20-ml syringe delivered intravenous infusions (160 μl) over a 6.0-s time frame. The system was interfaced with two IBM computers, each controlling drug delivery and recording data from six chambers. Subject assignment to chambers was counterbalanced by group, and testing occurred during the light phase of the cycle.

All control and lead-exposed test animals were deprived of water for 24 h prior to commencing shaping to lever press for a 0.500-mg/kg infusion of cocaine HCl (administered as a salt) on a fixed ratio (FR-1) schedule where each depression of the right lever activated the 20-ml syringe infusion pump and resulted in an infusion of cocaine and simultaneous illumination of the stimulus light above the lever. The houselights inside the test chambers were turned off during self-administration training and testing. A time-out period was imposed during the 6.0-s period of drug delivery and illumination of the stimulus light above the lever. Lever responding during this time-out period had no programmed consequences and was not included in the data reported here. Lever responses on the left ''inactive'' lever were recorded but had no programmed consequences. Once animals acquired the lever press response, formal testing operations began. During the initial 3-day phase of the investigation, control and lead-exposed animals were limited to 20-min access to water in the home cage immediately following cocaine self-administration testing. Each of the three test sessions were 2-h in duration, as were all other test sessions conducted throughout the remaining phases of the study. During this initial 3-day water-deprivation period, lever responding was maintained under an FR-1 schedule where a single lever response on the right ''active'' lever resulted in an intravenous infusion of 0.500 mg/kg cocaine. This FR-1 contingency also was in place during a subsequent 3-day period where testing was conducted under conditions of ad libitum access to water in the home cage. Following these successive FR-1 testing periods, for 7 days, all animals were shifted to an FR-2 baseline schedule of intravenous cocaine reinforcement where two active lever responses resulted in a delivery of 0.500 mg/kg cocaine.

Dose–effect testing began the day immediately following the final day of baseline testing. During the period of dose–effect testing, 0.500, 0.250, 0.125, 0.060, and 0.030 mg/kg/infusion were available on two successive days at each dose, with each dose presented in descending order. Between tests where subjects were allowed to self-administer these different cocaine doses, baseline conditions were reinstated for all animals for 2 days, i.e., 0.500 mg/kg cocaine/infusions were available for 2 days on an alternating schedule that afforded determination of stability of baseline responding over the course of dose–effect testing. Regardless of the dose made available during the 2-h daily testing regimen, before each session, the swivel and the catheter connecting between the infusion pump and the swivel were flushed with a 1-ml solution of 95% (v/v) ethanol, thus clearing the previous dose. The catheter was reconnected to the syringe pump containing the appropriate dosing solution and filled completely with the new drug solution. Once the jugular catheter was connected to the swivel, forming a closed delivery system, the pump was activated until the new dose was available to the animal for the initial daily cocaine infusion.

2.3. Tissue collection and analysis

After dose–effect testing was completed, blood and tissue samples were collected. Lead concentrations were measured via atomic absorption spectrophotometry as recently reported in detail from our laboratory (Dearth et al., 2003). Control and lead-exposed test animals were anesthetized with sodium pentobarbital (50 mg/kg ip). Following blood collection via cardiac puncture, each test animal was transcardiac perfused with a 0.1-M phosphate buffer. Following perfusion, brain was rapidly harvested along with kidney, liver, and tibia. To assure accuracy in measurements of tissue levels, certified standards (National Institutes of Health, Centers for Disease Control, and Wisconsin Blood Lead Certification Program) for blood lead were processed before and after analyses of tissue lead samples collected and reported here. Further, spiked samples were spaced intermittently (1 per 20 experimental samples) to insure adequate recovery. If, at any time, values from the standards were more than 5% above or below the certified mean or outside the 99% confidence interval, analysis of samples was stopped and recommenced following diagnosis of any problem with the lead analysis procedures.

2.4. Statistical analyses

Analysis of variance (ANOVA) tests were performed on food intake, body weight, and the behavioral (self-administration) data. In all cases, Newman–Keuls post hoc procedure for determining mean differences was employed where appropriate.

3. Results

We found evidence that lead exposure during gestation and lactation increases cocaine sensitivity when the drug is offered as a reinforcer much later in the adult cycle. These differences were observed although lead had cleared blood and brain tissue by the end of testing.

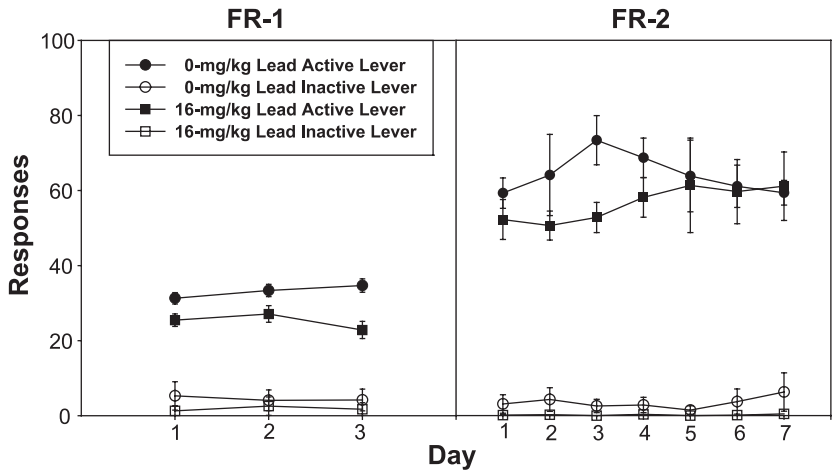

Fig. 1. Mean (S.E.M.) number of active (cocaine) and inactive lever responses for control ($n = 11$) and lead-exposed animals ($n = 11$) during acquisition under conditions of an FR-1 (left panel) and subsequently under conditions of an FR-2 (right panel).

3.1. Food intake and body weights

The analysis of mean weekly food intake immediately prior to testing did not yield significant results [mean ($\pm$ S.E.M.) intake: 256.2 ± 24.6 and 234.2 ± 16.3 g for control and lead groups, respectively; $P > .05$]. Similarly, the analysis of body weights at the time behavioral testing commenced did not show significant group differences [mean ($\pm$ S.E.M.) body weight: 408.8 ± 18.9 and 383.3 ± 10.2 g for control and lead groups, respectively; $P > .05$].

3.2. Cocaine self-administration

Examination of the initial training phases revealed that at the relative high baseline training dose of 0.500-mg/kg lead-exposed animals responded at lower rates than controls. That is, although not significantly different during the FR-1 water-deprivation period ($P > .05$), under conditions of ad libitum access to water, lead-exposed animals responded significantly less frequently on the active (cocaine) lever during FR-1 testing [$F(1,20) = 6.93$, $P < .05$] (left panel, Fig. 1). Post hoc analyses showed significant group separation on all 3 days where a single active lever press resulted in an infusion of 0.500 mg/kg cocaine ($P < .05$). Although group comparisons did not reach an acceptable level for significance on the analysis of inactive lever responding ($F < 1$), for both exposure conditions, on each of the 3 days of testing, significantly more responses were committed to the active lever than the inactive lever ($P < .01$).

The right panel of Fig. 1 presents active and inactive lever-response data for control and lead-exposed animals during the 7 days of baseline testing under conditions where a 0.500-mg/kg infusion of cocaine served as the reinforcer on an FR-2 schedule. The results from the

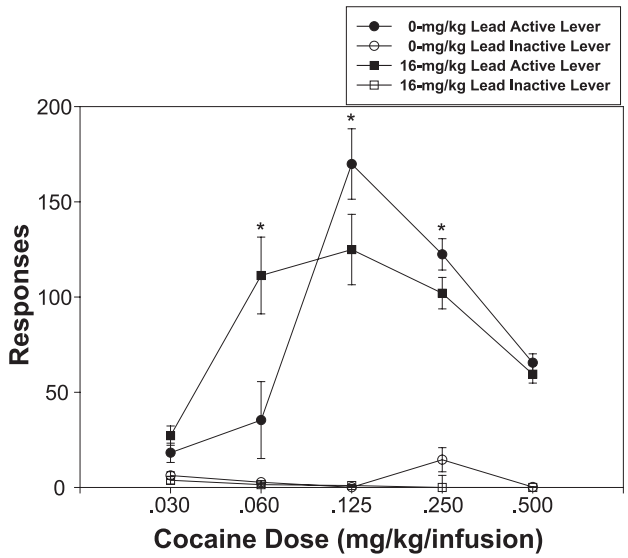

Fig. 2. Mean (S.E.M.) number of active (cocaine) and inactive lever responses for control ($n = 11$) and lead-exposed animals ($n = 11$) during the second 2-h test session at each dose of cocaine during dose–effect testing.

Table 1
Mean (S.E.M.) number of active (cocaine) and inactive lever responses for control ($n = 11$) and lead-exposed animals ($n = 11$) on the second day of alternating baseline training sessions (0.500 mg/kg cocaine/infusion) run prior to testing at each dose during dose–effect testing

Test dose (mg/kg/infusion)	Baseline responding (number of lever responses)	
	Control	Lead
0.030	56.0 (4.2), active	54.2 (4.2), active
	1.9 (1.3), inactive	0.1 (1.4), inactive
0.060	60.7 (4.4)	58.8 (4.6)
	3.0 (1.6)	0.2 (1.7)
0.125	61.6 (4.6)	59.5 (4.7)
	0.2 (0.1)	0.1 (0.1)
0.250	54.3 (4.0)	55.9 (4.0)
	3.4 (2.3)	0.8 (2.3)
0.500	56.5 (3.5)	55.4 (3.5)
	1.1 (0.5)	0.2 (0.6)

ANOVA performed on these data suggest further that perinatal lead exposure alters sensitivity to cocaine when metal-exposed offspring are tested as adults. Specifically, the Groups × Days interaction test of active lever responding was found to be significant [$F(6,120) = 5.03$, $P < .01$]. Post hoc analyses confirmed what is visually apparent from Fig. 1, i.e., lead-exposed animals made fewer lever presses than control animals initially ($P < .05$), but by the end of the FR-2 testing period, the groups converged and did not differ significantly ($P > .05$). Although active lever responding increased across days in both exposure conditions ($P < .05$), neither group separation nor a change in frequency of responding over days was evident regarding the inactive lever responding measure ($F < 1$).

Active (cocaine) and inactive lever responding from Day 2 of testing at each cocaine dose during the period of dose–effect testing is profiled in Fig. 2 for control and lead-exposed animals (second day data were analyzed to minimize carry-over effects). For both exposure conditions, active (cocaine) lever responding was found to be significantly greater than inactive lever responding at all doses, including the lowest cocaine dose of 0.030 mg/kg ($P < .01$). The repeated measures ANOVA performed on the number of active lever presses revealed that the Groups × Dose interaction effect

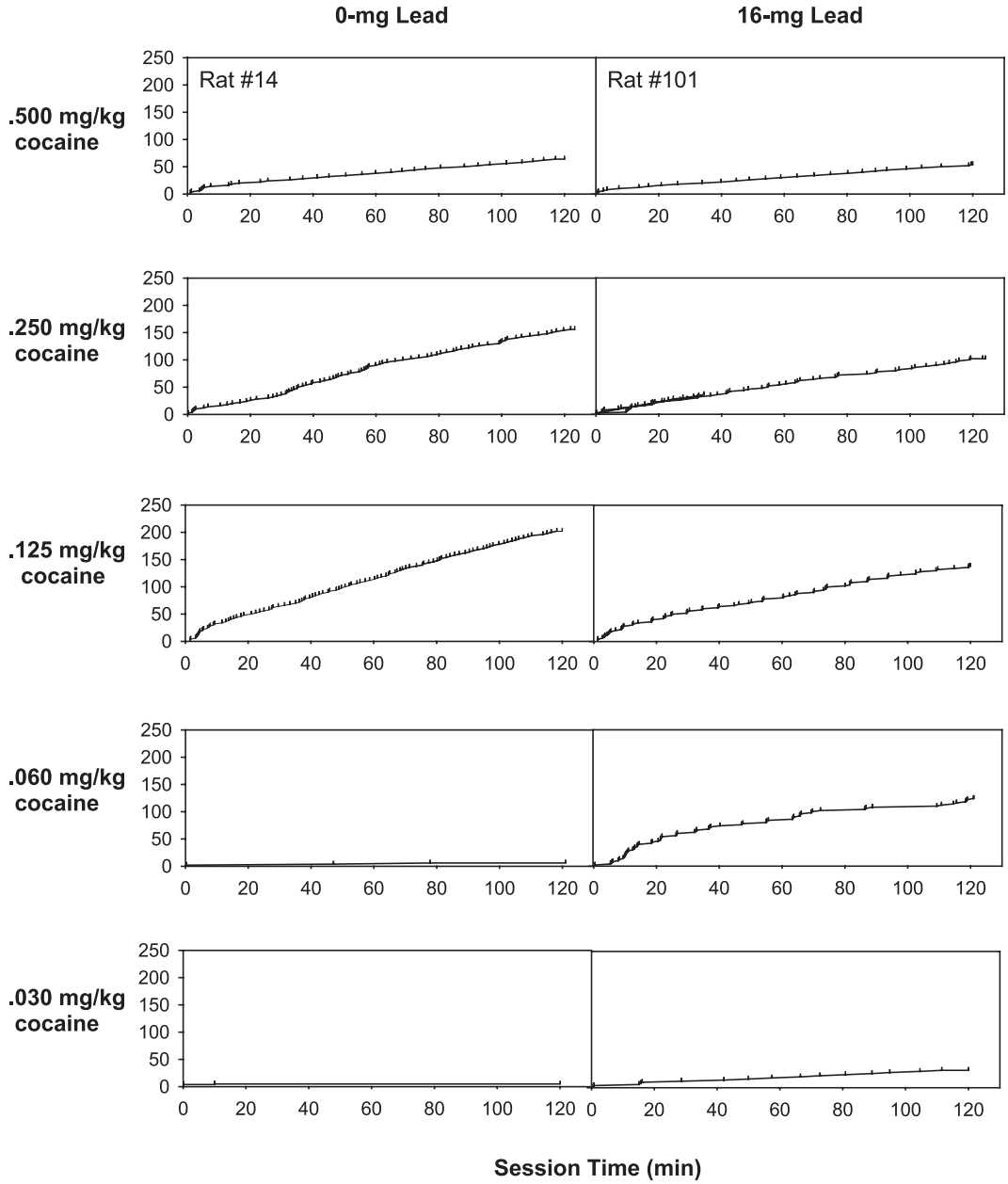

Fig. 3. Representative cumulative response records for a control animal (rat #14) and a lead-exposed animal (rat #101) during the second 2-h test session at each dose of cocaine.

was significant [$F(4,80) = 7.66$, $P < .01$]. Post hoc comparisons of group means indicated that control animals made more active lever responses than animals exposed to lead at doses of 0.125 and 0.250 mg/kg cocaine/infusion ($P < .05$). However, at the cocaine dose of 0.060 mg/kg/infusion, the lead group made significantly more active lever responses than the control group ($P < .01$). Additional comparisons showed that while active lever responding was not different for control animals at a cocaine dose of 0.030 mg/kg relative to a dose of 0.060 mg/kg ($P > .05$), lever responding for cocaine was significantly greater among lead-exposed animals at a dose of 0.060 mg/kg relative to the lowest dose of 0.030 mg/kg cocaine/infusion ($P < .01$). For both exposure conditions, active lever responding significantly increased at low doses of cocaine and then decreased as the dose increased further ($P < .05$).

With respect to inactive lever responding, neither the groups main effect [$F(1,20) = 3.29$, $P > .05$] nor the group interaction with dose [$F(4,80) = 2.23$, $P > .05$] were found to be significant. Unlike the case involving the active lever where response patterns changed markedly with increasing cocaine dose, inactive lever responding was stable over the course of dose–effect testing [$F(4,80) = 2.12$, $P > .05$].

It is of interest to note that during the period of dose–effect testing, baseline responding remained stable for both groups at the 0.500-mg/kg cocaine/infusion dose that was made available for 2 days on an alternating schedule with a particular test dose of the drug. Table 1 presents the group means for active and inactive lever responding on the second day 2-h training session run prior to self-administration testing at each of the five cocaine doses (0.030, 0.060, 0.125, 0.250, 0.500 mg/kg cocaine/infusion). The analyses of active and inactive lever responding on these alternating baseline training sessions completed prior to dose–effect testing failed to yield significance for group or dose comparisons (all Fs < 1.25; $P > .05$).

Fig. 3 presents representative cumulative response records of individual rats from the control condition and the lead-exposure condition. Each hash mark on the respective records indicates the time during the session when a response contingent cocaine infusion occurred, and the *y*-axis reflects the total cumulative infusions received during the 2-h test session. It is apparent from the representative individual subject data presented in Fig. 3, that 0.060 mg/kg cocaine intravenous self-administration responding was maintained at a much higher rate in the animal perinatally exposed to lead relative to the control animal.

3.3. Lead concentrations in tissue

Table 2 presents lead concentration data for dams, littermates, and test animals. It is evident among test animals that the behavioral effects observed here occurred although lead in blood and brain tissue (conventional markers of lead toxicity) had returned to control levels.

Table 2
Mean (S.E.M.) blood and tissue lead concentration values for dams, littermates, and test animals

	Control	Lead
Blood lead concentration (μg/dl)		
Dams		
Breeding	2.01 (0.5)	35.12 (6.2)*
10 days of gestation	2.99 (0.6)	28.10 (4.6)*
Parturition (PND 1)	1.04 (0.1)	35.66 (2.8)*
Weaning (PND 21)	1.18 (0.1)	27.49 (3.0)*
Littermates		
PND 1	1.09 (0.2)	53.24 (7.1)*
PND 21	1.12 (0.1)	12.45 (1.0)*
Test animals		
Termination	1.05 (0.1)	1.04 (0.1)
Tissue concentrations of lead (μg/g) for test animals		
Brain	< 0.01	< 0.01
Liver	< 0.01	< 0.01
Kidney	0.012 (0.002)	0.031 (0.010)*
Tibia	0.050 (0.010)	2.350 (0.210)*

See text for details.

* Control and lead-exposed animals were significantly different ($P < .05$).

4. Discussion

The results of this self-administration investigation showed sensitivity to cocaine was increased among adult male rats perinatally exposed to lead relative to controls. Specifically, during initial acquisition training where a high dose of cocaine (0.500 mg/kg/infusion) was used as the reinforcement outcome, lever responding for intravenous cocaine was at a lower rate for pups born to dams exposed to 16 mg lead/day via gavage throughout gestation and lactation, relative to controls. During subsequent dose–effect testing, lead-exposed animals sustained responding at a significantly greater rate than their control counterparts at a low dose of cocaine (0.060 mg/kg/infusion), yet once again at higher drug doses, cocaine was self-administered at lower rates in lead-exposed animals. These findings were observed in the absence of significant group differences in food intake or body weight. Although lead concentrations in kidney and bone (tibia) remained significantly elevated among lead-exposed animals at the conclusion of testing operations, the alterations in cocaine self-administration patterns apparent in this study were evident although lead amounts in blood and brain were at the level of controls.

It is noteworthy that the present changes produced by developmental lead exposure parallel findings from other investigations where chemical interventions have been employed to alter cocaine reinforcement value. In this regard, pharmacologic augmentation of cocaine sensitivity has been associated with diminished rates of self-administration at higher doses of cocaine. For instance, Caine et al. (2000) pretreated animals with the D_2-like agonists quinelorane or 7-OH-DPAT and found a downward shift in

cocaine self-administration at higher doses of the drug. One interpretation of such rate-reduction following drug potentiation is that regulation of drug intake reflects an attempt on the part of the animal to maintain drug levels within an optimal range (Lynch and Carroll, 2001; Wise et al., 1995). The central idea is that decreased responding on the descending limb of the dose–effect curve is a consequence of the diminishing reinforcement value inherent to drug satiation. That is, with more potent drug-delivery outcomes animals become satiated and further intake is contraindicated until levels fall below some desired point. It follows that agonist manipulations involving conventional drug challenges reduce self-administration responding by enhancing the satiating impact of the drug, at least at higher doses. With respect to the present findings, then, lower rates of responding for higher cocaine doses among lead-exposed animals are readily interpretable within the framework of contaminant-based increases in the reinforcing properties of cocaine.

A similar argument can be made regarding the finding reported here that perinatal lead exposure is associated with greater maintenance of self-administration responding at a low dose of cocaine (Fig. 2). Because developmental lead exposure results in increased sensitivity to the incentive value of cocaine, reinforced lever responding continues at a cocaine dose (e.g., 0.060 mg/kg/infusion) in lead-exposed animals that is insufficient to maintain responding among controls.

The finding of increased sensitivity to the reinforcing effects of cocaine in a dose–effect preparation is consistent with earlier published reports on the effects of perinatal lead exposure on relapse to drug-seeking, as well as cocaine-induced increases in locomotor activity. Nation et al. (2003) observed that, following initial cocaine acquisition training, adult animals developmentally exposed to lead self-administered significantly more saline injections than controls during an extinction period that commenced with a priming injection of 5 or 10 mg/kg cocaine. Elsewhere, Nation et al. (2000) recorded total distance traveled following repeated daily intraperitoneal injections of 10 mg/kg cocaine and noted that behavioral sensitization (augmented responding after successive administrations of the drug) was greater among rats perinatally exposed to lead. It would seem, then, that at least in experimental situations where cocaine is presented recurrently, perinatal lead exposure amplifies cocaine sensitivity, and this effect is enduring.

In addition to issues relating to relapse and activity, sensitization also is pertinent to the present self-administration findings. Hooks et al. (1994) and Schenk and Partridge (2000) have demonstrated that intraperitoneal injections of cocaine prior to or following intravenous self-administration training enhance the behavioral and neurochemical effects associated with cocaine. Elsewhere, Hemby et al. (1997) have shown that response-dependent intravenous cocaine self-administration progressively increases nucleus accumbens dopamine concentrations. In a related article, Phillips and Di Ciano (1996) observed sensitization of motor activity following repeated contingent and noncontingent intravenous administration of cocaine. Thus, it would seem that self-administering high doses of cocaine might sensitize the animal to lower doses when tested later. Because control and lead-exposed animals in the present investigation received multiple experiences with a relatively high intravenous dose of cocaine prior to being tested at lower doses, it must be acknowledged that the aforementioned behavioral sensitization produced by perinatal lead exposure (Nation et al., 2000) may have defined functional differences in drug sensitivity, rather than lead-induced alterations in the reinforcing value of cocaine per se. Moreover, this rationale speaks to the issue of directional differences associated with acute versus repeated cocaine administration in animals developmentally exposed to lead (cf. Miller et al., 2000; Nation et al., 2000). That is, acute or limited exposure to cocaine may be insufficient to produce sensitization, and perinatal lead exposure could result in drug attenuation (Miller et al., 2000, 2001). Conversely, sensitization effects associated with recurrent experience with cocaine may surmount initial differences in cocaine sensitivity and even augment the impact of the drug (Nation et al., 2000).

An alternative interpretive issue relates to potential perturbation of cocaine pharmacokinetics by early developmental lead exposure. Although it is clear from the results of the lead concentration in tissue assays that residues in blood and brain had returned to levels of controls, it is equally apparent that lead concentrations in kidney remained elevated in metal-exposed animals (Table 2). This raises questions concerning possible group differences in the elimination of cocaine or active cocaine metabolites such as benzoylecgonine. Such alterations in clearance in lead-exposed animals, of course, could affect the life of the drug at neural membrane sites. In addition, perinatal lead exposure may have selectively influenced other physiologic mechanisms such as lipid storage of the drug (Nayak et al., 1976; Reith et al., 1987), transfer rate of cocaine into blood or brain (Pan et al., 1991), or metabolic conversion of the drug (Ho et al., 1977), each of which could affect cocaine content in selective brain regions. Increased sensitivity to cocaine in lead-exposed animals, then, would derive more from availability than changes in drug action per se. Although it has been determined that lead exposure at the adult level does not alter cocaine pharmacokinetics (Nation et al., 1997), no corresponding developmental data are available. Consequently, the possibility that differences in delivery systems may have contributed to the patterns of separation observed here cannot be ruled out.

Although this study is restricted to a phenomenological presentation of the interactive behavioral relations between perinatal lead exposure and cocaine intake later in life, some mention of possible determinants may prove instructive. Along these lines, possible lead-related disturbances of dopaminergic neurotransmission are of interest. Both dopamine binding in the nucleus accumbens (Pokora et al., 1996)

and the number of spontaneously active dopamine neurons in the ventral tegmental area (Tavakoli-Nezhad et al., 2001) are decreased by postnatal lead exposure. Because dopamine activity in these brain regions is integrally involved in defining cocaine sensitivity (Kalivas, 1995b; Ranaldi and Wise, 2001; Wise and Bozarth, 1987), lead-related changes in dopamine action (e.g., up-regulatory processes) may have contributed to the pattern of results observed here. In addition, the potential role played by disturbances in glutamatergic function should not be overlooked in this study of perinatal lead/cocaine interactions. Glutamate is known to play a central role in defining cocaine sensitivity efficacy (Cornish et al., 1999; Kalivas, 1995a; Trujillo and Akil, 1995; Wolf, 1998). Because developmental lead alters presynaptic (Lasley and Gilbert, 1996) and postsynaptic (Lasley et al., 2001) glutamate transmitter operations, some consideration for the involvement of glutamate in lead-induced increases sensitivity to low doses of cocaine must be given. Curiously, although glutamate activity is critical to determining the primary reinforcing value (sensitivity) of cocaine (e.g., Cornish et al., 1999), glutamate appears to play no modulatory role in the conditioned reinforcement properties of cocaine (See et al., 2001). Perhaps the different effects of this transmitter on cocaine self-administration and conditioned place preference (CPP), at least to some degree, explains lead-related increased drug sensitivity in the present investigation and decreased sensitivity in an earlier report on CPP (Miller et al., 2000).

Other potential mechanisms contributing to lead-induced increases in cocaine sensitivity may include GABA-ergic systems. For instance, lead exposure limited to early development is sufficient to produce deficits in evoked GABA release (Lasley and Gilbert, 1996; Lasley et al., 1999). The resulting decrements in inhibitory transmitter availability could affect cocaine self-administration (Campbell et al., 1999; Roberts and Brebner, 2000), perhaps by elevating anxiety levels. Specifically, it is established that the $GABA_A$-like receptor subtype mediates anxiety (cf. Smith, 2002) and, in turn, elevated anxiety levels increase cocaine sensitivity (Goeders, 1997), perhaps through activation of the hypothalamic–pituitary–adrenal axis or GABA-mediated stimulation of dopamine pathways in the dorsal prefrontal cortex and limbic subcircuits (McFarland and Kalivas, 2001; Wolf, 1998). To the extent that developmental lead exposure disrupts GABA function and induces anxiety (Moreira et al., 2001), then, increased sensitivity to cocaine would be expected for the treatment condition. Whatever the mechanism of action, the changes occasioned by early lead exposure persist up to 9 months in the rat (Miller et al., 2001), and it must be considered that such metal-based disturbances in cocaine sensitivity may be permanent.

Finally, the finding that early lead exposure may augment the reinforcing value of cocaine is of central interest with respect to public health concerns. Insofar as lead exposure during pregnancy and nursing results in long-term increase in drug sensitivity, increased risk of cocaine addiction necessarily becomes more likely in those environments where lead distribution and contamination are widespread (Harwell et al., 1996). As indicated, the inner-city sectors of major metropolitan areas in North America continue to be burdened by elevated, unsafe lead levels (Harwell et al., 1996; Pirkle et al., 1998). Accordingly, it must be acknowledged that environmental contamination may contribute to the commonly reported high levels of drug abuse in inner-urban environments (Brody et al., 1994; Ensminger et al., 1997). Still, additional animal studies and confirmatory human investigations are required before statements along these lines can be made confidently.

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