Enhanced Acquisition of Cocaine Self-Administration in Rats Developmentally Exposed to Lead

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The rate of acquisition of drug self-administration may serve as a predictor of later drug-taking behavior, possibly influencing the vulnerability to use drugs. The present study examined the effects of perinatal (gestation/lactation) lead exposure on adult rates of acquisition of intravenous cocaine self-administration using an automated procedure that included both Pavlovian and operant components. For Experiment 1, female rats were gavaged daily with 0 or 16 mg lead for 30 days prior to breeding with nonexposed males. Metal administration continued through pregnancy and lactation and was discontinued at weaning (postnatal day (PND) 21). Animals born to control or lead-exposed dams subsequently were tested daily as adults in a preparation where sessions included an initial 3-h autoshaping period followed by a 3-h self-administration period where 0.20 mg/kg cocaine was delivered contingently. During autoshaping, intravenous cocaine infusions were paired with the extension and retraction of a lever, while infusions occurred during self-administration only when a lever press was executed (FR-1). The criterion for acquisition was a 2-day period during which a mean of 50 infusions/session occurred during self-administration. Animals were given 35 days to reach criterion. In Experiment 1, accelerated rates of acquisition of cocaine self-administration were evident for lead-exposed animals relative to controls. Overall, the number of self-administered cocaine infusions per session was significantly higher for lead-exposed rats as compared to control rats. Experiment 2 replicated Experiment 1 except that a higher dose of cocaine (0.80 mg/kg) was employed as the reinforcer, and 30 infusions/session was the set criterion. At the higher cocaine dose (Experiment 2), acquisition rates for control and lead-exposed animals were not markedly different, and significantly different infusion rates were not observed.
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INTRODUCTION

The deleterious effects of lead appear to begin *in utero*. Pregnant women with elevated blood lead levels give birth to children who have correspondingly high concentrations of lead in their bloodstream. In fact, during pregnancy, lead previously stored in bone appears to be liberated and redistributed to the vascular system (Gulson *et al*, 1997). Blood lead levels reach a peak during the second trimester at which point the metal is readily transferred to the fetus.

Lead is a particular threat to the fetus due to the ease with which it is absorbed by the placenta, crosses the under-developed blood–brain barrier, and penetrates the soft bone structure. Consequently, children born to lead-exposed mothers may be disposed in the fetal stage to develop lead-

induced impairments. Even in older children, there is increased brain lead absorption and decreased lead excretion relative to adults (Godwin, 2001). Additionally, whereas adults absorb only 10–20% of ingested lead, children absorb up to 50% into their bloodstream (Weizaecker, 2003). When ingested, or absorbed through the skin, lead can be carried in blood plasma, and bound to hemoglobin. Finally, although lead in blood may have a biologic half-life approximating 1 month, the half-life of lead in bone is estimated to be 20–30 years (Weizaecker, 2003). Accordingly, possible health consequences associated with early lead exposure may be long lasting.

In experiments where opiates have been presented repeatedly to animals perinatally exposed to lead, a decrease in sensitivity to the drug is often observed. For example, in an intravenous self-administration study, lead-exposed rats responded fewer times for a heroin reinforcer, at least at intermediate doses (Rocha *et al*, 2004). Supporting results were obtained when perinatally exposed animals were tested on a progressive-ratio task, that is, lead-exposed animals ceased lever pressing for heroin reinforcements at lower ratios than their control counterparts (Rocha *et al*, 2004).

In agreement with these findings, animals exposed perinatally to lead failed to show a morphine-induced conditioned place preference, suggesting a decreased rewarding sensitivity to the opiate (Miller et al, 2001).

In contrast to lead/opiate interactions, developmental lead exposure seems to potentiate the behavioral effects of cocaine. That is, perinatal lead exposure increases the stimulatory properties of cocaine when animals are tested in a locomotor chamber at either postnatal day (PND) 30 or PND 90 (Nation et al, 2000). Elsewhere, rats exposed developmentally to lead self-administered cocaine at doses too low to sustain responding in untreated controls (Nation et al, 2004; Valles et al, 2005). Also employing an intravenous self-administration model, Nation et al (2003) found that adult rats born to dams exposed to lead throughout gestation and lactation were more vulnerable than controls to drug reinstatement (relapse).

Although these latter studies on lead/cocaine interactions indicate that the reinforcer potency of cocaine is increased by developmental lead exposure, in order to obtain a more complete understanding of vulnerability to use cocaine, it is necessary to examine the drug acquisition phase per se. In the previous investigations of drug maintenance and relapse, the drug self-administration environment was necessarily manipulated in order to permit detailed assessments of parameters related to drug-selection and use, that is, various techniques such as shaping, a day or more of total food and/or water deprivation, priming, etc. were used to accelerate acquisition, therein permitting lengthier periods for evaluation of other, relevant issues. What was compromised was the ability to monitor the differential rates of learning for control and lead-exposed animals in a drug self-administration context that did not include experimenter intervention.

Accordingly, the purpose of the present project was to examine relative acquisition rates of drug (cocaine) self-administration for offspring (rats) born to dams exposed to 0 or 16 mg lead prior to breeding, and throughout gestation and lactation. In Experiment 1, adult control and lead-exposed animals were tested during daily sessions that involved an initial 3-h autoshaping component wherein 0.20 mg/kg cocaine infusions were paired with the extension and retraction of a lever (a Pavlovian procedure). During a subsequent 3-h self-administration component of each daily session, 0.20 mg/kg cocaine infusions were delivered only when a single lever press (FR-1) was executed (an operant procedure).

EXPERIMENT 1

Methods

Animals. All aspects of the research reported here were approved by the Texas A&M University Laboratory Animal Care Committee. For 30 days, adult female Sprague–Dawley rats (Harlan; Houston, TX) were exposed to 0 mg (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. This procedure has been used in our previous developmental lead studies to ensure stable blood/tissue levels (cf Nation et al, 2000, 2003, 2004; Rocha et al, 2004; Valles et al, 2005).

The present lead concentration was selected based on previous studies that found it produces differential behavioral effects while not altering dam weights or the locomotor ability of pups (see Miller et al, 2000). Following this 30-day toxicant exposure period, females were bred with nonexposed males. Once females tested positive for copulatory plugs, the males were removed from the home cage. Females continued to receive their daily dose of the control solution or lead acetate solution throughout the gestation and lactation periods. Standard rat chow (Teklad, Madison, WI) and tap water were available ad libitum for dams in the home cage. Litters were culled to eight pups on PND 1, and only one pup from each litter was used in the experiment in order to avoid confounds that are sometimes evident in studies involving toxic exposure (Holson and Pearce, 1992).

For control and lead-exposed dams, 100–150 μl of tail-blood was drawn at breeding, parturition (PND 1), and weaning (PND 21). In addition, at the point of termination of the experiment, the brain, kidney, liver, and bone (tibia) were harvested from test animals for lead concentration analyses. Littermates of test animals were killed on PND 1 and PND 21, and blood samples were collected for subsequent analyses.

The rate of pregnancy was not different between groups. On PND 21, pups used for testing were weaned and housed individually. All animals were maintained on a 12-h light/dark cycle. Testing commenced at approximately 10:00 h, 2 h into the 12-h light cycle.

Surgical procedures. Surgery was performed at PND 60, which is a point demonstrated to be well within the adult timeframe of behavioral change produced by developmental lead exposure (Miller et al, 2000, 2001; Nation et al, 2003, 2004). Using a backplate technique, implantation of chronic indwelling jugular catheters was performed using sterile techniques as described in detail elsewhere (Nation et al, 2003). The rats were allowed 5 days to recover from surgery before commencing cocaine self-administration testing. During this recovery period, each rat received in the home cage hourly intravenous (i.v.) infusions (200 μl) of a sterile saline solution containing heparin (1.25 U/ml) and penicillin G potassium (250 000 U/ml). Following recovery, over an 8 s time frame, animals received automated hourly infusions (213 μl) of heparinized saline in the home cage for the duration of the study. All animals received free access to food and water for 5 days while recovering from surgery. Subsequently, daily food was restricted to 18 g of standard rat chow in order to maintain animals at approximately 85% of the mean body weight of non-food-deprived littermates (not participating in the study). Moderate food restriction has been shown consistently to accelerate cocaine acquisition (Campbell and Carroll, 2001), and the procedure is recommended for autoshaping acquisition studies. Uncontaminated water was available ad libitum throughout the study. Animals were weighed daily prior to testing. Although initial individual pup body weights were higher for control than lead-exposed animals, no significant group differences in body weight were evident at the commencement of testing operations. Food was placed in home cages following the end of each daily testing session.

Apparatus. The 12 operant conditioning 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 i.v. infusions (160 µl) over a 6 s time frame. The system was interfaced with two IBM computers, each controlling drug delivery and recording data from six chambers.

Procedure. Autoshaping component: Control (Group 0-mg; $N = 7$) and lead-exposed (Group 16-mg; $N = 10$) animals were run in two squads, and subject assignment to chambers and squad was counterbalanced by group. Each of the 6-h experimental sessions consisted of two parts, an autoshaping, and a self-administration component. Testing was carried out for 7 days per week. For the first 3 h of Experiment 1, during the autoshaping component, testing commenced with the retractable lever drawn outside the reach or vision of the animal. After a 90-s time-out period, the retractable lever extended into the operant chamber at which point the animal received a 0.20 mg/kg cocaine infusion if it pressed the lever or after 15 s, whichever occurred first. Once again, a 90-s time-out period was instituted. As before, the active lever was then extended into the chamber and the animal was given 15 s to press the lever for an immediate infusion of 0.20 mg/kg cocaine, or, if no response occurred the animal received a noncontingent cocaine infusion of 0.20 mg/kg cocaine at the end of the 15-s period. This cycle repeated for the first 20 min of each hour for the initial 3 h (30 total cocaine infusions).

With the chamber house-light off, the stimulus light above the active (right) lever was lit for the 6-s duration of the infusion and terminated immediately after. The inactive (left) lever remained extended inside the chamber throughout the study. Responses on the inactive lever, as well as responses during an infusion, were recorded but had no programmed consequences. As indicated, a 0.20 mg/kg cocaine HCl infusion (160 µl) was delivered to the animal following each lever retraction regardless of whether the action was contingent or noncontingent. After the first 20 min of each hour, following the 10 cocaine infusions, all stimulus lights were extinguished and the active lever remained retracted for a 40-min time-out session, until testing recommenced at the beginning of the next hour.

Self-administration component: For the second 3-h component of the experiment, the retractable lever remained extended and 0.20 mg/kg cocaine infusions were contingent upon lever pressing under an FR-1 schedule. As before, responses on the left lever and responses during an infusion delivery were recorded, but had no programmed consequences. At the end of the 3-h self-administration period, testing was concluded for the day.

The criterion for acquisition of cocaine self-administration was a mean of 50 infusions per day over two consecutive daily self-administration sessions. This value is half of what has been set previously in studies that used twice the duration of testing time (ie 6-h autoshaping and 6-h self-administration) (Carroll and Lac, 1997, 1998). The cocaine dose (0.20 mg/kg) was chosen based on data from previous studies that show this dose is marginally reinfor-

cing, and does not produce satiation or motoric impairments (Campbell and Carroll, 2001).

In order to confirm patency during acquisition training, catheters were flushed twice daily with 0.20 ml of a heparinized saline solution; once prior to and once following each daily testing session. Catheters of questionable patency were flushed with 0.05 ml of sodium pentobarbital (7.50 mg/kg) followed by 0.20 ml of heparinized saline, and these animals were checked for immediate onset of brief anesthesia. At the end of the study, each animal in both exposure conditions received an i.v. infusion of 7.50 mg/kg sodium pentobarbital. Again, catheter patency was verified by rapid onset of brief anesthesia. Each of the seven control and 10 lead-exposed animals included in this report tested positive for open lines.

Drugs. The Research Technology Branch of the National Institute of Drug Abuse generously supplied the cocaine HCl. Heparinized saline served as the cocaine vehicle. Lead acetate and sodium acetate were obtained from Sigma-Aldrich Chemical Company (St Louis, MO).

Tissue collection and analyses. After animals recovered from patency verification, control (Group 0-mg) and lead-exposed (Group 16-mg) test animals were anesthetized with sodium pentobarbital (50 mg/kg i.p.). Following blood collection via cardiac puncture, brain was rapidly harvested along with the kidney, liver, and bone (tibia). Following collection of blood and tissue samples, lead residues were measured via atomic absorption spectrophotometry as described in a detailed report from our laboratory (Dearth *et al*, 2003).

Statistical procedures. The comparative rates of acquisition of cocaine self-administration were assessed using the Kaplan–Meier survival analysis, Breslow statistic (cf Lee, 1992). This analytical procedure is ideally suited for determining differences in rate with respect to animals reaching a set criterion (SPSS; Chicago, Il). In addition, an analysis of variance (ANOVA) test was performed on the mean number of active lever responses (infusions) and inactive lever responses for each group across the course of self-administration testing.

RESULTS

Acquisition of Cocaine Self-Administration

Figure 1 illustrates the cumulative percentage of rats in each exposure condition meeting criterion for the acquisition of cocaine self-administration (0.20 mg/kg/infusion). It is visually apparent that over the 35-day testing period, Group 16-mg animals were more likely to meet the requirements for acquisition of cocaine self-administration than controls. Indeed, even by the fifth day of acquisition training, a greater percentage of lead-exposed animals (two of 10 rats in the Group 16-mg) reached criterion than nonexposed animals (zero of seven rats in the Group 0-mg), and this pattern persisted throughout testing. This is especially evident at day 17, approximately mid-way through the 35-day testing period, where six of the 10 animals in the Group 16-mg had reached the acquisition criterion, but only one of seven animals in the Group 0-mg animals had reached criterion.
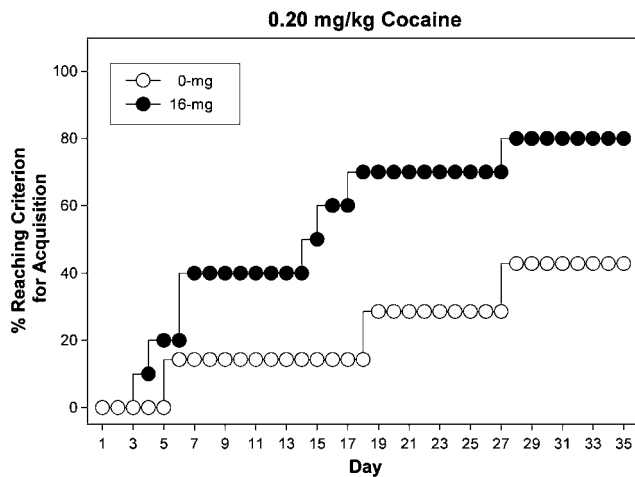
Figure 1 Cumulative percentage (%) of nonexposed (Group 0-mg lead/ $N=7$) and lead-exposed (Group 16-mg lead/$N=10$) rats meeting the criterion for the acquisition of cocaine (0.20 mg/kg/infusion) self-administration within the 35-day limit (Experiment 1). Open symbols and closed symbols represent the nonexposed and lead-exposed conditions, respectively.
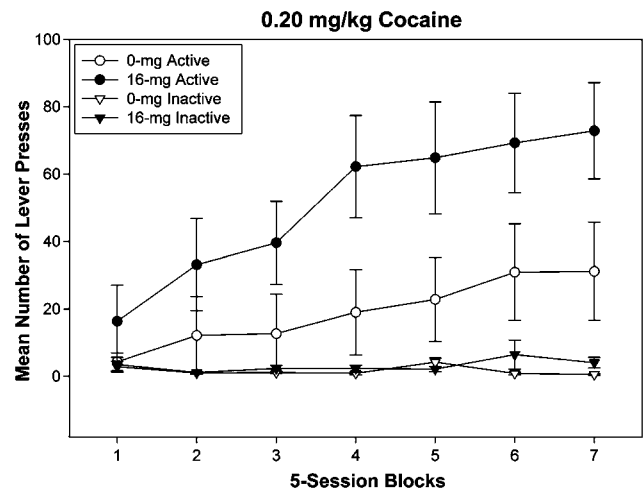

Figure 2 Mean active (0.20 mg/kg/infusion) and inactive lever responses for all animals in Group 0-mg lead ($N=7$) and Group 16-mg lead ($N=10$), across successive 5-session blocks (Experiment 1). Open symbols and closed symbols represent the nonexposed and lead-exposed conditions, respectively.

By the end of testing, three of seven rats reached the acquisition criterion in the Group 0-mg, whereas eight of 10 rats reached the acquisition criterion in the Group 16-mg. In addition, as assessed by survival analysis, it was found that acquisition rates (the point where animals reached criterion) were accelerated for Group 16-mg rats relative to Group 0-mg rats (Kaplan–Meier, Breslow statistic ($\chi^2 = 3.89$, $df = 1$, $p < 0.05$).

Figure 2 profiles the mean number of active (infusions) and inactive lever responses per five-session blocks for all animals in both exposure conditions. A 2 Groups (0-mg, 16-mg) $\times$ 2 Levers (active, inactive) $\times$ 7 Blocks of 5 Sessions (1–7) repeated measures ANOVA was performed on these data, with Levers and Blocks of 5 Sessions serving as within factors. Overall, the findings from this analysis revealed that lead-exposed rats self-administered cocaine at greater rates than control rats. That is, in addition to significant main effects for Levers ($F(1,15) = 14.95$, $p < 0.05$) and Blocks of 5 Sessions ($F(6,90) = 7.54$, $p < 0.05$), a significant main effect for Groups was found ($F(1,15) = 4.56$, $p < 0.05$). Further, it is apparent from Figure 2 that both groups maintained stable response rates at the end of the experiment.

Lead Concentrations in Tissues. Table 1 presents the mean (SEM) blood lead residue values for nonexposed (Group 0-mg) and lead-exposed (Group 16-mg) dams at breeding, parturition, and weaning. Blood lead concentrations are shown for littermates at PND 1 and PND 21, as well as for test animals at the termination of Experiment 1. As can be seen, for both groups of test animals, blood lead levels had fallen below detectable limits by day 35 of acquisition training ($<0.5\,\mu g/dl$), and in terms of the analyses performed on tissue samples taken from test animals, tissue concentrations were the same for both exposure conditions, with the exception that in tibia lead concentrations remained elevated in metal-exposed animals relative to controls; $p < 0.05$.

Table 1 Mean (SEM) Blood and Tissue Lead Concentration Values for Dams, Littermates, and Test Animals in Experiment 1

	Group 0-mg	Group 16-mg
Blood lead concentration ($\mu g/dl$)		
Dams		
Breeding	1.7 (0.2)	37.1 (0.6)*
Parturition (PND 1)	1.1 (0.1)	58.8 (0.3)*
Weaning (PND 21)	2.3 (0.003)	38.9 (0.3)*
Littermates		
PND 1	1.8 (0.03)	83.2 (0.2)*
PND 21	1.2 (0.01)	13.9 (0.03)*
Test animals		
Termination	<0.05	<0.05
Tissue concentrations of test animals at termination ($\mu g/g$)		
Brain	0.003 (0.001)	0.006 (0.002)
Kidney	0.010 (0.002)	0.034 (0.003)
Liver	0.004 (0.001)	0.006 (0.001)
Tibia	0.035 (0.002)	2.023 (0.317)*

The symbol * indicates that control and lead-exposed animals were significantly different ($p < 0.05$).

EXPERIMENT 2

Methods

The methods, apparatus, exposure regimen, surgical procedures, contingencies during testing, behavioral end points, and all other aspects of the research conducted for Experiment 2 were precisely as described in Experiment 1.

The difference was that in Experiment 2, a higher dose of cocaine was used (0.80 mg/kg/infusion), a value employed by Carroll and Lac (1997) to demonstrate that a greater drug dose results in more rats acquiring drug self-administration, and the mean number of days to meet the criterion decreases. Accordingly, forming the basis for this investigation was the issue that observed differences in Experiment 1 might be surmounted by using a high concentration of cocaine typically characteristic of values defining the descending end of the dose–effect curve (refer to Nation *et al*, 2004). In Experiment 2, there were 10 test animals in Group 0-mg and eight test animals in Group 16-mg.

RESULTS

Acquisition of Cocaine Self-Administration

Figure 3 illustrates the cumulative percentage of nonexposed (Group 0-mg) and lead-exposed (Group 16-mg) rats meeting criterion (30 lever presses; note the decrease in the infusion requirement to meet criterion at a dose of 0.80 mg/kg/infusion reflects the lower response rates commonly associated with higher doses of cocaine in self-administration studies (cf. Carroll and Lac, 1997)). As is visually apparent, the rate of acquisition for Group-16 mg reached asymptote before day 14 of acquisition and remained steady throughout testing. Whereas six out of eight lead-exposed animals reached acquisition by day 13, control animals did not reach a similar percentage until day 25 of testing. As a group, control animals showed a gradual progression to reach acquisition criterion, slowly surpassing acquisition rates for lead-exposed animals, ultimately achieving a cumulative percentage of 100% (10 out of 10) on day 33 of testing.

Although there was a trend toward more rapid acquisition by lead-exposed animals, in contrast to the pattern observed in Experiment 1 the rates of acquisition of cocaine self-administration were not significantly different in Experi-
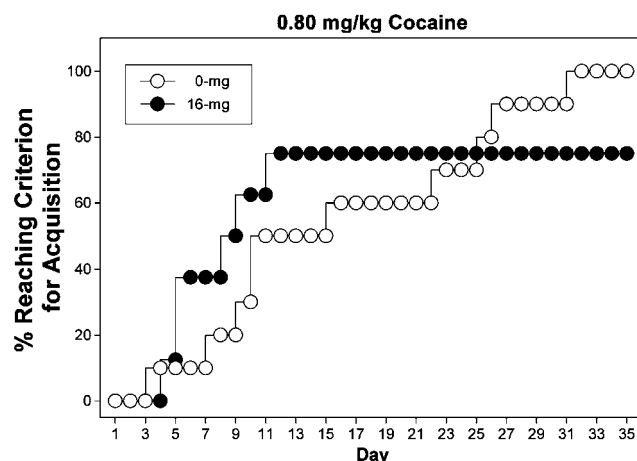
ment 2 (survival analysis; Kaplan–Meier, Breslow statistic ($\chi^2 = 0.45$, df = 1, $p > 0.05$)) and nor were overall infusion rates significantly different in Experiment 2 (Figure 4), unlike the case for Experiment 1. As in Experiment 1, once animals reached acquisition, stable responding was maintained.

Lead Concentrations in Tissues

The same dams gave birth to the animals tested in Experiment 1 and Experiment 2, and the animals tested across these two experiments were littermates. Accordingly, the Experiment 2 blood lead data for dams, and littermates not tested in either experiment, already have been profiled in Table 1 (top). Regarding Experiment 2 test animals (Table 2), the only substantial group differences with respect to lead accumulation in tissue was once again in the analysis of tibia, where greater lead residues were evident in Group 16-mg relative to Group 0-mg; $p < 0.05$. As in Experiment 1, at termination of testing, blood lead concentrations in both exposure conditions were $< 0.5 \mu g/dl$, that is, below the limits of detection.
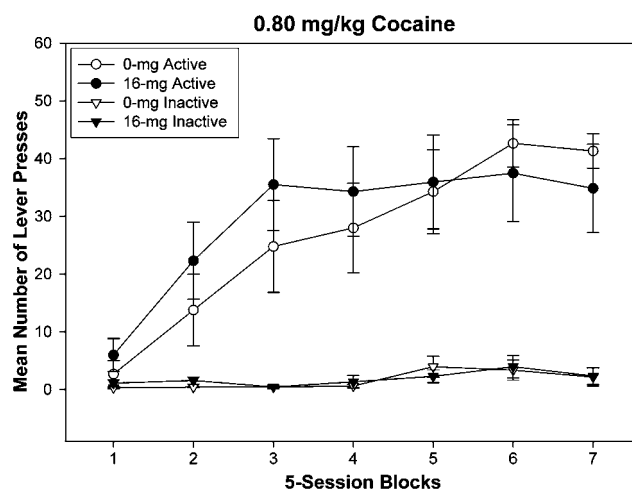

Figure 4 Mean active (0.80 mg/kg/infusion) and inactive lever responses for all animals in Group 0-mg lead ($N = 10$) and Group 16-mg lead ($N = 8$), across successive 5-session blocks (Experiment 2). Open symbols and closed symbols represent the nonexposed and lead-exposed conditions, respectively.

Table 2 Mean (SEM) Tissue Lead Concentration Values for Test Animals in Experiment 2

	Tissue lead concentrations of test animals at termination (µg/g)	
	Group 0-mg	**Group 16-mg**
Brain	0.004 (0.001)	0.007 (0.002)
Kidney	0.012 (0.007)	0.034 (0.004)
Liver	0.004 (0.001)	0.004 (0.001)
Tibia	0.031 (0.002)	1.47 (0.189)*

The symbol * indicates that control and lead-exposed animals were significantly different ($p < 0.05$).

Figure 3 Cumulative percentage (%) of nonexposed (Group 0-mg lead/$N = 10$) and lead-exposed (Group 16-mg lead/$N = 8$) rats meeting the criterion for the acquisition of cocaine (0.80 mg/kg/infusion) self-administration within the 35-day limit (Experiment 2). Open symbols and closed symbols represent the nonexposed and lead-exposed conditions, respectively.

DISCUSSION

Employing 0.20 mg/kg cocaine (i.v.) as the reinforcement outcome in a drug self-administration paradigm, the findings from Experiment 1 revealed that perinatal lead exposure resulted in a substantially greater percentage (80%) of rats reaching the criterion for acquisition over a 35-day training regimen relative to nonexposed controls (42%). Moreover, lead-exposed animals reached the acquisition criterion at a significantly more rapid rate than controls. Additional analyses revealed that at the 0.20 mg/kg/infusion dose, overall active lever responding for cocaine was greater for lead-exposed rats relative to control rats. When a higher cocaine dose (0.80 mg/kg) was substituted as the reinforcer in the self-administration model (Experiment 2), acquisition of self-administration was similar for both control and lead-exposed animals, with most animals meeting the criterion in each condition. In both experiments, lever responding was stable once animals reached criterion.

The fact that group differences in acquisition of cocaine self-administration and overall infusion rate were observed in Experiment 1 and not in Experiment 2 is not surprising, given that treatment manipulations in drug research typically are more likely to be manifested at lower unit doses. In effect, the higher cocaine dose used in Experiment 2 may have surmounted the lead-related effects and produced a ceiling effect that eclipsed the treatment effects that were clearly evident at the lower dose of cocaine.

The finding in Experiment 1 that developmental lead exposure resulted in enhanced acquisition of cocaine self-administration, as well as greater overall infusion rates, is important because animal models of acquisition of the sort employed here have predictive validity regarding possible vulnerability to drug abuse in humans. Along these lines, a number of interesting interpretive issues are presented by our results. Certainly, it is possible that the pattern of group separation may derive from lead-induced increases in the reinforcing properties of the drug, and therein the metal functionally elevates the cocaine dose. This line of reasoning agrees with a recent literature on perinatal lead/cocaine interactions where it has been shown that developmental lead exposure occasions increased sensitivity to the behavioral effects of cocaine. Previously, we mentioned that developmental lead exposure produces a displacement to the left in the cocaine dose–effect curve (Nation et al, 2004; Valles et al, 2005), increases drug seeking in a reinstatement paradigm (Nation et al, 2003), and heightens locomotor activation to cocaine administration (Nation et al, 2000). In all cases, these behavioral results in developmentally lead-exposed animals express an amplified response to cocaine relative to controls.

It is reasonable to expect that the changes in the reinforcing and stimulating properties of cocaine engendered by early lead exposure may be associated with direct changes in neural pathways associated with drug reward. Lead is known to target the mesolimbic dopamine system, most conspicuously projection neurons from the ventral tegmental area to the nucleus accumbens (Cory-Slechta, 1995; Tavakoli-Nezhad et al, 2001). Since dopamine activity along this circuit is critically involved in determining cocaine responsiveness (Ranaldi and Wise, 2001; Wise and Bozarth, 1987), functional disturbances in mesolimbic dopamine operations resulting from prenatal/postnatal lead presence may translate into an enduring increased sensitivity to cocaine. Also, there is the issue of the potential role played by glutamate in lead-related changes in cocaine self-administration. Apart from matters related to potential redefinition of drug reinforcer potency (Cornish et al, 1999; Trujillo and Akil, 1995; Wolf, 1998), glutamate is instrumental in learning and memory function (Nihei and Guilarte, 2001). Since developmental lead affects gene and protein expression of specific glutamate subunits in the morphologically immature brain (Guilarte, 1998; Guilarte and McGlothan, 2003; Guilarte and Miceli, 1992; Guilarte et al, 2003), undefined alterations in associative conditioning mechanisms may have contributed to the acquisition patterns observed here.

Other more indirect determinants of increased sensitivity to cocaine caused by perinatal lead exposure also should be considered. The fact that lead-exposed pups initially exhibited lower body weights than controls brings forth the question of early malnutrition on later self-administration of cocaine. And, disturbances in metabolic conversion, drug distribution/absorption, etc may persist for lengthy periods following early lead exposure. Further, it must be considered that heightened response rates exhibited by lead-exposed animals may derive from the aforementioned increase in activity that has been observed with animals exposed to the same regimen employed here (Nation et al, 2000).

Finally, some mention should be made of demographic variables that may influence lead/drug interactions. To this end, it is noted that risks for lead poisoning are especially pronounced among minorities residing in inner-city environments (Pellizzari et al, 1999). However, the situation is much more hydra-headed and complex than many public officials realize. For one thing, epidemiologic studies have shown that children in less socio-economically advantaged settings are more vulnerable to the effects of lead contamination than more advantaged children (cf Bellinger, 2004). In impoverished neighborhoods, it is estimated that 83% of the houses built before 1978 contain dangerous levels of lead in paint (CDC, 1997). Given this burden of elevated, unsafe lead levels is concentrated in inner-city sectors (Harwell et al, 1996; Pirkle et al, 1998), it is disquieting that drug abuse is commonly reported to be higher in these same urban communities (Brody et al, 1994; Ensminger et al, 1997). Drug abuse is not caused by environmental pollution—experiential history, psychosocial unrest, and innumerable societal factors are major determinants of this complicated health problem. Still, the scientific community and health-care providers should not ignore the growing literature that shows toxicants such as lead alter drug sensitivity.

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