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The effects of the $GABA_A$ antagonist bicuculline on cocaine self-administration in rats exposed to lead during gestation/lactation

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Abstract

The present investigation examined the effects of perinatal lead exposure on cocaine self-administration following a $GABA_A$ antagonist pretreatment. Female rats were exposed to either 0 or 16 mg lead daily for 30 days prior to breeding with unexposed males. Beginning on postnatal day (PND) 75, control (N=10) and lead-exposed (N=8) animals were trained to self-administer 0.50 mg/kg cocaine intravenously (IV). After stable responding was established, animals were tested at 0.03 and 0.06 mg/kg cocaine delivered intravenously (IV), combined with intraperitoneal (IP) administration of either saline, 0.50, 1.00 or 2.00 mg/kg bicuculline (a $GABA_A$ antagonist). The results showed that control animals increased self-administration responding at a cocaine dose of 0.06 mg/kg as bicuculline dose increased. Lead-exposed animals exhibited an opposite pattern, i.e., a decrease in active (cocaine) lever responding occurred as the bicuculline dose was increased. Results at the 0.03 mg/kg cocaine dose failed to show group separation, or significant changes consequent to the bicuculline pretreatment. The data suggest that GABA antagonism results in increased reward potency of a low dose of cocaine and further, that this effect is differentially expressed in animals exposed to perinatal lead.

Keywords: Cocaine; GABA; lead; Stress

1. Introduction

Studies of the effects of perinatal lead exposure on repeated cocaine administration reveal an apparent increase in drug sensitivity. For instance, Nation et al. (2000) observed enhanced cocaine-induced elevation in locomotor activity in animals perinatally exposed to lead. Other results from this laboratory indicate that animals tested in a reinstatement preparation exhibit an increased sensitivity relative to nonexposed animals at low doses of cocaine (Nation et al., 2003). Pertinent to the rationale for conducting the present research, in a recent cocaine self-administration investigation, animals exposed to 16 mg lead throughout gestation and lactation exhibited a displacement to the left in the cocaine dose–effect curve (Nation et al., 2004).

Due to the manifold nature of cocaine reinforcement mechanisms, several factors must be considered with respect to developmental lead/cocaine interactions. Of particular interest here is the fact that anxiogenic manipulations, specifically multiple stressful episodes, increase the functional reward value of cocaine in self-administration procedures (Goeders, 2002). Exposure to repeated stressful episodes increases cocaine-related changes in locomotion, accelerates drug acquisition, and enhances progressive ratio performance when cocaine serves as the reinforcement outcome (Covington and Miczek, 2001). Ostensibly, activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to a stressor increases circulating levels of plasma corticosterone, functionally altering the potency of cocaine at low doses (Goeders, 2002).

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Perhaps linked to this effect, GABA receptors are known to play a crucial role in the physiological response to a stressor (Nutt and Malizia, 2001), possibly due to forebrain pathways directly involved in stress-induced hormone secretion (Van de Kar and Blair, 1999). Stimulation of the $GABA_A$ receptor complex results in inhibition of adrenocorticotropin hormone (ACTH) secretion resulting from stressors, a decrease in the release of adrenocorticosteriods into circulation, and subsequently an alleviation or blockade of behavioral and physiological responses to stress (Yagi and Onaka, 1996). Stimulation of benzodiazepine receptors in the dorsal hippocampus and median raphe nucleus produce anxiolytic effects in social interaction tests and elevated plus-maze tests (Gonzalez et al., 1998), in all probability due to autoreceptor blockade leading to endogenous GABA mediated stimulation of post-synaptic $GABA_A$ receptors (Zarrindast et al., 2001). Elsewhere, it has been shown that intracranial antagonism of basolateral amygdala $GABA_A$ receptors using bicuculline methiodide (a $GABA_A$ antagonist) results in conditioned place avoidance (Thielen and Shekhar, 2002). Further, withdrawal of the $GABA_A$ neuroactive steroid allopregnalone has resulted in increases in anxiety in plus-maze tests in male and female rats alike (Gulinello et al., 2002; Smith, 2002). These data implicate the GABA receptor complex and HPA-axis as mediation sites for anxiety-induced behaviors.

Related to GABA/anxiety interactions, data from in vitro examinations indicate that lead may noncompetitively block voltage-dependent calcium channels and cause overall decreases in the amount of evoked GABA release from pre-synaptic terminals (Lasley et al., 1999; Lasley and Gilbert, 2002). This perturbation in GABA function may contribute to a variety of subsequent alterations in behavior thought to be modulated by GABA, i.e., anxiety. As previously mentioned, changes in anxiety may alter self-administration performance. Interestingly, animals developmentally exposed to lead exhibit increased baseline levels of anxiety as measured by behavioral methods such as the forced swim test (Moreira et al., 2001). Considering the disrupting effects of lead on GABA function (Lasley et al., 1999; Lasley and Gilbert, 2002; Leret et al., 2002), and the associated increase in anxiety resulting from lead exposure (Moreira et al., 2001; Yu et al., 1996), it would seem reasonable to examine possible lead/stress/GABA/cocaine interactions.

Specifically, insofar as selective $GABA_A$ antagonists increase anxiety levels in animals (Thielen and Shekhar, 2002), it is predicted that GABA antagonism and correlated increases in anxiety would mutually increase cocaine reward potency for both control and lead-exposed animals. The biphasic nature of the cocaine dose–effect curve suggests that an increase in drug potency should elevate responding at low doses, but once an optimal dose is reached further augmentation should decrease responding due to satiation effects (Lynch and Carroll, 2001). Therefore, for control animals, the administration of a $GABA_A$ antagonist, such as bicuculline, would be expected to increase cocaine self-administration at low doses of the drug because responding would be expected to remain on the ascending limb of the dose–effect curve. Lead-exposed animals also would experience a potentiation of reward potency from bicuculline pretreatment but instead would decrease responding due to their increased sensitivity to low doses of cocaine (Nation et al., 2004). This decrease would represent a functional shift in the reward value of cocaine into the range of the descending limb of the cocaine dose–effect curve.

The essential comparative issue in this investigation is that at a cocaine dose of 0.06 mg/kg, lead-exposed animals respond at high levels, while this level of the drug fails to maintain responding among control animals (Nation et al., 2004). For reasons noted, augmentation of drug reward potency by whatever means would be predicted to produce a different pattern of results for control and developmentally lead-exposed animals. With respect to bicuculline manipulations, nonexposed animals would manifest an increase in reward potency by increasing lever responding as bicuculline pretreatment dose increased. Conversely, lead-exposed animals would react to an increase in reward potency by decreasing lever responding as bicuculline pretreatment dose increased. A dose of 0.03 mg/kg was included in the present investigation because it produces almost no self-administration in both control and lead-exposed animals (Nation et al., 2004), much like saline substitution (unpublished observations). This dose is particularly low and most likely provides no inherent reinforcement value. Furthermore, no changes in self-administration patterns after bicuculline pretreatment in combination with 0.03 mg/kg would further the argument that bicuculline itself is not acting as a reinforcer.

2. Methods

2.1. Animals

The research design and conduct of the experiment were approved by the Texas A&M University Laboratory Animal Care Committee, and all aspects of the research followed the guidelines outlined in Principles of Laboratory Animal Care (National Institute of Public Health (NIH), 1996, publication No.85-23). Throughout the experiment, animals were maintained on a 12-h dark/light cycle consisting of lights on at 08:00 hours and lights off at 20:00 hours. Adult female Sprague–Dawley (Harlan; Houston, TX) rats (dams) were exposed to 0 (sodium acetate) or 16 mg lead (as lead acetate) daily via gavage, disregarding animal body weight. This approach has been used in our laboratory successfully in order to approximate environmental exposure to humans. Thus, for nonexposed (0 mg) animals, a 16 gauge [ga] gavage needle was used to administer a volume of 1.0 ml deionized water at a pH of 5.5 for 30 days prior to breeding. For lead-exposed (16

mg) animals, 16 mg lead was administered daily via gavage in the same volume of vehicle for 30 days prior to breeding.

Upon completion of the initial 30 day lead-exposure period, nonexposed males were introduced into the home cage of the dam and lead exposure continued. Once dams tested positive for copulatory plugs, males were removed from the breeding cage. The lead-exposure regimen for dams remained uninterrupted throughout breeding, gestation, and lactation. Pups were exposed to lead perinatally, having had transplacental exposure prenatally and no route of lead exposure other than the mother's milk supply postnatally. Dams were maintained on standard rat chow and tap water ad libitum throughout the experiment. Daily body weights and weekly food intake data were recorded.

On postnatal day (PND) 1, litters were culled to eight pups keeping the most males possible and using females if necessary to complete the litter. Only one male pup from each dam was used in the study in order to avoid any litter confounds that could arise (Holson and Pearce, 1992). Male pups were weaned from the dam on PND 21 and housed two or three to a cage and placed on ad libitum food and water with no further exposure to lead. On PND 50, pups were separated and individually housed for the remainder of the study. Each animal had ad libitum access to standard chow and tap water for the remainder of the study.

Dams had tail-blood drawn in a volume of 100–150 μl at the onset of breeding, at 10 days gestation and again at parturition. At weaning (PND 21 for offspring), blood was collected via cardiac puncture and brain, liver, kidney, and tibia samples were harvested from dams. Littermates were sacrificed at PND 1 and 21, and blood samples were collected for later analyses. On completion of the study, all test animals were sacrificed in order to obtain blood and tissue samples as described above.

2.2. Surgery

On PND 68, chronic indwelling jugular catheters were implanted in 12 control and 12 lead-exposed male offspring. Rats were anesthetized with separate injections of 50.00 mg/kg ketamine and 20.00 mg/kg sodium pentobarbital administered intraperitoneally (IP). A .01 interior diameter (ID) Silastic tubing (Dow Corning, Midland, MI) catheter was inserted into the right jugular vein and sutured to muscle tissue in the area of the vein. Using an 11 ga stainless steel tube as a guide, the catheter was passed subcutaneously through the body of the animal exiting the back between the scapulae. A backplate consisting of two stainless steel ovals separated by polypropylene mesh (Ethicon; Somereville, NJ) provided an anchor for 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 channel fluid swivel [22 ga] (Instech Labs, Plymouth Meeting, PA). The swivel design permitted an interlock with separate connecting arms located in the home cage and operant test chambers. The hinged arm allowed for a range of movement in either the home cage or test chamber. A .02 ID catheter continued from the top of the swivel to an infusion pump (Razel Scientific Instruments; Stamford, CT) that controlled the solution delivery. Animals were allowed 7 days to recover from surgery before commencing cocaine self-administration testing on PND 75. During this recovery period, each animal received in the home cage automated hourly intravenous (IV) infusions (200 μl) of a sterile saline solution containing heparin (1.25 IU/ml), penicillin g potassium (250,000 IU/ml), and streptokinase (8000 IU/ml). After self-administration sessions, cannulae were flushed with this solution, and then cleared with a subsequent infusion of 500 μl heparinized saline.

2.3. Apparatus

Twelve operant conditioning chambers (Model E10-10, Coulbourn, Allentown, PA) in sound attenuating cubicles served as the test apparatus. Each chamber contained two levers with a stimulus light located above each lever. Drug delivery to the animal was controlled by an infusion pump (Razel Scientific Instruments; Stamford, CT) in each chamber. A 20 ml syringe delivered IV infusions of vehicle/drug solutions in a volume of 160 μl over a 6.00 s time frame. Two IBM computers monitored and recorded drug deliveries from the chambers. Animals were run in two squads of 12 each, counterbalanced by group in terms of squad assignment and chamber. All behavioral testing occurred during the light phase of the dark/light cycle.

2.4. Behavioral testing

Baseline training commenced with active (right) lever presses resulting in infusions of 0.50 mg/kg doses of cocaine HCL (administered as the salt). Cocaine was suspended in a heparinized 0.9% saline solution. The schedule began as a fixed ratio (FR)-1 lever press (equaling one infusion) and continued as such until steady-state (<20% fluctuation over 7 days) responding was achieved following stable FR-1 baseline responding, and then animals were switched to an FR-2 until steady-state responding was evident (<20% fluctuation over 7 days). The dose of 0.50 mg/kg/infusion cocaine allowed for a rapid acquisition of the drug-response contingency. During this initial training period, animals were given an initial manual infusion by the experimenter at the onset of the session and were administered another manual infusion if no response was scored for a period longer than 15 min.

Prior to the self-administration session, the catheter connecting the infusion pump and the swivel were flushed with a 1 ml solution of 95% ethanol and a subsequent 1 ml solution of heparinized saline to clear the line. The catheter was then reconnected to the syringe pump containing a freshly mixed dosing solution and the line filled completely

with the new drug solution. After the jugular catheter was connected to the swivel, it formed a closed drug delivery system. The pump was then manually activated until the new solution was available to the animal after the initial active (right lever) press.

All sessions in the operant chambers were 2 h in duration. Responding at the appropriate FR on the active lever resulted in a cocaine infusion and a simultaneous illumination of the stimulus light positioned directly above the lever. Animals were allowed access to a maximum of 125 infusions during self-administration sessions. During training and testing, the houselights remained off. Lever responding at any time on the inactive (left) lever had no consequences but these responses were monitored and recorded. A time out period (6.00 s), in which further responding had no programmed consequences, was in effect during the duration of each infusion (160 μl over 6.00 s) and responses during this period were not included in the data analyses.

Dose–effect testing commenced after stable FR-2 baseline training was established. Cocaine test doses, GABA antagonist (bicuculline) test doses, and squad assignments, were counterbalanced across treatment conditions. Animals continued to run in two squads of 12 each. The schedule consisted of two days of testing with a combination of cocaine (0.03 or 0.06 mg/kg) [as indicated these doses were selected based on the previous data of Nation et al. (2004)] and the $GABA_A$ receptor antagonist bicuculline methobromide (either saline, 0.50, 1.00 or 2.00 mg/kg). Between each test combination were two interpolated baseline sessions (0.50 mg/kg cocaine/infusion), which were introduced in order to reestablish stable responding. Bicuculline methobromide was administered suspended in a 0.9% saline solution. Sessions continued until all combinations of 0.03 and 0.06 mg/kg cocaine and bicuculline had been completed. Bicuculline injections were administered IP, 10 min prior to the onset of testing.

Following the conclusion of the study, all animals were sacrificed using 50.00 mg/kg pentobarbital IP. Blood samples were taken via cardiac puncture. Brain, liver, kidney, and tibia were harvested and frozen at a temperature of −70 °C. Blood and tissue were later acid digested and analyzed for lead residues using atomic absorption spectrophotometry (Dearth et al., 2003).

2.5. Data analyses

Food intake and body weight data were analyzed for dams and offspring using separate Groups × Weeks analysis of variance (ANOVA) tests. Performance during testing sessions was analyzed with a 2 Groups (Group Control, Group Lead) × 2 Cocaine Doses (0.03 and 0.06 mg/kg) × 4 Bicuculline Doses (saline, 0.50, 1.00, and 2.00 mg/kg) × 2 Levers (Active, Inactive) repeated measures ANOVA, with Cocaine Doses, Bicuculline Doses, and Levers serving as within factors. Baseline responding was assessed using a 2 Groups × 8 Test Conditions × 2 Levers ANOVA. Neuman–Keuls post hoc test procedures were performed when appropriate. Number of total lever responses was used as the dependent measure and the significance level was set at $p<0.05$. Due to patency failures the group sample sizes were reduced to 10 for Group Control and 8 for Group Lead, and the analyses reported here were based on the data from these 18 animals that completed all testing combinations.

2.6. Drugs

Cocaine HCL was provided gratis by NIDA (Research Triangle Park, NC, USA). Bicuculline methobromide was purchased from Sigma-Aldrich (St. Louis, MO). Streptokinase and ampicillin sodium were purchased through the Texas A&M University Large Animal Veterinary Pharmacy.

3. Results

3.1. Body weights

Dam body weights were measured across a period of 11 weeks. Group Control and Group Lead dams showed mean body weights of 321.41±4.67 g and 314.36±5.67 g respectively at weaning and were not statistically significant $F<1$. Pup body weights were measured across a period of 7 weeks prior to onset of testing. ANOVA tests revealed no interaction or main effect for Groups $F<1$. Group Control and Group Lead test animals showed mean body weights of 368.0±14.19 g and 349.3±16.97 g respectively at onset of testing. Offspring (test animals) body weights throughout testing were measured for a period of 5 weeks. No interaction or main effect for Groups reached statistical significance $F<1$. Group Control and Group Lead showed mean body weights of 448.6±11.96 and 442.3±8.55 g, respectively, at termination of testing.

3.2. Food intake

Dam food intake was recorded and collapsed for a period of 10 weeks. Analysis of mean weekly consumption revealed no statistically significant interaction $F<1$ or main effect for Groups $F(1,23)=3.18$, $p<0.10$. Mean weekly food consumption scores for offspring were recorded for a period of 5 weeks prior to the onset of testing. No significant interaction $F<1$, or main effect for Groups $F<1$ were found.

3.3. Self-administration data

Based on the results of the 4-way interaction Groups × Cocaine Doses × Bicuculline Doses × Lever analyses, separate ANOVAs were performed on the 0.03 mg/kg

cocaine data and the 0.06 mg/kg cocaine data. A significant interaction (Groups × Cocaine Doses × Bicuculline Doses) [$F(1,48)=11.43$, $p<0.05$], and a significant main effect for Cocaine Doses were found $F(3,48)=8.66$, $p<0.05$. A significant effects also was also found for Lever $F(1,48)=127.73$, $p<0.05$, prompting an exclusion of Lever from any further analyses.

3.4. Baseline

As indicated, the baseline (0.50 mg/kg cocaine) data collected between the respective tests were analyzed using a Groups × Test Conditions × Levers repeated measures ANOVA. Although no group differences were found, a main effect for Lever did reach an acceptable level for statistical significance $F(1, 16)=116.53$, $p<0.05$. It is apparent from Fig. 1 that these differences occurred because of greater responding by both groups on the Active lever. There were no significant differences across Test Conditions, i.e., baseline responding remained stable over the course of dose–effect testing that involved cocaine/bicuculline combinations.

3.5. 0.03 mg/kg cocaine

The self-administration data for 0.03 mg/kg cocaine (Fig. 2) were examined further using a 2 Groups × 4 Bicuculline Doses repeated measures ANOVA. A significant Groups × Bicuculline Doses interaction effect was found $F(3, 48)=4.98$, $p<0.05$. Group Control animals showed significant decreases in lever responding from doses of 0.50 to 1.00 mg/kg bicuculline while Group Lead animals showed no changes in lever responding for any dose of bicuculline when tested at a cocaine dose of 0.03 mg/kg.

Table 1
Mean blood lead levels for group control and lead dams at breeding, gestation 10, PND 1 and 21

Dams	Group Control (μg/dl)	Group Lead (μg/dl)
Breeding	2.5±0.9	54.3±3.7*
Gestation Day 10	2.0±0.3	44.6±3.0*
PND 1	2.4±0.6	62.0±5.6*
PND 21	3.0±1.3	23.6±1.4*

Note. *Indicates statistical significance from Group Control at same sampling day; $p<0.05$.

3.6. 0.06 mg/kg cocaine

The 2 Groups × 4 Bicuculline Doses repeated measures ANOVA performed on the 0.06 mg/kg cocaine data (Fig. 3) revealed only a significant interaction effect $F(3, 48)=6.92$, $p<0.05$. Subsequent group comparisons indicated that Group Control animals made fewer active lever presses than Group Lead animals, when saline was administered IP; $F(1, 17)=10.42$, $p<0.05$. Group Lead animals made fewer active lever presses than Group Control animals at the 1.00 mg/kg dose of bicuculline $F(1, 17)=4.66$, $p<0.05$. Additional comparisons showed Group Control animals significantly increased cocaine self-administration responding when IP injections were

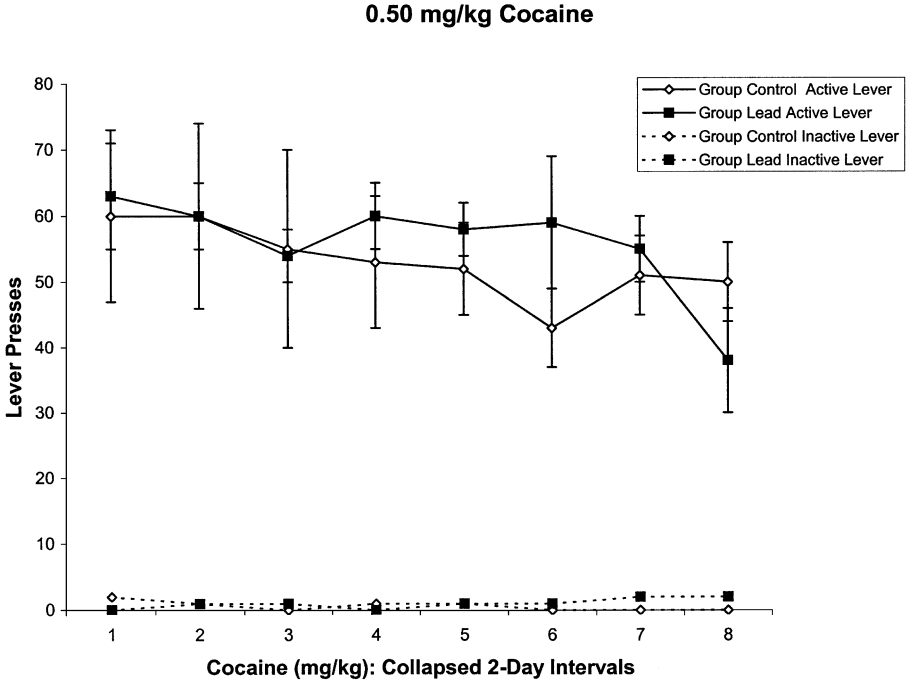

Fig. 1. Mean baseline lever press rates and standard error values for Group Control and Group Lead at 0.50 mg/kg/infusion cocaine. Average 2-day baseline session response rates were not statistically significant different at any point over the course of testing.

Table 2
Blood lead levels for group control and lead littermates at PND 1 and 21

Littermates	Group Control (μg/dl)	Group Lead (μg/dl)
PND 1	1.6±0.3	46.3±8.4*
PND 21	1.2±0.2	11.2±1.6*

Note. *Indicates statistical difference from Group Control on that sampling day; $p<0.05$.

changed from saline to a bicuculline dose of 1.00 mg/kg; $p<0.05$. In a directionally opposite manner, individual comparisons performed on Group Lead means showed significant decreases in active (cocaine) lever responding at bicuculline doses of 0.50 and 1.00 mg/kg, relative to saline; $p<0.05$.

3.7. Blood and tissue

It is apparent from Tables 1 and 2 that Group Lead dams and littermates showed greater concentrations of the metal in blood than Group Control animals. Due to an analytical error, terminal blood and tissue lead values are not available for animals that completed dose–effect testing. It is worth noting, however, that numerous developmental studies using exposure procedures identical to those employed here have shown no difference in blood, brain and liver lead concentrations upon completion of testing during the adult life-cycle (Nation et al., 2004, 2003; Rocha et al., 2004; Valles et al., 2003).

4. Discussion

Lead-exposed (Group Lead) animals receiving intravenous (IV) deliveries of 0.06 mg/kg cocaine, combined with saline administered intraperitoneally (IP), self-administered cocaine at greater levels than their nonexposed (Group Control) counterparts. Combinations of 0.03 mg/kg cocaine and saline showed no significant difference in responding between Group Control and Group Lead animals. It was further shown in the present investigation that increasing concentrations of bicuculline (IP) in combination with 0.06 mg/kg cocaine (IV) produced directionally opposite effects for Group Control and Group Lead animals, i.e., cocaine self-administration response rates for Group Control increased as bicuculline dose increased, but responding decreased for Group Lead animals as bicuculline dose increased.

It is noteworthy that the patterns of group responding involving combinations of saline/0.03 mg/kg cocaine (Fig. 2) and saline/0.06 mg/kg cocaine (Fig. 3) effectively replicate the findings reported by Nation et al. (2004), and therein validate the rationale that formed the basis for the present experiment. In the latter cocaine dose–effect study, animals exposed to control or lead-exposure regimens identical to those employed here, were tested for self-administration of cocaine presented alone (no bicuculline). Nation et al. (2004) found a dose of 0.03 mg/kg cocaine was insufficient to maintain self-admin-

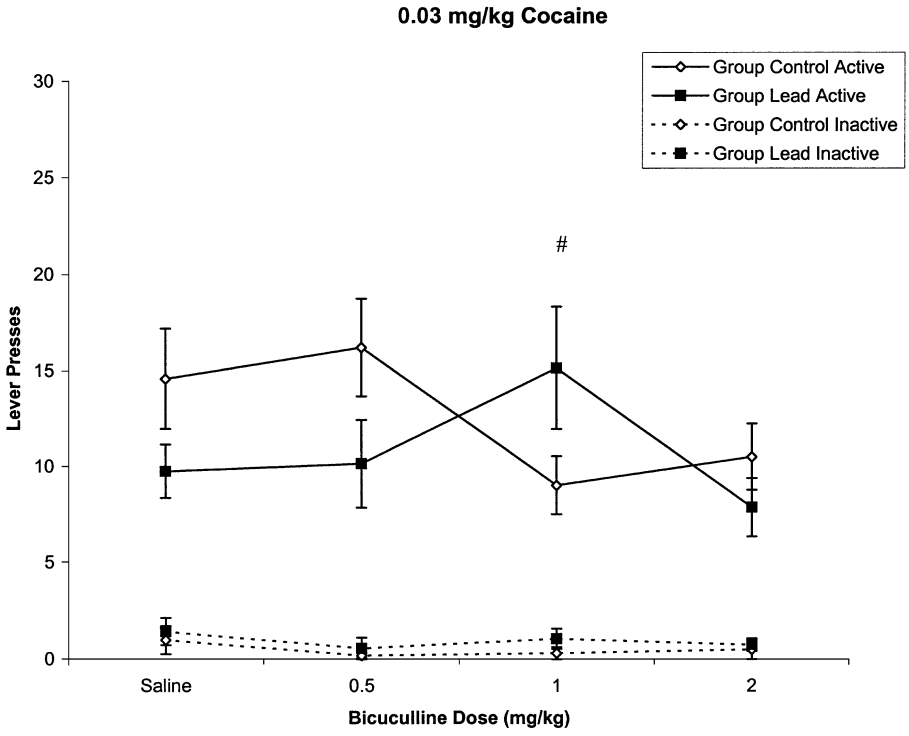

Fig. 2. Mean lever press rates and standard error values for Group Control and Group Lead at 0.03 mg/kg/infusion cocaine and different doses of bicuculline, averaged across 2-day sessions. The symbol # denotes difference from the bicuculline dose of 0.50 mg/kg within Group Control; $p<0.05$. Group Lead did not produce significantly altered response rates at any dose of bicuculline.

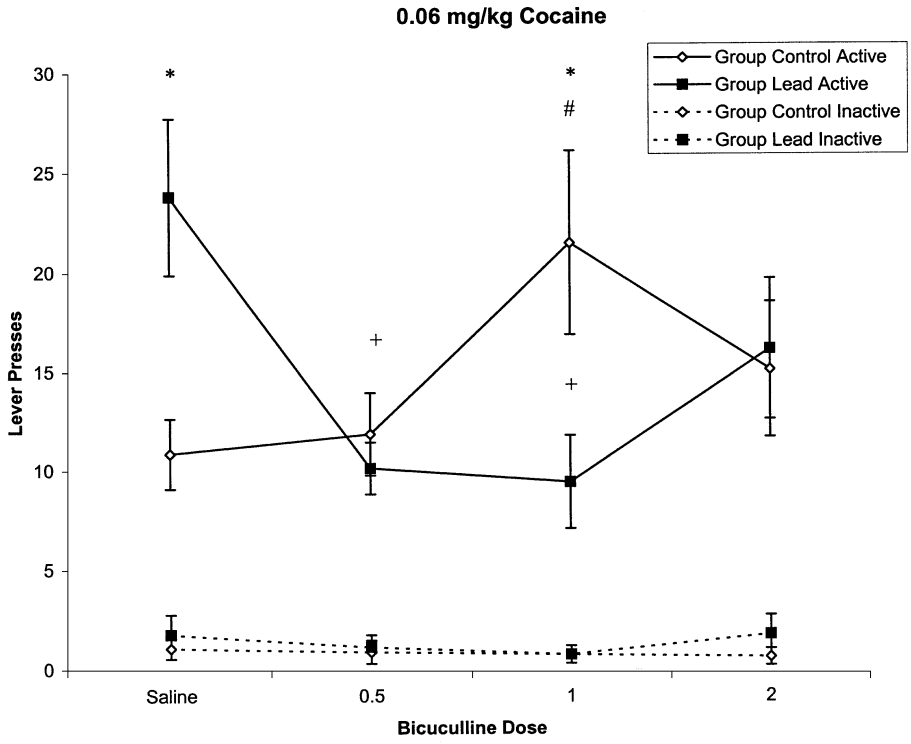

Fig. 3. Mean lever press rates and standard error values for Group Control and Group Lead at 0.06 mg/kg/infusion cocaine and different doses of bicuculline, averaged across 2-day sessions. The symbol * denotes statistically significant differences between Group Control and Group Lead Animals; $p<0.05$. The symbol # indicates statistically significant increases in response rates for Group Control animals relative to the saline condition; $p<0.05$. The symbol + indicates statistically significant decreases in responding for Group Lead relative to the saline condition; $p<0.05$.

istration responding in either control or lead-exposed groups. Further, the results of this earlier investigation showed that self-administration significantly increased from 0.03 to 0.06 mg/kg cocaine among lead-exposed animals, but an increase at 0.06 mg/kg cocaine was not evident in controls. Moreover, significantly greater response (infusion) rates were exhibited by lead-exposed animals at a dose of 0.06 mg/kg cocaine, relative to controls. This profile is identical to the one observed here where saline/cocaine treatments were functionally parallel to a cocaine-only test agenda, i.e., low response rates at 0.03 mg/kg and elevated self-administration responding in Group Lead animals at saline/0.06 mg/kg cocaine, coupled with the corresponding lack of an increase in Group Control animals at this combination, simply argues for the position taken by Nation et al. that 0.06 mg/kg cocaine is reinforcing for lead-exposed animals but not nonexposed controls.

As discussed, manipulation of the GABA receptor complex is known to alter anxiety and stress related behaviors (Nutt and Malizia, 2001; Yagi and Onaka, 1996), and anxiety potentially alters cocaine reinforcement potency (Goeders, 2002). Stimulation of $GABA_A$ and $GABA_B$ receptors results in an anxiolytic effect (Gonzalez et al., 1998) and ultimately attenuates cocaine reward (Brebner et al., 1999; David et al., 2001; Zarrindast et al., 2001). Consistent with this line of reasoning, the $GABA_A$ antagonist bicuculline is thought to possess anxiogenic properties and therein amplify cocaine reward values (Thielen and Shekhar, 2002).

Because lead contamination disrupts GABA availability by decreasing amounts of evoked release (Lasley et al., 1999; Lasley and Gilbert, 2002), and promotes dopamine binding in nucleus accumbens (Pokora et al., 1996), it is understandable that lead-exposed animals in the current investigation, as well as the earlier Nation et al. (2004) report, would maintain responding at a cocaine dose that failed to serve as an effective maintenance reward outcome for control animals.

The cocaine dose–effect curve is characterized by an ascending limb and a descending limb (Lynch and Carroll, 2001). Given that Group Control animals receiving saline injections self-administer cocaine infrequently at doses of 0.03 and 0.06 mg/kg cocaine, it follows that any increase in reward potency would occasion increased active-lever responding, at least up to some peak drug dose. In contrast, for animals developmentally exposed to lead, increases in reinforcement strength from their high-responding dose of 0.06 mg/kg cocaine would result in reduced lever pressing, i.e., they functionally would be responding on the descending limb of the dose–effect curve. Because bicuculline elevates anxiety and therein arguably enhances cocaine reward value, the behavioral data for 0.06 mg/kg cocaine are in line with the aforementioned predictions that Group

Control animals would show increasing self-administration numbers, while Group Lead animals would show decreasing responding due to the functionally higher reward value of 0.06 mg/kg cocaine at increasing concentrations of bicuculline. At a dose of 0.03 mg/kg the drug simply may have been too low to interact with bicuculline and alter lever responding for either group.

The data from this investigation suggest that GABA may play a modulatory role in defining the reinforcement effectiveness of cocaine, perhaps by altering anxiety related mechanisms, such as the hypothalamic–pituitary–adrenal (HPA)-axis, which are known to alter cocaine reward potency. Furthermore, this modulation of cocaine reward potency may be interacting with the changes in GABA function produced by lead exposure. Data from the 0.06 mg/kg cocaine dose underscore the response-altering effects of bicuculline in two groups of animals experiencing functionally different reward values for low doses of a psychomotor stimulant.

Additionally, our findings may be relevant to the human population, inasmuch as lead contamination continues to be a problem in industrialized nations, and particularly in urban areas (Ensminger et al., 1997; Harwell et al., 1996; Pirkle et al., 1998). Parallels between drug abuse and elevated risk for chronic lead exposure in the inner-city are cause for continuing investigations regarding possible pollutant/drug interactions. Children in particular are susceptible to the debilitating effects associated with lead toxicity. A fundamental concern in this and recent reports is that cognitive/behavioral deficits apparently are associated with lead contamination that falls within the currently allowable blood lead safety limits (Canfield et al., 2003). It remains to be determined how serious these and other health threats, including possible heightened vulnerability to drug abuse, are for young people and precisely at what level of exposure lead distribution poses a direct or indirect environmental concern.

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