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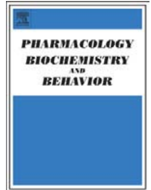

Prenatal lead exposure enhances methamphetamine sensitization in rats☆

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ABSTRACT

Adult female rats were exposed to lead-free sodium acetate via gavage [0 mg (vehicle control)] or to 16 mg lead as lead acetate for 30 days prior to breeding. Following confirmation of breeding, the female animals continued to be exposed to their respective doses throughout gestation and lactation. When weaned, 16 control and 16 lead-exposed offspring were placed on regular water and food (lead-exposure was discontinued) until postnatal day (PND) 70. At this time, one-half of the control animals and one-half of the lead-treatment animals received intraperitoneal (i.p.) injections of the vehicle (saline) for 10 successive days and the remaining animals in each exposure conditions received daily injections of 1.0 mg/kg (+)-methamphetamine (METH) for 10 days ($N=8$/group). Locomotion in automated chambers was monitored daily for 45 min post-injection.

Subsequently, during dose–effect testing, all animals received consecutive daily i.p. injections of 0, 1.0, 2.0, and then 4.0 mg/kg METH. The results of the experiment showed that both control and lead-exposed animals exhibited heightened locomotor activity (i.e. behavioral sensitization) to the repeated administration of 1.0 mg/kg METH. More importantly, animals developmentally (perinatally) exposed to lead showed more rapid sensitization than did their control counterparts. These data indicate that early lead exposure increases sensitivity to the locomotor-stimulating effects of METH. In contrast, identically exposed lead animals exhibit diminished METH dose–effect responding when tested in an intravenous (i.v.) self-administration paradigm [Rocha A., Valles R., Bratton G.R., Nation J.R. Developmental lead exposure alters methamphetamine self-administration in the male rat: acquisition and reinstatement. Drug Alcohol Depend 2008a;95:23–29, Rocha A., Valles R., Hart N., Bratton G.R., Nation J.R. Developmental lead exposure attenuates methamphetamine dose–effect self-administration performance and progressive ratio responding in the male rat. Pharmacol Biochem Behav 2008b;89:508–514].

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1. Introduction

Although atmospheric levels of lead in North America have fallen dramatically over the last several years, exposure to lead continues to be problematic. Especially in the inner cities and among minorities, an alarmingly high percentage of children register blood lead levels that exceed the allowable limits set forth by the Centers for Disease Control and Prevention in inner-urban areas (Kemp et al., 2007; Mielke, 1999; Pirkle et al., 1998). Inasmuch as blood lead levels within the so-called “safe” range (less than 10 µg/dl) have been shown to be associated with neurobehavioral impairment (cf, Hubbs-Tait et al., 2005; Lamphear et al., 2005) and deranged cognitive function (Bellinger, 2006; Canfield et al., 2003), there continues to be concern in the scientific community about the potential adverse effects of lead exposure.

In addition to the potential cognitive effects of lead, there is evidence to suggest that lead exposure may result in a predisposition to develop drug abuse. For several years, this laboratory has conducted a series of studies to characterize the interactive relations between developmental lead exposure and changes in sensitivity to psychoactive drugs. It has been observed that perinatal (gestation/lactation) lead exposure enhances locomotor activity (sensitization) to effects of cocaine even when lead exposure had been discontinued at weaning and testing did not occur until 60 days later (Nation et al., 2000). Consistent with these findings, and perhaps more importantly, perinatal lead exposure produces a leftward displacement in the dose–effect for intravenous (i.v.) self-administration responding for cocaine (Nation et al., 2004; Valles et al., 2005), and increases the chances for relapse in a reinstatement paradigm (Nation et al., 2003). Finally, Rocha et al. (2005) report that responding for self-administered cocaine is acquired more quickly in a preparation that combines

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noncontingent cocaine deliveries for 3 h prior to a 3 h contingent operant testing procedure. Thus, the overall pattern between prenatal lead and cocaine is one of lead-induced augmentation.

A key component of cocaine's biobehavioral effects relates to antagonism of membrane transporters for dopamine (Lin and Uhl, 2002; Rothman et al., 2001). In contrast, methamphetamine (METH) is a substrate for the dopamine transporters and induces the transporter to run in reverse, thereby increasing synaptic dopamine levels (Howell and Kimmel, 2008; Rothman et al., 2001). The use and abuse of METH appears to be a growing issue in the United States (Cho and Melega, 2002; Crèvecoeur et al., 2007) as well as worldwide (Anglin et al., 2000; Rawson and Condon, 2007). With regard to lead exposure and METH use, it is of concern that low socioeconomic status is significantly related to METH use (Iritani et al., 2007) and to lead exposure within the inner city (Ensminger et al., 1997; Kemp et al., 2007; Mielke, 1999; Mielke et al., 2008; Pirkle et al., 1998). Of specific interest herein was whether perinatal lead exposure would augment the locomotor effects of METH in a manner consistent with its effects on cocaine-induced hyperlocomotion. Accordingly, offspring from dams repeatedly exposed to 0 mg lead daily or 16 mg lead daily were tested during adulthood regarding changes in locomotor activity following repeated daily intraperitoneal (i.p.) administration of vehicle or 1.0 mg/kg METH, a protocol known to induce sensitization. This METH dose increases locomotion in rats, but it does not induce stereotypy (Hall et al., 2008). Following this sensitization test period, all test animals were administered 0.0, 1.0, 2.0, and then 4.0 mg/kg METH (i.p) on consecutive locomotion trials.

2. Methods

2.1. Animals

Animal maintenance and research were conducted in accordance with the guidelines provided by the Texas A&M University Laboratory Animal Care Committee, and the Public Health Service Policy outlined in the publication of the Guide for the Care and Use of Laboratory Animals (1996).

2.2. Lead exposure regimen

For 30 consecutive days, adult female (200–225 g) Sprague–Dawley rats (Harlan; Houston, TX) were exposed daily to 0 mg lead (sodium acetate) or 16 mg lead (as lead acetate) daily using a 18 ga gavage needle to administer the respective solutions in a volume of 1.0 ml of pH adjusted deionized water. This procedure has been used in previous developmental lead studies to ensure stable blood/tissue lead levels (cf. Nation et al., 2000, 2003, 2004; Rocha et al., 2004). The present lead dose was selected based on previous studies that found it produces differential behavioral effects while not altering dam body weight or the locomotor ability of pups (see Nation et al., 2000). Following the initial 30 day lead exposure period, females were bred to non-lead exposed males. Once females tested positive for copulatory plugs, the males were removed from the home cage. Rate of pregnancy did not differ between control and lead groups. Females continued to receive their daily doses of the control solution or lead acetate solution throughout the gestation and lactation periods. Standard rat chow (Teklad; Madison, WI) and tap water were continuously available for dams in the home cage. Litters were culled to a maximum of eight pups on PND 2 with the proviso that each group retained the maximum number of male pups. On PND 21, the litters were shifted to housing in groups of 2–3 per cage (males only). Only one pup from each litter was used to form the four groups of the experiment in order to avoid confounds that are sometimes evident in studies involving toxic exposure (Holson and Pearce, 1992). Starting on PND 70, rats were individually housed in a colony room with a 12 h light/dark cycle (lights off at 1000 h). Behavioral testing commenced on PND 70. Locomotion was measured at approximately 10:00 h, at the start of the dark cycle.

2.3. Apparatus

The assessment of locomotion was made in a set of 8 automated optical beam activity monitors (Model RXYZCM-16; Accuscan Instruments, Columbus, OH, USA). Each monitor was housed within a 40×40×30.5 cm acrylic cage. Activity monitors and cages were located in a sound-proof room with a 40 dB [SPL] white noise generator operating continuously. A multiplexor-analyzer monitored beam breaks from the optical beam activity monitors and tracked the simultaneous interruption of beams. The multiplexor-analyzer updated the animal's position in the acrylic cage every 10 ms using a 100% real-time conversion system. Computerized integration of the data obtained from the monitor afforded the recording of general activity using total distance traveled scores (in cm) as the primary dependent measure (Sandberg et al., 1987).

2.4. Procedure

Test animals were randomly selected from a given litter and then randomly assigned to one of four test groups. One-half of the control animals and one-half of the lead-treatment animals received intraperitoneal (i.p.) injections of the vehicle (saline) for 10 successive days and the remaining animals in each exposure conditions received daily injections of 1.0 mg/kg (+)-methamphetamine (METH) for 10 days ($N=8$/group). Animals receiving methamphetamine were administered daily i.p. injections of 1.0 mg/kg methamphetamine HCl expressed as the salt, while vehicle controls received saline (1.0 ml/kg volume). Methamphetamine was provided by Dr. Kevin Gormley of the Basic Research Division of NIDA. In this initial phase of the project, animals were tested during 1 h sessions each day for 10 successive days, in four squads of 8 rats (total = 32) counterbalanced by group (i.e. two rats from each lead-drug exposure condition were run in each squad). With the room lights off, animals were placed in their respective test chambers for a 15-min baseline-recording period on each test trial prior to receiving either a methamphetamine (1.0 mg/kg METH) or vehicle (0 mg/kg METH) injection. At the point of the injection, the room lights were turned on and the animal was placed back in the chamber immediately following the injection, at which time the room lights again were turned off. This procedure was employed in order to increase the discriminatory properties of the injections. Previous cocaine investigations (e.g., Post et al., 1981) have shown that contextual cues contribute to augmented responding associated with repeated drug administration. Insofar as administering the injections, placement in the test chambers, turning off the test room lights and other pre-injection correlates serve as conditioned stimuli, it is reasonable to assume that reinstatement of such events could alter locomotor responding (in the absence of the drug). We tested for such a possibility by administering a vehicle only (0 mg/kg METH) injection following initial sensitization testing (see procedures for Day 11 of testing). In all tests conducted in this study, total distance traveled (cm) was recorded preinjection for 15 min and for post-injection across successive 5-min intervals for 45 min. The 45 min test period used herein has been sufficient to detect dose-dependent differences between analogues of amphetamine that act on monoamine transporters (Wellman et al., 2009). On Days 11–14, all animals within each of the four groups received successive daily i.p. injections of 0, 1.0, 2.0, and 4.0 mg/kg METH.

2.5. Tissue sampling and analyses

For control and lead-exposed dams, 100–150 µl of tail-blood was drawn at breeding, parturition (PND 2), and weaning (PND 21) and analyzed for lead levels. In addition, at the point of termination of the

Table 1
Mean (SEM) blood and tissue lead concentration values for dams, littermates, and test animals.

Blood lead concentration (μg/dl)		
	Group 0-mg	Group 16-mg
Dams		
Postnatal day 2	2.53 (2.1)	77 (15.0)*
Postnatal day 21	1.96 (0.48)	44.1 (6.08)*
Littermates		
Postnatal day 2	0.76 (0.2)	75.5 (11.0)*
Blood post-experiment		
Methamphetamine	0.19 (0.007)	0.24 (0.04)
Vehicle only	0.19 (0.01)	0.28 (0.013)
Tissue concentrations of dams at weaning (μg/g)		
Brain	0.006 (0.001)	0.6 (0.07)*
Kidney	0.04 (0.034)	11.51 (0.57)*
Liver	0.007 (0.002)	0.87 (0.15)*
Tibia	0.11 (0.01)	127.2 (15.18)*

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

experiment, blood was taken from test animals for lead concentration analyses. Littermates of test animals were sacrificed on PND 2, and blood samples were collected for subsequent analyses. Dams were sacrificed at weaning with blood and tissue (brain, kidney, liver and bone) samples collected for subsequent analyses. The body weights (Mean ± SEM) of the control dams on PND 21 were 308 ± 4 g whereas those of the lead dams were 291 ± 8 g.

Blood lead and tissue residues were measured by inductively coupled plasma-mass spectroscopy on a Perkin Elmer DRC 2 instrument following acid digestion in a microwave. The ^{208}Pb isotope and ^{209}Bi were used as internal standards. Weighted linear calibration was performed with a blank and three external standards (0.05, 20, and 200 parts per billion) and was verified by analyzing NIST SRM 1640 (trace elements in water). Data were acquired in peak hopping mode, using the autolens feature and three replicate reads per determination. Verification of the calibration and baseline were performed after every group of 10 samples and at the end of the analytical run.

2.6. Data analyses

The overall design for the sensitization phase of the study was a split-plot (mixed) factorial consisting of the between-group factors of lead exposure (control versus lead) and methamphetamine dose (0 versus 1 mg/kg) and a within-group factor of time after injection (5 min bins over a 45 min period). The dose–effect behavioral data were analyzed using a split-plot (mixed) factorial design consisting of the between-group factors of lead exposure (control versus lead) and METH pretreatment dose (0 versus 1 mg/kg) and within-group factors of METH treatment dose (0, 1.0, 2.0, and 4.0 mg/kg) and time after injection (5 min bins over a 45 min period as well as total locomotion scores). The body weight and blood/tissue lead level data were analyzed using a complete factorial consisting of the between-group factors of lead exposure (control versus lead) and METH dose (0 versus 1.0 mg/kg). Statistical significance was deemed to be $p<0.05$ and the Bonferroni procedure was used to examine mean group differences.

3. Results

3.1. Body weights

Body weights were averaged for each animal in each group over the final 7 days prior to commencing activity testing (data not shown). ANOVA of these data revealed a significant effect of lead treatment (F (1,28) = 7.94, $p<0.009$). Lead-pretreated rats weighed an average (± SEM) of 366 g (± 5.1 g), whereas control rats weighed an average of 386 g (± 5.1 g). There were no significant effects of METH treatment nor was there an interaction between lead treatment and METH treatment factors on body weight.

3.2. Blood and tissue lead levels

As expected, dams exposed to lead exhibited a considerable body lead burden (Table 1). At the time of weaning, dams exhibited significant levels of lead in tibia, kidney, liver and brain as well as blood. Similarly, littermates showed significant blood levels of lead at PND 2 and PND 22. By the end of this experiment, blood lead levels in both control and lead groups were not different. Thus, the behavioral disturbances associated with perinatal lead exposure occurred at a time point far beyond that at which the lead burden had cleared from blood.

3.3. Methamphetamine sensitization

Fig. 1 depicts the changes in total distance traveled scores for rats treated on Days 1–10 with either vehicle or 1.0 mg METH. On Day 1, the METH groups exhibited a significant increase in locomotion that was identical for both control and lead-pretreated rats. Repeated administration of this fixed dose of METH resulted in significant sensitization, as evident in augmented locomotion scores across days. ANOVA of these data revealed a significant effect of METH treatment on locomotion ($F(1,28) = 208.6$, $p<0.0001$) as well as a significant effect of day ($F(9,252) = 23.57$, $p<0.0001$). While there was no significant overall effect of lead treatment, there was a significant interaction between the factors of lead treatment, METH treatment, and day ($F(9,252) = 2.964$, $p<0.002$). Subsequent contrasts indicated that lead exposed rats showed greater locomotion following METH administration than did control rats on days 3, 4 and 5 and suggest that the METH treated groups converged on day 6 and were comparable thereafter.

To further explore these data, the total distance traveled scores from Days 1, 5 and 10 were further analysed, as a function of 15 min time bin (see Fig. 2). On Day 1, there was noted a significant effect of drug ($F(1,28) = 34.2$, $p<0.002$) but no effect of group or any

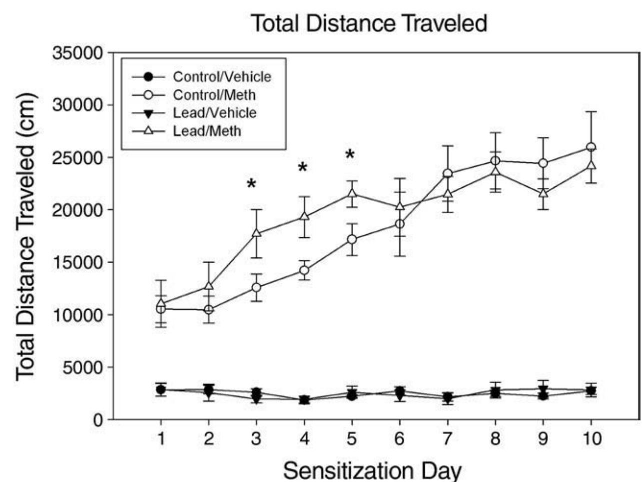

Fig. 1. Mean group changes in total distance traveled scores (cm) over a 45 min period for control and lead-pretreated rats injected daily with either vehicle (VEH) or 1.0 mg/kg METH ($N = 8$ per group) on Days 1–10. The bar above each symbol reflects the standard error of the mean for that value. Significant differences ($p<0.05$) between control and lead-pretreated groups are denoted by a *.

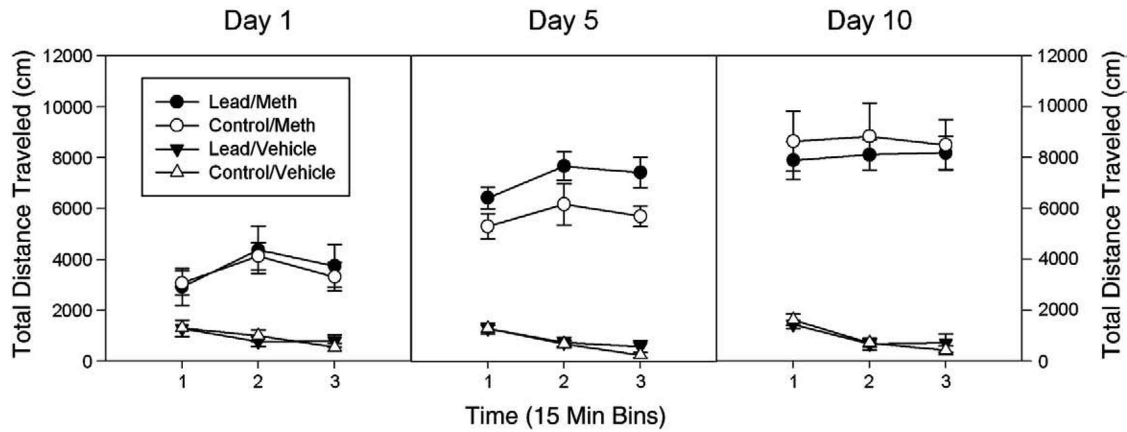

Fig. 2. Mean group changes in total distance traveled scores (cm) over three successive 15 min periods for control and lead-pretreated rats injected daily with either vehicle (VEH) or 1.0 mg/kg METH ($N=8$ per group) on Days 1, 5, and 10. The bar above each symbol reflects the standard error of the mean for that value.

interaction between group and drug or group, drug and time. On Day 5, the analyses indicated a significant effect of drug ($F(1,28)=269.3$, $p<0.0001$) and of group ($F(1,28)=5.2$, $p<0.0001$) but no interaction between group and drug or group, drug and time. By Day 10, the effect of drug was significant ($F(1,28)=134.6$, $p<0.0001$) whereas the effect of group was not.

On Day 11 (see Fig. 3: 0.0 mg/kg drug dose), all rats were treated with vehicle prior to the 45 min test period. Rats previously treated with METH showed significantly elevated locomotion scores that were similar for both control and lead groups. ANOVA of Day 11 locomotion data revealed a significant stimulatory effect of METH pretreatment on locomotion after vehicle treatment ($F(1,28)=15.47$, $p<0.001$), but no effect of lead group nor an interaction between METH pretreatment and lead group. This difference on Day 11 may reflect a degree of conditioned reactivity to METH, but it is unlikely due to a drug carryover effect, given the rapid clearance of METH in the rat (i.e. a half-life of approximately 1 h: cf. Rivière et al., 1999; Segal and Kuczenski, 2006).

3.4. Methamphetamine dose effect tests

Injection of control and lead-pretreated rats with an ascending dose series of 1.0, 2.0 and 4.0 mg/kg METH produced an inverted-U pattern in locomotion (Fig. 3). Because rats formerly treated with METH showed greater locomotion after vehicle, the locomotion data from Day 11 were used as a covariate for the dose–effect data for Days 12, 13 and 14. This split-plot ANOVA revealed a significant effect of METH dose which reflected a linear decrease in locomotion as METH dose increased from 1.0 to 4.0 mg/kg ($F(1,27)=13.306$, $p<0.001$). There was a significant interaction between METH pretreatment and dose ($F(2,54)=10.225$, $p<0.0001$) but no effects of lead exposure, METH group, nor a significant interaction between METH group and lead exposure. As expected, rats pretreated with 1.0 mg/kg METH for 10 days exhibited greater locomotion after injection of 1.0 mg/kg METH on Day 12 than did rats pretreated with vehicle. At 2.0 mg/kg METH, rats pretreated with vehicle on Days 1–10 showed a significant increase in locomotion, whereas rats pretreated with METH displayed a decrease in locomotion (relative to their scores after 1.0 mg/kg METH). At 4.0 mg/kg METH, all groups decreased their locomotion from that evident after 2.0 mg/kg METH.

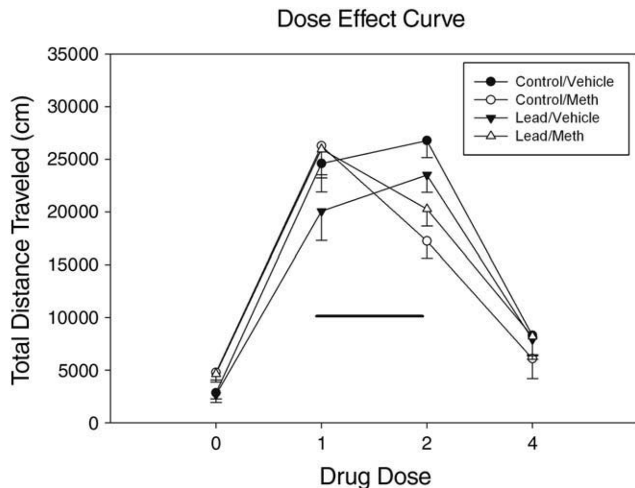

Fig. 3. Mean group total distance traveled scores (cm) for rats treated with 0, 1.0, 2.0 and 4.0 mg/kg METH starting on Day 11. The control and lead-pretreated groups ($N=8$ per group) in this panel were treated on Days 1–10 with either vehicle or 1.0 mg/kg METH. The bar above each symbol reflects the standard error of the mean for that value. Significant differences ($p<0.05$) between rats pretreated with VEH and rats pretreated with METH are denoted by a *.

4. Discussion

In the present study, rats exposed to lead during gestation and lactation showed an increased rate of development of locomotor sensitization during the first 5 days of METH administration. On Day 6 and thereafter control and lead-pretreated rats reached a similar plateau of locomotion in response to repeated daily METH treatments. The locomotor results are generally consistent with the augmented behavioral sensitization induced by perinatal lead in male rats exposed to morphine (Nation et al., 2000) and to cocaine (Nation et al., 2000). In the present study, this augmentation was short-lived and only apparent during the initial days of METH exposure. The short-lived duration of the difference between lead and control rats may reflect our choice of the 1.0 mg/kg METH dose, which induced rapid sensitization such that the control rats caught up with the lead rats by Day 6. As noted above, this dose is sufficiently high to induce sensitization, but not stereotypy (Hall et al., 2008). Of interest here is the fact that perinatal lead exerts a consistent pattern of augmentation of behavioral reactivity in spite of the widely diverging mechanisms of action of cocaine (a dopamine transporter antagonist), methamphetamine (a transporter substrate drug that releases dopamine, norepinephrine, and serotonin) and morphine (an indirect dopamine agonist via inactivation of GABA cells that innervate nucleus accumbens neurons).

With regard to the impact of perinatal lead exposure on intravenous self-administration, the profile becomes complex. A portion of the complexity reflects an interaction between developmental age and lead exposure. We reported that the enhanced sensitivity to cocaine following developmental lead exposure is opposite that noted with adult exposure, i.e., in adults lead exposure

decreases cocaine sensitivity (Nation et al., 1996). Additionally, there appear to be major differences between different drugs of abuse, especially cocaine and METH with regard to the impact of perinatal lead exposure on drug self-administration in adulthood. As noted above, perinatal lead exposure augments self-administration of cocaine (Nation et al., 2004; Rocha et al., 2005; Valles et al., 2005) and increases the chances for relapse in a reinstatement paradigm (Nation et al., 2003). In contrast, Rocha et al. (2008a) reported that perinatal lead exposure *retards* acquisition of a METH self-administration response and *decreases* relapse potential. Elsewhere, Rocha et al. (2008b) found that early lead exposure results in a *downward shift* in the METH self-administration dose–effect curve, and it also *decreased* progressive ratio responding for METH. These data point to lead-induced antagonism of METH action and in that regard are compatible with an earlier study of heroin self-administration (Rocha et al., 2004).

The present study indicates that perinatal lead augments METH locomotor sensitization as does cocaine, but does not indicate the locus or mechanism of action at which this effect occurs. The present study also does not indicate why this effect is different than that of METH self-administration (Rocha et al., 2008a,b). Although there is a sizable literature regarding the effects of postweaning lead exposure on relevant drug-related neural systems (refer to Cory-Slechta, 1995 D.A. Cory-Slechta, Relationships between lead-induced learning impairments and changes in dopaminergic, cholinergic, and glutamatergic neurotransmitter system functions, *Ann. Rev. Pharmacol. Toxicol.* 35 (1995), pp. 391–415. View Record in Scopus | Cited By in Scopus (103) Cory-Slechta, 1995), our understanding of the effects of preweaning lead exposure on neural mechanisms that are central to defining drug reactivity is limited (Devoto et al., 2001). Lead can alter meso-limbic dopamine function by reducing presynaptic autoreceptors or dopamine transporters and thus augment DA release, (Cory-Slechta, 1997; Pokora et al., 1996; Zuch et al., 1998). Postnatal lead, however, also alters neurochemical systems that in turn interact with mesolimbic dopamine. Lasley and Gilbert have shown, for example, that lead has the capacity to diminish hippocampal glutamate function as well as GABA release (Lasley and Gilbert, 1996). The multiple sites of action of lead in brain have the potential to complicate the analyses of changes in drug action (White et al., 2007). Even more importantly, almost no information exists regarding the potential enduring mechanistic changes caused by early lead exposure in instances where the lead exposure regimen has been discontinued, as was the case in the present study. Studies are underway to examine the impact of perinatal lead exposure on brain dopamine function.

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