Inorganic Lead Exposure in the Rat Activates Striatal cFOS Expression at Lower Blood Levels and Inhibits Amphetamine-Induced cFOS Expression at Higher Blood Levels

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ABSTRACT
The impact of inorganic lead exposure on dopamine (DA) neurotransmission in the basal ganglia was examined. Amphetamine (AMPH)-induced cFOS immunoreactivity (cFOS-IR) in the striatum was determined after a 3-week exposure to lead acetate (0, 50, or 250 ppm). On the 21st day of lead exposure, rats were challenged with AMPH (4 mg/kg i.p.) or saline vehicle (Veh) and were assayed for presence of cFOS-IR. In the untreated control (Con) group, AMPH challenge (Con/AMPH) increased cFOS-IR expression by approximately 35-fold over Veh challenge (Con/Veh) (P < 0.01). In the Pb50/Veh group, cFOS-IR expression was approximately 7-fold greater than in the Con/Veh group (P < 0.05). Given that there was negligible cFOS-IR expression in the Con/Veh group, this indicates that the Pb50 exposure induced cFOS expression. The increase in cFOS-IR in the Pb50/AMPH was also significant (P < 0.01), but it was not different from the Con/AMPH (P > 0.20). Neither the Pb250/Veh group nor the Pb250/AMPH group had a significant increase in cFOS-IR relative to Con/Veh (P > 0.20). These results indicate that chronic 50 ppm lead exposure induced a low but statistically significantly level of cFOS gene activation and that it did not affect the AMPH-induced cFOS activation. However, chronic 250 ppm lead exposure inhibited AMPH-induced activation of cFOS in the striatum by about 89%. Therefore, lead is capable of both activating cFOS expression at low levels of exposure (mean blood lead level 21.6 ± 1.9 μg/dl) and inhibiting AMPH-induced cFOS expression at higher levels of exposure (mean blood lead level 47.4 ± 2.6 μg/dl).

Numerous studies have shown that lead exposure alters the turnover or release of many classical neurotransmitters, including glutamate, acetylcholine, GABA, and DA (Minnema et al., 1986; Shao and Suszkiw, 1991; Cory-Slechta, 1995; Kala and Jadhav, 1995a,b; Braga et al., 1999; Lasley and Gilbert, 2002). The present study focuses on the effects of in vivo lead exposure on the midbrain DA system. It has been well established that the midbrain DA system is affected by lead exposure at clinically relevant blood lead levels in the rat (Cory-Slechta, 1995, 1997; Kala and Jadhav, 1995a,b; Tavakoli-Nezhad et al., 2001). The midbrain DA system is involved in cognition, attention, reward mechanisms, and motor function and has been shown to be an important participant in many neurological and psychiatric disorders. Abnormalities in the midbrain DA system are highly suspect in the etiology of attention-deficit hyperactivity disorder (Sagvolden and Sergeant, 1998; Solanto, 2002; DiMaio et al., 2003; Krause et al., 2003). Although the etiology of attention-deficit hyperactivity disorder (ADHD) is likely multifactorial (Davids et al., 2003; DiMaio et al., 2003), evidence suggests that lead exposure is a risk factor for the development of ADHD in an exposed subpopulation of ADHD patients (Minder et al., 1994; Tuthill, 1996; Canfield et al., 2003b). However, the precise nature of the

ABBREVIATIONS: DA, dopamine; ADHD, attention-deficit hyperactivity disorder; cFOS-IR, cFOS-immunoreactivity; NMDA, N-methyl-D-aspartate; CREB, cAMP response element-binding protein; Con, control; Veh, vehicle; AMPH, amphetamine; ANOVA, analysis of variance; SKF-38393, (±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride.
effects of lead on attention mechanisms, and the degree to which lead-induced attention deficits contribute to impaired learning, is a matter still under investigation (Cory-Slechta, 2003).

Kala and Jadhav (1995a) have reported that exposure to 50 ppm lead for 90 days resulted in a decrease in basal and K+-stimulated release of DA and its metabolites in the nucleus accumbens (i.e., ventral striatum). Jadhav and Ramesh (1997) have also reported that exposure to 50 ppm lead for 30 days resulted in a 43% decrease in tyrosine hydroxylase activity in the nucleus accumbens. These results suggest that the effects of drugs that elicit DA release may be altered by lead exposure.

Amphetamine has been used as a pharmacological tool for probing catecholamine release mechanisms. Amphetamine is an indirect DA agonist, and it competitively inhibits DA transporters and elicits catecholamine release via transport-mediated exchange, thereby increasing synaptic DA levels (Leviel, 2001). Devoto et al. (2001) showed that, in rats exposed to lead in vivo, amphetamine-induced DA release in the nucleus accumbens was significantly lower in the lead-exposed group (Devoto et al., 2001). It should also be noted that amphetamine and amphetamine-like drugs, such as methylphenidate, have been shown to be effective agents in the control of ADHD symptoms. Imaging studies of ADHD patients show forebrain abnormalities, particularly in striatal regions, and single photon emission computed tomography has shown an elevation in striatal dopamine transporter density in these patients (Krause et al., 2003).

Amphetamine has been shown to induce expression of cFOS in both the dorsal and ventral striatum (Graybiel et al., 1990). The amphetamine-induced expression of cFOS-IR has been shown to be dependent on both D1 and NMDA receptor activation (Robertson et al., 1991; Young et al., 1991; Berretta et al., 1992). D1 receptor activation increases cAMP, resulting in the phosphorylation of the cAMP responsive element-binding protein (CREB) and the induction of cFOS in striatal neurons (Das et al., 1997). Recently, lead exposure has been shown to induce cFOS in the rat striatum (Ramesh et al., 2001). Because lead exposure has been shown to affect the midbrain DA system in animal lead exposure models, alter basal forebrain DA release and amphetamine-elicted forebrain DA release, and also induce cFOS expression in the forebrain, we sought to determine whether chronic lead exposure would alter the amphetamine-induced expression of the cFOS gene in the striatum. This study examines the effects of chronic lead on the trans-synaptic DA modulation of gene expression in the rat striatum.

Materials and Methods

Animals and Drug Treatments. Animals were housed in facilities operated by the Department of Laboratory Animal Resources at Wayne State University and maintained according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) were 20 days old on the day of arrival. Animals received water and rat chow (Lab Diet 5001, PMI Nutrition International, LCC, Brentwood, MO) ad libitum. The day after arrival, the rats were weighed (mean body weight 45 ± 0.6 g; n = 62) and randomly assigned to treatment groups. The control group received purified water (controls), and the lead-treated groups received purified water containing either 50 or 250 ppm lead acetate. Twenty-one-day-old rats were maintained on the lead-treated water regimen for 3 weeks and weight gain was monitored. Exposure to these two concentrations of lead acetate induces clinically relevant blood lead concentrations (Cory-Slechta, 1995; Kala and Jadhav, 1995, 1997). This postweaning protocol may best model pica behavior and oral ingestion of lead by young children (Greene et al., 1992; Bayer et al., 1993). Tavakoli-Nealid et al. (2001) have reported that significant lead effects on the midbrain DA system can be observed at clinically relevant blood lead levels using this lead exposure protocol.

Drug Challenge. Data from our preliminary dose-response studies and from literature indicate that the effect of amphetamine (AMPH) on cFOS activation in the striatum is dose-dependent and that 4 mg/kg is an intermediate dose. The 4-mg/kg dose of AMPH was chosen so that lead-induced increases or decreases in cFOS gene activation would be detectable. Control and lead-treated rats were randomly assigned to receive an i.p. injection of either vehicle (normal saline) or d-amphetamine sulfate in normal saline (AMPH; 4 mg/kg i.p.). Before injections, rat cages were transferred from the animal quarters to a quiet laboratory, where the injections took place. After i.p. injection, all rats were returned to their home cage and maintained in the same location until sacrificed.

Tissue Preparation. Two hours after injections, rats were deeply anesthetized with chloral hydrate (400 mg/kg) and prepared for transcardial perfusion. Perfusion was initiated with ice-cold phosphate-buffered saline (0.1 M) containing heparin (5 USP units/ml) and maintained until the effusate ran clear, and then the rat was fixed with 4% paraformaldehyde in 0.1 M phosphate buffer (fixative). The brain tissue was postfixed for 2 h before transfer to 30% sucrose in fixative. The brains were stored at 4°C until they sunk to the bottom of the sucrose fixative. Brains were blocked using Tissue-Tek OCT compound (Sakura, Torrance CA) and mounted on a freezing cryostat stage. Coronal sections (40 μm in thickness) were serially cut using a cryostat (Histoslide 2000; Reichart-Jung, NuBlock, Germany) at −27°C. Brain sections were stored in cryoprotectant (see Drugs and Solutions) at −20°C until processed for detection of the cFOS protein with the anti-cFOS rabbit polyclonal IgG sc-52 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA).

Every third forebrain section containing the striatum was selected for immunohistological examination. Floating brain slices in 1:5000 cFOS antiseraum were maintained on orbital rocker overnight in a cold room at 4°C. Biotinylated goat anti-rabbit antibody (Vector Laboratories, Burlingame, CA) was used at 1:1000. Nuclear cFOS protein was visualized using the Vector Elite ABC reagents followed by 3',3-diaminobenzidine chromogen that stained the cFOS-labeled nuclei gray-black. The antibody specificity was tested in some sections by the deletion of the primary antibody. Under these circumstances, nuclear labeling was not observed.

Micrographs were taken with a Nikon Eclipse E600 with CoolSNAP Pro digital camera and transferred to Adobe Photoshop for digital photo processing. Digital photos were analyzed with Image-Pro Plus software (Media Cybernetics, Silver Springs, MD).

Blood and Brain Lead Determinations. The blood lead levels were measured in samples obtained by cardiac puncture in anesthetized rats. The electrolytic voltammetric stripping method was used for all blood lead determinations (LeadCare blood lead test kit, ESA, Inc. Chelmsford, MA). The blood lead level was determined from three levels of exposure: 0, 50, and 250 ppm. Brain lead levels were determined from 100- to 300-μg brain samples from a coronal section through forebrain tissue at approximately the mid-level of the striatum. The tissue was then digested in concentrated ultrapure nitric acid at 150°C overnight. Digests were analyzed in a Zeeman 5100 atomic absorption spectrometer (PerkinElmer Life and Analytical Sciences, Boston, MA) and compared with a lead standard curve that ranged from 0 to 100 μg/ml (lead atomic absorption standard; Aldrich Chemical Co., Milwaukee, WI). The groups of animals used for blood and brain lead level determinations were not included cFOS-IR study, but they were raised together in the same cages and therefore are representative of the latter group.
Lead Activates cFOS and Inhibits Amphetamine-Induced Expression

Analysis. To ensure that regional differences in cFOS expression were taken into account, the entire rostral-caudal extent of the striatum was analyzed for AMPH-induced cFOS gene activation. From the rostral to the caudal extent of the caudate-putamen, every third brain slice was examined for cFOS-positive neurons. Brain sections were digitally photographed at 100× magnification and analyzed for the presence of cFOS-positive neurons. cFOS-positive neurons were "manually" counted bilaterally with the assistance of Image-Pro Plus software. Each of the cFOS-positive nuclei were analyzed for the presence of cFOS-positive neurons. cFOS-positive sections were digitally photographed at 100x magnification and restricted our analysis to the dorsal striatum (caudate-putamen) in coronal brain sections corresponding to the coordinates from bregma 0.02 to 2.0. The dose of AMPH used in this study (4 mg/kg) activated neurons predominately in the medial half of the striatum.

The experiment examining a 4-mg/kg challenge dose of AMPH after 3 weeks of lead treatment was analyzed using a two-way ANOVA. There was a significant lead treatment effect (Lead: 0, 50, 250 ppm; P < 0.005), drug challenge effect (Veh/AMPH; P < 0.001), and lead treatment by drug challenge interaction (P < 0.001). However, Levene’s test indicated that there was significant heterogeneity of variance among the various groups (P < 0.001). Therefore, a nonparametric approach was used for further analysis. A nonparametric Kruskal-Wallis test indicated that there was still a significant difference among all groups (P < 0.001). Planned comparisons were made using the nonparametric Mann-Whitney U test. In control animals, saline challenge (Veh) did not cause a significant induction of cFOS (Figs. 1A and 2, Con/Veh: 6 ± 3 cells/section; n = 6). However, the level of the AMPH-induced expression of the cFOS gene was considerable. In the untreated control group, AMPH administration significantly increased the number of cFOS-IR-positive neurons located in the striatum (Figs. 1B and 2; Con/AMPH versus Con/Veh: 1301 ± 402 versus 31 ± 29 cells/section; P < 0.01, Mann-Whitney U test; n = 5 and 6, respectively). After Pb50 treatment, there was a significant basal activation of the cFOS gene in the saline-challenged group relative to control group (Figs. 1C and 2; Pb50/Veh versus Con/Veh: 223 ± 67 versus 31 ± 29 cells/section; P < 0.05; n = 5 and 6, respectively). However, Pb50 treatment had no effect on the AMPH-induced cFOS gene activation, because AMPH-injection still significantly increased cFOS-IR relative to the Pb50/Veh group (Figs. 1D and 2; Pb50/AMPH versus Pb50/Veh: 1801 ± 263 versus 223 ± 67 cells/section; P < 0.01; n = 5 each), and this level of gene activation was not significantly different from that observed after AMPH challenge in the untreated control group (Con/AMPH versus Pb50/AMPH, 1301 ± 402 versus 1801 ± 263 cells/section; P > 0.20; n = 5 each). In the Pb250 group, lead treatment did not activate the cFOS gene, because the count of cFOS-IR-positive cells in vehicle-challenged animals were not significantly different from the untreated control (Figs. 1E and 2; Pb250/Veh versus Con/Veh: 6 ± 5 versus 31 ± 29 cells/section; P > 0.50; n = 5

TABLE 1

<table>
<thead>
<tr>
<th>Tissue Weight or Lead Level</th>
<th>Lead Treatment Condition</th>
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<tr>
<td></td>
<td>0 ppm</td>
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<tr>
<td>Rat weight (g)</td>
<td>205 ± 9</td>
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<tr>
<td>Brain weight (g)</td>
<td>1.70 ± 0.05</td>
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<tr>
<td>Blood lead (µg/dl)</td>
<td>2.8 (n = 1)</td>
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<tr>
<td>Brain lead (ng/g)</td>
<td>&lt;1.4, B.D. (n = 15)</td>
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B.D., below limits of detection.

Kruskal-Wallis test, P < 0.001.

Results

The study examined a total of 62 treated rats. Thirty-one rats were used in immunohistochemistry experiments and an additional 31 rats were used to obtain blood and brain lead concentrations and brain weight. Although there was a trend toward reduced body and brain weight at 250 ppm, there was no significant difference found in the body or brain weight between the three groups. However, there was a significant exposure level-dependent difference in the blood and brain lead levels. The mean values (± S.E.M.) for body and brain weight and blood and brain lead concentrations are given in Table 1.

In preliminary experiments, the expression of AMPH-induced cFOS-IR was found to be dose-dependent. When the dose of AMPH was increased from 1 to 10 mg/kg, a corresponding increase in cFOS-IR was found. Saline challenge failed to increase the expression of cFOS-IR, as did AMPH in the absence of the primary cFOS antibody (data not shown). We found the 4-mg/kg dose of AMPH to induce an intermediate level of cFOS-IR. Expression of cFOS-IR was found throughout the rostral to caudal extent of the striatum. We restricted our analysis to the dorsal striatum (caudate-putamen) in coronal brain sections corresponding to the coordinates from bregma 0.02 to 2.0. The dose of AMPH used in this study (4 mg/kg) activated neurons predominately in the medial half of the striatum.

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and 6, respectively). Furthermore, in the Pb250-treated animals AMPH did not cause a significant induction of cFOS relative to vehicle-challenged controls (Pb250/AMPH versus Pb250/Veh; 148 ± 79 versus 6 ± 5; P > 0.20; n = 5 each). In contrast to the Pb50 treatment, the Pb250 treatment significantly reduced the AMPH-induced expression of cFOS-IR by approximately 89% relative to untreated control (Figs. 1F and 2; Pb250/AMPH versus Con/AMPH: 148 ± 79 versus 1301 ± 402; p < 0.005; n = 5 each).

**Discussion**

This study examines the impact of lead exposure on DA-modulated gene expression in the rat striatum. An approximate 7-fold increase in cFOS expression in rats treated with 50 ppm lead and not challenged with amphetamine was found. This indicates that low-level lead treatment can induce cFOS and is consistent with the study by Ramesh et al. (2001), which found that 3 months of exposure to 50 ppm lead caused an increase in striatal cFOS in rats. When rats treated with 50 ppm lead were challenged with amphetamine, the degree of cFOS activation was not significantly different from that of the untreated control group challenged with amphetamine. Therefore, at this exposure level, lead did not seem to impair D1 receptor-mediated nigrostriatal DA neurotransmission.

In contrast to the results from 50 ppm lead exposure, the 250 ppm level of lead exposure had no significant effect on basal cFOS levels. The 250 ppm level of lead exposure did, however, dramatically reduce the amphetamine-induced increase in cFOS-IR in the striatum relative to amphetamine-challenged untreated controls by about 89%. This finding strongly suggests that the 250 ppm lead exposure impaired DA neurotransmission. The precise site(s) for this lead-induced impairment is not known, but it could include an alteration in amphetamine-induced DA release or events “downstream” from the immediate drug action.

Lead has been shown to alter the turnover or release DA (Minnema et al., 1986; Cory-Slechta, 1995; Kala and Jadhav, 1995a) and glutamate (Braga et al., 1999; Lasley and Gilbert, 2002), both of which are required for the amphetamine-induced activation of striatal cFOS (Berretta et al., 1992; Kiba and Jayaraman, 1994; Liu et al., 1994). It has been reported that exposure to 50 ppm lead for 90 days resulted in a decrease in DA release in the nucleus accumbens (Kala and Jadhav, 1995a). Because a lead-induced decrease in the number of spontaneously active midbrain DA neurons, but not lead-induced DA neuron cell death, has been reported at low levels of exposure (i.e., 250 and 500 ppm) by Tavakoli-Nezhad et al. (2001), these findings indicate that lead alters the physiological function of DA neurons in a manner consistent with attenuated DA neurotransmission at the presynaptic level. It should be noted that the apparent lead-induced decrease in DA neurotransmission was demonstrated in the nucleus accumbens (or ventral striatum) and not the dorsal striatum.

Kant et al. (1984) studied the effects of lead exposure on amphetamine-stimulated DA release by using an extended period of exposure that included exposure of the dam before mating (1000 ppm lead acetate 70 days before mating), the gestational period (dam continued on 1000 ppm lead acetate), and the postnatal period (1000 ppm to the lactating dam and...
then the weanlings) up until the age of about 60 days old. Their study showed that there was no lead-based difference in amphetamine-stimulated DA release in striatal tissue minces (Kant et al., 1984). The protocol used by Kant et al. (1984) was, however, very different from that of the present study. More recently, Devoto et al. (2001) showed that the amphetamine-induced DA release in the nucleus accumbens was significantly lower in the lead-exposed (350 ppm lead acetate in utero until the day of testing) group relative to controls in rats. In the present study, it is tempting to speculate that the 250 ppm lead exposure may have decreased the amphetamine-induced release of DA in the striatum. However, given the very large magnitude of the impact of lead exposure on cFOS in the present study, the apparently smaller magnitude of the effect of lead on DA release in the nucleus accumbens reported by Devoto et al. (2001) may not completely explain our findings. It should also be noted that not only was a different nucleus studied (i.e., nucleus accumbens), but also the exposure protocol used by Devoto et al. (2001) was dissimilar to the one used in the present study. In particular, it involved a much more extensive developmental exposure that included both the prenatal and postnatal periods.

Pokora et al. (1996) used a postweaning exposure protocol similar to the one used in the present study to examine the time course of the effects of lead on DA D1-like and D2-like receptor binding in the striatum and nucleus accumbens. In the striatum, lead exposure at the 150 ppm level caused only a small and transient decrease in D1-like binding after 8 months of lead treatment (no longer significant after 12 months), but no effect at the earlier 2-week time point. The nucleus accumbens, however, showed a pronounced decrease in D1-like binding after 8 months, but this effect was transient (absent at the 12-month time point), and there was no effect at earlier the 2-week time point. A pronounced decrease in D2-like binding sites was also observed in the nucleus accumbens at the 150 ppm level of exposure for all time points measured. Pokora et al. (1996) concluded in this study that the nucleus accumbens was preferentially affected by lead relative to the striatum.

A microiontophoretic study by Pitts et al. (2002) examined the effects of 250 ppm postweaning lead exposure on type I nucleus accumbens neurons that are presumably medium spiny GABAergic neurons (Onn et al., 1994). After 3 weeks of lead exposure, they found that the sensitivity of neurons from lead-exposed animals to the DA D1 agonist SKF-38393 was significantly less that that of controls. This finding is consistent with a lead-induced decrease in DA D1 receptor sensitivity in a population of medium spiny neurons.

There is a complex distribution of DA receptors in the basal ganglia. The striatum and nucleus accumbens neurons that are presumably GABAergic neurons (Onn et al., 1994). After 3 weeks of lead exposure, they found that the sensitivity of neurons from lead-exposed animals to the DA D1 agonist SKF-38393 was significantly less that that of controls. This finding is consistent with a lead-induced decrease in DA D1 receptor sensitivity in a population of medium spiny neurons.

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The results of this study indicate that lead exposure adversely affects DA-regulated gene expression within the rat striatum at low levels of lead exposure and indicate that the striatum is sensitive to lead exposure at clinically relevant blood levels. These results also indicate that the exposure level is a critical determinant for the outcome for cFOS expression observed in the striatum. Further studies will be necessary to ascertain the relative importance of pre- and postsynaptic mechanisms in the effects of lead on cFOS expression within the striatum.

Acknowledgments

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