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Low-level lead exposure modulates effects of quinpirole and eticlopride on response rates in a fixed-interval schedule

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Abstract

Exposure to low levels of lead (Pb) results in a wide range of behavioral changes. These behavioral deficits of lead are modified by duration of exposure, level of exposure, and stage of exposure. The mesoaccumbens dopamine (DA) system appears to be critically involved in these alterations; however, the precise mechanisms are not completely understood. This study investigated the effects of systemic administrations of the dopamine D_2-like receptor agonist, quinpirole, and antagonist, eticlopride, on response rates of postweaning lead-exposed rats in a fixed-interval 1-minute (FI-1) schedule. Postweaning exposure to 50 ppm lead (lead acetate) resulted in increased response rates. The dopamine D_2-like agonist, quinpirole (0.05, 1.0, 3.0 mg/kg), reversed the effects of lead by reducing the response rates. However the antagonist, eticlopride (0.01 and 0.05), did not produce any marked modulation of the response rates of the lead group. Rather, systemic injections of eticlopride attenuated the response rates of control rats. The effects suggest that lead-induced alterations in FI responding are modulated by dopamine D_2-like mechanisms. Thus, postweaning, subchronic exposure to lead resulted in enhanced sensitivity to quinpirole administration and reduced sensitivity to eticlopride. These observations are consistent with attenuated dopaminergic activity.

Keywords: Lead; Dopamine; Fixed interval; D_2 receptors; Quinpirole; Eticlopride

1. Introduction

Lead exposure at blood levels ≥ 10 μg/dl in humans and animals interferes with different measures of behavior including cognitive functions (Bellinger et al., 1987, 1992). Although an association has been established between lead exposure and these behavioral impairments, unraveling the neurobiological basis remains an enigma. The mesoaccumbens dopamine system (which includes the nucleus accumbens) appears to be especially sensitive to lead exposure. Previous studies from this laboratory suggest that postweaning exposure to low levels of lead results in a net attenuation of dopamine availability in this circuitry (Jadhav and Ramesh, 1997; Kala and Jadhav, 1995a,b; Ramesh and Jadhav, 1998). Dopaminergic neurons with cell bodies in the ventral tegmental area terminate in the nucleus accumbens. The nucleus accumbens also receives dopaminergic projections from the cortical area and has been implicated in reward related mechanisms including natural reward processes like sex and food and in the development of addiction (Corrigall et al., 1992; Koob et al., 1998). The impact of lead exposure on this system may therefore suggest modulation of factors that control this pathway and may have implications including predisposition to addiction and the development of disease states associated with mesoaccumbens dopamine pathway.

In the nucleus accumbens of rats exposed to lead for 90 days, we have found associated with lead exposure decreased DA content, attenuated stimulus-induced DA release, and reduced activity of tyrosine hydroxylase, the rate-limiting enzyme in DA biosynthesis. Other studies have reported effects consonant with reduced dopaminergic availability following lead exposure (Buckey et al., 1997; Cory-Slechta and Widzowski, 1991; Lasley, 1992; Lasley and Lane, 1988; Leander, 1980; Nation and Burkey, 1994). Some of these studies suggest that the attenuating effects of lead on dopamine synthesis and release result from

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impaired autoreceptor-mediated regulatory activity. This hypothesis of net reduction in dopaminergic neurotransmission is also supported by studies showing up-regulation of dopamine D_2-like receptor density and enhanced receptor sensitivity following lead exposure (Cory-Slechta and Widzowski, 1991; Cory-Slechta et al., 1993; Widzowski et al., 1994). Two earlier studies also showed that lead attenuated both cocaine-induced increases in extracellular dopamine in the nucleus accumbens (Nation and Burkey, 1994) and the enhancing effects of cocaine on fixed-interval (FI) response rates (Buckey et al., 1997). The present study seeks to further investigate the nature of lead interactions with dopamine receptor mechanisms.

Fixed-interval schedule of reinforcement has been widely employed to assess lead toxicity in rodents and primates and has been shown to be a sensitive indicator of lead toxicity (Cory-Slechta, 1997). The nature of lead-induced changes in FI parameters depends on the duration of exposure, level of exposure, and the stage of exposure (Cory-Slechta, 1990). Generally, postweaning exposure paradigms that result in blood-lead level below 25 μg/dl increase response rates on FI schedules (Cory-Slechta et al., 1996). It has been suggested that performance in FI schedule is related to mesoaccumbens dopaminergic mechanisms. The microinjection of *n*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), the irreversible dopamine antagonist, into the nucleus accumbens decreased FI performance, an effect not replicated in the striatum (Cory-Slechta et al., 1997). These effects were reversed by the pharmacological activation of D_1 and D_2 receptors in the nucleus accumbens. As suggested by the authors, the results indicate a critical involvement of nucleus accumbens dopamine in FI responding.

The studies reported here examined the effects of dopamine D_2-like receptors in lead-induced changes in FI response rates under postweaning exposure conditions. It is pertinent to delineate the involvement of this class of receptors in lead toxicology and determine if such changes can underlie the associated behavioral deficits. Although there are studies suggesting an association between lead exposure and increased mesoaccumbens dopamine availability (Cory-Slechta et al., 1996; Pokora et al., 1996), our findings did not support that hypothesis. Rather, under postweaning exposure to lead, rats were more sensitive to the D_2-like agonist, quinpirole, which may be consistent with a net reduced dopamine bioavailability in this pathway. The variations in the findings may be connected with the different exposure duration and exposure levels utilized. As stated earlier the effects of lead vary depending on the time of exposure (developmental exposures versus postweaning), exposure duration (acute, subchronic, or chronic), and the level of exposure (Cory-Slechta, 1990; Cory-Slechta et al., 1996). In this study, we investigated the effects of lead under postweaning exposure to 50 ppm lead for 3 months on FI performance and the modulation by D_2 receptor selective agents.

2. Method

2.1. Animals

The experimental protocol was approved by the Institutional Animal Care and Use Committee. Twenty-one-day-old acclimatized male Long–Evans rats (Harlan, Indianapolis, IN) were randomly divided into two groups: control ($n = 12$) and lead-treated ($n = 18$). The control and lead-treated groups were provided 50 ppm sodium acetate (Sigma, St. Louis, MO) and 50 ppm lead acetate (Sigma), respectively, in drinking water for 90 days. This exposure paradigm has been established in our laboratory to produce environmentally relevant blood-lead levels and alter nucleus accumbens dopamine release and tissue dopamine content. Male Long–Evans rats have been routinely utilized in studies of lead behavioral and neurochemical studies (Cory-Slechta et al., 1996, 1997; Jadhav and Ramesh, 1997; Kala and Jadhav, 1995a,b). All solutions were prepared in deionized, distilled water. Animals had unrestricted access to a semipurified chow (Purina Mills, Richmond, IN) until they attained a body weight within the range of 200 to 250 g. This diet was formulated with reduced levels of metals known to interfere with lead absorption at the gastrointestinal level and has been routinely used in neurobehavioral studies (Cory-Slechta and Widzowski, 1991; Kala and Jadhav, 1995a,b). Body weights were subsequently maintained within 280 to 300 g by placing animals on a restricted diet. Animals were housed on a 12-h light/dark cycle. Rats were housed in groups of two in plastic cages. Weekly body weights and fluid intakes were monitored throughout the duration of the experiment.

2.2. Apparatus

The FI sessions were conducted in eight identical Plexiglas enclosed operant chambers (Coulbourn Instruments, Allentown, PA, Model E10-09). Chambers were equipped with two levers, a pellet delivery trough, and a house light that was turned on for the duration of the experiment. The levers were designated as right and left levers and were each equipped with three cue lights. Each chamber was equipped with a continuous white-noise generator to mask extraneous sounds, an audio cue, and a fan for ventilation. Protocol programming, execution, and data acquisition were conducted with the L2t2 software (Coulbourn Instruments).

2.3. Fixed-interval measurement procedures and pharmacological treatments

Measurements began after 30 days of exposure (approximately age 51) with the shaping of animals for lever pressing and pellet retrieval on a variable time (VT) schedule at an average of 90 s. Responses were reinforced

with a 45 mg food pellet (Bio-Serv, Frenchtown, NJ). The first response on the right lever following the initiation of the permutation changed the paradigm to a fixed ratio schedule (FR1). Each rat received a minimum of 70 pellets during the shaping protocols. All the rats were shaped in overnight sessions and two rats (one from each group) that did not learn lever pressing were taken through one additional overnight session each until a 70-response criterion was met. There were no differences in shaping between the control and the lead group. An FI-1 schedule was subsequently imposed at approximately 54 days of age. Three cue lights on the right lever were turned on and no consequences were programmed for incorrect responses on the left lever. Sessions were carried out 6 days a week from Monday to Saturday. Session duration was 30 min and individual rats went through one session per day. The lead exposure regimen continued throughout the duration of the experiment.

After 30 sessions on the FI schedule, the lead group was subdivided into three groups while the control group was divided into two groups of six rats each. Rats were divided as such so that groups in each exposure level received either quinpirole (RBI, Natick, MA) or eticlopride (RBI). This schedule of administration was used to avoid superimposing the effects of the agonist and antagonist that has been suggested to affect some previous studies (Pokora et al., 1996). The third lead group served as lead control and received no pharmacological treatments. The schedule of pharmacological interventions involved single intraperitoneal injections of 0.01, 0.05, 1.00, and 3.00 mg/kg body weights of either quinpirole or eticlopride, randomized across the dosing levels on individual rat basis. Rats were returned to their respective cages and response rates assessed 30 min postinjection. During the subsequent 6 days, no injections were given to the rats but the response rates were assessed. This protocol served two purposes: (1) the 6-day period served as a "washout" period, which was adequate since each group received only one kind of drug, albeit different doses, and (2) it permitted comparison between the changes in response rates following drug treatment to response rates before treatment. During the periods between successive injections, the response rates recovered to the preinjection levels. The lead control group received no treatment and was included so that changes due to lead alone can be observed for comparative analysis and to monitor performance of the rats. An injection volume of 1 ml/rat per dose was used. Doses were selected based on previous behavioral and pharmacological studies (Svenningson et al., 2000; Tizabi et al., 1999). Both quinpirole and eticlopride were prepared in deionized distilled water, because they are both soluble in water and thus no vehicle control was included in the study. At 1.0 and 3.0 mg/kg, eticlopride completely abolished responding in both groups of rats and thus the data are not included in the analysis. Blood samples were taken after cervical decapitation and lead values determined after the completion of the experiment as previously described (Kala and Jadhav, 1995a).

2.4. Data and statistical analysis

Blood-lead data were analyzed using a one-factor analysis of variance while response rate data preceding pharmacological interventions (first 30 sessions) were analyzed using a one-factor repeated measure analysis of variance (RMANOVA). Lead exposure was used as the predictor variable because the focus was to analyze for lead-related differences. Mean values were used for the statistical analysis of the overall response rates (ORRs). Where there were significant differences, post hoc analyses were performed using the Tukey all pairwise comparison test. Data for the pharmacological manipulations were analyzed using one-factor analysis of variance since a third lead-only group was included in the analysis. All statistical analyses were carried out with the Sigma Stat Statistical software (Version 2.0, Jandel Scientific, San Rafael, CA).

3. Results

3.1. Blood-lead levels, fluid intakes and animal body weights

The exposure protocol resulted in blood-lead levels of 2.5 ± 0.2 and 15.1 ± 0.4 μg/dl for control and lead-exposed groups, respectively, at the end of 90-day exposure. All animals gained weight during the experimental duration until caloric regulation was instituted and no differences were observed between the two groups. Fluid intakes also did not vary between the groups and reached a plateau by the 30th day of exposure. Thus, lead exposure did not result

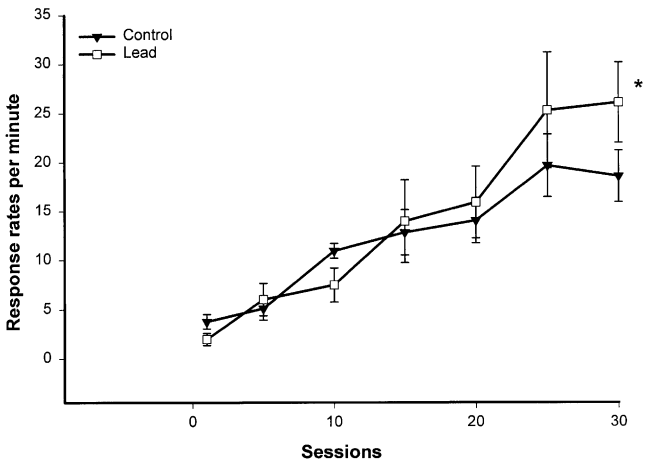

Fig. 1. ORRs for control (▼) and lead-exposed rats (□). (a). Response rates were measured after 30 days of exposure and following shaping of responses. Each data point represents the mean ± S.E.M. of 12 rats per group. * Statistical analysis of the first 30 sessions indicated treatment-related significant differences (one-factor RMANOVA, $F = 15.209$, $df = 1$, $P < .001$).

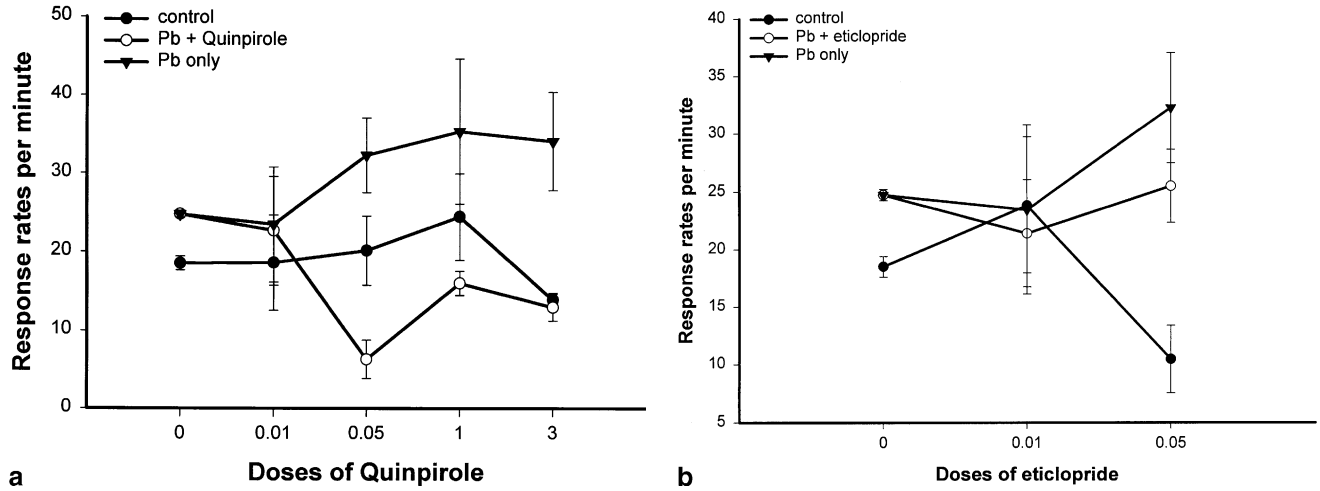

Fig. 2. (a) Changes in ORRs in control (●) and lead-treated rats (○) in the FI-1 schedule after quinpirole injections. A lead-only (without pharmacological treatment) group (▼) is included for comparisons. Response rates are given in responses per minute and each data point represents mean ± S.E.M. of six rats per group. Animals were assessed on the FI schedule 30 min postinjection. The baseline 0 (zero) point represents the mean ± S.E.M. for the last four sessions preceding the pharmacological interventions. Other baseline data representing sessions between the injections were similar. (b) Changes in ORRs in control (●) and lead-treated rats (○) in the FI-1 schedule after eticlopride injections. A lead control (without pharmacological treatment) group (▼) is included for comparison. Response rates are given in responses per minute and each data point represents mean ± S.E.M. of six rats per group. Animals were assessed on the FI schedule 30 min postinjection. The baseline 0 (zero) point represents the mean ± S.E.M. for the last four sessions preceding the pharmacological interventions. Other baseline data representing sessions between the injections were similar.

in any variations in fluid consumption or the eating habits of the rats. These observations are consistent with our previous findings that the employed exposure protocols do not alter fluid intake, body weight gain or caloric intake (Jadhav and Areola, 1997; Kala and Jadhav, 1995a).

3.2. Behavioral data

ORRs were calculated as the total number of responses divided by session duration (30 min), and were monitored without any pharmacological manipulations for the first 30 sessions (Fig. 1). Although there were temporal variations, lead exposure resulted in significantly higher response rates, $F(1, 29) = 15.209$, $P < .001$. These observations are consistent with previous findings (Cory-Slechta, 1990).

3.3. Quinpirole-induced modulation of FI performance

The administration of different concentrations of the dopamine D_2 agonist, quinpirole, affected response rates in both groups producing differential effects. In general, some degree of response rate decrease was noticed for all groups. The response rates of the lead-exposed and the no lead control were not affected significantly by 0.01 mg/kg quinpirole (Fig. 2a). However, the administration of 0.05 mg/kg quinpirole (Fig. 2a) produced a significant lowering of the response rates of the lead-exposed group as compared to the no lead control and lead control groups level, $F(2, 4) = 37.372$, $P < .001$. Similar observations were made when 1, $F(2, 4) = 10.473$, $P = .006$, and 3 mg/kg quinpirole, $F(2,4) = 8.858$, $P = .009$, were administered.

3.4. Eticlopride-induced modulation of FI performance

Treatment with 0.01 mg/kg eticlopride did not result in any significant changes in response rates between the groups, though the initial differences in response rates as a result of lead exposure still existed. However 0.05 mg/kg eticlopride produced significant lowering of the response rates of control rats, $F(2,4) = 22.189$, $P = .009$ (Fig. 2b). However, at 1 and 3 mg/kg eticlopride response rates were drastically reduced, almost abolishing all responding. Thus, the data are not included in this report.

In summary, response rates of the 50 ppm lead-exposed group were consistently higher than those of the controls prior to the administration of D_2 receptor modulators (Fig. 1). Administration of quinpirole, a dopamine D_2 agonist, reversed the enhanced response rates of lead-exposed rats significantly. In contrast, administration of eticlopride, a dopamine D_2 antagonist to lead-exposed rats did not result in significant changes in response rates (Fig. 2a and b).

4. Discussion

These studies tested the hypothesis that the modulation of dopaminergic mechanisms by postweaning low-level lead exposure is associated with the changes observed in FI responding. The hypothesis was designed to specifically investigate the involvement of D_2 receptors in FI responding in lead-exposed rats. The results indicate that low-level lead exposure modulates the effects of dopamine D_2 receptor selective agents on response rates of the imposed FI

schedule. The pattern of modulation may be consistent with decreased dopamine bioavailability.

This observation supports previous findings of impaired regulation of dopamine activity and autoreceptor-mediated release of dopamine in lead-treated rats, D_2 receptor supersensitivity, and up-regulation of D_2 receptors in the nucleus accumbens (Cory-Slechta and Widzowski, 1991; Lasley and Lane, 1988; Widzowski et al., 1994). Quinpirole altered response rates in lead-treated rats at all doses except the lowest (0.01 mg/kg) while causing minimal changes in the response rates of control rats. This enhanced sensitivity to dopamine agonist in lead-treated rats is similar to the findings of Leander (1980) where the enhanced response rates of D-amphetamine treated pigeons were attenuated by lead exposure. Similar observations were also made by Cory-Slechta et al. (1996) although the pattern of change differs. Cory-Slechta et al, (1996). reported a decrease in response rates following the administration of low doses of quinpirole in lead-exposed rats, a trend that was reversed back to control levels at 0.10 mg/kg. In this study, the decrease in response rates was sustained at all dosages (Fig. 2a). These differences may be due to differences in protocols. Although both studies utilized similar postweaning exposure paradigms, the duration of exposure differs. The study in question dissolved quinpirole in saline, made at least two injections of each dose, and made frequent saline injections between treatments. In this study, quinpirole was dissolved in water and only single injections of each were used in this study. Single injections were made to avoid chronic interactions of the receptors with the agonist and antagonist, so that acute treatment-related changes can be differentiated. Similarly, the response to 0.1 mg/kg quinpirole may be different from those of 1 and 3 mg/kg used in this study.

Our findings however, appear to differ from the studies suggesting receptor down-regulation (Cory-Slechta et al., 1996; Pokora et al., 1996) in lead exposed rats, because receptor down-regulation would be consistent with increased dopamine bioavailability and thus decreased sensitivity to agonists like quinpirole. As yet, we do not know the reasons for these differences although they might have resulted from differences in exposure level and duration. Dopamine receptors are known to undergo adaptive changes following chronic administration of agonist and antagonist (Cooper et al., 1991). Our working hypothesis that the subchronic administration of lead results in reduced central dopamine bioavailability will conceivably be consonant with dopamine receptor up-regulation. This up-regulation of dopamine receptors may thus explain the enhanced sensitivity observed when quinpirole, a dopamine agonist was administered. It is imperative to note that previous reports indicate region specificity and temporal changes in indices of dopaminergic transmission following postweaning low-level lead exposure (Kala and Jadhav, 1995a; Pokora et al., 1996). Thus, although the findings here tend to support one mechanism, the dynamics of change in dopaminergic mechanisms following lead insult require further investigation. It is also important to note that the findings under these postweaning exposure conditions may differ from developmental effects of lead.

Eticlopride did not exhibit any marked modulation of response rates in lead-treated rats (Fig. 2b) though response rates were altered in control rats. The fact that lead-treated rats did not exhibit any marked sensitivity to eticlopride at the doses utilized may suggest that lead-treated rats were simply not responsive to eticlopride at these doses, or because control rats were affected, it may indicate a lead-associated disruption in this mechanism, perhaps, a loss of sensitivity (subsensitivity). This also supports our working hypothesis as receptor up-regulation is expected to result in reduced sensitivity to further receptor inactivation by eticlopride, a D_2 receptor antagonist.

In conclusion, this study further extends the contention that changes in FI performance induced by postweaning low-level lead exposure may be mediated through dopaminergic pathways by mechanisms related to increased sensitivity to D_2 receptor agonists. As stated earlier, a role for autoreceptor-mediated events in lead toxicity have been suggested by previous studies (Cory-Slechta and Widzowski, 1991; Jadhav and Ramesh, 1997; Lasley and Lane, 1988; Ramesh and Jadhav, 1998; Widzowski et al., 1994). However, the contributing mechanisms are not clear. Autoreceptor regulation of synthesis and release can modulate the rate of tyrosine hydroxylation (Cooper et al., 1991). Findings consonant with this have been reported in our laboratory; decreased TH activity in the whole brain (Jadhav and Ramesh, 1997) and in the nucleus accumbens (Ramesh and Jadhav, 1998) have been demonstrated in rats similarly exposed to low levels of lead.

Also, as stated earlier, there are reports of enhanced dopaminergic activity in the nucleus accumbens of lead-exposed rats (Cory-Slechta et al., 1996; Pokora et al., 1996). Although there are notable procedural differences, the differences in results may indicate deregulations or alterations exerted by lead on other neurotransmitters in the neuronal circuitry affected by lead. This is important because inputs into the nucleus accumbens terminal region originate from dopamine cell bodies in the ventral tegmental area (VTA). This region also receives glutamatergic, nicotinic, and GABAergic inputs, which have been reported to modulate the functions of mesoaccumbens dopamine system. For example it is known that increased dopamine release in the nucleus accumbens by nicotine and other drugs of addiction is mediated by glutamatergic mechanisms (Schilstrom et al., 1998; Suaud-Chagny et al., 1992). Thus, the interactions of lead with mesolimbic dopaminergic neurons may be modulated or regulated by other neural mechanisms. Future studies of the mechanisms underlying lead behavioral toxicity need to include the potential involvement of other neurotransmitter systems that interact with dopamine systems.

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