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Morphine conditioned place preference is attenuated by perinatal lead exposure

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Abstract

The purpose of this investigation was to determine if perinatal lead exposure alters the conditioned reinforcing properties of morphine when offspring were tested as adults. Dams were gavaged daily with 0- (sodium acetate) or 16-mg lead (as lead acetate) for 30 days prior to breeding with nonexposed males. Administration continued through gestation and lactation and was discontinued at weaning (postnatal day [PND] 21). At PND 70 animals were tested in a conditioned place preference (CPP) preparation using 0.00, 0.60, 1.25, 2.50, or 5.00 mg/kg ip morphine as the unconditioned stimulus (US). Relative to controls, attenuation of CPP was evident in animals exposed to 16-mg lead at 1.25 and 2.50 mg/kg morphine. Analysis of blood lead concentration revealed that by the end of testing residue levels in metal-exposed animals had returned to control levels. However, data from littermates sacrificed well beyond the current testing period revealed that brain lead residues remained elevated in animals exposed to lead, even though the metal had gained clearance from blood. The present data suggest that early lead exposure may have an enduring impact on the reinforcing properties of morphine.

Keywords: Conditioned place preference; Developmental; Lead; Morphine

1. Introduction

Even with increased governmental regulation, lead contamination continues to be a major pollution problem in North America. Environmental distribution can stem from a number of sources including smelters and lead-based paints, and contaminant exposure is particularly a concern in inner-city areas (Harwell et al., 1996; Pirkle et al., 1994). In many urban communities, substandard living areas are populated by residents who have limited resources with respect to protecting themselves against health threats associated with toxicant exposure. In particular, children run an especially high risk of being exposed to the effects of lead, both acutely and chronically. Continuous exposure, even at low levels, via inhalation or ingestion on the part of a child may result in cognitive and physiological deficiencies that could last well into adulthood (Godwin, 2001). Moreover, lead distribution to the fetus or to a newborn may have lasting consequences with respect to behavioral and neurological function.

The prevalence of lead exposure in the urban environment coincides with a high incidence of drug use in these same areas (Ensminger et al., 1997). Pertinent to this issue, animal studies of chronic low-level lead exposure and drug use have yielded significant interaction effects. In the case of lead exposure in the adult organism, for example, it has been shown that locomotor sensitization to the effects of repeated cocaine administration is blunted in metal-exposed animals (Nation et al., 1996). In a like manner, morphine-induced locomotor sensitization is attenuated by adult lead exposure (Miller et al., 2000b).

A somewhat more complex pattern of results occurs when lead is presented developmentally. When female rats are exposed daily to 8- or 16-mg lead throughout gestation and lactation, the stimulatory (locomotor sensitization) effects associated with recurrent cocaine administration are augmented in their offspring (Nation et al., 2000). Seemingly at odds with this finding, data from a conditioned place preference (CPP) study employing cocaine as the reinforcing stimulus reflect a pattern of attenuation among animals exposed to lead during gestation/lactation

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(Miller et al., 2000a). Parallel antagonism has been observed in drug discrimination studies where it has been shown that developmental lead exposure is associated with a decrease in the hedonic properties of cocaine and selective dopamine agonists (Miller et al., 2001). Further, Miller et al. (2001) determined that the *k*-opioid agonist U69,593 produced a decrease in cocaine generalization in control animals, but comparable changes in groups perinatally exposed to lead were not evident. An attenuation of the withdrawal symptoms associated with morphine dependence also has been observed in rats exposed to lead during gestation and lactation (Kitchen and Kelly, 1993). Generally, a disruption of opioid receptor and endogenous ligand development, along with biological responses to opioids, seems to occur as a result of developmental lead toxicity (Kitchen, 1993). These data suggest that a neuronal alteration in the opioid system may take place for animals developmentally exposed to lead in addition to changes that are occasioned in cocaine/dopamine related circuitries.

Developing a more complete understanding of the underlying mechanisms that maintain substance abuse requires a variety of procedures that address the complexity of the systems involved. Testing the reinforcing properties of drug related stimuli may be accomplished using a CPP paradigm. In this procedure, the drug is administered immediately before the animal is introduced into an environment with unique olfactory, visual, and tactile stimuli. In combination with this manipulation, vehicle-only administrations are presented on alternate days and paired with a distinctively different context. Repeated pairings of drug and vehicle-only stimuli with their respective contextual components is followed by a test day where free access to either environment is provided to assess the side favored by the animal. The results of CPP testing demonstrate the extent to which the animal develops a preference for the drug-side of the apparatus. Because CPP is believed to index the importance of context and conditioned reinforcement in drug abuse (Hoffman, 1989), it is considered a valuable animal model for determining the abuse potential of numerous drugs, including opiates (Miller and Nation, 1997). Accordingly, to further examine the possible linkages between developmental lead exposure and changes in responsiveness to opiates, a CPP procedure was used in the present investigation to evaluate the effects of early contaminant exposure on the conditioned reinforcement properties of morphine.

2. Materials and 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 (NIH Publication No. 85–23). Adult female Sprague–Dawley rats (Harlan; Houston, TX) were exposed to either 0- (sodium acetate) or 16-mg lead acetate for a period of 30 days prior to breeding. Animals were gavaged daily using 16-gauge gavage needles in a solution of 1-ml deionized water. Nonexposed males were then paired with females until the presence of a copulatory plug confirmed successful breeding. Dams continued with their respective exposure regimens of either 0- or 16-mg lead solution throughout gestation and lactation. Tail-blood samples, in the amount of 100–150 μl, were taken from females at breeding, gestation day 10, and postnatal day (PND) 1. Dams were sacrificed at weaning (PND 21) and blood samples were collected.

On PND 1, litters were culled to eight, keeping the most males possible and filling out the litter with females. Pups remained with the dam until PND 21. Pups being used for testing purposes were weaned and double housed until PND 50. Beginning at PND 50, pups were single housed for the remainder of the study. Littermates were sacrificed at PND 1 and PND 21 and trunk blood from the animals was used to determine lead concentrations. Also, brains from littermates used in another investigation were harvested (see below). After weaning, all animals in this study were maintained on standard rat chow and given free access to tap water in the home cage. A 12/12-h light–dark cycle was used throughout the study. Weekly records of food consumption and body weights were kept until onset of testing. Daily body weights were recorded during testing operations.

2.2. Apparatus

Conditioning and testing were conducted in seven wooden shuttle boxes, each measuring $20 \times 60 \times 20$ cm. Half the apparatus consisted of white walls with a smooth white floor, the other half of black walls with a black sandpaper floor. During conditioning sessions, a removable partition separating the two equal-sized sides was placed in the center of the chambers. Animals were restricted to only one of the two compartments throughout these sessions.

During testing sessions, the partitions were removed and a $20 \times 10 \times 5$ cm wooden platform was placed 2 cm above the floor. This provided a division between the two areas while allowing free access to the two compartments. To adjust for the natural preference for the black side (cf. Miller and Nation, 1997), a 40-W light was positioned 50 cm above the black side of the chamber. These lamps provided the only illumination in the testing room. A 40-dB white noise generator was positioned in the testing room to mask any outside noise. Located at either end of the box was a microswitch connected to an IBM compatible computer. With the aid of a floor-tilt mechanism, a computer equipped with a previously written BASIC program continuously recorded the duration the animal spent on either side, as well as the number of entries into a given compartment.

2.3. Behavioral testing

All test animals in the experiment were experimentally naive and not used for any other research projects. On Day 1 of behavioral training (PND 70), animals were transferred from the colony to the testing room for 40 min for the purposes of habituating them to transportation, sound, and illumination of the testing room. They were not placed into the apparatus during the first day. Initial biases for the white or black chamber (pretest) were determined on Day 2 as noninjected control and lead-exposed (Group 0-Lead and Group 16-Lead, respectively) animals were given free access to either chamber for a 15-min period. On Days 3–10 intraperitoneal injections of either morphine or vehicle were given according to body weights (1 ml/kg). During conditioning, animals were placed on the side least preferred (defined as the side in which the animal spent the least amount of time on the Day 2 pretest), if a morphine injection was administered. Alternatively, if a vehicle injection (distilled water) was administered, the animal was placed on the side most preferred (defined as the side in which the animal spent the most amount of time on the Day 2 pretest). In all cases during conditioning, animals were injected and placed in their respective compartments for a 40-min period. Morphine and vehicle were presented on alternating days (8 total) and the injection received first was counterbalanced for type of injection (distilled water, morphine) and exposure regimen (control, lead). Animals were run in squads of seven, counterbalancing by dose and group assignment (Group 0-Lead, Group 16-Lead). In an effort to control for litter effects, only one pup/group was used from any dam (cf. Holson and Pearce, 1992). Separate groups of control and lead-exposed animals ($N = 7$/group) were conditioned with morphine doses of 0.00, 0.06, 1.25, 2.50, and 5.00 mg/kg. A posttest was conducted on Day 11 following the same procedure as the Day 2 pretest to determine if CPP had occurred.

2.4. Lead levels

Lead levels in dams were determined at PND 21, and as indicated, blood lead concentration in littermates was determined at PND 1 and PND 21. Twenty-four hours after the posttest (Day 11 of CPP testing) was conducted, blood collection procedures were carried out on test subjects to determine lead concentrations. Group 0-Lead and Group 16-Lead test animals were anesthetized with sodium pentobarbital (50.00 mg/kg ip), and blood was collected via cardiac puncture.

In addition, information on lead concentration in blood and brain at a time point well past the testing in this study was made available by littermates sacrificed in a separate investigation (cf. Nation et al., in press). For all assays, lead residue was measured via atomic absorption spectrophotometry as recently detailed in a report from our laboratory (Dearth et al., 2002).

2.5. Statistical analysis

Changes in time (measured in s), in the drug-paired chamber, defined the final conditioning scores (posttest minus pretest). A CPP occurred only when the mean group conditioning score was significantly different from the vehicle-only group (0 mg/kg). A 2 Exposure condition (Group 0-Lead, Group 16-Lead) × 5 Dose (0.00, 0.60, 1.25, 2.50, 5.00 mg/kg morphine) factorial ANOVA was performed on the conditioning scores. Newman–Keuls post hoc tests were used when applicable to determine the source of main effect and interaction differences ($P < .05$).

3. Results

3.1. Exposure regimen

Food intake data were collapsed over a 4-week period prior to the onset of behavioral testing. Analysis of mean weekly food consumption showed no significant group differences ($P > .05$). Group 0-Lead and Group 16-Lead means were 186.67 and 202.40 g, respectively.

Body weights were measured across the duration of the conditioning and test days (11 days). Group 0-Lead and Group 16-Lead displayed mean body weights of 370.93 and 378.13 g, respectively. Main effects from ANOVA on bodyweights by treatment (Group 0-Lead and Group 16-Lead) did not reach an acceptable level of significance. No interaction effects (Dose × Treatment) were present that reached an acceptable level of statistical significance ($P > .05$).

3.2. Morphine CPP

The data from Day 2 pretest, where initial biases for the white or black chambers was determined, revealed that for both Group 0-Lead and Group 16-Lead, more than 70% of the animals in each exposure condition preferred the black chamber. There were no significant differences with respect to the amount of time control animals (mean ± S.E.M. = 234.1 ± 58.7 s) and lead-exposed animals (mean ± S.E.M. = 258.5 ± 77.2 s) spent on the least-preferred (white chamber) side of the apparatus ($F < 1$).

The results of the conditioning scores recorded on test day 11 are presented in Fig. 1. The results of the 2 Exposure condition (Group 0-Lead, Group 16-Lead) × 5 Dose (0.00, 0.60, 1.25, 2.50, 5.00 mg/kg morphine) factorial ANOVA test performed on these data showed a significant main effect for dose [$F(4,60) = 7.84$, $P < .01$]. Post hoc analyses of means indicated that CPP (greater conditioning scores [s]) was evident among groups that received 1.25, 2.50, or 5.00 mg/kg morphine injections relative to animals that received injections of the vehicle only (0.00 dose) ($P < .01$). Also, the main effect for exposure condition reached an acceptable level for statistical significance [$F(1,60) = 6.48$, $P < .05$]. It is

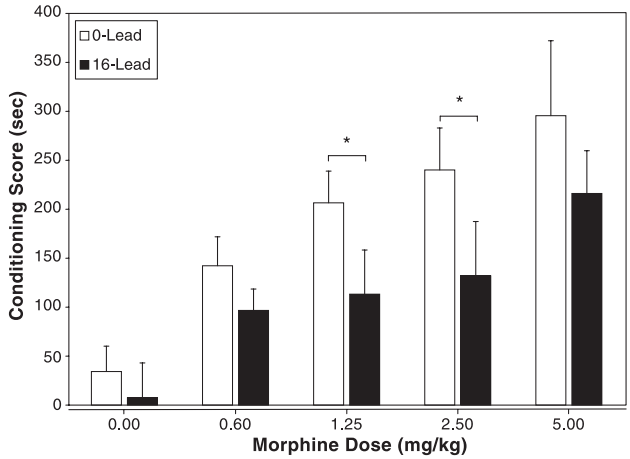

Fig. 1. Distribution of conditioning scores for Group 0-Lead and Group 16-Lead at each of the morphine doses (mg/kg). Scores were defined as the change in time (s) between pretest and posttest. * Indicates that Group 0-Lead spent significantly more time in the drug-paired chamber than Group 16-Lead ($P < .05$).

evident from visual inspection of Fig. 1 that this effect was due to the overall lower conditioning scores (decreased CPP) exhibited by Group 16-Lead animals (mean ± S.E.M. = 112.5 ± 31.2 s) relative to Group 0-Lead animals (mean ± S.E.M. = 183.9 ± 42.6 s).

The results of the simple effects analyses and post hoc analyses of group interaction means at each dose revealed that Group 0-Lead animals showed a CPP (significant increase in conditioning score relative to the vehicle-only test [0.00 mg/kg] for that exposure condition) at morphine doses of 0.60, 1.25, 2.50, and 5.00 mg/kg ($P < .05$). In addition, for Group 0-Lead animals it was found that conditioning scores were greater at 1.25, 2.50, and 5.00 mg/kg when compared to the 0.60 mg/kg condition; ($P < .05$). Although CPP was also observed among Group 16-Lead animals at morphine doses of 0.60, 0.125, 2.50, and 5.00 mg/kg ($P < .05$), only at the highest morphine dose of 5.00 mg/kg were conditioning scores found to be greater than the 0.60 mg/kg condition ($P < .05$). The overall pattern, then, was one wherein it required higher doses of morphine to produce separation by dose in lead-exposed animals relative to controls. This pattern of attenuation among Group 16-Lead animals is supported by findings from individual group comparisons at each dose where it was found that Group 16-Lead animals had lower conditioning scores at morphine doses of 1.25 and 2.50 mg/kg than their control counterparts ($P < .05$).

A previous investigation has shown that perinatal lead exposure, employing precisely the metal-exposure procedures used here, increases the locomotor stimulating properties of morphine (Miller et al., 2000b). However, no significant differences were noted between or among any of the exposure groups at any dose with respect to the number of times an animal entered the drug or vehicle-paired chamber (all Fs < 1).

3.3. Lead levels

Eight control animals and eight lead-exposed animals were randomly sampled (pups [$N = 16$]; dams [$N = 16$]) across the different exposure conditions and concentration in blood was determined for each exposure regimen. Dam blood lead levels showed significant differences at PND 21 between the two metal treatments [$F(1,14) = 33.65$, $P < .01$]. Mean blood lead levels of 0.01 ± 0.01 and 0.17 ± 0.03 μg/dl were observed for Group 0-Lead and Group 16-Lead, respectively. Lead concentrations for pups at PND 1 also showed significant differences [$F(1,14) = 86.62$, $P < .01$] with means of 0.01 ± 0.01 μg/dl for Group 0-Lead and 0.70 ± 0.07 μg/dl for Group 16-Lead. Blood lead values from pup samples taken at PND 21 also were significant [$F(1,14) = 51.90$, $P < .01$] with means of 0.01 ± 0.01 and 0.14 ± 0.02 μg/dl for Group 0-Lead and Group 16-Lead, respectively. Lead levels at termination of experimental procedures revealed no significant differences between exposure regimens as blood lead levels had fallen below detectable limits (< 0.01 ppm) for all animals that were used in the CPP testing procedure.

The results of the analyses performed on tissues collected from littermates sacrificed at a point after testing (see Nation et al., in press) also revealed that blood lead concentrations had returned to control levels (were below detectable limits). In contrast, brain lead levels remained significantly elevated even beyond PND 100 (means were 0.01 ± 0.01 and 0.04 ± 0.01 μg/g for Group 0-Lead littermates and Group 16-Lead littermates, respectively; $P < .01$).

4. Discussion

The results of this study found that morphine CPP was produced in control and lead-exposed animals in a dose-dependent fashion. More directly relevant to the rationale that formed the basis for conducting the present investigation, morphine CPP was attenuated by perinatal lead exposure. Specifically, following 8 days of conditioning in CPP chambers employing increasing doses of morphine administered intraperitoneally, animals born to dams exposed to 16-mg lead daily throughout gestation and lactation showed lower conditioning scores than their control counterparts. Significant decreases in the amount of time spent on the least-preferred [morphine] side for lead-exposed animals were observed at the 1.25 and 2.50 mg/kg dose of the drug. Further, while control animals exhibited greater place preference at 1.25, 2.50, and 5.00 mg/kg morphine relative to the 0.60 mg/kg dose, for animals developmentally exposed to lead, only at a morphine dose of 5.00 mg/kg were the conditioning scores greater than the 0.60 mg/kg dose. The overall pattern, then, was one that suggested perinatal lead exposure produced an attenuation of the conditioned reinforcing properties of morphine. These findings were obtained even though lead had gained clearance from blood

at the point when the final test was completed. It is worth noting that brain lead levels remained elevated in littermates that were sacrificed after the period of testing.

When our data are examined within the framework of other drug research findings, interesting parallels emerge. Most conspicuously, the period in the animal's life in which it is exposed to lead seems crucial in determining what the subsequent effects will be on drug-related behaviors. Adult lead exposure has produced significant attenuation of sensitization to the stimulatory effects of cocaine (Nation et al., 1996) and morphine (intraperitoneal) (Miller et al., 2000b). By way of contrast to the adult exposure case, enhancement of locomotion from repeated morphine and cocaine administration has been observed following developmental (perinatal) lead exposure (Nation et al., 2000; Miller et al., 2000b). Conversely, testing using perinatal lead treatments has shown attenuation but not a complete blockade of CPP in animals when varying doses of cocaine are used as the unconditioned stimulus [US] (Miller et al., 2000a). These latter cocaine results are congruent with our present findings that show perinatal lead exposure results in an attenuation of drug responsiveness when morphine is presented as the US.

The behavioral effects observed in this study may be accounted for, in part, by examining possible neurochemical disturbances produced by early lead exposure. Dopamine (DA) is believed to play a crucial role in both morphine self-administration (David et al., 2002) and morphine CPP (Manzanedo et al., 2001). Jeziorski and White (1995) also have found that DA antagonists attenuated the expression but not development of sensitization. Given that the dopaminergic system is known to be integral to the rewarding effects of numerous drugs including opiates, (Ranaldi and Wise, 2001; Vanderschuren and Kalivas, 2000; Wise and Bozarth, 1987), lead-induced changes in brain function and neurochemical operation may contribute to the resultant behaviors seen in this study. Along these lines, binding in the nucleus accumbens (NAC) (Pokora et al., 1996), and the number of active DA neurons in the ventral tegmental area (VTA) (Tavakoli-Nezhad et al., 2001) are both decreased by postnatal lead exposure.

In addition to factors relating to lead/DA interactions, developmental exposure to lead is known to be associated with impairments to glutamatergic systems (Cory-Slechta, 1995). Early lead exposure is known to increase the density of glutamate (GLU) receptors in response to a dramatic depletion of GLU availability (Lasley et al., 2001). Glutamate activity also is known to be involved in mediating opiate sensitivity (Jeziorski et al., 1994) and reinforcement and therefore merits attention when examining lead/morphine interactions. The ultimate role of other neurotransmitter systems as a result of lead-induced disturbances has yet to be determined but the modulation of morphine sensitivity by other neural systems must be considered.

CPP was selected as the behavioral endpoint for this study because it is generally accepted as a model for measuring the reinforcing properties of drugs. Although there are some disagreements in the literature regarding the relative procedural advantages associated with the use of biased or unbiased procedures, on the whole we believe that the biased procedure affords more reliable evidence of the strength of conditioned preference. In this regard, it is recognized that increased time spent on the least-preferred side of the apparatus may derive from elimination to the initial aversion to the drug-paired side of the test chamber. However, Calcagnetti and Schechter (1993) have shown that when the drug US is replaced with saline after conditioning, extinction occurs and a return to preconditioning preferences is evident. This suggests appetitive properties of the drug play a significant role in a CPP preparation employing biased conditioning procedures.

As indicated, CPP scores were determined on test days (when free access was allowed to either side) and were defined as some measurable preference of one side vs. the other. In this case, morphine produced rewarding effects for both control animals and lead-exposed animals but in the case of lead-exposed animals the amount of morphine required to show the same degree of CPP as controls was greater. Of potential practical significance is that antagonism of the acute rewarding properties of morphine displayed in this study may have implications for the selection of opiates. Animals that experience an attenuation of the rewarding effects of a drug may increase self-administration at high doses of a drug due to a need to maintain an optimal level of the reinforcing effects of that drug. This pattern of behavior could be interpreted within a theoretical framework linked to compensatory mechanisms. Lynch and Carroll (2001) have proposed that to maintain optimal drug levels, animals will self-administer at greater amounts when high doses are decreased in potency. In this regard, self-administration trials using developmental lead and morphine could potentially reveal patterns of antagonism that are manifest as a rightward shift in the dose–effect curve. That is, the rewarding efficacy of morphine at high doses could be reduced by neurological changes due to early lead contamination; consequently more frequent infusions of high doses of morphine would be necessary to achieve the same amount of reward experienced by control animals.

With respect to possible limitations of the present study, it must be acknowledged that the gavage technique used may have been a source of stress that contributed to the pattern of results reported here. There is some evidence that large volumes (>20 ml/kg) of the gavage vehicle can alter maternal behavior, and therein influence behavioral development (Brown et al., 2000). As noted, in the present investigation lead/vehicle only solutions were presented in 1-ml volumes, so the likelihood of such perturbations was minimal. Still, it would be of interest to compare the CPP behavior of gavage controls with a separate control group that receives no such treatment.

Finally, we note the implications of these findings are that drug users developmentally exposed to lead contaminants may be presented with increased health risks. Environ-

ments where lead levels continue to remain within unsafe ranges are particularly at risk. The offspring of those exposed during critical developmental periods could potentially be experiencing long-lasting changes in the efficacy of drugs possessing abuse liability. Accordingly, it must be considered that lead exposure early in the developmental period may ultimately relate to the elevated number of cases of drug abuse reported in urban areas where lead pollution continues to be a problem (Harwell et al., 1996).

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