Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 95 (2008) 23–29
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Developmental lead exposure alters methamphetamine self-administration in the male rat: Acquisition and reinstatement☆

Angelica Rocha[a], Rodrigo Valles[a], Gerald R. Bratton[b], Jack R. Nation[a,b,*]

[a] *Department of Psychology, Texas A&M University, College Station, TX 77843, United States*
[b] *Department of Veterinary Anatomy and Public Health, Texas A&M University, College Station, TX 77843, United States*

Received 9 August 2007; received in revised form 29 November 2007; accepted 1 December 2007
Available online 1 February 2008

Abstract

The rate of acquisition of drug self-administration and the return to drug seeking are important elements of the overall drug profile, and are essential factors in understanding risks associated with drug abuse. Experiment 1 examined the effects of perinatal (gestation/lactation) lead exposure on adult rates of acquisition of intravenous (i.v.) methamphetamine self-administration. Experiment 2 investigated the effects of perinatal lead exposure on drug-maintained responding in a reinstatement (relapse) paradigm. In Experiment 1, female rats were gavaged daily with 0 or 16 mg lead for 30 days prior to breeding with nonexposed males. Lead exposure continued through gestation and lactation and was discontinued at weaning (postnatal day [PND] 21). Male rats born to control or lead-exposed dams were tested daily as adults in an acquisition paradigm that incorporated both Pavlovian and operant components. An initial 3-h autoshaping period preceded a 3-h self-administration period. For 35 daily training sessions i.v. methamphetamine infusions [inf] (0.02 mg/kg) were paired with the extension and retraction of a lever (autoshaping), while inf occurred during self-administration only when a lever press was executed (FR-1). In Experiment 2 animals developmentally exposed to lead were trained on an FR-2 to self-administer methamphetamine (0.04 mg/kg/inf) and then placed on an extinction schedule prior to receiving intraperitoneal (i.p.) priming injections of saline, 0.50, 1.00, or 1.50 mg/kg methamphetamine. The findings from Experiment 1 showed that acquisition was delayed in rats born to lead-exposed dams gavaged daily with 16 mg lead throughout gestation and lactation when a 0.02-mg/kg/inf of methamphetamine served as the reinforcement outcome. Additional data from Experiment 2 indicated priming cues (injections of methamphetamine [i.p.]) administered after extinction were less likely to occasion a return to drug seeking (relapse) in the 16-mg group relative to the 0-mg control group. These results suggest perinatal lead exposure alters patterns of methamphetamine self-administration during the adult cycle.

Keywords: Autoshaping; Developmental lead; Methamphetamine; Self-administration

1. Introduction

With the forced removal of lead additives in the 1970s, North America has witnessed substantial declines in environmental lead concentrations over the past two decades. And although some in the public sector, and even within the scientific community, have assumed the public health threats associated with lead toxicity have been largely removed, it is clear that this is not the case (Hubbs-Tait et al., 2005). 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 (Kemp et al., 2007; Milke, 1999; Pirkle et al., 1998). Coupled with a compelling literature on developmental low-level lead-induced disturbance in cognitive function (Bellinger, 2006; Canfield et al., 2003), it is becoming increasingly apparent that a range of behaviors impacted by such early lead exposure may extend to include drug selection and use, and potentially may affect matters relating to addiction. For instance, developmental lead exposure has been shown to increase the acquisition and maintenance of cocaine self-administration at low doses of the drug when animals are tested as adults (Rocha et al., 2005; Valles et al., 2005), and it increases the likelihood of relapse in a cocaine self-administration setting (Nation et al., 2003). Elsewhere, the modulatory role of developmental lead exposure in the redefi-

☆ This research was supported by United States Public Health Grants DA13188 and MH65728.
* Corresponding author at: Department of Psychology, Texas A&M University, College Station, TX 77843, United States. Tel.: +1 979 845 2573; fax: +1 979 845 2573.
E-mail address: jrn@psyc.tamu.edu (J.R. Nation).

0376-8716/$ – see front matter.
doi:10.1016/j.drugalcdep.2007.12.003

nition of the reinforcing efficacy of heroin has been established (Rocha et al., 2004).

To date, no attempts have been made to explore potential interactive relations between early lead exposure and methamphetamine, a psychostimulant that currently is gaining distribution worldwide (Anglin et al., 2000; Yan et al., 2006). The psychoactive effects of methamphetamine are associated with disturbances in a variety of neurochemical pathways, but perhaps most conspicuously in dopaminergic and GABA-ergic systems. Both increased dopamine (DA) levels and decreased DA transporter (DAT) activity have been reported in rodents administered with methamphetamine (Broom and Yamamoto, 2005; Brown and Yamamoto, 2003; Cadet et al., 2003; but see Shepard et al., 2006). With respect to gamma-aminobutyric acid (GABA) and attendant anxiety-related involvement in the effects of methamphetamine administration, the anxiogenic compound yohimbine increases drug sensitivity (Shepard et al., 2004), and the GABA agonist baclofen attenuates the reinforcing effects of methamphetamine (e.g., Ranaldi and Poeggel, 2002). These data are of particular interest here inasmuch as lead exposure is known to decrease dopamine activity (Cory-Slechta, 1995; Devoto et al., 2001; Lasley and Lane, 1988) as well as GABA function (Lasley and Gilbert, 2002; Lasley et al., 1999).

Given the apparent links between lead exposure and neural mechanisms ostensibly involved in determining methamphetamine sensitivity, it seems reasonable to examine both the possible relationship between developmental lead exposure and the acquisition of methamphetamine self-administration responding, as well as the return to drug seeking following extinction (reinstatement [relapse]). It has been argued that the rate of acquisition of drug self-administration may serve as a predictor of later drug-taking behavior, possibly influencing the transition from drug use to addiction (refer to Rocha et al., 2005). Accordingly, in Experiment 1 an acquisition paradigm developed by Carroll and associates (Campbell and Carroll, 2001; Carroll and Lac, 1997) was employed to train lead-exposed and control animals to press a lever for a methamphetamine-reinforcement in a consistent manner, with minimal intrusions. In this preparation, Pavlovian conditioning is first used to shape behavior, then operant conditioning is tested in order to measure rate of methamphetamine acquisition in the animals. Experiment 2 focused on the effects of lead exposure on reinstatement responding which is considered to be a valid animal model of relapse (McFarland et al., 2003; Shalev et al., 2002; Yan et al., 2006). It is within this context that findings from Experiments 1 and 2 may have clinical implications for drug addiction. In both experiments the exposure regimen consisted of perinatal (gestation/lactation) lead exposure.

2. Experiment 1

2.1. Methods

2.1.1. 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 the Public Health Service Policy for the Care and Use of Laboratory Animals (PHS Policy, 1996). Adult female and male Sprague-Dawley rats (Harlan; Houston, TX) were used for breeding, and only male offspring were tested in this investigation.

2.1.2. Lead exposure regimen. For 30 days, adult female rats were exposed to 0 (sodium acetate) or 16 mg lead (as lead acetate) daily using a 16 ga gavage needle to administer the respective solutions in a volume of 1.0 ml deionized water. This procedure has been used in our previous developmental lead studies to ensure stable blood/tissue levels (cf. Miller et al., 2000; Nation et al., 2000, 2003; Rocha et al., 2004; Valles et al., 2005). The present lead concentration was selected based on previous investigations that found it produces differential behavioral effects while not altering dam weights or the locomotor ability of pups (Miller et al., 2000). Following this 30-day toxicant exposure period, females were bred with nonexposed males. Once females tested positive for copulatory plugs, males were removed from the home cage. Females continued to receive their daily dose of the control solution or lead acetate solution throughout the gestation and lactation periods. Standard rat chow (Teklad, Madison, WI) and tap water were available *ad libitum* for dams in the home cage. Litters were culled to eight pups on postnatal day (PND) 1, and only one pup from each litter was used in the experiment in order to avoid confounds that are sometimes evident in studies involving toxicant exposure (Holson and Pearce, 1992).

For control and lead-exposed dams, 100–150 μl of tail-blood was drawn at breeding, parturition (PND 1) and weaning (PND 21). In addition, at the point of termination of the experiment, brain, kidney, liver and bone (tibia) were harvested from test animals for lead concentration analyses. Littermates of test animals were sacrificed on PND 1 and PND 21, and blood samples were collected for subsequent analyses.

The rate of pregnancy was not different between groups. On PND 21, pups used for testing were weaned and housed individually. All animals were maintained on a 12-h light/dark cycle. Testing commenced at approximately 10:00 h, 2 h into the 12-h light cycle.

2.1.3. Surgical procedures. Surgery was performed on test offspring at PND 60, which is a point demonstrated to be within the adult timeframe of behavioral change produced by developmental lead exposure (Miller et al., 2000, 2001; Nation et al., 2000, 2003). Using a backplate surgical procedure, implantation of chronic indwelling jugular catheters was performed using sterile techniques as described in detail elsewhere (Nation et al., 2003). The rats were allowed 5 days to recover from surgery before commencing methamphetamine self-administration testing. During this recovery period, each rat received in the home cage hourly intravenous (i.v.) infusions [inf] (200 μl) of a sterile saline solution containing heparin (1.25 U/ml) and penicillin g potassium (250,000 U/ml). Following recovery, over an 8.00-s time frame, animals received automated hourly inf (213 μl) of heparinized saline in the home cage for the duration of the study. All animals received free access to food and water for 5 days while recovering from surgery. Subsequently, daily food was restricted to 18 g of standard rat chow in order to maintain animals at approximately 85% of their mean free-feeding body weight. This food-restriction regimen is similar to that used in other laboratories (e.g., Campbell and Carroll, 2001). Moderate food restriction consistently has been shown to accelerate methamphetamine acquisition (Roth and Carroll, 2004), and the procedure is recommended for autoshaping acquisition studies. Uncontaminated water was available *ad libitum* throughout the study. Animals were weighed daily prior to testing. Food was placed in home cages following the end of each daily testing session.

2.1.4. Apparatus. Twelve operant conditioning chambers (Model E10-10, Coulbourn, Allentown, PA) in sound attenuating cubicles served as the test apparatus. Each chamber had two levers and a stimulus light located above each lever. Infusion pumps (Razel Scientific Instruments; Stamford, CT) controlled drug delivery to each of the boxes. A 20-ml syringe delivered i.v. inf (160 μl) over a 6.00-s time frame. The system was interfaced with 2 IBM computers, each controlling drug delivery and recording data from 6 chambers.

2.1.5. Procedure.

2.1.5.1. Autoshaping component. Control (Group 0 mg; $n = 7$) and lead-exposed (Group 16 mg; $n = 8$) animals were run in two squads, and subject assignment to chambers and squad was counterbalanced by group. Each of the