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Research article

Differential behavioral effects of nicotine in adult male and female rats with a history of prenatal methamphetamine exposure

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HIGHLIGHTS

- Prenatal methamphetamine exposure resulted in decreased aversive effects of nicotine in adult male rats but not in adult female rats.
- Prenatal methamphetamine exposure did not influence nicotine-induced locomotor activity in either male or female adult rats.
- Prenatal methamphetamine exposure and gender differentially affected nicotine-induced behaviors such as nicotine-induced conditioned taste aversion and locomotor activity.

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ABSTRACT

The goal of the current study was to assess the effects of prenatal methamphetamine (MA)/saline exposure on nicotine-induced stimulant and aversive effects in both male and female adult rats. The aversive effects of nicotine were assessed using the nicotine-induced conditioned taste aversion model (0.4 mg/kg, base), while the stimulant effects of nicotine were measured by assessing changes in spontaneous locomotor activity after subcutaneous administration of different doses of nicotine (0, 0.1 & 0.4 mg/kg, base). The aversive effects of nicotine were significantly decreased in male, but not in female rats with a history of prenatal MA exposure compared to respective saline controls. No influence of prenatal MA exposure was observed on nicotine-induced increase in locomotor activity in either male or female rats. In conclusion, males with a history of prenatal MA exposure may be more vulnerable to nicotine addiction due to a decrease in nicotine-induced aversive effects.

1. Introduction

Tobacco smoking and the morbidity associated with it is a major burden on societies across the world [1]. However, factors increasing vulnerability to tobacco addiction are not fully understood. Over the last decade, there has been an increase in methamphetamine (MA) abuse by pregnant women [28]. In humans, infants exposed to MA *in utero* show a variety of motor, developmental, physical and cognitive abnormalities [14,24]. In animals, prenatal MA exposure resulted in increased amphetamine-induced conditioned place preference (CPP) in adult rats compared to controls [23]. Additionally, prenatal MA exposure increased sensitivity to anxiolytic effects of MA in adult rats compared to controls [18]. The above findings suggest that prenatal MA exposure influenced behavioral effects of drugs of abuse in the adult offspring. High rates of tobacco smoking are often observed amongst adult MA abusers [27]. However, it is not known if prenatal MA exposure increases vulnerability to tobacco addiction during adulthood.

Nicotine in tobacco smoke can result in both rewarding and aversive effects by binding to neuronal nicotinic receptors [12,26]. First time smokers often report aversive and unpleasant effects such as dizziness, headaches, palpitations, and vomiting upon first initiating smoking [5]. In fact, aversive effects of nicotine experienced by first-time smokers determine their vulnerability to nicotine addiction [16]. Thus, individuals that experience fewer or no aversive effects of nicotine are more likely to continue smoking. The goal of this study was to assess effects of prenatal MA exposure on nicotine-induced aversive effects in adult offspring using the nicotine-induced conditioned taste aversion model (CTA)

Abbreviations: CTA, conditioned taste aversion; CPP, conditioned place preference; MA, methamphetamine; NAcc, nucleus accumbens; hr, hours; mins, minutes; SD, Sprague Dawley.

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[21]. Nicotine is a psychomotor stimulant and increases locomotor activity, which is used as a measure of its reinforcing effects [2]. Therefore in this study, we also assessed effects of nicotine on locomotor activity in animals with a history of prenatal MA/saline exposure. We hypothesized that animals with a history of prenatal MA exposure compared to controls would be less sensitive to the aversive effects of nicotine and more responsive to nicotine-induced stimulant effects.

Previous work from our laboratory showed that prenatal MA exposure compared to controls resulted in significantly decreased basal spontaneous locomotor activity in adult female rats, but not in male rats [15]. Further, prenatal MA exposure compared to controls increased myocardial sensitivity to ischemic injury (larger infarct size and elevated end-diastolic pressure) in female rats, but not in male rats. Additionally male, but not female rats with a history of prenatal MA exposure compared to controls showed significantly greater amount of rearing after MA challenge during adulthood [20]. Overall, the above findings suggest that the effects of prenatal MA exposure can be gender specific. Thus, in this study we evaluated the effects of prenatal MA exposure on nicotine-induced stimulant and aversive effects in both adult male and female rats.

2. Materials and methods

2.1. Animals

Male and female Sprague Dawley (SD) rats were obtained from Charles River (Wilmington, MA) and a breeding colony was established at Ohio Northern University. Rats were housed 3–4/cage in a temperature- and humidity-controlled vivarium using a 12 hr light/dark cycle. Animals had unrestricted access to food and water, except during the nicotine-induced CTA experiment when they were water restricted (see experimental details described below). All procedures described in this application were approved by the university's institutional animal care and use committee.

2.2. Drugs

MA hydrochloride and (−)Nicotine hydrogen tartrate were obtained from Sigma-Aldrich (St. Louis, MO) and dissolved in saline (Hospira, Lake Forest, IL). Both drugs were administered subcutaneously (s.c.) in a volume of 1 ml/kg. The pH for nicotine was adjusted to 7.4 ± 0.5 with 0.1 M NaOH and nicotine doses are reported as base concentrations (0.1 and 0.4 mg/kg, base).

2.3. Prenatal MA/saline exposure

Prenatal MA/saline treatment has been previously described [15] (see Fig. 1A). Briefly, pregnant female rats were randomly assigned to either MA- (n = 15) or saline-treated (n = 15) groups. Pregnancy was defined by the presence of a vaginal plug [gestational day zero (GD 0)]. Daily MA (5 mg/kg; s.c.)/saline (1 ml/kg; s.c.) injections were initiated on GD 1 and continued until the day of delivery (GD 21 or GD 22), based on previously published studies [15,18,19]. Litter sizes were similar in MA- and saline-treated groups. Only one offspring (male or female) from each litter of the MA- and saline-treated groups was used for the study. Remaining animals from each litter were used for other studies. The day of delivery was counted as postnatal day (PND) 0 and experiments with nicotine were conducted in adult rats (PND 60–72 days).

2.4. Experimental design

Effects of nicotine-induced CTA in male (Experiment 1) and female (Experiment 2) rats with a history of prenatal MA/saline exposure

Adult male and female SD rats with a history of MA/saline exposure underwent nicotine-induced CTA as described below (see Fig. 1B). Animals were administered nicotine (0.4 mg/kg, base; s.c) on nicotine conditioning days and saline on saline conditioning days.

Effects of nicotine-induced locomotor activity in male (Experiment 3) and female (Experiment 4) rats with a history of prenatal MA/saline exposure

After completion of the nicotine-induced CTA experiment, adult male and female SD rats were used to assess the effects of nicotine/saline on locomotor activity using chambers described below. On day1, animals were habituated to the experimental room (15 mins) and testing chambers (20 mins). On days 2–4, locomotor activity was measured for 20 mins after nicotine/saline administration as follows: saline (1 ml/kg; s.c.; Day 2), nicotine (0.1 mg/kg, base; s.c.; Day 3) and nicotine (0.4 mg/kg, base; s.c.; Day 4). These nicotine doses were based on previously published studies [2,3]. Locomotor activity was measured for 20 mins because preliminary work in our laboratory showed that nicotine-induced (0.4 mg/kg, base; s.c.) increase in locomotor activity was observed in the first 10 mins and locomotor activity returned to basal levels within 20 mins. The lower dose of nicotine (0.1 mg/kg, base; s.c.) was used to see if animals with a history of prenatal MA exposure were more sensitive to the stimulant effects of nicotine compared to control animals.

2.5. Nicotine-induced CTA

The protocol for the nicotine-induced CTA model was adapted from previously published studies [4,21] (see Fig. 1B). Nicotine-induced CTA was divided into the following phases: water restriction phase (Days 1–5), Pre-test phase (Days 6–7), Conditioning phase (Days 8–15), Test phase (Days 17–18). During the experiment two flavored solutions (0.3% unsweetened cherry and grape Kool-Aid®) were used. Simultaneous access to the two flavored solutions during the Pre-test allowed for determination of the preferred flavored solution (consumed in greater amount), which was subsequently paired with nicotine during conditioning. The other flavored solution was paired with saline during conditioning. Animals had a total of eight conditioning sessions between Days 8–15 with one conditioning session/day (i.e. four days of conditioning with nicotine and four days with saline alternating with each other). Conditioning sessions were counterbalanced. On day 16, rats were allowed water access for 60 mins in the housing colony and no drugs were administered on that day to avoid carryover effects. Importantly, animals were not administered any drug on Pre-test and Test days. To account for side-preference, the Pre-test and Test was conducted over two days. Consumption of the flavored solutions and water was measured by weighing the bottles before and after animals had access to the respective solution on all days.

2.6. Locomotor activity

Locomotor activity in rats was measured using an Opto-M4 Auto-Track System (Columbus Instruments, Columbus, OH) made of Plexiglas compartments ($44 \times 44 \times 21$ cm) and equipped with 16 lasers (spaced 2.5 cm apart) on each axis. The total distance travelled by the rat was determined by the number of photobeam breaks, which were recorded by a computerized animal activity meter system (Auto Track).

3. Data analyses

Data from male and female rats was analyzed separately because total consumption of the two flavored solutions on the Pre-test and Test days in male rats was significantly greater than in female rats.