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Delayed extinction and stronger drug-primed reinstatement of methamphetamine seeking in rats prenatally exposed to morphine

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ABSTRACT

Prenatal morphine (PM) affects the development of brain reward system and cognitive function. The present study aimed to determine whether PM exposure increases the vulnerability to MA addiction. Pregnant Sprague-Dawley rats were administered saline or morphine during embryonic days 3–20. The acquisition, extinction and reinstatement of methamphetamine (MA) conditioned place preference (CPP) and intravenous self-administration (SA) paradigms were assessed in the male adult offspring. There was no difference in the acquisition and expression of MA CPP between saline- and PM-exposed rats, whereas PM-exposed rats exhibited slower extinction and greater MA priming-induced reinstatement of drug-seeking behavior than controls. Similarly, MA SA under progressive ratio and fixed ratio schedules was not affected by PM exposure, but PM-exposed rats required more extinction sessions to reach the extinction criteria and displayed more severe MA priming-, but not cue-induced, reinstatement. Such alterations in extinction and reinstatement were not present when PM-exposed rats were tested in an equivalent paradigm assessing operant responding for food pellets. Our results demonstrate that PM exposure did not affect the association memory formation during acquisition of MA CPP or SA, but impaired extinction learning and increased MA-primed reinstatement in both tasks. These findings suggest that the offspring of women using morphine or heroin during pregnancy might predict persistent MA seeking during extinction and enhanced propensity to MA relapse although they might not be more susceptible to the reinforcing effect of MA during initiation of drug use.

1. Introduction

Substance abuse during pregnancy is a serious and growing problem. Children born to heroin- or morphine-addicted mothers suffer from high mortality and central nervous system impairments (Ostrea & Ostrea, 1997; Yanai et al., 2003) and present long-term neuropsychological consequences associated with dysfunction in intellectual ability, lack of emotional control, and disturbances in memory (Ornoy, 2003). Similarly, animals prenatally exposed to morphine showed spatial learning deficits in the Morris water maze and both working and reference memory impairments in the radial arm maze (Gass, Osborne, Watson, Brown, & Olive, 2009; Yang et al., 2003).

In general, the children of addicts are more likely than the general population to develop an addiction to drugs. Although many risk factors may be involved, gestational morphine exposure seems to be one of risk factors which lead to the offspring more prone to drug addiction. Preclinical studies have shown that prenatal morphine (PM) exposure increases vulnerability to morphine-induced conditioned place preference (CPP) and behavioral sensitization (Gagin, Kook, Cohen, & Shavit, 1997; Wu, Chen, Tao, & Huang, 2009). Moreover, the enhanced cocaine or heroin self-administration (SA) has been observed in the adult offspring prenatally exposed to morphine (Ramsey, Niesink, & Van Ree, 1993). These findings suggest that PM exposure induces a long-lasting enhancement of the reinforcing effects of morphine and cocaine.

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However, it remains unclear if PM exposure affects reinforcing effects of other abused drugs.

Methamphetamine (MA) is a commonly abused illicit drug, releasing excess dopamine into the synaptic clefts of dopaminergic neurons (Volz, Fleckenstein, & Hanson, 2007). As an extremely powerful and addictive psychostimulant, animal models of MA addiction including behavioral sensitization, CPP and SA have been well established (Gass et al., 2009; Rogers, De Santis, & See, 2008; Tien, Ho, Loh, & Ma, 2007). The present study aimed to determine whether PM affects MA CPP and SA because these two preclinical tasks were commonly used to compare the individual vulnerability to drug addiction (Tzschentke, 2007). The progressive ratio (PR) schedule in SA was used to investigate the potential effect of PM exposure on the motivation for MA in the present study. The PR schedule is an effective tool for studying the reinforcing efficacy of abused substances. The final ratio completed is defined as the breaking point, reflecting the maximum effort that an animal will expend in order to receive a defined drug infusion (Richardson & Roberts, 1996).

Furthermore, the extinction–reinstatement procedures of these two tasks suitable to study drug craving and relapse (Gass et al., 2009; Mueller & Stewart, 2000; Shaham, Shalev, Lu, De Wit, & Stewart, 2003) were included. Extinction is referred to the reduced responding when the conditioned stimulus or the reinforcer is no longer present (Bossert, Marchant, Calu, & Shaham, 2013). After successful acquisition of MA CPP, the animals underwent the non-confined extinction, in which the gradual reduction of the time spent in initially preferred compartment when the drug reward was absent. Following extinction, CPP was reinstated with a priming injection of a lower dose of MA. In the MA SA task, the drug seeking behaviors were reinstated by the conditioned cue and drug priming infusion after the extinction training reached the criteria.

Finally, the acquisition, extinction and reinstatement phases in an equivalent paradigm assessing operant responding for food SA were examined to reveal if PM exposure produced the same effects on operant conditioning of natural reinforcers.

2. Materials and methods

2.1. Animals

Pregnant Sprague-Dawley rats (BioLASCO Taiwan Co., Ltd) and their male offspring were used in the experiments. The pregnant female rats (at E2), 10–12 weeks old and weighing 200–250 g, were shipped from animal breeding company. After arrival, the dams were acclimatized to a room with controlled temperature (25 °C), humidity (50 ± 10%) and a 12 h day-night cycle (light on 07:00–19:00 h) for 24 h before experimentation. Rat dams during gestation and nursing were kept individually in separate cages and their offspring were housed 2–3 per cage after weaning. All animals were provided with food (Western Lab 7001, Orange, CA, USA) and water *ad libitum*. All procedure for animal care was proved by the Institutional Animal Care and Use Committee of the National Health Research Institutes.

2.2. Chemicals

Morphine and methamphetamine hydrochloride were purchased from the Taiwan Food and Drug Administration, Taipei, Taiwan. Morphine was dissolved in distilled water and methamphetamine hydrochloride was dissolved in physiological saline (0.9% NaCl).

2.3. Prenatal morphine exposure

Pregnant female rats (at embryonic day 2, E2) were randomly assigned into the control and morphine groups and received vehicle or morphine (s.c.) during E3–E20. The control group received distilled water 1 ml/kg, *s.c.*, twice a day. The morphine group received morphine, 2 mg/kg (initial dose) to 4 mg/kg (final dose), *s.c.*, twice a day (increment of 1 mg/kg per week). All rats received drug injections during 8:30–9:00 and 16:30–17:00. The dosage was selected to produce overt toxicity, but not overdose deaths (Chiang, Hung, Lee, Yan, & Ho, 2010).

2.4. MA CPP

The apparatus and procedure were described as a previous report (Kuo, Chai, & Chen, 2011). Briefly, CPP apparatus consisted of a large box made of wood and was divided into two large compartments of equal size (45 × 45 × 30 cm) by a wooden partition. One end compartment was painted gray and the other was painted with black and white vertical stripes on the walls. An unpainted small compartment was (36 × 18 × 20 cm), protruding from the rear of the two large boxes, connected the two entrances to allow animals move freely in the all three compartments. The apparatus was situated in a brightly lit room about 60 cm from a one-way vision window, preventing the rats from seeing any of the cues in the room.

The CPP procedures consisted of five consecutive phases, pre-exposure, conditioning, test, extinction and MA priming-induced reinstatement. On the first day of the experiment, animals were placed in the small compartment and allowed to explore the all three compartments for 10 min. In this pre-exposure phase, animals were allowed to habituate to the whole apparatus and their possible unconditioned place preference for compartments was verified.

Next, the conditioning phase consisted of 4 daily sessions and each rat was injected with MA (2 mg/kg, i.p.) and saline on the alternate days. Animals were placed into the specific compartment immediately after the injections. CPP test was conducted 24 h after the last conditioning session and no drug infusion was given before the test. Animals were allowed to move freely in the whole apparatus for 20 min as the pre-exposure and the time they spent in each compartment was recorded for CPP test analysis.

Extinction and MA-primed reinstatement were conducted as the CPP test. Extinction included 4 daily sessions. The amount of time the animals lingered in each compartment was recorded. The MA priming-induced reinstatement was manipulated 24 h after the last extinction session and MA (1 mg/kg, i.p.) priming injection was given 30 min before placing animals into the small compartment.

2.5. MA self-administration procedures

2.5.1. Food pretraining

Rats were food-restricted (5 g/day) for 48 h prior to starting food training. After the initiation of food training, animals received 12 g rat chow per day, at least 30 min after the end of the food training session. During the 1 h training session, the animals were trained to press the lever for a single food pellet (45 mg; Bioserve) under fixed ratio 1 (FR1). Only one lever was extended into the operant testing chamber during the initial food training period. Animals took 3–4 days to meet the criteria (defined as earning 100 food pellets within the 1 h session for three consecutive days).

2.5.2. Intravenous catheterization surgery

The IV catheterization surgery was conducted at least 3 days after the free feeding. Animals were anesthetized with isoflurane