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Research report

Effect of prenatal methadone on reinstated behavioral sensitization induced by methamphetamine in adolescent rats

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HIGHLIGHTS

- Prenatal methadone enhances METH-induced increment in locomotor activity in rats.
- Prenatal methadone enhances the reinstated behavioral sensitization to METH in rats.
- Prenatal methadone increases the potential of addiction to METH in later life.

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ABSTRACT

It has been known that methadone maintenance treatment is the standard treatment of choice for pregnant opiate addicts. However, there are few data on newborn outcomes especially in the cross talk with other addictive agents. The present study was to investigate the effect of prenatal exposure to methadone on methamphetamine (METH)-induced behavioral sensitization as an indicator of drug addiction in later life. Pregnant rats received saline or methadone (7 mg/kg, s.c.) twice daily from E3 to E20. To induce behavioral sensitization, offspring (5 weeks old) were treated with METH (1 mg/kg, i.p.) or saline once daily for 5 consecutive days. Ninety-six hours (day 9) after the 5th treatment with METH or saline, animals received a single dose of METH (1 mg/kg, i.p.) or saline to induce the reinstated behavioral sensitization. Prenatal methadone treatment enhanced the level of development of locomotor behavioral sensitization to METH administration in adolescent rats. Prenatal methadone treatment also enhanced the reinstated locomotor behavioral sensitization in adolescent rats after the administration had ceased for 96 h. These results indicate that prenatal methadone exposure produces a persistent lesion in the dopaminergic system, as indicated by enhanced METH-induced locomotor behavioral sensitization (before drug abstinence) and reinstated locomotor behavioral sensitization (after short term drug abstinence) in adolescent rats. These findings show that prenatal methadone exposure may enhance susceptibility to the development of drug addiction in later life. This could provide a reference for drug usage such as methamphetamine in their offspring of pregnant woman who are treating with methadone.

1. Introduction

Methadone, a synthetic opioid, was developed in Germany in 1937, and it is first used to replace morphine for pain treatment. It usually comes in liquid form, which the patient drinks for the treatment of chronic pain [1]. Recently, methadone is used to treat for opiate addiction, and it currently remains the standard treatment for opiate addiction in pregnancy [2]. Evidence shows that chronic use of methadone causes addictive liability and respiratory depression in some subjects [3]. It has been reported that maternal methadone dosage is associated with neonatal abstinence

Abbreviations: E2, day 2 of gestation; i.p., intraperitoneal; METH, methamphetamine; P0, postnatal day 0; s.c., subcutaneous.

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syndrome score on the percentage of treatment for withdrawal and the duration of neonatal hospitalization [4]. These findings indicate that methadone in high doses would not be a good therapeutic agent for pregnant women. However, it is unclear that the effect of prenatal exposure to methadone on the central nervous system or cross interaction with other addictive drugs such as methamphetamine in later life.

Methamphetamine is a very addictive stimulant drug that activates certain systems in the brain. It is a member of amphetamine family, but the effects of methamphetamine are much more potent, longer lasting, and more harmful to the central nervous system [5]. It has been reported that repeated administration of methamphetamine produces a progressively enhanced and persistent behavioral response in rodents, a phenomenon called "behavioral sensitization" [6,7]. Behavioral sensitization is considered to be related to compulsive drug-seeking behavior [8]. Previous studies have indicated that once sensitization has developed, a challenge dose of methamphetamine exhibits behavioral hyperactivity (reinstatement of drug seeking behavior), characterized by increase in locomotor activity and stereotyped behaviors in animals [9–11]. Although the mechanism responsible for methamphetamine-induced behavioral sensitization remains unclear, it is believed that the mesolimbic dopaminergic system in the central nervous system plays a critical role in the development of behavioral sensitization [12,13].

Topographic overlaps between opioid and dopamine neurons are found in the central nervous system, suggesting that interactions exist between these two systems [14]. Previous studies have demonstrated that opioid systems are the targets for psychostimulants as well. For example, the opioid receptor antagonist naltrexone can attenuate methamphetamine-induced locomotor activity in mice [15] and the mu-opioid receptor knockout mice show insensitive to methamphetamine-induced behavioral sensitization [9,16]. The last decade, methadone maintenance treatment becomes the standard treatment of choice for pregnant opiate addicts [17,18]. Therefore, the effect of the earlier exposure to methadone on the central nervous system or the biochemical changes induced by other addictive agents should be respected.

The objective of this study was to determine whether the prenatal methadone treatment leads to a long-lasting change in the brain rewarding system which can enhance adolescent susceptibility to the development of addictive-like behavior in adolescent rats. The current results may represent a useful approach to study the interactions between prenatal methadone treatment and the development of drug addiction in later life, as well as the mechanisms involved.

2. Methods

2.1. Animals

Timed pregnant Sprague-Dawley rats (BioLASCO Taiwan Co., Ltd) arrived in the laboratory on day 2 of gestation (E2). Animals were maintained in a room with a 12 h light/dark cycle and at constant temperature (25 °C). All procedures for animal care were approved by the Institutional Animal Care and Use Committee of National Health Research Institutes or Fu Jen Catholic University at Taiwan. Every effort was made to minimize the number of animals used and their suffering.

2.2. Prenatal treatment

Pregnant Sprague-Dawley rats received methadone (7 mg/kg) by subcutaneous (s.c.) injection twice daily (9:00 and 17:00) from gestation E3 to E20. The control rats were injected with the same volume of sterile saline (1 ml/kg of body weight). The day of birth was defined as postnatal day 0 (P0). The offspring were weaned at P21 and four rats (2 prenatal methadone-treated and 2 prenatal saline-treated) per cage were housed after weaning. Sixteen rats from eight dams for each group were used in the present study.

2.3. Drug administration

Sixteen rats from the prenatal methadone or saline-treated group were further divided into two groups: one received 5 doses of the intraperitoneal (i.p.) injection of methamphetamine hydrochloride (METH; Taiwanese Food and Drug Administration, Taiwan, ROC) (1 mg/kg) (eight rats) and the other with saline (eight rats) on P35. METH was freshly dissolved in physiological saline before use.

Animals began a treatment schedule of 5 daily injections of METH (1 mg/kg, i.p.) to induce behavioral sensitization from day 1 (P35) to day 5 (P39). To reintroduce behavioral sensitization after short–term period of drug abstinence, animals received a single dose of 1 mg/kg METH (i.p.) on day 9 (P43, four days after repeated injection of METH) (Fig. 1).

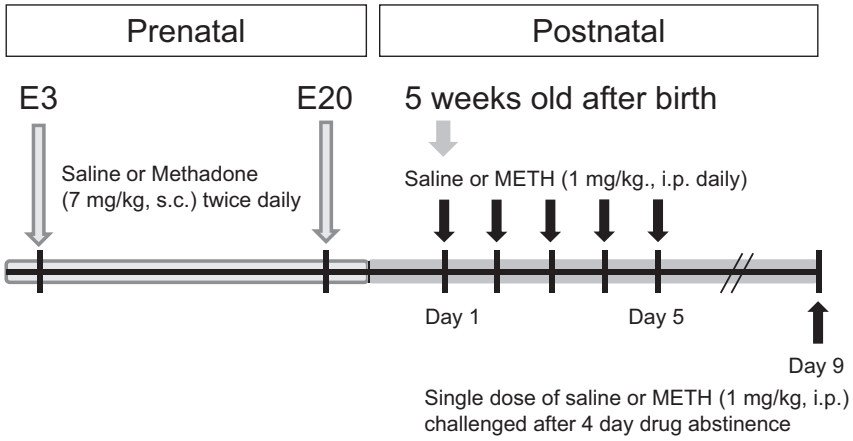

Fig. 1. Experimental procedure of drug administration. Pregnant Sprague-Dawley rats received methadone (7 mg/kg) or saline by s.c. injection twice daily from gestation E3 to E20. Animals began a treatment schedule of five daily injections of METH (1 mg/kg, i.p.) or saline to induce behavioral sensitization from day 1 (P35) to day 5 (P39). To reintroduce behavioral sensitization after short-term period of drug abstinence, animals received a single dose of 1 mg/kg METH (i.p.) or saline on day 9 (P43, 96 h after repeated injection of METH).