



Research report

The effect of early environmental manipulation on locomotor sensitivity and methamphetamine conditioned place preference reward

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H I G H L I G H T S

- Methamphetamine group developed a conditioned preference to the drug paired chamber.
- Separated animals did not exhibit increased meth conditioned place preference.
- Separated animals exhibited elevated activity in response to methamphetamine.
- Increased methamphetamine induced activity was more pronounced in males.
- No difference in mRNA levels was observed for DAT or NET.

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Early life stress leads to several effects on neurological development, affecting health and well-being later in life. Instances of child abuse and neglect are associated with higher rates of depression, risk taking behavior, and an increased risk of drug abuse later in life. This study used repeated neonatal separation of rat pups as a model of early life stress. Rat pups were either handled and weighed as controls or separated for 180 min per day during postnatal days 2–8. In adulthood, male and female rats were tested for methamphetamine conditioned place preference reward and methamphetamine induced locomotor activity. Tissue samples were collected and mRNA was quantified for the norepinephrine transporter in the prefrontal cortex and the dopamine transporter in the nucleus accumbens. Results indicated rats given methamphetamine formed a conditioned place preference, but there was no effect of early separation or sex. Separated males showed heightened methamphetamine-induced locomotor activity, but there was no effect of early separation for females. Overall females were more active than males in response to both saline and methamphetamine. No differences in mRNA levels were observed across any conditions. These results suggest early neonatal separation affects methamphetamine-induced locomotor activity in a sex-dependent manner but has no effects on methamphetamine conditioned place preference.

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1. Introduction

Stress early in development, such as childhood abuse or neglect, negatively impacts physical and mental health later in life. Correlational research suggests chronic life stress increases the likelihood of developing psychological disorders, such as anxiety, depression,

and substance abuse disorder. Although many studies have demonstrated this phenomenon, the underlying mechanisms remain difficult to study in the human population [1,2]. This increased vulnerability likely arises from multifaceted environmental interactions and biological changes which persist into adulthood. The time limitations, ethical constraints, and lack of satisfactory control groups considerably restrict human subjects research in this area.

Animal studies have helped elucidate many biological mechanisms of chronic early life stress. Maternal separation is a well-established model of early developmental stress. This paradigm takes advantage of a sensitive period during the development of the hypothalamic–pituitary–adrenal axis (HPA-axis). In rodents, during the first two weeks after birth, the dam regulates

Abbreviations: HPA-axis, hypothalamic–pituitary–adrenal axis; GR, glucocorticoid receptors; PND, post natal day; DAT, dopamine transporter; NET, norepinephrine transporter.

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the HPA-axis activity of her pups. Removing pups from the dam activates the HPA-axis and her presence ceases further activation of this system, indicating absence of the dam results in persistent release of stress hormones during this sensitive period [3]. Extended activation of the HPA-axis leads to long term changes which results in distinct biological and behavioral phenotypes in adulthood. However, the frequency and duration of HPA-axis activation required for long-term effects remains unclear, as animals can exhibit long-lasting alteration after a single, 24-h separation, or daily 1-h separation for one week [4,5].

Repeated maternal separation is associated with many long-term behavioral adaptations, including behavioral responses to drugs of abuse. After an acute stressor, separated animals exhibit an increased locomotor response to low doses of cocaine and amphetamine relative to handled and non-handled controls [6,7]. A large body of evidence additionally supports the role of early life stress leading to increased sensitivity to the rewarding properties of drugs of abuse. Separated animals acquire cocaine self-administration earlier and escalate their intake more rapidly relative to control animals [8,9]. Additionally, separated animals exhibit increased rewarding behavior to amphetamine in a conditioned place preference test [10]. Although the reasons for these behavioral effects are not completely understood, several alterations in brain reward systems have been characterized.

The effects of early life stress on drug reward are likely a result of changes in multiple neural systems. Most predominantly, the mesolimbic dopamine system regulates aspects of drug reward and drug craving [11]. Maternally separated animals exhibit several alterations throughout the mesolimbic and mesostriatal dopamine systems. Separated animals show elevated dopamine levels in the nucleus accumbens in response to an acute stressor, suggesting a possible hypersensitivity in dopamine release after a stressor [6]. Separated animals also exhibit decreased dopamine transporters in the nucleus accumbens core and striatum [6,7]. Decreased transporter availability may lead to a compromised ability to clear dopamine from the synapse leading to elevated dopamine levels. Interestingly, separated animals also exhibit increased dopamine release in the nucleus accumbens after an acute injection of cocaine or amphetamine, suggesting an increased sensitivity to the rewarding properties of these drugs may be due to changes in dopamine systems [12].

Although dopamine is an important neurotransmitter for regulating drug reward and sensitivity, effects of the dopamine system alone do not fully explain stimulant reward and locomotor activity. Noradrenergic systems have been implicated in stimulant reward and sensitivity. In particular, stimulation of $\alpha 1$ adrenergic receptors may facilitate dopamine release and associated psychostimulant locomotor activation and reward [13,14]. Separated animals exhibit several alterations in norepinephrine systems including enhanced stress-induced norepinephrine release in the hypothalamic paraventricular nucleus and reduced levels of the $\alpha 2$ adrenergic autoreceptors, relative to handled controls [15]. Thus, enhanced stress-induced noradrenergic activity in maternally separated rats may facilitate behavioral responses to psychostimulants.

Though the effects of early life stress on cocaine sensitivity are generally consistent [6,8,16], studies are mixed on the sensitivity of maternally separated animals to the locomotor activating effects of amphetamine [17–19]. Few studies have looked at the effects of early life stress on methamphetamine reward and locomotor activation [20–22]. Previously, we found increased sensitivity to the locomotor activating effects of a low (1.0 mg/kg) and medium (3.0 mg/kg) dose of methamphetamine in separated animals [23]. Other studies found no difference or attenuation in adolescent separated animals relative to controls in methamphetamine reward [20,21]. However, these studies were done in adolescent rats and not adult animals and did not include female animals.

To further examine the effect of early life stress on drug reward and locomotor sensitivity, this study examined the immediate locomotor response to methamphetamine and the rewarding properties of methamphetamine using a conditioned place preference paradigm in adult animals. To better elucidate the underlying mechanisms associated with early life stress, locomotor activity, and methamphetamine reward, we quantified mRNA for dopamine and norepinephrine transporters. We hypothesized that maternal separation would increase sensitivity to the locomotor activating and rewarding effects of methamphetamine and decrease expression of catecholamine transporters in the mesocorticolimbic system.

2. Materials and methods

2.1. Animals

Long-Evans rats (Charles River) were pair-housed in polypropylene cages and kept on 12:12 light/dark cycle with access to food and water *ad libitum*. Litters were derived from 12 male and female pairs bred in the facility. Pregnant dams were housed separately and remained untouched except for weekly cage changes. A total of 73 offspring, 34 males and 39 females, obtained from 10 litters, were used in the study.

2.2. Maternal separation

The day of birth was designated as postnatal day (PND) 0. Litters were culled or fostered on PND 1 to obtain roughly equal litter sizes of no more than 12 pups. Litters were randomly assigned as control or separated. Control litters were transported to the testing room and weighed, resulting in separation from the dam for approximately 15 min every day between PND 2 and 8. Separated litters were transported to the testing room, weighed, and housed individually at nest temperature (30–33 °C) by use of a heating pad for 3 h every day during PND 2–8. Two to four pups from each litter were left with the dam to minimize stress reaction from the dam, and these animals were not tested in the subsequent conditioned place preference experiment. Litters were left undisturbed, except for cage changes, from PND 9 to 20 and were weaned into same-sex pair-housing on PND 21. All rats remained pair-housed and handled weekly during cage changes until testing began on PND 60.

2.3. Conditioned place preference

Methamphetamine conditioned place preference began between PND 60–62. A three-compartment chamber (70 cm × 30 cm × 30 cm, *Kinder Scientific*) was used to condition animals. Each larger side compartment had a distinct wall color (black or white) and a distinct floor texture (bars or grid), whereas the smaller middle chamber was gray with a smooth floor. Total activity and time in each compartment were recorded by a photobeam tracking system (*Motor Monitor, Kinder Scientific*). Animals were habituated to the testing room for 30 min before experimental manipulation each day. Testing occurred over ten days as follows: day 1 – chamber habituation, days 2–9 – conditioning, day 10 – preference test. On day 1 of testing, animals were habituated to the testing apparatus for 30 min with free access to all chambers. After initial habituation, a single sample *t*-test that compared time spent in each chamber to 50% was run for each animal to determine if there was a baseline chamber preference. If animals spent significantly more than half of the habituation time in one chamber, the drug was paired with the non-preferred chamber. If animals did not display a preference, the drug-paired chamber was determined by random assignment. On days 2, 4, 6, and 8 animals were given saline injections and confined to the appropriate

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