Methamphetamine-induced Conditioned Place Preference is Facilitated by Estradiol Pretreatment in Female Mice

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Abstract

Ovarian hormones were well documented to modulate the dopamine release in the central dopaminergic systems. The dopamine-releasing effects in the nucleus accumbens, a major target of the mesolimbicortical dopaminergic system, were closely associated with the reinforcing effects of two psychomotor stimulants, cocaine and methamphetamine. This study aimed to examine the sex differences in the cocaine- and methamphetamine-reinforcing behavior, conditioned place preference. In addition, the modulating effects of estradiol and progesterone on methamphetamine-induced conditioned place preference were investigated in both sexes of adult gonadectomized mice. There was no sex difference in the sensitivity to the cocaine (5 mg/kg)-induced conditioned place preference. However, female mice exhibited a more potent methamphetamine (1 mg/kg)-induced conditioned place preference than did male mice. Moreover, pretreatment with estradiol for two consecutive days before the beginning of the conditioning and throughout the four daily conditionings (0.47 μg /day for totally six days) effectively facilitated methamphetamine-induced conditioned place preference in gonadectomized female mice, but not in gonadectomized male mice. Progesterone, under a similar treatment regimen (0.47 μg/day for six consecutive days), did not alter the methamphetamine-induced conditioned place preference in either sex of gonadectomized mice. Taken together, we conclude that the facilitating effects of estradiol on methamphetamine-induced conditioned place preference could be sex-dependent with an eminent sensitivity associated with the adult female mice.

Key Words: dopamine, sex, estrogens, methamphetamine, cocaine, conditioned place preference

Introduction

Classical conditioning paradigm is sensitive to treatments that act on the central rewarding pathway, specifically the mesolimbicortical dopaminergic system innervating the nucleus accumbens. For example, presentation of unconditioned stimuli during conditioning and presentation of the conditioned stimuli after conditioning both enhanced dopamine release in the nucleus accumbens (30). When an appetitive stimulus is repeatedly paired with specific cues, such cues may acquire conditioned properties that they can elicit subsequent approach responses. The preference for the environment containing the conditioned cues over a natural control environment is referred to as conditioned place preference (CPP). Amphetamine-induced CPP, in this regard, reveals the biased approach responses favoring the

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amphetamine-paired environment over the vehicle-paired environment via a classical conditioning procedure. Amphetamine-induced dopamine release in the nucleus accumbens was posited necessary and sufficient for acquiring the amphetamine-induced CPP (27, 28). First, the efficacy of amphetamine to support an intra-accumbens self-administration response was evident (22), indicating the appetitive propensity of amphetamine. Second, *in vivo* and *in vivo* administration of amphetamine induced a time-dependent increase in the extracellular concentration of dopamine in rat nucleus accumbens (25, 29). Third, CPP was observed with amphetamine infused directly into the core area of the nucleus accumbens (20). Finally, intra-accumbens pretreatment with either D_1 or D_2 dopamine antagonist, SCH 23390 or sulpiride, blocked the acquisition of the amphetamine-induced CPP in a dose-dependent manner (18).

Accrued evidence indicates the modulating effects of ovarian hormones on basal and/or psychomotor stimulant-induced dopamine release in the central dopaminergic system. Estradiol benzoate was found to increase amphetamine-stimulated nigrostriatal dopamine release (1, 9). Administration of amphetamine both *in vivo* and *in vitro* produced a greater dopamine release in the striatum on estrus as compared to them on proestrus and diestrus (3, 5). Moreover, estrogens were found to enhance dopamine release in the nucleus accumbens (26). Estradiol benzoate enhanced amphetamine-induced rotations, an index of dopamine release on the intact side, in a unilateral nigrostriatal projection-lesioned paradigm (2). Lately, we have demonstrated that estradiol may modulate methamphetamine-induced nigrostriatal dopamine toxicity (31, 32), in which the toxicity is closely associated with the dopamine releasing effects elicited by methamphetamine. Likewise, progesterone at low concentrations of 100 and 200 mM reduced K^+-stimulated striatal dopamine release *in vitro*, whereas high concentrations of 300 and 500 mM enhanced the dopamine release (8). We found that progesterone alone mitigated the methamphetamine-induced nigrostriatal dopamine depletions (31). Taken together, ovarian hormones were well known to exert the modulating effects on dopamine release primarily in central nigrostriatal dopaminergic system.

Methamphetamine, a potent amphetamine analog, and cocaine are abused drugs of choice in the local area. Both these psychomotor stimulants were reported to enhance the dopamine release in the nucleus accumbens (10) and to reliably establish CPP in rat models (12, 24). This study aimed to examine 1)sex differences in establishing methamphetamine- and cocaine-induced CPP in a mouse model, and 2) the modulating effects of two ovarian hormones, estradiol and progesterone, on the methamphetamine-induced CPP in two sexes of adult gonadectomized mice.

Materials and Methods

Subjects

Both sexes of C57BL/6J mice, approximately 8 weeks of age (NCKUCM Lab Animal Center, Tainan, Taiwan), were housed five in one plastic cage with free access to food (Purina Mouse Chow, Richmond, IN, USA) and tap water. The colony room was temperature-, humidity-controlled and maintained on a 12h light-dark cycle (lights on at 0700). Methamphetamine hydrochloride was purchased from NBCD in Taiwan and cocaine hydrochloride was purchased from Sigma Chemical Company (St. Louis, MO, USA). All experiments were conducted in a laboratory with the temperature maintained at 21±1°C. This study was performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All procedures were approved by the local Animal Care Committee at National Cheng Kung University College of Medicine.

Surgery and Hormonal Treatment

Male and female mice were gonadectomized bilaterally under 50 mg/kg, i.p., sodium pentobarbital (Nembutal, Abbott Laboratories, North Chicago, USA) anesthesia. Successful removal of female ovaries was confirmed by vaginal epithelial cell examination for eight consecutive days following surgery. Five weeks after gonadectomy, mice of each sex were randomly divided into three treatment groups. The first groups of each sex received daily injection, s.c., of estradiol benzoate (0.47 μg in 0.1ml sesame oil/day, Sigma Chemical Co., St. Louis, USA) for six days. The second groups received daily injection, s.c., of progesterone (0.47 μg in 0.1 ml sesame oil/day, Sigma Chemical Co., St. Louis, USA) for six days. Six doses of sesame oil (0.1 ml each, Sigma Chemical Co., St. Louis, USA) were administered subcutaneously to the last groups of mice, serving as controls. All these priming doses of ovarian hormones and vehicle were given around 0600. Training for methamphetamine-induced conditioned place preference started four hours after the third priming dose of ovarian hormones and vehicle.

Place Preference Apparatus

Methamphetamine- and cocaine-induced place preference conditioning trainings and tests were conducted in one of the four modular component units designed for mice (MedAssociates Inc., Georgia,

Vermont, USA). Each unit consisted of three Plexiglas compartments with a center chamber ($9 \times 13 \times 13$ cm) and two cue-distinct side chambers ($17 \times 13 \times 13$ cm). The side chambers provided three sets of distinctive cues: medium (approximately 160 Lux) vs. dim (approximately 40 Lux) light illumination, opaque black vs. opaque white walls and ceilings, and steel bar grid vs. wire-mesh floors. The center chamber was bright-lit with gray walls and ceiling and a gray platform floor. Automatic guillotine doors controlled passages between the center chamber and the side chambers. Two sets of cues, house light illumination and wall, ceiling color, were counterbalanced between units. Mouse location in each unit was monitored by photocell detectors aligned 1.5 cm above the floor across three compartments with 3 cm apart, connected via interface card to IBM-compatible PC and the time spent in each compartment was recorded and analyzed by MED-PC for Windows.

Conditioning Protocol

All compartments and bottom trays were deodorized by a thorough cleaning with an isopropyl alcohol (70%)-rinsed paper towel wiping and dry process before each training and testing. Habituation procedure was omitted due to 1) avoidance of a frequently-concerned pre-exposure-induced latent inhibition, 2) a proven unbiased design of these units by utilizing several batches of naive mice (approximately 14 each), all exhibiting comparable preference for side chambers across the four units, and 3) an added vehicle control group. On days 1 and 3, mice received an injection of methamphetamine hydrochloride (1 mg/kg, i.p.), cocaine hydrochloride (5 mg/kg, i.p.) or an equivalent volume of saline and were immediately confined in one randomly assigned compartment of the units for 30 min. On alternate days (days 2 and 4), mice received one saline injection and were immediately confined in the other compartment of their corresponding units for 30 min. On day 5, the day following the conclusion of the four-day conditioning training regimen, mice were placed in the center compartment of their corresponding units and started a 15-min preference test. Duration in second mice exploring in each of the three compartments was recorded in this preference test. Individual drug-induced CPP was represented by subtracting the time spent in vehicle-paired chambers from the time spent in drug-paired chambers.

Statistical Analyses

A reliable CPP established by 1 mg/kg methamphetamine and 5 mg/kg cocaine in intact mice was determined by using analysis of variance (ANOVA). Student *t*-tests were employed to examine the sex differences in methamphetamine- and cocaine-induced CPP in intact mice. The modulating effects of estradiol and progesterone on methamphetamine-induced CPP in each sex of adult gonadectomized mice were examined by ANOVA, followed by Scheffe post-hoc analyses if appropriate.

Results

A Notable Sex Difference in the Methamphetamine-Induced Conditioned Place Preference

Previous findings and our preliminary data have demonstrated that methamphetamine (at doses of 1 and 2 mg/kg) and cocaine (at doses of 5, 10, 15, 20 and 25 mg/kg) can be used to establish a reliable CPP in mouse models (19). Low doses of methamphetamine (1 mg/kg) and cocaine (5 mg/kg), thus, were used in an attempt to determine the sex differences in acquiring such drug-induced CPP. In addition, a small number of pairings (two pairings for drug and saline each) were performed in the conditioning protocol to avoid the possibility that such sex differences being overshadowed by the extremely robust reinforcing effects of the drugs. Saline-treated male (N=7) and female (N=7) mice demonstrated an unbiased preference (5.72±18.22 and 18.16±42.55 sec, respectively) between the odd day-training compartment and even day-training compartment. Both methamphetamine (1 mg/kg) and cocaine (5 mg/kg) reliably established conditioned place preference under the present regimen ($F(2,47)=6.01$, $P<0.0047$) (Fig. 1, Top panel). Following the completion of drug conditioning trainings, intact C57BL/6J male and female mice did not exhibit any difference in the acquisition of cocaine (5 mg/kg)-induced CPP (Fig. 1, Bottom panel). However, female C57BL/6J mice demonstrated a more potent methamphetamine-induced CPP as compared to male mice ($t_{(20)}=-2.33$, $P<0.0306$) (Fig. 1, Bottom panel).

Estradiol Effectively Enhances the Methamphetamine-Induced Conditioned Place Preference in Female, but not in Male Mice

While the sex difference in the sensitivity to methamphetamine-induced CPP was observed with female mice displaying a more potent methamphetamine-induced CPP, the roles of ovarian hormones in this CPP paradigm deserved a well-controlled study. In an attempt to avoid the endogenous ovarian confounds, both sexes of adult gonadectomized mice were used. The effects of six daily priming doses of estradiol benzoate (0.47 μg/day), progesterone (0.47 μg/ day), and sesame oil (0.1 ml/day) were examined

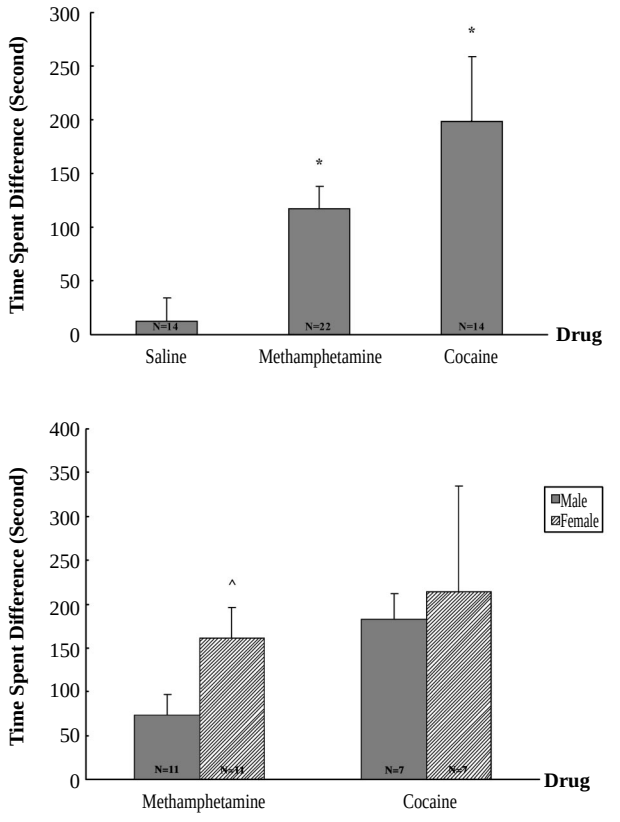

Fig. 1. Sex differences in methamphetamine-induced conditioned place preference and cocaine-induced conditioned place preference (Bottom). A four-day conditioning protocol was used with days 1 and 3 paired with methamphetamine (1 mg/kg) or cocaine (5 mg/kg) injection in one end compartment and days 2 and 4 paired with saline injection in the other end compartment. Drug-induced conditioned place preference was indicated by the time spent difference (subtracting the time spent in saline-associated compartment from the time spent in drug-associated compartment). Both methamphetamine and cocaine reliably established conditioned place preference (Top). *Significantly greater than the saline-treated controls. ^Significantly greater than the matched male mice.

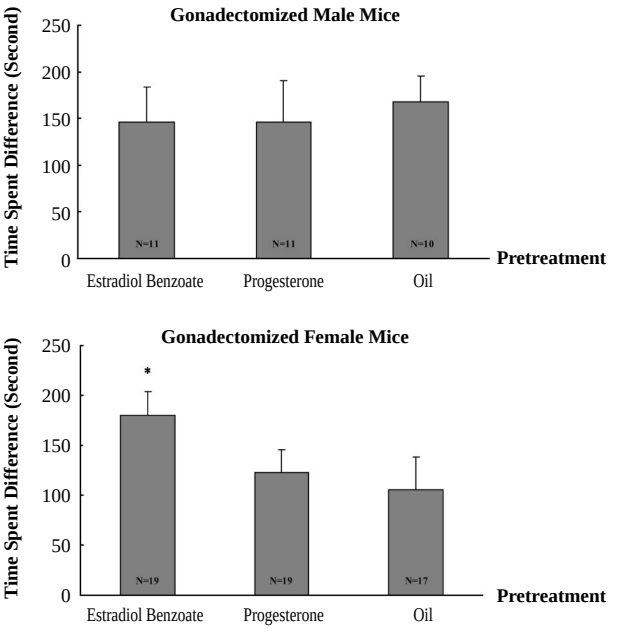

Fig. 2. Effects of estradiol and progesterone on modulating the methamphetamine-induced conditioned place preference in adult gonadectomized male (Top) and female (Bottom) mice. A four-day conditioning protocol was used with days 1 and 3 paired with methamphetamine (1 mg/kg) injection in one end compartment and days 2 and 4 paired with saline injection in the other end compartment. Drug-induced conditioned place preference was indicated by the time spent difference (subtracting the time spent in saline-associated compartment from the time spent in drug-associated compartment). *Significantly greater than sesame oil- and progesterone-pretreated mice.

in gonadectomized female and male mice. Pretreatment with progesterone did not seem to modulate the methamphetamine-induced CPP in gonadectomized female mice (Fig. 2, Bottom panel). Estradiol benzoate was found to effectively facilitate the methamphetamine-induced CPP in gonadectomized female mice ($F(2,52)=4.075$, $P<0.023$) (Fig. 2, Bottom panel). Likewise, it was of interest to note that sesame oil-pretreated ovariectomized female mice seemed to exhibit a weaker methamphetamine-induced CPP than intact female mice under a similar treatment protocol (Fig. 1, Bottom panel and Fig. 2, Bottom panel). Gonadectomized male mice receiving these pretreatments all exhibited comparable methamphetamine-induced CPP (Fig. 2, Top panel).

Discussion

We found that both sexes of mice responded similarly to the cocaine (5 mg/kg)-induced CPP, whereas female mice exhibited a more potent methamphetamine (1 mg/kg)-induced CPP as compared to male mice. This sex difference in the sensitivity to methamphetamine-induced CPP could be modulated by estradiol secretion due to our observation that estradiol pretreatment facilitated methamphetamine-induced CPP in female mice, not in male mice. The lack of estradiol effects on such place preference in gonadectomized male mice could be derived from three possibilities. First, estradiol can not modulate the underlying mechanism of the methamphetamine-induced place preference in adult male mice. Second, removal of male gonads may impair the performance in methamphetamine-induced CPP. The latter alternative appears to be less likely since the sesame oil-pretreated gonadectomized male mice demonstrated equivalent, if not more potent, methamphetamine-induced CPP than did intact male mice under a similar protocol. Third, estradiol can

not exert its potentiating effect, if any, in gonadectomized male mice due to the saturated performance of the methamphetamine-induced CPP in such mice. Given the findings that intact male mice appeared to exhibit a less potent methamphetamine-induced CPP than the gonadectomized male mice under a similar protocol, a male gonadal hormone, testosterone, is suspected to mitigate the magnitude of methamphetamine-induced CPP in this regard.

Many reports, to date, have addressed the distinctive modulating effects of estradiol on various central dopaminergic systems (7, 16). Dopamine receptor blockade were found sufficient to antagonize cocaine-induced drug-seeking behavior only in the dorsal prefrontal cortex (21). Thus, cocaine-induced dopamine-releasing effects in the dorsal prefrontal cortex could play a critical role in initiating the reinforcing effects and/or euphoric experience-activating effects associated with the drug. In contrast, dopamine release in the nucleus accumbens was responsible for the reinforcing effects of amphetamine (6, 11, 17). Given the findings that both amphetamine and methamphetamine enhanced dopamine release in the nucleus accumbens, methamphetamine was less effective than amphetamine in raising dopamine levels in the prefrontal cortex (23). In our results, female mice demonstrated a greater sensitivity to methamphetamine-induced CPP as compared to it in male mice, whereas both sexes exhibited comparable cocaine-induced CPP. Thus, we suspect that discrepancies in such sex-dependent sensitivity to cocaine- and methamphetamine-induced conditioned behavior could arise from variant, modulating effects of sex hormones on dopamine release in the nucleus accumbens and the prefrontal cortex. Nonetheless, sex differences in mouse sensitivity to cocaine-induced CPP can not be excluded by far unless the full dosage spectrum and various strains were examined. Although both sexes of rats exhibited similar psychomotor behavior, such as rotational behavior, stereotyped grooming, head-bobs, forelimb movements, and drug-elicited sensitization following methamphetamine and cocaine administration (4), we, hereby, showed the sex difference in sensitivity to the methamphetamine-induced conditioned behavior in a mouse model. This drug-induced conditioned behavior in mice can be used as an appropriate paradigm to examine the sex differences in psychomotor stimulant dependence and abuse.

Pretreatment with estradiol, not with progesterone, was found effective in facilitating the methamphetamine-induced CPP in gonadectomized female mice. However, estradiol or progesterone pretreatment did not significantly modulate the methamphetamine-induced CPP in gonadectomized male mice. Since surgical removal of gonads was conducted in adult mice in this study, it was reasonable to suspect that the functions of the anatomical substrates underlying this psychomotor stimulant-associated conditioned behavior are modulated by estradiol in a sex-specific manner. Previously, we reported that estradiol attenuated methamphetamine-induced nigrostriatal dopamine depletion only in adult female mice (31). Moreover, estradiol was found to produce a severe acute toxicity to methamphetamine exclusively in intact male mice (15). Furthermore, estrogen was reported to attenuate MPP(+)-induced in vivo dopamine release in gonadectomized female, but not male rats (13). Finally, nicotine-evoked dopamine release in the striatum was enhanced in estrogen-treated females, whereas decreased in estrogen-treated males (14). Along these lines of evidence, our results provide the evidence in support of the notion that estradiol can modulate the central dopaminergic functions via a sex-specific, not a general route. Estradiol may facilitate the methamphetamine-induced CPP via enhancing the reinforcing effects of methamphetamine and/or strengthening the association of environmental cues and methamphetamine-induced euphoria. Differential degrees in salience of environmental cues can be attempted in the present protocol to examine the effects of the latter possibility. Besides, further studies should be extended to determine the modulating effects of estradiol on methamphetamine-induced dopamine release in the nucleus accumbens in both sexes of gonadectomized mice.

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