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Methamphetamine-enhanced female sexual motivation is dependent on dopamine and progesterone signaling in the medial amygdala

Mary K. Holder [a,*,1], Shaun S. Veichweg [b], Jessica A. Mong [a,b]

[a] Program in Neuroscience, University of Maryland, Baltimore, School of Medicine, Baltimore, MD 21201, USA
[b] Department of Pharmacology, University of Maryland, Baltimore, School of Medicine, Baltimore, MD 21201, USA

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ABSTRACT

Methamphetamine (METH) is a psychomotor stimulant strongly associated with increases in sexual drive and impulsive sexual behaviors that often lead to unsafe sexual practices. In women METH users, such practices have been associated with increases in unplanned pregnancies and sexually transmitted diseases. Despite this significant heath concern, the neural mechanisms underlying this drug–sex association are not known. We previously established a rodent model of METH-facilitated female sexual behavior in which estradiol and progesterone interact with METH to increase motivational components of female behavior and neuronal activation in the posterodorsal medial amygdala (MePD) (Holder et al., 2010; Holder and Mong, 2010). The current study more directly examines the mechanisms underlying the drug–sex interaction. Here, we hypothesize that METH-induced increases in MePD dopamine signaling bridge the METH–hormone interaction. In support of this hypothesis, we found that excitotoxic lesions targeted to the MePD attenuated the METH-induced increases in proceptive behavior. Furthermore, infusion of a D1 agonist into the MePD increased proceptive behavior, while infusion of a D1 antagonist blocked the ability of METH to increase proceptive behaviors. Additionally, we found that METH-treatment increased progesterone receptor (PR) immunoreactivity in the MePD, suggesting an interaction between dopamine and progesterone signaling. Indeed, infusions of the PR antagonist, RU486, prevented METH-induced increases in sexual behavior. Thus, taken together, the current findings suggest that dopamine in the MePD modulates enhanced sexual motivation via an amplification of progesterone signaling and contributes to a better understanding of the neurobiology of drug-enhanced sexual behaviors.
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Introduction

Methamphetamine (METH) use among women is a burgeoning health concern as its abuse is significantly associated with high-risk sexual behaviors, leading to increased rates of sexually transmitted diseases such as HIV/AIDS and unplanned pregnancies among METH-addicted women (Corsi and Booth, 2008; Mansergh et al., 2006). Self-report studies have clearly established that METH use elicits heightened sexual drives, desires and sexual activities in women (Mansergh et al., 2006; Rawson et al., 2002; Semple et al., 2004a,b). However, self-reporting surveys do not allow direct testing of the cellular and molecular events underlying METH effects on sexual motivation; thus, the mechanisms by which METH induces female sexual motivation have remained unexplored. For this, rodent models are most appropriate as they can inform the physiological processes underlying the human experience (Blaustein, 2008; Pfaus et al., 2003).

Recently, several laboratories, including our own, have demonstrated that METH facilitates sexual motivation in female rodents (Guarraci, 2010; Winland et al., 2011). In our established model, repeated administration of METH more than doubles the frequency of proceptive (i.e. solicitation) behaviors and augments lordosis intensity. The METH-induced increase in proceptivity depends upon estradiol and progesterone (Holder et al., 2010), suggesting a convergence of ovarian steroids and METH actions.

The posterodorsal medial amygdala (MePD) is uniquely situated to act as a convergence point for METH and hormone actions as it has been implicated in the modulation of female sexual behavior (reviewed in Erskine, 1989). Our previous findings demonstrate that the combined administration of estradiol/progesterone and METH, over either treatment alone, increases neuronal activation and spinophilin protein expression (Holder et al., 2010; Holder and Mong, 2010) in the MePD. Additionally, exogenous estradiol/progesterone administration increases tyrosine hydroxylase (TH) expression in the MePD (Holder and Mong, 2010), suggesting an increase in catecholamine synthesis. METH increases the concentration of extracellular catecholamines by reversal of reuptake transporters (Fleckenstein et al., 2000; Fukui et al., 2003; Sulzer et al., 2005). Thus, increases in TH could further increase extracellular catecholamine concentrations and activation of

* Corresponding author at: 655 W. Baltimore Street, Baltimore, MD 21201, USA. Fax: +1 410 706 0032.
E-mail address: mhold001@umaryland.edu (M.K. Holder).
[1] Present address: Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, Amherst, MA, USA.

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dopamine and/or norepinephrine receptors. Activation of the dopamine D_1 receptor (D_1R) increases the transcriptional activation of progesterone receptors (PRs) (Bai et al., 1997; Denner et al., 1990; Mani et al., 1994a; Power et al., 1991), which are required for the expression of proceptive behaviors (Beach, 1942; McEwen et al., 1987; Pfaff, 1994; Whalen, 1974). Additionally, activation of the noradrenergic α_1 receptor (α_1R) can also facilitate sexual behavior by increasing PR activation (Chu and Etgen, 1999; Chu et al., 1999; Etgen, 1990; Gonzalez-Flores et al., 2004, 2007).

In the present study, we examined the role of the MePD in the METH-enhanced female sexual motivation. We then determined which of the candidate catecholaminergic receptors within the MePD mediated the enhanced sexual motivation. Importantly, within these analyses we established a potential mechanism through with METH and progesterone converge in the MePD to increase female sexual motivation.

Materials and methods

Animals

Adult female Sprague–Dawley rats (275–300 g) were purchased from Charles River Laboratories (Kingston, NY) and housed in the Laboratory Animal Facility of the Health Sciences Facilities at the University of Maryland, School of Medicine under a reversed 12 h:12 h dark:light cycle (lights off at 1000 h) with food and water available ad libitum. All animals were bilaterally ovariectomized under isoflurane anesthesia and allowed a 10–14 day recovery period following surgery. All procedures were approved by the University of Maryland, Baltimore Institutional Animal Care and Use Committee and were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Hormones and methamphetamine treatment

All injections were administered in accordance with the treatment procedures used in our previous studies (Holder et al., 2010; Holder and Mong, 2010). Forty-eight hours before the start of the experimental assay (e.g., behavioral testing or tissue collection), the animals were administered 5 μg 17-β-estradiol benzoate (EB, SC; Sigma Aldrich, St. Louis, MO) followed by 10 μg EB 24 h later. Four hours prior to experimental assay, the rats were injected with progesterone (P, 500 μg, SC; Sigma-Aldrich). During the three days of hormonal priming rats received a daily injection of METH (5 mg/kg/day, IP; Sigma-Aldrich) or saline vehicle. This dose and administration protocol of METH was previously demonstrated to facilitate female sexual motivation (Holder and Mong, 2010) and behaviors (Holder et al., 2010) without causing an increase in stereotypy or general locomotion at the time point of the experimental assay (Holder et al., 2010).

Sexual behavior

The behavioral tests were conducted under dim red light in the dark phase of the light cycle between 1300 and 1600 h, approximately 4 h after the last METH administration. Experimental females were placed in a 50 cm × 38 cm × 25 cm Plexiglas observation chamber with a sexually experienced male. Each behavioral test was recorded by a video camera and was completed when 10 mounts were received or when 15 min had elapsed. During the tests, the investigator remained at a consistent location approximately 0.5 m away from the observation chambers during all trials. An experimenter blind to the treatment groups scored the receptive and proceptive sexual behaviors as previously described (Holder et al., 2010; Holder and Mong, 2010). Briefly, the number of proceptive behaviors (hops, darts, and ear wiggling) that occurred in 10 min was quantified. Additionally, the quantitative (lordosis quotient; LQ) and qualitative (lordosis intensity score; LS) parameters of lordosis were scored as previously described (Holder et al., 2010).

Stereotaxic surgeries targeting posterodorsal medial amygdala

Animals were placed in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA) under isoflurane anesthesia, an incision was made to expose the skull, and holes were drilled at 3.1 mm posterior and ±3.7 mm lateral to Bregma on the skull surface (Guarraci et al., 2004) using a dremel drill (Dremel, Racine, WI). Bilateral neurotoxic lesions targeting the MePD were produced with injections of 0.4 μl of ibotenic acid (10.0 μg/μl in phosphate-buffered saline (PBS), Sigma) using a 5 μl Hamilton syringe (700 series, Hamilton, Reno, NV) lowered 9.3 mm ventral from the skull surface and delivered over a 10 min period. After each injection, the syringe was left in place for a minimum of 10 min. Sham lesions were performed using the same methods, but using vehicle injections. Following surgery, animals were allowed a 10–14 day recovery period. Animals were treated with METH (sham: n = 6, lesion: n = 6) or saline (sham: n = 6, lesion: n = 6) and EB/P as described above and tested for sexual behavior. For the cannulation experiments, chronic indwelling 25-gauge guide cannulae (Plastics One, Roanoke, VA) were bilaterally implanted into the MePD (3.1 mm posterior, ±3.7 mm lateral, and 8.0 mm ventral from Bregma) and affixed to the skull using dental acrylic. Dummy stylets were placed in the guide cannulae in order to keep them unobstructed.

Microinfusion experiments

Hormonally primed animals were treated as described in Table 1 or Supplemental Table 1. Animals used in the receptor experiments received daily infusions of one of the following: the dopamine D_1R/D_5R agonist SKF38393 (Sigma), the D2R agonist quinpirole (Sigma), the norepinephrine α1R agonist phenylephrine (Sigma) or the dopamine D_1R/D_5R antagonist SCH23390 (Sigma). Animals used in the PR experiment received one infusion of RU486 (Sigma) 30 min prior to progesterone injection. During the microinfusions, the dummy stylets were removed and replaced by 33 gauge microneedles that project 1.3 mm below the guide cannulae and were attached via polyethylene tubing to a 25 μl Hamilton syringe (700 series, Hamilton, Reno, NV) attached to a BASi Bee pump attached to a Bee Hive controller (Bioanalytical Systems, Inc., West Lafayette, IN). Infusions (0.5 μl) occurred over 5 min and the injectors remained in place for an additional 5 min to ensure diffusion away from the injector tips.

Dose response studies were conducted in order to determine the lowest effective dose of SCH23390 and SKF38393 (Supplemental Tables 1 and 2); doses were based on those that have been previously demonstrated to attenuate or facilitate lordosis behavior when infused into the third ventricle (Mani et al., 1994a). Based on the dose response results, 100 ng of both SCH23390 and SKF38393 was used in the microinfusion studies. Additionally, it should be noted that RU486 also inhibits glucocorticoid receptors at higher doses than for PR; its binding affinity is higher for PRs than for glucocorticoid receptors in the rodent brain (Etgen and Barfield, 1986; Vathy et al., 1989). Numerous studies have clearly demonstrated that the antiprogestin actions of RU486 in the ventromedial nucleus of the hypothalamus (VMN) abolish the expression of female sexual behaviors (Brown and Blaustein, 1984, 1986; Etgen and Barfield, 1986; Mani et al., 1994a,b, 1996; Vathy et al., 1987, 1989). The dose used in this study is ~100-fold less than that used to block PR action in the VMN to attenuated female sexual behavior (Mani et al., 1994a,b) so as to avoid actions at the glucocorticoid receptors.

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