Brain Research Bulletin 103 (2014) 49–53

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Acute estradiol treatment affects the expression of cocaine-induced conditioned place preference in ovariectomized female rats

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ARTICLE INFO

Article history:
Received 24 October 2013
Received in revised form 14 February 2014
Accepted 15 February 2014
Available online 22 February 2014

Keywords:
Estrogen
Cocaine
Reward
Ovariectomy
Dose–response
Locomotion

ABSTRACT

Women and female rodents are more responsive to the subjective effects of psychostimulant drugs of abuse compared to males. A growing body of literature supports a role for estradiol as a mechanism underlying these sex differences. However, little is known about the influence of acute elevations in levels of estradiol on drug conditioned behaviors. The aim of the present study was to evaluate the influence of an acute increase in systemic estradiol levels on the expression of cocaine conditioned place preference (CPP). Using a six day conditioning procedure, ovariectomized (OVX) female rats were conditioned with one of four doses of cocaine (2.5, 5, 10, or 15 mg/kg) to associate one of two large chambers of a CPP apparatus with cocaine or saline. Thirty minutes prior to the start of the CPP preference test, rats were pretreated with either 5 μg estradiol benzoate (EB) or peanut oil (PO). PO-treated rats expressed a significant preference for only the mid-range conditioning doses of cocaine (5 and 10 mg/kg). However, acute EB treatment resulted in a rightward shift in the cocaine dose–response curve; rats demonstrated a significant preference at only the moderate and high conditioning doses of cocaine (10 and 15 mg/kg). These findings demonstrate that acute elevations in estradiol may dampen the expression of conditioned responses to cocaine's secondary rewards at lower conditioning doses of the drug and facilitate CPP at higher doses while estradiol deficiency decreases the threshold dose of cocaine necessary to induce CPP.

1. Introduction

Cue reactivity and exposure to cues are important factors in continued drug use and relapse to former patterns of drug use (Childress et al., 1988; Epstein et al., 2009; O'Brien et al., 1990). Investigations into gender differences in reactivity to cocaine-associated cues have produced inconsistent results; some studies report greater cue reactivity in women (Elman et al., 2001; Robbins et al., 1999), one reports greater reactivity in men (Sterling et al., 2004), and another reports equivalent cue reactivity among men and women (Avants et al., 1995). Several methodological factors account for these discrepancies. A recent neuroimaging study highlights the importance of simultaneously collecting neural data along with self-report data during specific periods of the menstrual cycle and reports greater brain reactivity to conditioned cocaine cues in mid-follicular phase women than in men who were current cocaine abusers even though their self-reported craving responses did not differ (Volkow et al., 2011). Overall, these data strongly suggest that exposure to cocaine-associated environmental conditioned stimuli stimulates and/or increases the desire to use drugs in drug dependent individuals and this desire to use may be further enhanced in women during phases of the menstrual cycle during which high levels of circulating estrogen are predominant (O'Brien et al., 1977).

Evidence from drug self-administration studies in rodents has reliably demonstrated sex and hormonally modulated differences during all phases of the addiction process: acquisition, maintenance, and reinstatement (Anker and Carroll, 2011). Overall, these data show that female rats' operant behavior is more robust than males' during acquisition of cocaine self-administration, escalation of cocaine intake, and drug-primed and stress-induced reinstatement (Bard et al., 2000; Buffalari et al., 2012; Fuchs et al., 2005; Lynch et al., 2000; Lynch and Carroll, 1999; Roth and Carroll, 2004). Female rodents' response to cocaine also varies with their estrous cycle. Female rats in the estrus phase of the cycle display increased motivation to self-administer cocaine (Roberts et al., 1989) and increases in the intensity of cocaine-induced stereotypic and locomotor activities (Quinones-Jenab et al., 1999). Taken together, these

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http://dx.doi.org/10.1016/j.brainresbull.2014.02.002
0361-9230/

data suggest that increases in circulating levels of estradiol increase the motivation to self-administer cocaine and other behavioral subjective effects of the drug.

Studies manipulating circulating levels of estradiol in rodents have consistently demonstrated a key role for estrogen in enhancing the behavioral response to cocaine in females (Becker, 1999; Festa et al., 2004). For example, removal of endogenous ovarian hormones by ovariectomy (OVX) decreases acquisition rates of cocaine self-administration and cocaine-primed reinstatement of drug-seeking behavior. Moreover, replacement of estradiol, via chronic daily subcutaneous injections or via continuous release Silastic implant, restores cocaine self-administration rates to levels comparable with those of intact females' (Frye, 2007; Larson et al., 2005; Lynch et al., 2001). In summary, most studies have consistently shown that chronic sustained elevations in levels of estradiol increases cocaine self-administration.

The conditioned place preference (CPP) paradigm is used to determine the conditioned rewarding effects of drugs in rodents because the contextual cues used within the paradigm acquire secondary appetitive properties when paired with an addictive drug. Very few studies have used the CPP paradigm to investigate sex differences in the conditioned rewarding effects of cocaine and fewer still have examined the role of ovarian hormones. To date, only three investigations have examined the activational effects of estradiol on conditioned cocaine reward (Russo et al., 2003; Segarra et al., 2010; Twining et al., 2013). Through the use of slightly different methodologies, each of these studies examined the role of prolonged elevations in estradiol levels on cocaine-induced CPP and has provided some fundamental insight into our understanding of the influence of estradiol on learning drug–context associations. However, until now, the issue of the effects of acute elevations of estradiol on cocaine-induced CPP has remained unsettled. Therefore, the purpose of the present study was to examine the influence of a single acute increase in systemic estradiol levels on the expression of cocaine CPP.

2. Methods

2.1. Subjects

Eighty-three experimentally naïve, adult (60 day old), female, Long Evans rats (University of Texas at Arlington vivarium) were triple housed with same-sex cage mates in a temperature and humidity-controlled environment under a 12 h reversed light/dark cycle with lights on at 7 p.m. and off at 7 a.m. All animals had free access to food and water throughout the study and were maintained and cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All procedures were approved by the University of Texas at Arlington's Institutional Animal Care and Use Committee (IACUC) in accordance with AAALAC standards.

2.2. Ovariectomy

Rats were anesthetized with a 2–3% isoflurane-oxygen vapor mixture and ovariectomized (OVX) using a dorsal approach. Briefly, both flanks were shaved and swabbed with Betadine. The skin was opened with a 5 mm incision along the midline just below the ribs, and a 10 mm incision was made through the muscle ~1.5–2 cm lateral to the midline. The ovary was pulled through the incision. The tissue between the oviduct and uterus were clamped with a hemostat and a ligature was placed just below the hemostat. The ovary was removed with scissors and the hemostats released. This procedure was repeated on the contralateral side. Lastly, the muscle layer was sutured closed and the skin incision closed with 9 mm wound clips.

2.3. Vaginal lavage testing

Following a 4–5 day surgical recovery period, all rats underwent daily vaginal lavage testing for 8–10 consecutive days to confirm cessation of cycling. Vaginal secretion was collected with a plastic pipette filled with 10 μL of 0.9% $NaCl^{-}$ by inserting the tip into the rat vagina, but not deeply. Unstained material was observed under a light microscope. All ovariectomies performed were confirmed as complete and thus, no animals were eliminated on the basis of an incomplete procedure.

2.4. Estradiol treatment

Animals were assigned to one of two groups of hormone treatment: 0.1 ml peanut oil – vehicle (OVX); or 5 μg 17β-Estradiol 3 benzoate (EB; Sigma–Aldrich, St Louis, MO) dissolved in 0.1 ml peanut oil. Hormone treatment was delivered via subcutaneous (s.c.) injection only once; 30 min prior the test for conditioned place preference (see Fig. 1).

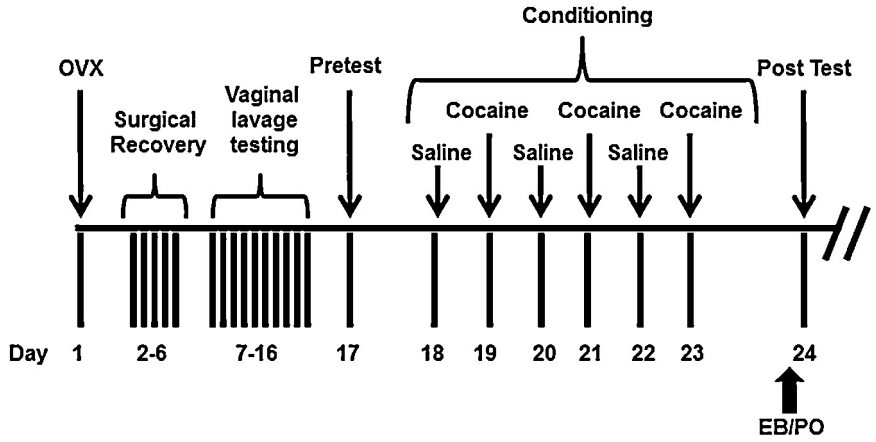

Fig. 1. Timeline of experimental procedures. All animals undergo ovariectomy (Day1; OVX) followed by a five day surgical recovery period (Days 2–6) after which they are subjected to ten days of vaginal lavage testing to confirm completion of OVX. The conditioned place preference protocol commences with a PreTest (Day 17) during which rats freely explore the entire apparatus in a drug-free state. Conditioning for Saline/Cocaine occurred over days 18–23; on alternating days OVX rats received injections of 0.9% saline or one of four doses of cocaine (2.5, 5, 10, or 15 mg/kg) and were confined to one chamber of the apparatus for 30 min. Thirty minutes prior to the test for conditioned preference (PostTest; Day 24), animals received an injection of EB (5 μg) or peanut oil (PO).