Hormones and Behavior 64 (2013) 573–578

Contents lists available at ScienceDirect

Hormones and Behavior

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

Impact of pubertal and adult estradiol treatments on cocaine self-administration

Adam N. Perry [a,1], Christel Westenbroek [a,1], Jill B. Becker [a,b,c,d,*]

[a] Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI 48109, USA
[b] Department of Psychology, University of Michigan, Ann Arbor, MI 48109, USA
[c] Neuroscience Program, University of Michigan, Ann Arbor, MI 48109, USA
[d] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 27 June 2013
Revised 16 August 2013
Accepted 20 August 2013
Available online 5 September 2013

Keywords:
Estradiol
Puberty
Organization
Cocaine self-administration
Sex differences
Acquisition
Motivation

ABSTRACT

Estradiol is thought to play a critical role in the increased vulnerability to psychostimulant abuse in women. Sex differences in the ability of estradiol to influence cocaine self-administration in adult rats have been hypothesized to depend upon pubertal estradiol exposure. The current study investigated whether the presence of gonadal hormones during puberty affected cocaine self-administration behavior and its sensitivity to adult estradiol treatment in male and female Sprague–Dawley rats. Subjects were gonadectomized or SHAM-operated at postnatal day (PD) 22, and received either OIL or estradiol benzoate (EB) during the approximate time of puberty (PD27 to PD37). Adult rats were subsequently treated with either EB or OIL 30 min before cocaine self-administration (0.3 mg/kg/inf) in order to examine the effects of pubertal manipulations on the estradiol sensitivity of acquisition on a fixed ratio (FR) 1 schedule, total intake on a FR5 schedule and motivation on a progressive ratio schedule. Adult EB treatment only affected cocaine self-administration in females, which is consistent with previous research. Adult EB treatment enhanced acquisition in all females irrespective of puberty manipulations. All females, except those treated with EB during puberty, displayed increased cocaine intake following adult EB treatment. Adult EB treatment only enhanced motivation in females that were intact during puberty, whereas those treated with EB during puberty showed reduced motivation. Therefore, the sensitivities of different self-administration behaviors to adult estradiol treatment are organized independently in females, with pubertal estradiol exerting a greater influence over motivational processes, and negligible effects on learning/acquisition.

Introduction

Men and women are differentially vulnerable to drugs of abuse. Even though more men than women use cocaine and psychotherapeutics, more women show dependence for these substances (Back et al., 2010; Cotto et al., 2010; Elman et al., 2001). The subjective effects of psychostimulants, like euphoria, desire, increased energy and intellectual efficiency, vary across the menstrual cycle. Thus, women report effects that are comparable to those of men when they are in the follicular phase and reduced during the luteal phase (Justice and de Wit, 1999, 2000a, 2000b). During the follicular phase, estradiol administration enhances, whereas progesterone attenuates, the subjective effects of psychostimulants (Justice and de Wit, 2000b). In men, the effects of estradiol on psychostimulant responses have not been examined and the effects of progesterone are ambiguous (Evans and Foltin, 2005; Evans, 2007; Fox et al., 2013; Sofuoglu et al., 2004). Furthermore, it is unclear whether the effects of ovarian hormones on subjective effects of drugs translate into different patterns of psychostimulant use between men and women (Reed et al., 2011; Sofuoglu et al., 2004).

In contrast, estradiol has been shown to have significant effects on drug self-administration in preclinical models, with the majority occurring selectively in females. Estradiol treatment facilitates acquisition of cocaine self-administration, increases cocaine intake and enhances motivation for cocaine in ovariectomized female rats, but has no apparent effects in males (Hu and Becker, 2008; Jackson et al., 2006; Lynch and Carroll, 2001). Male rats are quite capable of responding to estradiol, as it is one of the primary signals required for both the organization and activation of their reproductive behavior (McCarthy, 2008; Ogawa et al., 2000). Current views on sexual differentiation of the brain are largely based on the differentiation of reproductive behavior in males and females, which is driven in large part by perinatal testosterone exposure in males (but not females) and further refinement by sex-specific gonadal hormone profiles during puberty (McCarthy, 2008; Mccarthy and Arnold, 2011; Sisk and Zehr, 2005). During the perinatal period, estradiol primarily functions as a masculinizing hormone, whereas it becomes crucial for female differentiation during puberty (McCarthy, 2008; Stewart and Cygan, 1980).

* Corresponding author at: University of Michigan, 1050 MBNI, 205 Zina Pitcher Place, Ann Arbor, MI 48109, USA. Fax: +1 313 763 7480.
E-mail address: jbbecker@umich.edu (J.B. Becker).
[1] These authors contributed equally to this work.

0018-506X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yhbeh.2013.08.007

We have previously proposed that the expression of sex differences in motivated behaviors in adulthood are at least partly mediated by ovarian hormones secreted during puberty, which are essential for feminizing the mesocorticolimbic dopamine system (Becker, 2009). The current experiment was conducted to test whether pubertal estradiol exposure is necessary and/or sufficient for the subsequent feminization of cocaine self-administration behavior in adult rats. We predicted that the self-administration behavior of females would only be sensitive to adult estradiol treatment if they had also been exposed to estradiol during puberty. Conversely, we predicted that pubertal estradiol would not be sufficient to feminize behavior in males, possibly due to the prior masculinizing effects of perinatal testosterone/estradiol.

Methods

Animals

Sprague–Dawley rats purchased from Charles Rivers (Portage, MI) were gonadectomized (OVX/CAST) at postnatal day (PD) 22, or remained intact through puberty (pINTACT) (N = 51 per sex). Animals were housed in same-sex groups in standard laboratory cages (2–3 per cage) and maintained on a 14:10 (light:dark) reversed light cycle (lights off at 08:00) and provided free access to rat chow (Teklad Global 14% protein rodent maintenance diet) and carbon-filtered water in a temperature- and humidity-controlled vivarium. All experimental procedures were conducted between 09:00 and 16:00, were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were preapproved by the University of Michigan Committee on the Use and Care of Animals.

OVX/CAST animals received subcutaneous (s.c.) injections of either estradiol benzoate (EB) or the peanut oil vehicle (OIL) from PD27–37 (approximate time of puberty in females). Treatments consisted of OIL or a ramping EB regime (5, 10 and 15 mg/kg, s.c.) delivered over 3 days for 3 cycles with one day off between cycles. These groups were referred to as puberty EB (pEB) or puberty OIL (pOIL). The pINTACT animals were treated with OIL during PD27–37 and were subsequently OVX/CAST at PD67. Animals were weighed daily and the age at vaginal opening (for females) or preputial separation (for males) was determined. Estrogen reduces weight gain in both males and females and accelerates vaginal opening, so these measures were used to validate the effectiveness of pubertal gonadectomies and EB treatments.

Catheter surgeries

At PD74, all animals were fitted with indwelling jugular catheters connected to a back port. Catheters were constructed by gluing silastic tubing (Silastic tubing, 0.51 mm I.D. × 0.94 mm O.D., Dow Corning, Midland, MI) to an external guide cannula (22 Gauge guide cannula; Plastics One, Roanoke, VA) using cranioplastic cement. A polypropylene mesh was secured to the bottom of the cannula using this same cement. Rats received an injection of Buprenorphine (0.02 mg/kg, s.c.) 30 min before they were anesthetized with isoflurane (5% isoflurane in oxygen). The free end of the silastic tubing of the catheter apparatus was inserted into the right jugular vein of the animal and secured using 4.0 silk sutures around the tubing and the venous tissue. The catheter port exited dorsally from the animal. After successful implantation, the animal's catheter was flushed with 0.2 ml each of heparin (30 U/ml in 0.9% sterile saline) and gentamicin (3 mg/kg) to prevent clotting and infection, respectively. A dummy stylet was then inserted into the port opening. Two days after surgery, catheters were flushed with 0.2 ml of heparin (30 U/ml in 0.9% sterile saline) and gentamicin (3 mg/kg), and each day after that with gentamicin and heparin (3 mg/kg and 20 U/ml, resp.). Catheter patency was checked weekly using a solution of Pentothal® (thiopental sodium, 15 mg/ml, 0.15–0.25 ml in sterile water). Animals were allowed to recover for 5–7 days before the start of cocaine self-administration.

Table 1
Group names and corresponding timing of the hormone treatments (PD: postnatal day, EB: estradiol benzoate, CAST: castration, OVX: ovariectomy, SA: self-administration).

		Puberty	Adult				
	PD22	PD 27–37	PD67	SA		Group name	
Male (N = 51)	INTACT	OIL (N = 13)	CAST	OIL	Male	pINTACT-aOIL	(N = 7)
				EB	Male	pINTACT-aEB	(N = 6)
	CAST	OIL (N = 20)		OIL	Male	pOIL-aOIL	(N = 9)
				EB	Male	pOIL-aEB	(N = 11)
		EB (N = 18)		OIL	Male	pEB-aOIL	(N = 9)
				EB	Male	pEB-aEB	(N = 9)
Female (N = 51)	INTACT	OIL (N = 13)	OVX	OIL	Female	pINTACT-aOIL	(N = 7)
				EB	Female	pINTACT-aEB	(N = 6)
	OVX	OIL (N = 20)		OIL	Female	pOIL-aOIL	(N = 10)
				EB	Female	pOIL-aEB	(N = 10)
		EB (N = 18)		OIL	Female	pOIL-aOIL	(N = 8)
				EB	Female	pOIL-aEB	(N = 10)

Cocaine self-administration

Half of the animals in each puberty group (pOIL, pEB and pINTACT) were treated with OIL or EB (5 mg/kg, s.c.) 30 min before the start of each daily self-administration session, resulting in 12 final treatment groups: 2 sexes (male or female) × 3 puberty treatments (pOIL, pEB or pINTACT) × 2 adult treatments (aOIL or aEB). Group treatments and assignments are described in Table 1. Self-administration and adult hormone treatments were administered 5 days a week, followed by 2 days off as in previous experiments from this laboratory where EB enhanced cocaine-taking behavior (Hu et al., 2004; Jackson et al., 2006).

Self-administration was performed in standard operant chambers (Med Associates, Inc., Georgia, VT) where the animals could nose poke into the active hole for cocaine or in an inactive hole, which had no consequences. Rats were connected to the infusion syringe via a swivel mounted to a counter-balanced arm, which allowed animals to move freely in the testing environment. Animals were weighed prior to each self-administration session.

Subjects self-administered cocaine (0.3 mg/kg/inf) on a fixed ratio (FR) 1 schedule of reinforcement for the first 13 days. On the FR1 schedule, animals were required to perform one nose poke in the active hole in order to receive an infusion. Nose pokes in the inactive hole had no consequences. The FR1 tests were 2 h long, but terminated early once the animal received 100 infusions. Acquisition of cocaine self-administration was defined as three consecutive days with two times the number of active to inactive nose pokes. Animals were then tested on a progressive ratio (PR) schedule of reinforcement to determine breaking points (BPs). The PR requirement escalated through an exponential series: 1, 3, 6, 9, 12, 17, 24, 32, 42, 56, 73, 95, 124, 161, 208, 268… adapted from Richardson and Roberts (1996). A higher BP is an indication that the animal is more motivated for cocaine, as they are willing to work harder to obtain each subsequent infusion. The number of infusions, nose pokes in the active and inactive holes and the last completed ratio (BP) were recorded. The PR session terminated after 6 h, or earlier if 1 h elapsed without receiving an infusion.

Following the PR test, animals were transitioned to a FR5 schedule of reinforcement with daily tests consisting of 3 × 40 minute active sessions (i.e., house light illuminated indicating drug availability) separated by 2 × 15 minute inactive sessions (i.e., house light turned off signaling drug unavailability). There was also a 40-second delay following each infusion, during which time nose pokes in the active hole were recorded but did not result in any consequences. To investigate if chronic cocaine self-administration affected the motivation to take cocaine, animals were retested on the PR schedule after 18 days on the FR5 schedule.