Psychoneuroendocrinology (2015) 54, 1—13

Available online at www.sciencedirect.com

ScienceDirect

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

Understanding the cognitive impact of the contraceptive estrogen Ethinyl Estradiol: Tonic and cyclic administration impairs memory, and performance correlates with basal forebrain cholinergic system integrity

Sarah E. Mennenga[a,b], Julia E. Gerson[a,b], Stephanie V. Koebele[a,b], Melissa L. Kingston[a,b], Candy W.S. Tsang[a,b], Elizabeth B. Engler-Chiurazzi[a,b], Leslie C. Baxter[b,c], Heather A. Bimonte-Nelson[a,b,*]

[a] Department of Psychology, Arizona State University, Tempe, AZ 85287, USA
[b] Arizona Alzheimer's Consortium, Phoenix, AZ 85006, USA
[c] Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

Received 3 November 2014; received in revised form 30 December 2014; accepted 2 January 2015

KEYWORDS
Memory;
Ethinyl Estradiol;
Contraceptive;
Hormone

Summary Ethinyl Estradiol (EE), a synthetic, orally bio-available estrogen, is the most commonly prescribed form of estrogen in oral contraceptives, and is found in at least 30 different contraceptive formulations currently prescribed to women as well as hormone therapies prescribed to menopausal women. Thus, EE is prescribed clinically to women at ages ranging from puberty to reproductive senescence. Here, in two separate studies, the cognitive effects of cyclic or tonic EE administration following ovariectomy (Ovx) were evaluated in young female rats. Study I assessed the cognitive effects of low and high doses of EE, delivered tonically via a subcutaneous osmotic pump. Study II evaluated the cognitive effects of low, medium, and high doses of EE administered via a daily subcutaneous injection, modeling the daily rise and fall of serum EE levels with oral regimens. Study II also investigated the impact of low, medium and high doses of EE on the basal forebrain cholinergic system. The low and medium doses utilized here correspond to the range of doses currently used in clinical formulations, and the high dose corresponds to doses prescribed to a generation of women between 1960 and 1970, when oral contraceptives first became available. We evaluate cognition using a battery of maze tasks tapping several domains of spatial learning and memory as well as basal forebrain

* Corresponding author at: Arizona State University, Department of Psychology, P.O. Box 871104, Tempe, AZ 85287, USA. Tel.: +1 480 727 0766; fax: +1 480 965 8544.
E-mail address: Bimonte.Nelson@asu.edu (H.A. Bimonte-Nelson).

http://dx.doi.org/10.1016/j.psyneuen.2015.01.002

cholinergic integrity using immunohistochemistry and unbiased stereology to estimate the number of choline acetyltransferase (ChAT)-producing cells in the medial septum and vertical/diagonal bands. At the highest dose, EE treatment impaired multiple domains of spatial memory relative to vehicle treatment, regardless of administration method. When given cyclically at the low and medium doses, EE did not impact working memory, but transiently impaired reference memory during the learning phase of testing. Of the doses and regimens tested here, only EE at the highest dose impaired several domains of memory; tonic delivery of low EE, a dose that corresponds to the most popular doses used in the clinic today, did not impact cognition on any measure. Both medium and high injection doses of EE reduced the number of ChAt-immunoreactive cells in the basal forebrain, and cell population estimates in the vertical/diagonal bands negatively correlated with working memory errors.

1. Introduction

Ethinyl Estradiol (EE), a synthetic form of 17β-estradiol (E2), is the most common estrogen in hormonal contraceptives (Shively, 1998), and is the only estrogen used in the contraceptive pill. National surveys estimate that 10.6 million women between 2006 and 2010 (Jones et al., 2012), and 17.3% of all women between 2006 and 2008 (Mosher and Jones, 2010), used oral contraceptives. Over 30 contraceptive formulations contain EE (Curtis et al., 2005), including both oral regimens and non-oral, tonic delivery regimens, such as the transdermal patch and vaginal ring. EE is also found in hormone therapies (HT) for menopausal women, such as Estinyl™ and Femhrt™ (Curtis et al., 2005). Understanding the cognitive impact of estrogens is critical, as exogenous exposure to estrogens occurs throughout the adult lifespan through contraceptives and HT. Of note, EE is a synthetic analog to E2; however, these estrogens have different pharmacokinetic profiles (Coelingh Bennink, 2004). EE is more biologically active than E2 (Dickson and Eisenfeld, 1981) and cannot be converted to estrone or other weaker estrogens (Fotherby, 1996), whereas E2 can (Prokai-Tatrai and Prokai, 2005). These estrogens also have different binding profiles, which vary across species (Paradiso et al., 2001).

Although EE is among the most commonly prescribed estrogens for contraception, and is prescribed to women from puberty to post-menopause, most preclinical research on the cognitive impact of estrogens has focused on 17β-estradiol and other endogenous estrogens, and does not include EE (for reviews see: Bimonte-Nelson et al., 2010; Acosta et al., 2013). Methodically evaluating EE in a rodent model allows the opportunity to systematically control for many variables that could impact cognitive scores, including mode of administration, dosing, endogenous hormone variations, age, and diet.

There have been a few studies investigating the cognitive effects of EE as a contraceptive or HT, with effects that vary across memory domains. In human contraceptive users, no impact of EE-containing contraceptives was found on several tests measuring memory and concentration (Silber et al., 1987). Another study found enhanced verbal memory during the active compared to the inactive phase of oral contraceptives, although benefits were not seen on visuospatial measures (Mordecai et al., 2008). Importantly, although each of the contraceptive formulations used in these studies contained EE, other aspects of the formulations differed, including dose and the progestin component. Thus, it is difficult to decipher whether or to what extent EE was responsible for these effects. In studies investigating EE as a HT, cognitive effects depend on the domain as well. In aged, ovariectomized (Ovx) rhesus monkeys, EE improved spatial working memory (Lacreuse et al., 2002), but impaired face recognition (Lacreuse and Herndon, 2003), and had no impact on executive function (Lacreuse et al., 2004). An fMRI study of menopausal women found EE-containing HTs increased frontal cortex activation during a working memory task (Smith et al., 2006).

In women taking hormonal contraceptives, serum level patterns differ between once daily and tonic regimens. Oral contraceptives produce a cycle of serum levels throughout the day, with concentrations highest 1–2 h after ingestion of the pill (Devineni et al., 2007). Tonic hormone delivery via transdermal patches produces steady serum levels, unlike oral administration (Devineni et al., 2007). There is evidence for cognitive benefits of tonic estrogen delivery; in randomized, placebo-controlled studies on women with mild-moderate probable Alzheimer's disease, transdermal E2 positively affects multiple measures of cognition (Asthana et al., 1999; Wharton et al., 2011). A study evaluating transdermal versus oral contraceptives found no difference in quality of life, side effects or regularity of the menses; however, more transdermal patch users reported a favorable impact on ''daily activities'' (Sucato et al., 2011). Additionally, metabolism by the liver following oral estrogen administration is linked to increases in markers of thromboembolic side effects, whereas transdermal administration is not (Scarabin et al., 1997; Decensi et al., 2002; Post et al., 2003). In the current series of experiments, we assess both modes of administration.

Study I evaluated the cognitive effects of tonic EE, administered via subcutaneous pumps that deliver at a steady rate, resembling the tonic pattern of EE delivery from a transdermal patch or vaginal insert (Theeuwes and Yum, 1976; Curtis et al., 2005). We evaluated a low dose of EE, corresponding to the most popular doses currently prescribed to women, along with a high dose that is outside of the range of current formulations, but is representative of the high doses of EE that were previously present in contraceptives (Dhont, 2010). The high EE dose is also roughly one-tenth of a dose of E2 previously shown to enhance performance on spatial tasks (Talboom et al., 2008), to account