Psychoneuroendocrinology 90 (2018) 134–140

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

The association between estradiol levels, hormonal contraceptive use, and responsiveness to one-session-treatment for spider phobia in women

Bronwyn M. Graham[a,*], Sophie H. Li[a], Melissa J. Black[a], Lars-Göran Öst[b,c,d]

[a] School of Psychology, University of New South Wales, Sydney, Australia
[b] Department of Psychology, Stockholm University, Sweden
[c] Department of Clinical Neuroscience, Karolinska Institutet, Sweden
[d] Haukeland University Hospital, Bergen, Norway

ARTICLE INFO

Keywords:
Spider phobia
One-session-treatment
Exposure therapy
Estradiol
Hormonal contraception
Fear extinction

ABSTRACT

Preclinical studies have demonstrated that conditioned fear extinction is impaired in females with low endogenous levels of the sex hormone estradiol, due to menstrual fluctuations or hormonal contraceptive use. As fear extinction is a laboratory model of exposure therapy for anxiety and trauma disorders, here we assessed the hypothesis that treatment outcomes may be diminished when exposure therapy occurs during periods of low estradiol. 90 women with spider phobia (60 cycling and 30 using hormonal contraceptives) underwent a one-session exposure treatment for spider phobia, following which, serum estradiol levels were assessed. A median split in estradiol level was used to divide cycling participants into two groups; lower and higher estradiol. Behavioral avoidance and self-reported fear of spiders were measured pre-treatment, post-treatment, and at a 12 week follow-up assessment. Women using hormonal contraceptives exhibited a significantly slower rate of improvement across treatment, greater behavioral avoidance at post-treatment and follow-up, and fewer self-initiated post-treatment exposure tasks, relative to both groups of cycling women, who did not differ. No group differences in self-reported fear were evident. Correlational analyses revealed that across the whole sample, lower estradiol levels were associated with slower rates of improvement across treatment, and greater self-reported fear and behavioral avoidance at post-treatment, but not follow-up. These results provide the first evidence of an association between endogenous estradiol, hormonal contraceptive use, and exposure therapy outcomes in spider phobic women. Hormonal profile may partly account for variability in responsiveness to psychological treatments for anxiety and trauma disorders in women.

1. Introduction

Despite being the recommended psychological treatment for anxiety and trauma disorders (Stein and Craske, 2017), a proportion of individuals who receive exposure therapy remain symptomatic or experience symptom relapse (Holmes et al., 2014). Understanding the factors associated with variability in treatment responsiveness may point to means of improving treatment outcomes for individuals with anxiety and trauma disorders who fail to exhibit complete symptom remission. Exposure therapy can be modelled using fear extinction, a laboratory procedure in which a fear-eliciting conditioned stimulus (e.g., an image that was previously paired with shock) is presented without aversive outcome until fear responses reduce (Graham and Milad, 2011). Preclinical studies have revealed a role for sex hormones, particularly estradiol, in fear extinction. For example, in cycling female rats and non-anxious women, extinction is impaired during menstrual phases associated with low estradiol and progesterone, and enhanced during phases of high hormonal levels (Chang et al., 2009; Graham and Daher, 2016; Graham and Milad, 2013; Gruene et al., 2015; Li and Graham, 2016; Milad et al., 2009, 2010; Milligan-Saville and Graham, 2016; Pineles et al., 2016; Rey et al., 2014; Wegerer et al., 2014; White and Graham, 2016; Zeidan et al., 2011). Additionally, hormonal contraceptives suppress estradiol and progesterone synthesis and are associated with impaired extinction (Graham and Milad, 2013; White and Graham, 2016), and reduced discrimination between threatening and safe cues (Lonsdorf et al., 2015). Moreover, estradiol administration enhances extinction (Graham and Milad, 2013; Milad et al., 2009), whereas estrogen receptor antagonists impair extinction (Milad et al., 2009).

The relationship between estradiol and conditioned fear extinction has been replicated in laboratory studies of women with specific phobia (Li and Graham, 2016) and PTSD (Glover et al., 2012; although Pineles

* Corresponding author at: School of Psychology, The University of New South Wales Australia, Sydney, New South Wales, 2052, Australia.
E-mail address: bgraham@psy.unsw.edu.au (B.M. Graham).

https://doi.org/10.1016/j.psyneuen.2018.02.019
Received 5 December 2017; Received in revised form 14 January 2018; Accepted 19 February 2018

et al., 2016, reported that a combination of high progesterone and low estradiol predicted impaired extinction in women with PTSD). It has recently been hypothesized that women's estradiol levels during exposure therapy may be associated with treatment outcomes (Glover et al., 2015; Li and Graham, 2017). This hypothesis has not been tested – although fear extinction is an established model of exposure therapy, it is not therapeutic, and focuses on reducing artificially induced physiological fear responses rather than disorder-relevant symptoms. Moreover, there are methodological challenges in assessing this hypothesis, due to difficulties in reconciling women's cyclic hormonal fluctuations with the need for multiple exposure sessions to achieve symptom reduction. However, in the case of specific phobia, a single prolonged exposure therapy session, termed One-Session-Treatment (OST; founded by Lars-Göran Öst), produces large symptom reductions that are maintained over long follow-up periods (Öst, 1989; Davis et al., 2012). A meta-analysis of 30 randomized controlled trials demonstrated large effect sizes of OST for specific phobias when compared to either placebo or other active treatments (e.g., five sessions of exposure) (Davis et al., 2012). Capitalizing on the fact that OST occurs within a discrete hormonal phase, in the present study we assessed whether women's estradiol levels on the day of treatment, and hormonal contraceptive use, are associated with the outcomes of OST for spider phobia. We predicted that cycling women with higher estradiol would exhibit greater symptom improvement relative to those with lower estradiol and women using hormonal contraceptives. We focused on estradiol because the association between progesterone and extinction is inconsistent, likely due to progesterone having a biphasic role in extinction (Graham and Daher, 2016). Nonetheless, we also measured progesterone for exploratory purposes.

2. Methods and materials

2.1. Participants

Ninety women (mean age 22.3 years) were recruited via a public online research participation system. Eligible participants were non-pregnant, non-breastfeeding females, aged 18–35, with regular menstrual cycles (21–32 days) or using hormonal contraceptives, with a principle diagnosis of spider phobia, no psychosis, substance abuse, or bipolar disorder (comorbid anxiety and depression were permitted), no neurological or endocrinological conditions, and not using medication other than a selective serotonin reuptake inhibitor (SSRI). Participants identified as Caucasian/Australian (30), Asian (41), European (2), Arab (2), or mixed race (15).

Participants were using hormonal contraceptives (HrmC, n = 30; see Supplementary material for information on hormonal contraceptive formulations), or naturally cycling (NC; n = 60), and the latter were divided into two groups – those with higher (NC High Estradiol) and lower (NC Low Estradiol) estradiol, based on a median split in serum estradiol levels measured on the day of treatment. Based on self-reported number of days since the last onset of menstruation; 38.89% of NC Low Estradiol reported being in the early follicular phase of their cycle (days 1–7), 27.78% reported being in the late follicular phase (days 8–14), and 33.33% reported being in the luteal phase (day 15+). For NC High Estradiol, 12.5% reported being in the early follicular phase, 31.25% reported being in the late follicular phase, and 62.5% reported being in the luteal phase. See Supplementary material for analyses of outcomes based on self-reported menstrual phase.

Five participants (1 NC High Estradiol, 4 HrmC) were taking an SSRI. Fifty-eight participants had comorbid phobias (20 NC Low Estradiol, 23 NC High Estradiol, 15 HrmC). All participants completed the post-treatment assessment. Thirteen participants (2 NC High Estradiol, 6 NC Low Estradiol, and 5 HrmC) could not be contacted to return for the 12-week follow-up assessment (see Supplementary material for analysis of completers versus participants lost to follow up). Procedures were approved by the UNSW Human Research Ethics Committee, and were carried out in accordance with the standards of the Declaration of Helsinki. All participants provided written informed consent after the nature of the study was explained. As the study involved a therapeutic intervention, it was registered on ClinicalTrials.gov (NCT02622087; see supplement for the CONSORT diagram). Participants were reimbursed $70.

2.2. Primary outcome measure: behavioral approach test (BAT)

The BAT assesses behavioral avoidance of spiders, and required the participant to stand in front of a closed 3 × 3 m room containing a live spider (an adult Holconia), measuring 16 cm in diameter, housed in a transparent plastic container on a table at the far end of the room. The participant was asked to open the door and approach the spider, remove the lid, put a hand inside the container, and guide the spider over their hand. When the participant had completed all steps, or refused to progress to the next step, they were scored on a nine-point scale corresponding with the steps taken during the test (see Supplementary material for details).

2.3. Secondary outcome measure: spider phobia questionnaire (SPQ)

The SPQ (Klorman et al., 1974) consists of 31 true/false statements regarding participants' feelings, beliefs, and behavior around spiders, and assesses the verbal-cognitive component of spider phobia. Scores range between 0 (low fear) and 31 (high fear). Depressive symptoms were assessed using the Beck Depression Inventory-II (Beck et al., 1996) (BDI-II; see Supplementary material for details and analysis).

2.4. Serological assessment

Serum hormone concentrations were analyzed by Healthscope Pathology Services. Estradiol levels were analyzed using an ADVIA Centaur Enhanced Estradiol assay (Siemens), which is a competitive assay that measures serum estradiol concentrations up to 3000 pg/mL (11,010 pmol/L) with a limit of detection of 11.8 pg/mL (43.6 pmol/L) (intra-assay% CV 4.2; inter-assay% CV, 1.9). Progesterone levels were analyzed using an ADVIA Centaur Progesterone assay (Siemens), which is a competitive immunoassay that measures serum progesterone concentrations up to 60 ng/mL (190.8 nmol/L) with a minimum detectable concentration of 0.21 ng/mL (0.67 nmol/L) (intra-assay% CV 5.3; inter-assay% CV 2.7).

2.5. Procedure

The study took place at the UNSW Psychology Clinic over three sessions, which were conducted according to the OST manual for specific phobia (Davis et al., 2012). Clinicians (BMG, SL, and MB) were trained by L-GÖ.

Inclusion criteria was assessed by phone interview, and eligible participants were scheduled for a four hour assessment and treatment session commencing between 8:30–9:30 am. The screening and treating clinicians were different to ensure that the treating clinician remained blind to the participant's hormonal status. The assessment took one hour, during which the participant completed the SPQ, BDI-II, and pre-treatment BAT, as well as a structured clinical interview for specific phobia based on the ADIS-IV (Brown et al., 1994). The treatment immediately followed, which involved a series of graded exposure steps requiring the participant to interact with spiders. Two native Australian spider species were used (Argiope and Holconia; see Supplementary material for details). Participants who completed the full exposure hierarchy were exposed to a juvenile and adult of each species. Exposure commenced with a juvenile Argiope and individual steps involved holding the spider enclosure, catching the spider using a postcard and plastic cup, holding the caught spider close to the body and describing its appearance, touching the spider, and allowing the spider