Neurobiology of Learning and Memory 134 (2016) 339–348

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Estradiol levels in women predict skin conductance response but not valence and expectancy ratings in conditioned fear extinction

Emily C. White, Bronwyn M. Graham *

School of Psychology, University of New South Wales, Sydney, Australia

ARTICLE INFO

Article history:
Received 16 November 2015
Revised 31 July 2016
Accepted 17 August 2016
Available online 18 August 2016

Keywords:
Estrogen
Sex hormones
Menstrual cycle
Fear extinction
Anxiety
US expectancy

ABSTRACT

Anxiety disorders are more prevalent in women than men. One contributing factor may be the sex hormone estradiol, which is known to impact the long term recall of conditioned fear extinction, a laboratory procedure that forms the basis of exposure therapy for anxiety disorders. To date, the literature examining estradiol and fear extinction in humans has focused primarily on physiological measures of fear, such as skin conductance response (SCR) and fear potentiated startle. This is surprising, given that models of anxiety identify at least three important components: physiological symptoms, cognitive beliefs, and avoidance behavior. To help address this gap, we exposed women with naturally high ($n = 20$) or low estradiol ($n = 19$), women using hormonal contraceptives ($n = 16$), and a male control group ($n = 18$) to a fear extinction task, and measured SCR, US expectancy and CS valence ratings. During extinction recall, low estradiol was associated with greater recovery of SCR, but was not related to US expectancy or CS evaluation. Importantly, women using hormonal contraceptives showed a dissociation between SCR and cognitive beliefs: they exhibited a greater recovery of SCR during extinction recall, yet reported similar US expectancy and CS valence ratings to the other female groups. This divergence underscores the importance of assessing multiple measures of fear when examining the role of estradiol in human fear extinction, especially when considering the potential of estradiol as an enhancement for psychological treatments for anxiety disorders.

1. Introduction

Women are twice as likely as men to develop an anxiety disorder (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). They also experience greater symptom severity and chronicity, and poorer treatment outcomes, relative to men (Pigott, 2003). While we do not fully understand the mechanisms underlying this gender disparity, one contributing factor may be the influence of sex hormones. We know that sex differences in anxiety prevalence do not emerge until after puberty, suggesting that activation of gonadal hormones may be playing a role (Paus, Keshavan, & Giedd, 2008). Furthermore, fluctuations in the sex hormone estradiol have been shown to impact the long term recall of conditioned fear extinction (Chang et al., 2009; Graham & Milad, 2013; Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad et al., 2010; Zeidan et al., 2011). Fear conditioning and extinction are laboratory procedures that are widely used to understand the mechanisms underlying the acquisition and inhibition of fear. During differential conditioning, two neutral conditioned stimuli (CSs) (e.g. two images on a computer screen) are presented; one (the CS+) is paired with an aversive unconditioned stimulus (US) (e.g. a mild shock), while the other (the CS−) is never paired with the US. As the individual learns the relationship between the CS+ and the US, presentation of the CS+ evokes a conditioned fear response (e.g. increase in skin conductance). The conditioned fear is then extinguished by repeatedly presenting both CSs without the US, until fear responses to the CS+ subside. It is thought that this extinction process generates a new inhibitory memory which competes with the original fear conditioning memory (Bouton, 2004). The strength of the extinction memory can be tested by presenting the extinguished CS+ and the CS− after a delay: good extinction recall is evident by continual low levels of fear, while poor extinction recall is evident by an increase in fear responses to the CS+. Responses to the CS− typically remain low throughout extinction training and recall.

Evidence from naturally-cycling humans and rodents suggests that females in the low estradiol phase of their cycle show significantly poorer recall of fear extinction than females in the high estradiol phase (Chang et al., 2009; Graham & Milad, 2013; Gruene, Roberts, Thomas, Ronzio, & Shansky, 2015; Milad et al.,

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

http://dx.doi.org/10.1016/j.nlm.2016.08.011
1074-7427/

2009, 2010; Rey, Lipps, & Shansky, 2014; Zeidan et al., 2011). Similarly, women with PTSD who have low estradiol levels exhibit heighted startle responses during extinction training (Glover et al., 2012). Finally, pre-extinction estradiol treatment improves extinction recall in women with naturally low estradiol levels (Graham & Milad, 2013), while in rodents extinction recall is enhanced by estrogen agonists and impaired by estrogen antagonists (Chang et al., 2009; Milad et al., 2009; Zeidan et al., 2011).

Comparable results have been found for women using hormonal contraceptives, which suppress endogenous estradiol and progesterone. During extinction training, women using contraceptives show similar skin conductance responses (SCRs) to naturally cycling women (Graham & Milad, 2013; Lonsdorf et al., 2015; Merz et al., 2012), despite exhibiting greater neuronal differentiation to the CS+ and CS− during this phase (Merz et al., 2012). However, women using contraceptives show poorer extinction recall compared to naturally cycling women, either due to greater recovery of SCRs (Graham & Milad, 2013), or reduced SCR differentiation between the CS+ and CS− (Lonsdorf et al., 2015).

Fear extinction forms the basis of exposure therapy, which is an important component of Cognitive Behavioral Therapy (CBT), the gold standard treatment for anxiety disorders (Hofmann & Smits, 2008). Exposure therapy counteracts the pathological avoidance of feared stimuli and situations associated with anxiety disorders. However, established models of anxiety disorders (e.g. Beck, Emery, & Greenberg, 1985; Clark, 1986; Clark & Wells, 1995; Ehlers & Clark, 2000) also emphasize the crucial role of cognitions in the development and maintenance of clinical anxiety. According to these models, exaggerated beliefs regarding the likelihood and consequences of feared cues fuel both behavioral avoidance and the physiological sensations of anxiety (e.g. increased heart rate), which then reinforce exaggerated beliefs (Beck et al., 1985; Davey, 2006; Lovibond, 2006). Thus, anxiety disorders comprise at least three components: beliefs about the feared stimulus, physiological reactions, and behavioral responses. This is also in accordance with Lang's three-response system of fearful emotions, comprising verbal responses (cognitions and affect), physiological arousal, and avoidance behavior (Lang, 1985).

To date, the current literature examining sex hormones and fear extinction in humans has focused primarily on physiological measures of fear, such as skin conductance response (SCR) and fear-potentiated startle (but see Lonsdorf et al., 2015, which examined self-reported menstrual phase, oral contraceptive use, and cognitive responses in a context-dependent fear acquisition, extinction, and extinction retrieval/expression procedure). While these measures are important, it is also crucial to investigate the link between sex hormones and alternative response systems, such as beliefs about extinguished cues. Research indicates that Lang's three emotional response systems do not always converge, with different patterns of responses found across contexts and populations (Lang, 1985; Lang, Bradley, & Cuthbert, 1998). Therefore, assessing multiple measures of fear will help to develop a more robust understanding of the role of estradiol in fear extinction in humans. Such an understanding may help to shed light on the potential clinical utility of estradiol adjuncts to psychological treatments.

The aim of the current study was to investigate the relationship between estradiol and cognitive responses towards previously conditioned extinguished cues, in addition to its documented influence on physiological reactions to such cues. To achieve this, we exposed naturally cycling women with high and low levels of estradiol, women using hormonal contraceptives, plus a male control group, to a differential fear conditioning and extinction procedure. We measured SCR to cues, plus two verbal measures of fear responses: US expectancy (how much the CS predicts the occurrence of the US; Lovibond & Shanks, 2002), and CS evaluation (the change in the valence of the CS when it is paired with the US; De Houwer, Thomas, & Baeyens, 2001).

There is evidence that US expectancy is inflated in clinical anxiety (for a review, see Boddez et al., 2013). However, there is continued debate as to whether US expectancy and SCR are linked: some argue that SCR does not occur without contingency awareness of the CS-US relationship (e.g. Hamm & Vaitl, 1996; Hamm & Weike, 2005; Lovibond, 2004; Lovibond & Shanks, 2002; Purkis & Lipp, 2001; Sevenster, Beckers, & Kindt, 2014; Soeter & Kindt, 2010), while others suggest these two measures are dissociable (e.g. Esteves, Parra, Dimberg, & Ohman, 1994; Knight, Nguyen, & Bandettini, 2003, 2006; Schultz, Balderston, Geiger, & Helmstetter, 2013; Schultz & Helmstetter, 2010) and may reflect different neural circuitry (Bechara et al., 1995; Cacciaglia, Pohlack, Flor, & Nees, 2015; Knight, Waters, & Bandettini, 2009). Similarly, debate exists regarding whether CS evaluation is independent of contingency awareness (for reviews, see De Houwer, Baeyens, & Field, 2005; Field, 2000), although research specifically examining the relationship between evaluative conditioning and SCR is limited. Interestingly, there is some evidence that residual negative evaluation of the CS predicts self-reported fear post extinction (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004, 2007; Dirikx, Vansteenwegen, Eelen, & Hermans, 2009; Hermans et al., 2005; Zbozinek, Hermans, Prenoveau, Liao, & Craske, 2015), though it is not yet clear whether these findings are applicable to SCR (Zbozinek et al., 2015).

Given the above, we predict that as per past research, women with low levels of estradiol (either naturally or due to hormonal contraceptive use) will exhibit an increase in SCR during extinction recall, relative to women with high levels of estradiol. Specifically, we predict that women with low estradiol levels will exhibit a greater recovery of SCRs during extinction recall, expressed as a proportion of their maximum SCR conditioning strength (percent recovery of fear; Graham & Milad, 2013; Milad, Orr, Pitman, & Rauch, 2005; Milad et al., 2010; Zeidan et al., 2011). Importantly, if SCR is dependent on contingency awareness, then during extinction recall we would also expect women with low estradiol to rate the CS+ as more likely to be followed by shock, relative to women with high estradiol. Finally, if residual negative evaluation of the CS+ predicts poor extinction recall, then we would expect low estradiol women to rate the CS+ more negatively at the end of extinction (i.e. higher dislike ratings) than women with high estradiol.

2. Methods

2.1. Participants

Eighty-three participants (18–35 years old, mean age 22.2 years; 21 men) were recruited from first-year psychology courses and community advertisements (see Table 1 for demographics). Women reported regular menstrual cycles ($n = 45$) or were using hormonal contraceptives (Hrm-C; $n = 17$; see Table S1 in supplemental for details). Participants reported no history of DSM-V Axis I disorders and no history of endocrinologic conditions (e.g. polycystic ovary syndrome). Skin conductance recordings were visually inspected for movement artifacts during the experiment, leading to the exclusion of 8 participants (4 naturally cycling, 1 Hrm-C, and 3 male participants). Two additional participants were excluded because their skin conductance responses were greater than three standard deviations above the mean (2 naturally cycling participants), thus reducing the final sample to seventy-three participants (41.1% Caucasian, 52.1% Asian, 6.8% other). Once all the data had been collected, naturally cycling women were divided into high (H-EST) and low (L-EST) estradiol