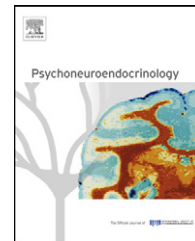




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Patients with premenstrual dysphoric disorder have increased startle modulation during anticipation in the late luteal phase period in comparison to control subjects

Elin Bannbers^{a,*}, Kristiina Kask^a, Johan Wikström^b, Victoria Risbrough^c, Inger Sundström Poromaa^a

^a Department of Women's and Children's Health, Uppsala University, SE - 751 85 Uppsala, Sweden

^b Department of Oncology, Radiology and Clinical Immunology, Uppsala University, 751 85 Uppsala, Sweden

^c Department of Psychiatry, University of California, San Diego, CA, USA

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Summary The acoustic startle response (ASR) is a withdrawal reflex to sudden or noxious auditory stimuli and, most importantly, an unbiased measure of emotional processing of appetitive and aversive stimuli. By exposing subjects to fearful situations, such as aversive pictures, the ASR may be enhanced, suggesting that amygdala modulates the startle circuit during threat situations. As one previous study, investigating affective modulation of the ASR in women with premenstrual dysphoric disorder (PMDD), discovered no difference during picture viewing it is possible that the mood changes observed in PMDD relate to anxious anticipation rather than to direct stimulus responding. Hence we sought to examine the effects of PMDD on picture anticipation and picture response.

Sixteen PMDD patients and 16 controls watched slide shows containing pleasant and unpleasant pictures and positive and negative anticipation stimuli during the follicular and luteal phase of the menstrual cycle. Simultaneously, semi-randomized startle probes (105 dB) were delivered and the ASR was assessed with electromyography.

Compared with control subjects, PMDD patients displayed an enhanced startle modulation by positive and negative anticipation stimuli in the luteal phase of the menstrual cycle. This finding was mainly driven by increased modulation in the luteal phase in comparison to the follicular phase among PMDD patients but also by an increased modulation in patients compared to controls during luteal phase. This suggests that the neural circuits underlying response to emotional anticipation are more sensitive during this period and emphasize the need of examining the neural correlates of anticipatory processes in women with PMDD.

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* Corresponding author. Tel.: +46 18 611 57 87; fax: +46 18 55 97 75.
E-mail address: elin.bannbers@kbh.uu.se (E. Bannbers).

Introduction

Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome and affects 3–8% of women of reproductive ages (Cunningham et al., 2009). The PMDD criteria require at least five symptoms, mainly affective, to be present in the luteal phase of most menstrual cycles and the symptoms should be severe enough to interfere with social and work functioning (Pearlstein, 2010). As symptoms occur only during ovulatory menstrual cycles (Cronje et al., 2004) or during progesterone administration (Segebladh et al., 2009), the ovarian steroids estradiol and progesterone have been implicated in the pathophysiology of the syndrome. However, although it is generally believed that ovarian hormones are involved in the etiology of PMDD, a number of menstrual cycle manipulation studies also suggest that a certain degree of anxious anticipation may be involved in the symptom provocation (Schmidt et al., 1991, 1998; Segebladh et al., 2009). Several lines of evidence suggest that amygdala reactivity is involved in the disorder. Women with PMDD have lower levels of prepulse inhibition than healthy controls during the late luteal phase (Kask et al., 2008) and female rats subjected to progesterone withdrawal display increased startle response paralleled by increased amygdala expression of α 4-subunit containing GABA_A receptors (Gulino et al., 2003). The amygdala is also rich in estradiol and progesterone receptors (Ostlund et al., 2003) and human post mortem studies indicate that the highest brain levels of progesterone are found in the amygdala (Bixo et al., 1997). Recently, a neurocircuitry model for PMDD was suggested, involving a premenstrual decrease in medial orbitofrontal cortex activity in association with a premenstrual increase in amygdala activity (Protopopescu et al., 2008).

The acoustic startle response (ASR) is a withdrawal reflex to sudden or noxious auditory stimuli which can be measured as an eye blink in humans or as a whole body response in laboratory animals (Davis, 2006). Prior studies in women with PMDD have indicated that these women have an increased baseline ASR (Kask et al., 2008). However, startle reactivity may also be used as an unbiased measure (at least compared to self report) of emotional processing of both appetitive and aversive stimuli (Lang et al., 2000). Animal studies as well as human studies show the ASR to be enhanced during arousal and fearful situations, such as during threat of shock or aversive pictures, while it is reduced when presented with rewarding stimuli such as pictures of food or erotica (Grillon and Baas, 2003; Baas et al., 2009). Studies investigating different anxiety disorders also show an enhanced startle magnitude during modulation of the ASR (Kaviani et al., 2004; Melzig et al., 2007). This enhancement by exposing subjects to aversive situations, suggest that amygdala modulates the startle circuit during threat situations (Lang et al., 2000; Pissioti et al., 2003). Importantly, startle reactivity is also dependent upon emotional valence, unlike other physiological measures of arousal (e.g. skin conductance) which are elevated in the presence of either highly rewarding or highly negative stimuli (Lang et al., 2000).

Prior studies have also investigated the effect of anticipation on startle magnitude by eliciting acoustic stimuli during specific cues prior to pleasant, neutral and unpleasant picture stimuli (Sabatinelli et al., 2001; Dichter et al., 2002; Nitschke et al., 2002). The results suggest that the expected

arousal by the upcoming picture elicits an elevated startle magnitude already during the anticipation phase (Sabatinelli et al., 2001; Dichter et al., 2002). Hence, each person is only anticipating what they are told will be an unpleasant or pleasant image, thus the construct of anxious anticipation is probed as opposed to the construct of stimulus-specific fear or aversion. One obvious utility of examining startle responses during instructed anticipation of an image type (either pleasant or unpleasant), is that startle reactivity is not dependent upon the image itself, thus differences in how subjects respond to a particular image based on different life experiences do not confound the interpretation of startle effects. Recent findings in functional magnetic resonance imaging (fMRI) also suggest that image anticipation tasks probe important anxiety neural substrates, namely the insular cortex and amygdala (Simmons et al., 2006, 2008).

To our knowledge, only one previous study has investigated the affective modulation of the ASR in women with PMDD. Although Epperson et al. (2007) found an increased baseline startle response during the luteal phase of the menstrual cycle, no differences between PMDD patients and controls were found during picture viewing (Epperson et al., 2007). However, the study was limited by a low number of subjects with complete data from both cycle phases and it is thus possible that a difference in affective modulation between the PMDD patients and controls was concealed by low power. In addition, it is also possible that the mood changes observed in PMDD may relate to anxious anticipation rather than to direct stimulus responding. We hypothesized that PMDD patients would display enhanced startle modulation during picture viewing as well as during image anticipation in comparison with control subjects. Hence, the aims were to evaluate startle modulation by pleasant and unpleasant pictures, as well as by anticipation of pleasant or unpleasant pictures, across the menstrual cycle in PMDD patients and controls.

Methods

Subjects

Fifty-one women complaining of premenstrual symptoms, recruited among patients at the outpatient ward of the Department of Obstetrics and Gynaecology, Uppsala University Hospital or by local newspaper advertisements, were screened for inclusion in the study. Of these, 22 women fulfilled the inclusion criteria and were included in the study.

Included patients met the criteria for PMDD diagnosis, defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, 1994). Patients were considered to have PMDD if they had a 100% increase in at least five symptoms during seven premenstrual days compared to seven mid-follicular days, associated with a clinically significant social and occupational impairment (Hammarbäck et al., 1989; Sundstrom et al., 1999). Diagnosis was based on daily, prospective symptom ratings on the Cyclicity Diagnoser (CD) scale during two cycles prior to inclusion (Hammarbäck et al., 1989; Sundstrom et al., 1999). The CD scale consists of nine negative mood parameters (depression, decreased interest in usual activities, fatigue, irritability, tension, mood swings, lability, difficulties in concentrating, and sleeping disturbances), two positive mood parameters

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