Physiological Correlates of Premenstrual Dysphoric Disorder (PMDD)

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Abstract Premenstrual dysphoric disorder (PMDD) is a mood disorder with onset of functionally impairing or distressing mood symptoms in the late luteal phase of the menstrual cycle. Psychophysiologic findings in PMDD broadly fall into two categories: vulnerability trait findings, thus categorized because they are present in the asymptomatic phases of the menstrual cycle, and state findings, which are only present in the symptomatic late luteal phase and which are potentially representative of the hormonal events and biological mechanisms that lead to PMDD. Trait vulnerability markers in PMDD include diminished cardiovascular stress responses, lower heart rate variability (reflecting increased vagal tone), and lower P300 amplitude, eventually suggesting that women with PMDD share a number of physiological correlates with related anxiety and mood disorders. State findings in PMDD include lower luteal phase prepulse inhibition and altered luteal phase emotion processing. Lower prepulse inhibition in the late luteal phase may be an important ovarian steroid-influenced indicative of altered serotonergic neurotransmission, of relevance for women with PMDD. Attempts to determine the neural correlates of emotion processing in the late luteal phase are thus far inconsistent, but promising.

Keywords Premenstrual dysphoric disorder · Estradiol · Progesterone · Prepulse inhibition · Emotion processing · Functional magnetic resonance imaging

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1 Introduction

Premenstrual dysphoric disorder (PMDD) is categorized as a mood disorder with onset of functionally impairing or distressing mood and physical symptoms in the late luteal phase of the menstrual cycle, a decline in symptom severity after onset of menstruation, and an absence of symptoms in the postmenstrual week (O'Brien et al. 2011). Hallmark mood symptoms include mood lability, irritability, anxiety, tension, and depression (O'Brien et al. 2011). The disorder affects roughly 5 % of women of reproductive age (Wittchen et al. 2002), and has a moderate heritability (Kendler et al. 1998).

PMDD is defined by the relation to the late luteal phase of the menstrual cycle. As progesterone is only present in the luteal phase, PMDD is commonly regarded as a disorder caused by the variation in (or mere presence) of progesterone levels. Research in support of this include findings of symptom relief during anovulatory cycles (Wyatt et al. 2004), the reinstatement of symptoms when add-back hormone therapy is administered together with gonadotropin-releasing hormone (GnRH) agonists (Segebladh et al. 2009), and findings of progestagen-induced mood symptoms in postmenopausal women (Andreen et al. 2003, 2005, 2006). Notably, no consistent hormonal differences between women with PMDD and healthy controls have been reported (Backstrom et al. 2003). Hence, the exact mechanism by which progesterone precipitates the symptoms of PMDD is unknown, although interactions with the serotonin (Jovanovic et al. 2006; Brown et al. 2009) and the GABAergic systems (Epperson et al. 2002; Sundstrom Poromaa et al. 2003) are plausible.

Estradiol and progesterone are both highly lipophilic and easily pass through the blood–brain barrier. In fact, animal studies and post-mortem studies in reproductive and postmenopausal women indicate that estradiol and progesterone are accumulated in the brain (Bixo et al. 1986, 1995, 1997), with the highest concentration of progesterone found in the amygdala (Bixo et al. 1997). The estradiol receptors (ERα and ERβ) and the progesterone receptors (PRA and PRB) are highly expressed in brain areas associated with reproductive function, such as the hypothalamus and the limbic system (for review, see (Gruber et al. 2002; Brinton et al. 2008). For example, the expression of the estradiol receptors has been demonstrated in the human amygdala, hippocampus, claustrum,

hypothalamus, and the cerebral cortex. Within the cerebral cortex, the most distinct expression of estradiol receptors is found in the temporal cortex (Osterlund et al. 2000a, b). The progesterone receptors are also distributed throughout the amygdala, hippocampus, hypothalamus, thalamus, and the frontal cortex (Kato et al. 1994; Bixo et al. 1997; Guerra-Araiza et al. 2000, 2002, 2003). The receptor distribution suggests that the ovarian hormones have the capability to modulate emotional processing, cognitive function, sensory input, attention, decision making, and motor function. Progesterone can also be metabolized into neuroactive steroids, among which allopregnanolone and pregnanolone are the two neurosteroids most studied in PMDD. Neurosteroids potentiate the $GABA_A$ receptor, where they increase hyperpolarization and act in a similar manner to barbiturates and benzodiazepines (Melcangi et al. 2011). As GABA is the major inhibitory transmitter in the central nervous system, acute administration of allopregnanolone has sedative, anxiolytic, and anticonvulsant properties (Melcangi et al. 2011). A functionally relevant amount of allopregnanolone is synthesized in the brain, but the main source of brain and serum allopregnanolone in nonpregnant women is the corpus luteum (Ottander et al. 2005).

Over the past years menstrual cycle studies have greatly improved in quality by use of counterbalanced, longitudinal designs, and by correct classification of menstrual cycle stage by use of hormonal levels and assessment of the luteinizing hormone surge rather than just the onset of menses. For this review, only studies where these design standards have been met have been included. The most relevant menstrual cycle contrast in PMDD women is obviously the late follicular phase (when patients are symptom-free) and the late luteal phase (when symptoms culminate). In addition, this review has only considered studies where PMDD diagnosis is based on criteria devised by the Diagnostic and Statistical Manual of Mental Disorders (DSM). Besides the typical symptom profile and a clear-cut impact on daily life, the diagnosis must also be confirmed by use of prospective daily symptom ratings. Unfortunately, many PMDD studies typically include relatively small sample sizes. While this is a problem in terms of statistical power or high probability of chance findings, it is also understandable as diagnostic procedures are time consuming and a large number of women need to be screened before the target population is reached.

2 Trait Vulnerability Markers

Life-time comorbidity with depressive and anxiety disorders is common in women with PMDD (Wittchen et al. 2002, 2003), and many PMDD women display typical vulnerability markers for psychiatric morbidity such as neurotic personality traits (Freeman et al. 1995; Gingnell et al. 2010) and history of violence or abuse (Girdler et al. 2003). Furthermore, several biochemical and neurophysiological abnormalities encountered in depressed or anxious patients are also found in women with PMDD. If such findings are present in the asymptomatic phases of the

menstrual cycle, they are commonly regarded as vulnerability traits for PMDD, or alternatively, vulnerability traits for the depressive and anxiety disorders that are commonly associated with PMDD.

2.1 Cardiovascular Stress Reactivity

Many women with PMDD state that their symptoms worsen during time periods of intense workload and stress (Sadler et al. 2010), and hypothetically, women with PMDD could have an altered stress response in comparison with healthy women (Perkonigg et al. 2004; Sadler et al. 2010). In a series of studies, Girdler and colleagues have reported on cardiovascular stress responses in healthy women and PMDD women across the menstrual cycle. Besides a lack of menstrual cycle influence on stress-induced hemodynamic responses such as cardiac output and peripheral resistance, women with PMDD also showed diminished diastolic blood pressure and heart rate responses and a tendency to blunted cardiac output to the stress tests, irrespective of cycle phase (Girdler et al. 1993). These findings were later partly replicated in a study where women with PMDD in both cycle phases had lower cardiac output and stroke volume and higher peripheral resistance during mental stress than healthy controls (Girdler et al. 1998). Further attempts to replicate these findings have either failed (van den Akker and Steptoe 1989; Girdler et al. 2003), or only been confirmed in women with PMDD who also had a history of abuse (Girdler et al. 2007). Although the positive physiological findings that have been reported are suggestive of trait vulnerability markers, it should also be noted that endocrine measures of stress, such as allopregnanolone levels, are elevated in PMDD women in the luteal phase (Girdler et al. 2001).

Heart rate variability (HRV) measures provide a sensitive noninvasive measure of cardiac autonomic regulation via the parasympathetic (vagal) and sympathetic nervous systems. Time domain variables of beat-to-beat variability of the heart rhythm are assumed to reflect mainly vagal tone while frequency domain variables, derived from power spectral analysis, can be used to distinguish between sympathetic and vagal predominance. While two studies have failed to demonstrate any difference between PMDD patients and controls (although within group differences in responsiveness to the menstrual cycle changes were reported) (Baker et al. 2008; de Zambotti et al. 2013), two studies have suggested lower heart rate variability, reflecting increased vagal tone, in PMDD women (Landen et al. 2004; Matsumoto et al. 2007). Again, these findings were not confined to the symptomatic late luteal phase. Instead, women with PMDD appear to have lower HRV indices across both cycle phases (Matsumoto et al. 2007) or only in the follicular phase (Landen et al. 2004). These findings support the notion that reduced HRV is a feature shared by a number of related psychiatric disorders that are characterized by symptoms such as depressed mood and anxiety, including PMDD. In addition, these findings imply that women with lower autonomic function regardless of the menstrual cycle are vulnerable to more severe premenstrual disorders.

2.2 Attention and Alertness

Event-related potentials (ERPs) are electroencephalogram (EEG) changes that are time locked to a stimulus event. One of the most prominent components of the ERP is the positive P300 waveform that occurs between 300 and 500 ms after stimulus onset. The P300 is thought to reflect higher processing of the psychological meaning of stimuli and the P300 amplitude is affected by numerous factors, including task or stimulus complexity, expectancy, vigilance, and attention. Two studies have investigated the P300 in women with PMDD, one reporting lower P300 amplitude to both auditory and visual stimuli in both menstrual cycle phases (Baker et al. 2010), and the other reporting longer P300 latency to auditory stimuli across both cycle phases in PMDD women (Ehlers et al. 1996). As PMDD women in the study by Baker and colleagues also performed poorly on a psychomotor vigilance task in the luteal phase, the authors suggested that women with PMDD allocated less attentional resources to the tasks than did controls at both symptomatic and symptom-free menstrual cycle phases, although response output processing (reaction times on the PVT) was only affected in the symptomatic phase (Ehlers et al. 1996).

Despite common reports of fatigue during the luteal phase, no difference in waking EEG power density in the theta/alpha range, as possible indicators of alertness (Cajochen et al. 1997; Baker et al. 2010), has been noted in PMDD women. Women with PMDD, however, are reported to have a lower saccadic eye velocity across both cycle phases (Sundstrom and Backstrom 1998).

2.3 Startle Response

The acoustic startle reflex is a withdrawal reflex to sudden or noxious auditory stimuli which can be measured as an eyeblink in humans or as a whole-body response in laboratory animals. This paradigm is a useful bridge between preclinical and human data, since it has a similar circuitry and pharmacology in humans as it does in animals. While healthy female controls do not show cyclic changes in this measure of physiologic arousal (Epperson et al. 2007), PMDD is associated with an increase in baseline startle magnitude, although it is unclear if this present in both cycle phases (Kask et al. 2008) or confined to the symptomatic late luteal phase (Epperson et al. 2007). Again, increased startle response is a feature shared by a range of anxiety disorders, but the relevance in PMDD is strengthened by the influence of ovarian steroids on the acoustic startle reflex (Toufexis et al 1999; Van den Buuse and Eikelis 2001; Vaillancourt et al. 2002; Byrnes et al. 2007) and by the fact that the startle response is increased in an animal model of PMDD (the progesterone withdrawal model) (Gulinello et al. 2003; Gulinello and Smith 2003). In addition, the acoustic startle response is also regulated by the agents thought to be critical to the etiology PMDD symptoms, notably

progesterone fluctuations and underlying alterations in inhibitory neurotransmission via the $GABA_A$ receptor (Gulinello et al. 2003; Gulinello and Smith 2003; Toufexis et al. 2004).

3 State Findings

As understood by the previous section, relatively few psychophysiology findings in PMDD women have been confined to the symptomatic late luteal phase. While trait findings are important for the overall understanding of PMDD, psychophysiology findings during the symptomatic phase would aid in our understanding of the biological mechanisms that lead to the symptom surfacing in the premenstrual phase.

3.1 Prepulse Inhibition

Prepulse inhibition of the startle magnitude is a sexually dimorphic measure which also varies across the menstrual cycle. In fact, it is one of the most reliable and consistent menstrual cycle findings that PPI is lower at times when estradiol and progesterone levels are high, such as during the mid-luteal phase of the menstrual cycle and in pregnancy (reviewed in (Kumari 2011)). In addition, women of childbearing ages have lower PPI than postmenopausal women (Bannbers et al. 2011), and the sex difference also disappears following menopause (Kumari et al. 2008).

Women with PMDD patients exhibit lower levels of PPI compared to control subjects in the luteal but not in the follicular phase (Kask et al. 2008). Furthermore, PMDD patients with pronounced anxiety and depression symptoms during the cycle in which they were tested had even more impaired PPI than less symptomatic patients (Kask et al. 2008). As variable hormone levels from menstrual cycle to menstrual cycle within individual subjects may result in variable symptom expressions (Wang et al. 1996), this finding underlies the assumption that the hormonal events that trigger PMDD symptoms in a specific menstrual cycle could also affect the circuits modulating PPI. The relevance of this measure for PMDD symptom expression is further strengthened by similar findings of low PPI in women suffering from depression and irritability while using combined oral contraceptives (Borgstrom et al. 2008).

While progesterone appears to be the most relevant hormone for PMDD, estradiol has been of greater interest in the field of PPI, presumably due to its role in schizophrenia (Gogos and Van den Buuse 2004; Gogos et al. 2006a, b, 2009; Guille et al. 2011; Hill et al. 2013; Thwaites et al. 2014; Wu et al. 2013). Menstrual phase-related variability in PPI has been suggested to be mediated by fluctuating estrogen level, based on the observations of more PPI in women during

the follicular, relative to the luteal, phase. Both estrogen receptors are found in the nucleus accumbens and amygdala (Gruber et al. 2002; Brinton et al. 2008) and other areas of the PPI circuit (Charitidi et al. 2012), and ERα has been suggested to play a key role (Charitidi et al. 2012). Estrogen induces a dose-dependent increase in PPI in ovariectomized rats (Van den Buuse and Eikelis 2001; Charitidi et al. 2012) and estrogen (or combined estrogen-progestagen) treatment in ovariectomized female rats may also prevent 5-HT_{1A-}, dopamine-, and NMDA receptor-induced disruptions of PPI (Gogos and Van den Buuse 2004; Gogos et al. 2010, 2012; Thwaites et al. 2014). Similar findings have also been obtained in females where estrogen treatment prevented buspirone-induced PPI deficits (Gogos et al. 2006a). However, treatment with 2 mg estradiol during the early follicular phase did not affect PPI in healthy women (Gogos et al. 2006b), and no direct correlations between estradiol levels and PPI have been reported (Kask et al. 2008b; Kumari et al. 2008,2010; Talledo et al. 2009; Bannbers et al. 2011). Hence, an alternative explanation to the menstrual cycle effects and the PMDD findings be equally well be that of progesterone-induced inhibition of estradiol effects in the luteal phase. Recently, a role for progesterone in PPI was also suggested (Kumari et al. 2010) as a larger increase in progesterone was associated with a smaller decrease in PPI from the follicular to the luteal phase, which could be of relevance for PMDD women. This effect is presumably mediated by the progesterone receptors, as GABA-active progesterone metabolites have no influence on PPI (Kask et al. 2009).

In terms of PMDD pathophysiology, the finding of reduced PPI in the symptomatic late luteal phase may suggest altered serotonergic or dopaminergic neurotransmission. Of these two, the serotonin system is by far the most researched in PMDD. A role for serotonin in PMDD is predominantly suggested by the fact that serotonin reuptake inhibitors (SSRI) can be used for treatment (Marjoribanks et al. 2013). Not only so, the SSRIs appear to have a distinctly different route of action in PMDD, as opposed to when it is used for depressive or anxiety disorders. For instance, it is equally effective when used intermittently, i.e., only during the luteal phase, or continuously, and the onset of action is reportedly as short as 14 hours after first drug intake (Landen et al. 2009). These temporal relationships suggest that SSRIs may facilitate serotonin transmission shortly after the onset of treatment in anger-modulating pathways, by increasing synaptic levels of serotonin (Landen et al. 2009). Further pharmacological challenges in PMDD women are, however, needed to establish the role of the serotonin system for the impaired late luteal phase PPI in PMDD women.

3.2 Emotion Processing: Startle Reactivity

Startle reactivity may also be used as an measure of emotional processing (Lang et al. 2000). Animal studies as well as human studies show the acoustic startle response to be enhanced during arousal and fearful situations, such as during threat

of shock, noxious noise, or aversive pictures, while it is reduced when presented with rewarding stimuli such as pictures of food or erotica (Lang and Davis 2006). Emotion-induced modulation of the startle response, as far as it has been studied, appears not to be different in women with PMDD, either in comparison with healthy controls or across menstrual cycle phases (Epperson et al. 2007; Bannbers et al. 2011). However, PMDD patients display an increased startle modulation by positive and negative anticipation stimuli in the late luteal phase. Possibly one reason why anticipation, as opposed to image viewing, results in an increased startle response in women with PMDD, could be that startle reactivity in this case 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. The latter may be of specific relevance in PMDD women, as women with a history of trauma, or PTSD, are more likely to experience PMDD (Wittchen et al. 2003; Pilver et al. 2011), and as PMDD women with a history of trauma have an abnormal neuroendocrine stress response (Girdler et al. 1998, 2003, 2007; Segebladh et al. 2011). Anticipation of negative events may be adaptive and promote behavior that increases the possibility for survival in response to threat, but could also be dysfunctional and initiate anxious responses also to nonthreatening stimuli (Grupe and Nitschke 2013). In the context of PMDD, the anticipation of the luteal phase symptoms has been shown to influence the severity of symptoms (Segebladh et al. 2009). Further, the increased startle modulation by positive and negative anticipation stimuli have later been validated by functional magnetic resonance imaging (fMRI), where women with PMDD had higher luteal phase reactivity in the anterior medial prefrontal cortex and dorsolateral prefrontal cortex during negative anticipation than healthy controls, while they did not differ from healthy controls in their response to the emotional images (Gingnell et al. 2013).

3.3 Emotion Processing: Functional Magnetic Resonance Imaging

A growing number of studies have attempted to pinpoint the neural correlates of the late luteal phase emotion processing in PMDD women. Most attention has been given to the hypothesized corticolimbic emotion processing network (reviewed by (Shin and Liberzon 2010)), where the amygdala and insula are activated by bottom-up emotional processes and the anterior cingulate cortex involved in top-down regulation. While increased amygdala reactivity characterizes negative affective states like anxiety and depression (Etkin and Wager 2007; Shin and Liberzon 2010), studies on amygdala reactivity in PMDD have thus far been inconsistent (Protopopescu et al. 2008; Gingnell et al. 2012, 2013), possibly because none of the paradigms used have tapped into the PMDD-specific symptomatology. Protopopescu et al. (2008) reported increased late luteal amygdala

reactivity in response to emotional words, but the results appeared to reflect alterations in reactivity over the menstrual cycle in healthy controls rather than in women with PMDD. Gingnell et al. (2012) reported a follicular phase increase in amygdala reactivity to emotional faces, whereas the expected luteal phase increase was only noted in a subgroup of PMDD patients who also had high trait anxiety. Furthermore, no differences in the amygdala and insula or ACC reactivity between patients and controls and no menstrual phase modulation were observed to negative emotional stimuli (Gingnell et al. 2013). Although these findings appear inconsistent and not specific to the late luteal phase, some details may be of importance for the understanding of PMDD. First, the increased bilateral amygdala reactivity in PMDD women during the follicular phase noted by Gingnell and colleagues was highly and positively correlated with progesterone levels, which was not the case in the healthy controls. While progesterone levels at this point of the menstrual cycle are low, and also not associated with mood worsening, women with PMDD are in general more sensitive to progesterone than controls (Schmidt et al. 1998). Hence, this finding may suggest that the amygdalae in PMDD women respond already at very low levels of progesterone. Indeed, the progesterone levels needed to induce amygdala reactivity in healthy women are approximately 20-fold higher (van Wingen et al. 2008). As progesterone receptors are present throughout the limbic system (Kato et al. 1994; Bixo et al. 1997; Guerra-Araiza et al. 2000, 2002, 2003) and progesterone concentrations are high in the amygdala (Bixo et al. 1997), the follicular phase increase in amygdala reactivity might reflect a trait-like sensitivity in the amygdala to low levels of progesterone, which is abolished in the luteal phase when ovarian steroid levels are increased. It has been suggested that tolerance to progesterone may develop during the luteal phase and that women with PMDD have an aberrant tolerance development (Backstrom et al. 2014). Although this hypothesis mainly relies on findings of GABAergic progesterone metabolites [GABA plays a major role in amygdala functioning (Roberto et al. 2012)], it is equally possible that progesterone receptors in the CNS may be saturated during the luteal phase and direct associative couplings between amygdala reactivity and small stress-induced changes in progesterone may not be detectable.

Yet another important issue is that the emotional stimuli used in startle and fMRI experiments may not have been specific enough to discriminate the PMDD women from healthy controls in the luteal phase, especially since amygdala reactivity is increased in the luteal phase already in healthy women (Andreano and Cahill 2010; Goldstein et al. 2010; Gingnell et al. 2012). Using a paradigm that contrasted brain reactivity in response to social as opposed to nonsocial aversive stimuli, women with PMDD displayed increased amygdala and insular cortex reactivity during the luteal phase which was paralleled by a reduced reactivity in areas previously reported to be involved in emotion regulation, i.e., the anterior cingulate cortex (Gingnell in press). Among women with PMDD reactivity in the amygdala increased between the follicular and luteal phase and was positively correlated to the progesterone increase across cycle phases (Gingnell in manuscript). Reactivity alterations in PMDD to social stimuli might thus be similar to

anxiety disorders with increased reactivity in the amygdala and insula but decreased reactivity in the regulatory parts of ACC which is restricted to symptom provoking situations (Shin and Liberzon 2010).

Attempts to use cognitive paradigms have thus far yielded trait-like findings across both cycle phases. For instance, Baller and colleagues (Baller et al. 2013) reported increased activity in the prefrontal cortex of women with PMDD as compared to healthy controls during a short-term memory task, but this effect was unrelated to hormonal levels. Using a nonemotional Go/NoGo-task, women with PMDD have also been reported to have lower parietal reactivity than healthy controls regardless of menstrual cycle phase (Bannbers et al. 2012).

4 Conclusion

Although PMDD is common, and although it is an important model for our understanding of how ovarian steroids influence mood and anxiety in women, the number of studies attempting to elucidate its pathophysiology is strikingly low. Most physiologic findings in PMDD women, such as altered cardiovascular responses to stress or decreased heart rate variability, have been reported in both cycle phases, suggesting that they represent vulnerability traits for PMDD, or alternatively, vulnerability traits for the depressive and anxiety disorders that are commonly associated with PMDD. Relatively few, and yet for the most part, unconfirmed findings have pinpointed the late luteal phase as the crucial determinant for differences between women with PMDD and healthy controls. Among these, lower prepulse inhibition in the late luteal phase may be an important ovarian steroid-influenced indicative of altered serotonergic neurotransmission, of relevance not only for women with PMDD but also for women suffering from mood and anxiety disorders. Attempts to determine the neural correlates of emotion processing in the late luteal phase are thus far inconsistent, but promising.

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