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Anxiety Sensitivity, the Menstrual Cycle, and Panic Disorder: A Putative Neuroendocrine and Psychological Interaction

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Abstract

The 2:1 female-to-male sex difference in the prevalence of Panic Disorder (PD) suggests that there is a sex-specific vulnerability involved in the etiology and/or maintenance of this disorder. The purpose of this paper is to present a new conceptual model, which emphasizes the interaction between a cognitive vulnerability for PD, anxiety sensitivity, and the effects of progesterone and its metabolite, allopregnanolone, on behavioral and physiological responses to stress during the premenstrual phase. This interaction is proposed to be a potential sex-specific pathway that may initiate and/or maintain panic and anxiety symptoms in women. This review paper presents preliminary evidence from both the human and animal literatures to support this new model. Specific topics reviewed include: psychopathology related to the menstrual cycle, anxiety sensitivity and its relationship to the menstrual cycle, PMS, and PMDD, anxiety-modulating effects of progesterone and its neuroactive metabolite, allopregnanolone, and how results from the neuroendocrine literature relate to psychopathology or symptoms associated with the menstrual cycle.

Keywords

Panic Disorder; Premenstrual Phase; Anxiety Sensitivity; Neurosteroids

1. Introduction

Disorders that involve dysregulation of anxiety systems such as Panic Disorder (PD) are as much as 2 times more prevalent in women than in men (McLean & Anderson, 2009), suggesting a sex-specific vulnerability is involved in the etiology and/or maintenance of this anxiety disorder. Identification of sex-specific stress-susceptible systems mediating anxiety symptoms and disorders would have important implications for prevention, assessment, treatment, and research. Ovarian hormonal changes occurring in the premenstrual phase of the menstrual cycle may constitute a neuromodulatory influence that contributes to the onset and maintenance of maladaptive or clinical anxiety in women. Indeed, periods of hormonal change or flux are associated with changes in affect and an increase in the occurrence or symptoms of a myriad of mental disorders (Brier et al., 1986; Freeman, 2003; Gonda et al., 2008; Kaspi et al., 1994; Kornstein et al., 2008).

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The premenstrual phase has been associated with an increase in negative psychological (e.g., anxiety, sadness, tension, affect lability) and physical symptoms (e.g., headaches, fatigue; Angst, Sellaro, Stolar, Merikangas, & Endicott, 2001; Asso, 1983; Bloch, Schmidt, & Rubinow, 1997; Logue & Moos, 1986), and at least one premenstrual symptom is experienced regularly across cycles by approximately 80% of women (Wittchen, Becket, Lieb, & Krause, 2002). Premenstrual Dysphoric Disorder (PMDD) is an extreme variant on the continuum of premenstrual symptoms with reported prevalence rates that range from 3–8% (Halbreich, Borenstein, Pearlstein, & Kahn, 2003). Although PMDD was originally conceptualized as a depressive disorder, premenstrual anxiety is a common symptom reported among affected women (Vickers & McNally, 2004). Additionally, pathophysiological and psychobiological links between PMDD and PD have been proposed (Vickers & McNally, 2004). Hence, fluctuations of hormones that accompany the premenstrual period are likely involved in the manifestation of Premenstrual Syndrome (PMS) and PMDD.

Here, we propose that the interactions between premenstrual hormone fluctuations, psychological or cognitive vulnerability factors (e.g., anxiety sensitivity), and external stressors (e.g., negative or stressful events), may interact in the development of clinical anxiety such as PD. In this review we present a new model for understanding these interactions and provide an overview of several different literatures that support this model. Included in this review are: 1) an overview of the literature on anxiety sensitivity, a cognitive vulnerability to anxiety disorders such as PD, and its relationship to the menstrual cycle, PMS, and PMDD; 2) literature on the anxiety-modulating effects of progesterone and its neuroactive metabolite allopregnanolone (also known as 3 α 5 α -tetra-hydro-progesterone or THP) in both laboratory rodents and women, particularly through THP effects on the GABA receptor; and 3) relate results from the neuroendocrine literature to psychopathology or symptoms associated with the menstrual cycle. Cumulatively, these topics provide preliminary evidence for the new conceptual model proposed here (see Figure 1), which emphasizes the association between anxiety sensitivity and the effects of progesterone and its metabolites on behavioral and physiological responses to stress during the premenstrual phase. This model is provided as a framework to guide future research on the examination of etiological and/or maintenance pathways specific to women with PD or clinical anxiety. Although this review focuses primarily on PD, this model could be tested with other anxiety disorders given that the 2:1 female-to-male sex difference exists for several anxiety disorders (e.g., Generalized Anxiety Disorder, Post Traumatic Stress Disorder, Agoraphobia; McLean & Anderson, 2009). Understanding sex-specific stress-susceptible systems could lead to the development of more targeted prevention and intervention programs for women.

2. Changes in progesterone across the menstrual cycle

Figure 2 depicts the changes in sex steroid levels across the human menstrual cycle. Normal menstrual cycles range from 25–35 days. In a 28-day cycle, menstruation begins on Day 1 and lasts, on average, for 5 days. During the menstrual phase (Days 1–5), estrogen and progesterone are at their lowest. Estrogen peaks and the follicle stimulating hormone (FSH) levels are low at Day 6, starting off the follicular phase (Days 6–12). During the follicular phase, estrogen declines and then rises again, progesterone levels remain low and steady, and the endometrium thickens. The ovulatory phase (Days 13–15) is characterized by a peak in luteinizing hormone and the fall of estrogen. The luteal phase runs from Days 16–23. The late luteal or premenstrual phase (Days 24–28) is characterized by a high level of progesterone, a moderate level of estrogen, and a gradual rise in FSH to begin developing a new set of follicles. Estrogen and progesterone decline at the end of the premenstrual phase as the next menstrual phase begins (Asso, 1983; Yen, 1999). For the purpose of this review,

it is important to note the trajectory of progesterone release. In sum, progesterone is low throughout menses and the follicular phase, rises steadily following ovulation and throughout the luteal phase, and then declines rapidly prior to the beginning of menstruation in the next cycle.

3. Psychopathology related to the menstrual cycle

A variety of psychological and physical symptoms have been correlated with different phases of the menstrual cycle. Commonly reported premenstrual changes include acne, constipation or diarrhea, fatigue, fluid retention, increased sex drive, headaches, insomnia, joint or muscle aches and pains, sweet or salty food cravings, affect lability, anxiety, bursts of energy, feeling of loss of control, irritability, poor concentration, sadness, and tension (Bloch, Schmidt, & Rubinow, 1997; Chrisler & Caplan, 2002; Logue & Moos, 1986; Freeman, 2003). Approximately 50–80% of women report that they experience at least some symptoms during the premenstrual phase (Halbreich, Borenstein, Pearlstein, & Kahn, 2003; Logue & Moos, 1986; Pearlstein & Stone, 1998; Wittchen, Becker, Lieb, & Krause, 2002). Prospective tracking of symptoms across three consecutive menstrual cycles among healthy women who did not meet criteria for PMDD revealed that 50.8% of the sample reported a 66% or greater increase in physical symptom severity from the follicular to the premenstrual phase (Gonda, Telek, Juhasz, Lazary, Vargha, & Bagdy, 2008). Additionally, this sample of women reported an increase in non-pathological anxiety, depressive, and obsessive-compulsive symptoms; somatization; neuroticism; and interpersonal sensitivity in the premenstrual versus the follicular phase (Gonda et al., 2008), suggesting that even healthy women experience a consistent fluctuation of affect across the menstrual cycle. However, some prospective studies following the same women over time have found little evidence for a consistent pattern of negative premenstrual symptom worsening as compared to other cycle phases, despite the fact that many of these women reported experiencing premenstrual syndrome in retrospective reports (Hardie, 1997; McFarlane and Williams, 1994). This highlights the importance of using prospective symptom tracking to identify menstrual cycle-related changes. Additionally, expectations related to the premenstrual phase have been shown to influence report of premenstrual symptoms (Klebanov & Jemmott, 1992). Specifically, women who were told they were in their premenstrual phase reported more symptoms as compared to women who were told they were in their intermenstrual phase, regardless of what phase they were actually in (Klebanov & Jemmott, 1992).

Premenstrual syndrome (PMS) is defined as a cyclical pattern of symptoms that cause some degree of impairment, occur premenstrually, and decline soon after the beginning of menses (Steiner, 1997; Freeman, 2003). Prevalence estimates for clinically significant PMS are between 13%–19% (Angst et al., 2001; Spitzer et al., 2000). Among women who report this cyclical pattern of premenstrual symptoms, only 3–8% rate these symptoms as disabling or severe (Asso, 1983; Halbreich et al., 2003; Logue & Moos, 1986). The extreme variant along the continuum of premenstrual symptoms is called Premenstrual Dysphoric Disorder (PMDD). In order to meet research criteria for PMDD according to the DSM-IV-TR: 1) symptoms must be present during most of the week prior to menstruation, diminish a few days after the onset of menstruation, and are completely absent the week following menstruation; 2) ≥ 5 symptoms must occur in most menstrual cycles during the last 12 months [(i.e., depressed mood, anxiety/tension, marked affective lability, anger/irritability, fatigue, appetite changes/food cravings, insomnia/hypersomnia, any physical symptom (e.g., headache, bloating), and feeling out of control)], and one of these symptoms must be either depressed mood, anxiety/tension, marked affective lability, or anger/irritability; 3) the symptoms significantly interfere with relationships, school/work, or usual activities; and 4) the symptoms are not an exacerbation of another mental or physical disorder (APA, 2000). Additionally, this pattern of symptoms and behavior must be confirmed by prospective daily

ratings for at least two consecutive menstrual cycles. Reported prevalence estimates for PMDD using strict DSM-IV-TR criteria range from 3–8% of women (Halbreich et al., 2003, Wittchen et al., 2002). Prospective studies examining symptom severity patterns among women meeting research criteria for PMDD found that the most frequent symptoms were anger/irritability, anxiety/tension, and affect lability (Bloch et al., 1997; Pearlstein, Yonkers, Fayyad, & Gillespie, 2005) and that symptoms were similar in severity and consistency across cycles within the same women during the premenstrual phase (Bloch et al., 1997).

Despite the fact that a minority of women who experience premenstrual symptoms meet criteria for PMDD, 55% of women reported that they experienced premenstrual symptoms that interfere with their usual activities in a large ($N = 1,744$) study (Barnard, Frayne, Skinner, & Sullivan, 2003), suggesting that the majority of women experience some degree of impairment. Furthermore, women who reported that they experienced any menstrual symptoms (bothered or being treated for abnormal periods, painful periods that interfered with their usual schedule, and/or experience of premenstrual symptoms) reported lower health status on the SF-36, which measures eight different health domains (e.g., physical functioning), compared to women who reported no menstrual symptoms. Upon examination of each type of menstrual symptom separately, premenstrual symptoms explained most of the variance in health status (Barnard et al., 2003). Degree of impairment is associated with symptom severity. Specifically, premenstrual symptom severity increases as impairment across several life domains increases (Robinson & Swindle, 2000). As compared to women with mild or no PMS, women with severe PMS or PMDD report a higher number of missed workdays due to health reasons or premenstrual symptoms, greater healthcare utilization and cost, increased productivity loss, greater impairment in social functioning, and lower health status (Borenstein, Dean, Leifke, Korner, & Yonkers, 2007; Robinson & Swindle, 2000). A large ($N = 1,194$) prospective study examining the economic burden of PMDD revealed that decreased productivity during the premenstrual phase was the most significant form of impairment affecting economic burden among women with PMDD as compared to women with mild premenstrual symptoms (Chawla, Swindle, Long, Kennedy, & Sternfeld, 2002). Additionally, a representative population-based survey among 11,648 women aged 18–55 across the U.S. found that women who reported any menstrual problems during the past year also reported an increase in frequency of anxiety, depression, insomnia, fatigue, and pain during the last 12 months, and were more likely to smoke, drink heavily, and be overweight or obese (Strine, Chapman, & Ahluwalia, 2005).

Along with psychological and physical symptoms, the premenstrual phase has been associated with various types of psychopathology, including a significant association between depressive symptoms and more severe premenstrual symptoms in non-clinical (Lane & Francis, 2003) and clinical (Halbreich & Endicott, 1985) samples, greater lifetime and concurrent comorbid diagnoses among women with PMDD (Kim, Gyulai, Freeman, Morrison, Baldassano, & Dube, 2004), and a greater likelihood of inpatient psychiatric hospital admission (Targum, Caputo, & Ball, 1991) and suicidal intent during the premenstrual phase (Logue & Moos, 1986), especially among individuals with PMDD (Wittchen et al., 2002). Lifetime prevalence of mood and anxiety disorders is higher among women with retrospectively assessed PMDD (Merikangas, Foeldenyi, & Angst, 1993) or with reported premenstrual complaints and prospectively confirmed PMDD as compared to healthy controls and community samples (Harrison, Endicott, Nee, Glick, & Rabkin, 1989; Pearlstein et al., 1990). Current comorbid diagnoses of major depression and anxiety are also more prevalent among women with PMDD as compared to controls [see Kim, Gyulai, Freeman, Morrison, Baldassano, & Dube (2004) for a review]. In Kim and colleagues (2004) review of the PMDD literature, reported current comorbid prevalence rates among women with PMDD were 12–25% for Major Depression, 25% for PD, 19–23% for Social Phobia, 11–13% for Obsessive-Compulsive Disorder, and 4–38% for Generalized Anxiety

Disorder. It should be noted, however, that ability to understand comorbidity between PMDD and other Axis-I disorders is limited due to the fact that many PMDD studies exclude women with concurrent Axis-I diagnoses, including some included in the Kim et al. (2004) review described above. Among women seeking treatment for PMS symptoms, 23% met criteria for a mood disorder, 7% met criteria for an anxiety disorder, and 8% met criteria for both (Bailey & Cohen, 1999). In this same study, the most common diagnoses were Dysthymia, Depression, and PD, respectively (Bailey & Cohen, 1999).

Studies have also found premenstrual exacerbation of symptoms in the context of other psychiatric disorders, particularly in women with depression and anxiety disorders. Specifically, 64% of women seeking treatment for depression reported a premenstrual exacerbation of symptoms and experienced longer depressive episodes ($M = 30.7$ months) as compared to women who did not report premenstrual exacerbation of symptoms ($M = 13.5$ months; Kornstein et al., 2008). In a study examining symptom history of individuals with agoraphobia and unexpected panic attacks, 51% of women reported experiencing increased anxiety symptoms and 33% reported increased frequency of panic attacks premenstrually (Breier, Charney, & Heninger, 1986). Similarly, 79% of women with PD reported that they experienced an exacerbation of anxiety premenstrually (Cook, Noyes, Garvey, Beach, Sobotka, & Chaudhry, 1990). Women with PD, who completed prospective daily diaries across two menstrual cycles, reported an exacerbation of anxiety and panic attacks during their premenstrual phase (Kaspi, Otto, Pollack, Eppinger, & Rosenbaum, 1994). In a different study, however, only women with PMS exhibited a premenstrual worsening of reported anxiety symptoms, and no menstrual cycle phase (late luteal vs. follicular) differences in anxiety ratings and panic attack frequency assessed daily across two menstrual cycles were found in women with PD or in controls (Stein, Schmidt, Rubinow, & Uhde, 1989). In a study examining suicidality in PD, women with PD who subjectively and retrospectively reported a premenstrual worsening of panic attack frequency and severity were more likely to have higher active suicidality scores as measured by the Schedule for Affective Disorders and Schizophrenia suicide subscale as compared to women with PD who did not report premenstrual worsening of symptoms (Basoglu, Cetin, Semiz, Agargun, & Abrinc, 2000). Similarly, premenstrual exacerbation of psychiatric symptoms have been reported in Bulimia (Gladis & Walsh, 1987), Obsessive-Compulsive Disorder (Labad, Menchon, Alonso, Segalas, Jimenez, & Vallejo, 2005), and Generalized Social Anxiety Disorder (Van Veen, Jonker, Van Vliet, & Zitman, 2009). Associations between medical disorders and the menstrual cycle have also been made, such as premenstrual exacerbations of symptoms in catamenial epilepsy, asthma, irritable bowel syndrome, and diabetes (see Case & Reid, 1998 for a review).

Although the etiology of PMDD is still unclear, there is some evidence to suggest that psychosocial stressors such as socioeconomic status, marital status, stressful life events, and perceived stress are related to PMDD. Married women were less likely to experience premenstrual symptoms as compared to single, separated, or divorced women (Logue & Moos, 1986). Similarly, socioeconomic status was related to premenstrual and menstrual symptom reporting, whereby women with greater income reported fewer premenstrual and menstrual symptoms (Logue & Moos, 1986). In a prospective study of women with varying levels of premenstrual symptoms, global perceived stress, averaged across the 5 days prior to menses, predicted premenstrual symptoms (Woods et al., 1998). Additionally, premenstrual symptoms also predicted perceived stress (Woods et al., 1998), suggesting a reciprocal relationship between stress and premenstrual symptoms. A prospective study of risk factors in a community sample of women not meeting full clinical diagnostic criteria for PMDD at baseline demonstrated that subthreshold PMDD diagnosis at baseline ($OR = 12.9$), experiencing a traumatic event ($OR = 3.6$), having an anxiety disorder at baseline ($OR = 3.4$), negative life events ($OR = 1.3$), and daily hassles ($OR = 1.7$) predicted increased risk

for meeting diagnostic criteria for PMDD at a followup 42 months later (Perkonig, Yonkers, Pfister, Lieb, & Wittchen, 2004). Additionally, traumatic events continued to increase the risk for a PMDD diagnosis at followup, even after controlling for subthreshold PMDD and anxiety disorder diagnosis at baseline and daily hassles (Perkonig et al., 2004), suggesting that stress may be an important factor in the etiology of PMDD. Taken together, these studies provide some evidence that external stressors play a role in the etiology of PMDD.

In summary, the majority of women report experiencing physical and psychological changes during the premenstrual phase associated with some degree of impairment and decreased health outcomes. Among these women, 13–19% report clinically significant PMS and 3–8% meet strict DSM-IV criteria for PMDD. Additionally, lifetime and current comorbid depression and anxiety diagnoses as well as premenstrual exacerbation of symptoms among women with depression and anxiety are common, suggesting that the changes in the premenstrual phase have a significant impact on the mental health of a large percentage of women. Lastly, chronic psychosocial stressors may interact with ovarian hormone changes to predict as well as exacerbate clinical levels of premenstrual symptoms.

4. Cognitive vulnerability to anxiety

Anxiety sensitivity (AS) is the tendency to respond fearfully to the occurrence of anxiety symptoms due to beliefs that certain bodily sensations may indicate harm or illness (McNally, 2002), and is an established cognitive risk factor for the development of PD (Donnell & McNally, 1989; Maller & Reiss, 1992; McNally & Lorenz, 1987). High AS individuals hold the belief that experiencing anxiety or fear will cause severe negative consequences (i.e., heart attack); are hypervigilant to stimuli that signal anxiety (i.e., increased heart rate); worry about becoming anxious; and avoid stimuli that provoke anxiety (McNally, 2002; Reiss, Peterson, Gursky, & McNally, 1986). A meta-analytic review of AS and anxiety disorders demonstrated that AS level is greater among individuals with anxiety disorders (i.e., PD, Social Phobia, Specific Phobia, Generalized Anxiety Disorder, Obsessive-Compulsive disorder, Post Traumatic Stress Disorder, and Agoraphobia without Panic) as compared to nonclinical controls (Olatunji & Wolitzky-Taylor, 2009). However, only PD patients differed significantly from those with Major Depressive Disorder; and only PD and Posttraumatic Stress Disorder differed significantly from other anxiety disorders (Olatunji & Wolitzky-Taylor, 1999), suggesting unique features of AS in PD.

AS has been measured using the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986), the Anxiety Sensitivity Index-Revised (ASI-R; Taylor & Cox, 1998), and the Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007). Later versions of the ASI have identified three separate dimensions of anxiety-related symptoms, including physical, cognitive, and social concerns (Taylor et al., 2007), and it has recently been suggested that AS may be taxonic in nature (i.e., categorical vs. dimensional), depicting two forms of AS, pathological and normative (Bernstein et al., 2006, 2007).

Individuals with high baseline AS scores were significantly more likely to experience frequent and intense panic attacks at prospective followups over 2 and 3 years and were more likely to develop anxiety disorder diagnoses (including PD) as compared to individuals with low baseline AS, above and beyond the effect of trait anxiety (Maller & Reiss, 1992; Schmidt, Zvolensky, & Maner, 2006) and negative affectivity (Zvolensky, Kotov, Antipova, & Schmidt, 2005). Additionally, experience of panic attacks has been correlated with an increase in AS at followup, suggesting reciprocal effects of AS and panic attacks (Li & Zinbarg, 2007). Collectively, these studies support AS as a unique risk factor for the development and maintenance of panic attacks.

Prior studies also support the unique contribution of AS to biological challenge reactivity (an external stressor induced in the laboratory). Individuals scoring high on AS demonstrate increased anxiety and fear responses to hyperventilation and CO₂ challenges in comparison to individuals low on AS (Donnell & McNally, 1989; McNally, 2002), above and beyond the effects of trait anxiety and history of panic (McNally, 1990). Reactivity to a CO₂ challenge uniquely predicted onset of spontaneous panic attacks during a 24-month followup in a non-clinical sample (Schmidt & Zvolensky, 2007). Furthermore, individuals who scored high on AS and had increased reactivity to a CO₂ challenge were more likely to report experiencing a spontaneous panic attack over followup in comparison to individuals with either high AS alone or increased reactivity to a CO₂ challenge alone (Schmidt & Zvolensky, 2007).

Consistent sex differences emerge in AS scores and panic appraisal. AS is elevated among females in comparison to males in university samples (Reis & McNally, 1995; Reis, Peterson, Gursky, & McNally, 1986; Stewart, Taylor, & Baker, 1997). Among patients with PD, females report higher AS, in general (Schmidt & Koselka, 2000), and score higher on the physical concerns subscale of the ASI as compared to men (Foot & Koszycki, 2004; Schmidt & Koselka, 2000). On a measure assessing panic appraisal, women with PD believed more strongly that experiencing a panic attack would lead to negative, physical, and loss of control consequences and estimated a higher likelihood of panic attack occurrence as compared to men (Schmidt & Koselka, 2000). Sex differences also emerge in psychological responses to a CO₂ challenge. In a non-clinical sample, women reported increased fear and panic symptoms in response to a CO₂ challenge and took longer to recover from negative emotions induced by the challenge as compared to men (Kelly, Forsyth, & Karekla, 2006). However, there were no sex differences in psychophysiological reactions to the challenge (e.g., skin conductance level and response, heart rate, frontalis EMG; Kelly et al., 2006).

To summarize, AS is an established risk factor for the development of anxiety disorders and panic attacks; and high AS is associated with increased panic-relevant responding to an external stressor (e.g., CO₂ challenge). Additionally, AS is a risk factor that is more pertinent to women than to men and plays an important role in the etiology and maintenance of anxiety and panic.

5. Menstrual cycle phase, external stressors, and anxiety among women

A small literature has examined the interaction between the menstrual cycle and an external stressor on anxiety response among normal individuals, individuals at risk for anxiety (e.g., high AS), and individuals with current clinical anxiety or PMDD. Normal females reported increased anxiety in response to a CO₂ challenge during the premenstrual phase as compared to the postmenstrual phase¹ (Fishman, Carr, Becket, & Rosenbaum, 1994). Sigmon, Fink, Rohan, and Hotovy (1996) conducted the first test of the interaction between AS (high vs. low) and menstrual phase [(premenstrual vs. intermenstrual (Days 8–22)] on psychophysiological reactivity to anxiety-provoking stimuli using a cross-sectional design. Women high and low on AS listened to descriptions of neutral and anxiety-provoking scenarios during either the premenstrual or intermenstrual phase of their cycles while psychophysiological data were recorded. High AS women measured in their premenstrual phase displayed greater skin conductance response frequency and magnitude in response to the anxiety scenes in comparison to high AS women assessed in the intermenstrual phase and low AS women assessed in either cycle phase, above and beyond the effects of baseline state anxiety and panic history (Sigmon et al., 1996). Although these results suggest

¹Fishman et al., (1994) did not specify whether the “postmenstrual phase” session occurred during the follicular or luteal phase.

preliminary support for an interaction between AS and menstrual cycle phase on psychophysiological responding to anxiety-provoking stimuli, this study is limited by its cross-sectional design. In a similar study, using a longitudinal design, women with PD exhibited greater skin conductance response magnitude while listening to anxiety-provoking scenes in comparison to controls when measured in the premenstrual phase, but not when the same women were assessed in the intermenstrual phase (Sigmon et al., 2000). In both Sigmon studies described above (Sigmon et al., 1996, 2000), baseline physiological arousal (i.e., skin conductance level averaged across a 5-minute baseline period) did not differ between women with and without PD or between women high and low on AS in either phase. These results suggest that autonomic reactivity to anxiety-provoking stimuli may be exacerbated premenstrually whereas general autonomic arousal may not fluctuate across the menstrual cycle.

In a small study of PD patients vs. controls, significant differences emerged across the menstrual cycle in response to a 35% CO₂ challenge. Women with PD, but not controls, had greater panic symptoms and higher self-reported anxiety in response to the challenge during the menstrual phase (Day 4) in comparison to the midluteal phase (Day 20; Perna, Brambilla, Aranio, & Bellodi, 1995). It is possible that the rapid decrease in progesterone in the premenstrual phase may prolong the sensitive period into the menstrual phase, or that the anxiolytic effects of progesterone and its metabolites following their increase in the luteal phase may serve as a protective factor.

PMDD patients display similar rates of panic compared to PD patients in biological challenge research, suggesting a shared pathophysiological or psychobiological process (see Vickers & McNally (2004) for a review). A greater proportion of women with PMDD experience a panic attack during a CO₂ challenge as compared to controls (Harrison et al., 1989b; Kent, Papp, Martinex, Browne, Coplan, Klein, & Gorman, 2001), regardless of cycle phase (Harrison et al., 1989b). Women with PMDD and women with PD experience comparable and elevated rates of actual panic attacks during CO₂ challenge relative to controls (Kent et al., 2001). Other panic provocation studies have demonstrated that women with premenstrual symptoms and women with PMDD experience increased rates of panic attacks following sodium lactate infusion as compared to controls (Facchinetti, Romano, Fava, & Genazzi, 1992; Sandberg, Endicott, Harrison, Nee, & Gorman, 1993). Although the exact link between these two disorders is unknown, ovarian hormonal changes (e.g., progesterone) and psychological vulnerability factors (e.g., AS) have been proposed (Vickers & McNally, 2004).

Thus, preliminary research suggests that healthy individuals, individuals at risk for clinical anxiety (i.e., high AS), and individuals with PD respond to an external stressor differently depending on what phase of the menstrual cycle they are currently in across between- and within-subjects study designs. Specifically, during the premenstrual phase (when progesterone is on its decline) and during the menstrual phase (soon after progesterone's decline), women exhibit greater anxiety in response to an external stressor. Additionally, women with premenstrual symptoms or PMDD experience panic attacks more frequently in response to an external stressor as compared to women without premenstrual symptoms.

6. Progesterone, allopregnanolone (3 α 5 α -THP), and the GABA_A receptor in animal models

Ovarian hormones and their metabolites have been shown to influence GABA_A receptor expression and, subsequently, anxiety behavior. The GABA_A receptor is essentially a group of five protein subunits (a pentomere) joined together to form a neuronal membrane ion channel that, when activated, opens to allow the negatively charged ion chloride (Cl⁻) to

enter the neuron and decrease the chance that an axon potential will occur. GABA receptors constitute the major inhibitory influence in the central nervous system. The GABA_A receptor has numerous protein subunits (designated α , β , γ , δ , ϵ , π , and θ), of which various combinations can join to form the pentomeric receptor. However, the GABA_A receptor always contains α and β subunits. Some of these subunits (α , β , and γ) have several isoforms; and slight changes in the amino acid makeup and, consequently, the shape and binding properties between individual subunit isoforms, determine the receptor's affinity for neurotransmitter, steroids, or drugs as well as the chance of ion channel opening and Cl⁻ conductance. Thus, changing from one of these isoforms to another can have a major effect on inhibitory tone. For example, decreased expression of the $\alpha 1$ subunit and increased expression of the $\alpha 4$ subunit reduce the response of the GABA_A receptor to diazepam (Follesa et al., 2000).

Allopregnanolone, or 3 α 5 α -tetra-hydro-progesterone (THP), is a neuroactive metabolite of progesterone that has been shown to be a potent positive modulator of GABA_A receptors, particularly at GABA_A receptors expressing the δ and α subunits. As such, this metabolite has the potential to change the dynamics of the major inhibitory neurotransmitter in the brain and, thus, to profoundly affect anxiety and other emotional behaviors. Because THP binds to and increases the activity of the GABA_A receptor and, therefore, enhances inhibition in brain regions, including limbic areas involved in emotional control, exposure to THP in the short term tends to have an anxiolytic effect in animal models (e.g., Frye & Walf, 2004). However, rapid withdrawal of THP induces particular subunit changes within the GABA_A receptor, which consequently make the receptor less sensitive to THP as well as anxiolytic drugs like benzodiazapines, leading to reduced limbic inhibition and consequently increased anxiety-like behavior (Follesa et al., 2000; Frye & Walf, 2002; Gulinello, Gong, Li, & Smith, 2001; Shen, Gong, Yuan, & Smith, 2005; Staley & Proctor, 1999; Stell, Brickley, Yang, Farrant, & Mody, 2003). Given that THP is a rapidly formed metabolite of progesterone, the amount circulating is contingent on the amount of circulating progesterone. Therefore, THP peaks during the luteal phase and rapidly declines at the end of the luteal phase and at the beginning of menstruation. This may underlie the onset of premenstrual symptoms as well as anxiety responses to stressful situations during this time.

Animal models support the role of progesterone and THP in anxiety behaviors (Frye & Walf, 2002; Frye & Walf, 2004; Gulinello, Orman, & Smith, 2003; Rhodes & Frye, 2001; Smith, Ruderman, Frue, Homanic, & Yuan, 2006; Walf, Sumida, & Frye, 2006). Progesterone administration to the amygdala of ovariectomized rats produces decreased anxiety and fear behaviors (Frye & Walf, 2004; Walf et al., 2006) and decreased pain responsiveness (Frye & Walf, 2004). Administration of THP to prepubertal mice also produces decreased anxiety as measured by more time spent in the open arm entries of an elevated plus maze (Smith, Ruderman, Frye, Homanics, & Yuan, 2006).

Among female pubertal rats, THP levels are at their highest in proestrous as compared to other stages of the estrous cycle (Frye & Bayon, 1999). Proestrous female rats display more anxiolytic (i.e., more time spent on the open arm portion of the elevated plus-maze) and more antidepressant (i.e., less time spent immobile in the Porsolt swim test) behaviors as compared to diestrous female and male rats (Frye & Walf, 2002). Administration of finasteride, which disrupts the enzymatic production of THP and thus decreases THP levels, attenuates these anxiolytic and antidepressant effects such that proestrus female rats spend less time in the open field (Frye & Walf, 2002; Rhodes & Frye, 2001; Walf et al., 2006), demonstrate increased freezing in response to shock (Rhodes & Frye, 2001; Walf et al., 2006), and spend more time immobile in the swim test following finasteride administration as compared to control rats (Frye & Walf, 2002; Walf et al., 2006). Some research has suggested that the anxiolytic effect of THP becomes anxiogenic only when the THP

withdrawal is paired with an aversive stimulus (Smith et al., 2006). Female mice undergoing THP withdrawal demonstrated increased anxiety (e.g., less time spent in open arm on an elevated plus maze) as compared to vehicle-administered control mice when a shock preceded the maze test (Smith et al., 2006). Alternatively, female mice undergoing THP withdrawal, who did not receive a shock preceding the maze test, did not demonstrate any significant differences on open arm time compared with vehicle-administered control mice (Smith et al., 2006). Additionally, female rats demonstrate an increased acoustic startle response and upregulation of the GABA_A-R $\alpha 4$ subunit as compared to vehicle-administered control female rats following progesterone withdrawal, whereas progesterone withdrawal in male rats did not increase acoustic startle response or change $\alpha 4$ levels as compared to control male rats (Gulinello, Orman, & Smith, 2003), suggesting sex-dependent differences in the $\alpha 4$ subunit expression during progesterone withdrawal. 48-hour administration of THP increased both $\alpha 4$ and δ subunit expression (Shen et al., 2005). Increased expression of both of these subunits has also been noted following progesterone treatment and in progesterone and THP withdrawal (Smith, Shen, Gong, & Zhou, 2007).

In summary, rat models support the hypothesis that THP influences GABA expression, particularly at the $\alpha 4$ and δ subunits, and subsequent behavior. Specifically, acute administration of THP in rat models decreases anxiety behavior, whereas withdrawal of THP increases anxiety behavior. Recent research suggests that the anxiolytic effect of THP becomes anxiogenic only when THP withdrawal is paired with an aversive stimulus, which provides support for the model proposed in this review.

7. Progesterone, THP, PMDD symptoms, and panic disorder in human females

Evidence on the relationship between progesterone levels and premenstrual symptoms has been inconsistent. Even though progesterone changes, particularly in the premenstrual phase, are hypothesized to underlie premenstrual symptoms, many studies examining hormone levels and daily symptom reports across the menstrual cycle found no relationship between progesterone level and premenstrual symptoms (Backstrom et al., 1983; Rubinow et al., 1988; Schmidt et al., 1991). These negative findings may result from methodological issues related to timing. For example, some studies have observed a relationship between progesterone levels and symptom scores time lagged 4–7 days throughout the menstrual cycle (Halbreich et al., 1986; Redei and Freeman, 1995), suggesting that hormonal changes occurring prior to the premenstrual phase may influence premenstrual symptom changes. In a study of women with PMS, assessed daily across two menstrual cycles, cycles with higher levels of THP in the luteal phase (14 days prior to menstruation) were associated with decreased irritability and increased ratings of cheerfulness, well-being, and energy as compared to cycles with lower levels of THP within the same woman (Wang, Seippel, Purdy, & Backstrom, 1996), providing support for the anxiolytic effects of THP. Another prospective longitudinal study of women with PMS demonstrated that progesterone levels were significantly lower in both the follicular and luteal phases as compared to controls and that THP was lower in the luteal phase for women with PMS vs. controls (Monteleone et al., 2000), suggesting that women with PMS may have an insufficient production of THP. However, increased THP levels have been shown to covary with symptom severity in women with PMS or PMDD (Backstrom et al., 2003). Specifically, symptoms of irritability and depression rise as THP levels rise following ovulation among women with PMDD with the greatest symptom severity occurring 5 days prior to the onset of menses (Backstrom et al., 2003), suggesting that among women with PMDD, the decline of THP during the premenstrual phase alone does not explain all premenstrual symptoms. It should be noted, however, that studies examining differences in THP levels between women with PMDD versus controls have been mixed (Andreen et al., 2009); and, it is difficult to draw a fixed

conclusion about the role of THP in PMDD other than to conclude that changes in THP over the menstrual cycle occur in PMDD. Perhaps a dysregulation of progesterone and/or THP rather than a net increase or decrease in absolute levels of THP is involved in the etiology of these disorders. In concordance with this, it has been suggested that differences in sensitivity to GABA_A receptor modulators (e.g., THP, benzodiazepines, alcohol) may differentiate women with PMDD from controls rather than differences in THP itself (Kask, Gulinello, Backstrom, Geyer, & Sundstrom-Poromaa, 2008). For example, women with PMDD demonstrated altered acute saccadic eye movement sensitivity in response to an alcohol infusion (e.g., a GABA_A receptor modulator) during the late luteal as compared to the follicular phase, whereas control women showed no differences between phases (Nyberg, Wahlstrom, Backstrom, & Poromaa, 2004).

Differences in progesterone and THP levels have been observed among women with PD across different phases of the menstrual cycle and among women with premenstrual symptoms or PMDD. Women with PD and agoraphobia demonstrated higher levels of progesterone in the mid-luteal phase (Day 22) and increased levels of THP during the follicular phase (Day 7) as compared to controls (Brambilla et al., 2003), which would indicate a negative rather than a positive influence of progesterone and THP in PD. However, severity of reported phobic symptoms improved from the follicular phase to the mid-luteal phase, which the authors posit may be related to the increase in progesterone and its metabolites following ovulation (Brambilla et al., 2003). This suggests there may be an insensitivity to elevated levels of progesterone and THP in PD that can be somewhat ameliorated by further increases following ovulation. THP levels decreased during panic attacks induced by sodium lactate and cholecystokinin tetrapeptide administrations (i.e., external biological stressors) among women with PD as compared to controls; however, there were no differences in THP levels between PD patients and controls following placebo administration (Strohle et al., 2003), suggesting that changes in neuroactive steroids may be involved in the pathophysiology of panic attacks among patients with PD.

In conclusion, although few studies have been completed to date, there is some evidence that progesterone and THP influence premenstrual symptoms among women with PMS or PMDD as well as the pathophysiology of panic attacks among women with PD; however, the mechanisms are not well understood. It may be that sensitivity to GABA_A receptors may be involved in menstrual cycle related changes in affect rather than hormone levels. Therefore, the model proposed in this review may serve only as a starting point for further exploration.

8. Conclusions and future directions

The 2:1 female-to-male sex difference in the prevalence of PD (McLean & Anderson, 2009) suggests that there is a sex-specific vulnerability involved in the etiology and/or maintenance of this disorder. This review began with a theoretical model to understand this sex-specific vulnerability. The model posits that anxiety sensitivity (AS), a cognitive vulnerability for PD (e.g., Schmidt & Zvolensky, 2007), interacts with ovarian hormonal changes that occur during the premenstrual phase of the menstrual cycle, which affects behavioral and physiological responses to stress, subsequently initiating or maintaining clinical panic and/or anxiety. Incorporation of an external stressor in this model pertains to evidence from both the animal (e.g., Smith et al., 2006) and human (e.g., Sigmon et al., 1996) literatures that an external anxiety-provoking stressor may be necessary to elicit increased anxiety premenstrually. High AS alone increases the risk for panic attacks and panic disorder (e.g., Schmidt et al., 2005) and, therefore, serves as an underlying vulnerability for potential future anxiety problems. Given that the premenstrual phase involves psychological and physical changes, high AS women may be more likely to

misinterpret these bodily sensations as dangerous, which primes them to be more reactive to external stressors and could (1) initiate the initial and subsequent uncued panic attack when under stress and (2) serve as a maintenance factor in PD.

Allopregnanolone or THP, a neuroactive metabolite of progesterone, rises and falls with progesterone levels during the menstrual cycle, with the sharpest rate of decline occurring during the premenstrual phase. THP is a potent positive modulator of GABA_A receptors, particularly at the δ and $\alpha 4$ subunits; and rat models have consistently demonstrated that THP changes influence anxiety behavior. Specifically, short-term exposure to THP has anxiolytic effects whereas rapid withdrawal (such as what is experienced during the premenstrual phase) induces particular subunit changes in the GABA_A receptor, which make it less effective and increase anxiety behaviors (Frye & Walf, 2002; Frye & Walf, 2004; Gulinello et al., 2003; Rhodes & Frye, 2001; Walf et al., 2006). Recent research provides initial support for part of the model proposed in this review. Specifically, female mice undergoing THP withdrawal paired with an aversive stimulus exhibited increased anxiety as compared to control mice; in contrast, female mice undergoing THP withdrawal without an aversive stimulus did not display any significant differences in anxiety behavior as compared to control mice (Smith et al., 2006).

The link between PD and PMDD also provides some initial support for the model proposed in this review. The premenstrual phase has been associated with a variety of physical and psychological changes that affect the majority of women, although only a minority (3–8%) meet strict DSM-IV criteria for PMDD (Halbreich et al., 2003). Although the etiology of PMDD is not entirely clear, psychosocial stressors such as perceived stress and traumatic events have been shown to predict a diagnosis of PMDD in longitudinal studies (Perkonig et al., 2004; Woods et al., 1998). Premenstrual exacerbation of panic and anxiety has been reported among women with PD (Breier et al., 1986; Cook et al., 1990; Kaspi et al., 1994), although the literature on this has been mixed (Stein et al., 1989). In addition, individuals with PMDD evidence similar rates of panic as compared to PD patients during a CO₂ challenge (Vickers & McNally, 2004). Although the exact link between these two disorders is unclear, AS and progesterone level changes have been proposed (Vickers & McNally, 2004).

The closest test to the proposed model thus far examined the interaction between AS (high vs. low) and menstrual cycle phase [intermenstrual (Days 8–22) vs. premenstrual] in response to a stressor induced in the laboratory (e.g., listening to anxiety provoking scenes). Women high on AS measured in their premenstrual phase displayed greater SCR frequency and magnitude in response to listening to anxiety scenes as compared to women high on AS assessed in the intermenstrual phase and low AS women assessed in either cycle phase (Sigmon et al., 1996). Other studies examining women with PD across different phases of the menstrual cycle in response to an external stressor have been consistent with the above pattern of findings (Perna et al., 1995; Sigmon et al., 2000). These studies, although consistent with the proposed model, are lacking a test of the proposed interaction between AS and progesterone/THP.

Understanding risk factors for anxiety specific to women would increase interventions focused on prevention. Specifically, prevention efforts targeting women at risk (high AS) could provide psychoeducation surrounding normal physical and psychological changes that occur in the premenstrual phase. Additionally, women who present with anxiety and panic complaints could be assessed for menstrual cycle fluctuations in the clinic in order to effectively tailor intervention strategies. Specifically, women who have premenstrual exacerbations in panic symptoms may benefit from an intensification of treatment during the premenstrual phase. For example, in panic control treatment (PCT; Craske & Barlow, 2008),

an empirically-supported cognitive-behavioral psychotherapy for PD, the frequency of interoceptive exposures to panic-relevant body sensations could be increased during the premenstrual phase and/or exposures to premenstrual-specific body sensations could be developed and added to the protocol.

Future research testing the proposed model would offer much insight into the etiology and maintenance of panic and anxiety for women. To our knowledge, no study has cumulatively looked at the interaction between AS and THP in response to a stressor longitudinally and in the prediction of clinical levels of anxiety. Additionally, examining differences in the rate of decline of progesterone and THP within this model is an important factor to explore.

Research Highlights

1. The premenstrual phase is associated with increased negative psychological symptoms.
2. Allopregnanolone, a neuroactive metabolite of progesterone, is a modulator of GABA_A receptors.
3. Allopregnanolone withdrawal paired with an aversive stimulus increases anxiety behaviors in mice.
4. Menstrual cycle phase may influence reactivity to an external stressor in women.
5. Anxiety sensitivity, ovarian hormonal changes, and stressors may interact to initiate/maintain clinical anxiety.

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Figure 1.
Proposed conceptual model

Figure 2.
Ovarian hormone fluctuations across the human menstrual cycle