



Histories of major depression and premenstrual dysphoric disorder: Evidence for phenotypic differences

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ABSTRACT

This study examined unique versus shared stress and pain-related phenotypes associated with premenstrual dysphoric disorder (PMDD) and prior major depressive disorder (MDD). Sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA)-axis measures were assessed at rest and during mental stress, as well as sensitivity to cold pressor and tourniquet ischemic pain tasks in four groups of women: (1) non-PMDD with no prior MDD ($N = 18$); (2) non-PMDD with prior MDD ($N = 9$); (3) PMDD with no prior MDD ($N = 17$); (4) PMDD with prior MDD ($N = 10$). PMDD women showed blunted SNS responses to stress compared to non-PMDD women, irrespective of prior MDD; while women with prior MDD showed exaggerated diastolic blood pressure responses to stress versus never depressed women, irrespective of PMDD. However, only in women with histories of MDD did PMDD women have lower cortisol concentrations than non-PMDD women, and only in non-PMDD women was MDD associated with reduced cold pressor pain sensitivity. These results suggest both unique phenotypic differences between women with PMDD and those with a history of MDD, but also indicate that histories of MDD may have special relevance for PMDD.

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1. Introduction

Mood disorders are highly prevalent in women throughout their lifetime (Pearlstein et al., 1997), being about twice as prevalent in women than men (Alexander et al., 2007; Halbreich and Kahn, 2001; Kessler et al., 1994; Pearlstein et al., 1997). One such mood disorder that affects females exclusively is premenstrual dysphoric disorder (PMDD). This disorder is characterized by premenstrual emotional and physical symptoms severe enough to interfere with function during the last week of the luteal phase of the menstrual cycle, but remit with the onset of menses. PMDD afflicts 5–7% of women in their reproductive years (Pearlstein and Steiner, 2008), and although the symptoms of PMDD are of shorter duration than those of other depressive disorders, the impact of PMDD symptoms on quality of life during the premenstrual luteal phase is equivalent to that seen with major depressive disorder (MDD), posttraumatic stress disorder, and panic disorder (Freeman and Sondheimer, 2003).

The underlying pathophysiologic mechanisms contributing to PMDD remain elusive. The lack of a consensus on the biological basis of PMDD and the lack of efficacy of selective serotonin reuptake inhibitors in up to 40% of PMDD women (Halbreich et al.,

2006; Steiner and Soares, 2008) speaks to the heterogeneity of PMDD and suggests that there may be clinically distinct subgroups of PMDD women with differing pathogeneses (Klatzkin et al., 2006a,b).

One such subgroup of PMDD women may be those with a history of MDD. A history of MDD has been reported in 30–70% of women with PMDD (Cohen et al., 2002; Pearlstein et al., 1990; Yonkers, 1997). Not only are PMDD women more likely to have experienced a prior episode of MDD (Harrison et al., 1989; Pearlstein et al., 1990), but they are also more likely to develop a future episode of MDD than are non-PMDD women (Hartlage et al., 2001; Roca et al., 1999). The high comorbidity of PMDD with histories of MDD has fueled debates in the literature regarding the nosology of the two disorders. For example, it has been suggested that (1) MDD may play a role in the etiology of PMDD (Kendler et al., 1998); (2) PMDD is in fact a distinct entity when compared to other depressive disorders such as MDD (Endicott et al., 1999); and (3) a history of MDD may have special biological relevance for PMDD symptomatology and responses to stress (Klatzkin et al., 2006b). Studies aimed at addressing the phenotypic similarities and differences seen in women with PMDD relative to women with histories of MDD may shed light on the extent of overlap in pathogenic pathways and, consequently, inform treatment for a large proportion of women with PMDD who are otherwise nonresponsive to current FDA-approved treatments (Halbreich, 2008).

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Since both PMDD and depressive disorders are associated with increased daily stress (Girdler et al., 1993, 1998), and are exacerbated by stressful life events (Kendler et al., 2004; Paddison et al., 1990), a pathogenic role of stress-responsive dysregulation has been implicated in both disorders (Cohen et al., 2002; Endicott, 1993; Harrison et al., 1989; Kendler et al., 1998; Pearlstein et al., 1990; Yonkers, 1997). Experimental studies examining stress responses in PMDD women have been scant, and results mixed. However, when considered together, the majority of evidence points toward decreased activation of the hypothalamic–pituitary–adrenal (HPA) and the sympathetic nervous system (SNS) axes in PMDD women relative to non-PMDD controls. For example, in both the follicular and luteal phases of the menstrual cycle, PMDD women show blunted heart rate (HR), blood pressure (BP), and cardiac output reactivity to a variety of laboratory psychological stressors relative to non-PMDD women (Girdler et al., 1993), suggesting blunted SNS activation to stressors. Similarly, PMDD women exhibit lower baseline and stress-induced β -endorphin levels (Chuong et al., 1985; Facchinetti et al., 1994; Giannini et al., 1990; Straneva et al., 2002), blunted adrenocorticotrophic hormone (ACTH) and cortisol responses to serotonergic challenges (Bancroft et al., 1991; Su et al., 1997), and lower cortisol levels during mental stress (Girdler et al., 1998), suggesting blunted HPA-axis activation.

That PMDD and MDD represent two distinctly different depressive disorders is supported by evidence suggesting differential dysregulation in the stress axes in women with PMDD versus women with current or prior depressive disorders. In contrast to the profile seen in PMDD, the overwhelming evidence in patients with current depression is for a hyperactive HPA-axis reflected in heightened baseline levels of corticotrophin releasing hormone (CRH), cortisol, β -endorphin, and ACTH (Carroll et al., 2007; Catalan et al., 1998; Galard et al., 2002; Gold et al., 1986a,b, 2005; Goodwin et al., 1993; Gotthardt et al., 1995; Heuser et al., 1996; Juruena et al., 2006; Krittayaphong et al., 1996; Wong et al., 2000; Young et al., 2001, 2000b). Upregulation of the SNS is also present in patients with current depression, reflected in increased baseline and stress-induced norepinephrine (NE), SBP, and HR compared to controls (Carney et al., 1999, 1988; Gold et al., 2005; Hamer et al., 2007; Lake et al., 1982; Lechin et al., 1995; Udupa et al., 2007; Veith et al., 1994; Volkens et al., 2003; Wong et al., 2000). With regard to SNS and HPA-axis functioning in euthymic individuals with a history of MDD, most studies, though not all (Ahrens et al., 2008), report hyperactivity of both stress axes (Broadley et al., 2005; Davydov et al., 2007; Kathol, 1985; Young et al., 2000a), indicating persistent dysregulation beyond the remission of the depressive disorder.

Another clinically significant aspect of both PMDD and MDD that may have relevance for the nosology of these mood disorders are the physical, or somatic symptoms that are common to both. Somatic symptoms such as breast tenderness, bloating, and joint or muscle pain are important features of PMDD and MDD and contribute to overall dysfunction (Steiner et al., 2001). Although laboratory-based methods of assessing pain sensitivity are positively related to clinical pain (Edwards and Fillingim, 1999; Fillingim et al., 1999), there are few studies assessing pain sensitivity in PMDD (Fillingim et al., 1995; Kuczmierczyk and Adams, 1986; Kuczmierczyk et al., 1986; Straneva et al., 2002) and MDD patients (Klauenberg et al., 2008; Bar et al., 2005, 2006; Dickens et al., 2003; Lautenbacher et al., 1994, 1999; Schwier et al., 2009; Terhaar et al., 2009).

Prior studies from our laboratory have shown that women with PMDD exhibit lower ischemic pain threshold and tolerance compared with controls in both the follicular and luteal phases of the menstrual cycle (Fillingim et al., 1995; Straneva et al., 2002), and others have shown that PMDD women endorse higher pain

intensity ratings in response to pressure pain irrespective of menstrual cycle phase (Kuczmierczyk and Adams, 1986; Kuczmierczyk et al., 1986). These results, taken together, suggest that PMDD is associated with enhanced pain sensitivity. In contrast, a systematic review and meta-analysis of the literature in MDD concluded that pain threshold was higher in individuals with current MDD compared to healthy controls (Dickens et al., 2003). More recent studies have assessed both threshold and tolerance to multiple experimental pain stimuli in depressed patients, and although findings have been mixed, taken together they indicate reduced sensitivity to experimental pain in MDD (Bar et al., 2005, 2006; Klauenberg et al., 2008; Lautenbacher et al., 1994, 1999; Schwier et al., 2009; Sindrup and Jensen, 1999; Terhaar et al., 2009). To the extent that pain sensitivity is modulated by stress-responsive systems (e.g. stress-induced analgesia) (al'Absi et al., 2002; Girdler et al., 2005; Maixner, 1991; Mechlin et al., 2005), diagnosis-related differences in stress responses may play a role in the experience of pain in both PMDD and MDD patients.

Consequently, the primary purpose of the current study was to examine evidence for common versus different phenotypic profiles related to SNS, HPA-axis and pain measures in women with PMDD and women with histories of MDD, and whether a history of MDD holds special relevance for PMDD women with respect to stress and pain profiles. Although a diagnosis of current MDD may be superimposed on the diagnosis of PMDD (American Psychiatric Association [DSM-IV], 1994), this comorbidity is less common than is a history of MDD in PMDD samples. Hence, our focus was on histories of MDD, and not current MDD in women with PMDD. While the present investigation is exploratory in nature, it is the first, to our knowledge, to approach this issue experimentally with the inclusion of four groups of women: (1) PMDD women with histories of MDD; (2) PMDD women with no history of MDD; (3) non-PMDD women with histories of MDD; and (4) non-PMDD women with no history of MDD. Diagnosis-related differences in phenotypes would be supported by statistical main effects of prior MDD or PMDD in the absence of PMDD \times Prior MDD interactions. On the other hand, if histories of MDD hold special relevance for the SNS, HPA-axis, and/or pain sensitivity measures in PMDD women (or if the effects of PMDD and prior MDD were additive), then we would anticipate PMDD \times Prior MDD interactions in these measures.

2. Methods

2.1. Participants

The sample of 54 women (19–51 years of age) who comprise this report represent a sub-sample of participants recruited for a larger, ongoing investigation. The participants in this substudy were specifically recruited via newspaper, radio, or posted advertisements to examine the influence of histories of MDD and PMDD diagnosis on pain sensitivity and stress responses. While it was not necessary to engage in selective recruitment efforts targeting PMDD women with histories of MDD, in order to recruit non-PMDD controls with prior MDD, a proportion of our advertisements targeted women with a prior major depressive episode. Since the ongoing parent project is not focused on histories of MDD, the participants comprising this report represent the final sample of participants for the substudy related to PMDD and histories of MDD and are composed of four groups: (1) non-PMDD women with no prior MDD ($N = 18$); (2) non-PMDD women with prior MDD ($N = 9$); (3) PMDD women with no prior MDD ($N = 17$); (4) PMDD women with prior MDD ($N = 10$).

Participants with a current Axis I psychiatric disorder were excluded (based on interview, see below) but referred for treatment. Also excluded was any woman who was pregnant or breastfeeding, had irregular menstrual cycles, was taking prescription medication (including oral contraceptives and psychotropics), had a cardiovascular disorder, a history of or a current chronic or acute pain condition, an endocrine disorder including diabetes or thyroid disorder, or other chronic medical illness. A diagnosis of MDD was based on a structured clinical interview (see below) with the requirement of one year in full remission. Participants in the prior MDD group were required to have had at least one prior episode of MDD, though they may also have had histories of minor depression, dysthymia, or adjustment disorder with depressed mood. The never depressed groups were free of any lifetime depressive illness, including minor depression and adjustment disorder. The protocol was approved by the Institution's Institutional Review Board, and all

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