Review

Gonadal steroid regulation of mood: The lessons of premenstrual syndrome ♠

David R. Rubinow *, Peter J. Schmidt

Behavioral Endocrinology Branch, National Institute of Mental Health, National Institutes of Health,
Department of Health and Human Services, Bethesda, MD 20892-1276, USA

Available online 2 May 2006

Abstract

New models for menstrual cycle-related mood disorders provide unique opportunities to gain insight into the processing of emotional information and the regulation of mood state by reproductive steroids. This paper reviews the role of reproductive steroids in affect regulation and in premenstrual dysphoric disorder (PMD), parses PMD into component processes that suggest potential mediating neurocircuitry, and highlights the importance of and potential contributors to the differential sensitivity that permits reproductive steroids to destabilize mood in some but not all women.

Keywords: Gonadal steroids; Mood; Depression; Hormones; Neurocircuitry; Emotion; PMS; Menstrual cycle; Cognition

1. Introduction

Menstrual cycle-related mood disorder—referred to in the literature as severe premenstrual syndrome, premenstrual dysphoria or premenstrual dysphoric disorder (PMD) (as it will be referred to in this paper)—represents an affective syndrome the appearance of which is confined to the luteal phase of the menstrual cycle and the symptoms of which are sufficiently severe to interfere with normal life activities. Unlike many disorders in medicine, the diagnosis is based less on the symptoms, which are non-specific, and more on the timing of the symptoms (in relation to the menstrual cycle); and it is the timing of symptoms that makes them so interesting and the subject, over the years, of great speculation. Since the menstrual cycle is a hormonal cycle reflecting endocrine activity at the hypothalamus, pituitary, and ovary, it was presumed that the symptoms of PMD must result from abnormal levels of some ovarian or menstrual cycle-dependent factor, much in the way that depression may result from other endocrinopathies like thyroid or pituitary adrenal dysfunction. Studies conducted, however, have overwhelmingly refuted the presumption that gonadal steroid levels are abnormal in women with PMD. PMD, nonetheless, has a tremendous amount to teach us about the role of hormones in affective dysregulation, but only if we abandon simple cause-and-effect, hormone deficiency-based models of behavioral regulation. Specifically, understanding PMD requires a model that must account for the timing of the symptoms, their emergence with time (appearing commonly in the late 20s or 30s), and their minimal expression in most women (only 5–10% of women have PMD). An attempt to model these characteristics, as follows, results in a re-conceptualization of PMD that better fits the data and that offers a teleological explanation for a syndrome that otherwise is mystifying in its appearance.

2. Why would one imagine that gonadal steroids would regulate affect?

This question is the easiest to answer, for the neuroregulatory effects of gonadal steroids are myriad, well known, and widely appreciated. Indeed, wherever one finds a system believed to play a role in the etiology or treatment of
depression, modulatory effects of gonadal steroids are observed as well. The neurotransmitter systems implicated in depression—serotonin, norepinephrine, dopamine, acetylcholine, GABA, glutamate—all are regulated by estradiol [40,41]. Estradiol’s regulation of the serotonergic system, for example, is extensive, involving serotonin synthesis (tryptophan hydroxylase), receptors [transcripts, protein, and binding] (e.g., 5-HT1A, 2A), and transporter [58]. Additionally, estrogen increases sensitivity to dopamine and cocaine and is believed to contribute to the increased vulnerability to substance abuse in women [34,35]. Recent hypotheses about mood dysregulation center on deficits in neuroplasticity and neuronal/glial survival, with attendant observations that cell survival proteins like Bcl-2 and BDNF are low in depression [24,38]. Stress decreases BDNF in animal models [8,25], and both Bcl-2 and BDNF are increased by antidepressants and mood stabilizers [38,49,50], effects also seen after exposure to estradiol [14,72]. Cell survival is regulated by the actions of several signal transduction systems, including ERK, Akt, WNT/beta catenin. In a brain region-specific fashion, estradiol increases ERK and cell survival in neurons (although it decreases both in glia) [55,69,79,85], increases AKT and neuronal survival [33,86,88], trkA [71], phospho CREB [88], and decreases GSK-3 beta [12]. Similar effects are seen with antidepressants and mood stabilizes on ERK (increased) and GSK-3 beta (decreased) [38]. Finally, estrogen appears to play a major role in neuronal excitability, as it directly and acutely (in seconds to minutes) modulates both calcium and potassium ion channel activity [44,54,77,87].

Similarly, many areas of the brain that have been implicated in depression, including prefrontal cortex (PFC), amygdala, hippocampus, striatum, and thalamus [17,21,22,52,53,66,74], contain estrogen receptors and are modulated by estradiol [1,10,15,41]. For example, in the first demonstration of the effects of estradiol and progesterone on cerebral blood flow in humans, Berman et al. [7] showed that both estrogen and progesterone increased cerebral blood flow in the dorsal lateral prefrontal cortex, inferior parietal lobule, and posterior inferior temporal cortex compared with a hypogonadal condition produced by a gonadotropin releasing hormone agonist. Finally, the importance of gonadal steroids in affective regulation is suggested by studies demonstrating the role of estradiol in stress amplification [65,67,82], of ER beta in anxiety in female rats [37] and of ER alpha in arousal [27]. It does not require a stretch of the imagination to posit that gonadal steroids could contribute to mood regulation, but how specifically might they contribute to PMD?

3. What is the role of gonadal steroids in PMD?

3.1. Are there luteal phase-specific mood and behavioral symptoms?

Given the absence of uniform definitions of premenstrual syndrome or menstrual cycle-related mood disorders, our first efforts were of necessity methodologic and directed toward development of operational criteria that could be used to diminish the heterogeneity of the samples selected for study. We developed an operational method for confirming (or disconfirming) the presence of luteal phase-specific mood symptoms [57]. These efforts contributed to the requirements for a specified degree of increase in symptom severity in the luteal phase compared with the follicular phase (NIMH PMS workshop criteria, 1984 [51]) and for the prospective documentation of symptom changes across the menstrual cycle (NIMH criteria and DSM-III-R criteria [19] for late luteal phase dysphoric disorder). The operational definition that we proposed was subsequently confirmed by Schnurr [62] as highly concordant with the effect size method for diagnosing significant menstrual cycle phase-specific changes in affective symptomatology.

3.2. Do luteal phase-specific physiologic abnormalities accompany the luteal phase-specific mood and behavioral symptoms in women with PMS?

Once investigators could agree on methods for sample selection, they could then reasonably attempt to test hypotheses about physiological disturbances accompanying or characterizing menstrual-related mood disorders. We demonstrated [56], consistent with some earlier investigators [4], that there were no diagnosis group-related differences in gonadotropins or gonadal steroids in patients with prospectively confirmed PMS compared with controls in whom the absence of menstrual cycle-related symptoms was prospectively confirmed. Our data, therefore, failed to support hypotheses of excesses or deficiencies of gonadal steroids (either progesterone or estrogen) in PMS.

3.3. Is the luteal phase necessary for the appearance of PMS?

If there was no obvious abnormality in the activity of the reproductive axis, was PMS in fact dependent on the menstrual cycle for its expression, or could it be dissociated from the luteal phase? We blinded women to their position in the menstrual cycle by administering the progesterone receptor antagonist RU 486 (which both precipitates menses and ends corpus luteal activity), alone or with human chorionic gonadotropin (hCG) (which preserves corpus luteal activity despite the precipitation of menses) [61]. Thus, after receiving the RU 486 (six days after the LH surge), subjects did not know whether they were in the follicular phase of the next cycle (RU 486 alone) or in the preserved luteal phase of the initial cycle (RU 486 + hCG; or placebo). Subjects in all three groups experienced highly comparable symptoms that were significantly greater than those seen in the follicular phase; i.e., women receiving RU 486 alone developed characteristic symptoms of PMS in the experimentally produced follicular phase of the next cycle. PMS, therefore, was not dependent on reproductive endocrine changes occurring in the mid-late luteal phase, as
we were able to eliminate those changes without influencing subsequent symptom development. This left open the question of whether events occurring earlier than the mid-luteal phase might nonetheless be influencing subsequent symptom development.

3.4. If you suppress ovarian activity, can you prevent the symptoms of PMD?

As the RU 486 study eliminated only the mid-luteal phase, PMD symptoms might have appeared consequent to reproductive-endocrine events occurring earlier in the menstrual cycle. To test this possibility, we performed “medical oophorectomies” by administering the GnRH agonist leuprolide acetate (Depot Lupron, 3.75 mg) in a placebo-controlled parallel design study in 20 women with PMD. Lupron but not placebo was highly effective in eliminating both symptom severity and cyclicity. (10/18 women responded to Lupron and 0/10 responded to placebo [60].) This confirmed similar observations by Bancroft et al. [5] and Mortola et al. [48] and suggested that PMD was dependent upon ovarian steroid production.

3.5. In those in whom ovarian suppression effectively prevents the expression of PMD, will exogenous administration of gonadal steroids (either estrogen or progesterone) precipitate the return of characteristic symptoms?

Eighteen women whose PMD symptoms were significantly attenuated or eliminated by Lupron-induced ovarian suppression were then continued on Lupron and received in addition (in a double-blind, crossover fashion) estradiol (four weeks followed by a fifth week in combination with progesterone to promote endometrial shedding) and progesterone (four weeks). Five of these women received one additional month of placebo “addback” to control for patients’ expectations, specifically the recognition that they were taking something new. Finally, the same regimen of Lupron-induced hypogonadism followed by sequential hormone replacement was performed in 15 control women, in whom the absence of menstrual cycle-related mood disturbances was confirmed with longitudinal ratings prior to study entry. The women with MRMD whose symptoms were successfully eliminated (or attenuated) by Lupron-induced hypogonadism experienced a return of symptoms on either estradiol or progesterone but not on placebo. Characteristically, symptoms returned within two weeks of initiating hormone replacement and remitted by the 4th week of administration. In the control women lacking a history of MRMD, however, neither the hypogonadal nor the hormone replacement conditions were associated with any perturbation of mood [60]. Consistent with the findings from our basal hormone studies, then, it appears that MRMD represents an abnormal response to normal hormone changes or levels rather than a “normal” response to a hormonal abnormality.

3.6. If gonadal steroids trigger PMD in some women, why do not they in all?

In many respects, this is a question that has widespread applicability throughout medicine: what results in a different phenotypic response to a given biological stimulus? What is the context of susceptibility? Certainly the context dependency of steroid action is well established. For example, the response to steroids is developmental stage-dependent: Toran–Allerand demonstrated that the effects of estradiol on neuronal proliferation are facilitatory early in development, inhibitory during adulthood, and facilitatory again in the face of brain injury [75]; Garey et al. [27] demonstrated that the effects on locomotion of estrogen receptor beta knockout are seen in old, but not young, animals; Miranda et al. [46] observed that estradiol modulates spine density in the dentate gyrus in old but not young female rats; and Adams et al. [2] demonstrated that the effect of estradiol to increase NMDA R1 receptor density/spine appears only in older rats. The target cell of steroid action is itself a context in which the presence of tissue-specific proteins dictates the effect of the steroid-activated receptor. Shang and Brown [64], for example, have shown that the tissue specificity of the selective estrogen receptor modulator tamoxifen—estrogen agonist-like effect in the uterus and estrogen antagonism in the breast—is mediated by the differential recruitment of the co-activators or co-repressors, respectively, in those tissues. Even within the same tissues, hormone responses will differ with cell type. For example, as noted above, estradiol increases MAP kinase and cell survival in a neuronal cell line and decreases MAP kinase and cell survival in glia [79,85].

An obvious source of differences in response phenotype is found in genotypic differences. Known polymorphisms in gonadal steroid receptors have been shown to alter receptor transcriptional efficiency (e.g., CAG repeat in exon 1 of the androgen receptor; proline insertion in intron 7 of the progesterone receptor) and to be associated with differential illness risk (i.e., prostate cancer, breast cancer) [6,28,78,84]. Additionally, the susceptibility to the disruptive effects of estradiol on reproductive development differs enormously (up to 100-fold) between mouse strains, with genotype contributing more to the variance than the dose of estradiol employed [73]. There is precedent, then, for inferring that polymorphisms in genes involved in the gonadal steroid signaling pathway or in gonadal steroid-regulated genes may alter the nature or strength of the steroid signal as well as the phenotype. While some earlier candidate gene studies did not find significant associations with PMD [43], we have recently identified a region of the ESR1 gene containing multiple polymorphic alleles that associated with PMD, thus lending support to the idea that the effects of multiple genes may interact in creating a dysphoric behavioral response to normal gonadal steroid levels. Additionally, Meaney and co-workers [42,80] have demonstrated that the behavioral phenotype can be determined by environment-induced alterations in the expression of the genome, an
modern neurobiological counterpart of the Yerkes–Dodson Curve [83], which suggested that either too much or too little stress impaired function. Weinberger and co-workers [45,76] have applied this concept to prefrontal cortical function and demonstrated that, depending upon a subject’s location on the curve relating prefrontal cortical dopamine and working memory, an increase in dopamine could produce either an improvement or deterioration in working memory. Robbins and colleagues’ [16] have introduced the element of regional and functional specificity to this formula, showing that while increased dopamine improves working memory, it impairs reversal learning in patients with Parkinson’s Disease. This ‘good-for-what’ qualifier of neurobiological manipulation is relevant for the effects of genetic polymorphisms (e.g., the MET allele of BDNF is associated with abnormal brain morphology, hippocampal function, and intracellular trafficking of BDNF and yet appears to be protective against the adverse, serotonin-related, developmental consequences of stress [26,31,81]) but finds particularly useful expression in the studies of Korol [36]. These investigations suggest that estradiol biases the selection of learning strategies in rodents, so that high estradiol conditions favor hippocampal function and place-based learning strategies, while low estradiol conditions favor striatal factors and response-based learning strategies. These findings suggest that different phases of the menstrual cycle may bias toward the activation or inhibition of specific neurocircuits and the selection of different information processing strategies. This concept is supported by preliminary studies performed with Karen Berman, demonstrating both altered prefrontal cortical-hippocampal connectivity during induced hypogonadism compared with during hormone replacement and altered activation of reward circuitry as a function of menstrual cycle phase; specifically, activation is greater in the follicular phase than in the luteal phase in the orbitofrontal cortex and amygdala during reward anticipation and in the midbrain, striatum, and left ventrolateral PFC during reward delivery [20]. The relevance of these observations becomes clear if we abandon the usual cataloging of symptoms associated with PMD and instead focus on affective information processing and regulation.

Premenstrual dysphoric disorder comprises the following disturbances (among others) during the luteal phase: (1) changes in valuation of or valence assignment to experiences; (2) increase in negative information processing bias; (3) inability to access/recall positive mood states or maintain positive mood state; (4) disturbances in arousal/reactivity; (5) inability to suppress negative responses; (6) inability to change affective state [59] (Rubinow et al., unpublished data). These processes are mediated by the balance of activation in interconnected brain regions (circuits) involving the prefrontal cortex (PFC), orbito frontal cortex, anterior cingulate (ACC), amygdala, striatum, and ventral tegmentum/nucleus accumbens. Excessive activation (e.g., amygdala) or deficient activation (PFC and ACC) of specific brain regions are associated with dysphoric states. For example, increased amygdalar activation (or inappropriate amygdalar activation) is associated with prolonged negative mood states and with trait vulnerability to experience depression [29,68]. The work of many investigators [18,23,30,32,39,76] makes abundantly clear that affective dysregulation can best be explained in the activation patterns of interconnected and reciprocal inhibitory brain regions rather than in the activity of any brain region in isolation. Deficient PFC activation, for example, may result in unrestrained amygdala activation [18], with aforementioned negative impact on mood, and in unrestrained stress-related dorsal raphe activation [3], with consequent amplification of the adverse biological and behavioral effects of stress. While stimulated PFC and amygdala function have not been examined in PMD, abnormal amygdala activation has been reported in association with deficient recognition of emotion and facial expressions, an abnormality that we have observed during the luteal phase in women with PMD (Rubinow et al., unpublished data). Disturbances observed in women with PMD during the luteal phase also may implicate other elements of the affective neurocircuitry. The negative bias/affective misperception could reflect the mis-assessment of emotional information seen with dysfunction of the normal balance between dorsal and ventral anterior cingulate cortical activity [11]. The failure to access positive mood states and to update frontal representations, and the consequent maladaptive behavioral response selection, may suggest dysfunctional reward circuitry, with impaired phasic mid-brain dopaminergic modulation of prefrontal cortical activity [47]. This possibility is enhanced by our observation of decreased capacity for emotional reappraisal and recovery in women with PMD (Dancer et al., unpublished data). Studies by Schultz and colleagues [63] demonstrate that a reward that is
smaller than that expected will actually inhibit the firing of dopamine neurons associated with the expectation of the reward. Thus, an affective misperception may contribute to as well as reflect the experience of anhedonia or dysphoria.

These findings then suggest the following: (1) cognitive and affective information processes may serve as probes to identify candidate circuits for the mediation of gonadal steroid-dependent affective dysregulation; (2) if gonadal steroids alter learning strategies, i.e., put specific regions on and offline and alter connectivity, they may disturb a delicate balance in those with trait vulnerability to experience affective dysregulation; (3) alternatively, those with PMD may have excessive or deficient gonadal steroid signaling that may alter the processing of stressors and lead to a dysregulated response [65] or altered learning that might favor the development of behavioral sensitization or steroid-dependent interocceptive cueing of behavioral states. Pursuit of these testable hypotheses in studies of PMD will advance our understanding of this disorder, illuminate mechanisms by which reproductive steroids may regulate a differential sensitivity that permits reproductive steroids to destabilize mood in some but not all women.

References


NIMH premenstrual syndrome workshop guidelines, National Institute of Mental Health, (not published), Rockville, MD, 1983.


