80

HORMONAL AND GENDER INFLUENCES ON MOOD REGULATION

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HISTORY AND MECHANISMS

Within the past 20 years, the putative role of gender and gonadal steroids in mood regulation has been transformed from the staple of stereotype to a critical locus of research in clinical neuroscience. This transformation reflects the impact of explosive advances in molecular endocrinology and basic neuroscience, both of which suggest the myriad and dramatic neuroregulatory effects of gonadal steroids. Although direct isomorphs between basic mechanisms and clinical observations are for the most part absent, our burgeoning knowledge of the cellular and central nervous system effects of gonadal steroids is offering new models for understanding the relevance of gender and gonadal steroids in mood regulation. In this chapter, we review some of the major findings in reproductive neuroscience, emphasize the context dependency of many of these findings, and suggest that similar contextual effects underlie the inability to demonstrate uniform effects of gender or gonadal steroids on mood and behavior.

Reproductive hormones have played a central historical role in the development of our understanding of the effects of hormones on brain and behavior. More than 2,000 years ago, Aristotle, in his biological treatise *Historia Animalium,* observed that castration of immature male birds prevents the development of characteristic male singing and sexual behavior (1). One hundred fifty years ago, Berthold (2) successfully transplanted testes in castrated roosters and reversed their hypogonadal symptoms, demonstrating that reproductive organs possess factors that can dramatically alter physiology and behavior. These observations culminated in the claims by nineteenth century organotherapists (e.g., Brown-Sequard) that the administration of ovarian or testicular extracts could treat a variety of mood disorders in humans, ranging from depression to the anergy of senescence (3,4). In the 1920s and 1930s, the active gonadal substances—testosterone, estradiol, and progesterone—were isolated and characterized.

In 1962, Jensen and Jacobsen (5) provided evidence that the effects of estradiol are mediated through a specific intracellular hormone-binding protein, the estrogen receptor (a concept originally proposed by Langley in 1905), and by 1966, the estrogen receptor became the first hormone receptor to be isolated and identified (6). An elegant scheme for the cellular effects of hormones was subsequently elaborated. As lipophilic factors, steroid hormones would diffuse into cells, where they would bind the intracytoplasmic receptor (in contrast to the membrane-bound receptors of neurotransmitters and peptide hormones); the receptor protein would then be phosphorylated to cause dissociation of a heat shock protein and uncapping of the DNA binding domain of the receptor, which would result in binding of the receptor (frequently after dimerization) to a response element on the DNA, transcription of messenger RNA (mRNA), and finally translation of the mRNA into proteins in the cell cytoplasm. Because an enormous array of proteins relevant to neural transmission (e.g., neurotransmitter synthetic and metabolic enzymes, neural peptides, receptor proteins, signal transduction proteins) were observed to be regulated by gonadal steroids, this ''genomic'' mechanism promised to explain at a cellular level many of the effects of reproductive steroids observed at the level of the organism. In the past 15 years, the elegant simplicity of this genomic mechanism has given way to a model for the actions of reproductive steroids that is more comprehensive, powerful, and complex. Examination of this complexity promotes both an appreciation for the rich neuroregulatory potential of reproductive steroids and a means for understanding the diverse and wide ranging behavioral responses to alterations in reproductive steroid levels.

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First, as the mechanics of transcription were elucidated, it became clear that activated steroid receptors influence transcription not as solitary agents but in combination with other intracellular proteins (7). These protein–protein interactions were such that an activated receptor might enhance, reduce, initiate, or terminate transcription of a particular gene solely as a function of the specific proteins with which it interacted (and the ability of these proteins to enhance or hinder the recruitment of the general transcription factor apparatus). The expression of these proteins—co-regulators (co-activators or co-repressors)—proved to be tissue-specific, and so suggested a means by which a hormone receptor modulator (e.g., tamoxifen) could act like an (estrogen) agonist in some tissues (e.g., bone) and like an (estrogen) antagonist in others (e.g., breast) (8,9). Another group of intracellular proteins, the co-integrators, provided a means by which classic hormone receptors could bind to and regulate sites other than hormone response elements [e.g., estrogen receptor (ER) or glucocorticoid receptor (GR) binding cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein and, subsequently, the activator protein 1 (AP-1) binding site)] (10), and competition for co-integrator or other transcriptional regulatory proteins was demonstrated as a mechanism by which even ligand-free hormone receptors could influence (e.g., squelch or interfere with) the transcriptional efficacy of other activated hormone receptors (11). Thus, both the intracellular hormone receptor environment and the extracellular hormone environment might dictate the response to hormone receptor activation.

Second, the hormone receptors were found to exist in different forms. For example, isoforms of the progesterone receptor, PR_A and PR_B (the latter of which contains a 164-amino acid N-terminal extension), have different distributions and biological actions (12). As another example, two separate forms of the estrogen receptor, ER_α and ER_β, are encoded on different chromosomes (6 and 14, respectively) and have different patterns of distribution in the brain, different affinity patterns for certain ligands, and a range of different actions (including those created by ER heterodimers) (13–15). Further, a variant of ER_β, ER_β, is expressed in the brain, where it can form heterodimers with the ER_α or ER_β receptors (16) and inhibit their transcriptional actions (17).

Third, a variety of substances (e.g., nerve growth factor, insulin) are capable of activating a steroid receptor even in the absence of ligand (18,19). This crosstalk is exemplified by the ability of dopamine to induce lordosis by activating the PR (20,21).

Fourth, the relatively slow "genomic" effects of gonadal steroids have been expanded in two dimensions: time, with a variety of rapid (seconds to minutes) effects observed, and targets, which now include ion channels and a variety of second-messenger systems. For example, estradiol increases the firing of neurons in the cerebral cortex and hippocampus (CA1) (22) and decreases firing in medial preoptic neurons (23). The activity of membrane receptors like the glutamate and γ-aminobutyric acid (GABA) receptors is acutely modulated by gonadal steroids (estradiol and the 5-α reduced metabolite of progesterone, allopregnanolone, respectively) (24,25). Estradiol binds to and modulates the maxi-K potassium channel (26), increases cAMP levels (27), activates membrane G proteins ($G_{\alpha q}$, $G_{\alpha s}$) (28), inhibits L-type calcium channels (via nonclassic receptor) (29), and immediately activates the mitogen-activated protein kinase (MAPK) pathway (albeit in a receptor-mediated fashion) (30). The effects observed are tissue- and even cell-specific (e.g., estradiol increases MAPK in neurons but decreases it in astrocytes (31) (Zhang et al., *unpublished data*). The increase in the number of described mechanisms by which gonadal steroids can affect cell function has paralleled the rapid growth in their observed effects. Consequently, with each of these newly identified actions (which are usually, but sometimes inaccurately, called *nongenomic*), one needs to examine multiple factors before inferring the mechanism of action: (a) the duration required to see the effect, (b) the impact on the effect of inhibitors of transcription and protein synthesis, (c) the presence (or absence) of intracellular hormone receptors, (d) the stereospecificity of ligand binding (to see if effects are mediated through a classic receptor), (e) the effect of hormone receptor blockers, and (f) the ability of the ligand to initiate the action from the cell membrane (i.e., when entry into the cell is blocked). This last requirement acknowledges the presence on the membrane of binding sites for gonadal steroids that appear to be physiologically relevant (32).

Fifth, gonadal steroids regulate cell survival. Neuroprotective effects of estradiol have been described in neurons grown in serum-free media or those exposed to glutamate, amyloid-β, hydrogen peroxide, or glucose deprivation (22). Some of these effects appear to lack stereospecificity (i.e., are not classic receptor-mediated) and may be attributable to the antioxidant properties of estradiol (33,34), although data from one report are consistent with a receptor-mediated effect (35). Gonadal steroids may also modulate cell survival through effects on cell survival proteins (e.g., Bcl-2, Bax), MAPK, or even amyloid precursor protein metabolism (31,36,37) (Zhang et al., *unpublished data*).

Sixth, some actions of gonadal steroids on brain appear to depend on context and developmental stage. Toran-Allerand (38) has shown that estrogen displays reciprocal interactions with growth factors and their receptors (e.g., p51 and trkA, neurotrophins) in such a way as to regulate, throughout development, the response to estrogen stimulation; estrogen stimulates its own receptor early in development, inhibits it during adulthood, and stimulates it again

in the context of brain injury. Additionally, we have demonstrated that the ability to modulate serotonin receptor subtype and GABA receptor subunit transcription in rat brain with exogenous administration of gonadal steroids or gonadal steroid receptor blockade largely depends on the developmental stage (e.g., last prenatal week vs. fourth postnatal week) during which the intervention occurs (39; Zhang et al., *unpublished data*).

Finally, the effects of gonadal steroids do not occur in isolation, but rather in exquisite interaction with the environment. Juraska (40), for example, demonstrated that the rearing environment (enriched vs. impoverished) dramatically influences sex differences in dendritic branching in the rat cortex and hippocampus. Further, the size of the spinal nucleus of the bulbocavernosus and the degree of adult male sexual behavior in rats is in part regulated by the amount of anogenital licking they receive as pups from their mothers, an activity that is elicited from the dames by the androgen the pups secrete in their urine (41).

SEXUAL DIMORPHISMS IN BRAIN STRUCTURE AND FUNCTION

In a highly influential article from the laboratory of C. W. Young, Phoenix et al. (42) demonstrated that exposure of the prenatal female guinea pig to androgens leads to defeminization of reproductive behavior in adulthood and increased sensitivity to androgen-induced male mating behavior. The authors interpreted these results as demonstrating an organizational effect of perinatal steroids on structure and subsequent behavioral function of the brain. These organizational effects, permanent changes in the brain consequent to exposure to gonadal steroids during small, critical windows of development, were contrasted with activational effects, which were impermanent effects that required continued exposure to gonadal steroids. This dichotomy was not uniformly accepted (43); Beach and Holz (44), who had demonstrated the effects on adult reproductive behavior of perinatal steroid manipulation and had interpreted them as derived from changes in gonadal morphology rather than brain function, referred to organizational effects as *imaginary brain mechanisms* (45). Nonetheless, by the late 1960s and early 1970s, the evidence for sexual dimorphisms in the brain that were organized by perinatal steroids was fairly compelling. Pfaff (46) demonstrated dimorphisms in rat brain in both gross and cellular morphology, with the dimorphisms altered by perinatal castration. Nottebohm and Arnold (47) showed that male song birds, who, in contrast to females, have the capacity to sing, had song control nuclei that were five to six times larger than comparable structures in the female. In two classic articles, Raisman and Field (48,49) demonstrated dimorphisms in neural connections; females showed a greater proportion of spine synapses in the preoptic area (48), and this dimorphism could be altered by perinatal steroid manipulation (49). Gorski et al. (50) identified in mammals a sexually dimorphic nucleus of the preoptic area that was two to six times larger in males than in females, and Rainbow et al. (51) demonstrated sexual differences in the response to gonadal steroids, with PR induction by estrogen seen more robustly in females than in males.

In subsequent years, sexual dimorphisms have been identified at all levels of the neuraxis and include differences in the following: nuclear volume; neuron number, size, density, morphology, and gene expression; neuritic outgrowth and arborization; synapse formation; glial number, morphology, and gene expression; and capacity for certain physiologic (e.g., cyclic gonadotropin secretion) and behavioral (e.g., song) activities (see refs. 52, 53 for review). For example, we observed that in comparison with male astrocytes, perinatal cortical astrocytes from female rats have more activated MAPK at baseline and are more sensitive to estradiol suppression of both MAPK and cell proliferation (Zhang et al., *unpublished data*). Additionally, we observed dramatic dimorphisms in the developmental pattern and amount of expression of the cell survival/death proteins Bcl-2 and Bax (Zhang et al., *unpublished data*). The wide scope of these sex differences has become less mystifying as gonadal steroids have been seen to regulate virtually all stages of brain development, from neurogenesis to neural migration, differentiation, synaptogenesis, survival, and death (53). Nonetheless, despite the elegance of sexually dimorphic brain organization as an explanation for dimorphic behaviors, the complexity of the process underlying the development of sexual dimorphisms has assumed daunting proportions. First, it is often difficult to interpret the meaning of the dimorphisms. For example, lesions of the sexually dimorphic nucleus of the preoptic area (SDN-POA) do not compromise male copulatory behavior (despite the role of the preoptic area in reproductive behavior) (54), and DeVries and Boyle (55) have suggested that sexual dimorphisms may in some cases mediate the same behavior (e.g., the same parental behavior in prairie voles is mediated by differences in vasopressin). Second, lack of parallelism across genders complicates ascription of dimorphisms to the presence or absence of a particular steroid hormone. For example, song behavior (usually seen only in males) develops in female zebra finches if they are administered androgen or estradiol perinatally, but males deprived of androgen perinatally show no disruption of song behavior as adults (56,57). Third, some sexual dimorphisms appear to be organized and are independent of subsequent steroid exposure (58); others are activated (i.e., are dependent on subsequent steroid exposure) but not organized (i.e., they are not permanently influenced by perinatal steroid manipulation) (59); and still others are both organized and activated (e.g., the perinatally androgenized female zebra finch requires androgen as an

adult to express song behavior) (55,60). Further, Reisert and Pilgrim (61) have evidence suggesting that dimorphisms in the course of development of mesencephalic and diencephalic neurons are under genetic control (i.e., they are determined well before the appearance of any differences in gonadal steroid levels), like the genetically determined pouch or scrotum in marsupials (62). Fourth, the activational–organizational dichotomy is far more fluid and plasticity is much greater than the concept of critical periods allows. In contrast to the female zebra finch (who shows no male song behavior if androgenized during adulthood only), the female canary receiving androgen during adulthood exhibits male song behavior and shows masculine morphologic changes in the vocal control nuclei, including marked dendritic branching (63,64). Not only is the timing of hormonal administration (and species of the animal) important in determining outcome, but the manner of administration may also dictate the response. For example, Sodersten (65) demonstrated that one can induce typical female behavior in gonadectomized adult male rats by pulsatile but not continuous administration of estradiol followed by progesterone. Complexities notwithstanding, gonadal steroids appear capable of programming gonadal steroid sensitive circuitry in the brain, behavioral capacities, and differential response to the same physiologic stimulus.

SEXUAL DIMORPHISMS IN HUMANS

Given the relative lack of access to the brain in human studies in comparison with similar investigations in animals, the existence of gender-related differences has provided a major source of inference about the role of gonadal steroids in brain function and behavior. Reported gender dimorphisms in psychiatry include the following: prevalence, phenomenology (including characteristic symptoms, age at onset, susceptibility to recurrence, stress responsivity), and treatment characteristics. Specific examples of such dimorphisms are presented below.

Depression

Studies consistently demonstrate a twofold increased prevalence of depression in women in comparison with men (66–69), and this increased prevalence has been observed in a variety of countries (68). A twofold to threefold increased prevalence of dysthymia and a threefold increase in seasonal affective disorder (70) in women have also been noted (71). Although bipolar illness is equally prevalent in men and women (66,72,73; see ref. 74 for review), prepubertal depression prevalence rates are not higher in girls (75,76), possibly reflecting ascertainment bias (depressed boys may be more likely to come to the attention of health care providers) or the possibility that prepubertal major depression is premonitory of bipolar illness (77). With some exceptions, fewer differences in age at onset (68,69,78–81; but see also refs. 82–85), type of symptoms, severity, and likelihood of chronicity and recurrence (68,69,78,82,86–88; but see also refs. 89–93) are seen between men and women. Women are more likely to present with anxiety, atypical symptoms, or somatic symptoms (70,78,78,82,91,93–95) and are more likely to report symptoms, particularly in self-ratings (70,78,95). They are also more likely to report antecedent stressful events (96,97) and manifest a more robust effect of stress on the likelihood depression developing during adolescence (98). Women display increased comorbidities of anxiety and eating disorders (83,99–101), thyroid disease (102,103), and migraine headaches (104), and a lower lifetime prevalence of substance abuse and dependence (82,83). Reported differences in treatment response characteristics in women in comparison with men include a poor response to tricyclics (105–108), particularly in younger women (106); a superior response to selective serotonin reuptake inhibitors or monoamine oxidase inhibitors (109,110); and a greater likelihood of response to triiodothyronine (T_3) augmentation (103). The extent to which these differences reflect gender-related differences in pharmacokinetics (111–117) remains to be determined. Finally, although the prevalence of bipolar disorder is comparable in men and women, rapid cycling is more likely to develop in women (74), and they may be more susceptible to antidepressant-induced rapid cycling (118).

Schizophrenia

Although prevalence rates of schizophrenia appear comparable in men and women, a variety of differences in phenomenology, course, and treatment response characteristics have been identified (111,119,120).

Most but not all (121) studies suggest that the onset of schizophrenia is later in women and that they have better premorbid function (20–40 vs. 17–30; 122–126). Although symptom patterns during acute psychosis do not appear to differ substantially by gender, a variety of studies suggest that deficit or negative symptoms occur more frequently in men (123,127–129), perhaps consistent with the increased incidence in men of abnormalities of brain structure (primarily the corpus callosum) (127,130–133) and cognitive impairment (134). The course of illness in women tends to be more benign, with higher levels of psychosocial function (124), less time in a psychotic state (135), fewer days of hospitalization and fewer readmissions (126, 136,137), less substance abuse (126,135,137), and less violence (aggressive episodes and completed suicide) (123, 138). Finally, consistent with a more benign course (at least until middle age), women are reported to respond to neuroleptics more quickly, more extensively, and at lower doses

(123,139–145). The extent to which this last observation reflects gender dimorphisms in pharmacokinetics (e.g., drug absorption, storage, distribution volume, clearance) versus pharmacodynamics awaits determination (112).

Physiologic Dimorphisms

The epidemiologic observations previously described are increasingly complemented by demonstrations of sexual dimorphisms in brain structure and physiology in humans. Structural and functional brain imaging studies, for example, have shown the following: (a) differences in functional organization of the brain, with brain activation response to rhyming task lateralized in men but not in women (146); (b) gender-specific decreases in regional brain volume (caudate in males and globus pallidus, putamen in females) during development (147); (c) increased neuronal density in the temporal cortex in women (148); (d) greater interhemispheric coordinated activation of brain regions in women (149); (e) larger-volume hypothalamic nucleus (INAH3) in men (150); (f) differences in both resting blood flow and the activation pattern accompanying self-induced mood change (151); (g) decreased serotonin (5-HT_2) binding in the frontal, parietal, temporal, and singular cortices in women (152); (h) differences in whole-brain serotonin synthesis (interpreted as decreased in women but possibly increased if corrected for plasma levels of free tryptophan (153); (i) greater and more symmetric cerebral blood flow in women (154–158); (j) greater asymmetry in the planum temporale in men (159); and (k) higher rates of brain glucose metabolism (19%) in women (160,161). The potential relevance of gonadal steroids in some of these differences has also been demonstrated with the same technologies. For example, Berman et al. (162) demonstrated that the normal pattern of cognitive task-activated cerebral blood flow is eliminated by induced hypogonadism and restored by replacement with estradiol or progesterone. These findings were supported by Shaywitz et al. (163), who demonstrated estrogen enhancement of cognitive task-stimulated brain regional activation on function magnetic resonance imaging (fMRI) in postmenopausal women. Additionally, Wong et al. (164) demonstrated in a small number of subjects that dopamine receptor density in the caudate (measured by positron emission tomography) varies as a function of the menstrual cycle (lower in the follicular phase). The contribution of these and other effects of gonadal steroids to observed gender dimorphisms must, obviously, await further determination.

MOOD DISORDERS RELATED TO REPRODUCTIVE ENDOCRINE FUNCTION

Given the complexity of the factors that affect gender throughout development, it is very difficult to infer the degree to which differential exposure to gonadal steroids determines gender-related behavioral differences. A better opportunity to determine the behavioral relevance of fluctuations in gonadal steroids is provided by mood disorders that appear linked to changes in levels of reproductive steroids. In the following section, we review the role of gonadal steroids in the precipitation and treatment of mood disorders by focusing on three disorders: premenstrual syndrome (PMS), postpartum depression (PPD), and perimenopausal depression.

Premenstrual Syndrome

Although Frank is credited with the first description of ''premenstrual tension'' in 1931, reports of mood and behavioral disturbances confined to the luteal phase of the menstrual cycle appeared earlier, in the medical literature of the nineteenth century. For example, in 1847, Dr. Ernst G. Von Feuchtersleben stated that ''the menses in sensitive women is almost always attended by mental uneasiness, irritability or sadness'' (165). Two years later, the organ transplantation studies of Berthold (2) demonstrated that the reproductive organs possess factors that can markedly alter physiology and behavior, an observation that culminated in the late nineteenth century in the practice by organotherapists of administering ground-up animal glands and organs to treat a wide array of diseases and ailments (4). In this context, the isolation and characterization of ovarian steroids in the early twentieth century led to the inevitable assumption that premenstrual tension is caused by an excess or deficiency of estrogen or progesterone. In the ensuing years, each new discovery in endocrinology gave rise to a new theory of PMS if the new endocrine factor could in any way be shown to influence or be influenced by the menstrual cycle or potentially mediate any of the myriad symptoms attributed to PMS. Despite the obvious appeal of hormonal excess or deficiency as an explanation for PMS, consistent demonstration of any hormonal abnormality was lacking. A major source of study inconsistency was identified in the 1980s (166)—namely, that samples of women with PMS were selected (diagnosed) with highly unreliable techniques (i.e., unconfirmed history). Without prospective demonstration of luteal phase-restricted symptom expression, samples selected were certain to include a large number of false-positives and so make it impossible to apply the data to the population with PMS (167). This requirement for prospective confirmation of luteal phase symptomatology was ultimately incorporated into diagnostic criteria for PMS (National Institute of Mental Health, *unpublished data,* 1983) and late luteal phase depressive disorder/premenstrual depressive disorder (168). Although the improved diagnostic methods used since the mid-1980s have ensured the comparability of samples selected for study, subsequent data, if anything, have provided fairly convincing evidence against

hormonal excess or deficiency as etiologically relevant in PMS.

Individual studies have identified diagnostic group-related differences in levels of reproductive hormones, but the most consistent and compelling data support the absence of such differences. We observed no diagnosis-related differences in plasma levels, areas under the curve, or patterns of hormone secretion for estradiol, progesterone, follicle-stimulating hormone (FSH), or luteinizing hormone (LH) (169), findings consistent with those of Backstrom et al. (170) in a comparison of patients with high and low degrees of cyclic mood change.

In recent additions to the conflicting literature, Wang et al. (171) observed increased estradiol and decreased progesterone levels in women with PMS, Redei and Freeman (172) reported nonsignificant increases in both estradiol and progesterone, and Facchinetti et al. (173) found no differences between subjects and controls in integrated progesterone levels. Results of studies of androgen levels have been similarly inconsistent, demonstrating both normal and decreased testosterone levels (174–176) and elevated and decreased free testosterone levels (175,176).

Recent speculations about the etiology of PMS have focused on putative abnormal neurosteroid levels. Observations central to these speculations include the following: (a) the GABA receptor (the presumed mediator of anxiolysis) is positively modulated by the 5-α and 5-β reduced metabolites of progesterone (allopregnanolone and pregnanolone, respectively) (25); (b) withdrawal of progesterone in rats produces anxiety and insensitivity to benzodiazepines secondary to withdrawal of allopregnanolone, with consequent induction of $GABA_A$ α_4 subunit levels and inhibition of GABA currents (177,178); (c) decreased plasma allopregnanolone levels are seen in major depressive disorder and in depression associated with alcohol withdrawal, with increased levels seen in plasma and cerebrospinal fluid following successful antidepressant treatment (179–182); (d) allopregnanolone has anxiolytic effects in several animal models of anxiety (183–185) and may be involved in the stress response (186); (e) antidepressants may promote the reductive activity of one of the neurosteroid synthetic enzymes (3-α-hydroxysteroid oxidoreductase) and thus favor the formation of allopregnanolone (187); (f) patients with PMS show differences in pregnanolone-modulated saccadic eye velocity and sedation in the luteal phase in comparison with controls (188) (although the reported differences seem attributable to a saccadic eye velocity response to vehicle in those with PMS and a blunted sedation response in the follicular phase in controls); (g) patients with severe PMS show blunted saccadic eye velocity and sedation responses to $GABA_A$-receptor agonists—pregnanolone (188) or midazolam (189)—in comparison with patients with mild PMS. Although one investigator observed decreased serum allopregnanolone levels in women with PMS in comparison with controls on menstrual cycle day 26 (190), other studies showed no diagnosis-related differences in allopregnanolone or pregnanolone (191,192) nor any difference in allopregnanolone levels in women with PMS before and after successful treatment with citalopram (193). Wang et al. (192) did find that if two cycles differed in area under the curve of a hormone by more than 10%, the cycle with the lower levels of allopregnanolone and higher levels of estradiol, pregnanolone, and pregnenolone sulfate was accompanied by more severe symptoms.

In sum, then, no consistent or convincing evidence is available that PMS is characterized by abnormal circulating plasma levels of gonadal steroids or gonadotropins or by hypothalamic–pituitary–ovarian axis dysfunction. Several studies do, however, suggest that levels of estradiol, progesterone, or neurosteroids (e.g., pregnenolone sulfate) may be correlated with symptom severity in women with PMS (171,194,195).

If one treats PMS with any of a number of therapies, one is never certain that the response seen is causally related to the pharmacologic (contrasted with the nonspecific) properties of the intervention employed. Therefore, we attempted to dissociate the symptoms of PMS from the menstrual cycle phase by targeting the menstrual cycle phase rather than the symptoms (196). We administered a progesterone receptor blocker (RU 486) with or without human chorionic gonadotropin (hCG) to women with PMS during the early luteal to midluteal phase. Within 2 days of administration, RU 486 caused menses (by blocking the endometrial progesterone receptors) and luteolysis and advanced the onset of the follicular phase of the next cycle. Addition of hCG does not alter the RU 486-induced menses but ''rescues'' or preserves the corpus luteum and permits a luteal phase of normal length. Consequently, after women experienced an RU 486-induced menses, they 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 first cycle (RU 486 plus hCG). Women in both groups experienced typical PMS symptoms despite the fact that the women receiving RU 486 were now symptomatic in the context of an experimentally advanced follicular phase. Hence, the endocrinology of the midluteal to late luteal phase is irrelevant to the symptoms of PMS, as this phase can be eliminated without influencing the appearance of PMS symptoms. This suggested two possibilities: mood symptoms in women with PMS were entrained to the menstrual cycle but not caused by it, or mood symptoms might be triggered in the luteal phase by reproductive endocrine events occurring earlier in the menstrual cycle, a possibility that was examined in a second study.

The gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate (Lupron) was administered for 3 months in a double-blinded, placebo-controlled, parallel-design study to 20 women with PMS. Women receiving Lupron, but not those receiving placebo, demonstrated a significant decrease in symptom severity and cyclicity, consistent with

several earlier demonstrations of the efficacy in PMS of medical or surgical oophorectomy (197,198). The ovulatory cycle, therefore, appears to be necessary for the expression of PMS (199).

To determine whether gonadal steroids were the factors that when removed resulted in the elimination of PMS, we added back estradiol and progesterone separately to women who continued to take Lupron and for whom Lupron alone successfully eliminated symptoms of PMS. Both estradiol and progesterone were associated with a return of symptoms typical of PMS. Symptoms were precipitated within 7 to 10 days and largely remitted by the end of the 4-week phase of addback. It does appear, therefore, that gonadal steroids can trigger symptoms of PMS, an observation that at first glance appears discordant with the lack of differences in gonadal steroid levels between women with PMS and controls. The reconciliation of these observations is found in the second part of the aforementioned study, in which a comparison group of women with confirmed absence of PMS received the same protocol of Lupron and hormone addback. The control women showed no perturbation of mood during Lupron-induced hypogonadism or during hormone addback with either progesterone or estradiol, despite achieving hormone levels comparable with those seen in the women with PMS. Women with PMS, therefore, are differentially sensitive to gonadal steroids such that they experience mood destabilization with levels or changes in gonadal steroids that are absolutely without effect on mood in women lacking a history of PMS. Gonadal steroids, then, are necessary but not sufficient for PMS. They can trigger PMS, but only in women, who, for undetermined reasons, are otherwise vulnerable to experience mood state destabilization (199). In other words, PMS represents an abnormal response to normal hormone levels.

Postpartum Depression

The literature examining the possible role of hormone abnormalities in postpartum is more exiguous than that for PMS. This literature, however, may be similarly distilled; the evidence for a reproductive hormone abnormality in PPD is scant (200–204, but see also ref. 205). Nonetheless, it is difficult to regard as irrelevant the enormous hormonal excursions occurring during the puerperium (with precipitous drops of estradiol and progesterone from levels of up to 15,000 pg/mL and 150 ng/mL, respectively, to hypogonadal levels in just 1 to 3 days). Analagous to our observations with PMS, it is possible that women with and those without PPD differ in sensitivity to puerperal hormone changes, not in the degree to which they occur. To test this hypothesis, we created a scaled-down model of the puerperium in which women received high-dose estradiol and progesterone for 2 months (superimposed on Lupron-induced gonadal suppression to permit comparability and stability of levels achieved), followed by a blinded, precipitous withdrawal of gonadal steroids and a consequent Lupron-induced hypogonadal state. This protocol was performed in two groups: euthymic women with a history of PPD occurring no more recently than 1 year before the study (PPD+) and controls lacking a history of depression (PPD−). In the first 2 weeks following withdrawal, the women with a history of PPD experienced a significant increase in measures of depression relative to baseline, with several subjects experiencing an increase in symptoms during the last few weeks of addback. No similar symptoms were experienced by the women lacking a history of PPD. Both the levels of hormones achieved and the change from peak to withdrawal-induced hypogonadism were comparable in the two groups. It appears, therefore, that like women with PMS, women with a history of PPD experience mood state destabilization in association with changes in levels of gonadal steroids that are without effect on mood in women lacking a history of PPD. The hormonal changes can trigger the mood state change, but only in a context of increased susceptibility to affective dysregulation.

Context

The differential sensitivity to gonadal steroids seen in women with a history of PMS or PPD emphasizes that the response to a biological signal cannot be inferred absent an understanding of the context in which the signal occurs. This context includes current physiologic and external environments, prior experience, past history of exposure to the stimulus, and genetic makeup. With the imminent mapping of the human genome, this last contextual determinant becomes of great practical interest as a potential explanation for the differential response to steroids. Data already exist from both animal and human studies in support of this hypothesis. Spearow et al. (206) demonstrated greater than 16-fold differences in sensitivity to estradiol (reproductive disruption) across six different mouse strains, with genotype accounting for more of the variation than the dose of estradiol. Similarly, strain/genetic (and task-dependent) differences in behavioral sensitivity to allopregnanolone were observed by Finn et al. (207). Huizenga et al. (208) demonstrated not only intraperson stability of baseline cortisol and feedback sensitivity (to dexamethasone), which suggests a genetic influence (209), but also a higher sensitivity to exogenously administered glucocorticoid (dexamethasone) in association with a polymorphism in exon 2 of the glucocorticoid receptor. Association studies suggest a progressively increased rate and severity of prostate cancer as the number of cytosine–adenine–guanosine (CAG) trinucleotide repeats in exon 1 of the androgen receptor decreases (210). This observation is accompanied by the recent observation that androgen receptors with decreased CAG repeats demonstrate increased transcriptional efficiency (211). Steroid receptor polymorphisms, then, may alter the steroid signaling pathway in such a way as to produce or

contribute to a different behavioral/phenotypic response to a hormone signal. As appealing as this explanation is for the differential sensitivity observed in PMS and PPD, the demonstrations in animal studies that perinatal steroid manipulations alter the organization of gonadal steroid-sensitive circuitry (42) and gonadal steroid-activated gene expression (212) caution us that gene–environment interactions may yield markedly different phenotypic expressions of the same genotype.

Hormones as Therapeutic Agents

An emerging area of interest is the use of gonadal steroids in the treatment of PPD (213) and the perimenopause. As in PPD, the evidence for a reproductive hormonal abnormality in perimenopausal depression is vanishingly small (214–216; Schmidt et al., *unpublished data*). Some (217–220) but not all (Schmidt et al., *unpublished data*) studies have observed lower plasma LH levels in postmenopausal depressed women, but no consistent group-related differences in gonadal steroids have been demonstrated. Similarly, despite claims for the antidepressant efficacy of estrogen dating back to the nineteenth century (4,221), reports of the effect of estradiol on mood in perimenopausal and postmenopausal women (222–226) have been inconsistent (227–229) and have been compromised by the failure to diagnose depression (as opposed to depressive symptoms, which have different causes and treatment response characteristics), the failure (with one exception; see ref. 226) to consider remediation of hot flushes as a confound in assessment of psychotropic efficacy, and the failure to assess efficacy in perimenopausal (vs. postmenopausal) women, a potentially important distinction identified by Montgomery et al. (222). These problems were addressed in a recent study that demonstrated the antidepressant efficacy of estradiol in perimenopausal women with major and minor depression (230,231). The antidepressant effects were further shown in the subsample of women with no hot flushes, so that the possibility that remediation of hot flush-induced sleep disturbance might indirectly improve mood was eliminated. A subsequent study has similarly demonstrated the psychotropic efficacy of estradiol in perimenopausal depression (C. Soares et al., *unpublished data*). These observations converge with *in vitro* and epidemiologic evidence for neuroprotective effects of estradiol in suggesting that gonadal steroids (and adrenal androgens) may enter the neuropsychiatric therapeutic armamentarium, either as primary or adjunctive agents. While not permitting an inference about the etiology of reproductive endocrine-related mood disorders, the psychotropic effects of hormones may help dissect neural pathways of relevance to the regulation of affect. Attempts to define the mechanisms underlying both the psychotropic effects of gonadal steroids and the differential response to endogenous gonadal steroids should help advance our efforts to illuminate the neurobiology of mood and mood disorders.

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