The nature and extent of the impact of gender and reproductive function on mood has been the subject of speculation and controversy for centuries. Over the past 50 years, however, it has become increasingly clear that not only is the brain a major target of reproductive steroid hormones, but additionally, the steroid hormones, as neuroregulators, create a context that influences a broad range of brain activities; i.e., neural actions and resultant behaviors are markedly different in the presence and absence of gonadal steroids. In turn, the actions of gonadal steroids are themselves context-dependent. Thus, even where it can be demonstrated that gonadal steroids trigger mood disorders, the triggers are normal levels of gonadal steroids (to be contrasted with the mood disturbances accompanying endocrinopathies), and the mood disorders appear only in a subset of susceptible individuals. The context specificity and differential susceptibility to affective dysregulation seen in women with reproductive endocrine–related mood disorders are undoubtedly important underlying characteristics of a wide range of psychiatric disorders in which the triggers have not yet been identified. Consequently, reproductive endocrine–related mood disorders offer unparalleled promise for the identification of those contextual variables that permit biological stimuli to differentially translate into depression in individuals at risk.
consider this phenomenon has been the keystone of the argument that reproductive endocrine–related mood disorders do not exist. The syllogism is as follows: The effects of reproductive hormones should be similar across individuals; not all individuals have the same behavioral concomitants of changes in reproductive endocrine function; therefore, reproductive hormones have nothing to do with behavior. In other words, if changes in reproductive steroids do not precipitate mood disorders in everyone, they must do so in no one. As will be shown below, this argument is fallacious and serves to obscure rather than clarify. Second, the principle that the response to a biologic stimulus depends upon the context in which the stimulus is administered is generalizable and underlies much of our physiology. Third, by understanding the means by which reproductive steroids can trigger affective change in some but not other women, we will be in a far more powerful position to understand the substrate underlying susceptibility to affective disorder in general, which is better conceptualized as a differential response to a stimulus rather than as a “deficiency” state. The remainder of this paper, then, will address the central question in reproductive psychiatry/neuroscience: how is it that reproductive steroids can trigger a depression, and why does this occur only in some individuals?

Reproductive steroids: modulators of brain function

The observed links between reproductive function and behavior date back at least several millennia to Aristotle, who noted that castration of immature male birds prevented the development of characteristic male singing and sexual behavior.1 By the end of the 19th century, Brown-Séquard and other “organotherapists” claimed that the administration of ground-up extracts from animal gonads could successfully treat a variety of human mood disorders, including depression and the anergy of senescence.2 In the 1920s and 1930s, the potential mediators of these effects—the steroid hormones estradiol, progesterone, and testosterone (and not sperm, as Brown-Séquard believed)—were isolated and characterized. Forty years later, Jensen and Jacobsen6 demonstrated that the actions of estradiol occurred through its binding to an intracellular protein, the estrogen receptor (ER), which was isolated and identified 4 years later.7 The means by which steroids influenced cell function were subsequently elaborated: after diffusing into the cell, the steroid bound and activated its receptor, a transcription factor that could then bind DNA and regulate the transcription of mRNA, which would then be translated into proteins in the cell cytoplasm. In this fashion, reproductive steroids were found to regulate the expression of a variety of proteins of relevance for neural function (eg, neurotransmitter synthetic and metabolic enzymes, neuropeptides, receptors, etc). More recently, advances in neuroscience (reviewed in the accompanying article by McEwen8) have demonstrated vastly more complex, broad-ranging, and powerful mechanisms for neural control by reproductive steroids, and have further uncovered several regulatory principles that help explain how a given steroid signal may elicit diverse behavioral responses. One inescapable, overarching principle is that the molecular and behavioral effects of steroids are highly context-dependent.

Cellular context

Data overwhelmingly suggest that the cell is a context that determines the response to a stimulus. First, steroid-activated receptors influence transcription not as solitary agents, but by forming combinations with other intracellular proteins.9 Some of these proteins, the coregulators, determine whether gene transcription is enhanced or suppressed by the activated receptor. Other proteins, the cointegrators, permit activated receptors to regulate genomic expression through sites (eg, activator protein, AP1) other than the classical DNA hormone response elements, thus expanding the range of genes
influenced by steroids. Many of these proteins are tissue specific, thus helping to explain how ER modulators (eg, tamoxifen and raloxifene) can act like agonists in some tissues (eg, bone) and like antagonists in other tissues (eg, breast). Second, different subtypes of the steroid receptors are either coded for on different genes (eg, estrogen receptors alpha and beta) or modified after transcription (eg, splice variants or progesterone receptor isoforms A and B). These subtypes have different distribution patterns in the brain, different affinities for ligands, and very different actions (including inhibition of the actions of other subtypes). Third, the relatively slow, “genomic” effects of reproductive steroids have been expanded in two dimensions: time, with a variety of rapid (seconds to minutes) “nongenomic” effects observed; and targets, which now include ion channels and second messengers. Once again, the effect observed depends upon the type of cell examined: estradiol activates the second messenger, mitogen-activated protein kinase (MAPK), in neurons, but decreases MAPK activation in cortical glia.

**Metabolic context**

As steroid hormones are highly homologous and serve as precursors for one another, the manner in which steroids are metabolized can markedly change the amplitude or nature of the steroid signal. Steroid metabolic enzymes, then, can contribute to the variance in a steroid signal in several ways. First, enzymes regulate the activation and potency of steroid hormones, as seen, for example, with the enzyme (5α-reductase) that converts testosterone into dihydrotestosterone (DHT), an androgen with fourfold greater affinity for the androgen receptor (AR) and fivefold greater stability. Second, enzymes determine the receptor system that is activated, as seen, for example, in the conversion by aromatase of testosterone (acting at the AR) to estradiol (acting at the ER). Third, the metabolism of steroids can facilitate or inhibit the accumulation of metabolites that may be neurotoxic, as seen, for example, with the ability of 5α-reductase to shunt testosterone away from the pathway leading to accumulation of estradiol, which can function as a neurotoxin. Fourth, enzymes may produce steroid metabolites that have a completely different neuromodulatory profile from that of the parent hormones, as seen, for example, with the conversion of progesterone to the neurosteroid allopregnanolone (by 5α-reductase and 3α-hydroxy steroid oxidoreductase [3α-HSOR]), a potent modulator of the γ-aminobutyric acid (GABA) receptor chloride ionophore. Finally, since many of the enzymes have multiple steroid substrates, the enzyme activity regulates the relative amounts of different behaviorally active metabolites; for example, 3α-HSOR both inactivates the androgen DHT and produces the neurosteroid allopregnanolone. Not only will different metabolic profiles activate or inhibit different receptor systems, but the consequence of the activation of a given steroid receptor will differ depending upon which hormones are present. Estradiol and cortisol, for example, exert opposing effects on AP1-modulated genes through interactions with the coactivator CBP/P300. A steroid hormone, then, may produce markedly different effects depending upon its metabolism and the hormonal context in which it is acting.

**Developmental/temporal context**

Perinatal reproductive steroids create a context that influences (organizes) brain development and the adult behavioral repertoire. Phoenix et al and Gorski et al showed that prenatal exposure of female guinea pigs or perinatal exposure of rats to androgens resulted in enhanced behavioral sensitivity (eg, increased sexual and aggressive behaviors) to androgens administered during adulthood. Thus, differences in early exposure to reproductive steroids created the capacity in adults for different behavioral responses to the same stimulus. The effects of reproductive steroids are also developmental stage-specific. Estradiol, for example, stimulates its own receptor early in development, inhibits it during adulthood, and stimulates it again in the context of brain injury. Modulatory effects of reproductive steroids also differ in old and young subjects (both animals and humans). For example, spine density in the dentate gyrus is modulated by estradiol in old but not young female rats. These age-dependent effects are particularly of interest given a burgeoning literature describing the ability of reproductive steroids to regulate cell death and survival through effects on cell survival proteins (eg, Bel-2, Bax), signal transduction (eg, MAPK, Akt), amyloid precursor protein metabolism, and free radical species generation. Effects on survival operate at both ends of the developmental spectrum. Early effects influence prun-
ing and the shaping of brain circuitry. Modulation of neural and glial survival during aging provides yet another means by which reproductive steroids may influence the susceptibility to neuropsychiatric illness, given the putative role of neurodegeneration in depression and its demonstrated role in Alzheimer’s disease.

Environmental context

The brain is a nonlinear transform system, in which the response to a stimulus can be altered as a function of past history or present environment. Multiple demonstrations of this process can be found in the animal literature. For example, behavioral sensitization refers to an amplified behavioral response (eg, aggression) to repeated exposure to a pharmacologic stimulus. Two elements of this process are of further interest. First, Antelman has suggested that even without repeated administration, exposure to certain drugs may yield an amplified response upon readministration, simply by virtue of the passage of time. There is a “memory” following exposure that alters the response when the stimulus is re-presented. Second, Post and coworkers have demonstrated that expression of behavioral sensitization may be context dependent, in that the exaggerated response elicited to cocaine in the test cage will not be manifest if, after sensitization is achieved, the cocaine is administered in the home cage. Both past experience and environment, then, may alter subsequent response. One of the most impressive demonstrations of experience-related alternations in context is provided by the work of Meaney and coworkers. These authors expanded the work of Levine and showed that the separation and handling of rat pups elicited licking and grooming behavior from mothers that differentially and permanently determined the nature of the offspring’s response to stressors. Meaney and coworkers then went on to demonstrate in cross-fostering studies that it was the maternal licking and grooming behavior, not the genetic factors, that influenced the licking and grooming behavior (as well as the stress responsivity) of the female offspring, and that the “adopted” licking and grooming behavior and stress responsivity were passed down to subsequent generations. This series of studies, then, demonstrates that maternal behavior can alter the developmental context, such that permanent and dramatic differences in response—from the transcriptional to the behavioral level—are programmed into the offspring. Several studies also demonstrate the exquisite sensitivity of reproductive physiology and behavior to environmental alterations during development. Ward and Weisz demonstrated that male offspring of a rat dam stressed during gestation were demasculinized, with lower testosterone levels (on critical gestational days) and deficient adult male mating behavior. Moore et al observed that the size of the sexually dimorphic spinal nucleus of the bulbocavernosus as well as adult male mating behavior were in part determined by maternal licking of the anogenital region of the pup, which in turn appeared to be elicited by androgens in the rat pup urine. Finally, reproductive hormones interact with environmental factors during development to determine the adult behavioral repertoire. Adult aggressive behavior in mice can be attenuated by prepubertal castration; the attenuation, however, is blunted to the extent to which the mouse has already been exposed to aggressive encounters. These examples demonstrate that current and past environments and experience can create a context in which the same hormonal or environmental stimulus may elicit any of a range of behavioral responses.

Gender context

Early hypotheses that the brain displays sex-related differences in structure and function were confirmed by the demonstrations by Pfaff of sexual dimorphisms in rat brain morphology and by Raisman and Field of sex-related differences in the synaptic density of the preoptic area in the rat. There is now an impressive literature detailing sexual dimorphisms at all levels of the neuroaxis, including differences in the following: nuclear volume; neuron number, size, density, morphology, and gene expression; signal transduction; neuronal neuritic branching patterns; synapse formation; and physiological and behavioral response. Given the ability of reproductive steroids to regulate virtually all stages of brain development, from neurogenesis to neural migration, differentiation, synaptogenesis, survival, and death, the wide range of brain dimorphisms is not surprising. Nonetheless, the source and significance of many of the dimorphisms are far from clear. For example, while exposure to reproductive steroids is believed to organize (perinatally) or activate (adulthood) most dimorphisms, Reisert and Pilgrim showed that dimorphisms in the course of development of embryonic mes-
encephalic and diencephalic neurons appear under genetic control (i.e., they are determined well before the appearance of any differences in reproductive steroid levels). Similarly, both the morphologic (e.g., neuritic extension) and functional (e.g., signal transduction) responses of cultured neurons and glia to reproductive steroids have been shown to display dramatic sexual dimorphisms despite exposure to identical levels of steroid, i.e., the dimorphic response cannot be attributed to differences in the steroid milieu of males and females. Additionally, the existence of brain sexual dimorphisms often is not translatable into gender-related differences in behavior. Still, the widespread dimorphisms in animals (as well as the demonstrations of sexual dimorphisms in brain structure and physiology in humans) provide a basis for inferring the mechanisms underlying reported gender dimorphisms in depression and other psychiatric disorders, i.e., differences in prevalence, phenomenology (including characteristic symptoms, age of onset, susceptibility to recurrence, and stress responsivity), and treatment response characteristics.

Sexual dimorphisms

Sexual dimorphisms in depression

Depression differs in women and men in a number of respects. Studies consistently demonstrate a twofold increased prevalence of depression in women compared with men, and this increased prevalence has been observed in a variety of countries. A two- to threefold increased prevalence of dysthymia and threefold increase in seasonal affective disorder in women has also been noted, while bipolar illness is equiprevalent in men and women (reviewed in reference 64).

Prepubertal depression prevalence rates are not higher in girls, 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. With some exceptions, the age of onset (but also see references 72 to 75), type of symptoms, severity, and likelihood of chronicity and recurrence (but also see references 79 to 83) display few differences between men and women. Women are more likely to present with anxiety, atypical symptoms, or somatic symptoms are more likely to report symptoms (particularly in self-ratings) are more likely to report antecedent stressful events and manifest a more robust effect of stress on the likelihood of developing depression during adolescence. Women also display increased comorbidity of anxiety and eating disorders, thyroid disease, and migraine headaches, as well as lower lifetime prevalence of substance abuse and dependence. Reported differences in treatment response characteristics in women compared with men include poor response to tricyclics, particularly in younger women, superior response to selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs) and a greater likelihood of response to triiodothyronine (T3) augmentation. The extent to which these differences reflect gender-related differences in pharmacokinetics remains to be determined. Finally, while the prevalence of bipolar disorder is comparable in men and women, women are more likely to develop rapid cycling and may be more susceptible to antidepressant-induced rapid cycling.

It is one matter to identify sex-related differences in depression and quite another to interpret their meaning. Specifically, one cannot infer that the observed differences are a product or a reflection of sex-specific biology. Sex-related differences in the prevalence of depression, for example, could occur consequent to increased number and severity of stressors experienced by women (e.g., greater demands to manage both home and vocational responsibilities; societal encouragement of conciliatory behavior and discouragement of expression of anger; a lack of social empowerment) or to social stigmatization of endorsement of depressive symptoms in men. Nonetheless, the potential for sex-dependent biology to play a significant role in affective and cognitive disorders is suggested by the following (described below): (i) sexual dimorphisms in brain structure and physiology have been identified in humans; (ii) reproductive steroids regulate brain function in humans in vivo; and (iii) reproductive steroids play a role in the precipitation and treatment of mood disorders that are linked to periods of reproductive endocrine change.

Brain sexual dimorphisms in humans

While a biological basis for sex-dependent differences in the susceptibility to or expression of depression has not been demonstrated, structural and functional imaging studies have identified a variety of sex-differences in
the human brain, including the following: (i) functional organization of the brain, with brain activation response to rhyming task lateralized in men but not women; (ii) gender-specific decreases in regional brain volume (caudate in men and globus pallidus, putamen in women) during development; (iii) increased neuronal density in the temporal cortex in women; (iv) greater interhemispheric coordinated activation of brain regions in women; (v) larger volume hypothalamic nucleus (interstitial nucleus of the anterior hypthalamus–3 [INAH–3]) in men; (vi) differences in both resting blood flow and the activation pattern accompanying self-induced mood change; (vii) decreased serotonin receptor 5-HT3 binding in the frontal, parietal, temporal, and cingulate cortices in women; (viii) differences in whole brain serotonin synthesis (interpreted as decreased in women but possibly increased if corrected for plasma free tryptophan levels); (ix) higher and more symmetric cerebral blood flow in women; (x) greater asymmetry in the planum temporale in men; and (xi) greater brain glucose metabolism (19%) in women. Data from several studies employing similar technologies suggest that reproductive steroids may mediate some of the observed dimorphisms.

Regulation of brain physiology by reproductive steroids

Berman et al demonstrated that the normal pattern of cognitive task–activated cerebral blood flow was eliminated by induced hypogonadism and restored by replacement with estradiol or progesterone, findings supported by Shaywitz et al, who demonstrated estrogen enhancement of cognitive task–stimulated brain regional activation (functional magnetic resonance imaging [fMRI]) in postmenopausal women. Wong et al demonstrated in a small number of subjects that dopamine receptor density in the caudate (measured by positron emission tomography [PET]) varied as a function of the menstrual cycle (lower in the follicular phase). Further, in two recent studies using paired-pulse transcranial magnetic stimulation, Smith et al showed that cortical facilitation was enhanced in the late follicular phase, while cortical inhibition was enhanced during the luteal phase, consistent with putative central excitatory effects of estradiol and inhibitory effects of progesterone metabolites.

Despite gender-related and reproductive steroid–related differences in brain physiology, it is the investigation of mood disorders linked to reproductive endocrine change that offers the greatest potential insight into the role of reproductive steroids in the regulation and dysregulation of affect.

Reproductive endocrine–related mood disorders

Premenstrual syndrome

While 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 19th 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.” As the symptoms of PMS occurred in a menstrual cycle phase–specific fashion (ie, only in the luteal phase), it was presumed that abnormalities in the hormonal constituents of the menstrual cycle (eg, estradiol, progesterone) must underlie PMS. Despite the appeal of this hormone excess or deficiency hypothesis, however, early studies of the putative hormonal etiologies of PMS were inconsistent in their conclusions. A major source of study inconsistency was identified in the 1980s, namely that samples of women with PMS were selected (diagnosed) with highly unreliable techniques (ie, unconfirmed history). Without prospective demonstration of luteal phase–restricted symptom expression, samples selected were certain to contain a large number of false positives, thus rendering the data obtained ungeneralizable to the population with PMS. This requirement for prospective confirmation of luteal phase symptomatology was ultimately incorporated into diagnostic criteria for PMS and late luteal phase dysphoric disorder (LLPDD)/premenstrual dysphoric disorder (PMDD). This requirement for prospective confirmation of luteal phase symptomatology was ultimately incorporated into diagnostic criteria for PMS and late luteal phase dysphoric disorder (LLPDD)/premenstrual dysphoric disorder (PMDD). While the use of these diagnostic criteria/guidelines has permitted greater homogeneity of samples across studies—a requirement for comparison and generalization of results obtained—data subsequently generated have provided little if any evidence for hormonal excess or deficiency as etiologically relevant in PMS. Indeed, more recent studies have, if anything, largely preserved the formerly observed inconsistency. For example, Wang et al observed increased estradiol and decreased progesterone levels in women with PMS. Redei and Freeman reported nonsignificant
increases in both estradiol and progesterone, while Facchinetti et al\textsuperscript{136} found no differences from controls in integrated progesterone levels. Results from studies of androgen levels have been similarly inconsistent, demonstrating both normal and decreased testosterone levels\textsuperscript{137-139} and elevated and decreased free testosterone levels.\textsuperscript{138,139} In conclusion, there is no consistent or convincing evidence 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 (eg, pregnenolone sulfate) may be correlated with symptom severity in women with PMS.\textsuperscript{134,140,141} (See references 142 and 143 for summaries of hormonal studies of PMS.)

If PMS is not due to a deficiency or excess of reproductive steroids (or of any other hormone studied to date), do these steroids play any role at all in the precipitation of the syndrome? We attempted to answer this question by posing four questions.

**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 luteum activity), alone or with human chorionic gonadotropin (hCG) (which preserves corpus luteum activity).\textsuperscript{146} Thus, after receiving the RU-486 (6 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). Subjects in all three groups (a placebo-only group was included) experienced highly comparable symptoms that were significantly greater than those seen in the follicular phase; ie, 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-late luteal phase might, nonetheless, be influencing subsequent symptom development.

**If you suppress ovarian activity, can you prevent the symptoms of PMS?**

As the RU-486 study eliminated only the mid-late luteal phase, PMS 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 gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate (3.75 mg) in a placebo-controlled parallel-design study in 20 women with PMS. Leuprolide but not placebo was highly effective in eliminating both symptom severity and cyclicity (10/18 women responded to leuprolide and 0/10 responded to placebo).\textsuperscript{145} This confirmed similar observations by Bancroft et al\textsuperscript{146} and Mortola et al,\textsuperscript{147} and suggested that PMS was indeed dependent upon ovarian steroid production.

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

Eighteen women whose PMS symptoms were significantly attenuated or eliminated by leuprolide-induced ovarian suppression were then continued on leuprolide and received in addition (in a double-blind, crossover fashion) estradiol (4 weeks followed by a fifth week in combination with progesterone to promote endometrial shedding) and progesterone (4 weeks). Five of these women received an additional 1 month of placebo “addback” in order to control for patients’ expectations, specifically the recognition that they were taking something new. Finally, the same regimen of leuprolide-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 PMS whose symptoms were successfully eliminated (or attenuated) by leuprolide-induced hypogonadism experienced significant return of symptoms on either estradiol or progesterone, but not on placebo. Characteristically, symptoms returned within 2 weeks of initiating hormone replace-
ment and remitted by the fourth week of administration. In the control women lacking a history of PMS, however, neither the hypogonadal nor the hormone replacement conditions were associated with any perturbation of mood.\textsuperscript{145} Consistent with the findings from our basal hormone studies,\textsuperscript{148} it appeared that PMS represents an abnormal response to normal hormone changes or levels rather than a “normal” response to a hormonal abnormality. This study, then, raised a fundamental question: Why do similar changes in or levels of gonadal steroids trigger mood deterioration in women with PMS, while showing no apparent effect on mood in women lacking this history?

What are the potential mechanisms underlying the increased vulnerability to gonadal steroid–triggered mood changes in women with PMS?

While mood disorders may be seen in association with the pathological function of certain endocrine organs (eg, adrenal, thyroid), mood disturbances precipitated by gonadal steroids in PMS appear in the context of normal ovarian function. There are several possible means by which otherwise normal steroid signals might elicit a change in behavioral state.

Altered set points for relevant neural systems (ie, a means of conferring vulnerability)

The serotonin systems are appealing candidates for conferring vulnerability to gonadal steroid–precipitated mood changes\textsuperscript{146}: gonadal steroids and serotonin display numerous reciprocal regulatory effects in the central nervous system (CNS); aggression against intruders by female rats (resident intruder model) varies with the estrous cycle, is ovarian steroid dependent, and is prevented by serotonin agonist antidepressants\textsuperscript{150}; serotonin has a role in behaviors (eg, appetite, impulsivity, mood, sleep, and sexual interest) that vary with the menstrual cycle in PMS; blunted endocrine responses to serotonergic agonists (eg, L-tryptophan, meta-chlorophenylpiperazine) have been described in PMS (although not confined to the luteal phase);\textsuperscript{151,152} serotonergic agonists have a role in behaviors (eg, appetite, impulsivity, mood, sleep, and sexual interest) that vary with the menstrual cycle in PMS; blunted endocrine responses to serotonergic agonists (eg, L-tryptophan, meta-chlorophenylpiperazine) have been described in PMS (although not confined to the luteal phase);\textsuperscript{151,152} serotonergic agonists are efficacious in the treatment of PMS,\textsuperscript{153} and the therapeutic efficacy of serotonin agonists can be reversed by tryptophan depletion\textsuperscript{154} or serotonin receptor blockade.\textsuperscript{155} While alterations in serotonin function are clearly relevant to the successful treatment of PMS symptoms, it remains unclear whether alterations in serotonin function underlie the predisposition to experience PMS. Future studies will await the development of receptor subtype specific agonists/antagonists and access to subtype-specific imaging ligands.

Polymorphisms in gonadal steroid signaling pathway proteins or in systems regulated by gonadal steroids

PMS offers an ideal opportunity to identify genetic contributions to the vulnerability for affective disturbance, since the offending stimuli (steroid triggers) are known. Several polymorphisms in gonadal steroid receptors have been shown to alter receptor transcriptional efficacy (eg, CAG repeat in exon 1 of the androgen receptor; progins insertion in intron 7 of the progesterone receptor) and to be associated with differential illness risk (ie, prostate cancer or breast cancer).\textsuperscript{156-159} Additionally, the susceptibility to the disruptive effects of estradiol on reproductive development differs enormously (up to 100-fold) between mouse strains, with the genotype contributing more to the variance than the dose of estradiol employed.\textsuperscript{160} There is precedent, then, for inferring that polymorphisms 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 phenotype. In genetic studies that we have performed to date in 125 women with PMS and 280 controls (C. Roca and B. Harlow, unpublished data), no differences were observed in the frequencies of the following polymorphisms: PvuII, XbaI, and TA repeat (estrogen receptor α); CAG repeat (androgen receptor); progins, CA repeat (progesterone receptor); T102C, His-Tyr (serotonin 2A receptor); Cys-Ser (serotonin 2C receptor). A significant difference has been identified, however, for the SLC6A4 promoter polymorphism of the serotonin transporter, with a higher frequency of the L (long) allele (associated with increased transport and increased response to SSRIs)\textsuperscript{161,162} in the women with PMS (C. Roca et al, unpublished data). This difference appears to reflect a lower than predicted frequency in the controls as well as a higher frequency in patients, suggesting that women with documented absence of any menstrual cycle–related mood symptoms (approximately 10% of the Harlow sample) may be protected from the development of symptoms and hence may be at least as informative as illness probands in providing clues to the genetic determinants of susceptibility.
Altered metabolism of gonadal steroids

The neurosteroid metabolites of progesterone (and androgens) are of considerable interest as possible mediators of the behavioral effects of gonadal steroids. Supportive observations are as follows: (i) the ring A–reduced metabolites of progesterone, allopregnanolone and pregnanolone, are allosteric modulators of the GABA<sub>A</sub> receptor/chloride ionophore<sup>21</sup>; (ii) withdrawal of progesterone in rats produces anxiety and insensitivity to benzodiazepines due to withdrawal of allopregnanolone, with consequent induction of GABA<sub>A</sub> alpha-4 subunit levels and inhibition of GABA currents<sup>163,164</sup>; (iii) decreased plasma allopregnanolone levels are seen in major depressive disorder and in depression associated with alcohol withdrawal, with an increase in levels seen in plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment<sup>165-167</sup>; (iv) allopregnanolone displays anxiolytic effects in several animal anxiety models<sup>168</sup> and may be involved in the stress response<sup>169</sup>; (v) antidepressants may promote the reductive activity of one of the neurosteroid synthetic enzymes (3α-HSOR), thus favoring the formation of allopregnanolone.<sup>170</sup> While we previously reported no differences in luteal phase allopregnanolone and pregnanolone levels in women with PMS compared with controls,<sup>171</sup> in an experimental model of postpartum depression (PPD), we observed a highly significant inverse correlation (r=0.92) between the change in allopregnanolone levels from weeks 6 to 8 of hormone addback and Beck depression ratings at week 8 of addback (see below).<sup>172</sup> This correlation reflected the high depression ratings in those women with a past history of PPD, whose allopregnanolone levels dropped or failed to increase during the last 2 weeks of high dose addback. These findings suggest that differences in the activity of the synthetic (or metabolic) enzymes for neurosteroids may translate into phenotypic differences.

At present, we do not understand the basis for the differential sensitivity seen in women with PMS: what permits levels or changes in reproductive steroids that are without effect on mood in women without a history of PMS to destabilize mood in those with a history of PMS? Nonetheless, the simultaneous requirement for a trigger (reproductive steroids) and an underlying vulnerability to mood state destabilization in PMS provides a model for thinking about affective disorders in general as well as other mood disorders (eg, postpartum depression) specifically linked to periods of reproductive endocrine change.

Postpartum depression

A reproductive endocrine–related mood disorder that is phenomenologically similar to major depression is PPD, the most prominent symptoms of which are sleep disturbance, excessive fatigue, sadness and anhedonia, excessive guilt or self blame, psychomotor disturbance, and suicidal ideation.<sup>173-175</sup> It does not appear that there is anything phenomenologically unique about the depression that occurs postpartum; rather, once again, it is the timing of the syndrome that makes it distinctive, in this case following delivery. However, variability in the definition of the interval during which PPD can develop (2 weeks to 3 months postpartum) in part accounts for the variable estimates of the incidence and prevalence of PPD. Prevalence rates for PPD vary between 8.3% and 14.9%,<sup>176-181</sup> While an increased prevalence of depression postpartum has not been clearly demonstrated (due, in part, again to varying intervals examined and a paucity of adequate control groups), it does appear that the relative risk of depression increases during the first few months postpartum.<sup>176,182-184</sup> While a variety of factors have been associated with the development of PPD, including personal or family history of psychiatric illness, marital disharmony, lack of confiding relationships, and number of life events in the previous year,<sup>185-187</sup> two are of particular interest. First, while some but not all studies show a prior history of affective illness as a risk factor for subsequent PPD,<sup>188-191</sup> women with PPD as their first depressive episode appear both less likely to experience a nonpuerperal depression and more likely to experience a subsequent PPD than women with nonpuerperal episodes.<sup>192</sup> Second, recent studies suggest that depressive symptoms during pregnancy may be associated with the development of PPD.<sup>184,189-191,193-195</sup> Any hypothetical role of reproductive steroids in PPD must account for the increase in depressive symptoms during pregnancy.

Studies have examined the relationship between PPD and reproductive steroids by measuring steroid levels (particularly estradiol and progesterone) or changes in levels during pregnancy and the postpartum. The results of these studies in general fail to show any consistent differences between women with PPD and controls.<sup>196</sup> Similarly, while thyroid dysfunction may contribute to postpartum mood dysregulation in a small group of women, it does not appear relevant for the majority of...
women with PPD. PPD, then, cannot be thought of as a simple hormonal excess or deficiency state. If there is no reproductive endocrine abnormality in women with PPD, and symptoms, at least in some cases, develop during pregnancy, could PPD represent an altered sensitivity to reproductive steroids in a subgroup of women? Supportive evidence for this role of differential sensitivity is drawn from two indirect sources. First, vulnerability to PPD appears to associate with vulnerability to other reproductive endocrine–related mood disorders. Several studies,\textsuperscript{197,198} for example, report marked elevations in the prevalence of a history of PPD (up to 68\%) in women with PMS, and high postpartum depressive scores have been associated with a history of PMS.\textsuperscript{199,200} Second, the relevance of reproductive steroids is suggested by recent reports of the efficacy of hormonal treatments of PPD. These reports suggest the acute\textsuperscript{201} and prophylactic\textsuperscript{202} antidepressant effects of estradiol in women with PPD, with the recurrence rate in the latter study reduced to 9\% from an anticipated rate of 35\% to 60\%.

Direct evidence in support of the role of reproductive steroids in the development of PPD comes from a study in which a scaled-down form of pregnancy and parturition was created in euthymic women with and without a history of PPD. Use of this model permitted examination of the role of reproductive steroids in postpartum mood symptoms without many of the factors that confound efforts to study PPD, including dramatic concurrent changes in other endocrine axes (eg, hypothalamic-pituitary-adrenal [HPA] axis), obstetrical pain and complications, varying levels of social support, and stress secondary to childbirth and motherhood. The GnRH agonist leuprolide acetate was used to suppress ovarian steroid production and create a stable hypogonadal baseline, following which supraphysiologic doses of estradiol and progesterone were administered for 2 months and then abruptly (and blindly) withdrawn. This methodology replicated (albeit on a smaller scale) both the elevated reproductive steroid levels seen during pregnancy and the precipitous decline in levels at parturition. Five of the eight women with a history of PPD, and none of the controls, developed significant mood symptoms during both hormone addback and withdrawal, findings consistent with observations that the incidence of depressive symptoms is increased during both the last trimester and postpartum. This study suggests a direct role for estradiol or progesterone or both in PPD and further demonstrates that women with a history of PPD are differentially sensitive to the mood-destabilizing effects of marked changes in levels of reproductive steroids.

**Conclusions**

The differential sensitivity to gonadal steroids seen in women with histories of PMS and PPD emphasizes that the response to a biological signal cannot be inferred without an understanding of the context in which the signal occurs. This context includes current physiological and external environments, prior experience, past history of exposure to the stimulus, and genetic makeup. With the mapping of the human genome, this last contextual determinant becomes of great practical interest as a potential explanation for differential response to steroids.

While genetic polymorphisms clearly influence the transcriptional, physiological, and behavioral responses to activated steroid receptors, it seems equally clear that genetic factors will contribute to, but not solely provide, the explanation for the differential sensitivity seen in women with PMS and PPD. Indeed, even where genetic strain differences are apparent in behavioral sensitivity to reproductive steroids, not all strain members demonstrate the observed steroid-stimulated behavior.\textsuperscript{150} Further, the observed alterations in reproductive steroid–sensitive neurocircuitry, reproductive steroid–activated gene expression, and adult behavior following differential exposure to perinatal steroids\textsuperscript{23,203,204} caution us that gene–environment interactions may yield markedly different phenotypic expressions of the same genotype. The variable influences on behavior, then, are not likely to reduce to simple, unitary explanations for the susceptibility to depression. Nonetheless, by recognizing that a biological stimulus may trigger an affective state change (operate as an affective trigger) only in a specific context of susceptibility, we are in a much better position to meaningfully explore and uncover the pathophysiology of depression. By illuminating the mechanisms underlying the differential sensitivity to reproductive steroids exemplified by women with PMS and PPD, we will significantly advance our understanding of the neurobiology of affective illness.
**Esteroides gonadales, cerebro y conducta: papel del contexto**

La naturaleza y extensión de la influencia del sexo y la función reproductora en el ánimo ha sido objeto por siglos de especulación y controversia. En los últimos 50 años; sin embargo, se ha demostrado cada vez con mayor claridad que no es sólo el cerebro el blanco principal de las hormonas esteroideas de la reproducción, sino que adicionalmente, las hormonas esteroideas – como neurorreguladores- dan origen a un contexto que influye en una amplia gama de actividades cerebrales. Por ejemplo, las acciones neurales y las conductas resultantes son marcadamente diferentes en presencia o ausencia de esteroides gonadales. A su vez, las acciones de los esteroides gonadales son por sí mismas dependientes del contexto. De este modo, aun cuando se pueda demostrar que los esteroides gonadales provocan trastornos del ánimo, esta provocación ocurre con niveles hormonales normales (en oposición a los trastornos del ánimo que acompañan a las endocrinopatías) y los trastornos del ánimo aparecen sólo en un subgrupo de individuos sensibles. La especificidad del contexto y la diferente susceptibilidad para la dis regulación afectiva que se observa en mujeres con trastornos del ánimo relacionados con el ciclo reproductor endocrino, son sin lugar a dudas importantes características que subyacen a una amplia gama de trastornos psiquiátricos en los que los factores genéticos y ambientales no han sido identificados. En consecuencia, los trastornos del ánimo relacionados con el ciclo reproductor endocrino ofrecen una esperanza sin igual para la identificación de aquellos variables del contexto que permiten que estímulos biológicos se transformen específicamente en depresión en individuos que están en riesgo.

**Stéroides gonadiques, cerveau et comportement : rôle du contexte**

La nature et l’importance de l’influence des fonctions sexuelles et reproductives sur l’humeur ont été l’objet de discussion et de controverse depuis des siècles. Cependant, depuis les 50 dernières années, il est devenu de plus en plus évident que non seulement le cerveau est une cible majeure des hormones stéroïdiennes de la reproduction, mais qu’en plus les hormones stéroïdiennes, en tant que neurorégulateurs, créent un contexte qui influe sur une large gamme d’activités cérébrales, c’est-à-dire qu’en fonction de la présence ou de l’absence des stéroides gonadiques, les effets neurologiques et les comportements en résultant sont très différents. De plus, les effets des hormones stéroïdiennes gonadiques dépendent eux-mêmes du contexte. Par conséquent, même quand il est possible de montrer que les hormones stéroïdiennes provoquent les troubles de l’humeur, ces derniers apparaissent pour des concentrations normales d’hormones stéroïdiennes (par opposition aux troubles de l’humeur qui accompagnent les endocrinopathies), et seulement dans un sous-groupe d’individus sensibles. La spécificité du contexte et la différence de sensibilité individuelle aux désordres affectifs, décrites chez des femmes ayant des troubles de l’humeur liés aux hormones de la reproduction, sont de toute évidence des particularités importantes sous-jacentes d’un large échantillon de troubles psychiatriques pour lesquels les facteurs déclenchants n’ont pas encore été identifiés. Par conséquent, les troubles de l’humeur liés aux hormones de la reproduction offrent une possibilité sans précédent d’identifier les variables de ce contexte qui permettent aux stimuli biologiques de se traduire de façon différente en dépression chez les individus à risque.

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