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Neurosteroids in the context of stress: Implications for depressive disorders

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Abstract

Animal models indicate that the neuroactive steroids 3α,5α-THP (allopregnanolone) and 3α,5α-THDOC (allotetrahydroDOC) are stress responsive, serving as homeostatic mechanisms in restoring normal GABAergic and hypothalamic-pituitary-adrenal (HPA) function following stress. While neurosteroid increases to stress are adaptive in the short term, animal models of chronic stress and depression find lower brain and plasma neurosteroid concentrations and alterations in neurosteroid responses to acute stressors. It has been suggested that disruption in this homeostatic mechanism may play a pathogenic role in some psychiatric disorders related to stress. In humans, neurosteroid depletion is consistently documented in patients with current depression and may reflect their greater chronic stress. Women with the depressive disorder, premenstrual dysphoric disorder (PMDD), have greater daily stress and a greater rate of traumatic stress. While results on baseline concentrations of neuroactive steroids in PMDD are mixed, PMDD women have diminished functional sensitivity of $GABA_A$ receptors and our laboratory has found blunted allopregnanolone responses to mental stress relative to non-PMDD controls. Similarly, euthymic women with histories of clinical depression, which may represent a large proportion of PMDD women, show more severe dysphoric mood symptoms and blunted allopregnanolone responses to stress versus never-depressed women. It is suggested that failure to mount an appropriate allopregnanolone response to stress may reflect the price of repeated biological adaptations to the increased life stress that is well documented in depressive disorders and altered allopregnanolone stress responsivity may also contribute to the dysregulation seen in HPA axis function in depression.

Keywords

Neurosteroids; Allopregnanolone; Stress; Premenstrual dysphoric disorder; Depressive disorders

1. Introduction

The concept of stress is as old as medical history itself, dating back at least to the time of Hippocrates who referred both to the suffering associated with disease (pathos) and to the toil (ponos) — the fight of the body to restore itself to normalcy (Hippocrates, 1923). In more recent history, both Walter Cannon (Cannon, 1939) and Claude Bernard (Bernard, 1949) described the ability of all organisms to maintain a constancy of their internal milieu or homeostasis, and 70 years ago Hans Selye, the pioneer of contemporary stress research, first

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described the General Adaptation Syndrome (GAS) as a chronological development of the response to stressors when their action is prolonged (Selye, 1936). While we will return to the concept of generalized biological responses to stress and stress response adaptation as a context to understand pathophysiological processes for neurosteroids in depressive disorders, it is of historical interest to point out here that Selye was the first to document the relatively immediate (within minutes) anesthetic and anticonvulsant properties of progesterone and related compounds administered itraperitoneally to rats (Selye, 1941, 1956). This provided the first evidence that endogenous steroid hormones could influence neuronal excitability on a time scale inconsistent with the classic genomic mechanisms of steroid action. The central nervous system effects of steroid hormones documented by Selye led him to speculate on whether the somnolence of pregnancy, premenstrual tension, and other clinical conditions accompanied by increased steroid-hormone production may find their explanation in that phenomenon (Selye, 1956).

In keeping with the early observations of Selye (1941, 1956) that steroid hormone metabolites could exert central effects within minutes of administration, Purdy and colleagues (Purdy et al., 1991; Barbaccia et al., 1996, 1997) were among the first to demonstrate in rat models that acute stress results in significant increases in both plasma and CNS concentrations of the 3α-hydroxy ring A-reduced steroid metabolites, 3α,5α-THP (allopregnanolone) and 3α,5α-THDOC (allotetrahydroDOC), in physiologic ranges known to enhance GABA receptor-activated Cl- currents (Purdy et al., 1991; Reddy, 2006).

The neuroactive steroids, allopregnanolone and allotetrahydroDOC, are among the most potent allosteric modulators of the $GABA_A$ receptors (nanomolar concentrations) via dose-dependent enhancement of GABA-induced Cl- ion channels (Morrow et al., 1987), and it is through this mechanism that they exert profound anxiolytic effects (Bitran et al., 1995; Brot et al., 1997; Bitran et al., 1999, 2000). Allopregnanolone is the A-ring reduced metabolite of progesterone and is synthesized not only in ovary and adrenals but also de novo in brain (Paul & Purdy, 1992). AllotetrahydroDOC, on the other hand, is derived exclusively from adrenal sources since its mineralocorticoid precursor, deoxycorticosterone (DOC), is synthesized in the adrenal zona fasciculate under the control of ACTH, with no evidence for de novo synthesis of allotetrahydroDOC in brain (Reddy, 2006). Both allopregnanolone and allotetrahydroDOC are highly lipophillic, and animal studies using adrenalectomized versus control rats have demonstrated that not only do peripherally produced concentrations of these neuroactive steroids following stress readily cross the blood–brain barrier, contributing significantly to stress-induced increases in central concentrations of both allopregnanolone and allotetrahydroDOC, but that the major proportion of brain allopregnanolone and allotetrahydroDOC increased by acute stress is produced by peripheral tissues (Purdy et al., 1991). The time course of peripheral versus central neurosteroid responses to stress in rats is quite distinct, however, with the peripheral increase in allopregnanolone being more delayed, peaking between 30 and 70 min following the onset of acute swim stress (Paul and Purdy, 1992; Barbaccia et al., 1998; see Fig. 1). It should be noted that, in contrast to this initial animal work on stress-induced allopregnanolone that relied on high performance liquid chromatography (HPLC) combined with radioimmunoassay (RIA) to measure neurosteroids, more recent studies by Purdy and colleagues (Vallee et al., 2000) using more sensitive and specific gas chromatography/mass spectrometry (GC/MS) methods found lower cortex concentrations of allopregnanolone in response to stress, though plasma allopregnanolone concentrations following acute swim stress remained equivalent to those measured by HPLC/RIA (Fig. 1). The greater central concentrations of allopregnanolone in the earlier studies using HPLC/RIA methods was presumably due to the detection of other related compounds (i.e., pregnenolone) in the brain (Vallee et al., 2000). Nonetheless, the central versus peripheral difference in time course to peak allopregnanolone concentrations in rat following stress remains.

2. Neuroactive steroid responses to stress: behavioral and endocrine adaptations

In rodents, the behavioral effects seen following administration of certain A-ring reduced steroid derivatives, particularly allopregnanolone and allotetrahydroDOC, including anxiolytic (Bitran et al., 1995; Akwa et al., 1999), anti-conflict (Perche et al., 2001; Pinna et al., 2003; Pibiri et al., 2006), antiseizure (Frye, 1995), and antinociceptive effects (Kavaliers & Wiebe, 1987; Wiebe & Kavaliers, 1988; Frye & Duncan, 1994), are consistent with an integrated and adaptive response to stress (Purdy et al., 1991). The pretreatment of animals with the 5α-reductase inhibitor, finasteride (an inhibitor of the rate limiting step in the conversion of progesterone and DOC to their metabolite precursors of allopregnanolone and allotetrahydroDOC) or the administration of GABA antagonists, bicuculline, or picrotoxin (Kavaliers & Wiebe, 1987; Wiebe & Kavaliers, 1988) eliminates many of these behavioral responses to stress, suggesting that these behavioral adaptations to acute stressors are mediated by the 5α-reduced neurosteroids (Reddy, 2003).

In addition to the adaptive short-term behavioral effects associated with increases in allopregnanolone and allotetrahydroDOC summarized above, animal models provide strong and consistent evidence that the A-ring reduced steroid metabolites also act as endogenous suppressors of the endocrine response to stress (Purdy et al., 1991). Specifically, neurosteroids appear to serve as endogenous homeostatic mechanisms restoring both normal GABAergic and hypothalamic-pituitary-adrenal (HPA) function following acute stress (Guo et al., 1995; Patchev et al., 1996; Barbaccia et al., 1998; Strous et al., 2006). Animal models indicate that acute stress results in a rapid decrease in GABAergic neurotransmission and that this reduction in inhibitory neurotransmission with stress is mediated by the $GABA_A$ receptor (Concas et al., 1988; Drugan et al., 1989; Biggio et al., 1990). While the decrease in GABAergic tone occurs immediately with the onset of acute stress, the increase in both plasma and brain allopregnanolone concentrations occur subsequent to both the stressor onset and the reduction in GABAergic neurotransmission, resulting in a functional correlation between endogenous allopregnanolone concentration in brain, the recovery of GABAergic transmission tone, and the disappearance of conflict behavior (i.e. anxiety) (Barbaccia et al., 1998).

Stress-induced increases in allopregnanolone and allotetrahydroDOC also serve to negatively modulate HPA axis activation, thereby facilitating the recovery of physiologic homeostasis following stressful stimuli. For example, using animal preparations, allopregnanolone, dose-dependently suppresses the hypothalamic release of GnRH in vitro. The effect is blocked by bicuculline, a $GABA_A$ receptor antagonist (Calogero et al., 1998), suggesting that hypothalamic suppression by allopregnanolone involves the $GABA_A$ receptor. Additionally, allopregnanolone and allotetrahydroDOC counteract the anxiogenic activity of corticotrophin-releasing factor (CRF) and attenuate methoxamine-stimulated CRF release in vitro in a dose-dependent fashion (Patchev et al., 1994). Several laboratories have also shown that the pretreatment of rats with allopregnanolone, allotetrahydroDOC, or progesterone significantly attenuates stress-induced increases in plasma ACTH and cortisol (Owens et al., 1992; Patchev et al., 1996) and that allopregnanolone affects the gene transcription of arginine vasopressin (AVP) in the paraventricular nucleus (PVN) of the hypothalamus in a pattern similar to that seen with glucocorticoids (Patchev et al., 1996). Increased GABAergic tone also inhibits hypophysiotropic CRF neurons (Owens et al., 1992). The significance of GABA modulation of CRF neurons is underscored by the evidence that CRF neurons in the locus coeruleus and throughout the CNS integrate the autonomic and behavioral responses to stress (Chrousos and Gold, 1992; Owens et al., 1992). Thus, endogenous allopregnanolone and allotetrahydroDOC represent homeostatic mechanisms in the context of adaptation to stress by limiting the extent and duration of reduction in GABAergic inhibitory transmission and activation of the HPA axis. Within this context, it has been suggested that disruption in this homeostatic mechanism

may play an etiopathogenetic role in some psychiatric disorders related to stress and often associated with increased adrenal glucocorticoid output (Barbaccia et al., 1998), the prototypical profile seen in human depression.

In addition to their role in restoring GABAergic tone and suppressing the acute endocrine stress response, animal models also indicate that the A-ring reduced neurosteroids provide long-term protection against adverse effects of early life stressful events. For example, in the validated animal paradigm of early life stress involving the repeated separation of ratpupsfromtheir mothersduring early post-natal life, administration of allotetrahydroDOC not only suppresses the stress vocalizations in maternally deprived rats following separation, but it also abolishes the anxiogenic behavioral after-affects of neonatal stress seen in deprived pups exposed to the plus-maze test (Patchev et al., 1997). Pretreatment with allopregnanolone or allotetrahydroDOC in rat pups also exerts long-term protection against HPA axis responses to stress since it abolishes the greater corticosterone response to subsequent acute stressors seen in neonatally deprived animals relative to never-deprived animals (Patchev et al., 1997; Mitev et al., 2003). Thus, allopregnanolone and allotetrahydroDOC may protect the developing brain against adverse emotional challenges, indicating a role for neurosteroids in the long-term control of behavioral and endocrine responsiveness to stress.

3. Stress dysregulation in neuroactive steroids: implications for depressive disorders

While neurohormonal activation in response to stress is adaptive in the short-term, long-term activation of such responses due to repeated or chronic stress may lead to persistent dysregulation in these stress-responsive factors and set the stage for subsequent illness. This was first documented by Selye in rats, when he described the chronologic development of the nonspecific response to stressors when their action is prolonged. He termed this the GAS (Selye, 1936, 1951, 1955, 1976), which involved a triphasic response: (i) the alarm reaction, in which adaptation has not yet been acquired; (ii) the stage of resistance, in which adaptation is optimum; and (iii) the stage of exhaustion, in which the acquired adaptation is lost (Selye, 1955). Selye subsequently described diseases of adaptation, including psychosomatic diseases as well as immunologic and inflammatory diseases, which depended primarily on excessive or inappropriate responses to stressors, where an essentially useful defensive reaction (e.g., HPA axis activation or emotional arousal in preparation for fight) can be the major cause of disease if the defense is inappropriate under the circumstances (Selye, 1976). While Selye's GAS was first described 70 years ago (Selye, 1936), it is briefly reviewed above because it provides a cornerstone to current conceptualizations on the development of stress-related illness in humans.

In humans, the price of repeated biological adaptations to stress has been termed allostatic load and refers to the long-term effect of physiologic responses to stress (McEwen, 1998). Allostatic load may be expressed as repeated elevations of neurohormonal stress mediators (e.g., cortisol, norepinephrine) over long periods, as a failure to adapt to the same stressor, as a failure to shut off the normal stress response, or as an inadequate hormonal response to stress that may allow other systems that are normally counter-regulated to become overactive (e.g., inadequate secretion of glucocorticoids, resulting in increased levels of inflammatory factors that are normally regulated by the glucocorticoids; McEwen and Seeman, 1999). It has been suggested that such hypoactivation of stress responses may result from a wearing out or exhaustion of the stress-responsive system due to long-term allostatic load (McEwen, 1998). Both animal and human studies indicate that chronic or severe stress exposure, especially early in life (Coplan et al., 1996), can result in persistent alterations in neurobiological systems that are stress responsive (Bremner & Vermetten, 2001; Heim et al., 2001). There is particularly compelling evidence that such long-term adaptation to either early life stress or to chronic on-

going stress occurs for HPA axis regulation (Lemieux & Coe, 1995; Resnick et al., 1995; Coplan et al., 1996; Ladd et al., 1996; Kaufman et al., 1997, Heim et al., 2001; Szikszay & Benedek, 1989; D'Amore et al., 1993; Heim et al., 2002; Bennett et al., 2004), and there is also evidence that it occurs for noradrenergic regulation (Bremner et al., 1996; Young & Breslau, 2004).

Similarly for neuroactive steroid responses to stress, it has been suggested that while such responses may be protective against the damaging effects of stress, dysregulation in the neurosteroid stress response may predispose individuals to the negative effects of stress (Poromaa et al., 2003), perhaps forming the basis for the development of mood disorders (Heim et al., 2001). This is supported, in part, by evidence from animals demonstrating that stressors that produce behavioral depression and anxiety not only alter neurosteroid levels but also regulate $GABA_A$ receptor expression and result in insensitivity to benzodiazepines and neurosteroids (Deutsch et al., 1994; Serra et al., 2000; Dong et al., 2001). Such alterations in $GABA_A$ receptor function, which we will return to later, could set the stage for dysphoric mood potentially resulting from chronic stress.

Indeed, and consistent with a greater allostatic load model (McEwen, 1998), it has been suggested that the neurosteroid depletion consistently documented in patients with depression is likely associated with chronic stress (Reddy, 2003). When compared with non-depressed controls, depressed patients have lower plasma and CSF concentrations of allopregnanolone (Romeo et al., 1998; Uzunova et al., 1998; Strohle et al., 1999, 2000; Nappi et al., 2001; Eser et al., 2006, Uzunova et al., 2006) but higher allotetrahydroDOC concentrations (Strohle et al., 1999, 2000), which may reflect differential alteration in the biosynthesis of deoxycorticosterone or its metabolites in depression (Strohle et al., 1999, 2000). The pathophysiological relevance of these altered neurosteroid concentrations in humans comes from studies showing inverse relationships between allopregnanolone concentrations and severity of the depressive illness (Uzunova et al., 1998; Nappi et al., 2001) and from other studies showing that clinically efficacious treatment with antidepressants is associated with increases in allopregnanolone (Uzunova et al., 1998; Romeo et al., 1998; Strohle et al., 1999, 2000) and decreases in allotetrahydroDOC (Strohle et al., 2000). The antidepressant-like effect of allopregnanolone is also well established in animal models (Khisti and Chopde, 2000; Khisti et al., 2000; Frye & Walf, 2002; Uzunova et al., 2003, 2004).

Although no studies to date have specifically examined the association of chronic stress with neuroactive steroid function in depressed patients, it could be argued that clinical depression is itself a chronic stressor; the link between chronic stress and neurosteroid depletion is supported in part by animal models showing that protracted long-term adaptation to the stress of social isolation, a characteristic feature of human depression (Prince et al., 1997; Roberts et al., 1997), is associated with anxiety, aggression, and decreased response to GABAmimetic drugs and with significantly lower brain and plasma neuroactive steroid concentrations, including allopregnanolone and allotetrahydroDOC (Serra et al., 2000; Guidoti et al., 2001; Dong et al., 2001). The finding that the expression of 5α-reductase (mRNA and protein) in mouse brain, the rate limiting enzyme in the conversion of progesterone to allopregnanolone, is down-regulated during protracted social isolation supports the view that chronic stress could alter neuroactive steroid synthesis (Reddy, 2006). Moreover, the persistent decreases in the concentrations of neuroactive steroids in the brain of rats exposed to long-term social isolation stress is also associated with a decrease in the function of brain $GABA_A$ receptors and with persistent alterations in neuroactive steroid responses to subsequent acute stressors (Serra et al., 2000). Similar to depressed patients, socially isolated animals respond to the anti-depressant fluoxetine with a normalization of allopregnanolone brain content (Guidoti et al., 2001).

In contrast to the diminished neuroactive steroid concentrations seen in chronically stressed rats, and consistent with the role of the neuroactive steroids as endogenous negative modulators of the HPA axis (Guo et al., 1995; Patchev et al., 1996), plasma corticosterone concentrations are elevated in isolated animals compared with controls (Serra et al., 2000). Thus, this profile of diminished neurosteroid concentrations coupled with elevated glucocorticoids in socially isolated animals is strikingly similar to that seen in patients with melancholic depression, since many depressed patients are also hypercortisolimic relative to non-depressed controls (e.g., Nemeroff, 1998; Young et al., 2000a, 2000b). Chronic activation of the HPA axis, including greater CRF concentrations and gene expression in depressed patients (Roy et al., 1987; Raadsheer et al., 1995; Nemeroff, 1998), is clearly implicated in the pathophysiology of depressive disorders (Nemeroff, 1998). While numerous mechanisms may contribute to HPA axis hyperactivation in depression, including dysregulation in glucocorticoid negative feedback mechanisms or altered circadian rhythm (von Bardeleben and Holsboer, 1988; Young and Veldhuis, 2006), diminished neuroactive function represents an additional candidate.

Both clinical and empirical evidence clearly indicates that stress plays a major, independent role in contributing to the onset and exacerbation of depressive disorders (Kendler et al., 1993; Brown et al., 1994; Frank et al., 1994). Consistent with the concept of allostatic load, the possibility exists that an inadequate neuroactive steroid response to stress may allow the HPA axis, which is normally counter-regulated by neurosteroids, to become overactive. Research on neuroactive steroid responses to stress in humans is scant. Genazzani and colleagues (1998) initially demonstrated in healthy men and women that both GnRH and CRF administration increased serum progesterone and allopregnanolone concentrations. In their study, plasma was sampled every 15 min for 120 min, with peak allopregnanolone responses to the endocrine GnRH and CRF challenge occurring at 45 and 60 min, respectively, post-challenge (see Fig. 2). Suppression of adrenal steroidogenesis with dexamethasone markedly reduced allopregnanolone, indicating that in humans both ovary and adrenal cortex are major sources of circulating allopregnanolone. Subsequent work by this group has yielded a similar time course to peak plasma allopregnanolone response to the endocrine CRF challenge in healthy male and female controls, although not in women with hypothalamic amenorrhea who fail to show any increase in allopregnanolone (Meczekalski et al., 2000) or in obese men and women who show an exaggerated allopregnanolone response to CRF infusions with an earlier peak (Menozzi et al., 2002). Taken together, the results of these endocrine challenge studies suggest that neuroactive steroids may increase in response to stress in healthy humans as they do in animals. If so, any alterations in neuroactive steroid responses to stress may play a pathophysiological role in the development or maintenance of stress-related disorders, including depressive disorders.

4. Baseline neuroactive steroids concentrations in premenstrual dysphoric disorder

Our laboratory has had the exciting opportunity to conduct some of the initial research on neuroactive steroid responses to mental stressors, particularly allopregnanolone, in women with depressive disorders. Our earliest work examined allopregnanolone concentrations and reactivity to laboratory stressors in women with premenstrual dysphoric disorder (PMDD). PMDD, a depressive disorder, is characterized by the cyclic recurrence during the luteal phase of the menstrual cycle of a variety of emotional and physical symptoms of sufficient severity to interfere with function. Importantly, in order to meet PMDD criteria as outlined in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV, 1994), there must be clear evidence of complete symptom remission shortly after the onset of menses. Consequently, PMDD is differentiated from the premenstrual exacerbation of a chronic depression, dysthymia, or other mood disturbance. Finally, PMDD must be confirmed by prospective daily symptoms records over a minimum of 2 months (DSM-IV, 1994). PMDD

afflicts 5−10% of women in their reproductive years (Cohen et al., 2002), and although the symptoms of PMDD are of shorter duration than those of other depressive disorders, the impact of PMDD symptoms on quality of life during the premenstrual luteal phase is equivalent to that seen with major depression, post-traumatic stress disorder, and panic disorder (Freeman & Sondheimer, 2003).

Due to the cyclical nature of the mood disturbance in PMDD, much early attention was paid to the pathophysiological role of the gonadal steroid hormones, particularly progesterone since it is elevated during the symptomatic luteal phase only and at very low concentrations during the follicular and ovulatory phases of the cycle. However, those studies found little evidence to support the view that either an excess or deficiency in progesterone or estradiol concentrations are etiologically relevant to the disorder (Rubinow & Schmidt, 1992), and the majority of controlled trials have failed to find that progesterone administration is efficacious in PMDD (Freeman et al., 1995; see Freeman, 2004, for review). Nonetheless, there is clearly evidence for an obligatory role of the gonadal steroid hormones in PMDD, since PMDD is evident only during the reproductive years (DSM-IV, 1994) and its associated behavioral and emotional symptoms are alleviated with ovarian suppression (Schmidt et al., 1998) or during spontaneous anovulatory cycles (Hammarback et al., 1991). Consequently, investigations into diagnosis-related differences in neuroactive metabolites of progesterone have been undertaken.

Alterations in allopregnanolone concentrations have received the greatest attention in PMDD research, since plasma levels of allopregnanolone follow closely those of progesterone during the symptomatic luteal phase. The anxiogenic $GABA_A$ receptor antagonists or partial agonists, such as dehydroepiadrosterone (DHEA), DHEA sulfate, pregnenolone, and pregnenolone sulfate have also been examined in PMDD, as well as the potential imbalance between these positive versus negative $GABA_A$ receptor modulators. Since retrospective reporting of premenstrual symptoms is associated with an overestimation of severity and with a high rate of false positive PMDD diagnoses (Marvan & Cortes-Iniestra, 2001), this review will be confined to the 6 studies to date that have examined neuroactive steroid concentrations in prospectively confirmed women with PMDD (see Table 1).

The earliest studies by Schmidt et al. (1994) and Wang et al. (1996), based on small samples of PMDD and control women reported no differences between patients and controls in either follicular or luteal phase plasma concentrations of the 3α-hydroxysteroid metabolites of progesterone, allopregnanolone, and pregnanolone or in pregnenolone sulfate, an anxiogenic inverse agonist at $GABA_A$ receptors. Furthermore, the Schmidt et al. (1994) study found no diagnosis-related differences in the allopregnanolone/pregnanolone ratio or in the ratios of allopregnanolone or pregnanolone to progesterone and found no association of neuroactive steroid concentrations with symptoms of depression or anxiety in PMDD women. In contrast to the study of Schmidt et al. (1994) that assessed neuroactive steroids at only 1 time point in a single luteal phase, in the study of Wang et al. (1996), that assessed plasma concentrations of neurosteroids and symptoms daily during the luteal phase of 2 consecutive cycles, more negative symptoms occurred in cycles higher in pregnenolone and pregnenolone sulfate, while more positive symptoms occurred in cycles higher in allopregnanolone and its precursor (5α-DHP).

In a larger sample of 35 PMDD women and 38 controls, Rapkin et al. (1997) reported that PMDD patients had lower luteal phase plasma concentrations of allopregnanolone and lower allopregnanolone/progesterone ratio than controls. Thus, the study of Rapkin and colleagues also suggested possible diagnosis-related differences in the conversion of progesterone to allopregnanolone. Lower allopregnanolone concentrations in PMDD women were also found in 2 subsequent studies. Monteleone et al. (2000) found lower plasma allopregnanolone in 28 women seeking help from a PMS clinic compared with non-help seeking controls during the

luteal but not in the follicular phase, and Lombardi et al. (2004) found that PMS women had lower baseline allopregnanolone levels in the luteal phase only, though higher testosterone, DHEA and a DHEA/allopregnanolone ratio in both cycle phases. In contrast to the studies reviewed above, the first study from our laboratory to assess plasma allopregnanolone concentrations in 25 PMDD women compared with 13 non-PMDD controls found that PMDD women had higher luteal phase plasma allopregnanolone concentrations and a greater allopregnanolone/progesterone ratio than controls.

Why might such discrepancies exist in the literature on neuroactive steroids in PMDD? Some methodological differences across studies that may, either independently or in combination, influence findings are also summarized in Table 1. One methodological factor involves differences in the diagnostic criteria employed for PMDD since only some of the existing studies relied on DSM criteria (Wang et al., 1996;Rapkin et al., 1997;Girdler et al., 2001), while others did not (Schmidt et al., 1994;Monteleone et al., 2000;Lombardi et al., 2004). Differences across studies in the assessment and inclusion or exclusion of women with current or past psychiatric illness might also impact on findings since histories of depression are more prevalent in PMDD populations (Pearlstein et al., 1990;Cohen et al., 2002), since reduced allopregnanolone concentrations are consistently found in patients with current depression as summarized above, and since our own work suggests that histories of depressive disorders impact on allopregnanolone concentrations, at least during stress (see below). Additionally, since changes in allopregnanolone concentrations parallel changes in progesterone concentrations, and since progesterone concentrations can vary markedly and change rapidly day-to-day in the luteal phase, study differences in the luteal phase sampling period may also contribute to discrepancies in the literature. This is supported by the study of Rapkin et al. (1997) where diagnosis-related differences in allopregnanolone concentration were examined at 2 time points in the luteal phase, days 19 and 26 of an idealized 28-day cycle. In that study, PMDD and non-PMDD groups were equivalent in their allopregnanolone concentrations on day 19 but not on day 26 of the cycle when PMDD women had significantly lower concentrations than non-PMDD controls. Finally, to the extent that allopregnanolone concentrations are responsive to venipuncture stress, then study differences in blood sampling procedures and/or other nonspecific effects associated with novelty of the laboratory or clinic environment may impact on diagnosis-related differences in allopregnanolone concentrations as our own work reviewed later in this paper suggests.

While our initial study (Girdler et al., 2001) that found higher, and not lower, luteal phase allopregnanolone concentrations in PMDD women was limited by the relatively small sample of non-PMDD control women, we did employed strict DSM diagnostic criteria to confirm PMDD status and used structured clinical interview to exclude both PMDD and non-PMDD women with any current Axis I diagnosis. To the best of our knowledge, our study was the only one to sample allopregnanolone using an indwelling intravenous line following a 25-min adaptation rest period, while the other studies appeared to have relied on single stick venipuncture. Although women with histories of Axis I disorders, particularly depression, were enrolled in our study, we did not control for potential diagnosis-related differences in the prevalence of histories of depression, nor did the majority of the studies summarized in Table 1. Our subsequent work, summarized below, suggests that histories of depression may impact on allopregnanolone concentrations in women.

5. HPA axis and $GABA_A$ receptor function in PMDD

With these procedural caveats in mind, it is important to point out that our findings for higher, and not lower, allopregnanolone concentrations in PMDD women is consistent with a number of other observations in PMDD populations. First, as reviewed above, allopregnanolone negatively modulates the HPA axis in animal models, and although null findings have been

reported (Su et al., 1997; Bloch et al., 2000; Lombardi et al., 2004) where diagnosis-related differences exist, they suggest blunted HPA axis function in PMDD. For example, a number of studies have reported lower circulating ACTH or cortisol concentrations in PMDD women (Rabin et al., 1990; Redei & Freeman, 1993; Girdler et al., 1998), increased ACTH response to ovine CRF (consistent with lower endogenous CRF; Rabin et al., 1990), a delayed (Steiner et al., 1999) or blunted HPA axis response to serotonergic agents (Bancroft et al., 1991; Su et al., 1997), and the absence of the normal plasma cortisol and ACTH response to exercise stress in the luteal phase that is seen in non-PMDD women (Roca et al., 2003). More compelling evidence that the greater allopregnanolone concentrations that we observed in PMDD women might negatively modulate HPA axis function in that population comes from our own results reported in Girdler et al. (2001), documenting significantly lower plasma cortisol concentrations in the PMDD women than the controls (5.8±0.6 vs. 7.7±0.7 μg/dL, respectively; $P<0.05$). Moreover, for the entire sample of women, higher luteal phase allopregnanolone tended to be associated with lower luteal phase cortisol concentrations ($r=-0.32$, $P=0.05$). Although it should be pointed out that higher allopregnanolone concentrations in obese subjects in response to a CRF challenge test was not found to be related to plasma cortisol concentrations (Menozzi et al., 2002).

Higher circulating concentrations of allopregnanolone are also consistent with the evidence for alterations in $GABA_A$ receptor function in PMDD as assessed via saccadic eye velocity (SEV) responses to benzodiazepines or $GABA_A$ agonists. Since benzodiazepines, acting via the $GABA_A$ receptor, are known to reduce SEV in a dose-dependent fashion (Hommer et al., 1986), SEV is believed to be a sensitive measure of benzodiazepine/$GABA_A$ receptor sensitivity in humans. Using placebo-controlled designs, Sundstrom and colleagues have shown in a series of studies that PMDD women show less of a reduction in SEV to intravenous diazepam (Sundstrom et al., 1997a), midazolam (Sundstrom et al., 1997b), and pregnanolone (Sundstrom et al., 1998) than non-PMDD controls. Behaviorally, PMDD women also generally report less sedation in response to the i.v. benzodiazepines (Sundstrom et al., 1997a, 1997b). The clinical significance of these results comes from their findings that when PMDD women are divided into lower versus higher symptom severity groups, the more severe PMDD symptom groups respond with less of a reduction in SEV (Sundstrom et al., 1997b, 1998) and with lower sedation ratings (Sundstrom et al., 1998) in response to benzodiazepines. Since there is no evidence that PMDD women differ in the density or affinity of peripheral benzodiazepine receptors, at least as measured on lymphocytes (Daly et al., 2001), the findings of Sundstrom and colleagues indicate diminished functional sensitivity of $GABA_A$ receptors in PMDD.

This is consistent with studies finding modest or no clinical efficacy with benzodiazepine treatment for PMDD (Schmidt et al., 1993; Freeman et al., 1995; Evans et al., 1998), though exceptions exist (Harrison et al., 1987), and with lack of clinical benefit associated with a progesterone intervention or with progesterone induction of supraphysiologic levels of 5α- and 5β-progesterone metabolites (Freeman et al., 1995; Vanselow et al., 1996; see Wyatt et al., 2001 for review). It is also consistent with the results of a placebo-controlled clinical trial of antidepressants that found that PMDD women who were classified as “improved” with treatment had significantly lower, and not higher, plasma allopregnanolone concentrations at post-treatment than PMDD women who did not improve (Freeman et al., 2002).

6. The neurosteroid withdrawal hypothesis in PMDD

The animal literature suggests that high concentrations of allopregnanolone may change the characteristics and function of the $GABA_A$ receptor. For example, studies in rats have shown that both in vitro and in vivo long-term exposure to high concentrations of positive allosteric modulators acting at various sites of the $GABA_A$ receptor results in a down-regulation of the

receptor through a reduction in the abundance of specific receptor subunit mRNAs (see Follesa et al., 2001, for review). Moreover, the changes in the abundance of the subunit mRNAs are associated with changes in $GABA_A$ function, since long-term exposure to progesterone and its metabolites results in reduced sensitivity of $GABA_A$ receptors to the administration of diazepam or allopregnanolone (Follesa et al., 1998; Concas et al., 1999; Follesa et al., 2001). If similar effects occur in human brain, then this mechanism could account for the reduced sensitivity to positive $GABA_A$ allosteric modulators documented in PMDD as summarized above.

Relatedly, because any potentially dysphoric effects of allopregnanolone in the luteal phase would occur following a period of relative allopregnanolone withdrawal in the follicular phase, animal models of allopregnanolone withdrawal have been developed to study neurosteroid mechanisms in PMDD (Gallo & Smith, 1993; Smith et al., 2006). The work of Smith and her colleagues has demonstrated that neurosteroid withdrawal results in a state of anxiety and to a relative insensitivity to the anxiolytic effects of benzodiazepines and that these effects appear to be mediated by an increase in the expression of the α4-containing $GABA_A$ receptor subunit in brain (Smith et al., 1998a, 1998b, 2006). Recently, Smith et al. (2006), examined withdrawal from naturally occurring high nocturnal concentrations of allopregnanolone in mice via the administration of finasteride for 3 days. In that study, only vehicle control mice showed the expected anxiolytic effects of allopregnanolone administration in the elevated plus maze paradigm, and this was true whether mice were tested in the presence or absence of an aversive auditory stimulus. In mice treated with finasteride, however, and in the presence of the aversive auditory stimulus, allopregnanolone administration had the opposite effect, eliciting significant decreases in open arm time and number of entries in the plus maze test, indicative of increased anxiety. These mice were also insensitive to benzodiazepine administration. In the absence of the aversive stimulus, allopregnanolone administration had no significant effect on behavior of finasteride-treated animals. These results indicate that both withdrawal from high concentrations of allopregnanolone, and aversive, stressful stimuli are necessary to reverse the normally anxiolytic effect of allopregnanolone to an anxiogenic action, and that this may come about through changes in the agonism properties of $GABA_A$ receptors following exposure to and withdrawal from allopregnanolone (Smith et al., 2006). That such a phenomenon might occur in PMDD women is supported by the work of Le Melledo et al. (2000) showing that exposure to flumazenil, a benzodiazepine receptor antagonist, in the luteal phase elicits marked increases in panic symptoms in PMDD women but not in non-PMDD controls. This effect is consistent with a shift in benzodiazepine sensitivity toward inverse agonism, as is seen with panic patients exposed to flumazenil (Nutt et al., 1990).

While speculative, our finding for increased luteal phase plasma allopregnanolone concentrations in PMDD women relative to non-PMDD women (Girdler et al., 2001), the work of Freeman et al. (2001), suggesting that clinical improvement with antidepressant treatment is associated with lower, and not higher, allopregnanolone concentrations in PMDD, the observation for positive correlations between luteal phase progesterone concentrations and premenstrual symptom severity in PMDD women but not controls (Redei & Freeman, 1995), and the work of Schmidt et al. (1998) demonstrating that administration of the parent compound, progesterone, precipitates the return of dysphoric symptoms in PMDD women whose symptoms had been minimized following ovarian suppression, an effect not seen in non-PMDD women, is consistent with the animal studies summarized above suggesting that allopregnanolone may actually reverse to increase anxiety rather than to act as anxiolytic under some conditions (i.e., in the context of stress) and in certain vulnerable individuals (Smith et al., 2006).

7. Allopregnanolone responses to stress in PMDD

To the extent that stress exposure modifies the effects of allopregnanolone on $GABA_A$ receptor function and behavior, as the animal work of Smith et al. (2006) suggests, then women who develop PMDD may be at increased vulnerability for dysregulation in allopregnanolone function. PMDD women report more stressful life events and that daily stressors have a greater impact on their lives than non-PMDD women (Girdler et al., 1993; Woods et al., 1997). PMDD women also report more traumatic life stress, including sexual and physical abuse histories (Paddison et al., 1990; Golding & Taylor, 1996, 2000; Girdler et al., 2003, 2007). Since allopregnanolone is stress responsive, at least in animal models (Purdy et al., 1991; Barbaccia et al., 1996, 1997), greater allostatic load in PMDD resulting from more severe life stress could contribute to the elevated allopregnanolone concentrations that we have seen in PMDD women (Girdler et al., 2001) and result in the documented alterations in $GABA_A$ receptor function in PMDD (Sundstrom et al., 1997a, 1997b, 1998), including alterations in the agonism properties of the $GABA_A$ receptor as animal models (Smith et al., 2006) and human studies of PMDD suggest (Le Melledo et al., 2000). This could then explain the seemingly paradoxical association between increasing allopregnanolone concentrations in the luteal phase and increased dysphoric mood states in PMDD. This is supported by a recent study (Andreen et al., 2006) in postmenopausal women given increasing sequential doses of oral micronized progesterone, where the corresponding increases in allopregnanolone concentrations were associated with the development of negative mood states, at least within physiologic ranges corresponding to the increase in allopregnanolone seen from the follicular to the early–mid luteal phase in normally cycling women (Genazzani et al., 1998).

Further evidence that alterations in allopregnanolone concentrations or mechanisms may reflect increased allostatic load in PMDD also comes from our first study of allopregnanolone in PMDD (Girdler et al., 2001), where we had the exciting opportunity to be the first laboratory to assess allopregnanolone reactivity to mental stress in humans. In the luteal phase, we sampled plasma allopregnanolone via indwelling i.v. at 2 time points, once following an extended baseline rest period (yielding the group differences in allopregnanolone concentrations and inverse relationship to plasma cortisol described earlier) and again ~ 17 min after the onset of a mental stressor battery involving speech preparation, delivery of a speech and a serial addition task. Allopregnanolone reactivity to mental stress was analyzed as change scores, subtracting baseline concentrations from stress concentrations. In the 24 PMDD women and 13 non-PMDD controls, we found a tendency ($P<0.010$) for the groups to differ in the direction of their allopregnanolone response to mental stress since only the controls showed the expected stress-induced increase in allopregnanolone (see Fig. 3). In fact, a full 83% of controls showed a stress-induced increase in allopregnanolone compared with only 42% of PMDD women ($P<0.05$). Moreover, lack of allopregnanolone responsiveness to stress in PMDD women was related to their greater baseline allopregnanolone concentrations since allopregnanolone reactivity and baseline concentrations were negatively correlated in the PMDD group ($r=-0.59$, $P<0.001$) but not in the controls ($r=-0.23$, $P=0.46$).

Our finding for dysregulation in the allopregnanolone response to mental stress in PMDD is consistent with earlier work from our laboratory, showing alterations in cardiovascular reactivity and plasma norepinephrine and cortisol concentrations at rest and during mental stressors in PMDD women relative to non-PMDD controls (Girdler et al., 1993, 1998). It is also consistent with the endocrine challenge work of Monteleone et al. (2000) and Lombardi et al. (2004) in PMDD women. Despite the fact that those investigators reported lower, and not higher, baseline allopregnanolone in PMDD (Table 1), in response to an ACTH stimulation test following dexamethasone suppression, PMDD women had a significantly blunted adrenal allopregnanolone response compared with controls during the luteal phase (see Fig. 4; Lombardi et al., 2004), and a blunted ovarian allopregnanolone response to a GnRH challenge

relative to controls (Monteleone et al., 2000). Taken together, these results indicate an impaired anxiolytic $GABA_A$-mediated response during stress in PMDD (Monteleone et al., 2000) that we suggest may be related to a greater allostatic load resulting from repeated biological adaptations to the greater daily stress and/or traumatic stress documented in women with PMDD. As described earlier (McEwen, 1998; McEwen & Seeman, 1999), increased allostatic load may be expressed as elevations of stress mediators over long periods, such as the greater baseline allopregnanolone that we documented or as an inadequate hormonal response to stress as documented in the blunted allopregnanolone responses to mental and pharmacological challenges in PMDD women.

8. Histories of depression and allopregnanolone stress responsivity

While our first study generated interesting preliminary data suggesting dysregulation in allopregnanolone reactivity to stress in PMDD, one significant limitation to our work and to all the work on allopregnanolone in PMDD that preceded it involves the failure to either assess or to control for group differences in prior histories of depression. Histories of depression, which are more prevalent in PMDD women (Cohen et al., 2002), may provide a context of vulnerability for the dysphoric effects associated with steroid hormones (Rubinow, 2005). For example, Bloch et al. (2000) demonstrated that euthymic women with a past history of postpartum depression experienced significant depression when exposed to high doses of hormone add-back and withdrawal, effects not seen in women with no prior history of depression. Divergent evidence suggests that in euthymic women, histories of depression are associated with persistent disturbance in HPA axis function (Young et al., 2000a, 2000b) as well as thyroid axis function (Pedersen et al., 1993) relative to never-depressed women.

Consequently, in our subsequent study (Klatzkin et al., 2006a), we set out to address the issue of whether the discrepancies that exist in the literature on diagnosis-related differences in allopregnanolone concentrations seen between PMDD and non-PMDD women may relate, in part, to a greater likelihood of prior depression in PMDD samples. Thus, we specifically recruited non-PMDD women with or without histories of depression, requiring greater than 7 months in full remission from depression for both PMDD and non-PMDD women. We compared 26 PMDD women with 39 non-PMDD controls; and based on structured interview, we classified 14 PMDD women (54%) and 17 non-PMDD women (44%) as having a history of a depressive disorder (69% with prior major depression, 19% with prior minor depression, 12% with prior adjustment disorder with depressed mood). No subject was taking any prescription medication and for both groups it had been, on average, 60 months since their last depressive episode. In confirmed luteal phases, we sampled plasma allopregnanolone immediately after venipuncture stress associated with the i.v. placement, again 25 min later after an extended baseline rest, and at 30 and 60 min following the onset of the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), a stressor battery involving speech and mental arithmetic lasting ~ 25 min. The TSST reliably induces large and consistent HPA axis responses (Kirschbaum et al., 1993, 1995a, 1995b). This time, by characterizing women based on prior depression, we found that all women with depression histories, regardless of PMDD diagnosis, showed alterations in their allopregnanolone responses to stress. Women with prior depression showed significant decreases in allopregnanolone from baseline to post-stress at both the 30- and 60-min time points ($P<0.005$) while women with no prior depression showed modest, though nonsignificant increases in allopregnanolone from baseline to post-stress (see Fig. 5). Nonetheless, the directional difference in allopregnanolone response to mental stress between the 2 groups was statistically different ($P<0.005$).

The lack of a significant increase in post-stress allopregnanolone in the never-depressed women is worth comment. While this study sampled for stress allopregnanolone 30 and 60 min following the onset of the mental stressor battery, modeling the sampling intervals on animal

studies (Purdy et al., 1991) and human endocrine challenge studies (Genazzani et al., 1998), the possibility exists that these intervals missed the peak allopregnanolone response to mental stress in human females. This is supported by the comparison of the stress-induced increase in allopregnanolone in the never-depressed women in the present study with the non-PMDD controls in our first study (Fig. 3), since the former group showed a response that was only 20% of what we observed in the non-PMDD controls when allopregnanolone was sampled earlier, at 17 min post-stress onset. This is also supported by recent preliminary data from our laboratory indicating that in healthy, non-PMDD females with no history of depression, peak allopregnanolone responses occur ~ 15 min after stress onset (unpublished data). Consequently, failure to capture peak allopregnanolone responses to stress may have contributed to our inability to detect PMDD-related differences in allopregnanolone stress responsivity in this second study (Klatzkin et al., 2006a). An alternative, though not mutually exclusive possibility, is that as part of the dysregulation in allopregnanolone stress responsivity, women with depressive disorders show a different time course of the allopregnanolone response to stress and this may contribute to the stress-induced decreases in allopregnanolone that we documented both in PMDD women (Fig. 3) and in women with histories of depression (Fig. 5).

In our second study (Klatzkin et al., 2006b), women with prior depression also failed to show the expected recovery in allopregnanolone from venipuncture stress to extended rest that was evident in never-depressed women (i.e., never-depressed women showed a decrease in allopregnanolone from venipuncture to extended baseline rest). Also, women with prior depression did not show the expected positive correlation between luteal phase progesterone and luteal phase allopregnanolone concentrations (r=0.16) that was seen in never-depressed women (r=0.37, P<0.005). This finding is similar to the absence of a relationship between progesterone and allopregnanolone documented in women with current post-partum dysphoria (Nappi et al., 2001) and documented in PMDD women relative to controls in the luteal phase (Monteleone et al., 2000), although that study did not assess histories of depression. Thus, what our initial study indicated was an effect of PMDD diagnosis on allopregnanolone responsivity to mental stress, our more recent work suggests may have reflected, at least in part, the greater prevalence rates of histories of depression in PMDD women.

One remarkable feature of these findings is that, on average, women had been in full remission from their prior depressive episode for ~ 5 years. Thus, these data suggest that histories of depression may be associated with persistent, long-term effects on allopregnanolone responsivity to stress and that the greater likelihood of prior depression in PMDD women may have contributed to previous findings for lower allopregnanolone concentrations or blunted allopregnanolone responsivity to challenge in PMDD women (Rapkin et al., 1997; Monteleone et al., 2000; Girdler et al., 2001; Lombardi et al., 2004). Moreover, to the extent that allopregnanolone negatively modulates the HPA axis following stress, then our results are also consistent with HPA axis abnormalities seen in depression, since it is well established that a large proportion of patients with melancholy depression are hypercortisolimic (Nemeroff, 1998) and show exaggerated HPA axis responses to mental stress (Heim et al., 2000; Young and Breslau, 2004). More relevant, euthymic women with a history of major depression show elevated diurnal salivary cortisol relative to never-depressed women (Young et al., 2000a, 2000b). Thus, the possibility exists that the hypercortisolimia frequently documented in depression may be an associated feature of the depleted allopregnanolone concentrations seen in patients with depression or the altered allopregnanolone response to stressors seen in our sample of women with depression histories.

9. Alterations in allopregnanolone responses to stress in prior depression: relevance to PMDD

Our findings for differences in allopregnanolone responsivity as a function of prior depression and not PMDD in our second study is not to say that depression-related alterations in allopregnanolone responsivity to challenge do not have special clinical relevance for PMDD women. First, 45−60% of PMDD women have a history of major depression (Pearlstein et al., 1990; Cohen et al., 2002). Second, in our study we also documented that women with histories of depression had more severe premenstrual symptoms than never-depressed women, including greater premenstrual depression ($P<0.005$), irritability ($P<0.001$), labile mood ($P<0.005$), and fatigue ($P<0.07$). Using multiple regression techniques, we then examined the degree to which allopregnanolone measures predicted premenstrual symptom severity in PMDD women with and without prior depression. Greater allopregnanolone levels at extended baseline rest (reflecting a failure to recover from venipuncture stress) was a significant predictor of greater premenstrual depression, irritability, and labile mood, while greater decreases in allopregnanolone at 30 min following stress was a significant predictor of greater premenstrual depression. Together these measures of allopregnanolone reactivity to stress accounted for a significant 30−54% of the variance in symptoms. But this was true only for PMDD women with depression histories. Allopregnanolone responsivity to stress did not predict premenstrual symptoms in PMDD women with no prior history of depression. Thus, the possibility exists that failure to recover from stressors or failure to mount an appropriate allopregnanolone response to stress reflects the price of repeated biological adaptations to the increased life stress that is well documented in PMDD women and may contribute to the greater emotional and behavioral impact of daily stressors in the large subgroup (45−60%) of PMDD with histories of depression. If confirmed, these results are consistent with more recent conceptualizations of PMDD as a heterogeneous disorder with respect to pathophysiological mechanisms (Halbreich, 2003).

10. Conclusions and future directions

In humans, as in animal models, it appears that allopregnanolone is responsive to HPA axis activation induced by pharmacological challenge or by mental stress. While animal models provide compelling evidence for the adaptive role of stress-induced allopregnanolone, in terms of both behavioral and neuroendocrine responses to acute stress, these studies also demonstrate that chronic stress, such as occurs in animal models of depression, results in persistent alterations in $GABA_A$ receptor function and neuroactive steroid responses to subsequent acute stress. The evidence for alterations in baseline neuroactive steroid concentrations in depressive disorders, combined with our preliminary work suggesting altered allopregnanolone reactivity to stress in women with depressive disorders, suggest that investigations into the role of neuroactive steroid stress responsivity and the regulatory role of such responses with regard to the HPA axis in the pathophysiology of depressive disorders in humans is indicated. While this represents an exciting and innovative approach to understanding causal factors in depressive illness, it will be important to proceed cautiously by first establishing reliable studies in healthy human males and females on the time course of the allopregnanolone response to stress, and to investigate other neuroactive steroids that are detectable in human plasma, are stress responsive, and are potent modulators of the $GABA_A$ receptor, including both positive modulators such as allotetrahydroDOC and negative modulators such as pregnenolone sulfate. The nature of the stressful stimuli in terms of duration, controllability and predictability, as well as gender and ethnicity, may be important modulators of neurosteroid responses to stress, since each of these factors has been shown to alter the magnitude and time course of other stress-responsive neuroendocrine factors. Some of these initial studies are currently underway in our laboratory (e.g., Girdler et al., 2006).

The establishment of a reliable neuroactive stress response profile in healthy humans, as has been done for the HPA axis response to social stress (e.g., Kirschbaum et al., 1993, 1995a, 1995b; Young et al., 2000a, 2000b), will be needed to address questions suggested by some of the recent work from our laboratory. For example, whether depressive illness results in long-term alterations in neurosteroid responsivity, persisting beyond remission of the depressive episode, and whether such dysregulation results in altered stress responsiveness to even mild stressors later, either directly or indirectly via homeostatic forces affecting the HPA axis, setting the stage for the recurrence of a depressive episode with stress. Such studies may have direct implications for treatment of depressive illness since selective serotonin reuptake inhibitors (SSRI), while the first line of pharmacotherapy for depressive disorders, do not show uniform efficacy for all depressive illness. This is especially true for PMDD where there is a 40% non-response rate to SSRI (e.g., Steiner et al., 1995; Pearlstein et al., 2000).

"Stress is the salt of life — few people would like to live an existence of no runs, not hits, no errors" (Selye, 1976). Thus, the role of the stress researcher may not be to focus on ways of eliminating stress from individuals' lives but to identify ways of maintaining adaptive biological and cognitive responses to life's stressors.

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Abbreviations

3α,5α-THP, allopregnanolone; 3α,5α-THDOC, allotetrahydroDOC; HPA, hypothalamic-pituitary-adrenal; PMDD, premenstrual dysphoric disorder.

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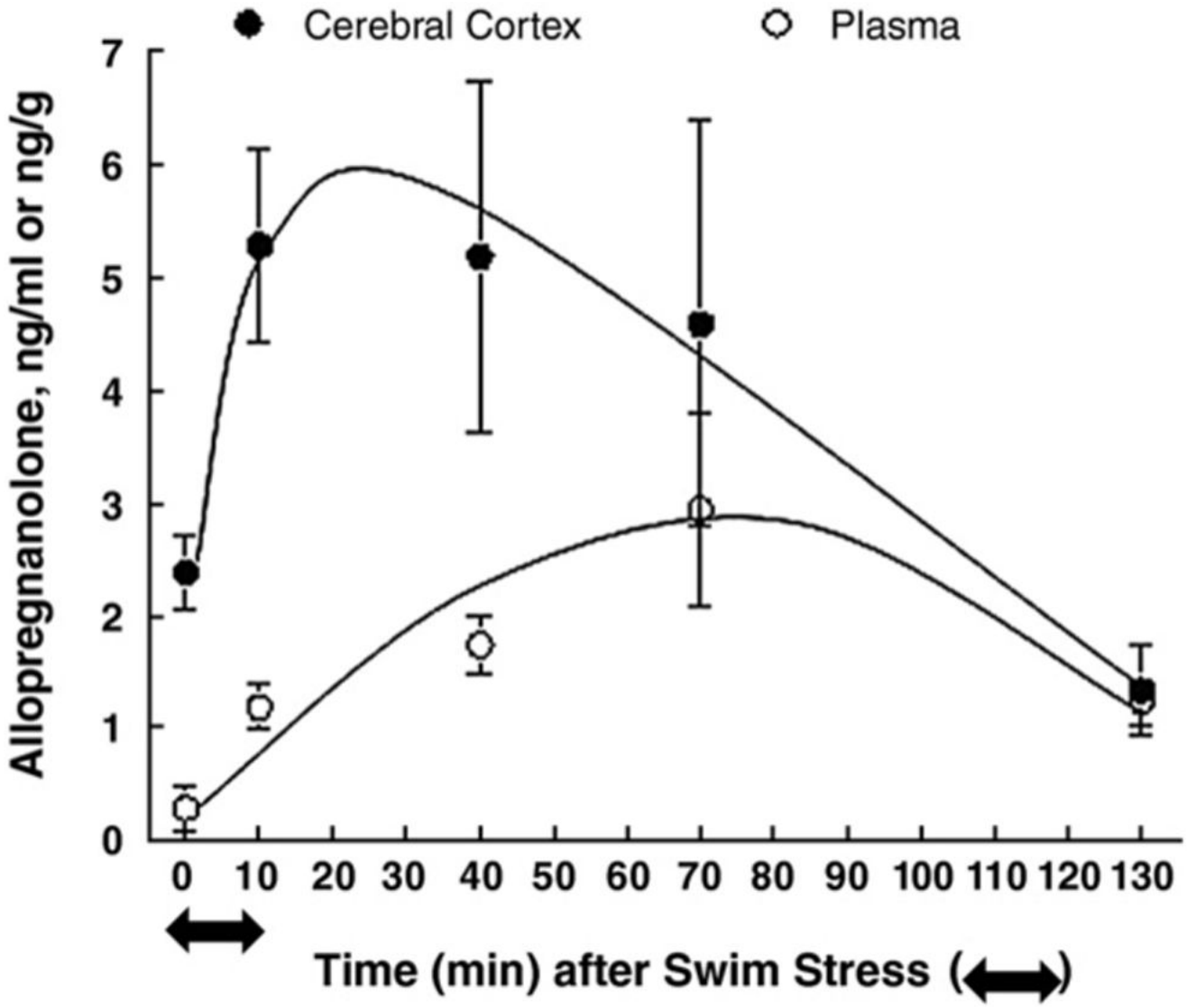

Fig. 1.

Allopregnanolone levels in plasma and brain of adult Sprague-Dawley male rats after acute swim stress. Rats were subjected to acute stress by swimming for 10 min in ambient temperature water. Allopregnanolone levels were measured by RIA after purification of the steroid by HPLC. The data represent the mean±SEM for 3 separate experiments (n=12 rats per time point) for the cerebral cortex and plasma. Stress-induced increases of allopregnanolone in the cerebral cortex and plasma were statistically significant at 10, 40, and 70 min after the initiation of swim stress compared with nonstressed levels at 0 time [analysis of variance (ANOVA), $P<0.05$; Tukey's honestly significant difference procedure (HSD), $P<0.05$]. Adapted from Purdy et al. (1991).

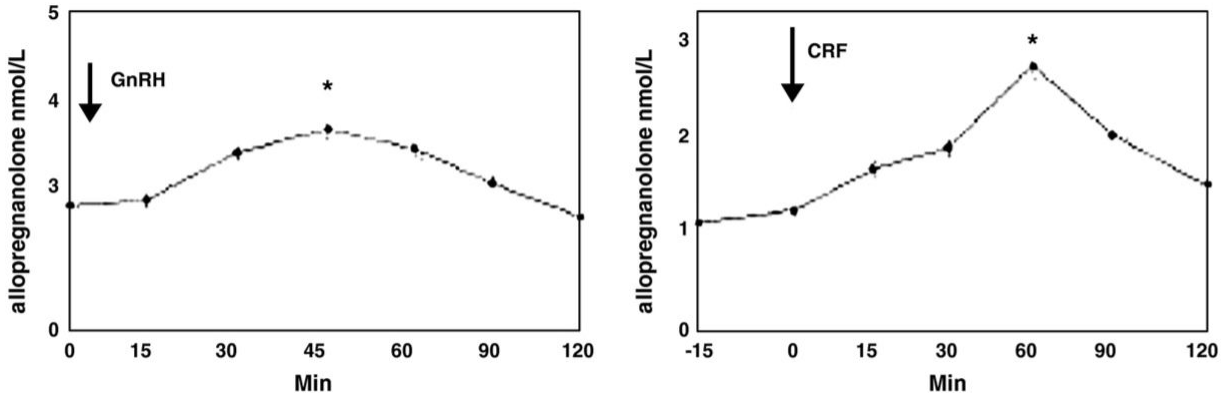

Fig. 2.

Mean±SEM allopregnanolone levels in response to the GnRH test (*, $P<0.01$ vs. 0 min) and in response to the CRF test (*, $P<0.01$ vs. 0 min). Adapted from Genazzani et al. (1998).

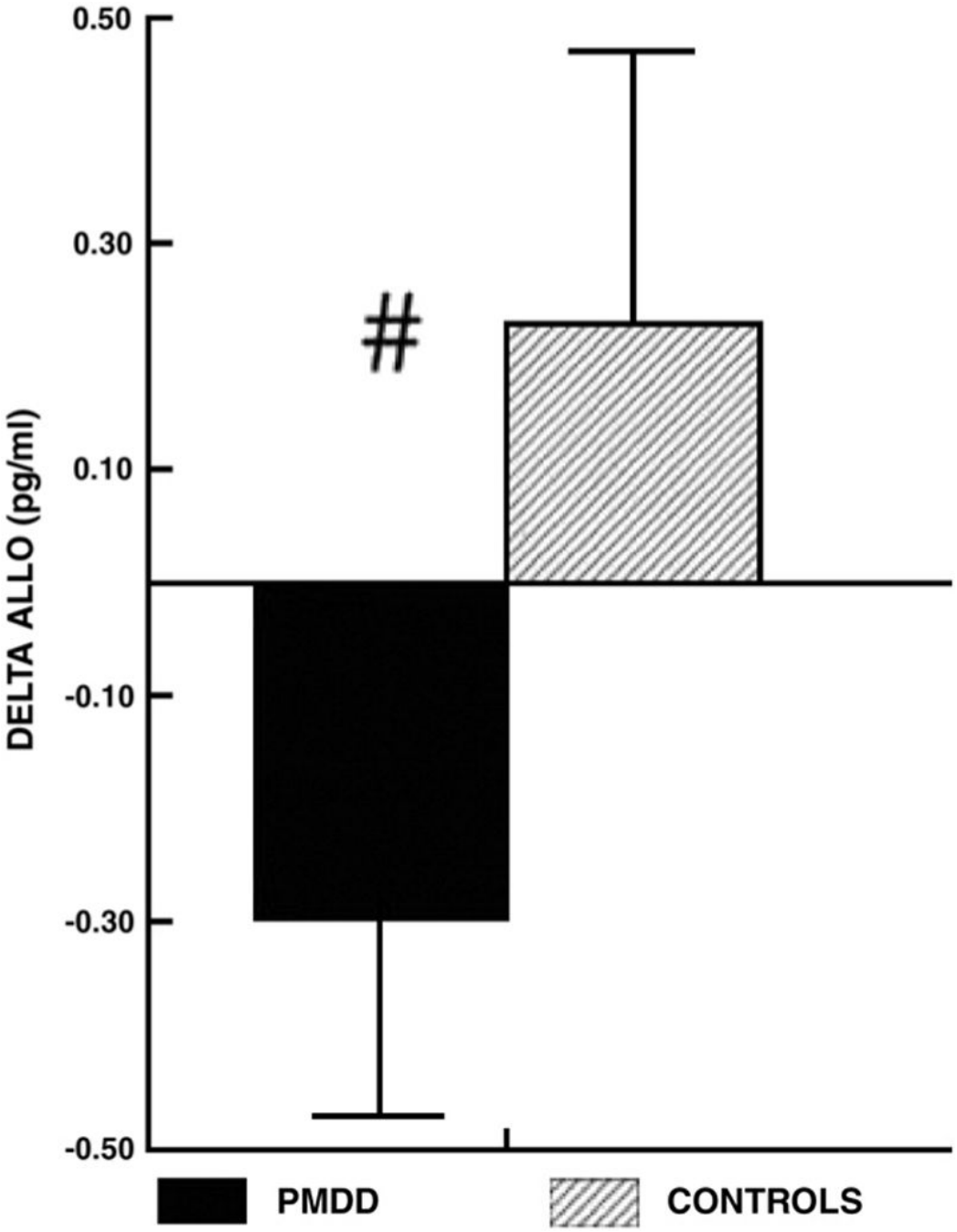

Fig. 3.
Mean (± SEM) change in luteal phase plasma allopregnanolone (ALLO) during stress in PMDD women and control subjects (#, $P<0.010$). From Girdler et al. (2001).

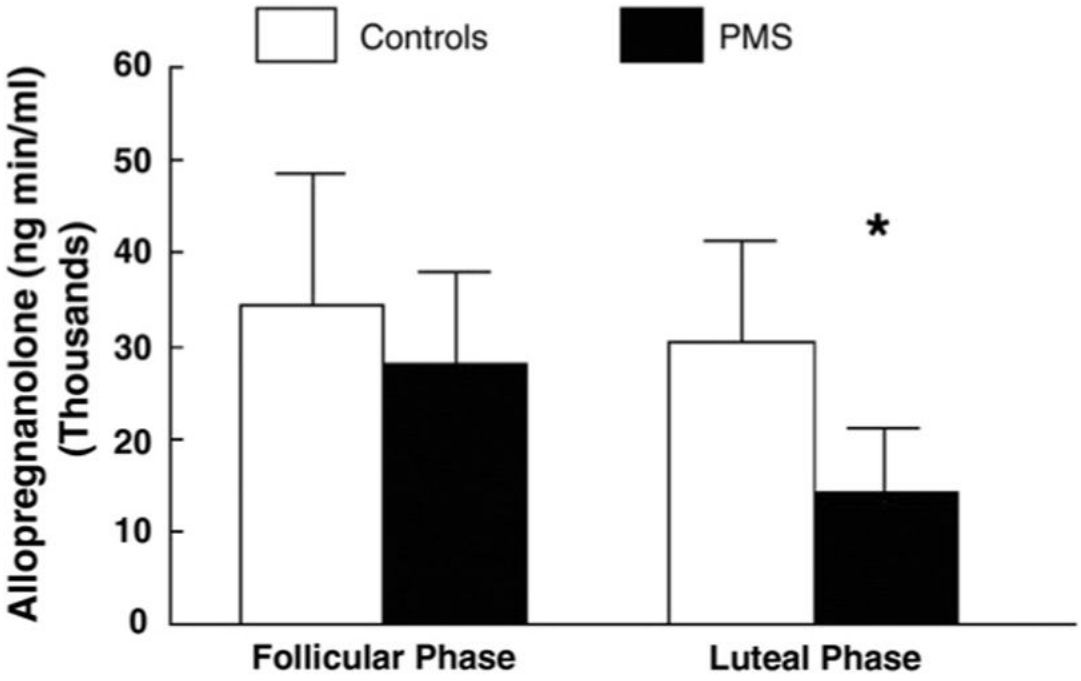

Fig. 4.

Allopregnanolone response to the adrenocorticotropic hormone (ACTH) test in patients with premenstrual syndrome (shaded bars) and in the control group (white bars) expressed as area under the curve (*, $P<0.05$). Adapted from Lombardi et al. (2004).

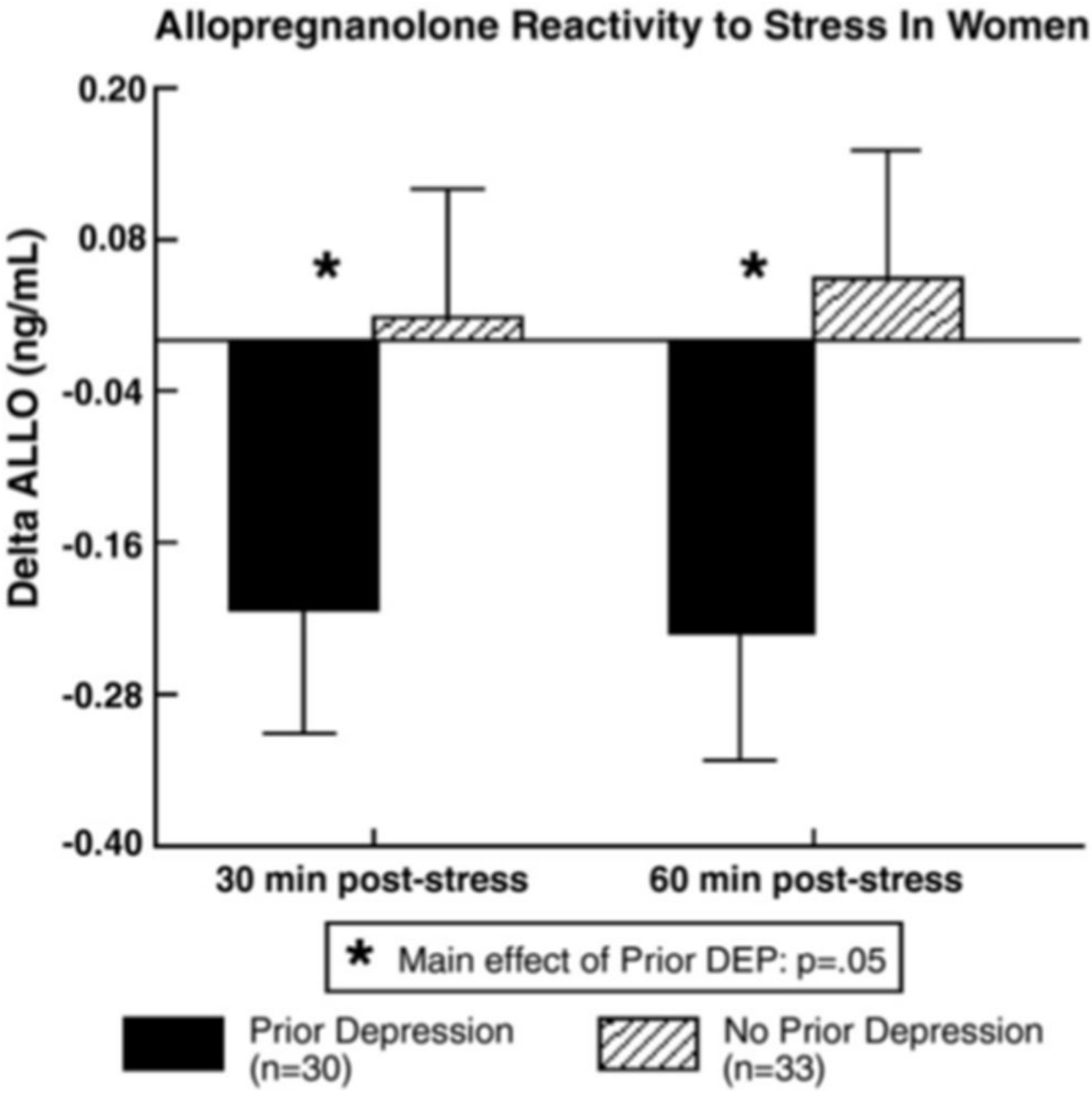

Fig. 5.
Change (stress−baseline) in allopregnanolone (ALLO) concentrations at 30 and 60 min post-stress in women as a function of histories of depression (DEP). From Klatzkin et al. (2006a).

Table 1

Summary of baseline neuroactive steroid findings in women with prospectively confirmed PMDD (P) compared with non-PMDD controls (C)

Study	Sample size	DSM criteria for PMDD	Current psych Dx	Prior psych Dx	Cycle days[a]	Number of cycles assessed	Results
Schmidt et al., 1994	P: 15	No	P: No	P: Yes	L: 20−24	1	L Allo: P=C
	C: 12		C: NA	C: NA			L Preg: P=C
Wang et al., 1996	P: 12	Yes	P: NA	P: NA	F: 1−4	2	F&L Allo: P=C
	C: 8		C: NA	C: NA	L: 10−27		F&L PE: P=C
							F&L PS: P=C
Rapkin et al., 1997	P: 35	Yes	P: No	P: No	L: 19 & 26	1	L Allo day 19: P=C
	C: 36		C: No	C: No			L Allo day 26: P<C
Monteleone et al., 2000	P: 28	No	P: No	P: NA	F: 5−8	3	F Allo: P=C
	C: 28		C: No	C: NA	L: 22−26		L Allo: P<C
Girdler et al., 2001	P: 25	Yes	P: No	P: Yes	L: 21−25	1	L Allo: P>C
	C: 13		C: No	C: Yes			
Lombardi et al., 2004	P: 20	No	P: No	P: No	F: 5−7	3	F Allo: P=C
	C: 20		C: No	C: No	L: 22−26		L Allo: P<C
							F&L: DHEA: P>C
							F&L: DHEAS, ANDR, PE: P=C

NA, not assessed; L, luteal phase; F, follicular phase; Psych Dx, psychiatric diagnosis; Allo, allopregnanolone; Preg, pregnanolone; PE, pregnenolone; PS, pregnenolone sulfate; DHEAS, dehydroepiandrosterone sulfate; ANDR, androstenedione.

[a]Reflects days adjusted to idealized 28-day cycle.