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The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women

Zenab Amin, Graeme F. Mason, Idil Cavus, John H. Krystal, Douglas L. Rothman, C. Neill Epperson *

Yale University, United States

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Abstract

A growing literature suggests that hormonal fluctuations occurring across the menstrual cycle, during and after pregnancy, and during the menopausal transition are associated with onset of affective disorders or exacerbation of existing disorders. This influence of the neuroendocrine system on psychiatric disorders is thought to be mediated by an abnormality in central nervous system response to neuroactive steroids such as estradiol, progesterone, and the progesterone derivative allopregnanolone (ALLO). This interplay is considerably complex as neuroactive steroids modulate the function of multiple neurotransmitter systems throughout various stages of development. While one could choose to study any number of steroid–neurotransmitter interactions, our group in addition to others has focused our investigative efforts on unraveling the contribution of neuroactive steroids to psychiatric syndromes and disorders via their modulation of gamma aminobutyric acid (GABA), the brain's major inhibitory neurotransmitter. The goal of this article is two-fold: to synthesize the clinical and preclinical research focusing on the interplay between neuroactive steroids and GABA as they relate to neuropsychiatric and substance use disorders in women and to integrate data from our laboratory using proton magnetic resonance spectroscopy into this context.

Keywords: Gamma aminobutyric acid; Depression; Magnetic resonance spectroscopy; Premenstrual dysphoric disorder; Postpartum depression; Menopause

1. Introduction

Reproductive hormones are hypothesized to be involved in the development and/or exacerbation of a broad range of neuropsychiatric disorders in women. Several affective disorders are associated with hormonal fluctuations across the menstrual cycle, during and after pregnancy, and during the menopausal transition, while some women experience exacerbation of existing disorders at these time points (Rapkin et al., 2002). Sex differences in other illnesses, such as substance abuse/addiction (Lynch et al., 2002) and menstrual cycle-related symptom patterns in seizure disorders (Reddy, 2004) may also be mediated, at least in part, by ovarian hormones. It is likely that sensitivity to changes in neurotransmitter function as a result of hormone fluctuations plays a large role in the etiology or exacerbation of these disorders (Backstrom et al., 2003; Steiner et al., 2003).

Neuroactive steroids such as estradiol, progesterone, and progesterone's metabolite allopregnanolone (ALLO) modulate the function of neurotransmitters implicated in affect regulation, cognition, and behavior. Estradiol enhances neuronal excitability in structures such as the hippocampus (Joels, 1997) via modulation of glutamatergic NMDA receptors (Smith et al., 1988; Smith, 1989; Foy et al., 1999). Estradiol is also thought to have antagonist activity at the gamma aminobutyric acid type A ($GABA_A$) receptor (Kelly et al., 2003). In contrast, the progesterone metabolite ALLO is a potent $GABA_A$ receptor agonist (review in Lambert et al., 2003) with anticonvulsant, hypnotic, and anxiolytic effects (Gruber and Huber, 2003). As the primary inhibitory neurotransmitter, GABA is released by neurons throughout the brain and has numerous interactions with other neurotransmitter systems (Bacci et al., 2005). Thus, substances which modulate GABA neurotransmission will not only alter the balance in neuronal excitation and inhibition but are likely to alter the activity of neurons from multiple systems. That the

* Corresponding author.
E-mail address: neill.epperson@yale.edu (C.N. Epperson).

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$GABA_A$ receptor, and to a lesser degree, the NMDA type glutamate receptor are sensitive to physiologic changes in estradiol and ALLO levels indicate that this area would be fertile ground for research in women's reproductive behavioral health.

Although animal studies provide much information on the mechanisms of neuroactive steroid effects, noninvasive methods are required to study their interactions with neurotransmitters in humans. To this end, our laboratory has utilized proton magnetic resonance spectroscopy (^{1}H MRS) to evaluate the interplay between cortical GABA concentrations and plasma neuroactive steroids in mediating mood and behavior during hormonal fluctuations across the female life cycle. In exploring the hypothesis that neuroactive steroid effects on GABA are critical to the pathogenesis and/or exacerbation of neuropsychiatric conditions occurring at specific points in the female reproductive life cycle, we will review the relevant literature and highlight published and unpublished data from our laboratory.

2. Premenstrual Dysphoric Disorder (PMDD)

Across the normal menstrual cycle, there are increasing levels of estrogen in the follicular phase, peaking just before ovulation at mid-cycle, followed by an increase in progesterone and relatively high estrogen levels in the mid-luteal phase. Just before menstruation (the start of the follicular phase), there are low levels of both of these ovarian hormones. Women diagnosed with premenstrual dysphoric disorder (PMDD) are symptomatic during the last half of the luteal phase, the week before menses, but may have onset of symptoms at or near ovulation. To meet criteria for PMDD and not premenstrual exacerbation of an ongoing psychiatric disturbance, women must have a symptom-free postmenstrual week during the early to mid-follicular phase. The hallmark symptoms of PMDD include irritability, mood lability, anxiety/tension, depressed mood, and decreased interest and pleasure. While one of these hallmark symptoms must be of at least moderate severity during the luteal phase and absent during the postmenstrual week, women are required to experience a total of 5 psychological and/or somatic symptoms with a similar pattern and severity to meet the DSM-IV research criteria for PMDD (American Psychiatric Association, 1994).

The primary hypothesis regarding the etiology of PMDD implicates the ovarian steroids estrogen and progesterone as well as neurosteroids such as ALLO, which can be made *de novo* by glia and some neurons in the central nervous system (CNS). Their fluctuation across the menstrual cycle offers an obvious trigger for the disorder and the onset of symptoms often follows the hormone increase in the mid-luteal phase. However, for some individuals symptom onset is concurrent with the decline in ovarian steroids and the majority of women with PMDD will experience peak symptoms two days prior to onset of menstrual flow (Pearlstein et al., 2005). Moreover, there is considerable within-subject variability regarding timing of onset and offset of mood and physical symptoms across cycles (Pearlstein et al., 2005). Thus, the timing of symptoms provides minimal clues to the role that neuroactive steroids play in the pathogenesis of PMDD, with the exception that ovulation itself appears to be critical to symptom onset.

Most studies have not found abnormal peripheral levels of estrogen or progesterone in PMDD patients compared to healthy women, but it is possible that normal hormonal fluctuation has atypical consequences in women with PMDD and/or peripheral measures are a poor assessment of CNS events. Because SSRIs are among the most effective treatments, with fluoxetine, sertraline, and paroxetine having received FDA approval for use in PMDD, researchers have focused on dysregulation of the serotonin system. According to several studies, individuals with PMDD show decreased post-synaptic serotonin responsivity and other abnormalities compared to controls during the symptomatic phase, while others have found altered serotonergic function across phases, suggesting vulnerability throughout the cycle (reviews in Kouri and Halbreich, 1997; Steiner and Pearlstein, 2000; Parry, 2001). In animals, estrogen and progesterone have been shown to modulate aspects of the serotonin system and may enhance serotonin transmission by several means, for example, by increasing serotonin synthesis and decreasing its metabolism (Bethea et al., 2002). Thus, ovarian steroid effects on the serotonin system may influence PMDD symptoms.

Clinically, progesterone has gained the reputation of being "depressogenic" in a subset of women (Bjorn et al., 2000; Andreen et al., 2003). Although progesterone modulates serotonin neurotransmission, it appears to have its most pronounced effects on the GABA system via its metabolite ALLO (3α-hydroxy-5α-pregnan-20-one). Neurosteroid modulation of GABAergic function has been a frequent target of investigation and is considered to be important to the pathogenesis of PMDD (reviews in Smith, 2001; Sundstrom Poromaa et al., 2003). Women with PMDD show decreased sedation with GABA agonists (the benzodiazepine midazolam and the neurosteroid pregnanolone) in the luteal phase compared to healthy women and reduced influence on saccadic eye velocity (SEV) in the follicular phase (Sundstrom et al., 1997; Sundstrom et al., 1998). One hypothesis is that SSRIs treat PMDD through their ability to alter activity of the 3α-hydroxysteroid dehydrogenase enzyme responsible for conversion of 5α-dihydroprogesterone to ALLO (Uzunov et al., 1996; Griffin and Mellon, 1999). Similarly, SSRI treatment normalized the above mentioned effects of GABA agonists on SEV in women with PMDD (Sundstrom and Backstrom, 1998). Several studies have found that women meeting criteria for PMDD or the less severe premenstrual syndrome (PMS) have reduced luteal (Rapkin et al., 1997) or follicular and luteal phase plasma levels of ALLO (Monteleone et al., 2000; Nyberg et al., 2005), which supports the theory that alterations in neurosteroid levels are important in PMDD. While other studies failed to find differences in plasma ALLO concentrations between women with PMDD or PMS and healthy controls (Schmidt et al., 1994; Wang et al., 1996; Epperson et al., 2002), higher luteal phase ALLO has been associated with a decrease in severity of PMS symptoms (Wang et al., 1996). In addition, animal studies suggest that peripheral levels of ALLO are not an accurate reflection of CNS levels under certain physiologic conditions (Paul and Purdy, 1992).

It is possible that psychiatric history may influence ALLO levels across the menstrual cycle in women with PMDD, and

most studies did not control for this variable. A recent study of response to mental stress found that women with a history of depression (a group of women with PMDD as well as controls) had blunted ALLO response to stress, while those in both groups without a history of depression did not (Klatzkin et al., 2006). Furthermore, women with a history of depression had no correlation between ALLO and progesterone levels and ALLO response predicted severity of PMDD symptoms only in women with past depression. Thus, past depression may be a better predictor of dysregulated ALLO response to stress than PMDD and further research is necessary regarding this relationship.

One possible interpretation of the literature regarding alterations in ALLO and/or GABAergic function in PMDD is that these factors underlie an imbalance in cortical excitation and inhibition, which contributes to the characteristic symptoms of PMDD. Providing support for this notion, a recent transcranial magnetic stimulation (TMS) study in humans found that although women with PMS and control subjects showed similar motor evoked potential response in the follicular phase, control subjects showed more inhibition and PMS subjects showed more facilitation in the luteal phase (Smith et al., 2003a,b). Such findings derived from the TMS paradigm suggest that, despite similar peripheral hormone levels, GABA inhibitory tone is enhanced during the luteal phase in healthy controls and decreased in women with PMS or that excitatory tone is increased in the women with PMS.

Another method to examine the contribution of GABA and neurosteroids to mood disorders in women is the noninvasive neuroimaging technique, ^{1}H MRS (proton magnetic resonance spectroscopy). The absence of radioactive ligands in this procedure allows for multiple scans over short periods of time and is therefore ideal for menstrual cycle studies and use in lactating women during the puerperium. We applied this method to measure occipital cortex GABA concentrations in the follicular phase (when ovarian steroids are low), the mid-luteal phase (when ovarian steroids are high) and the late-luteal phase (when ovarian steroids are declining) in a group of 9 women with PMDD and 14 healthy female controls. The interested reader can refer to Epperson et al. (2002) for more details regarding subjects and methods. Findings from this study indicate that women with PMDD have a deficiency in cortical GABA concentrations in the non-symptomatic follicular phase, although luteal phase levels do not differ between groups (Fig. 1). GABA levels in healthy controls were highest at the follicular phase time point and dropped in the luteal phase as plasma estradiol, progesterone, and ALLO increased. The opposite relationship between cortical GABA levels and plasma neuroactive steroid was seen in women with PMDD. In addition, while there was a significant correlation between GABA and ALLO in healthy controls, no such relationship was found for women with PMDD, suggesting an abnormal interplay between GABA and ALLO in women afflicted with this disorder (Epperson et al., 2002). Furthermore, an abnormality in brain response to neuroactive steroids in the follicular phase, in the absence of symptoms, implies an abnormal CNS response to ovarian hormones. Although women with PMDD and healthy controls "look similar" in the luteal phase with respect to cortical GABA concentrations, the cyclicity of GABA levels is out of synchronism, leading to a dramatically different behavioral presentation. Moreover, the finding of follicular phase differences between women with PMDD and healthy controls is not unique to our study (Sundstrom et al., 1997; Sundstrom et al., 1998; Monteleone et al., 2000; Nyberg et al., 2005).

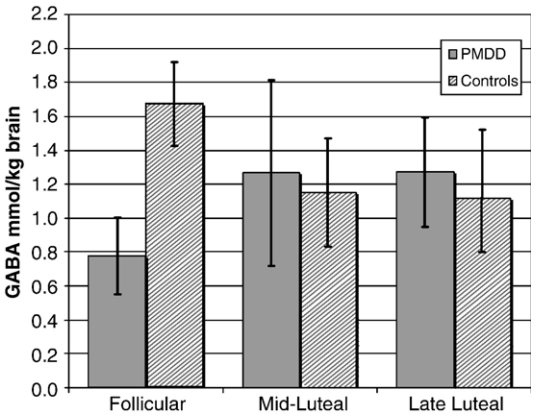

Fig. 1. Cortical GABA levels across the menstrual cycle in women with PMDD and healthy controls. The results of ^{1}H MRS scans in the follicular, mid-luteal and late-luteal phases of the menstrual cycle. Random effects modeling revealed a highly significant group (PMDD versus healthy control) by phase interaction ($p<0.0001$) explained mainly by follicular phase GABA levels ($p<0.0001$). Similar findings were seen in analysis of GABA levels for the entire subject sample. Adapted from Epperson et al. (2002).

The use of techniques such as TMS and ^{1}H MRS has enabled investigators to obtain more direct assessments of CNS excitability. However, more advanced neuroimaging techniques such as carbon-13 MRS, paired with genetic analyses of glutamate and GABA synthesis-related gene expression will allow investigators to probe the mechanism for alterations in GABA concentrations across the menstrual cycle in healthy and disordered women. Carbon-13 MRS allows detection of a naturally occurring, non-radioactive isotope of carbon, with which a substance such as glucose may be labeled and injected. Thus, with carbon-13 MRS, it is possible to measure rates of metabolism and neurochemical release in the brain (Mason et al., 1995; Shen et al., 1999; Sibson et al., 1998).

Even more direct assessment of amino acid neurotransmitter levels is possible in women undergoing neurosurgical assessment of their intractable epilepsy. Using microdialysis catheters implanted along with depth electrodes used for electroencephalographic (EEG) monitoring in ambulatory patients, Cavus et al. (2005) have measured GABA and glutamate levels in the extracellular fluid (ECF) from the seizure focus as well as from non-epileptic, "healthy" cortical tissue. In these non-epileptic, presumably healthy cortical areas, glutamate levels were similar in the follicular and luteal phases, while follicular phase GABA levels were significantly higher than luteal phase GABA (Cavus et al., 2004), which corresponds to the pattern seen in healthy controls undergoing ^{1}H MRS. Given that abnormalities in the neuroendocrine milieu are presumed responsible for periovulatory and perimenstrual clustering of

seizures, this technique could be extended to the investigation of the pathogenesis of catamenial epilepsy.

3. Substance use in women: smoking cessation

Women appear to be more vulnerable than men to the reinforcing effects of certain drugs such as nicotine (Lynch et al., 2002) and may have more difficulty quitting smoking (Bjornson et al., 1995; Wetter et al., 1999). Female smokers may be more likely than males to develop depressive symptoms when attempting smoking cessation (Killen et al., 2003), which can reduce the likelihood of success (Levine et al., 2003; Smith et al., 2003a,b). In addition, there is some evidence of menstrual cycle-related changes in smoking behavior, with the early follicular phase associated with fewer cravings or less cigarette use than other points of the cycle (Perkins et al., 2000; Pomerleau et al., 2000; Franklin et al., 2004). However, one previous study found that progesterone administration resulted in a decrease in craving for smoking as well as the subjective effects from smoking (Sofuoglu et al., 2001).

Interaction between nicotine, amino acid neurotransmitters, and neurosteroids may contribute to smoking behavior in female smokers. Nicotine is known to release glutamate and GABA in some brain areas (Barik and Wonnacott, 2006) and to diminish the inhibitory effects of GABA on long-term potentiation in the hippocampal CA1 region (Fujii et al., 2000). At high, anxiogenic doses nicotine enhances neurosteroidogenesis in rodents, leading to increased production of ALLO (Porcu et al., 2003). If this process occurs in humans, it is possible that women are more susceptible to nicotine's effects on neurosteroid production during the luteal phase than the follicular phase as a result of increase in progesterone availability for conversion to ALLO. Estradiol is also likely to contribute to differences in smoking behavior across the menstrual cycle. For example, nicotine alters metabolism of estradiol (Irwin et al., 1994), which has numerous effects in the CNS (Mellon and Griffin, 2002).

As mentioned, there is a relationship between smoking and GABA neurotransmission which may contribute to alterations in inhibitory/excitatory balance in smokers. Nicotine modulation of nicotinic acetylcholine receptors located on GABAergic interneurons induces GABA release (Fuxe et al., 1989) and nicotine enhances electrically evoked GABAergic transmission (Zhu and Chiappinelli, 1999). Nicotine's activation of brain reward centers is modulated by GABA (Mansvelder et al., 2002; Li et al., 2004) and $GABA_B$ agonists decrease nicotine self-administration in rodents (Markou et al., 2004; Paterson et al., 2004). Thus, an interaction is possible between smoking and menstrual cycle-related changes in GABA function.

We recently conducted a ^{1}H MRS study of short-term (48 h) smoking abstinence across the menstrual cycle (Epperson et al., 2005). Ten nicotine-dependent men, 6 nicotine-dependent women, 7 non-smoking men, and 13 non-smoking women were scanned in a 2.1 T magnet (Oxford Magnetic Technology, Oxford, England) to evaluate differences in cortical GABA as a result of sex, smoking status, and menstrual phase. While there were no significant effects of abstinence, female smokers showed decreased GABA levels in the follicular phase compared to female non-smokers and male smokers (Fig. 2). This was primarily due to a lack of cyclicity in cortical GABA level in female smokers compared to what is seen in healthy non-smoking women. We and others have previously found that luteal phase increases in ALLO (Epperson et al., 2002) and exogenous administration of benzodiazepines (Goddard et al., 2004) are associated with reductions in cortical GABA levels in healthy subjects, suggesting that agonist modulation of the $GABA_A$ receptor may reduce GABA synthesis. Although there is little available information regarding the mechanism of this decrease, it may be the result of an inhibitory effect on glutamic acid decarboxylase (GAD), which is involved in synthesizing GABA from glutamic acid. One study of long-term effects of benzodiazepine treatment during development in rodents found decreased GAD mRNA (Raol et al., 2005), though there are opposite results during tolerance in adult rodents (Izzo et al., 2001). A lack of GABA cyclicity in female smokers may be the result of smoking-induced alterations in neurosteroidogenesis and thus GABA neurotransmitter levels. Theoretically, such alterations in the cortical amino acid neurotransmission may render women at increased risk of affective disturbances during smoking abstinence, as the relationship between cortical inhibition and menstrual cycle-related steroid fluctuations is sub-optimum.

4. Psychiatric illness during pregnancy and postpartum

Symptoms of depression, psychosis, mania, suicidality, and anxiety disorders are common during pregnancy and the puerperium (Brandes et al., 2004; Brockington, 2004; Gavin et al., 2005; Heron et al., 2005; Lindahl et al., 2005). The dramatic rise and fall of neuroactive steroids during this time are likely to

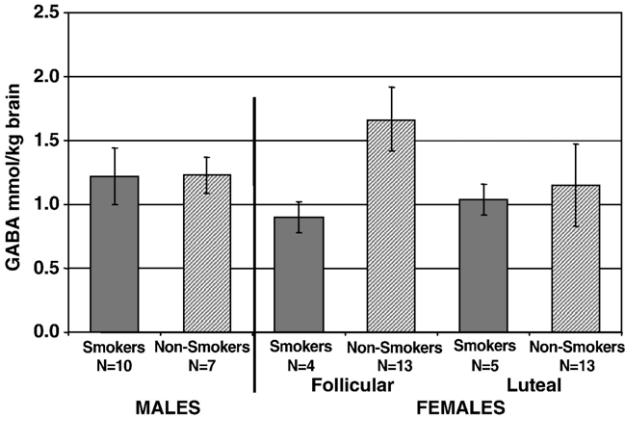

Fig. 2. Cortical GABA levels in male and female smokers and non-smokers. GABA levels from 5 of the 10 males with pre- and post-abstinence scans were averaged. Follicular and luteal phase GABA levels for 6 female smokers represent the average of the pre- and post-abstinence scans. GABA levels were obtained in 4 of the 6 women during the follicular phase and from 5 of the 6 women during the luteal phase. Two-way ANOVA analysis of sex and smoking effects on GABA levels revealed significant sex by smoking interaction ($p<0.0001$). Cortical GABA levels did not differ significantly between smoking and non-smoking men ($p=0.2$). Mixed model analysis showed a significant menstrual cycle phase by smoking interaction ($p=0.0001$). Adapted from Epperson et al. (2005).

have major effects on central nervous system function, and many of these disorders are associated with dysregulation of GABAergic function (Keverne, 1999; Brambilla et al., 2003; Nemeroff, 2003).

Using a model of pseudopregnancy in rats, Bitran and Solano (2005) have found that termination of pseudopregnancy after 10 days by ovariectomy decreased time spent in open arms of an elevated plus maze (an index of anxiety), while progesterone treatment increased it, suggesting anxiolysis. There was an interaction between pseudopregnancy termination and treatment with the benzodiazepine chlordiazepoxide such that pseudopregnancy caused an anxiogenic effect of chlordiazepoxide resulting in less time spent in open arms. It was hypothesized that pseudopregnancy resulted in a dependence on GABA agonists such as ALLO and that termination of pseudopregnancy resulted in ALLO withdrawal. However, it is also possible that chlordiazepoxide had sedative, not anxiogenic effects on the rats tested. In a related study, Bitran and Smith (2005) found that pseudopregnancy termination caused an increase in benzodiazepine receptors and a decrease in GABA-stimulated chloride influx in the hippocampus. Thus, withdrawal from hormones following pregnancy may result in increased arousal and reactivity, relating to anxiety in the postpartum period.

That increased ALLO levels during pregnancy have profound influences on the GABA system is supported by several other rodent studies. For example, another study in rats found that plasticity of $GABA_A$ receptors (measured by responsiveness to muscimol and subunit mRNA expression) during pregnancy and after delivery was functionally related to fluctuations in brain ALLO concentrations (Concas et al., 1998). In pregnant mice, GABA levels and turnover were found to be decreased during pregnancy in several brain regions and remained decreased at parturition (Smolen et al., 1993). It is possible that turnover decreased because of the decrease in GABA levels or may be the result of high levels of agonists such as ALLO.

Comparatively little research has evaluated interactions between GABA and neuroactive steroids during pregnancy in humans. Plasma levels of progesterone and its metabolites are known to increase across pregnancy and decrease in the postpartum (Gilbert Evans et al., 2005; Paoletti et al., 2006). Similar to what was found in mice, when comparing pregnant and nonpregnant women, cerebrospinal fluid GABA levels were lower in pregnant women and there were increased levels of prolactin, oxytocin, and the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (Altemus et al., 2004). When comparing pregnant women with and without postpartum negative mood, serum ALLO levels were significantly lower in women experiencing mood symptoms, but progesterone levels did not differ (Nappi et al., 2001). Similarly, ALLO and progesterone levels were significantly correlated only in euthymic women and there was a significant negative correlation between the Hamilton depression score and levels of serum ALLO. These findings provide additional evidence that GABA synthesis is downregulated by increased levels of ALLO during gestation and that women suffering from postpartum negative mood may have a deficiency in converting progesterone to ALLO.

These clinical and preclinical data as well as the phenomenon of increased risk of postpartum depression (PPD) in women with PMDD led our laboratory to extend our focus to the examination of occipital cortex GABA concentrations and plasma neuroactive steroids in the perinatal context (Epperson et al., 2006). Using the same ^{1}H MRS techniques as those for our menstrual cycle studies, we scanned 9 women diagnosed with PPD according to DSM-IV criteria, 14 postpartum healthy controls, and compared them to 10 healthy follicular phase women who served as controls in our PMDD study (Epperson et al., 2002) using the 2.1 T magnet. Follicular phase women were chosen based on having estradiol levels which were consistent with the early follicular phase and the puerperium. All postpartum women were scanned within 6 months of delivery and prior to resumption of menses. Consistent with previous studies (Smolen et al., 1993; Altemus et al., 2004) both cortical GABA and plasma ALLO concentrations were reduced in postpartum women (depressed: 1.39±0.29 mmol/kg GABA and 0.79±0.39 nmol/L ALLO; nondepressed: 1.11±0.27 GABA mmol/kg and 0.68±0.23 nmol/L ALLO) compared to follicular phase women (GABA: 1.69±0.25 mmol/kg; ALLO: 1.58±0.65 nmol/L). However, in contrast to one previous study (Nappi et al., 2001), there were no neuroendocrine differences between the two postpartum groups regardless of diagnosis(Fig. 3). Thus, it is possible that women with PPD have an irregular response to naturally occurring decreases in central GABA levels combined with decreased postpartum levels of ALLO. Although gas chromatography mass spectroscopy (GCS–MS), which is considered to be the most reliable method, was used to measure peripheral neurosteroid levels in our studies, when interpreting the relationship between central GABA concentrations and peripheral neurosteroids, it is important to remember that peripheral neurosteroid levels may not always be an accurate assessment of CNS levels. For example, enhanced conversion of progesterone to ALLO has been noted in the brain of adrenalectomized, ovariectomized rodents under conditions of stress, although peripheral ALLO levels were undetectable (Paul and Purdy, 1992).

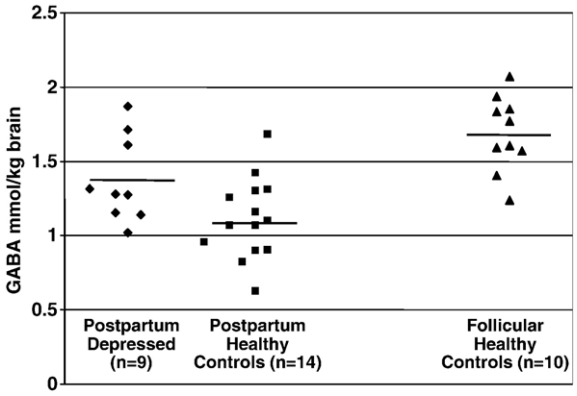

Fig. 3. Cortical GABA concentrations in women with postpartum depression, healthy postpartum women, and healthy cycling women. Occipital cortex GABA concentrations were compared among three groups (PPD, postpartum HC and follicular phase HC) using ANCOVA. The overall group effect was significant: $F(2,29)=11.98$, $p=0.002$. Adapted from Epperson et al. (2006).

5. Menopausal changes in mood

As with other periods of hormonal change, the transition to menopause may be marked by an increase in symptoms of depression and perimenstrual irritability, particularly in women with a history of PMS or PMDD (Freeman et al., 2004; Robinson, 2001). Although a number of neurotransmitter systems may be involved in perimenopausal mood symptoms, the continuity with mood disturbances occurring during other periods of hormonal fluctuation (Stewart and Boydell, 1993; Gregory et al., 2000; Freeman et al., 2004) indicates that there may be similar patterns of change in the GABA system in perimenopause as have been found in PMDD and PPD. Such changes may have implications for response to hormone therapy (HT) in this population.

Although randomized, placebo-controlled trials have demonstrated the efficacy of estrogen administration for depression during the perimenopause (Schmidt et al., 2000; Soares et al., 2001), it is unclear how estrogen exerts its positive effects on mood. Interestingly, estrogen's antidepressant effects appear to be dependent on reproductive status as depression in postmenopausal women is not responsive to estrogen treatment (ET; Morrison et al., 2004). Research suggests that the hormone modulates a number of neurotransmitters implicated in the regulation of affect, including acetylcholine, serotonin, dopamine, and norepinephrine (Melton, 1999). It is possible that estrogen has secondary effects on the GABA system through its diverse actions in the brain or that it has direct effects on GABA transmission. For example, there is animal data suggesting that estrogen rapidly uncouples $GABA_B$ receptors from G-protein-gated potassium channels (Kelly et al., 2003). In addition, estradiol decreases the expression of GAD in hippocampal neurons within 24 h, thus overall increasing the excitatory drive (Murphy et al., 1998). However, another study found that mRNA expression of GAD in the hippocampus is stimulated by estradiol administration in ovariectomized rats and suppressed by addition of progesterone (Weiland, 1992), but it has been hypothesized that estrogen's enhancement of GAD mRNA expression may have been a feedback response to initial declines in GAD and not indicative of estrogen's direct effects (Murphy et al., 1998).

To examine the impact of estrogen administration on GABAergic function in menopausal women, we recruited a cohort of women ages 49 to 55 who had no past or present history of Axis I disorder. In addition, they had no first-degree relatives with any Axis I disorder, excepting substance abuse/dependence. Women ranged from 6 weeks to 7 years (mean = 2.6 years; SD = 2.7 years) since their last menstrual period or last regular use of HT. Eight women were scanned using a 2.1 T magnet before and during transdermal ET at 75 μg dose. Participants underwent their second GABA measurement after an average of 11.4 (SD = 6.9) weeks of ET and showed a significant increase in plasma estradiol level, $t(7) = -2.39$, $p < 0.05$. There was substantial inter-individual variability in the pattern of GABA level changes from baseline to the second scan (Fig. 4), resulting in no significant difference between time points, $t(7) = -0.81$, $p = 0.44$. However, more women showed an increase in GABA than a decrease and evaluation of a larger sample of women may reveal effects of estrogen and whether the effects differ depending on duration of treatment. In addition, both peri- and postmenopausal women were included in the study so that the length of time of hypogonadism varied across participants, which may have influenced the observed variability and should be considered in future studies. Furthermore, data are required with regard to the effects of ET with daily or sequential progesterone therapy as these are common HT strategies prescribed for menopausal women.

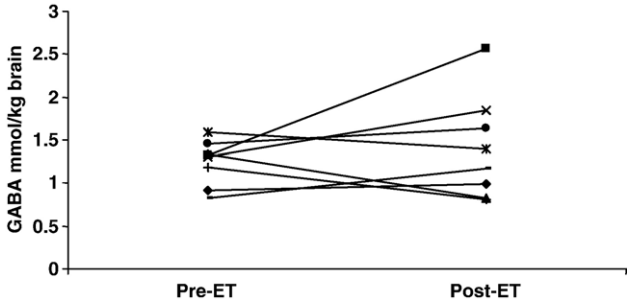

Fig. 4. Cortical GABA concentrations in menopausal women before and during estrogen treatment. Results from 8 women scanned at two time points (before and after beginning ET).

6. Summary

In conclusion, data suggest that relationships between neuroactive steroids and the GABA system may play a role in the etiology of several psychiatric disorders in women. While animal research provides much information regarding the interactions between these substances in the brain, noninvasive methods such as MRS can examine disruptions of the GABA system in humans. Overall, our MRS studies provide corroborating evidence that central GABA concentrations are dampened by exposure to endogenous or exogenous $GABA_A$ receptor agonists and that this relationship is dysregulated in women with PMDD and possibly nicotine addiction. Likewise, high concentrations of ALLO during pregnancy appear to downregulate GABA synthesis. This alteration in the neuroendocrine milieu may not be critical to the pathogenesis of postpartum depression but may mask a vulnerability to depression in certain women. Finally, the menopause provides a naturally occurring hypogonadal state in which to test the effects of short and long-term ET with and without concomitant use of progesterone on cortical GABA levels.

While these findings are of considerable interest and ^1H MRS provides a more direct assessment of endocrine-induced changes in central GABAergic function, our MRS studies have been limited to the occipital cortex, which is not typically implicated in the pathogenesis of neuropsychiatric disorders. However, the measurement of GABA by MRS depends strongly on magnetic field homogeneity in the volume of interest, the ability of the subject to hold still, and interference from lipid signals. The magnetic field homogeneity is better in the occipital cortex than in the areas of the brain that are traditionally of greater interest, the occipital cortex is near the

neck and therefore is closer to the pivot point of head motion, and there are fewer muscles at the back of the head. Thus, from a technical standpoint, it is easier to measure GABA in the occipital cortex. There are also growing reports of significant occipital changes in psychiatric disorders (e.g., Vawter et al., 2000). Nonetheless, MRS measurements of GABA in other areas of the brain will be crucial to understanding the implications of steroid-associated changes in GABA in neuropsychiatric disorders.

Another limitation of the ^{1}H MRS technique is that it provides a static measure of tissue GABA concentrations and thus neuroactive steroid modulation of GABA neuronal function. In the future, application of carbon-13 MRS would enable investigators to obtain a dynamic measure of glutamate–glutamine cycling between neurons and glia (Lebon et al., 2002; Shen et al., 1999) and the impact of neuroactive steroids on this process. There is evidence that glia are themselves modulated by sex steroids, particularly estrogen (Mor et al., 1999). Thus, alterations in estradiol concentrations may influence the balance in neuronal excitation/inhibition without directly modulating GABA or glutamate receptors or concentrations. While direct assessment of estrogen effects on glial morphology is not yet possible in the human laboratory, MRS techniques can be applied to glean information regarding hormonal effects on neuronal–glial interactions.

In summary, neuroendocrine modulation of GABAergic function appears to contribute to disturbances of mood and other psychiatric symptomatology across the female reproductive life cycle. While not yet conclusive, MRS data reviewed herein provide the basis for future studies examining this promising interplay between endocrine and brain systems.

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