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Steroid hormone fluctuations and $GABA_AR$ plasticity

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Summary Conditions of changing steroid hormone levels are a particularly vulnerable time for the manifestation of neurological disorders, including catamenial epilepsy, premenstrual syndrome (PMS), and postpartum depression. The pathophysiology of these disorders may be related to changes in neurosteroid levels, which can dramatically impact neuronal excitability. Robust changes in neurosteroid levels, such as those that occur following stress, over the ovarian cycle, and throughout pregnancy, profoundly alter GABAA receptor (GABAAR) structure and function and underlie the associated changes in neuronal excitability. A moderate and brief exposure to elevated neurosteroids, such as those that occur over the ovarian cycle and following an acute stressful episode, result in a decrease in GABAAR gamma2 subunit expression and an increase in GABAAR delta subunit expression. These changes are accompanied by a decrease in seizure susceptibility and decreased anxiety-like behavior in mice, demonstrating altered neuronal excitability associated with changes in the receptor composition. More robust changes in steroid hormone levels, such as those that occur throughout pregnancy, result in a decrease in both GABAAR gamma2 and delta subunit expression and are associated with an increase in neuronal excitability evident from the shift in the input-output relationship. Alterations in GABAAR subunit composition may represent a homeostatic mechanism to maintain an ideal level of inhibition in the face of fluctuating neurosteroid levels. Neurosteroids potentiate the effects of GABA on GABAARs, particularly those containing the delta subunit, and reorganization of these receptors may be necessary to prevent sedation and/or anaesthesia in the face of high levels of neurosteroids or to prevent hyperexcitability in the absence of these compounds. Alterations in GABAARs under conditions of altered steroid hormone levels result in measurable changes in neuronal excitability and dysregulation of GABAARs may play a role in steroid hormone-associated neurological disorders.

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Neurosteroids in the central nervous system (CNS)

Neurosteroids are neuroactive metabolites of steroid hormones, which can be synthesized in the peripheral and central nervous system, in both neurons and glial cells (Belelli and Lambert, 2005; Herd et al., 2007). Neurosteroids are synthesized *de novo* from cholesterol or converted from steroid hormone precursors (Stoffel-Wagner, 2001). Thus, fluctuations in steroid hormone levels result in local fluctuations in neurosteroid levels (Stoffel-Wagner, 2001). Altered levels of neurosteroids in the CNS are associated with numerous physiological (*e.g.*, ovarian cycle, pregnancy) and pathological (*e.g.*, stress) conditions. Some of these conditions are known to be associated with debilitating psychiatric and neurological disorders including premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS), catamenial epilepsy, menstrual migraine, postpartum depression, and anxiety (for review see (Backstrom et al., 2003)).

Steroid hormone-linked disorders in women share patterns of symptom manifestation, consisting of a worsening during the luteal phase, occurring just prior to or during menses, and/or at the time of ovulation (Backstrom et al., 2003; Smith et al., 2003; Sundstrom et al., 1999). Symptom manifestation in menstrual cycle-linked psychiatric and neurological disorders has been attributed to changes in steroid hormone levels. However, there are no consistent changes in hormone levels associated with steroid hormone-linked disorders (for review see (Backstrom et al., 2003)). Rather, it has been suggested that women with PMS/PMDD differ in brain sensitivity to neurosteroids (Backstrom et al., 2003). Administration and withdrawal of exogenous steroid hormones, designed to mimic the hormonal changes during pregnancy, result in symptoms of depression only in women with a history of postpartum depression (Bloch et al., 2000), suggesting that the withdrawal of reproductive hormones alone is not sufficient to induce symptoms of depression, but rather some women must be predisposed to postpartum depression. Consistent with this hypothesis, women with a history of postpartum depression exhibit differences in their sensitivities to steroid hormones (Wisner et al., 2002), suggesting that the site of neurosteroid action, namely the $GABA_A$ receptors ($GABA_A$Rs), might be altered in affected women.

Neurosteroids and $GABA_A$ receptors

The GABAergic system has been implicated in the pathophysiology of menstrual cycle-linked disorders (Backstrom et al., 2003; Smith et al., 2003; Sundstrom et al., 1999) as well as anxiety disorders (Bremner et al., 2000; Goddard et al., 2001; Malizia et al., 1998; Tiihonen et al., 1997). Benzodiazepines and the neuroactive steroids pregnanolone and allopregnanolone exert anxiolytic effects in patients with panic disorder (Herd et al., 2007; Mitchell et al., 2008; Smith et al., 2007; Strohle et al., 2002). In addition, withdrawal of positive allosteric modulators of $GABA_A$Rs, such as benzodiazepines, mimic the symptoms of ovarian cycle-linked neurological disorders, resulting in symptoms such as irritability, tension, increased anxiety, panic attacks, headaches, and even depression and seizures in women (Petursson, 1994). Consistent with the role of $GABA_A$Rs in menstrual cycle-linked disorders, PMS/PMDD patients are less sensitive to neurosteroids and benzodiazepines (Sundstrom et al., 1997, 1998).

$GABA_A$Rs are heteropentameric receptors composed of a combination of subunits, such as α1-6, β1-4, γ1-3, δ, ε, θ, and ρ1-2 (Olsen and Sieghart, 2008; Whiting et al., 1999), which dictate the anatomical distribution (Pirker et al., 2000), physiological properties, and pharmacology of the receptor (Hevers and Luddens, 1998; Mody and Pearce, 2004). For example, γ2 containing $GABA_A$Rs are widely distributed throughout the brain (Pirker et al., 2000; Wisden et al., 1992), localized synaptically, and mediate the "synaptic" or "phasic" form of GABAergic inhibition (Farrant and Nusser, 2005). In contrast, the δ subunit-containing $GABA_A$Rs are prevalent in the cerebellum, dentate gyrus, cortex, thalamus, and striatum (Peng et al., 2002, 2004; Pirker et al., 2000; Wisden et al., 1992), localized extrasynaptically (Nusser et al., 1998) or perisynaptically (Wei et al., 2003), and mediate the "tonic" form of GABAergic inhibition (Farrant and Nusser, 2005). We now know δ subunit-containing $GABA_A$Rs are more sensitive to neurosteroids in heterologous systems (Belelli et al., 2002; Belelli and Lambert, 2005; Brown et al., 2002; Mihalek et al., 1999; Spigelman et al., 2003; Wohlfarth et al., 2002) and these receptors are the major site of neurosteroid potentiation of the tonic current in dentate gyrus granule cells (Stell et al., 2003) (for review see (Walker and Semyanov, 2008)). However, the conserved site for neurosteroid binding has recently been discovered between the α and β interface of the $GABA_A$R (Hosie et al., 2006), in conflict with the pharmacological data demonstrating the enhanced neurosteroid potentiation of δ subunit-containing receptors. This discrepancy may be due to the fact that the δ subunit may act to alter the efficacy of neurosteroid potentiation rather than influence neurosteroid binding (Hosie et al., 2009).

$GABA_A$ receptor regulation by steroid hormones

While steroid hormone metabolites, derived from ovarian steroid hormones (progesterone) or stress steroid hormones (corticosterone), potentiate the effects of GABA on $GABA_A$Rs, particularly those containing δ subunits, there are also effects of steroid hormones and neurosteroids on $GABA_A$R subunit expression in rodents. The remainder of this review will focus on the steroid hormone regulation of $GABA_A$R structure and function in response to physiological conditions, such as pregnancy, stress, and the ovarian cycle, as well as discussing the pathophysiological consequences of the breakdown in this $GABA_A$R regulation.

Pregnancy

One of the most common physiological conditions associated with elevated steroid hormone levels is pregnancy. During pregnancy, progesterone levels rise approximately 200-fold (Backstrom et al., 2003) and, in addition, there are also large increases in the levels of the neuroactive steroids allopregnanolone and THDOC (Concas et al., 1998). Many studies investigating the changes in $GABA_A$R subunit expression

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Table 1 Steroid hormone-associated changes in GABAAR subunit expression and function.

	Optical density (a.u.)		Tonic inhibition	Phasic inhibition
	δ Expression	γ2 Expression	Tonic current (pA)	Peak amplitude (pA)
Ovarian cycle				
Estrus	0.37 ± 0.04	0.51 ± 0.02	29.8 ± 5.5	90.6 ± 13.4
Diestrus	0.53 ± 0.01*	0.34 ± 0.01 *	57.6 ± 10.2*	114.5 ± 20.5
Pregnancy				
Virgin	0.42 ± 0.03	0.55 ± 0.01	39.8 ± 4.4	76.4 ± 5.5
Pregnancy	0.28 ± 0.02*	0.37 ± 0.01*	19.7 ± 3.6*	45.4 ± 3.9*
Postpartum	0.42 ± 0.05	0.55 ± 0.01	40.4 ± 7.1	69.5 ± 6.9

Western blot analysis was performed on the total hippocampal membrane fraction and probed with an antibody for the $GABA_AR$ δ subunit or the $GABA_AR$ γ2 subunit. Optical density measurements are shown in Table 1 (left; Maguire et al., 2005; Maguire and Mody, 2008). Altered $GABA_AR$ subunit expression is associated with changes in GABAergic inhibition. The tonic GABAergic inhibition and peak amplitude of sIPSCs recorded in dentate gyrus granule cells is shown in Table 1 (right; Maguire et al., 2005; Maguire and Mody, 2008). * Denotes $p < 0.05$ using a one-way ANOVA. Estrous cycle and pregnancy data were analyzed separately, Maguire et al. (2005) and Maguire and Mody (2008), respectively.

* Denotes significance compared to estrus in the ovarian cycle studies and wild type virgin in the pregnancy studies.

related to pregnancy have relied on "pseudopregnancy" or progesterone withdrawal models. Progesterone withdrawal has been shown to increase expression of $GABA_AR$ α4 and δ expression in the hippocampus (Smith et al., 1998) and periaqueductal grey (PAG) (Griffiths and Lovick, 2005a). In addition, many studies have focused on changes in mRNA levels, which may not reflect changes in functional protein levels. $GABA_AR$ γ2 mRNA levels have been shown to be decreased during pregnancy in the cortex and hippocampus (Concas et al., 1998; Follesa et al., 1998) with no change in the levels of α1, α2, α3, α4, β1, β2, β3 (Concas et al., 1998; Follesa et al., 1998). These changes were blocked by finasteride treatment (Concas et al., 1998), suggesting that this regulation of $GABA_AR$s is mediated by neurosteroids.

In order to investigate changes in $GABA_AR$s associated with the highly elevated steroid hormone levels throughout pregnancy and postpartum in C57Bl/6 mice, we measured $GABA_AR$ subunit expression by Western blot analysis in the hippocampal membrane fraction to ensure only membrane-associated, functional receptors were analyzed. We demonstrated a decreased expression of the $GABA_AR$ δ subunit expression in the hippocampus at day 18 of pregnancy, which rebounds to virgin levels by 48 h postpartum (Table 1) (Maguire and Mody, 2008). The functional consequence of this decrease in the $GABA_AR$ δ subunit during pregnancy was analyzed by whole-cell patch clamp recording and corresponds to a decrease in the tonic inhibition mediated by these receptors in dentate gyrus granule cells (Table 1) (Maguire and Mody, 2008). Similarly, we detected a decrease in the $GABA_AR$ γ2 subunit in the hippocampus during pregnancy which corresponded to a decrease in the amplitude of spontaneous inhibitory postsynaptic potentials (sIPSCs) measured by whole-cell patch clamp recording, mediated predominantly by these receptors in dentate gyrus granule cells (Table 1) (Maguire and Mody, 2008). These alterations in $GABA_AR$s may be compensatory changes in response to the elevated levels of allopregnanolone throughout pregnancy, which become elevated to nearly 100 nM during pregnancy (Paul and Purdy, 1992), within the concentration range which causes sedation (80–160 nM) under normal conditions (Sundstrom et al., 1999). The rapid return of neurosteroid levels to pre-pregnancy levels is accompanied by a quick postpartum reversion of $GABA_AR$ expression and inhibition to control levels, likely to maintain an ideal level of inhibition throughout the postpartum period (Fig. 1). Our data suggest that $GABA_AR$s, which are sensitive to the high levels of neurosteroids which occur throughout pregnancy, likely become downregulated to prevent excess inhibition throughout pregnancy which may have adverse behavioral consequences. However, recently it was discovered that these same receptors undergo a different pattern of regulation throughout pregnancy in the rat (Sanna et al., 2009), suggesting that the regulation of $GABA_AR$s throughout pregnancy may be more complex than merely homeostatic plasticity and that there may also be species differences in steroid hormone-mediated $GABA_AR$ regulation.

We propose that a deficiency in $GABA_AR$ regulation throughout pregnancy and postpartum may predispose individuals to mood disorders associated with the postpartum period, such as postpartum depression (Fig. 1). The postpartum period is a particularly vulnerable period for mood disorders and this vulnerability is thought to be related to changing steroid hormone levels. However, it may not be the steroid hormones *per se* but rather the site of steroid hormone action in the CNS, namely the $GABA_AR$ δ subunit. Consistent with this hypothesis, the inability to properly regulate $GABA_AR$s during pregnancy and postpartum, as in mice that are deficient in the $GABA_AR$ δ subunit ($Gabrd^{-/-}$ mice), is associated with depression-like and abnormal maternal behaviors in these mice. $Gabrd^{-/-}$ mice exhibit depression-like behaviors 48 h postpartum assessed using the Porsolt forced swim test. In addition, postpartum $Gabrd^{-/-}$ mice fail to build a nest, they keep their pups at an increased distance from the mother, and exhibit an increase in the percentage of pups that die due to neglect and/or cannibalism (Maguire and Mody, 2008). Our data are consistent with the idea that the pathophysiology of postpartum depression may be related to the inability to properly regulate the expression of $GABA_AR$s throughout pregnancy and restore their function postpartum (Fig. 1).

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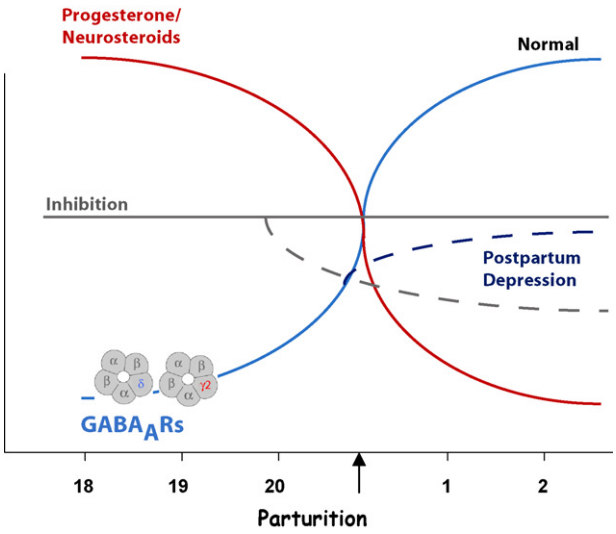

Figure 1 A model of GABAAR dysfunction in postpartum depression. In the face of elevated steroid hormone levels during late pregnancy, the neurosteroid sensitive GABA$_A$R δ and γ2 subunits must become downregulated to maintain a level of inhibition throughout pregnancy. At the time of parturition, as steroid hormone levels rapidly decline, the levels of GABA$_A$R δ and γ2 subunits must be recovered to pre-pregnancy levels to maintain an ideal level of inhibition throughout the postpartum period. Inability to regulate GABA$_A$Rs during the postpartum period (dotted line) may result in an imbalance between excitation and inhibition resulting in abnormal postpartum mood disorders, such as postpartum depression. Figure adapted from (Maguire et al., 2009).

Stress

Another condition known to elevate steroid hormone levels is stress. Stress activates the hypothalamic-pituitary-adrenal axis resulting in the release of corticosteroids, thus, resulting in an increase in both circulating and brain levels of the neuroactive steroids THDOC and allopregnanolone (Mcewen, 2002; Purdy et al., 1991; Reddy and Rogawski, 2002). Acute stress has been shown to increase THDOC levels (Barbaccia et al., 1996a, 2001) from 1–5 nM to 15–30 nM (Reddy and Rogawski, 2002); for review see (Reddy, 2003)) and allopregnanolone levels 8-fold (Purdy et al., 1991). However, stress-related neurosteroids exert complex actions on GABA$_A$Rs. Several studies, relying heavily on binding and uptake assays, have demonstrated changes in GABA$_A$R function following stress (Akinci and Johnston, 1993; Schwartz et al., 1987; Serra et al., 2000; Skerritt et al., 1981). For instance, acute stress has been shown to increase GABA receptor-mediated chloride influx (Schwartz et al., 1987), while a decrease in GABAergic function is associated with chronic stress (Serra et al., 2000). An acute swim stress enhances the binding of GABA agonists (Akinci and Johnston, 1993; Skerritt et al., 1981) and increases the seizure threshold induced by GABA antagonists (Pericic et al., 2001). It has been suggested that elevated THDOC levels following acute stress are responsible for the decreased seizure susceptibility (Reddy, 2003), such that the decreased seizure susceptibility is correlated with a 3-fold increase in circulating levels of THDOC (Reddy and Rogawski, 2002). However, elevated levels of neurosteroids following stress induce alterations in GABA$_A$Rs which may also contribute to altered neuronal excitability.

We demonstrate alterations in GABA$_A$R subunit expression following an acute stressful episode, which may function to maintain the balance between excitation and inhibition following stress. Mice subjected to a 2 min CO_2 stress exhibit an increase in GABA$_A$R δ subunit expression 30 min following the stressor (Maguire and Mody, 2007), which is associated with an increase in tonic GABAergic inhibition in dentate gyrus granule cells assessed by whole-cell patch clamp recording (Maguire and Mody, 2007). Previous binding studies have suggested that there is a decrease in GABAergic function 10 min following an acute stressful episode and that the increase in neurosteroid levels at 30 min following the stressor may serve to restore GABAergic function following stress (Barbaccia et al., 1996b). The dynamic regulation of GABA$_A$Rs in response to an acute stressor is a compensatory mechanism to cope with the stress and disruption in the regulation of GABA$_A$Rs in response to stress may underlie the stress-induced exacerbation of many psychiatric and neurological disorders.

Ovarian cycle

Changes in neuronal excitability and anxiety are associated with changes in steroid hormone levels over the ovarian cycle (Backstrom et al., 2003; Herzog et al., 1997, 2004), which have been attributed to changes in endogenous neurosteroid levels (Backstrom et al., 2003; Herzog et al., 1997, 2004). However, how neurosteroids alter neuronal excitability over the ovarian cycle is unclear, but is thought to involve actions of neurosteroids on GABA$_A$Rs. Changes in GABAergic inhibition over the ovarian cycle have been inferred from alterations in muscimol binding and changes in the sensitivity to neurosteroids and benzodiazepines over the estrous cycle (Aldahan et al., 1994; Martin and Williams, 1995; Molina-Hernandez and Tellez-Alcantara, 2001; Molina-Hernandez et al., 2001; Reddy and Kulkarni, 1999; Sundstrom et al., 1998). In addition to the direct effects of neurosteroids in potentiating the effects of GABA on GABA$_A$Rs, steroid hormones have also been shown to alter GABA$_A$R subunit composition. For example, short-term exposure to progesterone or allopregnanolone increases GABA$_A$R α4 and δ subunit expression in the hippocampus, with peak expression at 2–3 days of treatment (Gulinello et al., 2001; Hsu and Smith, 2003). Direct changes in GABA$_A$Rs over the estrous cycle of mice have been reported in the hippocampus (Maguire et al., 2005) as well as in the periaqueductal grey (Griffiths and Lovick, 2005a,b). Our data demonstrate an increase in the expression of the GABA$_A$R δ subunit and a decrease in GABA$_A$R γ2 subunit by Western blot analysis at times of the estrous cycle in mice characterized by elevated levels of the steroid hormone, progesterone (Table 1) (Maguire et al., 2005). These changes in GABA$_A$R subunit expression are correlated with elevated levels of progesterone (Maguire et al., 2005), and although the levels of allopregnanolone were not directly measured in this study, allopregnanolone levels have been shown to mirror changes in progesterone levels (in review (Paul and Purdy, 1992)). The increase in the GABA$_A$R δ subunit expression over the ovarian cycle is associated with an increase in the tonic inhibition measured by whole-cell patch clamp recording mediated by these receptors

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in dentate gyrus granule cells (Table 1). However, we do not see a change in the phasic component of GABAergic inhibition despite the decreased levels of $GABA_AR$ γ2 subunit expression. This is likely due to the fact that the synaptic receptors are saturated upon release of GABA or these receptors sit peri- or extrasynaptically where they would not sense synaptically released GABA. These changes in $GABA_AR$ structure and function over the ovarian cycle are associated with a decrease is seizure susceptibility, and a decrease in anxiety levels (Maguire et al., 2005). These data suggest that changes in neuronal excitability over the ovarian cycle may involve regulation of $GABA_ARs$ and dysregulation may play a role in PMS and/or PMDD.

Significance

Elucidating the neurosteroid-mediated alterations in $GABA_AR$ composition has altered the way that scientists think about steroid hormone-associated neuropsychiatric disorders. Previously, it was thought that steroid hormones acted solely through steroid hormone receptors to induce changes in gene transcription and that steroid hormone derivatives, or neurosteroids, exerted only acute effects on $GABA_ARs$. It is now clear that steroid hormones can alter $GABA_AR$ subunit composition and thereby alter GABAergic inhibition, independent of steroid hormone receptors (Maguire and Mody, 2007). Interestingly, acute exposure to steroid hormones/neurosteroids has a different effect than prolonged exposure to these same compounds, highlighting the bimodal effects of steroid hormones and their derivatives. For example, in response to a modest, brief increase in neurosteroid levels, such as over the ovarian cycle or following acute stress, there is an increase in the tonic inhibition with no change in the phasic component of inhibition. In contrast, in response to very high levels of neurosteroids for a prolonged period of time, such as during pregnancy, both the tonic and phasic components of inhibition become dampened. These dose-dependent changes in inhibition may be related to differences in the affinity of different receptors assemblies for neurosteroids. At low nanomolar concentrations, neurosteroids act preferentially at δ subunit-containing receptors which mediate the tonic component of inhibition. However, at higher concentrations neurosteroids can also activate γ2 subunit-containing receptors, which mediate the phasic form of inhibition. Therefore, the concentration and time of exposure of neurosteroids may have an effect $GABA_AR$ regulation. These alterations in $GABA_ARs$ likely play an important role in steroid hormone-associated changes in neuronal excitability and dysfunction in the regulation of $GABA_ARs$ by steroid hormones may play a role in steroid hormone-associated neuropsychiatric disorders (Longone et al., 2008; Girdler and Klatzkin, 2007), such as PMS, PMDD, and postpartum depression (Backstrom et al., 2003; Sundstrom et al., 1999).

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