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Allopregnanolone in premenstrual dysphoric disorder (PMDD): Evidence for dysregulated sensitivity to GABA-A receptor modulating neuroactive steroids across the menstrual cycle

Liisa Hantsoo[a,*], C. Neill Epperson[b]

[a] Department of Psychiatry & Behavioral Sciences, The Johns Hopkins University School of Medicine, 550 N, Broadway Street Baltimore, MD, 21205, USA
[b] Department of Psychiatry, University of Colorado School of Medicine Anschutz Medical Campus, 13001 E 17th Place, MS F546, Aurora, CO, 80045, USA

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ABSTRACT

Premenstrual dysphoric disorder (PMDD) is a severe mood disorder with core symptoms (affective lability, irritability, depressed mood, anxiety) and increased sensitivity to stress occurring in the luteal phase of the menstrual cycle. PMDD can be conceptualized as a disorder of suboptimal sensitivity to neuroactive steroid hormones (NASs). In this review, we describe the role of the NAS allopregnanolone (ALLO), a positive allosteric modulator of the $GABA_A$ receptor ($GABA_A$-R), in PMDD's pathophysiology. We review evidence of impaired interaction between ALLO and $GABA_A$-Rs in terms of affective symptom expression, with evidence from rodent and human studies. We discuss evidence of increased luteal phase stress sensitivity as a result of poor ALLO-GABA control of the HPA axis. Finally, we describe how treatments such as selective serotonin reuptake inhibitors (SSRIs) and new drugs targeting $GABA_A$-Rs provide evidence for impaired ALLO-GABA function in PMDD. In sum, the literature supports the hypothesis that PMDD pathophysiology is rooted in impaired $GABA_A$-R response to dynamic ALLO fluctuations across the menstrual cycle, manifesting in affective symptoms and poor regulation of physiologic stress response.

1. Introduction

PMDD is a unique cyclic mood disorder. Premenstrual dysphoric disorder (PMDD) is a severe mood disorder, unique in that symptoms emerge and remit with the hormonal fluctuations of the menstrual cycle. Symptoms emerge monthly in the luteal phase, roughly one to two weeks before menses, when sex steroid hormones are fluctuating. Symptoms quickly remit in the hormonally stable follicular phase of the menstrual cycle, the roughly two weeks between menses and ovulation. Symptoms then return with the following menstrual cycle's luteal phase. Characteristic PMDD symptoms include affective lability, irritability, depressed mood, anxiety, as well as decreased interest in usual activities, poor concentration, fatigability, change in appetite, sleep changes, sense of overwhelm, and physical symptoms such as breast tenderness, bloating or headaches (Epperson et al., 2012). The monthly waxing and waning of these symptoms produces distress and functional impairment totaling 24 days to up to 6 months annually (Hantsoo and Epperson, 2015). Across the roughly 450 menstrual cycles that a woman has in her lifetime (Halbreich et al., 2003), a woman who experiences PMDD symptoms for one week per cycle would experience 8.6 cumulative years of symptoms, similar to what someone with recurrent major depressive disorder would experience across their lifetime (Kessler and Walters, 1998). PMDD affects three to eight percent of women worldwide (Halbreich et al., 2003), roughly similar to the prevalence of generalized anxiety disorder or panic disorder (Altemus et al., 2014; Kessler et al., 2005; McLean et al., 2011).

PMDD is a disorder of suboptimal sensitivity to sex steroids. Reflected in symptom emergence during a hormonally dynamic phase of the menstrual cycle, PMDD's pathophysiology likely involves altered central nervous system (CNS) sensitivity to neuroactive steroid (NAS) hormones. NASs are steroid hormones produced in endocrine tissue or brain that interact with neuron receptors, such as the gamma-aminobutyric acid (GABA)-A receptor ($GABA_A$-R) or NMDA receptors. Examples of NASs are pregnenolone, progesterone, estradiol, and corticosterone. This review will focus on the NAS allopregnanolone (ALLO), a progesterone metabolite. ALLO acts as an allosteric modulator of the $GABA_A$-R to potentiate the effect of GABA, the main inhibitory neurotransmitter in the CNS. In this review, we describe the role of ALLO in PMDD's pathophysiology.

Stress response is altered in PMDD. Along with the core mood

* Corresponding author.
E-mail address: LHantso1@jhmi.edu (L. Hantsoo).

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symptoms of the luteal phase, women with PMDD experience increased sensitivity to stress during the luteal phase. This includes not only increased greater subjective perceived stress (Beddig et al., 2019; Petersen et al., 2016), but altered physiologic stress responsivity such as hypothalamic pituitary adrenal (HPA) axis function (Beddig et al., 2019; Girdler et al., 1998; Parry et al., 2000) and acoustic startle response (ASR) (Epperson et al., 2007; Hantsoo et al., 2015). In this review, we describe alterations in stress response among women with PMDD, particularly as related to interactions between the HPA and hypothalamic-pituitary-gonadal (HPG) axes.

2. Suboptimal sensitivity to allopregnanolone in PMDD

While there are multiple potential contributors to PMDD's etiology including genetic factors (Dubey et al., 2017) and psychosocial factors (Pilver et al., 2011), this review focuses on impaired CNS sensitivity to NASs. The timing of symptom onset and offset in PMDD implicates hormonal fluctuation as a critical component of PMDD's etiology. Paradoxically, women with PMDD cannot be distinguished from asymptomatic women in terms of peripheral ovarian hormone levels (Thys-Jacobs et al., 2008), including ALLO (Nguyen et al., 2017). Instead, it is hypothesized that women with PMDD have altered sensitivity at the receptor level to normal hormonal fluctuations across the menstrual cycle (Bäckström et al., 2011; MacKenzie and Maguire, 2014). The hormone sensitivity hypothesis proposes that PMDD represents an aberrant response to sex steroid hormones (Dubey et al., 2017; Schmidt et al., 1998). Growing evidence suggests that the hallmark symptoms of PMDD - mood lability, anxiety and irritability, often exacerbated by stress - reflect suboptimal $GABA_A$-R sensitivity to ALLO.

2.1. Progesterone's metabolite, allopregnanolone

Progesterone, a sex steroid secreted by the corpus luteum responsible for preparing the uterus for implantation, is low during the follicular phase, rises across the luteal phase, and drops rapidly in the late luteal phase just prior to menses. Its levels are mirrored by its metabolite, ALLO (Timby, 2012). ALLO is a potent positive allosteric modulator of the $GABA_A$-R; when it binds to its site on the receptor, it potentiates function by increasing Cl^- ion flux when GABA binds $GABA_A$-R (Chen et al., 2019; Lambert et al., 2009). ALLO thus has anxiolytic, anesthetic and sedative properties similar to barbiturates or benzodiazepines (Schüle et al., 2014).

2.1.1. ALLO synthesis from progesterone

ALLO is synthesized from progesterone in two steps: first, 5α-reductase converts progesterone to 5α-dihydroprogesterone (5α-DHP), then 3α hydroxysteroid dehydrogenase (3α-HSD) converts 5α-DHP to allopregnanolone (Agís-Balboa et al., 2006). Women with PMDD exhibited higher 5α-DHP in the mid-luteal phase than control women (Epperson et al., 2002), but there is no direct evidence to date that women with PMDD have alterations in the enzymatic pathway from progesterone to ALLO. Women with PMDD showed no differences in metabolic processing of exogenously administered estradiol or progesterone after ovarian suppression compared with controls (Nguyen et al., 2017). Further work in larger samples is needed to assess the function of these biosynthetic enzymes in PMDD.

2.1.2. ALLO levels and kinetics

While basal NAS levels do not differ between women with PMDD and controls at particular phases of the menstrual cycle (Nguyen et al., 2017; Thys-Jacobs et al., 2008), it is possible that there are differences in the dynamics of these hormones across the menstrual cycle in women with PMDD. ALLO exposure followed by rapid withdrawal may be a key factor in the etiology of PMDD (Smith et al., 2006). In an animal model of PMDD based on progesterone withdrawal, rats that rapidly withdrew from physiological doses of progesterone exhibited social withdrawal and anhedonia, symptoms characteristic of PMDD (Li et al., 2012). Indeed, when rate of decline of progesterone was manipulated in rodents, a rapid decline in plasma progesterone increased anxiety-like behavior, while a gradual progesterone decline did not (Doornbos et al., 2009).

Similar patterns are emerging from human studies. Dutasteride, a 5-alpha reductase inhibitor, prevented symptom onset in women with PMDD in a randomized, double-blind, placebo-controlled crossover study (Martinez et al., 2016). While the participants experienced luteal phase progesterone fluctuations, by blocking 5-alpha reductase's conversion of progesterone to ALLO, the researchers stabilized ALLO levels and reduced symptoms of irritability, low mood, anxiety, food cravings and bloating. This emphasizes that it is likely not the absolute level of ALLO, but changes in its levels across the luteal phase, that triggers PMDD symptoms. Indeed, a study that examined kinetics of progesterone levels across the luteal phase found differences in rates of change in progesterone between women with PMDD and asymptomatic controls (Lovick et al., 2017). In controls, progesterone levels gradually waned in the eight days prior to menses. In the women with premenstrual symptoms, progesterone levels remained stable until three days prior to menses, when they dropped sharply. This is similar to the rodent study in which an abrupt decline in progesterone produced anxiety symptoms while a gradual decline did not (Doornbos et al., 2009), although did not address why PMDD symptoms may also occur when ALLO levels are increasing (Martinez et al., 2016).

2.2. Animal models of PMDD are based on NAS withdrawal

Animal models of PMDD are based on withdrawal from progesterone or ALLO (Li et al., 2012; Smith et al., 2006). As described above, fluctuation in ALLO is thought to be a key trigger of PMDD symptoms (Martinez et al., 2016). In rodents, rapid withdrawal from progesterone or ALLO produces symptoms characteristic of PMDD, such as increased anxiety behavior (increased ASR, decreased open arm entries in elevated plus maze) (Gulinello and Smith, 2003; Smith et al., 2006) and depressive behavior (increased immobility in forced swim test, social withdrawal in social preference test, anhedonia in saccharin preference test) (Li et al., 2012). In these rodent models of PMDD, NAS withdrawal also alters $GABA_A$-R structure, detailed in the next section. Briefly, in female rats, progesterone exposure and withdrawal upregulated the α4 subunit of $GABA_A$-R (Smith et al., 1998b). Similarly, in a mouse model of PMDD, withdrawal from ALLO increased expression of the $GABA_A$-R α4 subunit eight-fold, accompanied by anxiety-like behaviors (Smith et al., 2006). Female rats withdrawn from chronic progesterone similarly exhibited upregulation of $GABA_A$-R α4 subunit expression, which was paralleled by elevated ASR (Gulinello et al., 2003). Importantly, progesterone withdrawal did not alter serotonin levels in rat cortex or hippocampus, indicating that PMDD symptoms may not be serotonin-driven (Li et al., 2012). These results from animal models also suggest that expression of the $GABA_A$-R subunits, such as α4, may be a key piece of PMDD pathophysiology.

2.3. Altered interaction between ALLO and $GABA_A$ receptors in PMDD

2.3.1. $GABA_A$-R subunits

$GABA_A$-Rs are composed of five subunits of nineteen (α1–α6, β1–β3, γ1–γ3, δ, ε, θ, π, ρ1–ρ3) (Chua and Chebib, 2017; Simon et al., 2004). $GABA_A$-R subunit expression is dynamic, and varies by sex and hormonal status (Bhandage et al., 2015; Maguire and Mody, 2008; Sanna et al., 2009). Different subunit combinations produce different sensitivity to pharmacologic compounds and NASs, i.e. structure informs function (Knoflach et al., 2018). While an exhaustive review of the $GABA_A$-R subunits is beyond the scope of this article (instead, see Belelli et al., 2006; Wang, 2011; Lee and Maguire, 2014), we describe several subunits potentially relevant to PMDD.

The α subunits of $GABA_A$-Rs are sensitive to NASs, enhancing

GABAergic current. α1-and α3-containing $GABA_A$-Rs are sensitive to low concentrations of ALLO, while α2-, α4-, α5-and α6-containing receptors are sensitive to higher ALLO concentrations (Belelli et al., 2002). The expression of the subunits themselves is also responsive to fluctuations in NASs. Administration of pregnanolone, an isomer of ALLO, increased α4 subunit expression in female rats over a 48-h period (Shen et al., 2005). Administration of progesterone over 21 days (mimicking the human menstrual cycle) followed by rapid withdrawal increased $GABA_A$-R α4 subunit expression by 2–3 fold in female rats within 24 h of withdrawal and increased anxiety, reflected in elevated ASR, in the rodent model of PMDD mentioned above (Gulinello et al., 2003). In another PMDD rodent model, withdrawal from ALLO via finasteride, a 5α-reductase inhibitor, increased expression of the $GABA_A$-R α4 subunit eight-fold, accompanied by anxiety-like behaviors (Smith et al., 2006). Other studies have also shown that increases in the α4 subunit are associated with increased anxiety behavior (Gulinello et al., 2001; Smith et al., 1998b).

δ-Containing $GABA_A$-Rs are also sensitive to NASs, particularly at low concentrations (Belelli et al., 2002). The δ subunit is involved in tonic inhibition, in which GABA "spillover" in the extracellular space produces a persistent activation of $GABA_A$-Rs, in contrast to the brief phasic inhibition resulting from presynaptic release of GABA (Farrant and Nusser, 2005). As mentioned above, administration of pregnanolone over 48 h influenced $GABA_A$-R subunit expression, increasing not only α4 subunits but increasing δ subunit expression four-to five-fold in female rats (Shen et al., 2005). Further, ALLO withdrawal produced anxiety behavior except in δ knockout mice (Smith et al., 2006). The δ subunits are thought to be involved in regulating anxiety-like behavior (Maguire et al., 2005).

Plasticity of $GABA_A$-Rs or their subunits in response to NAS fluctuations may be a key aspect of PMDD pathophysiology (MacKenzie and Maguire, 2014). However, findings at this point are limited to animal research. Animal data on other reproductive affective disorders (e.g. postpartum depression) suggest that mice that were not able to regulate $GABA_A$-R dynamics in response to the slow rise and rapid decrease in ALLO across pregnancy and postpartum showed depression-like behaviors postpartum (Maguire and Mody, 2008). In control mice, the rapid postpartum drop of NASs to pre-pregnancy levels was followed by an appropriate corresponding adjustment in number of functional $GABA_A$-Rs (Maguire and Mody, 2008). Together, rodent models suggest impaired $GABA_A$-R plasticity in response to NAS fluctuations in reproductive affective disorders such as postpartum depression and PMDD (Gallo and Smith, 1993; Gulinello et al., 2001; Reddy et al., 2012; Smith et al., 1998a; Sundstrom-Poromaa et al., 2002).

2.3.2. Evidence of altered interaction between ALLO and $GABA_A$-Rs in clinical studies

Although data is sparse relative to animal studies, women with PMDD show evidence of altered $GABA_A$-R response to ALLO. While intravenous administration of ALLO to healthy controls increased sedation and decreased maximal saccadic eye velocity (SEV; regulated by the $GABA_A$-R (Ball et al., 1991)), women with PMDD did not experience ALLO-induced sedation in the luteal phase and paradoxically experienced sedation in the follicular phase (Timby et al., 2016). As SEV is a measure of $GABA_A$-R sensitivity (Bixo et al., 2018), these findings suggest that women with PMDD have altered $GABA_A$-R function that changes across the menstrual cycle. Preliminary data from our laboratory also indicates that women with PMDD have elevated anxiety-potentiated startle (APS) in the luteal phase relative to controls in the luteal phase, suggestive of altered $GABA_A$-R function in the context of fluctuating ALLO levels (Hantsoo et al., 2015). Together, the findings in rodents and humans support the hypothesis that PMDD reflects a failure of $GABA_A$-R plasticity; the $GABA_A$-R in PMDD is unable to adapt its composition to changing ALLO levels across the menstrual cycle, resulting in affective symptoms and poor regulation of stress response.

3. Allopregnanolone and stress response in PMDD

3.1. The hypothalamic pituitary adrenal (HPA) axis

ALLO's sedative effects make it a critical aspect of acute stress response; it not only exerts calming effects, but regulates HPA axis response to acute stress (Cullinan et al., 2008). In the laboratory, a bolus injection of ALLO produces a subjective sense of sedation in healthy individuals (Kask et al., 2009). Accordingly, acute stress triggers an ALLO increase (Childs et al., 2010; Purdy et al., 1991), reflected both centrally in brain tissue and peripherally in blood (Klatzkin et al., 2006), peaking twenty to 60 min after stressor onset (Eser et al., 2005; Purdy et al., 1991). ALLO's role in acute stress response is to potentiate GABAergic transmission, promoting anxiolysis and attenuating stress response. ALLO attenuates corticotropin releasing factor (CRF) release from the hypothalamus, promoting negative feedback in the HPA axis to ultimately reduce adrenal gland cortisol secretion and restore homeostasis (Patchev et al., 1994; Turkmen et al., 2011).

Women with PMDD show altered HPA axis function, including lower cortisol levels during mental stress (Girdler et al., 2001; Huang et al., 2015) and higher baseline cortisol levels during the luteal phase (Rasgon et al., 2000) compared to controls. However, findings are mixed, with some reports of typical HPA function in women with PMDD (Lee et al., 2012), or altered HPA indicators only in a subset of PMDD women (Segebladh et al., 2013). For instance, only women with both PMDD and high serum ALLO levels exhibited blunted nocturnal cortisol levels (Segebladh et al., 2013). Women with premenstrual mood symptoms also show alterations in ALLO response to acute stress. ALLO release to HPA axis stimulation was blunted in women with premenstrual syndrome (PMS), a less severe syndrome than PMDD with fewer, milder symptoms (Lombardi et al., 2004). In that study, controls and women with PMS underwent dexamethasone suppression of the HPA axis followed by ACTH stimulation. Women with PMS had a smaller, delayed ALLO response to ACTH stimulation than controls, particularly in the luteal phase. This suggests that women with premenstrual mood syndromes may have dysregulated interaction between the hypothalamic pituitary gonadal (HPG) and HPA axes. If $GABA_A$-Rs fail to respond appropriately to fluctuating ALLO across the menstrual cycle in PMDD, it follows that these $GABA_A$-Rs may exert poor control over the HPA axis in PMDD (Gordon et al., 2015). This poor GABA regulation of the HPA axis may be reflected in the increased stress sensitivity of women with PMDD in the luteal phase of the menstrual cycle.

3.2. Acoustic startle response

3.2.1. Acoustic startle in animal models of PMDD

The startle reflex is an index of physiological arousal, and can be considered an aspect of stress response. As ASR is conserved across species, it is a highly translational tool and has been used in animal models of PMDD. As described above, progesterone or ALLO withdrawal are often used to model PMDD in rodents. In a rodent model of PMDD, progesterone withdrawal increased ASR and upregulated $GABA_A$-R α4 subunit expression (Gulinello et al., 2003). In this rodent model, the authors proposed that elevated ASR represented greater anxiety levels.

3.2.2. Acoustic startle in women with PMDD

Physiological arousal may be altered at points in the menstrual cycle among women with PMDD. During the follicular phase when ALLO levels are low, ASR was similar between healthy controls and women with PMDD, but in the luteal phase, PMDD women showed increased ASR (Epperson et al., 2007). In another study, women with PMDD had greater ASR in both phases of the menstrual cycle compared to controls, with ASR particularly accentuated in the luteal phase (Kask et al., 2008). Women with PMDD also had enhanced ASR in anticipation of

positive and negative images, compared with controls, during the luteal phase (Bannbers et al., 2011). Together, these ASR findings in women with PMDD show elevated physiologic arousal in the luteal phase, suggesting that ALLO action on $GABA_A$Rs is failing to moderate arousal.

3.2.3. Anxiety-potentiated and fear-potentiated startle

Anxiety potentiated startle (APS) is the potentiation of ASR during sustained anxious anticipation of a potential threat (Davis et al., 2010). APS is mediated by the $GABA_A$R-rich bed nucleus of the stria terminalis (BNST) (Davis, 2006; Davis et al., 2010; Lee and Davis, 1997; Sink et al., 2012). Fear-potentiated startle (FPS) is the phasic potentiation of ASR by an explicit and predictable threat, mediated by the amygdala (Alvarez et al., 2011). Intriguingly, in rodents ALLO dampens APS (operationalized as corticotrophin releasing factor (CRF)-enhanced startle) but not FPS (Toufexis et al., 2004). Ovariectomized rats injected with estradiol and progesterone showed a blunted CRF-enhanced startle compared with estradiol-only injected rats, an effect of progesterone mediated by ALLO (Toufexis et al., 2004). However, neither chronic progesterone nor acute ALLO affected FPS, indicating that ALLO's influence is specific to anticipatory anxiety as opposed to fear. APS may therefore serve as a marker of $GABA_A$-R sensitivity, as it is mediated by the ALLO-sensitive and GABA-R-rich BNST (Schmitz and Grillon, 2012). APS's sensitivity to ALLO makes it a potential marker for altered sensitivity to NASs in women with PMDD (Hantsoo et al., 2018). APS may broadly reflect altered stress sensitivity in PMDD, as the BNST coordinates HPA and HPG axes (Oyola and Handa, 2017). Indeed, women with PMDD often report that they are more reactive to stressors during the symptomatic luteal phase, feeling unable to dampen their response to external stimuli (Hantsoo and Epperson, 2015; Petersen et al., 2016).

3.3. Lifetime stress exposure

History of significant lifetime stress exposure is associated with PMDD. These include adverse childhood experiences (ACEs) such as chronic household dysfunction, and trauma such as abuse. Higher rates of stressful life events and childhood abuse have been reported among women with PMDD compared with women without PMDD (Bunevicius et al., 2005; Golding et al., 2000; Perkonigg et al., 2004; Wittchen et al., 2003). In a sample of nearly 4000 women, trauma history was associated with PMDD diagnosis (Pilver et al., 2011). Past emotional and physical abuse were strongly correlated with moderate to severe PMS in a longitudinal case-control study of over 3000 women (Bertone-Johnson et al., 2014a). The Nurses' Health Study cohort found a greater risk for moderate to severe PMS in women with histories of childhood emotional, physical or sexual abuse (Bertone-Johnson et al., 2014b). Research by Epperson and colleagues suggests that adverse childhood experiences (ACEs) may prime women for risk of mood disorders at points of hormonal fluctuation. For instance, women who had experienced multiple ACEs prior to puberty had a 2.3 times greater risk of incident major depression at the menopausal transition, compared with women with no ACE history (Epperson et al., 2017). Similarly, women who experienced multiple ACEs had dysregulated HPA axis function perinatally (Morrison et al., 2017). In line with Epperson's work, a similar pattern may hold for PMDD. That is, history of ACEs or trauma exposure may make some women more vulnerable to the effects of hormonal fluctuations across the menstrual cycle. One potential mechanism linking stress exposure history and PMDD is ALLO. While ALLO increases with acute stress (Crowley and Girdler, 2014; Klatzkin et al., 2006), after repeated or chronic stress, serum ALLO levels become blunted in rodents (Serra et al., 2007). Given the possible impact of childhood adversity on physiologic arousal regulation (Jovanovic et al., 2009), it is possible that the organizational effect of adversity early in life contributes to dysregulation of the HPA-HPG axes and their modulation by ovarian steroids.

4. Treatment

4.1. Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are the gold standard treatment for PMDD (Lovick, 2013). However, they exhibit unique properties when used for PMDD treatment, namely a rapid therapeutic effect and efficacy at low doses. In women with PMDD, SSRIs typically reduce symptoms over the course of one to three days, in contrast to the weeks often required for response to SSRIs in major depression (Landén and Thase, 2006; Steinberg et al., 2012). Using hourly mood ratings, nearly two-thirds of women with PMDD experienced a 50% reduction in symptoms relative to baseline within 2 days of luteal phase fluoxetine treatment (Steinberg et al., 2012). Similarly in placebo-controlled trials, luteal phase administration of sertraline (Yonkers et al., 2015) and paroxetine (Steiner et al., 2008) were more effective than placebo in reducing PMDD symptoms. SSRIs are also effective at low doses in PMDD, for instance, 25–50 mg sertraline (Kornstein et al., 2006) or 20 mg fluoxetine (Steinberg et al., 2012; Steiner et al., 2003).

These unique characteristics of SSRIs in PMDD treatment suggest that the therapeutic effect is not entirely serotonergic. One suggested mechanism is that SSRIs alter the conversion of progesterone to ALLO (Devall et al., 2015; Pinna et al., 2009). According to this hypothesis, SSRIs increase conversion of the progesterone metabolite 5α-dihydroprogesterone (5α-DHP) to ALLO, via SSRI action on enzymes that catalyze this conversion (Griffin and Mellon, 1999; Trauger et al., 2002). Here, the SSRI would be acting as a selective brain steroidogenic stimulant (SBSS) (Pinna et al., 2009, 2006). In fact, research in animals (Matsumoto et al., 2007; Pinna et al., 2006) and humans (Gracia et al., 2009; Pinna et al., 2009; Uzunova et al., 1998) suggest that SSRIs enhance ALLO biosynthesis. Clinically, an open-label trial of sertraline in women with severe PMS or PMDD found that the SSRI increased peripheral ALLO levels in women with low baseline ALLO, and decreased ALLO in women with high baseline levels (Gracia et al., 2009). However, more research is needed in this area.

4.2. GABA-modulating drugs

Breakthrough GABA-modulating drugs are being developed for affective disorders, particularly those such as PMDD and postpartum depression (PPD) whose etiology involves NASs. For instance, in March 2019 brexanolone (Zulresso®, Sage Therapeutics, Cambridge, MA, USA), a synthetic version of ALLO, was FDA-approved for postpartum depression (PPD). PPD is similar to PMDD in that NAS changes are believed to contribute to its onset, with ALLO as a key player (Osborne et al., 2017). ALLO levels rise steadily through pregnancy, then drop rapidly following parturition. This rapid withdrawal may, in vulnerable women, result in failure to appropriately upregulate in $GABA_A$-Rs that had gradually downregulated across pregnancy. In Phase II (Kanes et al., 2017) and Phase III clinical trials (Meltzer-Brody et al., 2018), brexanolone rapidly reduced PPD symptoms, within 60 h of administration. Again, this is a much more rapid response than seen with SSRIs for PPD treatment, which can take weeks for symptom relief (Hantsoo et al., 2014; Wisner et al., 2006) compared with < 3 days for brexanolone. By acting as a positive allosteric modulator of $GABA_A$-Rs, brexanolone exploits a mechanism that enables rapid symptom relief of PPD.

Sepranolone is a similar drug, currently in Phase II clinical trials for PMDD (sepranolone (UC1010), AsarinaPharma, Solna, Sweden). Sepranolone, or isoallopregnanolone (3b–OH–5a-pregnan- 20-one), is an ALLO isomer and GABA-A modulating steroid antagonist (GAMSA). It inhibits the effect of ALLO on $GABA_A$-Rs. In an initial placebo-controlled trial, sepranolone reduced PMDD mood symptom scores by 75% when administered in the luteal phase in women with PMDD (Bixo et al., 2017). Interestingly, sepranolone provided significant reduction in mood symptoms, but not physical symptoms (such as breast

tenderness, headaches, bloating) in PMDD.

Together, brexanolone and sepranolone represent cutting-edge treatment options for individuals experiencing mood symptoms related to NAS fluctuation. Continued evaluation of these drugs is needed, to reduce barriers to administration and access, and to determine for which patients these medications may be most effective, with attention to factors such as symptom profile, past psychiatric history, and lifetime stress exposure (Morrison et al., 2019; Payne and Maguire, 2019).

5. Conclusion

Evidence from animal and human literature suggests that PMDD's characteristic waxing and waning symptoms - mood lability, anxiety and irritability - reflect suboptimal $GABA_A$-R response to fluctuating levels of ALLO across the menstrual cycle. PMDD is modeled in rodents via NAS exposure and withdrawal (Gallo and Smith, 1993; Li et al., 2012; Schneider and Popik, 2009; S. Smith et al., 2006), with a rapid NAS withdrawal eliciting symptoms more than a gradual NAS decline (Doornbos et al., 2009). Similarly, women with PMDD have a more rapid late luteal phase drop in progesterone than control women (Lovick et al., 2017). NAS withdrawal may elicit symptoms due to its impact on $GABA_A$-Rs. Multiple studies have found that NAS withdrawal upregulates $GABA_A$-R α4 subunits in the rodent brain (Gulinello et al., 2003; S. Smith et al., 2006; Smith et al., 1998b). Beyond simple up- or downregulation of receptors, some suggest that NAS exposure and withdrawal induces a $GABA_A$-R subunit switch, as opposed to a change in GABA-R density (Shen et al., 2005). Human studies also suggest impaired $GABA_A$-R function in PMDD, including lack of ALLO-induced sedation in the luteal phase (Timby et al., 2016) and elevated APS in the luteal phase relative to controls (Hantsoo et al., 2015). Together, these rodent and human studies support the hypothesis that PMDD represents impaired $GABA_A$-R plasticity, with $GABA_A$-Rs failing to adapt their composition in response to changing ALLO levels across the menstrual cycle.

In addition to the core affective symptoms of PMDD, women with the diagnosis also evidence greater objective and subjective sensitivity to stress in the luteal phase. ALLO not only fluctuates across the menstrual cycle, but is released in response to stress. In response to stress, ALLO potentiates GABAergic transmission to promote anxiolysis, and regulates HPA axis function. Alterations in HPA axis response to stress in PMDD (Girdler et al., 2001; Huang et al., 2015; Rasgon et al., 2000; Segebladh et al., 2013) suggest that the disorder may include dysregulated interaction between the HPA and HPG axes, in specific, $GABA_A$Rs exerting poor control over the HPA axis (Gordon et al., 2015). Thus, impaired ALLO function in PMDD may be implicated in both symptom expression and elevated stress sensitivity.

Finally, treatment response in PMDD provides further evidence of altered ALLO-GABA function. SSRIs act rapidly in PMDD, taking effect over the course of days, as opposed to weeks required in other disorders such as major depressive disorder (Landén and Thase, 2006; Steinberg et al., 2012). A suggested mechanism is SSRI enhancement of ALLO biosynthesis from progesterone, stabilizing ALLO levels in the late luteal phase (Gracia et al., 2009; Pinna et al., 2009). However, double-blind controlled trials are needed to properly examine the impact of SSRIs on NAS levels across the menstrual cycle in PMDD. Sepranolone, a novel GABA-modulating drug that inhibits the effect of ALLO on $GABA_A$-Rs, reduced affective symptoms in randomized, double-blind, placebo-controlled study (Bixo et al., 2017). GABA modulating drugs may hold promise for PMDD treatment, but larger trials are needed. While SSRIs and sepranolone involve different mechanisms, both appear to impact ALLO-GABA function, suggesting that if ALLO levels are stabilized or ALLO activity at $GABA_A$-R is inhibited, symptoms diminish.

Future studies should continue to test the hypothesis that PMDD reflects impaired interaction between ALLO and $GABA_A$-R. Clarifying the role of NAS dynamics and $GABA_A$-R dynamics across the menstrual cycle, and mechanisms of SSRI action in PMDD, will lead to more effective and tailored treatments for the one in twenty women worldwide who suffer from PMDD.

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References

Agís-Balboa, R.C., Pinna, G., Zhubi, A., Maloku, E., Veldic, M., Costa, E., Guidotti, A., 2006. Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. Proc. Natl. Acad. Sci. U. S. A 103, 14602–14607. https://doi.org/10.1073/pnas.0606544103.

Altemus, M., Sarvaiya, N., Epperson, C.N., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35, 320–330. https://doi.org/10.1016/j.yfrne.2014.05.004.

Alvarez, R.P., Chen, G., Bodurka, J., Kaplan, R., Grillon, C., 2011. Phasic and sustained fear in humans elicits distinct patterns of brain activity. Neuroimage 55, 389–400. https://doi.org/10.1016/j.neuroimage.2010.11.057.

Bäckström, T., Haage, D., Löfgren, M., Johansson, I.M., Strömberg, J., Nyberg, S., Andréen, L., Ossewaarde, L., van Wingen, G.A., Turkmen, S., Bengtsson, S.K., 2011. Paradoxical effects of GABA-A modulators may explain sex steroid induced negative mood symptoms in some persons. Neuroscience 191, 46–54. https://doi.org/10.1016/j.neuroscience.2011.03.061.

Ball, D.M., Glue, P., Wilson, S., Nutt, D.J., 1991. Pharmacology of saccadic eye movements in man. 1. Effects of the benzodiazepine receptor ligands midazolam and flumazenil. Psychopharmacology 105, 361–367. https://doi.org/10.1007/bf02244431.

Bannbers, E., Kask, K., Wikström, J., Risbrough, V., Poromaa, I.S., 2011. Patients with premenstrual dysphoric disorder have increased startle modulation during anticipation in the late luteal phase period in comparison to control subjects. Psychoneuroendocrinology 36, 1184–1192. https://doi.org/10.1016/j.psyneuen.2011.02.011.

Beddig, T., Reinhard, I., Kuehner, C., 2019. Stress, mood, and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD). Psychoneuroendocrinology 109, 104372. https://doi.org/10.1016/j.psyneuen.2019.104372.

Belelli, D., Casula, A., Ling, A., Lambert, J.J., 2002. The influence of subunit composition on the interaction of neurosteroids with GABAA receptors. Neuropharmacol. GABAA Recept. Cell. Network Excitability 43, 651–661. https://doi.org/10.1016/S0028-3908(02)00172-7.

Belelli, D., Herd, M.B., Mitchell, E.A., Peden, D.R., Vardy, A.W., Gentet, L., Lambert, J.J., 2006. Neuroactive steroids and inhibitory neurotransmission: mechanisms of action and physiological relevance. Neurosci. Neuroactive Steroids: Old Players in a New Game 138, 821–829. https://doi.org/10.1016/j.neuroscience.2005.07.021.

Bertone-Johnson, E.R., Whitcomb, B.W., Missmer, S.A., Manson, J.E., Hankinson, S.E., Rich-Edwards, J.W., 2014a. Early life emotional, physical, and sexual abuse and the development of premenstrual syndrome: a longitudinal study. J. Womens Health 23, 729–739. https://doi.org/10.1089/jwh.2013.4674. 2002.

Bertone-Johnson, E.R., Whitcomb, B.W., Missmer, S.A., Manson, J.E., Hankinson, S.E., Rich-Edwards, J.W., 2014b. Early life emotional, physical, and sexual abuse and the development of premenstrual syndrome: a longitudinal study. J. Womens Health 23, 729–739. https://doi.org/10.1089/jwh.2013.4674. 2002.

Bhandage, A.K., Hellgren, C., Jin, Z., Olafsson, E.B., Sundström-Poromaa, I., Birnir, B., 2015. Expression of GABA receptors subunits in peripheral blood mononuclear cells is gender dependent, altered in pregnancy and modified by mental health. Acta Physiol. Oxf. Engl. 213, 575–585. https://doi.org/10.1111/apha.12440.

Bixo, M., Ekberg, K., Poromaa, I.S., Hirschberg, A.L., Jonasson, A.F., Andréen, L., Timby, E., Wulff, M., Ehrenborg, A., Bäckström, T., 2017. Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)-A randomized controlled trial. Psychoneuroendocrinology 80, 46–55. https://doi.org/10.1016/j.psyneuen.2017.02.031.

Bixo, M., Johansson, M., Timby, E., Michalski, L., Bäckström, T., 2018. Effects of GABA active steroids in the female brain with a focus on the premenstrual dysphoric disorder. J. Neuroendocrinol. 30. https://doi.org/10.1111/jne.12553.

Bunevicius, R., Hinderliter, A.L., Light, K.C., Leserman, J., Pedersen, C.A., Girdler, S.S., 2005. Histories of sexual abuse are associated with differential effects of clonidine on autonomic function in women with premenstrual dysphoric disorder. Biol. Psychol. 69, 281–296. https://doi.org/10.1016/j.biopsycho.2004.08.002.

Chen, Z.-W., Bracamontes, J.R., Budelier, M.M., Germann, A.L., Shin, D.J., Kathiresan, K., Qian, M.-X., Manion, B., Cheng, W.W.L., Reichert, D.E., Akk, G., Covey, D.F., Evers, A.S., 2019. Multiple functional neurosteroid binding sites on GABAA receptors. PLoS Biol. 17. https://doi.org/10.1371/journal.pbio.3000157.

Childs, E., Van Dam, N.T., de Wit, H., 2010. Effects of acute progesterone administration upon responses to acute psychosocial stress in men. Exp. Clin. Psychopharmacol 18, 78–86. https://doi.org/10.1037/a0018060.

Chua, H.C., Chebib, M., 2017. GABAA receptors and the diversity in their structure and pharmacology. Adv. Pharmacol. San Diego Calif 79, 1–34. https://doi.org/10.1016/bs.apha.2017.03.003.

Crowley, S.K., Girdler, S.S., 2014. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans?

Psychopharmacology 231, 3619–3634. https://doi.org/10.1007/s00213-014-3572-8.
Cullinan, W.E., Ziegler, D.R., Herman, J.P., 2008. Functional role of local GABAergic influences on the HPA axis. Brain Struct. Funct. 213, 63–72. https://doi.org/10.1007/s00429-008-0192-2.
Davis, M., 2006. Neural systems involved in fear and anxiety measured with fear-potentiated startle. Am. Psychol. 61, 741–756. https://doi.org/10.1037/0003-066X.61.8.741.
Davis, M., Walker, D.L., Miles, L., Grillon, C., 2010. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 35, 105–135. https://doi.org/10.1038/npp.2009.109.
Devall, A.J., Santos, J.M., Fry, J.P., Honour, J.W., Brandão, M.L., Lovick, T.A., 2015. Elevation of brain allopregnanolone rather than 5-HT release by short term, low dose fluoxetine treatment prevents the estrous cycle-linked increase in stress sensitivity in female rats. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 113–123. https://doi.org/10.1016/j.euroneuro.2014.11.017.
Doornbos, B., Fokkema, D.S., Molhoek, M., Tanke, M.A.C., Postema, F., Korf, J., 2009. Abrupt rather than gradual hormonal changes induce postpartum blues-like behavior in rats. Life Sci. 84, 69–74. https://doi.org/10.1016/j.lfs.2008.10.014.
Dubey, N., Hoffman, J.F., Schuebel, K., Yuan, Q., Martinez, P.E., Nieman, L.K., Rubinow, D.R., Schmidt, P.J., Goldman, D., 2017. The ESC/E(Z) complex, an effector of response to ovarian steroids, manifests an intrinsic difference in cells from women with premenstrual dysphoric disorder. Mol. Psychiatr. 22, 1172–1184. https://doi.org/10.1038/mp.2016.229.
Epperson, C., Pittman, B., Czarkowski, K.A., Stiklus, S., Krystal, J.H., Grillon, C., 2007. Luteal-phase Accentuation of acoustic startle response in women with premenstrual dysphoric disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 32, 2190–2198. https://doi.org/10.1038/sj.npp.1301351.
Epperson, C., Steiner, M., Hartlage, S.A., Eriksson, E., Schmidt, P.J., Jones, I., Yonkers, K.A., 2012. Premenstrual dysphoric disorder: evidence for a new category for DSM-5. Am. J. Psychiatr. 169, 465–475.
Epperson, C.N., Haga, K., Mason, G.F., Sellers, E., Gueorguieva, R., Zhang, W., Weiss, E., Rothman, D.L., Krystal, J.H., 2002. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. Arch. Gen. Psychiatr. 59, 851–858.
Epperson, C.N., Pittman, B., Czarkowski, K.A., Stiklus, S., Krystal, J.H., Grillon, C., 2007. Luteal-phase accentuation of acoustic startle response in women with premenstrual dysphoric disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 32, 2190–2198. https://doi.org/10.1038/sj.npp.1301351.
Epperson, C.N., Sammel, M.D., Bale, T.L., Kim, D.R., Conlin, S., Scalice, S., Freeman, K., Freeman, E.W., 2017. Adverse childhood experiences and risk for first-episode major depression during the menopause transition. J. Clin. Psychiatr. 78, 298–307. https://doi.org/10.4088/JCP.16m10662.
Eser, D., di Michele, F., Zwanzger, P., Pasini, A., Baghai, T.C., Schüle, C., Rupprecht, R., Romeo, E., 2005. Panic induction with cholecystokinin-tetrapeptide (CCK-4) Increases plasma concentrations of the neuroactive steroid 3alpha, 5alpha tetrahydrodeoxycorticosterone (3alpha, 5alpha-THDOC) in healthy volunteers. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 30, 192–195. https://doi.org/10.1038/sj.npp.1300572.
Farrant, M., Nusser, Z., 2005. Variations on an inhibitory theme: phasic and tonic activation of GABA A receptors. Nat. Rev. Neurosci. 6, 215–229. https://doi.org/10.1038/nrn1625.
Gallo, M.A., Smith, S.S., 1993. Progesterone withdrawal decreases latency to and increases duration of electrified prod burial: a possible rat model of PMS anxiety. Pharmacol. Biochem. Behav. 46, 897–904.
Girdler, S.S., Pedersen, C.A., Straneva, P.A., Leserman, J., Stanwyck, C.L., Benjamin, S., Light, K.C., 1998. Dysregulation of cardiovascular and neuroendocrine responses to stress in premenstrual dysphoric disorder. Psychiatr. Res. 81, 163–178.
Girdler, S.S., Straneva, P.A., Light, K.C., Pedersen, C.A., Morrow, A.L., 2001. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. Biol. Psychiatr. 49, 788–797.
Golding, J.M., Taylor, D.L., Menard, L., King, M.J., 2000. Prevalence of sexual abuse history in a sample of women seeking treatment for premenstrual syndrome. J. Psychosom. Obstet. Gynaecol. 21, 69–80.
Gordon, J.L., Girdler, S.S., Meltzer-Brody, S.E., Stika, C.S., Thurston, R.C., Clark, C.T., Prairie, B.A., Moses-Kolko, E., Joffe, H., Wisner, K.L., 2015. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. Am. J. Psychiatr. 172, 227–236. https://doi.org/10.1176/appi.ajp.2014.14070918.
Gracia, C.R., Freeman, E.W., Sammel, M.D., Lin, H., Sheng, L., Frye, C., 2009. Allopregnanolone levels before and after selective serotonin reuptake inhibitor treatment of premenstrual symptoms. J. Clin. Psychopharmacol. 29, 403–405. https://doi.org/10.1097/JCP.0b013e3181ad8825.
Griffin, L.D., Mellon, S.H., 1999. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. Proc. Natl. Acad. Sci. U. S. A 96, 13512–13517.
Gulinello, M., Gong, Q.H., Li, X., Smith, S.S., 2001. Short-term exposure to a neuroactive steroid increases alpha4 GABA(A) receptor subunit levels in association with increased anxiety in the female rat. Brain Res. 910, 55–66.
Gulinello, M., Orman, R., Smith, S.S., 2003. Sex differences in anxiety, sensorimotor gating and expression of the alpha4 subunit of the GABAA receptor in the amygdala after progesterone withdrawal. Eur. J. Neurosci. 17, 641–648.
Gulinello, M., Smith, S.S., 2003. Anxiogenic effects of neurosteroid exposure: sex differences and altered GABAA receptor pharmacology in adult rats. J. Pharmacol. Exp. Therapeut. 305, 541–548. https://doi.org/10.1124/jpet.102.045120.
Halbreich, U., Borenstein, J., Pearlstein, T., Kahn, L.S., 2003. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). Psychoneuroendocrinology 28 (Suppl. 3), 1–23.
Hantsoo, L., Epperson, C.N., 2015. Premenstrual dysphoric disorder: epidemiology and treatment. Curr. Psychiatr. Rep. 17, 87. https://doi.org/10.1007/s11920-015-0628-3.
Hantsoo, L., Golden, C.E.M., Kornfield, S., Grillon, C., Epperson, C.N., 2018. Startling differences: using the acoustic startle response to study sex differences and neurosteroids in affective disorders. Curr. Psychiatr. Rep. 20, 40. https://doi.org/10.1007/s11920-018-0906-y.
Hantsoo, L., Grillon, C., Epperson, C.N., 2015. Dysregulated luteal phase startle response in premenstrual dysphoric disorder is corrected by luteal sertraline treatment. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 40.
Hantsoo, L., Ward-O'Brien, D., Czarkowski, K.A., Gueorguieva, R., Price, L.H., Epperson, C.N., 2014. A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. Psychopharmacology 231, 939–948. https://doi.org/10.1007/s00213-013-3316-1.
Huang, Y., Zhou, R., Wu, M., Wang, Q., Zhao, Y., 2015. Premenstrual syndrome is associated with blunted cortisol reactivity to the TSST. Stress Amst. Neth. 1–9. https://doi.org/10.3109/10253890.2014.999234.
Jovanovic, T., Blanding, N.Q., Norrholm, S.D., Duncan, E., Bradley, B., Ressler, K.J., 2009. Childhood abuse is associated with increased startle reactivity in adulthood. Depress. Anxiety 26, 1018–1026. https://doi.org/10.1002/da.20599.
Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., Doherty, J., Epperson, C.N., Deligiannidis, K.M., Riesenberg, R., Hoffmann, E., Rubinow, D., Jonas, J., Paul, S., Meltzer-Brody, S., 2017. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet Lond. Engl. https://doi.org/10.1016/S0140-6736(17)31264-3.
Kask, K., Gulinello, M., Bäckström, T., Geyer, M.A., Sundström-Poromaa, I., 2008. Patients with premenstrual dysphoric disorder have increased startle response across both cycle phases and lower levels of prepulse inhibition during the late luteal phase of the menstrual cycle. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 33, 2283–2290. https://doi.org/10.1038/sj.npp.1301599.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatr. 62, 593–602. https://doi.org/10.1001/archpsyc.62.6.593.
Kessler, R.C., Walters, E.E., 1998. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity. Survey. Depress. Anxiety 7, 3–14.
Klatzkin, R.R., Morrow, A.L., Light, K.C., Pedersen, C.A., Girdler, S.S., 2006. Associations of histories of depression and PMDD diagnosis with allopregnanolone concentrations following the oral administration of micronized progesterone. Psychoneuroendocrinology 31, 1208–1219. https://doi.org/10.1016/j.psyneuen.2006.09.002.
Knoflach, F., Hernandez, M.-C., Bertrand, D., 2018. Methods for the discovery of novel compounds modulating a gamma-aminobutyric acid receptor type A neurotransmission. J. Vis. Exp. JoVE. https://doi.org/10.3791/57842.
Kornstein, S.G., Pearlstein, T.B., Fayyad, R., Farfel, G.M., Gillespie, J.A., 2006. Low-dose sertraline in the treatment of moderate-to-severe premenstrual syndrome: efficacy of 3 dosing strategies. J. Clin. Psychiatr. 67, 1624–1632.
Lambert, J.J., Cooper, M.A., Simmons, R.D.J., Weir, C.J., Belelli, D., 2009. Neurosteroids: endogenous allosteric modulators of GABA(A) receptors. Psychoneuroendocrinology 34 (Suppl. 1), S48–S58. https://doi.org/10.1016/j.psyneuen.2009.08.009.
Landén, M., Thase, M.E., 2006. A model to explain the therapeutic effects of serotonin reuptake inhibitors: the role of 5-HT2 receptors. Psychopharmacol. Bull. 39, 147–166.
Lee, E.E., Nieman, L.K., Martinez, P.E., Harsh, V.L., Rubinow, D.R., Schmidt, P.J., 2012. ACTH and cortisol response to Dex/CRH testing in women with and without premenstrual dysphoria during GnRH agonist-induced hypogonadism and ovarian steroid replacement. J. Clin. Endocrinol. Metab. 97, 1887–1896. https://doi.org/10.1210/jc.2011-3451.
Lee, V., Maguire, J., 2014. The impact of tonic GABAA receptor-mediated inhibition on neuronal excitability varies across brain region and cell type. Front. Neural Circ. 8. https://doi.org/10.3389/fncir.2014.00003.
Lee, Y., Davis, M., 1997. Role of the hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. J. Neurosci. Off. J. Soc. Neurosci. 17, 6434–6446.
Li, Y., Pehrson, A.L., Budac, D.P., Sánchez, C., Gulinello, M., 2012. A rodent model of premenstrual dysphoria: progesterone withdrawal induces depression-like behavior that is differentially sensitive to classes of antidepressants. Behav. Brain Res. 234, 238–247. https://doi.org/10.1016/j.bbr.2012.06.034.
Lombardi, I., Luisi, S., Quirici, B., Monteleone, P., Bernardi, F., Liut, M., Casarosa, E., Palumbo, M., Petraglia, F., Genazzani, A.R., 2004. Adrenal response to adrenocorticotropic hormone stimulation in patients with premenstrual syndrome. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 18, 79–87.
Lovick, T., 2013. SSRIs and the female brain–potential for utilizing steroid-stimulating properties to treat menstrual cycle-linked dysphorias. J. Psychopharmacol. Oxf. Engl. 27, 1180–1185. https://doi.org/10.1177/0269881113490327.
Lovick, T.A., Guapo, V.G., Anselmo-Franci, J.A., Loureiro, C.M., Faleiros, M.C.M., Del Ben, C.M., Brandão, M.L., 2017. A specific profile of luteal phase progesterone is associated with the development of premenstrual symptoms. Psychoneuroendocrinology 75, 83–90. https://doi.org/10.1016/j.psyneuen.2016.10.024.
MacKenzie, G., Maguire, J., 2014. The role of ovarian hormone-derived neurosteroids on

the regulation of GABAA receptors in affective disorders. Psychopharmacology 231, 3333–3342. https://doi.org/10.1007/s00213-013-3423-z.
Maguire, J., Mody, I., 2008. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 59, 207–213. https://doi.org/10.1016/j.neuron.2008.06.019.
Maguire, J.L., Stell, B.M., Rafizadeh, M., Mody, I., 2005. Ovarian cycle–linked changes in GABA A receptors mediating tonic inhibition alter seizure susceptibility and anxiety. Nat. Neurosci. 8, 797–804. https://doi.org/10.1038/nn1469.
Martinez, P.E., Rubinow, D.R., Nieman, L.K., Koziol, D.E., Morrow, A.L., Schiller, C.E., Cintron, D., Thompson, K.D., Khine, K.K., Schmidt, P.J., 2016. 5α-Reductase inhibition prevents the luteal phase increase in plasma allopregnanolone levels and mitigates symptoms in women with premenstrual dysphoric disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 41, 1093–1102. https://doi.org/10.1038/npp.2015.246.
Matsumoto, K., Puia, G., Dong, E., Pinna, G., 2007. GABA(A) receptor neurotransmission dysfunction in a mouse model of social isolation-induced stress: possible insights into a non-serotonergic mechanism of action of SSRIs in mood and anxiety disorders. Stress Amst. Neth. 10, 3–12. https://doi.org/10.1080/10253890701200997.
McLean, C.P., Asnaani, A., Litz, B.T., Hofmann, S.G., 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J. Psychiatr. Res. 45, 1027–1035. https://doi.org/10.1016/j.jpsychires.2011.03.006.
Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C.N., Deligiannidis, K.M., Rubinow, D.R., Li, H., Sankoh, A.J., Clemson, C., Schacterle, A., Jonas, J., Kanes, S., 2018. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Lond. Engl. 392, 1058–1070. https://doi.org/10.1016/S0140-6736(18)31551-4.
Morrison, K.E., Cole, A.B., Thompson, S.M., Bale, T.L., 2019. Brexanolone for the treatment of patients with postpartum depression. Drugs Today Barc. Spain 55, 537–544. https://doi.org/10.1358/dot.2019.55.9.3040864. 1998.
Morrison, K.E., Epperson, C.N., Sammel, M.D., Ewing, G., Podcasy, J.S., Hantsoo, L., Kim, D.R., Bale, T.L., 2017. Preadolescent adversity programs a disrupted maternal stress reactivity in humans and mice. Biol. Psychiatr. 81, 693–701. https://doi.org/10.1016/j.biopsych.2016.08.027.
Nguyen, T.V., Reuter, J.M., Gaikwad, N.W., Rotroff, D.M., Kucera, H.R., Motsinger-Reif, A., Smith, C.P., Nieman, L.K., Rubinow, D.R., Kaddurah-Daouk, R., Schmidt, P.J., 2017. The steroid metabolome in women with premenstrual dysphoric disorder during GnRH agonist-induced ovarian suppression: effects of estradiol and progesterone addback. Transl. Psychiatry 7, e1193. https://doi.org/10.1038/tp.2017.146.
Osborne, L.M., Gispen, F., Sanyal, A., Yenokyan, G., Meilman, S., Payne, J.L., 2017. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. Psychoneuroendocrinology 79, 116–121. https://doi.org/10.1016/j.psyneuen.2017.02.012.
Oyola, M.G., Handa, R.J., 2017. Hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes: sex differences in regulation of stress responsivity. Stress Amst. Neth. 20, 476–494. https://doi.org/10.1080/10253890.2017.1369523.
Parry, B.L., Javeed, S., Laughlin, G.A., Hauger, R., Clopton, P., 2000. Cortisol circadian rhythms during the menstrual cycle and with sleep deprivation in premenstrual dysphoric disorder and normal control subjects. Biol. Psychiatr. 48, 920–931. https://doi.org/10.1016/s0006-3223(00)00876-3.
Patchev, V.K., Shoaib, M., Holsboer, F., Almeida, O.F., 1994. The neurosteroid tetrahydroprogesterone counteracts corticotropin-releasing hormone-induced anxiety and alters the release and gene expression of corticotropin-releasing hormone in the rat hypothalamus. Neuroscience 62, 265–271.
Payne, J.L., Maguire, J., 2019. Pathophysiological mechanisms implicated in postpartum depression. Front. Neuroendocrinol. 52, 165–180. https://doi.org/10.1016/j.yfrne.2018.12.001.
Perkonigg, A., Yonkers, K.A., Pfister, H., Lieb, R., Wittchen, H.-U., 2004. Risk factors for premenstrual dysphoric disorder in a community sample of young women: the role of traumatic events and posttraumatic stress disorder. J. Clin. Psychiatr. 65, 1314–1322.
Petersen, N., London, E.D., Liang, L., Ghahremani, D.G., Gerards, R., Goldman, L., Rapkin, A.J., 2016. Emotion regulation in women with premenstrual dysphoric disorder. Arch. Womens Ment. Health 19, 891–898. https://doi.org/10.1007/s00737-016-0634-4.
Pilver, C.E., Levy, B.R., Libby, D.J., Desai, R.A., 2011. Posttraumatic stress disorder and trauma characteristics are correlates of premenstrual dysphoric disorder. Arch. Womens Ment. Health 14, 383–393. https://doi.org/10.1007/s00737-011-0232-4.
Pinna, G., Costa, E., Guidotti, A., 2009. SSRIs act as selective brain steroidogenic stimulants (SBSSs) at low doses that are inactive on 5-HT reuptake. Curr. Opin. Pharmacol. 9, 24–30. https://doi.org/10.1016/j.coph.2008.12.006.
Pinna, G., Costa, E., Guidotti, A., 2006. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. Psychopharmacology 186, 362–372. https://doi.org/10.1007/s00213-005-0213-2.
Purdy, R.H., Morrow, A.L., Moore Jr., P.H., Paul, S.M., 1991. Stress-induced elevations of gamma-aminobutyric acid type A receptor-active steroids in the rat brain. Proc. Natl. Acad. Sci. U. S. A 88, 4553–4557.
Rasgon, N., McGuire, M., Tanavoli, S., Fairbanks, L., Rapkin, A., 2000. Neuroendocrine response to an intravenous L-tryptophan challenge in women with premenstrual syndrome. Fertil. Steril. 73, 144–149.
Reddy, D.S., Gould, J., Gangisetty, O., 2012. A mouse kindling model of perimenstrual catamenial epilepsy. J. Pharmacol. Exp. Therapeut. 341, 784–793. https://doi.org/10.1124/jpet.112.192377.
Sanna, E., Mostallino, M.C., Murru, L., Carta, M., Talani, G., Zucca, S., Mura, M.L., Maciocco, E., Biggio, G., 2009. Changes in expression and function of extrasynaptic GABAA receptors in the rat Hippocampus during pregnancy and after delivery. J. Neurosci. 29, 1755–1765. https://doi.org/10.1523/JNEUROSCI.3684-08.2009.
Schmidt, P.J., Nieman, L.K., Danaceau, M.A., Adams, L.F., Rubinow, D.R., 1998. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N. Engl. J. Med. 338, 209–216. https://doi.org/10.1056/NEJM199801223380401.
Schmitz, A., Grillon, C., 2012. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nat. Protoc. 7, 527–532. https://doi.org/10.1038/nprot.2012.001.
Schneider, T., Popik, P., 2009. An animal model of premenstrual dysphoric disorder sensitive to antidepressants. Curr. Protoc. Neurosci. https://doi.org/10.1002/0471142301.ns0931s46. (Chapter 9), Unit 9.31.
Schüle, C., Nothdurfter, C., Rupprecht, R., 2014. The role of allopregnanolone in depression and anxiety. Prog. Neurobiol. 113, 79–87. https://doi.org/10.1016/j.pneurobio.2013.09.003.
Segebladh, B., Bannbers, E., Moby, L., Nyberg, S., Bixo, M., Bäckström, T., Sundström Poromaa, I., 2013. Allopregnanolone serum concentrations and diurnal cortisol secretion in women with premenstrual dysphoric disorder. Arch. Womens Ment. Health. https://doi.org/10.1007/s00737-013-0327-1.
Serra, M., Sanna, E., Mostallino, M.C., Biggio, G., 2007. Social isolation stress and neuroactive steroids. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 17, 1–11. https://doi.org/10.1016/j.euroneuro.2006.03.004.
Shen, H., Gong, Q.H., Yuan, M., Smith, S.S., 2005. Short-term steroid treatment increases δ GABAA receptor subunit expression in rat CA1 hippocampus: pharmacological and behavioral effects. Neuropharmacology 49, 573–586. https://doi.org/10.1016/j.neuropharm.2005.04.026.
Simon, J., Wakimoto, H., Fujita, N., Lalande, M., Barnard, E.A., 2004. Analysis of the set of GABA(A) receptor genes in the human genome. J. Biol. Chem. 279, 41422–41435. https://doi.org/10.1074/jbc.M401354200.
Sink, K.S., Walker, D.L., Freeman, S.M., Flandreau, E.I., Ressler, K.J., Davis, M., 2012. Effects of continuously enhanced corticotropin releasing factor expression within the bed nucleus of the stria terminalis on conditioned and unconditioned anxiety. Mol. Psychiatr. https://doi.org/10.1038/mp.2011.188.
Smith, Ruderman, Y., Frye, C., Homanics, G., Yuan, M., 2006a. Steroid withdrawal in the mouse results in anxiogenic effects of 3alpha,5beta-THP: a possible model of premenstrual dysphoric disorder. Psychopharmacology 186, 323–333. https://doi.org/10.1007/s00213-005-0168-3.
Smith, S., Ruderman, Y., Frye, C., Homanics, G., Yuan, M., 2006b. Steroid withdrawal in the mouse results in anxiogenic effects of 3alpha,5beta-THP: a possible model of premenstrual dysphoric disorder. Psychopharmacology 186, 323–333. https://doi.org/10.1007/s00213-005-0168-3.
Smith, S.S., Gong, Q.H., Hsu, F.C., Markowitz, R.S., ffrench-Mullen, J.M., Li, X., 1998a. GABA(A) receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. Nature 392, 926–930. https://doi.org/10.1038/31948.
Smith, S.S., Gong, Q.H., Li, X., Moran, M.H., Bitran, D., Frye, C.A., Hsu, F.C., 1998b. Withdrawal from 3alpha-OH-5alpha-pregnan-20-One using a pseudopregnancy model alters the kinetics of hippocampal GABAA-gated current and increases the GABAA receptor alpha4 subunit in association with increased anxiety. J. Neurosci. Off. J. Soc. Neurosci. 18, 5275–5284.
Steinberg, E.M., Cardoso, G.M.P., Martinez, P.E., Rubinow, D.R., Schmidt, P.J., 2012. Rapid response to fluoxetine in women with premenstrual dysphoric disorder. Depress. Anxiety 29, 531–540. https://doi.org/10.1002/da.21959.
Steiner, M., Brown, E., Trzepacz, P., Dillon, J., Berger, C., Carter, D., Reid, R., Stewart, D., 2003. Fluoxetine improves functional work capacity in women with premenstrual dysphoric disorder. Arch. Womens Ment. Health 6, 71–77. https://doi.org/10.1007/s00737-002-0162-2.
Steiner, M., Ravindran, A.V., LeMelledo, J.-M., Carter, D., Huang, J.O., Anonychuk, A.M., Simpson, S.D., 2008. Luteal phase Administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. J. Clin. Psychiatr. 69, 991–998.
Sundstrom-Poromaa, I., Smith, D.H., Gong, Q.H., Sabado, T.N., Li, X., Light, A., Wiedmann, M., Williams, K., Smith, S.S., 2002. Hormonally regulated alpha(4)beta(2)delta GABA(A) receptors are a target for alcohol. Nat. Neurosci. 5, 721–722. https://doi.org/10.1038/nn888.
Thys-Jacobs, S., McMahon, D., Bilezikian, J.P., 2008. Differences in free estradiol and sex hormone-binding globulin in women with and without premenstrual dysphoric disorder. J. Clin. Endocrinol. Metab. 93, 96–102. https://doi.org/10.1210/jc.2007-1726.
Timby, E., 2012. Allopregnanolone effects in women : clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. https://doi.org/10.1111/j.1600-0412.2012.01435_1.x.
Timby, E., Bäckström, T., Nyberg, S., Stenlund, H., Wihlbäck, A.-C.N., Bixo, M., 2016. Women with premenstrual dysphoric disorder have altered sensitivity to allopregnanolone over the menstrual cycle compared to controls-a pilot study. Psychopharmacology (Berl. https://doi.org/10.1007/s00213-016-4258-1.
Toufexis, D.J., Davis, C., Hammond, A., Davis, M., 2004. Progesterone attenuates corticotropin-releasing factor-enhanced but not fear-potentiated startle via the activity of its neuroactive metabolite, allopregnanolone. J. Neurosci. Off. J. Soc. Neurosci. 24, 10280–10287. https://doi.org/10.1523/JNEUROSCI.1386-04.2004.
Trauger, J.W., Jiang, A., Stearns, B.A., LoGrasso, P.V., 2002. Kinetics of allopregnanolone formation catalyzed by human 3 alpha-hydroxysteroid dehydrogenase type III (AKR1C2). Biochemistry 41, 13451–13459.
Turkmen, S., Backstrom, T., Wahlstrom, G., Andreen, L., Johansson, I.-M., 2011. Tolerance to allopregnanolone with focus on the GABA-A receptor. Br. J. Pharmacol. 162, 311–327. https://doi.org/10.1111/j.1476-5381.2010.01059.x.
Uzunova, V., Sheline, Y., Davis, J.M., Rasmusson, A., Uzunov, D.P., Costa, E., Guidotti, A., 1998. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc. Natl.

Acad. Sci. U. S. A 95, 3239–3244. https://doi.org/10.1073/pnas.95.6.3239.
Wang, M., 2011. Neurosteroids and GABA-A receptor function. Front. Endocrinol. 2. https://doi.org/10.3389/fendo.2011.00044.
Wisner, K.L., Hanusa, B.H., Perel, J.M., Peindl, K.S., Piontek, C.M., Sit, D.K.Y., Findling, R.L., Moses-Kolko, E.L., 2006. Postpartum depression: a randomized trial of sertraline versus nortriptyline. J. Clin. Psychopharmacol. 26, 353–360. https://doi.org/10.1097/01.jcp.0000227706.56870.dd.
Wittchen, H.-U., Perkonigg, A., Pfister, H., 2003. Trauma and PTSD - an overlooked pathogenic pathway for premenstrual dysphoric disorder? Arch. Womens Ment. Health 6, 293–297. https://doi.org/10.1007/s00737-003-0028-2.
Yonkers, K.A., Kornstein, S.G., Gueorguieva, R., Merry, B., Van Steenburgh, K., Altemus, M., 2015. Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: a randomized clinical trial. JAMA Psychiatr. 72, 1037–1044. https://doi.org/10.1001/jamapsychiatry.2015.1472.