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EDITED BY
Ana Valea,
Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca,
Romania

REVIEWED BY
Mara Carsote,
Carol Davila University of Medicine and Pharmacy, Romania
Claudiu Eduard Nistor,
Carol Davila University of Medicine and Pharmacy, Romania

*CORRESPONDENCE
Sheng Wei
✉ weisheng@sdutcm.edu.cn
Wei Liu
✉ Lw_1369@163.com

†These authors have contributed equally to this work and share first authorship

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Role of allopregnanolone-mediated γ-aminobutyric acid A receptor sensitivity in the pathogenesis of premenstrual dysphoric disorder: Toward precise targets for translational medicine and drug development

Qian Gao[1,2,3†], Wei Sun[1,2†], Yue-Rui Wang[1,2,3†], Zi-Fa Li[1,2], Feng Zhao[1,2], Xi-Wen Geng[1,2,3], Kai-Yong Xu[1], Dan Chen[1], Kun Liu[1,2,3], Ying Xing[1,2,3], Wei Liu[4]* and Sheng Wei[1,2,3]*

[1]Experimental Center, Shandong University of Traditional Chinese Medicine, Jinan, China, [2]Key Laboratory of Traditional Chinese Medicine Classical Theory, Ministry of Education, Shandong University of Traditional Chinese Medicine, Jinan, China, [3]Chinese Medicine and Brain Science Core Facility, Shandong University of Traditional Chinese Medicine, Jinan, China, [4]Department of Encephalopathy, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China

Premenstrual dysphoric disorder (PMDD) can be conceptualized as a disorder of suboptimal sensitivity to neuroactive steroid hormones. Its core symptoms (emotional instability, irritability, depression, and anxiety) are related to the increase of stress sensitivity due to the fluctuation of hormone level in luteal phase of the menstrual cycle. In this review, we describe the emotional regulatory effect of allopregnanolone (ALLO), and summarize the relationship between ALLO and γ-aminobutyric acid A ($GABA_A$) receptor subunits based on rodent experiments and clinical observations. A rapid decrease in ALLO reduces the sensitivity of $GABA_A$ receptor, and reduces the chloride influx, hindered the inhibitory effect of GABAergic neurons on pyramidal neurons, and then increased the excitability of pyramidal neurons, resulting in PMDD-like behavior. Finally, we discuss in depth the treatment of PMDD with targeted $GABA_A$ receptors, hoping to find a precise target for drug development and subsequent clinical application. In conclusion, PMDD pathophysiology is rooted in $GABA_A$ receptor sensitivity changes caused by rapid changes in ALLO levels. Targeting $GABA_A$ receptors may alleviate the occurrence of PMDD.

KEYWORDS

premenstrual dysphoric disorder, premenstrual syndrome, pathogenesis, allopregnanolone, γ-aminobutyric acid A receptor, subunit

1. Introduction

Premenstrual syndrome (PMS) refers to a series of physical and emotional symptoms that women of childbearing age regularly experience before menstruation, such as anxiety, quick temper, excessive breast tenderness, increased or decreased appetite, nausea, vomiting, acne, low back pain, or fainting (1). Premenstrual dysphoric disorder (PMDD) is a debilitating subtype of PMS, and the typical symptoms of PMDD include emotional instability, irritability, depression, anxiety, decreased interest in daily activities, inattention, fatigue, appetite changes, sleep changes, feeling overwhelmed, and other emotional symptoms, with physical symptoms such as headache, edema, and breast pain (2, 3). The American Psychiatric Association published the diagnostic criteria for PMDD in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (4). The essential features of premenstrual dysphoric disorder are the expression of mood lability, irritability, dysphoria, and anxiety symptoms that occur repeatedly during the premenstrual phase of the cycle and remit around the onset of menses or shortly thereafter. These symptoms may be accompanied by behavioral and physical symptoms. Symptoms must have occurred in most of the menstrual cycles during the past year and must have an adverse effect on work or social functioning (5). Symptoms must appear in the last week before menstruation begins, and begin to improve within a few days after menstruation begins. Given that the menstrual cycle lasts 4 weeks, few weeks after menstruation almost coincides with the week preceding menstruation in which PMS/PMDD symptoms manifest. At least five symptoms must appear, including a "core" symptom (obvious emotional instability, irritability, depression, or anxiety) and other potential symptoms, including decreased interest in daily activities, difficulty in focusing, insufficient energy, sleep or appetite change, feeling overwhelmed or out of control, and physical symptoms. The incidence rate of PMS is 30–40%, and the incidence rate of PMDD is 3–8% (6, 7). The rates of long-term and 12-month suicidal thoughts in patients with PMDD were 45.8 and 18.6%, respectively (8). It is particularly necessary to find a way to treat PMDD.

At present, the first-line drugs for treatment of PMS/PMDD are selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, and paroxetine (9, 10). The effective response rate of PMS/PMDD to SSRIs is 60–90%, while that to placebo is 30–40% (11, 12). However, symptoms such as nausea, weakness, drowsiness, fatigue, decreased libido, and sweating are side effects of SSRIs. Because of the long half-life of SSRIs, these symptoms usually become more and more serious and last for several weeks (13). Because of these adverse side effects, there is poor patient compliance with SSRI treatment, and many PMDD patients choose to terminate the therapy. Therefore, it is urgent to find alternative or supplementary therapeutic methods or discover new treatment targets for PMDD.

In recent years, studies have found that the symptoms of PMDD are greatly affected by the fluctuation of neurosteroids during the menstrual cycle (14). It is well known that the progesterone content in normal animals will decrease sharply, and the estrogen in normal animals will remain at a stable low level, during the late period of estrus. At this stage, some animals have a strong sensitivity to the rapid decline of progesterone level in their bodies, usually showing obvious depression and PMDD-like behavior (15). Therefore, the rapid decrease of progesterone content in the luteal phase may be a trigger factor for female animals to be vulnerable to psychological stress. At the same time, the rapid decrease of progesterone content in the luteal phase is also a major feature of PMDD. Therefore, it is a method to treat PMDD by supplementing progesterone level to delay the rapid decline of progesterone. As a metabolite of progesterone, allopregnanolone (ALLO) has received therapeutic approval for postpartum depression (PPD) (16), which is similar to PMDD and also related to the abnormal changes of hormone in the key period of female reproductive physiological cycle. Further studies (17–19) show that ALLO is a positive allosteric modulator of the γ-aminobutyric acid A ($GABA_A$) receptor. The therapeutic effect of ALLO supplementation against PMDD may be achieved by regulating the expression and function of $GABA_A$ receptor. Therefore, this article will review the pathogenesis of PMDD caused by ALLO-mediated changes in $GABA_A$ receptor sensitivity, with the aim of finding precise targets for drug development and subsequent clinical applications.

2. Effect of ALLO on emotional regulation

Neurosteroids are key molecules in the central nervous system that regulate neural function. Through the interaction with ion channel-coupled receptors, they can quickly change neural excitability. Neurosteroids are produced in the brain and peripheral nervous system, and also some endocrine glands (adrenal glands and gonads) in the body that produce steroidal compounds or steroidal substances with neural activity, including glucocorticoids, mineralocorticoids, progesterone, androgens, and estrogen (20). Neurosteroids are widely involved in human physiological and pathological processes. In the menstrual cycle and other physiological processes, the level of neurosteroids fluctuates, and mental diseases such as depression and anxiety are closely related to neurosteroids and their receptors (21).

The neurosteroid tetrahydroprogesterone, also known as allopregnanolone (ALLO), is a metabolite of progesterone, and its existence has been verified through the use of human brain tissue and animal experiments (22). At present, both neurons and glial cells are capable of synthesizing neurosteroids including ALLO (23, 24), and their synthesis pathways in the brain are roughly similar to those in the periphery (22): Cholesterol is transported to the inner mitochondrial membrane through the 18-kDa transport protein TSPO, and then through the cytochrome P450 cholesterol side-chain lyase P450 (P450scc) to produce pregnenolone. Progesterone is produced from pregnenolone by 3β-hydroxysteroid dehydrogenase (3β-HSD) metabolism, and then, the metabolized products are gradually reduced by 5α-reductase and 3α-HSD (25–27). The formation process is shown in Figure 1. The serum level of ALLO in women of normal childbearing age ranges from 0.2 to 0.5 nmol/L in the follicular phase, increases to 4 nmol/L in the middle luteal phase (28), and fluctuates in the range of 0.9–2 nmol/L in the late luteal phase (29–31). However, compared with the ALLO concentration corresponding to the normal luteal phase level, both high and low levels of ALLO can cause more severe emotional changes, which illustrates the bimodal effect or inverted U model of change of ALLO on emotion (32).

It has been observed in animal experiments that ALLO has a two-way emotional regulation effect (33). Low-dose ALLO increases

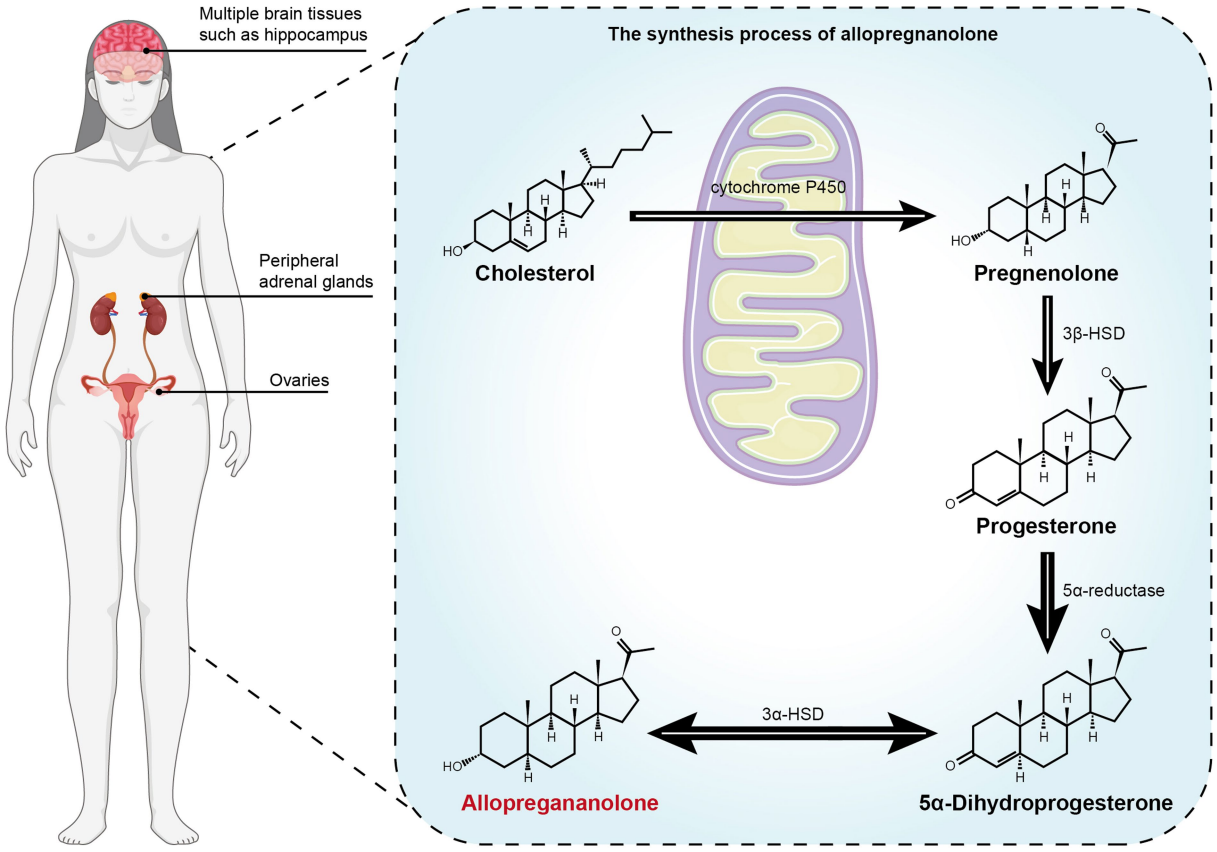

FIGURE 1
The metabolism process of the precursor cholesterol to allopregnanolone. Cholesterol is transported to the inner mitochondrial membrane through the 18-kDa transport protein TSPO, and then through the cytochrome P450 cholesterol side-chain lyase P450 (P450scc) to produce pregnenolone. Progesterone is produced from pregnenolone by 3β-hydroxysteroid dehydrogenase (3β-HSD) metabolism, and then the metabolized products are gradually reduced by 5α-reductase and 3α-HSD (25). Allo is synthesized in brain (such as hippocampus), adrenal gland and gonad (24, 27).

the PMDD-like behavior of female mice, while high-dose ALLO reduces aggressive behaviors (34). However, in healthy women, negative emotional reactions triggered by changes in ALLO levels have not been observed (35). One possible reason why ALLO changes cause negative emotions is the plasticity of the $GABA_A$ receptor, because the composition and pharmacological properties of $GABA_A$ receptor subunits have been shown to change with different reproductive states (36). The $GABA_A$ receptor is an ion channel receptor related to ALLO, and ALLO shows high affinity for most $GABA_A$ receptor subtypes (37), which can enhance the GABA evoked chloride current through increasing the frequency and/or duration of openings of the GABA-gated chloride channel (38–40).

3. Fluctuations in ALLO levels are key triggers for PMDD symptoms

PMDD can be traced back to female puberty, and it is closely related to the periodic changes of female ovarian function. The negative emotional changes of PMDD patients started from ovulation in a menstrual cycle, and gradually presented and significantly increased with the production of corpus luteum, especially about the last 5 days of corpus luteum period, the symptoms gradually relieved or disappeared after menstruation. Clinical studies have gradually revealed that ovarian hormones play an important role in the pathogenesis of PMDD, especially estradiol and progesterone metabolite ALLO, and a series of hormone therapies have been derived from them (41).

Although ALLO plays an important role in PMS/PMDD, its relationship is not very clear. Compared with the normal situation, does the level of ALLO in PMS/PMDD patients increase or decrease? There is no consensus on how the level of ALLO changes in patients with PMDD after cure. Some studies have shown that the remission of PMS/PMDD symptoms is related to the reduction of ALLO level. After treating PMS with sertraline and desipramine, Freeman et al. found that PMS symptoms were related to a reduction in ALLO levels (42). A similar conclusion appeared after the use of the gonadotropin-releasing hormone agonist buserelin to induce ovarian suppression, and it was found that low-dose buserelin can ameliorate negative mood symptoms (43). However, under the environment of excluding the influence of estrogen and simulating progesterone during the luteal phase, the average serum level of ALLO in the PMDD group was not significantly different from that in the control group (44). Nevertheless, TV Nguyen et al. found that the increase of the content of neurosteroids in luteal phase, rather than the basic

level, mediates the onset of female symptoms of PMDD, because blocking 5 α Reductase activity can reduce the onset of PMDD symptoms (44). A study using the 5α-reductase inhibitor dutasteride to treat PMDD found that patients who received high doses (2.5 mg/day) of dutasteride experienced relief of the core symptoms of the luteal phase after drug treatment, and the level of ALLO in the luteal phase was lower than that in the follicular phase. In contrast, there were lower levels of ALLO in the follicular phase than in the luteal phase for patients who received low-dose (0.5 mg/day) dutasteride and placebo (45).

Although this study suggests that hindering the conversion of progesterone to ALLO can alleviate the core symptoms of PMDD, in most studies, PMDD symptoms were alleviated when ALLO levels were increased (35, 46). Some studies found that the level of ALLO in women with PMS in the luteal phase was lower than that in healthy women whose ALLO was significantly higher in the luteal phase as compared to the follicular phase (47, 48). However, another study showed that in the follicular phase, there was no significant difference in the levels of ALLO between the PMS group and control group (49). These results showed that the decrease in the ALLO level in the luteal phase may be one of the biological factors that contribute to anger and depression in PMS patients. Some studies divided PMS patients with different ALLO levels into high, medium, and low groups, with 2.55 ng/ml as the baseline (50). After treatment with sertraline, it was found that the change in ALLO levels was associated with specific emotional symptoms, such as depression, loss of control, and helplessness. Sertraline increased the ALLO levels in the low baseline group, and it ameliorated the above-described emotional symptoms. In the middle baseline group, the negative mood symptoms were also ameliorated, but the ALLO level did not significantly change. In the high baseline group, the level of ALLO decreased, with only slight amelioration of symptoms (50). The relevance between ALLO and PMS/PMDD was confirmed by the reversal of ALLO concentration after intervention with anti-depression drugs. The level of ALLO significantly increased in brain tissue after fluoxetine administration (51). The application of low-dose fluoxetine can prevent ALLO from oxidizing to 5α-dihydroprogesterone (5α-DHP) without affecting the reuptake of 5-HT (52). Short-term low-dose fluoxetine intervention in the late luteal phase can increase the concentration of ALLO in the brain and prevent the onset of PMDD (10).

Although the above evidences have different conclusions, it is confirmed that the fluctuation of ovarian steroid hormone level can indeed affect the pathogenesis of PMDD. The luteal phase is both the period of PMDD onset and the period of rapid decrease of progesterone, so the fluctuation of the level of neurosteroids may be the key trigger factor affecting the onset of PMDD (53). At the same time, Yan Li proposed the animal model of PMDD based on withdrawal of progesterone or ALLO (54). In rodent experiments, the rapid withdrawal of ALLO will produce symptoms characterized by PMDD, such as increased anxiety behavior (increased acute start response, decreased the opening arm entry time in the elevated plus-maze test) (55) and depressive behavior (increased suspension immobility time in forced swimming test, social withdrawal in social preference test, and lack of pleasure in sugar water preference test) (54).

4. ALLO-mediated $GABA_A$ receptor sensitivity is involved in key mechanisms of PMDD

4.1. Physiological properties of the $GABA_A$ receptor

The $GABA_A$ receptor is a transmembrane protein complex. After binding with GABA or the appropriate agonists, it can play a regulatory role by regulating the flow of chloride ions, so as to hyperpolarize neurons. $GABA_A$ receptors are composed of 19 subunits (α1–α6, β1–β3, γ1–γ3, δ1, ε1, θ, π1, and ρ1–ρ3) from eight subunit families (56, 57). The assembling of different subunits results in different receptor characteristics in different brain regions. The subunits closely related to PMDD are mainly α, δ, and γ subunits. Receptors containing the α4, α6, and δ subunits mediate persistent tonic suppression in low extrasynaptic concentrations of GABA. In high post-synaptic GABA concentrations, the α1, α2, α3, and γ subunit receptors mediate rapid and short-term phase inhibition (58–60). Compared with postsynaptic receptors that require high concentrations of GABA to activate, there is a lower activation threshold for extrasynaptic receptors. ALLO can enhance phasic and tonic inhibition by combining synapses and extrasynaptic $GABA_A$ receptors (37). Under physiological conditions, $GABA_A$ receptor activation hyperpolarized the neurons and inhibited the excitability through to influx of chloride ions. The tonic inhibitory current produces a greater amount of charge transfer, and thus, regulating the expression of receptors containing the α4, α6, and δ subunits is an effective method to reduce the excitability of neurons (61).

4.2. The key evidence of interaction between ALLO and $GABA_A$ receptor-saccadic eye velocity

Saccadic eye velocity (SEV) is rapid, steplike, conjugate changes of gaze, the purpose of which is calculate the speed of centralizing objects of interest on the fovea (62). SEV is controlled by frontal lobe, substantia nigra, superior colliculus, pontine reticular formation, and cerebellum, and there are a lot of $GABA_A$ receptors in these regions. It has been shown to be a reliable neurophysiological tool for the assessment of $GABA_A$ receptor sensitivity (63). Therefore, the results of SEV experiment can be used as evidence for the interaction between ALLO and $GABA_A$ receptor. Allopregnanolone has been shown to dose-dependently decrease SEV and increase subjective sedation in humans (64). Therefore, the sensitivity of $GABA_A$ receptor related to the fluctuation of ALLO may be the cause of PMDD.

4.3. Altered $GABA_A$ receptor sensitivity in PMDD pathogenesis

4.3.1. ALLO affects the expression of $GABA_A$ receptor subunits

The expression of $GABA_A$ receptor subunits, such as α4, may be a key point under PMDD pathophysiology (65–67). The expression of

the extrasynaptic $GABA_A$ receptor is significantly affected by fluctuations in the concentration of extracellular ALLO (10). The expression of the δ subunit decreased after intervention with the 5α-reductase inhibitor finasteride (68). Before fluoxetine administration, GABA decreased, and expression of the α4 subunit increased in the brain area of rats developed as a PMDD model. After fluoxetine administration, the ALLO concentration and α4 subunit expression level reversed (69, 70). After progesterone withdrawal in a PMDD rat model, it was observed that the expression of the α4 and δ subunits in the brain increased, which led to changes in neuronal excitability and induced PMDD-like behavior in rats (10). It was also observed that the mRNA expression of the $GABA_A$ receptor α4 and δ subunits decreased in the brain of depressed patients (71). Recently found in the studies of rats have found that the periaqueductal gray (PAG) substance, which is involved in the regulation of fear responses, is involved in the pathogenesis of PMDD (72). GABAergic neurons are widely distributed in the dorsolateral area of the PAG. The progesterone level in female rats sharply decreased in the late estrus period, and the expression of $GABA_A$ receptor α4, β1, and δ subunits in the PAG area was upregulated, which enhances the excitability of neural circuits in the PAG area and induces anxiety and panic (73).

The α4, β, and δ subunits of the $GABA_A$ receptor are mainly expressed in the dentate gyrus and thalamus (28). The effect of upregulation of subunit expression on granule cells of the dentate gyrus was significantly higher than that on pyramidal cells of the CA1 region (68). Electrophysiology also confirmed that the GABA current mediated by ALLO enhancement in granule cells of the dentate gyrus was higher than that in pyramidal cells of the CA1 region (68). It has been reported that the increased expression of the δ subunit in the striatum may be a protective mechanism that compensates for the increased excitability of neurons (74).

ALLO has a strong mediating effect on the expression of the δ and α4 subunits of the $GABA_A$ receptor (17, 37). It is currently known that there are two types of binding sites of ALLO on the $GABA_A$ receptor: (1) one that enhances the effects of steroids and is in the α subunit in the cavity of the basal transmembrane structure and (2) one that directly activates the receptor-gated channel and is located between the α and β subunit interfaces (75–78). ALLO works by enhancing sites at low levels and can directly activate receptors at high levels. Although there is no research suggesting that the ALLO binding site is related to the δ subunit, the ability of ALLO to potentiate GABAA receptors is greater when these receptors contain the delta subunit (79, 80).

4.3.2. ALLO affects the function of $GABA_A$ receptor subunits

The negative emotional symptoms of women with PMDD are caused by the contradictory effects of the change in the $GABA_A$ receptor mediated by ALLO (81). Martinez et al. (45) proposed that it is the changes in the level of neurosteroids that cause the adjustment in the $GABA_A$ receptor. The regulation of ALLO on the receptors is inseparable from the plasticity of the receptors themselves. The plasticity of the $GABA_A$ receptor refers to the selective changes in the composition of subunits in different regions due to the changes in the reproductive cycle (64, 68).

Animal experiments have confirmed that the expression of the $GABA_A$ receptor subunits periodically changes under physiological conditions. The expression of the δ subunit protein and mRNA in the high progesterone period is higher than that in the low progesterone period, especially in the hippocampal dentate gyrus (68). In the PMDD animal model, it was observed that the expression of the α4 subunit in the hippocampus was upregulated, the affinity for benzodiazepines decreased, and anxiety-like behaviors appeared at the same time (82). It is known that the δ subunits preferentially combine with α4 subunits, which contain benzodiazepine binding sites between the α and γ subunit interface. Therefore, the increase in the expression of the α4 and δ subunits leads to a decrease in the receptor affinity for benzodiazepines due to the γ subunit being replaced by the δ subunit and suppressing the release of GABA, resulting in PMDD-like behavior in rats (83).

The plasticity of the $GABA_A$ receptor is impaired and its receptor subunits cannot adapt to the fluctuation of ALLO during the menstrual cycle, resulting in the pathogenesis of PMDD (17). Neurophysiological experiments showed that expression of the $GABA_A$ receptor α4, β2, and δ subunits increased 30 min after treatment with ALLO and GABA, and reached a peak after 48 h, while expression of the $GABA_A$ receptor α4, β2, and δ subunits on the cell membrane surface did not increase 48 h after treatment with GABA alone (61). GABA acts as a partial agonist on the $GABA_A$ receptor α4, β2, and δ subunits, and ALLO can increase the potency of GABA acting on the receptor, which may explain the high affinity of ALLO for the α4 and δ subunits (61, 76). Therefore, the sensitivity of the $GABA_A$ receptor to ALLO refers to the ability to respond to fluctuations in ALLO levels. The compositional conditions of this response ability include $GABA_A$ receptor affinity for ALLO, and the inherent plasticity of the receptor.

Summarizing the above studies, the following assumptions are put forward: due to the high affinity of ALLO for the extrasynaptic $GABA_A$ receptor, when the level of ALLO decreases, the expression of the α4, β, and δ subunits increases. When the level of ALLO increases, the α4, β, and δ subunits do not return to normal and show impaired plasticity. This mediates the effect of ALLO on the receptors and causes the inhibitory neurons to be inhibited. Neurons exhibit disinhibition and a net effect of excitability, which then affects emotional changes. The changes in ALLO levels affect the expression of the α4 and δ subunits, which leads to increased sensitivity of the extrasynaptic $GABA_A$ receptor to ALLO. One of the results is that ALLO becomes a trigger point that easily affects women's moods and can lead to disorders. This result is not only related to genetics, but is also subject to the effects of stress (84).

5. ALLO-mediated $GABA_A$ receptor: The most viable potential drug target for alleviating PMDD

At present, there are mainly two types of clinical drugs targeting $GABA_A$ receptors: $GABA_A$ receptor-regulated steroid antagonists (sepranolone) and $GABA_A$ receptor-selective positive allosteric modulators [brexanolone, ganaxolone, and SAGE-217 (zuranolone)].

Sepranolone (or isoallopregnanolone) is a metabolite of ALLO that is a $GABA_A$ receptor-modulating steroid antagonist that can selectively inhibit the enhancement of $GABA_A$ receptor-induced current mediated by neurosteroids on the $GABA_A$ receptor. Currently, phase II clinical trials for PMDD are underway. In preclinical studies, it has been shown that sepranolone inhibits the effect of ALLO on

$GABA_A$ receptor chloride uptake mediated by GABA *in vitro* (85). Satisfactory clinical effects have been obtained with the drug and high safety. Emotional symptoms were satisfactorily relieved, but there was no effect on physical symptoms (17). There were no obvious side effects in clinical trials. The only thing to be noted is that subcutaneous administration produced injection site reactions during the luteal phase (86).

$GABA_A$ receptor-selective positive allosteric modulator antidepressants can cause conformational changes in receptors and regulate the affinity of receptors for GABA. Examples of such antidepressants are brexanolone, ganaxolone, and SAGE-217 (zuranolone). Brexanolone (allopregnanolone) is approved by the FDA for postpartum depression (PPD). The pathogenesis of PPD is similar to that of PMDD. The rapid decline of ALLO levels is considered to be the cause of its pathogenesis, and ALLO is the key factor (87). Clinical trials have shown that brexanolone can significantly reduce the depression score of patients with moderate to severe PPD. The most common side effects are headache, dizziness, and sleepiness (16, 88). This drug is used to treat PPD through intravenous infusion for 60 h under continuous medical supervision because of the risks of severe sedation, hypnosis, loss of consciousness, and deep respiratory arrest (89). Ganaxolone and SAGE-217 (zuranolone) are synthetic analogs of ALLO. Ganaxolone is a synthetic 3β-methyl ALLO derivative with sedative effects that can be used as an adjuvant drug for PMDD (90). Preclinical studies have shown that SAGE-217 can exhibit 30–60% oral bioavailability in rodents and demonstrate clear pharmacodynamic effects, consistent with $GABA_A$ receptor activity, following oral administration (91). In a phase I clinical trial, oral administration of SAGE-217 was well tolerated without severe adverse reactions (92). In a double-blind phase II clinical trial, MDD patients treated with SAGE-217 for 14 days exhibited significantly reduced depressive symptoms (71). At present, SAGE-217 has entered a number of phase II clinical trials and is expected to become a new drug for the treatment of major depression and PMDD. In conclusion, the ALLO-$GABA_A$ receptor remains as the most promising target for the treatment of PMDD.

6. Conclusion and prospects

ALLO is strongly associated with some specific female mental disorders, such as PMS/PMDD (93), catamenial epilepsy (94), menstrually related and postmenopausal migraine (95), and PPD (16, 96). At present, there are few clinical and animal experiments, and the specific mechanism of action is still unclear. After summarizing the above contents, we can draw a conjecture: when the decrease in ALLO is too rapid, there is an increase in the expression of GABAA receptor subunits and decrease in the sensitivity (decreased affinity, reduced plasticity), leading to a decrease in chloride influx, which, in turn, inhibits the release of GABA from GABAergic interneurons, reduces the inhibition of pyramidal neurons, and then increases the excitability of pyramidal neurons, leading to the development of PMDD. The ALLO-mediated GABAA receptor remains the main pathogenic factor of PMDD (Figure 2). ALLO is a positive allosteric modulator of $GABA_A$ receptor. When ALLO binds to $GABA_A$ receptor, it will enhance the GABA evoked chloride current through increasing the frequency and/or duration of openings of the GABA-gated chloride channel (40). Under normal physiological conditions, $GABA_A$ receptor changes normally with the fluctuation of ALLO in the menstrual cycle. When ALLO decreases too fast, the binding rate of ALLO and $GABA_A$ receptor decreases, or the plasticity of $GABA_A$ receptor is impaired, leading to the decrease of chloride influx. GABAergic interneurons release less GABA, reducing the inhibition of pyramidal neurons (disinhibition of inhibitory neurons), enhancing the excitability of pyramidal neurons, and leading to the occurrence of PMDD. ALLO-mediated $GABA_A$ receptor sensitivity is still the main pathogenic factor of PMDD. $GABA_A$ receptor (conformation and affinity to GABA), ALLO (elevated level), and the change of $GABA_A$ receptor mediated by ALLO receptor may be the therapeutic target of PMDD. Based on the study of changes in ALLO levels related to PMDD, the following conclusions are drawn: (1) The changes in the levels of ALLO participate in the onset of PMDD as a trigger factor for emotional symptoms; (2) The absolute level of ALLO is not the conclusive cause of the onset of PMDD, but rather, the focus should be on the $GABA_A$ receptor; (3) The level of ALLO cause changes in the expression and function of $GABA_A$ receptor subunits in the brain, which results in increasing sensitivity to ALLO in women with PMDD (97). The sensitivity of the $GABA_A$ receptor for ALLO fluctuations refers to the affinity of the $GABA_A$ receptor to ALLO and the plasticity of the receptor. The rapid decline of ALLO leads to the decrease of the affinity between ALLO and $GABA_A$ receptor and the impairment of the plasticity of $GABA_A$ receptor. Therefore, PMDD leads to the decrease of sensitivity of $GABA_A$ receptor to ALLO fluctuation and the increase of pressure sensitivity; and (4) Women with PMDD change their response to ALLO under stress.

A goal of future research is to deeply understand the mechanism related to the GABA receptor and ALLO and deeply explore this mechanism so as to develop more effective therapeutic drugs with fewer side effects. However, because the interventions for the treatment of PMDD are mainly chemical drugs, their side effects are extensive. Complementary and alternative medicine represented by traditional Chinese medicine has unique advantages in the treatment of emotional diseases. TCM compounds and active ingredients can act on brain areas that control emotions *via* multiple targets and channels, and acupuncture can activate specific neural circuits and neuroendocrine pathways, thereby ameliorating PMDD symptoms. In the future, research in this field can be directed toward revealing the neural circuit and neuroendocrine mechanism of Chinese herbal compound in the pathogenesis of PMDD and clarified the interventional pathways and targets of complementary and alternative therapies at this level. Then, we will focus on the main components that may play a role in the drug effect. Through the isotope labeling method/virus tracing method, we will deeply explore whether the effective components play a role by influencing the GABAergic nervous system, and how the specific mechanism is. In short, $GABA_A$ receptor is a very potential target. Comprehensive exploration in this field will further reveal the possible neurobiological mechanism, thus promoting the development of translational medicine and drugs.

Author contributions

QG, WS, and Y-RW: writing original draft. Z-FL: data collection. FZ and X-WG: writing—reviewing and editing. K-YX and DC: conceptualization and methodology. KL and YX:

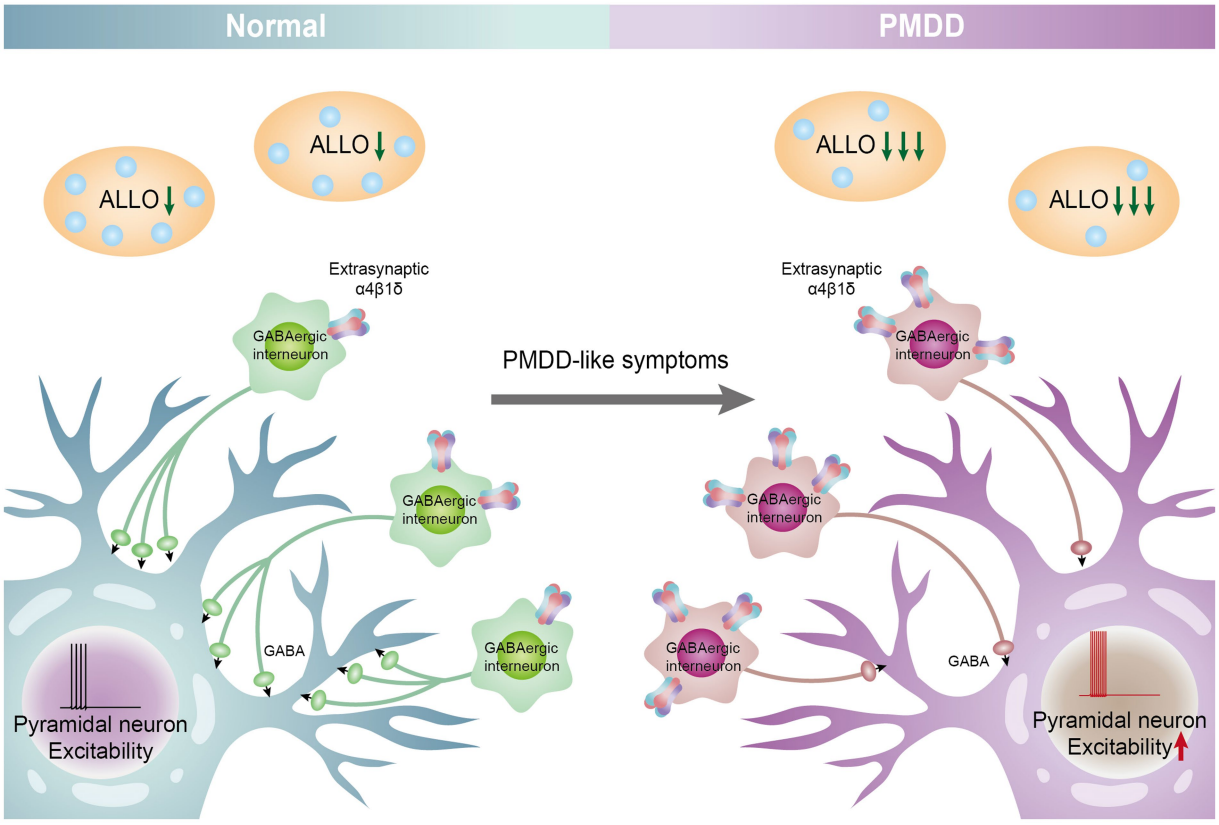

FIGURE 2
ALLO-mediated $GABA_A$ receptor subunit sensitivity participates in the pathogenesis of PMDD. When the decrease in ALLO is too rapid, there is an increase in the expression of $GABA_A$ receptor α4 β subunits (10) and decreases in the sensitivity (decreased affinity, reduced plasticity), and leading to a decrease in chloride influx, which, in turn, inhibits the release of GABA from GABAergic interneurons, reduces the inhibition of pyramidal neurons, and then increases the excitability of pyramidal neurons, leading to the development of PMDD. The ALLO-mediated $GABA_A$ receptor remains the main pathogenic factor of PMDD.

visualization. WL and SW: project administration, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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