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Review

Allopregnanolone in mood disorders: Mechanism and therapeutic development

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ABSTRACT

The neuroactive steroid allopregnanolone (ALLO) is an endogenous positive allosteric modulator of GABA type A receptor ($GABA_AR$), and the down-regulation of its biosynthesis have been attributed to the development of mood disorders, such as depression, anxiety and post-traumatic stress disorder (PTSD). ALLO mediated depression/anxiety involves GABAergic mechanisms and appears to be related to brain-derived neurotrophic factor (BDNF), dopamine receptor, glutamate neurotransmission, and Ca^{2+} channel. In the clinical, brexanolone, as a newly developed intravenous ALLO preparation, has been approved for the treatment of postpartum depression (PPD). In addition, traditional antidepressants such as selective serotonin reuptake inhibitor (SSRI) could reverse ALLO decline. Recently, the translocation protein (TSPO, 18 kDa), which involves in the speed-limiting step of ALLO synthesis, and ALLO derivatization have been identified as new directions for antidepressant therapy. This review provides an overview of ALLO researches in animal model and patients, discusses its role in the development and treatment of depression/anxiety, and directs its therapeutic potential in future.

1. Introduction

Mood disorders are the most common types of neuropsychiatric illness and increasingly becoming a major cause of disability. Among them, depression and anxiety are the most devastating diseases, which affect the patients' cognition and memory, leading to poor life quality [1–3]. The World Health Organization (WHO) survey found that the prevalence of mood disorders has increased rapidly in the past decade, patients with depression and anxiety accounting for 4.4% and 3.6% of the global population, respectively [4]. Although depression and anxiety are classified as two different diseases according to diagnostic criteria, both have similar clinical characteristics and treatment [5]. In clinical, anxious depression is a common syndrome, manifesting in nearly half of patients suffering from both depression and anxiety [6,7]. Nowadays, there still lacks effective treatments for depression and anxiety. Therefore, it is urgent to research and develop new antidepressants.

Allopregnanolone (3α, 5α-tetrahydroprogesterone, ALLO) is a member of the neurosteroid family. Various studies demonstrated that depressive and anxiety-like behaviors are associated with changes in ALLO level and return to normal after effective antidepressant treatment [8–12], suggesting the pathophysiological role and therapeutic potentials of ALLO in depression and anxiety. Brexanolone, a newly developed intravenous ALLO preparation, has been approved by the United States Food and Drug Administration (FDA) in 2019 for the treatment of severe

Abbreviations: ALLO, allopregnanolone; $GABA_AR$, GABA type A receptor; PTSD, post-traumatic stress disorder; BDNF, brain-derived neurotrophic factor; SSRI, selective serotonin reuptake inhibitor; PPD, postpartum depression; TSPO, the translocation protein; WHO, World Health Organization; FDA, Food and Drug Administration; P-450scc, the side chains of cytochrome-P-450 enzyme; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-DHP, 5α-dihydroprogesterone; 3α-HSD, 3α-hydroxysteroid dehydrogenase; PFC, prefrontal cortex; MDD, major depressive disorder; mPFC, medial prefrontal cortex; TrkB, Tropomyosin receptor kinase B; NMDA, N-methyl-D-aspartic acid; ACh–M1, acetylcholine M1; VDCC, voltage dependent calcium channel; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; HPA, hypothalamic-pituitary-adrenal; NAcc, nucleus accumbens; FST, forced swimming test; KSS, Kami Shoyo-san; RU-38486, mifepristone; VTA, ventral tegmental area; OFT, open field test; EPM, elevated plus-maze; IOMO, Morinda officinalis; SPS, single prolonged stress; FEWP, Free and Easy Wanderer Plus; HAMD-17, 17-item Hamilton Rating Scale for Depression; 5-HT, 5-hydroxytryptamine.

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postpartum depression (PPD) [13,14].

Here, we review ALLO researches in animal models and depression/anxiety patients, to explore its role in the development of depression/anxiety and therapeutic potential, and to discuss the future direction.

2. Synthesis of ALLO

Synthesis of neurosteroids begins with cholesterol or steroidal precursors (Fig. 1). The first step is the transport of cholesterol onto inner mitochondrial membrane, which is mediated by the translocation protein (TSPO, 18 kDa) located on the outer mitochondrial membrane. On inner mitochondrial membrane, cholesterol is cleaved through the side chains of cytochrome-P-450 enzyme (P450scc) and metabolized to pregnenolone, a precursor to all neurosteroids, which is converted to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD). Then, progesterone is reduced to 5α-dihydroprogesterone (5α-DHP) under the action of rate-limiting enzyme 5α-reductase, a key step in ALLO synthesis. Finally, 3α-hydroxysteroid dehydrogenase (3α-HSD) catalyzed the reduction of 5α-DHP to ALLO [15]. Remarkably, ALLO can also be oxidized to 5α-DHP *via* 3α-HSD.

3. Target of ALLO

3.1. GABA type A receptor ($GABA_AR$) is the main target of ALLO

GABA is an inhibitory neurotransmitter, which is released from the vesicle and activates the GABA receptor family in the postsynaptic membrane, acting as a neuronal suppressor [16]. It's been hypothesized that GABAergic deficits are associated with the occurrence of a variety of depression [17]. In major depressive disorder (MDD) and chronic stress, the imbalance of excitation and inhibition in prefrontal cortex (PFC) is related to the occurrence of depression [18,19]. Previous studies showed that GABA concentrations in the occipital cortex and PFC were significantly lower in patients with MDD [20,21], severe PPD [22] and postmenopausal women with depression [23]. Similarly, the output of GABAergic neurons in the medial prefrontal cortex (mPFC), as well as the expression of genes and proteins associated with GABA synthesis and transporters decreased in depressed mice with chronic mild emergency [24]. These results suggested that the stimulation of $GABA_AR$, the main type of GABA receptor, in PFC may be a novel strategy for antidepressant therapy [25].

ALLO is an endogenous positive allosteric regulator of both synaptic and extra-synaptic $GABA_ARs$ [26], which prolongs the decay time of GABA-gated ion channels, resulting in lengthening the opening time of GABA-activated chloride channels and enhancing the inhibitory effect of neurons [25,27]. The antidepressant/antianxiety effects of ALLO strongly correlate with fluctuations of $GABA_AR$ function and plasticity. The $GABA_AR$ agonists, diazepam and muscimol, had synergistic effects on ALLO-induced antianxiety in animal models of depression [28,29], whereas $GABA_AR$ antagonists flumazenil, bicuculline, and picrotoxin attenuated the anti-anxiety effects of ALLO [28–30]. These results corroborated that the antidepressant/antianxiety effects of ALLO are mediated by stimulation of $GABA_ARs$.

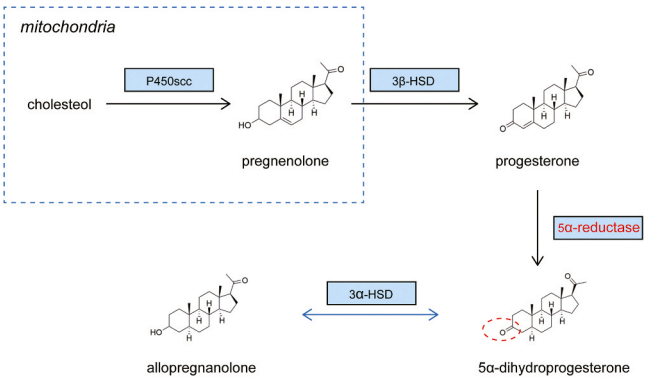

Fig. 1. Synthesis of neurosteroids. [15] (1) The transport of cholesterol across mitochondria. (2) Cholesterol is metabolized to pregnenolone by cytochrome-P-450 enzyme (P450scc). (3) Pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD). (4) Progesterone is reduced to 5α-dihydroprogesterone (5α-DHP) by rate-limiting enzyme 5α-reductase. (5) 3α-hydroxysteroid dehydrogenase (3α-HSD) catalyzes the reduction of 5α- DHP to ALLO.

3.2. ALLO-induced antidepressant effects through elevation of brain-derived neurotrophic factor (BDNF)

BDNF, a member of the "neurotrophic protein" family, is a critical mediator of neuronal plasticity including neurogenesis, synaptogenesis and neuronal maturation [31]. Stress and depression have been reported to reduce BDNF level significantly in the hippocampus and cerebral cortex of depressed animal models and clinical patients [32–35]. Mice lacking BDNF after birth due to a genetic mutation showed a tendency to be anxious [36,37]. Infusion of BDNF into the hippocampus, on the other hand, induced antidepressant effects [38].

Various studies have been conducted to explore the relationship between antidepressant effects of ALLO and BDNF. When ALLO was infused into the PFC of a depressed rat model, the BDNF mRNA expression in the hippocampus increased [39]. Chen et al. [40] found that ALLO up-regulated the BDNF mRNA in the midbrain of 6-hydroxydopamine--damaged mice. In addition, BDNF may be involved in the neurosteroids mediated regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Intraperitoneal injection of ALLO simultaneously changed the HPA axis activity and BDNF level in hippocampus and hypothalamus in adult male rats [41]. Because BDNF binds to tropomyosin receptor kinase B (TrkB), ALLO-induced antidepressant-like effects through BDNF might be blocked by TrkB antagonists. To test this, Shirayama et al. reported that ANA-12, a TrkB antagonist, blocked the antidepressant-like effect of ALLO in learned helplessness rat model, suggesting that BDNF-TrkB signaling plays a role in antidepressant effects of ALLO [42]. However, activation of BDNF-TrkB signaling is not subject to the modulation of $GABA_A$ receptors. Studies confirmed that antidepressant effects of ketamine, scopolamine, and LY341495, have very similar molecular mechanism to that of ALLO [43–45]. All these compounds promote glutamate release through inhibition on the N-methyl-D-aspartic acid (NMDA) receptor or acetylcholine M1 (ACh–M1) receptor or metabotropic glutamate (mGlu) receptor, and activate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which then stimulates the voltage-dependent calcium channels (VDCCs) to induce Ca^{2+} influx, and finally activate the BDNF-TrkB signaling to produce antidepressant effects [46].

3.3. Other targets

In contrast to BDNF, there is negative correlation between dopamine level and depressive-like behaviors [47–49]. Evidence suggested that the dopamine delivery system was involved in antidepressant effects of ALLO [50]. ALLO reduces basal dopamine level in the PFC and nucleus accumbens (NAcc) in a dose-dependent manner [51]. Finasteride, an inhibitor of 5α-reductase (the key enzyme in ALLO synthesis), significantly reduced ALLO in the cortex, while increased the dopamine output in acute stress response [52]. Bortolato and his colleagues revealed that in social isolation rearing rats (a model of early chronic psychosocial stress), 5α-reductase level decreased in both NAcc and mPFC, along with an increase of dopamine level [53]. These results implied that ALLO might regulate dopamine level during both acute and chronic stress. The administration of leropiril, a dopamine D-2 receptor antagonist, abolished the antidepressant effect of ALLO in the forced swimming test (FST), while dopamine D-1 receptor antagonist SCH23390 did not, suggesting that antidepressant effects of ALLO was largely dependent on dopamine D-2 receptor [50]. Kami Shoyo-san (KSS), a traditional

Chinese herb used to treat menopausal anxiety, was reported to have anti-anxiety effects through neurosteroid synthesis [54]. Recently, Guo et al. [55,56] found that administration of either ALLO or KSS improved anxious-like behaviors and raised endogenous ALLO level in mice brain. The application of SCH23390 almost completely eliminated the pharmacological effect of KSS. Therefore, the administration of KSS promoted the downstream cascade of ALLO. Dopaminergic D1 receptor mediated signaling in the brain to reverse the endogenous brain ALLO reduction in females with socially related behavioral deficits. However, the mechanism of the interaction between dopamine and ALLO is less studied, which needs further exploration.

Hu et al. [57] used L-type calcium channels antagonist, verapamil, to block ALLO-mediated inhibition of presynaptic glutamate release in rat mPFC. In addition, Wang et al. [58] found that calcium channel blockers La^{3+} or nifedipine attenuated ALLO-induced Ca^{2+} elevation in rats, and bicuculline and picrotoxin also had similar effects. Mechanisms of antidepressant effects of ALLO have been summarized in Fig. 2. Apart from $GABA_A$Rs, involvement of other possible mechanisms in ALLO-induced antidepressant effects warrants further investigation.

4. Depressive/anxiety-like behaviors are associated with changes in ALLO level

A large number of studies have linked ALLO to the pathophysiology of depression and anxiety. Depression and anxiety may be related to the reduced endogenous ALLO synthesis. It was found that patients with post-traumatic stress disorder (PTSD) had lower ALLO than those in the normal control [59]. It has been reported that treatment of finasteride (a selective inhibitor of 5α-reductase) in animals, resulting in reduced formation of GABAergic neuroactive steroids [52,60–64], significant increase of immobility duration in the FST [65–68], and depressive/anxiety-like behaviors. Similarly, finasteride has also been proved to inhibit hippocampal neurogenesis (a mechanism that may also lead to the occurrence of depression) in male mice [69]. However, more researches are needed to investigate the mechanism of finasteride-induced depression. In a clinical study, Melcangi et al. [70] assessed neuroactive steroids level in both cerebrospinal fluid and plasma of three post-finasteride patients. Compared with healthy controls, post-finasteride patients had lower ALLO level and showed persistent depressive symptoms. Agis-balboa et al. [71] measured the level of neurosteroids in the PFC in patients with depression and found that the level of 5α-reductase type I was down-regulated, which suggested that GABAergic neurotransmitter deficit induced by the down-regulation of ALLO synthesis in the brain may contribute to depression.

In addition, the progesterone receptor antagonist mifepristone (RU-38486) and CDB-4124 increased the immobility duration of FST in mice [72]. In clinical trials, studies have confirmed that ALLO and progesterone level are associated with depression in women during the premenstrual phase [73,74]. As a steroidal precursor of ALLO synthesis, progesterone has similar pharmacological mechanisms to ALLO. A decrease in progesterone levels directly contributes to depression, reminding us that increasing progesterone level in patients may alleviate depression.

Social isolation rearing caused a significant reduction of ALLO in the cerebral cortex, hippocampus and plasma, as well as low function of $GABA_A$Rs [53,75,76]. In the serum and hippocampus of male Wistar rat models socially isolated for 6 and 10 weeks, endogenous ALLO level decreased and were negatively correlated with isolation time. And the immobility duration of FST in these rats was higher than that in housing and treatment groups [77]. Furthermore, the reduced ALLO during social isolation lead to stronger contextual fear responses and impaired fear extinction in mice, which could be used as a model for PTSD [75]. These studies suggested that the decline in endogenous ALLO is a major cause of depression.

In the brains of animal depression model, there are regional differences in ALLO content. Dong et al. [78] found that the content of ALLO reduced in the brain of rats socially isolated for 6 weeks due to a decrease in 5α-reductase. The expression of 5α-reductase type I mRNA was the highest in olfactory bulb, and the lowest in cerebellum. The olfactory bulbectomized rat model is a well-known animal model of depression [79]. The high ALLO levels in the olfactory bulb may be the reason for the significant imbalance of ALLO content after the removal of the olfactory bulb in rats, which resulting in depression. In mice socially isolated for 4 weeks, 5α-reductase type I mRNA was specifically down-regulated in glutamatergic pyramidal neurons in the amygdala, which might explain their aggressive and anxious behaviors [80]. Uzunova et al. [81] analyzed ALLO content in the brain, amygdala and frontal cortex in olfactory-bulbectomized rats. Interestingly, ALLO significantly increased in cerebral cortex, and decreased in amygdala

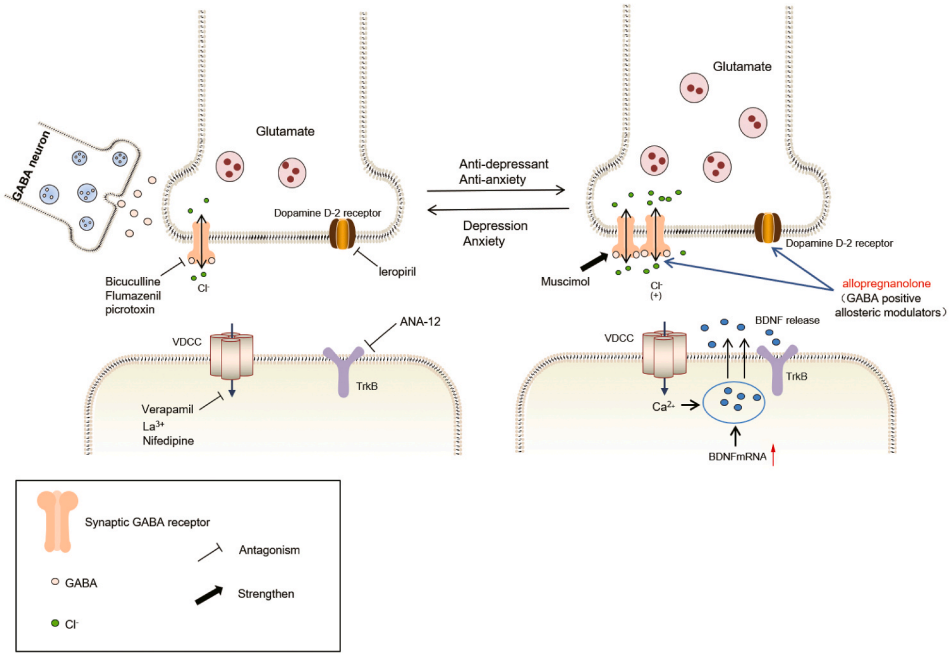

Fig. 2. Mechanism of antidepressant effects of ALLO. ALLO is an endogenous positive allosteric regulator of $GABA_A$Rs, by interacting with $GABA_A$R sites, and it makes the opening time of GABA-activated chloride channels longer and enhances the inhibitory effect of neurons [25,27]. $GABA_A$R antagonists, bicucullin [28], flumazenil [28–30] and picrotoxin [29] have antagonistic effects towards ALLO-mediated antianxiety, while $GABA_A$R agonist, muscimol [28,29], enhanced the anti-anxiety effects. The burst of glutamate causes the release of BDNF. The BDNF mRNA expression up-regulated by ALLO in depression models [39,40], and antidepressant effects induced by BDNF was blocked by TrkB antagonist, ANA-12 [42]. Antidepressant effects of ALLO were also dependent on dopamine D-2 receptor. Leropiril, a dopamine D-2 receptor antagonist, enhanced depressed-like behaviors in rats [50]. In addition, ALLO-induced Ca^{2+} elevation was dependent on L-type calcium channels [57]. Calcium channel blockers verapamil [57], La^{3+} [58] or nifedipine [58] attenuate ALLO-induced Ca^{2+} elevation.

and frontal cortex, but in hippocampus, no significantly change was observed. Therefore, the amygdala plays a key role in ALLO related depression [82].

In addition, after inhibiting ALLO synthesis in the midbrain ventral tegmental area (VTA) of female rats, open field test (OFT, a test analyzed locomotion, anxiety and stereotypical behaviors in rodents.) and elevated plus maze (EPM, a test for measuring anxiety-like behaviors), were performed to assess anxiety behaviors [83,84]. It was found that the central entry time in the open field and the time of opening arms in EPM were both significantly reduced, which suggested the antianxiety ability of female rats deteriorated [85].

ALLO level during pregnancy also affected the onset of depression. In the ovariectomized rat model, the withdrawal of ALLO increased the immobility duration of FST, and showed depressive-like symptoms [86,87]. Also, at the end of pregnancy in animals, administration of ALLO reduced depressive/anxiety-like behaviors in newborn rats and in adulthood [88], in contrast, lowering ALLO level increased the anxiety-like behaviors of young female guinea pigs under the new environment [89], indicating that ALLO level directly affects fetal depressive/anxiety-like behaviors. In addition, a decrease in neurosteroid levels after preterm delivery reduced the specific $GABA_AR$ subtype expression involved in neurosteroids binding, ultimately reducing ALLO generation [90]. Similarly, in human, the drastic change of ALLO level during pregnancy is closely related to PPD, which will be introduced in the following section (The pathophysiology role of ALLO and GABA in PPD). In a word, changes in ALLO level not only affect the occurrence of depressive/anxiety-like behaviors, but also participate in the pathogenesis of depression.

5. The role of ALLO in antidepressant therapy

Neuroactive steroids have been shown to be modulators of the pathophysiology of mood disorders, and to be associated with their treatment [91]. Direct administration of ALLO has confirmed antidepressant effects in both rodents and humans [92] with reduction in the immobility duration of FST [93–98] and increase in the firing rate of lateral septal neurons [99]. Neuroactive steroids also positively regulated the firing activity of dorsal raphe nucleus neurons in rats, with sex differences [100–102], which paved the way for treating mood disorders in women.

As mentioned above, there are regional differences in ALLO content in the brain, and the antidepressant effects of ALLO are also region-specific, correlating with the different distribution of $GABA_ARs$ [103]. The hippocampus and amygdala are key sites for regulating emotional behavior. An infusion of ALLO in the central district of hippocampus or amygdala of a depressed rat model produced antidepressant-like effects [104,105]. In addition, injection of ALLO into NAcc could also reduce the immobility duration of FST [106,107]. Nelson et al. [108] found that S-norfluoxetine or pregnanolone directly infused into the basolateral amygdala reduced aggressive behaviors of a socially isolated mouse, with elevated ALLO level in the amygdala and hippocampus. However, injecting these compounds into the striatum had no such effects.

Numerous antidepressant drugs in clinic, as shown in Table 1, have been demonstrated to restore ALLO to the normal level in animal or patients. Selective serotonin reuptake inhibitor (SSRI) is the preferred treatment for depression. Its antidepressant effects of SSRI [9] may be associated with the increase of ALLO in the brain or plasma.

In preclinical studies, drugs such as fluoxetine [109–117], olanzapine [12,118,119] and clozapine [125,127] have been shown to produce antidepressant effects and increase ALLO level in rodents. In the olfactory-bulbectomized rat depression model, some chronic antidepressants such as desipramine, sertraline, and venlafaxine, could reverse a regional imbalance in ALLO level in brain [117]. Pinna G et al. [113–115] found that fluoxetine administration reversed the decrease of ALLO and aggressive behaviors in socially isolated mice. In a subsequent experiment, low-dose and short-term fluoxetine administration increased the ALLO concentration in the brain, and prevented an increase in spontaneous cyclically related anxiety-like behaviors in female rats [119], which will facilitate its development as a means of alleviating premenstrual symptoms in women.

Table 1
The effects of antidepressant drugs in clinic are proved to be linked with the increase of ALLO in human or animals for diseases such as depression or anxiety.

Drugs[a]	Targets	Diseases	Test subjects
Fluoxetine	SSRI	Depression, anxiety	Mice [109–111], rats [112–117], human [9,10]
Sertraline	SSRI	Depression	Rats [113,118]
Fluvoxamine	SSRI	Depression	Human [9]
Paroxetine	SSRI	Depression, anxiety	Mice [119]
Mirtazapine	5-HT2/5-HT3 antagonist	Depression	Rats [120], human [11]
Olanzapine	5-HT2 antagonist, Dopamine D2 receptor antagonist	Depression, anxiety, schizophrenia	Mice [12], rats [12,121,122], human [12]
Clozapine	A serotonin antagonist	Schizophrenia	Rats [121,123]
Carbamazepine	A monoamine oxidase inhibitor	Convulsions, depression	Rats [124], human [125,126]
Desipramine	A monoamine oxidase inhibitor	Depression	Rats [113]
Venlafaxine	An inhibitor of the uptake of both serotonin and noradrenaline	Depression	Rats [113]
Brexanolone	A positive allosteric modulator of $GABA_AR$	PPD	Women [127–129]

5-HT: 5-hydroxytryptamine.
[a] The antidepressant drugs approved by FDA from 1980 to 2019.

In a study, SSRIs such as fluoxetine, sertraline and paroxetine could directly alter the activity of ALLO biosynthetic enzyme, affecting endogenous ALLO content [130]. Two studies demonstrated that mirtazapine and fluoxetine enhanced ALLO levels in rats by acting on microsomal dehydrogenase to inhibit oxidation of ALLO to 5α-DHP [11,116]. This is a new site of action for SSRIs, shedding new light on the development of new antidepressants.

In the clinical trial, patients with MDD showed alleviated symptoms after receiving fluoxetine or fluvoxamine, which was associated with the restoration of ALLO to the normal level in the cerebrospinal fluid [9]. Studies have confirmed that 5α-reductase mRNA and endogenous ALLO expression decreased in the brain during alcohol withdrawal [131,132], while fluoxetine could reduce the degree of depression in patients treated with alcohol withdrawal by restoring ALLO [10].

In addition to monotherapies, combination of antidepressants now makes them more effective in clinical settings [133]. Studies have shown that the rise of ALLO level in brain is linked to the effectiveness of antidepressant combination. Fluoxetine, olanzapine and 17-β estradiol in combination, for example, produced antidepressant effects and increased the neuroactive steroids levels in the hippocampus of rats [117,134,135]. Second, the anticonvulsant carbamazepine could increase the amount of ALLO in rat brains [124]. It could be used as a potentiator in patients with depression who didn't respond to tricyclic antidepressants or SSRIs [125,126].

6. Role of ALLO in antianxiety therapy

Similar to antidepressant effects, ALLO showed an antianxiety effect in the light/dark transition [136], EPM [137,138], burying behavior test [139], mirrored chamber behavior test [140], OFT [141] and ultrasonic vocalization [142,143]. Bitran et al. [138] evaluated the effects of changes in progesterone metabolites in the EPM in female rats, and found that ALLO and pregnanolone induced antianxiety effects. In follow-up experiments, they further confirmed that the antianxiety

effects of progesterone were due to its biotransformation into ALLO, which later enhanced $GABA_AR$-mediated function [144,145]. Darbr et al. [146] carried out research on the influence of ALLO changes at birth on neurodevelopment in male Wistar rats, and found that the rats given finasteride showed anxiety-related behaviors in adulthood, while ALLO administration could reduce such behaviors, which suggested that endogenous ALLO level in newborns could affect anxiety-related scores.

The antianxiety effect also varies with the injection sites of ALLO. Research suggested that the amygdala mediated the antianxiety mechanism of ALLO [147]. Injecting ALLO into the amygdala and mPFC of rats showed antianxiety effects, but not in the hippocampus [148]. However, some studies showed that the injection of neuroactive steroids into the dorsal (CA1) hippocampus and lateral septum produced an antianxiety effect [149,150]. And stimulating mitochondrial benzodiazepine receptor in the hippocampus to activate ALLO synthesis also had an antianxiety-like effect [151]. So the antianxiety effect of ALLO in the hippocampus seems to depend on its subtle structure. Frye CA et al. [152–155] has reported that the midbrain VTA is also closely related to the antianxiety effect of ALLO. Infusing VTA with an inhibitor blocked the metabolism of progesterone to ALLO, reducing social and emotional behaviors in female rats, while infusing ALLO enhanced antianxiety effects in rats.

In a randomized controlled trial, Sripada et al. [156,157] investigated the neural mechanisms underlying ALLO effects on mood. The results showed that, compared with placebo, ALLO reduced activity in regions associated with negative emotions, as well as connectivity between regions. These regions are closely related to the pathophysiological effects of anxiety disorders, suggesting that ALLO is a drug intervention target for anxiety disorders.

Therefore, ALLO is considered to be one of the most promising targets in antidepressant and antianxiety treatment in the future.

7. Role of ALLO in antidepressant/antianxiety effects of plant preparations and natural extracts

Recently, more and more attention has been paid to the application of plant preparations and natural extracts in antidepressant/antianxiety-like behaviors, the mechanisms of which are closely related to the synthesis of neurosteroids. The antidepressant/anxiolytic-like activities of ginsenosides [158–160] and Radix Paeoniae Alba [161–163] were associated with restoring ALLO synthesis. Inulin-type oligosaccharides of *Morinda officinalis* (IOMO) could relieve symptoms in animal depression models [164,165]. Qiu et al. [166] reported that IOMO improved PTSD-like behaviors on EPM and reversed significant decline of ALLO in the PFC, hippocampus and amygdala in single prolonged stress (SPS) model. Resveratrol is a naturally occurring polyphenolic compound with antidepressant, anti-anxiety [167–169] and anti-PTSD activities [170]. Zhang et al. [171] examined the progesterone and ALLO level in foot shock stress mice after resveratrol administration and found that ALLO was increased in the PFC and hippocampus. Puerarin, a flavonoid glycoside extracted from *Pueraria*, was reported to possess the antidepressant [172–174] and antianxiety [119] activities. Puerarin could improve the anxiety-related behaviors associated with PTSD in the freezing response and EPM, and reverse the decline of neurosteroids in the PFC and hippocampus of rats [175]. Free and Easy Wanderer Plus (FEWP) is a multi-herbal preparation used to treat mood disorders [54,176–179]. FEWP improved the behavioral deficits of SPS models in the contextual fear paradigm and EPM tests, increasing the ALLO levels in the PFC and hippocampus [180]. All the above experimental results indicated that ALLO biosynthesis appeared to be involved in the mechanisms of anxiolytic-like activity of these natural products.

8. ALLO and PPD

As a specific type of MDD, PPD is one of the most common complications of childbirth. Globally, the prevalence of PPD in women during pregnancy or after childbirth is about 20% [181,182]. There are many possible causes for PPD, such as epigenetic changes, hormonal fluctuations during pregnancy, GABAergic signaling dysregulation, and neuroinflammatory responses [183]. Multiple evidences verified that changes in GABAergic signal transduction and neuroactive steroid concentrations after pregnancy were associated with PPD [184–186].

8.1. The pathophysiology role of ALLO and GABA in PPD

Nappi et al. [187] tested the serum ALLO level in women with PPD to find that its concentration was significantly low. Bloch et al. [188] simulated the administration and withdrawal of exogenous estrogen and progesterone during pregnancy, and found both gonadal steroids were directly involved in the development of PPD. ALLO is a metabolite of progesterone, which level can reflect the fluctuation of progesterone during pregnancy and is a potential biomarker for PPD. A number of studies have revealed fluctuations of ALLO throughout pregnancy and the postpartum period, rising rapidly in the body during pregnancy and falling immediately after childbirth, and the abnormal level of ALLO was linked to the onset of PPD [189–192]. Consistent with the above results, in one study, serum ALLO level was negatively correlated with depression scores in women in the third trimester of pregnancy [193]. In recent clinical statistics, the risk of PPD was reduced by 63% for every 1 ng/mL increase of ALLO in the second trimester, and lower serum ALLO was strong indicator of PPD [194], suggesting that the determination of serum ALLO could applied for PPD predication and prevention [195].

The increase in neurosteroids during pregnancy and the immediate plunge after childbirth affected the plasticity of $GABA_ARs$ [196,197]. Moreover, the fluctuations in $GABA_AR$ subunits expression and function during pregnancy and postpartum have been observed in animal models [198,199]. Maguire et al. [200] established $GABA_AR$ deficient mice, the *Gabrd*$^{-/-}$ mice showing depressive/anxiety-like symptoms during the postpartum period. These behaviors were ameliorated by a $GABA_AR$ delta-subunit-selective agonist, suggesting that disfunction of $GABA_AR$ contributed to PPD, and $GABA_AR$ subunit could be a potential target for the treatment of PPD in the future. Overall, these data implied that dramatic changes in neurosteroid levels, ALLO in particular, during pregnancy disrupt GABA signaling resulting in PPD. Therefore, manipulation of ALLO may be a potential therapy for PPD.

8.2. ALLO used to treat PPD

Most current treatments for PPD stem from an extension of MDD treatment. SSRIs are the most common first-line PPD drugs, as well as serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, estradiol and progestin interventions [182]. Although the above therapies can alleviate PPD to some extent, they also have disadvantages such as low cure rate, slow onset, serious adverse effects and subsequent likelihood of drug intolerance, which limit their clinical applications [201–204].

Based on the GABAergic hypothesis and the link between ALLO and PPD, ALLO is expected to be a new treatment for PPD. Brexanolone injection is a newly developed, proprietary, β-cyclodextrin-based intravenous ALLO injection approved by FDA for the clinical treatment of PPD in women [13,14].

A recent open label proof-of-concept study confirmed that brexanolone had a good tolerance and anti-PPD activity. The study administered brexanolone to four severe PPD women who scored $\geq$ 20 on 17-item Hamilton Rating Scale for Depression (HAMD-17), followed by safety monitoring and efficacy evaluation. The results showed that brexanolone showed good tolerability in these four patients without serious adverse reactions, and encouragingly, the total score of HAMD-17 decreased at the end of infusion (60_{th} hour) and at the final evaluation point (84_{th} hour) [127]. Subsequently, a double-blind, randomized, placebo-controlled phase II study and phase III clinical trial of brexanolone therapy were carried out in women with severe PPD. The results

showed that, compared with placebo, infusion of brexanolone resulted in a significant reduction in the HAMD-17 total score were achieved 60 hours after brexanlone infusion in women with severe PPD. In both studies, adverse drug reactions were mild to moderate, characterized by sedation, lethargy, headache, dry mouth, and loss of consciousness. These side effects are thought to be related to the rate and frequency of drug infusion. A small number of patients (percentage) required discontinuation of treatment due to excessive sedation or loss of consciousness, but recovered within a short period of time [128,129].

The meta-analysis of a randomized controlled trial of brexanolone for PPD showed a rapid antidepressant effect lasting at least 1 week [205], which was similar to the antidepressant response of single ketamine infusion in MDD [206]. Cooper et al. [207] compared the efficacy of brexanolone and SSRIs in the treatment of PPD. According to the results reported by patients and clinicians, the baseline variation in brexanolone on HAMD-17 was greater than that of SSRIs at all time points. Thus, brexanolone has faster and consistent efficacy compared with SSRIs. Moreover, in terms of cost effectiveness in treating PPD, brexanolone was more economically effective compared to SSRIs [208]. Taken together, brexanolone is an effective new treatment for PPD.

However, because of the wide range of liver metabolism *via* non-cytochrome P450 proteins pathway, such as ketone reduction, glucosalaldehyde acidification, sulfonation and other pharmacokinetic properties, brexanolone can only be administered by intravenous injection, which leads to the clinical inaccessibility of the drug. Therefore, in the follow-up studies on anti-PPD, the development of convenient brexanolone delivery methods, such as oral and sublingual are urgently needed [209].

9. Conclusion and future directions

As a member of the neurosteroid family, ALLO plays an important role in the development and treatment of mood disorders. Both animals and people with depression and anxiety have low level of ALLO, and some antidepressant agents, such as fluoxetine, olanzapine, clozapine have been shown to have antidepressant and antianxiety effects by restoring ALLO. In addition, the release of brexanolone, a proprietary injection, marks a new milestone in PDD therapy. Nowadays, TSPO ligands and ALLO derivatives have become the new research direction in antidepressant treatment.

9.1. TSPO has become a new target for antidepression and antianxiety therapy

Based on the rate-limiting step of endogenous ALLO formation, the transport of cholesterol across mitochondrial membranes relies on TSPO, which has recently been identified as a novel target for antidepressant therapy. TSPO, originally known as a peripheral benzodiazepine receptor [210,211], mediates the transport of cholesterol into the mitochondria. Owen et al. [212] found that esterified cholesterol accumulated in rats with TSPO mutation, along with a significant reduction of ALLO in the cerebral cortex. Studies have indicated that TSPO overexpression in the hippocampus increased the synthesis of progesterone and ALLO. In particular, TSPO overexpression in hippocampal CA1 region improved lipopolysaccharide-induced cognitive dysfunction in mice [213]. Another study showed that TSPO overexpression in the dentate gyrus of the hippocampus in mice produced antidepressant, antianxiety and anti-PTSD effects, which were mediated by up-regulation of ALLO synthesis, while these beneficial effects were blocked by selective TSPO antagonist PK11195 [214,215]. These findings demonstrated that disfunction of TSPO is associated with mood disorders, and TSPO may be a promising target for antidepressant/antianxiety therapy.

Etifoxine, the first TSPO ligand, showed antianxiety activity in a clinical trial [216]. Its antianxiety effect was found to be attributed to the enhancement of endogenous neurosteroid synthesis [217,218]. XBD173 (AC-5216, Emapunil), a novel TSPO ligand, promoted the synthesis of neurosteroids. The antidepressant, antianxiety and anti-PTSD effects of XBD173 have been shown to be related to a rise in the newly synthesized ALLO [219–222]. In diabetic rats, XBD173 showed antidepressant-like activity that was blocked by PK11195 [223]. Compared with benzodiazepines, XBD173 did not cause sedation or withdrawal symptoms even seven days after administration [224–226]. Therefore, XBD173 is an effective clinical psychotropic drug with a promising application prospect, and now it has passed stage II clinical trials.

ZBD-2, an analog of XBD173 [227,228], and YL-IPA08 [229,230], recently designed TSPO ligands, had been shown to have antidepressant, antianxiety and anti-PTSD-like effects in animals. In subsequent studies, they were proved to be effective on PPD model [231,232]. After YL-IPA08 administration, the levels of neurosteroids in the brain of PPD rats returned to normal [232].

Based on the original strategy of non-peptide prototype design of dipeptide drugs, Gudasheva et al. [233–235] designed the first dipeptide TSPO ligand GD-23 (N-carbobenzoxy-L-tryptophanyl-L-isoleucine amide). In pharmacological tests, GD-23 showed anti-anxiety activity, which was blocked by PK11195, trilostane (a selective inhibitor of 3β-HSD) and finasteride (a selective inhibitor of 5α-reductase).

9.2. ALLO derivatization is a new direction in antidepressants research

Ganaxolone and SAGE-217 (zuranolone) were synthetic analogs of ALLO, acting as $GABA_AR$ positive allosteric modulators.

Ganaxolone, a synthetic 3β-methyl derivative of ALLO, has been shown to be well tolerated and safe in clinical trials for epilepsy [236]. And it has been shown to improve behavioral deficits in mice with PTSD, however, in following phase II clinic trial, no significant difference was observed compare to placebo [237,238]. In addition, a recent open-label study showed that ganaxolone had a sedative effect, which may be applied as an adjunct to antidepressant therapy [239].

Recently, SAGE-217 has shown excellent pharmacokinetic properties in clinical trials [182,240]. A preclinical study demonstrated that SAGE-217 enhanced the levels and transport of $GABA_AR$, as well as its oral bioavailability and efficacy in the central nervous system [241]. The safety and pharmacokinetics of SAGE-217 after oral administration were evaluated in phase I, double-blind, placebo-controlled, single ascending dose and multiple ascending dose studies, and the results showed that SAGE-217 was well tolerated and has no serious adverse reactions [242]. In a double-blind phase II clinical trial, patients with MDD who were prescribed SAGE-217 for 14 days showed significant reduction in depressive symptoms [243]. Currently, SAGE-217 has entered several phase II clinical programs and is expected to be a novel drug for major depression and PPD.

Thus, neuroactive steroids, especially ALLO, still are promising targets for the treatment of mood disorders.

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CRediT authorship contribution statement

SC drafted the first version of the manuscript; **YY, LG, XL and SC** revised and edited the manuscript; **SC** collected and organized the references; **YY** approved the final version of the paper.

Declaration of Competing Interest

The authors declare no competing interests.

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