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Revealing GABA Induced Depression: Dual Validation of Animal Experiments and Clinical Data

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Abstract: At present, the scientific research field has conducted in-depth research on its pathogenesis, and a large number of studies have shown that Gamma-Aminobutyric Acid (GABA) ergic neuronal downregulation plays a key role in the pathogenesis of major depression. As a critical inhibitory neurotransmitter in the central nervous system, the abnormal downregulation of GABA neurons will break the balance of the neurotransmitter system. This disruption subsequently interferes with the normal transmission and regulation of neural signals, ultimately leading to multifaceted abnormalities in emotional, cognitive, and physiological functions—processes that collectively drive the onset and progression of major depression. This article reviews the existing experimental evidence of GABA's influence on the development of depression, and provides the basis for further research.

Keywords: GABA, depression, Sprague-Dawley rats, GAD67, Postmenopausal women

1. Introduction

Major Depressive Disorder (MDD) is a serious mental disorder affecting over 300 million people worldwide and is one of the main causes of disability [1]. GABA, a naturally occurring non-protein amino acid, plays a crucial role in the central nervous system and is used by approximately 30% of synaptic sites for information transmission. GABA is synthesized through a specific biochemical pathway, where glutamine produced by astrocytes is decomposed into glutamate and catalyzed by Glutamate Decarboxylase (GAD) [2]. The released GABA binds to the receptors of postsynaptic neurons, such as GABAA, GABAB, and GABAC [3]. GABA can also be translocated into synaptic vesicles, transferred to presynaptic neurons, or metabolized into succinic semialdehyde (SSA) in astrocytes [4]. Although some previous studies have shown a significant association between the down regulation of GABA and depression, and it mainly works in postmenopausal women. From the perspective of the overall experimental evidence system, there is still a lack of sufficient experimental evidence. In view of this, this article aims to systematically sort out and deeply review the existing experimental evidence regarding the association between GABA and depression, with the expectation of providing a more comprehensive and in-depth theoretical basis and experimental evidence for further exploring the pathogenesis of depression and developing new treatment strategies.

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2. Clinical evidence of GABA's association with depression

2.1. Behavioral model

Sprague-Dawley rats are crucial in behavioral and neurobiological research for understanding the link between neural mechanisms and behavioral manifestations. Studies have shown that animals with congenital helpless behavior (cH) are unable to escape current shock exposure, with GABA transporter GAT3 expression significantly downregulated in cLH rats. Scholars such as M Zink[5]have further analyzed the molecular mechanism behind this phenomenon in depth. It was found that in cLH rats, the expression of the GABA transporter GAT3 was significantly downregulated [5].

This finding supports the hypothesis that "glial function is impaired in depression," providing a deeper understanding of the pathogenesis of depression at the molecular level. The unpredictable foot shock (uFS) model is also widely used in research. C57BL/6J mice were used as experimental subjects, and after a single uFS stimulation, they exhibited a significant increase in anxiety-related behaviors. Electrophysiological techniques revealed that the excitability of GABA neurons in the ventral tegmental area (VTA) of the mice was significantly enhanced [6]. Chemogenetic methods were used to inhibit anxiety-related behaviors in the mice, revealing a close relationship between excitability changes and anxiety-related behaviors, providing important experimental evidence for a deeper understanding of neural mechanisms related to depression.

2.2. Gene knockout and transgenic animal research

Glutamic Acid Decarboxylase 67 (GAD67), as a γ-Aminobutyric Acid (GABA) synthesizing enzyme, plays a crucial role in the nervous system. Its function is closely related to various neurotransmitter receptors such as the n-Methyl-D-Aspartate (NMDA) receptor and the Cannabinoid Receptor 1. Karen Müller Smith's study on Gad67GFP knock-in mice revealed a significant reduction in GABAergic neurons, abnormal swimming and anxiety behaviors, and a profound impact on animal behavioral regulation. The abnormality of the GAD67 gene may affect GABAergic neurons [3]. Additionally, Sven Nullmeier focused on male mice with GAD67 single gene deletion (GAD67+/GFP mice) [7]. The study found that mice with social behavior defects, reduced interaction, and increased immobility time in a forced swimming test may exhibit depression-like behavior. This highlights the importance of the GAD67 gene in maintaining normal social behavior and emotional regulation. Sun Mi Gu et al. used a mouse model to thoroughly evaluate the effects of GAD67 knocks on depression-like behavior and anxiety through forced swimming tests and elevated maze tests [8]. On this basis, we further explored the role of GAD67 knockdown on Conditioned Place Preference (CPP) induced by ketamine and JWH-018. The results show that GAD67 knockdown in the dorsal striatum of mice can significantly increase depression-like behavior, providing an important experimental basis for in-depth understanding of the molecular mechanism of GAD67 in the regulation of emotion-related behavior.

2.3. Clinical evidence

Research indicates that depression linked to GABA dysfunction is more common in postpartum women and certain young populations. A study involving 19 postmenopausal women with depression and 13 healthy controls found that GABA+ levels were higher in these women. The study used H-MRS, Hamilton Rating Scale, and Gannet software to analyze the association [9]. The study found lower GABA+ levels in ACC/mPFC of postmenopausal women with depression, suggesting a possible link between GABAergic system dysfunction and depression. The study involved 30 sedentary overweight or obese women, with the intervention group taking 200 mg of

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GABA daily. Both groups adhered to physical exercise for 90 days. The study was evaluated in three stages: the baseline stage (T0) before the trial, the mid-study stage (T45) on the 45th day, and the end-of-study stage (T90) on the 90th day [10]. The intervention group showed positive changes in sleep, emotions, and mental state, with a decrease in negative emotions and a more positive mental state. The DASS-21 scale showed a significant improvement in depression. The HRV analysis showed increased parasympathetic nervous system dominance, suggesting GABA supplementation positively impacts physical functions. Previous studies have found depression disorders related to abnormal GABA function more prevalent among postpartum women and young patients.

In the newly reported sample analysis ($P = 0.003$), the researchers found that young individuals with depression had significantly lower GABA levels than healthy controls (HC). After the combined analysis of the two samples ($P = 0.003$), the same result was obtained: the level of GABA in the depressed youth group was significantly lower than that in the healthy control group. This important finding further confirms the presence of abnormally reduced GABA levels in depressed youth and provides critical in vivo quantitative data support for further research into the neurobiological mechanisms of depression [11].

3. Related drug research

Currently, the anti-depression drugs targeting GABA (γ-aminobutyric acid) available on the market mainly include the following categories.

3.1. Positive allosteric modulators of GABAA receptors (PAMs)

3.1.1. Brexanolone (SAGE-547)

Brexanolone exerts a rapid antidepressant effect by enhancing GABAA receptor function. The HUMMINGBIRD project, comprising one phase 2 and two phase 3 double-blind randomized controlled trials, has established brexanolone as the only U.S. Food and Drug Administration (FDA)-approved drug for postpartum depression (PPD). A post-hoc analysis comparing the efficacy of brexanolone at a rate of 90μg/kg/h (BRX90) with that of the placebo has revealed that patients in the BRX90 group respond more quickly in the assessment of depression and clinical improvement. The cumulative response rates on the Hamilton Rating Scale for Depression-17 (HAMD-17) and the Clinical Global Impression-Improvement (CGI-I) scale within 60 hours are higher. The improvement in symptoms of anxiety, somatization, and insomnia from 24 hours to 30 days is also more significant. While exploratory findings are limited by insufficient sample size, results collectively confirm that BRX90 rapidly relieves depressive, anxiety, and insomnia symptoms in women with PPD [12].

3.1.2. Zuranolone (SAGE-2170)

Zuranolone (SAGE-217, CS-2797), the world's first oral GABAA receptor agonist, has an EC50 of 296 nM for the α1β2γ2 subtype and 163 nM for the α4β3δ subtype, showing great potential in the treatment of depression. A double-blind Phase 3 trial enrolled 196 women with severe postpartum depression (PPD) and randomly assigned them at a 1:1 ratio to receive either 50 mg/d of zuranolone or a placebo for 14 days. The primary endpoint was the change from baseline in total HAM-D score on Day 15, with secondary endpoints including HAM-D score changes at multiple time points, CGI-S score on Day 15, and adverse event (AE) monitoring. The results showed that 86.7% of the patients completed the 45-day study. The least squares mean (LSM) change in the HAM-D score on Day 15 for the zuranolone group (-15.6) was significantly better than that of the placebo group

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(-11.6), with meaningful improvements at multiple time points and a better CGI-S score. Common AEs were somnolence, dizziness, and sedation, with no serious safety events, indicating that zuranolone can effectively improve PPD symptoms, has good tolerability, and holds substantial therapeutic value [13].

3.2. GABA modulator: γ-Hydroxybutyric acid (GHB)

A study on 16 healthy men found that γ-Hydroxybutyric acid (GHB), a GHB-/GABAB receptor agonist, has dual effects of stimulation and sedation, causing euphoria and disinhibition, and enhancing vitality. It promotes donation behavior among low prosocial individuals but does not affect social and cognitive functions. GHB only increases plasma progesterone levels without affecting other hormones, suggesting that GHB/GABAB receptors and progesterone may play a crucial role in its regulation [14].

3.3. Drugs that indirectly regulate the GABA system

3.3.1. Diazepam

Diazepam, a medication, works by binding to specific GABA receptor sites, increasing the affinity between GABA and the receptor. This leads to increased chloride ion channel opening, allowing more chloride ions to enter neurons, enhancing GABA's inhibitory effect. A study on 101 patients with depression found significant differences in diazepam test results. High trait anxiety patients relieved depression without sedation, while low trait anxiety patients showed sedation with less improvement. This suggests differences in pathophysiological mechanisms among patients with different trait anxiety levels [15].

3.3.2. Lorazepam

Lorazepam mainly binds to benzodiazepine receptors in the central nervous system, potentiating the inhibitory effect of gamma-aminobutyric acid (GABA), follow table 1. In a multicenter double-blind parallel controlled study, 112 primary care patients with mixed anxiety and depression who met the criteria of MADRS $\geqslant$ 21 points and CAS $\geqslant$ 11 points were enrolled to demonstrate the therapeutic effect of lorazepam over a 6-week period. Results demonstrated that, aside from a significant early anti-anxiety effect observed in the elderly subgroup, MADRS, CAS, and Clinical Global Impression scale scores all showed continuous improvement from baseline throughout treatment. In terms of safety, lorazepam has a prominent sedative effect. Given the consensus on the short-term use of benzodiazepine drugs, this study confirms that this drug maintains continuous effectiveness after 6 weeks of treatment, providing an important basis for the selection of clinical medication regimens [16].

Table 1: Drugs based on non-alcoholic fatty liver

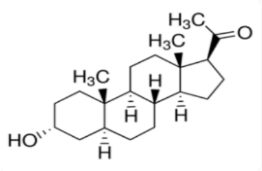
Category	Name of drug	Chemical Structure	Clinical progression
PAMs	Brexanolone		Phrase IIIclinical trial

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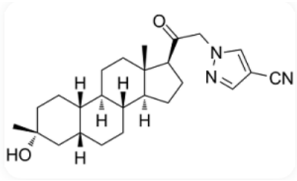
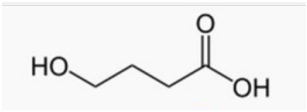
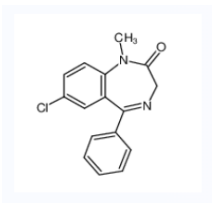
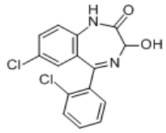
Table 1: (continued)

	Zuranolone		Phrase III clinical trial
GABA modulator	GHB		Phrase III clinical trial
Benzodiazepines	Diazepam		Approved listing
	Lorazepam		Stop listing

4. Conclusion

This review systematically synthesizes experimental evidence of GABA's impact on depression in animal and human studies. In animal experiments, down regulating GABAergic neurons leads to depressive - like behaviors and neural abnormalities, showing its role in promoting such behaviors. In human investigations, advanced magnetic resonance - based techniques prove GABAergic system dysfunction and reduced neuron activity in depressed patients, supporting the link to depression. However, a notable limitation persists in clinical research: the lack of precise stratification of depression patient subgroups. In addition, among the aforementioned drugs, Brexanolone and Zuranolone are regarded as anti-postpartum depression drugs mainly targeting the GABA target. Despite subtle differences in their mechanisms of action, both drugs precisely target the GABAA receptor, opening up new avenues for the treatment of postpartum depression and providing important options for personalized clinical medication. γ-hydroxybutyric acid, an agonist of GHB-/GABAB receptors, has both stimulating and sedative effects, improving mood and prosocial behavior. Diazepam enhances GABA inhibitory effect, eliciting different responses in patients with different trait anxieties. Lorazepam relieves anxiety by enhancing GABA inhibitory effect, showing significant early effects in elderly patients but with sedative effects and short-term use limitations. These drugs act on the GABA system through multiple pathways, providing diverse strategies for the treatment of depression.

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