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The Mechanism of Propofol in Treating Depression-like Behaviors Based on Network Pharmacology and Experimental Validation

Jiarong Wang [1], Jinchen Xiang [1], Xuemei Han [2], Xueliang Shang [1]

[1] School of Psychology and Mental Health, North China University of Science and Technology, Tangshan Hebei, 063210, China
[2] School of Basic Medical Sciences, Hebei Key Laboratory for Chronic Diseases, Tangshan Key Laboratory for Preclinical and Basic Research on Chronic Diseases, North China University of Science and Technology, Tangshan Hebei, 063210, China

Abstract: Objective: To explore the potential mechanism of propofol in improving antidepressant-like behavior through network pharmacology and animal experimental validation, providing theoretical and experimental support for the development of novel antidepressant drugs based on propofol. Methods: 1. The targets of propofol and the disease targets of depression were screened through Swiss Target prediction, Super-pred, SEA, Drugbank, CTD, GeneCards, OMIM, and TTD databases. A protein-protein interaction (PPI) network was constructed, and the core targets were screened and visualized using CytoScape 3.10.2 software. Additionally, GO and KEGG enrichment analyses of the intersection targets were performed using the Metascape database. 2. Thirty male C57BL/6 mice were randomly divided into the CON group, LH model group, and PRO treatment group, with 10 mice in each group. The sucrose preference test, forced swim test, and tail suspension test were conducted to determine whether the depression model was successfully established and to assess the improvement effect of propofol on antidepressant-like behavior. 3. The pathological morphological changes of hippocampal neurons in the three groups of mice were observed through HE staining experiments. The expression of mGluR5 protein in the hippocampus was analyzed by Western blot. Results: 1. Network pharmacology analysis indicated that propofol may exert antidepressant effects by acting on core genes such as ALB, ESR1, NFKB1, HSP90AB1, and EGFR. These core target genes were mainly enriched in biological processes such as synaptic transmission and membrane potential regulation; they involved cellular components such as GABA receptor complexes and synaptic membranes; and they included molecular functions such as neurotransmitter receptor activity. Additionally, propofol may exert antidepressant effects through signaling pathways such as neuroactive ligand-receptor interaction, morphine addiction, and GABAergic synapse. 2. Compared with the CON group, the sucrose preference rate of mice in the LH model group significantly decreased, while the immobility time in the forced swim test and tail suspension test significantly increased. Compared with the LH model group, the sucrose preference rate of mice in the PRO treatment group significantly increased, and the immobility time significantly decreased. 3. The HE results showed that compared with the CON group, the number of neurons in the LH group decreased, with loose arrangement, pycnotic and deeply stained nuclei with blurred boundaries. However, the number of necrotic neurons in the PRO group significantly decreased. The Western blot results showed that compared with the CON group, the expression level of mGluR5 protein in the LH model group significantly increased, while it significantly decreased in the PRO treatment group compared with the LH model group. Conclusion: Propofol may exert antidepressant effects by regulating the expression of mGluR5, improving antidepressant-like behavior, and reducing hippocampal neuronal necrosis.

Keywords: Network Pharmacology; Propofol; Depression; GRM5; mGluR5.

1. Introduction

Depression is a persistent chronic mental disorder that not only leads to continuous emotional distress, anhedonia, hopelessness, and helplessness at the psychological level but also accompanies severe cognitive impairments such as decline in learning and memory, and slowed thinking, and may even be comorbid with other physical diseases [1]. As a global mental health issue, depression affects over 300 million people and poses a severe threat to public health [2]. However, current antidepressant medications face numerous challenges in terms of efficacy and safety. Traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), although alleviating depressive symptoms to some extent, are widely characterized by slow onset of action, significant side effects, and high relapse rates upon discontinuation [3]. These issues not only limit the widespread application of these drugs but also increase the treatment difficulty and economic burden for patients. Therefore, the development of novel antidepressants, particularly those with rapid onset, low side effects, and stable therapeutic effects, has become a crucial issue that urgently needs to be addressed in the field of antidepressant therapy [4].

Propofol, a commonly used anesthetic in clinical practice, has been shown in studies to alleviate emotional disturbances in patients with refractory depression [5] and to improve anhedonia symptoms in chronic restraint stress (CRS) mice [6]. That is, besides its anesthetic and sedative effects, propofol may also possess potential antidepressant properties. This discovery will provide a new direction for the treatment of depression.

Network pharmacology, as an emerging research methodology [7], has demonstrated significant advantages in screening active ingredients of traditional Chinese medicines and their compound prescriptions, as well as in predicting targets of action. This study aims to explore possible targets of propofol in the treatment of depression using network pharmacological techniques and to validate these findings through subsequent animal experiments, thereby providing new perspectives and ideas for depression research.

2. Materials and Methods

2.1. Animals

Thirty male C57BL/6 mice, aged 6-8 weeks, weighing 18-25 grams, and of SPF grade, were purchased from the Experimental Animal Center of North China University of Science and Technology. This animal experiment was approved by the Experimental Animal Ethics Committee of North China University of Science and Technology with the ethical approval number SQ2022193.

2.2. Main Reagents and Instruments

Propofol medium- and long-chain fatty acid injection (10 mg/ml, 5C221104, Guangdong Jiabo), saline (M24032603, Sichuan Kelun Baijian'an), 4% paraformaldehyde solution (XG1050, Biosharp), 10% chloral hydrate (PH1818, Phygene), potent RIPA lysis buffer (ES-8148, Beyotime), PMSF (ST506, Beyotime), protein Marker (Cat. ZS-PR24001, Zhongshi Tongchuang), PVDF membrane (68505100, Mork), mGluR5 antibody (ET1609-36, 1:1000, Hua Bio), β-actin antibody (AC026, 1:100,000, AB clonal), goat anti-rabbit secondary antibody (S1002, 1:5,000, Report), hypersensitive ECL luminescent solution (RW0601, ReportBio), centrifuge (model TGL-16M, Hunan Xiangyi), upright microscope (Leica, Germany), dehydrator (Donatello, DIPATH, Italy), embedding machine (JB-P5, Wuhan Junjie Electronic Company), electrophoresis and membrane transfer apparatus (model EPS-300, Shanghai Tianneng Company), and Gel imaging system (Baygene, 710mini).

2.3. Methods

2.3.1. Screening of Propofol Target Sites

The SMILE serial number of propofol was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and imported into Swiss Target Prediction (http://www.swisstargetprediction.ch/) to obtain targets. Targets were retrieved by searching for "propofol" in the Super-Pred (https://prediction.charite.de/), SEA (https://sea. bkslab.org/), and Drugbank (https://go.drugbank.com/) databases. After deduplication, the targets were converted into gene names through the Uniprot database (https://www. uniprot.org/).

2.3.2. Screening of Depression-Related Targets

Depression targets were retrieved by searching for "depression" in the GeneCards (https://www.genecards.o-rg/), CTD (https://ctdbase.org/), TTD (https://db.idrblab.net/), and OMIM (https://omim.org/) databases.

2.3.3. Intersection of Propofol Target Sites and Depression-Related Target Genes

The Venny 2.1.0 online mapping platform (https://bioinfogp. cnb.csic.es/tools/venny/) was used to find the intersection between the above two types of targets, obtaining potential targets of propofol in depression and creating a Venny diagram.

2.3.4. Construction of Protein-Protein Interaction Network Diagram

The intersection target genes were imported into the STRING database (https://string-db.org/, 11.5) with "Homo sapiens" as the species and a minimum interaction threshold of "medium confidence" set at 0.4. Isolated points were hidden to generate a protein-protein interaction (PPI) network diagram. The obtained data were then imported into Cytoscape 3.10.2 software, and the target values were calculated using six algorithms (betweenness centrality, closeness centrality, degree centrality, eigenvector centrality, average connectivity, and network centrality) from the CytoNCA plugin. Targets with values exceeding the median for all algorithms were selected as key targets, and a core target diagram was constructed.

2.3.5. GO Enrichment Analysis and KEGG Pathway Enrichment Analysis

The core targets were imported into the Metascape database (https://metascape.org/) for gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis. GO analysis included biological processes (BP), cellular components (CC), and molecular functions (MF). The top 10 GO analysis entries and top 20 KEGG analysis entries were selected and imported into the Microbioinformatics online mapping platform (www.bioinformatics.com.cn) for visualization.

2.3.6. Preparation of Animal Models

Mice were randomly divided into three groups of 10 each: the CON group (saline, 100 mg/kg), the LH model group (saline, 100 mg/kg), and the PRO-treated group (propofol, 100 mg/kg). After a 7-day acclimation period, the LH model was induced in the LH and PRO groups by administering 180 footshocks at 0.5 mA, lasting 5-10 seconds with an interval of 1-15 seconds, using a shuttle box daily for one week. The CON group did not receive footshocks. From the 3rd to the 7th day of modeling, mice in each group received intraperitoneal injections of propofol or saline, respectively.

2.3.7. Sucrose Preference Test

The sucrose preference test was conducted to assess anhedonia in the animals. During the test, mice were given two bottles of sucrose solution for 24 hours and then, after a 24-hour fast with no access to water, were presented with one bottle of sucrose solution and one bottle of water for 2 hours, with the proportion of sucrose solution consumed being measured. Notably, sucrose preference rates were assessed both before and after the induction of the LH model.

2.3.8. Forced Swim Test

The forced swim test was used to evaluate behavioral despair in the animals. Mice were placed in a transparent plastic cylindrical container (40 cm height, 25 cm diameter, with water at a depth of 30 cm) and observed for 6 minutes. The duration of immobility, defined as the cessation of struggling and near stillness, was recorded in the last 4 minutes.

2.3.9. Tail Suspension Test

Mice were suspended by their tails, approximately 2 cm from the tail root, using adhesive tape attached to a hanging device 50 cm above the ground, placing them in an inverted position. The cumulative duration of immobility was recorded over the last 4 minutes of the total 6-minute test period.

2.3.10. Hippocampal Tissue Harvesting and Slice Preparation

After completing the behavioral tests, mice were intraperitoneally injected with 10% chloral hydrate (10 mg/kg) the following day. Once deeply anesthetized, they underwent in vivo cardiac perfusion. The whole brain was collected for slicing after perfusion with 4% paraformaldehyde, while the hippocampus was harvested and stored at -80°C without paraformaldehyde perfusion. The whole brain was trimmed, rinsed overnight with running water, and then subjected to dehydration, clearing, wax immersion, and embedding to form wax blocks. Subsequently, slicing, mounting, picking, and baking were performed, and the prepared slices were stored at room temperature for subsequent HE staining experiments.

2.3.11. HE Staining Experiment

The prepared slices were sequentially placed in xylene, gradient alcohol, and distilled water, followed by staining with hematoxylin and eosin. After dehydration in gradient alcohol and clearing in xylene, the slices were mounted with neutral gum and observed and photographed under a light microscope.

2.3.12. Western Blot

The prepared hippocampal tissues were placed in a pre-cooled glass homogenizer and homogenized on ice with the addition of strong lysis buffer RIPA and PMSF. The homogenate was centrifuged at 12,000 r/min at 4°C for 20 minutes. Protein loading buffer was added to the supernatant, which was then mixed by low-speed centrifugation and boiled for 10 minutes. Additionally, a portion of the supernatant was reserved for protein concentration determination.

SDS-PAGE gels were prepared according to the manufacturer's instructions, and the denatured protein samples were injected into the lanes for electrophoresis and membrane transfer. The PVDF membrane was then blocked, incubated with primary and secondary antibodies, and finally developed with ECL chemiluminescent solution in a developer to detect and save the results.

2.3.13. Statistical Analysis

Experimental results are presented as mean ± standard error of the mean (M±SEM). One-Way ANOVA was performed using SPSS 22.0. If homogeneity of variances was assumed, Bonferroni post-hoc tests were conducted; otherwise, Tamhane post-hoc tests were used. Differences were considered statistically significant at $P < 0.05$ (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$; #: $p < 0.05$, ##: $p < 0.01$, ###: $p < 0.001$).

3. Experimental Results

3.1. Venny Analysis of Propofol and Depression Targets

Using the Swiss Target prediction, Super-pred, SEA, and Drugbank databases, we obtained 107, 73, 27, and 36 targets for propofol, respectively. After deduplication, a total of 214 targets were identified. For depression-related targets, we retrieved 1467, 3949, 620, 161, and 276 targets from the CTD, GeneCards, OMIM, TTD, and Drugbank databases, respectively, yielding a total of 5713 unique targets after deduplication. A Venn diagram (Figure. 1A) was created using the online tool Venny 2.1.0, revealing 150 overlapping target genes, which are hypothesized to be potential targets for propofol in the treatment of depression.

3.2. Analysis of PPI Network and Core Target Interaction Network for Propofol's Targets in Depression

The 150 overlapping targets were imported into the STRING database to generate a protein-protein interaction (PPI) network (Figure. 1B). To further understand the interactions among these targets, the data were imported into Cytoscape 3.10.2 to construct a core target interaction network (Figure. 1C). The top 10 potential core target genes for propofol's action on depression were identified as ALB, NFKB1, ESR1, EGFR, HSP90AB1, MAOB, GABR1, GABBR2, GABRB2, and CYP1A1.

3.3. GO Enrichment Analysis and KEGG Pathway Enrichment Analysis

To further elucidate the biological functions of the potential target genes of propofol in depression, GO functional and KEGG pathway enrichment analyses were performed. The GO enrichment analysis results (Figure. 1D) showed that the biological processes of the target genes were concentrated in chemical synaptic transmission, synaptic and trans-synaptic signaling, and regulation of postsynaptic membrane potential. The cellular components involved mainly included GABA-A receptor complex, postsynaptic membrane, and postsynapse. The molecular functions of the target genes primarily involved neurotransmitter receptor activity, GABA receptor activity, and extracellular ligand-gated monoatomic ion channel activity (Figure. 1E). KEGG enrichment analysis identified 131 pathways, and the top 20 pathways based on gene count and p-value were selected to create a bubble plot (Figure. 1F). The main signaling pathways involved included Neuroactive ligand-receptor interaction, Morphine addiction, Retrograde endocannabinoid signaling, Calcium signaling pathway, Chemical carcinogenesis - receptor activation, Nicotine addiction, GABAergic synapse, and Serotonergic synapse.

3.4. Effects of Propofol on Depressive-like Behavior

The sucrose preference test revealed (Figure. 2A) that there were no differences in sucrose preference levels among the groups before modeling, indicating a high degree of homogeneity conducive to the experiment. After modeling, the sucrose preference rate in the LH group was significantly lower than that in the CON group ($p < 0.001$), while the PRO group showed a significantly higher level than the LH group ($p < 0.001$) (one-way ANOVA, $F_{(2, 27)} = 32.656$, $p < 0.001$). This validated the successful induction of depressive-like phenotypes using the learned helplessness model and demonstrated the improvement effect of propofol on the decreased sucrose preference rate in depressed mice. In the tail suspension test and forced swimming test (Figure. 2B, 2C), the immobility time of LH mice was significantly longer than that of the CON group ($p < 0.001$, $p < 0.01$), while the PRO group showed a significant reduction in immobility time after propofol treatment, which was significantly shorter than that of the LH group ($p < 0.001$, $p < 0.05$) (one-way ANOVA, $F_{(2, 27)} = 54.241$, $p < 0.001$; $F_{(2, 27)} = 22.68$, $p < 0.001$).

3.5. Effects of Propofol on Neurons in the Hippocampal Region

HE staining results (Figure. 2D) showed that hippocampal neurons in the CON group were neatly arranged with full and round nuclei and clear chromatin. In contrast, neurons in the LH group, especially in the CA3 and DG regions, showed a decrease in number, loose arrangement, and the presence of numerous pycnotic nuclei with deep staining and blurred boundaries, indicating neuronal necrosis. However, the study found that propofol could significantly reverse these pathological changes. Visual inspection revealed a reduction in the number of necrotic neurons in the CA3 and DG regions of the PRO group, restoring the normal state of neurons to some extent.

3.6. Effects of Propofol on mGluR5 Protein Expression

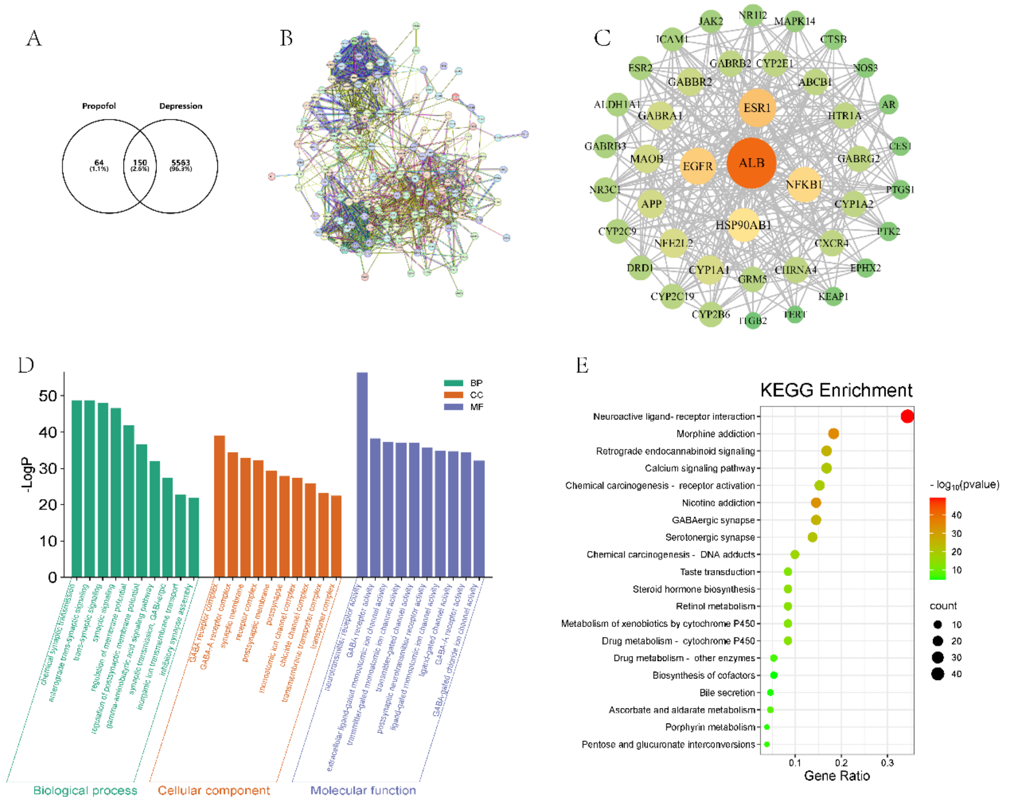

Fig 1. Results of propofol on Network pharmacology. (A) The venny diagram. (B) The PPI diagram of intersection targets. (C) The diagram of core intersection targets. (D) The diagram of GO function enrichment analysis. (E) The diagram of KEGG pathway enrichment analysis.

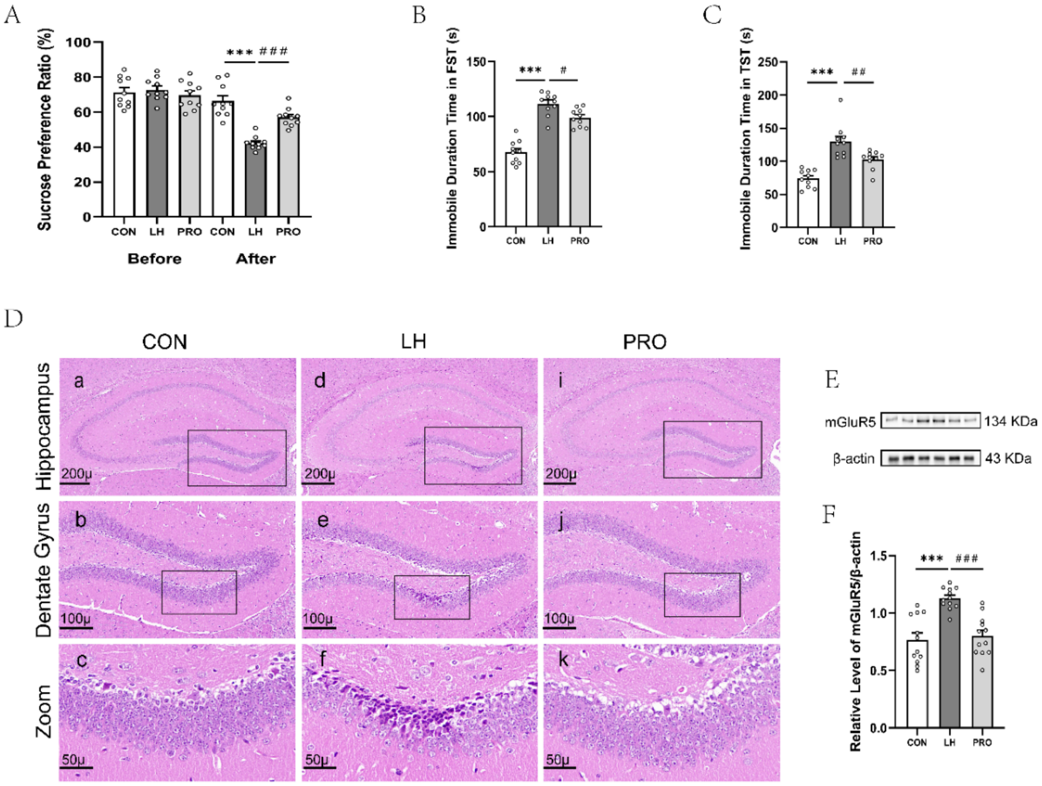

Fig 2. Results of animal experiments. (A) The sucrose preference percentage in the SPT. (B) Duration of immobility in the FST, n = 10 in every group. (C) Duration of immobility in the TST, n = 10 in every group. (D) The representative photographs of HE stained in hippocampus and dentate gyrus, n = 10 in every group. Scar bar = 200 μm in the above three figures, scar bar = 100 μm in the middle three figures, scar bar = 50 μm in the below three figures. (E) Representative bands of mGluR5 proteins. (F) The expression values of mGluR5 and it is normalized with β-actin, n = 4 in every group.

All data are presented as Mean ± SEM. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$ comparison between the LH group and the CON group; #: $p < 0.05$, ##: $p < 0.01$, ###: $p < 0.001$comparison between the PRO group and the LH group.

Western blot analysis showed the expression levels of mGluR5 protein in hippocampal neurons (Figure. 2E, 2F). Compared with the CON group, the relative expression level of mGluR5 in the LH group was significantly increased ($p < 0.001$). However, compared with the LH group, the relative expression level of mGluR5 in the PRO-treated group was significantly decreased ($p < 0.001$) (one-way ANOVA, $F_{(2, 57)} = 30.915$, $p < 0.001$).

4. Discussion

In recent years, the incidence of depression has risen significantly, with a global patient population exceeding 350 million, posing a pressing public health issue. Despite the complex and incompletely understood pathogenesis of depression [8], pharmacological therapy remains the primary treatment for moderate to severe depression. However, traditional antidepressants have relatively low cure rates, making the development of novel, safe, and efficient antidepressants particularly crucial. In 2019, Esketamine was approved by the United States Food and Drug Administration (FDA) for the treatment of depression [9], opening a new perspective for researchers as anesthetics may emerge as novel antidepressants.

Propofol, a widely used anesthetic and a GABA-A receptor antagonist, significantly enhances its inhibitory function by specifically acting on GABA-a receptors and promoting chloride ion (CI-) influx [10]. As research progresses, scholars have discovered that propofol exhibits neuroprotective effects such as reducing oxidative stress, inhibiting cellular apoptosis, and anti-inflammatory properties [11]. It can significantly improve the Hamilton Depression Rating Scale scores of patients with refractory depression and rapidly alleviate depressive symptoms [5]. Furthermore, animal experiments have found that propofol acts on dopamine transporters, regulating dopamine levels in the synaptic cleft, thereby effectively alleviating anhedonia symptoms [6]. Huang Zhili et al. revealed the potential role of glutamatergic neurons during propofol anesthesia. They found that during propofol anesthesia induction, the excitability of glutamatergic neurons in the paraventricular thalamus (PVT) sharply decreased during loss of consciousness and significantly increased during consciousness recovery [12], suggesting that glutamatergic neurons may be one of the key regulatory targets of propofol's antidepressant effects. Despite the immense potential of propofol in treating depression, related research is still relatively scarce.

To delve deeper into the potential mechanisms of propofol in treating depression, this study utilized network pharmacological methods to screen out 42 core target genes closely related to propofol's antidepressant effects, among which the GRM5 gene (encoding the metabolic glutamate receptor 5 protein, mGluR5) caught our attention. mGluR5 plays a crucial role in the development of various psychiatric disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, and anxiety disorders [13]. Further, Gene Ontology (GO) analysis revealed that the biological processes and cellular components regulated by propofol's target genes primarily focus on synapses, while the molecular functions are mostly related to neurotransmitters and receptor ligands. This finding resonates with the results of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, where the Neuroactive ligand-receptor interaction pathway was the most enriched, further emphasizing the key role of neurotransmitter receptors in propofol's antidepressant mechanism. Combining previous research on propofol's effects on glutamatergic neurons, this study focused on mGluR5 as a potential target and explored its specific role in propofol's antidepressant effects.

Due to its good reliability and validity, the Learning Helplessness model (LH) has become an important tool for screening antidepressants in recent years. This model exposes animals to unavoidable aversive environments, simulating the development of human depression, and assesses learned helplessness through escape failure rates. Animal experiments showed that C57 mice exhibited decreased sucrose preference and increased immobility time after seven consecutive days of footshock. These changes were significantly reversed after propofol treatment, not only validating the successful establishment of the depression model but also demonstrating propofol's effectiveness in improving depressive-like behaviors in mice. Hippocampal neuronal damage is considered the physiological basis of depression [14]. This study found that neuronal necrosis was exacerbated in the LH group but improved in the propofol-treated group, indicating that propofol reduced hippocampal neuronal necrosis.

In recent years, glutamatergic dysfunction has garnered extensive attention in the field of neurological disorders [15,16,17,18]. Researchers have discovered that mGluR5 is involved in synaptic transmission and regulates synaptic plasticity during the rapid antidepressant effects of ketamine [19]. mGluR5 is widely distributed in the brains of humans and rodents, including the cerebral cortex, hippocampus, olfactory bulb, striatum, and thalamus. This receptor is primarily located on the postsynaptic membrane but also exists on the presynaptic membrane and in astrocytes. mGluR5 initiates classical signaling pathways by coupling with Gαq/11 proteins, thereby regulating cellular activities such as membrane receptor activity, gene transcription, and protein synthesis. Additionally, it can affect synaptic plasticity by recruiting β-arrestin [20]. On the postsynaptic membrane, mGluR5 regulates the internalization of AMPA receptors (AMPARs) through various mechanisms, thereby mediating long-term depression (LTD). Currently, multiple studies have confirmed that mGluR5 is a potential therapeutic target for central nervous system disorders [21]. Building on this, our study further found that under depressive conditions, the relative expression level of mGluR5 in the hippocampus was higher than normal. However, after propofol treatment, the expression level of mGluR5 returned to normal. This finding suggests that propofol may reduce hippocampal neuronal necrosis by downregulating mGluR5 expression, thereby alleviating depressive-like behaviors.

However, this study has some limitations, such as not measuring escape failure rates to verify the validity of the LH model, a relatively small experimental sample size, and a lack of direct verification of GRM5 expression at the genetic level. These shortcomings need to be addressed in future research.

In summary, this study preliminary explores the potential mechanisms of propofol in treating depression through an integrated approach encompassing network pharmacology, animal experiments, and molecular biology experiments. Experimental results indicate that propofol may ameliorate depressive symptoms by downregulating the expression of mGluR5 and reducing hippocampal neuronal necrosis. In the future, we will delve deeper into the specific mechanisms by which mGluR5 contributes to the antidepressant effects of propofol, aiming to provide novel strategies and methodologies for the treatment of depression.

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