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Case Control Study
Cognitive dysfunction in schizophrenia patients caused by down-regulation of γ-aminobutyric acid receptor subunits

Chen X et al. GABA receptor subunits in schizophrenia
Abstract

BACKGROUND
The expression pattern of gamma aminobutyric acid (GABA) receptor subunits are commonly altered in patients with schizophrenia, which may lead to nerve excitation/inhibition problems, affecting cognition, emotion, and behavior.

AIM
To explore GABA receptor expression and its relationship with schizophrenia and to provide insights into more effective treatments.

METHODS
This case-control study enrolled 126 patients with schizophrenia treated at our hospital and 126 healthy volunteers who underwent physical examinations at our hospital during the same period. The expression levels of the GABA receptor subunits were detected using 1H-magnetic resonance spectroscopy. The recognized cognitive battery tool, the MATRICS Consensus Cognitive Battery, was used to evaluate the scores for various dimensions of cognitive function. The correlation between GABA receptor subunit downregulation and schizophrenia was also analyzed.

RESULTS
Significant differences in GABA receptor subunit levels were found between the case and control groups ($P < 0.05$). A significant difference was also found between the case and control groups in terms of cognitive function measures, including attention/alertness and learning ability ($P < 0.05$). Specifically, as the expression levels of GABRA1 ($\alpha 1$ subunit gene), GABRB2 ($\beta 2$ subunit gene), GABRD ($\delta$ subunit), and GABRE ($\varepsilon$ subunit) decreased, the severity of the patients’ condition increased gradually, indicating a positive correlation between the downregulation of these 4 receptor subunits and schizophrenia ($P < 0.05$). However, the expression levels of GABRA5 ($\alpha 5$ subunit gene) and GABRA6 ($\alpha 6$ subunit gene) showed no significant correlation with schizophrenia ($P > 0.05$).
CONCLUSION
Downregulation of the GABA receptor subunits is positively correlated with schizophrenia. In other words, when GABA receptor subunits are downregulated in patients, cognitive impairment becomes more severe.

Key Words: Cognitive function; Schizophrenia; Downregulation; Gamma-aminobutyric acid receptor subunits; Correlation

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Core Tip: The levels of gamma-aminobutyric acid (GABA) receptor subunits differ between the brains of patients with schizophrenia and those of healthy individuals. Patients with schizophrenia show cognitive impairments due to problems with attention, memory, social cognition, and executive functions. Furthermore, downregulation of the GABA receptor subunits GABRA1, GABRB1, GABRD, and GABRE is positively correlated with declining cognitive function in schizophrenia patients. No significant correlation was found between the subunit expression levels of GABRA5 and GABRA6.

INTRODUCTION
Schizophrenia is a complex and devastating genetic psychiatric disorder worldwide, with high relapse and disability rates and a lifelong prevalence of 1%[1]. It is primarily characterized by disturbances in perception, thought, emotion, and behavior, with discoordination between the environment and mental activities[2]. It often begins in early adulthood, showing a slow and protracted course[3]. Some patients may experience a cognitive decline, which not only causes great suffering to
the patients and their families, but also imposes a heavy economic burden on society.

Schizophrenia has complex clinical features, including positive (delusions, hallucinations, and thought disorders) and negative symptoms (blunted affect and social withdrawal)[4]. Cognitive impairment, including attention, working memory, executive function, and social cognition, is a core symptom that includes both the psychological and social aspects of cognition[5]. There is a strong correlation between cognitive impairment and long-term outcomes in patients with schizophrenia, as cognitive impairment appears before other psychiatric symptoms[6]. Therefore, cognitive function can be used to predict disease progression and treatment response to treatment[7]. In recent years, patients with cognitive impairment have received increasing attention.

Gamma aminobutyric acid (GABA) is a primary inhibitory neurotransmitter[8], found in approximately 50% of central synapses, which plays an important role in controlling neuronal excitability[9]. In addition to its distribution in various parts of the brain, GABA is associated with a variety of higher brain functions such as attention, working memory, emotions, and motor inhibition. The hypothesis of GABA deficiency in schizophrenia has been established over the past 30 years[10]. In 1972, Roberts proposed, for the first time, a correlation between schizophrenia and GABA system deficiency through his study on the interaction between GABA and DA in the basal ganglia[11]. Based on this, other researchers have established a theory of the interactions between GABA and dopamine in the striatum and marginal system, suggesting a weakened inhibitory effect of GABA on dopamine activity, leading to abnormal behavior[12]. Numerous studies have implicated the GABAergic neurotransmitter system in the pathogenesis of schizophrenia, according to numerous studies[13].

The association between GABA receptor gene clusters and schizophrenia has become a popular research topic in recent years[14]. Currently, several genes related to the GABA hypothesis of schizophrenia have received increasing attention, including GABRA1 (α1 subunit gene), GABRB2 (β2 subunit gene), GABRA5 (α5 subunit gene), GABRA6 (α6 subunit gene), GABRD (δ subunit), and GABRE (ε
This study aimed to investigate the relationship between schizophrenia and the downregulation of GABA receptor subunits and to analyze how GABA receptor subunit expression levels correlate with schizophrenia symptoms and severity.

**MATERIALS AND METHODS**

*General information*

Data from 196 patients with schizophrenia who were admitted in our hospital from March 2022 to August 2023 were collected retrospectively. A total of 126 patients were selected as the case group based on the inclusion and exclusion criteria, while 126 healthy volunteers matched for age, sex, and education level, who underwent physical examination at our hospital in the same time period were randomly selected as the healthy control group. Data on age, sex, body mass index (BMI), education, living environment, type of schizophrenia, Brief Psychiatric Rating Scale (BPRS) score, smoking history, drinking history, and complications were collected for both groups.

*Inclusion and exclusion criteria*

The inclusion criteria for schizophrenia patients were:

1. Patients diagnosed with schizophrenia in accordance with the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; (2) Age 18-50 years, with no abnormalities in a routine blood examination; and (3) The main type of schizophrenia was the paranoid type. Exclusion criteria were as follows: (1) Patients with diabetes, thyroid disease, hypertension, cardiovascular disease, or other diseases that could adversely affect their microbiota; (2) Recent diarrhea and pregnancy or breastfeeding; and (3) Over one month of olanzapine, aripiprazole, quetiapine, and haloperidol administration.

The inclusion criteria for healthy controls were as follows: (1) No mental illness; (2) 18-50 years old; and (3) Primary school education or above, able to understand the research content. The exclusion criteria were:

1. Mental retardation or other serious mental disorders; (2) Organic brain or other serious somatic diseases; (3) History of drug or alcohol abuse; and (4) Mental retardation.
Detection of GABA receptor subunit levels

Blood samples were collected from patients with schizophrenia and healthy controls to determine the expression levels of GABA receptor subunits. The expression levels of GABA receptor subunits were detected using 1H-magnetic resonance spectroscopy (1H-MRS), at each visit, using the same 1H-MRS pulse sequences and equipment. By comparing the differences in GABA receptor subunit expression levels between patients with schizophrenia and healthy controls, further analyses were conducted to determine their relevance to schizophrenia. Additionally, the relationship between GABA receptor subunit expression levels and disease progression was analyzed based on the severity of patients' symptoms.

Cognitive function scores

The first step in assessing the cognitive function scores was to determine whether patients were conscious. The severity of consciousness impairment was evaluated using the MATRICS Consensus Cognitive Battery (MCCB). MCCB Data Quality Assurance was assured by ensuring that each tester who interacted with the patients was trained in the administration and scoring of the MCCB through video and group sessions. If the patient was conscious, cognitive dysfunction was assessed using the BPRS[20]. Examination results can be used to determine whether patients have cognitive dysfunction and to further assess their cognitive function.

Statistical analysis

Statistical software (SPSS 26.0) was used to analyze the data. Continuous data is represented as the mean ± SD, and comparisons were conducted using the t-test. Categorical data is represented in the form of \( n (%) \), and comparisons were made using the \( \chi^2 \) test. Statistical significance was set at \( P < 0.05 \).

RESULTS

Comparison of baseline data results
As shown in Table 1, both the case and control groups were demographically and clinically similar. Baseline data, including age, sex, BMI, living environment, comorbidities, and years of education, did not show statistically significant differences ($P > 0.05$) between the two groups. A flowchart of the study is shown in Figure 1.

Comparison of GABA receptor subunit expression levels
As shown in Table 2, in contrast to healthy controls, patients with schizophrenia showed downregulated expression of GABA receptor subunits, which correlated with the risk of schizophrenia. In schizophrenia patients, GABRA1, Gabrb2, GABRD, and GABRE expression levels were significantly lower than those in the healthy control group ($P < 0.05$), whereas the expression levels of the GABRA5 and GABRA6 subunits were not significantly different from those in the healthy control group ($P > 0.05$).

Comparison of cognitive scores
Figure 2 shows a comparison of cognitive scores between the two groups. The case group scored significantly lower than the healthy control group ($P < 0.001$) in all four cognitive domains. The ability to process information quickly, maintain working memory, learn words, and solve problems is a part of the cognitive process. A significant difference was observed between the two groups in the visual learning domain of visual learning ($P = 0.026$). However, there were no significant differences in the attention/alertness domains ($P = 0.73$).

Correlation analysis between downregulation of GABA receptor subunits and cognitive behavior in patients with schizophrenia
In this study, we examined the correlation between four GABA receptor subunits, with significant differences between the two groups of patients, and six cognitive domains of the MCCB (ability to process information efficiently, be attentive, maintain working memory, learn words, acquire visual perception, reason, and
solve problems). In healthy controls, there was no correlation between the downregulation of GABA receptor subunits and cognitive function ($P > 0.05$).

**Correlation analysis of GABA receptor subunit downregulation and information processing speed**

Table 3 shows a positive correlation between information processing speed and the downregulation of the four receptor subunits in schizophrenia patients, with correlation coefficients for GABRA1 ($r = 0.871$, $P = 0.023$), GABRB2 ($r = 0.731$, $P = 0.016$), GABRD ($r = 0.641$, $P = 0.032$), and GABRE ($r = 0.543$, $P = 0.018$).

**Correlation analysis of GABA receptor subunit downregulation and verbal learning**

As shown in Table 4, GABRA1, GABRB2, GABRD, and GABRE were not significantly correlated with word learning ($P > 0.05$) and only GABRA1 was downregulated ($r = 0.734$, $P = 0.023$).

**Correlation analysis of GABA receptor subunit downregulation and working memory**

As shown in Table 5, the downregulation of GABRA1 ($r = 0.467$, $P = 0.047$) and GABRB2 ($r = 0.734$, $P = 0.023$) was significantly positively correlated with working memory, while GABRD and GABRE were not correlated ($P > 0.05$).

**Correlation analysis of GABA receptor subunit downregulation and attention/vigilance visual learning**

As shown in Table 6, only the GABRE ($r = 0.532$, $P = 0.038$) was associated with attention/vigilance in visual learning. GABRA1, GABRB2, and GABRD levels were positively correlated ($P > 0.05$).

**Correlation analysis of GABA receptor subunit downregulation and reasoning and problem solving**
As shown in Table 7, GABRB2 \( (r = 0.992, P = 0.098) \), GABRD \( (r = 1.386, P < 0.001) \), and GABRE \( (r = 0.747, P = 0.004) \) were positively associated with reasoning and problem solving, whereas GABRA1 and GABRA1 were not correlated \( (P > 0.05) \).

**Correlation analysis of GABA receptor subunit downregulation and social cognition**

As shown in Table 8, GABRB2 and GABRE were not significantly correlated with social cognition \( (P > 0.05) \). However, GABRA1 \( (r = 0.871, P = 0.006) \) and GABRD were significantly downregulated \( (r = 0.752, P = 0.049) \).

**DISCUSSION**

In schizophrenia, a person’s senses, emotions, and behaviors are chronically and severely affected\(^{[21]}\). Individuals with schizophrenia have impaired ability to distinguish reality from imagination\(^{[22]}\). It may be difficult for them to engage in normal social behaviors because of their slow responses and behavioral withdrawal. Medical professionals classify schizophrenia as a disorder rather than a disease by medical professionals\(^{[23,24]}\). Most cases occur in young or primed individuals. It includes physical, mental, emotional, and behavioral disorders; however, the patient has no evidence of coma or mental retardation\(^{[25,26]}\). The pathogenesis of schizophrenia is complex and various hypotheses have been proposed. Recent studies have gradually shifted classical focus from the dopamine hypothesis to the GABA hypothesis. Signal transmission between most nerve cells in the central nervous system is primarily mediated by glutamate excitation and GABA inhibition model\(^{[27]}\). GABA is produced from glutamate under the action of glutamate decarboxylase, and is abundantly expressed in the central nervous system\(^{[28]}\). Cl\(^-\) are pumped out through the Na\(^+\)/K\(^+\)/Cl\(^-\) pump transporter, which reduces the intracellular Cl\(^-\) concentration and causes the hyperpolarization of neurons. Failure to maintain the glutamate-GABA balance may be related to schizophrenia, epilepsy, and anxiety\(^{[29]}\). Glutamate-GABA regulates the neuronal excitation-inhibition balance, which can cause neurodegenerative diseases and cognitive impairment\(^{[30]}\). Reversing GABA imbalance, inhibiting the activation of the nuclear factor kappa-
light-chain-enhancer of activated B cells signaling pathway, and inhibiting the release of interleukin-6 and tumor necrosis factor-alpha can improve cognitive impairment\[^{31}\].

Patients with schizophrenia often experience cognitive impairments, such as difficulty integrating information, memory loss, and difficulty paying attention. Most individuals with cognitive dysfunction further experience memory decline as a primary symptom\[^{32}\]. In addition, schizophrenia impairs executive function, visuospatial ability, comprehension, and numeracy. Age affects both general and social cognition\[^{33}\]. The incidence of cognitive dysfunction increases with the aging population grows\[^{34}\]. Several clinical studies have demonstrated a correlation between schizophrenia and cognitive function. Interventions targeting cognition, emotions, and social aspects have shown promising results\[^{35}\]. This study observed a substantial decline in various cognitive aspects of patients with schizophrenia. Compared to healthy individuals, we observed impairments in learning, memory, fine motor skills, social cognition, working memory, category fluency, information processing, and kinetic energy. These results suggest an association between cognitive function and schizophrenia, similar to the results of the above study.

In addition, this study found that the downregulation of the GABA receptor subunit strongly affects schizophrenia symptoms and the risk of development. This finding supports the important role of the GABA system in the pathogenesis of schizophrenia, which is consistent with previous studies\[^{36}\]. GABA is one of the most important inhibitory neurotransmitters in the central nervous system and plays a neuroregulatory role by binding to its receptors\[^{37}\]. Changes in the expression of GABA receptor subunits may affect the inhibitory effect on neurons, leading to a variety of symptoms in patients with schizophrenia. According to these results, the downregulation of GABRA1, GABRB2, GABRD, GABRE, and other subunits may affect GABA receptor function, thereby affecting neuronal inhibitory effects\[^{38}\]. Such changes may promote neuronal instability, leading to abnormalities in thinking, emotions, and behavior in people with schizophrenia. In addition, the expression levels of GABA receptor subunits may also be influenced by environmental factors,
such as drugs, diet, and stress, which may also be involved in the pathogenesis of schizophrenia.

Limitations
This study has several limitations. Firstly, we only explored the correlation between GABA receptor subunits and schizophrenia in terms of gene expression, and the small sample size led to genetic analysis being the only method used to determine the results. Therefore, our study is only in the initial stages of exploring the relationships between genetic alterations. More comprehensive studies on these genes are needed to determine their exact roles in schizophrenia. Furthermore, other possible factors (such as environmental factors and nerve cell apoptosis, etc.) were not investigated. The pathogenesis of schizophrenia can be understood better by examining the effects of various factors. Further research is required to determine the interactions between different GABA receptor subunits and their effects on schizophrenia.

CONCLUSION
In conclusion, this study found that the downregulation of GABA receptor subunits is closely related to the risk and symptom severity of schizophrenia, providing a new perspective to further understand the pathogenesis of schizophrenia. Future studies are needed to further investigate the abnormal expression levels and function of GABA receptor subunits and the relationship between GABA receptor subunits and environmental factors, nerve cell apoptosis, and other factors to reveal the pathogenesis of schizophrenia more comprehensively. At the same time, the development of therapeutic strategies targeting GABA receptor subunits also needs further research and practice. Overall, the results of this study suggest that the downregulation of GABA receptor subunits is closely associated with the risk of onset and symptom severity in schizophrenia. These findings contribute to a deeper understanding of schizophrenia pathogenesis and provide a theoretical basis for developing new treatment strategies. Researchers must account for the effects of various factors on schizophrenia to better understand its pathogenesis.
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