ORIGINAL RESEARCH

Electroconvulsive Therapy Reduces Protein Expression Level of EP300 and Improves Psychiatric Symptoms and Disturbance of Thought in Patients with Schizophrenia

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Objective: Although electroconvulsive therapy (ECT) has been employed as an effective treatment strategy and to improve mental symptoms in schizophrenia (SCZ), its action mechanisms remain unclear. Our previous study found that some genes and biological pathways were closely related to ECT through genetic technology analysis, such as LTP pathway and *EP300*. This study combined with healthy controls and symptomatology analysis to further explore the changes of expression of EP300 protein in treatment and related symptoms of SCZ.

Methods: One hundred and one patients with SCZ and 45 healthy controls (HCs) were enrolled in this study. Patients with SCZ received acute courses of 6 times bilateral ECT. The peripheral blood of patients with SCZ (BECT: before ECT; AECT: after ECT) and the HCs was collected to calculate the changes of expression level of EP300 protein by enzyme-linked immunosorbent assay. The Positive and Negative Symptoms Scale (PANSS) was used to evaluate the severity of symptoms of SCZ patients and the efficiency of the ECT.

Results: There was a statistical difference of EP300 protein expression in patients with SCZ (BECT and AECT) (F = 114.5, $p < 0.05$). ECT reduced plasma expression level of EP300 protein in patients with SCZ, which was not statistically different from that in HCs (t = 4.47, $p = 0.20$). The change of the expression level of EP300 protein in patients with SCZ (BECT and AECT) has a positive correlation with reduction rate of positive symptoms (r = 0.228, $p < 0.05$) and disturbance of thought (r = 0.219, $p < 0.05$).

Conclusion: Our study suggests that the expression level of EP300 protein has a significant change in patients with SCZ treating with ECT, and EP300 may have some connections with positive symptoms and disturbance thought of patients with SCZ.

Keywords: EP300, electroconvulsive therapy, schizophrenia

Introduction

With a global prevalence of about 1%, schizophrenia (SCZ) is a common severe mental illness caused by multiple factors.[1] Antipsychotic medication therapy is the first choice in the treatment of SCZ currently, but approximately 30% of patients with SCZ do not respond to standard antipsychotic treatment.[2]

Electroconvulsive therapy (ECT) is one of the most commonly used physical therapies for acute and severe mental illness. Compared with antipsychotic medications, ECT is more effective and has more significant relief of psychiatric symptoms.[3] Studies have shown that ECT in combination with antipsychotic medication can provide rapid relief from severe psychiatric symptoms and better control of the condition.[4] Many existing studies have explored the potential

biological mechanisms of ECT in terms of gene expression, but the specific mechanisms of ECT improving psychiatric symptoms are still unknown.

The *EP300* is located at 22q13, encoding the E1A binding protein P300, a histone acetyltransferase (HAT), which can catalyze the acetylation of multiple substrates such as histone.[5] It could interact with multiple transcription factors and regulate cell growth, differentiation, cell cycle, and maintenance of genomic stability.[6,7] A study[8] identified 350 epigenetic genes associated with SCZ and intellectual disability in 108 chromosomal regions through GWAS. Eight alleles, including *EP300*, were found to be associated with cognitive impairment through analysis of alleles at these loci. Similarly, the common mutation of *EP300* (rs9607782) was found to be associated with IQ, episodic memory and attention in patients with SCZ. A mutation burden test[9] found that a different mutation load spectrum in the exon region of the *EP300* was associated with SCZ. Our preliminary study[10] identified *EP300* as a core gene through analyzing the transcriptome sequencing data in 8 schizophrenic patients (BECT and AECT) and 8 healthy controls. We subsequently confirmed this finding by comparing the mRNA expression in different brain regions in patients with SCZ and healthy controls using a public database, and found that *EP300* mRNA expression increased in patients with SCZ.[10] These findings seem to indicate that *EP300* plays an important role in the improvement of psychiatric symptoms in ECT.

This study aims to further reveal the potential mechanism of ECT in treating SCZ by comparing the plasma expression level of EP300 protein before and after ECT and its relationship with psychiatric symptoms. Our hypotheses: 1) there is a difference in the expression level of EP300 protein between patients with schizophrenia and healthy controls before ECT. 2) ECT can improve psychiatric symptoms and change the expression of EP300 protein in patients with schizophrenia. 3) There are correlations between psychiatric symptoms and the expression level of EP300 protein in patients with schizophrenia.

Materials and Methods

Participants

All the 101 patients with SCZ were recruited in the Fourth People's Hospital of Yibin, PR China. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV), Patient Edition (SCID-P)[11] were used to diagnose by two professional trained psychiatrists. All recruited patients met the enrollment criteria: 1) Age from 18 to 60 years old; 2) The severity of symptoms was accessed by the Positive and Negative Syndrome Scale (PANSS),[12] and total scores at the baseline were 60 or more; 3) ECT was not applied during the last 6 months. The exclusion criteria: The severity physical illnesses including neurologic abnormalities, brain injuries and other related diseases to induce mental symptoms, other mental disorders like dementia and fail to understand the content. The 45 HCs were all recruited from the local area by advertisement and accepted the SCID Non-Patient Edition (SCID-NP)[11] to affirm the absence of any mental disorders. All the participants were Han Chinese from the Sichuan province of China. The study was approved by the local Institutional Ethics Committee (IRB number: KY201990). All subjects provided informed consent for participation in the study.

ECT

ECT was applied to all the patients by using the Thymatron IV instrument (Somatics, Lake Bluff, IL, USA). The treatment course of ECT was 6 times, 3 times a week. The patients were evoked using bilateral electrical stimulation with an initial electrical dose that based on 2/3 of their age, and subsequent dosing was performed according to seizure morphology adequacy. EEG was used to monitor and assess the patient's seizures. The indicators for reference included the peak heart rate, EEG endpoint, average seizure energy index, etc., and all the parameters were recommended by instruction of Thymatron. Before ECT, patients received etomidate (0.16–0.2 mg/kg) to reach anesthesia status, succinylcholine (1.0 mg/kg) for muscle-relaxing and atropine sulfate (0.01 mL/kg) to reduce airway secretion by intravenous injection. The entire treatment process was monitored by professional anesthesiologists to prevent serious side effects such as asphyxia and arrhythmia. During ECT, all patients were taking antipsychotic medications and the dose of antipsychotic medications did not change.

Assessment of Clinical Symptoms

Clinical symptoms of SCZ patients were assessed using PANSS at baseline and the end of ECT. Positive and Negative Syndrome Scale (PANSS) contains 30 items including seven positive symptom items and seven negative symptom items, each scored from 1 to 7; higher scores indicate more severe symptoms.[13] The internal consistency reliability was 0.87 and the internal consistency reliability of all dimensions ranged from 0.74 to 0.90.[13] Two trained clinical psychiatrists conducted the scale evaluations. Repeated assessment analysis showed that the inter-observer correlation coefficient of the scale evaluations remained >0.8.

The reduction rate of PANSS was defined as (PANSS score at baseline − PANSS score at the end of ECT)/(PANSS score at baseline − 30) ×100%, the reduction rate of each factor of PANSS scale = (factor score before ECT − factor score after ECT)/(factor score before ECT − N) × 100%, N was the base score of each factor. The change of the expression of EP300 protein = EP300 at baseline − EP300 after ECT. The reduction rate was indicated as: >75% indicated complete remission, 50–75% indicated significant improvement[3] so response to ECT was defined as the reduction rate of PANSS ≥50% and all the patients met the criterion.

Sample Preparation

The peripheral blood of the patients with SCZ was collected before and after ECT in anticoagulation tubes. The peripheral blood of HCs was collected at the time of enrollment. After isolating the plasma of the peripheral blood samples of the patients with SCZ and HCs, all the samples were stored in −80°C immediately, which would be used for the ELISA experiments.

Elisa Experiments

The concentrations of EP300 protein in the plasma samples of 101 patients with SCZ treated with 6 times ECT were measured by the EP300 ELISA kit (ELISA Kit which produced by Jiangsu Meimian Industrial Co., Ltd) before and after ECT, and the changes of the expression of EP300 protein before and after ECT were calculated. The expression level of EP300 protein in HCs was also measured by the ELISA Kit.

Statistical Analyses

The chi-square test was used to examine the differences of age, gender, marital status and resident areas in patients (BECT&AECT) and HCs; t-test was used to examine the differences of educated years in patients (BECT&AECT) and HCs. After controlling variables such as age, gender, disease process, covariance analysis was used to examine the expression level of EP300 protein between patients (AECT) and HCs (with control the age, educated year). Repeated measure analysis of variance was used to examine the change of expression level of EP300 in patients (BECT and AECT), ROC analysis was applied to test that the expression level of EP300 protein could predict the curative effect of ECT, and all the data normality all tested by quantile–quantile plot. After controlling variables such as age, gender, and disease process, the correlation analysis was used to examine the correlation between the change of the expression level of EP300 protein in plasma and the reduction rate of PANSS scores of patients with SCZ. SPSS version 23 (IBM Corp., Armonk, NY, USA) was used to all the data analysis. $p < 0.05$ was the statistical significant threshold.

Results

Description of Clinical Information

The demographic differences and statistic results are shown in Table 1 and Table 2. There was no statistical variability between patients with SCZ and HCs in age, gender, educated years, marriage status and urban-rural differences. Among the 101 patients with SCZ, 25 patients had the family history of psychosis, 29 patients had smoking history and 6 patients had drinking history. Before ECT, they all received the antipsychotic medication treatment, and PANSS scores and other clinical information are shown in Table 3.

The Expression Level of EP300 Protein in Patients with SCZ (BECT&AECT) and HCs

The expression level of EP300 protein in patients with SCZ group plasma before ECT was 173.62 ± 30.75ng/mL, while the expression level of EP300 protein in plasma of patients with SCZ group after ECT was 117.65 ± 30.35 ng/mL. After

Table 1 Demographic and Clinical Date of Patients (BECT) and HCs

Variables	Patients with SCZ (N=101)		F	p
	BECT	AECT		
Gender (male/female)	56/45	56/45		
Age, mean	37.59± 11.37	37.59± 11.37		
Educated years	8.64±4.08	8.64±4.08		
Married (%)	56.12%	56.12%		
Urban & rural (%)	29.59%	29.59%		
Chlorpromazine equivalent during ECT(mg)	306.20±102.76	306.20±102.76		
EP300 level (ng/mL)	173.62±30.75	117.65±30.35	114.50	<0.05

Abbreviations: P, P value; BECT, before ECT; AECT, after ECT.

Table 2 Demographic and Clinical Date of Patients (AECT) and HCs

Variables	HCs (N=45)	Patients AECT (N=101)	X^2/t	P
Gender (male/female)	56/45	56/45	0.459	0.498
Age, mean	38.00±8.65	37.59± 11.37	t=0.21	0.832
Educated years	12.56±3.40	8.64±4.08		<0.01
Married (%)	20%	56.12%		<0.01
Urban & rural (%)	86.6%	29.59%		<0.01
Chlorpromazine equivalent during ECT(mg)	–	306.20±102.76		
EP300 level (ng/mL)	106.03±35.11	117.65±30.35	4.47	0.20

Abbreviations: HCs, health controls; P, P value; AECT, after ECT.

Table 3 Clinical Scale and Related Information of Patients with SCZ Before and After ECT

	Scale Score	BECT (Mean ± Standard Deviation)	AECT (Mean ± Standard Deviation)	Difference (Mean ± Standard Deviation)	P
PANSS	Total Score	72.94±17.75	45.88±11.15	27.06±17.33	<0.001
	General psychiatric symptoms	34.69±9.36	24.45±5.08	10.25±9.33	<0.001
	Positive symptoms	20.51±7.41	9.55±3.28	10.96±7.22	<0.001
	Negative symptoms	17.73±6.98	11.88±5.36	5.85±6.96	<0.001
	Lack of reaction	8.37±3.63	6.41±2.81	1.97±3.56	<0.001
	Thought disorder	10.19±4.81	5.34±1.69	4.85±4.36	<0.001
	Activating	5.20±2.36	3.52±0.87	1.68±2.24	<0.001
	Paranoid aggressive	8.51±3.75	3.98±1.83	4.53±3.75	<0.001
	Depression	7.31±3.60	6.17±2.29	1.14±3.63	<0.001

Note: Clinical scale and related information of patients with SCZ before and after ECT.
Abbreviations: ECT, electroconvulsive therapy; BECT, schizophrenia patients before ECT; AECT, schizophrenia patients after ECT; P, P value.

ECT, there was a statistically significant change on the expression level of EP300 protein in the plasma of patients with SCZ (F = 114.50, $p < 0.05$) and the difference value was 55.97 ± 42.74ng/mL (Table 1 and Table 2). The correlation analysis showed that there was no statistically significant correlation between the change of the expression level of EP300 protein and antipsychotic medications in patients (control the age, educated years) ($p > 0.05$). The expression level of EP300 protein in HC was 106.03 ± 35.11ng/mL. Besides, there was a statistically significant difference on the expression level of EP300 protein in patients with SCZ (BECT) and HCs (t = 10.48, $p < 0.05$). After the ECT, the expression level of EP300 protein in patients with SCZ reduced a lot and the reduced protein expression level was not significantly different from that of HCs (t = 4.47, $p > 0.05$) (Figure 1).
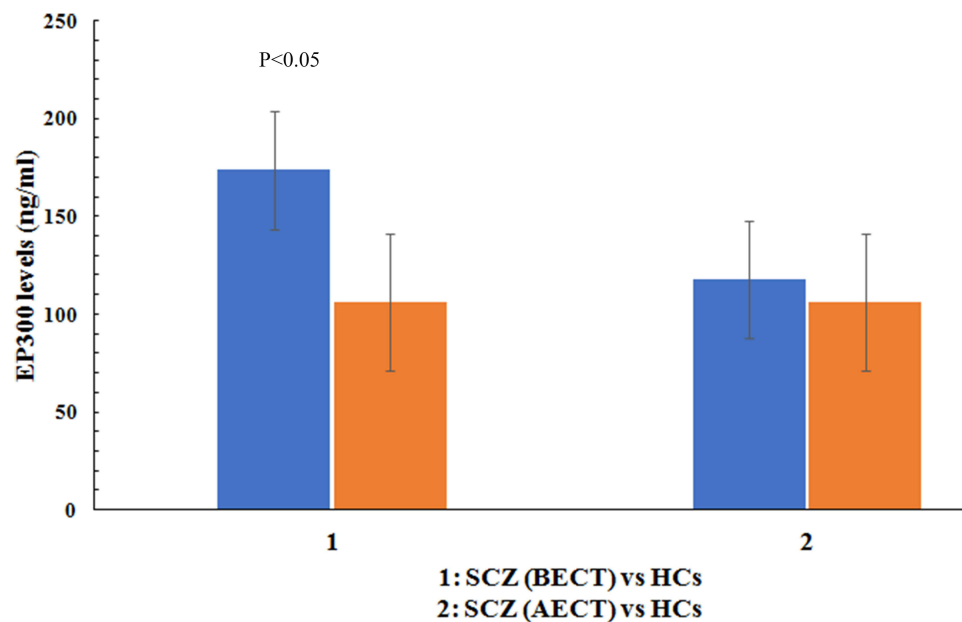
Figure 1 1: Compare the EP300 levels between SCZ patients (BECT) and HCs; 2: Compare the EP300 levels between SCZ patients (BECT) and HCs.
Abbreviations: ECT, electroconvulsive therapy; BECT, schizophrenia patients before ECT; AECT, schizophrenia patients after ECT; HCs, health controls; P, P value.

The Correlation Analysis of the Change of the Expression Level of EP300 Protein and PANSS Scores in Patients with SCZ

After controlling variables such as age, gender, disease process, the correlation analysis between the change of the expression level of EP300 protein in plasma and the reduction rate of PANSS scores of patients with SCZ showed that the change of the expression level of EP300 protein in patients with SCZ group (BECT and AECT) had a positive correlation with the reduction rate of positive symptoms ($r = 0.228$, $p < 0.05$) and the reduction rate of disturbance of thought (r = 0.219, $p < 0.05$) (Table 4). Besides, the relevant scatter plots (Supplementary Figures 1–9) also showed the same result.

Discussion

We found that *EP300* may be involved in the underlying biological mechanism of SCZ and ECT. This is the first study to show changes on the plasma expression level of EP300 protein and improvements on related psychiatric symptoms in patients with SCZ treated with ECT.

SCZ is a debilitating psychiatric disorder characterized by delusions, hallucinations, cognitive impairment, and symptoms related to social dysfunction.[14] SCZ has been linked to *EP300*. GWAS identified 108 chromosomal regions associated with SCZ risk that spanned 350 genes including EP300.[15] In addition, a study[16] on placental polygenic risk score and DNA methylation in the third trimester of pregnancy found that abnormal methylation at the *EP300* locus was associated with the incidence of SCZ, and prenatal adverse environment had a great influence on DNA methylation.

Table 4 Correlation Analysis of the Change of EP300 Protein Expression and the Reduction Rate of PANSS in Patients with SCZ

Project	Total Score	Positive Symptoms	Negative Symptoms	General Psychiatric Symptoms	Lack of Reaction	Disturbance of Thought	Irritability	Paranoid Aggressive	Depression
The change of EP300 protein expression (ng/mL)	0.061	0.228*	−0.173	0.058	−0.094	0.219*	0.107	0.022	0.058
P	0.294	0.015	0.183	0.350	0.515	0.026	0.166	0.803	0.415

Note: *P < 0.05, the PANSS scale and symptom cluster involved in the project are the reduction rate before and after ECT.

Meanwhile, SCZ is considered as a neurodevelopmental disorder, many risk genes have an impact on both early brain development and adult neurogenesis.[17,18] Some evidence[19,20] suggests that dysregulation of adult neurogenesis is associated with psychiatric disorders such as schizophrenia. A recent study[21] found that olanzapine increased neural chemorepulsant-Draxin expression in the adult rat hippocampus, which is an inhibitory axon guiding factor and local chemorepulsive glycoprotein involved in neuronal migration and neurite growth in the developing brain.[22–24] Besides, it is reported[25] that in children and adolescents with a neurodevelopmental disorder or neurodevelopmental difficulties, the onset of psychosis is likely to be characterized by positive symptoms (eg, grandiose ideas, perceptual abnormalities, disorganized communication) and disorganized symptoms (eg, odd behavior or appearance, bizarre thinking), which means that the positive symptoms of SCZ may be related to neurodevelopmental disorders. Interestingly, *EP300* was found to be closely related to neurodevelopmental disorders. Yue Li et al[26] found elevated protein synthesis of histone acetyltransferase EP300 and ubiquitination-mediated degradation of histone deacetylase HDAC1 in adult hippocampal neural stem cells (NSCs) after knockout (KO) of fragile X mental retardation (FMR1) gene in 2-month-old mice, resulting in NSC depletion, leading to cognitive impairment in adult mice. Meanwhile, reducing the activities of EP300 to rebalance histone acetylation rescued both neurogenesis and cognitive deficits in mature adult fragile X mental retardation protein (FMRP)-deficient mice.[26] As an EP300 inhibitor, curcumin also reversed impaired hippocampal neurogenesis and cognition in animals.[26] Studies found that EP300 could activate transcription of P16,[27,28] a CDK4/6 inhibitor, which could lead to cell cycle arrest and neurogenesis decline[27,29] and was associated with aging and cognitive impairment.[28] In addition, Xuelian et al[30] performed a genome-wide analysis of HDAC3 occupancy and transcriptome profiling, and found that HDAC3 repressed promyelinating programs through epigenetic silencing while coordinating with p300 histone acetyltransferase to activate myelination-inhibitory programs, which suggested that EP300 may also play an important role in inhibiting myelination in peripheral nerve cells. This study also found that elevated plasma expression level of EP300 protein in patients with SCZ, combined with the mentioned above, we speculate that increased expression level of EP300 protein may lead to neurodevelopmental disorder such as defects in proliferation and differentiation of NSCs, arrest of the cell cycle, decline of neurogenesis and abnormal myelination, so that the patients with SCZ show positive symptoms.

A previous study[31] has shown that abnormal activation in prefrontal areas engaged during working memory may be critical to disorganized thought-processing in patients with schizophrenia-like psychosis of epilepsy, which means that disturbance of thought may be related to cognitive dysfunctions. Existing studies have also suggested that EP300 is closely related to cognitive functions such as memory. Cyclic AMP-responsive element-binding protein-1 (CREB1) is involved in learning and memory.[32] The *EP300* encodes the histone acetyltransferase E1A binding protein P300 (EP300), which is a coactivator of CREB1[33] and is associated with cognitive functions such as episodic memory and memory speed.[34] In animal studies, declarative memory is associated with histone acetylation, the level of which is regulated by EP300.[35] While in human studies, EP300 plays a key role in neuronal plasticity and cognitive function, and mutations or abnormalities in *EP300* can cause Rubinstein Tabby syndrome characterized by a typical facial dysmorphism, distal limb abnormalities, and intellectual disability.[36] Therefore, we speculate that cognitive dysfunction related to EP300 abnormalities may lead to disturbance of thought in patients with SCZ.

In this study, we found that the plasma expression level of EP300 protein was significantly higher in patients with SCZ than that in healthy controls, which was consistent with our previous study finding that the EP300 mRNA expression in the cerebellum of patients with SCZ was significantly higher than that of healthy subjects in the public database, and the change of EP300 protein before and after ECT was positively correlated with the reduction rate of positive symptoms and disturbance of thought. Combined with the above mentioned, it is speculated that the overexpression level of EP300 protein in patients with SCZ leads to neurodevelopmental disorders in SCZ, resulting in cognitive impairment, delusions and other positive symptoms. ECT can reduce the expression level of EP300 protein and thus improve the disturbance of thought and positive symptoms of patients with SCZ.

There are still some limitations and deficiencies in our study. Firstly, all patients who received ECT were also taking antipsychotic medications, which may interfere with the scale results. Second, there is a lack of data on cognitive function tests in patients with SCZ, and more comprehensive cognitive testings are needed to explore the relationship

between EP300 and cognitive scores. Third, patients with SCZ who did not receive ECT were not enrolled in this study, the comparison between patients who have received and who have not received ECT could better reflect the effect of ECT on the expression of EP300 protein. Fourthly, the sample sizes between schizophrenia patients and HCs were different, which may affect the statistical results, and future studies should recruit equal numbers of schizophrenia patients and healthy controls.

Conclusion

Our study found that compared with HC, the expression level of EP300 protein in SCZ patients abnormally increased. ECT can significantly reduce the expression level of EP300 protein in plasma of patients with SCZ, and the reduced protein expression level is not significantly different from that of HC. The change of the expression level of EP300 protein has some connections with positive symptoms and disturbance thought, suggesting that ECT may play a role in treating SCZ by affecting the expression of EP300 protein.

Ethics Statement

The study was approved by the Fourth People's Hospital of Yibin Ethics Committee (IRB number: KY201990). This study was conducted in accordance with the Declaration of Helsinki. All subjects provided informed consent for all participants.

Disclosure

The authors report no conflicts of interest in this work.

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