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Association of Plasma Pro-Brain-Derived Neurotrophic Factor (proBDNF)/Mature Brain-Derived Neurotrophic Factor (mBDNF) Levels with *BDNF* Gene Val66Met Polymorphism in Alcohol Dependence

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: In a previous study, we reported that pro-brain-derived neurotrophic factor (proBDNF) was involved in the pathology of alcohol dependence, and the single-nucleotide polymorphism (SNP) Val66Met was located at the prodomain of the brain-derived neurotrophic factor gene (*BDNF*). This polymorphism has been reported to affect intracellular trafficking and activity-dependent secretion of BDNF. Our present research investigated the relationships between the *BDNF* Val66Met polymorphism and the plasma levels of proBDNF and mature brain-derived neurotrophic factor (mBDNF) in patients with alcohol dependence.

Material/Methods: The *BDNF* gene Val66Met polymorphism was genotyped in 59 alcohol-dependent patients and 37 age- and sex-matched controls, and the plasma levels of proBDNF and mBDNF were assessed by enzyme-linked immunosorbent assay in all participants.

Results: No association was found between the *BDNF* gene Val66Met polymorphism and alcohol dependence ($P>0.05$). In comparison with the control group, the level of plasma proBDNF in the alcohol-dependence group was notably increased ($Z=-2.228$, $P=0.026$), while the level of mBDNF was remarkedly decreased ($Z=-2.014$, $P=0.044$). In the alcohol-dependence group, significant associations were not found between the Val66Met polymorphisms and proBDNF and mBDNF plasma levels ($P>0.05$). The plasma level of proBDNF was positively correlated with the average daily alcohol consumption in the last month ($r=0.344$, $P=0.008$) and drinking history ($r=0.317$, $P=0.014$), while the plasma level of mBDNF had negative effects ($r=-0.361$, $P=0.005$, with the average daily alcohol consumption; $r=-0.427$, $P=0.001$, with drinking history).

Conclusions: The *BDNF* gene Val66Met polymorphism does not appear to affect the secretion of proBDNF and mBDNF in Chinese patients with alcohol dependence. Furthermore, this study reconfirmed that the plasma levels of proBDNF and mBDNF were correlated with the average daily alcohol consumption in the last month and with drinking history.

Keywords: Alcohol Abstinence • Brain-Derived Neurotrophic Factor • Polymorphism, Single Nucleotide • Protein Precursors

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Background

Alcohol is widely perceived as a neurotoxic agent that can harm physical and mental health and lead to serious damage to social function, professional function, and social adaptability. The effect of ethanol on the central nervous system is ebriety. The degree of ebriety caused by long-term alcohol consumption gradually declines, which is called tolerance. Individuals who continue to drink are considered to have alcohol dependence. Chronic and heavy alcohol exposure causes neurodegeneration and reduces the regeneration of neurons.

Brain-derived neurotrophic factor (BDNF) has an important role in the survival, growth, differentiation, and development of neurons, and it also participates in the development of substance addiction [1]. The single-nucleotide polymorphism (SNP) rs6265 is the substitution of valine for methionine (Val66Met) at the 66th codon of the *BDNF* gene, and the Met allele is considered to alter intracellular proBDNF trafficking and packaging, thereby altering the regulated secretion of mature BDNF (mBDNF) [2]. The polymorphism plays a part in the incidence of alcohol dependence [3,4]. We previously reported that the pro-brain-derived neurotrophic factor (proBDNF)/mBDNF ratio was altered in alcohol dependence [5]. However, whether the mutation of *BDNF* rs6265 leads to the change of proBDNF/mBDNF ratio in patients with alcohol dependence has rarely been studied in the Chinese Han population. ProBDNF and mBDNF have opposite biological processes [6], and we hypothesize that the mutation leads to a change in the proBDNF/mBDNF level, which results in the pathology of alcohol dependence.

Material and Methods

Study Participants

Study approval was granted by the Ethics Committee of Yunnan Mental Hospital Institution. Fifty-nine alcohol-dependent patients who were hospitalized in Yunnan Mental Hospital between September and November 2019 were recruited. Three senior psychiatrists used the Chinese version of the Mini International Neuropsychiatric Interview and the scale of alcohol use disorders identification test (AUDIT) to confirm that the patients met the diagnosis of alcohol dependence according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria. Individuals with comorbidity with other non-nicotine substance abuse or dependence or with psychiatric disorders were excluded.

The control group consisted of 37 healthy subjects who underwent routine physical examinations at the Yunnan Psychiatric Hospital during the same period. Individuals were excluded from the control group if they met the diagnostic criteria for alcohol abuse or dependence in the past or if their average daily alcohol consumption was more than 100 g during the previous 3 months. Individuals were also excluded if they met the diagnostic criteria for schizophrenia or schizoaffective disorder or for a mood disorder according to ICD-10.

All participants were from the same city (Kunming City, Yunnan Province), and demographic information was matched between the alcohol-dependence group and the control group.

BDNF Val66Met Polymorphism Genotyping

The next morning after hospitalization, 2-5 mL of peripheral blood was collected into anticoagulant tubes, and 200 µL of blood was used for genomic DNA extraction by using a Blood Genomic DNA Extraction Kit (Tiangen Biochemical Technology, Beijing, cat. no. DP348). The following primers were used:
forward: 5'-GGTGAGAAGAGTGATGACCA-3',
reverse: 5'-GCCAGCCAATTCTCTTTTTG-3'.
The PCR conditions were 95°C for 5 min; 34 cycles of 95°C for 30 s, 60°C for 30 s, and 72°C for 30 s; and 72°C for 10 min. ABI7500 was conducted for genotyping. FinchTV (https://www.ch.cam.ac.uk/computing/software/finchtv) was applied to analyze the sequence.

Determination of proBDNF and mBDNF Concentrations with ELISA

The blood samples were centrifuged at 1500 *g* for 10 min, and the plasma was frozen at -80°C for later analysis. The ELISA process was as follows [7,8]. The capture antibody (2 µg/mL, protein G-purified mouse anti-mBDNF monoclonal antibody, B34D10) was diluted in the coating buffer (50 mM carbonate), and 100 µL of capture antibody was added immediately to each well of the microplate. The microplate was incubated at 37°C for 1 h. The plate was then washed with phosphate-buffered saline 3 times. Next, 150 µL of blocking buffer (phosphate-buffered saline and bovine serum albumin) was added to each well, and the plate was again incubated for 1 h at 37°C. The standard mBDNF was diluted in a range from 2 to 0.125 ng/mL. One hundred microliters of diluted plasma was put into each well, and the plate was incubated at 37°C for 1 h. Then, the plate was washed with wash buffer 4 times. The next steps were to dilute the detecting antibody to 2.5 µg/mL in sample diluent and to add 100 µL to each well. The plate was incubated at 37°C for 1 h once more. The plate was washed 4 times with wash buffer, and the previous step was then repeated. Next, 100 µL of freshly prepared 3,3',5,5'-tetramethylbenzidine substrate was added to each well, and color was allowed to develop for 10 to 15 min. Finally, 1 N sulfuric acid was used to stop the color reaction. The absorbance at 450 nm was measured with a microplate reader (Model

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Table 1. Genotype distributions of rs6265 in alcohol-dependent patients and controls.

	N	Genotype (N, frequency%)			Allele (N, frequency%)	
		Val/Val	Val/Met	Met/Met	Val	Met
Patients	59	17 (28.81)	33 (55.93)	9 (15.26)	67 (56.80)	51 (43.20)
Controls	37	8 (21.62)	20 (54.05)	9 (24.33)	36 (48.60)	38 (51.40)
χ^2		1.46			1.21	
P		0.48			0.27	

P was calculated by Pearson chi-squared test.

Sunrise, TECAN, Germany) to determine the BDNF concentration according to the standard curve. To determine the specificity of the kit, mBDNF, proBDNF, nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) at 1 ng/mL or 0 to 20 ng/mL were added in the incubation step. The plasma level of proBDNF was determined by DuoSet human ELISA Development System (R&D, cat. no. DY3175) according to the manufacturer's instructions.

Statistical Analysis

SPSS version 19.0 (IBM, USA) was used for data analysis. The Hardy-Weinberg equilibrium was evaluated by chi-square test. The AUDIT scores and drinking life were expressed as mean±standard error (SE). The data for age, average ethanol consumption, and mBDNF and proBDNF ELISA results were expressed as median (M) plus the interquartile range (IQR [P25, P75]), and the Mann-Whitney *U* test was used to analyze the data. One-way ANOVA was used to analyze the data of comparisons among different genotypes of *BDNF* gene rs6265 and plasma proBDNF and mBDNF levels. Associations of the average daily ethanol consumption and drinking history with proBDNF and mBDNF levels were assessed using Spearman's correlation test. $P<0.05$ (2-tailed) was considered as statistically significant.

Results

Demographic and Clinical Information

A total of 59 patients with alcohol dependence were included in the study. The patients' median age was 44 (37, 49) years and ranged from 23 to 60 years old; the AUDIT score was 29.64±4.11 points (mean±SE); average alcohol consumption last month was converted to a median pure alcohol concentration of 500 (350, 600) g; duration of drinking alcohol was 20.695±1.043 years (mean±SE). The 37 cases in the control group had a median age of 38 (30, 49.5) years, ranging from 23 to 59 years. There was no statistically significant difference in age distribution between the 2 groups ($P=0.15$).

Genotyping and Linkage Disequilibrium Evaluation

There were no differences in the genotype distribution or allele frequencies of rs6265 between the patients and controls ($P>0.05$). No significant deviation was found in the analysis of the Hardy-Weinberg equilibrium.

Association Between BDNF Gene rs6265 and Susceptibility to Alcohol Dependence

Table 1 provides the allele and genotype frequencies of *BDNF* SNP (rs6265) in the alcohol-dependent patients and controls. There were no statistically significant differences between the 2 groups in genotype distributions of rs6265 ($P>0.05$).

Plasma Levels of ProBDNF and MBDNF in Patients Compared with Controls

The median plasma level of proBDNF in the alcohol-dependent patients was 508.57 (378.97, 687.87) pg/mL, and the median plasma level of proBDNF in the controls was 404.06 (319.87, 597.54) pg/mL. The plasma level of proBDNF in the alcohol-dependent patients was remarkably higher than in the control participants ($Z=-2.228$, $P=0.026$, Mann-Whitney *U* test, Figure 1A). The median plasma level of mBDNF in the alcohol-dependent patients was 241.93 (155.67, 416.54) ng/mL, and the median plasma level of mBDNF in the controls was 295.67 (216.50, 530.31) ng/mL. The plasma level of mBDNF in the alcohol-dependent patients was significantly lower than in the control participants ($Z=-2.014$, $P=0.044$, Mann-Whitney *U* test, Figure 1B).

Genotypes of BDNF Gene rs6265 and Plasma proBDNF and mBDNF Levels in Alcohol-Dependent Patients

Figure 2A and 2B illustrate the comparisons among different genotypes of *BDNF* gene rs6265 and plasma proBDNF and mBDNF levels in alcohol-dependent patients. There were 17 carriers of the GG genotype, 33 carriers of the AG genotype, and 9 carriers of the AA genotype. No significant differences were found among different genotypes of *BDNF* gene rs6265

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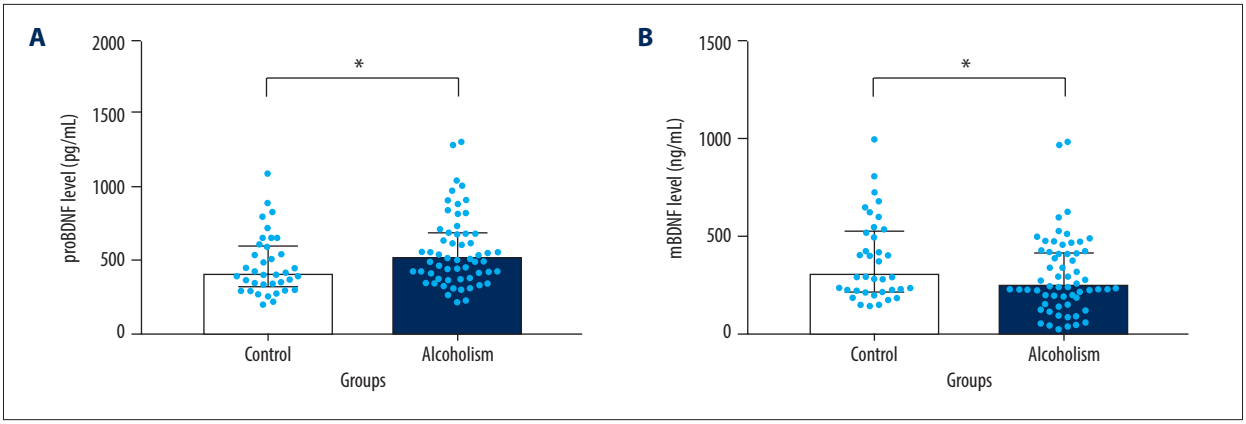

Figure 1. The plasma level of proBDNF was increased and mBDNF was decreased in the patients with alcohol dependence compared with controls. (**A**) The plasma level of proBDNF in the patients was significantly higher than in the controls (Z=-2.228, P=0.026, Mann-Whitney U test). (**B**) The plasma level of mBDNF in the patients was significantly reduced compared with the controls (Z=-2.014, P=0.044, Mann-Whitney U test). mBDNF – mature brain-derived neurotrophic factor; proBDNF – pro-brain-derived neurotrophic factor.

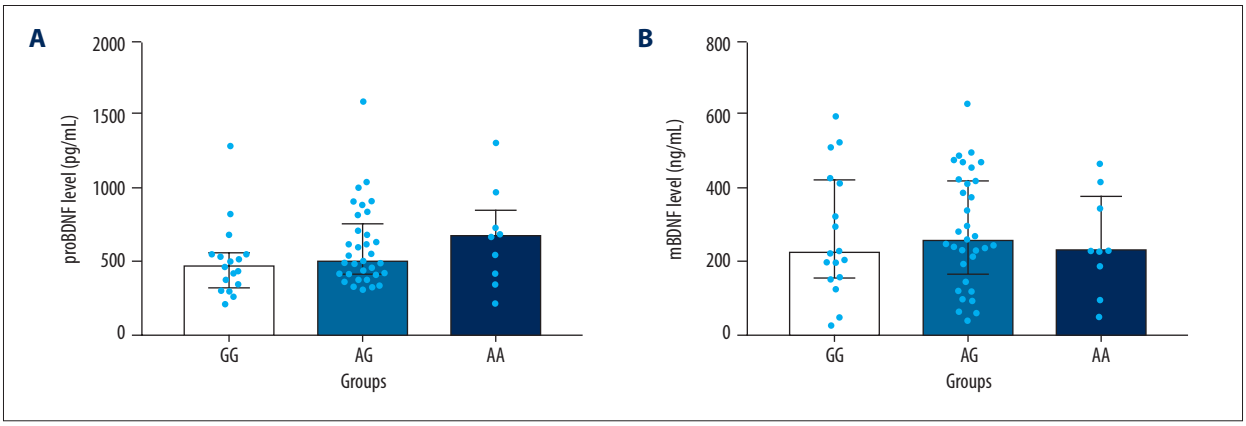

Figure 2. Comparisons between *BDNF* gene rs6265 and plasma proBDNF and mBDNF levels in alcohol-dependent patients. No significant differences were found between *BDNF* gene rs6265 and proBDNF level (**A**) or mBDNF level (**B**) in alcohol-dependent patients (One-way ANOVA, P>0.05). mBDNF – mature brain-derived neurotrophic factor; proBDNF – pro-brain-derived neurotrophic factor.

and the proBDNF level ($F_{2,56}$=1.056, P=0.3548, **Figure 2A**) and mBDNF level ($F_{2,56}$=0.229, P=0.796, **Figure 2B**) in alcohol-dependent patients (1-way ANOVA test).

Plasma proBDNF and mBDNF Levels and the Average Daily Alcohol Consumption in the Last Month in Alcohol-Dependent Patients

The plasma proBDNF level was directly correlated to the average daily alcohol consumption in the past month in the alcohol-dependent patients, as shown in **Figure 3A** (r=0.344, P=0.008, Spearman's correlation test). The plasma mBDNF level was negatively correlated with the average daily alcohol consumption in the past month (r=-0.361, P=0.005, Spearman's correlation test; **Figure 3B**).

Plasma proBDNF and mBDNF Levels and Drinking History in the Alcohol-Dependent Patients

The plasma proBDNF level in the alcohol-dependent patients was positively correlated with drinking history (r=0.317, P=0.014, Spearman's correlation test; **Figure 4A**), and the plasma mBDNF level was negatively correlated with the drinking history (r=-0.427, P=0.001, Spearman's correlation test; **Figure 4B**).

Discussion

BDNF can induce the direct differentiation of neural precursor cells, promote the proliferation of neurons, and promote the development and maturation of the nervous system. In adults, BDNF exhibits a wide range of neurotrophic and neuroprotective

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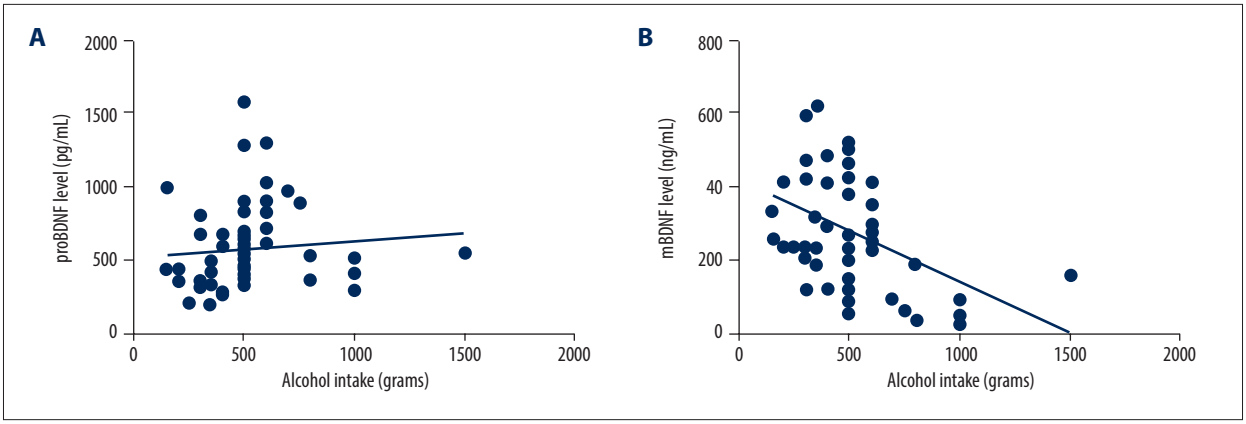

Figure 3. Correlations of plasma proBDNF and mBDNF levels with average daily ethanol consumption in the patients with alcohol dependence. Statistical analysis was performed with Spearman's correlation test. (**A**) proBDNF (r=0.344, P=0.008) had a significant positive correlation with average daily ethanol consumption. (**B**) mBDNF (r=-0.361, P=0.005) had a significant negative correlation with total alcohol consumption. mBDNF – mature brain-derived neurotrophic factor; proBDNF – pro-brain-derived neurotrophic factor.

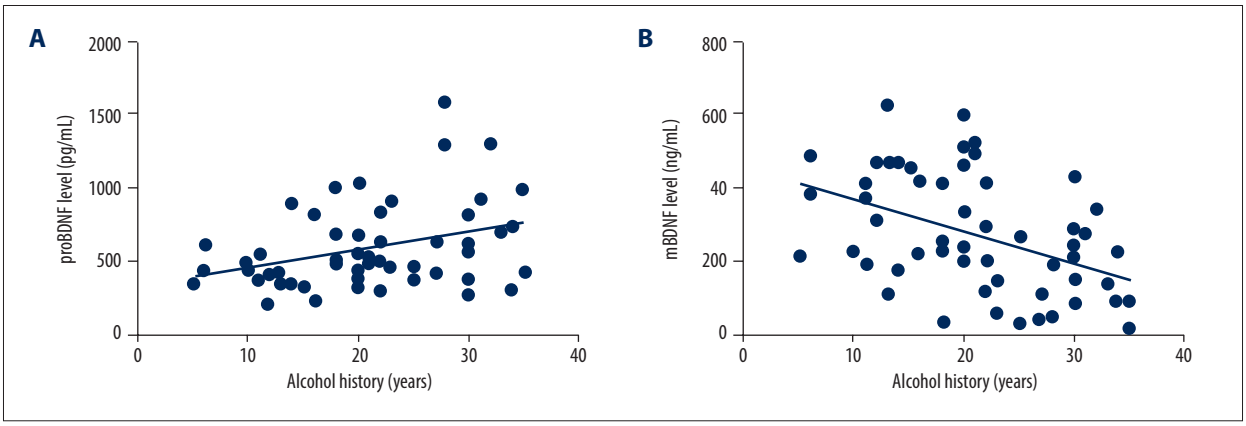

Figure 4. Correlations of plasma proBDNF and mBDNF levels with alcohol drinking history. Statistical analysis was performed with Spearman's correlation test. (**A**) proBDNF (r=0.317, P=0.014) had a significant positive correlation with average daily ethanol consumption. (**B**) mBDNF (r=-0.427, P=0.001) had a significant negative correlation with total alcohol consumption. mBDNF – mature brain-derived neurotrophic factor; proBDNF – pro-brain-derived neurotrophic factor.

roles, and it plays an active role in the survival of neurons and the maintenance of normal physiological functions. The current study showed that the level of plasma proBDNF in alcohol-dependent patients was markedly higher than in the control group and the level of plasma mBDNF was notably lower. These results suggest that in patients with alcohol dependence, long-term consumption of a large amount of alcohol activates the proBDNF/p75NTR/sortilin signaling pathway, which causes neuronal apoptosis and inhibits neuron regeneration. Some studies have shown that alcohol can interfere with the balance of multiple neural circuits, tamper with the reward circuits in the brain, and cause and maintain excessive drinking behaviors [9,10]. The formation of the proBDNF/p75NTR/sortilin complex activates c-Jun N-terminal kinase (JNK) [11], which leads in turn to neuronal apoptosis. So, the elevation of proBDNF level in alcohol-dependent patients may lead to neuronal apoptosis via the JNK pathway and potentially cause impairment of cognition and social function. The combination of mBDNF and TrkB forms a receptor dimer, which leads to the autophosphorylation of TrkB and subsequent activation of intracellular signaling cascades (including MAPK, PI3K/Akt, and Rho pathways), and plays an anti-apoptotic role [12]. More importantly, the mBDNF/TrkB complex activates GTPases to promote the synthesis of actin and the stability of microtubules required for the growth of nerve fibers [13]. To summarize, both proBDNF and mBDNF play roles in the pathophysiology of alcohol dependence through different, even opposite ways.

BDNF gene rs6265 is located in the coding axon region. It is a well-known functional polymorphism of the *BDNF* gene and has been studied extensively. Studies reported that methionine replaces valine in the *BDNF* gene Val66Met polymorphism. This

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change alters the transportation and packaging of proBDNF, resulting in a reduction in the activity-dependent secretion of BDNF in neuronal dendrites [2,14,15]. Met68BDNF mice were found to consume excessive amounts of alcohol [4,16].

In this study, we did not find that *BDNF* gene rs6265 was associated with the incidence of alcohol dependence in the Chinese Han population. This finding accorded with some studies [17,18], but it was inconsistent with others [19-21]. In their umbrella review based on more than 150 meta-analyses on substance use disorders, Lopez-Leon et al. [22] reported that the *BDNF* gene had an odds ratio higher than 2 for methamphetamine dependence, but not for alcohol dependence. Another meta-analysis showed that 8 studies on rs6265 and alcoholism were inconsistent [23], and the discrepancies were mainly caused by the differences between European and Asian races. Therefore, the role of *BDNF* gene rs6265 in alcohol dependence needs to be verified in a large sample. In the current study, we found that in the alcohol-dependent patients only, the level of proBDNF in the plasma with Met/Met (AA) genotype was slightly higher than that with Val/Val (GG) and Val/Met (AG) genotypes, while the level of mBDNF was slightly lower; however, it did not reach statistical significance. Mature BDNF was cleaved from proBDNF by furin, plasmin, and specific metalloproteases, but the levels of its cleavage enzymes were not assayed in this study. We infer that there are many factors affecting the levels of proBDNF and mBDNF. In addition to the functional polymorphisms located at the proBDNF cleavage site, changes in the enzymes under pathological conditions may have a role [24], which will be a topic in our future research.

The results also revealed that the level of proBDNF in the plasma was not only positively correlated with the average amount of alcohol consumed daily in the last month, but was also directly associated with the number of years of alcohol intake. Meanwhile, mBDNF was not only negatively correlated with the average daily alcohol consumption in the last month, but also negatively correlated with the number of years of alcohol consumption. Long-term and excessive alcohol consumption is suggested to elevate the proBDNF level and activate apoptosis cascades, which is confirmed by neuroimaging findings of volume lost in the cerebral cortex and subcortical structure, including gray and white matter atrophy, in alcohol-dependent patients. Autopsy results also revealed abnormal gray and white matter volume reduction in multiple brain regions [25,26].

Limitations

The sample size of this study was small, and only 1 polymorphism of the *BDNF* gene was detected, which limits the power to detect important associations and may bias our results.

Conclusions

In summary, the correlation between the rs6265 polymorphism of the *BDNF* gene and the incidence of alcohol dependence was not been found, and the *BDNF* gene Val66Met polymorphism did not appear to affect the secretion of proBDNF and mBDNF in Chinese patients with alcohol dependence. However, we further confirmed that the BDNF signaling pathway can be studied as a stable regulatory pathway for alcohol addiction.

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Conflicts of Interest

None.

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