Original Article

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Posttraumatic stress disorder eliminates association of *TrkB rs1187327* with HDL-C in Chinese Han adolescents

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Summary **Tropomyosin-related kinase receptor B (TrkB) has been observed to be a common player in posttraumatic stress disorder (PTSD) and the regulation of serum lipids levels. However, interplays of PTSD with TrkB on serum lipids levels have not been explored yet. This study was to investigate the interplays of PTSD and *TrkB rs1187327* on serum lipid profiles. Variants of *TrkB rs1187327* of 709 high school students were identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analyses and verified by DNA sequencing. The PTSD Checklist Civilian Version (PCL-C) was used to assess PTSD. Colorimetric methods were used to determine the serum levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and glucose. The results show that the GG homozygotes had a significantly higher level of HDL-C than the A allele carriers of *TrkB rs1187327* after the adjustment for gender, age and body mass index (BMI) (1.44 ± 0.299 mmol/L *vs*. 1.39 ± 0.266 mmol/L, $p = 0.036$). When PTSD was taken into account, the higher than the A allele carriers level of HDL-C of the GG homozygotes was observed significant after the adjustment for gender, age and BMI only in the subjects without PTSD (1.44 ± 0.293 mmol/L *vs*. 1.39 ± 0.267 mmol/L, $p = 0.030$), but not in the subjects with PTSD. These results suggest that the A allele of *TrkB rs1187327* may be associated with decreased levels of serum HDL-C in general healthy adolescents, but not in adolescents with PTSD.**

Keywords: BDNF-TrkB, SNP, lipids, PCR-RFLP

1. Introduction

Post-traumatic stress disorder (PTSD) is a prevalent, chronic and disabling anxiety disorder (*1*). It usually develops following exposures to traumatic events such as natural disasters, threatened deaths, serious injuries and sexual violence, and is characterized by an inability to extinguish fear memories (*2-4*). Evidences have been reported for a strong link between PTSD and higher prevalence of cardiovascular diseases (CVD) (*5,6*). Meanwhile, abnormalities of serum lipid profiles are the major traditional risk factors of CVD, which include increased levels of serum triglycerides (TG), total cholesterol (TC) and more widely recognized low-density lipoprotein cholesterol (LDL-C), and decreased levels of high-density lipoprotein cholesterol (HDL-C) (*7,8*). Moreover, it was found that the levels of TC, TG and LDL-C were elevated but the level of HDL-C was reduced in war veterans with chronic PTSD when compared with healthy control subjects (*9-11*). However, in other studies, no significant differences were found in the levels of serum TC, LDL-C and HDL-C between veterans with and without PTSD (*12*). The mechanisms of these discrepancies have not been elucidated yet.

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins, which can exert its functions by

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activating the tropomyosin-related kinase receptor B (TrkB) (*13*), the high affinity receptor of BDNF. It was observed that BDNF was associated with memory and learning (*14*). Decreased levels of BDNF in various brain regions have been reported to be involved in psychiatric disorders and neurodegenerative pathogeneses (*15*). Single-nucleotide polymorphisms (SNPs) at the gene of BDNF were demonstrated to be indispensable to establish genetic risk factors for the onset and development of mental disorders including PTSD (*16*). For example, the SNP of Val66Met polymorphism has been confirmed to be related with PTSD (*17*). This polymorphism was tested to be associated with impaired fear extinction that was an indispensable character of PTSD (*18*). Moreover, previous studies have demonstrated that BDNF plays an important role in the regulation of glucose and lipids metabolisms. It was revealed that the serum level of BDNF was positively correlated with the serum levels of TG, TC and LDL-C (*19-21*). On the other hand, the transgenic mice overexpressing *TrkB* gene were reported to have enhanced ability to extinct fear memories (*22*), although this effect was not confirmed by the knockout of the gene because it resulted in that mice rarely survived beyond three weeks and the rest survived mice had serious health problems (*23,24*). Furthermore, the association of TrkB with serum lipid profiles has also been revealed. It was reported that there was a decreasing trend of HDL-C level in the transgenic mice overexpressing *TrkB* when compared with the control mice (*25*). All these evidences suggest that TrkB is involved in not only the development of PTSD but also the regulation of serum lipid profiles. Exploring the interactions between PTSD and TrkB on serum lipid profiles may provide novel insights into the regulation of lipoprotein metabolisms and the pathophysiological mechanism of dyslipidemia. Therefore, we hypothesized that PTSD may affect the association of TrkB with the levels of serum lipids. To test our hypothesis in the present study, the effect of PTSD on the levels of serum lipids was analyzed in high school students with different genotypes of the *rs1187327* polymorphism at the gene of *TrkB* (*TrkB rs1187327*) 6 months after Wenchuan earthquake, a catastrophic disaster occurred on May 12, 2008. The earthquake, measuring 8.0 on the Richter scale, extended about 10 thousand km^2, destroyed about 6.5 million houses and left about 15 million people evacuated from their homes. According to the official statistics, 69 thousand people were confirmed dead and 37 thousand people injured. *TrkB rs1187327* polymorphism was selected in this study because it had been frequently studied and may have an effect on splicing or expression (*26*). In addition, studies have shown that *TrkB rs1187327* may contribute to the risk of mental diseases (*27,28*). To our knowledge, interactions between PTSD and *TrkB rs1187327* on the levels of serum lipids have not been explored before.

2. Materials and Methods

2.1. *Study population*

This study was conducted at the 6th month after the 2008 Wenchuan Earthquake in a boarding high school situated 10 kilometers away from the epicenter of the earthquake. The earthquake destroyed almost all the buildings at the school. The students lived and studied in temporary houses after the earthquake before their school was rebuilt.

The students were selected from grade 11 for this study. A total of 746 students participated in the questionnaire survey, 737 (98.8%) of the students completed the questionnaire. A total of 709 students were finally included in the study. The other students were excluded because (*i*) they did not complete all the questionnaires in the survey; (*ii*) they provided more than one answers for single-answer question, and/or no answers were chosen for any questions; (*iii*) their blood were not sampled because of personal reasons; and (*iv*) they had diseases, medications or other interferences that influenced serum lipid profiles or PTSD. The included 709 students were all Chinese Han people. All the students and their guardians provided written consents. This study was approved by the Human Ethics Committee of Sichuan University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2. *Measurements*

The measurement instrument consisted of two parts. The first part was used to assess demographic characteristics including gender, age, height and weight. Body mass index (BMI) was calculated. In the second part, the PTSD Checklist Civilian Version (PCL-C) was used to assess the symptoms of PTSD. It consists of 17 items based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (ASM-IV) criteria (*27*), with a total score from 17 to 85 (*28*). Cronbach's α coefficient of the PCL-C ranged from 0.891 to 0.894 in the present study. The score of 50 was selected as cut-off point for PTSD (*29-31*).

2.3. *DNA extraction and genotyping*

Peripheral venous blood was sampled into sterile anticoagulant tubes. Genomic DNA was extracted using Wizard Genomic DNA Purification Kit (Tiandz, China) according to the procedure provided by the manufacture. *TrkB rs1187327* was genotyped by polymerase chain reaction restriction-fragment length polymorphism (PCR-RFLP) method and verified by

Table 1. Distribution of the genotypes of *TrkB rs1187327*

Genotype	Total *n* (%)	Hardy-Weinberg *p*	Males *n* (%)	Females *n* (%)	*p*†
AA	125 (17.6)		60 (19.2)	65 (16.4)	
AG	342 (48.2)	0.987	153 (49.0)	189 (47.6)	0.401
GG	242 (34.1)		99 (31.7)	143 (36.0)	

† Males *vs*. females by Chi-Square tests.

Table 2. Prevalence of PTSD in the subjects with different genotypes of *TrkB rs1187327*

PTSD	AX			GG		
	All (%)	Males (%)	Females (%)	All (%)	Males (%)	Females (%)
With	48 (10.3)	14 (6.6)	34 (13.4)#	27 (11.2)	4 (4.0)	23 (16.1)#
Without	419 (89.7)	199 (93.4)	22 (86.6)	215 (88.8)	95 (96.0)	120 (89.3)

Data are expressed as *n* (%). #$p < 0.05$ when compared with that of the male students.

DNA sequencing. The DNA fragments containing *TrkB rs1187327* were amplified using primers of 5'-GATGTTGAGCAGGCGTGATA-3' (forward) and 5'-GCAACACACAACTTGCTGAAA-3' (reverse). DNA templates were denatured at 95°C for 5 min followed by 30 cycles consisting of denaturing at 95°C for 30 s, annealing at 56°C for 30 s and extension at 72°C for 30 s, with a final extension at 72°C for 5 min. The 341 bp PCR products were incubated with 4 units of *Eco*47I (Shanghai) at 37°C for 12 hours. The digested fragments were then separated by electrophoresis on 2% agarose gel. The separated DNA fragments were 341 bp for the AA genotype, and 245 and 96 bp for the GG genotype.

2.4. *Blood collection and serum lipids analyses*

Venous blood samples were collected between 7:00 a.m. and 8:00 a.m. after twelve-hour fasting. Enzymatic methods were used to determine the serum concentrations of TC, TG and glucose. HDL-C concentration was measured enzymatically after phosphotungstic-Mg^{2+} precipitation of apolipoprotein B-containing lipoproteins. LDL-C concentration was quantified in the semi-automated biochemistry analyzer by the polyvinyl sulfate precipitation method. All biochemical parameters were measured three times, and the average values were used for statistical analyses.

2.5. *Statistical analyses*

All the data are presented as mean ± standard deviation (SD) unless otherwise stated. The χ^2 goodness-of-fit test was performed to assess whether the genotypes of *TrkB rs1187327* were in the Hardy-Weinberg equilibrium. Chi-square tests were used to analyze the distribution of genotypes and PTSD prevalence between the male and female subjects, or PTSD prevalence between the subjects with different genotypes of *TrkB rs1187327*. One-way ANOVAs were used to evaluate the differences of serum lipid levels and the related metabolic indices in the subjects with different genotypes of *TrkB rs1187327* before the adjustment for age, gender and BMI as covariates. Analyses of covariance (ANCOVA) with age, gender and BMI as covariates were used to analyze the differences of TC, TG, HDL-C, LDL-C and glucose in subjects with and without PTSD or/and with different genotypes of *TrkB rs1187327*. Age, gender and BMI were used as covariates because impacts of these variables were observed on serum lipids concentrations (*12,32*). All statistical analyses were 2-tailed with $p \leq 0.05$ as the level of significance.

3. Results

3.1. *Distribution of the genotypes of TrkB rs1187327*

As shown in Table 1, there was no significant deviation from Hardy-Weinberg equilibrium in the distribution of the genotypes of *TrkB rs1187327* ($p = 0.987$). Moreover, no significant differences were found of the genotypes between the male and female subjects ($p = 0.401$).

3.2. *Prevalence of PTSD in the subjects with different genotypes of TrkB rs1187327*

For the further analyses, the AA homozygotes were combined with the heterozygotes and designated as the A allele carriers (AA/AG) because of the limited number. The prevalence of PTSD is shown in Table 2 for the subjects with different genotypes of *TrkB rs1187327*. There was no significant difference between the GG homozygotes and the A allele carriers in the all subjects, the male subjects or the female ones. However, the female subjects had higher prevalence of PTSD than the male subjects in both the GG homozygotes (*p*

Table 3. Anthropometric and biochemical characteristics of the subjects with different genotypes of *TrkB rs1187327*

Variables	AX, *n* = 467	GG, *n* = 242	*p*-Value	ANCOVA, *p*-Value[a]
Gender: female, *n* (%)	254 (54.4%)	143 (59.1%)	0.012	–
Age, year	16.9 ± 0.574	16.9 ± 0.613	0.370	–
BMI, kg/m^2	20.2 ± 2.21	20.4 ± 2.48	0.368	–
TC, mmol/L	3.56 ± 0.559	3.64 ± 0.600	0.178	0.178
TG, mmol/L	1.10 ± 0.419	1.14 ± 0.479	0.074	0.613
HDL-C, mmol/L	1.39 ± 0.266	1.44 ± 0.299	0.119	0.036
LDL-C, mmol/L	1.66 ± 0.476	1.68 ± 0.511	0.702	0.858
Glucose, mmol/L	5.08 ± 0.422	5.06 ± 0.460	0.374	0.619

BMI: body mass index; TG: triglycerides; TC: total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ANCOVA : analysis of covariance. [a] Analyses of covariance with the adjustment for age, gender and BMI.

Table 4. Effects of PTSD on the association of *TrkB rs1187327* with anthropometric and biochemical characteristics

Variables	Group	AX	GG	*p*-Value[a]	ANCOVA, *p*-Value[a,b]
Gender: female, *n* (%)	Control	220 (52.5%)	120 (70.8%)	0.450	–
	PTSD	34 (55.8%)	23 (85.2%)	0.260	–
Age, year	Control	16.9 ± 0.571	16.9 ± 0.608	0.459	–
	PTSD	16.9 ± 0.598	17.0 ± 0.649	0.525	–
BMI, kg/m^2	Control	20.1 ± 2.18	20.2 ± 2.31	0.870	–
	PTSD	21.0 ± 2.32	22.1 ± 3.17	0.130	–
TC, mmol/L	Control	3.54 ± 0.547	3.62 ± 0.592	0.122	0.128
	PTSD	3.72 ± 0.631	3.77 ± 0.661	0.740	0.798
TG, mmol/L	Control	1.08 ± 0.376	1.12 ± 0.447	0.030	0.351
	PTSD	1.29 ± 0.665	1.29 ± 0.671	0.890	0.277
HDL-C, mmol/L	Control	1.39 ± 0.267	1.44 ± 0.293	0.229	0.030
	PTSD	1.41 ± 0.263	1.41 ± 0.340	0.247	0.866
LDL-C, mmol/L	Control	1.65 ± 0.463	1.67 ± 0.474	0.629	0.853
	PTSD	1.72 ± 0.577	1.78 ± 0.621	0.878	0.880
Glucose, mmol/L	Control	5.09 ± 0.427	5.06 ± 0.439	0.566	0.623
	PTSD	5.00 ± 0.371	4.99 ± 0.466	0.358	0.895

[a] Comparisons of those between the GG homozygotes and the A allele carriers in the control or PTSD subjects. [b] Analyses of covariance with the adjustment for gender, age and BMI.

= 0.003) and the A allele carriers (p = 0.016).

3.3. *Anthropometric and biochemical characteristics of the subjects with different genotypes of TrkB rs1187327*

As presented in Table 3, there were no significant differences of the serum lipids levels between the GG homozygotes and the A allele carriers before the adjustment for age, gender and BMI. However, the GG homozygotes had a significantly higher level of HDL-C than the A allele carriers after the adjustment for gender, age and BMI although no other differences were observed after the adjustment.

3.4. *Effects of PTSD on the association of TrkB rs1187327 with anthropometric and biochemical characteristics*

Table 4 presented the anthropometric and biochemical characteristics of the subjects with different genotypes of *TrkB rs1187327* and with or without PTSD. Before the adjustment for age, gender and BMI, the GG homozygotes without PTSD had significantly higher level of TG than the A allele carriers without PTSD. No other significant differences were observed between the GG homozygotes and the A allele carriers in control or PTSD subjects. After the adjustment of age, gender and BMI, the GG homozygotes had significantly higher level of HDL-C than the A allele carriers only in the control subjects, but not in the subjects with PTSD. No other significant differences were tested between the GG homozygotes and the A allele carriers in control or PTSD subjects.

4. Discussion

BDNF-TrkB signaling pathway has been found to play an important role in lipid metabolism (*19*). However, the association of TrkB with serum lipid profiles has not been explored yet in human being, although it has been reported that there is a decreasing trend of HDL-C level in the transgenic mice overexpressing *TrkB* when compared with the control mice (*25*). Moreover, BDNF-TrkB signaling pathway has also been found to be an important player in the development of PTSD after stressed (*15-17*). Therefore, exploring the interplays of TrkB with PTSD on serum lipid profiles may provide novel insights into the mechanism of the regulation of serum lipids levels and pathophysiology of CVD,

especially in the subjects with PTSD. However, these interplays have not reported yet. In the present study, the association of *TrkB rs1187327* with the levels of serum lipids was investigated in high school students with or without PTSD. The results demonstrated that the GG homozygotes of *TrkB rs1187327* had significantly higher levels of HDL-C than the A allele carriers after the adjustment for gender, age and BMI (Table 3). When PTSD was taken into account, the higher than the A allele carriers levels of HDL-C of the GG homozygotes were observed significant after the adjustment for gender, age and BMI only in the subject without PTSD, but not in the subjects with PTSD (Table 4). These results suggest that *TrkB rs1187327* may be associated with the serum level of HDL-C and PTSD can modify and eliminate the association.

Plasma BDNF was found to be correlated with TG levels (*33*). In contrast, the expression of *TrkB* in endothelium was reduced in atherosclerotic lesions in the patients with high levels of TC, TG, LDL-C and glucose, when compared with that in the subjects with normal lipid profiles (*34*). Low levels of BDNF were reported to be in concurrence with reduced glucose metabolism and decreased HDL-C levels in Chinese people (*35,36*). However, a decreasing trend of HDL-C level was observed in the transgenic mice overexpressing *TrkB* when compared with the control mice (*25*). All these evidences suggest associations of TrkB with serum lipid profiles although they are indirect and inconstant. In the present study, the levels of HDL-C of the GG homozygotes were observed significant higher than the A allele carriers after the adjustment for gender, age and BMI only in the subject without PTSD, but not in the subjects with PTSD (Table 4). This result may be one of the explanations of the inconsistent relationship reported before between TrkB and the levels of serum lipids, and suggest that psychological factors such as PTSD need to be taken into account when the relationship is investigated. *TrkB rs1187327* is located in introns (*26*). The structure and the related functions of the encoded protein should not be changed. However, it has been observed that *TrkB rs1187327* is associated with psychiatric disorders such as bipolar disorder (*26*) and Alzheimer's disease (*37*). Therefore, the mutants of *TrkB rs1187327* may play a role in splicing or expression levels (*26*). Other mechanism such as linkage disequilibrium is also needed to be taken into account. There were some limitations in the present study. Firstly, serum levels of TrkB were not measured. Secondly, the levels of *TrkB* mRNA were not tested.

In conclusion, there may be some interplays of *TrkB rs1187327* with PTSD on serum lipid profiles, together with age, gender and BMI. After the adjustment of age, gender and BMI, the GG homozygotes had a significantly higher level of HDL-C than the A allele carriers. When PTSD was taken into account, the GG homozygotes had significantly higher levels of HDL-C than the A allele carriers only in the control subjects, but not in the subjects with PTSD. These results suggest that the A allele of *TrkB rs1187327* may be associated with decreased level of serum HDL-C in general healthy adolescents, but not in adolescents with PTSD. This finding of the present study may provide new insights into the regulations of serum lipids levels and their mechanisms, and pave the way to precision medical intervention to reduce risks of cardiovascular diseases in young subjects, especially those with different genotypes of *TrkB rs1187327* and with or without PTSD.

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