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Association of NPSR1 rs324981 polymorphism and treatment response to antidepressants in Chinese Han population with generalized anxiety disorder

Qianqian He [a], Zhongxia Shen [a], Lie Ren [a], Xing Wang [a], Mincai Qian [a], Jianying Zhu [b], Xinhua Shen [a, *]

[a] Department of Neurosis and Psychosomatic Diseases, Huzhou 3rd Hospital, Huzhou, Zhejiang, 313000, PR China
[b] Department of Radiology, Huzhou 3rd Hospital, Huzhou, 313000, PR China

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ABSTRACT

In previous studies, neuropeptide S (NPS) and its cognate receptor (NPSR) have been involved in the pathogenesis of anxiety disorders in previous studies. Here, we aimed to investigate the association of NPSR1 polymorphism with generalized anxiety disorder (GAD) and its treatment response in Chinese Han population. Three hundred and thirty seven patients and one hundred and seventy seven healthy controls were involved in our study for 8 weeks. Further, Hamilton Anxiety Scale (HAMA) was used to assess anxiety symptom at baseline and the 1st, 2nd, 4th, 8th week. And all participants were genotyped for NPSR1 (rs324981) variants by polymerase chain reaction. Using Repeated-measures analysis, it showed significant reduction on HAMA scores in patients treated with escitalopram ($F = 1.03$, $P = 0.362$) and venlafaxine ($F = 0.27$, $P = 0.763$) respectively through 8 weeks treatment. Additionally, patients with AA and TT homozygous genotypes treated with venlafaxine XR had a higher reduction of HAMA scores compared to AT heterozygotic carriers ($F = 4.18$, $P = 0.004$), while no significant differences were found in patients treated with escitalopram ($F = 1.05$, $P = 0.383$). Thus, our study provides preliminary evidence that NPSR1 AA and TT homozygous genotypes have better treatment responses to venlafaxine XR in Chinese GAD patients, but not to escitalopram. Further studies are needed to verify the observation.

1. Introduction

Generalized anxiety disorder (GAD) is defined by persistent excessive worry , uncontrollable anticipatory anxiety and somatic symptomatology [1], which significantly reduce the quality of life for patients with GAD and leads to their functional impairment in social, occupational, and daily life [2]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the most common and representative drugs widely used for the treatment of GAD in clinic [3].

Neuropeptide S (NPS) and its cognate receptor (NPSR) have been attracting a great deal of attention for their role of a promising and novel pathomechanism of anxiety disorders recently [4–6]. NPS is a recognized peptide transmitter that modulates emotional and cognitive functions in the brain [7] and affects numerous neuroendocrine, behavioral, and inflammatory responses via its G protein-coupled cell surface Neuropeptide S Receptor 1 (NPSR1) [8,9]. The NPS/NPSR system were reported to have associations with a wide range of neuropsychiatric phenotypes and biological functions, including panic disorders [4,10], psychological stress [11], fear responses [12], obsessive-compulsive disorder (OCD) [5], wakefulness [13], food intake [14], learning and memory processes [15], drug abuse [16]. It was also reported that the mice and rats whose amygdala or tracerebroventricular were injected with NPS have shown to produce strong anxiolytic-like or panicolytic-like actions [17–21], contrary to these conclusions, NPS could weaken the fear expression and accelerate the extinction of fear memories in mice and rats [19,22]. Besides, some studies indicated that the mice whose NPSR was knocked out (NPSR(−/−)) or treated with NPSR antagonists (SHA68) behaved severe anxiety [22,23].

* Corresponding author.
E-mail addresses: heqianqian205@163.com, heqianqian205@foxmail.com (Q. He), snowszx@sina.com (Z. Shen), renliemeidu@126.com (L. Ren), 1439612777@qq.com (X. Wang), 1311956613@qq.com (M. Qian), 54037360@qq.com (J. Zhu), prozac1216@sina.com (X. Shen).

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However, there were also opposite conclusions that the rodents with panic and post-traumatic stress disorders showed less anxiolytic-like effects after treated by NPSR agonists and the NPSR(−/−) mice did not show an anxiogenic-like phenotype [24]. Although anxiolytic-like activities of the NPS/NPSR system have been researched in these studies, the gene mechanism remains not fully clear. Some studies indicated that the SNP rs324981 of human NPSR1 that reduced agonist might be related to panic disorder, and the variant of Ile107 (T-allele) was over expressed compared to Asn107 (A-allele) in patients with panic disorder [4,10].

These studies suggest there exists a correlation between NPS/NPSR and GAD, and NPS is therefore deemed to be a potent anxiolytic compound [17]. As we know, there have been no consistent examinations for the association of NPSR1 polymorphisms and GAD in Asian population. In the study, we explore the association between the NPSR1 polymorphism and GAD as well as the treatment response to anti-anxiety drugs in Chinese Han population.

2. Materials and methods

2.1. Participants

One hundred and forty six patients of Chinese Han ethnicity diagnosed with GAD, who met Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 2000), were recruited from Huzhou 3rd Hospital. The age for all patients was from 18 to 65 (42 males, 104 females). And they had a minimal score of 14 on the HAMA score. Exclusion criteria included severe physical diseases such as liver, kidney or cardiovascular disease, any comorbid psychiatric disorders such as schizophrenia, bipolar disorder, epilepsy, dementia and so on, personality disorders diagnosed by the DSM-IV or substance use disorders, pregnant or lactating women. Those participants who received any psychoactive drugs or other antidepressants, as well as any psychotherapy within two months at the beginning of the study were also excluded. One hundred and seventy seven healthy participants aging from 18 to 65 (57 males and 152 females) were recruited without any mental illness defined by DSM-IV and with a HAMA-14 total score ≤ 7 as control groups. This study protocol was approved by the Research Ethics Review Board of Huzhou 3rd Hospital (Zhejiang, China). Written informed consent was obtained from all participants.

2.2. Design

All patients were administered venlafaxine XR (75–225 mg/day) or escitalopram (10–20 mg/day) according to local clinical practice during the 8-week study. Other antidepressants were forbidden and short-acting pills including Zopiclone and Zolpidem were permitted for insomnia. The changes of HAMA scores were assessed at baseline and on the first, second, fourth and eighth week in patients treated with escitalopram or venlafaxine by trained physicians. And the interrater consistency was good (ICC>0.80). Response was defined by the reduction of HAMA≥50% and non-response was defined by the reduction of HAMA< 50% at different treatment period. And remission was defined by HAMA scores ≤7 and non-remission was defined by HAMA scores >7.

2.3. Genotyping

Peripheral venous blood for genomic studies was collected from all patients and healthy controls in ethylenediaminetetraacetic acid (EDTA) tubes. And then we extracted the genomic DNA from venous blood using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China) and stored them at −80 °C according to the manufacturer's instructions.

Genotyping of NPSR1 was performed with the PCR-restriction fragment length polymorphism (PCR-RFLP) and direct sequencing (GenScript Corp., Nanjing, China) and the single nucleotide polymorphisms (SNPs) of NPSR1 Asn107Ile variant (rs324981) genes were detected and amplified using PCR. Then PCR products of SNP (rs324981) were digested with AseI restriction enzyme and resolved in 3% agarose gel. The sequences of all forward primers of NPSR1 (rs324981) were 5′-GCTTTGCATTTCCTCAGTGG-3′ and reverse primers were 5′-ATTTGTGGCTCGTTTGTGTTTTCT-3′, which were verified according to the GenBank database.

2.4. Statistical analysis

All statistical analyses were carried out using SPSS statistical analysis software (version 19.0; IBM SPSS, Chicago, IL, USA). Comparisons of the allele and genotype frequencies between cases and controls were performed using $\chi 2$ test. Hardy-Weinberg equilibrium (HWE) was evaluated for genotypes. Repeated-measures ANOVAs were used to analyse the changes of clinical variables between and within case groups and its interaction over 8 weeks in patients treated with different drugs. All tests were two-tailed, and P values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Comparison of NPSR polymorphism between case group and control group

Eighty one patients were treated with venlafaxine and three patients were dropped out. Sixty four patients were treated with escitalopram and five patients were dropped out. Thus, One hundred and thirty seven patients (36 males, 101 females) completed the study in the end and nine patients were dropped during the study due to the unwilling to continue or side effects. The NPSR genotypes were in accordance with Hardy-Weinberg equilibrium (HWE) ($P = 0.696$ by χ^2). It showed no significant differences in the frequencies of A and T allele ($P > 0.05$) between the case group and control group. Besides, no statistical frequency differences were found in AA, TT and AT genotypes ($P > 0.05$) between the two groups. Further we did not find of significance frequencies differences of NPSR1 allele and genotype in male or female participants between the case group and control group. See Table 1.

Table 1
Allele and genotype frequencies and the association of gender between case and control groups.

	Gene/genotype	Case (n = 137)		Control (n = 177)		χ2	*P*-value
		n	%	n	%		
NPSR1	A	118	42.14	152	42.93	0.014	0.872
	T	162	57.86	202	57.06		
	AA	22	16.10	35	19.80	1.539	0.463
	AT	74	54.00	82	46.30		
	TT	41	29.90	60	33.90		
NPSR1 Male	A	24	33.33	44	40.00	1.009	0.270
	T	48	66.67	66	60.00		
	AA	5	13.90	8	14.50	1.572	0.078
	AT	14	38.90	28	50.90		
	TT	17	47.20	19	34.50		
NPSR1 Female	A	94	46.53	108	44.26	0.148	0.634
	T	108	53.47	136	55.74		
	AA	17	16.80	27	22.10	5.102	0.078
	AT	60	59.40	54	44.30		
	TT	24	23.80	41	33.60		