Int J Clin Exp Pathol 2016;9(11):11944-11950
www.ijcep.com /ISSN:1936-2625/IJCEP0035313

Original Article

Relationship between 5-hydroxytryptamine (serotonin) type 3 receptor and nausea and vomiting

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Received July 8, 2016; Accepted July 20, 2016; Epub November 1, 2016; Published November 15, 2016

Abstract: Objective: The 5-hydroxytryptamine (serotonin) type 3 receptor (HTR3) plays an important role in the regulation of nausea and vomiting. This study investigated whether common genomic variations rs3758987 and rs4938058 of B subunits of HTR3 (*HTR3B*) were associated with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting in a Chinese Han population. Methods: A cohort of 175 patients with acute myeloid leukemia (AML) were enrolled in this study. *HTR3B* gene polymorphisms rs3758987 and rs4938058 were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach. Chi-square test was employed to analyze the differences of genotype and allele distributions. Results: The GG genotype of rs3758987 might significantly increased the incidence of both grade 3/4 nausea and vomiting in codominant and dominant models, allelic analysis also showed significant association with G allele ($P<0.05$). For rs4938058, G allele carriers appeared to be more susceptible to experience grade 3/4 vomiting. However, no significant association had been found between *HTR3B* gene polymorphisms with the incidence of delayed CINV. Conclusion: *HTR3B* common genetic variants rs3758987 and rs4938058 were significantly associated with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting in a Chinese Han population.

Keywords: *HTR3B*, polymorphism, CINV, ondansetron

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is the major adverse effect of cancer patients treated with highly emetogenic chemotherapy [1]. It has an obvious effect on the daily functioning and quality of life of patients [2]. A major study performed by Lopez-Jimenez have indicated that more than half of acute myeloid leukemia (AML) patients experience emesis after high-dose cytarabine chemotherapy [3]. CINV is generally divided into two types: acute CINV which occurs within 24 hours after chemotherapy with poor control and delayed CINV persisting from 24 to 120 hours after chemotherapy [4]. And delayed CINV may have more severe impact on patients than that with acute CINV [5]. Although more effective, convenient, and well-tolerated means have been performed to prevent CINV, substantial minority of patients continues to have suboptimal antiemetic control. Therefore, additional treatment approaches are needed.

5-hydroxytryptamine (serotonin) type 3 (5-HT3) receptor belongs to the Cys-loop superfamily of ligand-gated ion channels (LGICs). This ion channel is cation-selective and mediates neuronal depolarization and excitation within the central and peripheral nervous systems [6]. In human, 5-HT3 subunits are encoded by five genes containing *HTR3A-E.* Among these subunits, 5-HT3A and 5-HT3B have been studied moat extensively. Particularly, the genes encoding the subunits 5-HT3A and 5-HT3B are located close together on human chromosome 11q23.1. 5-HT3 have been reported to significantly reduce postoperative nausea and vomiting (PONV), but there are still over 35% of patients treated with ondasertron experience PONV [7]. The reason for the different response is probably individual differences in the biotransformation and disposition of 5-HT3 receptor antagonists, which may be caused by gene polymorphisms related to pharmacokinetics [7, 8].

Table 1. Primer sequences of *HTR3B* gene rs3758987 and rs4938058 polymorphisms

SNP	Primer sequences		Size (bp)
rs3758987	Upstream	5'-AAGAGCCCAAGAACCACT-3'	284
	Downstream	5'-TTCTCCCTTTGGTTCTGC-3'	
rs4938058	Upstream	5'-CCTTATGGTCCATCTGTG-3'	253
	Downstream	5'-GAGGCTGAGGCAGGAGAA-3'	

5-HT3B receptor gene is also known as *HTR3B*. Genetic variations in *HTR3B* have been reported to influence the clinical outcome related to nausea and vomiting. Studies have been performed by Tremblay PB and Tanaka M et al., which confirm the hypothesis that patients with genetic variations in the *HTR3B* gene may respond differently to antiemetic treatment [9, 10].

As our knowledge, no studies have been performed relating genetic variants to severity of CINV. Therefore, in the present study, we explored the association of *HTR3B* gene polymorphisms (rs3758987 and rs4938058) with antiemetic therapeutic efficacy of ondansetron in Chinese cancer patients with high-dose of cytarabine chemotherapy.

Patients and methods

Study population

A cohort of 175 patients were enrolled in this present study, which were diagnosed as acute myeloid leukemia (AML) in Chinese PLA General Hospital from June 2013 to May 2014. This research was consented and approved by Ethics committee of Chinese PLA General Hospital. Sample collection is conformed to ethics criteria of national human genome research. Informed consent was obtained from all parents or their guardians. All participants were Chinese Han population.

All patients were treated with a high dose of cytarabine (1.5 g/m^2 up to 3 days) monotherapy. Thirty minutes before the beginning of chemotherapy, ondansetron 8 mg intravenously and following by 24 mg ondansetron by continuous infusion lasting until 12 hours after the end of the cytarabine infusion were given to the patients. Ondansetron (8 mg IV) once per day until 2 days after the end of chemotherapy were the standard antiemetic therapy for prevention of delayed CINV. Besides, patients who had concomitant diseases that might cause nausea or vomiting, took other antiemetics, experienced nausea or vomiting or received radiotherapy within 24 hours before the start of chemotherapy were excluded.

Nausea and vomiting assessment

Every patient completed a daily record up to 5 days, beginning with the first day of chemotherapy. The following information was collected, containing the number of episodes of vomiting, the 0-100 scale of nausea visual analog scale (NVAS) [11]. Acute CINV was categorized and divided into grade 1/2 and grade 3/4 based on the National Cancer Institute Common Toxicity Criteria v.3 (NCI CTC v.3) [12]. Additionally, delayed CINV were examined as yes or no, in which patients without delayed vomiting and/or had <5 score on the NVAS scale were defined as patients without delayed emesis (no), instead were patients without delayed emesis (yes) [13, 14].

Genotyping of HTR3B polymorphisms

Peripheral venous blood was collected from every patient, anticoagulated by 0.5% EDTA (pH 8.0). Genomic DNA was extracted by DNA extraction kit (Tiangen, Beijing, China), and stored at -20°C for standby application.

The polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method was carried out for the genotyping of *HTR3B* gene rs3758987 and rs4938058 polymorphisms. Primer sequences were designed by Primer Premier 5.0, and synthesized by Sangon Biotech (Shanghai, China) (**Table 1**). PCR amplification was performed in a total volume of 25 μl. Then the amplified PCR products of rs3758987 and rs4938058 were digested with Csp6I and Ppu10I respectively. Finally, digested DNA products were then analyzed by 2% agarose gel electrophoresis and visualized by UV light.

Statistical analysis

The data analysis was performed by PASW statistics 18.0 statistical software. Hardy-Weinberg equilibrium (HWE) was assessed to test the representativeness of participant. Geno-

Table 2. Basic clinical characteristics of the ACI patients (n=175)

Characteristic	n (%)
Age (years old)	
<43	89 (50.86)
>43	86 (49.14)
Sex	
Male	73 (41.71)
Female	102 (58.29)
History of smoking	
Yes	106 (60.57)
No	69 (39.43)
History of drinking	
Yes	110 (62.86)
No	65 (37.14)
BSA, m	
≤1.677	68 (38.86)
>1.677	107 (61.14)
BMI	
Underweight + normal	115 (65.71)
Overweight + obese	60 (34.29)

Note: BMI = body mass index; BSA = body surface area.

Table 3. The incidence of acute and delayed CINV in AMI patients after high-dosage cytarabine chemotherapy

Parameters	n	%
Acute nausea		
Grade 1/2	85	48.57
Grade 3/4	90	51.43
Acute vomiting		
Grade 1/2	75	42.86
Grade 3/4	100	57.14
Delayed CINV		
None	91	52.00
Yes	84	48.00

type and allele frequencies of *HTR3B* gene rs3758987 and rs4938058 polymorphisms were estimated by direct counting. Hardy-Weinberg equilibrium (HWE) was also assessed to test the representativeness of population. Differences of the polymorphisms distributions between groups were compared via Chi-square test. The differences had statistical significance when $P<0.05$.

Results

Characteristics analysis of patients

A cohort of 175 patients were enrolled in this study. **Table 2** presented the characteristics of all patients. Among the patients with AML, more of them had a history of smoking and drinking. Besides, more patients had low body surface area (BSA) and their body mass index (BMI) tended to be underweight or normal. The presence of nausea and vomiting during the acute and delayed phase was summarized in **Table 3**. In the acute phase, 51.43% of AML patients were in grade 3/4 nausea, while 57.14% of all patients were in grade 3/4 vomiting. And 48% patients experienced nausea and/or vomiting in the delayed phase.

Association of the HTR3B polymorphisms with the incidence of Grade 3/4 CINV

As shown in **Table 4**, the genotype and allele frequencies of *HTR3B* gene polymorphisms were calculated by direct counting. The distributions of the two polymorphisms rs3758987 and rs4938058 were all confirmed to HWE, which indicated the representativeness of the patients.

For rs3758987, patients with GG genotype had a higher risk to experience grade 3/4 nausea and vomiting, and the differences were statistically significant ($P=0.017$, $P=0.039$). In dominant model analysis, significant differences in the grade 3/4 nausea and grade 3/4 vomiting were also observed between the GG genotype and others without GG genotype ($P=0.008$, $P=0.012$). The allelic frequencies analysis indicated that patients of G allele carriers were more susceptible to experience grade 3/4 nausea and grade 3/4 vomiting. However, no significant differences were presented in the incidence of delayed CINV among different rs3758987 genotypes and alleles ($P>0.05$).

In refer to rs4938058, the genotype differences were also analyzed in three models: codominant, dominant, recessive. No significant differences in genotype distribution frequencies were found in the incidence of acute nausea and vomiting ($P>0.05$). However, the allelic frequencies analysis showed that AMI patients of the G allele carriers had higher risk to experience grade 3/4 vomiting ($P=0.026$).

Discussion

Nausea and vomiting are difficult symptoms to manage in patients with advanced cancer or chemotherapy. Despite newer agents, CINV is still a distressing side effect to a proportion of

Table 4. Effects of *HTR3B* polymorphisms on the antiemetic therapeutic efficacy of ondansetron in AML patients

	Genotype	Acute Nausea, n (%)			Vomiting, n (%)			Delayed CINV, n (%)		*P*
		Grade 1/2	Grade 3/4	*P*	Grade 1/2	Grade 3/4	*P*	Grade 1/2	Grade 3/4	
rs3758987										
Co	GG	23 (27.06)	42 (46.67)	0.017	19 (25.33)	44 (44.00)	0.039	29 (31.87)	33 (39.28)	0.394
	GA	44 (51.76)	38 (42.22)		41 (54.67)	41 (41.00)		44 (48.35)	40 (47.62)	
	AA	18 (21.18)	10 (11.11)		15 (20.00)	15 (15.00)		18 (19.78)	11 (13.10)	
Do	GG	23 (27.06)	42 (46.67)	0.008	19 (25.33)	44 (44.00)	0.012	29 (31.87)	33 (39.28)	0.344
	GA+AA	62 (72.94)	48 (53.33)		56 (74.67)	56 (56.00)		62 (68.13)	51 (60.72)	
Re	GG+GA	67 (78.82)	80 (88.89)	0.098	60 (80.00)	85 (85.00)	0.422	73 (80.22)	73 (86.90)	0.309
	AA	18 (21.18)	10 (11.11)		15 (20.00)	15 (15.00)		18 (19.78)	11 (13.10)	
Allele	G	90 (52.94)	122 (67.78)	0.006	79 (52.67)	129 (64.50)	0.028	102 (56.04)	106 (63.10)	0.192
	A	80 (47.06)	58 (32.22)		71 (47.33)	71 (35.50)		80 (43.96)	62 (36.90)	
rs4938058										
Co	AA	41 (48.23)	36 (40.00)	0.387	37 (49.33)	36 (36.00)	0.094	38 (41.76)	26 (30.95)	0.246
	AG	32 (37.65)	35 (38.89)		29 (38.67)	41 (41.00)		34 (37.36)	33 (39.29)	
	GG	12 (14.12)	19 (21.11)		9 (12.00)	23 (23.00)		19 (20.88)	25 (29.76)	
Do	AA	41 (48.23)	36 (40.00)	0.290	37 (49.33)	36 (36.00)	0.089	38 (41.76)	26 (30.95)	0.159
	AG+GG	44 (51.77)	54 (60.00)		38 (50.67)	64 (64.00)		53 (58.24)	58 (69.05)	
Re	AA+AG	73 (85.88)	71 (78.89)	0.242	66 (88.00)	77 (77.00)	0.076	72 (79.12)	59 (70.24)	0.222
	GG	12 (14.12)	19 (21.11)		9 (12.00)	23 (23.00)		19 (20.88)	25 (29.76)	
Allele	A	114 (67.06)	107 (59.44)	0.151	103 (68.67)	113 (56.50)	0.026	110 (60.44)	85 (50.60)	0.068
	G	56 (32.94)	73 (40.56)		47 (31.33)	87 (43.50)		72 (39.56)	83 (49.40)	

Note: Co = codominant; Do = dominant; Re = recessive.

patients undergoing systemic anti-cancer therapy [15]. CINV can result in various conditions such as dehydration, malnutrition, and even treatment non-response, which may significantly affects patients' quality of life [16]. Traditionally, CINV is always divided into two groups of acute and delayed CINV. But recently, breakthrough CINV is defined if nausea and vomiting cannot be controlled effectively with prophylactic antiemetics [17]. Therefore, additional treatment approaches are imminent.

Olanzapine is a single agent antipsychotic medication which can help relieve psychotic depression [18]. Besides, it also is an inhibitors of serotonergic 5-HT2a, 5-HT2c, 5-HT3, 5-HT6 receptors, dopaminergic D1, D2, D3, and D4 receptors, alpha-1 adrenergic receptors, histaminic H1 receptors, and multiple muscarinic receptors [19]. The current recommended antiemetic treatment for acute and delayed CINV, in the setting of moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC), is ondansetron and dexamethasone [20]. Ondansetron is the first 5-hydroxytriptamine-3 receptor antagonists (5-HT3RAs) and has been widely used in hospitals, which is reported to significantly improve the control of CINV [5].

The HTR3 plays crucial roles in promoting nausea and vomiting, initiated from the central and peripheral nervous systems. The influence of the HTR3 on chemotherapy- and radiotherapy-induced vomiting has attracted particular research interest, in which researches has suggested its involving in chemotherapy-induced CINV [21]. Human *HTR3B* gene encodes a protein subunit of HTR3 [22], but the functional effects of *HTR3B* polymorphisms has not been sufficiently studied. Previous studies showed that genetic variations of the *HTR3* subunits may affect the expression or function of the HTR3 complex, as well as serotonin signaling. It might increase the affected individuals' predisposition to certain disease that are modulated by serotonin signaling or the efficacy of treatments for these diseases [23]. Variations will likely affect protein's expression, stability and function, if it is within the regulatory region of the gene and causes changes in the amino acid sequence of the encoded protein [24, 25]. Sequence variations in the coding regions of genes can still exert an effect on the stability of the transcript and/or signaling, even if the amino acid sequence can be altered [26-28]. A previous study has suggested *HTR3B* gene variations as predictors for the efficacy of anti-

emetic treatment in Caucasian patients with cancer [9]. However, there are no data available for the association of *HTR3B* gene rs3758987 and rs4938058 polymorphisms with chemotherapy-induced nausea and vomiting in Chinese Han population.

In the current study, we found that ondansetron treatment prevented acute grade 3/4 nausea in only 48.57% of AML patients and prevented acute grade 3/4 vomiting in 42.86% of the patients after high-dose cytarabine chemotherapy. Besides, in the delayed phase, 52% of the patients didn't experience nausea and/or vomiting after ondansetron treatment. By contrast, the curative of ondansetron were lower than those reported of other antiemetic drugs, such as palonosertron, although ondansetron has been considered as a standard therapy for AML patients in China [29]. In addition, our results found that there were no significant association between *HTR3B* gene rs3758987 and rs4938058 polymorphisms and the incidence of delayed CINV in Chinese patients with AMI. But the allelic analysis demonstrated that both rs3758987 and rs4938058 were associated with the incidence of grade 3/4 vomiting, while only rs3758987 allele distribution was related to the incidence of grade 3/4 nausea in our cohort. Besides, we also analyzed the genotype distributions of two polymorphisms in three models. And we found that GG genotype of rs3758987 might significant increased the incidence of both grade 3/4 nausea and vomiting in codominant and dominant models, while no significant association was found for rs4938058. In the previous study, rs3758987 has been studied on the relationship with postoperative vomiting in Chinese Han patients and significant association has been detected [30]. All results confirmed the role of rs3758987 on human nausea and vomiting.

In conclusion, we identified in a Chinese Han population common genetic variants of *HTR3B* (rs3758987 and rs4938058) that was associated with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting. However, there were also limitations in this study; for example, the environmental factors were not be considered for the studies on therapeutic efficacy. And the sample size of our study was relatively small in this study. Therefore, the results data are preliminary, and studies with larger and different populations are required for further validation.

Disclosure of conflict of interest

None.

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