

Lack of Association between TRP Gene Polymorphisms and Complication of Medication Overuse Headache in Migraine Patients

Masaaki Ishibashi^{1,2}, Hideyo Kasai³, Hirotaka Katoh^{3,4} and Masakazu Ishii^{1,2*}

¹Division of Physiology and Pathology, Faculty of Pharmaceutical Sciences, Teikyo Heisei University, Nakano-ku, Tokyo, Japan.

²Division of Physiology and Pathology, Showa University School of Pharmacy, Shinagawa-ku, Tokyo, Japan.

³Department of Neurology, Showa University School of Medicine, Shinagawa-ku, Tokyo, Japan.

⁴Kuramae Kato Medical Clinic, 3-4-9 Kuramae, Taito-ku, Tokyo, Japan.

*Correspondence:

Masakazu Ishii, PhD, Division of Physiology and Pathology Faculty of Pharmaceutical Sciences, Teikyo Heisei University, 4-21-2 Nakano, Nakano-ku, Tokyo 164-8530, Japan, Tel: +81-3-5860-4038; E-mail: masakazu.ishii@thu.ac.jp.

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ABSTRACT

Purpose: We studied the association between the polymorphisms of TRP channels, such as TRPV1 (vanilloid 1), TRPM2 (melastatin 2), TRPM8 (melastatin 8) and TRPA1 (ankyrin 1), and the complications of medication overuse headache (MOH) in patients with migraines.

Methods: Forty-seven migraine patients (6 males and 41 females; 36.4 ± 10.3 years) and 22 MOH patients (1 male and 21 females; 39.6 ± 9.9 years) who had migraines participated in this study. The genotypes for the TRPV1 (rs222747, rs222749 and rs8065080), TRPM2 (rs1556314), TRPM8 (rs10166942 and rs11562975) and TRPA1 (rs920829 and rs11988795) gene polymorphisms were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods.

Results: No significant differences were observed in the genotype distributions of TRPV1, TRPM2, TRPM8 or TRPA1 between migraines and MOH.

Conclusion: TRP gene polymorphisms were not involved in the aggravation of migraines due to the overuse of medication.

Keywords

Medication overuse headache, Migraine, Polymorphism, TRP channels.

Introduction

Medication overuse headache (MOH) is a chronic headache which develops following overuse of acute headache medication and vanishes after withdrawal. Migraine patients are particularly prone to developing MOH [1-3]. Moreover, MOH patients, in contrast to migraine patients, have a higher percentage of comorbidity with depression [3-5]. It is important to prevent the complications of MOH in patients with migraine, as the complication of MOH leads

to a markedly decreased quality of life for patients [1].

The antioxidant capacity in patients with MOH or migraines is lower than in healthy controls; this suggests enhanced vulnerability to oxidative stress during headache [6]. Interestingly, nitric oxide (NO) metabolites and lipid peroxidation are increased during a migraine attack in platelets, in contrast to headache-free periods [7]. Thus, oxidative stress may be increased with increased frequency of headache in patients with migraines. Therefore, it is possible that an increase in oxidative stress may contribute to the aggravation of migraines due to medication overuse. However, catalase (CAT), superoxide dismutase (SOD) and glutathione

peroxidase (GPX) gene polymorphisms did not contribute to the aggravation of migraines due to the overuse of medication [8].

Transient receptor potential (TRP) channels, including TRPA1 (Ankyrin 1) [9], TRPV1 (Vanilloid 1) [9], TRPM2 (Melastatin 2) [10] and TRPM8 (Melastatin 8) [11], were identified as oxidative stress-sensitive Ca²⁺-permeable channels and were expressed in the trigeminal ganglion [12]. Calcitonin gene-related polypeptide (CGRP) is a potent vasodilator and is released from the trigeminal ganglion via TRPA1 and TRPV1 activation [13]. Interestingly, in MOH model animals, triptan increased CGRP levels [14]. Therefore, the oxidative stress may stimulate the CGRP release via these TRP channels' activation in trigeminal neurons, and stimulate headache pain.

However, few studies have been performed focusing on the genetic polymorphisms associated with oxidative stress-sensing TRP channels. Therefore, we carried out the present study to investigate the contributions of TRP gene polymorphisms in the complication of MOH in patients with migraines.

Methods

Subjects

We enrolled 47 migraine (6 males and 41 females; 5 with migraines with an aura (MA), 36 with migraines without an aura (MO), and 6 with MA + MO; 36.4 ± 10.3 years) and 22 MOH (1 male and 21 females; 1 with MA and 21 with MO; 39.6 ± 9.9 years) patients who were admitted to the Department of Neurology in the outpatient clinic of Showa University East Hospital, Tokyo, Japan, between May 2010 and January 2011. These patients had participated in a previous study, in which the incidence of depression was shown to be significantly higher in MOH patients than in migraine patients ($P < 0.001$) [5]. The overused medications were combination analgesics in 14 patients (64%), analgesics in 9 patients (41%) and triptans in 2 patients (9%) [15].

Migraines were diagnosed according to the International Classification of Headache Disorders, 2nd Edition (ICHD-II) in 2004 [16]. We also confirmed with an interview that the migraine patients in the present study had not previously overused medication. The revised ICHD-II criteria were used for the diagnosis of MOH [1]. MOH patients were asked about primary headaches by headache specialists. Moreover, headache specialists confirmed primary headaches after the recovery of patients from MOH, according to the ICHD-II criteria. Although the subjects included in the present study were not only patients with migraines but also patients with migraines and tension-type headaches, patients with tension-type headaches only were excluded from this study. We used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to diagnose major depressive disorder [17].

All patients were Japanese. We enrolled all patients with migraines and patients with MOH who provided informed consent for this study, and did not select patients. This clinical study was approved by the Ethics Committee for Genome Research of Showa University.

Genotyping

Genomic DNA was extracted from whole blood using NucleoSpin Blood QuickPure (NIPPON Genetics Co., Ltd., Tokyo, Japan). The gene polymorphisms of transient receptor potential vanilloid receptor 1 (TRPV1, rs222747 [18], rs222749 [18] and rs8065080 [19]), transient receptor potential melastatin 2 (TRPM2, rs1556314), transient receptor potential melastatin 8 (TRPM8, rs10166942 and rs11562975) and transient receptor potential ankyrin 1 (TRPA1, rs920829 and rs11988795) were studied. These genotyping assays were performed on a maximum of 20 samples plus positive control. Primer sequences, restriction enzymes and expected fragment sizes of 8 gene polymorphisms are shown in Table 1. The PCR products or restriction enzyme-treated PCR fragments were run on 3% agarose gels and stained with ethidium bromide.

Statistical analysis

Categorical variables were analyzed by χ^2 test using Excel Statistics (Excel Toukei) 2008 for Windows (Social Survey Research Information Co., Tokyo, Japan). Values of $P < 0.05$ were considered significant.

Results

The genotype frequencies are shown in Table 2. The genotypic distributions of rs222747 (G/G vs G/C vs C/C, $P = 0.067$), rs222749 (C/C vs C/T vs T/T, $P = 0.605$), rs8065080 (C/C vs C/T vs T/T, $P = 0.871$), rs1556314 (T/T vs T/G vs G/G, $P = 0.586$), rs10166942 (C/C vs C/G vs G/G, $P = 0.732$), rs11562975 (C/C vs C/G vs G/G, $P = 0.492$), rs920829 (A/A vs A/G vs G/G, $P = 0.701$) and rs11988795 (C/C vs C/T vs T/T, $P = 0.926$) were not significantly different between migraine patients and MOH patients (Table 2).

Discussion

In the present study, no association was observed between polymorphisms of TRP genes and the complication of MOH in patients with migraine.

TRPM8 is activated by a broad range of modulator compounds, including cold and cooling compounds such as menthol [20]. Moreover, TRPM8 is expressed in the trigeminal ganglion and dorsal root ganglion, and involved in cold-induced pain [20,21]. TRPM8 is also known to be involved in cutaneous allodynia [20], which was observed in many migraine patients [22]. Recent studies suggest that the association at rs10166942 in TRPM8 is specific for migraines compared with non-migraine headache [23]. However, in the present study, no relationship was observed between TRPM8 gene polymorphisms (rs10166942 and rs11562975) and the complication of MOH in migraine patients.

We previously reported that depression is a risk factor for the complication of medication overuse headache in migraine patients [5]. Cupini et al. implicated that the excess of psychiatric comorbidity in patients with MOH can be related either to medication overuse or to chronification of headache [24]. In a questionnaire study of bipolar patients, Mahmood et al. found that 26% fulfilled the criteria for a diagnosis of migraine [25].

Polymorphism		Primer	Restriction enzyme	Product size (bp)
TRPV1	(rs222747)	5'-AGT TTG GAG GCC GGT GGT TC-3'	BsaBI	G: 431
		5'-TCC TCT CCC ATG CCA TCA GC-3'		C: 269 and 162
	(rs222749)	5'-CGG CGT GGT GGC TGC TGC A-3'	Sau96I	T: 329 and 92
		5'-TAG CCC AGA AGC CAG ACC AC-3'		C: 229, 100 and 92
	(rs8065080)	5'-CAA GTC CTG GAG CTC ATT TCA-3'	Hpy99I	T: 486
		5'-GCC CTG ACC CAG GTA TGT GTA-3'		C: 292 and 194
TRPM2	(rs1556314)	5'-ATG CTT GCT CTC AGC CTT CAG A-3'	BamHI	G: 496
		5'-GCA GCC TAA GAT AGA GCA TGT G-3'		T: 296 and 200
TRPM8	(rs10166942)	5'-GAG TTT TTA GTC CTA GGA CC-3'	MseI	C: 349
		5'-TGC AAA GGC AGA GAG ATT TG-3'		T: 100 and 249
	(rs11562975)	5'-GGC ATA ATG TGA TTG AAC CCA AAG T-3'	PflMI	G: 179
		5'-GTG TGT GGT TGT TGT CCA GGA TGT A-3'		C: 160 and 19
TRPA1	(rs920829)	5'-ACT CTA GTG GAA GGC AAG TAC C-3'	HhaI	A: 186
		5'-ACA AAC CAA AAT CTG CAA TGC TG-3'		G: 174 and 12
	(rs11988795)	5'-CTA TGT GCT TAC GTG ATG CAA C-3'	TaqI	C: 156
		5'-TTG ATA AAT GGC AAA AGT TGA TCC TTC TTT TCT CA-3'		T: 126 and 30

Table 1: Primers and restriction enzymes used for genotyping.

			Subjects		Migraine		MOH		P value
			n = 69	(%)	n = 47	(%)	n = 22	(%)	
TRPV1	rs222747	G/G	16	23.2	9	19.1	7	31.8	0.067
		G/C	36	52.2	29	61.7	7	31.8	
		C/C	17	24.6	9	19.1	8	36.4	
	rs222749	C/C	43	62.3	28	59.6	15	68.2	0.605
		C/T	24	34.8	18	38.3	6	27.3	
		T/T	2	2.9	1	2.1	1	4.5	
	rs8065080	C/C	30	43.5	20	42.6	10	45.5	0.871
C/T		34	49.3	24	51.1	10	45.5		
T/T		5	7.2	3	6.4	2	9.1		
TRPM2	rs1556314	T/T	47	68.1	31	66.0	16	72.7	0.586
		T/G	20	29.0	14	29.8	6	27.3	
		G/G	2	2.9	2	4.3	0	0.0	
TRPM8	rs10166942	C/C	19	27.5	14	29.8	5	22.7	0.732
		C/G	33	47.8	21	44.7	12	54.5	
		G/G	17	24.6	12	25.5	5	22.7	
	rs11562975	C/C	0	0.0	0	0.0	0	0.0	0.492
		C/G	26	37.7	19	40.4	7	31.8	
TRPA1	rs920829	A/A	2	2.9	1	2.1	1	4.5	0.701
		A/G	42	60.9	30	63.8	12	54.5	
		G/G	25	36.2	16	34.0	9	40.9	
	rs11988795	C/C	17	24.6	11	23.4	6	27.3	0.926
		C/T	43	62.3	30	63.8	13	59.1	
		T/T	9	13.0	6	12.8	3	13.6	

Table 2: Genotype distribution of gene polymorphisms.

Moreover, Xu et al. suggested that TRPM2 polymorphism (rs1556314) is associated with bipolar disorder in case-control and family datasets [26]. However, we could not find an association between TRPM2 polymorphism (rs1556314) and the complication of MOH in migraine patients.

Nerve growth factor (NGF) has been implicated in the generation and modulation of pain [27]. Moreover, NGF was elevated in cerebral spinal fluid in chronic migraine patients [28]. NGF stimulated the TRPA1 but not TRPM8 expression in dorsal root ganglion neurons [29]. Malin et al. reported that TRPV1 and TRPA1 activities and expression are stimulated by NGF due to inflammation [30]. In addition, oxidative stress is known to induce the gene expression of NGF in astrocyte culture [31]. Therefore, the increased oxidative stress may stimulate not only TRPV1 and TRPA1 channel activities, but also the expression of both TRPV1 and TRPA1 channels via induction of NGF.

Further genetic studies are required to identify target genes for oxidative stress in the complication of MOH in migraine patients. In addition, because the small sample size was a limiting factor in the present study, larger genetic studies are required to identify target gene polymorphisms that may be associated with the complication of MOH in migraine patients.

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