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ORIGINAL ARTICLE

Human organic cation transporter (*OCT1* and *OCT2*) gene polymorphisms and therapeutic effects of metformin

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Abstract Organic cation transporters (OCTs) are responsible for the hepatic and renal transport of metformin. In this study we analyzed variants of *OCT1* and *OCT2* genes in 33 patients (24 responders and nine non-responders) based on the hypothesis that polymorphisms in both genes contribute to large inter-patient variability in the clinical efficacy of metformin. The sequences of the 5′-flanking and coding regions of the two genes of interest were screened by single-strand conformation polymorphism (SSCP) analysis. To compare the causative factors between responders and non-responders, we performed stepwise discriminant functional analysis. Age, body mass index (BMI) and treatment with lipid-lowering agents were demonstrated as positive predictors, and two mutations in the *OCT1* gene, –43T > G in intron 1 and 408Met > Val (1222A > G) in exon 7, were negative and positive predictors, respectively, for the efficacy of metformin; the predictive accuracy was 55.5% ($P < 0.05$). Subsequent study indicated that OCT1 mRNA levels tended to be lower in human livers with the 408Met (1222A) variant, though the differences did not reach the level of significance. In this study it is suggested that *OCT1* and *OCT2* gene polymorphisms have little contribution to the clinical efficacy of metformin.

Keywords Metformin · OCT1 · OCT2 · Polymorphisms · Pharmacokinetics · Pharmacodynamics

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Introduction

Metformin is one of the most commonly used drugs for the treatment of type 2 diabetes, but we sometimes encounter patients who do not respond sufficiently, even under approved dosage conditions (e.g., 500–750 mg/day in Japan). Although the effects of metformin on glycemic control and lipids have been reported to be dose dependent, recent pharmacogenomic studies indicate that genetic polymorphisms of drug-metabolizing enzymes and transporters should be taken into consideration when large inter-patient variability in the intensity and duration of both drug effects and side effects is observed. Among various pharmacokinetic-related genes, since renal secretion, not hepatic metabolism, is the major route of elimination of metformin, the contribution of genetic variations in drug transporters is of interest.

Human organic cation transporters (OCTs; OCT1–3) are poly-specific transporters of small and hydrophilic

organic cations, including toxic substances, endogenous compounds (e.g., dopamine and serotonin), and clinically used drugs (e.g., procainamide and amantadine) (Jonker and Schinkel 2004). Among the OCT family, OCT1 is expressed predominantly in the basolateral membrane of hepatocytes, and mouse Oct1, which is homologically and functionally similar to OCT1, is responsible for the hepatic uptake of metformin (Wang et al. 2002, 2003). Although the precise mechanism of the action of metformin remains unclear, it is believed that hepatic uptake is an essential step in reducing hepatic glucose production as well as the occurrence of life-threatening side effects such as lactic acidosis (Hundal et al. 2000; Stumvoll et al. 1995; Wang et al. 2002). Recently, a number of single nucleotide polymorphisms (SNPs) has been identified in the *OCT1* gene. Some of these SNPs have been found to be associated with altered in vitro transport activity (Hundal et al. 2000; Sakata et al. 2003; Shu et al. 2003; Takeuchi et al. 2003).

In the kidney, OCT2, another subfamily of the OCT family, is expressed on the basolateral membrane of the proximal tubule epithelium and is involved in the uptake of many xenobiotics from the bloodstream into renal epithelial cells (Jonker and Schinkel 2004). Kimura et al. (2005) demonstrated that metformin is a good substrate for OCT2, using HEK293 cells expressing OCT2. Similar to those in the *OCT1* gene, functionally different variants have been identified in the *OCT2* gene (Leabman et al. 2002).

We hypothesized that large inter-patient variability in the clinical efficacy of metformin may occur as a result of variations in *OCT1* and/or *OCT2*. In this report we evaluated the functional significance of genetic polymorphisms of *OCT1* and *OCT2* genes with regard to the efficacy of metformin in patients with type 2 diabetes. To date, no study has addressed the genotype–phenotype relationship in light of *OCT* in humans.

Materials and methods

Study subjects

Thirty-three patients (nine men and 24 women; mean age 60 years, range 29–73 years) treated with metformin for at least 1 month were enrolled. We excluded patients who discontinued metformin because of adverse effects (e.g., diarrhea and headache). There are no generally accepted criteria in the clinical cut-off point to divide patients into responders and non-responders. Thus, we selected the criteria empirically, based on our clinical experiences and a previous report (Takei et al. 2001) as follows: (1) responders [$n = 24$; mean age 62 years, range 29–73 years; mean body mass index (BMI) 25.4 kg/m^2, range 20.4–34.5 kg/m^2], i.e., those whose HbA_{1c} levels had decreased by more than 0.5% from the baseline within 3 months of metformin therapy and had remained low for more than 3 months; and (2) non-responders ($n = 9$; mean age 56 years, range 34–69 years; mean BMI 25.1 kg/m^2, range 17.8–30.6 kg/m^2), i.e., those for whom either metformin therapy had been discontinued within 3 months and/or after another hypoglycemic drug (e.g., sulfonylurea) had been added to the therapy because of insufficient improvement in HbA_{1c} levels. Eighteen of the responders and six of the non-responders were treated with the maximum approved daily dose in Japan (i.e., 750 mg/day). Eight of the responders and four of the non-responders received metformin monotherapy, and others were co-medicated with sulfonylurea, α-glycosidase inhibitor or insulin. This study was approved by the Ethics Review Board of the Faculty of Medicine, Tottori University, and all subjects gave informed consent before participating.

Identification of variants in *OCT1* and *OCT2* genes

Genomic DNA was extracted from peripheral blood. The primer design was based on the sequence of the 5'-flanking region and the intron/exon junction of *OCT1* and *OCT2* genes (GenBank accession number AL353625 for *OCT1*, AL162582 for *OCT2*). Primers were designed to divide all 11 exons of each gene into fragments of approximately 350 bp so that mutations could be screened by subsequent single-strand conformation polymorphism (SSCP) analysis. Polymerase chain reaction (PCR) products were sequenced either directly or after subcloning on an ABI 3100 automatic sequencer (Applied Biosystems, Foster City, VA, USA).

Quantitative real-time PCR

Total RNA was extracted with an RNAeasy kit (Qiagen, Hilden, Germany) from 58 human liver samples (33 Caucasian and 25 Japanese non-diabetic donors), and reverse transcribed into cDNA using oligo dT primers and reverse transcriptase. OCT1 mRNA was quantified by real-time PCR using an ABI PRISM 7700 sequence detector (Applied Biosystems) with SYBR-green detection of reaction products. Primers for OCT1 mRNA were directed at a sequence that spans the junction of exons 9 and 10, corresponding to open reading frame 1437–1509; 5′-CAC

CCCCTTCATAGTCTTCAG-3′ (forward) and 5′-GCC CAACACCGCAAACAAAAT-3′ (reverse). The copy number of the transcript was measured against the copy-number standard curve of cloned target templates consisting of serial tenfold dilution points. β_2-microglobulin mRNA was used as the reference gene for OCT1 mRNA.

Statistical analysis

The significance of differences in allelic frequency was calculated by χ^2 analysis using 2×2 contingency tables. Statistical differences among the data for each group were determined by analysis of variance (ANOVA), followed by the Fisher least significant difference test. To compare the causative factors between responders and non-responders, we performed stepwise discriminant functional analysis. At each step, improvement in the χ^2 and the P values was used to check whether the variable entered at that step significantly improved the discrimination. The independent variables were as follows: polymorphisms, gender, age, duration of disease, types and numbers of co-medicated anti-hyperglycemic drugs, daily dose of metformin, BMI, aspartate aminotransferase, alanine aminotransferase, total cholesterol, high-density lipoprotein (HDL) and treatment with lipid-lowering agents (statins and fibrates). Data are shown as means ± SDs. A P value <0.05 was considered to be significant.

Results

Although the time course of change in the mean daily dose of metformin (milligrams per kilogram per day) and the initial level of HbA_{1c} did not differ between the two groups, the mean HbA_{1c} level was significantly lower in the responder group than in the non-responder group during metformin therapy (Fig. 1).

To identify polymorphisms, we performed PCR–SSCP analysis of all 11 exons of the two genes of interest (*OCT1* and *OCT2*), using DNA obtained from all patients, and the allelic frequency was compared between the responder and non-responder groups. In the *OCT1* gene, 11 polymorphisms were detected by SSCP analysis and identified by subsequent sequencing; none were novel polymorphisms (Table 1). Of these, five SNPs resulted in the following amino acid substitutions: 123C > G (41Phe > Leu), 350C > T (117Pro > Leu), 480C > G (160Phe > Leu), 1022C > T (341Pro > Leu), and 1222A > G (408Met > Val). Although 480C > G, 1022C > T, and 1222A > G variants had a relatively high incidence, 123C > G and 350C > T were observed in one patient as heterozygosity. In the *OCT2* gene, two non-synonymous variants were observed: 602C > T (201Thr > Met) and 808G > T (270Ala > Ser). Altogether, there were no remarkable differences in the prevalence of any mutation between responders and non-responders.

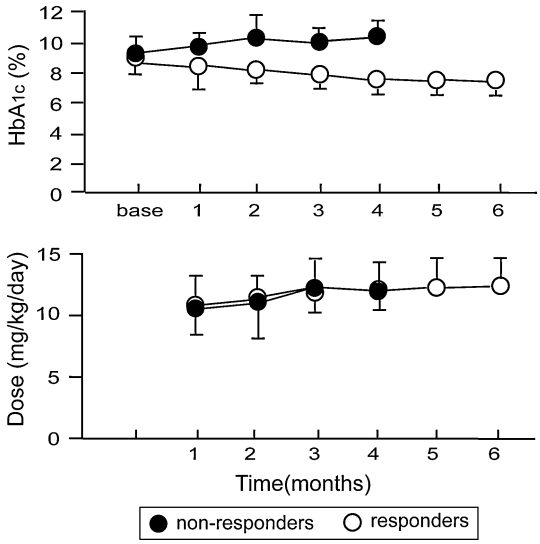

Fig. 1 Time course of changes in HbA_{1c} and metformin daily dose during the observation period in responders and non-responders

The result of discriminant functional analysis is shown in Table 2. Variables selected by the discriminant process were age, BMI, treatment with lipid-lowering agents and two mutations in the *OCT1* gene (–43T > G and 1222A > G). Other variables, such as duration of disease, daily dose of metformin, and types of co-medicated anti-hyperglycemic drugs, had no significant effect on the discrimination. Although age, BMI and treatment with lipid-lowering agents were demonstrated as positive predictors, –43T > G and 1222A > G (408Met > Val) were negative and positive predictors, respectively, for the efficacy of metformin. Total predictive accuracy using these factors was 55.5% ($\chi^2 = 5.59$, $P < 0.05$).

As shown in Table 1, since the frequency of the 408Met allele tended to be higher in non-responders than in responders (0.28 vs 0.19), and since the non-synonymous 408Met > Val variant was selected as a positive predictor, we next examined the association of the 408Met > Val (1222A > G) variant with the expression of OCT1 mRNA in the human liver samples (Fig. 2). Of 58 samples, we analyzed 31 that were homozygotes for the –43T variant (–43T/T). The mean (± SD) hepatic expression level of OCT1 in homozygotes for 408Met (1222A/1222A), heterozygotes for

Table 1 Summary of *OCT1* and *OCT2* gene polymorphisms

Gene	Location	Position[a]	Allele[a]	Nucleotide sequence	Amino acid substitution	Allelic frequency (95% CI)	
						Responders (n = 24)	Non-responders (n = 9)
OCT1	Exon 1	123	C	tcttCctgg	41Phe > Leu	0.98 (0.94–1.02)	1.000
			G	tcttGctgg		0.02 (–0.02–0.06)	0.000
		156	T	agagTcctg	Ser52	0.58 (0.44–0.72)	0.44 (0.21–0.67)
			C	agagCcctg		0.42 (0.28–0.56)	0.56 (0.33–0.79)
		243	C	cgggCgagg	Gly81	1.000	0.94 (0.84–1.05)
			T	cgggTgagg		0.000	0.06 (–0.05–0.16)
		350	C	ctgcCgctg	117Pro > Leu	1.000	0.94 (0.84–1.05)
			T	ctgcTgctg		0.000	0.06 (–0.05–0.16)
	Intron 1	–43	T	atggTtctg	–	0.42 (0.28–0.56)	0.33 (0.12–0.55)
			G	atggGtctg		0.58 (0.44–0.72)	0.67 (0.45–0.89)
	Exon 2	480	C	tcttCtttg	160Phe > Leu	0.88 (0.78–0.97)	0.83 (0.66–1.01)
			G	tcttGtttg		0.13 (0.03–0.22)	0.17 (–0.01–0.34)
	Exon 6	1022	C	acgcCgcgc	341 Pro > Leu	0.81 (0.70–0.92)	0.89 (0.74–1.03)
			T	acgcTgcgc		0.19 (0.08–0.30)	0.11 (–0.03–0.26)
	Exon 7	1222	A	ggccAtgtc	408Met > Val	0.19 (0.08–0.30)	0.28 (0.07–0.49)
			G	ggccGtgtc		0.81 (0.70–0.92)	0.72 (0.52–0.93)
	Inron 7	+8	Deletion	(ggtaagtt)0		0.81 (0.70–0.92)	0.72 (0.52–0.93)
				(ggtaagtt)1		0.19 (0.08–0.30)	0.28 (0.07–0.49)
	Intron 10	+26	C	actcCgagg		0.98 (0.94–1.02)	1.000
			T	actcTgagg		0.02 (–0.02–0.06)	0.000
		–21	C	ccaaCttt		0.46 (0.32–0.60)	0.39 (0.16–0.61)
			T	ccaaTttt		0.54 (0.40–0.68)	0.61 (0.39–0.84)
OCT2	Exon 3	602	C	tataCgtgg	201Thr > Met	0.98 (0.94–1.02)	0.94 (0.84–1.05)
			T	tataTgtgg		0.02 (–0.02–0.06)	0.06 (–0.05–0.16)
	Exon 4	808	G	agttGctct	270Ala > Ser	0.92 (0.88–0.96)	0.94 (0.84–1.05)
			T	agttTctct		0.08 (0.04–0.12)	0.06 (–0.05–0.16)

[a] Position is relative to the ATG start site, and the reference allele for each gene was obtained from the GenBank accession numbers AL353625 for OCT1 and AL162582 for OCT2

408Met > Val (1222A/1222G), and homozygotes for 408Val (1222G/1222G) was 0.69 ± 0.43, 0.92 ± 0.53, and 1.01 ± 0.66, respectively. Although the hepatic expression of OCT1 tended to be lower in livers with the 408Met (1222A) variant, the differences did not reach the level of significance. In the –43T > G variant, the mean OCT1 expression level in –43T/T (n = 18), –43T/G (n = 8), and –43G/G (n = 10) samples (all harbored the 1222G/1222G allele) was 1.01 ± 0.70, 1.04 ± 0.34, and 1.46 ± 0.53, respectively.

Table 2 Stepwise discriminant functional analysis of the efficacy of metformin

Variable	Coefficient	χ^2 value	P
Age	0.09	5.59	0.05
BMI	0.23		
Treatment with lipid-lowering agents	2.25		
–43T > G (intron 1)	–2.35		
408Met > Val (exon 7)	2.51		

Predictive accuracy = 55.5%

Discussion

In this study we first analyzed mutations in *OCT1* and *OCT2* and then examined the association between polymorphisms in these two genes and the efficacy of metformin, because in vitro studies have indicated that OCT1 and OCT2 are responsible, respectively, for the hepatic and renal transport of metformin (Kimura et al. 2005; Wang et al. 2002, 2003). In contrast to studies in vitro and with animals, there are no data from human studies on the contribution of these polymorphisms to the phenotypes of metformin.

In the *OCT1* gene, all non-synonymous variants except 41Phe > Leu and 117Pro > Leu have already been identified in some racial populations, with a frequency of 0.005–0.81 (Kerb et al. 2002; Shu et al. 2003). The 41Phe > Leu and 117Pro > Leu allele frequencies were relatively low (0.004), and they have already been reported in a Japanese population (Itoda et al. 2004). Recent expression studies have indicated that 341Pro > Leu had decreased ability to transport test compounds, while 160Phe > Leu and 408Met > Val were unchanged (Kerb et al. 2002; Sakata et al. 2003;

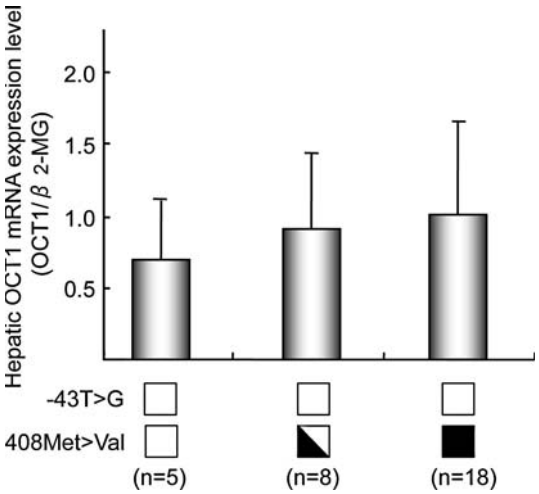

Fig. 2 Hepatic OCT1 mRNA expression levels with regard to the 408Met > Val (1222A > G) variant. Among 58 samples, 31, which were homozygotes for the –43T variant (–43T/T), were analyzed. *Open squares*, *partially filled squares* and *closed squares* correspond to patients homozygous for the 408Met (1222A) allele and heterozygous and homozygous for the 408Val (1222G) allele

Shu et al. 2003). Interestingly, the 341Pro > Leu variant was observed in Asian and African American populations but not in Caucasians (Shu et al. 2003); however, there was no difference in the allele frequency of 341Pro > Leu between responders and non-responders to metformin therapy in this study.

In contrast to those in the *OCT1* gene, it appears that the number of non-synonymous variants in the *OCT2* gene and their allelic frequencies were lower than in other known drug transporter genes such as *MDR1*, *MRP1*, *MRP2*, and *OATP-C* (Nishizato et al. 2003). These observations are consistent with the finding of a lower frequency of non-synonymous variants in ethnically diverse genomic DNA samples (Leabman et al. 2002). Recent population-genetic analysis has demonstrated that selection has acted against amino acid changes in OCT2 (Leabman et al. 2002), suggesting that OCT2 is relatively intolerant of non-synonymous changes. In general, the less frequent non-synonymous variants resulted in more significant and deleterious functional changes. However, the 270Ala > Ser variant was reported to exhibit subtle functional differences from the reference form of OCT2 (Leabman et al. 2002).

Although there were no remarkable differences in the prevalence of any mutation sites between responders and non-responders, we next carried out discriminant functional analysis including not only genetic polymorphisms but also the patients' background. As shown in Table 2, age, BMI and treatment with lipid-lowering agents were demonstrated as positive predictors of metformin efficacy. These observations are partially in agreement with the findings by Knowler et al. (2002), that metformin was less effective in subjects with lower BMI or a lower fasting plasma glucose concentration. BMI > 25 kg/m^2 is defined as obesity in Japan; 66.7% of responders and 44.4% of non-responders were obese in this study. Although the precise mechanism is unknown, these data suggest that metformin is more effective in the case of obesity-induced insulin resistance that is higher fasting plasma glucose. The contribution of lipid-lowering agents was somewhat unexpected, because metformin therapy has been reported to improve both glycemic control and lipid concentrations (i.e., plasma total and low-density lipoprotein cholesterol and triglyceride) in patients with non-insulin-dependent diabetes mellitus (DeFronzo and Goodman 1995). However, in our study, 12 responders and two non-responders were treated with lipid-lowering agents, and most of these patients (11/12 responders and 1/2 non-responders) used HMG-CoA reductase inhibitors (statins). Several studies have shown that low-density lipoprotein (LDL) size rather than plasma LDL level is more correlated with insulin resistance and eventual progression of coronary heart disease (Rizzo and Berneis 2006). Although the efficacy of modifying LDL size is different among agents (fluvastatin and atorvastatin seem to be much more effective agents than pravastatin and simvastatin), statins moderately lower all LDL subclasses, and, somehow, this process seems to make metformin more effective.

Since –43T > G and 408Met > Val (1222A > G) variants were identified as negative and positive predictors, respectively, for the clinical effectiveness of metformin, we evaluated the functional significance of the latter non-synonymous variant in the expression of OCT1 mRNA, using human liver samples. Our findings indicate that samples with the 408Met (1222A) allele tended to be associated with a reduced expression level, as compared with those without the 408Met allele; however, the difference did not reach significance. A recent study using site-directed mutagenesis has indicated that point mutations in the predicted ninth transmembrane domain such as 1222A > G (408Met > Val) do not lead to functional changes (Kerb et al. 2002). We also measured OCT1 mRNA expression with regard to the non-coding –43T > G variant; however, no significant effect was observed. In the present study, the predicted accuracy is still insufficient for its clinical application (i.e., 55.5%). Thus, if these observations are taken into consideration, the contribution of polymorphisms in

OCT1 and *OCT2* genes to metformin efficacy may not be as significant as our expectations had led us to believe. However, since a non-synonymous variant 408Met > Val is often observed simultaneously with other non-synonymous variants (Shu et al. 2003), further in vitro and in vivo studies with regard to the haplotypic consideration, including the non-coding region, are needed to elucidate the functional properties of the variants identified in this study.

While data from only 24 responders and nine non-responders were used, this preliminary investigation is the first study addressing the genotype–phenotype relationship of OCTs in the efficacy of metformin. However, obviously, the small number of patients is a drawback in our study. For example, co-medication of other anti-hyperglycemic drugs in both groups made it difficult for us to judge whether the decreases in HbA_{1c} levels in the responders are attributable to the metformin effect. Clearly, definition of the clinical cut-off point is also essential to divide patients into the two groups correctly. In order to overcome these problems, it is clear that the results in this study should be confirmed in a population study involving large numbers of patients. Nevertheless, this report provides for the possibility of OCTs' functions in humans.

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