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REVIEW

Interindividual and interethnic variability in drug disposition: polymorphisms in organic anion transporting polypeptide 1B1 (OATP1B1; *SLCO1B1*)

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OATP1B1 (*SLCO1B1*) is predominantly expressed at the basolateral membrane of hepatocytes and is critically important for the hepatic uptake and clearance of numerous drug substrates and endogenous compounds. In general, the organic anion transporting polypeptides (OATP; *SLCO*) represent a superfamily of uptake transporters that mediate the sodium-independent transport of a diverse range of amphipathic organic compounds including bile salts, steroid conjugates, thyroid hormones, anionic peptides, numerous drugs and other xenobiotic substances. OATP1B1 is highly polymorphic and a number of relevant and ethnically dependent polymorphisms have been identified and functionally characterized. In particular, the *SLCO1B1* 521T>C and 388A>G polymorphisms are commonly occurring variants in ethnically diverse populations and numerous *in vitro* and clinical studies have evaluated the consequences of these variants to interindividual differences in drug disposition and response. OATP1B1 is particularly important for the disposition of HMG-CoA reductase inhibitors, or statins, as it is known to efficiently transport most statins to their site of action within hepatocytes. Many studies have focused on the consequences of OATP1B1 variants to statin disposition *in vitro* and *in vivo* and would suggest that genetic variability in *SLCO1B1* has important implications for statin pharmacokinetics, risk for statin-induced myopathy, and modulation of statin treatment response. This review describes what is currently known regarding *SLCO1B1* genotype, OATP1B1 protein expression and interindividual and interethnic consequences to drug disposition, with particular focus on statin pharmacokinetics and implications for drug response and toxicity.

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Tables of Links

TARGETS	
Transporters [2]	OATP (SLCO)
ABCG2 (BCRP)	OATP1B1 (SLCO1B1)
BSEP (ABCB11)	OATP1B3 (SLCO1B3)
MATE	OATP2B1
MDR	OCT
MRP	**Enzymes** [3]
NTCP	HMG-CoA reductase
OAT	

LIGANDS	
Atorvastatin	Methotrexate
Atrasentan	Pitavastatin
Cholesterol	Pravastatin
Docetaxel	Rifampicin
Estrone-3-sulfate	Rosuvastatin
Fluvastatin	Simvastatin
Lovastatin	Valsartan

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

Organic anion-transporting polypeptide 1B1 (OATP1B1; *SLCO1B1*) is a membrane transport protein of the organic anion-transporting polypeptide (OATP) transporter superfamily [4, 5]. It functions as a sodium-independent uptake transporter for a broad range of endogenous and xenobiotic compounds with diverse characteristics [4, 6]. Substrates tend to be primarily organic anions with a molecular weight greater than 300 Da, but some substrates may be neutral or even positively charged [7]. OATP1B1 is a genetically polymorphic transporter and is predominantly expressed on the sinusoidal (basolateral) membrane of human hepatocytes (Figure 1A) [8–10]. Recent studies have demonstrated OATP1B1 and its related counterpart OATP1B3 to be amongst the most highly expressed uptake or efflux membrane transporters expressed in the liver [11, 12]. Thus, OATP1B1 plays a major, clinically important role in the hepatic uptake and clearance of many drugs. Functionally relevant and ethnically-dependent polymorphisms in *SLCO1B1* have been identified and characterized. Clinical studies have confirmed OATP1B1 variants to be associated with alterations in the pharmacokinetics of substrate drugs, treatment response, and risk for drug-induced toxicities. This review provides an update on the role of *SLCO1B1* polymorphisms to interindividual and interethnic variability in drug disposition and response.

SLCO1B1 genetic variability

To date, >45 nonsynonymous (NS) sequence variants have been identified in *SLCO1B1* [13, 14], some of which are clinically important due to their altered function [15, 16] (Table 1). The first systematic study of *SLCO1B1* variants identified 14 NS single-nucleotide polymorphisms (SNPs) in 15 haplotypes, many of which (217T>C, 245T>C, 467A>G, 521T>C, 1058T>C, 1294A>G, 1463G>C, 1964A>G) were associated with markedly decreased OATP1B1 transport activity *in vitro* for prototypical substrates such as estrone sulfate and estradiol-17β-D-glucuronide [10]. Moreover, genotypic frequencies were dependent on race in a population of European- and African-Americans. In particular, the 521T>C (rs4149056) SNP, resulting in substitution of alanine for valine at amino acid position 174, was common in European-Americans with an allele frequency of 14% but much less so in African-Americans at 2%. Conversely, the 388A>G (rs2306283) variant, resulting in an asparagine to aspartic acid amino acid change at amino acid position 130 located in the extracellular region of the transporter, was seen predominantly in African-Americans with an allele frequency of 74% but significantly less so in European-Americans at 30%. Additional population genetic studies demonstrate *SLCO1B1* variants exhibit marked differences in their ethnically defined allele frequencies amongst major geographical regions. Pasanen *et al.* [17] investigated the frequencies of 12 SNPs in *SLCO1B1*, including 5 NS variants and two promoter variants, in 941 individuals from 52 populations including Africa, the Middle East, Asia, Europe, Oceania and the Americas (Amerindians). Consistent with initial reports, the low-activity haplotypes *5 (388A/521C) and *15 (388G/521C) have a combined frequency of approximately 15–20% in Europeans, 10–15% in Asians and 2% in sub-Saharan Africans. The *1B (388G) haplotype has a frequency of approximately 26% in Europeans, 39% in South/Central Asians, 63% in East Asians, and as high as 77% in sub-Saharan Africans.

The 521T>C variant, located in exon 5, resulted in significantly decreased OATP1B1 membrane expression by Western blot analysis and cell surface biotinylation experiments, resulting in ~75% decreased uptake transport activity toward estrone-3-sulfate and estradiol-17β-D-glucuronide *in vitro* [10]. Consistent with its decreased membrane expression, the 521T>C SNP affected mainly the maximum transport velocity in comparison to substrate affinity [10]. The deleterious functional consequence of the 521T>C variant was confirmed in subsequent studies with a diverse list of OATP1B1 substrates, including rifampin, pravastatin, atorvastatin, rosuvastatin, atrasentan, ezetimibe glucuronide, methotrexate and docetaxel [9, 13, 18–22]. Another common variant associated with potentially altered transport activity of OATP1B1 is 388A>G (*1b), located in exon 4, but the functional consequences of this variant remain controversial. Quantitative PCR and immunoblotting studies in liver

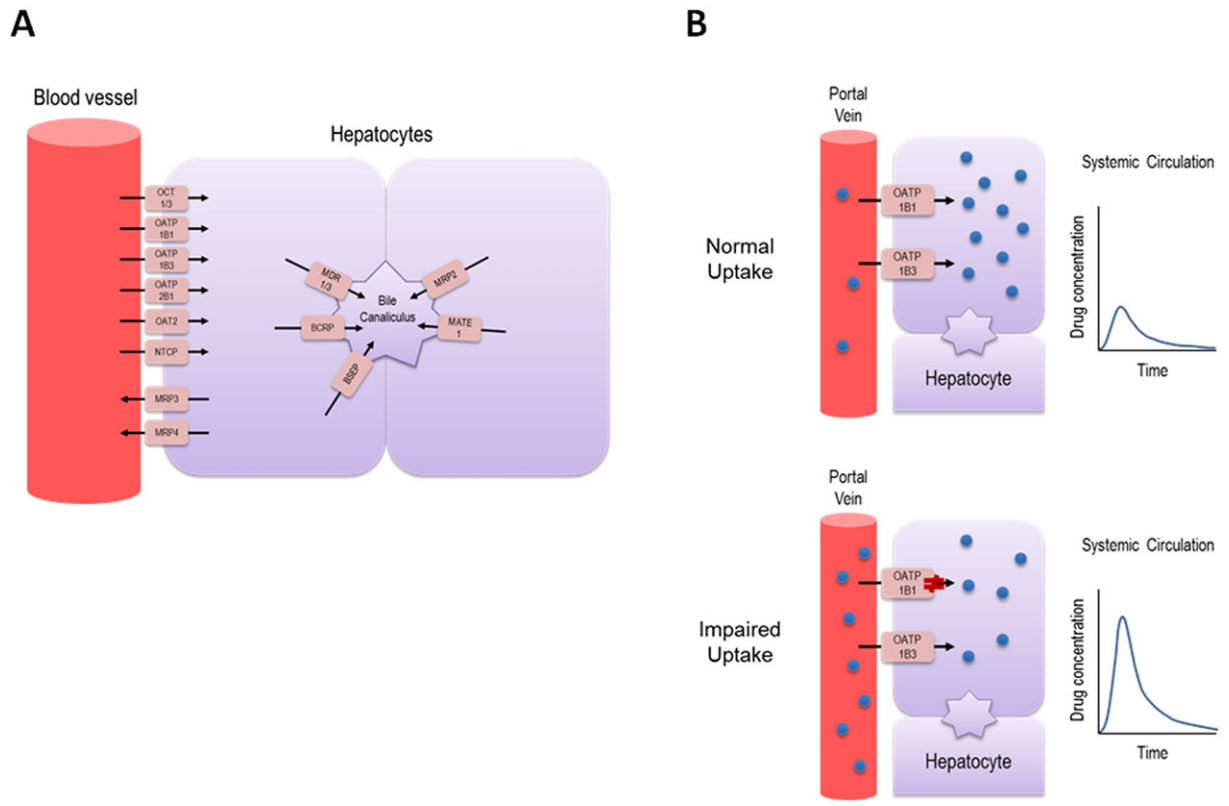

Figure 1

Summary of transporters expressed in human hepatocytes involved in mediating drug uptake and efflux (A), and illustration of the impact of *SLCO1B1* genetic variation on drug disposition *in vivo* (B). Individuals carrying a dysfunctional genetic variant in *SLCO1B1* results in impaired hepatocellular uptake of drug substrates as compared to wild type individuals, leading to significantly increased plasma exposure, which may increase risk for drug-induced adverse effectsBCRP, breast cancer resistance protein; BSEP, bile salt export pump; MATE, multidrug and toxin extrusion; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; NTCP, sodium/taurocholate co-transporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter

samples have demonstrated the 388A>G variant to be significantly associated with increased OATP1B1 expression, suggesting increased functional activity for this variant [12, 23].

Indeed, 388A>G and 521T>C form four distinct haplotypes: *1A (388A/521T), *1B (388G/521T), *5 (388A/521C) and *15 (388G/521C) [17, 24]. In general, the OATP1B1*5 and *15 genotypes confer significantly impaired hepatic uptake [9, 20, 21, 25], resulting in an increased systemic exposure of substrates (Figure 1B), whereas OATP1B1*1B has been associated with decreased systemic exposure due to enhanced hepatic uptake, including statins such as atorvastatin and pravastatin [23, 26, 27]. However, additional studies on the functional consequences of the *1B haplotype have yielded conflicting results in its activity as several studies demonstrated no significant differences in *1A versus *1B for evaluated substrates, such as estrone-3-sulfate, estradiol-17β-D-glucuronide, and docetaxel [9, 10, 18], and even opposite results with increased plasma exposure of pitavastatin for those with the *1B haplotype, suggesting reduced activity for this variant [28, 29]. Additional studies to fully characterize the functional consequences of the 388A>G variant are warranted. Interestingly, coexisting null function mutations in *SLCO1B1* and *SLCO1B3* which resulted in complete and simultaneous deficiencies of both hepatic OATP1B1 and OATP1B3 have been linked to families with Rotor syndrome, a rare, benign hereditary syndrome characterized by conjugated hyperbilirubinemia, coproporphyrinuria and strongly reduced liver uptake of many diagnostic compounds, including cholescintigraphic tracers [30].

While common OATP1B1 variants have received the most attention, rare *SLCO1B1* genotypes may also have functional consequences *in vivo*. Ramsey *et al.* [13] identified 93 SNPs in *SLCO1B1* in 699 patients, of which 15 were NS SNPs. Three NS SNPs (388A>G, 463C>A and 521T>C) were common, with a minor allele frequency (MAF) >5%, one (1929A>C) had low frequency (MAF 1%–5%), and 11 were rare (MAF < 1%). In examining the impact of rare and common *SLCO1B1* variants on drug response, this group noted rare *SLCO1B1* NS variants were associated with reduced methotrexate clearance. In a multivariate analysis, *SLCO1B1* variants accounted for 10.7% of population variability in methotrexate clearance. The *5 and *15 haplotypes and two rare novel haplotypes, *23 (211G>A) and *31 (388A>G/1463G>C), were associated with low methotrexate clearance. Interestingly, though, while common NS variants accounted for the majority of that variability, rare damaging NS variants comprised 17.8% of *SLCO1B1*'s effects with larger effect sizes than common variants,

Table 1

Selected SLCO1B1 polymorphisms

Nucleotide change	rs number	Amino acid change	*In vitro* function	*In vivo* function	Caucasians	African-Americans	Asians
c.217T>C	rs56101265	p.F73L	Decreased		0–2	0	0
c.245T>C	rs56061388	p.V82A	Decreased		0–2	0	0
c.388A>G	rs2306283	p.N130D	Increased or unchanged	Decreased AUC pravastatin, atorvastatin Increased AUC pitavastatin	30–45	72–83	59–86
c.452A>G	rs2306282	p.N151S			0–3	0–2	0–4
c.463C>A	rs11045819	p.P155T	Unchanged		13–23	2–10	0–3
c.467A>G	rs72559745	p.E156G	Decreased		0–2	0	0
c.521T>C	rs4149056	p.V174A	Decreased	Increased AUC statins Increased risk statin-induced myopathy Decreased lipid lowering efficacy	8–20	1–8	8–16
c.578T>G	rs72559746	p.L193R	Decreased		<0.3		
c.733A>G	rs11045852	p.I245V			0	0–7	0
c.1007C>G	rs72559747	p.P336R	Unchanged		0		1
c.1058T>C	rs55901008	p.I353T	Decreased		0–2	0	0
c.1200C>G	rs59113707	p.F400L			0	2	0
c.1294A>G	rs56387224	p.N432D	Decreased or unchanged		0–1	0	0
c.1385A>G	rs72559748	p.D462G	Unchanged		0–1	0	0
c.1463G>C	rs59502379	p.G488A	Decreased		0	3–9	0
c.1495A>G	rs74064213	p.I499V				6	
c.1929A>C	rs34671512	p.L643F	Unchanged		3–9	5–13	0–1
c.1964A>G	rs56199088	p.D655G	Decreased		0–2	0	0
c.2000A>G	rs55737008	p.E667G	Unchanged		0–2	0–34	0

suggesting rare variants are likely to have an important effect on pharmacogenetic phenotypes [13].

Ethnic variability in OATP1B1 expression

It has been demonstrated that *SLCO1B1* variants are associated with altered OATP1B1 liver expression but until recently, little was known regarding interethnic differences in OATP1B1 expression. Peng *et al.* [12] utilized a targeted quantitative proteomic approach to determine hepatic protein concentrations of transporters including OATP1B1 in a panel of human livers (n = 141) across ethnic groups, including Caucasians, Asians and African-Americans. Interestingly, when compared across ethnicity and accounting for genotype, the hepatic expression levels of OATP1B1 were higher in Asians relative to Caucasians, while there were too few African-American samples to draw any conclusions. Accordingly, additional potential explanations include regulatory or epigenetic modifications that are ethnically-dependent that result in race-dependent differences in OATP1B1 expression that are independent of OATP1B1 genotype. Furthermore, the effects of *SLCO1B1* polymorphisms on OATP1B1 hepatic abundance were examined by comparing the protein concentrations of different allelic variants. OATP1B1 hepatic protein expression was significantly associated with genotype as 388A>G expression was significantly higher than wild type 388A>A. This is in concordance with a previous study that had noted the 388A>G variant to be associated with increased OATP1B1 hepatic protein expression [23]. But, interestingly, there was no difference in protein expression between 521T>C and wild type 521T>T. However, it should be noted that the proposed mechanism of impaired function for the 521T>C variant is a mistrafficking defect that results in significantly decreased cell surface expression as total absolute protein content for the 521T>C compared to the *1a wild type allele was equivalent [10].

Effects of *SLCO1B1* polymorphisms on pharmacokinetics and drug disposition

Features of the clinical pharmacokinetics of statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, are amongst the most commonly prescribed drugs worldwide and used as antihyperlipidemic agents in the treatment of hypercholesterolemia and the primary and secondary prevention of coronary artery disease [31, 32]. However, their use has been associated with adverse drug effects including severe muscle-related side effects such as rhabdomyolysis and myopathy [33]. Statins are partly (pravastatin and rosuvastatin) or rarely (other statins) eliminated into the urine through the kidneys in an unchanged form; they are mainly delivered within hepatocytes to their site of action in inhibiting HMG-CoA reductase by uptake transporters and eliminated into the bile by efflux transporters with minimal metabolism [33–35]. Many statins are well known to be substrates of hepatic uptake transporters, including OATP1B1, OATP1B3 and OATP2B1 [36]. However, studies have suggested OATP1B1 to be the major hepatic OATP to be involved in hepatic uptake and clearance. For example, the contribution of OATP1B1 to the overall hepatic uptake of pitavastatin and rosuvastatin was estimated to be 92% [37] and 77% [38], respectively.

OATP1B1 is thus considered the major transporter involved in the hepatic uptake of statins. However, several OATP1B1 genetic variants have been found to be associated with impaired uptake activity of numerous drug substrates, including statins, most notably the commonly occurring 521T>C variant. In a number of clinical studies, subjects with the *SLCO1B1* 521T>C polymorphism have demonstrated reduced nonrenal (hepatic) clearance of pravastatin [24, 39–41], rosuvastatin [42–45], atorvastatin [42, 45, 46], simvastatin acid [45, 47–49] and pitavastatin [50], as compared with subjects with the *SLCO1B1* wild-type alleles. The clinical consequences of individuals carrying loss of function *SLCO1B1* alleles have also been noted with regard to statin-induced adverse effects. A genome-wide association study (GWAS) identified an intronic variant in *SLCO1B1* in near complete linkage disequilibrium ($r^2 = 0.97$) with the *SLCO1B1* 521T>C allele to be the single most important predictor of simvastatin-associated myopathy risk in the SEARCH trial in patients who received high-dose 80 mg simvastatin [51]. The odds ratio for myopathy risk due to *SLCO1B1* 521T>C was 4.5 for heterozygous carriers and 16.9 for homozygous carriers. These results were replicated in 10 000 patients who received 40 mg simvastatin in the Heart Protection Study, demonstrating a myopathy odds ratio of 2.6 for each copy of the 521T>C allele. The vast majority of the subjects in this study were Caucasian and the study conclusions may have more important implications for Caucasian and Asian populations as the genotypic frequency of the 521T>C allele approaches 15–20% in these ethnic populations, whereas they are significantly less common in African-American and Hispanic populations. The association between the 521T>C SNP and statin adverse events was subsequently confirmed for simvastatin and also demonstrated for atorvastatin, but not associated in subjects taking pravastatin, suggesting the risk for statin-induced adverse events modulated by OATP1B1 genotype is influenced by the choice of statin being administered [52]. Furthermore, in the setting of *SLCO1B1* 521T>C genotype, gender has been reported to also contribute to interindividual variability in pharmacokinetics and treatment efficacy of statins [53, 54].

The functional consequences of the *SLCO1B1* 388A>G polymorphism (*SLCO1B1*1b*) has also been evaluated. Maeda *et al.* [27] showed a good correlation with the **1b* allele among the area under the plasma concentration–time curve (AUC) values of pravastatin, valsartan and temocapril in a three-period crossover pharmacokinetic study. When oral administration of these drugs was performed separately in each period in 23 healthy subjects with carriers of *SLCO1B1* 388A>G and/or 521T>C variants, the subjects with 388A>G revealed higher nonrenal clearance, representing the hepatic uptake clearance of pravastatin, and increased transport activity compared to the **1a* allele. This would be consistent with studies demonstrating increased protein expression for those who carry the *1b allele [12, 23]. While this higher nonrenal (hepatic) clearance in subjects with 388A>G was also observed when pravastatin or lovastatin was used in Caucasians [26, 41, 55], and pitavastatin in Koreans [56], other conflicting studies have demonstrated either no differences or even opposite differences to the **1a* allele such as with rosuvastatin in Caucasians [44], Koreans [57] and Chinese patients [43], pitavastatin in Chinese [29], or simvastatin acid in Koreans [49]. Further adequately powered studies should be conducted to assess the influence of *SLCO1B1* 388A>G genotype on statin pharmacokinetics and determine whether this has any clinical implications for statin response and risk for adverse effects.

There is also data regarding the influence of OATP1B1 genotype to statin response. In short-term clinical studies of less than 3 months, when compared to those who are wild-type, the *SLCO1B1* 521T>C variant was associated with modest increases in LDL-cholesterol for patients receiving pravastatin, but not rosuvastatin [58–61]. This is consistent with the impaired function of this variant resulting in reduced hepatic uptake and thus decreased inhibition of HMG-CoA reductase within hepatocytes. A more recent population-based study confirmed a statistically significant association with lower statin-induced total cholesterol reduction in those with *SLCO1B1* 521T>C genotype and receiving either simvastatin, pravastatin, lovastatin or fluvastatin [40]. No effect was noted for atorvastatin. Assessment of achievement of treatment goals according to published cardiovascular guidelines showed a lower rate of successful treatment for those harbouring the *SLCO1B1* 521T>C variant and receiving either simvastatin or pravastatin. The *SLCO1B1* 388A>G variant has generally not been associated with significant changes in LDL or total cholesterol response [40, 62, 63].

Ethnic variability in the pharmacokinetics of statins

Ethnic variability has been observed in the plasma exposures of statins between Caucasians and Asians or between Caucasians and African-American populations. For example, a

higher systemic plasma exposure of pravastatin was observed in Caucasians as compared with African-Americans [41] and plasma exposure of rosuvastatin was higher in Asians than that in Caucasians living in the same environments, Singapore [64] or the United States [44]. When Caucasians and African-Americans were compared after a single oral 40 mg dose of pravastatin was administrated, a higher plasma exposure of pravastatin was observed in Caucasians as compared with African-Americans [41]. The CL/F (oral clearance) in African-Americans was 1.4 times higher than in Caucasians. This significant ethnic variability was still observed even after adjusting for *SLCO1B1* 521T>C and 388A>G genotypes, gender, and BSA, and assay sensitivity as covariates, suggesting other genetic or non-genetic factors may contribute to the interethnic and interindividual variability in pravastatin disposition [41].

Systemic exposure to rosuvastatin was observed to be approximately two-fold higher in Japanese subjects living in Japan compared with white subjects in Western Europe or the United States [65–67]. A population pharmacokinetic analysis revealed that the apparent oral clearance of rosuvastatin was reduced by 44% in Asian subjects, mainly Japanese subjects living in Japan, compared to Caucasian subjects living in the UK, Europe or the USA [68]. Moreover, clinical rosuvastatin pharmacokinetic studies have been conducted with subjects living in the same environment, either Singapore or the US [44, 64]. When the pharmacokinetics of rosuvastatin in Asians were compared with those in Caucasian subjects living in the same environment, a remarkable difference in plasma AUC values between Caucasians and Asians was confirmed. Rosuvastatin plasma exposure was significantly higher in Asians and similar to that in Japanese populations and *SLCO1B1* genotypes (388A>G or 521T>C) did not account for the observed pharmacokinetic differences. Rosuvastatin exposure was higher in subjects carrying the *SLCO1B1* 521C allele compared with that in non-carriers of this allele, but since the allele frequency of this variant is similar in Asians and Caucasians, interethnic differences in statin disposition cannot be explained by *SLCO1B1* genotype alone [44]. Based on the data from these collective studies, in the US, the recommended initial dose of rosuvastatin for Asians is 5 mg, which is half of the dose recommended for Caucasians.

Interestingly, a common nonsynonymous variant, 421C>A (rs2231142; p. Gln141Lys) resulting in significantly decreased transport activity, in *ABCG2* (BCRP), an efflux transporter localized to the apical membranes of hepatocytes and intestinal enterocytes and capable of statin transport, may partially explain interethnic differences in rosuvastatin exposure between Asians and Caucasians [44, 69, 70]. The frequency of 421C>A in *ABCG2* is lower in Caucasians (~9–14%) than in Asians (~35%) [70, 71]. Birmingham *et al.* [45] recently assessed plasma exposure of atorvastatin, rosuvastatin and simvastatin in Caucasian and Asian subjects. Polymorphisms in *SLCO1B1* 521T>C or *ABCG2* 421C>A were associated with higher exposure to rosuvastatin, atorvastatin and simvastatin acid across ethnic populations. However, in individuals carrying wild-type alleles for both *SLCO1B1* and *ABCG2*, plasma AUC still appeared to be higher for rosuvastatin, atorvastatin and simvastatin acid in Chinese and Japanese subjects compared with Caucasians, respectively. Therefore, despite the differences in the frequency of the *ABCG2* 421C>A allele amongst Asians and Caucasians, this alone does not explain the increased plasma exposure of statins in Asians when compared to Caucasians. Tomita *et al.* [72] conducted quantitative pharmacokinetic analyses of published studies to date evaluating statin plasma exposure in Asian and Caucasian populations. They suggest that OATP1B1-mediated hepatic intrinsic uptake clearance, where the ratio of OATP1B1 activity in Japanese/Caucasians is 0.584 and is independent of *SLCO1B1* genotype, may explain the ethnic variability in plasma AUCs of statins. However, the reasons underlying ethnic differences in OATP1B1 activity are not understood. An analysis of cell surface protein expression levels of OATP1B1 in liver samples from Caucasians and Asians may help to support this hypothesis regarding differences in intrinsic activity.

Conclusion

OATP1B1 is an important hepatic drug uptake transporter that can mediate the uptake and clearance of numerous endogenous compounds and drugs. It is also highly polymorphic and a number of functionally relevant and ethnically dependent polymorphisms have been identified and characterized. In this review, we describe what is currently known regarding *SLCO1B1* genotype, OATP1B1 protein expression, and the resulting interindividual and interethnic consequences to drug disposition, focusing particularly on statin pharmacokinetics and drug response in populations of Caucasian, African-American and Asian subjects. *SLCO1B1* genotype significantly influences statin pharmacokinetics, risk for statin-induced adverse effects such as myopathy, and the treatment efficacy of certain statins. However, *SLCO1B1* genotype alone does not entirely account for observed significant differences in plasma statin exposure amongst ethnic groups. Additional studies focused on delineating the membrane-specific expression of OATP1B1 amongst these groups may help to clarify these differences.

Competing Interests

The authors have no competing interests to declare.

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