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MOLECULAR BASIS OF ETHNIC DIFFERENCES IN DRUG DISPOSITION AND RESPONSE

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■ **Abstract** Ethnicity is an important demographic variable contributing to interindividual variability in drug metabolism and response. In this rapidly expanding research area many genetic factors that account for the effects of ethnicity on pharmacokinetics, pharmacodynamics, and drug safety have been identified. This review focuses on recent developments that have improved understanding of the molecular mechanisms responsible for such interethnic differences. Genetic variations that may provide a molecular basis for ethnic differences in drug metabolizing enzymes (CYP 2C9, 2C19, 2D6, and 3A4), drug transporter (P-glycoprotein), drug receptors (adrenoceptors), and other functionally important proteins (eNOS and G proteins) are discussed. A better understanding of the molecular basis underlying ethnic differences in drug metabolism, transport, and response will contribute to improved individualization of drug therapy.

INTRODUCTION

The term ethnicity is a multidimensional classification that encompasses shared origins, social background, culture, and environment (1, 2). Ethnicity is an important determinant of drug metabolism and response and therefore contributes to interindividual variability. The definition of ethnicity, encompassing both genetic and environmental factors, is different from that of race (2). It is generally recognized that the effects of ethnicity on drug metabolism and response are determined by both genetic and environmental factors to a varying extent, depending on the ethnic groups and probe drugs studied (3–8a). Increased research in population pharmacogenetics (3–13) has led to the coining of terms "pharmacoanthropology" (14) and "ethnopharmacology" (11).

DRUG METABOLIZING ENZYMES

CYP2C Subfamily

In human liver microsomes the cytochrome P-450 (CYP) 2C subfamily is second in quantity only to the P-450 3A subfamily (15). Its four known members are CYP 2C8, 2C9, 2C18, and 2C19 (16, 17). Of these, CYP 2C9 and 2C19 are the predominant *CYP2C* gene products. Comparison of the amino-terminal amino acid sequence of CYP2C9 shows that it differs from CYP2C19 by only two residues (16). Genetic variations in both CYP2C9 and 2C19 have clinical significance.

CYP2C9 CYP2C9 contributes ~20% of total hepatic P-450 content (18) and is one of the important drug metabolizing enzymes in humans (19). It has many clinically relevant substrates, including the oral anticoagulants warfarin and acenocoumarol, the oral hypoglycemics tolbutamide and glipizide, the anticonvulsant phenytoin, the loop diuretic torsemide, the angiotensin II–receptor antagonist losartan, the HMG-CoA inhibitor fluvastatin, and a number of nonsteroidal anti-inflammatory drugs (NSAIDs) (16, 19).

An early study of tolbutamide metabolism suggested that ~30% of subjects were poor metabolizers (PMs) (20). However, many subsequent studies, including a survey of tolbutamide oxidation capacity in 106 unrelated Australian participants that failed to find a single PM (21), indicated that the frequency of the CYP2C9 PM phenotype is low (22–29).

The gene encoding CYP2C9 protein is localized on chromosome 10 (30), has 9 exons, and is ~55 kb in size (GenBank accession numbers: L16877–L16883) (31). *CYP2C9* cDNA encodes a protein of 490 amino acids. There appear to be at least two naturally occurring variants: the wild-type $Arg^{144}Ile^{359}$ (designated *CYP2C9*1*), $Cys^{144}Ile^{359}$ (designated *CYP2C9*2*), and $Arg^{144}Leu^{359}$ (designated *CYP2C9*3*). The *CYP2C9*2* allelic variant has an exchange of $C^{430} \rightarrow T$ in exon 3, and *CYP2C9*3* has an exchange of $A^{1075} \rightarrow C$ in exon 7. In vitro studies have shown that the allelic variants of *CYP2C9* differ in their affinity (K_m) and/or intrinsic clearance (V_{max}/K_m) for different substrates of CYP2C9 (21, 24, 32–35). For example, the *CYP2C9*2* variant was found to be associated with impaired 6- and 7-hydroxylation of *S*-warfarin (21, 32). However, other studies found that this variant resulted in a small or negligible decrease in the V_{max} for tolbutamide (21, 24, 32, 36), did not alter CYP2C9-mediated methyl hydroxylation of torsemide (34), and had little effect on *S*-warfarin hydroxylation (36, 37). In clinical studies individuals heterozygous for *CYP2C9*1/*2* required a 20% lower mean maintenance dose of warfarin to maintain therapeutic anticoagulation than wild-type homozygotes (38). Individuals homozygous for *CYP2C9*2* had 58.2% higher mean phenytoin trough levels than *CYP2C9*1* homozygotes (26).

The *CYP2C9*3* variant has been found to have a pronounced reduction in catalytic activity across all CYP2C9 substrates. In vitro evidence revealed that the product of the *CYP2C9*3* variant had a significantly lower maximum catalytic rate

(with lower V_{max} value) and/or lower affinity (with higher K_m value) for *S*-warfarin, tolbutamide, and phenytoin than the wild-type form (18, 21, 24, 33, 36, 39). Individuals homozygous for *CYP2C*3* have been identified to be PMs of *S*-warfarin (25), phenytoin (23, 26, 40), glipizide (40), tolbutamide (23, 24, 41), and losartan (23, 27). Also, in individuals heterozygous for *CYP2C9*3* decreased metabolic clearance of phenytoin (26, 42, 43), *S*-warfarin (25, 28, 29, 38, 44, 45), and acenocoumarol (45a) was reported. Thus, the *CYP2C9*3* variant is a major genetic determinant of variability in the disposition of CYP2C9 substrates.

The relationship between ethnicity and CYP2C9 expression or activity is less clear. Using an immunochemical approach to quantify P-450 content, Shimada et al found that P-450 2C (principally CYP2C9) was not different in Caucasian and Japanese liver microsomes (n = 30 each) (15). A limited number of in vivo studies suggested that African Americans had slower hepatic metabolism of oral phenytoin than Caucasian Americans (46). Caucasians (American or German) had a higher mean K_m value (5.7–6.8 μg/ml; here estimated from population pharmacokinetic data) for phenytoin than did East Asians (Chinese or Japanese) (2.2–3.2 μg/ml) (47), but there are few studies comparing the disposition of CYP2C9 substrate drugs in different ethnic groups.

More recently, analysis of *CYP2C9* polymorphisms has been performed across various ethnic groups. The allelic frequencies of both *CYP2C9* variants (**2* and **3*) in different ethnic groups are summarized in Table 1. The *CYP2C9*2* variant is present only in black (∼3%) and white (∼10%) populations and is absent or

TABLE 1 Ethnic distribution of the *CYP2C9* allelic variants[a]

	Cys^{144} (*2)		**Leu^{359} (*3)**		
Ethnicity	**n**	**%**	**n**	**%**	**References**
Asians					
Chinese	466	0.0	426	2.1	24, 48
Japanese	1394	0.0	1394	1.9	18, 42, 44, 49, 50[b]
Korean	1148	0.0	1148	1.1	47a
Total	3008	0.0	2968	1.6	
Blacks					
American	1098	2.9	500	0.8	24, 51[b]
Caucasians					
American	370	10.0	1512	7.9	18, 24, 51[b]
British	588	14.1	400	9.5	28, 38, 52
German	988	11.3	734	7.8	53, 54
Swedish	860	10.7	860	7.4	55
Turkish	998	10.6	998	10.0	26
Total	3804	11.3	4504	8.4	

[a]n, combined number of the total alleles tested; %, percent of the allelic variants.

[b]UI Schwarz, EF Choo, GK Dresser, CM Stein, AJJ Wood, DM Roden, GR Wilkinson, RB Kim. 2000, unpublished data.

extremely rare in East Asians (18, 24, 26, 28, 38, 42, 44, 47a, 48–55), suggesting that any effects of this variant on CYP2C9-mediated drug metabolism are likely to be negligible in East Asians. White subjects from many parts of the world have a significantly higher frequency of both *CYP2C9*2* and **3* (∼10%) than Asian or black subjects. Asian individuals homozygous for *CYP2C9*3* were rare, and less than ∼2% of the Asians were heterozygous for this allelic variant. Because of both the greater frequency of the *CYP2C9*3* allele in white (∼8%) than East Asian (∼2%) or black (∼1%) populations and the effects of gene dosage on CYP2C9 activity (26, 28, 45), we would anticipate that concentrations of CYP2C9 substrate drugs would, on average, be higher in whites, assuming expressed levels of the protein are comparable.

Ethnicity affects the average warfarin dose required to maintain therapeutic anticoagulation (56). However, in contrast to what would be predicted from ethnic differences in the frequency of the *CYP2C9*3* allele, white patients require higher warfarin doses than Asians to attain a comparable anticoagulant effect. Chinese patients required a ∼50% lower average maintenance dose of warfarin (3.3 mg/day) than white patients (6.1 mg/day) to obtain comparable anticoagulation [international normalized ratio (INR): 2.0–2.5] (57). The average maintenance dose of warfarin for Japanese patients with heart disease (3.3 mg/day) is also much lower than that for American patients (4.9 mg/day) (44). These data imply that known CYP2C9 polymorphisms account for only part of the ethnic differences in sensitivity to warfarin. Similarly, because of a higher frequency of *CYP2C9*3*, we would anticipate that whites would have a higher incidence of hypoglycemia induced by tolbutamide or glipizide, and a higher risk of warfarin-induced bleeding complications (28, 28a) than blacks or Asians taking similar doses; there is, however, little information regarding the effect of ethnicity on response to these drugs.

Recently, an Asp(GA<u>C</u>)^{360}Glu (GA<u>G</u>) polymorphism was identified in 5 of 110 African Americans with an allele frequency of 2.3% (58). Interestingly, another new *CYP2C9* variant A<u>T</u>T (Ile^{359}) → A<u>C</u>T (Thr^{359}) was identified in 32 Japanese patients with epilepsy but not in 100 healthy Japanese subjects (59). Both polymorphic amino acid residues are close to the *CYP2C9*3* variant and lie within the putative substrate recognition site 5 (SRS 5) in the CYP2 family (60), but their functional significance is as yet unknown.

CYP2C19 Impaired 4′-hydroxylation of *S*-mephenytoin in humans is a good example of how polymorphisms can affect drug metabolism and alter clinical response (61–66). Most of the population in any ethnic group can be phenotyped as extensive metabolizers (EMs) based on their ability to oxidize *S*-mephenytoin or other CYP2C19 substrates. However, because of a metabolic defect resulting from genetic variations in *CYP2C19*, some individuals cluster outside of the normal distribution and can be classified as PMs. CYP2C19 is a clinically important enzyme that catalyzes the metabolism of several frequently prescribed drugs (16, 67) such as diazepam, some barbiturates, tricyclic antidepressants, proguanil, and omeprazole and its structural analogs.

CYP2C19 is a protein of 490 amino acids encoded by the *CYP2C19* gene, which has 9 exons (GenBank accession numbers: L31506, L31507, L32982, and L32983) (68) and is mapped to chromosome $10q^{24}$ (69). CYP2C19 activity exhibits marked genetic polymorphism, and at least nine allelic variants have been identified (for the nomenclature, go to: http://www.imm.ki.se/CYPalleles/cyp2c19.htm). The two common alleles that result in a nonfunctional enzyme are null alleles. The first allelic variant, *CYP2C19*2* (previously designated *m1*), is a $G^{681} \rightarrow A$ point mutation in exon 5 that introduces an aberrant splice site resulting in an alteration of the reading frame of the mRNA and a truncated nonfunctional protein (70). A second common defective allele, *CYP2C19*3* (previously termed *m2*), a $G^{636} \rightarrow A$ single base transition in exon 4, produces a premature stop codon (71, 72). These two allelic variants account for almost all PMs in East Asians and blacks (73–75), but in whites ~10% of the PM alleles have not yet been identified (73).

Several studies indicate that there are pronounced ethnic variations in the frequency of *CYP2C19* genotypes and phenotypes among different populations (reviewed in 12, 73–77). Recently, we have summarized global data on allelic, genotypic, and phenotypic frequencies of *CYP2C19* in white populations of European descent, black populations of African descent, and Chinese populations of Asian origin (73–75). As shown in Table 2, the frequency of *CYP2C19*2* in the Chinese population (30%) is twice that in black (17%) or white (15%) populations, and *CYP2C19*3* occurs in approximately 5% of Chinese but less than 1% of blacks or whites.

In addition to ethnic differences in the frequency of CYP2C19 polymorphisms, enzyme activity also varies. Zhang et al found no significant difference in diazepam clearance in Chinese EMs and PMs of *S*-mephenytoin (78). Both EM and PM phenotypes had a diazepam clearance that was comparable to the range observed in white PMs and was half that of white EMs (78–80). These data imply that many Chinese EMs are heterozygotes (80, 81). As shown in Table 2, within the EM subgroups, the proportion of heterozygotes in Chinese is approximately 50%, twice that in whites. The low clearance of diazepam in Chinese EMs (78) and anecdotal evidence that "many Hong Kong physicians routinely prescribe smaller diazepam doses for Chinese than for Caucasians" (82) could thus be explained by the higher

TABLE 2 Allelic, genotypic, and phenotypic *CYP2C19* frequencies in different ethnic groups (73–75)

	Phenotype		**Genotype**			**Allele**			
	n	**PM (%)**	**n**	**PM (%)**	***wt/m* (%)[a]**	**n**	****1* (%)**	****2* (%)**	****3* (%)**
Blacks	922	3.9	966	3.7	29.0	1932	82.3	17.3	0.4
Chinese	1555	13.6	573	13.8	49.8	1146	64.7	30.0	5.1
Caucasians	3990	2.8	1356	2.1	26.0	2712	85.3	14.7	0.04

[a]*wt/m*, the proportion of heterozygotes in the EM subgroups.

frequency of CYP2C19 PMs and heterozygous EMs in the Chinese population. Similarly, the higher proportion of *CYP2C19*2* and **3* heterozygotes in Chinese EMs may be the molecular explanation for the observation that Caucasian EMs were more efficient at metabolizing omeprazole than Chinese EMs (62, 83–86) or Koreans (86). CYP2C19 also appears to be the major enzyme that activates the antimalarial drug proguanil to produce its therapeutically active metabolite cycloguanil (87). However, failure of proguanil's malaria chemoprophylaxis was not more likely in populations with a higher frequency of CYP2C19 PMs and *CYP2C19*2* and **3* heterozygotes, such as in Melanesians living in the Vanuatu islands, where malaria is endemic (88), suggesting that metabolic pathways other than CYP2C19 may be important or that the parent compound proguanil has significant intrinsic efficacy against malaria, independent of the active metabolite, cycloguanil.

CYP2D6

CYP2D6 is of clinical relevance because the gene encoding this enzyme is highly polymorphic (for more information, go to http://www.imm.ki.se/CYPalleles/cyp2d6.htm). At least 70 *CYP2D6* alleles are responsible for the ~200-fold variability in the metabolism of 100 or more drugs (89). Among the common allelic variants, the functional alleles include *CYP2D6*1* (wild-type), **2*, **9*, **10*, and **17*, whereas almost all the remainder are nonfunctional. Several mechanisms are responsible for genetic variability in *CYP2D6*. These include whole gene deletion (e.g. *CYP2D6*5*, a 12.1-kb deletion that includes the entire *CYP2D6* gene), gene duplication or multiplication [e.g. *CYP2D6*1* × n; **2* × n (n = 1, . . . ,13); **4* × 2, and **35* × 2], single nucleotide polymorphisms alone or in combination, deletion or insertion of single or multiple base(s), gene conversion (e.g. *CYP2D6*36*), and repeats (e.g. *CYP2D6*30*). Most of the known variant alleles are inactive and produce the PM phenotype, which appears to be rare (~1%) in most Asian populations, more common in whites (5%–10%) (12, 13, 90), and varies in black populations of African descent (0%–19%) (8, 91). Genotype-phenotype relationship studies have demonstrated that determination of the seven most common allelic variants, **2*, **3*, **4*, **5*, **6*, **9*, and **10*, resulted in a correct phenotype assignment for nearly 100% of all patients of European descent (92, 93). Based on the known *CYP2D6* genotype-phenotype relationships, individuals can be phenotyped into four potential subgroups: ultrarapid metabolizers, extensive metabolizers (EMs), intermediate metabolizers, and poor metabolizers (PMs). Theoretically, ultrarapid metabolizers carry at least three active alleles, and the molecular bases for this phenotype are functional alleles with more than one gene copy; EMs are defined by the presence of the two functional *CYP2D6* alleles (**1*, **2*, **9*, **10*, and **17*); intermediate metabolizers carry only one active allele (frequently **2*, **9*, or **10*); and PMs lack functional *CYP2D6* alleles. Compared with the wild-type allele **1*, active alleles **2*, **9*, **10*, and **17* are functional but have a moderately decreased CYP2D6 enzyme activity (93–102).

Significant ethnic differences have been demonstrated in: (*a*) the population frequency of the PM phenotype; (*b*) the distribution patterns of the metabolic ratio (MR) within individuals with the EM phenotype; (*c*) in vitro and in vivo metabolism of CYP2D6 substrates; (*d*) phenotype-genotype correlations; (*e*) the effects of gene-dosage on the metabolism and response to drugs that are substrates for CYP2D6; and (*f*) the population frequency of allelic variants.

In an in vitro study, Caucasian liver microsome preparations tended to have higher CYP2D6 content and higher bufuralol (a substrate of CYP2D6) 1′-hydroxylase activity than microsomes of Japanese origin (n = 30 each) (15). The frequency distribution of the debrisoquine MRs in Chinese EMs was shifted to the right (higher values) compared with Swedish EMs. Most Chinese EMs (∼66%) had a MR >1, whereas a smaller proportion of Swedish EMs (∼20%) had a MR >1 (103), and the hydroxylation of debrisoquine was slower in Chinese EMs than white EMs (104). This ethnic difference would be expected to also occur with other CYP2D6 substrates. For example, the mean clearance of desipramine, a substrate of CYP2D6, was considerably lower in Chinese EMs than in white EMs (105). Also, the production of morphine from CYP2D6-catalyzed *O*-demethylation of codeine was lower in Chinese EMs than Caucasian EMs (106–108). Recently, we demonstrated that codeine's apparent clearance and partial metabolic clearance via *O*-demethylation are significantly higher in white American EMs than in Chinese EMs, and that when codeine was co-administrated with quinidine (a potent inhibitor of CYP2D6) the inhibition of the production of codeine *O*-demethylated metabolite, morphine, is markedly greater in whites than in Chinese. The respiratory depressant effect caused by morphine after administration of codeine is significantly greater in Caucasians than in Chinese, before and after quinidine (108). These data suggest that although East Asians rarely have the CYP2D6 PM phenotype, within the EM population they have lower levels of CYP2D6 activity than Caucasian EMs.

Among different East Asian ethnic groups significant variations in CYP2D6 activity exist. Ishizaki and colleagues used metoprolol as a probe for CYP2D6 phenotyping and observed that the distribution of metoprolol MRs in Chinese EMs was also shifted to the right compared with Japanese or Korean EMs (109–110). The distribution of the metoprolol MRs in Korean EMs was similar to that in Japanese (110), whereas the proportion of EMs with MRs >1 in Chinese (66%) (103) was twice that than in Koreans (∼33%) (111). Consistent with the findings by both Horai et al (109) and Sohn et al (110), Chinese have a significantly lower ability to *O*-demethylate codeine than Japanese and Koreans (112). The allele *CYP2D6*10* is a $Pro^{34} \rightarrow$ Ser substitution in the proline-rich region near the NH_2-terminal that results in impaired folding capacity of the enzyme so that although it is functional, it has decreased activity (96). As shown in Table 3, *CYP2D6*10* is more frequent in East Asians such as Chinese (51–70%), Japanese (∼40%), and Koreans (51%) than in either whites (1–7%) or blacks (1–9%) (92–94, 96, 100, 111, 112a, 113–118, 121, 123, 124, 126, 131, 134). Thus, the more common occurrence of allele **10* is likely to contribute to the decreased CYP2D6 activity in East Asians. The

TABLE 3 Ethnic distribution of the major *CYP2D6* alleles[a]

	n	**1*	**2*	**3*	**4*	**5*	**6*	**9*	**10*	**17*	**M × N*	References
Asians												
Chinese	248			0.0	0.8	1.2			70.0		0.9	113
	226	26.9	13.4			5.7			50.7		1.3	96
	238	22.7	8.0		0.0	4.6			64.7			114
Japanese	196	42.3	9.2		0.5	6.1			40.8			100
	324	40.1	13.0	0.0	0.0	6.2			38.6	0.0		115
	412	43.0	12.3		0.2	4.5			38.1		1.0	112a
Korean	304	49.0							51.0		0.3	111
Blacks												
American	88	28.0	24.0	1.0	5.0	9.0			1.0	29.0	1.0	116
	492	83.0[b]		0.6	7.3	6.9			5.2	26.0	2.4	117, 118
	482	90.4[b]		0.2	9.3							119
	254	84.6[b]		0.4	9.1	5.9						120
Ethiopian	244			0.0	1.2	3.3			8.6	9.0	16.0	121
Tanzanian	216	27.8	40.0	0.0	0.9	6.3	0.0		3.8	17.0	3.4	94
	392			0.0	4.0						2.5	122
Zimbabwean	160	85.6[b]	9.9	0.0	2.5	3.8		0.0	5.6	34.0	0.9	123, 124
Whites												
American	416	37.0	33.7	1.0	17.5	3.8	1.0	2.9	1.9	0.2	1.1	93
	112				17.8	0.9						125
	928	76.0[b]		1.2	18.1	2.9			4.0	0.0	2.3	117, 118
	928	78.3[b]		1.0	20.7							119
	252	66.7[b]		2.4	28.6	2.4						120
British	1332	33.4	32.9	1.8	18.9	7.3	1.4	2.6	1.4	0.1		126
Danish	650	76.8[b]		2.0	20.6	0.6						127
	480	72.3[b]		2.5	18.1	5.2						128
Estonian	302	76.2[b]		2.3	21.5						0.7	129
Finnish	604	81.5[b]		2.2	12.8	1.7		0.3			1.2	130
German	390	35.6	33.6	1.0	19.5	4.1	1.3	2.1	2.1	0.0	1.6	131
	1154	36.4	32.4	2.0	20.7	2.0	0.9	1.8	1.5		1.9	92
Russian	408	83.8[b]		1.2	15.0							132
Swedish	496	75.0[b]		2.0	23.0							133
	166	83.0[b]		1.0	16.0							133
Turkish	808	37.1	35.3	0.0	11.3	1.5	0.7	0.6	6.1	1.1	5.6	134

[a]Data are presented as *n* and percent, where n = total number of the alleles tested. **M × N*: duplication, amplification or multiplication of the alleles, referred to **1 × N* or **2 × N*, not including **4 × N* because of lack of functional significance. Functional alleles are **1*, **2*, **9*, **10*, and **17*; the remaining are nonfunctional.

[b]Overestimated because the *CYP2D6*1* (wild-type) frequency was calculated from the number of polymorphic alleles detected. The empty cells mean that no data are available now.

significant difference in the frequencies of alleles **1* and **10* in Chinese and Japanese subjects might contribute to the ethnic differences in CYP2D6 activity levels between these two populations (96, 100, 112a, 113–115). The rarity of the inactive allele, *CYP2D6*4*, in East Asians (100, 112a, 113–115) is thought to be associated with a low frequency of the PM phenotype (∼1%). The active allele *CYP2D6*2* has frequently been found to be the variant associated with gene duplication or multiplication and thus significantly increased levels of CYP2D6 activity (134a). The lower frequency of the **2* allele could also contribute to the lower enzyme activity in East Asians (96, 100, 112a, 114, 115) compared with whites (92, 93, 126, 131, 134).

In black African populations the frequency of the CYP2D6 PM phenotype has varied in different studies (0–19%), depending on the ethnic group and probe drug studied (8, 91). In EMs a high proportion of individuals had a debrisoquine MR >1 in Zimbabwe (49–59%) (94, 123, 124) and Ethiopia (37%) (121). Marked variations in CYP2D6 activity are present among different black African ethnic groups, but overall, CYP2D6 activity is lower than in whites [e.g. ∼21% of Swedish EMs had a debrisoquine MR >1 (135)]. Ethnic differences in the frequency of the **17* allele may explain these observations. The CYP2D6*17 was found to have 20% of the wild-type CYP2D6 activity and altered affinity for CYP2D6 substrates such as bufuralol and codeine (99, 123). As shown in Table 3, although *CYP2D6*17* appears to be relatively African-specific (93, 94, 115–118, 121, 123, 124, 126, 131, 134), substantial variability in the **17* allele frequency occurs among different black African populations (9–34%) (94, 116–118, 121, 123, 124) and could partly explain the large variation in the frequency of the CYP2D6 PM phenotype (0–19%) reported in studies that used different probe substrates. In addition, variability in the frequency of the nonfunctional **4* allele (94, 116–124) may contribute to the varying frequency of the CYP2D6 PM phenotype in different black populations. Thus, the fact that CYP2D6 PMs are more common in Caucasians than in most black populations is likely to be due to the higher frequency of the nonfunctional **4* and **3* alleles in whites (92–94, 116–134), whereas the lower CYP2D6 activity in black EMs may be due to a significantly higher frequency of the **17* allele (see Table 3).

CYP3A4

The P-450 3A subfamily is the predominant P-450 isoform in human liver (∼30% of total P-450 content) (15) and contains three known members (17), P-450 3A4, 3A5, and 3A7, that are expressed in several organs important in drug metabolism and disposition. CYP3A4 is abundantly present in human liver and small intestine (15, 136) and contributes to the metabolism of ∼50% of commonly used drugs including nifedipine, cyclosporine, erythromycin, midazolam, alprazolam, and triazolam (136–141). It is important to note that interindividual variation in the levels of CYP3A4 expression is high, up to ∼20-fold or more (15, 142–145), and may account for the wide range of interindividual variability in the disposition of drugs metabolized by this enzyme (145–149).

TABLE 4 Studies of CYP3A4 substrates in different ethnic groups

Substrate	Parameters	Results	References
Alprazolam	CL_o, CL_s	Lower in Asians than Caucasians	150
	CL_o, CL_s	Similar in American-born Asians and native Asians	150
Cerivastatin	AUC, C_{max}	Similar in blacks, Japanese, and Caucasians	151
Cyclosporine	PK	Similar in healthy African and Caucasian Americans	152
	AUC	Lower in African- than Caucasian-American patients	153, 154
Erythromycin	AUC, $t^1/_2$	Similar in Koreans and Caucasians[a]	155
Midazolam	CL, CL/F, F	Similar in African- and Caucasian Americans	156
Nifedipine	AUC	Threefold higher in South Asians than Caucasians	157, 158
	CL_s	77% higher in Caucasians than Asian Indians	159
	AUC, $t^1/_2$	Similar in Malaysians and Asian Indians	160
	AUC, $t^1/_2$	1.4-fold higher in Koreans than Caucasians[a]	155
	$C_{min,ss}$	Similar in black West Indians and Caucasians	161
	AUC, $t^1/_2$	Similar in Nigerians and South Asians	162
	AUC, $t^1/_2$	81% higher in Nigerians than Caucasians[a]	162
Triazolam	CL_o, CL_m	Similar in Asian Indians and Caucasians	163

AUC, area under the plasma concentration–time curve with extrapolation to infinity; CL_o, oral clearance; CL_m, partial metabolic clearance; CL_s, systemic clearance; C_{max}, peak concentration; $t^1/_2$, terminal half-life; F, bioavailability; PK, pharmacokinetics (parameters); $C_{min,ss}$, trough concentration at steady state.

[a]Normalized for body weight.

Interethnic differences in CYP3A4-mediated drug metabolism have been studied in vitro and in different populations. Caucasian liver microsomes had higher nifedipine oxidase activity and significantly higher testosterone 6β-hydroxylase activity than Japanese samples (n = 30 each). Hepatic P-450 3A (principally P-450 3A4) content correlated well with nifedipine oxidation (r = 0.79) and testosterone 6β-hydroxylation (r = 0.81) activities. Also, CYP3A4-mediated metabolic activation of aflatoxin B1 and sterigmatocystin correlated well with microsomal P-450 3A content (r = 0.78 and 0.83, respectively) and was significantly higher in Caucasian than in Japanese samples (15). As summarized in Table 4, the apparent oral clearance of alprazolam was found to be similar in native and American-born Asians, but to be significantly higher in Caucasians than in Asians (150). Similarly, the area under the plasma concentration–time curve of nifedipine was significantly higher in Asians than Caucasians (155, 157–159). The ability to metabolize oral nifedipine was similar in Asian Indians and Malaysians who resided in the same geographic area (160) and codeine *N*-demethylation, mediated by CYP3A4 (164), was more extensive in Caucasian than Chinese subjects (106). These data suggest that CYP3A4 activity may be higher in Caucasians than other populations. However, such an ethnic variation may be substrate-dependent, since erythromycin *N*-demethylation did not show a good correlation with the content of hepatic P-450 3A (r = 0.28) (15), and no difference was present between Asians and Caucasians when erythromycin (155), triazolam (163) or cerivastatin (151) were used as metabolic markers of CYP3A4 activity.

Conflicting results have been found when CYP3A4-catalyzed oxidation of nifedipine (161, 162) was compared in black and white subjects. The metabolism of cerivastatin (151) and midazolam (156) does not differ between blacks and whites. Based on published data (see Table 4), ethnic comparisons with different CYP3A4 substrates have yielded inconsistent results that are difficult to interpret and may reflect an interplay of genetic and environmental factors.

An early in vivo study of nifedipine oxidation showed an apparent bimodality of the area under the plasma concentration–time curve of nifedipine after a 20 mg oral dose in 53 healthy Dutch individuals (165). Subsequent studies, however, in a larger number of subjects, did not confirm this finding (137, 147, 148, 158, 166), suggesting that nifedipine's metabolism is unlikely to be governed by genetic variations that result in the presence or absence of enzyme activity, such as occurs with CYP2C19 and CYP2D6.

The *CYP3A4* gene was mapped on chromosome $7q^{22.1}$ (167–171) and found to be ∼27 kb long, with 13 exons and 12 introns (172). The sequence of *CYP3A4* cDNA obtained from hepatic libraries has been extensively examined (GenBank accession numbers: M18907 for the *CYP3A4* cDNA, and D11131 for its 5′-flanking region) (168, 172–176). To date, at least four *CYP3A4* allelic variants have been identified (for more information on the nomenclature, go to http://www.imm.ki.se/CYPalleles/cyp3a4.htm). The first common *CYP3A4* allelic variant is an A to G transition in the 5′ promotor region at position −290 (from the transcription initiation site) (177), altering the 10-bp nifedipine-specific response element localized at −287 to −296 of the 5′ regulatory region (172). This allele (previously termed *CYP3A4-V* and now designated as *CYP3A4*1B*) was found to be more common in patients with prostate cancer of a more invasive clinical stage than patients with a low-level clinical stage (177), and to be over-represented in patients with leukemia (178). Recent studies indicate that this allelic variant results in a modest reduction in hepatic CYP3A4 activity (156) but does not significantly alter the metabolism of CYP3A4 substrate drugs (179–181), although there are marked differences in frequency among various ethnic populations (181a). The frequency of *CYP3A4*1B* was low in white and Hispanic subjects (3.6–11.0%) (177, 179, 181a, 182), absent in Chinese and Japanese subjects (179, 182, 183), and much higher in black subjects (53.0–69.0%) (179, 181a, 182, 183).

A second allelic variant of the *CYP3A4* gene was found in exon 7 (a $Ser^{222}Pro$ substitution) and designated *CYP3A4*2* (183). This allele was uncommon in 55 white subjects (2.7%), and was not observed in black or Chinese groups of similar size (183). Using a baculovirus-directed cDNA expression system, the intrinsic clearance (V_{max}/K_m) for nifedipine oxidation was decreased approximately six- to ninefold with the variant enzyme compared with the wild-type enzyme, but was not significantly different for testosterone 6β-hydroxylation (183). The *CYP3A4*2* allele may encode a variant enzyme with substrate-dependent altered kinetics, but because it is uncommon, this variant is not likely to contribute substantially to ethnic variations in CYP3A4 activity. Taken together, ethnic differences in the disposition of CYP3A4 substrate drugs are poorly characterized and inconsistent, and currently recognized molecular variations in the *CYP3A4* gene do not appear to

contribute substantially to interindividual variability in the disposition of CYP3A4 substrate drugs.

DRUG TRANSPORTER

P-Glycoprotein

There is increasing evidence that drug metabolism alone does not account for the observed interindividual variability in drug disposition or response (184), but that other processes, including drug transport, are important determinants of drug disposition. Although a number of drug transporters have been shown to play a key role in drug disposition (184–186; RB Kim & GR Wilkinson, submitted for publication), P-glycoprotein (P-gp), the *MDR1* gene product, is one of the best studied and characterized.

Although initial interest in P-gp focused on its role as a mediator of multidrug resistance (MDR) in tumor cells, recent studies have demonstrated its more general role in drug disposition (184–188). P-gp is expressed in many tissues other than tumor cells, particularly those associated with excretory function (189), such as the canalicular domain of hepatocytes and the (luminal) brush border membrane of both intestinal epithelial cells and renal proximal tubule cells. P-gp is an ATP-dependent drug efflux pump, actively transporting many structurally diverse compounds from the inside to the outside of cells against a concentration gradient. Its apical distribution in cells results in decreased drug absorption from the gut lumen and enhanced drug excretion into bile and urine. Moreover, expression of P-gp in the capillary endothelium of the blood-brain barrier prevents penetration of substrate drugs into the central nervous system. Accordingly, P-gp plays an important role in drug absorption, distribution, and excretion. Of importance for drug disposition is that P-gp and CYP3A4 are frequently co-expressed in the same cells and share a large number of substrates and modulators (139). The disposition of such drugs is thus affected by both transport and metabolism (184).

Variability in P-gp-mediated drug transport in the gastrointestinal tract alters the oral bioavailability (F) of P-gp substrates (7, 186, 190). Such effects are seen most easily when either hepatic or extrahepatic drug metabolism is negligible (188). Ethnic variation in P-gp activity has not been widely studied. Lindholm et al investigated the effects of demographic factors on the pharmacokinetics of cyclosporine, a drug that is a substrate for both P-gp and CYP3A4, in 187 kidney transplant recipients, and found that the oral bioavailability of cyclosporine was significantly lower in blacks ($n = 58$, mean $= 30.9\%$) than whites ($n = 86$, mean $= 39.6\%$) or Hispanics ($n = 40$, mean $= 42.1\%$), with no ethnic variation in clearance and volume of distribution at steady state (V_{ss}) (153). Because a 10-fold variation in the levels of intestinal CYP3A4 had no clear effect on oral cyclosporine pharmacokinetics, Lown and colleagues postulated that intestinal P-gp transport activity was the major determinant of bioavailability and

C_{max} of cyclosporine (190), so that patients with lower levels of intestinal P-gp had higher bioavailability and higher C_{max}, and vice versa. Furthermore, the concentration/dose ratio of tacrolimus (also a substrate of CYP3A4 and P-gp) was correlated with the mRNA expression of MDR1 but not CYP3A4 (191). Like cyclosporine (153, 154, 192, 193), higher doses of tacrolimus were required in blacks than whites to attain similar plasma levels (194), suggesting a lower oral bioavailability of tacrolimus. Although there is no supporting evidence, one explanation for the lower bioavailability of cyclosporine and tacrolimus would be greater P-gp-mediated drug transport in blacks. We found no difference in the disposition of cyclosporine in healthy black and white men studied on a controlled diet (CM Stein, AJ Sadeque, JJ Murray, C Wandel, RB Kim, et al, manuscript submitted). Recently, we found that the oral clearance of fexofenadine (a P-gp substrate that is not metabolized) exhibited ~10-fold interindividual variation and tended to be slightly higher in white women than in black women (195). However, additional studies with larger sample sizes will be required to define the relationship between ethnicity and P-gp activity. The interrelationship between CYP3A4 and P-gp, and the effects of environmental factors such as diet, make defining ethnic differences in P-gp-mediated drug disposition difficult.

The *MDR1* gene encoding P-gp is located on chromosome $7q^{21}$ (196), with 28 exons encoding a protein of 1280 amino acids. Significant information about the structure-function analysis of P-gp has recently been summarized (197). Some naturally occurring polymorphisms of the *MDR1* gene have been found to correlate with potential clinical effects (198), or with the levels of intestinal *MDR1* expression and uptake of orally administered digoxin (a substrate of P-gp) (188). We are currently examining the hypothesis that allelic variants of *MDR1* might be associated with interindividual or interethnic variations in the disposition of P-gp drug substrates. Using PCR-based single-stranded conformational polymorphism (SSCP) methods, we found that a number of single nucleotide polymorphisms exist in multiple exons and the 5′-flanking promotor region of the *MDR1* gene in Japanese, black, and white American populations, and that these point mutations are distributed differently among the ethnic groups (198a). Indeed, genetic variability in *MDR1* appears to be more frequent than previously thought. Future genotype-phenotype relationship studies may provide additional insights into the role of P-gp as a determinant of interindividual or interethnic variability in drug response.

DRUG RECEPTORS

α-Adrenergic Receptor

The α-adrenergic receptor (α-AR) family comprises two subfamilies (α_1-AR and α_2-AR). Three subtypes of each have been identified pharmacologically and through molecular cloning: α_{1A} (formerly α_{1C}), α_{1B}, α_{1D} (formerly $\alpha_{1A/D}$), α_{2A}, α_{2B}, and α_{2C} (199, 200). Evidence suggests that the human α_{1A}-AR predominates

in arteries (201), whereas all three α_1-AR subtypes (in particular α_{1A} and α_{1B}) are expressed in veins (201) and peripheral blood lymphocytes (202). The major α_1-AR subtypes mediating vasoconstriction and regulating peripheral vascular resistance are α_{1A} and α_{1B}.

Several studies have demonstrated that blacks have greater vascular reactivity in response to α-adrenergic stimuli than whites (203–208). The vascular responses to intrabrachial artery infusion of phenylephrine (an α_1-AR agonist) and to cold stress (a stimulator of endogenous norepinephrine release) were compared in African-American and Caucasian normotensive men (207–208) and α_1-AR-mediated vasoconstrictor reactivity was significantly increased in blacks. The response in the superficial dorsal hand vein to local infusion of phenylephrine was reported to be blunted in normotensive blacks (209). The different results may be due to the site of drug action (artery versus vein), because the responsiveness of different types of blood vessel differs quantitatively (210).

Known polymorphisms of the human α_{1B}-AR are rare and appear to not be associated with the interindividual variations in response to phenylephrine (211, 212). Although African Americans had a significantly lower frequency of the amino acid variant Cys^{492} of the α_{1A}-AR than Caucasian Americans, this polymorphism was not associated with hypertension and its effects on sensitivity to phenylephrine are not known (213). At present, the mechanisms underlying the increased α-adrenergic vascular sensitivity in African Americans are unknown.

β-Adrenergic Receptor

Three different β-adrenergic receptor (β-AR) subtypes have been cloned and pharmacologically characterized: β_1, β_2, and β_3 (200, 214). The presence of a putative fourth β-AR subtype (β_4) has been proposed based on recent pharmacological studies in human and rat cardiac tissue (200). Although both β_1-AR and β_2-AR subtypes co-exist in the human cardiovascular system (200, 215), β_1-ARs predominate. Many studies have revealed that β_1-AR-mediated effects include exercise-induced increase in heart rate and systolic blood pressure, as well as renin release (for reviews, see 215–217), whereas β_2-AR-mediated responses include a decrease in total peripheral resistance and diastolic blood pressure (215).

β1-Adrenergic Receptor (β1-AR) Ethnic differences in β-AR-mediated responses to drugs have been extensively investigated among Caucasians, East Asians, and blacks of African descent (4). Compared with Caucasian men, Chinese men had a greater sensitivity to the effects of propranolol, a nonselective β-AR antagonist, which produced a greater reduction in mean arterial blood pressure and exercise-induced tachycardia (218) and greater suppression of exercise-induced plasma renin release (a β_1-AR-mediated effect) (219). By contrast, normotensive blacks had decreased sensitivity to isoproterenol (a nonselective β-AR agonist) compared with whites, before and after β-blockade with propranolol (220). Furthermore, clinical observations from many investigations have indicated that

black patients with hypertension respond less well to monotherapy with several β-AR blockers (221), including the nonselective β-blockers propranolol (222) and nadolol (223), and the β_1-selective blocker atenolol (222–226). Decreased sensitivity to β-AR antagonists may be associated with the lower levels of plasma renin activity and higher proportion of low-renin hypertension found in blacks (4).

The human β_1-AR is a protein of 477 amino acid residues encoded by an intronless gene (227, 228) localized on chromosome $10q^{24–26}$ (227). Recently, 18 single nucleotide polymorphisms have been identified in the human β_1-AR gene, 17 of which are located in the *N*-terminal and *C*-terminal region of the coding exon, resulting in 7 amino acid substitutions (229). Two common allelic variants of the human β_1-AR gene, $A^{145}G$ (or $Ser^{49}Gly$) and $C^{1165}G$ (or $Arg^{389}Gly$), were identified (228–234). The first variant Gly^{49} was associated with a decreased mortality risk in patients with congestive heart failure (230) and was observed significantly more frequently in a group of patients with idiopathic dilated cardiomyopathy (229). However, no ethnic differences in the frequency of this allelic variant existed among African Americans, Caucasians, and Chinese (233). A second common variant Gly^{389} receptor was found to have a decreased receptor-G_s-protein interaction and reduced cyclic AMP production following exposure to agonist (232), suggesting that this variant receptor exhibits diminished response to a β_1-AR agonist in vitro. In vivo studies to determine the functional significance of the $Arg^{389}Gly$ β_1-AR polymorphism in humans are underway, and a preliminary population-based case-control study shows no association of this polymorphism with essential hypertension in African Americans or Caucasian Americans (234a). The frequency of the variant Gly^{389} receptor is significantly higher in African Americans (42%) than in Caucasian Americans (25%), Chinese (27%), or Hispanics (33%) (234b). The physiological significance of ethnic differences in the frequency of the Gly^{389} variant β_1-AR, which is characterized as a loss-of-function polymorphism in vitro (232), is uncertain.

β2-Adrenergic Receptor (β2-AR) The human β_2-AR is a protein of 413 amino acids that is encoded by an intronless gene mapped to chromosome $5q^{31–32}$ (235) and is distributed in the vascular smooth muscle cells of atria, ventricles, some arterioles (e.g. coronary and skeletal muscle vessels), and systemic veins (215). Selective β_2-AR agonists produce vasodilation in humans. Thus, enhanced blood pressure responses to stress in blacks might be the result of blunted β_2-AR-mediated vasodilation. In the human dorsal hand vein attenuated β_2-AR-mediated vasodilation was observed in Asian Indians who resided in the United States compared with white Americans (236). We and others have compared forearm blood flow responses to isoproterenol in young black and white American normotensive men and found that responses were markedly blunted in blacks (220, 237–240). Endothelial release of NO has recently been found to contribute to the vasodilator effect of β_2-AR stimulation (240–244). However, the vasodilator effect of isoproterenol was attenuated in normotensive black subjects both before and after N^G-monomethyl-L-arginine (an eNOS inhibitor) (240). Thus, the decreased vasodilator response

to isoproterenol in blacks is independent of the NO component of isoproterenol-induced vasorelaxation. The ethnic differences in β_2-AR-mediated vasodilation raise the possibility that β_2-AR polymorphisms may play a role.

Recently, two common naturally occurring allelic variants of the β_2-AR, $A^{46}G$ (or $Arg^{16}Gly$) and $C^{79}G$ (or $Gln^{27}Glu$), have been identified and their functional significance characterized (245). In contrast to the findings in vitro (246, 247), clinical studies showed that the Gly^{16} variant is resistant to isoproterenol-induced desensitization (248, 248a). The Gly^{16} variant, however, was associated with attenuated systemic vasodilation in response to intravenous infusion of a selective β_2-AR agonist in normotensive Australian (249) and normotensive American white subjects (250). The Glu^{27} β_2-AR variant is resistant to agonist-stimulated β_2-AR desensitization in vitro (246–248), and in vivo is associated with greater vasodilator responses to isoproterenol (248a, 251). There are ethnic differences in the distribution of the two common β_2-AR polymorphisms (252, 253), with a significantly lower frequency of the variant Glu^{27} allele, approximately 18%, in normotensive and hypertensive African Americans compared with Caucasian Americans ($\sim$35%). Whether the decreased frequency of the Glu^{27} allele in blacks contributes significantly to their attenuated responses to β-AR agonists such as isoproterenol is currently under investigation.

OTHER FUNCTIONALLY IMPORTANT PROTEINS

Endothelial Nitric Oxide Synthase

Since the identification in 1987 of NO as a biological mediator, there has been an explosion of information about the physiological, pathophysiological, pharmacological, and therapeutic roles played by this molecule. NO is synthesized from L-arginine and molecular oxygen by the constitutive enzyme endothelial nitric oxide synthase (eNOS) that is expressed in the endothelium. NO diffuses from the endothelium into vascular smooth muscle cells, where it increases the levels of cGMP by stimulating soluble guanylate cyclase (GC), resulting in vascular relaxation (254). The release of NO by the endothelium contributes to basal vascular tone (255) and regulates blood flow and blood pressure (256). Recently, interethnic variations in NO-mediated responses to vasodilators such as acetylcholine, methacholine, bradykinin, and sodium nitroprusside, have been extensively assessed (239, 240, 257–259). Blacks were found to have markedly decreased NO-dependent vasodilator responses to acetylcholine (240, 258), methacholine (239), bradykinin (259), and sodium nitroprusside (an exogenous NO donor) (239, 240, 257), suggesting decreased cGMP-mediated vasorelaxation in blacks. In addition, blacks were found to have a reduced NO-dependent vasodilation during mental stress (257), and N^G-monomethyl-L-arginine significantly inhibited the stress-induced increase in the forearm blood flow in whites but not in blacks (257). Together, these data indicate that blacks have less endothelium-dependent and endothelium-independent NO-mediated vasodilation than whites.

The enzyme eNOS is encoded by the *NOS3* gene of 26 exons that is located on chromosome $7q^{35–36}$ (260). A common missense mutation was identified as a $G^{894}T$ single base exchange at the genomic position 1917 in exon 7 (or at position 894 in its cDNA sequence), producing an amino acid substitution ($Glu^{298}Asp$). Preliminary in vivo observations suggest that acetylcholine-mediated, endothelium-dependent vasodilator responses are attenuated in healthy white Americans homozygous for the Asp^{298} variant compared with the wild-type homozygotes (261). The vasoconstrictor response to phenylephrine was also significantly higher in the variant 894T carriers (TT and GT) of French origin than in the GG carriers (262). These data suggest that the Asp^{298} (or 894T) variant of eNOS might be functionally important, resulting in decreased vasodilation. African Americans have a lower frequency of the variant Asp^{298} allele than Caucasian Americans (14.3% versus 35.3%) (263). Thus, this polymorphism would not explain the reduced vascular response to NO in African Americans.

Pertussis Toxin–Sensitive G_i-Type Protein

GTP binding proteins (G proteins) comprise a superfamily of ubiquitous signal-transducing proteins that participate in many intracellular signaling cascades and mediate the functional responses to numerous agonists. G proteins are heterotrimers with α, β, and γ subunits. A frequent genetic polymorphism ($C^{825}T$) has recently been identified by Siffert et al (264) in exon 10 of the *GNB3* gene (chromosome $12p^{13}$) (265) encoding the β_3 subunit of pertussis toxin–sensitive G_i-type protein. This single nucleotide polymorphism is related to alternative splicing of exon 9, resulting in the loss of 41 amino acids, which results in increased sensitivity to agonists that stimulate intracellular signaling through the pertussis toxin–sensitive G protein (264). Because of the large number of receptors, including adrenoceptors that function through G protein interactions, functional polymorphisms might have important pathophysiological consequences.

Case-control studies suggest that the allelic 825T variant is associated with increased blood pressure in German (264, 266, 267) and Australian Caucasians (268) and black Caribbeans of West African descent (269), but not in Japanese (270–272), aboriginal Oji-Cree Canadians (273), French individuals (274), and African Americans (275), suggesting potential ethnic differences in the nature of genetic susceptibility loci. Furthermore, this variant was associated with left-ventricular hypertrophy in a Spanish (276) but not a German (277) population with hypertension. The 825T polymorphism was also associated with lower renin levels (266) and obesity in some studies (278–282a) but not in others (268).

α_2-ARs are coupled to pertussis toxin–sensitive G_i protein and mediate vasoconstriction (283, 284). α_2-AR-mediated coronary blood flow was significantly decreased in subjects with the *GNB3* 825T allele (285), but dorsal hand vein constrictor responses were not different (286). Individuals of African descent have a higher frequency of the 825T allele than Caucasians (79% versus 33%) (269, 278),

and the 825T allele was associated with hypertension in black Caribbeans of West-African descent (269) but not in African Americans (275).

SUMMARY AND FUTURE DIRECTIONS

Human P-450 enzymes associated with drug metabolism belong mainly to the CYP families CYP1, CYP2, and CYP3. The major forms (percent of total P-450 content) include CYP 3A (∼30%), 2C (∼20%), 1A2 (∼13%), 2E1 (∼7%), 2A6 (∼4%), and 2D6 (∼2%) (15). Approximately 40% of human P-450-mediated drug metabolism is catalyzed by polymorphic enzymes (134), and ∼50% of commonly used drugs are metabolized by CYP3A4 (140). The greatest variability in the levels of enzyme activity is found with CYP 2D6 and 2C enzymes because of frequently occurring functionally significant polymorphisms (136). In this review, the relationship between such polymorphisms and ethnicity has been discussed. Other phase I and phase II drug metabolizing enzymes have been extensively reviewed elsewhere (11, 67, 287–290).

In addition, drug transporters (e.g. P-gp) function as drug efflux pumps in intestine, liver, and kidney and play an important role in drug absorption, distribution, and excretion. P-gp and CYP3A4 are commonly co-expressed in the same tissues and share substrate specificity. Thus, for many drugs both metabolism and transport are important determinants of disposition. Conclusive evidence for ethnic variations in the P-gp transporter activity is not available but is an intriguing possibility.

Ethnic differences in β-AR-mediated responses exist. Sensitivity to propranolol is greater in Chinese, and β_2-AR-mediated vasodilation is attenuated in African Americans compared with Caucasians. There are ethnic differences in the distribution of functionally significant polymorphisms, but the molecular basis for ethnic differences in vascular response is undefined.

NO plays an important role in the regulation of basal vascular tone and vasodilation. Evidence suggests that African Americans have attenuated NO-mediated (both endothelium-dependent and -independent) vasodilation compared with white Americans. However, the genetic or environmental explanations for this ethnic variation remain unclear.

A common genetic polymorphism of the G_i protein β_3-subunit gene (*GNB3*) $C^{825}T$ is associated with hypertension, low renin levels, and obesity in some but not all populations of different ethnic backgrounds. In addition, the existence of an 825T allele predicted selective α_2-AR-mediated coronary vasoconstriction. Although blacks have a higher allele frequency of 825T, the clinical significance is unknown.

In summary, proteins that determine drug disposition and response, such as drug-metabolizing enzymes, drug transporters, and drug receptors, are the products of the genes encoding them. The study of their molecular genetics may provide a clearer understanding of ethnic differences in drug response. The principal focus so far has been on drug metabolism and drug receptors. Future directions include

(*a*) characterizing the in vivo functional significance of known polymorphisms, (*b*) comparing phenotypic and genotypic characterization among multiple ethnic groups, (*c*) identifying new polymorphisms in genes that regulate drug disposition or response, and (*d*) defining the relative contribution of genetic and environmental factors to ethnic variations in drug response.

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