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Autonomic Nervous System Pharmacogenomics: A Progress Report

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***Abstract*——Pharmacogenetics, the inherited basis for interindividual differences in drug response, has rapidly expanded with the advent of new molecular tools and the sequencing of the human genome, yielding pharmacogenomics. We review here recent ideas and findings regarding pharmacogenomics of components of the autonomic nervous system, in particular, neuronal nicotinic acetylcholine receptors, postsynaptic receptors with which the parasympathetic and sympathetic neurotransmitters, acetylcholine (ACh) and norepinephrine, respectively, interact. The receptor subtypes that mediate these responses, M_{1-3} muscarinic cholinergic receptors (mAChRs), and $\alpha_{1A,B,D}$-, $\alpha_{2A,B,C}$-, and $\beta_{1,2,3}$-adrenergic receptors (AR), show highly variable expression of genetic variants; variants of mAChRs and α_1-ARs are relatively rare, whereas α_2-AR and β-AR subtype variants are quite common. The largest amount of data is available regarding variants of the latter ARs and represents efforts to associate certain receptor genotypes, most commonly, single nucleotide polymorphisms, with particular phenotypes (e.g., cardiovascular and metabolic responses). In vitro and in vivo studies have yielded inconsistent results; definitive conclusions are limited. We identify several conceptual and methodological problems with available data: sample size,**

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ethnicity, tissue differences, coding versus noncoding variants, limited studies of haplotypes, and interaction among variants. Thus, although progress has been made in identifying genetic variation that influences drug response for autonomic nervous system components, we are still at the early stages of defining the most critical genetic determinants and their role in human physiology and pharmacology.

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I. Introduction

The autonomic nervous system (ANS[1]) is responsible for maintaining homeostasis; it controls heart rate, body temperature, blood pressure (BP), metabolism, circulation, respiration, and digestion. Before discussing the pharmacogenetics of the ANS, we believe that it is useful to briefly review some aspects of autonomic anatomy and physiology. The ANS is primarily an efferent system that transmits impulses from the central nervous system (CNS) to regulate peripheral organ systems, such as the heart, lung, vasculature, and gastrointestinal tract.

The two major components of the ANS, the parasympathetic and sympathetic systems, use different end-organ neurotransmitters, acetylcholine (ACh) for the former and norepinephrine (NE) (with a few exceptions) for the latter. Both components of the ANS have synapses in ganglia with ACh as the neurotransmitter between the neurons that originate in the CNS and those that are postganglionic efferents. Most organs receive both sympathetic and parasympathetic innervation, which mediates opposing actions.

Neurotransmission in the ganglia occurs via nicotinic ACh receptors (nAChRs). In the parasympathetic system, the postganglionic neurotransmitter ACh activates muscarinic ACh receptors (mAChRs), whereas in the sympathetic system the postganglionic neurotransmitter NE acts at adrenergic receptors (adrenoceptors, ARs). Most of the current, clinically useful autonomic drugs act on the postsynaptic receptors. The classic view of ANS function, with control exclusively by ACh and NE, changed in recent decades to encompass new concepts in neurotransmission, including neuromodulation and cotransmission (Brading, 1999; Vinken and Bruyn, 1999). The list of putative cotransmitters/neuromodulators in the ANS includes dopamine, ATP and other nucleotides, angiotensin II, and neuropeptides such as neuropeptide Y, enkephalin, somatostatin, and vasoactive intestinal peptide (Lundberg, 1996; Burnstock, 1997; Vinken and Bruyn, 1999; Boehm and Kubista, 2002). Target cell response regulated by the ANS is further complicated by participation of multiple subtypes of neurotransmitter receptors.

The focus of this article is to review recent findings and ideas regarding ANS pharmacogenomics, the inherited basis for interindividual differences in drug response, in particular in humans (for a recent general overview of pharmacogenomics, see Evans and McLeod, 2003). Given the large number of known biosynthetic and degradation enzymes, transporters, receptors, and signaling components that contribute to activation of the parasympathetic and sympathetic systems (e.g., preganglionic neurons, ganglia, postganglionic neurons, effector cells), the topic of ANS pharmacogenomics is a very large one. There are many potential sources of genetic variation that might contribute to interindividual differences in response. We have chosen to focus on autonomic receptors, with an emphasis on the "classic" neurotransmitter receptors. We emphasize the influence of human polymorphisms on drug response and, in some cases, susceptibility to common diseases. Since most of the clinically useful autonomic drugs act on receptors with which ACh and NE interact, these receptors and in vitro and in vivo drug responses at these receptors will be the main focus of this review.

II. Cholinergic Receptors

A. Nicotinic Cholinergic Receptors

Neuronal nAChRs, ligand-gated ion channels that mediate fast-signal transmission, have a pentameric structure comprising homomeric α or heteromeric α and β subunits (Fig. 1). Functional neuronal nAChRs are composed of two α and three β subunits with "duplex" (α/β) or "triplex" ($\alpha_x\alpha_y\beta$ or $\alpha\beta_x\beta_y$) conformations (De Biasi, 2002). In humans, eight α subunits (α2-α7, α9, and α10) and three β subunits (β2–β4) have been cloned, but the in vivo subunit composition and the functional role of most nAChRs is still uncertain. Autonomic ganglia express α3, α4, α5, α7, β2, and β4 subunits (Table 1) (De Biasi, 2002; Skok, 2002; Tassonyi et al., 2002). The homomeric α7 and the heteromeric α3β4 appear to be prevalent in autonomic ganglia (Taylor, 2001; Skok, 2002; Tassonyi et al., 2002). The varying combinations of the distinct subunits could give rise to large numbers of nAChRs differing in their pharmacological and electrophysiological properties (De Biasi, 2002).

Numerous polymorphisms have been identified in α3, α4, α5, α7, β2, and β4 subunits (Table 2) (Steinlein et al., 1995; Weiland et al., 2000; Duga et al., 2001; Lev-Lehman et al., 2001; Leonard et al., 2002; Lueders et al., 2002). The nAChR genes for the β4, α3, and α5 subunits

[1]Abbreviations: ANS, autonomic nervous system; BP, blood pressure; CNS, central nervous system; ACh, acetylcholine; NE, norepinephrine; nAChR, nicotinic ACh receptor; mAChR, muscarinic ACh receptor; AR, adrenergic receptors; SNP, single nucleotide polymorphism; GPCR, G protein-coupled receptor; AC, adenylyl cyclase; UTR, untranslated region; EPI, epinephrine; RFLP, restriction fragment length polymorphism; IDCM, idiopathic dilated cardiomyopathy; HASM, human airway smooth muscle; CGP12177, 4-[3-[(1,1-dimethylethyl)amino]2-hydroxypropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one.

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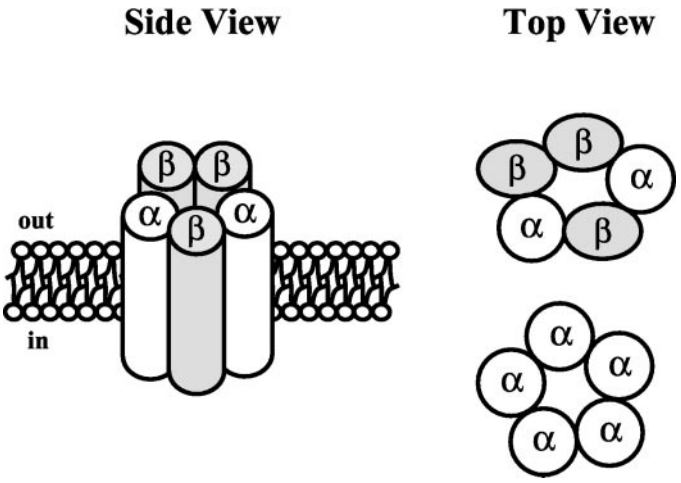

FIG. 1. Structural schematic of the nicotinic acetylcholine receptor. Left panel shows side view of the pentameric receptor. Cylinders represent transmembrane domains. Right panel shows top view of the putative assembly of heteromeric and homomeric receptors. Adapted from Weiland et al. (2000).

TABLE 1
Human nicotinic receptor subunits and muscarinic cholinergic receptors expressed in ganglia and/or effector cells of the ANS

Receptor/ Subunit	Gene Symbol	GenBank Accession Number[a]	Chromosome Location (Locus)[a]
α3	CHRNA3	NM_000743	15q24
α4	CHRNA4	NM_000744	20q13.2-q13.3
α5	CHRNA5	NM_000745	15q24
α7	CHRNA7	NM_000746	15q14
β2	CHRNB2	NM_000748	1q21.3
β4	CHRNB4	NM_000750	15q24
M_1	CHRM1	NM_000738	11q13
M_2	CHRM2	NM_000739	7q31-q35
M_3	CHRM3	NM_000740	1q41-q44

[a] National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

are clustered on chromosome 15q24, and until recently, the gene structures (i.e., exact genomic size and exon-intron boundaries) and the organization of the gene cluster were unknown, making comprehensive mutational analysis difficult (Weiland et al., 2000; Duga et al., 2001). The three genes in the cluster are physically linked (Raimondi et al., 1992), and the genes for the α3 and α5 subunits partially overlap at their 3′ ends (Duga et al., 2001). The genes in the cluster have been reported to be coexpressed, and regulatory elements that influence transcription of both the α3 and β4 genes have been identified (Deneris et al., 2000). Although the gene for the α7 nAChR subunit is not part of a cluster per se, it is partially duplicated, further complicating genetic analyses (Gault et al., 1998).

Some of the identified polymorphisms have been associated with neurologic disorders, including nocturnal frontal lobe epilepsy and schizophrenia (Weiland et al., 2000; Lueders et al., 2002); however, no evidence has been provided that such polymorphisms selectively alter ANS function. In vitro, a nonsynonymous coding single nucleotide polymorphism (SNP) in the α4 subunit, Ser248Phe (743 C→T), located in the second transmembrane domain, exhibits faster desensitization upon activation by ACh and slower recovery from the desensitized state compared with the wild-type receptor (Weiland et al., 1996). Additionally, an insertion polymorphism of a Leu (776 ±GCT), between amino acids 259 and 260 of the α4 subunit and located in the C-terminal end of the second transmembrane domain, alters receptor function when coexpressed with the β2 subunit in oocytes (Steinlein et al., 1997). ACh-evoked currents were greater in the wild-type receptor compared with the variant, thereby reducing receptor permeability to calcium (Steinlein et al., 1997). A β2 subunit variant that alters receptor function has also been detected in the second transmembrane domain; this variant, Val287Met (1025 G→A), when coexpressed with α4 subunits in oocytes exhibits a 10-fold increase in sensitivity to ACh (Phillips et al., 2001). Several promoter variants in the α7 subunit have been shown to alter transcription, as measured by luciferase reporter gene assay (Leonard et al., 2002). Variants at −86, −92, −143, −178, −194, and −241 base pairs, decreased transcription in vitro, with the −86-base pair variant showing the greatest decrease (20%) (Leonard et al., 2002). Variants in the transmembrane domain, which potentially line the pore of the receptor channel, and promoter variants, which could alter receptor levels, require future study as related to ANS function and disease.

Recent studies using knockout mice suggest that the α3, α7, β2, and β4 nAChR subunits are important for normal autonomic function. When disrupted alone or in combination, they cause mild to severe autonomic dysfunction and, in some cases, lead to increased mortality (Xu et al., 1999a,b; Franceschini et al., 2000). An Ala529Thr polymorphism in murine α4 subunits has been shown to alter receptor function and response to nicotine and makes α4 a promising candidate worthy of further investigation (Dobelis et al., 2002; Tritto et al., 2002). The identification of four novel polymorphisms in the β4, α3, α5 gene cluster on chromosome 15q24 (Duga et al., 2001) suggests that further polymorphisms may yet be identified. Recent evidence that both α3 and β4 subunits, which are prevalent in autonomic ganglia, are polymorphic in humans provides additional candidates for variations in autonomic function (Lev-Lehman et al., 2001). These polymorphisms, as well as those reported in Table 2, may prove to be important in modifying receptor function in the ANS.

B. Muscarinic Cholinergic Receptors

In humans, five subtypes of mAChR have been identified (M_1-M_5). Muscarinic AChRs are members of the large superfamily of G protein-coupled receptors (GPCRs) (Fredriksson et al., 2003). GPCRs share a common overall structure characterized by seven transmembrane domains with three extracellular and three intracellular loop domains, an extracellular N-terminal and an intracellular C-terminal tail. The transmembrane domains are more highly conserved than are the loops or

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TABLE 2
SNPs identified in human nAChR subunits[a]

Gene	Nucleotide Change	Amino Acid Change	Population	Reference
CHRNA3[b]	±CTG*	Leu between amino acid 22–23	ADNFLE patients and control subjects (German)	Rempel et al., 1998
	238 ±CTG, 345 A→G, 477 G→A, 831 C→T	Leu17 insertion, Val52Val, Leu96Leu, Tyr214Tyr	Family study of MMIHS and controls (Italian)	Lev-Lehman et al., 2001
CHRNA4	743 C→T	Ser248Phe	Kindred for ADNFLE (Australian)	Steinlein et al., 1995
	755 C→T	Ser252Leu	Family study of ADNFLE (Japanese)	Hirose et al., 1999
	828 G→A	Thr276Thr	Normal subjects (Japanese)	Akiyoshi et al., 2000
	*	Ser413Leu, Gln397Pro	Alzheimer's disease patients and controls, (Japanese)	Kawamata and Shimohama, 2002
	776 ±GCT	Leu (between amino acid 259–260)	ADNFLE family study (Norwegian)	Steinlein et al., 1997
CHRNA5	−34 T→C, +211 A→G	Intron 1, intron 3	ADNFLE patients and controls (Italian)	Duga et al., 2001
CHRNA7	654 C→T, 690 G→A, 1269 C→T, 1335 C→T	Synonymous SNPs*	Control subjects (Caucasian, African American, Hispanic, or Asian)	Gault et al., 1998
	−86 C→T, −92 G→A, −143 G→A, −178 ±G, −194 G→C	Promoter variants, 1 bp deletion	Schizophrenic patients and controls of varying ethnicity	Leonard et al., 2002
CHRNB2	1025 G→A	Val287Met	ADNFLE family study (Scottish)	Phillips et al., 2001
	1025 G→C	Val287Leu	ADNFLE family study (Italian)	De Fusco et al., 2000
CHRNB4[b]	392 C→T, 526 C→T, 538 A→G, 573 C→T, 840 C→T, 1519 A→G	Thr81Ile, Arg136Trp, Ser140Gly, Ser151Ser, Ile240Ile, Met467Val	Family study of MMIHS and controls (Italian)	Lev-Lehman et al., 2001

ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy; bp, base pair; MMIHS: megacystis-microcolon-hypoperistalsis syndrome.
*Nucleotide or amino acid not reported.
[a] Not an exhaustive list, but highlights SNPs in the coding or promoter region of nAChR subunit genes (many more are found in the intronic and untranslated regions[b]).

the N- and C-terminal tails. GPCRs couple to various effectors via heterotrimeric ($\alpha\beta\gamma$) G proteins that elicit responses via actions of both α and $\beta\gamma$ subunits. Among mAChRs, M_2 and M_4 preferentially couple to $G_{i/o}$ and, in turn, lead to inhibition of adenylyl cyclase (AC), activation of inwardly rectifying K^+ channels, and inhibition of voltage-dependent Ca^{2+} channels. M_1, M_3, and M_5 preferentially couple to $G_{q/11}$, which leads to activation of phospholipase C and the generation of diacylglycerol, which activates protein kinase C, and inositol phosphates, particularly inositol 1,4,5-trisphosphate, which mobilizes intracellular calcium. The mAChRs are present on postganglionic fibers and target cells that include epithelium, submucosal glands, and smooth muscle cells. In humans, M_1, M_2, and M_3 receptors have been identified as the targets of parasympathetic stimulation (Table 1) (Roux et al., 1998; Dhein et al., 2001; Hoffman and Taylor, 2001b; Walch et al., 2001). The M_2 receptor subtype predominates in both the heart and airway smooth muscle, although M_1 and M_3 receptors are also expressed in those tissues (Roux et al., 1998; Brodde et al., 2001a). M_1 and M_3, involved in ACh-induced vasodilation, are expressed in both vascular endothelium and smooth muscle (Walch et al., 2001).

In terms of identification of genetic variation in mAChRs, samples from 245 individuals (Coriell Collection, Coriell Institute for Medical Research, Camden, NJ) have been genotyped for the M_1 receptor; although 15 SNPs were identified, only 1 yielded a nonsynonymous SNP (Cys417Arg) that may have functional consequences (Lucas et al., 2001). In a screening of M_2 and M_3 receptor genes in normal and asthmatic subjects, no polymorphic variation was found in the M_3 receptor (Fenech and Hall, 2002). Two synonymous SNPs were identified in the coding region of the M_2 receptor, and one common polymorphism (65% frequency) was identified in the 3′ untranslated region (UTR) (1696 T→A); this latter polymorphism does not alter known transcription factor recognition sites (Fenech and Hall, 2002). More recently, Donfack et al. (2003) screened the entire 1.2-kilobase promoter region of the M_3 receptor in a well characterized, highly inbred population (> 700 individuals) and identified four SNPs and two short-tandem repeat polymorphisms. Although there was no association with asthma, there was a significant nonrandom transmission of haplotypes to individuals with skin test reactivity to cockroach allergens, suggesting a role for this gene in atopic disorders. Thus, mAChRs expressed in the ANS appear to be highly conserved. The functional significance of the identified SNPs, including their impact on drug responses, has yet to be determined.

III. Adrenergic Receptors

The sympathetic postganglionic neurotransmitter NE acts at both α- and β-ARs. These two receptor types were

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zoriginally hypothesized based on the effects of NE, epinephrine (EPI), and other adrenergic amines at peripheral sympathetic sites (Ahlquist, 1948). The major AR classes were further subdivided on functional and anatomical grounds: α-AR-mediated effects, such as vasoconstriction, were considered α_1-AR effects, in part based on actions of agonists and antagonists that could differentiate such responses from α_2-AR effects, which mediate feedback inhibition by NE on its release from presynaptic terminals (Docherty, 1998). Similarly, the β_1-AR-mediated effects on the force and rate of contraction in the heart were differentiated from β_2-AR-mediated effects, such as promotion of smooth muscle relaxation in the bronchi and vessels. Subsequent research showed that this classification scheme based on anatomic distribution is overly simplistic: many, probably most, organs have β_1- and β_2-ARs as well as α_1- and α_2-ARs. Molecular cloning definitively identified the existence of three α_1-AR subtypes: α_{1A}, α_{1B}, and α_{1D}; three α_2-AR subtypes: α_{2A}, α_{2B}, and α_{2C}; and three β-AR subtypes: β_1, β_2, and β_3 (Table 3). Although some evidence has been presented to suggest there may be additional ARs, no definitive proof for their existence has been provided (Granneman, 2001; Guimaraes and Moura, 2001).

All ARs are GPCRs that link to heterotrimeric G proteins. Each major type shows preference for a particular class of G proteins, i.e., α_1-AR-G_q, α_2-AR-G_i, β_2-AR-G_s. GPCRs in general and ARs in particular are characterized by relatively rapid (seconds to minutes) agonist-promoted activation, although certain actions, especially those involving transcriptional events, may not be detected for several hours. Agonist-promoted responses are subject to desensitization, which can occur either rapidly (seconds to minutes) or more slowly (minutes to hours). Multiple mechanisms are involved in desensitization, including such rapid events as receptor phosphorylation (by both G protein receptor kinases, and by signaling kinases, such as protein kinases A or C) (Luttrell and Lefkowitz, 2002) and receptor sequestration and uncoupling from G proteins, as well as more slowly occurring events, such as receptor endocytosis/internalization and degradation, which leads to a loss (down-regulation) of receptor number (Tsao et al., 2001). As will be discussed subsequently, genetic variants of ARs can influence receptor expression, activation, or desensitization.

TABLE 3
Human adrenergic receptors expressed in effector cells of the ANS

Receptor	Gene Symbol	GenBank Accession Number[a]	Chromosome Location (Locus)[a]
α_{1A}AR	ADRA1A	NM_000680	8p21-p11.2
α_{1B}AR	ADRA1B	NM_000679	5q23-q32
α_{1D}AR	ADRA1D	NM_000678	20p13
α_{2A}AR	ADRA2A	NM_000681	10q24-q26
α_{2B}AR	ADRA2B	NM_000682	2p13-q13
α_{2C}AR	ADRA2C	NM_000683	4p16
β_1AR	ADRB1	NM_000684	10q24-q26
β_2AR	ADRB2	NM_000024	5q31-q32
β_3AR	ADRB3	NM_000025	8p12-p11.2

[a] National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

A. α_1-Adrenergic Receptors

α_1-ARs regulate many physiological processes, including smooth muscle contraction (e.g., vascular tone), myocardial inotropy, and hepatic glucose metabolism (Brodde et al., 2001a; Guimaraes and Moura, 2001; Piascik and Perez, 2001; Koshimizu et al., 2002). Each of the α_1-AR subtypes shows linkage to G_q and activate phospholipase C, but differences have been noted in signaling capacities (Theroux et al., 1996) and regulation of gene expression (Gonzalez-Cabrera et al., 2003). Genetic variants have been identified for α_{1A}- and α_{1B}-ARs, but to date, there is no published information regarding genetic variations of human α_{1D}-ARs (Table 4).

1. α_{1A}-Adrenergic Receptors. The α_{1A}-AR subtype is the predominant α_1-AR in heart and in certain parts of the vasculature (e.g., arteries) (Docherty, 1998; Rudner et al., 1999; Brodde et al., 2001a). A relatively common nonsynonymous variant, Arg492Cys (1441 C→T), has been identified with allelic frequencies of ~30 and ~54% in African Americans and Caucasian Americans, respectively (Table 5) (Xie et al., 1999a). Sequencing efforts have failed to reveal other common variants (i.e., with frequencies >5%) especially in the coding sequence (D. T. O'Connor, unpublished observation). The Arg492Cys variant, found in the carboxy-terminal tail (Fig. 2), has no apparent phenotype in terms of alterations in binding affinity or receptor-mediated calcium signaling when stably expressed in cells (Shibata et al., 1996). Consistent with the lack of impact on biologic function, the Arg492Cys variant shows no association with hypertension, clozapine-induced urinary incontinence, or benign prostatic hypertrophy (Shibata et al., 1996; Xie et al., 1999a; Hsu et al., 2000). In contrast with these earlier results, a recent study of 16 subjects suggested that young, healthy men with the CC genotype at position 492 have a longer PR interval on EKG (Snapir et al., 2003a). Although the number of subjects was quite small, these findings suggest that additional in vitro and in vivo studies of the 492 variant may be warranted.

2. α_{1B}-Adrenergic Receptors. The long arm of chromosome 5 has been implicated in BP regulation and contains a cluster of genes that are potential candidates in hypertension (Krushkal et al., 1998). This chromosomal region includes the genes for the α_{1B}-AR, β_2-AR, and D_1 dopamine receptors. Since stimulation of the α_{1B}-AR results in vasoconstriction and BP elevation (Leech and Faber, 1996), Buscher et al. (1999b) investigated the presence and possible association of α_{1B}-AR polymorphisms, BP, and response to the α-agonist phenylephrine in patients with essential hypertension and their first-degree relatives. Two silent SNPs were identified in exon 1 but there was no significant association with BP or other functional activities measured. Analy-

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TABLE 4
α_1- and α_2-AR SNPs and in vitro/in vivo drug responses

Amino Acid Change	Nucleotide Change	Drug Response Studied	Genetic Association Noted	Reference
α_{1A}-AR				
Arg492Cys	1441 C→T	Binding affinity or signal transduction	No	Shibata et al., 1996
α_{1B}-AR				
Gly183Gly	549 G→A	BP, response to phenylephrine	No	Buscher et al., 1999b
Lys294Lys	882 G→A	BP, response to phenylephrine	No	Buscher et al., 1999b
α_{2A}-AR				
−261/HhaI RFLP	G→A	Density or affinity determined by radioligand binding	No	Bono et al., 1996
Asn251Lys	753 C→G	Enhanced G_i coupling	Yes	Small et al., 2000a
α_{2B}-AR				
Glu-Glu-Glu	Del301–303	Decreased agonist-promoted desensitization and phosphorylation of receptor	Yes	Small et al., 2001
Glu-Glu-Glu	Del301–303	Blunted coronary blood flow increased in response to EPI infusion	Yes	Snapir et al., 2003a
α_{2C}-AR				
Gly-Ala-Gly-Pro	Del322–325	Decrease in high-affinity binding; decreased agonist-induced coupling to G_i	Yes	Small et al., 2000b

TABLE 5
*Nonsynonymous adrenergic receptor polymorphisms and allele frequencies**

Receptor	Amino Acid Change	Caucasian	African American	Asian	Hispanic
α_{1A}-AR	Arg492Cys	0.54[a]	0.30[a]	0.10[b]	
α_{2A}-AR	Asn251Lys	0.004[c]	0.05[c]		
α_{2B}-AR	Glu-Glu-Glu, Del301–303	0.31[d]	0.12[d]		
α_{2C}-AR	Gly-Ala-Gly-Pro, Del322–325	0.04[e,f]	0.38–0.41[e,f]		
β_1-AR	Ser49Gly	0.11–0.15**[g,h,i,j]	0.13,0.29[j,k]	0.15[j]	
	Gly389Arg	0.24–0.28[f,i,j,l,m,n,o]	0.42–0.44[f,j,n]	0.26–0.29[j,n]	0.33[n]
β_2-AR	Gly16Arg	0.51–0.66[p,q]	0.51[p]	0.41[p]	
	Gln27Glu	0.35[p]	0.21[p]	0.07[p]	
	Val34Met	0.01[r]			
	Thr164Ile	0.05[r]			
β_3-AR	Trp64Arg	0.08[s]	0.10–0.12[s,t]	0.18[u]	0.13–0.16[s,v]

* Allelic frequencies are shown for the various adrenergic receptor subtypes. Data reported for subjects from the United States and Europe were assumed to represent Caucasian unless stated otherwise.
** Several studies cited detected the Ser49Gly variant at >10% allelic frequency, but Podlowski et al., (2000) did not detect this variant.
[a] (Xie et al., 1999a); [b] (Shibata et al., 1996); [c] (Small et al., 2000a); [d] (Small et al., 2001); [e] (Small et al., 2000b); [f] (Small et al., 2002); [g] (Wenzel et al., 2000); [h] (Borjesson et al., 2000); [i] (Maqbool et al., 1999); [j] (Moore et al., 1999); [k] (Johnson and Terra, 2002); [l] (Mason et al., 1999); [m] (Podlowski et al., 2000); [n] (Xie et al., 2001); [o] (Buscher et al., 2001); [p] (Xie et al., 1999b); [q] (Buscher et al., 2002); [r] (Reihsaus et al., 1993); [s] (Walston et al., 1995); [t] (Lowe et al., 2001); [u] (Kawamura et al., 2001); [v] (Corbalan et al., 2002b).

ses of exon 2, which encodes regions of the receptor distal to the third intracellular loop, also failed to reveal the presence of common SNPs. Two synonymous α_{1B}-AR SNPs (at nucleotides 534 and 549, Ile178Ile and Gly183Gly, respectively) also appear not to be associated with heart rate or systolic or diastolic BP (McCaffery et al., 2002). Functional studies have demonstrated the importance of the third intracellular loop of the α_{1B}-AR, specifically alanine 293, in coupling to G proteins and response to agonist (Cotecchia et al., 1990; Kjelsberg et al., 1992); however, nonsynonymous polymorphisms in this region have yet to be identified. Genetic variation in noncoding regions of the α_{1B}-AR has not been reported, but may prove difficult to define with precision given the large size of the intron between exons 1 and 2 (Ramarao et al., 1992).

We conclude that evidence thus far (Tables 4 and 5) suggests that, overall, except for the α_{1A}-AR Arg492Cys variant, there are neither a large number of nor highly frequent coding region nonsynonymous polymorphisms in α_1-ARs, and if present, they have little functional importance and appear not to be associated with diseases with altered function of the ANS.

B. α_2-Adrenergic Receptors

Sequence variations within the coding region of each α_2-AR gene (α_{2A}, α_{2B}, and α_{2C}) have been identified in humans (Fig. 2; Tables 4 and 5) (Small and Liggett, 2001). α_2-ARs couple, in large part via their third intracellular loop, to $G_{i/o}$ proteins that inhibit cAMP production through AC, inhibit Ca^{2+} channels, and activate K^+ channels (Docherty, 1998). The third intracellular loop of the α_2-AR subtypes is also important for agonist-induced desensitization (Eason and Liggett, 1992). Although α_2-ARs are known to regulate ANS function, in particular sympathetic outflow from the CNS and the release of NE at sympathetic nerve terminals, studies using genetically engineered mice have helped identify the role of each α_2-AR subtype (Philipp et al., 2002). Hein et al. (1999) demonstrated that the α_{2A}- and α_{2C}-ARs are required for presynaptic regulation of transmitter release from sympathetic nerves in the heart and from the CNS, results consistent with findings in vascular smooth muscle (Docherty, 1998; Philipp et al., 2002). The vascular endothelium expresses α_{2A}- and α_{2C}-ARs, which participate in the regulation of vascular tone (Guimaraes and Moura, 2001). The α_{2A}- and α_{2C}-ARs

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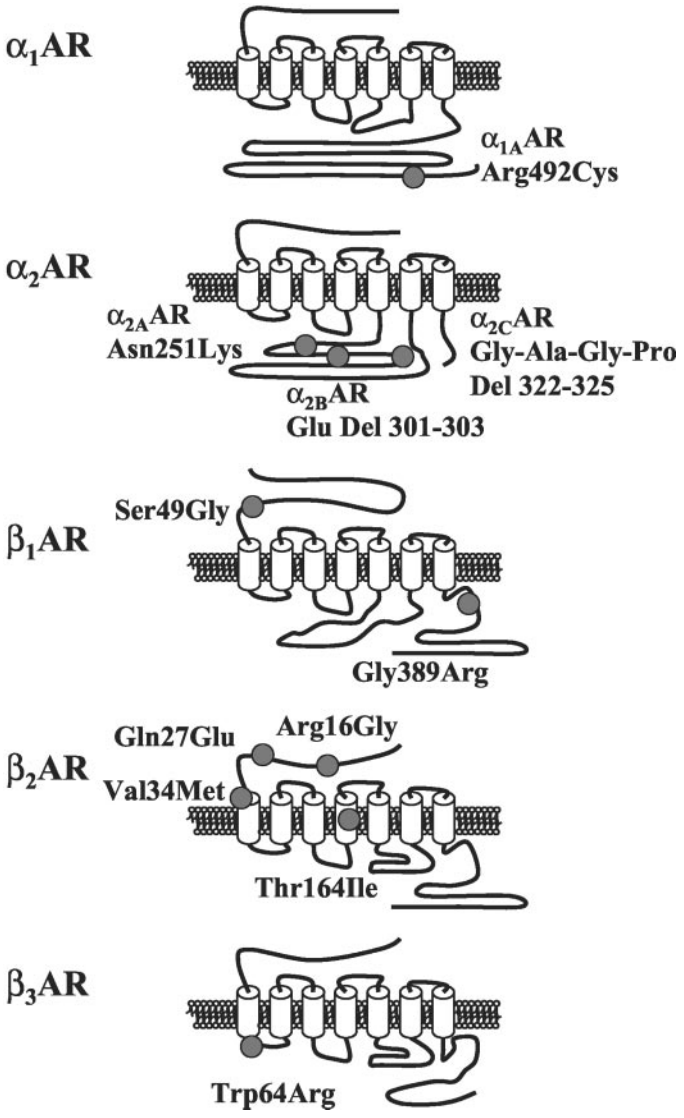

FIG. 2. Schematic of α- and β-adrenergic receptor structures and locations of nonsynonymous coding polymorphisms (denoted by gray circles). Cylinders represent transmembrane domains, loops correspond to extracellular or intracellular domains oriented to the top or bottom of the schematic, respectively.

may have a role in heart failure progression (Brede et al., 2002; Small et al., 2002). By contrast with the presynaptic location of the α_{2A}- and α_{2C}-ARs, α_{2B}-ARs are found postsynaptically (Docherty, 1998; Philipp et al., 2002).

1. α_{2A}-Adrenergic Receptors. Several polymorphisms have been identified in the 5′UTR, the coding region, and the 3′UTR of the α_{2A}-AR gene (Small and Liggett, 2001). Only the Asn251Lys (753 C→G) polymorphism in the third intracellular loop has been investigated mechanistically; this polymorphism alters function by enhancing agonist-promoted G_i coupling (Fig. 2; Table 4) (Small et al., 2000a). In the 5′UTR of the α_{2A}-AR, one can identify an HhaI restriction fragment length polymorphism (RFLP) (−261 G→A), but radioligand binding studies reveal no differences in receptor density or affinity with this RFLP (Bono et al., 1996). An association between hypertension and another RFLP, one generated by Bsu36I (location unknown), has also been investigated; no disease associations were identified, but the allelic frequencies differ between U.S. and Japanese populations (Sun et al., 1992; Umemura et al., 1994). In the 3′UTR, one can identify an RFLP with the restriction enzyme DraI; several studies suggested a relationship between this DraI RFLP and hypertension in African Americans or Caucasians (Lockette et al., 1995; Svetkey et al., 1996). Freeman et al. (1995) found a significant association between the DraI RFLP and increased catecholamine-induced platelet aggregation, increased heart rate in response to lower body negative pressure, and decreased sodium excretion induced by immersion in thermal neutral water. In a group of 147 hypertensive patients, the DraI RFLP polymorphism, although not associated with BP or a family history of hypertension, was significantly associated with several measures indicative of altered lipid or glucose metabolism, including lower levels of HbA_1 and HbA_{1C}, lower levels of total cholesterol, and similar trends, albeit not statistically significant differences, in serum levels of glucose, triglycerides, and low-density lipoprotein cholesterol (Michel et al., 1999). These results led the authors to conclude that alleles at the α_{2A}-AR locus may contribute to interindividual differences in the regulation of lipid and glucose metabolism (Michel et al., 1999).

The latter results likely relate to the ability of the α_{2A}-AR to regulate lipid mobilization, particularly inhibition of fatty acid mobilization from adipose tissue (Lafontan and Berlan, 1995). Garenc et al. (2002) investigated another α_{2A}-AR polymorphism, −1291 C→G, located in the 5′UTR of the gene, and its association with body fat accumulation. Using Caucasian or African American subjects who participated in the HERITAGE Family Study (HEalth, RIsk factors, exercise Training And GEnetics, (Bouchard et al., 1995)), the authors found that the −1291 C→G polymorphism showed ethnic differences in allele frequency (Caucasian Americans, 0.27; African Americans, 0.66), association in male subjects with greater trunk-to-extremity skinfold ratio, and decreased trunk-to-extremity skinfold ratio and abdominal visceral fat in African American women (Garenc et al., 2002). These results suggest a role for the α_{2A}-AR in determining the propensity to store abdominal fat, independent of total body fat. In a population of unrelated Swedish men, Rosmond et al. (2002) assessed the impact of the α_{2A}-AR −1291 C→G polymorphism on lipid metabolism and plasma concentrations of glucose, insulin, and other hormones. Heterozygotes were found to have higher dexamethasone-stimulated salivary cortisol levels, as well as higher fasting glucose levels. Perhaps the α_{2A}-AR −1291 C→G polymorphism alters function of an enhancer or regulatory element that helps control receptor expression, thereby contributing to altered physiological responses. However, no results have documented this. The above-mentioned studies suggest

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a role for the α_{2A}-AR and influence of the −1291 C→G polymorphism in lipid metabolism, but more data are needed.

2. α_{2B}-Adrenergic Receptors. Activation of α_{2B}-ARs present in vascular smooth muscle cells contribute to vascular tone via vasoconstriction (Link et al., 1996). A highly acidic stretch of amino acids in the third intracellular loop of the α_{2B}-AR (Fig. 2; Table 4) has been shown to be important for agonist-promoted receptor phosphorylation and desensitization by G protein receptor kinases (Jewell-Motz and Liggett, 1995). Studies with transfected cells revealed a decrease in agonist-promoted desensitization and phosphorylation of the Del301–303 (9 Glu) receptors compared with wild-type receptors (Small et al., 2001). The deletion of the three glutamic acids in this region (residues 301–303) is more common in Caucasians (31%) than in African Americans (12%) (Table 5) (Small et al., 2001).

The Del301–303 receptor would be predicted to show greater α_{2B}-AR-mediated responses, a prediction that is supported by some in vivo data. Snapir et al. (2001) confirmed that the deletion genotype was not associated with hypertension, but suggested that it was a novel risk factor for acute coronary events. This intriguing observation may relate to altered cardiovascular physiology and pharmacology. A significant association was identified between the deletion polymorphism and decreased flow-mediated dilation of the brachial and carotid arteries, an indicator of subclinical atherosclerosis (Heinonen et al., 2002). Additionally, the α_{2B}-AR deletion polymorphism has been associated with blunted coronary blood flow increases in response to EPI infusion (i.e., increased vasoconstriction) (Snapir et al., 2003a). As a follow-up that confirms and extends the earlier findings (Snapir et al., 2001), a recent study showed that the Del301–303 receptor is associated with nonthrombotic fatal (prehospital) acute myocardial infarction and an increased risk for sudden cardiac death in white men, especially those under the age of 55 (Snapir et al., 2003b).

The glutamic acid-rich region of the α_{2B}-AR has also been the focus of studies related to its impact on metabolism. Several AR subtypes are expressed in adipocytes, and these ARs influence adipocyte metabolism and growth (Lafontan et al., 1997). Heinonen et al. (1999) found that the basal metabolic rate was lower in obese subjects homozygous for the short allele (Glu9/Glu9) than for the long allele (Glu12/Glu12). The authors suggested that this polymorphism might contribute to variation in basal metabolic rate and to the pathogenesis of obesity. Sivenius et al. (2001) investigated the short form of the Glu variant on changes in body weight in nondiabetic and type 2 diabetic subjects and found that the short allele was associated with an increase in body weight among nondiabetic subjects. More recently, in young, healthy Japanese individuals, no association among the deletion variant and body mass index, plasma glucose, or insulin concentrations, or family history of diabetes or obesity was found; however, the short allele was associated with low- and very low-frequency R-R spectral analysis of heart rate variability, as well as a significantly higher index of sympathetic nervous system activity and a lower index of parasympathetic nervous system activity (Suzuki et al., 2003). This alteration in ANS function may contribute to metabolic disorders.

The interactive effect of the Glu deletion (heterozygous Glu12/Glu9 allele) in the α_{2B}-AR and a Trp64Arg polymorphism in the β_3-AR (to be described below) on energy metabolism and body composition has been examined in healthy women; a significant interaction of the α_{2B}- and the β_3-AR variants with greater fat mass and percentage of fat was identified (Dionne et al., 2001). Such results suggest that these two AR variants interact in the regulation of body composition, but studies in larger and more ethnically diverse populations are required. In addition, studies that directly assess the pharmacologic response of the variant receptor in adipose cells would be of interest. Since such cells can be obtained by biopsy and used for studies ex vivo (Lafontan et al., 1995, 1997), they provide a readily available source to directly assess the impact of α_{2B}-AR variants.

3. α_{2C}-Adrenergic Receptors. The α_{2C}-AR plays an important role in presynaptic control of neurotransmitter release from sympathetic nerves in the heart and central neurons and postjunctional regulation of vascular tone (Hein et al., 1999). Small et al. (2000b) identified a deletion variant that lacks 12 nucleotides and 4 encoded amino acids (Gly-Ala-Gly-Pro; Del322–325 in the receptor protein sequence) in the third intracellular loop of the α_{2C}-AR (Fig. 2; Table 4) and found a higher allelic frequency in African Americans (0.38) than in Caucasians (0.04) (Table 5) (Small et al., 2000b). When stably expressed in Chinese hamster ovary cells and compared with the wild-type receptor, the Del322–325 variant shows a decrease in high-affinity agonist binding, agonist-induced coupling to the G_i protein, inhibition of AC, and coupling to the stimulation of mitogen-activated protein kinase and inositol phosphate production. A recent study in heart failure patients investigated the combination of the α_{2C}-AR deletion variant (Del322–325) and a β_1-AR polymorphism (Gly389Arg), the latter of which shows an increased function in vitro (Small et al., 2002). The α_{2C}-AR variant was shown to contribute to more severe disease. In addition, the authors hypothesized that the two variants would act synergistically to increase synaptic NE release and enhance receptor function at the myocyte, thereby increasing the risk for heart failure. Indeed, African American individuals possessing both variants were at greater risk of heart failure (Small et al., 2002). However, we are not aware of published data that directly document altered functional activity of α_{2C}-ARs (Del322–325) (other than in vitro signaling pathways),

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particularly the impact on NE release (Small et al., 2000b).

Overall, the data suggest that α_2-ARs contribute to altered physiology and pharmacologic responses, but the work is still at a relatively early stage. Moreover, it will be important to consider interactions between α_2-AR variants and other genetic loci. The study by Dionne et al. (2001), and others (Small et al., 2002), highlights the potential importance of interactions between variants of different classes of ARs and perhaps with those of other signaling molecules (Naber et al., 2003) and disease genes as contributors to complex, polygenic traits.

C. β-Adrenergic Receptors

β-AR receptors regulate numerous functional responses, including heart rate and contractility, smooth muscle relaxation, and multiple metabolic events. All three of the β-AR subtypes, β_1, β_2, and β_3, couple to G_s and activate AC. However, recent data suggest differences in downstream signals and events activated by the three β-ARs (Lefkowitz et al., 2002; Ma and Huang, 2002). As discussed above, increases in catecholamines promote β-AR feedback regulation, i.e., desensitization and receptor down-regulation (Kohout and Lefkowitz, 2003). The β-AR subtypes differ in the extent to which they undergo such regulation with β_2-AR being the most susceptible (Suzuki et al., 1992; Lafontan et al., 1995; Zhou et al., 1995; Rousseau et al., 1996; Summers et al., 1997; Broadley, 1999).

1. β_1-Adrenergic Receptors. The β_1-AR is the predominant β-AR subtype in the heart; it is also found in the kidney, adipocytes, and other tissues (Brodde et al., 2001a; Hoffman and Taylor, 2001a). Numerous SNPs have been identified in the N- and C-terminal coding regions of the β_1-AR as well as in the 5′UTR (Podlowski et al., 2000; Wenzel et al., 2000). Podlowski and colleagues (2000) proposed that seven of these lead to amino acid changes and result in 11 different genotypes, but detailed examination of most of the variants has not been described. Two common coding SNPs have been reported for the β_1-AR: Ser49Gly (145 A→G), located in the extracellular N-terminal domain (Gly allele frequency in Caucasians and Asians, ~15% and in African Americans, ~30%), and Arg389Gly (1165 G→C), located in the intracellular C-terminal domain (Gly allele frequency in Caucasians and Asians, ~25% and African Americans, ~40%) (Fig. 2; Table 5) (Maqbool et al., 1999; Mason et al., 1999; Tesson et al., 1999; Borjesson et al., 2000; Podlowski et al., 2000; Wenzel et al., 2000; Johnson and Terra, 2002). Recent data have demonstrated that Ser49Gly and Arg389Gly are in linkage disequilibrium; the Gly49Gly389 combination rarely occurs (Johnson et al., 2003). Functional studies in vitro have demonstrated differences in Ser49 and Gly49 β_1-ARs: the Gly49 variant yields higher basal and agonist-stimulated AC activities and greater agonist-promoted down-regulation (Levin et al., 2002; Rathz et al., 2002) (Table 6). The Arg389Gly polymorphism is of particular interest because it is in a region important for G protein coupling (Mason et al., 1999), as discussed further below.

Due to the predominant role of β_1-ARs in the heart, heritable interindividual differences in cardiovascular function have been proposed to arise from variation in this gene, but the data are inconsistent. In studies assessing possible associations of the Ser49Gly β_1-AR polymorphism and hemodynamic parameters, including BP and heart rate, a significant association was identified in individuals of European American descent (McCaffery et al., 2002) or Chinese and Japanese descent (Ranade et al., 2002), but not in patients with ischemic heart disease (Humma et al., 2001). Ranade et al. (2002) assessed >1000 individuals of Chinese and Japanese descent and found that heterozygous individuals had resting heart rates intermediate between those of either homozygote (Ser49 being higher and Gly49 lower). In contrast, no association between the Ser49Gly β_1-AR polymorphism and hypertension was noted in a Scandinavian population (Bengtsson et al., 2001) nor in relation to the cardiostimulant (right atrial) effects of NE in a group of patients with coronary artery disease (Molenaar et al., 2002).

The allelic distribution of the β_1-AR Ser49Gly polymorphism has been associated with long-term survival (decreased mortality risk in subjects with Gly49) of patients with congestive heart failure (Borjesson et al., 2000). This finding may relate to results from in vitro studies that show increased desensitization and down-regulation of the Gly49 variant (Levin et al., 2002; Rathz et al., 2002), consistent with the idea that β_1-AR blockade or desensitization is protective in heart failure (Bristow, 2000). However, contradictory data have been reported: Podlowski et al. (2000) found the β_1-AR Ser49Gly polymorphism more frequently in patients with idiopathic dilated cardiomyopathy (IDCM). Interestingly, a polymorphism in the 5′UTR of the β_1-AR located at nucleotide −2146 (T→C), reported to be in strong linkage disequilibrium with the Ser49Gly polymorphism, has also been associated with IDCM (Wenzel et al., 2000).

The β_1-AR polymorphism at amino acid position 389 yields either Gly or Arg with allele frequencies of 0.26 and 0.74 in Caucasians, respectively (Mason et al., 1999). In vitro studies revealed that Arg389 receptors appear to have a gain of function: higher basal and agonist-stimulated AC activities and greater agonist-promoted binding, which is consistent with enhanced coupling to G_s leading to increased AC activity (Mason et al., 1999). In vivo studies have yielded inconsistent results for this variant, especially with respect to its gain of function. In studies with adipocytes, Ryden et al. (2001) found no differences in sensitivity or maximum lipolytic capacity of adrenergic agonists; radioligand binding was similar between the genotypes. In contrast,

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TABLE 6
Common β_1-AR coding SNPs and in vitro/in vivo drug responses

Amino Acid Change	Nucleotide Change	Drug Response Studied	Genetic Association Noted	Reference
Ser49Gly	145 A→G	Increased basal and agonist-stimulated AC	Yes	Levin et al., 2002
Ser49Gly	145 A→G	Increased agonist-promoted down-regulation	Yes	Levin et al., 2002; Rathz et al., 2002
Ser49Gly or Gly389Arg	145 A→G 1165 G→C	Potency/efficacy of NE cardiostimulant effects in right atrium of patients with CAD with/without β_1AR blockade	No	Molenaar et al., 2002
Gly389Arg	1165G→C	Arg389 increased basal and agonist-stimulated AC, increased agonist-promoted binding	Yes	Mason et al., 1999
Gly389Arg	1165G→C	Catecholamine-induced lipolysis (adipocytes)	No	Ryden et al., 2001
Gly389Arg	1165G→C	Inotropic potency of NE (myocardial tissue)	Yes	Sandilands et al., 2003
Gly389Arg	1165G→C	Hemodynamic response to NE	No	Snapir et al., 2003a
Gly389Arg	1165G→C	BP or heart rate with/without β_1AR blockade	No	O'Shaughnessy et al., 2000
Gly389Arg	1165G→C	Arg389 larger decrease in resting systolic and mean arterial BP when treated with β-blocker (atenolol)	Yes	Sofowora et al., 2003
Ser49Gly, Gly389Arg, and haplotype pair	145 A→G 1165 G→C	Metoprolol treatment: Arg389 homozygotes greater reduction in DBP, haplotype pair (Ser49Arg389/Ser49Arg389) significant predictor of decrease in DBP	Yes	Johnson et al., 2003

CAD, coronary artery disease; DBP, diastolic blood pressure.

Sandilands et al. (2003) studied isolated right atrial strips and found small but significant differences in the inotropic potency of the β_1-AR depending on genotype at position 389; the authors found greater inotropic effects of NE and increased basal and agonist-stimulated cAMP levels in tissues from Arg389 homozygotes, results consistent with findings from the earlier in vitro data (Mason et al., 1999).

There are other in vivo data regarding the physiological impact of the Arg389Gly β_1-AR polymorphism, but again the results have been variable. In an investigation of heritability and the influence of stress, the Arg389Gly polymorphism was associated with higher resting systolic and diastolic BP and a larger diastolic response to mental challenge in individuals of European American descent (McCaffery et al., 2002). Other workers, however, found no impact of this polymorphism on exercise (β_1-AR)-induced, work-load dependent increases in heart rate or on resting heart rate (Buscher et al., 2001; Xie et al., 2001; Ranade et al., 2002). In contrast, individuals with symptomatic ischemic heart disease have been reported to show an association between the Arg389Gly β_1-AR polymorphism and various hemodynamic measures (Humma et al., 2001). Although the polymorphism does not seem to influence hemodynamic responses to EPI or NE (Molenaar et al., 2002; Snapir et al., 2003a), individuals homozygous for Arg389 show larger decreases in BP (but not heart rate) when treated with β-blockers (Johnson et al., 2003; Sofowora et al., 2003). The latter results are at variance with earlier findings, showing that the 389 variant appears not to influence BP or heart rate response in hypertensive patients treated chronically with β_1-AR blockers (O'Shaughnessy et al., 2000), although this was a retrospective study with a different design compared with the more recent reports that found a "positive" result.

Other studies have assessed the possible role of β_1-AR variants at position 389 and cardiovascular disease. In a study of men with a coronary event and matched controls, no significant association was found with the Arg389Gly polymorphism (White et al., 2002). In patients with DCM, the Gly389 polymorphism suppressed the occurrence of ventricular tachycardia, suggesting that this allele confers a decreased risk of sudden death (Iwai et al., 2002). However, no association was found between overall occurrence of IDCM and the Arg389Gly polymorphism (Tesson et al., 1999; Podlowski et al., 2000). The Arg389Gly β_1-AR polymorphism appears to have a synergistic effect with the α_{2C}-AR deletion (Del322–325) polymorphism in promoting the progression of heart failure in African Americans (Small et al., 2002). The latter authors hypothesized that α_{2C}- and β_1-AR polymorphisms act synergistically to increase synaptic NE release and yield enhanced receptor function, respectively, so as to decrease cardiac function and promote progression of heart failure. Left ventricular mass, an important cardiovascular risk factor, was

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shown to be associated with the Arg389Gly polymorphism; in patients with renal failure, homozygous Gly389 individuals have greater left ventricular mass (Stanton et al., 2002). Although data from Scandinavian individuals suggest that the Arg389 allele increases risk to develop hypertension and influences heart rate (Bengtsson et al., 2001), similar associations have not been noted in other population groups (O'Shaughnessy et al., 2000; Ranade et al., 2002).

Overall, as recently reviewed (Michel and Insel, 2003), inconclusive results have been obtained regarding the physiological relevance of the β_1-AR polymorphisms. Further work is necessary to define the exact nature of the relationship between the in vitro and in vivo results and the role these β_1-AR polymorphisms, perhaps as haplotypes, play in disease and drug response (Table 6) (Hein, 2001; Jones and Montgomery, 2002; Johnson et al., 2003; Michel and Insel, 2003).

2. β_2-Adrenergic Receptors.

a. β_2-Adrenergic Receptor Polymorphisms and Haplotypes. Although β_2-ARs are expressed in the heart at lower concentrations than are the β_1-AR subtype, they are more numerous in many other sites, including vascular, bronchial, and gastrointestinal smooth muscle, glands, leukocytes, and hepatocytes (Hoffman and Taylor, 2001a). In contrast with results for certain other ARs, in particular α_1-AR (see above), β_2-ARs are highly polymorphic. Nine different SNPs have been identified in the coding region of the β_2-AR, four of which are nonsynonymous: Arg16Gly (46 A→G), Gln27Glu (79 C→G), Val34Met (100 G→A), and Thr164Ile (491 C→T) (Fig. 2; Table 8) (Reihsaus et al., 1993). At least nine variants have been identified in the 5′UTR of the β_2-AR, some of which are in linkage disequilibrium with the Arg16Gly and Gln27Glu polymorphisms (McGraw et al., 1998; Scott et al., 1999; Yamada et al., 1999; Drysdale et al., 2000). Of particular interest is a SNP at −47 (T→C), Arg19Cys, which is located within a short, open reading frame, termed the 5′ leader cistron, and encodes a putative peptide that regulates receptor expression at the translational level (see below) (Parola and Kobilka, 1994; McGraw et al., 1998). The 13 SNPs in the promoter and coding regions of the β_2-AR gene were found organized into 12 principal haplotypes of a potential 8192 (2^{13}) combinations, but of the 12 haplotypes only 4 are relatively common (Table 7) (Drysdale et al., 2000). Marked interethnic differences in allelic frequency have been described for certain individual SNPs and for the various β_2-AR haplotypes (Tables 5 and 7) (Drysdale et al., 2000). For example, the Gln27Glu β_2-AR polymorphism shows substantial interethnic variability, e.g., Caucasian (0.35), African American (0.21), and Chinese individuals (0.07) (Xie et al., 1999b), whereas the Arg16Gly β_2-AR polymorphism shows less interethnic differences: Caucasian (0.54), African American (0.51), and Chinese individuals (0.41) (Xie et al., 1999b) (Table 5). The Val34Met- and the Thr164Ile-β_2-AR polymor-

TABLE 7
Most common haplotypes and frequencies (>5%) in several populations

Nucleotide	−1023	−709	−654	−468	−406	−367	−47	−20	46	79	252	491	523	Ca	A A	As	H-L
Alleles	G/A	C/A	G/A	C/G	C/T	T/C	T/C	T/C	G/A	C/G	G/A	C/T	C/A				
Location	5′	5′	5′	5′	5′	5′	5′LC	5′	Gly16Arg	Gln27Glu	syn	Thr164Ile	syn				
Haplotype:																	
1	A	C	G	C	C	T	T	T	A	C	G	C	C	0.7[a]	25.0[a]	12.5[a]	10.0[a]
2	A	C	G	G	C	C	C	C	G	G	G	C	C	48.3	6.3	10.0	26.7
4	G	C	A	C	C	T	T	T	A	C	G	C	C	33.0	29.7	45.0	40.0
6	G	C	G	C	C	T	T	T	G	C	A	C	A	13.2	31.3	30.0	13.3

Nucleotide number is based on the first nucleotide of the start codon being + 1. The frequencies are reported for the indicated populations as follows: Ca, Caucasian; A A, African American; As, Asian; H-L, Hispanic-Latino. Alleles, the two nucleotide possibilities at each SNP position. 5′,5′ upstream of the β_2AR open reading frame; 5′LC, 5′ leader cistron; Syn, synonymous SNP. Adapted from Drysdale et al., 2000.

[a] Frequency is shown by percentage.

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phisms occur at low allelic frequencies (<1% and <5%, respectively). No homozygous Ile164 individuals have been identified, perhaps because this variant is lethal when homozygously expressed (Reihsaus et al., 1993; Brodde et al., 2001b; Makimoto et al., 2001).

The impact of the coding sequence variants of the β_2-AR has been reviewed with regard to some aspects of function and disease associations, and interested readers should consult these reviews: (Buscher et al., 1999a; Liggett, 2000a,b; Silverman et al., 2001; Fenech and Hall, 2002; Joos and Sandford, 2002; Palmer et al., 2002; Taylor and Kennedy, 2002; Wood, 2002; Small et al., 2003). We will emphasize the role of variant receptors in drug responses (especially cardiovascular responses) in vitro and in vivo.

b. 5′ Noncoding β_2-Adrenergic Receptor Polymorphisms and Receptor Expression. Promoter polymorphisms alone and in concert with coding region polymorphisms (haplotypes) have the potential to alter receptor expression (McGraw et al., 1998; Scott et al., 1999; Drysdale et al., 2000; Johnatty et al., 2002). In vitro, the Arg19Cys (−47 T→C) polymorphism located in the 5′ leader cistron increases receptor protein but not mRNA levels, consistent with the idea that this variant regulates receptor expression at the translational level (Parola and Kobilka, 1994; McGraw et al., 1998). In human airway smooth muscle (HASM) cells that natively express β_2-ARs, receptor expression was approximately 2-fold higher in cells bearing Cys19 compared with the Arg19 variant (McGraw et al., 1998). Drysdale et al. (2000) examined the two most common homozygous haplotypes (termed 2/2 and 4/4) (Table 7) in a transient expression system. These haplotypes, which express either Arg or Cys (−47 T→C) in the 5′ leader cistron, Arg- or Gly-16, and Gln- or Glu27, as well as other differences in 5′UTR nucleotides, differentially express both mRNA and protein levels of β_2-AR (Drysdale et al., 2000). Such results contrast with findings that emphasize the purely translational effect of the Arg19Cys variant (McGraw et al., 1998) and suggest that the additional 5′UTR polymorphisms found in the haplotypes likely influence mRNA expression. Moreover, as recently shown by Johnatty et al. (2002), no single 5′UTR polymorphism is predictive of haplotype effects on transcription.

c. β_2-Adrenergic Receptor Polymorphisms, Desensitization, and Down-Regulation. The two major nonsynonymous SNPs in the β_2-AR, Arg16Gly and Gln27Glu, are located in the extracellular amino terminus at sites that had not been recognized as important for β_2-AR function before the identification of the SNPs. Initial efforts involved studies of each of these and revealed that neither influenced receptor binding or G_s coupling, but instead impacted on receptor desensitization (Table 8). Green et al. (1994) used site-directed mutagenesis and recombinant expression of the polymorphic receptors in Chinese hamster fibroblasts to investigate the functional properties of the variants. The Arg16Gly β_2-AR had increased agonist-promoted down-regulation; the Gln27Glu β_2-AR was resistant to such down-regulation; and the combination of Arg16Gly and Gln27Glu β_2-ARs resembled Arg16Gly alone, i.e., demonstrating increased agonist-promoted down-regulation compared with wild-type (Arg16, Gln27) β_2-AR (Green et al., 1994).

Primary cultures of HASM cells expressing the variants yielded similar results (Green et al., 1995): enhanced agonist-promoted down-regulation in cells expressing Gly16, and blunted down-regulation/desensitization in cells that expressed Glu27 β_2-ARs (Green et al., 1995). Other data show that HASM cells containing at least one Glu27 allele (equivalent to the presence of the Gly16Glu27 haplotype) have greater acute and chronic isoproterenol-stimulated desensitization of cell stiffness, measured by magnetic twisting cytometry, and of cAMP accumulation compared with cells with Gln27 (Moore et al., 2000). In contrast with earlier data, Moore et al. (2000) observed that HASM cells with Gly16Gln27 showed *less* desensitization to isoproterenol, whereas cells with the Arg19 allele (−47 T→C), and presumably Glu27 because of linkage disequilibrium between Arg19 (−47 T→C) and Glu27 (McGraw et al., 1998; Drysdale et al., 2000; Moore et al., 2000), had *greater* desensitization to isoproterenol-stimulated cAMP formation and cell stiffness. There is no clear explanation for the differing results between the older and more recent studies involving the use of HASM cells that express different ARs. However, it is worth noting that early in vitro studies involved the use of receptors that contained combinations of polymorphisms that rarely occur naturally. Due to linkage disequilibrium, subjects who are Glu27 homozygotes are virtually always Gly16 homozygotes, implying that re-

TABLE 8
Common β_2-AR coding SNPs and in vitro drug responses.

Amino Acid Change	Nucleotide Change	Drug Response Studied	Reference
Arg16Gly	46A→G	Gly16 increased agonist-promoted down-regulation; others find Gly16 may be resistant to desensitization	Green et al., 1994, 1995; Chong et al., 2000; Moore et al., 2000
Gln27Glu	79C→G	Glu27 resistant to, or blunted, down-regulation	Green et al., 1994, 1995; Chong et al., 2000; Moore et al., 2000
Val34Met	100G→A	No functional effect reported	
Thr164Ile	491C→T	Decreased functional coupling to Gs; decreased sequestration	Green et al., 1993, 2001; Turki et al., 1996; Buscher et al., 2002

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sults with that combination are more relevant to the in vivo setting (Dewar et al., 1998; Johnson and Terra, 2002; Bruck et al., 2003).

Others have obtained inconsistent results, especially using cells isolated from human subjects, with regard to impact of the Gly16 and Glu27 variants on desensitization. A small study (10 healthy, male Japanese subjects) found that procaterol (β_2-AR agonist)-stimulated cAMP levels in peripheral blood mononuclear cells were suppressed after 5 days of oral procaterol, a suppression that was greater in Gly16 than Arg16 homozygotes (i.e., greater desensitization) (Makimoto et al., 2001). In mononuclear leukocytes isolated from patients with cystic fibrosis, Buscher et al. (2002) observed a decrease in isoproterenol-stimulated cAMP generation in cells from patients with Gly16. In contrast, Chong et al. (2000) investigated the ability of isoproterenol to inhibit histamine release from human lung mast cells and found that compared with wild-type (Arg16 and Gln27), the Gly16 and Glu27 forms of the receptor were *both resistant* to desensitization. In an examination of ex vivo (lymphocytes) and in vivo (bronchoprotection) function of β_2-ARs in asthmatic patients, Lipworth et al. (1999b) assessed β_2-AR binding density, binding affinity, basal and isoproterenol-stimulated cAMP response, and the protective effect of a single dose of inhaled formoterol against methacholine-induced bronchoconstriction and found that β_2-AR polymorphisms at positions 16 and 27 did not influence cAMP response or functional antagonism. Subsequent work by the same group using peripheral blood mononuclear cells from 96 individuals with asthma showed that no single polymorphism (in particular those at positions 16 and 27) or haplotype was correlated with levels of β_2-AR expression or cAMP response to isoproterenol (Lipworth et al., 2002). Thus, taken together, some recent findings with native human cells contrast with data from transfected cell systems and provide less consistent evidence that Gly16, alone or together with Glu27, is necessarily associated with greater desensitization or with a decrease in agonist-promoted responses. This issue will perhaps best be resolved by more thorough study of cells from subjects with different haplotypes.

The Thr164Ile β_2-AR polymorphism, located in the fourth transmembrane spanning domain, has decreased functional coupling to G_s, as measured by ligand binding and AC assays under basal or agonist-stimulated conditions (Green et al., 1993, 2001; Buscher et al., 2002), and when overexpressed in the hearts of transgenic mice, shows decreased biochemical and physiological activity (Table 8) (Turki et al., 1996). Similarly, isoproterenol-stimulated IgE-mediated release of histamine from human lung mast cells was blunted in preparations that were heterozygous Thr164Ile compared with homozygous Thr164Thr (Kay et al., 2003). Terbutaline-promoted inotropic and chronotropic responses are blunted in humans with the Thr164Ile variant (Brodde et al., 2001b), results consistent with the observed signaling defects in vitro but not as predicted by the reduction in agonist-promoted β_2-AR sequestration observed with the Ile164 variant (Green et al., 1993).

Thus, overall, the available data indicate that the effects of the individual polymorphisms on desensitization do not always yield the same result in vivo as they do in vitro. Additionally, it appears that the polymorphisms differentially influence desensitization depending on the tissue where the polymorphism(s) is/are expressed (as will be described subsequently). With the existence of several common haplotypes (Table 7), perhaps more clear-cut results (and definitive conclusions) will be possible if studies emphasize analyses of the most common haplotypes.

d. β_2-Adrenergic Receptor Polymorphisms and Hypertension. As noted above in the discussion of α_{1B}-ARs, the long arm of chromosome 5 contains a cluster of potential candidate genes for hypertension, including the β_2-AR (Krushkal et al., 1998). Given the role of β_2-ARs as regulators of vasodilation in many vascular beds, it is thus not surprising that studies have been conducted to test the hypothesis that those receptors are the responsible candidate gene (Table 9). Of particular note are results of studies with relatively large sample sizes. For example, Ranade et al. (2001) found a small, but significant, association between the Gly16 allele and essential hypertension in a population of Chinese origin (>800 subjects), with the Arg16Gly polymorphism accounting for ~1% of the variance in systolic and diastolic BP. Bray et al. (2000) studied subjects from Rochester, Minnesota, including 55 pedigrees containing one or more sibling pairs discordant for systolic BP and 298 nuclear families (1283 individuals) and found that compared with Arg16 homozygotes, Gly16 homozygotes had higher diastolic BP and that the Arg16Gly polymorphism accounted for ~2% of the variance in diastolic BP. In addition, Glu27 homozygotes had significantly higher systolic BP and mean arterial pressure compared with Gln27 homozygotes. Although the Gly16 variant was significantly associated with an increased BP or risk for hypertension in that population and others (Kotanko et al., 1997; Gratze et al., 1999; Ranade et al., 2001), other researchers have not observed such an association (Herrmann et al., 2000; Xie et al., 2000; Dishy et al., 2001; Ranade et al., 2001; Tomaszewski et al., 2002; Heckbert et al., 2003). Indeed, some have found an opposite result and proposed that, at least in certain populations, Arg16 is associated with hypertension (Timmermann et al., 1998; Busjahn et al., 2000) or with higher systolic BP in younger people (age <50 years) (Castellano et al., 2003). We conclude that overall, despite numerous studies involving several thousand individuals of different ethnicity, it seems unlikely that particular β_2-AR polymorphisms are universally important for the development of hypertension.

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TABLE 9
β_2-AR coding SNPs and hypertension

Amino Acid Change	Genetic Association Noted	Reference
Arg16Gly	Gly16 associated with hypertension (African Caribbean, 136 hypertensive and 81 normotensive)	Kotanko et al., 1997
Arg16Gly	Arg16 associated with hypertensive family-history; risk analysis implicated Arg16 (23 hypertensive and 22 normotensive families)	Timmermann et al., 1998
Arg16Gly	Gly16 associated with increase in BP (57 normotensive Austrian Caucasians)	Gratze et al., 1999
Arg16Gly, Gln27Glu	No association with hypertension (African American, n = 283, or Caucasian, n = 380)	Xie et al., 2000
Arg16Gly	No association with hypertension or hemodynamic measures (African-American or Caucasian, 243 subjects)	Herrmann et al., 2000
Arg16Gly, Gln27Glu	Gly16, Glu27 small, but significant, association with hypertension and BP (~300 families)	Bray et al., 2000
Arg16Gly	Arg16 associated with higher BP and greater risk of hypertension (166 pairs of German twins: 100 mono- and 66 di-zygotic twins)	Busjahn et al., 2000
Arg16Gly	Gly16 significantly associated with essential hypertension (Chinese, >800)	Ranade et al., 2001
Arg16Gly, Gln27Glu, Thr164Ile, haplotypes	No association with hypertension, SBP, or DBP (Polish pedigree, 638 subjects)	Tomaszewski et al., 2002
Arg16Gly, Gln27Glu, haplotypes	Association of BP with various genotypes in younger subjects only (aged <50) (571 subjects, random sample general population)	Castellano et al., 2003
Arg16Gly, Gln27Glu	No association with hypertension (808 African American and 4441 Caucasians)	Heckbert et al., 2003

SBP, systolic blood pressure; DBP, diastolic blood pressure.

e. β_2-Adrenergic Receptor Polymorphisms and Vascular Responses to Agonists. The Arg16Gly and Gln27Glu polymorphisms influence vascular response to agonist administration, but the data are not consistent, perhaps because of tissue-specific differences (Table 10). Some investigators have noted blunting of β_2-AR-mediated vasodilatory responses (i.e., greater vasoconstriction) in Gly16 subjects in various vascular beds (Gratze et al., 1999; Hoit et al., 2000; Snapir et al., 2003a). Other investigators have obtained different results: homozygotes for Gly16 or Glu27 (the former expected to be more prone to, and the latter resistant to, down-regulation) were both reported to have *higher* basal- and a *greater* increase in isoproterenol-stimulated- forearm (arterial) blood flow, and *greater* isoproterenol-stimulated dorsal hand vein dilation compared with Arg16 or Gln27 homozygotes (Cockcroft et al., 2000; Dishy et al., 2001). In a study of dorsal hand veins, Dishy et al. (2001) found that Glu27 homozygotes had higher maximal venodilation in response to isoproterenol than did Gln27 homozygotes, and subjects homozygous for Arg16 had almost complete desensitization, whereas those homozygous for Gly16 did not desensitize, the latter results contrasting with in vitro data, discussed in the previous section. Bruck et al. (2003) evaluated cardiac (versus vascular) responses and assessed receptor desensitization more directly: subjects with variants at positions 16 and 27 were administered daily terbutaline and showed similar extents of desensitization of chronotropic or inotropic responses to infused terbutaline after 2 weeks treatment, but subjects with Glu27 developed desensitization more slowly. In contrast, Gly16 did not influence either the rate or extent of desensitization of cardiac responses. Thus, these latter results, related to cardiac function, contrast with both in vitro findings as well as with results for peripheral vascular responses, especially with respect to impact of Arg16Gly on desensitization in vivo. Such contrasting results suggest that β_2-AR polymorphisms exhibit tissue-specific effects in terms of impact on drug responses. Assessment of the role of β_2-AR haplotypes on such responses should prove of interest.

In addition, the status of (patho)physiological changes in vascular responses related to aging needs to be taken into account. This was demonstrated by the recent re-

TABLE 10
β_2-AR coding SNPs and cardiovascular drug responses

Amino Acid Change	Drug Response Studied and Response Observed	Reference
Arg16Gly	Gly16: decreased vasodilatory response to salbutamol	Gratze et al., 1999
Arg16Gly	Gly16 and terbutaline treatment: limb blood flow was less, vascular resistance greater, SBP and DBP greater, no difference in HR	Hoit et al., 2000
Arg16Gly,Gln27Glu	Gly16, Glu27: higher basal blood flow in forearm (arterial); greater iso-stimulated increase in forearm and dorsal hand vein blood flow	Cockcroft et al., 2000
Arg16Gly, Gln27Glu	Arg16: associated with vascular response in dorsal hand vein: complete iso-stimulated desensitization; Glu27: higher iso-stimulated venodilation	Dishy et al., 2001
Arg16Gly	Gly16: greater iso-induced forearm blood flow; l-NMMA eliminated this effect	Garovic et al., 2003
Arg16Gly, Gln27Glu	Daily terbutaline treatment: similar desensitization of HR increase with Arg16Gly, Gln27Glu; Glu27 develops desensitization more slowly	Bruck et al., 2003
Arg16Gly	Gly16: greater EPI-promoted increase in DBP	Snapir et al., 2003a
Arg16Gly, Gln27Glu	Glu27 allele: greater number of good responder CHF patients with carvedilol treatment (i.e., LVEF, LVFS) vs. Gln27	Kaye et al., 2003

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; iso, isoproterenol; l-NMMA, *N*γ-monomethyl-l-arginine; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

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sults of Castellano et al. (2003), who noted association of the Arg16 variant (especially in combination with Gln27) and higher systolic BP, in particular in subjects below the age of 50. It is well known that aging is associated with a decrease in β_2-AR-mediated responses (Vestal et al., 1979; Pan et al., 1986; Lakatta, 2003), and thus, genetic variants in β_2-ARs would be predicted to have a greater impact on physiology and pathophysiology in younger subjects. This idea is one that has not been widely appreciated by investigators who have studied β-AR variants.

f. β_2-Adrenergic Receptor Polymorphisms and Congestive Heart Failure. Patients with congestive heart failure who have Thr164Ile have a significantly reduced survival and depressed exercise capacity (Liggett, 1998; Wagoner et al., 2000), results consistent with findings in transgenic mice that have this variant targeted to the heart (Turki et al., 1996). Healthy individuals with Ile164 show a blunting of the maximal increase in heart rate and a shortening of the duration of electromechanical systole induced by terbutaline (Brodde et al., 2001b). These studies suggest that blunted cardiac β_2-AR responsiveness in subjects with Thr164Ile may contribute to the decreased survival of heart failure patients who have this variant. We are unaware of data that document a contribution of the more common β_2-AR variants or haplotypes to development or progression of congestive heart failure. However, it has recently been reported that heart failure patients homozygous for the Gln27 allele were less likely to respond to the β-adrenergic antagonist carvedilol than were those with the Glu27 allele (Kaye et al., 2003). Such results, which were not observed for the position 16 alleles, suggest a possible contribution of Gln27 in influencing response to carvedilol and perhaps other β-adrenergic blockers used for treatment of heart failure. Such ideas will need to be tested in other patients with this widely prevalent disorder.

g. β_2-Adrenergic Receptor Polymorphisms and Obesity. The SNP at −47 (T→C), Arg19Cys, and the Arg16Gly and Gln27Glu variants of the β_2-AR have been associated with obesity-related phenotypes and may be risk factors in obesity or the propensity to gain weight (Large et al., 1997; Hellstrom et al., 1999; Yamada et al., 1999; Hoffstedt et al., 2001; Corbalan et al., 2002a; Ellsworth et al., 2002; van Rossum et al., 2002). Lipolytic measurements in fat cells from homozygous or heterozygous Gly16 individuals yielded a 5-fold increase in agonist sensitivity compared with the response in cells from Arg16 homozygotes, as measured by terbutaline-induced release of glycerol (Large et al., 1997). Freshly isolated subcutaneous fat cells that were heterozygous for Thr164Ile had a severalfold higher lipolytic EC_{50} of terbutaline compared with homozygous Thr164 cells (Hoffstedt et al., 2001). Since few studies have directly examined the effects of the β_2-AR variants in adipose tissue, such variants, especially haplotypes, should be further investigated in terms of impact on adipocyte function and obesity.

h. β_2-Adrenergic Receptor Polymorphisms and Asthma. Numerous association studies have been carried out with respect to β_2-AR SNPs and asthma (Liggett, 2000a; Silverman et al., 2001; Fenech and Hall, 2002; Joos and Sandford, 2002; Palmer et al., 2002; Taylor and Kennedy, 2002; Small et al., 2003). Overall, the data suggest that β_2-AR polymorphisms, especially Arg16Gly, may play a role in airway hyperresponsiveness, bronchodilator sensitivity and response to β-agonist, long-term use of β-agonist, and tolerance (Table 11) (Turki et al., 1995; Martinez et al., 1997; Tan et al., 1997; D'Amato et al., 1998; Kotani et al., 1999; Fowler et al., 2000; Israel et al., 2000; Lima et al., 2000; Taylor et al., 2000a). Future studies will need to identify individuals at risk for the development of asthma in addition to patient populations that are likely or unlikely to respond to treatment or experience adverse side effects (Silver-

TABLE 11
Examples of influence of β_2-AR SNPs on drug responses in asthma

Amino Acid Change	Drug Response Studied	Reference
Arg16Gly	Greater bronchodilator desensitization with 4-wk formoterol treatment of Gly16 vs. Arg16 homozygotes	Tan et al., 1997
Arg16Gly	FEV_1 response to albuterol more likely in Arg16 homozygotes and Arg16Gly heterozygotes vs. Gly16 homozygotes	Martinez et al., 1997
Arg16Gly, Gln27Glu	Response to fenoterol treatment (asthma control) similar between genotypes	Hancox et al., 1998
Arg16Gly	Albuterol-evoked FEV_1 was higher and more rapid in Arg16 homozygotes vs. Gly16 carriers	Lima et al., 1999
Arg16Gly	Lower airway responsiveness to salbutamol in Gly16 vs. Arg16 homozygotes or Arg16Gly heterozygotes	Kotani et al., 1999
Arg16Gly, Gln27Glu	No association between genotype and desensitization to short- or long-acting β_2-agonists (formoterol vs. terbutaline)	Lipworth et al., 1999a
Arg16Gly	Poor FEV_1 vs. albuterol concentration relationship associated with Gly16	Lima et al., 2000
Arg16Gly	No association between functional antagonism of methacholine-induced bronchoconstriction with formoterol or salmeterol and genotype	Lipworth et al., 2000
Arg16Gly	Decline in peak expiratory flow with regular albuterol use in Arg16 vs. Gly16 homozygotes	Israel et al., 2000
Arg16Gly	No association between tolerance to regular salmeterol and genotype	Taylor et al., 2000b
Arg16Gly	More frequent exacerbations during salbutamol treatment of Arg16 vs. Gly16 homozygotes or Arg16Gly heterozygotes	Taylor et al., 2000a
Haplotype pairs	Albuterol-evoked FEV_1 improvement related to haplotype pairs (i.e., Arg19Cys (−47), Arg16Gly, Gln27Glu)	Drysdale et al., 2000

FEV_1, forced expiratory volume in 1 s.

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man et al., 2001; Fenech and Hall, 2002; Joos and Sandford, 2002; Palmer et al., 2002; Taylor and Kennedy, 2002; Small et al., 2003).

3. β_3-Adrenergic Receptors. β_3-AR are expressed predominantly in adipose tissue and are involved in the regulation of lipolysis and thermogenesis; they are also found in the gastrointestinal tract and regulate smooth muscle relaxation (Krief et al., 1993; Summers et al., 1997). Sequence analysis of the β_3-AR gene has identified three exons and two introns (Lelias et al., 1993; van Spronsen et al., 1993). A widely investigated SNP of the β_3-AR is at nucleotide 827 (T→C) and results in an amino acid change, Trp64Arg, in the first intracellular loop (Fig. 2) (Walston et al., 1995). Additional variants of the β_3-AR have been identified at nucleotide 1856 (G→T) in one of the introns and nucleotide 3139 (G→C) near the 3′ noncoding end of the gene; these variants are strongly associated with the SNP at position 827 (Trp64Arg) and comprise two haplotypes (Hoffstedt et al., 1999; Silver et al., 1999). The β_3-AR Trp64Arg polymorphism shows varying allelic frequencies in subjects with different ethnicities: 0.08 in Caucasians, 0.10 in African Americans, 0.13 in Mexican Americans, 0.16 in Spanish subjects, 0.18 in Japanese Americans, and 0.31 in Pima Indians (Table 5) (Walston et al., 1995; Kawamura et al., 2001; Lowe et al., 2001; Corbalan et al., 2002b).

Subjects who are heterozygous for the Trp64Arg β_3-AR polymorphism show increased sensitivity to the pressor effects of infused NE compared with individuals homozygous for the Trp64 β_3-AR (Melis et al., 2002). Assessment of ANS activity during supine rest and standing has shown that individuals heterozygous for the Trp64Arg allele have lower resting ANS activity compared with subjects homozygous for the Trp64 allele (Shihara et al., 1999).

Studies that have investigated functional effects of the Trp64Arg β_3-AR polymorphism have yielded variable results. Transfected Chinese hamster ovary cells with Trp64- or Arg64-containing β_3-ARs showed no significant differences in agonist binding properties or stimulation of cellular cAMP accumulation between the two receptor variants (Candelore et al., 1996). In contrast, Pietri-Rouxel et al. (1997) found decreased maximal cAMP accumulation in response to several agonists in transfected cells stably expressing Arg64 compared with Trp64 β_3-AR. Spontaneous and agonist- or glucose-stimulated secretion of insulin were also decreased in Arg64 versus Trp64 β_3-AR-expressing cells (Perfetti et al., 2001). Isogaya et al. (2002) failed to find differences in agonist affinities or stimulated cAMP responses in COS-7 cells transfected with Arg64- and Trp64-containing β_3-ARs, but they did observe enhanced cAMP response to isoproterenol and CGP12177, a selective β_3-AR agonist, when the Arg64-containing β_3-AR was coexpressed with adenylyl cyclase 3, suggesting that signal transduction by the two alleles may differ depending on downstream components.

Several groups have studied the Trp64Arg β_3-AR polymorphism in native tissues. In studies of lipolysis in isolated visceral white fat cells incubated with NE or CGP12177, Trp64Arg heterozygotes and Trp64 homozygotes yielded similar results (no Arg64 homozygotes were identified) (Li et al., 1996). In omental adipose tissue, Hoffstedt et al. (1999) found differences between the Trp64- or Arg64-haplotypes (827T/1856G/3139G or 827C/1856T/3139C, respectively) in terms of the half-maximum effective agonist concentration (EC_{50}) for CGP12177: the Arg64 haplotype showed a 10-fold decrease in sensitivity. This finding may help explain some of the divergent conclusions on the biochemical effects of the Trp64Arg β_3-AR polymorphism; the codon 64 variant may not play a key functional role by itself but instead may be in linkage disequilibrium with a functional variant elsewhere in the gene. Individuals homozygous for Arg64 secrete less insulin in response to a glucose infusion and have higher fasting glucose levels and lower glucose effectiveness compared with Trp64 homozygotes (Walston et al., 2000). Such effects may contribute to the earlier onset of type 2 diabetes observed for individuals with the Arg64 β_3-AR allele (Walston et al., 1995).

Numerous studies have evaluated the association, or lack thereof, between the β_3-AR Trp64Arg polymorphism and metabolic disorders, such as obesity and type 2 diabetes (Arner and Hoffstedt, 1999). The results have been inconsistent: some studies find an association between the β_3-AR Trp64Arg polymorphism and obesity or type 2 diabetes (Kurokawa et al., 2001; Oizumi et al., 2001; Marti et al., 2002), whereas others report no association (Ghosh et al., 1999; Oeveren van-Dybicz et al., 2001; Rawson et al., 2002). It is difficult to identify a clear reason for the discrepant results, although gender, age, and ethnicity may influence or modify the effect of the Trp64Arg β_3-AR polymorphism and risk and onset of type 2 diabetes or obesity (Walston et al., 1995; Corella et al., 2001; Kawamura et al., 2001; Corbalan et al., 2002b).

The Trp64Arg β_3-AR and the α_{2B}-AR Glu deletion variant interact; when combined, these two variants are associated with greater fat mass and percentage of body fat (Dionne et al., 2001). More recently, potentially important interactions between the Trp64Arg β_3-AR polymorphism and other candidate genes for metabolic disorders have been identified, including synergism with the −3826 A→G promoter polymorphism of the uncoupling protein 1 gene, which is associated with decreased sympathetic nervous system activity and a tendency to gain weight (Sivenius et al., 2000; Shihara et al., 2001). In women, a significant interaction between the Trp64Arg β_3-AR polymorphism and the lipoprotein lipase gene (H+/H+ genotype) has been associated with a higher body mass index (Corella et al., 2001). A novel

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polymorphism of the human type 2 deiodinase gene (Thr92Ala) was found to interact significantly with the Trp64Arg β_3-AR polymorphism and is also associated with an increased body mass index (Mentuccia et al., 2002).

Overall, it appears that the Trp64Arg β_3-AR polymorphism can influence β_3-AR function both in vitro and in vivo and thereby influence lipid metabolism and perhaps onset or frequency of various metabolic disorders. The synergistic interactions between the Trp64Arg β_3-AR polymorphism and other gene variants may prove important for defining the functional roles of this receptor polymorphism.

IV. Summary and Conclusions

Many clinically useful drugs act on receptors of the ANS. Genetic polymorphisms in these receptors can contribute to differences in drug response (i.e., pharmacodynamics), as shown by certain examples discussed here. Understanding the interaction between particular drugs and the underlying genetic variation among individuals is likely to prove extremely important for pharmacology, especially for clinical pharmacology, in the future, as well as for other aspects of medical practice (Collins et al., 2003; Evans and McLeod, 2003). The ultimate goal of pharmacogenomic studies is to provide new strategies for optimizing and individualizing drug therapy based on a patient's genetic determinants of pharmacokinetics, drug efficacy, and toxicity. Few genes that underlie genetically complex traits have been identified compared with the number of single genes that mediate simple Mendelian traits (Glazier et al., 2002; Guttmacher and Collins, 2002; Korstanje and Paigen, 2002). Almost certainly, the vast majority of pharmacologic phenotypes are polygenic and thus is determined by interacting genes involved in multiple pathways of drug action. This creates considerable complexity in terms of defining unique and individualized patterns of genes mediating drug responses. The problem of attempting to individualize therapy is compounded by the fact that many of the most common and chronic diseases, in particular disorders that are treated by drugs active on components of the ANS, are genetically complex (e.g., hypertension, diabetes mellitus, and asthma). It is thus a daunting task to identify the full complement of genes that influence response to a given drug, especially in chronic polygenic diseases. Although progress has been made in the beginning to identify sources of genetic variation that influence drug response, we are still at the early stages of identifying the most critical genetic determinants. Thus, although the goal of optimizing drug therapy (in particular for drugs acting on the ANS) for individual patients is laudable, much work remains before this goal can be achieved.

In attempting to identify functionally important genetic variants, one is faced with choosing (testing) many possible sources of variation: synonymous or nonsynonymous variants, coding or noncoding SNPs, single or multiple variants (haplotypes), etc. Recently, it has been suggested that complex traits result more often from noncoding and regulatory variants than from coding sequence variants (Glazier et al., 2002; Korstanje and Paigen, 2002). In coding regions, the functional consequences are more readily assessed by investigating protein function. Interpreting the consequences of noncoding sequence variants is more complicated, because the relationship among promoter or regulatory elements, gene expression level, and phenotype is less well understood and not as readily amenable to experimental analysis.

To date, most studies of ANS receptors have emphasized the impact of individual, nonsynonymous, coding region SNPs or deletions. As we noted in several places in this review, different investigators commonly do not obtain concordant results regarding the effect of a particular variant. This may be attributable to experimental differences in terms of end points being assessed and quantified, ethnic background of the subjects, or specific tissues being studied. Several studies suggest that there can be large ethnic differences in the expression of genetic variants that relate to ANS receptors (Xie et al., 1999a,b, 2000, 2001; Evans et al., 2001; Garenc et al., 2002; Small et al., 2003), and for this reason ethnicity should be clearly defined (Shriver et al., 1997; Hoggart et al., 2003). Our bias is that the use of genetic markers to define ethnicity may prove critical for helping to define the role of ethnicity in autonomic receptor responses and, importantly, in optimization of therapy of drugs that act on those receptors.

The genetic background of a tissue or cell line can complicate analyses of genetic variants (Cockcroft et al., 2000; Hoit et al., 2000; Ryden et al., 2002). Although many studies have focused on associations between genotype and phenotype, detailed functional studies are limited with respect to the biological impact of most of the polymorphisms we have discussed. More importantly, there has been little confirmation by multiple investigators of key conclusions drawn from both in vitro and in vivo studies. One potentially useful approach to help define the in vivo significance of a particular variant will be to test the impact of replacement of the variant nucleotide of one phenotypic variant to another using animal models, such as transgenic or knock-in mice, ideally with tissue-specific, conditional expression (Glazier et al., 2002). However, ultimately studies in humans, especially in vivo, perhaps using relatively noninvasive strategies, will provide the most definitive answers regarding physiological and pharmacological roles of specific variants.

Signaling components outside the receptors of the ANS that may influence drug response should not be ignored. Some evidence suggests that the GNAS1 locus, which encodes the $G_{\alpha s}$ protein, may carry a synonymous

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variant (393 C→T, Ile131Ile) that influences BP variation and response to β-blockade in essential hypertension (Jia et al., 1999) and maximal orthostatic change in systolic BP after standing (Tabara et al., 2002). The latter variant, as well as a common G protein β3 variant (825 C→T), influences the prevalence and risk for orthostatic hypotension (Tabara et al., 2002). The G protein β_3 gene polymorphism (825 C→T) has also been shown to influence G_i protein receptor-mediated signal transduction (Ryden et al., 2002; Naber et al., 2003; Siffert, 2003). Depending on the stoichiometry among signaling components, it is likely that the most profound physiological and pharmacological effects will derive from genetic variants that alter activity or expression of the components that are most critical for determining potency and efficacy of responses to drugs (Ostrom et al., 2000, 2002; Rana et al., 2001).

It is increasingly recognized that it can be very difficult to link one SNP to a disease unless it has a major functional effect. Therefore, individual SNPs may have poor predictive power as pharmacogenetic loci for complex multigenic traits, such as the types we have described herein. Analysis of haplotypes is thus likely to prove important for defining important associations between phenotypes (i.e., drug response) and genetic variation. However, we believe one should approach these and other genomic analyses with a degree of skepticism. It is worth remembering that somatic cell genetic variants have proven of key importance in understanding certain polygenic disorders such as cancer (Calvert and Frucht, 2002; Balmain et al., 2003). In light of this, analyses for somatic cell variants in key pharmacologic targets may prove of interest (Erickson, 2003). Since it is sometimes difficult to estimate the exact effect of size a polymorphism will have on function, future studies will need to be appropriately powered to detect significant associations and linkage (Cardon et al., 2000; Jones and Montgomery, 2002). Approaches that use "natural" genetic cohorts, such as large pedigrees and twins, may prove useful to help define contributions of particular variants, but to date, very few studies have used such populations to assess ANS receptor signaling components.

V. Outlook

The basis for interindividual differences in drug response for targets of the ANS has advanced greatly in the past 5 to 10 years, but there is still much work to be done. Progress in phenotyping and genotyping should ultimately improve disease prediction, diagnosis, and prognosis, as well as yield new classification of disease and guide the choice of drugs and doses. The goal of individualization of therapy, especially for drugs active on the ANS, is laudable but still seems many years away. There are significant challenges that involve methodology, patient selection, statistical analyses, and the difficulties inherent in definitively linking and associating genotype and phenotype. Since all of these challenges are finite, we remain optimistic that the goal of individualized therapy for drugs that act via the ANS should be attainable. The key unanswered question is how long it will take to reach that goal.

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