

THE EFFECT OF COMMON POLYMORPHISMS OF THE β_2 -ADRENERGIC RECEPTOR ON AGONIST-MEDIATED VASCULAR DESENSITIZATION

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ABSTRACT

Background With continuous exposure to β_2 -adrenergic agonists, vascular tissue becomes desensitized to agonist-mediated vasodilatation. We studied the effects of two common polymorphisms of the β_2 -adrenergic receptor, one at codon 16 and one at codon 27, on agonist-mediated vasodilatation and desensitization in the vascular bed.

Methods We studied 26 healthy subjects who were selected to represent three genotypes: 7 were homozygous for the alleles encoding Arg16 and Gln27, 8 were homozygous for the alleles encoding Gly16 and Gln27, and 11 were homozygous for the alleles encoding Gly16 and Glu27. Vascular responses were assessed by measuring changes in the diameter of a dorsal hand vein. A dose-response curve of the effect of the β_2 -adrenergic-receptor agonist isoproterenol was constructed (dose range, 4 to 480 ng per minute). Desensitization was then induced by a 2-hour continuous infusion of isoproterenol, and venodilatation was measured 30, 60, 90, and 120 minutes after the start of the infusion.

Results Subjects who were homozygous for Arg16 had almost complete desensitization; venodilatation in response to isoproterenol in this group decreased from a mean (\pm SE) of 44 ± 11 percent to 8 ± 4 percent ($P=0.006$). In contrast, subjects who were homozygous for Gly16 did not have significant desensitization, irrespective of the amino acid encoded by codon 27. Subjects who were homozygous for Glu27 had higher maximal venodilatation in response to isoproterenol than those who were homozygous for Gln27 (86 ± 13 percent vs. 54 ± 8 percent, $P=0.03$).

Conclusions The Arg16 polymorphism of the β_2 -adrenergic receptor is associated with enhanced agonist-mediated desensitization in the vasculature, and the Glu27 polymorphism is associated with increased agonist-mediated responsiveness. Therefore, polymorphisms of the β_2 -adrenergic receptor are potentially important determinants of the vascular response to stress. (N Engl J Med 2001;345:1030-5.)

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IN humans, the β_2 -adrenergic receptor mediates physiologic responses, including vasodilatation, bronchial smooth-muscle relaxation, and lipolysis, in various tissues.¹ Altered mediation of vascular responses by this receptor may play a part in the pathogenesis of hypertension; blunted vasodilative responses to β_2 -adrenergic-receptor agonists have been found in persons with hypertension²⁻⁴ and in normotensive black Americans,⁵ members of a

group in which the prevalence of hypertension is high.^{6,7}

Several polymorphisms that have been described in the gene encoding the human β_2 -adrenergic receptor⁸ affect the function of the receptor in vitro. Specifically, the substitution of glycine for arginine at position 16 (Gly16) was associated with enhanced agonist-induced desensitization, and the substitution of glutamic acid for glutamine at position 27 (Glu27) was associated with resistance to desensitization, relative to the responses associated with the products of wild-type alleles (Arg16 and Gln27, respectively).^{9,10}

Studies of the effects of polymorphisms of the β_2 -adrenergic receptor on vascular reactivity in healthy subjects showed enhanced vasodilatation in response to isoproterenol in subjects who were homozygous for Glu27,¹¹ whereas vasodilatation after the systemic administration of a β_2 -adrenergic-receptor agonist was blunted in those who were homozygous for Gly16.^{12,13} The mechanism responsible for these alterations in agonist-mediated responses in vivo was thought to be the alterations in desensitization that had been observed in vitro in association with these polymorphisms.

There is marked linkage disequilibrium between the polymorphisms at codons 16 and 27 of the β_2 -adrenergic receptor.^{14,15} Thus, almost all persons who are homozygous for Glu27 are also homozygous for Gly16, whereas persons who are homozygous for Gly16 can be homozygous for Gln27, homozygous for Glu27, or heterozygous at codon 27. Studies addressing the effects of these polymorphisms on vascular reactivity have examined either codon 16 or codon 27 in isolation, seldom taking into account the strong linkage disequilibrium between the two polymorphisms. This is a crucial consideration, however, since according to the in vitro data, Gly16 and Glu27 may have opposite effects on agonist-mediated desensitization of the β_2 -adrenergic receptor.

The effects of the Arg16 and Gly16 polymorphisms and the Gln27 and Glu27 polymorphisms on agonist-mediated vascular desensitization in vivo remain unknown. Effects on agonist-induced desensitization in the vasculature that are mediated by these poly-

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morphisms may influence the adrenergic regulation of vascular tone and blood pressure. We conducted a study to determine the effects of polymorphisms of the β_2 -adrenergic receptor at codons 16 and 27 on agonist-induced venodilatation and desensitization in the human vasculature, while controlling for the various possible genotypes.

METHODS

Subjects

The study protocol was approved by the institutional review board of Vanderbilt University, and the subjects gave written informed consent. We determined the genotype of 400 volunteers with respect to the β_2 -adrenergic-receptor alleles of interest. The alleles encoding Arg16, Gly16, Gln27, and Glu27 were identified by single-strand conformation polymorphism analysis with the use of the polymerase chain reaction, as previously described.¹⁵ Twenty-five percent of the people examined were homozygous for the alleles encoding Arg16 and Gln27, 12 percent were homozygous for the alleles encoding Gly16 and Glu27, and 8 percent were homozygous for the alleles encoding Gly16 and Gln27. These persons then underwent screening to determine their eligibility for the study: persons of either sex were eligible if they were healthy, were not smokers, were residents of Nashville, were 18 to 50 years of age, and had no clinically significant abnormalities according to their history and the results of physical examination and laboratory testing. Consecutive, eligible subjects with one of the three genotypes of interest were asked to participate; 26 consented. Seven of these 26 subjects were homozygous for Arg16 and Gln27, 8 were homozygous for Gly16 and Gln27, and 11 were homozygous for Gly16 and Glu27.

The subjects received a controlled diet containing 150 mmol sodium and 70 mmol potassium daily for five days before the day on which the study was to be conducted. Adherence to the diet was confirmed by analysis of a 24-hour urine specimen collected the day before the study day. The subjects took no medications for at least two weeks and abstained from coffee and alcohol for five days before the study day. The night before the study, the subjects were admitted to the General Clinical Research Center of Vanderbilt University. The subjects remained in a supine position throughout the study.

Measurement of Vascular Responses

The study protocol is shown in Figure 1. Vascular responses were measured in a dorsal hand vein with the use of a linear variable differential transformer,¹⁶ as previously described.¹⁷ This instrument, which is mounted on the hand, measures and records changes in the diameter of the vein. All the subjects underwent testing at the same time of day and in the same room, which was maintained at a constant temperature. The subjects rested on a comfortable bed. After three stable base-line measurements of hand-vein diameter had been obtained, drug infusions were started in the vein on which the linear variable differential transformer was mounted. The α -adrenergic agonist phenylephrine (Elkins-Sinn, Cherry Hill, N.J.) was administered in increasing doses (from 24 to 6000 ng per minute), until the dose that caused approximately 70 percent constriction of the hand vein was identified. Pilot studies in six subjects had shown that the constriction induced by phenylephrine according to this protocol was stable. This dose of phenylephrine was then used to produce stable constriction during the remainder of the experiment. The dose-response curve for isoproterenol (Abbott Laboratories, North Chicago, Ill.) was then determined, as follows. Up to eight doses of isoproterenol (4 to 480 ng per minute for five minutes) were infused, and the response of the hand vein was measured.

The heart rate was continuously monitored with a bedside cardiac monitor (Dinamap MPS, Johnson and Johnson Medical, Tampa, Fla.), and blood pressure was measured in the arm on the side

opposite the side receiving the hand-vein infusion, by means of the same semiautomated device (Dinamap MPS). The heart rate and blood pressure were recorded during the last minute of infusion of each dose of isoproterenol. The infusion of isoproterenol was discontinued if there was a persistent increase in the heart rate of 10 or more beats per minute above the base-line value.

Desensitization

The initial assessment of the isoproterenol dose-response curve was followed by a washout period of 20 minutes, during which saline was infused and hand-vein measurements returned to base line. Next, a continuous infusion of isoproterenol to induce desensitization (mean [\pm SE] dose, 133 ± 12 ng per minute; range, 30 to 240) was administered for two hours. For each subject, the desensitizing dose chosen was the dose that resulted in venodilatation of approximately 50 percent and was determined from the subject's dose-response curve for isoproterenol. There was no significant difference among the three groups of subjects in the desensitizing dose used (geometric mean, 81 ng per minute [95 percent confidence interval, 50 to 133] in the subjects who were homozygous for Arg16 and Gln27; 141 ng per minute [95 percent confidence interval, 114 to 178] in those who were homozygous for Gly16 and Gln27; and 129 ng per minute [95 percent confidence interval, 91 to 180] in those who were homozygous for Gly16 and Glu27). The hand-vein response was measured 30, 60, 90, and 120 minutes after the start of the infusion of isoproterenol. Administration of the dose of phenylephrine that caused 70 percent constriction, as determined in each subject, was resumed 15 minutes before each measurement of the hand-vein response. This dose of phenylephrine did not differ significantly among the three groups of subjects (geometric mean, 893 ng per minute [95 percent confidence interval, 230 to 3475] in the subjects who were homozygous for Arg16 and Gln27; 956 ng per minute [95 percent confidence interval, 578 to 1556] in those who were homozygous for Gly16 and Gln27; and 767 ng per minute [95 percent confidence interval, 277 to 2123] in those who were homozygous for Gly16 and Glu27).

This method of desensitization was adapted from one described by Vincent et al.,¹⁸ who induced desensitization to isoproterenol in a dorsal hand vein by a continuous, four-hour infusion of isoproterenol at a dose of 271 ng per minute. In pilot studies, we had observed that when isoproterenol at a dose of 240 ng per minute (in three subjects) or saline (in three subjects) was infused for up to four hours, desensitization of the response to isoproterenol was complete within two hours and the response to saline remained unchanged. However, when the infusions lasted longer than two hours, the venodilative response in the subjects receiving saline also decreased, a response that would confound the assessment of agonist-induced desensitization. Isoproterenol at a dose of 240 ng per minute caused systemic effects (palpitations and tachycardia), whereas a lower dose (120 ng per minute infused for two hours) induced desensitization without causing systemic effects. The findings in the subjects who participated in the pilot study are not included in the data reported here.

The investigators who performed the hand-vein measurements were aware of the subjects' genotypes, since the subjects were recruited according to genotype. The experiments were not blocked according to genotype.

Statistical Analysis

Venoconstriction was expressed as the percentage reduction in the diameter of the hand vein from its maximal diameter during dilatation at base line. Venodilatation was expressed as the percentage reversal of the phenylephrine-induced constriction.¹⁶ Regression analysis was used to define the line of best fit through the linear portion of the isoproterenol dose-response curve. The dose of isoproterenol that caused 20 percent venodilatation was calculated for each subject. The maximal venodilative response to isoproterenol for each dose-response curve was recorded. These values were considered measures of vascular sensitivity and were compared among the subjects.

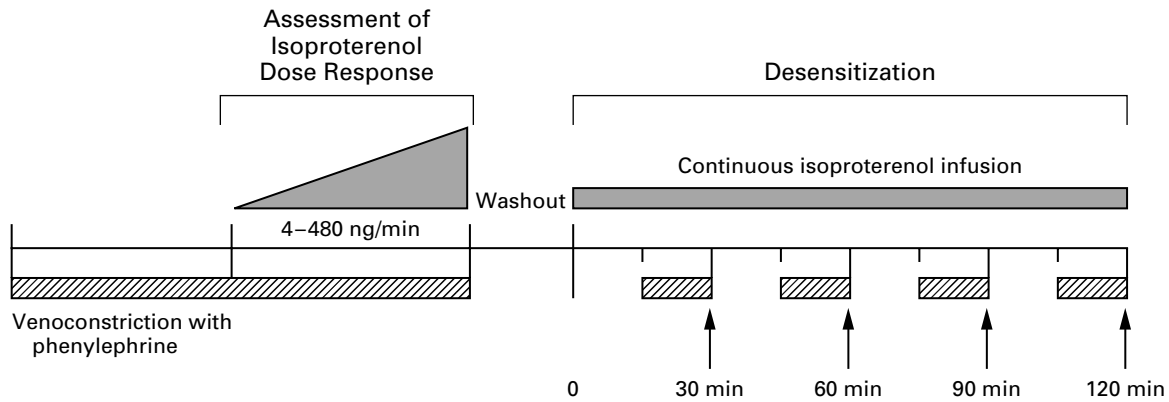


Figure 1. Study Protocol.

The shaded bars represent isoproterenol administration, and the hatched bars phenylephrine administration. Arrows indicate the points at which the response to isoproterenol was measured.

Data on the doses of isoproterenol required for 20 percent venodilatation were log-transformed before analysis and expressed as geometric means with 95 percent confidence intervals. Venodilatation in response to the dose of isoproterenol subsequently used for desensitization was measured during the initial assessment of the dose-response curve and 30, 60, 90, and 120 minutes after the start of the continuous isoproterenol infusion; the results were then compared among the subjects within each of the three genotype groups by linear-model, repeated-measures analysis of variance. One-way analysis of variance was used to compare normally distributed base-line and hemodynamic measurements among the three groups. The Kruskal-Wallis test was used to analyze data that were not normally distributed. The SPSS statistical software program (version 10.0, SPSS, Chicago) was used for all analyses. All tests were two-tailed. P values of less than 0.05 were considered to indicate statistical significance. The results are expressed as means \pm SE.

RESULTS

There were no significant differences in demographic characteristics among the three groups of subjects (Table 1). The subjects who were homozygous for Glu27 had a significantly higher maximal response to isoproterenol than the subjects who were homozygous for Gln27, regardless of the amino acid present at position 16 (86 ± 13 percent vs. 54 ± 8 percent, $P=0.03$) (Table 2). There was no significant difference in maximal isoproterenol-induced vasodilatation between the two groups of subjects who were homozygous for Gln27 ($P=0.66$). The dose of isoproterenol required for 20 percent venodilatation and the dose causing maximal venodilatation did not differ significantly among the three groups ($P=0.10$ and $P=0.19$, respectively).

Continuous infusion of isoproterenol resulted in desensitization, observed as a significant decrease in venodilatation over time, in the subjects who were homozygous for Arg16 ($P=0.006$ by analysis of variance) but not in the two groups of subjects who were homozygous for Gly16, irrespective of the ami-

TABLE 1. CHARACTERISTICS OF THE SUBJECTS ACCORDING TO GENOTYPE.*

CHARACTERISTIC	HOMOZYGOUS FOR Arg16 AND Gln27 (N=7)	HOMOZYGOUS FOR Gly16 AND Gln27 (N=8)	HOMOZYGOUS FOR Gly16 AND Glu27 (N=11)
Age (yr)	28 \pm 2	30 \pm 3	35 \pm 3
Sex (M/F)	5/2	3/5	6/5
Body-mass index†	25.5 \pm 1.5	22.6 \pm 1.2	26.6 \pm 1.5

*Plus-minus values are means \pm SE.

†Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

no acid at position 27 (Fig. 2). In the subjects who were homozygous for Arg16 and Gln27, desensitization occurred rapidly: venodilatation in response to isoproterenol decreased significantly within 30 minutes (from 44 ± 11 percent to 17 ± 7 percent, $P=0.02$) and reached its nadir 90 minutes after the start of the infusion (Fig. 2).

At the highest dose of isoproterenol infused, systolic blood pressure increased by a small amount over the values at rest in all three groups ($P=0.02$ by repeated-measures analysis of variance for all three groups considered together). In an analysis of each group separately, the change was significant only in the group of subjects who were homozygous for Glu27 (110 ± 4 mm Hg vs. 118 ± 5 mm Hg, $P=0.02$ by the paired t-test) (Table 3). However, there was no significant interaction between the increase in systolic blood pressure during isoproterenol infusion and

TABLE 2. EFFECT OF GENOTYPE ON THE VENODILATIVE RESPONSE TO ISOPROTERENOL BEFORE DESENSITIZATION.*

VARIABLE	HOMOZYGOUS FOR Arg16 AND Gln27 (N=7)	HOMOZYGOUS FOR Gly16 AND Gln27 (N=8)	HOMOZYGOUS FOR Gly16 AND Glu27 (N=11)
Maximal venodilative response to isoproterenol (%) [†]	50±11	57±11	86±13 [‡]
Dose of isoproterenol producing 20% venodilatation (ng/min)	43 (7–276)	62 (25–159)	16 (6–40)
Dose of isoproterenol producing maximal venodilatation (ng/min)	81 (19–350)	195 (132–288)	170 (94–302)

*Plus–minus values are means ±SE. The doses of isoproterenol are the geometric means; the values in parentheses are the 95 percent confidence intervals.

[†]The venodilative response is expressed as the percentage reversal of phenylephrine-induced vasoconstriction.

[‡]P=0.03 for the comparison of subjects who were homozygous for Glu27 with those who were homozygous for Gln27 (maximal venodilative response, 54±8 percent).

the genotype (P=0.27 by repeated-measures analysis of variance). Hemodynamic values measured before infusion were similar in the three groups (Table 3).

DISCUSSION

Our study of β_2 -adrenergic–receptor polymorphisms shows that subjects homozygous for Arg16 and Gln27 have enhanced agonist-mediated desensitization, according to measurements of vascular responses in the dorsal hand vein, whereas subjects homozygous for Gly16 (irrespective of the amino acid at position 27) have resistance to agonist-mediated desensitization.

The modulation of vascular desensitization and responsiveness by β_2 -adrenergic–receptor agonists has important clinical implications for responses to sympathetic nervous system stimulation, both under physiologic conditions (e.g., exercise and mental stress) and in diseases such as hypertension, preeclampsia, and congestive heart failure. The vasodilative effect of epinephrine, a β_2 -adrenergic–receptor agonist, normally blunts the increase in blood pressure induced by its α -adrenergic stimulation under conditions of exercise, mental stress, and other sympathetic stimuli. Thus, persons who are most sensitive to desensitization to the β_2 -adrenergic effects of epinephrine (those who are homozygous for Arg16) and persons with increased vasodilative responses to epinephrine (those who are homozygous for Glu27) will have altered responses during sympathetic stimulation. We have previously shown that vasodilative responses to iso-

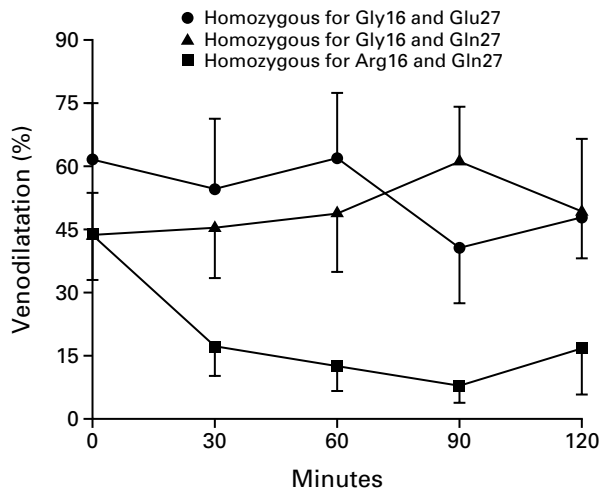


Figure 2. Mean (±SE) Venodilatation during Continuous Infusion of Isoproterenol (Desensitization) in the Three Groups of Subjects.

There was a significant interaction between genotype and the response to continuous infusion of isoproterenol (P=0.03 by repeated-measures analysis of variance). Subjects who were homozygous for Arg16 and Gln27 had significant desensitization (P=0.006), whereas subjects who were homozygous for Gly16 and Gln27 and those who were homozygous for Gly16 and Glu27 did not have desensitization over time (P=0.56 and P=0.11, respectively).

proterenol in healthy blacks are blunted as compared with the responses in whites.⁵ Blacks have also been shown to have greater increases in blood pressure in response to mental stress than whites,¹⁹ another indication of the reduced vasodilative response to endogenous β_2 -adrenergic agonists in blacks. Homozygosity for Glu27, which is associated with enhanced vasodilatation in response to β_2 -adrenergic agonists, is less prevalent in blacks than in whites,¹⁵ a difference that thus may contribute to the different vascular responses in the two groups.

Increased sympathetic activity with increased catecholamine concentrations in the blood may be associated with hypertension, especially in young persons.²⁰ Thus, long-term exposure to elevated concentrations of catecholamines in combination with desensitization to the β_2 -adrenergic, vasodilative effects of epinephrine may increase blood pressure, because under these conditions the α -adrenergic pressor effect of epinephrine and norepinephrine would be unopposed by vasodilatation.

Increased sympathetic activity and enhanced vasoconstriction have also been implicated in the pathogenesis of preeclampsia.²¹ We recently reported that homozygosity for Glu27 appears to protect Hispanic women from preeclampsia,²² a finding in keeping with our observation of enhanced vasodilatation in

TABLE 3. HEART RATE AND BLOOD PRESSURE BEFORE AND DURING INFUSION OF ISOPROTERENOL.*

VARIABLE	HOMOZYGOUS FOR Arg16 AND Gln27 (N=7)		HOMOZYGOUS FOR Gly16 AND Gln27 (N=8)		HOMOZYGOUS FOR Gly16 AND Glu27 (N=11)	
	BEFORE INFUSION	MAXIMAL ISOPROTERENOL DOSE	BEFORE INFUSION	MAXIMAL ISOPROTERENOL DOSE	BEFORE INFUSION	MAXIMAL ISOPROTERENOL DOSE
	Heart rate (beats/min)	61±4	63±3	67±4	69±4	59±3
Systolic blood pressure (mm Hg)†	112±4	116±3	106±5	109±4	110±4	118±5‡
Diastolic blood pressure (mm Hg)	67±4	63±4	65±4	63±3	64±1	60±1

*Values are means ±SE.

†P=0.02 for the change in systolic blood pressure from the value at rest to the value at the maximal dose of isoproterenol in all three groups (by repeated-measures analysis of variance).

‡P=0.02 for the change in systolic blood pressure from the value at rest to the value at the maximal dose of isoproterenol in the subjects who were homozygous for Gly16 and Glu27 (by the paired t-test).

association with this genotype. β_2 -Adrenergic receptors are also expressed in the heart and contribute to the inotropic effects of endogenous catecholamines.²³ Thus, if the polymorphisms we studied have similar effects on desensitization in other tissues, including the heart, they may influence the clinical course and survival of patients with congestive heart failure.

Our findings differ from those of Green et al., who performed in vitro studies in bronchial smooth-muscle cells.¹⁰ In these studies, the allele encoding Gly16 was associated with an increase in agonist-mediated down-regulation of the β_2 -adrenergic receptor, and the allele encoding Glu27 was associated with resistance to agonist-induced desensitization. More recently, however, a study of lung mast cells²⁴ showed that β_2 -adrenergic-receptor polymorphisms had effects on desensitization that were similar to those observed in the current study.

In vivo studies of the effect of these polymorphisms on the response to prolonged treatment with inhaled β_2 -adrenergic agonists in persons with asthma have had conflicting results. An initial study²⁵ found that persons who were homozygous for Gly16 had significantly greater bronchodilative desensitization than those who were homozygous for Arg16, a finding consistent with data from in vitro studies. However, a larger and more recent study found that persons with asthma who were homozygous for Arg16 had significantly lower responses to an inhaled β_2 -adrenergic agonist after 16 weeks of regular use than did persons who were homozygous for Gly16.²⁶ Another group of investigators recently reported a higher incidence of exacerbation of asthma in persons who were homozygous for Arg16 than in those who were heterozygous or homozygous for Gly16 during long-term therapy with inhaled β_2 -adrenergic agonists.²⁷ These results are concordant with our find-

ings with respect to the effect of homozygosity for Arg16 on desensitization in the vascular bed.

We found an enhanced vasodilative response to isoproterenol in subjects who were homozygous for Glu27. In a study in which subjects were not selected according to genotype, vascular responses mediated by β_2 -adrenergic receptors were enhanced in the subjects who were homozygous for Glu27.¹¹ The investigators hypothesized that this was the result of relative resistance to agonist-mediated desensitization in these subjects. However, our data indicate that in fact it is the allele encoding Arg16 that determines vascular desensitization and that persons who are homozygous for Gly16, whether they are homozygous for Gln27 or for Glu27, have a resistance to desensitization. Thus, our findings emphasize the importance of taking into account haplotypes, rather than just a single polymorphism, when defining functional significance in vivo. Recently, a polymorphism in the promoter region of the gene encoding the β_2 -adrenergic receptor, one that is associated with increased receptor expression under base-line conditions, was found to be in strong linkage disequilibrium with the Glu27 polymorphism,²⁸ thus offering a possible mechanistic explanation for this phenomenon.

Because we assessed vascular responses by measuring changes in the diameter of a hand vein, we cannot directly extrapolate our results to other tissues. However, the hand vein has been used extensively as a pharmacodynamic model for investigating agonist-receptor relations in vivo while avoiding the effects of systemic exposure to agonists and the consequent, confounding reflex responses. In addition, venous desensitization is important in its own right, since as the chief capacitance compartment, the venous bed has profound effects on cardiac filling, which in turn is an important determinant of cardiac output, espe-

cially in patients with heart failure. It will be important to extend these studies to larger populations and other tissues, although such in vivo studies are technically challenging.

In conclusion, homozygosity for the Arg16 polymorphism of the β_2 -adrenergic receptor is associated with rapid agonist-mediated vascular desensitization, whereas homozygosity for the Glu27 polymorphism is associated with enhanced agonist-mediated vasodilatation in healthy subjects. These findings have important implications for the understanding of the genetic regulation of responses mediated by β_2 -adrenergic receptors, both in the cardiovascular system and in other tissues.

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