Published in final edited form as:

Pharmacogenomics. 2009 October ; 10(10): 1581. doi:10.2217/pgs.09.92.

***GRK5* Gln41Leu polymorphism is not associated with sensitivity to β_1 -adrenergic blockade in humans**

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Abstract

Aims—A common, functionally significant polymorphism in *GRK5* (Gln41Leu) encodes a gain-of-function enzyme that enhances desensitization of the β_1 -adrenergic receptor. *GRK5* Leu41 has been postulated to confer endogenous ‘genetic β -blockade’ and contribute to an attenuated response to β -blockers in black subjects. The effects of this *GRK5* variant on sensitivity to a β -blocker have not been studied in humans. We hypothesized that the *GRK5* Gln41Leu variant contributes to interindividual variability in response to β -blockade and to the ethnic difference in sensitivity between black and Caucasian individuals.

Materials & methods—We measured the heart rate at rest and during a graded incremental exercise in 154 healthy subjects (85 white and 69 black) before and after an oral administration of 25 mg atenolol. We determined the genotypes of *GRK5* (Gln41Leu), β_1 -adrenergic receptor (*ADRB1* Ser49Gly and Arg389Gly) genotypes and plasma atenolol concentrations. The effects of genotype and covariates on sensitivity to atenolol, measured as the reduction in exercise-induced tachycardia, were determined using multiple regression analyses.

Results—The minor allele frequency of *GRK5* Leu41 was 32.6% in blacks and 0% in whites. Black individuals were less sensitive to atenolol than white individuals ($p \leq 0.011$) but this was not explained by the *GRK5* genotype. The *GRK5* genotype had no effect on resting heart rate before ($p = 0.61$) and after adjustment for age, sex, ethnicity, atenolol concentrations, BMI and *ADRB1* genotypes ($p = 0.81$). The decrease in heart rate after atenolol administration did not differ significantly according to the *GRK5* genotype at rest or after exercise, before (all $p > 0.14$) and after statistical adjustment for covariates (all $p > 0.17$).

Conclusion—The *GRK5* Gln41Leu polymorphism does not affect sensitivity to the β_1 -adrenergic blocker, atenolol, during acute physiological adrenergic stimulation, nor does it contribute to the ethnic differences in sensitivity to atenolol among black and Caucasian individuals.

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Financial & competing interests disclosure

This study was supported by the following grants: P01 HL56693, a Pharmacogenetics Research Network Grant (U01 HL65962) and the Vanderbilt CTSA grant 1 UL1 RR024975. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Keywords

β -blockade; atenolol; ethnicity; *GRK5*; pharmacogenetics

β -adrenergic receptor antagonists (β -blockers) are effective in the treatment of ischemic heart disease, heart failure and hypertension, and are among the most widely prescribed drugs [1, 2]. There are marked interindividual and ethnic differences in responsiveness to β -blockers [3]. Variation in the gene encoding the β_1 -adrenergic receptor (β_1 -AR), *ADRB1*, affects response to β -blockers *in vivo* [4–7]; however, we recently reported that such variation does not account for ethnic differences in sensitivity to a β_1 -blocker between black and white individuals [8].

Despite their widespread use, the mechanisms underlying the interindividual and ethnic differences in response to β -blockers are poorly understood [9]. Recently, Liggett *et al.* characterized a functionally significant genetic polymorphism in *GRK5*, a member of a family of serine/threonine kinases that phosphorylate and thus desensitize G-protein-coupled receptors (GPCRs) [10]. This *GRK5* Gln41Leu polymorphism, present in approximately 40% of black and 2% of white individuals [10], encodes a gain-of-function enzyme that enhances desensitization of the β_1 -AR *in vitro*. Studies in transfected cells and transgenic mice expressing *Grk5* Leu41 demonstrated that increased β_1 -AR desensitization resulted in attenuated responses after prolonged exposure to an adrenergic agonist and, similar to pharmacological β -blockade, protected against experimental catecholamine-induced cardiomyopathy, a phenotype described as ‘genetic endogenous β -blockade’ [10,11].

Since the *GRK5* Leu41 variant is 20-fold more common in black than white subjects, it has been suggested as a mechanistic explanation for attenuated responses to β -blockade in black individuals [10]. However, the effect of the *GRK5* genotype on sensitivity to β -blockers has not been studied in humans.

Therefore, we examined the effect of the *GRK5* genotype on response to a β_1 -blocker in a highly controlled setting, using a robust measure of sensitivity to β_1 -blockade – the reduction of exercise-induced tachycardia. Our hypothesis was that the *GRK5* Gln41Leu variant attenuates responses to β -blockade and contributes to ethnic differences in sensitivity between black and white individuals.

Materials & methods

Subjects & protocol

The study protocol was approved by the Institutional Review Board of the Vanderbilt University Medical Center (TN, USA) and subjects gave written informed consent. All subjects contributed data to a previous study and details of the study design and methods have been published [8]. Briefly, unrelated black and white American subjects were eligible to participate if they were between the ages of 18–50 years and had no clinically significant abnormality based on medical history, physical examination, electrocardiogram and routine laboratory testing. Subjects were free of medications for at least 1 week. They also received an alcohol- and caffeine-free diet for 6 days prior to the study, which provided 150 mmol of sodium, 70 mmol of potassium and 600 mmol of calcium daily.

Subjects performed graded incremental exercise on a supine bicycle ergometer (at 25, 50 and 75 W for 2 min each) before and 2.5 h after oral administration of 25 mg atenolol (Milan Pharmaceuticals Inc., WV, USA). A digitized electrocardiogram was recorded on a personal computer at 500 MHz using the Windaq software (v. 2.20; Data Instruments Inc., OH, USA).

Genotyping & plasma atenolol concentrations

Genotyping for *GRK5* A122T (rs17098707), corresponding to the Gln41Leu amino acid change in the translated protein, was performed by allelic discrimination with an on-demand TaqMan® 5'-nuclease assay (C-15852506_10) on an ABI 7900 real-time PCR system (Applied Biosystems, CA, USA) using validated TaqMan probes (Applied Biosystems) and a 95% quality value threshold. Genotyping for the two *ADRB1* SNPs, rs1801252 and rs1801253 (corresponding to Ser49Gly, Arg389Gly), was performed by TaqMan assay as previously described [8]. The genotyping success rate was 94.5, 99.4 and 93.3% for Ser49Gly, *ADRB1* Arg389Gly and *GRK5* Leu41, respectively. Plasma atenolol concentrations were determined by high-performance liquid chromatography as previously described [4].

Data analysis & statistics

Heart rate was determined from the computerized ECG recordings as the mean heart rate during the second minute of each exercise step. To examine the effect of the *GRK5* genotype and potential confounders on atenolol response, multiple linear-regression analyses were performed for the following response variables:

- Absolute reduction in heart rate after atenolol at rest;
- Absolute reduction in heart rate after atenolol at maximal exercise (75 W);
- Reduction in heart-rate area under the curve (AUC) after atenolol [8].

This analysis was adjusted for the corresponding heart rate (or heart-rate AUC) before atenolol, age, sex, ethnicity, BMI, *S*-atenolol plasma concentrations, and *ADRB1* Ser49Gly and Arg389Gly genotypes. Analyses were performed with the statistical software R [101]. Assuming a mean heart-rate reduction at 75 W of 13.6 ± 8.4 beats per minute (bpm) [8] and a *GRK5* Gln41Leu carrier rate of 55% among black subjects (corresponding to a minor allele frequency of approximately 0.35), a sample size of 63 black subjects would provide 80 and 90% power at an α value of 0.05 to detect a difference of 6 and 7 bpm respectively, among *GRK5* genotype groups.

Results

Subject characteristics & genotypes

We studied 154 healthy subjects (85 white individuals and 69 black individuals). The subject characteristics are shown in Table 1. There were proportionally more black than white female subjects (68.1% compared with 47.1%) and black subjects had a higher BMI (26.9 ± 6.3 kg/m² compared with 24.3 ± 3.8 kg/m²; $p = 0.004$) than white subjects.

The minor allele frequencies for *GRK5* (0 and 32.6% in white and black subjects, respectively; $p < 0.001$) were in the expected range and genotype distributions (85/0/0 and 29/35/5 for Gln/Gln, Gln/Leu and Leu/Leu in white and black subjects, respectively) conformed to the Hardy-Weinberg equilibrium ($\chi^2 = 1.64$; $p = 0.20$ for blacks).

Effects of *GRK5*: resting & exercise measures before atenolol

The *GRK5* genotype had no effect on baseline cardiovascular measures before ($p = 0.61$) and after adjustment for age, ethnicity, sex, BMI, and *ADRB1* Arg389Gly and Ser49Gly genotypes (all $p = 0.81$). Similarly, the *GRK5* genotype did not affect the increase in heart rate during exercise, as assessed by the heart-rate AUC, before ($p = 0.12$) and after ($p = 0.80$) adjustment for covariates.

Effects of *GRK5*: resting & exercise measures after atenolol

The *GRK5* genotype did not affect the atenolol-induced decrease in heart rate at rest or at maximal exercise before adjustment ($p = 0.14$ and $p = 0.31$ at rest and at 75 W, respectively; Figure 1A) or after adjustment for covariates ($p = 0.44$ and $p = 0.80$ at rest and at 75 W, respectively; Table 2). Similarly, the summary measure of atenolol effect during the entire exercise period, the AUC of the atenolol-induced reduction in heart rate, was not associated with the *GRK5* genotype before ($p = 0.29$) or after adjustment for covariates ($p = 0.17$). When only black subjects were considered, there was again no effect of the *GRK5* genotype at rest or at maximal exercise before adjustment ($p = 0.43$ and $p = 0.71$ at rest and at 75 W, respectively; Figure 1B) or after adjustment for covariates ($p = 0.65$ and $p = 0.91$ at rest and at 75 W, respectively). The AUC of the atenolol-induced reduction in heart rate when only black subjects were considered was not associated with the *GRK5* genotype before ($p = 0.49$) or after ($p = 0.35$) adjustment for covariates.

As shown in our previous analysis [8], atenolol reduced heart rates to a greater extent in white than in black subjects at rest (mean adjusted difference: 4.4 bpm; 95% CI: 1.7–7.2 bpm, $p = 0.002$; Table 2) and at maximal exercise (mean adjusted difference: 4.0 mmHg; 95% CI: 0.9–7.0, $p = 0.011$; Table 2), corresponding to a 1.4–1.8-fold greater decrease in heart rate in whites compared with blacks. Similarly, we confirmed our previous findings that *S*-atenolol plasma concentrations, male gender and *ADRB1* Arg389Gly genotype were associated with a greater heart-rate reduction after atenolol consumption (Table 2).

Discussion

This is the first study to examine the effects of a functional genetic variant in *GRK5* on β -blocker sensitivity in humans. Our main findings are that the presence of the *GRK5* Leu41 allele does not affect the response to a β -blocker during acute adrenergic stimulation in healthy subjects, nor does it contribute to the differences in sensitivity observed between black and white individuals.

Since there are no selective antagonists for specific *GRK* subtypes, the functional role of *GRK* subtypes in healthy humans can only be extrapolated from animal studies (mainly in knock-out mice) and quantitative data on protein and mRNA expression in human hearts. Both *GRK2* and *GRK5* are abundantly expressed in the normal human heart, in approximately similar amounts, depending on the location within the four heart chambers [12,13]. Both mediate β_1 -adrenoceptor phosphorylation and β -arrestin recruitment, resulting in the uncoupling from G-proteins, and therefore are believed to act as physiological regulators of β -AR activity [14]. β_1 -AR desensitization also occurs in normal subjects after short-term physiological or pharmacological sympathetic stimulation [15]. Thus, *GRK2* and *GRK5* are likely to contribute to the physiological desensitization of β_1 -ARs in humans.

The *GRK5* Gln41Leu variant encodes a gain-of-function enzyme resulting in enhanced *in vitro* desensitization of the β_1 -AR [10]. Transfected cells expressing the Leu41 variant show enhanced desensitization and a 33% lower maximal response after prolonged agonist stimulation than Gln41-expressing cells [10]. Similarly, *in vivo* phenotypic differences are observed following stimulation with an agonist. The dose response to isoproterenol is shifted to the right in transgenic mice expressing *Grk5* Leu41, and after prolonged infusion of isoproterenol there is enhanced desensitization and a faster decline in myocardial contractility [10]. In keeping with this enhanced desensitization of adrenergic responses, *Grk5* Leu41 transgenic mice are protected from chronic catecholamine-induced cardiomyopathy [10], a phenotype that mimics pharmacological β -blockade.

There is little information regarding the effects of the *GRK5* Gln41Leu variant in humans. In patients with heart failure, *GRK5* Leu41 is associated with improved survival. Moreover, in contrast with *GRK5* Gln41 homozygotes, β -blocker therapy does not improve the outcome (death or heart transplantation) in carriers of the Leu41 allele [10]. The observations in transgenic mice and in patients with heart failure are compatible with the concept of endogenous genetic β -blockade mediated by enhanced desensitization to adrenergic stimulation as a result of the variant *GRK5* Leu41 [10]. Thus, we hypothesized that in individuals carrying the Leu41 allele, the increase in heart rate in response to exercise would be attenuated (analogous to the shifted dose response to isoproterenol in the animal model) and that responses to atenolol would be smaller (since there would already be a phenotype analogous to endogenous β -blockade). The latter hypothesis was based on the fact that the Leu41 allele is much more common in African-Americans, a group in whom attenuated responses to β -blockers have been reported [16].

We previously demonstrated that attenuated responses to atenolol in black compared with white subjects were not explained by common *ADRB1* variants, although these variants did affect responses to atenolol [8]. Thus, in view of its functional characteristics and ethnic distribution, the *GRK5* Gln41Leu variant was considered a potential explanation for the ethnic difference in sensitivity to β -blockade. However, we found that *GRK5* Leu41 did not affect the attenuation of exercise-induced tachycardia by atenolol, nor did it contribute to ethnic differences in sensitivity to atenolol – depending on the exercise stage, white subjects had a 1.4–1.8-fold greater reduction in heart rate, a finding that was not affected after adjusting for the *GRK5* genotype. Specific components of the study design warrant consideration in the interpretation of the results.

Our study had a number of strengths that maximized our ability to detect a genetic signal, as indeed we did for *ADRB1* variants. These include the assessment of sensitivity to β -blockade using a robust measure (attenuation of exercise-induced tachycardia [17]), a carefully controlled setting, a physiological stimulus, statistical adjustment for potential genetic and environmental confounding variables, and the selection of healthy individuals to minimize the confounding effect of disease and concomitant medications on the outcome. The adrenergic stimulus (6 min of incremental exercise) represents acute, intensive β_1 -AR stimulation, and it could be argued that more prolonged adrenergic stimulation would be more likely to elucidate an effect on desensitization. However, desensitization can occur rapidly during adrenergic stimulation [15], and even at rest there is some chronic downregulation of β -receptors in humans [18]. Nevertheless, we cannot exclude the possibility that the *GRK5* Gln41Leu polymorphism could have different effects on sensitivity to β -blockers under conditions of chronic excessive sympathetic stimulation, as occurs in patients with heart failure, for example.

In human myocytes from failing hearts, *GRKs* are upregulated and contribute to chronic β_1 -AR desensitization. Upregulation of the different *GRK* subtypes is dynamic, complex and affected by the exact localization within the heart, concomitant drug therapy and disease stage. In heart failure, the *GRK2* subtype appears to be upregulated to a greater extent than *GRK5* [12,13], suggesting that the relative contribution of *GRK5* to total *GRK* activity is lower than in the nonfailing myocardium. Thus, since the precise physiological role and regulation of the *GRK5* subtype in human hearts in health and disease is poorly characterized, we cannot extrapolate our findings to subjects substantially different from our study group, such as elderly subjects, cardiac patients or patients on chronic β -blocker therapy, or disease states such as heart failure.

Our study was sufficiently powered to detect differences of approximately 40% in maximal heart-rate reduction among the *GRK5* genotype groups, a magnitude similar to the ethnic difference and is potentially clinically meaningful. Larger cohorts will be necessary to exclude

smaller genotype effects; however, if present, the clinical relevance of such smaller genotype effects would be uncertain.

Conclusion

Our results suggest that the *GRK5* Gln41Leu polymorphism does not affect sensitivity to the β_1 -adrenergic blocker atenolol during acute physiological adrenergic stimulation, nor does it contribute to the ethnic differences observed in sensitivity to atenolol.

Executive summary

- A polymorphism in *GRK5*, Gln41Leu, markedly alters desensitization in response to agonist in cell and animal models.
- The *GRK5* Leu41 variant confers a phenotype of ‘endogenous β -blockade’ and has been postulated to account for attenuated responses to β -blockers in African-Americans.
- We studied the effect of *GRK5* Gln41Leu genotype on response to atenolol (measured as a reduction in exercise-induced tachycardia) in 154 healthy subjects performing a graded exercise test in a highly controlled setting.
- *GRK5* genotype had no effect on baseline cardiovascular measures before ($p = 0.61$) and after adjustment for age, ethnicity, sex, BMI and *ADRB1* Arg389Gly and Ser49Gly genotypes (all $p = 0.81$).
- *GRK5* genotype did not affect the increase in heart rate during exercise, as assessed by the heart-rate area under the curve, before ($p = 0.12$) and after adjustment for covariates ($p = 0.80$).
- *GRK5* genotype did not affect the atenolol-induced decrease in heart rate at rest ($p = 0.14$) or at maximal exercise (75 W, $p = 0.31$) before or after adjustment for covariates ($p = 0.44$ and $p = 0.80$, respectively).
- *GRK5* genotype did not affect the atenolol-induced reduction in heart rate during the entire exercise period, as assessed by the summary measure, heart-rate area under the curve, before ($p = 0.29$) and after adjustment for covariates ($p = 0.17$).
- Ethnicity, sex, atenolol plasma concentrations, and *ADRB1* genotype independently affected response to atenolol.
- In conclusion, *GRK5* Gln41Leu polymorphism does not affect sensitivity to the β_1 -adrenergic blocker atenolol during acute adrenergic stimulation.

Future perspective

Studies examining the effect of the *GRK5* genotype on adrenergic stimulation and β -blockade in models of chronic, moderate-intensity adrenergic stimulation will be of interest. In addition, ethnic differences in response to acute β_1 -blockade remain unexplained. Therefore, future studies could focus on other candidate genes in the β_1 -AR signal-transduction pathway with polymorphisms whose prevalence differs significantly among ethnicities.

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Figure 1. Heart rate reduction after atenolol administration in *GRK5* genotypes

(A) Unadjusted reduction in heart rate at rest and incremental exercise in *GRK5* Gln41Leu genotypes after atenolol administration for both black and white subjects. Data points represent the unadjusted mean reduction in heart rate in the three genotype groups; error bars represent standard deviation. There was no significant difference between genotypes at any point (all $p > 0.14$), and the area under the curve was not significantly different among genotypes ($p = 0.29$). (B) Unadjusted reduction in heart rate at rest and incremental exercise in *GRK5* Gln41Leu genotypes after atenolol administration for black subjects only. Data points represent the unadjusted mean reduction in heart rate in the three genotype groups; error bars represent standard deviation. There was no significant difference between genotypes at any point (all p

> 0.33), and the area under the curve was not significantly different among genotypes ($p = 0.49$).

Table 1

Characteristics of white and black subjects

Parameter	White subjects	Black subjects	p-value
n	85	69	
Female	40 (47.1%)	47 (68.1%)	0.009
Age in years (range)	27.0 ± 6.4 (19–50)	25.9 ± 6.0 (19–50)	0.30
BMI (kg/m ²)	24.3 ± 3.8	26.9 ± 6.3	0.004
Heart rate (bpm)	67.8 ± 7.5	67.5 ± 8.4	0.78
Systolic blood pressure (mmHg)	109.9 ± 11.4	112.5 ± 12.1	0.18
Diastolic blood pressure (mmHg)	64.0 ± 6.8	66.2 ± 7.5	0.06
<i>ADRB1</i> Ser49Gly genotype			
Ser/Ser (n)	66 (77.6%)	39 (56.5%)	0.04
Ser/Gly (n)	19 (22.4%)	25 (36.2%)	
Gly/Gly (n)	0 (0%)	5 (7.2%)	
<i>ADRB1</i> Arg389Gly genotype			
Arg/Arg (n)	44 (51.8%)	21 (30.4%)	0.029
Arg/Gly (n)	32 (37.6%)	37 (53.6%)	
Gly/Gly (n)	9 (10.6%)	11 (15.9%)	
<i>GRK5</i> genotype			
Gln/Gln (n)	85 (100.0%)	29 (42.0%)	<0.001
Gln/Leu (n)	0	35 (50.7%)	
Leu/Leu (n)	0	5 (7.3%)	

Continuous variables are represented as mean ± standard deviation. p-values are for ethnic comparisons.

Effect of genotype, ethnicity and covariates on atenolol-induced reduction in heart rate (at rest, 75 w exercise and heart rate area under the curve.

Table 2

Covariate	Decrease in heart rate after atenolol (bpm)		Decrease in heart rate AUC after atenolol (bpm/min)	
	Rest	Maximum exercise (75 W)	Rest	Maximum exercise (75 W)
	β^* (95% CI)	p -value	β^* (95% CI)	p -value
Preatenolol heart rate/AUC	0.4 (0.3, 0.5)	<0.001	0.4 (0.3, 0.5)	<0.001
Age	0.0 (-0.1, 0.2)	0.77	0.1 (-0.1, 0.3)	0.38
Ethnicity	-4.4 (-7.2, -1.7)	0.002	-4.0 (-7.0, -0.9)	0.011
Sex	1.2 (-.08, 3.3)	0.25	5.6 (3.0, 8.1)	<0.001
BMI	0.0 (-0.2, 0.2)	0.70	0.2 (0.0, 0.5)	0.045
S-atenolol concentration	0.0 (0.0, 0.10)	0.10	0.1 (0.0, 0.1)	<0.001
ADRB1 Arg389 allele	0.9 (-0.6, 2.5)	0.24	2.3 (0.6, 4.0)	0.008
ADRB1 Ser49 allele	0.0 (-1.9, 2.0)	0.97	2.5 (0.3, 4.7)	0.029
GRK5 Gln49Leu [‡]	1.9 (-1.0, 4.9)	0.44 [§]	-0.1 (-3.3, 3.2)	0.80 [§]
GRK5 Leu49Leu [‡]	0.6 (-5.1, 6.3)	0.44 [§]	1.9 (-4.1, 7.9)	0.80 [§]

* Regression coefficients with their respective 95% CI. Genotypes were coded 0–2 representing the number of ADRB1 Arg389 and Ser49 alleles.

[‡] Compared with the reference group with GRK5 Gln49Gln genotype. Sex and ethnicity were coded 0/1 for female/male and black/white, respectively, so that the correlation coefficients reflect sex and ethnic differences, respectively.

[§] Overall p-value for categorical model.

AUC: Area under the curve; CI: Confidence interval