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Angaben zur Veröffentlichung / Publication details:

Raake, Philip, Walter J. Koch, and Patrick Most. 2011. "Polymorphisms present in G-protein-coupled receptor kinases and their effect on β-blocker treatment." Pharmacogenomics 12 (3): 295–97. https://doi.org/10.2217/pgs.11.13.

Polymorphisms present in G-protein-coupled receptor kinases and their effect on β-blocker treatment

KEYWORDS: β-adrenergic receptor blocker ■ genetic variant ■ G-protein-coupled receptor kinase ■ heart failure

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G-protein-coupled receptor kinases as central regulators of β-adrenergic signaling in healthy & failing hearts

Heart failure is a major worldwide health problem and its incidence in the Western world is projected to rise as the median life expectancy increases [1]. Critical for cardiac function in the heart failure state is neurohumoral regulation, especially the β-adrenergic receptor system. Cardiac β-adrenergic receptors allow close regulation of short-term cardiac function; G-protein-coupled receptor kinases (GRKs) regulate β-adrenergic receptor signaling, thereby controlling longer-term inotropic and lusitropic state [2,3]. GRK2 is the major GRK in the heart, with GRK3 and GRK5 also being present [2,3]. In failing hearts, levels of GRK2 and GRK5 were found to be upregulated [4]. GRK2, and GRK3 phosphorylate and desensitize G-protein-coupled receptors by translocating to the plasma membrane via binding to the βγ-subunits (G βγ) of heterotrimeric G proteins [2]. GRK5 is constitutively membrane-bound and also contributes to the desensitization of β-adrenergic receptor signaling [2]. Phosphorylation of β-adrenergic receptors by GRKs results in binding of β-arrestins, thereby preventing further stimulation of Gαs-proteins by β-adrenergic receptor agonists [2,5]. Abnormal β-adrenergic receptor inotropic responsiveness leads to an increased sympathetic drive, with subsequent upregulation of tissue and plasma catecholamines in an attempt to stimulate myocardial contractile function [2,6]. This sustains a vicious cycle as the chronic stimulation of cardiac β-adrenergic receptors perpetuates a loss of signaling due, in part, to a marked upregulation of GRKs, which desensitizes β-adrenergic receptors in the heart through phosphorylation [4,7].

Genetic *GRK5* polymorphisms altering β-adrenergic receptor blocker sensitivity

In heart failure patients, this vicious cycle leading to β-adrenergic receptor dysfunction can be interrupted with the pharmacological β-adrenergic receptor blockade, which augments heart failure survival [8,9]. Increased GRK activity should therefore naturally mimic pharmacological β-adrenergic receptor blocker effects. Identifying genetic variants in the known GRKs regulating β-adrenergic receptor signaling could therefore indentify potential patients showing different responsiveness to β-adrenergic receptor blocker treatment [10]. Screening for genetic variants found no common nonsynonymous polymorphisms in *GRK2* but identified four allelic variants of *GRK5* [10,11]. Liggett *et al.* discovered that the polymorphisms at amino acid positions 304, 536 and 542 were rare in the general population, while the polymorphism in amino acid 41 was also infrequent in Caucasians, but a substantial allele frequency was detected in African–Americans [10,11]. Leu 41 is located in the regulatory domain and not in the catalytic domain, therefore precluding any differences in kinase activity [10]. However, expression of the Leu 41 variant in hamster ovarian cells revealed increased agonist-promoted desensitization of β-adrenergic 1 and 2 receptor subtypes [10,11]. The Leu 41 variant promotes accelerated uncoupling from adenylyl cyclase and in addition facilitates β-adrenergic receptor internalization [10,11]. Therefore, this variant promotes an accelerated loss of β-adrenergic receptor signaling in living cells upon receptor stimulation [10–12]. Transgenic mice expressing the human Leu 41 *GRK5* variant demonstrated no overt phenotype, but revealed an accelerated decrease upon catecholaminergic

stimulation, suggesting decreased sensitivity of cardiac β-adrenergic receptors to the respective agonist [10,11]. Furthermore, Leu 41 expressing mice were protected from the adverse effects of chronic isoproterenol stimulation via osmotic minipumps; these effects were comparable to treatment with propranolol, an unselective β-adrenergic receptor blocker [10,11]. So far, these results are observational with no direct clinical importance.

Clinical relevance & potential implications of genetic *GRK* variants

The relevance of the Leu 41 *GRK5* variant was therefore further evaluated in 375 African–Americans; in this cohort the allele was found to be rather frequent (>40% allele carriers) [10,11]. Interestingly, the likeliness of heart failure is independent of this allele variant [10,11]. However, once heart failure has occurred, the Leu 41 variant protects against the progression of the disease to a similar extent as the use of a β-adrenergic receptor blocker treatment [10,11]. In addition, longer transplant-free survival was observed in Leu 41 carriers not prescribed β-adrenergic receptor blockers compared to β-adrenergic receptor blocker naive *GRK5* wild-type allele carriers [10,11]. Interestingly, no additive effect regarding β-adrenergic receptor blocker treatment could be identified in patients carrying the *GRK5* Leu 41 variant [10,11]. However, these results were drawn from a small, single center sample population [10]. With β-blocker treatment not being randomized, the study outcome might potentially be biased by β-blocker intolerance or β-blocker intake for other conditions than cardiac dysfunction [10]. Prospective, larger scale, multicenter, randomized studies will have to confirm these data and might further substantiate this gene–drug interaction [10].

Still the mechanism is a matter of debate as Spinelli *et al.* recently published data demonstrating the *GRK5* Leu 41 polymorphism being significantly more frequent in Takotsubo patients than in controls (21 vs 6%) [13,14]. These data indicate that the *GRK5* Leu 41 polymorphism may predispose to cardic dysfunction caused by sudden and recurring adrenergic rushes [13,14], which is contrary to the abovementioned preclinical results demonstrating protection of Leu 41 *GRK5* transgenic mice against catecholaminergic cardiomyopathy [11]. In addition, clinical β-adrenergic receptor blocker treatment and genetic ablation of *GRK2* in a mouse model of ischemic cardiomyopathy allow for the improvement of cardiac function, which is associated with resensitisation of β-adrenergic receptor signaling [4]. Taken together, these results indicate that slight changes in the β-adrenergic receptor–GRK interactome might cause profound differences in the outcome and raise doubt regarding the theory that the clinical effect of the Leu 41 *GRK5* variant is merely caused by uncoupling β-adrenergic receptors. Therefore, the Leu 41 *GRK5* variant might benefit its carrier beyond β-adrenergic receptor signaling, and previously unrecognized signaling effects might allow for a true mechanistic explanation.

Summary

In summary, these studies are of potential clinical importance considering the interindividual variation that occurs in response to β-adrenergic receptor blocker treatment in heart failure treatment. Identifying Leu 41 carriers would allow waiving β-adrenergic receptor blockade in these selected patients, avoiding potential harmful effects despite lack of therapeutic efficiency. Future efforts to identify the genetic variants in individual drug response to heart failure therapeutics, further underscore the significance of pharmacogenomics and develop the scientific findings of selected gene–drug interactions towards personalized medicine.

Financial & competing interests disclosure

This work was supported in part by grants from the Deutsche Forschungsgemeinschaft (RA 1668/3-1 to Philip W Raake and PM 562/1-1 to Patrick Most). This study was further supported by grants from the NIH (RO1 HL92130 and RO1 HL92130-02 S1 to Patrick Most). Walter J Koch is the WW Smith Professor of Medicine and this research was supported by his NIH grants R01 HL61690, R01 HL56205 and P01 HL075443 (Project 2). 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.

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