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

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 (Gβγ) 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]. Ligglet et al. discovered that the polymorphisms at amino acid positions 304, 536 and 542 were rare in the general population, while the polymorphism at amino acid 41 was also infrequent in Caucasians, but a substantial allele frequency was detected in African–Americans [10,11]. Leu 41 variant in hamster ovarian cells revealed an accelerated decrease upon catecholaminergic blocker treatment [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.
agonist carrying the results demonstrating protection of Leu 41 is contrary to the abovementioned preclinical ter sample population these results were drawn from a small, single cen- scale, multicenter, randomized studies will have to confirm these data and might further substantiate this gene–drug interaction.

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 pre-
scribed 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 cen-
ter 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].

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Bibliography


