Clinical implications of pharmacogenomics of β1-adrenoceptor for anaesthesia

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Abstract

Genetic polymorphisms within the β1-adrenoceptor are common within the population and whilst not directly causative of disease, accumulating evidence supports that they have significant molecular and clinical effects including altering the response to inotropes and β-blockers as well as altering exercise capacity. Herewith, we summarise current evidence as relevant to anaesthetists treating patients with heart failure.

Introduction

Anaesthetists are perhaps more aware of the impact of hereditary factors on response to drugs due to the conditions of suxamethonium apnoea and malignant hyperthermia, but it is comparatively unusual that one pauses to consider that genetic factors affect the response to drugs. The field of pharmacogenetics can be traced back to Pythagoras in 510 BC who noted that the response to ingestion of fava beans varied between individuals; a condition which would later be identified as glucose-6-phosphate deficiency [1].

At a molecular level, ligands cause a change in the activity of a receptor which causes a physiological effect. Full agonists increase the activity of the receptor, partial agonists also

activate the receptor but are unable to elicit a maximal response, inverse agonists decrease the intrinsic activity of the receptor whilst antagonists occupy the orthosteric binding site preventing the binding of full agonists, partial agonists and inverse agonists thus preventing their effects but have no intrinsic activity themselves.

The β1-adrenoceptor is a G protein-coupled receptor (GPCR) composed of 7 transmembrane domains with 3 intracellular and 3 extracellular loops. It was originally thought that when an agonist binds to a GPCR it causes the Gα subunit to exchange GDP for GTP and then activate downstream signalling pathways. It has subsequently been shown that this is an oversimplification. GPCRs can adopt a range of conformations[2] and in addition can signal via the Gβγ and β-arrestins. β-arrestins are adaptor proteins initially recognised to mediate receptor endocytosis and desensitisation but now recognised to have a signalling role also[3]. The binding of drugs to the orthosteric binding pocket influences that probability distribution of conformations[4,5, 6,7] and therefore the propensity of the receptor to activate specific downstream signalling partners. Rather than being simply on or off, receptors should be viewed as multiple signalling conformations with different ligands promoting different conformations leading to the conceptualisation of them as sophisticated allosteric microprocessors[8]. Carvedilol for example preferentially activates β-arrestin[9] which may be responsible for the superior effects of carvedilol when compared to other beta-blockers[9, 10]. This ability where certain ligands preferentially activate specific downstream signalling is known as ligand directed signalling bias.

The β1-adrenoceptor has chronotropic, lusitropic and inotropic effects on the heart as well actions on the kidney. Drugs acting on the β1-adrenoceptor are important in the management of

heart failure, ischemic heart disease and hypertension. We highlight the impact of genetic differences on response to drugs acting on the β1-adrenoceptor.

A single nucleotide polymorphism (SNP) is a single base difference in DNA which may cause an amino acid difference in the protein such differences can be significant risk factors for disease, effect prognosis and response to treatment. Significant polymorphisms include at position 49 serine or glycine and at 389 arginine or glycine[11]. These polymorphisms affect the extracellular terminus and the intracellular tail respectively (Figure 1). The terms wildtype and mutant are sometimes used, this is complex because the alternatives are common within the population hence the description as polymorphisms rather than mutations. Several rare polymorphisms including Ala29Thr, Arg31Gln, Ala59Ser, Arg399Cys, His402Arg, Thr404Ala and Pro418Ala have been recorded[12,13]. Studies of these polymorphisms are more limited given their rarity. Given that the Ser49Gly and Arg389Gly variants are common within the general population, it is unlikely that they are the primary cause of cardiovascular disease, but they may be significant in polygenic conditions with complex environmental interaction or significant determinants of response to treatment.

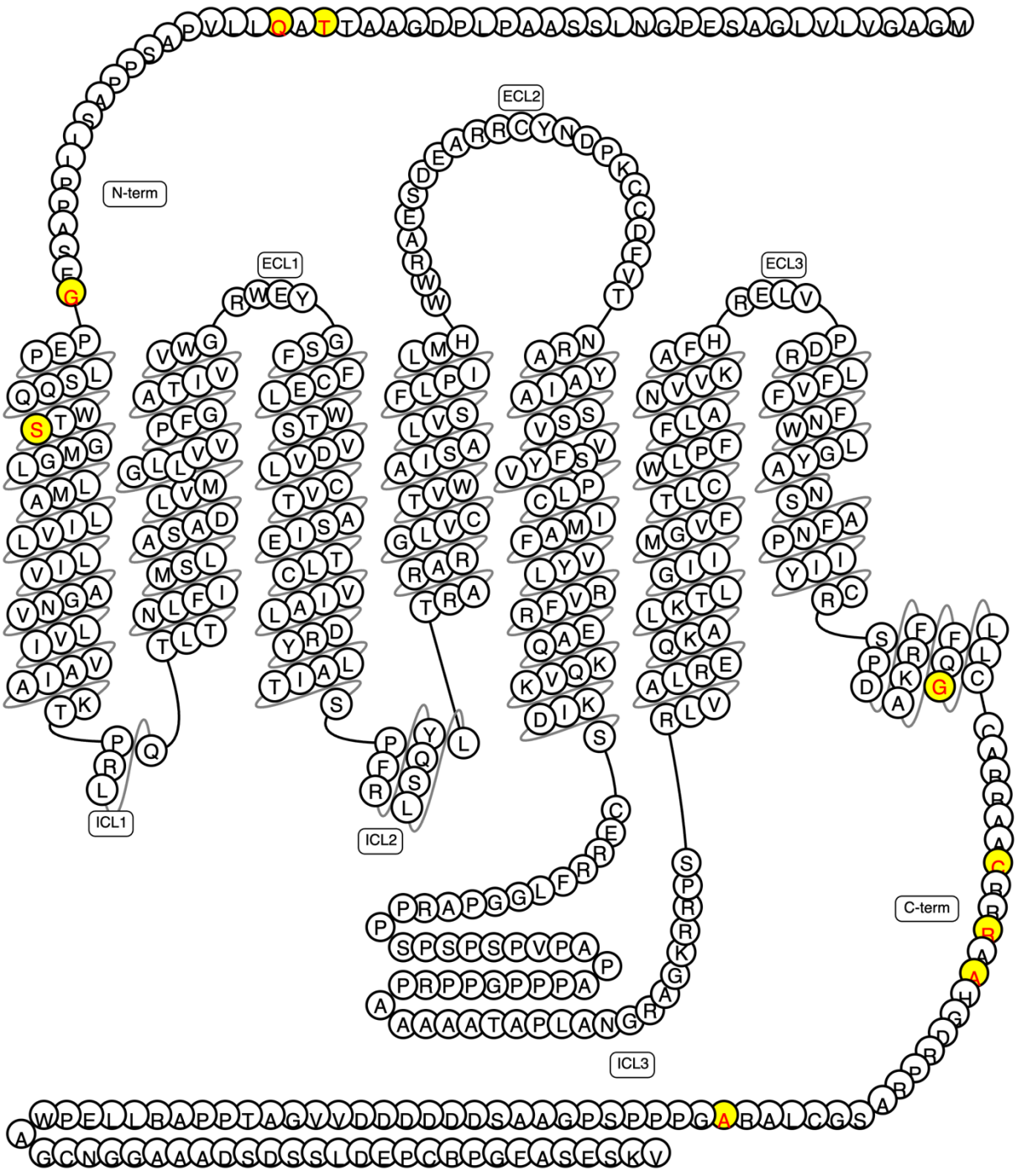

Figure 1 - A diagram of the β1-adrenoceptor showing the positions of the known polymorphisms concentrated around the extracellular and intracellular regions. Polymorphisms shown at all sites. Drawn with https://gpcrdb.org/construct/design

The Gly389 polymorphism decreases basal signalling of β1-adrenoceptor and attenuates the response to inotropes

The Gly389 polymorphism predominates in humans[14] but Arg 389 is heavily conserved across species[15]. The Arg389 polymorphism is associated with significantly greater basal activity as well as agonist induced stimulation of adenylyl cyclase[16]. This polymorphism lies within the intracellular tail of the receptor within the putative G protein-binding region and appears to increase affinity for the Gαs protein[16].

The Arg389Gly polymorphism shows significantly different prevalence in different ethnicities with lowest among African-Americans (58%) compared with Chinese (74%)[17]. This has been suggested to be the mechanistic reason for the higher rates of heart failure in African-Americans.

The polymorphism at codon 389 significantly affects response to inotropes. Transgenic mice overexpressing Arg389 show early enhanced contractility and response to dobutamine but later progression to cardiac failure[18]. Similar results are seen in healthy human volunteers, with subjected homozygous for Arg389 showing greater inotropic responses to dobutamine[19]. Arg389 heart show reduced contractility in response to propranolol whilst Gly389 hearts show a significantly attenuated response[18]. The Arg389 polymorphism is associated with greater response to both positive and negative inotropes acting on the β1-adrencoceptor with Gly389 blunting both responses.

The SNP affecting the amino acid at position 389 of the β1-adrenoceptor may also alter the bias of signalling; that is the degree to which signalling occurs down different downstream signalling pathways. Carvedilol behaves as a neutral antagonist with both Gly389 and Arg389 whilst bucindolol acts as an inverse agonist with Arg389 but neutral antagonist with Gly389[20]. The findings with respect to carvedilol are conflicting with other studies suggesting significant ligand directed signalling bias towards β-arrestin[9].

Cardiac tissue taken from patient homozygous for the Arg389 polymorphism is associated with a greater elevation in cAMP in response to noradrenaline as well as a greater inotropic response compared with tissue from patients homozygous for Gly389[21] although other studies have failed to show such as difference[22]. Transgenic rodent studies may not be translated into humans due to the higher resting adrenergic tone in rodents. In cardiac failure patients awaiting heart transplantation, the homozygosity for the Arg389 genotype is associated with significantly greater exercise capacity and VO_2peak[23].

The polymorphism at codon 389 has not be convincingly associated with a diseased state. Case-control studies have not shown the Arg389Gly to be significantly associated with idiopathtic dilated cardiomyopathy[14] or as independent risk factor for heart failure[24]. Arg389 has been associated with higher blood pressure and heart rate than Gly389[25,26] but other studies have been unable to reproduce this[27,28,29]. Arg389 is associated with increase LV mass[30].

The Arg389Gly polymorphism has been associated with treatment response. The Gly389 polymorphism is associated with a decreased response to the antihypertensive effect of β-

blockers[29]. Gly389 is a significant risk factor for VF but treatment with β-blocker appears to obliterate this risk[31]. Homozygosity for the Arg389 polymorphism has been found to be predictive for greater response to β-blocker in acute coronary syndrome [32]. Studies in hypertension have been conflicting [33,34]. These findings may reflect difference with the chosen β-blocker with subtle differences in their pharmacology; no significant difference was detected with bisoprolol but a significant difference was seen with carvedilol and there is some evidence that carvedilol favours β-arrestin biased signalling[9]. Gly389 appears to be associated with a more favourable response to rate control in atrial fibrillation[35].

Gly49 is associated with exaggerated response to agonists

At a molecular level, the Gly49 polymorphism is associated with increased agonist affinity as well as constitutive activity and greater response to isoprenaline as well as a greater response to metoprolol which has inverse agonist activity[36]. Gly49 is associated with greater agonist induced desensitisation[36]. This process of β-arrestin recruitment and internalisation also involves transactivation of epidermal growth factor receptor (EGFR) to produce cardioprotective effects[37], it has been predicted that Gly49 therefore confers greater cardioprotective signalling[31]. Transactivation occurs when an agonist bound receptor activates a second independent of the ligand for the second receptor.

SNPs in the β1-adrenoceptor also alter the propensity for post-translational modifications with Ser49 undergoing O-glycosylation whereas Gly49 does not[12]. The O-glycosylation appears to protect against proteolytic cleavage[12]. Ser49 is relatively resistant to agonist-induced

downregulation which appears to be related to a lower rate of degradation following internalisation[38].

Gly49 is associated with idiopathic dilated cardiomyopathy[13]. Homozygosity of Ser49 or Arg389 is associated with poor prognosis in heart failure with reduced ejection fraction (HFrEF) [39,40,41] Patients receiving heart transplants with allografts homozygous for Ser49 show greater exercise capacity post-transplant[42]. The Gly49 polymorphism appears protective against ventricular fibrillation following myocardial infarction[31].

In a cohort of patients being screened for primary hyperaldosteronism in primary care, patients who were homozygous for the Ser49 variant had higher renin levels than those carrying the Gly49 variant[43]. This finding supports the conclusion that the SNP is physiologically significant in altering the function of the receptor but also that a polymorphism in the β1-adrenoceptor may impact the response to drugs not only acting at the β1-adrenoceptor but also on other pathways such as the renin-angiotensin-aldosterone system (RAAS). However, evidence of β1-adrenoceptor polymorphisms impacting response to ACE inhibitors is currently lacking although there is some evidence that β2-adrenoceptor polymorphisms might have an impact [44].

Conclusion

The Arg389 polymorphism is associated with more pronounced responses to β1-agonists and antagonists. Although it does not appear to be directly pathogenic, it appears to have other clinically meaningful effects such as effecting the propensity of patient suffering a myocardial infarction to suffer arrhythmic complications and the peak oxygen consumption of heart failure

patients undergoing cardiopulmonary exercise testing. The polymorphism at codon 49 may has impacts on arrhythmia risk, response to inotropes and alters signalling via the RAAS system. In addition, there is evidence to suggest that both polymorphisms as well as quantitative effects, qualitatively impact signalling through the modulation of signalling bias. Several rarer polymorphisms have been discovered but remain unexplored. With the rise of personalised medicine and increasing utilisation of genetic information in routine clinical practice, we may be approaching an era where inotrope prescribing can be genetically informed.

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