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Conducting the G-protein Coupled Receptor (GPCR) Signaling Symphony in Cardiovascular Diseases: New Therapeutic Approaches

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Abstract

G protein-coupled receptors (GPCRs) are a virtually ubiquitous class of membrane-bound receptors, which functionally couple hormone or neurotransmitter signals to physiological responses. Dysregulation of GPCR signaling contributes to the pathophysiology of a host of cardiovascular disorders. Pharmacological agents targeting GPCRs have been established as therapeutic options for decades. Nevertheless, the persistent burden of cardiovascular diseases necessitates improved treatments. To that end, exciting drug development efforts have begun to focus on novel compounds that discriminately activate particular GPCR signaling pathways.

Introduction

Straddling the plasma membrane of cells in nearly every tissue and organ of the human body, G protein-coupled receptors (GPCRs) are a conduit for transmitting signals from the external milieu into intracellular responses. That roughly 30–50% of marketed drugs target GPCRs or GPCR-associated mechanisms strongly attests to their biological and clinical significance[1–3]. In the cardiovascular system, GPCRs modulate critical functional parameters such as heart rate, vascular tone, contractility, and blood volume. Abnormal GPCR signaling is a common feature of many chronic cardiovascular pathologies such as hypertension[4], heart failure (HF) [5,6], and cardiomyopathy[7], thus establishing GPCR-directed pharmaceuticals among the most successful components of the modern pharmacopoeia.

The classical notion of GPCR signaling posited that receptors shuttle between “on” and “off” states in the presence or absence of agonist, respectively[8]. The active state entailed a conformational change in the receptor, allowing association with intracellular heterotrimeric G proteins and activation of downstream effectors. Such a simplified paradigm, however, is inadequate to explain the growing complexity of the GPCR signalosome, which includes receptor desensitization and downregulation, allosteric modulation, partial agonism, and ligand bias[3,9,10].

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As our understanding of structure-function relationships in GPCR activation continues to evolve, it is enticing to speculate that translational application of this information will produce improved cardiovascular therapeutics. We may have only scratched the surface of this endeavor, considering that approximately 1/3 of nearly 200 cardiac GPCRs are “orphans”[11], and only a small portion of over 800 GPCR family members are targets of extant drugs[12]. Moreover, two of the most important cardiovascular GPCRs, β -adrenergic receptors (β -AR) and angiotensin II type 1 receptors (AT1R), are among the best described examples of biased ligand signaling[10], which may be exploited to produce novel benefit from established targets. In this mini-review, we will discuss current GPCR pharmacotherapy in cardiovascular diseases and introduce promising avenues for future drug development.

β -Adrenergic Receptors

Whether the underlying pathophysiology is weakened heart muscle secondary to myocardial infarction, or increased afterload as in hypertension or HF, pharmacological inhibition of β -ARs has proven a remarkably successful treatment strategy for a host of cardiovascular indications over the past five decades[13]. The biological effect produced by “ β -blockers”, eponymously named for their mechanism of action, primarily depends on receptor tissue distribution as well as drug-receptor subtype affinity. All three subtypes of β -ARs, β_1 , β_2 , and β_3 , have been identified in human myocardium, though β_1 -ARs predominate and are principally responsible for the positive inotropic and chronotropic effects of catecholamines[14,15]. In peripheral vascular beds, β_2 -ARs modulate resistance by stimulating vasorelaxation[16], while β_3 -ARs are most commonly associated with lipolysis in adipose tissue and may mediate conditional vasodilation[17].

At a most elemental level, agonist-bound GPCRs effect downstream responses through activation of various cognate G proteins. For instance, β_1 -ARs enhance cardiac contractility by coupling exclusively to G_{α_s} , which stimulates protein kinase A via cyclic AMP. By comparison, β_2 -ARs alternately signal through G_{α_i} , which reduces cytosolic cyclic AMP, as well as G_{α_s} , thus permitting opposing regulation of heart function to suit the situation[18]. Interestingly, β_2 -AR agonism may hold therapeutic promise, particularly in combination with β_1 -AR blockers[19]. β_3 -ARs also couple to G_{α_i} , and appear to be relatively resistant to desensitization, perhaps accounting for the observed cardioprotective properties of this receptor subtype[20].

It should be emphasized that the β -AR signaling described above refers to acute or intermittent stimulation only. Chronic β -AR activation, as seen in many cardiovascular diseases[21], leads to biochemical and molecular alterations highlighted by reduced receptor sensitivity and expression[5,22]. The critical step in such desensitization is phosphorylation of key residues on the receptor's cytoplasmic tail by G protein coupled receptor kinase (GRK) upon its binding to $G_{\beta\gamma}$ subunits[23]. Recent work from our lab and others suggests that pharmacological or gene therapy-based inhibition of $G_{\beta\gamma}$ -GRK2 interaction ameliorates HF progression [24–27]. GRK-mediated receptor phosphorylation is the signal to recruit β -arrestin to the receptor and prevent recoupling of the dissociated cognate G protein[28]. In this manner, GRKs and β -arrestins provide classic negative feedback to β -AR hyperstimulation. Furthermore, it is becoming widely appreciated that by facilitating the assembly of macromolecular signaling complexes, β -arrestins direct a number of additional second messenger pathways[29,30].

β -AR transactivation of epidermal growth factor receptor (EGFR) is one such “non-canonical” GPCR pathway with particular relevance to cardiovascular physiology. Indeed, β -arrestin can activate mitogenic extracellular-signal receptor kinase (ERK), through EGFR

transactivation, independent of G proteins[31]. In a heart disease model, chronic isoproterenol infusion of mice overexpressing mutant β_1 -ARs lacking GRK phosphorylation sites experience pronounced cardiac myocyte apoptosis and left ventricular dilatation compared to control animals[32]. The implication of this result is that absent β -arrestin-mediated anti-apoptotic ERK stimulation, as observed with the mutant β_1 -ARs, unmitigated G_{α_s} signaling exaggerates cardiotoxicity.

Despite the necessarily reductionist nature of experimentation, not only has the pleiotropism of β_1 -ARs become clear[33], but also that of β_2 -ARs[34,35] and AT₁Rs[36,37]. Inherent to the modern conception of GPCR signaling is that individual receptor types assume differential conformations according to the bound agonist. Therefore, it is the aim of ongoing drug development efforts to exploit these principles by producing “biased ligands” [38]. Such compounds would, for instance, produce “functional selectivity” by preferentially activating β -arrestin cardioprotective signaling over the G protein dependent pathway (Figure 1). By comparison, the prescription of β_1 -selective blocker metoprolol, indicated for post myocardial infarction and HF[39,40], presumably inhibits both deleterious G_{α_s} signaling as well as beneficial β -arrestin pathways.

It is particularly noteworthy that β -AR biased agonists are not merely chimerical hopes. In fact, the β -blockers alprenolol and carvedilol transactivate EGFR and ERK, while simultaneously antagonizing the G protein pathway[41]. Unique among available β -blockers, carvedilol activates β -arrestin signaling through β_2 -ARs as well.[42] Objective evaluation requires observing that carvedilol also exhibits α_1 -AR blocking properties[43], so it remains to be seen whether G protein-independent signaling contributes to the superior efficacy profile of carvedilol[44]. Nevertheless, auspicious results to date indicate that the next generation of therapeutic drugs will likely incorporate biased agonism.

Angiotensin II Receptors

The other major cardiovascular GPCR that is effectively targeted by modern pharmacology is the AT₁R. As the primary effector hormone of the Renin-Angiotensin-Aldosterone System (RAAS), Angiotensin II (Ang II) regulates blood pressure by controlling salt and water homeostasis, aldosterone secretion, and vasoconstriction[45]. Ang II receptors are found on a variety of cell types, including cardiac myocytes and fibroblasts, coronary artery and vascular smooth muscle cells, and endothelial cells[46–52]. Although two subtypes of Ang II receptor have been cloned, AT₁[53,54] and AT₂[55], the AT₁R subtype mediates most of the physiological effects of Ang II. In binding to AT₁Rs, Ang II initiates a dizzying array of intracellular pathways, from traditional G protein signaling through G_{α_q} subunits, to G protein-independent activation of nonreceptor tyrosine kinases and NAD(P)H oxidase[56]. Of these, the most familiar is G_{α_q} stimulation of phospholipase C, producing inositol-1,4,5-triphosphate (IP₃) and diacylglycerol (DAG), thus mobilizing intracellular Ca^{2+} release and Protein Kinase C, respectively[57–60]. The functional correlate is positive inotropy and chronotropy in cardiac muscle, in addition to smooth muscle contraction in blood vessels[61].

Just as elevated plasma catecholamines feature in the progression of HF, it has been well documented that upregulation of RAAS activity contributes to the pathogenesis of hypertension, HF, and atherosclerosis[62,63]. Sequelae of prolonged Ang II exposure include fibrosis, necrosis, myocyte hypertrophy, and ventricular remodeling[49,64,65]. Clinical trials have recapitulated laboratory findings demonstrating that blocking the primary enzyme responsible for Ang II production, angiotensin converting enzyme (ACE), or AT₁Rs, compellingly ameliorates cardiac remodeling and prolongs survival in multiple cardiovascular complications[66–69]. Elevated levels of angiotensin-derived heptapeptide,

angiotensin-(1–7), which appears to counteract hypertension, hypertrophy, and fibrosis, have been observed secondary to inhibition of ACE or AT₁Rs, signifying an advantageous mechanism of action apart from reduced AT₁R stimulation[70].

AT₁Rs are desensitized by GRK phosphorylation and β -arrestin recruitment, thus attenuating pernicious outcomes from prolonged receptor activation. Similar to β ARs, GRK/ β -arrestin signal transduction proceeds from phosphorylated AT₁Rs, as in the activation of ERK-mediated cell survival after mechanical stretch[36]. Differential activation of downstream signaling pathways appears to be dictated by the pattern of phosphorylation at key residues on the cytoplasmic tail of the AT₁R[10]. Moreover, systematic substitution of side chain amino acids in the Ang II peptide uncovered discrete effects on AT₁R phosphorylation and downstream signaling cascades[71]. Taken together, these properties substantiate the conceptual framework of functional selectivity for novel AT₁R drug discovery.

The provenance of TRV120027, a synthetic drug that concurrently antagonizes AT₁R G protein signaling and stimulates β -arrestin pathways (Figure 2), offers an illuminating case in point. Proof of principle had been previously established by Sar¹, Ile⁴, Ile⁸-AngII (SII), an Ang II analogue that does not induce AT₁R/G protein coupling, yet does trigger ERK stimulation through β -arrestin[72]. Furthermore, the pool of ERK activated by SII selectively accumulates in the cytosol of cardiac myocytes, in contrast to nuclear migration of Ang II-stimulated ERK[73]. Despite evidence of biased agonism, SII has a K_d roughly 300-fold higher than Ang II for AT₁R[71], complicating efforts to perform physiological assessments in vivo. Systematic evaluation of SII-based peptides led to the identification of a compound with superior potency and efficacy, TRV120027[74]. Indeed, TRV120027 reduced blood pressure while augmenting cardiac output in a canine HF model[75], justifying its progression to clinical trials for HF treatment.

The integration of cardiovascular, renal, and autonomic nervous systems in cardiovascular pathology suggest that optimal therapies should modulate signaling in multiple tissues. For example, this premise underlies the allure of GRKs as diagnostic and therapeutic targets[26,76]. β -AR and AT₁R signaling are functionally intertwined, perhaps reflecting both heterodimerization between the two receptors[77], as well as common upstream activation by sympathetic nervous system (SNS) output. Interaction between β -ARs and AT₁Rs has become increasingly apparent as downstream signaling pathways are progressively delineated. In fact, adrenergic stimulation of cardiac fibroblasts promotes the formation of AT₁R/serotonin 5-HT_{2B} receptor complexes, thereby producing cardiomyocyte hypertrophy in a paracrine manner[78]. Such data furnish mechanistic insight of SNS or RAAS blockade efficacy in HF [79]. Moreover, they portend the possibility of a single compound targeting either β -ARs or AT₁Rs, yet functionally directing both adrenergic and Ang II activity, without the need for combination therapy.

Conclusion

Many of the successes in the annals of drug development involve agents targeting cardiovascular GPCRs (Table 1). In particular, drugs directed at β -AR or AT₁R signaling remain standards of treatment for a host of heart maladies. However, cardiovascular diseases continue to impose enormous health and financial burdens. The next advance in treatment may well emerge from our evolving comprehension of ligand-receptor interactions, along with their associated downstream effectors and divergent signaling pathways. Indeed, GRK inhibition has improved cardiac performance in a number of preclinical models. Furthermore, it is anticipated that fine-tuning of GPCR signaling with biased ligands will

provide a superior treatment option by mitigating detrimental signaling cascades without compromising beneficial pathways.

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Figure 1. Generalized Schematic of Conventional and Biased Cardiac β_1 -AR Signaling

Epinephrine and norepinephrine enhance myocardial contractility, heart rate, and apoptosis through G_{α_s} -coupled signaling pathways in heart (black arrows). Furthermore, these catecholamines can activate an anti-apoptotic cascade independent of G_{α_s} (green arrows). Putative biased ligands induce cardioprotection by exclusively promoting the G protein coupled receptor kinase (GRK) and β -arrestin-mediated pathway (green arrows).

Figure 2. Generalized Schematic of Conventional and Biased AT₁R Signaling

Ang II stimulation of AT₁Rs produces vasoconstriction and augmented contractility in the vasculature and myocardium, respectively (black arrows). Biased ligands (e.g. TRV120027) selectively promote G protein coupled receptor kinase (GRK) and β-arrestin-mediated signaling, thereby enhancing myocardial contractility and reducing vasoconstriction (green arrows).

Table 1Representative β -AR and RAS Cardiovascular GPCR Therapeutics

Drug Class	GPCR Target	Physiological Effect	Clinical Indication(s)
Non-selective β -Blockers (e.g. Propranolol)	β_1 - and β_2 -ARs	↓ Heart Rate ↓ Myocardial Contractility Bronchoconstriction	Angina Arrhythmias Hypertension
β_1 -Selective Blocker (e.g. Metoprolol)	β_1 -ARs	↓ Heart Rate ↓ Myocardial Contractility	Angina Heart Failure Hypertension
Non-selective β -Blockers with Intrinsic Sympathomimetic Activity (e.g. Pindolol)	β_1 - and β_2 -ARs	↓ Heart Rate ↓ Myocardial Contractility Blood Vessel Relaxation	Arrhythmias Hypertension
β_1 -blocker with Direct Vasodilator Activity (e.g. Nebivolol)	β_1 -ARs	↓ Heart Rate ↓ Myocardial Contractility Nitric Oxide-mediated Vasodilation	Hypertension
β -Blockers with α -activity (e.g. Carvedilol)	β_1 - and β_2 -ARs α_1 -ARs	Antioxidant properties ↓ Heart Rate ↓ Myocardial Contractility Vasodilation	Heart Failure Hypertension
Angiotensin II Receptor Blockers (e.g. Losartan)	AT1Rs	↓ Vasoconstriction ↓ Aldosterone secretion	Hypertension
Angiotensin I Converting Enzyme Inhibitors (e.g. Captopril)	Upstream of AT1Rs	↓ Angiotensin II ↓ Vasoconstriction ↓ Aldosterone secretion	Hypertension Heart Failure