Heart Failure Reviews (2020) 25:343–354
https://doi.org/10.1007/s10741-019-09825-x

β-Adrenergic receptor, an essential target in cardiovascular diseases

Daniel Chikere Ali[1] · Muhammad Naveed[2] · Andrew Gordon[3] · Fatima Majeed[4] · Muhammad Saeed[5] · Michael I. Ogbuke[6] · Muhammad Atif[7] · Hafiz Muhammad Zubair[8] · Li Changxing[9]

Published online: 13 August 2019

Abstract

β-Adrenergic receptors (βARs) belong to a large family of cell surface receptors known as G protein–coupled receptors (GPCRs). They are coupled to Gs protein (Gαs) for the activation of adenylyl cyclase (AC) yielding cyclic AMP ($_C$AMP), and this provides valuable responses, which can affect the cardiac function such as injury. The binding of an agonist to βAR enhances conformation changes that lead to the Gαs subtype of heterotrimeric G protein which is the AC stimulatory G protein for activation of $_C$AMP in the cells. However, cardiovascular diseases (CVD) have been reported as having an increased rate of death and β1AR, and β2AR are a promising tool that improves the regulatory function in the cardiovascular system (CVS) via signaling. It increases the Gα level, which activates βAR kinase (βARK) that affects and enhances the progression of heart failure (HF) through the activation of cardiomyocyte βARs. We also explained that an increase in GPCR kinases (GRKs) would practically improve the HF pathogenesis and this occurs via the desensitization of βARs, which causes the loss of contractile reserve. The consistency or overstimulation of catecholamines contributes to CVD such as stroke, HF, and cardiac hypertrophy. When there is a decrease in catecholamine responsiveness, it causes aging in old people because the reduction of βAR sensitivity and density in the myocardium enhances downregulation of βARs to AC in the human heart.

Keywords Cardiovascular disease · Heart failure · β-Adrenergic receptor · Catecholamines · Adenylyl cyclase · GPCR

Introduction

Cardiovascular diseases include the heart and blood vessel; others are stroke, cardiomyopathy, congenital heart disease, and hypertension, and these are the leading causes of death in America [1]. Heart failure is associated with impaired cardiac vagal responsiveness [2] and it is common and costly to manage. It was assumed that there is a total of 1–3% of health care expenditure in North America, Western Europe, and Latin America with 5% complications in the adult patients admitted in US and European hospitals [3]. Heart failure is a progressive CVD with a rapidly growing public health problem and is the leading cause of mortality and morbidity with over 26 million people worldwide and more than 14 million people in Europe [4, 5] and nearly 8.26 million Americans having 32.8% of the cardiovascular-related deaths [6]. It was

✉ Li Changxing
lcx1535@163.com

[1] Department of Microbiological and Biochemical Pharmacy, School of Life Science, China Pharmaceutical University, Nanjing 210009, Jiangsu Province, People's Republic of China

[2] Department of Clinical Pharmacology, School of Pharmacy, Nanjing Medical University, 211166, Nanjing, Jiangsu Province, People's Republic of China

[3] Department of Pharmacognosy, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, Jiangsu Province, People's Republic of China

[4] Department of Nutrition and Food Hygiene, School of Public Health, Nanjing Medical University, Nanjing 211166, Jiangsu Province, People's Republic of China

[5] Faculty of Animal Production and Technology, The Cholistan University of Veterinary and Animal Sciences, Bahawalpur, 6300 Punjab Province, Pakistan

[6] Department of Pharmacy, School of Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu Province 210009, People's Republic of China

[7] Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur 63100, Punjab Province, Pakistan

[8] Department of Pharmacology, School of Basic Medical Sciences, Nanjing Medical University, Nanjing 211166, Jiangsu Province, People's Republic of China

[9] Department of Human Anatomy, Medical College of Qinghai University, Xining 810000, Qinghai Province, People's Republic of China

revealed that heart failure (HF) contributed to approximately 5% of all deaths in the UK [7]. It was also suggested that 30% of patients diagnosed have HF and chronic obstructive airway disease (COPD) [8]. β-Adrenergic receptors (βARs) are a member of the superfamily of G protein–coupled receptors (GPCRs); it is involved in the regulation of physiological processes such as hormonal homeostasis, metabolism, cell growth, and sensory perception [9]. GPCRs are membrane protein and their structural determination, purification, expression, and crystallization help in new drug discovery [10, 11]. It is the largest single family of proteins and is made up of 4% of those coded by the human genome. The most important of GPCR means of technology is the structure-based design of agonist and antagonist ligands which helps to determine the design of new ligands [12, 13]. Reports showed that about 50–60% of all existing medicines are believed to target GPCRs [14].

There are several subtypes of βARs including β1, β2, and β3. β1 and β2 are vital in the regulation of excitation-contraction coupling of a myocardium. However, the β1AR comprises 75–80% of βARs found in the heart. β2AR is expressed in the kidney, lung, and blood vessel and also in the heart and comprises 20–25% of cardiac βARs while β3AR is found in the adipose tissue and very little amount in the heart [15]. β-Adrenergic receptors play a major role in the cardiac functions via signaling transduction controlled by the G protein–coupled receptor kinase (GRK) phosphorylation interactions. The therapeutic capability of a βAR in disease regulation such as cardiovascular diseases (CVDs) is of great importance [16, 17]. When the cardiac βAR signaling is not functioning properly, the circulation of epinephrine levels and downregulation which are expressed on the cardiac myocytes can increase [18]. The continuous activation of the adrenergic receptor is capable of contributing to HF pathogenesis [19]. GPCR signaling pathways are the major prescription for CVD because ligand binding induces conformation changes in the GPCR that could disrupt the interaction of ions between a third cytoplasmic loop and a sixth transmembrane segment, and this brings about coupling with heterotrimeric G protein composed of three subunits: α, β, and γ [20]. The three subtypes of βARs are coupled to Gαs and cyclic AMP ($_C$AMP)–related pathways, and it is signaling to proceed through G protein–independent mechanism [21]. It is reported that βAR activation stimulates adenylyl cyclase (AC) activity through G proteins which enhance the formation of $_C$AMP in the myocardium [22]. Ligands can bind to a targeted site through the extracellular face in the center of the seven helices of hydrogen bonding or charged residue to interact with the natural ligand [23]. The binding effect is because the adrenergic receptor superfamily is a member of the G protein–coupled receptor, which is a membrane receptor that can activate heterotrimeric G proteins. However, signaling by GPCR is normally interfered and disrupted by the GRKs. Moreover, GRKs play a major role in the regulation of adrenergic responses via a mechanism independent from G proteins.

The aging in cardiac βAR response is a result of the downregulation of β1AR, and a decreased sensitivity of βARs by isoproterenol enhances conformational changes in the catecholamine-stimulated AC activity in the cardiovascular system (CVS) [24]. The current effective treatments of CVDs have been developed in a diverse approach called drug therapy [25]. Apart from drug therapy, some classes of the molecule were fully developed as an alternative to replace skeletal and cardiovascular systems. Few of the approved drug therapy are very effective in the treatments of cardiovascular disease [26]. The main aim and objective of this review will focus on evaluating the capability of βARs associated with cardiovascular diseases.

βARs in heart failure

The failing of the human heart is adrenergically hyperactivated which determines the cardiac functions/performance [27, 28]. Heart failure is a large pathophysiological syndrome which results from the primary defect that identified the capability of the heart to fill or eject blood appropriately [29]. The human β2AR is expressed in the pulmonary and cardiac myocyte tissues and is a therapeutic target for asthma and heart failure [30]. βARs remain a major regulator of cardiac function out of over 200 GPCRs in the heart [31]. The continuous/increased activation of adrenergic in the failing heart helps to maintain cardiac function, but the chronic adrenergic stimulation contributes to myocardial dysfunction and ventricular remodeling.

The aging process also induces structural and functional changes including myocyte hypertrophy and subsequent increase in myocardial fibrosis, wall thickness, and extracellular matrix remodeling with diastolic dysfunction via reduced active fillings of the left ventricle [32]. In the interface between sympathetic nervous system (SNS) and CVS, βARs control the progression of HF and any unnecessary changes in βAR signaling which will result in the reduction of the β1AR level to half and a sharp increase of the Gα level, and this will elevate βARK1 functions [9].

An exciting role of sympathetic activation in HF due to elevated myocardial βARK1 level and βAR desensitization in the dysfunctional heart is called protective mechanisms; such mechanisms will worsen the physiological deterioration caused by excess catecholamine stimulation, and chronic use of β-agonists in the HF is harmful [33]. β1AR third intracellular loop consists of the phosphorylation motif for basophilic protein kinase C (PKC) and phosphorylation attributed to protein kinase A (PKA). Catecholamines help the heart to perform its function by activating cardiac βAR [34]. If there is persistent activation of the adrenergic receptor by chemical or biological effects, myocardial damages such as cardiac hypertrophy, fibrosis, and apoptosis can be induced [35]. β2AR

stimulation determines the antiapoptotic cardiac outcomes in the heart [36]. However, cardiac hypertrophy is the leading cause of HF, and once cardiac hypertrophy develops, it progressed to heart failure. βAR stimulation increases oxidative stress in the heart and cerebral artery, and it can induce different cytoskeletal and functional modifications through modification of several parts of the βAR signaling transduction pathways. The cardiac dysfunction due to stimulation of βARs induces vascular dysfunction by the disruption of the actin cytoskeleton in vascular smooth muscle cells [35].

β-Adrenergic modeling

Receptors have been discovered to possess the ability to bind compounds known as a ligand to obtain chemical information contained in these compounds and convert them into a biological response [37]. β-Blocker has the potential to antagonize the toxic effect of norepinephrine at the cardiomyocyte which can promote cellular remodeling of the heart for effective hemodynamics [38]. β-Adrenergic receptor subtype acts via signaling cascade to modulate cardiac function and remodeling [39]. βAR is a member of the GPCR superfamily of a receptor which enhances the regulation of various functions and processes of the CVS via signaling pathways. βAR subgroups such as β1AR, β2AR, and β3AR are fully established with their respective functions while β4AR is still not fully confirmed with viable functions. The functions of β1AR, β2AR, and β3AR are different affinities for different ligands which enhance variable activation of each subgroup [40]. The β2-adrenergic is an important tool used to regulate function in various cells and help in the treatment of CVD [41]. The application of GPCR modeling of β-adrenergic for melanin-concentrating hormone receptors was used to predict agonist-induced changes in β2AR binding pockets. The ligand binding initiates a significant variation of the protein backbone in several receptor conformations via elastic network normal mode analysis (EN-NMA) methods. The backbone conformations generated with EN-NMA can shift from the original homology occurred in cytoplasmic parts of the GPCR bundle and the ligand-binding region [42]. Moreover, the contraction of the vestibule on the extracellular side results in the formation of G protein binding pockets on the intracellular side and in turn initiates intracellular signaling. β2-adrenergic-based A2A AR model is more effective in the binding site cavity than dopamine and when applied in in silico ligand screening can stabilize ligands inside the binding pockets [43].

The effects of β-adrenergic in cardiovascular disease

Cardiac function is a complex dynamic system that strongly optimizes the circulation of blood via the vascular bed of the tissue. Neurohormonal mechanisms during HF are regarded as a progressive disease that was dominantly proceeded with the symptom as a result of activation of neurohormonal mechanisms that reduce cardiac dysfunction such as vasopressin, endothelin, nervous system, aldosterone system, and natriuretic peptide [24]. GPCRs are known for their therapeutic targets as among receptors that can respond to aminergic hormones such as epinephrine. Catecholamines including epinephrine and norepinephrine are GPCRs which have two subfamilies (α and β) and have different ligand and downstream signaling processing [44]. The production of catecholamine increases norepinephrine release in response to a stimulus [45]. The decrease in catecholamine responsiveness in elderly persons is a result of aging and the reduction of βAR sensitivity, and density in the myocardium contributed to downregulation and βARs to AC in the human heart [24].

Nevertheless, the most vital target of adrenergic stimulation is the heart and its activation causes a tremendous increase in heart rate (chronotropic), relaxation (lusitropy), and contractility (inotropy) [22]. The βAR signaling pathway is a key factor during the progression of HF between the sympathetic nervous system (SNS) and the cardiovascular system. However, when there is an improper function, the βAR signaling will result in a reduction of the β1AR level by 50%. These changes will significantly bring about the decline in βAR signaling and sustained elevation of catecholamine will emerge [9]. When β-adrenergic is overstimulated into catecholamine in the backbone, it causes CVD, stroke, HF, and cardiac hypertrophy. The prolonged activation of βARs because of different stressors induces myocardial damage such as necrosis/apoptosis, fibrosis, and cardiac hypertrophy.

Cardiac hypertrophy is the leading cause of HF [35]. The fibrosis is a major factor in heart disease due to several structural changes which occur following pathological stimuli to the cardiovascular system. The structural changes may result in the contraction of the myocardium whereas the excessive accumulation of fibrillar collagen by fibrosis is a result of myocyte death, hypertrophy, and stimulation through the various numbers of hormones. The fibroblasts are activated to form myofibroblasts and produce excess collagen called TGF-β2 and angiotensin II (Ang II). The TGF-β2 and Ang II in the process act in the synergistic pathways to interfere with the normal structure and function of the myocardium region [46]. Irrespective of the fact that GPCR can activate a pathway that is capable of elevating Ca^{2+} in the intracellular, the Ca^{2+} mobilization helps in β2-adrenergic receptor-mediated resistance in response [47]. Prolonged βAR stimulation also increase the phosphorylation of extracellular signal-regulated kinase (ERK). This increases the c-fos and c-myc in the cerebral arteries, and c-fos expression equally increases phosphorylation of ERK in the heart [35]. β-Adrenergic signaling has various pathways when crosstalk with other signaling pathways can activate both cardiostimulatory (Gs) and cardioinhibitory (Gi) pathways in order to regulate gene

transcription and apoptosis or hypertrophy as shown in Fig. 1 [48]. The Gi-biased β1AR signaling can effectively protect the cardiomyocytes against induced apoptosis, and inhibition of Gi signaling may hinder cardiac response to certain diseases like ischemia and myocardial infarction (MI) [49].

GRK2 can modulate signaling because of physiological function via regulation of myocardium insulin signaling and can increase the level of GPRK2 in cardiomyocytes that lead to cell death following acute ischemic injury. The upregulation of GRK2 in cardiomyocytes increases GRK2 which on the other hand leads after to cardiac stress [50]. β2AR signaling contributes to the failing heart while β1AR expression is downregulated [51]. The downregulation results in the removal of the active receptor from the cell surface as a mechanism for cell signaling which occurs due to the phosphorylation of serine and threonine residues on intracellular domains of a βAR by protein kinase A (PKA) which is the key enzyme for cardiac function [48].

The age-related reduction or decline in the response of β-adrenergic has an impact in lowering the contractile function indicating the reduction in βAR density [52]. However, the catecholamine response is depressed in the ischemic and failing heart due to an increase myocardial βARK1 which revealed that the desensitization of βARs could protect the heart against chronic activation [33]. βARs are stimulated by catecholamines, and they are located in almost all peripheral tissue membranes [53]. The use of βARs of antagonists can potentially block the chronic activation of the βARs by norepinephrine. Recent studies confirmed that when βARK1 is upregulated, it results in the first feedback response mechanisms for initiation of SNS activity due to the βARK1 expression in the heart. This is stimulated by βARK1exposure to catecholamine that could serve as a therapeutic target for the treatment of HF or a failing heart [33].

The production of catecholamine increases norepinephrine release in response to a stimulus. The decrease in catecholamine results in aging while the reduction of βAR sensitivity and density in the myocardium contributed to downregulation leading to a decrease in response to AC in the human heart. Adrenergic stimulation enhanced chronotropy, lusitropy, and inotropy, and β-adrenergic signaling crosstalk with other signaling pathways can activate both Gs and Gi in order to regulate gene transcription and apoptosis or hypertrophy. Prolonged βAR stimulation also increases the phosphorylation of ERK. This increases the c-fos and c-myc in the cerebral arteries, and c-fos expression equally increases phosphorylation of ERK in the heart. The myocardial contraction and relaxation are determined by the rise and fall of cytosolic Ca^{2+} in cardiac myocytes. When β-adrenergic is overstimulated into catecholamine, it causes HF and cardiac hypertrophy. The prolonged activation of βARs under stress induces myocardial damage such as apoptosis.

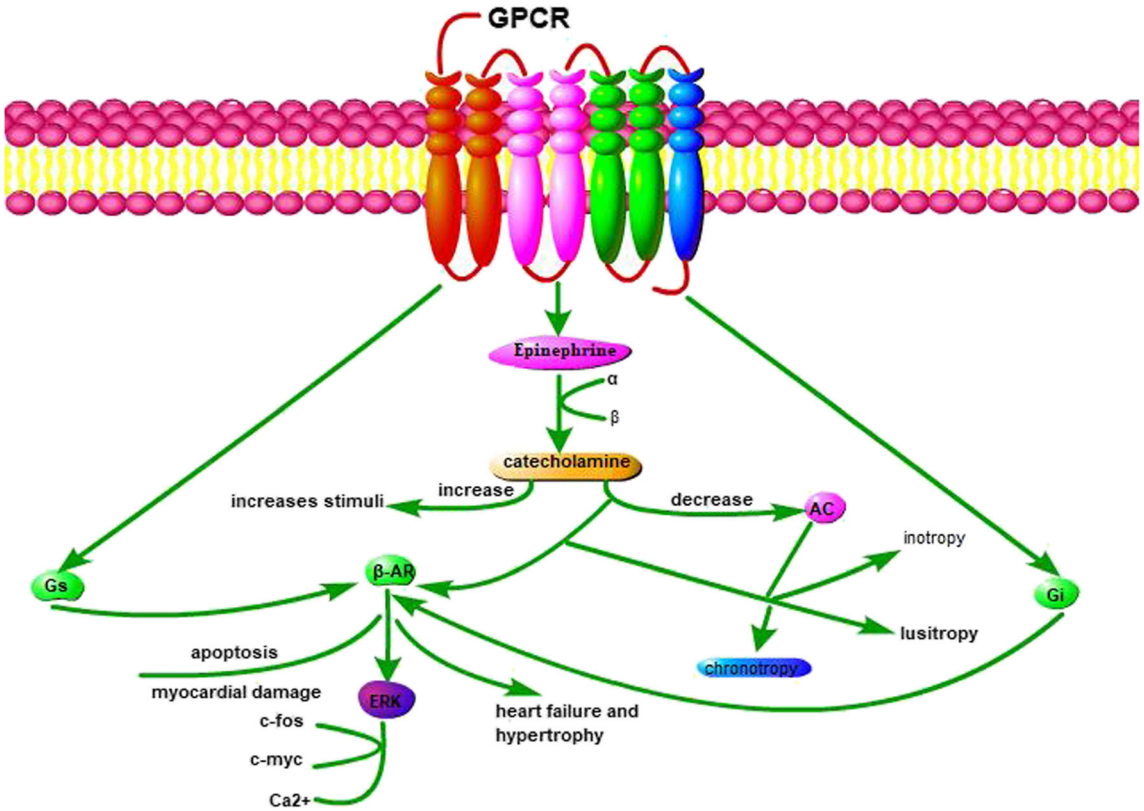

Fig. 1 A diagram describing the effects of β-adrenergic in cardiovascular disease

βAR signaling

GPCR ligands bind to a targeted site through the extracellular face in the center of the seven helices of hydrogen bonding or charged residue to interact with the natural ligand [23]. βARs elevate catecholamine secretion from the adrenal glands [54]. Catecholamines derived from the amino acid called tyrosine determine the response ability, and βAR signaling is controlled by the GRKs [36]. βARs mediate the catecholamine-induced activation of AC via the G protein and can bind to epinephrine with up to 30-fold of affinity than it can bind to norepinephrine. β1AR, β2AR, and β3AR are heptahelical GPCRs that mediate physiological responses to the norepinephrine and epinephrine. However, β1 and β2 are expressed in the heart and can effectively regulate cardiac function in an animal [55]. The β2-adrenergic receptor site is perfectly arranged to bind organic molecules and is primarily found in smooth muscle tissue [44]. β3AR signaling acts as counterbalance "brake" against adrenergic overstimulation, and it maintains cardiac sympathovagal balance by reinforcing vagal tone. β3AR also possess coronary and peripheral vasodilatation and may have pleiotropic on the cardiac system that may prevent arteriosclerosis [56]. β2AR was the first GPCR to be cloned, and it is the most studied GPCR due to its signaling and regulation potentials and is called prototypical GPCR [57]. The stimulation of βARs produces a viable effect through the activation of G protein [58]. The β1AR and β2AR are capable of coupling to Gs which helps signal pathways since β2AR can be coupled to the inhibitory G (Gi) protein for a $_{C}$AMP response [59]. In $_{C}$AMP-dependent β2AR signaling, AC mediates the hydrolysis of ATP into $_{C}$AMP that can activate the protein kinase known as PKA which in turn phosphorylates various intracellular substrate for effective function [57]. While β1AR stimulation by catecholamines will push for dissociation of the stimulatory G protein and alpha subunit (Gαs) from Gβγ, Gαs is responsible for the stimulation of AC yielding $_{C}$AMP. Gβγ activates downstream effectors present in cardiac signaling regulation. The stimulation of β3AR has an important effect in β1AR, and β2AR stimulation through Gαs activation is thereby increasing the generation of $_{C}$AMP and the activation of the PKA as shown in Fig. 2 [60, 61]. The dysfunction of the AC system is favored when the Gi protein is abnormal, and AC revealed that decentralization and uncoupling are induced, increasing GRK level. Furthermore, an increase in GRK2 in the heart elevates the development of the conspicuous failing heart [62]. Once adrenergic signaling is altered, it will activate a dilatation and decreased contractility [63] which remains an important expectation of HF and helps in downregulation and cardiotoxic signaling [64].

β1AR signaling is necessary for both normal and disease heart function, due to dysregulation of an injured or stressed myocardium which is the core value of HF. βAR dysregulation results in upregulation and as such causes the loss of βAR responsiveness which prevails via both chronic receptor desensitization and downregulation and usually takes place due to SNS activity. GRKs phosphorylate activated receptors and initiate desensitization in order to control overstimulation [50]. The β3AR are mainly found in the myocardium and endothelium, which played a major role in CVD via modulating cardiac function and angiogenesis. β3AR possess multiple roles including vasodilation, metabolism, and relaxation to cardiac contractility, contributing to the potential therapeutic methods in heart disease. As a result, β3AR are coupled with Gαi which may be responsible for the prevention of overactivation of β1AR and β2AR [61]. It was reported that a specific adrenergic receptor mediates several catecholamine responses in energy metabolism [65]. β1 and β2 are homologous receptors which can activate the G protein, enhancing stimulatory effect for adenylyl cyclase (GS) via signaling as a result of β1AR and β2AR for biological effects. The β1AR can stimulate the heart rate and strengthen myocyte contraction while β2AR chronotropic and chronic stimulation of β1AR produces myocyte hypertrophy and apoptosis, and β2AR promotes cell survival [66, 67]. There are differences in their signaling pathways and cellular responses of types of βARs [9]. The differences in β1 and β2 receptor show that the β2 receptor has potential to couple together with Gs and Gi while β1 receptor couples only Gs and Gi enhanced by PKA-mediated β2 receptor phosphorylation [68]. For example, it is readily stimulated by β1AR than β2AR signaling [66]. The selective stimulation of β1 and β2 of AC with downregulation of β1 and β2, respectively, was a result that the β2 receptor was partially uncoupled from the previous events in the β2AR pathway [69].

The stimulation of βARs activates G protein whereas β1AR and β2AR are capable of coupling to Gs to Gi for a $_{C}$AMP response. During β2AR signaling, AC mediates the hydrolysis of ATP into $_{C}$AMP and then activates PKA which in turn phosphorylates various intracellular substrates for effective function. Therefore, β1AR stimulation by catecholamines will form Gαs from Gβγ and Gαs that are responsible for the stimulation of AC yielding $_{C}$AMP. Gβγ activates downstream effectors present in cardiac signaling regulation. The stimulation of β3AR through Gαs activation also increases $_{C}$AMP and the activation of the PKA. The dysfunction of the AC is favored when the Gi protein is abnormal, and AC increases GRK level. β1 and β2 can activate the G stimulatory (GS) protein effect for AC via signaling through β1AR and β2AR for biological effects. The β1AR can stimulate the heart rate and strengthen myocyte contraction while β2AR chronotropic and chronic stimulation of β1AR produces myocyte hypertrophy and apoptosis while β2AR also

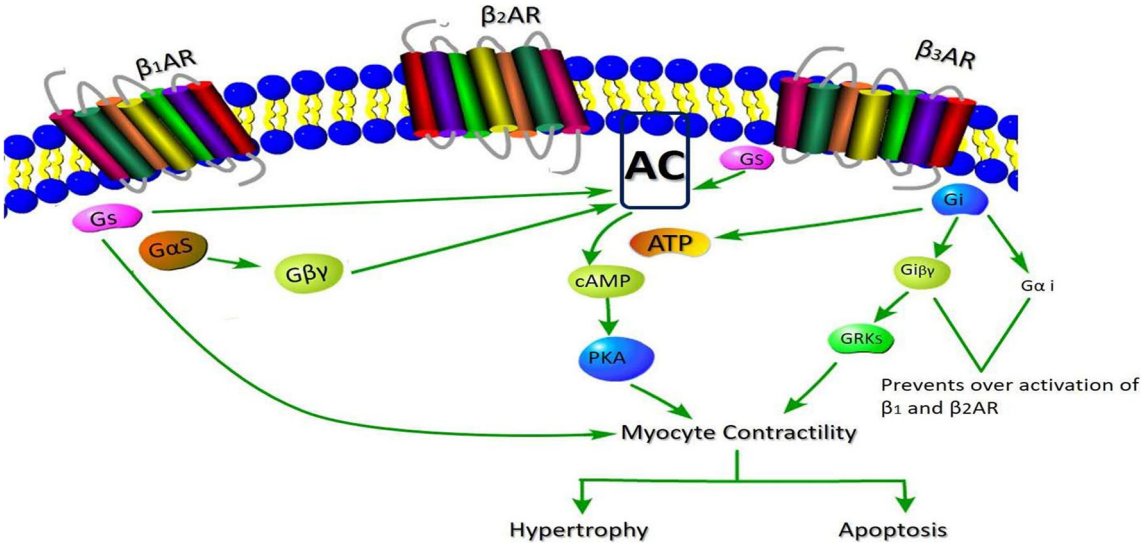

Fig. 2 The diagram of βAR signaling

promotes cell survival. The β3AR modulate cardiac function and angiogenesis and enhance cardiac contractility, and as a result, β3AR are coupled with Gαi which could prevent overactivation of β1AR and β2AR.

β-Adrenergic signaling in cardiovascular diseases

β1AR and β2AR are expressed and distributed at the cell surface to the detached region which enhances effective signaling to Gαi [38]. All βARs (β1AR, β2AR, and β3AR) are expressed in cardiomyocytes [70]. The G protein is a heterotrimer of α, β, and γ subunits of Gα, Gβ, and Gγ, respectively, and it is inactive when binding to guanosine diphosphate (GDP) but most active while binding to guanosine triphosphate (GTP). The βAR signaling and HF progression resulted due to Gβγ-mediated signaling via desensitizing kinases called GRK2 and phosphoinositide 3-kinase (PI3K) [71, 72]. GRK2 is protective for the cell through incrementing ATP production and promoting mitogenesis [73], and GRK regulates adrenergic responses via a mechanism independent from G protein [24]. Once β2-adrenergic is coupled to downstream excitatory Gαs protein, it will activate AC yielding $_{C}$AMP, producing inotropic and chronotropic responses that result in cardiac injury and [1]; at the molecular level, the process is derived by receptor phosphorylation via GRKs [29]. This will cause $_{C}$AMP-mediated PKA activations to Ca^{2+} mediating cardiac contraction in order to increase the cardiac output [31] and causes ventricular wall motion [70] by activating cardiomyocyte βARs [59].

Therefore, upon stimulation of cardiomyocytes, βAR will bind to the stimulatory G (Gs) protein and alpha subunit (Gαs) which then activate adenylyl cyclase [9]. βAR stimulation elevates cardiac contractility, and if the βAR stimulation persists, toxicity that will affect cardiomyocytes which causes maladaptive cardiac remodeling and development of HF is enhanced. In this process, GRK helps to restrain catecholamine-mediated adrenergic signaling via receptor decentralization [74]. The aging in cardiac βAR response is because of the downregulation of β1AR, and a decreased sensitivity of βARs by isoproterenol results in conformational changes in the catecholamine-stimulated AC activity in the cardiovascular system [24]. Additionally, adenylyl cyclase as a transmembrane protein possesses two hydrophobic and two cytoplasmic domains that can convert ATP to $_{C}$AMP once stimulated with βARs [75]. The cyclic nucleotide phosphodiesterases (PDEs) are responsible for catalyzing the hydrolysis of $_{C}$AMP and $_{C}$GMP via regulating the intracellular concentrations of the cyclic nucleotide. Phosphodiesterases are significantly upregulated in HF, which is an indelicate β-adrenergic response as a result of hydrolysis of $_{C}$AMP in cardiomyocytes [2]. Then, the upregulation of GRK2 and resultant βAR desensitization are effective in the heart, but once there is a sustained elevation, it will significantly affect maladaptive cardiac remodeling and heart failure. In the failing heart, adrenergic overdriving proceeds early in the progression to HF; this shows that there are increased catecholamine levels before heart failure. The overexpression of GRK2 initiates Gi-biased signaling that neutralizes cardiac contractile response to βAR stimulation of a pertussis toxin (PTX)–sensitive manner in GRK2 transgenic mice and cultured mouse cardiomyocytes [49].

GRK modulation in the heart

G protein receptor kinase 2 (GRK2) has the potential to modulate cardiac adrenergic signaling [74]. GRKs interact with agonist activation of GPCRs to affect receptor

phosphorylation which enhances impairment of receptor signaling or desensitization [76]. The role of GRK2 in regulating cytoskeletal components is to modulate cellular migration in physiological function in the inflammatory response during cardiac disease [77]. GRK is a promising therapeutic target and can regulate adult hearts through the modulation of chronotropic, inotropic, and hypertrophic signaling of 7-transmembrane spanning neurohormone receptors, but adult HF can be caused by the downregulation and desensitization of βARs [78]. GRK modulation processes are an essential characteristic that is responsible for alleviating cardiovascular dysfunction in cell culture and animal models, and GRK modulation can effectively improve human health [79]. The composite channel of control of GRK2 stability explains that the tight modulation plays a pragmatic role in GPCR signaling [80]. SNS is maladaptively activated because of the sustained reduction in cardiac output, and this increases secretion and reduces cardiac catecholamine reuptake [73]. The decrease in cardiac output by SNS response is a result of GPCR activity in different types of cell and tissue beyond the heart. When SNS is activated, there is a remarkable increase in the heart rate and contractility via catecholaminergic stimulation of cardiac βARs, and in the human myocardium, the β1 and β2 subgroups induce a positive chronotropic and inotropic adrenergic effects via Gs coupling [79]. Once β2AR are stimulated, they will produce effects called inotropic, lusitropic, chronotropic, and dromotropic which are capable of activating both Gs proteins, and this will cause β2AR to switch its signaling from Gs to Gi proteins when phosphorylated by PKA [36, 67]. Therefore, the stimulation of βAR pathway in the heart activates Gs protein, and this increases $_{C}$AMP, PKA-dependent phosphorylation, and modulation that help in myocardial contractility including L-type Ca^{2+} channels, troponin, and ATPase inhibitory protein [51]. The $_{C}$AMP is phosphorylation-dependent leading to the enhancement of active Ca^{2+} transport. The active Ca^{2+} channels are mediated by the sarcoplasmic reticulum (SR) via ATPase enzymes which act as an energy transducer and translocator of Ca^{2+} ion, tightly coupled with ATP hydrolysis through the formation and decomposition of an acyl-phosphorylated phosphoenzyme which is the cytosolic enzymes found in the cardiac muscle [56, 81]. In this process, the βAR stimulation activates GRK2 which is the necessary mechanism of self-regulation of adrenergic stimulation [51]. An increase in GRKs amplifies the HF pathogenesis by the desensitization of βARs, and this lead to the losses of contractile reserve [82]. GRK activation in the heart provides targets for effective GRK modulation in human therapy, and there are several levels of sequence in the tissue distribution like GRK2 and GRK3 for the regulation of endothelin, thrombin, and α1-adrenergic receptor (α1 AR) in the human heart. GPCR signaling is firmly controlled by cytosolic GRKs and can translocate to or target agonist-bound GPCRs, which initiate and phosphorylate the receptor [62, 77]. GRK2 is a cell death kinase in the heart, and its targets promote ischemic injury whereas their inhibition by the peptide inhibitor called βARKct contains the carboxyl-terminal domain of bovine GRK2 for cardioprotection found in Fig. 3 [83].

GRK2 has the potential to modulate cardiac adrenergic signaling. When SNS is activated, there is a remarkable increase in the heart rate and contractility via catecholaminergic stimulation of cardiac βARs and the human myocardium. β2AR activates both Gs proteins causing β2AR to switch its signaling from Gs to Gi proteins when phosphorylated by PKA which increases $_{C}$AMP. The $_{C}$AMP initiates active Ca^{2+} transport by ATPase enzymes tightly coupled with ATP. An increase in GRKs amplifies the HF/cell death which promotes ischemic injury whereas βARKct undergoes inhibition leading to the prevention of myocardial damage and heart preservation.

βAR agonist

Agonists help to determine different maximal responses through their intrinsic activity that can produce full agonists through the intrinsic activity value, and fraction of agonists may completely stimulate partial agonists [84]. Fluorescence spectroscopy studies suggested that β2AR are the sequential binding model of agonists, the partial agonist and dopamine have rapid binding, and a full agonist, noradrenaline, possesses biphasic binding kinetics [85]. β1- and β2-adrenergic receptors and the studies of the structural nature of receptor activation are found not only in rhodopsin but also in agonist-bound structures of β1- and β2-adrenergic receptors. βAR downregulation or desensitization mechanism contributes to the heart-related reduction in βAR response to agonists [52]. Agonist bounds to a receptor and stabilizes [23]. GPCRs are mainly modulated by the diverse spectrum of drugs ranging from full agonists to the partial agonists, antagonists, and inverse agonists [86]. It merely showed that when ligands bind to both serines, they would dominantly act as agonists. When ligands do not bind to both serines, they are termed as antagonists [87]. The crystal structure of β2AR has detail information on classical GPCR drug target, and it belongs to rhodopsin-like GPCR [88]. The 3D structure of β2AR helps to predict specific binding sites of the agonists and antagonists to β2AR [87]. Then, an agonist binds to βAR; it will initiate conformation changes that provide receptor coupling to Gsα subtype of heterotrimeric G protein which is the AC stimulatory G protein for activation of $_{C}$AMP in the cells found in Fig. 4 [31]. Gi-biased β2AR signaling is agonist stimulation-dependent, and β2AR stimulation with zinterol leads to a full contractile response. β2AR phosphorylation by PKA mediates coupling to Gs and Gi, and β2AR physiological signaling

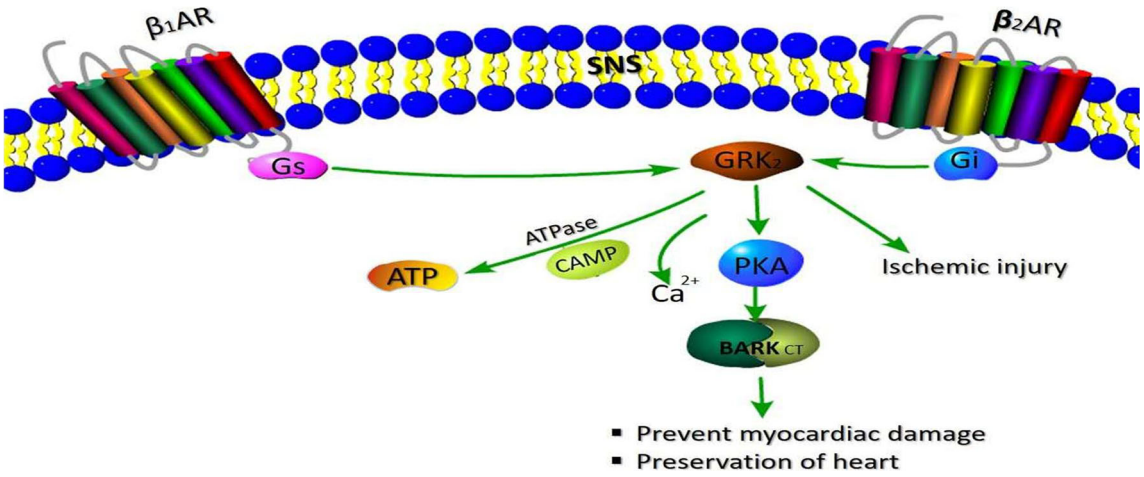

Fig. 3 GRK modulation in the heart

through GRK-mediated phosphorylation involves the regulation of β2AR couple to Gi signaling in the heart [49]. β2AR possess a strong affinity for the agonist isoprenaline which is more efficient when coupled to Gs [11]. βARs are agonist-promoted decentralization and downregulation which decrease regulatory effector response to activate agonist stimulation initiated by the receptor phosphorylation known as GRKs [89].

The structure of β2AR consists of several ligands; there are atomic binding modes of inverse agonists and antagonists while the agonists activate the signaling pathways and increase basal activities [88]. The activation of the β2AR by catecholamine agonists and ligand binding provides that agonists activate GPCRs via a conformation intermediate [90]. The different agonist-binding sites using salbutamol, epinephrine, and isoprenaline bind in a conformation, which allows them to form a strong hydrogen-bonding network with all three of the conserved TM5 serines. β2 agonists exhibit cross-reactivity with the other ARs which causes side effects and increased heart rate and blood pressure [87]. The activation and internalization of GPCRs have an impact on normal cellular physiology and alterations in heart failure. Overexpression of cofilin mutant can alter the level of β2AR phosphorylation following agonist stimulation which enhances internalization during isoprenaline stimulation [91].

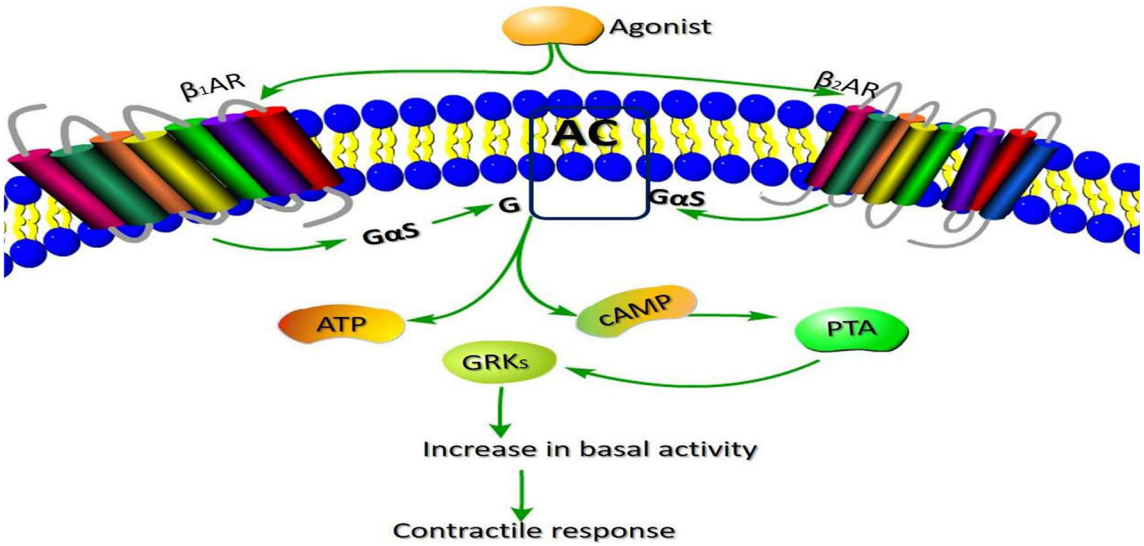

Fig. 4 The diagram which explains that when an agonist binds to βAR, it will initiate conformational changes that provide receptor coupling to Gαs subtype of heterotrimeric G protein which is the AC stimulatory G protein catalyzed by ATP into $_{C}$AMP in the cells. β2AR phosphorylation by PKA mediates coupling to Gs and Gi, and β2AR physiological signaling through GRK-mediated phosphorylation involves the regulation of β2AR couple to Gi signaling in the heart. βAR agonist-promoted decentralization and downregulation which decrease regulatory effector response to activate agonist stimulation initiated by GRKs that may lead to an increase in basal activities and contractile response through signaling pathways

Heart failure therapy

Heart failure is a common CVD with poor prognosis which develops when the heart is not capable of pumping blood and maintaining tissue perfusion [92]. Drugs capable of interacting with GPCRs are regulated via the activation status of heterotrimeric G protein [93]. Beta-blocker is regarded as a cornerstone of HF treatment which has shown a tremendous 10 to 40% reduction in mortality rate and hospitalization in 1 year [94, 95]. β-Blockers positively reduce the mortality in patients with systolic dysfunction and chronic HF [96] and are classified into three categories: sotalol, propranolol, nadolol, and timolol are the first category and referred to as a nonselective agent. β1 and β2 blocking receptors have an impact in influencing the heart rate, conduction, and contractility whereas the blocking of β2-receptors causes smooth muscle contraction. The second category is known as cardioselective (bisoprolol, celiprolol, atenolol, and metoprolol), and they are in low dose but can block receptors in higher doses. The third category possesses vasodilatory features and is either selective or nonselective (nebivolol and carvedilol), respectively, [95]. β1-receptor blocker has advance effects in the treatment of human heart failure [97].

Furthermore, βAR blockade served as standard therapy for cardiac failure [98]. β2AR blocker serves as therapy, and when adrenergic signaling is altered, it will activate a dilatation and decreased contractility [63]. Irrespective of angiotensin-converting enzyme (ACE) inhibition, there is possible hindrance showing that either the syndrome itself or ACE inhibition probably upregulates the alternative pathway which is useful in chronic HF with an inhibitor possibly possessing long-term restriction of all plasma levels and can retrogress in the left ventricular function [99]. The preventive treatment is using pharmacological therapy with beta-blockers, ACE inhibitors for the prevention of recurrent MI, and intensive monitoring to delay disease progression [28]. In animal models, β-blockers blunt apoptosis and cardiac remodeling associated failure, inhibit β1-adrenergic receptor internationalization, and can prevent PKA-dependent Ca^{2+} leak from the sarcoplasmic reticulum. β1-receptor blocker and ACE inhibitors can be combined consistently to improve HF symptoms. When ACE inhibitors are applied, they could reduce cardiac hypertrophic remodeling and fibrosis [97]. Beta-blockers are adequately protected from chronically increased catecholamines, leading to upregulation of β-receptors, and its exposure induces downregulation and desensitization of β-receptors where inotropy provides longer term left ventricular systolic dysfunction. The use of β-blockers is associated with significant survival in a patient with HF.

There is a concerning caution by the American Heart Association (AHA) before the regulation of HF advocate when using β-blockers in patients with symptomatic reactive airway diseases. The outcome of β-blockers is possibly attenuated by beta-agonists [100, 101]. It also recommends that the use of β-blockade in all patients with chronic HF can reduce systolic function without contradicting to β-blockers, and the β-blockers shall not undergo conversion during hospitalization for worsening heart failure [102]. Before MI and in patients with HF, treating the patients with blockers prevents reinfarction, hospitalization for HF, and premature death [103]. The Nobel Prize honor Sir James Black has shown that the advert effect of adrenergic stimulation via blocking the cardiac β-receptors will cause inhibitory effects on the sinus node (chronotropic effect), atrioventricular node (dromotropic effect), and myocardial contractility (inotropic effect) [95]. β-Blockers are convinced to reduce the risk of stroke drastically [104].

Conclusions

The βAR signaling pathway determines the progression of HF between the SNS and the CVS through the regulatory function in various cells. Heart failure is still a public health problem in the USA. When there is stimulation of cardiomyocytes, βAR will bind to the Gs protein and Gα subunit of the Gαs which then activate adenylyl cyclase. The cell death in cardiac βAR response via downregulation of β1AR and decrease in sensitivity of βARs affect conformational changes in the catecholamine-stimulated AC activity in the cardiovascular systems. In this review, we described that once there is a change in adrenergic signaling, it will activate a dilatation and decreased contractility. It was also established that when adrenergic signaling is altered, β2AR blocker will enable a dilatation and reduced contractility.

Acknowledgments We are very grateful to Ali Ozoemena for his unalloyed pieces of advice to complete this article. We are thankful to Chinese Scholarship Council (CSC) for funding our research scholar FATIMA Majeed in her doctorate studies. Furthermore, all the authors of the manuscript also thank and acknowledge their respective Universities and Institutes.

Funding information The Qinghai Science and Technology Department Project (Nos. 2018-ZJ-730 & 2019-SF-134) supported this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Rudomanova V, Blaxall BC (2017) Targeting GPCR-Gβγ-GRK2 signaling as a novel strategy for treating cardiorenal pathologies. Biochim Biophys Acta (BBA) - Mol Basis Dis 1863(8):1883–1892

2. Li D, Paterson DJ (2016) Cyclic nucleotide regulation of cardiac sympatho-vagal responsiveness. J Physiol 594(14):3993–4008
3. Rankin J, Rowen D, Howe A, Cleland JG, Whitty JA (2019) Valuing health–related quality of life in heart failure: a systematic review of methods to derive quality–adjusted life years (QALYs) in trial-based cost–utility analyses. Heart Fail Rev 24(4): 549–563
4. Morris JH, Chen L (2019) Exercise training and heart failure: a review of the literature. Card Fail Rev 5(1):57–61
5. Guha K, McDonagh T (2013) Heart failure epidemiology: European perspective. Curr Cardiol Rev 9(2):123–127
6. Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B, Mukherjee D, Lichstein E (2013) Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMj 346:f55
7. Jeyanantham K, Kotecha D, Thanki D, Dekker R, Lane DA (2017) Effects of cognitive behavioural therapy for depression in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev 22(6):731–741
8. Nadar SK, Shaikh MM (2019) Biomarkers in routine heart failure clinical care. Card Fail Rev 5(1):50
9. Madamanchi A (2007) β-Adrenergic receptor signaling in cardiac function and heart failure. McGill J Med 10(2):99
10. Chen J-Z, Wang J, Xie X-Q (2007) GPCR structure-based virtual screening approach for CB2 antagonist search. J Chem Inf Model 47(4):1626–1637
11. Shoichet BK, Kobilka BK (2012) Structure-based drug screening for G-protein-coupled receptors. Trends Pharmacol Sci 33(5): 268–272
12. Jacobson KA (2015) New paradigms in GPCR drug discovery. Biochem Pharmacol 98(4):541–555
13. Santulli G (2015) The adrenergic system in cardiovascular metabolism and aging. In: The cardiovascular adrenergic system. Springer, Cham. pp 97–116
14. Dolatshad NF, Hellen N, Jabbour RJ, Harding SE, Földes G (2015) G-protein coupled receptor signaling in pluripotent stem cell-derived cardiovascular cells: implications for disease modeling. Front Cell Dev Biol 3:76
15. Woo AYH, Xiao R-P (2012) β-Adrenergic receptor subtype signaling in heart: from bench to bedside. Acta Pharmacol Sin 33(3):335
16. Kamal FA, Travers JG, Blaxall BC (2012) G protein–coupled receptor kinases in cardiovascular disease: why "where" matters. Trends Cardiovasc Med 22(8):213–219
17. Kim YH, Oh SO, Kim CD (2016) Biased agonism of G protein–coupled receptors: a potential therapeutic strategy of cardiovascular diseases. Cardiovascular Pharmacology:Open Access 5(4): 1–7
18. Cresci S, Kelly RJ, Cappola TP, Diwan A, Dries D, Kardia SL, Dorn GW (2009) Clinical and genetic modifiers of long-term survival in heart failure. J Am Coll Cardiol 54(5):432–444
19. Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, Rohde LE (2008) Impact of β1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol 102(6):726–732
20. Salazar NC, Chen J, Rockman HA (2007) Cardiac GPCRs: GPCR signaling in healthy and failing hearts. Biochim Biophys Acta Biomembr 1768(4):1006–1018
21. Ciccarelli M, Sorriento D, Coscioni E, Iaccarino G, Santulli G (2017) Adrenergic receptors. In: Endocrinology of the heart in health and disease. Elsevier, pp 285–315
22. Corbi G, Conti V, Russomanno G, Longobardi G, Furgi G, Filippelli A, Ferrara N (2013) Adrenergic signaling and oxidative stress: a role for sirtuins? Front Physiol 4:324
23. Congreve M, Langmead CJ, Mason JS, Marshall FH (2011) Progress in structure based drug design for G protein-coupled receptors. J Med Chem 54(13):4283–4311
24. Santulli G, Iaccarino G (2016) Adrenergic signaling in heart failure and cardiovascular aging. Maturitas 93:65–72
25. Stern CS, Lebowitz J (2010) Latest drug developments in the field of cardiovascular disease. Int J Angiol 19(03):e100–e105
26. Sarkhel S, Sharon A, Trivedi V, Maulik PR, Singh MM, Venugopalan P, Ray S (2003) Structure-based drug design: synthesis, crystal structure, biological evaluation and docking studies of mono-and bis-benzo [b] oxepines as non-steroidal estrogens. Bioorg Med Chem 11(23):5025–5033
27. Rengo G, Lymperopoulos A, Zincarelli C, Femminella G, Liccardo D, Pagano G, De Lucia C, Cannavo A, Gargiulo P, Ferrara N (2012) Blockade of β-adrenoceptors restores the GRK2-mediated adrenal α2-adrenoceptor–catecholamine production axis in heart failure. Br J Pharmacol 166(8):2430–2440
28. O'connell J (2000) The economic burden of heart failure. Clin Cardiol 23(S3):III6–III10
29. Siryk-Bathgate A, Dabul S, Lymperopoulos A (2013) Current and future G protein-coupled receptor signaling targets for heart failure therapy. Drug Des Devel Ther 7:1209
30. Manna M, Niemelä M, Tynkkynen J, Javanainen M, Kulig W, Müller DJ, Rog T, Vattulainen I (2016) Mechanism of allosteric regulation of β2-adrenergic receptor by cholesterol. Elife 5:e18432
31. Vasudevan NT, Mohan ML, Goswami SK, Prasad SVN (2011) Regulation of β-adrenergic receptor function: an emphasis on receptor resensitization. Cell Cycle 10(21):3684–3691
32. Cannatà A, Marcon G, Cimmino G, Camparini L, Ciucci G, Sinagra G, Loffredo FS (2017) Role of circulating factors in cardiac aging. J Thorac Dis 9(Suppl 1):S17–S29
33. White DC, Hata JA, Shah AS, Glower DD, Lefkowitz RJ, Koch WJ (2000) Preservation of myocardial β-adrenergic receptor signaling delays the development of heart failure after myocardial infarction. Proc Natl Acad Sci 97(10): 5428–5433
34. Park M, Steinberg SF (2018) Carvedilol prevents redox inactivation of cardiomyocyte B1-adrenergic receptors. JACC Basic Transl Sci 3(4):521–532
35. Shin E, Ko KS, Rhee BD, Han J, Kim N (2014) Different effects of prolonged β-adrenergic stimulation on heart and cerebral artery. Integr Med Res 3(4):204–210
36. de Lucia C, Femminella GD, Gambino G, Pagano G, Allocca E, Rengo C, Silvestri C, Leosco D, Ferrara N, Rengo G (2014) Adrenal adrenoceptors in heart failure. Front Physiol 5:246
37. Strachan RT (2009) P90 ribosomal S6 kinase 2 (RSK2) directly phosphorylates the 5–HT2A serotonin receptor thereby modulating signaling. Case Western Reserve University (Thesis 42103)
38. Johnson J, Liggett S (2011) Cardiovascular pharmacogenomics of adrenergic receptor signaling: clinical implications and future directions. Clin Pharmacol Ther 89(3):366–378
39. Fajardo G, Zhao M, Urashima T, Farahani S, Hu D-Q, Reddy S, Bernstein D (2013) Deletion of the β2-adrenergic receptor prevents the development of cardiomyopathy in mice. J Mol Cell Cardiol 63:155–164
40. De Lucia C, Eguchi A, Koch WJ (2018) New insights in cardiac β-adrenergic signaling during heart failure and aging. Front Pharmacol 9:904
41. Jones SM, Hiller FC, Jacobi SE, Foreman SK, Pittman LM, Cornett LE (2003) Enhanced β 2-adrenergic receptor (β 2 AR) signaling by adeno-associated viral (AAV)-mediated gene transfer. BMC Pharmacol 3(1):15
42. Katritch V, Rueda M, Lam PCH, Yeager M, Abagyan R (2010) GPCR 3D homology models for ligand screening: lessons learned

from blind predictions of adenosine A2a receptor complex. Proteins: Struct, Funct, Bioinf 78(1):197–211
43. Yuzlenko O, Kieć-Kononowicz K (2009) Molecular modeling of A1 and A2A adenosine receptors: comparison of rhodopsin-and β2-adrenergic-based homology models through the docking studies. J Comput Chem 30(1):14–32
44. Kolb P, Rosenbaum DM, Irwin JJ, Fung JJ, Kobilka BK, Shoichet BK (2009) Structure-based discovery of β2-adrenergic receptor ligands. Proc Natl Acad Sci 106(16):6843–6848
45. Corbi G, Conti V, Russomanno G, Rengo G, Vitulli P, Ciccarelli AL, Filippelli A, Ferrara N (2012) Is physical activity able to modify oxidative damage in cardiovascular aging? Oxidative Med Cell Longev 2012:1–6
46. Samuel CS, Unemori EN, Mookerjee I, Bathgate RA, Layfield SL, Mak J, Tregear GW, Du X-J (2004) Relaxin modulates cardiac fibroblast proliferation, differentiation, and collagen production and reverses cardiac fibrosis in vivo. Endocrinology 145(9): 4125–4133
47. Stallaert W, Dorn JF, Van Der Westhuizen E, Audet M, Bouvier M (2012) Impedance responses reveal β2-adrenergic receptor signaling pluridimensionality and allow classification of ligands with distinct signaling profiles. PLoS One 7(1):e29420
48. Bernstein D, Fajardo G, Zhao M (2011) The role of β-adrenergic receptors in heart failure: differential regulation of cardiotoxicity and cardioprotection. Prog Pediatr Cardiol 31(1):35–38
49. Zhu W, Petrashevskaya N, Ren S, Zhao A, Chakir K, Gao E, Chuprun JK, Wang Y, Talan M, Dorn GW (2012) Gi-biased β2AR signaling links GRK2 upregulation to heart failure novelty and significance. Circ Res 110(2):265–274
50. Cannavo A, Liccardo D, Koch WJ (2013) Targeting cardiac β-adrenergic signaling via GRK2 inhibition for heart failure therapy. Front Physiol 4:264
51. Barrese V, Taglialatela M (2013) New advances in beta-blocker therapy in heart failure. Front Physiol 4:323
52. Ferrara N, Komici K, Corbi G, Pagano G, Furgi G, Rengo C, Femminella GD, Leosco D, Bonaduce D (2014) β-Adrenergic receptor responsiveness in aging heart and clinical implications. Front Physiol 4:396
53. Rath G, Balligand J-L, Chantal D (2012) Vasodilatory mechanisms of beta receptor blockade. Curr Hypertens Rep 14(4):310–317
54. Lymperopoulos A, Rengo G, Koch WJ (2007) Adrenal adrenoceptors in heart failure: fine-tuning cardiac stimulation. Trends Mol Med 13(12):503–511
55. Xiang Y, Devic E, Kobilka B (2002) The PDZ binding motif of the β1 adrenergic receptor modulates receptor trafficking and signaling in cardiac myocytes. J Biol Chem 277(37):33783–33790
56. Zaugg M, Schaub MC (2008) β3-adrenergic receptor subtype signaling in senescent heart nitric oxide intoxication or "endogenous" β blockade for protection? Anesthesiology: The Journal of the American Society of Anesthesiologists, 109(6):956–959
57. Gao Z-G, Jacobson KA (2017) Purinergic signaling in mast cell degranulation and asthma. Front Pharmacol 8:947
58. Zhang W, Yano N, Deng M, Mao Q, Shaw SK, Tseng Y-T (2011) β-Adrenergic receptor-PI3K signaling crosstalk in mouse heart: elucidation of immediate downstream signaling cascades. PLoS One 6(10):e26581
59. Liggett SB (2001) β-Adrenergic receptors in the failing heart: the good, the bad, and the unknown. J Clin Invest 107(8):947–948
60. Lymperopoulos A, Negussie S (2013) βArrestins in cardiac G protein-coupled receptor signaling and function: partners in crime or "good cop, bad cop"? Int J Mol Sci 14(12):24726–24741
61. Cannavo A, Koch WJ (2017) Targeting β3-adrenergic receptors in the heart: selective agonism and β-blockade. J Cardiovasc Pharmacol 69(2):71–78
62. Penela P, Murga C, Ribas C, Tutor AS, Peregrín S, Mayor F Jr (2006) Mechanisms of regulation of G protein-coupled receptor kinases (GRKs) and cardiovascular disease. Cardiovasc Res 69(1):46–56
63. Kaufman BD, Shaddy RE (2007) Beta-adrenergic receptor blockade and pediatric dilated cardiomyopathy. Prog Pediatr Cardiol 24(1):51–57
64. Bernstein D (2018) Cardiovascular receptors and signaling in heart failure. In: Heart Failure in the Child and Young Adult. Elsevier, pp 21–31.
65. Rosmond R, Ukkola O, Chagnon M, Bouchard C, Björntorp P (2000) Polymorphisms of the β2-adrenergic receptor gene (ADRB2) in relation to cardiovascular risk factors in men. J Intern Med 248(3):239–244
66. Richter W, Day P, Agrawal R, Bruss MD, Granier S, Wang YL, Rasmussen SG, Horner K, Wang P, Lei T (2008) Signaling from β1-and β2-adrenergic receptors is defined by differential interactions with PDE4. EMBO J 27(2):384–393
67. Bristow MR (2000) β-Adrenergic receptor blockade in chronic heart failure. Circulation 101(5):558–569
68. Lohse MJ, Engelhardt S, Eschenhagen T (2003) What is the role of β-adrenergic signaling in heart failure? Circ Res 93(10):896–906
69. Bristow M, Hershberger R, Port JD, Minobe W, Rasmussen R (1989) Beta 1-and beta 2-adrenergic receptor-mediated adenylate cyclase stimulation in nonfailing and failing human ventricular myocardium. Mol Pharmacol 35(3):295–303
70. Makaritsis K, Triposkiadis F (2015) Beta adrenergic receptors. In: Introduction to translational cardiovascular research. Springer, pp 73–89.
71. Kamal FA, Smrcka AV, Blaxall BC (2011) Taking the heart failure battle inside the cell: small molecule targeting of Gβγ subunits. J Mol Cell Cardiol 51(4):462–467
72. Zhang P, Mende U (2011) Regulators of G-protein signaling in the heart and their potential as therapeutic targets. Circ Res 109(3): 320–333
73. Ciccarelli M, Santulli G, Pascale V, Trimarco B, Iaccarino G (2013) Adrenergic receptors and metabolism: role in development of cardiovascular disease. Front Physiol 4:265
74. Zhang Y, Matkovich SJ, Duan X, Gold JI, Koch WJ, Dorn GW II (2011) Nuclear effects of G-protein receptor kinase 5 on histone deacetylase 5–regulated gene transcription in heart failure. Gene Expr 4:659–668
75. Ho D, Yan L, Iwatsubo K, Vatner DE, Vatner SF (2010) Modulation of β-adrenergic receptor signaling in heart failure and longevity: targeting adenylyl cyclase type 5. Heart Fail Rev 15(5):495–512
76. Métayé T, Gibelin H, Perdrisot R, Kraimps J-L (2005) Pathophysiological roles of G-protein-coupled receptor kinases. Cell Signal 17(8):917–928
77. Grisanti LA, Schumacher SM, Tilley DG, Koch WJ (2018) Designer approaches for G protein–coupled receptor modulation for cardiovascular disease. JACC Basic Transl Sci 3(4):550–562
78. Franco A, Zhang L, Matkovich SJ, Kovacs A, Dorn GW II (2018) G-protein receptor kinases 2, 5 and 6 redundantly modulate smoothened-GATA transcriptional crosstalk in fetal mouse hearts. J Mol Cell Cardiol 121:60–68
79. Belmonte SL, Blaxall BC (2011) G protein coupled receptor kinases as therapeutic targets in cardiovascular disease. Circ Res 109(3):309–319
80. Elorza A, Penela P, Sarnago S, Mayor F (2003) MAPK-dependent degradation of G protein-coupled receptor kinase 2. J Biol Chem 278(31):29164–29173
81. Nediani C, Formigli L, Perna A, Ibba-Manneschi L, Zecchi-Orlandini S, Fiorillo C, Ponziani V, Cecchi C, Liguori P, Fratini G (2000) Early changes induced in the left ventricle by pressure

overload. An experimental study on swine heart. J Mol Cell Cardiol 32(1):131–142
82. Pfleger JM, Gross P, Johnson J, Gao E, Houser SR, Koch WJ (2018) G protein-coupled receptor kinase 2 impairs fatty acid metabolism in the failing heart through novel mechanisms. J Mol Cell Cardiol 124:100
83. Chen M, Sato PY, Chuprun JK, Peroutka RJ, Otis NJ, Ibetti J, Pan S, Sheu S–S, Gao E, Koch WJ (2013) Pro-death signaling of GRK2 in cardiac myocytes after ischemic stress occurs via ERK-dependent, Hsp90–mediated mitochondrial targeting. Circ Res. 112(8): 1121–1134
84. Walker J, Penn R, Hanania N, Dickey B, Bond R (2011) New perspectives regarding β2-adrenoceptor ligands in the treatment of asthma. Br J Pharmacol 163(1):18–28
85. Selvam B, Wereszczynski J, Tikhonova IG (2012) Comparison of dynamics of extracellular accesses to the β1 and β2 adrenoceptors binding sites uncovers the potential of kinetic basis of antagonist selectivity. Chem Biol Drug Des 80(2):215–226
86. Swaminath G, Lee TW, Kobilka B (2003) Identification of an allosteric binding site for Zn2+ on the β2 adrenergic receptor. J Biol Chem 278(1):352–356
87. Freddolino PL, Kalani MYS, Vaidehi N, Floriano WB, Hall SE, Trabanino RJ, Kam VWT, Goddard WA (2004) Predicted 3D structure for the human β2 adrenergic receptor and its binding site for agonists and antagonists. Proc Natl Acad Sci 101(9):2736–2741
88. Chan HS, Filipek S, Yuan S (2016) The principles of ligand specificity on beta-2-adrenergic receptor. Sci Rep 6:34736
89. Hatton R, Cvjeticanin A, Lymperopoulos A (2015) The adrenergic system of the adrenal glands as a remote control of cardiac function. J Cardiovasc Dis 5:394–397
90. Swaminath G, Deupi X, Lee TW, Zhu W, Thian FS, Kobilka TS, Kobilka B (2005) Probing the β2 adrenoceptor binding site with catechol reveals differences in binding and activation by agonists and partial agonists. J Biol Chem 280(23):22165–22171
91. Volovyk ZM, Wolf MJ, Prasad SVN, Rockman HA (2006) Agonist-stimulated β-adrenergic receptor internalization requires dynamic cytoskeletal actin turnover. J Biol Chem 281:9773–9780
92. Tsuda T, Takefuji M, Wettschureck N, Kotani K, Morimoto R, Okumura T, Kaur H, Eguchi S, Sakaguchi T, Ishihama S (2017) Corticotropin releasing hormone receptor 2 exacerbates chronic cardiac dysfunction. J Exp Med 214(7):1877–1888
93. Sato M (2013) Roles of accessory proteins for heterotrimeric G-protein in the development of cardiovascular diseases. Circ J 77(10):2455–2461
94. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC (2009) Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol 53(2):184–192
95. Albouaini K, Andron M, Alahmar A, Egred M (2007) Beta-blockers use in patients with chronic obstructive pulmonary disease and concomitant cardiovascular conditions. Int J Chron Obstruct Pulmon Dis 2(4):535–540
96. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 362(9377):7–13
97. Kang M, Chung KY, Walker JW (2007) G-protein coupled receptor signaling in myocardium: not for the faint of heart. Physiology 22(3):174–184
98. Liggett SB, Cresci S, Kelly RJ, Syed FM, Matkovich SJ, Hahn HS, Diwan A, Martini JS, Sparks L, Parekh RR (2008) A GRK5 polymorphism that inhibits β-adrenergic receptor signaling is protective in heart failure. Nat Med 14(5):510–517
99. Petrie MC, Padmanabhan N, McDonald JE, Hillier C, Connell JM, McMurray JJ (2001) Angiotensin converting enzyme (ACE) and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. J Am Coll Cardiol 37(4):1056–1061
100. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ (2009) Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 11(2):130–139
101. Rutten FH, Cramer MJM, Lammers JWJ, Grobbee DE, Hoes AW (2006) Heart failure and chronic obstructive pulmonary disease: an ignored combination? Eur J Heart Fail 8(7):706–711
102. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M (2004) Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol 43(9):1534–1541
103. Lindholm LH, Carlberg B, Samuelsson O (2005) Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 366(9496):1545–1553
104. Pose-Reino A, Pena-Seijo M (2007) Should beta-blockers remain first choice in the treatment of primary hypertension? Med Clin 129(19):733–735