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Insulin and β adrenergic receptor signaling: Cross talk in heart

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Abstract

Recent advances show that insulin may affect β adrenergic receptor (βAR) signaling in heart, to modulate cardiac function in clinically relevant states such as diabetes and heart failure. Conversely, activation of βAR regulates cardiac glucose uptake and promotes insulin resistance in HF. We discussed recent characterization on the interaction between cardiac insulin receptor and βAR in myocardium, in which insulin stimulation cross talk with cardiac βAR via insulin receptor substrate-dependent and G protein receptor kinase 2-mediated phosphorylation of β_2AR. The insulin-induced phosphorylation promotes β_2AR coupling to G_i and expression of phosphodiesterase 4, which inhibit cardiac adrenergic signaling and compromise cardiac contractile function. These progresses might support new approaches for effectively prevention or treatment of obesity-or diabetes-related heart failure.

Keywords

Insulin; adrenergic receptor; diabetes; heart failure; GRK2

Sympathetic Nervous Activity and Insulin Resistance in Heart Failure

Insulin regulates a broad range of function in the heart including cardiac metabolism, myocyte survival, and cardiac growth (Figure 1 and Box 1). Insulin promotes glucose uptake in cardiomyocytes through activation of an InsR-mediated phosphatidylinositol 3-kinase

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(PI3K)-Akt pathway, which mobilizes glucose transporter 4 (GLUT4) vesicles to the cell surface for glucose uptake [1]. Interestingly, stimulation of βAR in heart also induces an additive effect on insulin-induced glucose uptake; and this effect is mediated by phosphorylation of Akt in threonine 308 through protein kinase A (PKA)/Ca^{2+}-dependent pathway [2, 3]. On the cellular level, stimulation with either insulin or catecholamines antagonizes the ability of the other to activate glucose transport and to modulate cardiomyocyte survival [4, 5]. These observations suggest a counter-regulation between insulin and βAR signaling in heart. Recently, a functional membrane complex consisting of insulin receptor (InsR) and β_2AR has been characterized [6, 7], providing a biochemical basis for intimate cross talk between cardiac insulin and β adrenergic regulatory systems. In this review, this novel complex and other progresses in understanding of the connection between cardiac insulin and βAR signaling is summarized, and the implications in the pathophysiology of heart diseases such as diabetes-related heart failure (HF) will be discussed.

In the absence of systemic metabolic disorders, cardiac insulin resistance (IR) can develop in congestive and ischemic HF most likely due to the elevated sympathetic nervous system (SNS) activity (Table 1) [8]. IR can be classified into two categories: failure of InsR in promoting intracellular signals such as Akt activity or an impaired translocation of GLUT4 to the cell surface despite increases in intracellular Akt activity. In both scenarios, dysregulation of the InsR-Akt signal may compromise the ability of myocardium to cope with stresses or exacerbate cardiac phenotype in HF [9]. The SNS effects on cardiomyocytes are mediated by βAR activation. Chronic β_2AR stimulation under the elevated SNS activity leads to sustained activation of Akt through PKA/$Ca^{2+}$and PI3K-dependent pathways, which decreases GLUT4 expression and GLUT4 translocation to the plasma membrane and compromises the ability of insulin to promote glucose uptake [10, 11]. CHF is associated with IR characterized by both fasting and stimulated hyperinsulinemia, which can drive chronic stimulation of the InsR signaling [12]. Accordingly, expression of constitutive active PI3K and Akt in cardiomyocytes compromises the insulin-induced GLUT4-dependent glucose uptake [13]. Abnormal insulin signaling plays an essential role in the development of HF, including cardiac cell survival, hypertrophy, and fibrosis [14]. In the late stage of HF, IR develops in both cardiac and peripheral tissues such as skeletal muscle, fat, and liver [15], and presents a poor prognosis of HF associated with worsening cardiac function and increasing mortality. Treatment with β-blockers including metoprolol and carvedilol antagonizes isoproterenol-induced IR and cardiac dysfunction, with non-selective βAR antagonist carvedilol displaying a greater efficiency [10, 16, 17]. Meanwhile, restoration of cardiac output after left ventricular assist devices improves glycemic control and decreases insulin requirements in patients with advanced CHF [18]. Together, these studies indicate that IR emerges as an important index along with βAR desensitization in management of HF with metabolic disorders.

Desensitization of Cardiac βARs in Heart Failure

In congestive and failing ischemic hearts, loss of cardiac output leads to compensatory increase in the SNS activity that stimulates cardiac βARs, which enhance cardiac contractility. Persistent and excessive stimulation with catecholamines promotes

phosphorylation of βARs by PKA and GRK that leads to receptor desensitization and endocytosis in cardiomyocytes (Table 1). In a classic paradigm, HF displays a selective downregulation of β_1AR that is often associated with an upregulation of GRK2 and G_i. In contrast, the expression of β_2AR is not altered (Figure 2 and Box 2). The mechanism for selective downregulation of β_1AR is not clear; though it is generally considered a mechanism that removes excessive and persistent toxic pro-apoptotic β_1AR signaling that is detrimental to myocardium [19]. Thus, selective β-blocker against β_1AR such as metaprolol has been developed to block the receptor activity in HF. One of clinical outcomes in an effective β-blocker therapy is to restore β_1AR density in myocardium, which may play a role in restoring cardiac contractility and cardiac reserve in response to catecholamines. The apparent paradox between toxic β_1AR signal and the recovered β_1AR density after therapy is not fully understood. Recent evidence suggests that GPCR including β_2AR can continue to signal from the endosome after agonist-induced endocytosis [20]; and the signal induced by endosomal β_1AR is shown to promote hypertrophy in cardiomyocytes [21]. Studies show that in adaptive HF cardiac β_1AR is shifted from the cell surface to the endosome without significant decrease in receptor density [22]. Therefore, one can argue that endosomal β_1AR potentially transduces detrimental signaling to promote cardiac remodeling during the development of HF; and β-blocker therapy is to eliminate toxic endosomal β_1AR signaling and restore normal β_1AR signaling from the plasma membrane.

In comparison, the expression of cardiac β_2AR is not decreased during HF. A loss of caveolae leads to redistribution of β_2AR from t-tubular membrane to crest membrane [23]. In HF, stimulation of β_2AR promotes a redistributed cAMP-PKA signaling in cardiomyocytes for contractile response [23–25]. Meanwhile, an upregulation of G_i is often associated with enhanced β_2AR-Gi signaling in HF. The enhanced β_2AR-G_i signaling leading to Akt activation can protect against myocyte apoptosis, and consequently slow down the progression of cardiomyopathy [26]. Therefore, a combined therapy of β_1AR blocker and β_2AR agonist has been proposed for treatment of HF. Despite its beneficial effects in myocardium, the same β_2AR-G_i coupling could blunt the G_s-mediated stimulation of contractile support, contributing to contractile defect in failing hearts [27]. Thus, the status of β_2AR-G_i coupling can potentially shape the overall output of cardiac βAR signaling under different pathological circumstances.

Hyperinsulinemia Promotes Desensitization of Cardiac βAR

Diabetes mellitus (DM) is an important predictor of HF independent of concomitant hypertension or coronary artery diseases [28]. One of the hallmarks in DM is insulin resistance and associated hyperinsulinemia. In metabolic syndromes including obesity and diabetes, InsR is no longer responsive to insulin stimulation that promotes glucose uptake in skeletal muscle, fat, and liver. General IR is often associated with nutrition overload such as free fatty acids and cholesterol, together with systemic inflammation. General IR is accompanied by compensatory increases in insulin released from the pancreas, which leads to high levels of insulin in the plasma [29]. In diabetes, metabolic stress can lead to cardiomyopathy via depressing Akt signaling and activate Foxo1-mediated gene expression [9]. Meanwhile, inflammation, oxidative stress, and mitochondria dysfunction also contribute to the development of cardiomyopathy [30]. However, whether hyperinsulinemia

play a role in diabetic cardiomyopathy and heart failure is not well established. Previous studies have shown a direct relationship between insulin signaling and cardiac contractility [31]. The newly characterized InsR and β_2AR complex in myocardium brings new prospects to the issue [32–34]. In this new paradigm, insulin stimulates recruitment of GRK2 to InsR in an IRS2-dependent manner, and promotes GRK2-mediated phosphorylation of β_2AR [32], through which insulin inhibits cardiac contractility by promoting a G_i-biased β_2-adrenergic signaling (Table 1 and Figure 3). Insulin also promotes dissociation of the InsR-β_2AR complex and β_2AR internalization to attenuate β-adrenergic stimulation of contractile responses in cardiomyocytes [6].

It's noteworthy that short-term HFD feeding leads to decreases in cardiac functional reserve and mitochondrial ROS production in response to β-adrenergic stimulation without significant alteration in β_1AR and β_2AR expression, cardiac structure, and cardiac function [34, 35]. This decrease in cardiac functional reserve is associated with significant increases in the levels of phosphorylation of β_2AR at PKA and GRK sites. Genetic deletion of the β_2AR preserves adrenergic response and cardiac contractile reserve in HFD-fed mice [34]. These observations suggest that hyperinsulinemia drives phosphorylation of the β_2AR for coupling to G_i protein to compromises cardiac adrenergic stimulation. Clinically, diabetic patients show decreases in exercise tolerance and blunted inotropic responses to dobutamine stimulation before the onset of overt cardiac dysfunction, suggesting that the cardiac β-adrenergic system is compromised [36]. Therefore, exercise intolerance and blunted inotropic response to adrenergic stimulation can be considered as early signs of diabetic cardiomyopathy, and the insulin-adrenergic signaling network can offer potential targets for early intervention to prevent cardiac complications.

Meanwhile, the PDE-mediated degradation of cAMP recently emerged as a previously underappreciated mechanism in the desensitization of cardiac βAR signaling [37, 38]. Insulin promotes an InsR-IRS-GRK2-and β-arrestin2-dependent transactivation of a β_2AR-ERK signaling cascade to induce PDE4 expression in cardiomyocytes. An increased PDE4 expression is also observed in atrial biopsies from patients with cardiac diseases and diabetes relative to those patients without diabetes [33]. The PDE4-dependent cAMP hydrolysis counterbalances the βAR-induced cAMP signal. Inhibition of PDE4 activity recovers the receptor-induced cAMP signal and rescues contractile response to adrenergic stimulation in HFD heart [33]. Pharmacological inhibition of β_2AR or GRK2, or genetic deletion of β_2AR or β-arrestin2 significantly attenuate insulin-induced phosphorylation of ERK and induction of PDE4D, and prevent diabetes-related contractile dysfunction [33]. Thus, hyperinsulinemia may contribute to the impairment of adrenergic signaling via the increasing expression of PDE4D in heart. Accordingly, aggressive glycemic control with insulin secretagogues displays adverse outcomes in comorbidity of HF and diabetes [39]. Together, these observations suggest that hyperinsulinemia can directly act on myocardium and promote desensitization of adrenergic signaling by inducing PKA and GRK phosphorylation of β_2AR to increase G_i coupling and the expression of PDE4D.

Hyperinsulinemia also leads to increase in activity of the sympathetic nervous system (SNS) [40]. This could be a compensatory mechanism in response to the inhibitory effects of insulin on cardiac βAR signal and reduced cardiac contractility and output. Alternatively,

increased free fatty acid in metabolic disorders is also associated with elevated SNS activity that drives cardiac βARs. The elevated levels of catecholamines further antagonize insulin's action, which leads to worsen cardiac IR and energy metabolism in CHF [10]. Chronic hyperinsulinemia can also work with hyperlipidemia and inflammation to drive IR in heart. Together, hyperinsulinemia and SNS activity are integrated via activation of the InsR-β_2AR signaling network to promote the development of HF. The relationship between DM and congestive HF (CHF) are bidirectional since CHF and DM often coexist with overlapping pathophysiological processes [41–43].

GRK2 Serves as a Nexus linking IR and βAR Desensitization

GRK2 emerges as a critical nexus to connect cardiac InsR and adrenergic signaling (Table 1). Following stimulation by catecholamines or insulin, GRK2 shuttles from the cytosol to the plasma membrane to desensitize βAR and InsR, respectively [4, 32].

After catecholamine stimulation, GRK2 is activated and recruited to βARs through binding to $G_{\beta\gamma}$ subunits on the plasma membrane, which allows GRK2 to phosphorylate receptor and other substrates such as PI3K to promote receptor endocytosis [44]. Chronic adrenergic stimulation is a signaling abnormality that also leads to the upregulation of GRK2 in HF [45]. Disruption of GRK2 binding to $G_{\beta\gamma}$ or deletion of GRK2 prevents βAR endocytosis induced by catecholamines [46]. Thus, inhibition of GRK2 has been proposed for HF therapy. A peptide that disrupts GRK2 binding to $G_{\beta\gamma}$ has been effective in treatment of various models of HF, including rodents and pigs [46]. More recently, a small molecule paroxetine, which is a FDA approved selective serotonin reuptake inhibitor, has been characterized as a selective GRK2 inhibitor [47]. Inhibition of GRK2 with paroxetine has been effective in modulation of βAR signaling pathway in cardiomyocytes, and in treatment of HF after transverse aortic constriction [47, 48].

Biochemical evidence suggests that GRK2 binds to IRS1/2 upon acute insulin stimulation, which facilitates phosphorylation of both InsR and IRS1/2, and prevents excessive insulin stimulation [49]. However, in HFD feeding model, the elevated expression of GRK2 promotes IR via inhibition of tyrosine phosphorylation and activation of IRS1/2 [33, 49]. The upregulated GRK2 also impairs myocardial glucose uptake before cardiac dilation, and the reduced function is evident (Table 1), indicating a metabolic remodeling at early stages of HF [50, 51]. Accordingly, overexpression of GRK2 has been shown to reduce myocardial insulin signaling. In germline GRK2 heterozygous knockout mice, insulin sensitivity is preserved in aging mice or when these animals are placed on a high fat diet (HFD) [52]. Genetic ablation of GRK2 is effective in ameliorating IR and glucose intolerance in an animal model of HFD-induced diabetes [53]. Thus, GRK2 serves as a crucial node in integrating cardiac metabolic and contractile regulation.

Early data implicates that GRK2 mediates adrenergic-induced IR and that inhibition of GRK2 leads to increased insulin sensitivity both in cells and in animal model of IR [45]. On the other hands, treatment with insulin promotes GRK2-mediated phosphorylation of β_2AR, which leads to β_2AR-G_i coupling to inhibit cardiac adrenergic signal. Both insulin and catecholamines also promote expression of GRK2. Depending on clinical onset conditions,

GRK2 can be activated by catecholamines and/or hyperinsulinemia, and acts as a critical node linking insulin and adrenergic signal in control of contractility and cardiac metabolism, and promotes IR and βAR desensitization in heart. Genetic and pharmacological inhibition of GRK2 displays beneficial effects including ameliorating hyperglycemia and glucose intolerance, and improving cardiac function in HFD mice [33, 53, 54]. It's worth mentioning that pharmacological inhibition of β_2AR with carvedilol partially attenuates the expression levels of cardiac GRK2, which may contribute to the improved cardiac function and glucose tolerance [33]. Moreover, the GRK2 inhibitor paroxetine largely reverses cardiac fibrosis and apoptosis, suggesting a necessary role of GRK2 in the adverse remodeling in diabetic cardiomyopathy. Therefore, targeting GRK2 may provide dual benefits by normalizing adrenergic signaling and metabolic function in HF, particularly in HF with comorbidity of metabolic disorders such as obesity and diabetes.

Hyperinsulinemia Promotes Cardiac Remodeling: Hypertrophy and Fibrosis

Cardiac hypertrophy is defined as an increment of ventricular mass resulting from increased cardiomyocyte size, and is an adaptive response of the heart to increased hemodynamic load due to either physiological stresses or pathological states [55]. Insulin is an anabolic hormone that promotes protein synthesis, cell growth, and hypertrophy. Insulin and insulin-like growth factor 1 (IGF-1) receptors differentially modulate cardiac growth in an IRS1/2-dependent manner at resting conditions and following exercise training [56]. Genetic deletion of InsR in cardiomyocytes leads to a 30% reduction in heart size associated with diminished Akt phosphorylation [57].

Chronic hyperinsulinemia is shown to increase myocardial mass and reduce cardiac output in rats [58]. Recent evidence shows that cardiac insulin signaling is hyperactive in a pathological hypertrophic model induced by pressure overload [55]. Genetic inhibition of the InsR-Akt1 signaling pathway substantially attenuates hypertrophy, adverse remodeling, and dysfunction following transverse aortic constriction [55, 59–62]. Thus, activation of InsR signaling in pressure overload model appears to promote detrimental pathological hypertrophy. The underlying mechanism of distinct roles of InsR in physiological (exercise) and pathological cardiac hypertrophy is not well understood. One of the potential factors is co-activation of cardiac ARs in pathological conditions, Stimulation of both α_1ARs and βARs promote pathological cardiac hypertrophy [63]; and βAR stimulation promotes hypertrophic growth via an Akt-dependent mechanism [60, 64]. In a TAC model, while the elevation of SNS activity drives the cardiac βAR to increase cardiac contractility and compensatory cardiac output, it also promotes persistent activation of PI3K and Akt via stimulation of β_2AR [65]. This signaling cascade may be involved and/or dependent on co-activation of InsR in the InsR-β_2AR complex. Activation of InsR, PI3K, and Akt is necessary for cardiac hypertrophy, indicating an early compensatory role of InsR activation in a TAC heart. Meanwhile, persistent activation of PI3K and Akt also promotes cardiac IR [13], which compromises cardiac metabolism and the ability of myocyte survival in responding to stress, contributing to maladaptation in HF development. While both IR and hyperactive InsR occur in a TAC heart, the mechanisms underlying the development of these two connected features are not understood. In addition, in pathological cardiac hypertrophy, cytotoxic β_1AR signal, the renin-angiotensin-aldosterone system (RAAS), reactive oxygen

species (ROS), and inflammation all promote cardiac maladaptive remodeling (e.g. cardiac apoptosis and fibrosis) [66]. These factors can also promote cardiac and general IR to exacerbate HF failure. For example, Angiotensin II abolishes insulin-induced tyrosine phosphorylation of IRS-1, activation of Akt, and GLUT4 translocation to the plasma membrane [67]. Multiple serine phosphorylation events are involving in the negative modulation of insulin signaling by Angiotensin II, which is consistent with the observation of the association of insulin resistance with cardiac hypertrophy [68].

Interestingly, in a recent study with HFD feeding, deletion of the β_2AR gene prevents myocardial fibrosis and apoptosis, further supporting the involvement of adrenergic signaling in adverse cardiac remodeling in pathological hypertrophy [33]. In HFD heart, hyperinsulinemia promotes activation of cardiac InsR to induce Akt and ERK1/2 activity. Deletion of β_2AR gene blocks Akt and ERK1/2 activity and cardiac fibrosis in HFD heart, indicating that hyperinsulinemia may promote β_2AR-dependent Akt and ERK1/2 activity through activation of the newly characterized InsR-β_2AR complex. However, genetic and pharmacological inhibition of the β_2AR does not prevent pathological cardiac hypertrophy in HFD mice; thus pathological cardiac hypertrophy in this model is not dependent on β_2AR, InsR, and Akt signaling [33]. Besides the SNS, the RAAS is activated in obese animals with IR; and an activated RAAS can also promote the development of pathological cardiac hypertrophy [69]. It is noteworthy that the detrimental role of β_2AR involved in fibrosis in diabetic hearts is distinct from the traditional beneficial role of β_2AR relative to cardiac toxicity induced by the β_1AR [27, 70]. Thus, one should be cautious when designing therapeutic strategies that target the cardiac insulin-adrenergic signaling network.

Together, in TAC heart with elevated SNS activity, stimulation of β_2AR induces the InsR-dependent Akt activity to promote cardiac hypertrophy probably as an early adaptation whereas the development of IR may contribute to maladaptive response. In contrast, in HFD heart with hyperinsulinemia, insulin-induced β_2AR-dependent ERK and Akt signaling does not contribute to cardiac hypertrophy; instead, the insulin-induced activation of InsR-β_2AR signaling may promote fibrosis in HFD heart. Further dissection of signaling processes of the InsR-β_2AR complex induced by SNS activity or hyperinsulinemia will help us to understand distinct consequences in myocardium in pathological conditions in different animal models.

Chronic βAR Stimulation and IR Promotes Oxidative Stress

Oxidative stress represents another common insult to promote cardiac remodeling in HF (Table 2). Stimulation of adrenergic signaling promotes mitochondria fission via increased PKA phosphorylation of Drp1, a key enzyme involved in mitofusion [71]. The fragmented mitochondria usually lead to less effective respiratory chain reaction [72]. Thus, acute β-adrenergic stimulation increases the production of ROS[35]; and transgenic activation of βAR leads to an elevation of NADPH oxidase activity with greater ROS production [73]. Meanwhile, cardiac glycogen utility involves a complex interplay between multiple signaling pathways including insulin-dependent glycogen synthesis [74], βAR-dependent glycogen breakdown [75], and AMPK [76]. In HF, chronic activation of the SNS promotes cardiac IR, which leads to metabolic switch from glucose to fatty acids due to reduced usage

of glucose in myocardium [8]. Increased burning of fatty acids increases production of ROS in mitochondria, contributing to damage of myocytes (Table 2).

On the other side, insulin signaling is essential to maintain mitochondria integrity via regulating mitophagy, a process that clears dysfunctional mitochondria. In cardiac muscle, activation of PI3K increases myocardial fatty acid oxidation capacity, whereas impaired PI3K signaling leads to cardiac mitochondrial dysfunction and prevents mitochondrial adaptations in response to physiological hypertrophic stimuli [77]. IR can potentially lead to accumulation of dysfunctional mitochondria and further exacerbate production and accumulation of ROS in myocytes [77]. Therefore, the subjects with metabolic syndrome that is associated with prolonged metabolic stress and SNS activity are prone to develop cardiovascular diseases due in part to increased ROS production [78]. Consequently, an increasing insulin sensitivity by Sirt1 is able to counteract oxidative stress [79]. Blocking βAR by nebivolol in IR transgenic rats significantly promotes Akt activation and endothelial NO synthase (eNOS), resulting in reduction of oxidant stress [80].

Insulin and βAR Signaling in Ischemia and Reperfusion

In myocardial I/R, the elevated SNS activity drives β_1AR signaling that plays a detrimental role in cardiac injury (Table 2) [81]. β-blockers have favorable effects on the outcome of ischemic heart diseases [82, 83]. However, the cardiac β_2AR-G_i-Akt signaling is traditionally considered beneficial to myocardium relative to cardiac toxicity induced by β_1AR signaling [27]. β_2AR agonist promotes Akt activity to protect against myocyte apoptosis induced by oxidative stress or overactivated β_1AR signaling in I/R [84–86]. Meanwhile, stimulation of β_2AR with formoterol also activates eNOS and augments NO bioavailability, which attenuates myocardial cell death after I/R [87].

It’s well known that insulin possesses cardioprotective effects in I/R injury (Table 2) [88–90]. In an isolated rat heart, insulin attenuates isoproterenol-induced cardiac dysfunction and cell injury in I/R [90]. Recent studies show that insulin promotes βAR phosphorylation and attenuates catecholamine-sensitive adenylyl cyclases [6, 34]. Thus, the cardioprotective effects of insulin in I/R might be due in part to the insulin-induced G_i-biased β_2AR signaling, which counters cardiac toxicity induced by β_1AR. In agreement, administration of glucose insulin potassium (GIK) in acute ischemia improves hemodynamic performance and reduces mortality. These effects are also associated with suppression of myocardial fatty acid oxidation, greater glucose consumption, increased SERCA2a and phospholamban mRNA expression [91, 92]. In contrary, long-term βAR stimulation inhibits insulin-induced phosphorylation of ERK1/2 and JNK [2], which are required for insulin to exert its protective effect against the hypoxia-induced activation of pro-apoptotic caspase-3 [2]. Together, these data suggests that the correlation between cardiac sympathetic function and insulin sensitivity contributes to IR and subsequently outcomes in failing ischemic human hearts, supporting the use of insulin and/or a combination of selective β_1AR-blocker and β_2AR agonist in treatment of acute I/R injury.

Concluding Remarks and future perspectives

Both insulin and β_2AR signaling may play either detrimental or protective roles depending on the pathological settings in heart. The elevated SNS activity resulting in enhanced stimulation of βARs is a typical feature of HF. Altered myocardial insulin signaling has also emerged as a potential pathophysiological mechanism that contributes to dysregulation of cardiac metabolism and the development of HF. Modification of cardiac metabolism is a fascinating field of investigation for the development of new treatments of myocardial dysfunction. The recent observation of direct interaction between InsR and βAR provides new insight into InsR-and β_2AR-mediated signaling induced by DM-associated hyperinsulinemia and/or the elevated SNS activity. Thus, focusing on the interactions between insulin and adrenergic signaling systems might help in the understanding of the relationship between IR and the SNS activity in type 2 diabetes-associated HF. For example, what roles do the insulin-adrenergic signaling network play in cardiac hypertrophy, fibrosis, and metabolism in HF? It is effective to target insulin receptor or β_2AR in comorbidity of heart diseases and metabolic disorders? Moreover, GRK2 acts as a central node that links both insulin and adrenergic regulation; can we target GRK2 as an effective treatment of heart diseases associated with metabolic disorders such as type 2 DM?

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BOX 1

Insulin Signaling in the Heart

Insulin is a pleiotropic hormone with various effects on glucose metabolism, the central nervous system, immune system, and cardiovascular system. InsR are highly abundant in the heart [93]. Activated InsR recruits and phosphorylates insulin receptor substrate (IRS) proteins, which in turn activate a complex signal transduction network, including phosphatidyl-inositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways such as extracellular-regulated kinase 1/2 (ERK1/2). Akt regulates the translocation of vesicles containing glucose transporter 4 (GLUT4), which enhances glucose uptake, whereas mTOR activation promotes lipogenesis and protein synthesis[93]. In addition, short-term insulin stimulation also activates pro-survival Akt to inhibit apoptotic signaling, and to inhibit autophagy by activating other intracellular signaling intermediates such as mTOR, S6 kinase (S6K), forkhead transcription factors 1/3(FOXO1/3), glycogen synthase kinase 3β (GSK3β) and nitric oxide synthase 2 (NOS2). The MAPK-ERK1/2-dependent branch of insulin signaling pathway increases the expression of genes that modulate biological processes such as differentiation and proliferation [93].

BOX 2

β-Adrenergic Receptor Signaling in the Heart

Sympathetic activation increases cardiac output through the release of catecholamines. The effects of catecholamines on myocardium are primarily mediated by βAR activation. There are three subtypes of βARs: β_1AR, β_2AR, and β_3AR. In the heart, nonselective βAR stimulation activates the G_s-AC-cAMP cascade, leading to PKA-dependent phosphorylation of a set of regulatory proteins involved in cardiac excitation-contraction coupling and energy metabolism, and resulting in greater contractility. However, activation of β_2AR can also promote a coupling switch from G_s to G_i pathway [27]. The coupling of β_2AR to G_i is under the influence of GRK-and PKA-and/or PKC-mediated phosphorylation [85]. The β_2AR-G_i signaling pathway plays a crucial role in the regulation of cell proliferation and protection against cardiomyocyte apoptosis via transactivation of a PI3K-Akt signaling pathway. The β_2AR-G_i signaling pathway also attenuates the βAR-G_s-mediated inotropic response via inhibition of AC activity [86]. Meanwhile, adrenergic signaling also activates PKA and Akt to promote glucose uptake in heart[10, 11]. The shared cellular functions suggest insulin signaling and adrenergic signaling can potentially converge together in the heart.

Trends

1. Insulin plays bidirectional roles in cardiac metabolism and contractile function depending on pathophysiological states.
2. Chronic hyperinsulinemia impairs cardiac contractile function by inducing a G_i-biased β_2AR signaling and upregulation of phosphodiesterase 4D (PDE4D) expression in heart.
3. Inhibition of β_2AR is effective in rescuing cardiac dysfunction but not in preventing cardiac hypertrophy in diabetic mice.
4. GRK2acts as a node, linking insulin and βAR signaling in cardiac metabolism and cardiac contractile function, thus serving as a potential target for treatment of diabetes-related HF.
5. Early intervention by targeting the insulin-adrenergic signaling network may be effective in preventing cardiac complications in diabetes.

Outstanding Questions

1. What roles do the insulin-adrenergic signaling network play in cardiac hypertrophy, fibrosis, and metabolism in HF?
2. What roles do βAR agonists and β-blockers have in cardiac insulin sensitivity in diabetes?
3. Is insulin treatment detrimental in HF with type 2 diabetes?
4. Will non-selective βAR antagonists be more effective than selective β_1AR antagonists in treatment of HF with diabetes?
5. Can inhibition of GRK2 be an effective therapeutic strategy in controlling diabetic cardiac dysfunction?

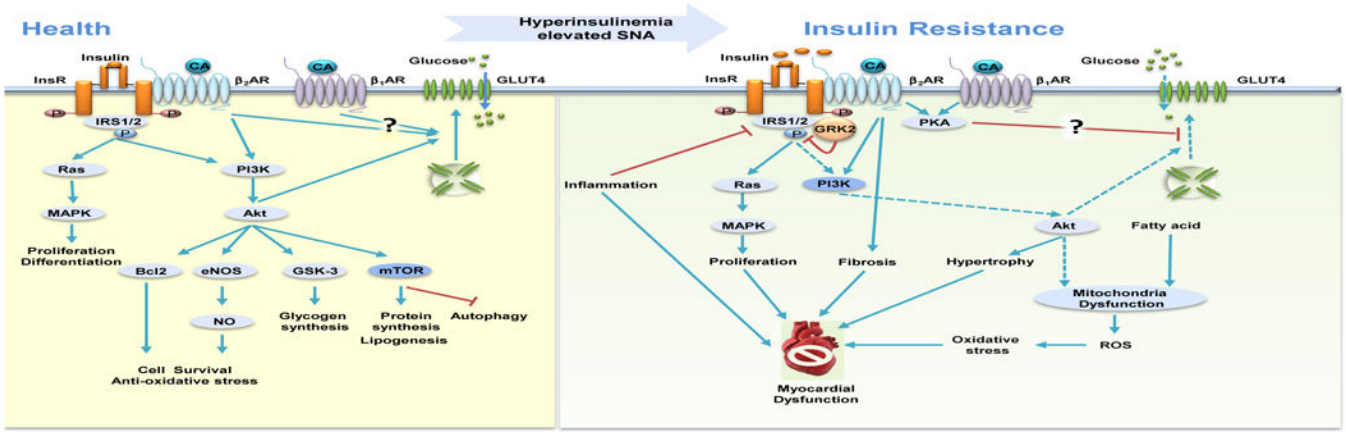

Figure 1. Insulin signaling and insulin resistance in heart

Insulin stimulates metabolic, mitogenic, and anti-apoptotic pathways via activation of insulin receptor (InsR)-insulin receptor substrates 1 and 2 (IRS1/2) cascades. In heart failure, insulin resistance leads to impaired Akt activation and/or transportation of GLUT4 to the plasma membrane for glucose uptake. Abbreviations: βAR, β adrenergic receptor; Bcl-2, B-cell lymphoma 2; CA, catecholamine; eNOS, endothelial nitric oxidase; ERK1/2, extracellular-regulated kinase 1/2; G_i, inhibitory regulative G-protein; GLUT4, glucose transporter 4; GRK2, G protein receptor kinase 2; G_s, stimulatory G protein; GSK, glycogen synthase kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NO, nitric oxide; PI3K, phosphatidyl-inositol 3-kinase; PKA, protein kinase A; Ras, rat sarcoma; ROS, reactive oxygen species; SNA, sympathetic nervous activity. The blue lines indicate stimulatory actions, the blue dash lines indicate impaired stimulation; the red lines indicate inhibitory actions.

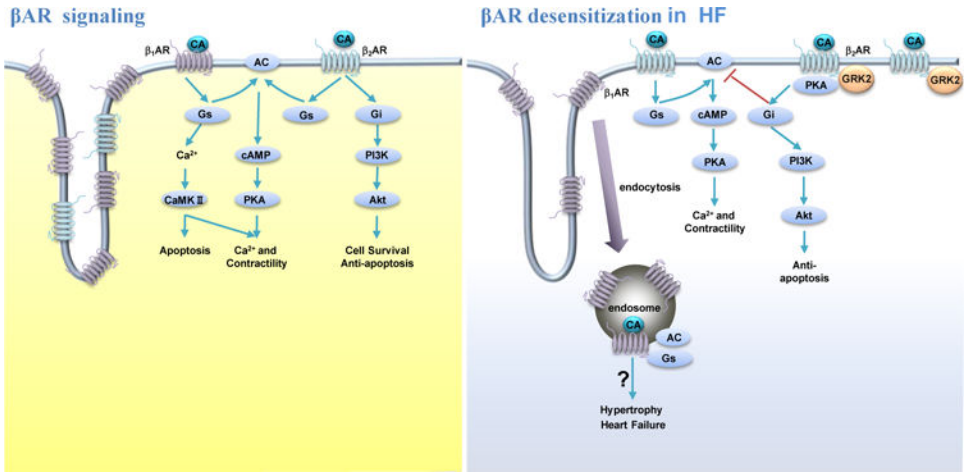

Figure 2. βAR signaling and βAR desensitization in heart failure

Activation of βARs by catecholamines induces production of cAMP through the G_S-AC cascade, which promotes PKA activity for cellular responses in cardiomyocytes. In heart failure, β_1AK undergoes endocytosis whereas β_2AK is relocated from t-tubular to crest membrane. The enhanced β_2AR-G_i coupling attenuates βAR-induced cAMP signal in cardiomyocytes. Abbreviations: AC, adenylyl cyclase; βAR, β adrenergic receptor; CA, catecholamine; CaMKII, calmodulin-dependent kinase; cAMP, cyclic monophosphate adenosine; G_i, inhibitory regulative G-protein; GRK2, G protein receptor kinase 2; G_s, stimulatory G protein; PI3K, phosphatidyl-inositol 3-kinase; PKA, protein kinase A; GRK2, G protein receptor kinase 2.

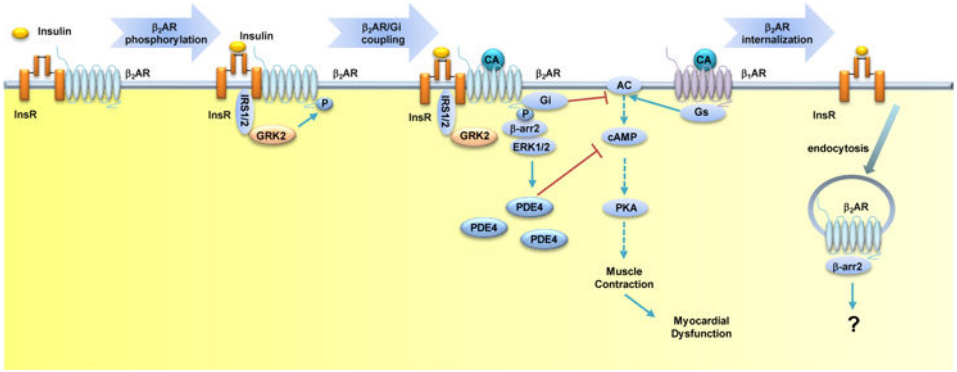

Figure 3. Insulin induces βAR desensitization in heart

InsR and β_2AR form a complex in the heart. Insulin stimulates recruitment of GRK2 to InsR in an IRS-dependent manner, which promotes β_2AR phosphorylation. The phosphorylated β_2AR couples to G_i and induces expression of PDE4D, both of which attenuates βAR signaling in cardiomyocytes. In addition, the phosphorylated β_2AR also undergoes internalization. Together, hyperinsulinemia contributes to cardiac dysfunction via desensitization of βAR signaling. Abbreviations: AC, G_s-adenylyl cyclase; βAR, β adrenergic receptor; β-arr2, β-arrestin2; CA, catecholamine; cAMP, cyclic monophosphate adenosine; ERK1/2, extracellular-regulated kinase 1/2; G_i, inhibitory regulative G-protein; GRK2, G protein receptor kinase 2; G_s, stimulatory G protein; InsR, insulin receptor; IRS1/2, insulin receptor substrates 1 and 2; PKA, protein kinase A; PDE4D, phosphodiesterase 4D.

Table 1

βAR and Insulin regulate cardiac metabolic, structure, and function in HF

	Glucose Uptake and IR	Cardiac Contractility	Cardiac Hypertrophy	Cardiac Fibrosis
βAR (acute)	Insulin-induced glucose uptake ↑ (PKA/Ca^{2+}-dependent Akt308 phosphorylation↓ 2)	↑ (cAMP/PKA↑)		
ßAR (chronic)	IR↑ (PKA/Ca^{2+} and PI3K-dependent Akt phosphorylation↑ 10, 11, 16, 17)	↓ (βAR endocytosis, 44–47)	↑ (Akt/GSK-3β signaling↑, $G_{\beta\gamma}$/ERK↑, fibroblast-derived IGF-1↑ 58, 61–63)	
GRK2	IR↑ (IRS-1 phosphorylation↑ 4, 51, 52)	↓ (βAR endocytosis, 44–47)		
Insulin	IR↑ (persistent PI3K-Akt↑, GLUT4 function↓ 12, 13, 14)	↓ (β_2AR phosphorylation mediated Gi-biased β_2-adrenergic signaling↑, β_2AR-dependent PDE4 expression↑ 6, 32–34)	↑ (Akt phosphorylation↑, PPARγ-PI3K/Akt-NO signaling pathway↑ β_2AR and Akt independent? 33, 53, 55, 57)	↑ (β_2AR dependent? 33)

Table 2

βAR and insulin regulate cardiac oxidative stress in I/R.

	Oxidative Stress	**Cardioprotective Effect in I/R**
βAR	↑ (mitochondria fission↑, NADPH oxidase activity↑, ROS↑ 35, 69, 71)	↓ β_1AR detrimental (cAMP and PKA, metabolism disorder 79); ↑ β_2AR protective (Akt phosphorylation↑, apoptosis↓, β_1AR signaling↓, eNOS↑ 82–85)
βAR blocker	↓(Akt and eNOS↑ 78)	↑ (Akt phosphorylation↑, miR-199a-3p and miR-214 ↑ 80)
insulin	↓ (mitochondria integrity↑, fatty acid oxidation capacity↑, ROS↓ 75)	↑ (fatty acid oxidation↓, glucose consumption↑, oxidative stress↓, Gi-biased β_2AR signaling? 86–90)