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REVIEW

Pathological cardiac hypertrophy: the synergy of adenylyl cyclases inhibition in cardiac and immune cells during chronic catecholamine stress

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Abstract

Response to stressors in our environment and daily lives is an adaptation conserved through evolution as it is beneficial in enhancing the survival and continuity of humans. Although stressors have evolved, the drastic physiological response they elicit still remains unchanged. The chronic secretion and circulation of catecholamines to produce physical responses when they are not required may result in pathological consequences which affect cardiac function drastically. This review seeks to point out the probable implication of chronic stress in inducing an inflammation disorder in the heart. We discussed the likely synergy of a G protein-independent stimuli signaling via β_2-adrenergic receptors in both cardiomyocytes and immune cells during chronic catecholamine stress. To explain this synergy, we hypothesized the possibility of adenylyl cyclases having a regulatory effect on G protein-coupled receptor kinases. This was based on the negative correlations they exhibit during normal cardiac function and heart failures. As such, the downregulation of adenylyl cyclases in cardiomyocytes and immune cells during chronic catecholamine stress enhances the expressions of G protein-coupled receptor kinases. In addition, we explain the maladaptive roles played by G protein-coupled receptor kinase and extracellular signal-regulated kinase in the synergistic cascade that pathologically remodels the heart. Finally, we highlighted the therapeutic potentials of an adenylyl cyclases stimulator to attenuate pathological cardiac hypertrophy (PCH) and improve cardiac function in patients developing cardiac disorders due to chronic catecholamine stress.

Keywords Chronic stress · Catecholamines · β-Adrenergic receptors · Adenylyl cyclase · G protein-coupled receptor kinase · Inflammation · Pathological cardiac hypertrophy

Introduction

Human's response to stress is an adaptation mechanism that has been conserved throughout evolution. Unlike in the modern day, the stressors encountered in the past were often imminent life-threatening dangers, for examples, predators and natural disasters. These stressors elicited physiological responses in the cardiovascular and respiratory system to enable freeze, fight, or flight. These responses enhanced man's survival from such dangers and increased their chances for procreation to ensure continuity [1]. The risk of injury and subsequent exposure to pathogens during fighting or fleeing suggests immune responses are as well stimulated by catecholamines for timely defense and healing. Today, the same stressors are still experienced; however, they are often foreseen and have measures put in place to mitigate their effect.

Regardless, the complexity of our modern-day lives, its demands and problems such as mortgage loans, examinations, work, and a dysfunctional family, among others, create psychosocial stressors which stimulate the same physiological responses even when the presumed threat (e.g., an academic examination) does not require a drastic physical response as before.

Stress can have a great toll on an individual's health [2]. Depending on its characteristics and duration, it can be categorized as acute stress, episodic acute stress, and chronic

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stress [3]. The continuous secretion and circulation of catecholamines to produce physical responses when they are not required may result in pathological consequences such as psychiatric illness [4], cancer metastasis [5], takotsubo cardiomyopathy [6], as well as, compromise the immune system [7, 8].

This review from an immunological and cardiovascular perspective seeks to point out a probable implication of chronic stress in inducing an inflammation disorder in the heart. We initially summarized the known signaling of the β-adrenergic receptors (βARs) in normal state and under chronic catecholamine stress. And also, we provided an overview of the diverse roles played by adenylyl cyclases (ACs) and G protein-coupled receptor kinases (GRKs) in cardiac function and hypertrophy, and in the immune system. The aforementioned discussions were then reconciled to explain the possibility of an unusual synergy of stimuli signaling between cardiomyocytes and some immune cells, which is mediated by the β_2-adrenergic receptors (β_2ARs) during chronic catecholamine stress. This led to the hypothesis that GRKs are possibly regulated by ACs in the myocytes and the cellular components of the immune system. As such, the downregulation of ACs during chronic stress enables the GRKs to engage in the maladaptive activation of extracellular signal-regulated kinase (ERK) 1/2. ERK1/2 in turn maladaptively activates transcription factors for cardiac hypertrophy and inflammatory response; a synergy that pathologically remodels the heart. Furthermore, an attempt is made to address the controversies regarding the functions of the ACs 5 and 6 during stress. Finally, the therapeutic potentials of an ACs stimulator for attenuating chronic stress-induced pathological remodeling of the heart were highlighted as a prospect drug.

Catecholamines and adrenergic receptors

Adrenergic receptors (ARs) currently have two subtypes, alpha (α) and beta (β), with various subunits (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, and β_3) [9–13]. These subunits are structurally very similar and belong to G protein-coupled receptors (GPCRs). They are distinctively expressed in various organs, serving as the binding sites for catecholamines: dopamine, norepinephrine, and epinephrine secreted in the adrenal medulla to modulate specific physiological responses. In cardiomyocytes and some components of innate and adaptive immunity (macrophages, neutrophils, and lymphocytes), βARs are known to be well expressed. This facilitates their interaction with circulating catecholamines to fine-tune contraction of the myocardium depending on the momentary demands of the body, as well as, the regulation of responses of the immune cells [14–16]. β_1AR expressions in the heart are like four times more in comparison to the expression of β_2AR in a healthy human heart [17, 18]. A controversy regarding the expression of β_2AR in the heart was stirred up when Myagmar et al. reported β_2AR are rarely present in myocytes but are abundant in non-myocytes [19]. This is contradictory to most of the finding in research works from the past decades to date [6, 20–24]. Nonetheless, this could have been due to the fact that β_2ARs are densely expressed in apical ventricular cardiomyocytes as compared to basal cardiomyocytes of the same heart [6, 25], and therefore, if cardiomyocytes are isolated from any other part of the ventricle besides the apex to assess β_2AR expression in the heart, the receptor may be found rarely expressed as reported. β_3AR is primarily expressed in adipose tissues where it plays vital roles in energy metabolism [26, 27]. The differential expression of βAR in innate and adaptive immunity has been reviewed elsewhere [28, 29].

With regard to their affinities to catecholamines, the β_3AR has the least compared to β_1AR and β_2AR. Norepinephrine has 20-fold higher affinity for the β_1AR compared to the β_2AR, likely because of the expression of β_1AR outnumbers β_2AR in the heart. Notably, β_1AR directs stimuli signals only via stimulatory G protein ($G_{\alpha s}$) upon being stimulated by norepinephrine [30, 31]. In contrast, epinephrine has higher affinity for the β_2AR than the β_1AR, despite β_2AR being outnumbered [6]. And also, the pleiotropic nature of β_2AR enables it to direct stimuli signals to Gαs at normal physiological state just as β_1AR does, and to inhibitory G protein ($G_{\alpha i}$) during stress [6, 32, 33]. It is a well-known fact that the phenomenon of inducing β_2AR to traffic stimuli via $G_{\alpha i}$ is epinephrine specific. This may explain the differences in epinephrine's affinities for β_1AR and β_2AR [30, 31].

Catecholamines—βARs downstream stimuli signaling cascade

Stressors invoke an influx in circulating catecholamines which stimulate βARs and triggers diverse intracellular pathways [18]. In a normal state, the stimulation of β_1AR and β_2AR activates AC by coupling to Gαs. AC in turn converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) which facilitates signaling via protein kinase A (PKA). PKA regulates the L-type Ca^{2+} channel (LTCC) through phosphorylation to ensure the rhythmic contraction of myocardium [34]. Besides activating PKA, cAMP is also responsible for activating the exchange protein directly activated by cAMP (Epac). Epac regulates several pivotal processes and is implicated in enhancing cardiac contraction and hypertrophy [35, 36]. Similar to myocytes, the cAMP–PKA/Epac signaling pathway is classically used in the immune system to help maintain homeostasis in immune responses in order to avoid exacerbation of disease conditions and aid timely recovery [37–39]. However, systemic elevation of epinephrine distorts these signaling cascades by stimulating the β_2AR to switch coupling from $G_{\alpha s}$ to $G_{\alpha i}$ upon phosphorylation of the receptor by PKA in negative feedback. This results in the downregulation of ACs and elevation of GRKs

expressions. Upon being upregulated, the GRK2 translocates to the cell membrane to phosphorylate β_1AR to initiate homologous desensitization process by recruiting β-arrestins-1 [40–43]. Phosphorylation by PKA can independently desensitize βARs without recruiting β-arrestin-1 [40, 44–46]; however, it occurs slowly and it is not as significant as GRK2–*β*-arrestin-1 mediated uncoupling [47, 48]. The β_1AR becomes irresponsive to stimuli, and it is downregulated by lysosomal degradation or recycled back into the cell membrane through dephosphorylation (Fig. 1) [49–51]. Intriguingly, the GRKs which are modulators of the desensitization of the βARs in cardiomyocytes and immune cells have also been found to actively facilitate inflammatory and immune responses in rheumatoid arthritis [37]. Also, there is evidence of immune response-enhancing rapid desensitization of βARs, where, IL-1 is found activating $G_{\alpha i}$ [52], and enabling intracellular elevation of GRK2 [53]. The suppression of the AC7 in macrophages, monocytes, dendritic cells, and B cells may be the probable underlying factor encouraging these.

Besides the fact that epinephrine has more affinity for the β_2AR, the β_1AR and its mRNA are mostly downregulated during high catecholamine stress [54]. These may explain why the β_2ARs are mostly found mediating stimuli signaling during chronic stress-induced pathological conditions of the heart.

β_2AR overstimulation in cardiomyocytes

By mechanotransduction, the hearts of pregnant women and athletes adjust and adapt to cardiac pressure overload. To be able to do this, their cardiomyocytes undergo pressure overload-induced cardiac hypertrophy which is mediated by Akt/Protein kinase B (PKB) [55]. This is categorized as a physiological cardiac hypertrophy, as the increase in cardiac size is accompanied by normal cardiac morphology with a sustained or an enhanced cardiac function [56]. Depending on the nature of the stimuli, its intensity, and the duration of the overloading stimuli, the enlargement in the myocardium can be sustained, reversible, or detrimental [57]. During hypertensive stress, high concentrations of catecholamine overstimulate the β_2AR and induce the receptor to switch coupling to $G_{\alpha i}$. $G_{\alpha i}$ signals via mitogen-activated protein kinase (MAPK) to transcription factors in an attempt to prevent cardiac insult [6, 58]. However, if the stress remains chronic, the hyperstimulation of the β_2AR causes maladaptive myocyte hypertrophy and consequently, cardiac injury and dysfunction—creating a pathological condition [59, 60].

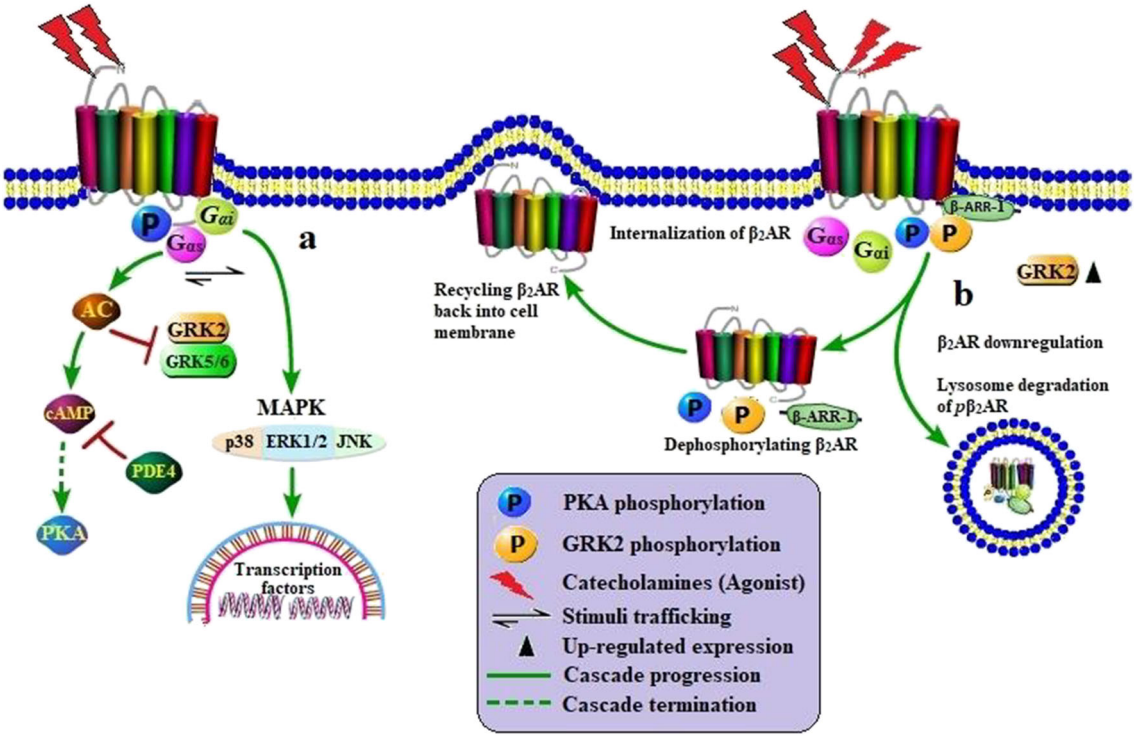

Fig. 1 Schematic illustration of βARs desensitization in cardiomyocytes and immune cells. (a) AC imposing inhibitory effects on GRKs, while together with PDE4, regulates cAMP concentration in cytosol. During acute influx of catecholamines, β_2AR signaling via $G_{\alpha i}$ more than $G_{\alpha s}$ upon being phosphorylated by PKA. AC is uncoupled from $G_{\alpha s}$ and stimuli is trafficked via $G_{\alpha i}$–MAPK to temporarily reduce cardiac contractility for protection against cardiac insult. p38, JNK, and ERK1/2 are types of MAPK and are involved in the activation of transcription factor distinctively. (b) Homologous and heterologous desensitization of βARs are induced by GRK2–β-arrestin-1 and PKA phosphorylation respectively, due to overstimulation of the receptor. At this point, mostly β_1ARs becomes dysfunctional and irresponsive to stimuli from SNS, and are either recycled back into membrane or degraded by lysosome

This is associated with a marked cardiomyocyte necrosis, fibrotic remodeling of the myocardium and arrhythmias which progresses to heart failure [61]. To attenuate this, βAR blockers (β-blocker) have been employed over the years as first-line therapy to mitigate overstimulation of the receptors and help improve cardiac function in failing hearts [62, 63]. Nevertheless, there are still concerns regarding its effectiveness in reducing mortality in high blood pressure patients as compared to calcium-channel blockers [64].

β_2AR overstimulation in immune cells

In the last decades, researches conducted to elucidate the underlying cause of heart failures have implicated the maladaptive involvement of the immune system in the exacerbation of cardiac dysfunction. The profound expression of β_2AR in macrophage, T, and B lymphocytes facilitates crosstalk with the sympathetic nervous system [65–67]. Signaling via β_2AR-$G_{\alpha s}$ increases intracellular cAMP and suppresses the immune response by inhibiting secretion of the proinflammatory cytokines, interleukin (IL)-1β, IL-2, IL-6, tumor necrosis factor alpha (TNFα), and interferon gamma (IFN-γ) and in contrast, enhances secretion of anti-inflammatory cytokine IL-10 [68, 69]. Regardless, during chronic hyperstimulation of β_2AR, this phenomenon is reversed as β_2AR traffics stimuli via $G_{\alpha i}$ which inhibits ACs from synthesizing cAMP [70]. This abolishes the inhibitory effect cAMP poses on immune response and permits the production of proinflammatory cytokine IL-1β and TNFα among others. A sustained upregulation of IL-1β and TNFα together activate nuclear factor NF-kB pathway, a prototypical inflammatory pathway [71]. As such, prolonged excitation of β_2AR in immune cells results in a homeostatic breach and exacerbates any inflammation, obstructing timely reparative and healing activities of the immune components [72–74].

Roles of ACs and cAMP in cardiomyocytes and cellular components of the immune system

ACs play an irreplaceable role in converting ATP to cAMP, an essential second messenger that facilitates the progression of stimuli signaling at the post-receptor level. In mammals, there are ten isoforms of ACs named sequentially, AC1–AC10. Beside the AC10 which is soluble, cytosolic, and activated by bicarbonate and calcium ions [75, 76], the ACs 1–9 isoforms are transmembrane and are activated in normal physiological states via βARs–$G_{\alpha s}$ coupling.

Sadana and Dessauer reviewed ACs 1–9 extensively, discussing their classification and biochemistry and their distinctive distributions in mammalian tissues and organs as well as their respective functions [77]. The myocardium has the isoforms AC5 and AC6 dominating, mainly to regulate heart rate and cardiac contractility [78, 79]. AC5 and AC6 are differentially expressed with respect to aging, cardiac pressure overload, and subcellular localization [80–82].

AC5 and AC6 play unsettled roles in regulating cardiac function and are still being researched on; nonetheless, their commonly known function is to synthesize sufficient cAMP needed to stimulate chronotropic and inotropic responses in the myocardium. The distinct roles of the AC5 and the AC6 in the response to cardiac stress remain controversial. There are research reports that have suggested that the AC5 knockout (AC5 KO) mice are resistant to chronic stress [83–85], while the deletion of AC6 does increase mortality in prolonged catecholamine stress [86]. The major role played by AC6 in calcium channel modulation [87] may explain why its deletion has such detrimental effects. However, not all studies support the beneficial effects of AC5 KO. This was demonstrated by Esposito et al. when they reported that cardiac function is improved during exercise upon overexpression of AC5 in the hearts of transgenic mice [88]. Regardless, the adverse effect of AC5 overexpression in the heart is observed during chronic βARs stimulation. In the normal state, hearts which have the AC5 overexpressed are found to have a key pro-hypertrophic pathway, i.e. nuclear factor of activated T-cells (NFATs) highly expressed [89]. This was not observed in the hearts with overexpression of the AC6 [90]. Thus, hearts with the overexpression of AC5 seem to be predisposed to cardiac hypertrophy. Despite the differences in the roles played by the AC5 and the AC6 in the heart, they both improve cardiac function in the failing heart when their expressions are restored in myocytes that had their ACs levels downregulated previously [91].

In immune cells, the isoform AC7 is responsible for synthesizing and regulating cAMP concentration. From an immunological perspective, researchers have reported the contradictory roles of cAMP in the immune system, such as, it being immunosuppressive in almost all cellular components of the immune system; as it specifically inhibits proliferation of T cell, the activation of B and T cells, the chemotaxis of neutrophils and the production of proinflammatory cytokines by macrophages and T cells [92–95]. Yet though, others have proven the essential role of cAMP in optimizing of the immune response [96–99]. Duan et al. demonstrated the regulatory roles of AC7 and cAMP in both the innate and adaptive immune system, where they proved that AC7 KO mice had hyperactive and detrimental inflammatory responses [100]. The paradoxical functions of cAMP in the immune system may have to do with its concentration and duration; most likely, an acute influx and signaling of cAMP being beneficial, while detrimental when it prolongs.

Phosphodiesterases (PDEs) which are activated by PKA in a negative feedback [101], complements the efforts of ACs in regulating cAMP by degrading excess cAMP. There are 11

isoforms of PDEs and they have been extensively reviewed elsewhere [102].

Regulatory role of GRKs in the cardiac and immune system

GRK isoforms (GRK1–GRK7) regulate signal mediating activities of GPCRs strictly through phosphorylating the receptor when activated. Changes in their expression and activity have been observed to play pivotal roles in cardiac hypertrophy, heart failure and immune cells specifically involved in disease conditions [103]. Phosphorylation of βARs by a specific GRK isoform is dependent on the concentration of the agonist and the duration of receptor sensitization. GRK2 phosphorylates βARs when they are overstimulated during catecholamine stress to desensitize the receptor [40]. In patients with hypertension and chronic heart failure, abnormal increases in GRK2 expression in cardiomyocytes have been reported. This is characterized by a decrease in activities of AC [41], and thus, a decrease in cardiac inotropy and function. However, an improved cardiac function is restored consequently upon a decrease in intracellular GRK2 expression. This is the main aim of β-blockers—to improve cardiac function by reducing the levels of GRK2 [104]. Interestingly, during chronic heart failure, there is a simultaneous upregulation of GRK2 expression in CD4+ T cells and B cells which are well known to be involved in disease pathogenesis [104, 105]. In this regard, alteration in cardiac proteins can be assessed by the use of peripheral lymphocytes, thus, bypassing the challenge of myocardium biopsy [106].

Besides GRK2, the isoforms GRK5/6 are implicated in cardiac function during chronic catecholamine stress. Although their functions are still being uncovered, they have been reported to be mostly playing maladaptive roles rather than being cardioprotective [107]. Unlike GRK2, GRK5/6 phosphorylation of βARs permits binding of β-arrestin-2 at the C-terminus. This uncouples $G_{\alpha i}$ and $G_{\alpha s}$ from the receptor and enables signal progression in a G protein-independent manner. By this non-canonical signaling pathway, GRK5/6 is able to activate ERK1/2 in a maladaptive manner [108], to regulate the transcription factors, cardiac hypertrophy, NF-kB, and NFATs [107, 109, 110].

The maladaptive activation of these transcription factors results in increased cardiomyocyte necrosis and elicits a hyperactive immune response which exacerbates the disease condition, leading to pathological remodeling of the heart. Indeed, GRK5 KO has been proven to be cardioprotective against pathological cardiac hypertrophy (PCH) and heart failure [111]. Other researchers have intensively reviewed the roles played by GRKs in cardiac hypertrophy elsewhere [112, 113].

Aftermath of β_1AR desensitization & down-regulation

Intracellular elevation GRK2 due to the suppression of AC affects the expression of the β_1AR right from gene level [114], by either tampering with their mRNA transcription rate, translational efficiency, or destabilizing their mRNA while desensitizing the receptors expressed in the membrane, thereby, downregulating and decreasing the total amount of βARs present in the membrane. These result in the irresponsiveness of βARs, mostly β_1AR, to further stimuli from SNS. An increase in the activities of GRK2 by three- to fourfolds have been reported in catecholamine-induced impairment of βARs at the end-point of cardiovascular diseases in humans and animal models [115–117]. Contrarily, downregulation of GRK2 in failing and dysfunctional myocardium does improve cardiac function [118, 119]. Proinflammatory immune responses involving the secretion of TNFα, IL-1, and IL-6 are heightened and hyperactive at this point and subsequently, activates NF-kB pathway.

Conclusion and perspectives

Cardiac hypertrophy is meant to be a physiological adaptation, adjusting the heart's function to suit pressure overload mostly experienced by athletes and pregnant women. However, chronic stress which is associated with the excessive firing of catecholamines by SNS leads to the overstimulation of βARs in the heart, causing them to become dysfunctional and scaffolds a signaling cascade that turns a physiologically adaptive hypertrophied heart into a pathologically remodeled maladaptive heart.

During cardiac pressure overload, GRK2–β-arrestin-1 mediates internalization and desensitization of dysfunctional βARs to halt the progression of signaling. Meanwhile, this does not seem to be the case during chronic catecholamine stress, because stimuli signaling progresses and the heart becomes maladaptively remodeled.

To elucidate the probable mechanism permitting the progression of signaling βARs, we hypothesize that ACs may have a regulatory effect on the GRKs, thereby, inhibiting their expressions and activities in cardiac and immune cells when the ACs is actively expressed. As such, downregulation of ACs eliminates this inhibitory effect and encourages βARs to be phosphorylated by GRKs. This is based on the facts that, despite the discrepancies in the cardioprotective roles ACs 5 and 6 [85, 86], they are both found to be downregulated in myocardial hypertrophy, hypertension, and heart failure [120–123]. Also, in immune cells, the deficiency of AC7 results in hyperactive immune response [100]. At these

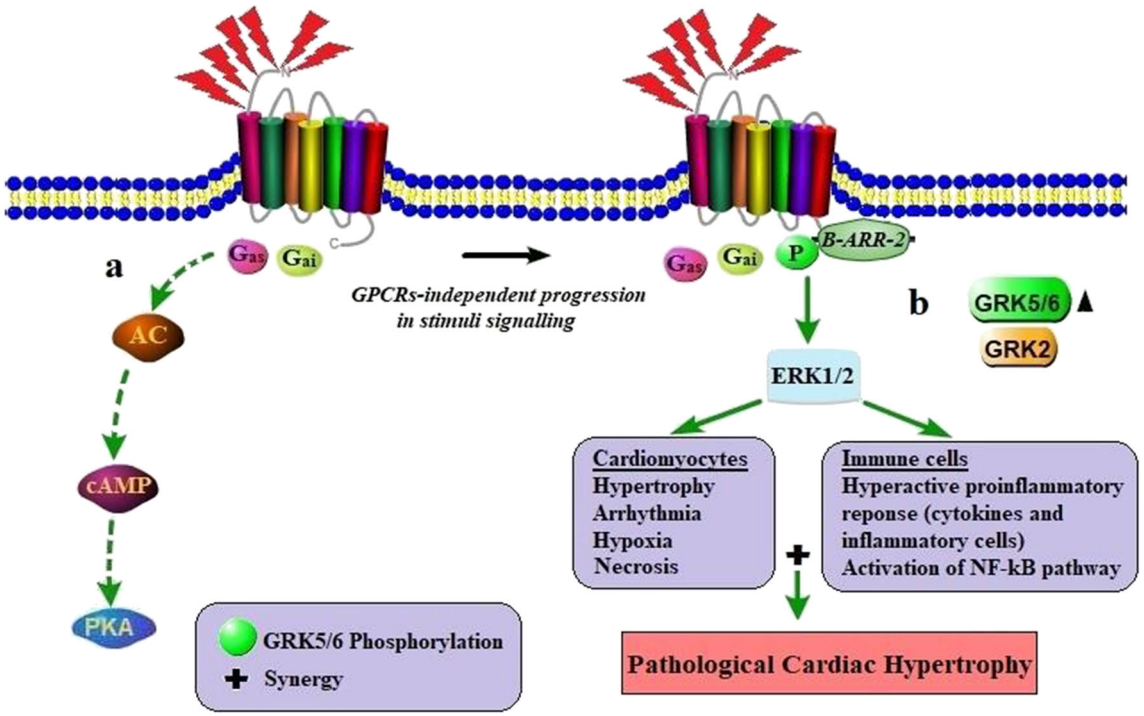

Fig. 2 Hypothetical schematic illustration of signaling cascade resulting in pathological cardiac hypertrophy. (a) GPCRs being completely uncoupled from β_2AR and a momentarily termination of signaling due to chronic catecholamine stress. AC expression in cytosol is downregulated, abolishing its inhibitory effect on GRKs. (b) GRKs upregulate and translocate to cell membrane. GRK5–β-arrestin-2 phosphorylate β_2ARs to facilitate a G-protein-independent signal progression in cardiac and immune cell and maladaptively activates ERK1/2 which induces transcription factors in the respective cells for the pathological remodeling of the heart

instances when ACs are downregulated, GRK2 is found upregulated and impeding proper cardiac function. Hence, to rescue cardiac function in these instances, β-blockers are administered to hypertensive patients to reduce GRK2 [104], and consequently increase AC to improve cardiac function.

Furthermore, prolonged inhibition of AC during chronic catecholamine stress might be enabling GRK5/6–β-arrestin-2 phosphorylation of β_2AR to facilitate G protein-independent signaling progression, [124, 125] rather than halting stimuli signals as GRK2 does. In this manner, GRK5/6 is able to activate ERK1/2, [108] not in the classical way that ensures it plays adaptive roles in the immune system and cardioprotection [126, 127]. Instead, it maladaptively invokes and persistently sustains activation of cardiac hypertrophic transcription factors, NFATs, myocyte enhancer factor 2 (MEF2), GATA4, Csx/Nkx2–5, and NF-kB pathway [128, 129]. The maladaptive activation of GATA4, MEF2, and Csx/Nkx2–5 by ERK1/2 may induce excessive myocyte hypertrophy and cause myocyte necrosis. This stimulates proinflammatory responses, IL-1β, IL-6, and TNFα. The proinflammatory cytokines IL-1β and TNFα proceed to activate NF-kB inflammatory pathway, which also gets sustained by activities of ERK1/2 [129].

In summary, the synergistic cascade due to the inhibition of ACs in cardiomyocytes and immune cells when their β_2ARs are overstimulated during chronic catecholamine stress begins with; the upregulation of the GRKs which initiates a GPCR-independent activation of ERK1/2 in a maladaptive manner. ERK1/2 then activates cardiac hypertrophy transcription factors and causes an abnormally marked myocyte hypertrophy which results in arrhythmias and hypoxia. Hypoxia and the excessive enlargement of the cardiomyocytes cause necrosis. Necrosis of the cardiomyocytes elicits immune responses in an attempt to repress the cell deaths. However, due to the downregulation of the AC7 which modulates immune responses, hyperactive immune responses are invoked without modulations. This results in the prolonged bias secretion of proinflammatory cytokines (IL-1β, IL-6, and TNFα) and finally the activation of the inflammatory pathway NF-kB which exacerbates the myocyte necrosis and pathologically remodels the heart. This is evidenced by a marked fibrosis (Fig. 2).

In conclusion, there is a negative correlation between the ACs and the GRKs in cardiomyocytes and immune cells during normal cardiac function and heart failures. ACs 5 and 6 are upregulated while GRKs are downregulated in healthy hearts, and the reverse is observed during heart failures. However, upon inhibiting GRKs with β-blockers, the upregulation of the ACs improves cardiac function. The fact that a restoration in the expression of ACs after they have been previously depleted restores cardiac function suggests ACs could be the target of a stimulator that can specifically stimulate and

activate ACs independent of βARs- $G_{\alpha s}$ coupling. This activator of ACs could help attenuate hypertrophic cardiomyopathy and improve cardiac function during heart failure. However, controversies on the roles of the ACs 5 and 6 on pressure overload hypertrophy might have hindered the novel discoveries and recommendations made on the therapeutic potentials of drugs that target ACs, from being translated into the pharmaceuticals and clinical care [54, 86, 130]. Nevertheless, it is important to note that reports on the adverse effects of ACs 5 and 6 on the heart were observed when these two isoforms were overexpressed in the heart of transgenic mice [89, 90]. In addition, with the exception of AC5 KO mice which exhibited improved cardiac function [82–84], AC6 KO mice had poor cardiac function [[86], as did AC7 KO mice which also experienced hyperactive and detrimental inflammatory responses [100]. Beside these findings, most research reports have suggested the restoration and normalization of the expressions of ACs after they have been previously depleted, have positive effects on chronotropic and inotropic of the heart, and the modulation of immune responses [91, 100, 131, 132]. Therefore, if ACs stimulators are developed and are administered in appropriate dosages as required to avoid their overexpression in myocytes and immune cells, they are likely to improve cardiac functions in individuals experiencing chronic stress while preventing the occurrence of a pathological cardiac hypertrophy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have conflicts of interest.

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