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REVIEW

Special Topic - CALCIUM SIGNALING

# β-adrenergic regulation of $Ca^{2+}$ signaling in heart cells

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**Abstract** β-adrenergic receptors (βARs) play significant roles in regulating $Ca^{2+}$ signaling in cardiac myocytes, thus holding a key function in modulating heart performance. βARs regulate the influx of extracellular $Ca^{2+}$ and the release and uptake of $Ca^{2+}$ from the sarcoplasmic reticulum (SR) by activating key components such as L-type calcium channels (LTCCs), ryanodine receptors (RyRs) and phospholamban (PLN), mediated by the phosphorylation actions by protein kinase A (PKA). In cardiac myocytes, the presence of $\beta_2$AR provides a protective mechanism against potential overstimulation of $\beta_1$AR, which may aid in the restoration of cardiac dysfunctions. Understanding the $Ca^{2+}$ regulatory signaling pathways of βARs in cardiac myocytes and the differences among various βAR subtypes are crucial in cardiology and hold great potential for developing treatments for heart diseases.

**Keywords** β-adrenergic receptor (βAR), $Ca^{2+}$ signaling, Cardiac myocytes, Compartmentalization

## INTRODUCTION

β-adrenergic receptors (βARs) belong to the G protein-coupled receptor (GPCR) superfamily, and are essential for regulating the function of the cardiovascular system. βARs are activated by catecholamines released from sympathetic nerve terminals and adrenal medulla under stress conditions, which increase heart rate and blood pumping capability of the heart (Bers 2002). The positive chronotropic, dromotropic and inotropic effects ensure the energy supply of emergent needs.

Currently, there are three identified subtypes of βARs ($\beta_1$AR, $\beta_2$AR, $\beta_3$AR), while the existence of a fourth subtype ($\beta_4$AR) is still a subject of debate (Gauthier *et al.* 1996). These three isoforms exhibit different affinities for different ligands, rendering the selectivity of isoform activation (Bristow *et al.* 1986). The ratio of $\beta_1$AR/$\beta_2$AR expression in the healthy human heart is approximately 4:1, while the expression of $\beta_3$AR is minimal. Both $\beta_1$AR and $\beta_2$AR respond to catecholamine stimulation and mediate positive inotropic effects in heart cells. $\beta_1$AR plays a dominant role in increasing chronotropy and inotropy in cardiac myocytes, whereas $\beta_2$AR produces only modest chronotropic effects (Xiang and Kobilka 2003; Xiao *et al.* 2006).

Epinephrine and norepinephrine are native catecholamine ligands of βARs (Bunemann *et al.* 1999; Hain *et al.* 1995; Nikolaev *et al.* 2006; Nikolaev *et al.* 2010). With catecholamine binding, βARs undergo conformational changes that enable its coupling to heterotrimeric G proteins, resulting in the substitution of the GDP on the $G_\alpha$ subunit of G-proteins by GTP and subsequent dissociation of $G_{\beta\gamma}$ subunits (Wess 1997). $G_\alpha$-GTP then stimulates adenylyl cyclase (AC) to catalyze the formation of cyclic AMP (cAMP). cAMP regulates a wide variety of cellular processes through activating a variety of downstream signaling molecules, including protein kinase A (PKA). PKA phosphorylates L-type $Ca^{2+}$ channels (LTCCs) in the cell membrane or T-tubules, ryanodine receptor (RyR) $Ca^{2+}$ release channels and phospholamban (PLN) in the sarcoplasmic reticulum (SR),

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and thereby up-regulates LTCC $Ca^{2+}$ influx, SR $Ca^{2+}$ release and cytosolic $Ca^{2+}$ uptake (Fig. 1).

## REGULATION OF LTCC

LTCCs are the predominant mediator of $Ca^{2+}$ influx in the cardiomyocytes playing an initiation role in the excitation-contraction coupling. In general, LTCCs are composed of $\alpha_1$, $\alpha_2$, β, δ and γ subunits. $\alpha_1$ is the pore-forming subunit with voltage sensors. $\alpha_2/\delta$ and β subunits modulate the expression, voltage dependence and gating kinetics of the channel (Bodi *et al.* 2005).

Several PKA phosphorylation sites in the $\alpha_1$ subunit have been identified (Fu *et al.* 2014; Hulme *et al.* 2006; Yang *et al.* 2016). βAR agonists, such as isoproterenol, increase the phosphorylation level of S1928 in the distal C-terminal domain (Hulme *et al.* 2006), which can be blocked by βAR antagonists. Interestingly, LTCCs with S1928 mutated to alanine still retain 70%–80% response to βAR stimulation, indicating that S1928 is not the major phosphorylation site for βAR stimulation (Benitah *et al.* 2010; Ganesan *et al.* 2006; Hulme *et al.* 2003, 2006). S1700 and T1704 located at the interface between the proximal and distal C-terminal domain are also phosphorylated in βAR regulation of LTCCs (Fu *et al.* 2013, 2014). Again, mutations of both S1700 and T1704 cannot eliminate βAR effects (Fu *et al.* 2013).

The regulatory $\beta_2$ subunit plays a crucial role in LTCCs regulation in response to βAR stimulation (Haase *et al.* 1993). S478 and S479 were identified as the phosphorylation sites of PKA in $\beta_2$ subunit (Gerhardstein *et al.* 1999). Mutating S478 and S479 to alanine in the $\beta_2$ subunit inhibits PKA-mediated $Ca^{2+}$ current increase in transfected cells (Bunemann *et al.* 1999). This result suggests that phosphorylation of S478 or S479 contributes to PKA-mediated regulation of LTCCs.

Monomeric G proteins, such as Rem and Rad, function as endogenous LTCC inhibitors (Beguin *et al.* 2001; Finlin *et al.* 2003). Recent analysis from a proximity proteomics screen provided solid evidence that Rad is enriched in the LTCC microenvironment but is depleted during β-adrenergic stimulation. Phosphorylation by PKA decreases Rad affinity for β subunits and increases LTCC open probability (Liu *et al.* 2020). Four serines in Rad have been identified as PKA phosphorylation sites, and mutation of these four serines or disrupting the interaction between LTCC β subunit and Rad reduced heart rate and basal contractility, and greatly diminished β-adrenergic contractile response (Papa *et al.* 2022, 2024).

A kinase anchoring protein 15 (AKAP15) is a lipid-anchored protein with a single amphipathic helix that binds PKA. AKAP15 colocalizes and associates with LTCC in T-tubules (Gray *et al.* 1998). PKA tethered to a

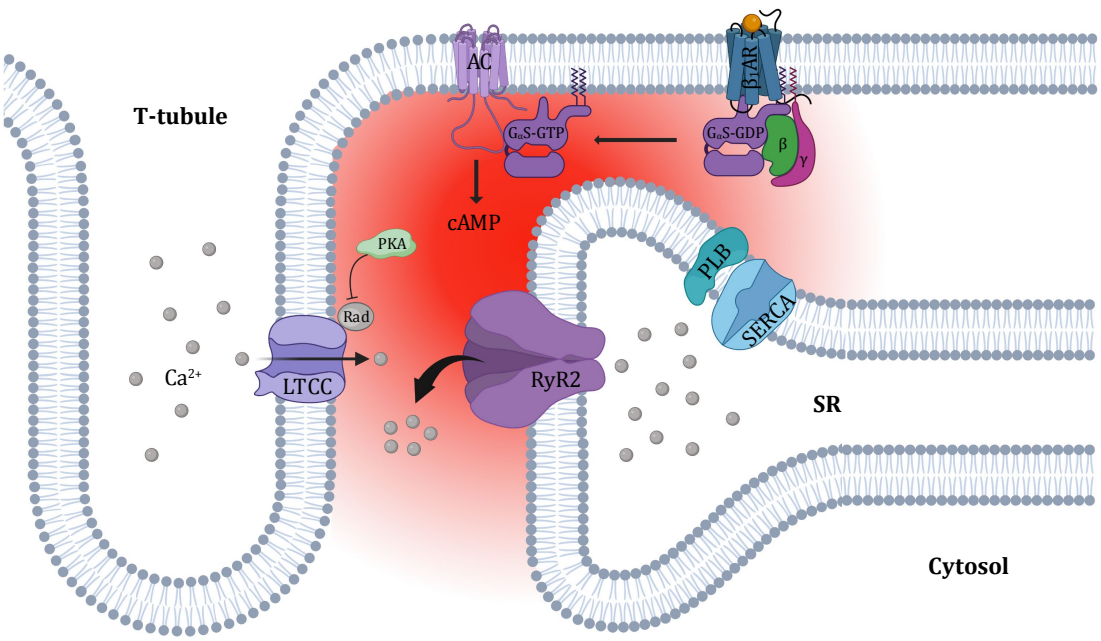


**Fig. 1** Illustration of β-adrenergic regulation of $Ca^{2+}$ signaling in heart cells

leucine zipper motif in the C-terminal domain of the LTCC $\alpha_1$ subunit via AKAP15 (Hulme *et al.* 2002), which is essential for β-adrenergic regulation of LTCC (Hulme *et al.* 2003).

LTCCs are also phosphorylated by $Ca^{2+}$/calmodulin-dependent kinase II (CaMKII). CaMKII is activated by βAR stimulation via guanine nucleotide exchange protein directly activated by cAMP (Epac) (Curran *et al.* 2007; Grimm and Brown 2010). Mutations at sites S1512 and S1570 of $\alpha_1$ subunit (Hudmon *et al.* 2005) and T498 of β2 subunit (Koval *et al.* 2010) reduce $Ca^{2+}$ influx.

Besides, cardiac phosphatase activities also play important roles in the regulation of $Ca^{2+}$ homeostasis. Phosphatase type 1 (PP1) and 2A (PP2A) are the major isotypes of cardiac phosphatases, comprising over 90% of the protein phosphatases in cardiomyocytes (Lüss *et al.* 2000). PP1 is reported to contribute to the dephosphorylation of LTCC, RyR, and PLB. Whereas, PP2A is mainly involved in the dephosphorylation of myofibrillar proteins, including troponin I and myosin-binding protein C (Metzger and Westfall 2004).

In recent years, a few proteins have been reported to modify the β-adrenergic regulation of LTCCs. Sphingosine-1-phosphate (S1P), a circulating bioactive sphingolipid, has been implicated in the regulation of several cellular processes including cardiac $Ca^{2+}$ handling (Means and Brown 2009). S1P does not affect the basal LTCC current, but partially reverses the regulation of βAR activation on LTCCs through a signaling pathway involving the interaction between P21-activated kinase 1 (Pak1) and protein phosphatase 2A (PP2A) (Egom *et al.* 2016). Ahnak functions as a suppressor of LTCCs by sequestering the $\beta_2$ subunit through a strong binding to the LTCC $\beta_2$ subunit (Hohaus *et al.* 2002). Rem GTPase interacts with LTCC $\beta_2$ subunit and inhibits LTCC currents. The inhibitor effects can be rescued by LTCC activators such as BayK8644, but not by the βAR stimulation (Xu *et al.* 2010). Besides the functional coupling regulators, there were some structural coupling factors, such as Bridging Integrator 1 (BIN1) and caveolin-3. BIN1 is essential for the localization of LTCCs to T-tubules in cardiomyocytes and affects LTCC regulation by βAR stimulation (Kumari *et al.* 2018). In heart cells, a subpopulation of LTCCs localizes in caveolae. Caveolae are specialized membrane microdomains and are supported by the structural protein caveolin-3. It is well known that $\beta_2$AR is enriched in caveolae. There is evidence showing that regulation of LTCCs by $\beta_2$AR, but not $\beta_1$AR, is eliminated when caveolae were disrupted (Balijepalli *et al.* 2006). This indicates that LTCCs are coupled to $\beta_1$AR signaling outside of caveolae.

## REGULATION OF RyRs

RyRs are major $Ca^{2+}$ release channels in the SR of striated myocytes or endoplasmic reticulum (ER) of other cells. RyRs bind to ryanodine in their open state. Early studies using radiolabeled ryanodine have shown that phosphorylation of RyR2 by PKA increased channel activity (Takasago *et al.* 1991). However, the identification of the phosphorylation site critical for βAR response has been highly controversial. It has been proposed that the phosphorylation of S2808 by PKA sensitizes the response of RyRs to cytosolic $Ca^{2+}$ change (Wehrens *et al.* 2004a). However, the mouse model harboring the S2808A mutation has normal inotropic and chronotropic responses to βAR stimulation (MacDonnell *et al.* 2008). S2808A cardiomyocytes exhibit blunted enhancement of systolic $Ca^{2+}$ transients at 3 Hz but not at lower frequencies (Benkusky *et al.* 2007). There is also evidence that the phosphorylation of S2030 by PKA enhances RyR2 responsiveness to luminal $Ca^{2+}$ (Xiao *et al.* 2005, 2007). However, data from different labs questioned Ser2030 as a physiological PKA phosphorylation site (Huke and Bers 2008; Wehrens *et al.* 2006).

Besides PKA-mediated phosphorylation, βAR-activated CaMKII specifically phosphorylates S2815 in RyRs (Kushnir *et al.* 2010; Wehrens *et al.* 2004b). Phosphorylation at S2815 increases the open probability of RyR2 by sensitizing the channel (Wehrens *et al.* 2004b). While cardiac-specific CaMKII overexpression enhances SR $Ca^{2+}$ fractional release (Maier *et al.* 2003), cardiac-specific inhibition of CaMKII reduces isoproterenol-induced responses in SR $Ca^{2+}$ release and heart rate (Wu *et al.* 2009).

In intact cells, βAR modulation of RyR function is difficult to measure, because βAR also increases LTCC $Ca^{2+}$ current and SR $Ca^{2+}$ loading. With a high-affinity $Ca^{2+}$ indicator combined with a slow $Ca^{2+}$ buffer agent EGTA to elicit $Ca^{2+}$ spikes, it is demonstrated that isoproterenol synchronizes the $Ca^{2+}$ release from RyR clusters (Song *et al.* 2001). When the SR $Ca^{2+}$ load and $Ca^{2+}$ current were controlled, isoproterenol stimulation of $\beta_1$AR accelerates SR $Ca^{2+}$ release kinetics without altering the amplitude of $Ca^{2+}$ transients (Ginsburg and Bers 2004), agreeing well with the PKA-mediated synchronization of RyR $Ca^{2+}$ release (Lakatta 2004; Wang and Wehrens 2010). However, experiments using UV photolysis to activate RyRs showed that isoproterenol enhances both the speed and the magnitude of $Ca^{2+}$ transients in cells with controlled SR $Ca^{2+}$ load (Ogrodnik and Niggli 2010). Using the loose-sealed patch clamp to trigger individual RyR $Ca^{2+}$ release units, manifested as a $Ca^{2+}$ spark, we observed that selective

 

βAR stimulation enhances the amplitude of triggered sparks in an LTCC unitary current-independent manner. The $Ca^{2+}$ release flux that underlies a $Ca^{2+}$ spark is enhanced when the SR $Ca^{2+}$ content is controlled to a comparable level. These results demonstrate unequivocally that the activation of RyRs is expedited and synchronized under βAR stimulation (Zhou *et al.* 2009).

## REGULATION OF PLN

The rapid removal of $Ca^{2+}$ from the cytoplasm is primarily facilitated by the sarco(endo)plasmic reticulum $Ca^{2+}$ ATPase SERCA2a, which pumps $Ca^{2+}$ back into the SR cavity and thus controls the amount of $Ca^{2+}$ in the SR (Zhihao *et al.* 2020). PLB is the endogenous regulatory protein of SERCA2a activity and is the only regulatory protein of SERCA2a that is directly involved in the development of heart disease, including heart failure (Shanmugam *et al.* 2011; Weber *et al.* 2021).

There are two phosphorylation sites in PLN, Ser16 and Thr17, which are phosphorylated by PKA and CaMKII respectively (Kuschel *et al.* 1999; Simmerman *et al.* 1986; Xiao *et al.* 1994). Experiments with phosphorylation of PLN at either site increase SR $Ca^{2+}$ load, and thus enhance SR $Ca^{2+}$ release and accelerate cardiomyocyte relaxation (Li *et al.* 2002). Different from that of Ser16, the phosphorylation of Thr17 by $\beta_1$AR is enhanced with increased frequency of electrical stimulation possibly because frequency-dependent accumulation of intracellular $Ca^{2+}$ facilities CaMKII activation (Hagemann *et al.* 2000).

## DIFFERENCE BETWEEN $\beta_1$AR AND $\beta_2$AR SIGNALING

The amino acid sequences of human $\beta_1$AR and $\beta_2$AR share only 71% identity in the transmembrane domains and 54% identity overall (Dixon *et al.* 1986). In the heart, $\beta_1$AR-activated cAMP signaling increases the phosphorylation of sarcolemmal LTCCs and a multitude of intracellular regulatory proteins, including RyR, PLB and myofilaments (Xiao 2001). However, $\beta_2$AR-mediated cAMP signaling specifically modulates LTCCs without affecting PLB and myofilaments in most mammalian species (Fig. 2) (Xiao and Lakatta 1993). Although in the human heart, $\beta_2$AR stimulation increases PKA-dependent phosphorylation of intracellular regulatory proteins, its effects are much smaller than that induced by $\beta_1$AR stimulation (Altschuld *et al.* 1995). Furthermore, $\beta_2$ARs are expressed preferentially in the

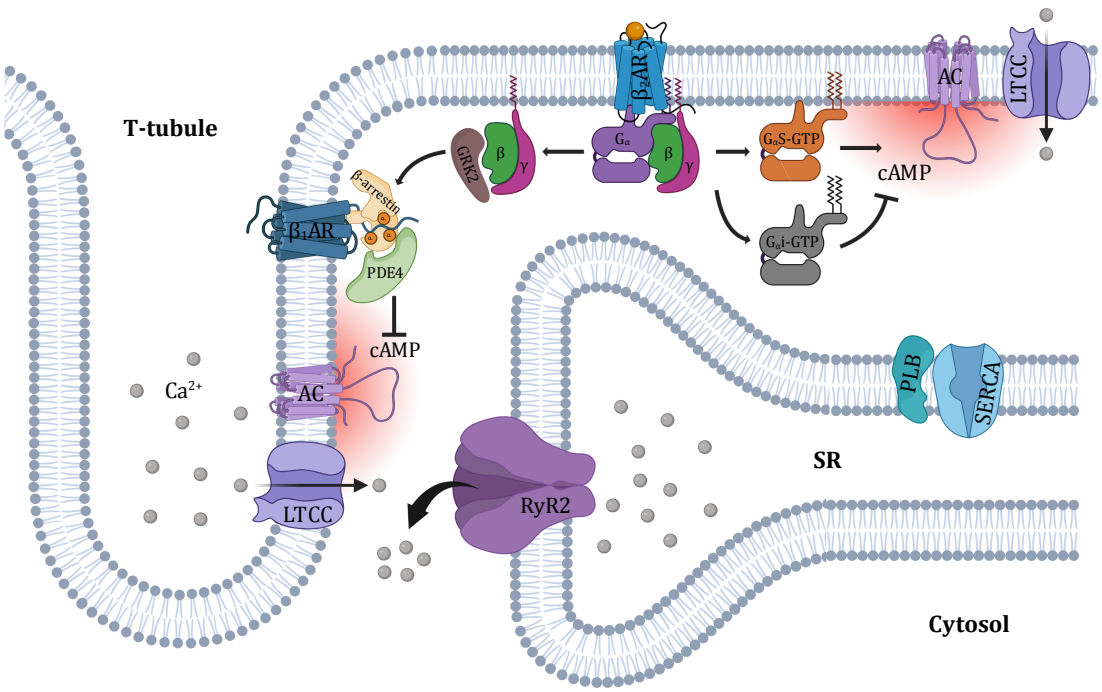


**Fig. 2** Illustration of compartmentalized $\beta_2$AR-cAMP signaling in heart cells

T-Tubule membrane, while $\beta_1$ARs are distributed in both T-tubules and surface membrane (Nikolaev *et al.* 2010).

βARs are G protein-coupled receptors. $\beta_1$AR and $\beta_2$AR both couple to $G_s$ protein, while $\beta_2$AR also couples to $G_i$ protein (Fig. 2). Selective $\beta_2$AR stimulation by zinterol does not enhance cardiomyocyte contraction in both wild-type (WT) mice and transgenic mice overexpressing human $\beta_2$AR (TG4) (Zhou *et al.* 1999). After incubating cells with pertussis toxin (PTX), which abrogates $G_i/G_o$ function via ADP ribosylation, zinterol markedly increases contraction amplitude in both WT and TG4 cardiomyocytes, which can be completely abolished by the specific $\beta_2$AR antagonist (Xiao *et al.* 1999). In cell-attached patch clamp experiment, $\beta_2$AR agonist in bath solution outside the patch pipette cannot cause a discernible change in LTCC activity in the patch membrane, while local $\beta_2$AR agonist in the pipette markedly increases the open probability of the patched channel. This sophisticated experiment indicates that $\beta_2$AR signaling is confined in a highly localized microdomain. After PTX treatment, the channels in the patch membrane became responsive to agonist in the bath solution, suggesting that $G_i$ plays an essential role in the compartmentalized $\beta_2$AR signaling (Chen-Izu *et al.* 2000).

In addition to the impact of $G_i$ protein, it is proposed that $\beta_2$ARs reside in caveolae, which compartmentalize $\beta_2$AR signaling. Indeed, caveolin-3 is of vital importance for the localization of $\beta_2$AR and compartmentation of $\beta_2$AR-cAMP signaling in healthy cardiomyocytes (Wright *et al.* 2014). Also, phosphodiesterase 4D (PDE4D) is recruited by β-arrestin2 to the vicinity of $\beta_2$AR. Its hydrolysis of cAMP restricts the spatial diffusion of $\beta_2$AR-activated cAMP signal (Fischmeister *et al.* 2006; Richter *et al.* 2008; Shi *et al.* 2017). Endogenous catecholamine ligands of βARs, epinephrine and norepinephrine, induced distinct $\beta_2$AR signaling through G protein-coupled receptor kinase 2 (GRK2) phosphorylation and selective binding of $G_s$ or $G_i$ (Heubach *et al.* 2004; Wang *et al.* 2008), which further revealed the complexity of $\beta_2$AR downstream signaling.

## $\beta_2$AR-MEDIATED OFFSIDE COMPARTMENTALIZATION OF $\beta_1$AR SIGNALING

Accumulative evidence suggests that $\beta_1$AR and $\beta_2$AR pathways may have crosstalk. The activation of $\beta_2$AR has been found to blunt the signaling of $\beta_1$AR in failing heart cells (He *et al.* 2005). In transgenic mice overexpressing $\beta_2$ARs, the contractility of cardiomyocytes is enhanced through spontaneous $\beta_2$AR-cAMP signaling. However, these cells lose their ability to respond to $\beta_1$AR stimulation (Zhang *et al.* 2000).

Recently, we have analyzed the interaction between $\beta_2$AR and $\beta_1$AR signaling. While isoproterenol normally up-regulates $Ca^{2+}$ transients during cardiomyocyte excitation, salbutamol, a selective $\beta_2$AR agonist, hinders the ability of isoproterenol to regulate $Ca^{2+}$ transients (Yang *et al.* 2019). This effect can be eliminated either by rolipram, a PDE4 inhibitor, or by peptides that antagonize β-arrestin1. In the rat model harboring mutations of the phosphorylation sites in the C-terminus of $\beta_1$AR, a putative binding domain for β-arrestin1 and GRK2, $\beta_2$AR agonist no longer interferes with $\beta_1$AR signaling. This study suggests that $\beta_2$AR stimulation activates GRK2 to phosphorylate the C-terminus of $\beta_1$AR, facilitates the recruitment of PDE4 to the phosphorylated $\beta_1$AR, and compartmentalizes $\beta_1$AR-cAMP signals within a sub-membrane nanodomain, preventing the PKA-dependent regulation of RyR and PLB. Because the compartmentalization of the $\beta_1$AR pathway is rendered by the $\beta_2$AR pathway in an offside manner, this signaling process is described as “offside compartmentalization” (Fig. 2) (Yang *et al.* 2019).

It is important to mention that the activation of offside compartmentalization can occur *in vivo* through the use of epinephrine, which hinders the regulation of heart contraction by norepinephrine (Yang *et al.* 2020). Epinephrine exhibits a limited preference for $\beta_2$AR over $\beta_1$AR as an adrenal hormone (Baker 2010), while norepinephrine predominantly stimulates β- and $\alpha_1$ARs as a sympathetic neurotransmitter (Minneman *et al.* 1981) and exhibits selectivity for $\beta_1$AR over $\beta_2$AR due to different entrance pathways to the extracellular binding pockets (Xu *et al.* 2021). Epinephrine and a less quantity of norepinephrine are tonically released from the adrenal glands (Paur *et al.* 2012). As prolonged activation of $\beta_1$AR leads to cytotoxicity (Wu *et al.* 2017; Zhu *et al.* 2003), the offside compartmentalization initiated by $\beta_2$AR signaling can serve as a negative feed-forward mechanism preventing the tonic $\beta_1$AR activation by circulating catecholamines. Under the offside compartmentalization, βAR signaling is still able to synchronize SR $Ca^{2+}$ release by up-regulating LTCC $Ca^{2+}$ influx (Yang *et al.* 2020) and enhance the transient response of $\beta_1$AR to norepinephrine during sympathetic excitation. Hence, in contrast to the robust and predictable E-C coupling regulation through overall $\beta_1$AR signaling, the compartmentalized βAR regulation of E-C coupling, while being moderate, exhibits an "autoadaptive" nature in response to various physiological and pathological circumstances.

 

## PATHOLOGICAL IMPLICATIONS

While βARs play essential roles in the physiological operation of $Ca^{2+}$ signaling, their malfunction is implicated in a variety of pathological processes. Prolonged $\beta_1$AR stimulation induces apoptosis in a CaMKII-dependent manner, and $\beta_2$AR blockade exaggerates $\beta_1$AR-induced apoptosis (Communal *et al.* 1999) possibly due to the absence of offside compartmentalization. In contrast, stimulation of $\beta_2$AR protects cardiac myocytes against a wide range of apoptotic insults, including enhanced $\beta_1$AR signaling, hypoxic treatment or induction of reactive oxygen species (ROS) (Zhu *et al.* 2001). Inhibition of $\beta_2$AR-activated $G_i$–$G_{\beta\gamma}$–PI3K–PKB signaling eliminates these protective effects, and transforms $\beta_2$AR signaling from anti-apoptotic to pro-apoptotic (Zhu *et al.* 2001; Chesley *et al.* 2000). Emerging evidence suggests that mitogen-activated protein kinase (MAPK) and extracellular signal-regulated protein kinases (ERK1 and ERK2) are also involved in $\beta_2$AR-mediated anti-apoptotic signaling (Shizukuda and Buttrick 2002).

During the early-stage development of heart failure, the sympathetic nervous system adjusts its activity to increase cardiac output to compensate for the alterations of cardiac and peripheral hemodynamics (Toschi-Dias *et al.* 2017). However, the continuous hemodynamic stress promotes the chronic release of catecholamines. The elevated level of catecholamine (Bristow *et al.* 1982; Ungerer *et al.* 1993) leads to sustained and toxic $\beta_1$AR-CaMKII signaling, which exacerbates the decline in cardiac function as observed in mid- and late-stages of heart failure (Brede *et al.* 2002; Johnson and Antoons 2018; Zhu *et al.* 2003).

## CONCLUDING REMARKS

Heart disease is the leading cause of death globally. β-adrenergic signaling plays a pivotal role in the modulation of cardiac function in physiological and pathological conditions. Understanding the molecular mechanism of β-adrenergic signaling is fundamental for heart disease therapy. A recent discovery of Rad, a novel endogenous regulator of LTCC, brought new insights into the βAR-cAMP-PKA signaling pathway, and well explained the controversial evidence on the functional phosphorylation sites on LTCC subunits. It is well known that $\beta_1$AR mediates global cAMP signaling while $\beta_2$AR generates localized cAMP signaling. Recent findings suggest that $\beta_2$AR may also blunt $\beta_1$AR signaling through GRK2 mediated "offside compartmentalization" mechanism, which can also serve as a negative feed-forward mechanism preventing the cell toxicity of tonic $\beta_1$AR activation by circulating catecholamines. This underscores the critical protective role of $\beta_2$AR against the detrimental effects of $\beta_1$AR overstimulation. Further discoveries of βAR signaling mechanisms will contribute to novel and effective diagnostic and therapeutic heart disease targets.

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**Compliance with Ethical Standards**

**Conflict of interest** Bo Yang, Shi-Qiang Wang and Hua-Qian Yang declare that there is no conflict of interests.

**Human and animal rights and informed consent** This article does not contain any studies with human or animal subjects performed by the any of the authors.



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