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Antiarrhythmic mechanisms of beta blocker therapy

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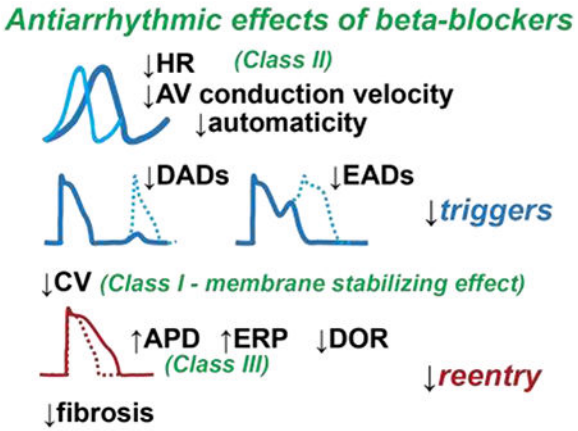
Abstract

Sympathetic activity plays an important role in modulation of cardiac rhythm. Indeed, while exerting positive tropic effects in response to physiologic and pathologic stressors, β-adrenergic stimulation influences cardiac electrophysiology and can lead to disturbances of the heart rhythm and potentially lethal arrhythmias, particularly in pathological settings. For this reason, β-blockers are widely utilized clinically as antiarrhythmics. In this review, the molecular mechanisms of β-adrenergic action in the heart, the cellular and tissue level cardiac responses to β-adrenergic stimulation, and the clinical use of β-blockers as antiarrhythmic agents are reviewed. We emphasize the complex interaction between cardiomyocyte signaling, contraction, and electrophysiology occurring over multiple time- and spatial-scales during pathophysiological responses to β-adrenergic stimulation. An integrated understanding of this complex system is essential for optimizing therapies aimed at preventing arrhythmias.

Graphical Abstract



Keywords

Autonomic drugs; arrhythmia; sympathetic stimulation; heart failure; beta-blockers

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1. Overview: the role of β-adrenergic activation in the heart

The sympathetic nervous system plays a key role in the neurohormonal control of cardiovascular function. It mediates neuronal and hormonal responses to fear, stress, or exercise by regulating cardiovascular function to meet the increasing demands of the body with a commensurate rapid increase in cardiac output (fight or flight response) (Cannon, 1915). The fight or flight response is initiated by release of norepinephrine (NE), from the cardiac sympathetic nerves, and epinephrine (Epi), from the adrenal medulla, which bind to β-adrenergic receptors (β-ARs) on cardiomyocytes. This triggers a signaling cascade leading to increase in cAMP and consequent PKA activation and phosphorylation of a myriad of targets, which orchestrate the physiological response of the heart: increase in heart rate and conduction velocity, and increased force of contraction and speed of relaxation (Bers, 2002). Although these responses are necessary to meet physical demands, excessive β-AR stimulation is also associated with electrophysiological abnormalities, leading to sometimes lethal disturbances of the cardiac rhythm, particularly in the setting of underlying cardiovascular disease (Ripplinger et al., 2016). Indeed, pharmacological agents with β-AR antagonism (class II antiarrhythmics or drugs with some β-AR blocking action, like amiodarone) are effective antiarrhythmics in many conditions (January et al., 2014; Al-Khatib et al., 2018). Here we review the intracellular pathways of β-adrenergic action, the mechanisms of cellular and tissue level regulation of cardiac electrical activity and arrhythmia, and the evidence for clinical antiarrhythmic indications for β-blocker therapy in cardiac diseases and arrhythmias, such as atrial fibrillation (AF), myocardial infarction (MI), and heart failure (HF). We suggest key questions and aspects that future experimentation and clinical studies should address to improve personalization of β-blockade therapy to varying arrhythmia types and patient groups.

2. Molecular mechanisms of β-adrenergic action

β-ARs are members of the G protein-coupled receptor superfamily. In the heart, at least two types of β-ARs are expressed, whereby β_1-ARs account for the majority (~80%) and β_2-ARs comprise ~20% of cardiac β-ARs (Bristow et al., 1986; Xiao, 2001). β_1-ARs have been shown to initiate a cell-wide response, whereas β_2-ARs are localized in caveolae and associated preferentially with L-type Ca^{2+} (Ca) channels (Xiao, 2001).

Binding of NE or Epi to β_1-ARs activate stimulatory G proteins (G_s). The Gα subunit of the G_s protein ($G_s\alpha$) binds to and activates adenylyl cyclase (AC), which catalyzes the conversion of adenosine triphosphate (ATP) into the second messenger cyclic adenosine monophosphate (cAMP). cAMP also activates protein kinase A (PKA), which then phosphorylates several downstream targets in both contractile cells and in the conduction system, including L-type Ca channels, phospholamban (PLB), ryanodine receptors (RyRs), and myofilament proteins including troponin I (Figure 1). These proteins enable the coupling of cell excitation to contraction by increasing the amount of intracellular Ca at each systole (to augment contraction) and by decreasing the myofilament Ca sensitivity (to speed relaxation) (Bers, 2002). cAMP also binds directly to hyperpolarization-activated cyclic nucleotide gated (HCN) channels, predominantly expressed in cardiac nodal cells, to increase the pacemaker current I_f, which contributes to increased heart rate.

The documented effects of cardiac β_2-AR activation are species-dependent, and vary with the developmental or pathophysiological state of the heart (reviewed in (Xiao, 2001)). β_2-ARs couple with G_s at baseline, but in some conditions, they couple with the G inhibitory (G_i) proteins, whereby the latter releases the activated $G_i\alpha$ subunit to inhibit AC activity. The localization of β_2-ARs in caveolae, closely associated with Ca channels (Figure 1), and the additional G_i pathway are thought to play a role in reshaping the spatiotemporal pattern of the G_s-AC-cAMP signaling and might have consequences on the kinetic (mismatch) between Ca and K^+ (K) channel responses to adrenergic activation. The G_i pathway also delivers G_s-independent signals, i.e., cell survival signals through a G_i-G$\beta\gamma$-PI3K-Akt pathway that could be important in counteracting the detrimental effects of chronic β-AR activation (see also Section 5).

β_3-ARs are expressed to much lesser degree, and their function in the heart has been poorly investigated (Cannavo & Koch, 2017). Whereas species differences have been reported, in human ventricle, β_3-ARs mainly couple with $G_s\alpha_i$ proteins, and thus can counteract the effects of β_1-AR and β_2-AR activation (see also Section 5).

3. Cellular and tissue level β-adrenergic responses

3.1 Physiological responses

Sympathetic activation leads to increased heart rate (chronotropy), force of contraction (inotropy), speed of relaxation (lusitropy), and conduction (dromotropy). Positive chronotropy is mediated by phosphorylation-dependent changes in intracellular Ca handling as well as by cAMP-mediated increases in I_f (DiFrancesco & Tortora, 1991), which together accelerate diastolic depolarization in the sinoatrial (SA) node via the membrane and Ca coupled clocks (Lakatta & DiFrancesco, 2009), leading to faster impulse generation. Faster heart rates and K channel phosphorylation typically abbreviate cardiac repolarization (Bartos et al., 2015; Grandi et al., 2017), necessary to accommodate shorter cycle lengths, by counter-balancing the I_{CaL} increase necessary for enhancing contractility.

Increased myocardial contractility is mediated by cytosolic Ca increase, which increases the fraction of bound myosin and actin filaments, and is primarily due to enhancement of L-type Ca current (I_{CaL}) and PLB and RyR phosphorylation (Bers, 2002). Enhanced I_{CaL} leads to increased transmembrane ‘trigger’ Ca initiating the Ca-induced-Ca-release process, whereas phosphorylation of PLB and RyRs contributes to increased sarcoplasmic reticulum (SR) Ca uptake and release, respectively (Figure 1). Enhanced Ca and PLB phosphorylation favor faster relaxation via accelerated SR Ca reuptake. Phosphorylation of troponin I also contributes to positive lusitropy by accelerating dissociation of Ca from the myofilaments. This reduction in myofilament Ca sensitivity would, by itself, be expected to decrease contractility, but it is outweighed by the dramatic increase in intracellular Ca available for contraction (Bers, 2002).

The positive dromotropic effect includes increased SA nodal and atrioventricular (AV) nodal conduction velocity primarily mediated by increased I_{CaL}, which is a key component of the SA and AV nodal action potential upstroke (Bartos et al., 2015). Conduction velocity of the ventricular myocardium may also increase with β-AR activation (Wallace & Sarnoff, 1964;

Ng et al., 2007; Ajijola et al., 2017). PKA-mediated phosphorylation of I_{Na} may be involved (Herren et al., 2013) (see Section 3.2), but modulation of gap junctions is also a likely contributor (Figure 1, reviewed in (Campbell et al., 2014)). In the short-term, β-AR activation and increased cAMP impact phosphorylation and assembly of connexin43 (Cx43) (TenBroek et al., 2001; Somekawa et al., 2005), whereas more long-term effects may be due to adrenergically-mediated alterations in Cx43 turnover or expression (Salameh et al., 2006).

3.2 Arrhythmogenic mechanisms of β-adrenergic action: ionic bases

The complex cardiac electrophysiological and Ca handling consequences of sympathetic activation involve changes in transmembrane potential homeostasis via both direct influences on sarcolemmal ion channels and transporters as well as indirect changes in Ca signaling that acutely regulate transmembrane fluxes and can lead to remodeling in the chronic (pathologic) setting.

cAMP/PKA signaling modulates several ion currents including I_{Na}, I_{CaL}, I_K, as well as I_f in nodal cells (increased I_f expression in the working myocardium in disease may also result in ectopic activity that can be targeted by β-AR blockade). PKA-dependent phosphorylation of I_{Na} potentiates the current via both gating changes (Zhou et al., 2000) and by enhancing channel trafficking (Zhou et al., 2002).This may contribute to the sympathetically-mediated increase in conduction velocity and formation of reentrant arrhythmias after MI, which is often characterized by myocardial depolarization (Nattel et al., 2007). Late I_{Na} is also increased upon β-AR activation, mediated by both PKA and CaMKII (Wagner et al., 2006) increases (Hegyi et al., 2018). Thus, β-AR stimulation may enhance late I_{Na}, lengthen the AP, and increase the propensity to arrhythmogenic early afterdepolarizations (EADs), especially in disease states when late I_{Na} is enhanced (Clancy & Rudy, 1999).

I_{CaL} enhancement subsequent to PKA-dependent phosphorylation has been associated with prolonged AP and increased tendency for EADs, due to I_{CaL} reactivation during the AP plateau (phase 2 EADs) (Weiss et al., 2010). Increased Ca influx and consequent increase in Ca load, needed for positive inotropy, also favors spontaneous SR Ca release and Na/Ca exchange-mediated depolarization before or after completion of repolarization, leading to phase 3 EADs or delayed afterdepolarizations (DADs) (Bers, 2008), respectively. PKA-mediated phosphorylation of RyRs enhances their Ca sensitivity, which also favors DADs. Indeed, in genetically linked catecholaminergic polymorphic ventricular tachycardia (CPVT), DAD-induced arrhythmia is triggered by high sympathetic tone (for example during exercise) in patients with no myocardial damage (Laitinen et al., 2001).

K currents are also enhanced by cAMP/PKA signaling to counteract AP prolongation and limit Ca loading. Sympathetic stimulation modulates the delayed rectifier K current (Bartos et al., 2017). Under basal conditions the slowly activating I_{Ks} density is much lower than the rapidly activating component I_{Kr} in humans and other large mammals (Jost et al., 2007). However, β-AR stimulation increases I_{Ks} more than I_{Kr} (Banyasz et al., 2014) and counteracts I_{CaL} enhancement to prevent potentially harmful action potential duration (APD) prolongation. Indeed, exercise and stress are typI_{CaL} arrhythmia triggers in congenital type 1 long QT syndrome (LQTS), linked to I_{Ks} loss of function (Schwartz et al., 2001), and can be prevented by β-AR blockade (Vincent et al., 2009). In a recent study, computer simulations

showed that increasing the I_{Ks}/I_{Kr} ratio, without changing the resulting APD, limits EAD occurrence in response to perturbations. This suggests the intriguing notion that I_{Ks} is more effective than I_{Kr} in stabilizing APD and suppressing EADs (Devenyi et al., 2017). The kinetic mismatch between faster phosphorylation-mediated activation of I_{CaL} and slower I_{Ks} increase upon β-AR activation transiently perturbs the balance of inward and outward currents (Liu et al., 2012). Computational modeling and simulations showed that this current imbalance that favors depolarization can prolong APD and favor EADs transiently (Xie et al., 2013).

At the tissue level, shorter APD and thus ERP can facilitate reentrant excitation, which is also promoted by structural changes such as fibrosis (Section 3.4) leading to slower impulse propagation. Spatial and temporal heterogeneity of PKA-dependent effects on depolarizing vs. repolarizing currents can also amplify dispersion of repolarization (DOR), thus increasing the likelihood for unidirectional conduction block and subsequent reentrant activity. Furthermore, faster I_{CaL} activation (vs. I_{Ks}) upon rapid β-AR stimuli transiently steepens APD restitution leading to spiral wave breakup and precipitating breakdown of ventricular tachycardia (VT) into ventricular fibrillation (VF) (Xie et al., 2014). Thus, the cellular triggering mechanisms discussed above combined with the tissue-level reentrant substrate can set the stage for β-AR arrhythmogenesis.

3.3 Arrhythmogenic mechanisms of β-adrenergic action: nerve remodeling in disease

The heart is extensively innervated (Pauza et al., 2002a; Pauza et al., 2002b), and recent detailed analysis of nerve-cardiomyocyte interaction has suggested that the sympathetic nerve-to-myocyte ratio is similar to the capillary-to-myocyte ratio (Freeman et al., 2014; Zaglia & Mongillo, 2017). Indeed, in the normal heart, it appears as if nearly every cardiomyocyte is in contact with one or more sympathetic nerves (Freeman et al., 2014; Zaglia & Mongillo, 2017). This density is not uniform, however, as there exist gradients in innervation from base to apex and from epi- to endocardium (Kawano et al., 2003). Importantly, cardiac sympathetic innervation undergoes extensive functional and anatomical remodeling during cardiovascular disease. Remodeling of sympathetic neurotransmission is arrhythmogenic and is associated with both hyper- and hypo-innervation as well as altered neurotransmitter content and release.

Regional hyper-innervation was one of the first identified forms of neural remodeling that was linked to arrhythmias in humans (Cao et al., 2000), and has now been well documented in various cardiac pathologies, including MI, HF, and AF (reviewed in (Chen et al., 2001)). The underlying mechanisms by which hyperinnervation leads to arrhythmia are likely due to excess NE release in a localized region of the heart, which exacerbates the cellular and tissue-level arrhythmogenic processes described above (Section 3.2). Indeed, our group demonstrated the mechanisms by which localized sympathetic stimulation leads to the generation of ventricular ectopic beats via synchronization of SR Ca overload and release (Myles et al., 2012). Excess catecholamines are also linked to downregulation of K currents and prolonged ventricular APD (Aflaki et al., 2014). Furthermore, both hyper-innervation and chronically elevated sympathetic drive present in cardiovascular disease can lead to decreased β-AR responsiveness and G-protein uncoupling (Soltysinska et al., 2011), which

may in turn lead to further elevations in sympathetic activity, thus perpetuating a vicious cycle of elevated sympathetic tone.

Many studies on the links between hyper-innervation and arrhythmia have focused on ventricular arrhythmias in MI or HF. However, hyper-innervation has also been documented in patients with chronic AF (Nguyen et al., 2009) and may be important in the initiation and maintenance of atrial tachyarrhythmias. Indeed, modulating autonomic function to reduce innervation or sympathetic activity has shown useful for AF control (reviewed in (Chen et al., 2014)), yet β-blockers are not typically used in AF rhythm control (see Section 4). Histological studies of the human pulmonary vein–left atrium junction showed that numerous autonomic nerves are present (Tan et al., 2006; Vaitkevicius et al., 2009), and that there is a mix of adrenergic and cholinergic fibers, suggesting that complex spatio-temporal interactions between sympathetic and parasympathetic activity may be involved in AF.

Paradoxically, sympathetic hypo-innervation (or denervation) is also linked to ventricular arrhythmias. Indeed, recent clinical studies have suggested that the degree of viable denervated myocardium is an independent predictor of ventricular arrhythmia risk and cardiac arrest (Boogers et al., 2010; Nishisato et al., 2010; Fallavollita et al., 2014). One explanation of these findings may be that any abnormal heterogeneity in sympathetic transmission is arrhythmogenic (Rubart & Zipes, 2005). Chronic hypo-innervation may also result in upregulation of β-ARs and adrenergic super-sensitivity of the myocardium, meaning that supra-physiological responses may occur with normal catecholamine exposure. Recent data from murine models suggests that the infarct remains devoid of sympathetic fibers following MI (Gardner & Habecker, 2013), and our group demonstrated that these denervated infarcts are in fact super-sensitive to adrenergic agonists, leading to electrophysiological heterogeneity and triggered activity (Gardner et al., 2015). Therefore, β-blockers may have significant anti-arrhythmic value even in denervated conditions.

3.4 Arrhythmogenic mechanisms of β-adrenergic action: hypertrophy and fibrosis

Cardiomyocyte hypertrophy and increased fibrosis are hallmarks of cardiovascular disease and both aspects of remodeling are associated with arrhythmias. Indeed, both organ enlargement and fibrotic remodeling create a vulnerable structural reentrant substrate, by generating longer conduction pathways for reentry, slowing conduction, and imposing unexcitable barriers that facilitate arrhythmia initiation and maintenance. Several studies have shown that β-AR agonists, including NE and isoproterenol, as well as β_1-AR overexpression can produce cardiac hypertrophy and fibrosis *in vivo* (Engelhardt et al., 1999). Although myocyte hypertrophy may be an adaptive response to the increase in work load caused by myocardial β_1-AR stimulation, there is evidence that direct adrenergic signaling may also be involved. In a seminal study in cultured cardiomyocytes, Simpson showed that NE-induced myocyte hypertrophy is mediated by α1-adrenergic receptors (Simpson, 1983). More recent work suggests that β_1-AR signaling may also be involved. Pare and colleagues demonstrated that PKA phosphorylates a pool of perinuclear RyR2s, leading to increased local Ca, which in turn activates the pro-hypertrophic calcineurin-nuclear factor of activated T-cells transcription factor pathway (Pare et al., 2005). Cardiac non-myocytes, including fibroblasts also have adrenergic receptors, and stimulation of β_2-

ARs in human and rodent cardiac fibroblasts leads to increased proliferation (Long et al, 1993; Turner et al, 2003). This raises the intriguing possibility that direct β-AR signaling in fibroblasts could be an important contributor to fibrosis in MI and HF and may explain some of the anti-fibrotic effects observed with β-blocker treatment.

4. Indications for clinical use of β-blockers

It is evident that β-blocker therapy may antagonize multiple direct and indirect arrhythmogenic effects of increased sympathetic activity. Depending on the arrhythmia type, β-blockers reduce proarrhythmic risk by preventing sympathetically-mediated triggers, functional reentrant substrates, and slowing of the SA- and AV-nodal rates. Table 1 lists currently used β-blockers, their mechanisms of action and therapeutic uses, including specific indications for arrhythmia.

β-blockers are a cornerstone of anti-arrhythmic drug therapy. β-blockers are generally safe agents that effectively suppress ventricular ectopic beats and arrhythmia, and prevent sudden cardiac death in a wide array of cardiac diseases (Al-Khatib et al., 2018). According to guidelines, β-blockers are indicated in all patients, except those with AV block, bradycardia, or asthma, and recommended in all HF patients regardless of baseline rhythm, β-blockers are also used for control of ventricular rates to avoid rapid irregular ventricular activation due to rapid and irregular atrial firing during AF (January et al., 2014).

AF.

β-blockers are first line therapy for ventricular rate control in AF (January et al., 2014). They act by slowing conduction through the AV node, have been proven superior in ventricular rate control especially with exercise, and are preferred to digoxin and Ca channel blockers in patients with MI or HF. β-blockers may be avoided in patients with chronic pulmonary disease and at risk of bronchoconstriction. In acute AF settings, intravenous administration of esmolol, propranolol, and metoprolol has been shown effective; in chronic AF, oral administration of β-blockers, including atenolol, bisoprolol, metoprolol, nadolol, propranolol, and sotalol (a K channel blocker), is effective for ventricular rate control (January et al., 2014). Of note, comparison of different β-blockers demonstrated that carvedilol is less effective than metoprolol for rate control (Vittorio et al., 2008).

β-blockers have a weak antiarrhythmic action compared to Class I (Na channel blockers) and Class III agents (K channel blockers), and are not generally considered as atrial rhythm control agents (January et al., 2014). However, β-blockers may be beneficial in some patients in combination with an antiarrhythmic drug. Note that Class III amiodarone, the most effective rhythm control agent in patients with AF, is also a β-AR antagonist. β-blockers may be helpful for AF prevention in patients with adrenergically-mediated AF, for example linked to stress or anxiety, and in patients following cardiothoracic surgery, with likely elevated postoperative sympathetic tone. On the other hand, they could be detrimental in vagally-mediated AF. Further, β-blockers have been shown to prevent the occurrence of AF in patients with systolic HF (Nasr et al., 2007).

MI.

β-blockers are known to decrease mortality both during acute MI and with long-term administration following MI. Many randomized clinical studies of β-blockers were performed prior to routine anti-platelet and statin therapy, so the absolute benefit may be lower, but initial clinical trials indicated a 10-25% reduction in mortality in patients treated with timolol, metoprolol, atenolol, or propranolol (Norwegian Multicenter Study, 1981; Hjalmarson et al., 1983; 1986; Chadda et al., 1986). Current recommendations for acute MI include cardioselective oral β-blockers, such as metoprolol or atenolol. For long-term administration after MI, agents that lack sympathomimetic activity are preferred (Antman et al., 2004; Antman et al., 2008).

β-blockade effects include (i) decreased myocardial oxygen demand and reduction of ischemic burden, due to lowering of heart rate, myocardial contractility, and blood pressure; (ii) prevention of maladaptive ventricular remodeling and failure, and (iii) decreased risk of VF and sudden cardiac death, as demonstrated in both experimental and clinical studies. Specific anti-arrhythmic effects may include lengthening of the ventricular effective refractory period, suppression of triggered activity and automaticity, attenuation of electrophysiological heterogeneity (e.g., caused by MI-induced hypo- or hyper-innervation), and slowing of heart rate. Recent experimental evidence also suggests that sympathetic nerve activity can modulate conduction through putative reentrant circuits in the infarct border zone, making them more prone to conduction block (Ajijola et al., 2017), suggesting another possible anti-arrhythmic mechanism of β-blockade following MI.

HF.

β-blockers are a mainstay of HF therapy (Yancy et al., 2013; Yancy et al., 2017). Three β-blockers, carvedilol (Packer et al., 2001), metoprolol (1999b), and bisoprolol (1999a), have been studied in clinical trials, whereby chronic treatment has been demonstrated to improve symptoms, reduce hospitalization, and enhance survival when used in addition to diuretics and angiotensin converting enzyme (ACE) inhibitors. β-blockers are only contraindicated in acute decompensated setting, whereby the negative inotropy is detrimental. β-blockers prevent sudden cardiac death in patients with systolic HF and reduce all-cause mortality, i.e., adverse effects of catecholamine stimulation, including increases in heart rate and myocardial energy requirements, maladaptive remodeling due to cell hypertrophy and death, fibrosis, proarrhythmia, and inappropriate stimulation of other pathways such as the renin-angiotensin-aldosterone system.

HF-induced remodeling involves key nodes of the cAMP/PKA signaling cascade, including downregulation of β_1- (~60%) and upregulation in β_2- (~40%) and β_3-AR, switching from G_s to G_i coupling, and activation of G protein-independent pathways, as recently reviewed (de Lucia et al., 2018). Extensive ionic remodeling also occurs (Nattel et al., 2007; Bartos et al., 2015) and involves downregulation of several K channels, i.e., those carrying I_{Kr}, I_{Ks}, I_{K1}, and I_{to} and consequent AP prolongation, increased risk for EADs, and increased DOR and dispersion of refractoriness. Ca handling abnormalities in HF include increased spontaneous Ca release and risk for DADs (Bers, 2006). Alterations in gap junction and structural remodeling (Burchfield et al., 2013), involving myocyte hypertrophy, organ

dilation, and fibrosis, contribute to slowing of conduction that can lead to unidirectional conduction block and predispose to reentry. Thus, the antiarrhythmic action of β-blockers in HF might be mediated by attenuating both the triggers and the functional or structural arrhythmia substrates.

LQTS.

β-blockers are a mainstay of treatment for LQTS (Ackerman et al., 2017). β-blockers are recommended in patients diagnosed with LQTS, and should be considered in patients that carry a causative LQTS mutation but have normal QT interval. Increased sympathetic tone (e.g., during exercise) is one of the most important arrhythmia triggers in LQT1 (which is caused by mutations in the *KCNQ1* gene leading to reduction in I_{Ks} current), and can be prevented by β-blockers (Schwartz et al., 2001; Vincent et al., 2009). In LQT2 (caused by loss of function of I_{Kr}), β-blockers are thought to be less effective than in LQT1. Recent studies comparing efficacy of different β-blockers, reviewed in (Ackerman et al., 2017), showed that propranolol and nadolol were similarly effective, whereas metoprolol had significantly less anti-arrhythmic efficacy. Importantly, when comparing the efficacy of different β-blocking agents independently for LQT1 and for LQT2, nadolol had the greatest efficacy among the more severely affected LQT2 patient group. It has been shown that β-blockers reduce risk in LQT3 patients (Wilde et al., 2016), despite prior studies indicating that β-blockers were not as effective in LQT3 as compared to LQT1 or LQT2.

CPVT.

CPVT is caused by defective inter-domain interaction within the RyR2 (Yamamoto et al., 2000), which enhances arrhythmias by promoting diastolic Ca leak. First-line treatment for CPVT patients includes exercise restriction and β-blockade (with agents lacking intrinsic sympathomimetic activity) (Ackerman et al., 2017). According to guidelines, β-blockers are recommended in all CPVT patients with documented ventricular arrhythmias (either spontaneous or stress-induced), and should be considered for asymptomatic mutation carriers even after a negative exercise stress test. Left cardiac sympathetic denervation might be an option for CPVT patients that are intolerant to β-blockers, but its efficacy remains to be fully assessed. Preliminary data on a small group of CPVT patients suggest that flecainide (a Na channel blocker known to interact with RyRs) significantly reduces arrhythmias and should be considered in combination with β-blockers when arrhythmia control is incomplete (Kannankeril et al., 2017). An implantable cardioverter-defibrillator (ICD) is indicated in patients that do not respond to β-blockade and flecainide (Ackerman et al., 2017).

5. Key future work

While available experimental and clinical evidence supports an important role of β-AR antagonism in counteracting acute and chronic detrimental effects of β-AR stimulation, important key questions remain to be addressed, that could pave the way for major new developments in β-blockade strategies and their therapeutic uses in cardiac disease and arrhythmia.

Exploiting drugs' receptor-specific β-AR agonism and antagonism.

While acute activation of β_1- and β_2-ARs exerts positive tropic actions, chronic activation of β_1-ARs causes (mal)adaptive effects including cardiac hypertrophy and fibrosis, and cell death, which contribute to the development of HF, and lethal arrhythmias. On the other hand, long term stimulation of β_2-ARs improves myocyte survival and overall cardiac function (Xiao, 2001). Further, while the functional significance of β_3-ARs is incompletely understood, preclinical studies showed that β_3-ARs can activate different signaling pathways that can protect the heart. For example, stimulation of β_3-ARs activates a downstream NO-GC-cGMP pathway that limits Ca influx and is thought to be cardioprotective (Cannavo & Koch, 2017). Thus, sustained activation of β_2- and β_3-ARs combined with β_1-AR blockade could be a new receptor-specific therapeutic approach for the chronic HF treatment. In addition to the cardioprotective effects of β_2- and β_3-AR stimulation, activation of β_2-AR stimulation has direct vasodilatory effects, and β_3-AR activation has been shown to increase lipolysis and may also have antidepressant activity (Ferrer-Lorente et al., 2005; Consoli et al., 2007). Thus, such antagonist/agonist drugs could have myriad positive effects in patients with cardiovascular disease (see Table 1).

Targeting compartmentalized signaling.

There is solid evidence that activation of β-ARs can generate spatially restricted pools of cAMP that in turn lead to localized intracellular (rather than global) PKA activation and result in specific downstream functional effects (Surdo et al., 2017). For example, the intensity, duration, and spatial range of cAMP signals is strongly modulated by cAMP-degrading phosphodiesterase activity and localization (Zaccolo & Pozzan, 2002; Surdo et al., 2017). Thus, using drugs that target specific cAMP pools, rather than affecting global intracellular cAMP levels, could be a promising strategy to improve therapeutic specificity (Zaccolo, 2009). This requires detailed understanding of the spatial organization, regulation and functional role of cAMP compartments. Furthermore, even in the presence of uniform cAMP signals, distinct domains of PKA-phosphorylated proteins can be obtained due to subcellular heterogeneity in protein phosphatase distribution (Burdyga et al., 2018), leading to differential phosphorylation of various downstream PKA targets that promote specific cardiac responses. For example, activation of protein phosphatase 1 in human HF opposes increased kinase activity and attenuates arrhythmogenic Ca leak (Fischer et al., 2018). Real-time imaging of cAMP and resulting PKA activity using FRET-based sensors has greatly contributed to our understanding of compartmentalized cAMP signaling (Zaccolo & Pozzan, 2002; Surdo et al., 2017). In particular, novel sensors targeted to protein complexes involved in excitation-contraction coupling have begun to address crucial questions regarding the size and spatial distribution of distinct cAMP compartments, the magnitude and kinetics of cAMP signals within each compartment, and the specific role of individual compartments in regulating cell function (Nikolaev et al., 2010; Surdo et al., 2017). For example, β_2-ARs were shown to be concentrated in the transverse tubules, leading to localized cAMP signal in healthy cells. In HF, however, these receptors were redistributed to the cell crest, leading to diffuse receptor-mediated cAMP signaling (Nikolaev et al., 2010). These approaches have provided original insight into the regulation of cardiac excitation and contraction in health and disease with profound implications for therapy (Surdo et al., 2017).

Evaluating the interaction between β-AR and other signaling pathways.

A clear link has been established between enhanced sympathetic activation and ventricular arrhythmias in both animal models and humans with cardiac disease. Excessive β-AR activation is well documented in HF, but the complex and multifaceted nature of the disease suggests that multiple other signaling pathways are perturbed. Notably, many of them might crosstalk with the β-AR system. For example, the renin-angiotensin-aldosterone system (RAAS) is also chronically active in HF. Experimental evidence indicates both that β-AR blockade may diminish activity of the RAAS, and that targeting the RAAS may reduce sympathetic nerve activity (Goldsmith, 2004), suggesting that combination therapy that suppresses each individual system involves a virtuous (negative feedback) cycle.

Stimulation of various signaling pathways, altered metabolism, and increased oxidative stress and their complex interactions may exert electrophysiological abnormalities acutely, and accumulation of these changes (e.g., in chronic pathological settings) may cause prolonged alterations in cardiac signal transduction and gene expression. In cardiac myocytes, β-adrenergic stimulation, via both direct (EPAC, NO)(Pereira et al., 2017) and indirect (increased Ca) mechanisms, enhances the activity of the Ca/calmodulin-dependent protein kinase (CaMKII), which is overexpressed and hyper-activated in HF, and critically regulates cellular subsystems participating in acute mechanical and electrical abnormalities in HF and models of adrenergic stimulation as well as long term cardiac remodeling in HF (Grandi & Dobrev, 2018). CaMKII phosphorylates a number of downstream targets that play important roles in excitation-contraction coupling (Figure 1), and many of these proteins are also targets of PKA-dependent phosphorylation. The relative contribution of these kinases to proarrhythmic functional alterations has begun to be defined. For example, it has been shown that while both kinases are involved in RyR dysregulation in human hypertrophy, in end stage human HF, CaMKII predominates to induce arrhythmogenic Ca leak (Fischer et al., 2013). Recent data also revealed differential modulations of I_{NaL} by PKA and CaMKII at different phases of the action potential (Hegyi et al., 2018). It has been hypothesized that in HF, synergy between CaMKII upregulation and altered Na and Ca fluxes can lead to a vicious (positive feedback) cycle perpetuating the arrhythmia, which is further accentuated during β-adrenergic stimulation. Thus, β-AR blockade could counteract arrhythmias via both direct effects and by de-escalating the synergistic interaction between CaMKII and β-AR signaling (Bers, 2005).

Understanding sex-based differences.

There are well-known sex differences in male and female cardiac electrophysiological properties (Ambrosi et al., 2013). For example, women have a prolonged baseline APD and QT interval, which lead to increased risk for drug-induced torsades de pointe (TdP) in females (Pham et al., 2001; Salama & Bett, 2014; Kurokawa et al., 2016). Moreover, the mechanisms of arrhythmias in HF may also differ between males and females, with cells from male failing hearts demonstrating an increase in Ca leak, spark frequency, and triggered activity compared to failing female cells (Fischer et al., 2016). Interestingly, normal male rabbit hearts also have a stronger, and more arrhythmogenic response to β-AR stimulation, showing an increase in triggered activity, despite similar increases in diastolic Ca leak (Hoeker et al., 2014). Further, heart rate variability studies suggest underlying sex

differences in autonomic control of the cardiovascular system, whereby women have higher degrees of parasympathetic activation, whereas sympathetic-mediated responses predominate in men (Pothineni et al., 2016). This has been associated with an increased propensity in women of AF due to extensive vagal innervation of the atrial muscle sleeves extending into the pulmonary veins. Furthermore, the ORBIT-AF registry revealed lower rates of use of β-blockers as rate-control agents in women (as opposed to digoxin) (Piccini et al., 2016), though the reason is unknown. These observations also suggest that there may be significant sex differences in efficacy of β-blocker therapy for arrhythmia prevention. Interestingly, in the MERIT-HF study, which assessed the efficacy of metoprolol, the 23% of women included were the only subgroup in which no favorable effect on mortality was observed (although the women in this study were still 37% less likely to die than men) (Group, 1999). Yet, post-hoc analyses of MERIT-HF and other studies do not show sex differences in mortality with β-blocker therapy for HF (Ghali et al., 2002). Importantly, while these data regarding mortality do not indicate whether these deaths were arrhythmic in nature, the mixed observations suggest an urgent need to better understand the mechanisms of underlying sex differences, which may suggest more personalized approaches to β-blocker therapy.

6. Conclusions

The effects of β-adrenergic stimulation on cardiac electrical activity and remodeling involve structural and functional changes occurring over multiple time- and spatial-scales. While significant progress has been made towards understanding the role of β-AR signaling in heart disease and arrhythmias, a comprehensive quantitative and functional understanding of the role of autonomic stimulation in normal cardiac electrophysiology and life-threatening arrhythmias is still lacking. We contend that defining the structural and functional anatomy of cardiac innervation, and linking neural structure and function to multiscale cardiac electrophysiology, e.g., via computational modeling approaches and simulation (Morotti & Grandi, 2018), is a necessary step to improve our understanding of this complex system. Integrating these data from the sub-cellular, tissue, and multi-organ levels could accelerate our understanding of the complex network of pathways involved, predict mechanisms underlying the interaction between adrenergic activation and the functional cardiac substrate, and facilitate identification and specific targeting of arrhythmia provoking conditions by autonomic drugs.

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Highlights

- β-blockers are effective antiarrhythmics in many conditions, including heart failure, myocardial infarction, and atrial fibrillation
- β-adrenergic action on cardiac function is complex, and involves structural and functional changes occurring over multiple time- and spatial-scales.
- Exploiting drugs' receptor-specific drug action, targeting compartmentalized signaling, and understanding sex differences in drug responses are key aspects that future studies should address to improve personalization of β-blockade therapy to varying arrhythmia types and patient groups.

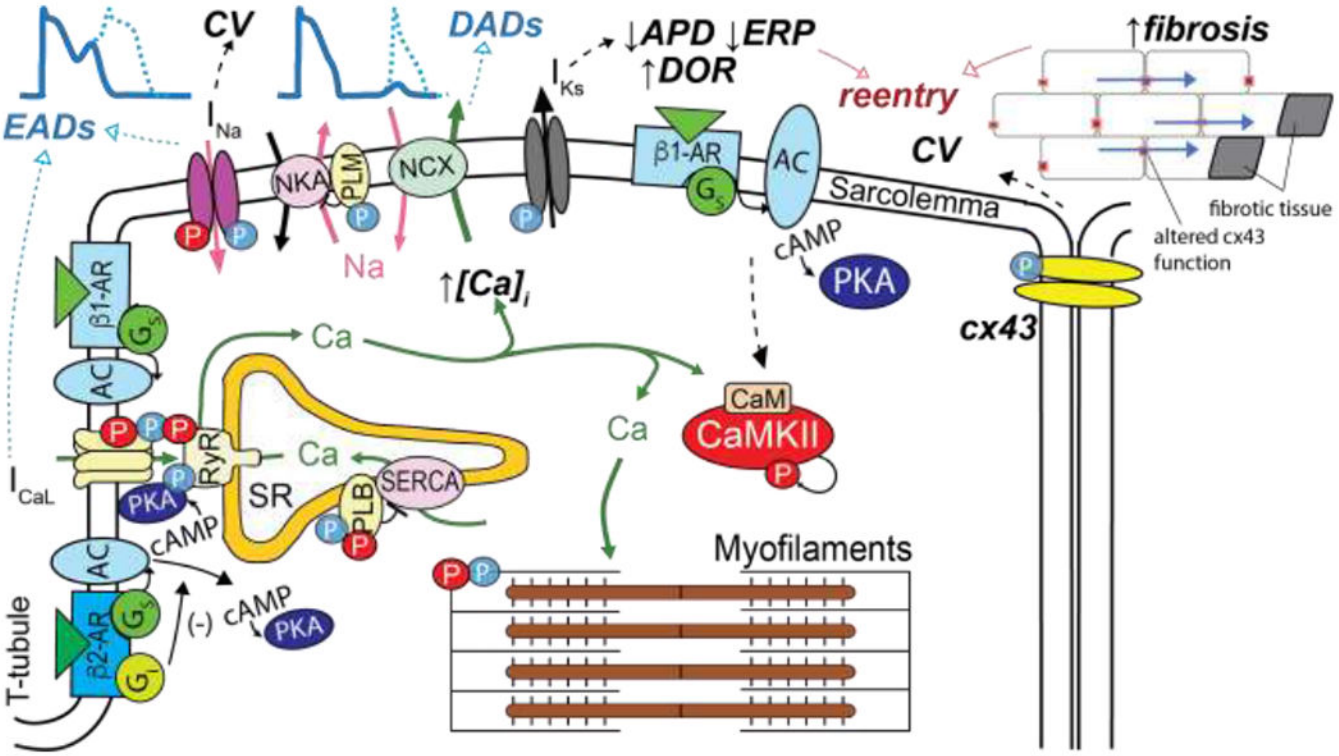

Figure 1: Molecular and cellular mechanisms of β-adrenergic action.

Schematic of the main cellular processes linking β-adrenergic activation (and β-adrenergic receptor specific signaling) to increased propensity for arrhythmia. Protein kinase A (PKA) phosphorylates multiple targets (blue symbol "P") that directly affect membrane electrophysiology and Ca signals. These include the L-type Ca channel (carrying I_{CaL}), ryanodine receptor (RyR), phospolamban (PLB) that regulates the sarcoplasmic reticulum Ca pump (SERCA), phospolemman (PLM) that regulates the Na/KATPase (NKA), the sarcolemmal Na and K channels (carrying I_{Na} and I_{Ks}), myofilament proteins, and connexin 43 (cx43). These downstream effects of β-adrenergic action facilitate the development of ectopic activity (EADs and DADs) and functional reentry (shortened action potential duration, APD and effective refractory period, ERP, increased dispersion of repolarization, DOR, and altered conduction, CV). β-adrenergic activation is also involved in structural remodeling (e.g., fibrosis) that facilitates the formation of a structural reentrant substrate. CaMKII is a central player in cardiac disease and adrenergically-mediated arrhythmia; its activity is enhanced by β-adrenergic activation via both increases in Ca and cAMP, and leads to increased phosphorylation of many of the same PKA targets (red symbol "P").

Table 1 –

Mechanisms of action and therapeutic uses of β-blockers.

Currently used β-blockers, their mechanisms of action (including β-AR receptor sensitivity), other extra-cardiac actions, and therapeutic uses are listed. Specific indications for arrhythmia are in red, and indication for HF, MI and AF are in blue. Information compiled from (Brunton et al., 2018).

Agent	Mechanism of Action	Therapeutic use
Non-selective β-adrenergic antagonists (*first generation*):		
Propranolol	Equal affinity for β1 and β2. Membrane stabilizing effect.	Used for: hypertension, angina, supraventricular arrhythmia, ventricular arrhythmia, MI.
Nadolol	Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.	Used for: Hypertension, angina, LQTS.
Timolol	Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.	Hypertension, congestive HF, acute MI.
β_1-selective adrenergic antagonists (*second generation*):		
Metoprolol	No sympathomimetic or membrane stabilizing activity.	Used for: essential hypertension, angina, tachycardia, HF, vasovagal syncope, secondary prevention after MI
Atenolol	No sympathomimetic or membrane stabilizing activity.	Used for: hypertension, coronary heart disease, arrhythmias, angina, reduces risk of complications after MI
Esmolol	Little sympathomimetic activity, no membrane-stabilizing activity.	Used when short duration is desired or in critically ill patients where rapid withdrawal may be necessary.
Acebutolol	Some sympathomimetic and membrane stabilizing activity.	Used for hypertension, atrial and ventricular arrhythmias, acute MI in high-risk patients
Bisoprolol	No sympathomimetic or membrane stabilizing activity. Higher degree of β1 selectivity than metoprolol or atenolol.	Used for: HF, hypertension, MI, arrhythmias
β-adrenergic antagonists with additional cardiovascular effects (*third generation* - *also possess vasodilatory actions*)		
Labetalol	Competitive antagonist to α1 and β receptors (β1 and β2). Partial agonist activity at β2 and also inhibits neuronal uptake of NE (cocaine-like).	Used for chronic hypertension or hypertensive emergencies
Carvedilol	Blocks α1, β1, and β2 similar to labetalol, but also has anti-oxidant and anti-inflammatory properties. Has membrane-stabilizing action, but no sympathomimetic activity.	Produces vasodilation and anti-inflammatory effects may help treatment of HF. Approved for use in hypertension, congestive HF, and LV dysfunction after MI
Celiprolol	β1 antagonist. β2 partial agonist. Also α2 antagonist and promotes NO production.	Reduces HR and blood pressure. Used to treat hypertension and angina
Nebivolol	β1 antagonist with endothelial NO-mediated vasodilatory action.	Also has antioxidant action and neutral or favorable effects on carbohydrate and lipid metabolism. Approved for the treatment of hypertension