Chapter 2
Adrenergic Receptor Signaling Pathways in the Regulation of Apoptosis and Autophagy in the Heart

Jessica MacLean and Kishore B. S. Pasumarthi

Abstract Despite the discovery of several new therapeutic interventions, heart disease remains the number one cause of death worldwide. Many forms of heart disease are associated with loss of functional heart muscle cells, cardiac hypertrophy, remodeling and chamber dilation as well as deterioration in cardiac function. Significant changes in the levels of mediators regulating apoptosis and autophagy have been reported in both patients and experimental models of heart disease. Endogenous catecholamines, norepinephrine and epinephrine have been shown to play a critical role in cell death and pro-survival pathways in the heart by binding to $\beta 1$-, $\beta 2$- and $\alpha 1$- adrenergic receptors (ARs). While there is scant information on the mechanisms regulating cell death and pro-survival pathways, a deeper understanding of these processes and their interplay is essential for development of new therapies for patients suffering from heart disease. Here, we have briefly reviewed various signal transduction mechanisms linking adrenergic receptors with apoptosis and autophagy in the heart. Notably, elevated plasma levels of norepinephrine or $\beta 1$-AR autoantibodies can induce apoptosis via stimulation of the $\beta 1$-AR/cAMP/protein kinase A dependent and independent pathways and activation of $\beta 2$- or $\alpha 1$-ARs can have pro-survival functions in cardiomyocytes. Whereas both AR agonists and antagonists can either increase or decrease autophagy depending on the cardiovascular cell type and experimental model system used. In addition, we have provided a comprehensive survey of the literature relevant to the effects of various adrenergic drugs on the signaling mechanisms regulating apoptosis and autophagy and discussed the relevance of these events in heart disease.

Keywords Cell death and survival pathways · Heart disease · Adrenergic receptors · Catecholamines · Adrenergic receptor agonists and α- and β-adrenergic receptor blockers

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Introduction

The adrenergic system consists of the endogenous catecholamines norepinephrine and epinephrine and the adrenergic receptors. Norepinephrine from nerve endings and epinephrine from the adrenal gland are secreted when the sympathetic nervous system is activated [1]. The systemic effects of the sympathetic nervous system, particularly on the heart and circulatory system, enable the human body's fight or flight response. To this end, sympathetic activation elicits an increased heart rate, increased contractility and relaxation of the heart, and it causes vasoconstriction with a subsequent increase in blood pressure. These effects are caused by the actions of epinephrine and norepinephrine on the adrenergic receptors [2]. Given that norepinephrine is the catecholamine released at the cardiac sympathetic nerve terminals, it can modulate the heart's activity more directly than epinephrine which is released by the adrenal glands in a systemic manner [2, 3]. In addition, some of the norepinephrine released from the postganglionic fibers innervating the heart can also reach the general circulation when it is produced in large amounts in the myocardium [2, 4]. Primarily epinephrine, as well as a small amount of norepinephrine, are produced by chromaffin cells located in the medulla of the adrenal glands [3, 4]. Under normal physiological circumstances 80% of catecholamine production will consist of epinephrine with the remaining 20% being norepinephrine [2].

Heart failure results from the heart's inability to function effectively as a pump due to diseases such as a myocardial infarction or ischemia. Chronic activation of adrenergic signaling is an important feature of many forms of heart disease. Elevated plasma norepinephrine levels in individuals with heart failure are strongly correlated with decreased survival and increased risk of death from chronic heart failure [5]. In heart failure, overactivation of the sympathetic system occurs with the primary goal of maintaining cardiac output in the failing heart [1, 4]. A study by Chidsey et al. [6] was one of the first to highlight the association between heart failure and increased functioning of sympathetic nervous system, as illustrated by higher norepinephrine secretion [6]. Decreased cardiac output in heart failure patients can also impact on the clearance of catecholamines from the plasma, and this, along with increased activation of the adrenal gland further contributes to increased catecholamines in the plasma of heart failure patients [2]. In untreated heart failure patients, the levels of circulating norepinephrine can reach approximately 50 times when compared to those in normal individuals who are exercising to their maximum ability [2, 7]. Plasma levels of norepinephrine in patients with congestive heart failure are significantly higher than those reported for angina patients with no clinical features of heart failure [8, 9]. Elevated epinephrine and norepinephrine levels have also been found in patients with hypertension [10]. In addition to the overactivation of adrenergic system in heart failure, decreased cardiac output increases production of angiotensin II and endothelin, which collectively promote systemic vasoconstriction and increase the afterload. These systemic changes further reduce ejection fraction and cardiac output, and the cycle repeats. The downward spiral is continued until a new steady

state is reached in which cardiac output is lower and afterload is higher than optimal for normal activity.

Despite the discovery of several therapeutic interventions, heart failure due to ischemia remains the number one cause of death worldwide [11]. In adults, cardiomyocytes (CMs) that die in response to aging and pathological insults are replaced by scar tissue instead of new muscle cells [12, 13]. While recent reports suggest an intrinsic capacity for the mammalian myocardium to regenerate via endogenous stem/progenitor cells, the magnitude of such response appears to be minimal and not yet realized in CV patients [14, 15]. Current therapies can increase the life expectancy of end-stage heart failure patients by 2–3 years [16]. Considering these issues, a deeper understanding of molecular mechanisms regulating cell death and survival is essential to combat the increasing burden of heart failure. Studies from multiple laboratories revealed that ischemia and cytotoxic levels of catecholamines can induce autophagy and programmed cell death or apoptosis in many forms of heart disease [17–19]. These two events can account in part for the loss of function in the diseased heart. In this chapter, we have briefly reviewed various signal transduction mechanisms linking adrenergic receptors with apoptosis and autophagy in the heart. In addition, we have provided a brief survey of the literature related to the effects of adrenergic receptor blockers on apoptosis and autophagy in the heart. Subsequently, we have identified some important research questions for future studies.

Adrenergic Receptors in the Heart

Norepinephrine and epinephrine elicit their effects by binding to α- and β-adrenergic receptors (AR). The β-adrenergic receptors (β-ARs) that are located in the mammalian heart are of three subtypes β1, β2, and β3 [20]. Under normal physiological circumstances only β1 and β2 receptors are active [1, 21]. Additionally, α1-ARs of the subtypes 1A, 1B, and 1D are also present in the heart, although their levels of expression are lower than the β-ARs. α1-AR subtypes 1A and 1B are found on cardiomyocytes whereas 1D receptors are found on smooth muscle cells in the coronary arteries. The role of α1-ARs in the heart is not well defined, but studies have shown that they have a protective effect against apoptosis and necrosis and these receptors are also reported to increase the strength of cardiac contractions. Through interactions with α1-ARs in blood vessels epinephrine and norepinephrine can elicit vasoconstriction [1, 22].

Both β1- and β2-ARs are coupled to adenylyl cyclase (AC) through the stimulatory G protein, G_s. Activation of AC leads to an increase in the intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP) which can subsequently activate protein kinase A (PKA). β2-ARs can also interact with the inhibitory G protein, G_i. Under normal conditions, cardiomyocytes predominantly express the β1 subtype, whereas cardiac fibroblasts predominantly express the β2 subtype [23–27]. The β3-ARs are believed to interact with the G_i protein and subsequently inhibit the activation of adenylyl cyclase, ultimately resulting in myocardial

relaxation. These receptors are thought to counteract the effects that the β1- and β2-ARs have on heart rate, conduction speed and inotropy. However, the β3-AR mediated actions are more relevant in disease states as these receptors become activated in response to higher concentrations norepinephrine compared with β1- or β2-ARs [28].

In the failing heart, the adrenergic signalling system changes in response to chronically increased levels of catecholamines. During heart failure, the ratio of β1 to β2 receptors changes from 3:1 to 1:1. Additionally, β1-AR expression at the plasma membrane is decreased and both β1- and β2-ARs become uncoupled from their associated G proteins and this process is termed as β-AR desensitization [2, 29]. The expression level of α1-ARs has been found to either remain constant or increase during heart failure [22].

Role of Adrenergic Receptor Signaling in the Regulation of Apoptosis and Autophagy in the Heart

Apoptosis is a controlled form of cell death. Unlike necrotic cell death where the contents of a dying cell leak out, apoptotic cells are not detrimental to surrounding cells nor do they initiate an inflammatory response [30]. Apoptosis is initiated by a cascade of caspase enzymes ultimately leading to the cleavage of critical proteins required for cell survival and the release of caspase activated DNAse enzymes. Subsequently, cells undergoing apoptosis shrink, lose their cytoskeleton and the cellular DNA is fragmented to the nucleosomal level. Apoptotic cells are then phagocytosed by surrounding cells or macrophages which recognize specific proteins on the surface of dying cells [30]. Autophagy is a cellular process activated in response to cellular stress and is also active in a form of non-apoptotic programmed cell death known as autophagic cell death [23]. Levine and Kroemer [31] suggested that autophagy is an adaptive mechanism used by cells to deal with injurious cellular components such as injured organelles or aggregates of protein. The pathway by which autophagy occurs can be different according to the cell type/environment [31]. The adrenergic signaling pathways associated with cardiovascular apoptosis and autophagy are discussed in subsequent sections.

Chronic catecholamine stimulation can lead to apoptosis in the heart [26, 32, 33]. When cardiomyocytes die, cardiac fibroblasts proliferate to maintain the architecture of the heart and this results in pathological remodeling and contributes to the development of heart failure [34]. Norepinephrine-induced apoptosis occurs via stimulation of the β1-AR and subsequent activation of cAMP-PKA signaling as well as via PKA independent pathways (Fig. 2.1). Conversely, activation of the β2-AR opposes apoptosis. The anti-apoptotic actions of the β2-AR stimulation occur via activation of the G_i protein and subsequent phosphoinositide-3-kinase (PI3K) and Akt activity [2, 32, 33, 35, 36] (Fig. 2.1). The p38 MAP kinase, a known downstream target of PKA, has been shown to play both pro- and anti-apoptotic roles in β-AR
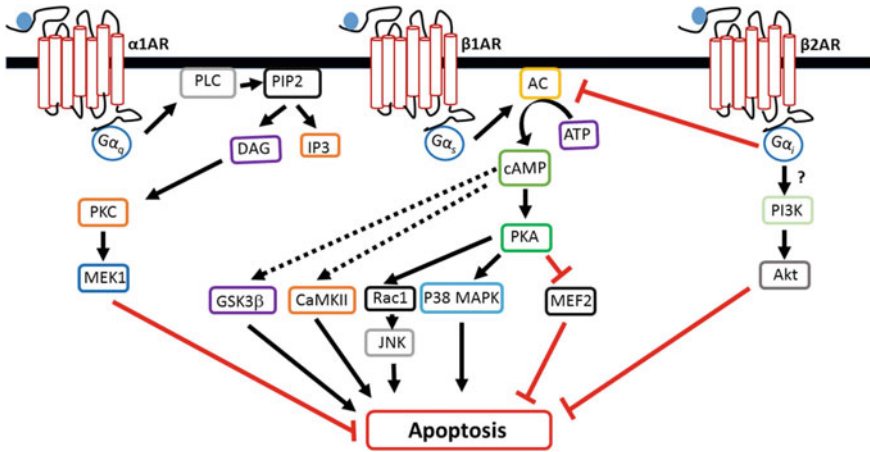
Fig. 2.1 Schematic diagram depicting various mediators involved in the adrenergic receptor (AR) agonist mediated effects on apoptosis in the heart. PLC: phospholipase C; PIP2: phosphotidyl inositol 4,5 biphosphate; IP3: inositol triphosphate; DAG: diacyl glycerol; PKC: protein kinase C; MEK1: mitogen activated protein kinase kinase; AC: adenylyl cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A, p38 MAPK: p38 mitogen activated protein kinase, MEF2: myocyte enhancer factor 2; CaMKII: calcium dependent calmodulin kinase II; GSK3β: glycogen synthase kinase 3β; JNK: c-Jun N-terminal kinase; PI3K: phosphotidyl inositol-3 kinase and Akt: protein kinase B. Unknown signaling connections are indicated by question marks. Solid black arrows indicate the stimulatory events, dashed lines with arrowheads indicate stimulatory events that occur independent of PKA and solid red lines indicate inhibitory events

mediated apoptosis in cardiomyocytes [37, 38]. Notably, chronic stimulation of β1-ARs can also promote cardiomyocyte apoptosis independent of PKA via activation of Ca^{2+}/calmodulin kinase II (CaMKII) [39]. Other studies found that stimulation of β1-ARs can increase cardiomyocyte apoptosis via activation of either Rac1/c-jun N-terminal kinase pathway [40] or GSK-3β [41]. Stimulation of the β1-ARs in neonatal cardiomyocyte cultures by isoproterenol (ISO) or 8-Br-cAMP induced apoptosis [35]. Notably, ISO induced apoptosis could be blocked by co-treatment with a PKA inhibitor and 8-Br-cAMP induced apoptosis was blocked by co-treatment with an α1-AR agonist, phenylephrine via the $G_{\alpha q}$/PKC/MEK-1 pathway (Fig. 2.1) [35].

In addition to the increased levels of catecholamines, autoantibodies against the β1-ARs are frequently generated in patients with dilated cardiomyopathy [42] and experimental models of heart disease [43]. Recent studies indicated that myocardial damage is sufficient to stimulate the generation of β1-AR specific autoantibodies in rats subjected for aortic banding or adriamycin treatment [43] and the long-term presence of these antibodies can significantly decrease cardiac function [44]. While these autoantibodies were shown to activate canonical β1-AR associated cAMP and PKA signaling pathway, sustained stimulation of β1-ARs with these antibodies was shown to increase levels of activated caspase-3 and cardiomyocytes apoptosis [45, 46]. Notably, β1-AR autoantibodies were also shown to increase the cardiomyocyte

endoplasmic reticulum stress and apoptosis via β1-AR coupled CaMKII, p38 MAPK and ATF6 pathway [47]. Long-term exposure to β1-AR autoantibodies was also shown to decrease the myocardial autophagy response and the cardiac dysfunction associated with autoantibodies could be reversed by upregulation of autophagy using the mTOR inhibitor, rapamycin [48].

Consistent with a role for adrenergic receptor signaling in the modulation of cardiomyocyte autophagy, stimulation of β-ARs using a non-selective agonist, isoproterenol was shown to activate Epac1 and increase autophagy in mouse hearts as well as primary rat cardiomyocytes [49]. Notably, pharmacological inhibition or germline deletion of Epac1 prevented the induction of β-AR mediated remodeling and cardiomyocyte autophagy in response to isoproterenol treatment. Specifically, it was shown that agonist actions on β-ARs can activate Epac1 via cAMP, leading to activation of Rap2B and phospholipase C which subsequently activate the Ca^{2+}/CaMKKβ/AMPK pathway (Fig. 2.2). This pathway is proposed to inhibit mTORC1 and thereby stimulate autophagy [49]. In this scenario, autophagy is proposed to be an adaptive response of cardiomyocytes to oppose the effects of Epac1 induced pathological cardiac remodeling [49]. Activation of the β2-ARs in adult rat cardiac fibroblasts by both isoproterenol and salbutamol (a β2-AR selective agonist) stimulated autophagy (Fig. 2.2), which augmented type I collagen degradation [23]. This study proposed that autophagy in response to high levels of catecholamines
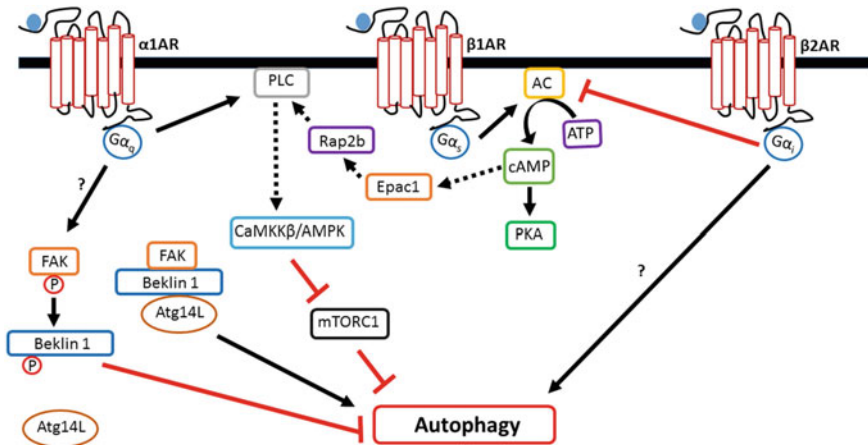

Fig. 2.2 Schematic diagram depicting various mediators involved in the adrenergic receptor (AR) agonist mediated effects on autophagy in the heart. FAK: focal adhesion kinase; Atg14L: autophagy related gene 14-like; AC: adenylyl cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; Epac1: exchange protein directly activated by cAMP 1; PLC: phospholipase C; CaMKKβ: calcium dependent calmodulin kinase kinase β; AMPK: 5' adenosine monophosphate-activated protein kinase; mTORC1: mammalian target of rapamycin 1. Unknown signaling connections are indicated by question marks. Solid black arrows indicate the stimulatory events, dashed lines with arrowheads indicate stimulatory events that occur independent of PKA and solid red lines indicate inhibitory events

may be an attempt to decrease the fibrosis by balancing the changes in extracellular matrix composition resulting from increased adrenergic stimulation [23]. A recent study demonstrated that stimulation of α1-ARs with phenylephrine in cardiomyocyte cultures or in vivo can suppress autophagy and promote hypertrophy (Fig. 2.2) via focal adhesion kinase mediated phosphorylation of Beclin1 and subsequent disruption of Beclin1-Atg14L interaction required for autophagosome formation (Fig. 2.2) [50]. While these observations underscore the importance of α1-AR signaling mediated suppression of cardiomyocyte autophagy in compensatory hypertrophy, it is not known whether this pathway plays any regulatory role in pathological hypertrophy and heart failure.

β-AR Blockers and Heart Disease

Three generations of β-AR blocking drugs have been developed over the past several decades. The first generation of β-blockers are non-selective, meaning that they block both the β1- and β2-AR subtypes. These drugs include propranolol, nadolol and timolol. The second generation β-blockers bind preferentially to the β1-AR subtype and include metoprolol, atenolol and bisoprolol. The third-generation blockers are either selective for the β1 subtype (e.g. celiprolol and nebivolol) or non-selective (e.g. carvedilol). Importantly, the third-generation blockers can also cause vasodilation in the periphery. Carvedilol does so by blocking the α1-AR, while nebivolol elicits this effect by interacting with the endothelium and increasing production of nitric oxide (NO) [28, 51]. Additionally, carvedilol also has antioxidant properties due to its ability to "scavenge free radicals" [52, 53]. β-blockers are effective in treating chronic heart failure as can be seen by their ability to mitigate adverse left ventricular remodeling, decreasing heart rate which then decreases the amount of oxygen required by the heart and the workload of the heart. These outcomes are accomplished by decreasing the toxic actions of the elevated levels of norepinephrine, upregulating the number of β-ARs, among others [1, 2].

The difference in β-AR selectivity between the various β-blockers must be considered when selecting a drug for clinical use. The majority of the "therapeutic actions" of these drugs are due to interactions with β1-ARs, whereas many "adverse effects" are caused by interactions with the β2-AR such as blockade of this receptor in lungs can lead to bronchoconstriction [52]. This interaction has important implications for selecting an appropriate β-blocker for patients suffering from both heart disease and asthma [54, 55]. Additionally, it is important to note that while some drugs are cardioselective by preferentially binding to the β1-AR, such selectivity can be overcome at higher doses as in the case with metoprolol. Nebivolol was found to be more cardioselective compared to other β-blockers such as metoprolol or bisoprolol [52, 56]. The ability of third generation β-blockers to cause vasodilation may be of use in certain circumstances, as discussed below.

A meta-analysis conducted on the use of atenolol to treat uncomplicated hypertension found that it had no impact on the occurrence of myocardial infarction or

mortality compared to placebo or no treatment, despite an ability to decrease blood pressure [57]. It was found that treatment of hypertension with third generation β-blockers had lower incidence of mortality compared with atenolol [57, 58]. Okamoto et al. investigated the actions of nebivolol versus metoprolol on hypertension in patients with autonomic failure to distinguish the β-AR effects from the vasodilatory effects through increasing NO. Nebivolol was able to significantly decrease the systolic blood pressure compared to control whereas metoprolol did not, and thus the authors concluded that nebivolol elicited these antihypertensive effects independent of its actions at the β1-AR [59]. Although another study found that nebivolol decreased the incidence of cardiovascular events more effectively than did metoprolol in patients with acute myocardial infarction (MI) and left ventricular dysfunction, there was no large difference between treatment with metoprolol and treatment with carvedilol with respect to cardiovascular events, nor was there a difference between the carvedilol and nebivolol groups [60]. The authors of this study suggest that carvedilol may be less effective in MI patients since blocking of β2-ARs can impair the pro-survival pathways [33]. Whereas, β2-AR blocking, and antioxidant properties of carvedilol are thought to be beneficial for the treatment of heart failure patients since β2-AR levels and oxidative stress are elevated in those patients [60]. Based on recent reports, it may be beneficial to keep both β2- and α1-AR signaling pathways intact in acute MI patients, as stimulation of β2-AR can increase autophagy and collagen degradation in cardiac fibroblasts [23] and α1-AR stimulation can promote hypertrophy by decreasing cardiomyocyte autophagy [50]. It is possible that blocking both β2- and α1-AR pathways in acute MI patients using carvedilol may lead to precocious fibrosis and impaired compensatory hypertrophic responses in addition to loss of pro-survival signals (Figs. 2.1 and 2.2), subsequently increasing adverse cardiovascular events. Thus, more research should be conducted to confirm the effects of these new generation β-blockers on pathways linking autophagy and apoptosis in addition to a clear focus on clinical outcomes.

New Mechanistic Insights for the Actions of β-AR Blockers in the Regulation of Apoptosis and Autophagy

It is clear from both experimental and clinical literature that β-AR blockers are highly effective in decreasing cardiac workload, oxidative stress, apoptosis, remodeling and arrhythmias in animal models or patients suffering from heart disease. Although β-AR blockers were initially not preferred for the treatment of heart failure due to their negative inotropic effects, positive results from clinical trials combined with new findings related to the novel actions of these drugs have increased a great deal of interest in the development of new generation drugs for the treatment of several forms of heart disease. Notably, the third-generation β-AR blockers nebivolol and carvedilol are also shown to act as antioxidants and increase the activity of endothelial

nitric oxide synthase (NOS). These additional features are helpful since heart disease is often accompanied by oxidative stress [61, 62].

Carvedilol has been implicated in modulating levels of microRNAs (miR), which are known to repress the expression of certain genes following transcription [61]. A study by Xu et al. [63] found that carvedilol upregulated miR-133 in the infarcted rat heart as well as in hydrogen peroxide treated neonatal rat cardiomyocyte cultures [63]. Further, co-treatment of cardiomyocyte cultures with hydrogen peroxide and carvedilol resulted in suppression of caspase 9 expression and associated apoptosis which were normally seen with peroxide treatment alone [63]. However, the mechanistic link between carvedilol treatment and miR-133 upregulation is yet to be established. Activation of β1-ARs in neonatal cardiomyocyte cultures using ISO was shown to induced apoptosis via cAMP/PKA mediated suppression of myocyte enhancer factor 2 (MEF2) transcriptional activity and expression of pro-survival genes such as KLF6 [24]. Whereas, inhibition of β-ARs using atenolol enhanced the MEF2 transcriptional activity and promoted cardiomyocyte survival (Fig. 2..1) [34]. Although clinical use of atenolol over other β-AR blockers in the treatment of hypertension is debated [57, 58], new findings related to atenolol mediated pro-survival pathways could be of use shortly after a myocardial infarction as this could prevent cardiomyocyte apoptosis and the subsequent pathological remodeling [34].

Ahmet and colleagues investigated the long-term effects of β1-AR antagonism in combination with β2-AR agonism using a rat model of chronic heart failure over a period of one year [64]. Rats treated in this manner had a 34% increase in survival when compared to rats that were not treated. Left ventricular remodeling and function were improved with the combination treatment. Additionally, the size of the infarct did not increase, and cardiomyocyte apoptosis was significantly decreased in the combination treatment group [64]. In a rat model of coronary artery ligation and cardioplegia-induced cardiac arrest, carvedilol treatment was found to decrease the amount of cardiomyocyte apoptosis that occurred following the cardioplegia and subsequent reoxygenation via activation of PI3K and MEK (mitogen activated protein kinase kinase) [65]. These observations underscore the potential for carvedilol to be used prior to cardiac surgery for prevention of cardiomyocyte apoptosis. Using a rat model of acute MI, another study found that carvedilol treatment can mitigate the upregulation of toll like receptor 4 (TLR-4) that is commonly seen following an infarction. TLR4 activates inflammatory pathways and has been implicated in pro-apoptotic signaling in the infarcted heart, suggesting this may be the mechanism by which carvedilol decreases apoptosis [66].

Compared to the effects of β-AR blockers on apoptosis, there is scant information on the effects of these drugs on autophagy in the heart. In a rat cardiac resuscitation model, treatment with a short acting β1-AR blocker, esmolol, was effective in reducing the levels of epinephrine induced cardiomyocyte apoptosis, and this protective effect was also correlated with a significant reduction in cardiomyocyte autophagy, as evidenced by reductions in Beclin-1 and parkin expression levels [67]. In a mouse model of pressure-overload induced cardiac dysfunction, treatment with metoprolol (β1-AR blocker) in combination with quiliqiangxin (QL; a Chinese herbal medication) over a 4-week period significantly improved cardiac function, decreased

remodeling and apoptosis compared to QL treatment alone [68]. Although QL+ metoprolol treatment was effective in reducing the levels of an autophagy marker protein (LC3-II) in the diseased heart when compared to no drug treatment group, this combination was not as effective as other combination treatments such as QL+ an angiotensin II receptor blocker or an angiotensin converting enzyme inhibitor [68]. In contrast to the suppressive effects of esmolol and metoprolol on autophagy, an earlier study showed that acute treatment of healthy rats with propranolol (a non-selective β-AR blocker) can significantly increase the volume fraction and density of autophagic vacuoles (AVs) in the left ventricular myocardium compared to the control hearts within 2–4 h after treatment. This study suggested that autophagy is an early cardiac adaptation response to reduced workload since similar effects on AVs were also observed after acute treatment with a calcium channel blocking drug vera-pamil [69]. Similar to the effects of propranolol on AVs, treatment of rats subjected to acute MI with carvedilol for 2 weeks also revealed a significant increase in the number of AVs, autophagy- and anti-apoptosis related proteins (e.g. Beclin-1 and Bcl-XL) in the infarct region and the region bordering infarction compared to those regions in untreated MI hearts [70]. Notably, treatment of non-cardiac HepG2 cells with propranolol in the absence or presence of a β2-AR agonist clenbuterol signifi-cantly increased the LC3-II protein levels [71]. However, propranolol treated HepG2 cells also revealed a significant increase in SQSTM1/p62 protein levels as well as a significant decrease in the number of autolysosomes suggesting that autophagosome flux was blocked at late stages such as lysosomal fusion, acidification or protease digestion [71]. Future studies on autophagosome flux with regards to the status of SQSTM1/p62 levels and autolysosome formation may provide additional insights into the mechanisms underlying protective effects of β-AR blockers in different cardiovascular cell types.

Conclusion

Here, we provide evidence from the literature that adrenergic signaling plays a critical role in the regulation of apoptosis and autophagy in cardiovascular system and both adrenergic receptor agonists and antagonists can be used to modulate the levels of apoptosis and autophagy in the heart. Although common signaling mediators can be readily identified for both pathways, more work needs to be done to define the relationship between apoptosis and autophagy and their relative significance in the context of cardiovascular disease. Some studies suggest that upregulation of autophagy can improve cardiac function [72] while other studies suggest that downregulation of autophagy may be beneficial during disease states [73, 74]. It has also been suggested that inadequate autophagy responses may contribute to cardiac dysfunction [75]. Some in vitro studies suggest that the degree of ischemic injury may dictate the manifestations of autophagy, apoptosis and necrosis in the heart. For example, mild ischemic injury may result in autophagy and apoptosis whereas moderate or severe ischemia may cause apoptosis and necrosis [76]. Thus,

it is generally thought that autophagy can be an early adaptive response to disease and increased autophagy can delay the onset of both apoptotic and necrotic cell death. However, increased autophagy is not always associated with a concomitant decrease in apoptosis as seen with the in vitro effects of different adrenergic receptor agonists and antagonists on these processes. A better understanding of molecular events involved in autophagy and apoptosis and the interplay between these pathways in heart disease as well as additional mechanistic information related to the effects of adrenergic drugs specifically on these processes will enable us to develop efficacious treatments.

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