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REVIEW ARTICLE

Angiotensin-converting enzyme 2–Angiotensin 1-7/1-9 system: novel promising targets for heart failure treatment

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ABSTRACT

Cardiac remodeling (cardiac hypertrophy and fibrosis) is a hallmark of heart failure (HF). It can be induced by the abnormal elevation of several endogenous factors including angiotensin II (Ang II), which is generated from its precursor angiotensin I (Ang I) by the action of angiotensin-converting enzyme. The inhibition of this enzyme or the blockade of the Ang II receptors demonstrated a high clinical value against the progression of HF. Ang I and Ang II may also be converted into angiotensin 1-7 (Ang 1-7) and angiotensin 1-9 (Ang 1-9), respectively, by the action of angiotensin-converting enzyme 2. Both derivatives demonstrated a promising anti-cardiac remodeling activity especially against the detrimental effects of Ang II. This manuscript thoroughly reviews the available in vitro and in vivo data on Ang 1-7 and Ang 1-9 in the context of the treatment of HF and discusses the associated molecular mechanisms and the trials to clinically utilize Ang 1-7 mimetics for the treatment of that disease.

INTRODUCTION

Heart failure (HF) is a common cause for disability and death worldwide. According to a global epidemiological study in the year 2012, the prevalence of HF was over 23 million worldwide, with a lifetime risk of developing the disease to be one in five, and a 5-year mortality rate that is higher than in many types of cancers [1].

Heart failure is a progressive chronic disease that is generally characterized by an imbalance between cardiac output and the metabolic demand of the body. It usually results from diminished contractility of the myocardium (systolic dysfunction), inadequate filling of the heart (diastolic dysfunction), or more often a combination of both dysfunctions. Several underlying disease conditions have long been identified to stand behind cardiac dysfunctions, including myocardial infarctions (MI), chronic ischemia, dilated cardiomyopathy, ventricular hypertrophy (which results from chronic pressure overload or volume overload), cardiac valves stenosis, and pericardial diseases. Any of the aforementioned diseases can weaken cardiac contractility and so can reduce cardiac output, leading to a persistent activation of the sympathetic nervous system (SNS) and concomitantly a reduction in the renal blood perfusion, which in turn activates the renin–angiotensin II (Ang II)–aldosterone system (RAAS), resulting in increased Ang II generation and aldosterone secretion. Both agents mediate several events associated with cardiac remodeling, such as hypertrophy and fibrosis [2]. Although the activation of RAAS and SNS in the early stages of HF development may partially improve cardiac function, the persistent elevation of Ang II levels and SNS activation eventually lead to the detrimental, irreversible, and progressive cardiac remodeling (*Figure 1*) [3,4]. In

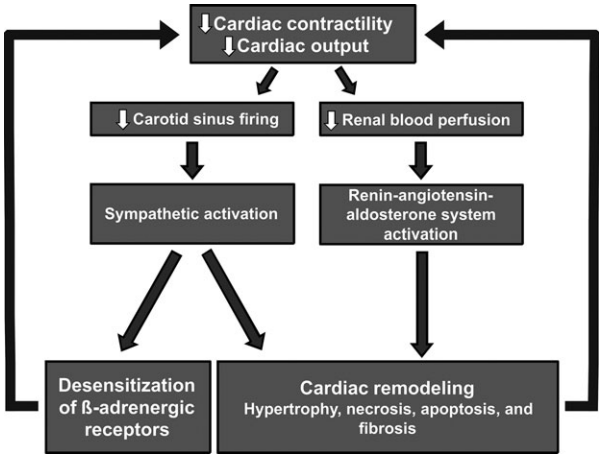

Figure 1 Vicious circle of heart failure. The reduction of the cardiac output, due to several underlying etiologies, induces the activation of the sympathetic nervous system and RAAS, which eventually results in the desensitization of the β-adrenergic receptors and in cardiac remodeling, and consequently in further reduction of the cardiac output. Modified from Maack et al. [4]. RAAS, renin–Ang II–aldosterone system.

addition, among the many types of bioactive molecules secreted by the cardiac cells are the components of the RAAS system, including angiotensinogen, renin, and the angiotensin-converting enzyme (ACE). This allows local generation of Ang II in the microenvironment of cardiac fibroblasts (CF) and cardiomyocytes (CM), which might be central in the maintenance of myocardial homeostasis as well as in the pathogenesis of HF [5].

ANG II

Ang II is the active end product of the RAAS, where angiotensinogen is converted by renin into angiotensin I, which is then cleaved by the ACE into Ang II. Two isotypes of Ang II receptors (AT1R and AT2R) have been identified. Both belong to the G protein-coupled receptor (GPCR) superfamily. In healthy adult individuals, Ang II exerts its biological functions mainly via activation of the AT1R [6], where AT1R is expressed in different cardiac cell types including CF [7], CM [8], and vascular smooth muscle cells [9]. Ang II has been the subject for numerous intensive researches and review articles over the last few decades, which revealed the great significance of this mediator in the pathogenesis of HF, and raised our awareness for the necessity to target it by various pharmacological approaches. In this section, some of the major issues on Ang II are highlighted; however, for more details, the reader is advised to refer to the following selected review articles [10–15].

Role of Ang II in the development of heart failure

In patients with HF, the levels of Ang II in the circulation, myocardium, and the central nervous system are increased [16,17]. Beside the fact that Ang II induces hypertrophy in CM [18], Ang II also induces the differentiation of CF into myofibroblasts [19], and it stimulates these cells to deposit increasing amounts of ECM proteins [20] and to secret profibrotic mediators such as transforming growth factor-β (TGF-β), endothelin-1, matrix metalloproteinases (MMPs), and connective tissue growth factor (CTGF) [21–23]. Ang II is widely believed to mediate some of these fibrogenic effects, at least in part, via the chronic induction of reactive oxygen species generation in the myocardium of patients with HF [24–29].

Ang II as a drug target

The interest in the targeting of RAAS system started in the early 1970s, when seminal studies were published showing that the inhibition of ACE reduced the pressor effects of angiotensin I [30,31]. The year 1978 witnessed the birth of the first member of the clinically used ACE inhibitor (ACE-I) class captopril, which was labeled until that time by the code SQ 14225, and it was introduced to the pharmaceutical market as an antihypertensive drug [32]. Several analogues of captopril were later on synthesized and were introduced in the clinical practice over the successive decades, and demonstrated an outstanding success on the control of blood pressure. This class was intensively investigated by many preclinical and clinical studies, which revealed that ACE-I was not just a casual antihypertensive class, but rather a class that deserves to be an indispensible corner stone not only in the treatment of hypertension but also for the management of HF. The acknowledgment of ACE-I's values compelled the development of other drug classes that target the angiotensin system, including the angiotensin receptor blockers (ARBs) and renin inhibitors. The superiority of the anti-RAAS classes over one another is still controversial [33,34].

The clinical values for the use of these classes in the management of HF were in the subject of many comprehensive review articles. In summary, clinical data demonstrated that ACE-I and ARBs can significantly

slow the progression of HF and reduce cardiovascular mortality; therefore, the current American College of Cardiology/American Heart Association guidelines recommend the use of these drugs for all stages of HF unless a contraindication exists. Numerous studies clearly demonstrated that the inhibition of RAAS system significantly reduced the cardiac remodeling associated with several underlying diseases, which is characterized by a reduction in both cardiac fibrosis and CM hypertrophy [10,35,36].

Besides Ang II, other derivatives of angiotensinogen were discovered such as angiotensin 1-7 (Ang 1-7) and angiotensin 1-9 (Ang 1-9). These derivatives attracted much interest and were in the focus many extensive studies as discussed below.

ANGIOTENSIN-CONVERTING ENZYME 2

The interest in the role of angiotensin-converting enzyme 2 (ACE2) in cardiology research had evolved during the early 2000s, when it was discovered that normal human cardiac tissue expresses this enzyme, and that the expression is upregulated along with the development of HF, and also following MI in both humans and rats [37,38]. At that time, many researchers tried to address the fundamental question whether ACE2 is a casual player in the pathogenesis of HF or a cardioprotectant. That question was so pressing based on the previous recognition of the core role of the renin–Ang II–aldosterone system in the pathogenesis of HF. Crackower et al. were among the first who challenged this question in a well-designed animal model-based study. They showed that the disrupting mutation of ACE2 gene in mice significantly deteriorated the cardiac contractility. Importantly, this was associated with an increase in both the amount of Ang II and the level of expression of the hypoxia-induced gene in the cardiac tissue. In accordance, when ACE gene was ablated in the ACE2 mutant mice, the cardiac phenotype was preserved [39]. These findings were only partially contradicted by data provided by Gurley et al. on an ACE2 null mouse model, as they showed that ACE2-deficient mice had rather normal cardiac dimensions and function, but they exhibited a modest increase in blood pressure as compared with the control animals. However, upon Ang II infusion, ACE2-deficient mice were more prone to hypertension, and they exhibited a marked accumulation of Ang II in the kidneys. The authors agreed with Crackower et al. regarding the proposed cardioprotective function of ACE2, and they proposed that ACE2 is able to prevent the Ang II-induced hypertension via Ang II metabolism. However, the authors denied any evidence for a direct role for ACE2 on the cardiac function and structure [40]. These conclusions were reinforced by the reports showing that ACE2 is the primary metabolic pathway for the conversion of Ang II into Ang 1-7, which interestingly antagonizes the fibrotic and proliferative effects of Ang II as detailed below [41]. However, taking into account that Ang II can induce cardiac fibrosis and hypertrophy (as discussed above) implied that ACE2 can indirectly protect against cardiac remodeling. This was clearly demonstrated by several publications, where ACE2 gene transfer by lentiviruses prevented the hypertension-induced cardiac hypertrophy and fibrosis in animal models of hypertension, whether spontaneous or Ang II induced [42–44]. Moreover, Wang et al. showed in a recent study that mice with heterozygous loss of ACE2 were significantly more prone to pressure overload-induced left ventricular dilation, decline in systolic and diastolic functions, increased myocardial hypertrophy and fibrosis, and increased expression of pathological genes. In the same time, these animals experienced promoted deteriorating effects for Ang II-induced diastolic dysfunction with preserved systolic function that was associated with an increased NADPH oxidase activity and myocardial fibrosis. At the molecular level, the cardiac cells of heterozygous ACE2-deficient mice exhibited an increased phosphorylation of ERK1/2, JNK1/2, and STAT3. These animals also suffered increased vascular fibrosis and stiffness and vascular oxidative stress [17].

Interestingly, the famous antihypertensive drug class ACE-Is do not inhibit ACE2, thus preserving the beneficial effects of this enzyme [45]. Gallagher et al. showed that both Ang II and endothelin-1 separately mediate a ERK1/2-dependent downregulation of ACE2 expression in CM and to a lesser extent in CF. This effect could be antagonized by the AT1R blocker losartan [46].

Taken together, the reviewed data above demonstrated that ACE2 could decrease the plasma levels of Ang II, and thereby might protect against the detrimental effects of Ang II on the cardiac tissue and blood pressure.

Angiotensin 1-7, the metabolite of ACE2

Beside the cardioprotective effects for ACE2 that is dependent on the elimination of Ang II, ACE2 received more appreciation upon the discovery of its role in the

generation of the heptapeptide Ang 1-7. This angiotensin derivative can be generated either directly from Ang I or from Ang II. In the first pathway, Ang I is hydrolyzed directly by prolylendopeptidase or neutral endopeptidase EC 3.4.24.11 into Ang 1-7 [47,48]. In the other pathway, Ang II is converted into Ang 1-7 by prolylcarboxypeptidase or ACE2 [49]. Ang 1-7 has been the subject of intensive research during the last two decades, which revealed much of its values in protection against various cardiac diseases as detailed below.

Ang 1-7 protects against arrhythmias

In the year 1997, Neves et al. [50] reported that Ang 1-7 can prolong the duration of ventricular tachycardia and ventricular fibrillation. However, these finding were later on opposed by several research groups like Ferreira et al., who reported in an animal model that Ang 1-7 did not only protect against ischemia/reperfusion injury but also against the associated ventricular arrhythmias. In addition, their article showed that Ang 1-7 significantly improved the myocardial functions via a receptor-dependent pathway involving the secretion of prostaglandins and bradykinin [51,52]. Moreover, other studies demonstrated that Ang 1-7 could induce the secretion of atrial natriuretic peptide (ANP), which could stand behind its ability to prevent the acute electrical remodeling in canines with acute and chronic atrial tachycardia [53,54]. Other studies demonstrated that the administration of Ang 1-7 to dogs with long-term atrial tachycardia could prevent atrial fibrosis and atrial fibrillation [55].

Ang 1-7 protects against the deleterious effects of Ang II

Later on, Iwata et al. reported that Ang 1-7 could exhibit an antifibrotic and antihypertrophic activity via specific binding sites on CF, through which it antagonized the Ang II-induced collagen synthesis. Importantly, the study demonstrated that these binding sites are distinct from AT1R and AT2R [56]. In consistence with these findings, Grobe et al. [57] reported that co-infusion of Ang 1-7 along with Ang II in rats significantly diminished the Ang II-induced interstitial fibrosis and myocyte hypertrophy. In vitro, treatment of CF with Ang 1-7 antagonized the stimulatory effects of Ang II on CF proliferation and collagen deposition [58]. In addition, a recent study demonstrated that Ang 1-7 blocks the Ang II-induced oxidative stress and by that it inhibits the respective CM autophagy and the associated cardiac remodeling [59].

Ang 1-7 protects against isoproterenol-induced cardiac remodeling

Several reports in mouse models demonstrated protective effects for Ang 1-7 against isoproterenol-induced cardiac hypertrophy and fibrosis [60,61]. Shah et al. presented in vivo evidence that this effect might be associated with the ability of Ang 1-7 to induce the secretion of ANP. The author further supported their findings by similar in vitro results [62].

Ang 1-7 protects against hypertension-induced heart failure

Grobe et al. reported that chronic administration of Ang 1-7 abrogated the cardiac fibrosis in deoxycorticosterone acetate (DOCA)-salt model of hypertension. The protective effect was independent of blood pressure and without any effect of cardiac hypertrophy [63]. However, Santiago et al. reported in a similar animal model that overexpression of Ang 1-7 could protect not only against cardiac fibrosis but also against cardiac hypertrophy. In the same time, it attenuated the elevation of blood pressure following DOCA-salt hypertension [64]. Also in agreement, Mercure et al. [65] showed that transgenic mice overexpressing Ang 1-7 exhibited less ventricular hypertrophy and fibrosis as compared to control animals in response to a hypertensive challenge.

Ang 1-7 enhances cardiac function

In addition, some studies on rat models of HF showed that Ang 1-7 could produce a positive inotropic effects and an enhancement of calcium transient in the left ventricular CM. Interestingly, this effect was selective for the diseased cells [66,67].

Ang 1-7 protects against diabetes-induced cardiac remodeling

Besides cardioprotection against the effects of pro-cardioremodeling mediators, the long-term administration of Ang 1-7 significantly reduced cardiac fibrosis and hypertrophy in animal models of type 2 diabetes [68,69].

The above-discussed data on Ang 1-7 showed that it can protect against cardiac arrhythmias and also prevent the development of HF whether induced by Ang II, the sympathomimetic activity of isoproterenol, salt retention hypertension, or hyperglycemia, besides the direct enhancement of cardiac function.

Molecular mechanisms for Ang 1-7

Ang 1-7 receptors. Ang 1-7 is proposed to function via the GPCR Mas and the orphan receptors Mas-related gene (Mrg) receptor family [70,71]. The genetic deletion of Mas receptors deteriorated the cardiac functions during ischemia–reperfusion of isolated perfused mouse hearts and increased the depositing of collagen in the hearts of such mice when subjected to physical exercise [72,73]. In addition, it was found that physical training increases the formation of Ang 1-7 and the expression of Mas receptors in spontaneously hypertensive rats [74].

Although the majority of articles on Ang 1-7 stress that Mas receptors are the main receptors for Ang 1-7, and focus on the investigation of the downstream signal transduction pathways, Tetzner et al. recently published some interesting data telling us that this is not the whole story, but rather another receptor type can also play a significant role, which is the GPCR Mrg member D (MrgD), that is coupled to $G\alpha_s$. When activated, these receptors can initiate a signal transduction pathway via activation of adenylyl cyclase and the generation of cAMP and the subsequent protein kinase A (PKA) activation [75], which has been already reported to inhibit CM hypertrophy [76].

Signal transduction pathways operated by Ang 1-7. When activated by Ang 1-7, Mas receptors operate via ERK1/2 signal transduction pathway resulting in the down-regulation of the intermediate-conductance Ca^{2+}-activated K^+ channels (KCa3.1). Interestingly, the expression of these channels can be upregulated by Ang II, and they mediate at least in part the Ang II-induced CF proliferation and differentiation into myofibroblasts; therefore, KCa3.1 are believed to play an important role in the fibrotic functions of Ang II in cardiac tissue [77–79]. In addition, the deletion of Mas receptors in mice hearts led to a significant increase in collagen types I/III and fibronectin in different regions of the heart, besides a decline in the levels of both MMP-2 and MMP-9. This was associated with an increase in ERK1/2 and p38 phosphorylation and a decline in cardiac functions [80,81].

McCollum et al. [58] demonstrated that Ang 1-7 attenuated endothelin-1 or Ang II-induced ERK1/ERK2 phosphorylation, beside blocking the increase in the expression of cyclo-oxygenase-2 and prostaglandin synthase by endothelin-1. In the same year, these researchers reported that Ang 1-7 upregulated the MAPK phosphatase dual-specificity phosphatase-1 (DUSP-1), in the time that Ang II had no effects of that enzyme, implying that Ang 1-7 antagonizes Ang II-induced ERK activation via DUSP-1 [82]. In agreement, another mechanistic study by Carver et al. showed, in a rat model of Ang II-induced hypertension, that Ang 1-7 significantly reduced the Ang II-induced perivascular and interstitial fibrosis. This was associated with an upregulation of DUSP-1 and a prevention of Ang II-induced Smad2/3 phosphorylation independently of TGF-β [83]. Tao et al. tried to gain a more insight to the mechanism by which Ang 1-7 regulates the phosphorylation of ERK1/2 in cultured rat CF. They investigated the role of an upstream negative regulator for ERK1/2 phosphorylations, which is the redox-sensitive protein tyrosine phosphatase Src homology2-containing inositol phosphatase 1 (SHP-1). Initially, the authors showed that overexpression of SHP-1 significantly reduced the Ang II-induced phosphorylation of c-Src and ERK1/2 (downstream target of c-Src). In addition, it inhibited the production of TGF-β1 and collagen I/III. Then, they demonstrated that Ang 1-7 was able to increase the activity of SHP-1 via Mas receptor-operated pathway [84]. In a close context, the cardioprotective effects for Ang 1-7 against diabetes-induced cardiac fibrosis and hypertrophy were attributed to the suppression of the growth-promoting pathways in the heart, which was indicated to by lower phosphorylation levels of p38MAPK, ERK1/2, and JNK1/2 [68]. Moreover, Giani et al. demonstrated in an in vivo rat model that Ang 1-7 can increase the phosphorylation of STAT3 and STAT4a/5b through AT1R, while it inhibited ERK1/2 and Rho kinase phosphorylation via Mas receptors; however, the authors did not provide a convincing explanation on how Ang 1-7 may operate AT1R producing an antagonistic action for Ang II [85]. Another signaling pathway for Ang 1-7 was reported in CM, where Ang 1-7 mediates, through Mas receptors, a calcium-dependent synthesis of nitric oxide (NO) that initiates a guanosine 3′,5′-cyclic monophosphate (cGMP)-dependent activation of calcineurin/nuclear factor of activated T-cell signaling (NFAT) cascade. This pathway was linked with the protective effect for Ang 1-7 against Ang II-induced CM hypertrophy [86,87]. In parallel, the positive inotropic effect of Ang 1-7 on HF CM and the associated enhancement of calcium transient in these cells were also linked to the Mas-mediated NO generation [66]. Moreover, the cardioprotective effects of Ang 1-7 against hypertrophy has been at least partly attributed to its ability to increase ANP secretion at high atrial pacing via the

Mas/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway and the activation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and sodium/hydrogen exchanger-1 [62]. This pathway and the resulting induction of ANP secretion have been linked to the anti-arrhythmic effects of Ang 1-7 [53].

Taken together, the overexpression of ACE2 and the subsequent generation of Ang 1-7 in the failing heart sound to be a desperate reflex to counteract the detrimental actions of Ang II, where the activation of Mas receptors by Ang 1-7 antagonize the Ang II-dependent ERK1/2 phosphorylation and the subsequent CF proliferation and differentiation. In addition, Ang 1-7 inhibit CM hypertrophy via the activation of NO–cGMP–calcineurin–NFAT pathway, and the PI3K–Akt–CAMKII-dependent ANP secretion. The major signaling pathways are illustrated in *Figure 2*.

Ang 1-7 mimetic

By cumulative evidences for the favorable effects of Ang 1-7 on the cardiac tissues, several projects tried to investigate the drugability of this target using AVE-0991, the first nonpeptide Ang 1-7 mimetic [88]. Ferreira et al. were the first to report in the year 2007 that AVE-0991 can attenuate postischemic HF via a mechanism involving the activation of Mas receptors and a subsequent release of NO [89]. This was followed by a series of publications that reported beneficial effects for this drug against cardiac remodeling induced by hyperglycemia, isoproterenol, Ang II, ischemia, and oxidative stress [90–94].

Angiotensin 1-9

Angiotensin-converting enzyme 2 may in addition convert Ang I into Ang 1-9, which is also believed to possess direct protective effects against cardiac remodeling. Interestingly, ACE can further convert Ang 1-9 into Ang 1-7 [45,95]. Ocaranza et al. showed that a post-MI continuous infusion of Ang 1-9 for 2 weeks might suppress CM hypertrophy. This effect was associated with a significant decline in the activity of ACE enzyme and the plasma levels of Ang II. To exclude a potential effect for Ang 1-7, the researchers showed that the beneficial effects of Ang 1-9 was not abrogated by the concomitant administration of a Mas receptor blocker. Moreover, they showed that the administration of the AT1R blocker candesartan or the ACE-I enalapril in cardiac infarcted rats greatly increased the plasma levels of Ang 1-9, which was associated with the prevention of ventricular hypertrophy. In addition, they provided in vitro evidence that Ang 1-9 could inhibit CM hypertrophy induced by norepinephrine and insulin-like growth factor-1 (IGF-1) [96]. Flores-Munoz et al. demonstrated by radio-ligand binding assay that Ang 1-9 is able to bind AT2R and that the in vitro pharmacological blockade of these receptors reduced the antihypertrophic effects of Ang 1-9, suggesting that the cardioprotective effects of Ang 1-9 could be mainly mediated via AT2R [97,98]. Furthermore, they showed in vivo that Ang 1-9 had no effects on the blood pressure of spontaneous hypertensive rats; however, it demonstrated in vivo and in vitro an AT2R-mediated antifibrotic activity both in vivo and in vitro [99]. Interestingly, Ocaranza et al. published data showing that Ang 1-9 can reverse hypertension induced by either Ang II or renal artery clipping; in addition, it could reverse some of the detrimental remodeling effects for hypertension including cardiac and aortic wall myocardial hypertrophy, oxidative stress, collagen deposition, fibrosis, and the expression of the pro-cardiac remodeling TGF-β1 protein. Again, these favorable effects were mediated by AT2R and were completely independent of angiotensin-(1-7)/Mas receptor axis [95]. Similar favorable effects for Ang 1-9 were reported against diabetes-induced cardiomyopathy in a rat model based on the induction of diabetes by the administration of streptozocin. Here, Ang 1-9 suppressed the oxidative stress and the generation of pro-inflammatory cytokines in the cardiac tissue. In addition, it inhibited ACE and suppressed the generation of Ang II there. These effects were dependent neither of glucose and insulin levels, nor of Ang 1-7/Mas axis, but rather were mediated by Ang 1-9/AT2R axis [100]. Furthermore, post-MI treatment of mice with a viral vector carrying Ang 1-9 gene prevented sudden cardiac death and greatly reserved left ventricular functions. Interestingly, the authors reported that Ang 1-9 gene delivery resulted in a complete restoration of ejection fraction, end-systolic volume, and end-systolic pressure. In addition, they reported that stroke volume and cardiac output were significantly improved in comparison with the sham mice. The authors also investigated the direct effect of Ang-(1-9) on isolated CM, where it demonstrated a positive inotropic effect that was associated with an increase in calcium transient amplitude and contractility, which was believed to be dependent on the activation of PKA [101].

It can be learned from the discussed data above that Ang 1-9 could protect against cardiac remodeling either indirectly by being biotransformed into Ang 1-7

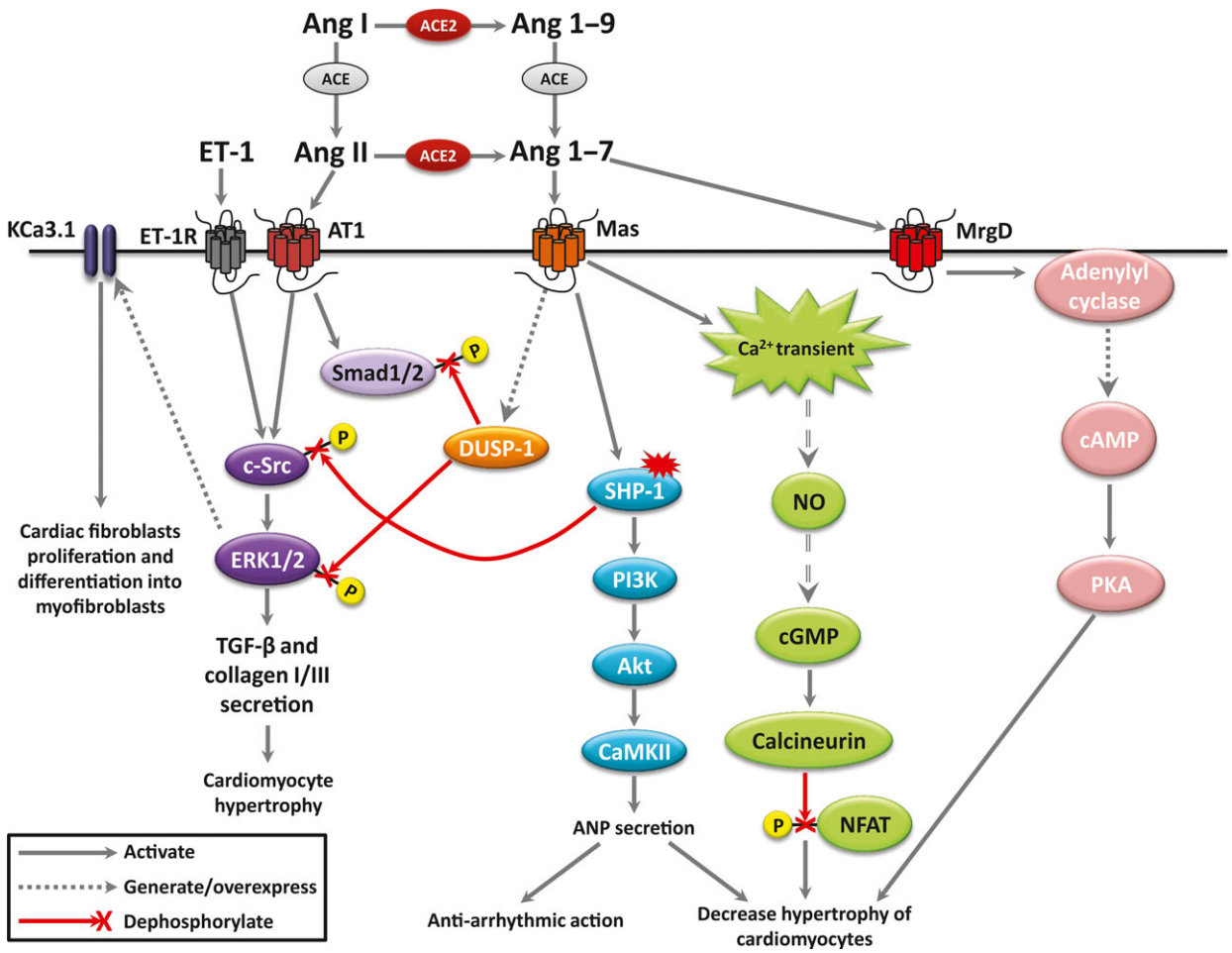

Figure 2 Summary of the main signaling pathways operated by Ang 1-7 that protects against cardiac remodeling and arrhythmias. ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting enzyme inhibitor; Akt: protein kinase B: Ang 1-7: angiotensin 1-7; Ang 1-9: angiotensin 1-9; Ang I: angiotensin I; Ang II: angiotensin II; ANP: atrial natriuretic peptide; AT1R: angiotensin II receptors type 1; AT2R: angiotensin II receptors type 2; CaMKII: Ca2+/calmodulin-dependent kinase II; CF: cardiac fibroblasts; cGMP: guanosine 3′,5′-cyclic monophosphate; CM: cardiomyocytes; DUSP-1: dual-specificity phosphatase-1; KCa3.1: intermediate-conductance Ca2+-activated K+ channels; Mrg: Mas-related gene receptor; MrgD: Mas-related gene receptor member D; NFAT: nuclear factor of activated T-cell signaling cascade; NO: nitric oxide; PI3K: phosphatidylinositol 3-kinase; PKA: protein kinase A; SHP-1: Src homology2-containing inositol phosphatase-1; TGF-β: transforming growth factor-β.

or directly via activation of AT2R. Through these receptors, Ang 1-9 can prevent cardiac remodeling triggered either by Ang II, norepinephrine, IGF-1, hyperglycemia, or hypertension. In addition, it may restore cardiac function following MI.

CONCLUSION

Ang II is a major player in the development cardiac hypertrophy and fibrosis associated with cardiac remodeling. Although the targeting of this mediator by ACE-Is and AT1R blockers demonstrated great clinical benefits, yet such approaches could not completely stop the progression of HF. As a self-saving measure, the failing heart may overexpress ACE2 which can metabolize Ang II. This action may in one hand decrease the plasma levels of Ang II and on the other hand convert Ang II into Ang 1-7, which functions via Mas and MrgD receptors to protect against cardiac remodeling induced by Ang II, sympathetic activation, hypertension, or hyperglycemia. Moreover, Ang 1-7 may improve cardiac function and protects against

arrhythmias. In the same time, ACE2 may metabolize Ang I into Ang 1-9 which might mediate a cardioprotective activity via AT2R. The development of novel drug molecules that can mimic the actions of Ang 1-7 or Ang1-9 might comprise a real opportunity for a pioneering pharmacotherapeutic approach for HF and it might add a significant clinical value to the currently in use medications.

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CONFLICT OF INTEREST

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ABBREVIATIONS

HF – heart failure
ACC – American College of Cardiology
ACE – angiotensin-converting enzyme
ACE2 – angiotensin-converting enzyme 2
ACE-I – angiotensin-converting enzyme inhibitor
AHA – American Heart Association
Akt – protein kinase B
Ang 1-7 – angiotensin 1-7
Ang 1-9 – angiotensin 1-9
Ang I – angiotensin I
Ang II – angiotensin II
ANP – atrial natriuretic peptide
ARBs – angiotensin receptor blockers
AT1R – angiotensin II receptors type 1
AT2R – angiotensin II receptors type 2
CaMKII – Ca^{2+}/calmodulin-dependent kinase II
CF – cardiac fibroblasts
cGMP – guanosine 3′,5′-cyclic monophosphate
CM – cardiomyocytes
CTGF – connective tissue growth factor
DOCA – deoxycorticosterone acetate
DUSP-1 – dual-specificity phosphatase-1
GPCR – G protein-coupled receptor
IGF-1 – insulin-like growth factor-1
KCa3.1 – intermediate-conductance Ca^{2+}-activated K^{+} channels
MI – myocardial infarctions
MMPs – matrix metalloproteinases
Mrg – Mas-related gene receptor
MrgD – Mas-related gene receptor member D
NFAT – nuclear factor of activated T-cell signaling cascade
NO – nitric oxide
PI3K – phosphatidylinositol 3-kinase
PKA – protein kinase A
RAAS – renin–Ang II–aldosterone system
ROS – reactive oxygen species
SHP-1 – Src homology2-containing inositol phosphatase-1
SNS – sympathetic nervous system
TGF-β – transforming growth factor-β

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