



Review

Novel players in cardioprotection: Insulin like growth factor-1, angiotensin-(1–7) and angiotensin-(1–9)



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ABSTRACT

Insulin-like growth factor-1, angiotensin-(1–7) and angiotensin-(1–9) have been proposed to be important mediators in cardioprotection. A large body of evidence indicates that insulin like growth factor-1 has pleiotropic actions in the heart (i.e., contractility, metabolism, hypertrophy, autophagy, senescence and cell death) and, conversely, its deficiency is associated with impaired cardiac function. Recently, we reported that insulin like growth factor-1 receptor is also located in plasma membrane invaginations with perinuclear localization, highlighting the role of nuclear Ca²⁺ signaling in the heart. In parallel, angiotensin-(1–7) and angiotensin (1–9) acting through Mas receptor and angiotensin type 2 receptor have emerged as a novel anti-hypertensive molecules promoting vasodilatation and preventing heart hypertrophy. In this review we discuss the scientific evidence available regarding insulin-like growth factor-1, angiotensin-(1–7) and angiotensin-(1–9) in cardioprotection and its potential application as novel therapeutic targets for treating cardiac diseases.

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Abbreviations: AA, arachidonic acid (AA); ACE, angiotensin converting enzyme; ACE 2, angiotensin converting enzyme 2; AMPK, AMP-activated protein kinase; Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1–7), angiotensin-(1–7); Ang-(1–9), angiotensin (1–9); ARB, angiotensin receptor blockers; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; ATIP1, AT2R-interacting protein 1; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular diseases; DUSP-1, dual-specificity phosphatase-1; eNOS, endothelial nitric oxide synthase; ERK, extracellular-regulated kinase; GH, growth hormone; GPCR, G-protein coupled receptor; HF, heart failure; HT, hypertension; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; IGF-BPs, IGF binding proteins; IGF1, IGF-1 deficiency; IκB, inhibitor of NF-κB; InsP₃, inositol 1,4,5-trisphosphate; IR, insulin receptor; IRS-1, IR substrate-1; MasR, Mas receptor; MI, myocardial infarction; mTOR, mechanistic target of rapamycin; NO, nitric oxide; PI3K, phosphatidylinositol-3 kinase; PLA2, phospholipase A2; PLC, phospholipase C; PTP, protein tyrosine phosphatase; RAS, renin-angiotensin system; rhIGF-1, recombinant human IGF-1; ROS, reactive oxygen species; SERCA2, sarco(endo)plasmic reticulum Ca²⁺ ATPase 2; STZ, streptozotocin; VSMC, vascular smooth muscle cells.

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1. Cardiovascular diseases

Cardiovascular diseases (CVD) are a group of diseases of the heart and blood vessels and they include hypertension (HT), coronary heart disease (CHD), heart failure (HF), angina, myocardial infarction (MI), congenital heart disease, stroke, among others. According to the World Health Organization (WHO), chronic diseases, such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes, are the leading cause of mortality in the world [1]. Of the 57 million global deaths in 2008, 17 million or 30%, were due to CVD [1]. HT, defined as having systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at two or more office visits or current use of blood pressure (BP)-lowering medications [2,3], remains the predominant risk factor for cardiovascular (CV) mortality worldwide [4,5]. Globally, 7.6 million premature deaths and 92 million disability adjusted life-years are attributable to elevated BP [4]. All epidemiological studies show that the risk of adverse CV outcomes, such as stroke, MI, CHD, HF, atrial fibrillation and kidney disease, increase progressively with increasing BP [6,7]. Clinical trials demonstrate that lowering BP reduces such risks [6]. Thus, even small improvements in the treatment of HT could result in widespread CV benefit.

HT induces alteration in small artery structure, mainly eutrophic remodeling, which alters arterial function [8]. This involves a reduction of the lumen diameter by an inward encroachment of the arterial wall [9]. In some conditions, eutrophic remodeling is replaced by a hypertrophic remodeling. In this case, as a consequence of a media thickening to encroach on the lumen, an increase in the media cross-sectional area and media/lumen ratio was observed [9,10]. In patients, angiotensin converting enzyme (ACE) inhibitors [11–13], angiotensin receptor blockers (ARB) [11,12,14] and Ca^{2+} channel antagonists [15] reverse the eutrophic inward remodeling.

Cardiac remodeling is defined as alteration in the structure (dimensions, mass, shape) of the heart in response to hemodynamic load and/or cardiac injury in association with neurohumoral activation. Cardiac remodeling may be described as physiologic (adaptive) or pathologic (maladaptive) [16,17]. Physiologic remodeling is triggered by exercise or pregnancy. This type of remodeling is mediated by insulin-like growth factor-1 (IGF-1) and is reversible [18]. On the other hand, pathologic remodeling may occur with pressure overload (e.g., aortic stenosis, HT), volume overload (e.g., valvular regurgitation), or following cardiac injury (e.g., MI). Initially these changes are compensatory mechanisms which help to maintain ejection performance and heart function. But if noxious stimuli persist, these changes become maladaptive [19]. Pathological remodeling is irreversible and it is frequently associated with an overactivation of renin angiotensin system (RAS) and/or adrenergic system [20]. Ventricular wall thickening due to cardiomyocyte hypertrophy is observed after both MI and chronically hemodynamic overload. If stressful stimuli continue, the heart dilates and cavity walls thin, triggering a systolic dysfunction [21]. These structural changes eventually lead to cardiomyocyte death and their replacement by fibrous tissue, phenomena known as cardiac remodeling [19,21]. Finally, cardiac remodeling results in HF. Therefore, slowing or

reversing remodeling has become an important goal of HF therapy [16].

Emerging evidence suggests beneficial effects of IGF-1 [18], angiotensin-(1–7) [(Ang-(1–7))] and angiotensin-(1–9) [Ang-(1–9)] [22] on the CV system. This review summarizes our current understanding regarding their signaling pathways focused on cardiac function. Furthermore, new potential therapeutic targets and patent applications for the diagnosis/treatment for treating CVD are also discussed. This information reinforces the concept that therapeutic interventions focused on this matter are actually an interesting field for future pharmacological research and clinical studies.

2. Role of insulin like growth factor-1 on the cardiovascular system

2.1. IGF-1 and IGF-1 receptor

IGF-1 is a 70-amino acid polypeptide (~7.6 kDa) and shares ~60% structure homology with IGF-2 and ~50% with pro-insulin [23]. IGF-1 is produced by many tissues, but mainly synthesized in the liver. Moreover, it is the major mediator of the anabolic and growth-promoting effects of hypothalamic growth hormone (GH) acting as a key physiological regulator of the IGF-1/GH axis in several tissues including the CV system (Fig. 1) [24]. The IGF-1 serum levels are regulated for their association with IGF-binding proteins (IGFBPs), particularly IGFBP3 which bounds ~90% of circulating IGF-1 controlling its bioavailability and half-life [25], highlighting the role of the IGF-1/IGFBP3 axis as a predictor of clinical outcomes in HF [26].

The IGF-1 receptor 1 (IGF-1R) is a cell-surface tetrameric tyrosine kinase receptor, cloned and sequenced for the first time in 1986 [27]. IGF-1R is composed of two extracellular α -subunits and two transmembrane β -subunits. The heterotetrameric complex $\alpha_2\beta_2$ (~400 kDa) is synthesized from a unique gene (*Igf-1 receptor*), which is located on chromosome 15 and contains 21 exons in humans. Interestingly, there is no evidence of alternative splicing of exon 11 in the *Igf-1 receptor* gene even though it has been reported in the human insulin receptor (*Ir*) gene and proposed as mechanism responsible for the specificity of IGF-1 and insulin signaling in physiology and disease [28]. *IGF-1R* mRNA encodes for a protein synthesized as a ~180 kDa precursor which is then glycosylated, dimerized and proteolytically processed to yield the mature $\alpha_2\beta_2$ receptor [29]. The most mammalian cells express both the IGF-1R and the IR. Thus, based on the high sequence identity (~58%) between IGF-1R and IR, they can heterodimerize forming IGF-1R/IR hybrid receptors (Fig. 1) [30]. On this regard, Slabby et al. proposed that IGF-1R/IR hybrid receptors have low insulin and high IGF-1 affinity, independent of the IR splice variant [31]. Moreover, IGF-1R may also form heterodimer with the epidermal growth factor receptor [32]. However, the physiological and/or pathophysiological roles of these hybrid receptors are still unclear [28,33]. Several works using different experimental approaches (e.g., ligand competition assay or bioluminescence resonance energy transfer, intact cells or solubilized receptors and ^{125}I -IGF-1 as tracer) have estab-

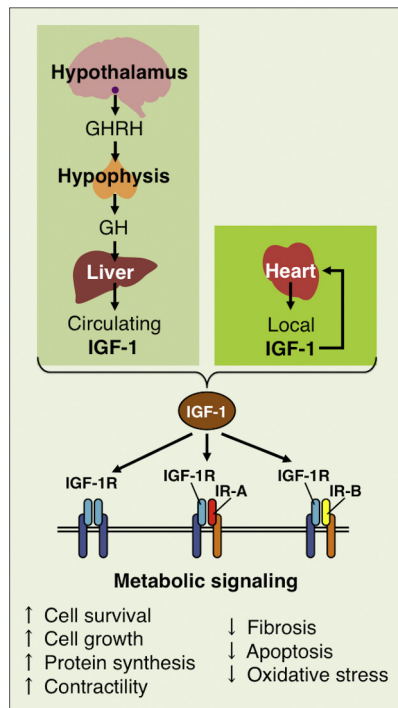


Fig. 1. Physiological and biological effects of IGF-1. IGF-1 is mainly produced in the liver by the growth-hormone-releasing hormone (GHRH)/growth hormone (GH) axis, and also release locally in the heart. IGF-1 activates the insulin-like growth factor receptor 1 (IGF-1R) and hybrids receptors composed either by heterodimers IGF-1R/insulin receptor A (IR-A) or IGF-1R/insulin receptor B (IR-B) depending on their binding affinity. IGF-1R activation promotes cell survival and growth, protein synthesis and contractility. In parallel, IGF-1 inhibits apoptosis and oxidative stress.

lished that the binding affinity of IGF-1 for IGF-1R is near 0.2–2.2 nM [34–37].

2.2. IGF-1R signaling pathways

IGF-1R activation following binding of IGF-1 to the α -subunit subsequently induces IGF-1R β -subunit autophosphorylation triggering several intracellular responses associated with cardiac regulation of cell growth, autophagy, metabolism, aging and apoptosis [18]. The activated IGF-1R tyrosine kinase phosphorylates several intracellular substrates such as IR substrate-1 (IRS-1) and Src homology 2 domain containing family members that act as docking proteins for downstream signaling molecules. Two canonical pathways related to IGF-1-signaling have been described, the phosphatidylinositol-3 kinase (PI3K)/Akt and the extracellular-regulated kinase (ERK) branches [29,38]. Mice with IGF-1R cardiomyocyte-specific knockout showed normal cardiac development, but the hypertrophic response to 5 weeks exercise swim training was prevented, suggesting that AMP-activated protein kinase (AMPK), might antagonize Akt-mediated physiological cardiac hypertrophy induced by IGF-1 [39]. In this sense, McMullen et al. previously showed that mice overexpressing cardiomyocyte-specific IGF-1R exhibited PI3K (p110 α)-mediated physiological cardiac hypertrophy, suggesting the first functional link in vivo between IGF-1 and cardiac growth [40]. On the other hand, IGF-1 has also cardiac antiapoptotic effects mediated by activation of the PI3K/Akt/mechanistic target of rapamycin (mTOR) pathway which induces the phosphorylation-mediated Bad inactivation, whereas its prosurvival effects are linked to activation of Ras/Raf/MEK/ERK signaling pathway

[18]. Interestingly, IGF-1-induced antiapoptotic effects also are blocked by PD098059 (MEK inhibitor) in rat cardiomyocytes [41]. Therefore, experimental evidence suggests a complex crosstalk between both IGF-1-induced canonical signaling pathways in the heart.

As we mentioned before, IGF-1 activates the PI3K/mTOR axis [18]. mTOR also participates as a key negative regulator of autophagy [42], biological process that maintains the cellular homeostasis regulating the organelle turnover, protein degradation, and recycling of intracellular components during cellular stress or nutrient starvation. This effect also emerges as a therapeutic target of clinical relevance on CV biology [43]. Recently, Troncoso et al. showed that IGF-1 negatively modulates nutrient deprivation-induced cardiac autophagy involving activation of the Akt/mTOR and AMPK/mTOR signaling pathways, which in turn promoted the mitochondrial activity [44,45]. Despite the apparent physiological association between IGF-1 and insulin axis they activate differentially the Akt1 and Akt2 isoforms, respectively. Akt1 is associated with normal cardiac growth, whereas Akt2 is linked to cardiomyocyte survival and metabolism [46]. Interestingly, both insulin and IGF-1 increase the mitochondrial activity in cultured rat cardiomyocytes [45,47] raising new questions regarding the complex interplay between their downstream signaling pathways. In this context, the manipulation of the ratio IGF-1R/IR affects hybrid receptor formation and insulin sensitivity in endothelial cells [48,49]. Thus, despite of evidence described above, we cannot rule out the essential role of the endothelium in maintaining an adequate function on the CV system [50].

Both IGF-1R and IR play a key role in determining the bioavailability of nitric oxide (NO) and, therefore, regulate the endothelial function [51]. IGF-1 induces NO release in rat renal inter-lobar artery [52], vascular smooth muscle cells (VSMC) [53] and human umbilical vein endothelial cells, however its effect is less potent (~40%) compared to insulin NO production [54]. Similar to the observed in cardiomyocytes, IGF-1 activates the PI3K/Akt pathway which promotes phosphorylation of the endothelial isoform of nitric oxide synthase (eNOS) [55] that catalyzes the conversion of L-arginine to L-citrulline and generating NO [56]. In parallel, binding of IGF-1 to IGF-1R also leads to Ras/Raf/MEK/ERK signaling pathway which is associated with VSMC proliferation, migration and regulation of atherosclerotic plaque stability [57,58].

Despite that classical IGF-1/Akt/ERK axis signaling has been well established [29,38,39,41], there is evidence regarding the involvement of a non-canonical G protein-mediated pathway in several cell types [59–63], including cardiomyocytes [64–66]. In this context, IGF-1 can also activate via the pertussis toxin-sensitive heterotrimeric G protein the phospholipase C (PLC) and, subsequently increases the intracellular levels of inositol-1,4,5-triphosphate (InsP₃) which activates InsP₃ receptors producing nucleoplasmic [64] and cytoplasmic [65] Ca²⁺ increases. Moreover, IGF-1-dependent hypertrophy is mediated by G $\beta\gamma$ -subunits/Ca²⁺/PKC α /ERK pathway [66], associated with increased [³H]-leucine uptake in cultured rat cardiomyocytes [67]. Recently, Ibarra et al. [64] proposed a novel structural organization model, suggesting that IGF-1R is located in plasma membrane invaginations extremely close to the nucleus, potentially as extensions of the transverse tubule (T-tubule) system to selectively raise local nuclear Ca²⁺ signaling in cardiomyocytes. Thus, future basic and clinical research should be conducted considering that HF has been associated with defective T-tubule organization, decreased contractility [68–70] and cardiomyocyte apoptosis [71], findings that provide a new insight on cardiac physiology and suggest important

future areas for investigation regarding the role of IGF-1 on CVD.

2.3. IGF-1 and cardiovascular diseases

The assumption that IGF-1 system down-regulation is coincident with a prolonged life span in mammals has not been fully elucidated [72]. However, patients with IGF-1 deficiency (Laron syndrome) exhibit reduced life expectancy related to stroke and CVD [73] but maintain heart dimension and function after IGF-1 replacement therapy [74]. Lewis dwarf rats (a GH/IGF-1 deficient model) exhibit cardiac atrophy, defective diastolic function and impaired cardiac contractility [75], similar to the pattern observed in mouse with lower circulating IGF-1 levels, which were linked to reduced sensitivity to aging-associated cardiomyocyte dysfunction [76]. Moreover, a mouse model of liver-specific inducible deletion of IGF-1 gene (LI-IGF-1^{-/-}) showed left ventricular dilatation and negatively affected post MI cardiac remodeling [77]. However, a large body of evidence has been established regarding deleterious effects of IGF-1 signaling network in cancer cells, promoting their growth and resistance to apoptosis [78,79], emerging new questions about the specific role (cardioprotective/oncogenic) of IGF-1 in several tissues. Studies specifically addressing the IGF-1 signaling in the heart have shown that local IGF-1 expression protects mouse cardiomyocytes from oxidative and hypertrophic stresses, reducing reactive oxygen species (ROS) levels and apoptosis triggered by angiotensin II (Ang II) and preventing Ang II-induced hypertrophic response [80]. In the same model, IGF-1 protects the heart from oxidative stress through SirT1/JNK1 axis, suggesting new treatment perspectives during aging and HF [81]. Interestingly, Huynh et al. showed that cardiac-specific IGF-1R protected against cardiac fibrosis and diastolic dysfunction in a streptozotocin (STZ)-induced mouse model of diabetes in vivo [82]. On the other hand, IGF-1 improved high-fat diet-induced cardiac dysfunction preventing the defective insulin signaling, mitochondrial damage and apoptosis [83]. From a physiological point of view, IGF-1 also increases cardiac contractility (inotropic response) promoted by Ca²⁺ release [84,85]. Moreover, IGF-1 promotes the sarco(endo)plasmic reticulum Ca²⁺ ATPase 2 (SERCA2) activity which increases the Ca²⁺ re-uptake to endoplasmic reticulum, improving the contractility in conditions of HT [86,87]. Fig. 2 summarizes the currently available data regarding IGF-1 effects on CV system.

3. Protective role of non-canonical RAS in the treatment of cardiovascular diseases

The RAS plays an important role in the initiation and progression of tissue injuries in the CVD. However, the protective actions of the RAS on the CV system have been demonstrated. The so-called protective arm of the RAS includes the Mas receptor (MasR) and Ang II type 2 receptor (AT2R), which is often characterized by opposite effects compared to Ang II type 1 receptor (AT1R). Nowadays, it is well accepted that both MasR and AT2R participate in the protective arm of RAS with an emerging potential in tissue protection and regeneration [88].

3.1. Angiotensin-(1–7) and angiotensin-(1–9): new players of the non-canonical RAS

One of the major risk factors for developing any CV is HT [89], and thus the RAS is closely related to the CV homeostasis. The classic view of RAS has been broadened since the discovery of the peptides Ang-(1–7) and Ang-(1–9), revealing a counterregulatory action for Ang-(1–7) and Ang-(1–9) in front of Ang II actions [22,90]. The metabolism of angiotensin peptides has been recently reviewed [22]. The classic pathway of RAS involves the enzymatic activity of the protease renin and the cleavage of the peptide angiotensinogen

to angiotensin I (Ang I). Then, Ang I is hydrolyzed by ACE, leading to the formation of the octapeptide Ang II, which has vasoconstrictor activity and induces the release of aldosterone from the cortex of adrenal glands through AT1R. Alternatively, the carboxypeptidase angiotensin converting enzyme 2 (ACE2) can hydrolyze Ang I and Ang II to the peptides Ang-(1–9) or Ang-(1–7), respectively. Likewise, Ang-(1–9) can be metabolized to Ang-(1–7) by ACE. The last discovered member of RAS, alamandine, is formed by decarboxylation of asparagine to alanine in Ang-(1–7) or by hydrolysis of angiotensin A (Ang A) by ACE2. The biological action of Ang-(1–7) and Ang-(1–9) relies upon their binding to MasR and AT2R, respectively [91,92] (Fig. 3).

3.2. Mas signaling pathways

MasR is a G-protein coupled receptor (GPCR) discovered in 1986 and initially misidentified as a proto-oncogene [93,94]. The human MasR is a 325-amino acid polypeptide which share high identity (~91%) with its rat and mouse homologous [94–96]. MasR was the first member identified of the Mas-related GPCR family [97] which also includes the alamandine receptor MrgprD and at least other 50 proteins [97,98]. MasR is highly expressed in brain and testis tissues and to a lesser extent in heart, kidney, lung, liver, spleen, tongue and skeletal muscle [99]. Interestingly, there are remarkable changes in MasR expression in different cardiac physiological and pathological states [100]. In terms of biological function, MasR was rapidly but erroneously associated to RAS as Ang II receptor [101] and it took fifteen years for MasR to be completely identified as Ang-(1–7) receptor after rigorous biochemical (radioligand assays) and functional analyses, evaluating release of arachidonic acid (AA) and relaxation of aorta rings [92]. The use of Ang-(1–7) agonist CGEN-856S [102] and the antagonist A-779 [103] as well as overexpression studies have helped to elucidate the intracellular signaling triggered by MasR. Possibly, the most relevant intracellular signaling pathway activated by MasR upon the binding of Ang-(1–7) is the activation of phospholipase A2 (PLA2)/arachidonic acid (AA) pathway. The stimulation with Ang-(1–7) of CHO and COS cells transfected with MasR induces a significant increase in AA release, which is not limited by AT1R or AT2R antagonists (ibersartan and PD123319, respectively) but it is blocked by MasR antagonist A-779 [92]. This mechanism is the most plausible explanation for the relaxing properties of Ang-(1–7) on vessels. The other major pathway activated by MasR is the PI3K/Akt cascade. Through this pathway, MasR signaling induces eNOS phosphorylation and activation and the concomitant NO release in CHO cells and in MasR cDNA-stably transfected endothelial cells [104] as well as in dog left atria [105]. Moreover, MasR also increases migration in human renal carcinoma cell lines [106]. Reinforcing this concept, it was recently shown that activation of MasR by Ang-(1–7) in skeletal muscle prevents Ang II-induced atrophy which is blocked by MK-2206 (Akt inhibitor) [107]. In addition, MasR/PI3K/Akt pathway increases PPAR γ activity promoting adipogenesis [108], evidence that highlights a novel counterregulatory action of Ang-(1–7) over Ang II. On the other hand, MasR has also been related to the insulin signaling in several tissues and cells [109–111], modifying the phosphorylation state of JAK/STAT, PI3K/Akt and IRS proteins signaling networks, improving the insulin sensitivity and increasing the glucose uptake, although some of these actions are mediated by interactions with AT1R and AT2R. For a deeper understanding of Ang-(1–7)/MasR participation on insulin signaling please see the recent review published by Dominici et al. [112]. Finally, constitutive activity of MasR induces intracellular Ca²⁺ signals that are activated in response to the coupling of the receptor to G_q/G₁₁ proteins, stimulating the activation of PKC, which in turn increases the expression of AT1R [113]. Moreover, increasing the heart availability of Ang-(1–7) in a transgenic rat model induces a potentiation

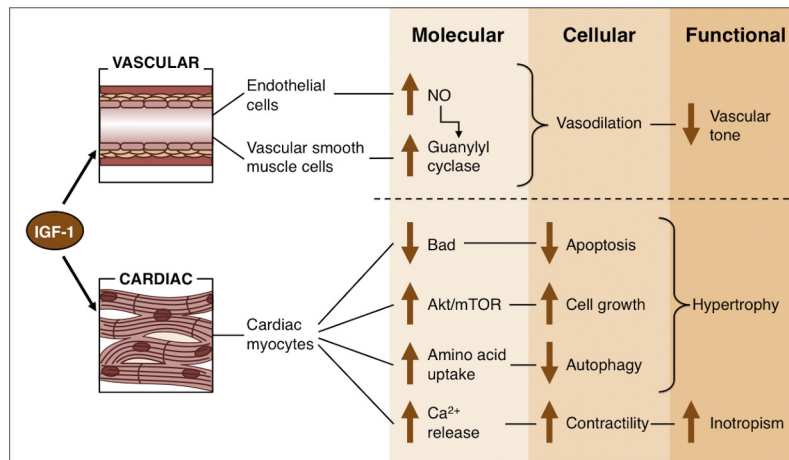


Fig. 2. Cardiovascular effects of IGF-1. This growth factor elicits vasodilatation due to activation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) release from the vasculature towards vascular smooth muscle cells. On the other hand, IGF-1 induces cardiomyocyte hypertrophy triggered by increasing cell growth and stimulating amino acid uptake. Moreover, IGF-1 promotes Bad-mediated apoptosis inhibition and activation of Akt/mTOR pathway which suppresses autophagy. IGF-1 also elicits cardiac contractility associated with stimulation of inotropism and Ca²⁺ release.

of Ca²⁺ handling, seen as higher Ca²⁺ transient amplitude, faster Ca²⁺ uptake, and increased expression of SERCA2 [114]. Accordingly, the absence of MasR in cardiomyocytes from MasR-KO mice elicits opposite effects over Ca²⁺ handling [114]. However, the par-

ticipation of MasR agonists on Ca²⁺ management is still unclear [115,116]. On this regard, as the majority of GPCRs, MasR shows a response depending on the agonist used [117]. Thus, with the exception of CGEN-856S, the agonists (peptidic or not) that stim-

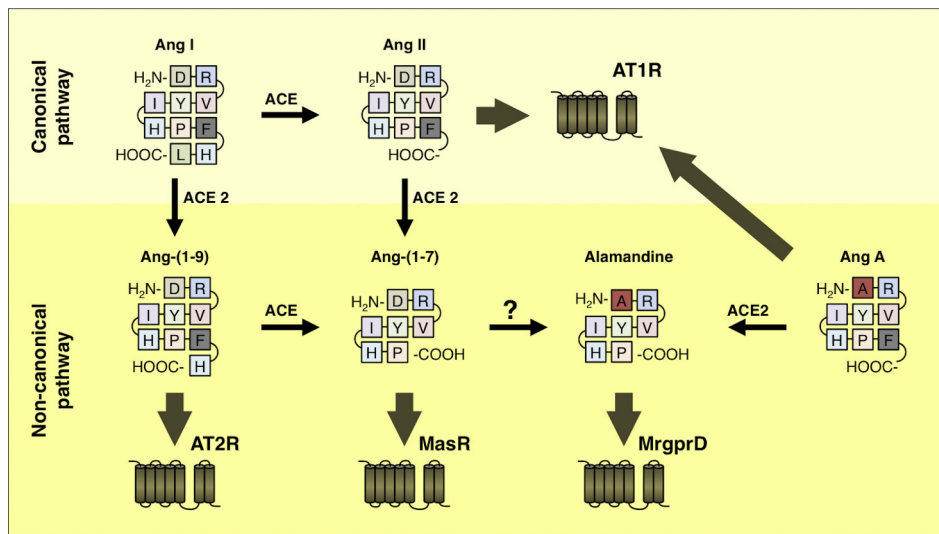


Fig. 3. Canonical and non-canonical signaling of the renin-angiotensin system (RAS). The RAS canonical pathway involves the processing of angiotensinogen to angiotensin I (Ang I) by renin enzyme (not shown in the picture). Subsequently, the angiotensin converting enzyme (ACE) hydrolyzes Ang I leading to Ang II formation, which in turn activates the Ang II receptor type I (AT1R). In the non-canonical RAS pathway, the angiotensin converting enzyme homologue (ACE2) produces both Ang-(1-9) and Ang-(1-7) from Ang I and Ang II, respectively. ACE can cleave the last two amino acids from Ang-(1-9) and generates Ang-(1-7). Moreover, alamanidine can be formed by the change of the aspartic acid of Ang-(1-7) to alanine (unknown enzyme) and also by the ACE2-mediated hydrolysis of angiotensin A (Ang A). Ang A, Ang-(1-9), Ang-(1-7) and alamanidine, bind to their membrane receptor AT1R, Ang II receptor type II (AT2R), Mas receptor (MasR) and Mas-related G-protein coupled receptor member D (MrgprD), respectively.

Table 1
Cardiovascular protection of Ang-(1-7)/MasR and Ang-(1-9)/AT2R axis.

Parameters	Ang-(1-7) by MasR	Ang-(1-9) by AT2R	Reference
ACE activity	=	↓	[146,205]
Ang II levels	↓	↓	[146,205]
Hypertension	↓	↓	[146,206]
Hypertrophy	↓	↓	[122,123,126,127,146,160,161,169]
Fibrosis	↓	↓	[146,163,207]
Oxidative stress	↓	↓	[146,208]
Proliferation	↓	↓	[122,146,163]
Vasodilation	↓	↓	[209]
Apoptosis	↓	?	[210]
NO release	↑	↑↑	[165]

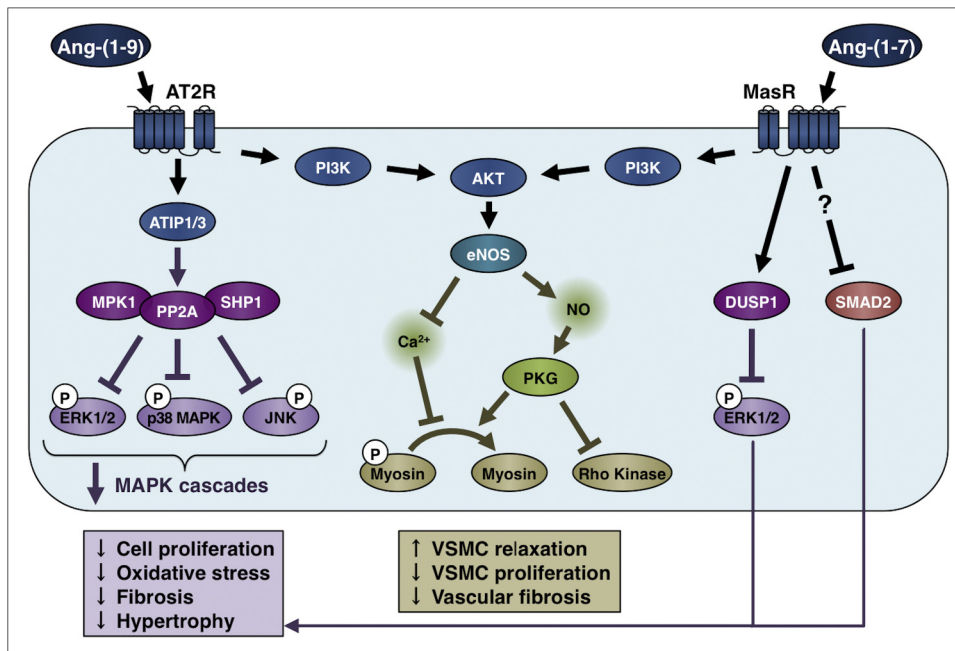


Fig. 4. Intracellular signaling of Mas and AT2 receptors. The binding of Ang-(1–9) and Ang-(1–7) to their receptors, AT2R and MasR, respectively, activates several intracellular cascades that promote vascular and cardiac protection. Activation of Mas receptor (MasR) inhibits the DUSP1-dependent ERK1/2 pathway. Also, MasR inhibits the Smad2 transcription factor by unknown mechanism. AT2R also inhibits p38 MAPK and JNK through the activation of phosphatases MKP1, PP2A and SHP1. This is considered as the main counter-regulatory mechanism of Ang-(1–9)/AT2R pathway against Ang II functions. Both receptor MasR and AT2R converge in the activation of PI3K/Akt pathway, and activation of endothelial nitric oxide synthase (eNOS), increasing nitric oxide (NO) availability.

ulate PI3K/Akt or PLA2/AA pathways are not the same as the ones that elicits intracellular Ca^{2+} concentration increases [97] (Fig. 4).

3.3. Angiotensin-(1–7) and cardiovascular diseases

The actions of Ang-(1–7) on CV biology was firstly assessed 25 years ago in dog hearts [118]. After the identification of MasR as the main receptor for Ang-(1–7) [92], the protective role of Ang-(1–7)/MasR axis has been shown in endothelial dysfunction [119], global ischemia [120], ischemia/reperfusion (I/R) [116], MI [121], cardiac remodeling [122] and HF [123]. It is widely known that I/R induces arrhythmias and contractile dysfunction in cardiac cells and that Ang-(1–7) has a cardioprotective role. In vitro studies showed that Ang-(1–7) improves Ca^{2+} homeostasis in cardiomyocytes subjected to simulated I/R [116]. Regarding to defective electrical coupling in cardiac cells and ischemia-associated arrhythmias, Ang-(1–7) improves cardiomyocyte communication and might improve impulse propagation [124]. In rats that underwent MI by coronary artery ligation, the posterior infusion of Ang-(1–7) by 8 weeks diminished the cross-sectional area of cardiomyocytes [125]. The effect of Ang-(1–7) on cardiomyocyte growth is replicated in other MI and HT animal models [122,123,126] possibly driven by the activation of a dual-specificity phosphatase-1 (DUSP-1) [122] that in turns reduces the activity of the ERK1/2 [127]. Interestingly, when the non-peptide agonist AVE0991 is used instead of Ang-(1–7), the mechanisms of cardioprotection against myocardial hypertrophy depends on the inhibition of TGF- β 1/Smad2 signaling [128], reflecting the bias response of MasR [115,117]. Ang-(1–7) attenuates the development of HF after MI [34,38] and also in pressure-overloaded ACE2-null mice [123]. Moreover, the expression of ACE2/Ang-(1–7) is increased in rats with HF after pressure-overload [129] but reversed by enalapril in MI driven HF [130]. The biomechanical stress produced by pressure-overload in the ACE2-null mice increased the expression of PKC α and phosphorylation grade of ERK1/2, STAT3, Akt, and GSK3 β , all effects that were blunted by the infusion of Ang-(1–7),

recovering all cardiac functions [123]. Interestingly, the beneficial actions of Ang-(1–7) on HF seems not to be restricted to cardiac tissue, since the heptapeptide inhibits the activity of the dorsolateral neurons of midbrain periaqueductal gray zone in the brain of rats provoking a significant decreased in HF [131].

3.4. Angiotensin type 2 receptor (AT2R)

AT2R is a GPCR which shares 34% sequence identity with AT1R [132]. Human *AGTR2* gene, located on the long arm of X chromosome exhibits a 72% homology with rat AT2R, mainly due to a divergence in the amino terminus region [133]. Moreover, AT2R gene consists of three exons with an uninterrupted coding region that codes a 363-aminoacid protein [134]. AT2R is widely expressed in the fetus but in most tissues AT2R levels decline in the neonatal period [135] respect to AT1R [136]. AT2R is expressed in the adult kidney, adrenal cortex, heart (cardiomyocytes and cardiac fibroblasts) and vasculature (aorta, coronary and resistant arteries), and predominate over AT1R in specific sites such as the uterus, ovary, adrenal medulla and in discrete areas of the brain [135,137].

AT1R mediates most of the harmful effects of Ang II, while AT2R has opposite effects [136]. AT2R-dependent cell signaling and effects are less studied than those of the AT1R [138,139], but has vasodilation, anti-proliferative and anti-inflammatory effects [140,141]. Moreover, recent studies showed that AT2R regulates BP, cardiac hypertrophy and fibrosis, and cell death after MI [142,143]. Such effects could be mediated by increased production of NO and vasodilation [144–146].

3.5. AT2R signaling pathways

AT2R activation triggers the NO-cGMP dependent signaling pathway through bradykinin or by increasing eNOS activity or expression [147]. AT2R activation induces protein tyrosine phosphatases (PTP), I κ B (NF- κ B inhibitor) and ATF2 transcription factor phosphorylation, and JNK, p38MAPK, ERK1/2 and

Table 2
Patents describing the use of IGF-1 in the treatment of cardiovascular diseases.

Authors	Title	Description	Patent application numbers
Mandrusov E., Consigny P., Hossainy SFA, Mirzaee D.	Stent for increasing blood flow to ischemic tissues and a method of using the same.	Stent containing IGF-1 as an angiogenic substance.	US6660034 (X6), US2004071861 (A1), US7625593 (B2), US2010047315 (A1), US7867549 (B2)
Gluckman P., Skottner A.	Use of human IGF-1 to treat cardiac disorders	IGF-1 to treat cardiomyopathy, myocarditis, inflammation or myocardial ischaemia and infarction	WO9211865 (A1), AT150316 (T), AU1166992 (A), AU657729 (B2), CA2099257 (A1), DE69218406 (T2), DK0566641 (T3), EP0566641 (B1), ES2101833 (T3), GR3023614 (T3), IE914392 (A1), IL100585 (A), JPH06504286 (A), JP3566283 (B2), NZ241108 (A), ZA9109977 (A), EP0501937 (B1)
Pittenger MF, Gordon SL, Mackay AM.	Cardiac muscle regeneration using mesenchymal stem cells	Use of IGF-1 to differentiate mesenchymal stem cells to cardiac myocytes	WO9903973 (A1), DK1007631 (T4), AU8401498 (A), ES2251773 (T5), AT307195 (T), CA2296704 (C), JP2002511094 (A), JP4562816 (B2), DE69831957 (T3), EP1007631 (A4), EP1007631 (B2)
Libbus I, Ross J, Girouard SD.	Cell therapy and neural stimulation for cardiac repair	IGF-1 as an angiogenic protein to promote cell therapy for cardiac repair	US7548780 (B2), US7548780 (X6)
Jameson BA, Baserga R.	IGF-1 analogs	Short peptides which function as analogs of IGF-1 to prevent restenosis of the coronary arteries after angioplasty	WO9323067 (A1), CA2135306 (A1), EP0639981 (A4), AU4238493 (A), JPH07508025 (A)
Mueller RL, Chee UH	Method and devices for heart treatment.	A method of treating a patient at risk of loss of cardiac function by cardiac ischemia by IGF-1 administration in the heart	US2004254451 (A1), US7392077 (B2)
Zhou M.	Cardiac muscle function and manipulation	A method for providing a therapeutic treatment for heart failure by administration of neuregulin together with IGF-1	US7964555 (B2), WO0037095 (A1), AT442156 (T), AU2422400 (A), EP1158998 (B1), ES2318909 (T3), ES2392596 (T3), EP2027869 (B1), EP2351573 (A1), US2006199767 (A1), US2007129296 (A1), US2007264254 (A1), US7612164 (B2), US7226907 (B1)
Anversa P.	Methods and compositions for the repair and/or regeneration of damaged myocardium.	Use of IGF-1 to treat cardiac stem cells prior to administration of the medicament to the patient.	US2006239983 (A1), US7862810 (B2), US2013288962 (A1), WO2007100530 (A3), US2011152835 (A1), US8663627 (B2), JP2009527482 (A), JP5292106 (B2), EP2001998 (B1), CN101460610 (B), CA2642564 (A1), AU2007221361 (B2)
Clark RG, Jin H, Paoni NF, Yang R.	Treatment of congestive heart failure	Methods of enhancing myocardial contractility and cardiac performance in a mammal with congestive heart failure by administering a combination of growth hormone (GH) and insulin-like growth factor (IGF-I)	WO9528174 (A1), AT208209 (T), AU691273 (B2), AU2195695 (A), LV12966 (B), DE69523747 (T2), JPH09512008 (A), JP3473623 (B2), EP0755265 (B1), CA2185998 (C), ES2167427 (T3), HK1003418 (A1), DK0755265 (T3), PT755265 (E)
Gluckman P, Skottner A.	Use of insulin-like growth factor and medicaments thereof in promoting cardiac muscle synthesis and preventing/treating heart disorders	Use of IGF-1 to treat cardiac problems included myocardial infarct, cardiomyopathies and heart failure	WO9211865 (A1), AT150316 (T), AU1166992 (A), AU657729 (B2), CA2099257 (A1), DE69218406 (T2), DK0566641 (T3), EP0566641 (B1), ES2101833 (T3), GR3023614 (T3), IE914392 (A1), IL100585 (A), JPH06504286 (A), JP3566283 (B2), ZA9109977 (A), EP0501937 (B1), US5434134 (A)
Hammond HK, Kelly TL.	Techniques and compositions for treating heart failure and ventricular remodeling by in vivo delivery of angiogenic transgenes	A method for treating a patient suffering from congestive heart failure, comprising delivering a vector to the heart containing a gene encoding IGF-1	WO9850079 (A3), KR20070005030 (A), CA2289600 (C), EP0980428 (A2), CN1267331 (A), JP2002515065 (A), AU7173598 (A)
Webster KA.	Methods, compositions, cells, and kits for treating ischemic injury	Methods, compositions, cells and kits based on stem cells, when injected into ischemic tissue of mammals, can be protected by preconditioning of the ischemic tissue with hypoxia-regulated human VEGF and human IGF-1	WO2012064920 (A1), US2013236433 (A1), EP2637702 (A4)
Hammond HK, Gao MH.	Systemic delivery and regulated expression of paracrine genes for cardiovascular diseases and other conditions	Methods for treating, cardiovascular diseases using a IGF-1 encoding gene	WO2013123094 (A2), KR20140124403 (A), JP2015508760 (A), EP2814513 (A2), CN104220098 (A), CA2864100 (A1), AU2013221615 (A1)

Table 2 (Continued)

Authors	Title	Description	Patent application numbers
Terzic A., Behfar A.	Treating cardiovascular tissue	Methods and materials for treating cardiovascular tissue using stem cells and IGF-1	WO2006015127 (A9), US2012178164 (A1), US8962320 (B2), US2008213214 (A1), US8173118 (B2), EP2269461 (A1), EP1786471 (B1)
Yitzhack S.	Homing of donor cells to a target zone in tissue using active therapeutics or substances	A method for inducing vascular growth in tissue of a mammal using IGF-1	US2003129750 (A1), KR20040038757 (A), AU2003255220 (A1), CA2447190 (A1), JP2004149533 (A)
Eugene Basu MS, Kuo HC.	Methods and compositions for treating post-myocardial infarction damage	Methods and compositions for treating post-myocardial infarction damage using IGF-1	US8187621 (B2), US2012237477 (A1), US8609126 (B2), WO2007145909 (A3), JP2009539839 (A), JP5595729 (B2), EP2040673 (A2)
Barton ER.	IGF-1 proteins and therapeutic uses thereof	Techniques using pro-IGF-1 for increasing IGF-1 activity for treating or preventing a disease or disorder mediated by IGF-1	WO2014012025 (A3)
Anversa P, Kajstura J, Leri A.	Treatment of heart disease	Methods, compositions and kits for treating cardiac stem cells with IGF-1 to be administered to a subject with cardiovascular diseases such as heart failure, myocardial infarction and an age-related cardiomyopathy	EP2498796 (A4), WO2011057249 (A3), US2012321595 (A1)
Caplice N.	IGF1 for myocardial repair	Methods for treating an individual having an acute myocardial infarction and IGF-1 eluting stents useful for treating such individuals	US2011245915 (A1)
Glass DJ.	IGF-1 and IGF-2 chimeric polypeptides and therapeutic uses thereof	A chimeric protein comprising an IGF1 and an IGF2 component to treat myocardial infarction	US2009175864 (A1), US7781404 (B2), US2006223753 (A1), US7521211 (B2)
Miyatake K, Komamura K, Kiyoto; S.	Novel method for treating chronic severe heart failure by using insulin-like growth factor-1 (IGF-1)	Method for treating chronic severe heart failure by using insulin-like growth factor-1 (IGF-1)	US2009012499 (A1), WO2006085631 (A3), EP1846021 (A2), JP2008529968 (A)
Das GS, Haider N.	Method and system for treating heart failure	A system and method for treating heart failure by direct or indirect delivery of human insulin like growth factor 1 (hIGF-1)	US2008103457 (A1), WO2006076342 (A3), EP1841443 (A4).
Delafontaine P.	Methods and compositions for treatment of atherosclerosis	Methods and compositions for treating subject having atherosclerosis by administering insulin like growth factor-1 (IGF-1)	US2008020982 (A1), US2010267619 (A1)

STAT3 dephosphorylation. These signaling pathways are associated to anti-proliferative and anti-inflammatory effects and cell death [139,148–150]. AT2R activation also triggers relaxation by inhibition RhoA/Rho kinase pathway and by opening the large-conductance Ca^{2+} -activated K^+ channels in VSMC [148,151]. The AT2R also enhances the activity of PTP, vanadate-sensitive phosphatases MKP1 (DUSP1), SHP1 (PTPN6) and PP2A [152,153]; AA release and inhibits cell growth (Fig. 4).

Nouet et al. identified a protein that interacts specifically with the C-terminal tail of the AT2R, the AT2R-interacting protein 1 (ATIP1) [154]. ATIP1 specifically interacts with AT2R but not with AT1R, β_2 -adrenergic receptor or bradykinin receptor [154,155]. Five ATIP isoforms (ATIP1, 2, 3a, 3b and 4) have been identified [156]. Orthologues of rat ATIP3b and 4 have been detected in humans [157]. In a broad range of normal and cancer cell lines, ATIP1 working with AT2R inhibits growth factor-induced and Ang II-induced cell proliferation via MAPK inhibition [155,156,158,159] (Fig. 4). AT2R activation decreases AT1R expression in VSMC. Therefore, agonist binding to AT2R may counter regulate the AT1R mediated effect on CV remodeling. Recently, Ang-(1–9) has shown to be a biologically active peptide within the counter-regulatory axis of the RAS by binding to the AT2R [91] and induces prevention and regression of CV remodeling in HT and MI [22,106,160,161].

3.6. Angiotensin-(1–9) and cardiovascular diseases

Until 2006 all the information regarding Ang-(1–9) indicated that this peptide did not have biological properties. However, there are increasing evidence showing that Ang-(1–9) has CV effects

in vivo and in vitro by activating AT2R [22,160,162,163]. In DOCA-salt hypertensive rats, Ang-(1–9) plasma levels and both plasma and aortic wall ACE2 activities are significantly decreased. However, treatment with a Rho kinase inhibitor, fasudil, reduces BP and increases ACE2 activity in plasma and aortic wall [164]. Moreover, chronic administration of Ang-(1–9) significantly reduces BP in 2 models of HT, Ang II infusion and Goldblatt (2K-1C) models [146]. Furthermore, vascular remodeling gene levels were normalized and eNOS mRNA levels was increased upon chronic administration of Ang-(1–9), suggesting also a vascular protective action of Ang-(1–9) [146]. Ang-(1–9) infusion improved vasorelaxation and NO levels on spontaneously hypertensive stroke prone rats [163]. It has been showed that Ang-(1–9) increases NO bioavailability by stimulating bradykinin release [165,166] and by the increase in NADPH oxidase-4 expression [163], that has been previously associated with endothelium promoted vasodilation by the release of NO [167]. Ang-(1–9) also stimulated atrial natriuretic peptide secretion through the AT2R/PI3K/Akt/NO/cGMP signaling pathway [162]. In addition to NO, the release of the vasodilator arachidonic acid may be also implicated [168]. However, the mechanism by which Ang-(1–9) causes those effects remains to be elucidated.

Ang-(1–9) levels positively correlates with ACE2 activity and heart function in MI rats. Plasma Ang-(1–9) levels and left ventricular ACE2 activities increase significantly when MI rats were treated with the ACE inhibitor enalapril [130]. Ocaranza et al. [160] also showed that Ang-(1–9) regulates cardiac hypertrophy in vivo and in vitro. In MI rats, the treatment with enalapril or the AT1R antagonist candesartan prevented heart hypertrophy and increased plasma Ang-(1–9) levels. These levels correlated inversely with different

Table 3
Patents describing the use of Ang-(1–9) and Ang-(1–7) in the treatment of cardiovascular diseases.

Authors	Title	Description	Patent application numbers
Ocaranza MP, Jalil JE, Lavandero S, Chiong M, Míchea LF.	Use of angiotensin 1–9 in combination in order to prevent arterial hypertension	Angiotensin-(1–9) for the preparation of drugs for treating arterial hypertension and/or inducing vasodilatation	WO2013149355 (A1)
Ocaranza MP, Lavandero S, Jalil J, Chiong M.	Pharmaceutical composition containing angiotensin-(1–9) for cardiovascular, pulmonary and/or cerebral treatment	Pharmaceutical composition containing angiotensin-(1–9) used to treat cardiovascular, remodeling	WO2010069090 (A3), EP2377544 (B1), US2012172301 (A1), ES2525811 (T3)
Alterman M, Hallberg A, Subbaiah AM.	Bicyclic angiotensin II agonists	Bicyclic compounds as selective agonists of the AT2 receptor for the treatment of cardiovascular disorders	US2009069382 (A1), US8357710 (B2), WO2006109058 (A1), MX2007012633 (A), KR20080011282 (A), KR101488812 (B1), JP2013067631 (A), JP2008535900 (A), JP5179349 (B2), JP5179349 (B2), EP1869009 (A1), CN101193881 (A), CA2603254 (C), AU2006235708 (B2)
Alterman; M, Hallberg; AR.	Tricyclic compounds useful as angiotensin II agonists	Tricyclic compounds as selective agonists of the AT2 receptor for the treatment of cardiovascular disorders	US2004167176 (A1), US7652054 (X6), WO02096883 (A1), AT372987 (T), AU2002257970 (B2), CA2449150 (C), CN1529697 (B), DE60222409 (T2), DK1395566 (T3), EP1395566 (A1), EP1395566 (B1), ES2295339 (T3), MXPA03011693 (A), US2009326026 (A1), US8124638 (B2)
Matos JR.	Cyclodextrin derivative salts	Chiral salts comprising anionic cyclodextrin derivatives with particular types of non-metal cations to deliver Ang-(1–9)	US2014046061 (A1)
de Vries L, Nelemans SA, Rinck R, Rocks AJM, Moll GN.	Novel angiotensin type 2 (AT2) receptor agonists and uses thereof	Cyclic peptides that are agonists of the Ang II type 2 receptor (AT2 receptor)	WO2012070936 (A1), EP2455388 (A1), US2014094400 (A1), KR20130099178 (A), JP2014503506 (A), EP2643342 (A1), CN103314006 (A), CA2818299 (A1), AU2011332397 (A1)
McCarthy TD, Naylor A.	Heterocyclic compounds and methods for their use	Heterocyclic compounds derived from pyrrolidine and azetidine compounds useful for antagonising angiotensin II type 2 (AT2) receptor	US2014378430 (A1), JP2015507636 (A), EP2800738 (A1), CN104271553 (A), CA2860577 (A1), AU2013202982 (A1)
Franklin R.	Compositions and methods for treatment of peripheral vascular disease	Compositions and methods for the treatment of peripheral vascular disease based on the use of angiotensin-(1–7) peptides or functional equivalents	US2013210726 (A1), US2013237478 (A1), KR20140140546 (A), JP2015508759 (A), EP2819687 (A1), CN104394878 (A), CA2863699 (A1), AU2013216910 (A1)
García Pérez MA.	Pharmaceutical composition comprising an angiotensin II-receptor antagonist and a calcium channel blocker for the treatment of arterial hypertension	Pharmaceutical composition containing a calcium channel blocking agent and one angiotensin II-receptor antagonist	WO2014119989 (A3); MX2013001277 (A)
Millan RD, Santos RA, Frezad FJ, Nadu AP.	Formulation comprising Angiotensin-(1–7) analogues and cyclodextrin	Angiotensin-(1–7) and its analogues and derivatives in cyclodextrin and the microencapsulation in biodegradable polymers and liposomes to be used in the treatment of arterial hypertension and other cardiovascular diseases	EP1450842 (A2), EP1450842 (B1); WO03039434 (A3); US2010158995 (A1); US2005069533 (A1); US7723304 (B2); MXPA04004313 (A); KR20110042029 (A); KR101246608 (B1); KR20040089078 (A); JP2011037868 (A); JP2005511577 (A); EP2356995 (A3); CN1599620 (A); CN100525830 (C); CA2466232 (A1); BR0105509 (A); AU2002349190 (A1)
Santos RA, Vilas Boas SK, Braga J, Frezard F, Sinisterra R, Silva Neiva C, Lautner R, Fraga Da Silva R.	(Argo)N-angiotensin-(1–7) peptide and pharmaceutical compositions for treating diseases	(Argo)N-angiotensin-(1–7) peptide which is produced by the insertion of at least one arginine amino acid in the amino-terminal position of Ang (1–7), for treating hypertension and other diseases	WO2014040158 (A1)
Franklin R, Stern W, Vryhof A.	Oral formulations of angiotensin	Provides various formulations for oral delivery of angiotensin peptides	WO2014043693 (A1)
Haas M, Kluskens LD, Kuipers A, Rink R, Nelemans SA, Moll Gert N.	Cyclic angiotensin analogs	Cyclised analogs having Ang(1–8) agonistic or antagonistic activity and cyclised Ang(1–7) analogs with agonistic or antagonistic activity to treat hypertension	US2010055146 (A1), US8835375 (B2), WO2008018792 (A3), NZ574876 (A), WO2008130217 (A1), EP2057184 (B1), DK2057184 (T3), CN101573373 (B), CA2660208 (C), AU2007282221 (B2), AT497969 (T)
Sinisterra RD, Ferreira CF, Santos RA, Silva LI, Barros F, Goulart PP, Leite AM.	Process for the preparation of compositions of AT1 receptor antagonist and angiotensin-(1–7)	Pharmaceutical composition containing a AT1 receptor antagonist(s) and angiotensin (1–7) for treating hypertension, cardiovascular diseases, heart hypertrophy, heart failure, coronary diseases, such as angina pectoris, endothelial disorder or endothelial lesions	US2010144624 (A1), US8653031 (B2), WO2008052295 (A1)

Table 3 (Continued)

Authors	Title	Description	Patent application numbers
Tijssma EJ, Driessen-Levels A, Hendriks M.	Angiotensin-(1–7) eluting polymer-coated medical device to reduce restenosis and improve endothelial cell function	Vascular stents with polymer coatings designed to control the release of angiotensin-(1–7) receptor agonists	EP1802361 (B1), US2006088572 (A1), US7176261 (B2), AT448813 (T), WO2006047289 (A3)
Tijssma EJ, Driessen-Levels A.	Angiotensin (1–7) eluting stent	Medical devices with polymer coatings designed to control the release of bioactive agents in combination with angiotensin-(1–7) receptor agonists	WO2008052179 (A3), EP2114479 (A2), US2010055147 (A1)
Alterman M, Wu X, Hallberg A.	New tricyclic angiotensin II agonists	Tricyclic compounds which are useful as selective agonists of the AT2 receptor for the treatment of cardiovascular disorders	EP1869023 (B1), WO2006109048 (A1), US2009042931 (A1), US8080571 (B2), MX2007012634 (A), KR20080009275 (A), KR101429484 (B1), JP2013040208 (A), JP2008535898 (A), JP5202301 (B2), ES2395194 (T3), DK1869023 (T3), CN101193886 (A), CN101193886 (B), CA2604797 (C), AU2006235698 (B2), AT540947 (T)
Santos RA, Veloso Brant S, De Faria R, Silva I, Barros F, Frezard FJG, Dos Reis, AM, De Franca LR, Ferreira AJ, Sinisterra R, Campagnole MJ, De Oliveira WN, De Castro M.	Use of Mas G-protein-coupled receptor agonists and antagonists, as apoptotic-activity modulators for study, prevention and treatment of diseases	Use of Mas G-protein-coupled receptor agonists and antagonists for treatment of diseases	US2008312129 (A1), WO2007000036 (A3), BRPI0502497 (A), EP1904087 (A2), JP2008546811 (A), CN101247818 (A), CA2613126 (A1), JP2013075911 (A),
Santos RA, Sousa SH, Alvarez JI, Matos M, Siqueira A, Rodrigues FL, Bader M, Alenina N, Sinisterra RD.	Use of Mas-G-protein-coupled receptor agonists in the treatment of the metabolic syndrome, its components and its complications	Use of Mas-G- protein-coupled receptor agonists for the control, prevention and treatment of the body levels of triglycerides, cholesterol and glucose, as well as of hypertension	WO2007121546 (A8), BRPI0602366 (A), EP2018185 (A1), US2009221498 (A1), US8586054 (B2)
Roks JM, Pinto YM, Henning RH, Van Gilst WH.	Use of angiotensin-(1–7) for preventing and/or reducing the formation of neointima	An implantable device for releasing angiotensin-(1–7) to prevent and/or reduce the formation of neointima	WO2006049490 (A1), US2005142130 (A1), CA2582048 (A1), JP2008513442 (A), EP1799245 (A1)
Heitsch H.	p-thienylbenzylamides as agonists of angiotensin-(1–7) receptors, and methods of their preparation and use	p-thienylbenzylamides as potent agonists of angiotensin-(1–7) receptors and are useful to treat and/or prevent hypertension, cardiac hypertrophy, cardiac insufficiency, coronary heart diseases, such as angina pectoris; and endothelial dysfunction or endothelial damage	US2003144343 (A1), US6984660 (X6), WO20072569 (A1), US2002188139 (A1), US6538144 (B2), DE10112041 (A1), EP1370548 (B1), JP2004527507 (A), JP4291578 (B2), AT316968 (T), CA2440647 (A1), MXPA03007635 (A), AR035781 (A1), PE09102002 (A1)
Hallberg A, Alterman M, Subbaiah AMU.	New bicyclic angiotensin II agonists	Bicyclic compounds as selective agonists of the AT2 receptor for the treatment of cardiovascular disorders	WO2004046128 (A1), AU2003286251 (A1)
Heitsch H, Wiemer G.	1-(p-thienylbenzyl)imidazoles as agonists of angiotensin (1–7) receptors, processes for their preparation, their use, and pharmaceutical preparations comprising them	1-(p-thienylbenzyl)imidazoles as potent agonists of angiotensin (1–7) for the treatment and prophylaxis of high blood pressure, cardiac hypertrophy, cardiac insufficiency, coronary heart diseases such as angina pectoris, cardiac infarct, vascular restenosis after angioplasty, cardiomyopathies, endothelial dysfunction or endothelial damage, and arterial and venous thromboses	WO0068226 (A1), YU78601 (A), US2001018449 (A1), US6429222 (B2), US6235766 (B1), US2002077344 (A1), TR200103171 (T2), SK15942001 (A3), RU2247121 (C2), PL351609 (A1), NZ515242 (A), NO20015309 (A), JP2002544130 (A), HU0201311 (A3), HRP20010814 (A2), HK1045519 (A1), EP1185527 (B1), EE200100572 (A), CZ20013907 (A3), CN1349530 (A), CN1158279 (C), CA2373010 (A1), BR0010248 (A), AU4753600 (A), AU775244 (B2), AT300535 (T), AR023837 (A1)

cardiac hypertrophy markers, even after adjusting for BP reduction [160]. Furthermore, chronic administration of Ang-(1–9) to MI rats prevented cardiac hypertrophy [160]. These effects of Ang-(1–9) seem to be mediated by the AT2R, but not by Ang-(1–7) [161,163,169]. Interestingly, Ang-(1–9) treatment also alleviated STZ-induced cardiomyopathy and attenuated myocardial dysfunction [170].

Table 1 shows a comparison of the pharmacological effects of Ang-(1–7) and Ang-(1–9) on the CV system.

4. Conclusions and therapeutic perspectives

Recombinant human IGF-1 (rhIGF-1) is available for human use. In 2005, the Food and Drug Administration (FDA) approved the use

of Mecasermin (INN, trade name Increlex), a recombinant DNA-derived human IGF-1 produced in *Escherichia coli* manufactured by Tercica Inc., for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary IGF-1 deficiency (IGFD). Severe primary IGFD includes patients with mutations in the GH receptor, post-GH receptor signaling pathway, IGF-1 gene defects, or have developed neutralizing antibodies to GH, and therefore, they cannot be expected to respond adequately to exogenous GH treatment [171,172]. This drug is not to be confused with mecasermin rinfabate (trade name Iplex, which was previously called SomatoKine), which is a combination of rhIGF-1 and IGFBP-3. IGFBP-3 serves to prolong the action of IGF-1 in the human body [173]. Iplex was approved by FDA in 2005 to Insmad Inc. Besides IGFD, several clinical trials have evaluated the use of IGF-1 for treatment of type 2 diabetes [174,175], hyperinsulin-

ism [176–178], amyotrophic lateral sclerosis [179], HIV metabolic disease [180], X-linked severe combined immunodeficiency [181], Rett syndrome [182,183], retinopathy of prematurity [184], wound healing [185], myotonic muscular dystrophy [186,187], Duchenne muscular dystrophy [188], multiple sclerosis [189], Crohn disease [190], Laron syndrome [191], anorexia nervosa [192,193], severe burn injury, patellar tendinopathy [194], cystic fibrosis [195], and autism spectrum disorder [196]. However, only 2 clinical trials have used rhIGF-1 for treating CVD, one in MI [197] and the other in the modification of CV risk factors [198]. In spite of few clinical applications, 23 patent applications described the use of IGF-1 in the treatment of CVD (Table 2). Six patent applications are related to the use of IGF-1 in cardiac stem cell treatment, 5 to treat vascular disorders, and 12 to treat several cardiac disorders. However, none of these uses have been tested in clinical trials yet.

Drugs which block RAS have proven a major advance in CV medicine. ACE inhibitors and AT1R selective antagonists are widely used as first line treatment in HT, HF and diabetic nephropathy [199]. Although ACE inhibitors and AT1R antagonists block the same system, experimental evidence suggests that their mechanisms of action also involve the increase of Ang-(1–9) levels [22,130]. Moreover, the Ang-(1–9)/AT2R axis has risen as a new alternative for treatment of CVD. There are currently three new AT2R agonists with the potential to become a usable drug: (1) Compound 21 (C21), a small nonpeptide molecule developed by Vicore Pharma, Gothenburg, Sweden [200]; (2) a cyclic Ang II derivative (LP2) developed by Lanthio Pharma, Groningen, the Netherlands [201]; and (3) Ang II derivatives with single amino acid in the sequence substituted by the respective β -amino acid [202]. On the other hand, there are currently two MarR agonists: (1) CGEN-856S, a small nonpeptide molecule developed by Comugen Ltd., Tel Aviv, Israel [203]; and (2) AVE 0991 (5-formyl-4-methoxy-2-phenyl-1[[4-[2-ethylaminocarbonylsulfonamido]-5-isobutyl-3-thienyl]-phenyl]-methyl]-imidazole), a small nonpeptide molecule developed by Aventis Pharma Deutschland GmbH, Frankfurt/Main, Germany [204]. None of the above 5 drugs were assayed in clinical trials. In Table 3 are depicted 14 patent applications related to the use of Ang-(1–9) and Ang-(1–7) in the treatment of CVD. Two patent applications are related to Ang II antagonism, 4 to AT2R agonists, 9 and 3 to Ang-(1–7) and Ang-(1–9) for treating several CVD, respectively. Major translational challenges still remain in this exciting area, but patients with CVD are likely to benefit from these efforts.

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References

- WHO. www.who.int/gho/ncd/en/index.html Global Health Observatory (GHO), 2013.
- K.K. Proia, A.B. Thota, G.J. Njie, R.K. Finnie, D.P. Hopkins, Q. Mukhtar, N.P. Pronk, D. Zeigler, T.E. Kottke, K.J. Rask, D.T. Lackland, J.F. Brooks, L.T. Braun, T. Cooksey, Team-based care and improved blood pressure control: a community guide systematic review, *Am. J. Prev. Med.* 47 (2014) 86–99.
- A.S. Go, D. Mozaffarian, V.L. Roger, E.J. Benjamin, J.D. Berry, M.J. Blaha, S. Dai, E.S. Ford, C.S. Fox, S. Franco, H.J. Fullerton, C. Gillespie, S.M. Hailpern, J.A. Heit, V.J. Howard, M.D. Huffman, S.E. Judd, B.M. Kissela, S.J. Kittner, D.T. Lackland, J.H. Lichtman, L.D. Lisabeth, R.H. Mackey, D.J. Magid, G.M. Marcus, A. Marelli, D.B. Matchar, D.K. McGuire, E.R. Mohler 3rd, C.S. Moy, M.E. Mussolino, R.W. Neumar, G. Nichol, D.K. Pandey, N.P. Paynter, M.J. Reeves, P.D. Sorlie, J. Stein, A. Towfighi, T.N. Turan, S.S. Virani, N.D. Wong, D. Woo, M.B. Turner, Heart disease and stroke statistics–2014 update: a report from the American Heart Association, *Circulation* 129 (2014) e28–e292.
- C.M. Lawes, H. Vander, S. oorn, A. Rodgers, Global burden of blood-pressure-related disease, 2001, *Lancet* 371 (2008) 1513–1518.
- D. Susic, E.D. Frohlich, Hypertensive cardiovascular and renal disease and target organ damage: lessons from animal models, *Cardiorenal Med.* 1 (2011) 139–146.
- A.V. Chobanian, G.L. Bakris, H.R. Black, W.C.ushman, L.A. Green, J.L.J. Izzo, D.W. Jones, B.J. Materson, S. Oparil, J.T.J. Wright, E.J. Rocella, Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure, *Hypertension* 42 (2003) 1206–1252.
- A.S. Go, D. Mozaffarian, V.L. Roger, E.J. Benjamin, J.D. Berry, W.B. Borden, D.M. Bravata, S. Dai, E.S. Ford, C.S. Fox, S. Franco, H.J. Fullerton, C. Gillespie, S.M. Hailpern, J.A. Heit, V.J. Howard, M.D. Huffman, B.M. Kissela, S.J. Kittner, D.T. Lackland, J.H. Lichtman, L.D. Lisabeth, D. Magid, G.M. Marcus, A. Marelli, D.B. Matchar, D.K. McGuire, E.R. Mohler, C.S. Moy, M.E. Mussolino, G. Nichol, N.P. Paynter, P.J. Schreiner, P.D. Sorlie, J. Stein, T.N. Turan, S.S. Virani, N.D. Wong, D. Woo, M.B. Turner, Heart disease and stroke statistics–2013 update: a report from the American Heart Association, *Circulation* 127 (2013) e6–e245.
- A.S. Greenstein, A. Price, K. Sonoyama, A. Paisley, K. Khavandi, S. Withers, L. Shaw, O. Paniagua, R.A. Malik, A.M. Heagerty, Eutrophic remodeling of small arteries in type 1 diabetes mellitus is enabled by metabolic control: a 10-year follow-up study, *Hypertension* 54 (2009) 134–141.
- M. De, J.G. ey, P.M. Schiffers, R.H. Hilgers, M.M. Sanders, Toward functional genomics of flow-induced outward remodeling of resistance arteries, *Am. J. Physiol. Heart Circ. Physiol.* 288 (2005) H1022–H1027.
- K. Sonoyama, A. Greenstein, A. Price, K. Khavandi, T. Heagerty, Vascular remodeling: implications for small artery function and target organ damage, *Ther. Adv. Cardiovasc. Dis.* 1 (2007) 129–137.
- D. Rizzoni, E. Porteri, G. Bettoni, A. Piccoli, M. Castellano, M.L. Muesan, G. Pasini, D. Guelfi, E.A. Rosei, Effects of candesartan cilexetil and enalapril on structural alterations and endothelial function in small resistance arteries of spontaneously hypertensive rats, *J. Cardiovasc. Pharmacol.* 32 (1998) 798–806.
- D. Rizzoni, E. Porteri, A. Piccoli, M. Castellano, G. Bettoni, M.L. Muesan, G. Pasini, D. Guelfi, M.J. Mulvany, R. Agabiti, E. osei, Effects of losartan and enalapril on small artery structure in hypertensive rats, *Hypertension* 32 (1998) 305–310.
- N.K. Thybo, N. Stephens, A. Cooper, C. Aalkjaer, A.M. Heagerty, M.J. Mulvany, Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension, *Hypertension* 25 (1995) 474–481.
- E.L. Schiffrin, J.B. Park, H.D. Intengan, R.M. Touyz, Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan, *Circulation* 101 (2000) 1653–1659.
- E. Porteri, D. Rizzoni, A. Piccoli, M. Castellano, G. Bettoni, M.L. Muesan, G. Pasini, D. Guelfi, R. Zulli, E.A. Rosei, Effects of hypotensive and non-hypotensive doses of manidipine on structure, responses to endothelin-1 and ICAM-1 production in mesenteric small resistance arteries of spontaneously hypertensive rats, *Blood Pressure* 7 (1998) 324–330.
- J.N. Cohn, R. Ferrari, N. Sharpe, Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an international forum on cardiac remodeling, *J. Am. Coll. Cardiol.* 35 (2000) 569–582.
- G.W. Dorn, R. 2nd, J. obbins, P.H. Sugden, Phenotyping hypertrophy: eschew obfuscation, *Circ. Res.* 92 (2003) 1171–1175.
- R. Troncoso, C. Ibarra, J.M. Vicencio, E. Jaimovich, S. Lavandero, New insights into IGF-1 signaling in the heart, *Trends Endocrinol. Metab.* 25 (2014) 128–137.
- L.H. Opie, P.J. Commerford, B.J. Gersh, M.A. Pfeffer, Controversies in ventricular remodelling, *Lancet* 367 (2006) 356–367.
- H.D. Intengan, E.L. Schiffrin, Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants, *Hypertension* 36 (2000) 312–318.
- M.J. Davies, A macro and micro view of coronary vascular insult in ischemic heart disease, *Circulation* 82 (1990) I138–46.
- M.P. Ocaranza, L. Michea, M. Chiong, C.F. Lagos, S. Lavandero, J.E. Jalil, Recent insights and therapeutic perspectives of angiotensin-(1–9) in the cardiovascular system, *Clin. Sci. (Lond.)* 127 (2014) 549–557.
- M. De, P. eys, J. Whittaker, Structural biology of insulin and IGF receptors: implications for drug design, *Nat. Rev. Drug Discovery* 1 (2002) 769–783.
- A. Colao, The GH-IGF-I axis and the cardiovascular system: clinical implications, *Clin. Endocrinol. (Oxf)* 69 (2008) 347–358.
- J.A. Janssen, A.J. Varewijck, IGF-IR targeted therapy: past, present and future, *Front. Endocrinol. (Lausanne)* 5 (2014) 224.
- S. Watanabe, T. Tamura, K. Ono, H. Horiuchi, T. Kimura, T. Kita, Y. Furukawa, Insulin-like growth factor axis (insulin-like growth factor-I/insulin-like growth factor-binding protein-3) as a prognostic predictor of heart failure: association with adiponectin, *Eur. J. Heart Fail* 12 (2010) 1214–1222.
- A. Ullrich, A. Gray, A.W. Tam, T. Yang-Feng, M. Tsubokawa, C. Collins, W. Henzel, T. Le Bon, S. Kathuria, E. Chen, et al., Insulin-like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity, *EMBO J.* 5 (1986) 2503–2512.

- [28] A. Belfiore, F. Frasca, G. Pandini, L. Sciacca, R. Vigneri, Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease, *Endocr. Rev.* 30 (2009) 586–623.
- [29] T.E. Adams, V.C. Epa, T.P. Garrett, C.W. Ward, Structure and function of the type 1 insulin-like growth factor receptor, *Cell. Mol. Life Sci.* 57 (2000) 1050–1093.
- [30] A.J. Varewijck, J.A. Janssen, Insulin and its analogues and their affinities for the IGF1 receptor, *Endocr. Relat. Cancer* 19 (2012) F63–F75.
- [31] R. Slaaby, L. Schaffer, I. Lautrup-Larsen, A.S. Andersen, A.C. Shaw, L.S. Mathiasen, J. Brandt, Hybrid receptors formed by insulin receptor (IR) and insulin-like growth factor 1 receptor (IGF-IR) have low insulin and high IGF-1 affinity irrespective of the IR splice variant, *J. Biol. Chem.* 281 (2006) 25869–25874.
- [32] F. Morgillo, J.K. Woo, E.S. Kim, W.K. Hong, H.Y. Lee, Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib, *Cancer Res.* 66 (2006) 10100–10111.
- [33] J. van der Veecken, S. Oliveira, R.M. Schifferers, G. Storm, P.M. van Bergen En Henegouwen, R.C. Roovers, Crosstalk between epidermal growth factor receptor- and insulin-like growth factor-1 receptor signaling: implications for cancer therapy, *Curr. Cancer Drug Targets* 9 (2009) 748–760.
- [34] S. Benyoucef, K.H. Surinya, D. Hadaschik, K. Siddle, Characterization of insulin/IGF hybrid receptors: contributions of the insulin receptor L2 and Fn1 domains and the alternatively spliced exon 11 sequence to ligand binding and receptor activation, *Biochem. J.* 403 (2007) 603–613.
- [35] G. Pandini, F. Frasca, R. Mineo, L. Sciacca, R. Vigneri, A. Belfiore, Insulin/insulin-like growth factor 1 hybrid receptors have different biological characteristics depending on the insulin receptor isoform involved, *J. Biol. Chem.* 277 (2002) 39684–39695.
- [36] L. Sciacca, M.F. Cassarino, M. Genua, G. Pandini, R. Le Moli, S. Squatrito, R. Vigneri, Insulin analogues differently activate insulin receptor isoforms and post-receptor signalling, *Diabetologia* 53 (2010) 1743–1753.
- [37] M.R. Sommerfeld, G. Muller, G. Tschank, G. Seipke, P. Habermann, R. Kurrle, N. Tennagels, In vitro metabolic and mitogenic signaling of insulin arginine and its metabolites, *PLoS One* 5 (2010) e9540.
- [38] C.W. Ward, T.P. Garrett, N.M. McKern, M. Lou, L.J. Cosgrove, L.G. Sparrow, M.J. Frenkel, P.A. Hoynes, T.C. Elleman, T.E. Adams, G.O. Lovrecz, L.J. Lawrence, P.A. Tulloch, The three dimensional structure of the type I insulin-like growth factor receptor, *Mol. Pathol.* 54 (2001) 125–132.
- [39] J. Kim, A.R. Wende, S. Sena, H.A. Theobald, J. Soto, C. Sloan, B.E. Wayment, S.E. Litwin, M. Holzenberger, D. LeRoith, E.D. Abel, Insulin-like growth factor 1 receptor signaling is required for exercise-induced cardiac hypertrophy, *Mol. Endocrinol.* 22 (2008) 2531–2543.
- [40] J.R. McMullen, T. Shioi, W.Y. Huang, L. Zhang, O. Tarnavski, E. Bisping, M. Schinke, S. Kong, M.C. Sherwood, J. Brown, L. Riggi, P.M. Kang, S. Izumo, The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway, *J. Biol. Chem.* 279 (2004) 4782–4793.
- [41] R. Foncea, A. Galvez, V. Perez, M.P. Morales, A. Calixto, J. Melendez, F. Gonzalez-Jara, G. Diaz-Araya, M. Sapag-Hagar, P.H. Sugden, D. LeRoith, S. Lavandero, Extracellular regulated kinase, but not protein kinase C, is an antiapoptotic signal of insulin-like growth factor-1 on cultured cardiac myocytes, *Biochem. Biophys. Res. Commun.* 273 (2000) 736–744.
- [42] Y.C. Kim, K.L. Guan, mTOR: a pharmacologic target for autophagy regulation, *J. Clin. Invest.* 125 (2015) 25–32.
- [43] S. Lavandero, M. Chiong, B.A. Rothermel, J.A. Hill, Autophagy in cardiovascular biology, *J. Clin. Invest.* 125 (2015) 55–64.
- [44] R. Troncoso, J.M. Vicencio, V. Parra, A. Nemchenko, Y. Kawashima, C. Del, A. ampo, B. Toro, P.K. Battiprolu, P. Aranguiz, M. Chiong, S. Yakar, T.G. Gillette, J.A. Hill, E.D. Abel, D. Leroith, S. Lavandero, Energy-preserving effects of IGF-1 antagonist starvation-induced cardiac autophagy, *Cardiovasc. Res.* 93 (2012) 320–329.
- [45] R. Troncoso, J. Diaz-Elizondo, S.P. Espinoza, M.F. Navarro-Marquez, A.P. Oyarzun, J.A. Riquelme, I. Garcia-Carvajal, G. Diaz-Araya, L. Garcia, J.A. Hill, S. Lavandero, Regulation of cardiac autophagy by insulin-like growth factor 1, *IUBMB Life* 65 (2013) 593–601.
- [46] A.J. Muslin, Akt2: a critical regulator of cardiomyocyte survival and metabolism, *Pediatr. Cardiol.* 32 (2011) 317–322.
- [47] V. Parra, H.E. Verdejo, M. Iglewski, A. Del Campo, R. Troncoso, D. Jones, Y. Zhu, J. Kuzmicic, C. Pennanen, C. Lopez-Crisosto, F. Jana, J. Ferreira, E. Noguera, M. Chiong, D.A. Bernlohr, A. Klip, J.A. Hill, B.A. Rothermel, E.D. Abel, A. Zorzano, S. Lavandero, Insulin stimulates mitochondrial fusion and function in cardiomyocytes via the Akt-mTOR-NFkappaB-OPA-1 signaling pathway, *Diabetes* 63 (2014) 75–88.
- [48] A. Abbas, H. Imrie, H. Viswambharan, P. Sukumar, A. Rajwani, R.M. Cubbon, M. Gage, J. Smith, S. Galloway, N. Yuldesheva, M. Kahn, S. Xuan, P.J. Grant, K.M. Channon, D.J. Beech, S.B. Wheatcroft, M.T. Kearney, The insulin-like growth factor-1 receptor is a negative regulator of nitric oxide bioavailability and insulin sensitivity in the endothelium, *Diabetes* 60 (2011) 2169–2178.
- [49] H. Imrie, H. Viswambharan, P. Sukumar, A. Abbas, R.M. Cubbon, N. Yuldasheva, M. Gage, J. Smith, S. Galloway, A. Skromna, S.T. Rashid, T.S. Futers, S. Xuan, V.K. Gatenby, P.J. Grant, K.M. Channon, D.J. Beech, S.B. Wheatcroft, M.T. Kearney, Novel role of the IGF-1 receptor in endothelial function and repair: studies in endothelium-targeted IGF-1 receptor transgenic mice, *Diabetes* 61 (2012) 2359–2368.
- [50] H. Cai, D.G. Harrison, Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress, *Circ. Res.* 87 (2000) 840–844.
- [51] V.K. Gatenby, H. Imrie, M. Kearney, The IGF-1 receptor and regulation of nitric oxide bioavailability and insulin signalling in the endothelium, *Pflugers Arch.* 465 (2013) 1065–1074.
- [52] H. Tsukahara, D.V. Gordienko, B. Tonshoff, M.C. Gelato, M.S. Goligorsky, Direct demonstration of insulin-like growth factor-1-induced nitric oxide production by endothelial cells, *Kidney Int.* 45 (1994) 598–604.
- [53] R. Muniyappa, M.F. Walsh, J.S. Rangi, R.M. Zayas, P.R. Standley, J.L. Ram, J.R. Sowers, Insulin like growth factor 1 increases vascular smooth muscle nitric oxide production, *Life Sci.* 61 (1997) 925–931.
- [54] G. Zeng, M.J. Quon, Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells, *J. Clin. Invest.* 98 (1996) 894–898.
- [55] S. Dimmeler, I. Fleming, B. Fisslthaler, C. Hermann, R. Busse, A.M. Zeiher, Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation, *Nature* 399 (1999) 601–605.
- [56] M.A. Potenza, F. Addabbo, M. Montagnani, Vascular actions of insulin with implications for endothelial dysfunction, *Am. J. Physiol. Endocrinol. Metab.* 297 (2009) E568–E577.
- [57] S.Y. Shai, S. Sukhanov, Y. Higashi, C. Vaughn, C.J. Rosen, P. Delafontaine, Low circulating insulin-like growth factor I increases atherosclerosis in ApoE-deficient mice, *Am. J. Physiol. Heart Circ. Physiol.* 300 (2011) H1898–H1906.
- [58] J. Wang, A. Razuvaev, L. Folkersen, E. Hedin, J. Roy, K. Brismar, U. Hedin, The expression of IGFs and IGF binding proteins in human carotid atherosclerosis, and the possible role of IGF binding protein-1 in the regulation of smooth muscle cell proliferation, *Atherosclerosis* 220 (2012) 102–109.
- [59] S. Dalle, W. Ricketts, T. Imamura, P. Vollenweider, J.M. Olefsky, Insulin and insulin-like growth factor I receptors utilize different G protein signaling components, *J. Biol. Chem.* 276 (2001) 15688–15695.
- [60] H. Hallak, A.E. Seiler, J.S. Green, B.N. Ross, R. Rubin, Association of heterotrimeric G(i) with the insulin-like growth factor-I receptor. Release of G(beta gamma) subunits upon receptor activation, *J. Biol. Chem.* 275 (2000) 2255–2258.
- [61] J.F. Kuemmerle, K.S. Murthy, Coupling of the insulin-like growth factor-I receptor tyrosine kinase to Gi2 in human intestinal smooth muscle: Gbetagamma-dependent mitogen-activated protein kinase activation and growth, *J. Biol. Chem.* 276 (2001) 7187–7194.
- [62] L.M. Luttrell, T. van Biesen, B.E. Hawes, W.J. Koch, K. Touhara, R.J. Lefkowitz, G beta gamma subunits mediate mitogen-activated protein kinase activation by the tyrosine kinase insulin-like growth factor 1 receptor, *J. Biol. Chem.* 270 (1995) 16495–16498.
- [63] R. Perrault, P. Zahradka, Identification of novel signalling roles and targets for G(alpha) and G(beta gamma) downstream of the insulin-like growth factor 1 receptor in vascular smooth muscle cells, *Biochem. J.* 450 (2013) 209–219.
- [64] C. Ibarra, J.M. Vicencio, M. Estrada, Y. Lin, P. Rocco, P. Rebellato, J.P. Munoz, J. Garcia-Prieto, A.F. Quest, M. Chiong, S.M. Davidson, I. Bulatovic, K.H. Grinnemo, O. Larsson, G. Szabadkai, P. Uhlen, E. Jaimovich, S. Lavandero, Local control of nuclear calcium signaling in cardiac myocytes by perinuclear microdomains of sarcolemmal insulin-like growth factor 1 receptors, *Circ. Res.* 112 (2013) 236–245.
- [65] C. Ibarra, M. Estrada, L. Carrasco, M. Chiong, J.L. Liberona, C. Cardenas, G. Diaz-Araya, E. Jaimovich, S. Lavandero, Insulin-like growth factor-1 induces an inositol 1,4,5-trisphosphate-dependent increase in nuclear and cytosolic calcium in cultured rat cardiac myocytes, *J. Biol. Chem.* 279 (2004) 7554–7565.
- [66] L. Carrasco, P. Cepa, P. Rocco, D. Pena-Oyarzun, P. Rivera-Mejias, C. Sotomayor-Flores, C. Quiroga, A. Criollo, C. Ibarra, M. Chiong, S. Lavandero, Role of heterotrimeric G protein and calcium in cardiomyocyte hypertrophy induced by IGF-1, *J. Cell. Biochem.* 115 (2014) 712–720.
- [67] H. Ito, M. Hiroe, Y. Hirata, M. Tsujino, S. Adachi, M. Shichiri, A. Koike, A. Nogami, F. Marumo, Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes, *Circulation* 87 (1993) 1715–1721.
- [68] C. Crocini, R. Coppini, C. Ferrantini, P. Yan, L.M. Loew, C. Tesi, E. Cerbai, C. Poggesi, F.S. Pavone, L. Sacconi, Defects in T-tubular electrical activity underlie local alterations of calcium release in heart failure, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 15196–15201.
- [69] D.J. Crossman, A.A. Young, P.N. Ruygrok, G.P. Nason, D. Baddeley, C. Soeller, M.B. Cannell, T-tubule disease: relationship between t-tubule organization and regional contractile performance in human dilated cardiomyopathy, *J. Mol. Cell. Cardiol.* 84 (2015) 170–178.
- [70] S. Wei, A. Guo, B. Chen, W. Kutschke, Y.P. Xie, K. Zimmerman, R.M. Weiss, M.E. Anderson, H. Cheng, L.S. Song, T-tubule remodeling during transition from hypertrophy to heart failure, *Circ. Res.* 107 (2010) 520–531.
- [71] G. Takemura, M. Kanoh, S. Minatoguchi, H. Fujiwara, Cardiomyocyte apoptosis in the failing heart—a critical review from definition and classification of cell death, *Int. J. Cardiol.* 167 (2013) 2373–2386.
- [72] Z. Ungvari, A. Csizsar, The emerging role of IGF-1 deficiency in cardiovascular aging: recent advances, *J. Gerontol. A Biol. Sci. Med. Sci.* 67 (2012) 599–610.
- [73] J. Guevara-Aguirre, P. Balasubramanian, M. Guevara-Aguirre, M. Wei, F. Madia, C.W. Cheng, D. Hwang, A. Martin-Montalvo, J. Saavedra, S. Ingles, R. de Cabo, P. Cohen, V.D. Longo, Growth hormone receptor deficiency is

- associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans, *Sci. Transl. Med.* 3 (2011), 70ra13.
- [74] M. Scheinowitz, M.S. Feinberg, Z. Laron, IGF-I replacement therapy in children with congenital IGF-I deficiency (Laron syndrome) maintains heart dimension and function, *Growth Horm. IGF Res.* 19 (2009) 280–282.
- [75] L. Groban, M. Lin, K.A. Kassik, R.L. Ingram, W.E. Sonntag, Early-onset growth hormone deficiency results in diastolic dysfunction in adult-life and is prevented by growth hormone supplementation, *Growth Horm. IGF Res.* 21 (2011) 81–88.
- [76] F. Feihl, L. Liaudet, B.I. Levy, B. Waeber, Hypertension and microvascular remodelling, *Cardiovasc. Res.* 78 (2008) 274–285.
- [77] M. Scharin Tang, B. Redfors, M. Lindbom, J. Svensson, T. Ramunddal, C. Ohlsson, Y. Shao, E. Omerovic, Importance of circulating IGF-1 for normal cardiac morphology, function and post infarction remodeling, *Growth Horm. IGF Res.* 22 (2012) 206–211.
- [78] R. Malaguarnera, A. Belfiore, The emerging role of insulin and insulin-like growth factor signaling in cancer stem cells, *Front. Endocrinol. (Lausanne)* 5 (2014) 10.
- [79] E.J. Gallagher, D. LeRoith, The proliferating role of insulin and insulin-like growth factors in cancer, *Trends Endocrinol. Metab.* 21 (2010) 610–618.
- [80] M. Vinciguerra, M.P. Santini, W.C. Claycomb, A.G. Ladurner, N. Rosenthal, Local IGF-1 isoform protects cardiomyocytes from hypertrophic and oxidative stresses via SirT1 activity, *Aging (Albany NY)* 2 (2010) 43–62.
- [81] M. Vinciguerra, M.P. Santini, C. Martinez, V. Paziienza, W.C. Claycomb, A. Giuliani, N. Rosenthal, mIGF-1/JNK1/SirT1 signaling confers protection against oxidative stress in the heart, *Aging Cell* 11 (2012) 139–149.
- [82] K. Huynh, J.R. McMullen, T.L. Julius, J.W. Tan, J.E. Love, N. Cemerlang, H. Kiriazis, X.J. Du, R.H. Ritchie, Cardiac-specific IGF-1 receptor transgenic expression protects against cardiac fibrosis and diastolic dysfunction in a mouse model of diabetic cardiomyopathy, *Diabetes* 59 (2010) 1512–1520.
- [83] Y. Zhang, M. Yuan, K.M. Bradley, F. Dong, P. Anversa, J. Ren, Insulin-like growth factor 1 alleviates high-fat diet-induced myocardial contractile dysfunction: role of insulin signaling and mitochondrial function, *Hypertension* 59 (2012) 680–693.
- [84] N.S. Freestone, S. Ribaric, W.T. Mason, The effect of insulin-like growth factor-1 on adult rat cardiac contractility, *Mol. Cell. Biochem.* 163–164 (1996) 223–229.
- [85] S. Kinugawa, H. Tsutsui, T. Ide, R. Nakamura, K. Arimura, K. Egashira, A. Takeshita, Positive inotropic effect of insulin-like growth factor-1 on normal and failing cardiac myocytes, *Cardiovasc. Res.* 43 (1999) 157–164.
- [86] S.J. Kim, M. Abdellatif, S. Koul, G.J. Crystal, Chronic treatment with insulin-like growth factor 1 enhances myocyte contraction by upregulation of Akt-SERCA2a signaling pathway, *Am. J. Physiol. Heart Circ. Physiol.* 295 (2008) H130–H135.
- [87] S. Kinugawa, H. Tsutsui, S. Satoh, M. Takahashi, T. Ide, K. Igarashi, K. Arimura, K. Egashira, A. Takeshita, Role of Ca²⁺ availability to myofibrilaments and their sensitivity to Ca²⁺ in myocyte contractile dysfunction in heart failure, *Cardiovasc. Res.* 44 (1999) 398–406.
- [88] U.M. Steckelings, T. Unger, Angiotensin II type 2 receptor agonists—where should they be applied, *Expert Opin. Invest. Drugs* 21 (2012) 763–766.
- [89] D. Mozaffarian, E.J. Benjamin, A.S. Go, D.K. Arnett, M.J. Blaha, M. Cushman, S. de Ferranti, J.P. Despres, H.J. Fullerton, V.J. Howard, M.D. Huffman, S.E. Judd, B.M. Kissela, D.T. Lackland, J.H. Lichtman, L.D. Lisabeth, S. Liu, R.H. Mackey, D.B. Matchar, D.K. McGuire, E.R. Mohler 3rd, C.S. Moy, P. Muntner, M.E. Mussolino, K. Nasir, R.W. Neumar, G. Nichol, L. Palaniappan, D.K. Pandey, M.J. Reeves, C.J. Rodriguez, P.D. Sorlie, J. Stein, A. Towfighi, T.N. Turan, S.S. Virani, J.Z. Willey, D. Woo, R.W. Yeh, M.B. Turner, Heart disease and stroke statistics—2015 update: a report from the American Heart Association, *Circulation* 131 (2015) e29–e322.
- [90] A.J. Ferreira, R.A. Santos, Cardiovascular actions of angiotensin-(1–7), *Braz. J. Med. Biol. Res.* 38 (2005) 499–507.
- [91] M. Flores-Munoz, N.J. Smith, C. Haggerty, G. Milligan, S.A. Nicklin, Angiotensin1–9 antagonises pro-hypertrophic signalling in cardiomyocytes via the angiotensin type 2 receptor, *J. Physiol.* 589 (2011) 939–951.
- [92] R.A. Santos, Simoes, S. e, A.C. ilva, C. Maric, D.M. Silva, R.P. Machado, B. de, I. uhr, S. Heringer-Walther, S.V. Pinheiro, M.T. Lopes, M. Bader, E.P. Mendes, V.S. Lemos, M.J. Campagnole-Santos, H.P. Schultheiss, R. Speth, T. Walther, Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas, *Proc. Natl. Acad. Sci. U. S. A.* 100 (2003) 8258–8263.
- [93] M. Sharif, N. Sasakawa, M.R. Hanley, Malignant transformation by G protein-coupled hormone receptors, *Mol. Cell. Endocrinol.* 100 (1994) 115–119.
- [94] D. Young, G. Waitches, C. Birchmeier, O. Fasano, M. Wigler, Isolation and characterization of a new cellular oncogene encoding a protein with function on multiple potential transmembrane domains, *Cell* 45 (1986) 711–719.
- [95] R. Metzger, M. Bader, T. Ludwig, C. Berberich, B. Bunnemann, D. Ganten, Expression of the mouse and rat mas proto-oncogene in the brain and peripheral tissues, *FEBS Lett.* 357 (1995) 27–32.
- [96] D. Young, K. O'Neill, T. Jessell, M. Wigler, Characterization of the rat mas oncogene and its high-level expression in the hippocampus and cerebral cortex of rat brain, *Proc. Natl. Acad. Sci. U. S. A.* 85 (1988) 5339–5342.
- [97] M. Bader, N. Alenina, M.A. Andrade-Navarro, R.A. Santos, MAS and its related G protein-coupled receptors, *Mrgprs, Pharmacol. Rev.* 66 (2014) 1080–1105.
- [98] R.Q. Lautner, D.C. Villela, R.A. Fraga-Silva, N. Silva, T. Verano-Braga, F. Costa-Fraga, J. Jankowski, V. Jankowski, F. Sousa, A. Alzamora, E. Soares, C. Barbosa, F. Kjeldsen, A. Oliveira, J. Braga, S. Savergnini, G. Maia, A.B. Peluso, D. Passos-Silva, A. Ferreira, F. Alves, A. Martins, M. Raizada, R. Paula, D. Motta-Santos, F. Klempin, A. Pimenta, N. Alenina, R. Sinisterra, M. Bader, M.J. Campagnole-Santos, R.A. Santos, Discovery and characterization of alamandine: a novel component of the renin-angiotensin system, *Circ. Res.* 112 (2013) 1104–1111.
- [99] N. Alenina, P. Xu, B. Rentzsch, E.L. Patkin, M. Bader, Genetically altered animal models for Mas and angiotensin-(1–7), *Exp. Physiol.* 93 (2008) 528–537.
- [100] M.F. Dias-Peixoto, A.J. Ferreira, P.W. Almeida, V.B. Braga, D.C. Coutinho, D.S. Melo, F. Gomes, A. ilho, M.B. Melo, L. Greco, M.J. Campagnole-Santos, R.F. Lima, R.A. Santos, S. Guatimosim, The cardiac expression of Mas receptor is responsive to different physiological and pathological stimuli, *Peptides* 35 (2012) 196–201.
- [101] T.R. Jackson, L.A. Blair, J. Marshall, M. Goedert, M.R. Hanley, The mas oncogene encodes an angiotensin receptor, *Nature* 335 (1988) 437–440.
- [102] S.Q. Savergnini, D. Janzer, M.B. Carvalho, A.J. Ferreira, G.A. Silva, F.D. Marques, A.A. Peluso, M. Beiman, G. Cojocar, Y. Cohen, A.P. Almeida, G. Rotman, R.A. Santos, The novel Mas agonist, CGEN-8565, attenuates isoproterenol-induced cardiac remodeling and myocardial infarction injury in rats, *PLoS One* 8 (2013) e57757.
- [103] R.A. Santos, M.J. Campagnole-Santos, N.C. Baracho, M.A. Fontes, L.C. Silva, L.A. Neves, D.R. Oliveira, S.M. Caligorne, A.R. Rodrigues, C. Gropen Junior, et al., Characterization of a new angiotensin antagonist selective for angiotensin-(1–7): evidence that the actions of angiotensin-(1–7) are mediated by specific angiotensin receptors, *Brain Res. Bull.* 35 (1994) 293–298.
- [104] W.O. Sampaio, Souza, S. dos, R.A. Santos, R. Faria-Silva, M. da, M. ata, L.T. achado, E.L. Schiffrin, R.M. Touyz, Angiotensin-(1–7) through receptor Mas mediates endothelial nitric oxide synthase activation via Akt-dependent pathways, *Hypertension* 49 (2007) 185–192.
- [105] J. Zhao, E. Liu, G. Li, L. Qi, J. Li, W. Yang, Effects of the angiotensin-(1–7)/Mas/PI3K/Akt/nitric oxide axis and the possible role of atrial natriuretic peptide in an acute atrial tachycardia canine model, *J. Renin Angiotensin Aldosterone Syst.* (2014).
- [106] S. Zheng, Y. Yang, R. Song, X. Yang, H. Liu, Q. Ma, L. Yang, R. Meng, T. Tao, S. Wang, J. He, Ang-(1–7) promotes the migration and invasion of human renal cell carcinoma cells via Mas-mediated AKT signaling pathway, *Biochem. Biophys. Res. Commun.* 460 (2015) 333–340.
- [107] F. Cisternas, M.G. Morales, C. Meneses, F. Simon, E. Brandan, J. Abrigo, Y. Vazquez, C. Cabello-Verrugio, Angiotensin-(1–7) decreases skeletal muscle atrophy induced by angiotensin II through a Mas receptor-dependent mechanism, *Clin. Sci. (Lond.)* 128 (2015) 307–319.
- [108] A. Than, M.K. Leow, P. Chen, Control of adipogenesis by the autocrine interplays between angiotensin 1–7/Mas receptor and angiotensin II/AT1 receptor signaling pathways, *J. Biol. Chem.* 288 (2013) 15520–15531.
- [109] J.F. Giani, M.M. Gironacci, M.C. Munoz, C. Pena, D. Turyn, F.P. Dominici, Angiotensin-(1–7) stimulates the phosphorylation of JAK2, IRS-1 and Akt in rat heart in vivo: role of the AT1 and Mas receptors, *Am. J. Physiol. Heart Circ. Physiol.* 293 (2007) H1154–H1163.
- [110] M.C. Munoz, J.F. Giani, F.P. Dominici, Angiotensin-(1–7) stimulates the phosphorylation of Akt in rat extracardiac tissues in vivo via receptor Mas, *Regul. Pept.* 161 (2010) 1–7.
- [111] T. Verano-Braga, V. Schwammle, M. Sylvester, D.G. Passos-Silva, A.A. Peluso, G.M. Etelvino, R.A. Santos, P. Roepstorff, Time-resolved quantitative phosphoproteomics: new insights into Angiotensin-(1–7) signaling networks in human endothelial cells, *J. Proteome Res.* 11 (2012) 3370–3381.
- [112] F.P. Dominici, V. Burghi, M.C. Munoz, J.F. Giani, Modulation of the action of insulin by angiotensin-(1–7), *Clin. Sci. (Lond.)* 126 (2014) 613–630.
- [113] M. Canals, L. Jenkins, E. Kellett, G. Milligan, Up-regulation of the angiotensin II type 1 receptor by the MAS proto-oncogene is due to constitutive activation of Gq/G11 by MAS, *J. Biol. Chem.* 281 (2006) 16757–16767.
- [114] E.R. Gomes, R.A. Santos, S. Guatimosim, Angiotensin-(1–7)-mediated signaling in cardiomyocytes, *Int. J. Hypertens* 2012 (2012) 493129.
- [115] K.C. Tirupula, R. Desnoyer, R.C. Speth, S.S. Karnik, Atypical signaling and functional desensitization response of MAS receptor to peptide ligands, *PLoS One* 9 (2014) e103520.
- [116] L. Wang, D. Luo, X. Liao, J. He, C. Liu, C. Yang, H. Ma, Ang-(1–7) offers cytoprotection against ischemia-reperfusion injury by restoring intracellular calcium homeostasis, *J. Cardiovasc. Pharmacol.* 63 (2014) 259–264.
- [117] T. Kenakin, A. Christopoulos, Signalling bias in new drug discovery: detection, quantification and therapeutic impact, *Nat. Rev. Drug Discovery* 12 (2013) 205–216.
- [118] R.A. Santos, J.M. Brum, K.B. Brosnihan, C.M. Ferrario, The renin-angiotensin system during acute myocardial ischemia in dogs, *Hypertension* 15 (1990) 1121–127.
- [119] C. Peiro, S. Vallejo, F. Gembardt, V. Azcutia, S. Heringer-Walther, L. Rodriguez-Manas, H.P. Schultheiss, C.F. Sanchez-Ferrer, T. Walther, Endothelial dysfunction through genetic deletion or inhibition of the G protein-coupled receptor Mas: a new target to improve endothelial function, *J. Hypertens* 25 (2007) 2421–2425.
- [120] C.H. Castro, R.A. Santos, A.J. Ferreira, M. Bader, N. Alenina, A.P. Almeida, Effects of genetic deletion of angiotensin-(1–7) receptor Mas on cardiac function during ischemia/reperfusion in the isolated perfused mouse heart, *Life Sci.* 80 (2006) 264–268.

- [121] Y. Wang, C. Qian, A.J. Roks, D. Westermann, S.M. Schumacher, F. Escher, R.G. Schoemaker, T.L. Reudelhuber, W.H. van Gilst, H.P. Schultheiss, C. Tschope, T. Walther, Circulating rather than cardiac angiotensin-(1–7) stimulates cardioprotection after myocardial infarction, *Circ. Heart Fail* 3 (2010) 286–293.
- [122] L.T. McCollum, P.E. Gallagher, E. Ann Tallant, Angiotensin-(1–7) attenuates angiotensin II-induced cardiac remodeling associated with upregulation of dual-specificity phosphatase 1, *Am. J. Physiol. Heart Circ. Physiol.* 302 (2012) H801–810.
- [123] V.B. Patel, S. Bodiga, D. Fan, S.K. Das, Z. Wang, W. Wang, R. Basu, J. Zhong, Z. Kassiri, G.Y. Oudit, Cardioprotective effects mediated by angiotensin II type 1 receptor blockade and enhancing angiotensin 1–7 in experimental heart failure in angiotensin-converting enzyme 2-null mice, *Hypertension* 59 (2012) 1195–1203.
- [124] W.C. De Mello, Angiotensin (1–7) re-establishes impulse conduction in cardiac muscle during ischaemia-reperfusion. The role of the sodium pump, *J. Renin Angiotensin Aldosterone Syst.* 5 (2004) 203–208.
- [125] A.E. Loot, A.J. Roks, R.H. Henning, R.A. Tio, A.J. Suurmeijer, F. Boomsma, G. van, W.H. IJst, Angiotensin-(1–7) attenuates the development of heart failure after myocardial infarction in rats, *Circulation* 105 (2002) 1548–1550.
- [126] C. Mercure, A. Yogi, G.E. Callera, A.B. Aranha, M. Bader, A.J. Ferreira, R.A. Santos, T. Walther, R.M. Touyz, T.L. Reudelhuber, Angiotensin(1–7) blunts hypertensive cardiac remodeling by a direct effect on the heart, *Circ. Res.* 103 (2008) 1319–1326.
- [127] E.A. Tallant, C.M. Ferrario, P.E. Gallagher, Angiotensin-(1–7) inhibits growth of cardiac myocytes through activation of the mas receptor, *Am. J. Physiol. Heart Circ. Physiol.* 289 (2005) H1560–H1566.
- [128] J.G. He, S.L. Chen, Y.Y. Huang, Y.L. Chen, Y.G. Dong, H. Ma, The nonpeptide AVE0991 attenuates myocardial hypertrophy as induced by angiotensin II through downregulation of transforming growth factor-beta1/Smad2 expression, *Heart Vessels* 25 (2010) 438–443.
- [129] B. Liang, Y. Li, Z. Han, J. Xue, Y. Zhang, S. Jia, C. Wang, CE2-Ang (1–7) axis is induced in pressure overloaded rat model, *Int. J. Clin. Exp. Pathol.* 8 (2015) 1443–1450.
- [130] M.P. Ocaranza, I. Godoy, J.E. Jalil, M. Varas, P. Collantes, M. Pinto, M. Roman, C. Ramirez, M. Copaja, G. Diaz-Araya, P. Castro, S. Lavandero, Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat, *Hypertension* 48 (2006) 572–578.
- [131] J. Xing, J. Lu, J. Li, Role of angiotensin-(1–7) and Mas-R-nNOS pathways in amplified neuronal activity of dorsolateral periaqueductal gray after chronic heart failure, *Neurosci. Lett.* 563 (2014) 6–11.
- [132] E. Kaschina, T. Unger, Angiotensin AT1/AT2 receptors: regulation, signalling and function, *Blood Pressure* 12 (2003) 70–88.
- [133] Y. Kambayashi, S. Bardhan, K. Takahashi, S. Tsuzuki, H. Inui, T. Hamakubo, T. Inagami, Molecular cloning of a novel angiotensin II receptor isoform involved in phosphotyrosine phosphatase inhibition, *J. Biol. Chem.* 268 (1993) 24543–24546.
- [134] H. Funke-Kaiser, J. Reinemund, U.M. Steckelings, T. Unger, Adapter proteins and promoter regulation of the angiotensin AT2 receptor—implications for cardiac pathophysiology, *J. Renin Angiotensin Aldosterone Syst.* 11 (2010) 7–17.
- [135] S.H. Padia, R.M. Carey, AT2 receptors: beneficial counter-regulatory role in cardiovascular and renal function, *PLugers Arch.* 465 (2013) 99–110.
- [136] M. Horiuchi, M. Akishita, V.J. Dzau, Recent progress in angiotensin II type 2 receptor research in the cardiovascular system, *Hypertension* 33 (1999) 613–621.
- [137] G. Faria-Costa, A. Leite-Moreira, T. Henriques-Coelho, Cardiovascular effects of the angiotensin type 2 receptor, *Rev. Port. Cardiol.* 33 (2014) 439–449.
- [138] C. Savoia, F. Tabet, G. Yao, E.L. Schiffrin, R.M. Touyz, Negative regulation of RhoA/Rho kinase by angiotensin II type 2 receptor in vascular smooth muscle cells: role in angiotensin II-induced vasodilation in stroke-prone spontaneously hypertensive rats, *J. Hypertens* 23 (2005) 1037–1045.
- [139] C. Hu, A. Dandapat, J. Chen, Y. Liu, P.L. Hermonat, R.M. Carey, J.L. Mehta, Over-expression of angiotensin II type 2 receptor (agr2) reduces atherogenesis and modulates LOX-1, endothelial nitric oxide synthase and heme-oxygenase-1 expression, *Atherosclerosis* 199 (2008) 288–294.
- [140] R.M. Touyz, E.L. Schiffrin, Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells, *Pharmacol. Rev.* 52 (2000) 639–672.
- [141] D. Henion, N. Kubis, B.I. Levy, Physiological and pathophysiological functions of the AT(2) subtype receptor of angiotensin II: from large arteries to the microcirculation, *Hypertension* 38 (2001) 1150–1157.
- [142] Y. Li, X.H. Li, H. Yuan, Angiotensin II type-2 receptor-specific effects on the cardiovascular system, *Cardiovasc. Diagn. Ther.* 2 (2012) 56–62.
- [143] F.M. Tavares, I.B. da Silva, D.A. Gomes, M.L. Barreto-Chaves, Angiotensin II type 2 receptor (AT2R) is associated with increased tolerance of the hyperthyroid heart to ischemia-reperfusion, *Cardiovasc. Drugs Ther.* 27 (2013) 393–402.
- [144] J. Varagic, S. Ahmad, S. Nagata, C.M. Ferrario, ACE2: angiotensin II/angiotensin-(1–7) balance in cardiac and renal injury, *Curr. Hypertens Rep.* 16 (2014) 420.
- [145] M.P. Ocaranza, L. Michea, M. Chiong, S. Lavandero, J.E.R. Jalil, eply, dissociating angiotensin 1–9 antidiabetic cardiovascular remodeling effects from those on blood pressure, *J. Hypertens* 32 (2014) 1719–1721.
- [146] M.P. Ocaranza, J. Moya, V. Barrientos, R. Alzamora, D. Hevia, C. Morales, M. Pinto, N. Escudero, L. Garcia, U. Novoa, P. Ayala, G. Diaz-Araya, I. Godoy, M. Chiong, S. Lavandero, J.E. Jalil, L. Michea, Angiotensin-(1–9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II axis, *J. Hypertens* 32 (2014) 771–783.
- [147] P.M. Abadir, R.M. Carey, H.M. Siragy, Angiotensin AT2 receptors directly stimulate renal nitric oxide in bradykinin B2-receptor-null mice, *Hypertension* 42 (2003) 600–604.
- [148] C. Savoia, T. Ebrahimian, Y. He, J.P. Gratton, E.L. Schiffrin, R.M. Touyz, Angiotensin II/AT2 receptor-induced vasodilation in stroke-prone spontaneously hypertensive rats involves nitric oxide and cGMP-dependent protein kinase, *J. Hypertens* 24 (2006) 2417–2422.
- [149] A. Dandapat, C.P. Hu, J. Chen, Y. Liu, J.A. Khan, F. Remeo, R.M. Carey, P.L. Hermonat, J.L. Mehta, Over-expression of angiotensin II type 2 receptor (agr2) decreases collagen accumulation in atherosclerotic plaque, *Biochem. Biophys. Res. Commun.* 366 (2008) 871–877.
- [150] P. Brassard, F. Amiri, E.L. Schiffrin, Combined angiotensin II type 1 and type 2 receptor blockade on vascular remodeling and matrix metalloproteinases in resistance arteries, *Hypertension* 46 (2005) 598–606.
- [151] C. Dimitropoulou, R.E. White, L. Fuchs, H. Zhang, J.D. Catravas, G.O. Carrier, I.I. Angiotensin, relaxes microvessels via the AT(2) receptor and Ca(2+)-activated K(+) (BK(Ca)) channels, *Hypertension* 37 (2001) 301–307.
- [152] M. Horiuchi, W. Hayashida, T. Kambe, T. Yamada, V.J. Dzau, Angiotensin type 2 receptor dephosphorylates Bcl-2 by activating mitogen-activated protein kinase phosphatase-1 and induces apoptosis, *J. Biol. Chem.* 272 (1997) 19022–19026.
- [153] K. Bedecs, N. Elbaz, M. Sutren, M. Masson, C. Susini, A.D. Strosberg, C. Nahmias, Angiotensin II type 2 receptors mediate inhibition of mitogen-activated protein kinase cascade and functional activation of SHP-1 tyrosine phosphatase, *Biochem. J.* 325 (Pt 2) (1997) 449–454.
- [154] S. Nouet, N. Amzallag, J.M. Li, S. Louis, I. Seitz, T.X. Cui, A.M. Alleaume, B. Di, M. enedetto, C. Boden, M. Masson, A.D. Strosberg, M. Horiuchi, P.O. Couraud, C. Nahmias, Trans-inactivation of receptor tyrosine kinases by novel angiotensin II AT2 receptor-interacting protein, ATIP, *J. Biol. Chem.* 279 (2004) 28989–28997.
- [155] C.J. Wruck, H. Funke-Kaiser, T. Pufe, H. Kusserow, M. Menk, J.H. Scheff, M.L. Kruse, M. Stoll, T. Unger, Regulation of transport of the angiotensin AT2 receptor by a novel membrane-associated Golgi protein, *Arterioscler. Thromb. Vasc. Biol.* 25 (2005) 57–64.
- [156] B. Di, M. enedetto, I. Bieche, F. Deshayes, S. Vacher, S. Nouet, V. Collura, I. Seitz, S. Louis, P. Pineau, D. Amsellem-Ouazana, P.O. Couraud, A.D. Strosberg, D. Stoppa-Lyonnet, R. Lidereau, C. Nahmias, Structural organization and expression of human MTUS1, a candidate 8p22 tumor suppressor gene encoding a family of angiotensin II AT2 receptor-interacting proteins, *ATIP, Gene* 380 (2006) 127–136.
- [157] M.A. Krezel, L.A. Rezmans, N. Varghaye, J. Pete, A.G. Frauman, S.N. Louis, Gene sequencing and tissue expression of unknown isoforms of an angiotensin II type 2 receptor interacting protein, ATIP, in the rat, *Biosci. Biotechnol. Biochem.* 75 (2011) 414–418.
- [158] T. Kinjo, M. Isomura, T. Iwamasa, Y. Nakamura, Molecular cloning and characterization of two novel genes on chromosome 8p21.3, *J. Hum. Genet.* 45 (2000) 12–17.
- [159] S. Seibold, C. Rudroff, M. Weber, J. Galle, C. Wanner, M. Marx, Identification of a new tumor suppressor gene located at chromosome 8p21. 3–22, *FASEB J.* 17 (2003) 1180–1182.
- [160] M.P. Ocaranza, S. Lavandero, J.E. Jalil, J. Moya, M. Pinto, U. Novoa, F. Apablaza, L. Gonzalez, C. Hernandez, M. Varas, R. Lopez, I. Godoy, H. Verdejo, M. Chiong, Angiotensin-(1–9) regulates cardiac hypertrophy in vivo and in vitro, *J. Hypertens* 28 (2010) 1054–1064.
- [161] M. Flores-Munoz, B.M. Godinho, A. Almalik, S.A. Nicklin, Adenoviral delivery of angiotensin-(1–7) or angiotensin-(1–9) inhibits cardiomyocyte hypertrophy via the mas or angiotensin type 2 receptor, *PLoS One* 7 (2012) e45564.
- [162] S.A. Cha, B.M. Park, S. Gao, S.H. Kim, Stimulation of ANP by angiotensin-(1–9) via the angiotensin type 2 receptor, *Life Sci.* 93 (2013) 934–940.
- [163] M. Flores-Munoz, L.M. Work, K. Douglas, L. Denby, A.F. Dominiczak, D. Graham, S.A. Nicklin, Angiotensin-(1–9) attenuates cardiac fibrosis in the stroke-prone spontaneously hypertensive rat via the angiotensin type 2 receptor, *Hypertension* 59 (2012) 300–307.
- [164] M.P. Ocaranza, P. Rivera, U. Novoa, M. Pinto, L. Gonzalez, M. Chiong, S. Lavandero, J.E. Jalil, Rho kinase inhibition activates the homologous angiotensin-converting enzyme-angiotensin-(1–9) axis in experimental hypertension, *J. Hypertens* 29 (2011) 706–715.
- [165] E.G. Erdos, H.L. Jackman, V. Brovkovich, F. Tan, P.A. Deddish, Products of angiotensin I hydrolysis by human cardiac enzymes potentiate bradykinin, *J. Mol. Cell. Cardiol.* 34 (2002) 1569–1576.
- [166] H.L. Jackman, M.G. Massad, M. Sekosan, F. Tan, V. Brovkovich, B.M. Marcic, E.G. Erdos, Angiotensin 1–9 and 1–7 release in human heart: role of cathepsin A, *Hypertension* 39 (2002) 976–981.
- [167] R. Ray, C.E. Murdoch, M. Wang, C.X. Santos, M. Zhang, S. Alom-Ruiz, N. Anilkumar, A. Ouattara, A.C. Cave, S.J. Walker, D.J. Grieve, R.L. Charles, P. Eaton, A.C. Brewer, A.M. Shah, Endothelial Nox4 NADPH oxidase enhances vasodilatation and reduces blood pressure in vivo, *Arterioscler. Thromb. Vasc. Biol.* 31 (2011) 1368–1376.

- [168] Z. Chen, F. Tan, E.G. Erdos, P.A. Deddish, Hydrolysis of angiotensin peptides by human angiotensin I-converting enzyme and the resensitization of B2 kinin receptors, *Hypertension* 46 (2005) 1368–1373.
- [169] M. Flores-Munoz, N.J. Smith, C. Haggerty, G. Milligan, S.A. Nicklin, Angiotensin-1-9 antagonises pro-hypertrophic signalling in cardiomyocytes via the angiotensin type 2 receptor, *J. Physiol.* 589 (2011) 939–951.
- [170] H. Zheng, S.Y. Pu, X.F. Fan, X.S. Li, Y. Zhang, J. Yuan, Y.F. Zhang, J.L. Yang, Treatment with angiotensin-(1–9) alleviates the cardiomyopathy in streptozotocin-induced diabetic rats, *Biochem. Pharmacol.* 95 (2015) 38–45.
- [171] D. Fintini, C. Brufani, M. Cappa, Profile of mecamermin for the long-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency, *Ther. Clin. Risk Manag.* 5 (2009) 553–559.
- [172] R.G. Rosenfeld, IGF-1 therapy in growth disorders, *Eur. J. Endocrinol.* 157 (Suppl. 1) (2007) S57–S60.
- [173] S.F. Kemp, J.L. Fowlkes, K.M. Thraillkill, Efficacy and safety of mecamermin rinfabate, *Expert Opin. Biol. Ther.* 6 (2006) 533–538.
- [174] Hoeybye C., Metabolic effects of GH and IGF-I in growth hormone deficient (GHD) and diabetes and impaired glucose tolerance (IGT). <https://www.clinicaltrials.gov/ct2/show/NCT01020955?term=IGF-1&rank=30> 2009.
- [175] FDA Office of Orphan Products Development. Study of recombinant human insulin-like growth factor I in patients with severe insulin resistance. <https://www.clinicaltrials.gov/ct2/show/NCT00004419?term=IGF-1&rank=140> 1999.
- [176] FDA Office of Orphan Products Development. Short term study of recombinant human insulin-like growth factor I in children with hyperinsulinism. <https://www.clinicaltrials.gov/ct2/show/NCT00004825?term=IGF-1&rank=120> 2000.
- [177] FDA Office of Orphan Products Development. Dose ranging study of recombinant human insulin-like growth factor I in children with hyperinsulinism. <https://www.clinicaltrials.gov/ct2/show/NCT00004699?term=IGF-1&rank=135> 2000.
- [178] FDA Office of Orphan Products Development. Phase II long term, randomized study of recombinant human insulin-like growth factor I in children with hyperinsulinism. <https://www.clinicaltrials.gov/ct2/show/NCT00004700?term=IGF-1&rank=136> 2000.
- [179] Mayo Clinic Insulin-like growth factor-1 in amyotrophic lateral sclerosis (ALS) trial. <https://www.clinicaltrials.gov/ct2/show/NCT00035815?term=IGF-1&rank=38> 2002.
- [180] Kim R. Effects of IGF-I in HIV metabolic disease. <https://www.clinicaltrials.gov/ct2/show/NCT01329744?term=IGF-1&rank=139> 2011.
- [181] NIAID NloAaId. Treatment for growth failure in patients with X-linked severe combined immunodeficiency: Phase 2 study of insulin-like growth factor-1. <https://www.clinicaltrials.gov/ct2/show/NCT00490100?term=IGF-1&rank=9> 2007.
- [182] Kaufmann W. Treatment of Rett syndrome with recombinant human IGF-1. <https://www.clinicaltrials.gov/ct2/show/NCT01777542?term=IGF-1&rank=18> 2013.
- [183] Kaufmann W. Treatment of Rett syndrome with rhIGF-1 (Mecasermin [rDNA] injection). <https://www.clinicaltrials.gov/ct2/show/NCT01253317?term=IGF-1&rank=28> 2010.
- [184] Shire IGF-1/IGFBP3 prevention of retinopathy of prematurity. <https://www.clinicaltrials.gov/ct2/show/NCT01096784?term=IGF-1&rank=23> 2010.
- [185] The University of Texas Medical Branch G. Assessment of mechanisms of improved wound healing. <https://www.clinicaltrials.gov/ct2/show/NCT00673309?term=IGF-1&rank=50> 2007.
- [186] Moxley RT. Effects of SomatoKine (Iplex) recombinant human insulin-like growth factor-1/recombinant human insulin-like growth factor-binding protein-3 (rhIGF-1/rhIGFBP-3) in myotonic dystrophy type 1 (DM1). <https://www.clinicaltrials.gov/ct2/show/NCT00233519?term=IGF-1&rank=33> 2005.
- [187] Inmed Incorporated Safety and efficacy study of recombinant human insulin-like growth factor-1/recombinant human insulin-like growth factor binding protein-3 (rhIGF-1/rhIGFBP-3) in myotonic dystrophy type 1. <https://www.clinicaltrials.gov/ct2/show/NCT00577577?term=IGF-1&rank=200> 2007.
- [188] Children's Hospital Medical Center C. Safety and efficacy study of IGF-1 in Duchenne muscular dystrophy. <https://www.clinicaltrials.gov/ct2/show/NCT01207908?term=IGF-1&rank=3> 2012.
- [189] National Institutes of Health Clinical Center (CC). A 48-week (24-week baseline followed by a 24-week treatment) phase II pilot study of the tolerability and effect/efficacy of subcutaneously administered insulin-like growth factor-1 (rhIGF) (CEP-151) in multiple sclerosis (MS) patients. <https://www.clinicaltrials.gov/ct2/show/NCT00001669?term=IGF-1&rank=199> 1999.
- [190] Nationwide Children's Hospital. Effect of Increlex® on children with Crohn disease. <https://www.clinicaltrials.gov/ct2/show/NCT00764699?term=IGF-1&rank=301> 2008.
- [191] Inmed Incorporated IGF-1/IGFBP-3 therapy in children and adolescents with growth hormone insensitivity syndrome (GHIS) such as Laron syndrome. <https://www.clinicaltrials.gov/ct2/show/NCT00368173?term=IGF-1&rank=326> 2006.
- [192] Klibanski A. Effects of anorexia nervosa on peak bone mass. <https://www.clinicaltrials.gov/ct2/show/NCT01301183?term=IGF-1&rank=66> 2011.
- [193] Misra M. Effects of rhIGF-1 on bone metabolism in adolescent girls with anorexia nervosa (814). <https://www.clinicaltrials.gov/ct2/show/NCT00720122?term=IGF-1&rank=116> 2008.
- [194] Hansen M. Patellar tendinopathy – effect of training and enhancement of the collagen synthesis by insulin-like growth factor-I (IGF-I). <https://www.clinicaltrials.gov/ct2/show/NCT01834989?term=IGF-1&rank=59> 2013.
- [195] Wilson TA. IGF-1 therapy in patients with cystic fibrosis. <https://www.clinicaltrials.gov/ct2/show/NCT00566241?term=IGF-1&rank=4> 2007.
- [196] Kolevzon A. A pilot treatment study of insulin-like growth factor-1 (IGF-1) in autism spectrum disorder. <https://www.clinicaltrials.gov/ct2/show/NCT01970345?term=IGF-1&rank=2> 2013.
- [197] Caplice N. Evaluation of the safety and efficacy of using insulin-like growth factor-1 in patients with a heart attack (RESUS-AMI). <https://www.clinicaltrials.gov/ct2/show/NCT01438086?term=IGF-1&rank=44> 2011.
- [198] Columbia University Differential effects of rhGH vs. rhIGF-1 on cardiovascular risk factors. <https://www.clinicaltrials.gov/ct2/show/NCT00684957?term=IGF-1&rank=60> 2008.
- [199] C. Werner, M. Baumhakel, K.K. Teo, R. Schmieder, J. Mann, T. Unger, S. Yusuf, M. Bohm, RAS blockade with ARB and ACE inhibitors: current perspective on rationale and patient selection, *Clin. Res. Cardiol.* 97 (2008) 418–431.
- [200] Y. Wan, C. Wallinder, B. Plouffe, H. Beaudry, A.K. Mahalingam, X. Wu, B. Johansson, M. Holm, M. Botoros, A. Karlen, A. Pettersson, F. Nyberg, L. Fandriks, N. Gallo-Payet, A. Hallberg, M. Alterman, Design, synthesis, and biological evaluation of the first selective nonpeptide AT2 receptor agonist, *J. Med. Chem.* 47 (2004) 5995–6008.
- [201] G.T. Wagenaar, Laghmani, H. el, M. Fidler, R.M. Sengers, V. de, Y.P. Isser, V. de, L. ries, R. Rink, A.J. Roks, G. Folkerts, F.J. Walther, Agonists of MAS oncogene and angiotensin II type 2 receptors attenuate cardiopulmonary disease in rats with neonatal hyperoxia-induced lung injury, *Am. J. Physiol. Lung Cell. Mol. Physiol.* 305 (2013) L341–L351.
- [202] E.S. Jones, M.P. Del Borgo, J.F. Kirsch, D. Clayton, S. Bosnyak, I. Welungoda, N. Hausler, S. Unabia, P. Perlmutter, W.G. Thomas, M.I. Aguilar, R.E. Widdop, A single beta-amino acid substitution to angiotensin II confers AT2 receptor selectivity and vascular function, *Hypertension* 57 (2011) 570–576.
- [203] R. Shemesh, A. Toporik, Z. Levine, I. Hecht, G. Rotman, A. Wool, D. Dahary, E. Gofer, Y. Kliger, M.A. Soffer, A. Rosenberg, D. Eshel, Y. Cohen, Discovery and validation of novel peptide agonists for G-protein-coupled receptors, *J. Biol. Chem.* 283 (2008) 34643–34649.
- [204] G. Wiemer, L.W. Dobrucki, F.R. Louka, T. Malinski, H. Heitsch, AVE 0991, a nonpeptide mimic of the effects of angiotensin-(1–7) on the endothelium, *Hypertension* 40 (2002) 847–852.
- [205] A.C. Mendes, A.J. Ferreira, S.V. Pinheiro, R.A. Santos, Chronic infusion of angiotensin-(1–7) reduces heart angiotensin II levels in rats, *Regul. Pept.* 125 (2005) 29–34.
- [206] N.M. Santiago, P.S. Guimaraes, R.A. Sirvente, L.A. Oliveira, M.C. Irigoyen, R.A. Santos, M.J. Campagnole-Santos, Lifetime overproduction of circulating Angiotensin-(1–7) attenuates deoxycorticosterone acetate-salt hypertension-induced cardiac dysfunction and remodeling, *Hypertension* 55 (2010) 889–896.
- [207] A.M. Papinska, N.M. Mordwinkin, C.J. Meeks, S.S. Jadhav, K.E. Rodgers, Angiotensin-(1–7) administration benefits cardiac, renal, and progenitor cell function in db/db mice, *Br. J. Pharmacol.* (2015).
- [208] X.X. Liao, R.X. Guo, H. Ma, L.C. Wang, Z.H. Chen, C.T. Yang, J.Q. Feng, Effects of angiotensin-(1–7) on oxidative stress and functional changes of isolated rat hearts induced by ischemia-reperfusion, *Nan Fang Yi Ke Da Xue Xue Bao* 28 (2008) 1345–1348.
- [209] R. Faria-Silva, F.V. Duarte, R.A. Santos, Short-term angiotensin(1–7) receptor MAS stimulation improves endothelial function in normotensive rats, *Hypertension* 46 (2005) 948–952.
- [210] H.Z. Liu, C.Y. Gao, X.Q. Wang, H.X. Fu, H.H. Yang, X.P. Wang, Y.H. Liu, M.W. Li, Z.M. Niu, G.Y. Dai, D.T. Qi, Y. Zhang, Angiotensin(1–7) attenuates left ventricular dysfunction and myocardial apoptosis on rat model of adriamycin-induced dilated cardiomyopathy, *Zhonghua Xin Xue Guan Bing Za Zhi* 40 (2012) 219–224.