Chapter 11
The Renin Angiotensin System and Diabetes

Ana Cristina Simões e Silva, Rodrigo Novaes Ferreira, and Aline Silva Miranda

Abstract The Renin Angiotensin System (RAS) is clearly implicated in the physiopathology of diabetes mellitus (DM). The frequent association of diabetes mellitus (DM) with hypertension, retinopathy, nephropathy, and cardiovascular disease has implicated the RAS in the initiation and progression of these complications of DM. This has been supported by clinical trials in which RAS inhibitors significantly reduced the incidence of vascular complications in DM patients. The main RAS mediator, Angiotensin II (Ang II), exerts several deleterious actions in patients with DM, including increase in insulin resistance, endothelial damage and deterioration of renal function. On the other hand, only few studies have reported the potential protective role of the stimulation of the conter-regulatory RAS axis formed by the enzyme homologue to ACE, ACE2, the heptapeptide Angiotensin-(1-7) [Ang-(1-7)] and its receptor, the proto-oncogene Mas. In this review, we report recent experimental and clinical evidence in relation to ACE2 stimulation and Mas receptor agonists as potential therapeutic targets for DM.

Keywords Diabetes mellitus • Renin angiotensin system • Angiotensin II • Angiotensin-(1-7) • ACE2 • Mas receptor • Diabetic nephropathy

A.C. Simões e Silva, M.D., Ph.D. (✉)
Department of Pediatrics, Unit of Pediatric Nephrology, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil

Interdisciplinary Laboratory of Medical Investigation, Faculty of Medicine, UFMG, Belo Horizonte, CEP 30130-100, Brazil
e-mail: acssilva@hotmail.com; ana@medicina.ufmg.br

R.N. Ferreira, Ph.D. • A.S. Miranda
Laboratory of Neurobiology, Department of Morphology, Institute of Biological Sciences, UFMG, Belo Horizonte, Brazil

Interdisciplinary Laboratory of Medical Investigation, Faculty of Medicine, UFMG, Belo Horizonte, CEP 30130-100, Brazil

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11.1 Introduction

The renin-angiotensin system (RAS) has been implicated in complications linked with diabetes mellitus, including insulin resistance, endothelial damage and diabetic nephropathy [1–3]. Measurements of the RAS components in diabetic patients have shown conflicting results: some have found elevated levels, others, reduced, and others yet, found no change [4–6]. The picture can be further confusing given the activity of local and independently regulated RASs [7, 8]. However, the significant reno and cardioprotection that have been achieved by blockade of the RAS with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARAs) are strong compelling evidence for the role of the RAS in this disease [2, 9, 10].

Many studies have shown that Angiotensin (Ang) II exerts physiological and biochemical actions that may contribute to cardiovascular and renal damage [11]. The Angiotensin type 1 (AT_1) receptor mediates the main actions of Ang II [12]. Over the recent past, our view of Ang II has changed from being a simple vasoconstrictor to that of a complex growth factor mediating effects through diverse signaling pathways [8]. It has also become clear that Ang II is a key player in vascular inflammation. Through increased generation of reactive oxygen species (ROS) and activation of redox-sensitive transcription factors, Ang II promotes expression of cell adhesion molecules and induces synthesis of proinflammatory mediators and growth factors [8, 12]. These processes increased vascular permeability, leukocyte recruitment and fibrosis leading to tissue injury and structural remodeling. Targeting some of these signaling events with novel therapeutic strategies may provide important tissue protection in many forms of cardiovascular, renal and metabolic diseases.

On the other hand, it was originally thought that Ang II mediates all actions of the RAS. Over the past few years, other angiotensin peptides, like Ang III, Ang IV, and especially Ang-(1-7), were shown to selectively mediate different RAS effects [11, 13]. In regard to Ang-(1-7), this heptapeptide can be formed from Ang I by neutral-endopepdidase 24.11 or prolyl-endopeptidase or from Ang II via prolyl-endopeptidase, prolylcarboxypeptidase [14] or mainly by ACE2, an enzyme homologue to ACE [15, 16]. Ang-(1-7) binds to a G-protein coupled receptor, named Mas receptor [17], and, in general, plays a counter-regulatory role in the RAS by opposing the vascular and proliferative effects of Ang II [11, 13]. Currently, RAS is conceived as a system formed by two opposite axes: the first and classical one composed by ACE, Ang II and AT_1 receptor and the second and counter-regulatory axis comprising ACE2, Ang-(1-7) and Mas receptor [11, 13]. Experimental studies clearly support a role for the counter-regulatory RAS axis in diabetes. However, a limited number of studies have evaluated the components of ACE2-Ang-(1-7)-Mas receptor axis in diabetic patients [18–25], and the majority of them investigated only ACE2 [18–20, 23–25]. In this chapter, we report evidence for the role of ACE2-Ang-(1-7)-Mas receptor axis in diabetes mellitus and its complications, including poor glycemic control, diabetic nephropathy and cardiovascular alterations.

11.2 Role of ACE2-Angiotensin-(1-7)-Mas Axis in Glycemic Control

Identification of a local pancreatic RAS has led to a better understanding of the role of the RAS in the physiopathology of diabetes. RAS blockers seem to be able to reverse Ang-II-induced impairment in insulin sensitivity, insulin secretion, and pancreatic β-cell function [26–29]. However, the role of RAS blockers in this context is an ongoing matter of debate due to studies showing the inefficiency of RAS blockers in controlling hyperglycemic symptoms [30, 31].

On the other hand, ACE2 has received significant attention over the past years, being considered a promising target due to its beneficial role in glycemic control [32]. ACE2 was discovered in 2000 and shares 42% sequence homology with ACE, but cannot be inhibited by ACE inhibitors [15, 16].ACE2 gene is located on the Xchromosome and cleaves various substrates, including Ang II, angiotensin I (Ang I), apelin, neurotensin, and des-Arg bradykinin with the highest catalytic efficiency towards Ang II [15, 16]. Indeed, ACE2 is the main enzyme responsible for the conversion of Ang II into Ang-(1-7) in many organs and tissues [33].

ACE2 overexpression has been shown to reverse the detrimental phenotypes in cardiovascular disease [34, 35], diabetes [36, 37],and its related complications, an effect known to occur by suppressing the overactive Ang II levels [38]. The beneficial effects of ACE2 have been attributed to its capacity to increase Ang-(1-7) levels [15, 16, 33]. It has reported that Ang-(1-7) improves insulin sensitivity and glucose tolerance in experimental animal models, possibly by stimulating the insulin signaling via Mas receptor [39, 40]. Supporting this hypothesis, mice with genetic deletion of Mas receptor exhibit disturbances in glucose and lipid metabolism [41]. Furthermore, the increase in circulating levels of Ang-(1-7) improves glucose tolerance and dyslipidemia [42]. Even under physiological conditions, mice with genetic deletion of ACE2 progressively reduce insulin secretion and glucose tolerance [43]. However, when these knockout animals were under a high-fat high-sucrose diet,the degree of glucose intolerance is higher than in wild type mice [44]. This effect was attributed to the reduced skeletal muscle levels of GLUT4 and myocyte enhancer factor 2A expression [44]. It should be mentioned that the administration of Ang-(1-7) restored glucose tolerance [44]. These results support the importance of Ang-(1-7) signaling in maintaining glucose tolerance and insulin sensitivity.

The importance of the counter-regulatory ACE2-Ang-(1-7)-Mas axis in maintaining pancreatic β-cell function has been investigated in vitro [45]. The results showed that an upregulation in the expression of ACE2 and of Mas is associated with an increase in insulin secretion at high glucose concentrations [45]. In experimental models of diabetes, ACE2 levels decrease as the disease progresses, leading to an uninhibited rise in the activity of the classical ACE-Ang II-AT_1 axis [36, 46]. Thus, it can be speculated that, as the Ang II levels increase in hyperglycemic state, ACE2 is also upregulated as a compensatory mechanism and aids in the degradation and reduction of Ang II. Moreover, ACE2 gene therapy and the administration of

ACE2 activators, including xanthenone and diminazene aceturate [47], exerted beneficial effects in the face of diabetes [36, 48] and its complications [49, 50].

Various mechanisms have been proposed by which ACE2 elicits opposing effects on Ang II signaling. Oxidative stress has been reported to be one of the predisposing factors of pancreatic β-cell dysfunction during hyperglycemic states [51, 52]. Ang II activates reactive oxygen species (ROS) [53]. ACE2 over expression reduced oxidative stress and corrected Ang II-induced imbalance in the relationship between the expressions of AT_1 receptor and of ACE2 [37]. Both mechanisms improved glycemic control [37]. Pharmacological inhibition of ACE2 and of Mas receptor increased ROS formation induced by Ang II [54], further supporting the hypothesis that ACE2 reduces thecapacity of Ang II to form ROSby converting Ang II into Ang-(1-7).

Other mechanisms of impaired glucose homeostasis include endoplasmic reticulum stress, tissue fibrosis and inflammation [55–57]. The lack of ACE2 has been reported to exacerbate fibrosis and inflammation in the kidney [58, 59]and in the heart [60], whereas the overexpression of ACE2 decreased fibrosis in the heart [61], lungs [62], and pancreas [63].Moreover, Ang-(1-7) improved insulin sensibility, at least in part, via its anti-inflammatory properties in the liver [64].This effect was also associated with an up regulation in ACE2 expression in the liver. On the other hand, there are scarce information on the role of ACE2-Ang-(1-7)-Mas axis in preventing fibrosis in pancreatic islets [63]. The role of ACE2 in modulating endoplasmic reticulum stress, fibrosis, and inflammation in the islets warrants further investigation.

Figure 11.1 summarizes the main actions of the classical and the counter-regulatory RAS axes in the control of the glycemia and of the insulin secretion.

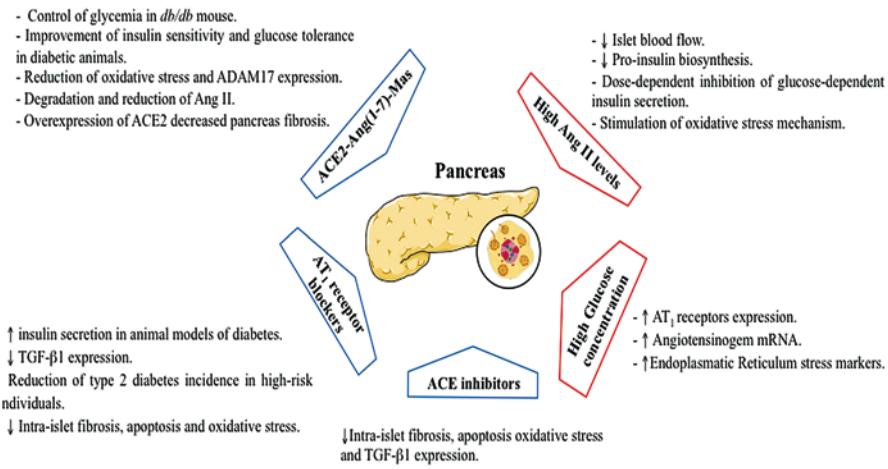

Fig. 11.1 The role of components of the classical and the counter regulatory renin-angiotensisn system axes in the control of glycemia Nd of the insulin secretion

11.3 Role of ACE2-Ang-(1-7)-Mas Receptor Axis in Diabetic Nephropathy

Diabetic nephropathy is one of the most common causes of end-stage renal disease and one of the main complications of diabetes, but the factors responsible for the development of diabetic nephropathy have not been fully elucidated [65].

There is growing interest in a possible role of ACE2 in diabetic kidney disease [19, 46, 65]. Activation of the classical RAS axis, ACE-Ang II- AT_1 receptor, is widely believed to contribute to kidney injury in diabetes [66]. ACE2 may act as a negative regulator of the classical RAS axis, exerting a renoprotective action [65]. Obese *db/db* mice (C57BLKS/JLepr) have been used as a model of type 2 diabetes, and their lean littermates (*db/m*) have served as nondiabetic controls [18, 19, 24, 65]. In renal cortical tubules of *db/db* mice, the pattern of ACE and ACE2 expression was characterized by low ACE, but increased ACE2 protein [65]. These alterations in ACE2 protein in renal tubules from diabetic mice are accompanied by corresponding changes in enzymatic activity [19]. Ye and co-workers [24]examined the localization of ACE and ACE2 in the glomerulus of control and diabetic mice. The glomerulus is the site of the nephron where the lesions of diabetic nephropathy appear earlier, and an increase in glomerular permeability is an early manifestation of diabetic kidney disease as reflected by the presence of albuminuria. The authors found that in glomeruli from *db/db* mice, ACE staining was higher than in control mice, while strong ACE2 staining in glomeruli from diabetic mice was less frequently seen than in controls [24]. In addition, the same research group reported that chronic blockade of ACE2 with the enzyme inhibitor, MLN-4760, in control or diabetic mice produced albuminuria and matrix proteins deposition [18]. In this regard, Wong and co-workers [67] examined the effect of deletion of the *ACE2* gene on diabetic kidney injury. In this study, ACE2 knockout mice [$ACE2^{-/-}$]were crossed with Akita mice ($Ins2^{WT/C96Y}$), a model of type 1 diabetes mellitus, and four groups of mice were studied at 3 months of age: $ACE2^{+/y}Ins2^{WT/WT}$, $ACE2^{-/y}Ins2^{WT/WT}$, $ACE2^{+/y}Ins2^{WT/C96Y}$, and $ACE2^{-/y}Ins2^{WT/C96Y}$. $ACE2^{-/y}Ins2^{WT/C96Y}$ mice exhibited increased mesangial matrix scores, glomerular basement membrane thicknesses, glomerular deposit of fibronectin and a twofold augmentation in the urinary albumin excretion rate compared with $ACE2^{+/y}Ins2^{WT/C96Y}$ [67]. The treatment with an AT_1 receptor blocker, irbesartan, reversed the alterations in renal histology and reduced proteinuria in $ACE2^{-/y}Ins2^{WT/C96Y}$ mice [67]. More recently, ACE2 knockout mice with streptozotocin-induced diabetes presented an increase in serum creatinine, urea levels and albuminuria in comparison with wild type diabetic animals [66]. In addition, glomerular and tubulointerstitial injuries and macrophage infiltration were significantly more severe inACE2 knockout mice than in wild type controls. AT_1receptor blocked with olmersartan attenuated the effects of ACE2 deficiency, but only partially [66]. Taken together, these studies suggested that ACE2 plays a protective role in the diabetic kidney, and ACE2 is an important determinant of diabetic nephropathy.

Some studies have also suggested a close correlation between albuminuria and ACE2. The treatment of HK-2 cells with bovine serum albumin has led to significant changes in ACE/ACE2 expression favoring Ang II formation [52]. More recently, Marquez and co-workers [68] showed that insulin increases ACE2 gene, protein expression, and enzymatic activity in cultured podocytes and these increases were maintained over time. In the presence of albumin, the beneficial effect of insulin on ACE2 expression and activity disappeared [68]. Therefore, ACE2 reduction might increase urinary albumin excretion, while albuminuria, in turn, could disrupt the balance of ACE/ACE2 expression [68]. In this regard, Riera and co-workers [69] studied the non-obese diabetic mice model, since these animals develop autoimmune diabetes that resembles human type 1 diabetes. At an early stage of diabetes, diabetic mice exhibited tenfold increase in urinary albumin excretion, glomerular enlargement, increased glomerular filtration rate and higher blood pressure in comparison to controls [69]. At a later stage, diabetic mice had a 20-fold increase in albuminuria, mesangial expansion and reduced podocyte number. Circulating and urine ACE2 activity were markedly increased at early and late stage of diabetes. Insulin administration prevented albuminuria, markedly reduced GFR, blood pressure, and glomerular enlargement at the early stage; and prevented mesangial expansion and the reduced podocyte number at the late stage of diabetes. The increase in serum and urine ACE2 activity was normalized by insulin administration at the early and late stages of diabetes. The authors conclude that diabetic mice develop features of early kidney disease associated with increased activity of ACE2 in both serum and urine and these alterations can be completely prevented by the administration of insulin.

Ang-(1-7) has also a role in experimental models of diabetes. The administration of Ang-(1-7) was able to normalize creatinine clearance and significantly attenuate proteinuria in Zucker diabetic fattyrats, a model of type 2 diabetes and diabetic nephropathy [70]. Diabetic rats treated with Ang-(1-7) displayed markedly reduction in renal fibrosis, presenting levels of extracellular matrix proteins similar to control animals [70]. Levels of TNF-α, IL-6, endothelin-1, and hypoxia inducible factor (HIF)-1α in the kidneys were also decreased to levels similar of those of control animals. The same effect was observed in renal and urinary levels of neutrophil gelatinase-associated lipocalin (NGAL), a marker of kidney damage [70]. Accordingly, chronic infusion of Ang-(1-7) also had significant protective effects in leptin deficient *db/db* mice, another model of type2 diabetes and diabetic nephropathy [25]. Animals treated with Ang-(1-7) for 28 days normalized urinary albumin excretion and significantly decreased kidney weight and mesangial expansion. Phosphorylation of STAT3 and renal fibrosis were also significantly reduced, as well macrophage infiltration in perirenal adipose tissue [71]. These findings suggest that both elevated levels of Ang II and decreased levels of Ang-(1-7) may contribute to renal damage [68].

In contrast to experimental studies, limited data were obtained in regard to ACE2-Ang-(1-7)-Mas axis in patients with diabetic nephropathy [22]. Most studies measured urinary levels of ACE2 in patients with type 2 diabetes [18, 20, 23, 24] and few others investigated mRNA and/or protein expression for ACE2 in human renal tissue [21, 25].

Concerning the studies that measured ACE2 in urine, Park and co-wotkers investigated whether urinary ACE2 levels are associated with abnormal glucosehomeostasis and urinary albumin excretion [23]. The authors found that urinary ACE2 levels were an independent predictor of microalbuminuria afteradjusting for other clinical risk factors in patients with type 2 diabetes [23]. In patients with type 2 diabetes and chronic kidney disease, Abe and co-workers showed that the treatment with the AT_1 receptor antagonist olmesartansignificantly increases urinary ACE2 levels independently of blood pressure andplasma aldosterone levels and reduces albuminuria, urinary liver-type fatty acidbinding protein, and plasma aldosterone levels [18]. The authors raised the possibility that increased ACE2 contributes to renoprotection elicited by olmesartan [18]. More recently, Liang and co-workers reported that urinary levels of ACE2 are increased in type 2 diabetic patients with various degrees of albuminuria [20]. Furthermore, the treatment with RAS inhibitors reduced urinary ACE2 excretion [20]. The authors concluded that urinary ACE2 measurement mightpotentially function as a marker for monitoring the metabolic status and therapeutic response to RAS inhibitors in diabetes [20]. Only one study investigated ACE2 in patients with type 1 diabetes and found that urinary ACE2 activity and protein expression are increased prior to the onset of clinical complications [19]. None of these studies have investigated the mechanisms that promote the elevation of ACE2 in the urine of diabetic patients. A possible explanation is that the augmentation of urinary ACE2 levels might be a compensatory mechanism in response to kidney injury in diabetic patients.

In regard to the evaluation of Ang-(1-7) and Mas receptor in diabetic patients, Mizuiri and co-workers reported that the proximal tubules from type 2 diabetic patients with nephropathy exhibited higherexpression of ACE and lower expression of ACE2, Ang-(1-7) and Mas receptor in comparison to healthy controls and to patients with minimal change nephrotic syndrome [21].

Figure 11.2 displays the effects of the classical and the counter-regulatory RAS axes in diabetic nephropathy.

11.4 Role of ACE2-Ang-(1-7)-Mas Receptor Axis in Diabetic Cardiovascular Disease

Diabetes mellitus is associated with substantial risk of heart failure and has been described as the leading cause of morbidity and mortality related with cardiovascular diseases (CVD) worldwide. Diabetic CVD includes myocardial infarction, mainly associated with premature atherosclerosis, and diabetic cardiomyopathy, characterized by left ventricular (LV) remodeling and dysfunction, both leading to heart failure [72, 73]. Indeed, diabetes has been considered not only a risk factor for CVD, but also a cardiovascular event equivalent, since diabetic subjects had a risk of cardiovascular complications similar to patients with previous myocardial infarction [74]. Accordingly, diabetic patients with myocardial infarction have worse prognosis than non-diabetic patients with myocardial infarction [75].

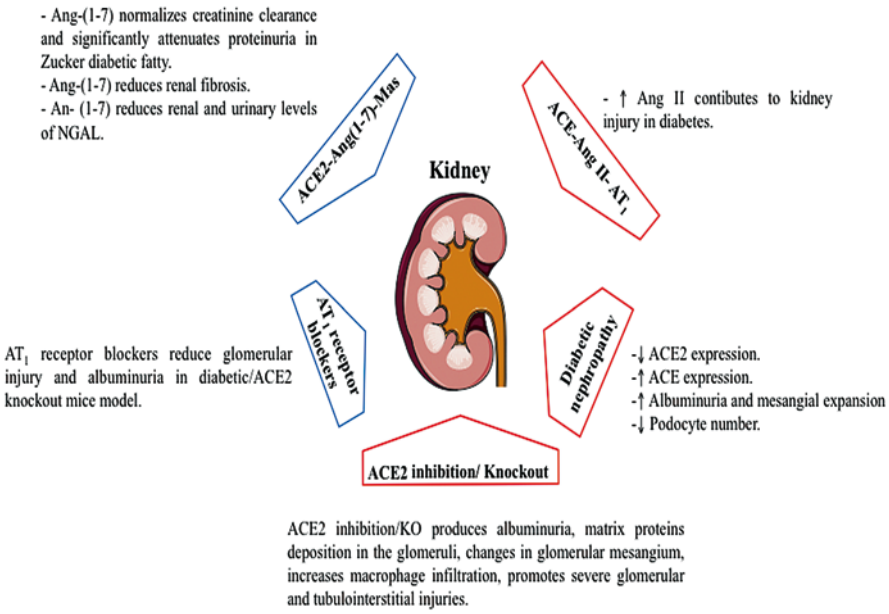

Fig. 11.2 The role of components of the classical and the counter regulatory renin-angiotensisn system axes in diabetic nephropathy

The pathophysiological mechanisms underlying diabetic CVD remain poorly elucidated. The discover that RAS key components are also locally expressed in different organs, including the heart, opens the road for the hypothesis that RAS exerted both hemodynamic and non-hemodynamic effects [76]. In fact, RAS components, including renin, angiotensinogen, ACE and Ang II receptors, were upregulated in the heart after cardiac injury, volume overload, myocardial infarction, and heart failure [77–80]. In the context of diabetes, over the past decades, clinical and experimental studies have been linked the classical RAS axis to diabetic CVD pathophysiology. For instance, ACE inhibitors, like perindopril, and AT_1 receptor blockers improved cardiovascular morbidity and mortality in patients with diabetes [81, 82] and prevented atherosclerosis and myocardial infarction in diabetic apolipoprotein E-deficient mice and in a streptozotocin-induced diabetes model [83–85]. There is evidence that Ang II by binding to its AT_1 receptors might mediate cardiovascular damage by inducing reactive oxygen species generation, tissue inflammation, fibrosis, and apoptosis [83, 84, 86–89].

A more modern concept has been supported that diabetic CVD depends on a balance between both RAS axes, the classical (ACE-Ang II-AT_1 receptor) and the counter-regulatory (ACE2-Ang-(1-7)-Mas receptor) [50, 90, 91].In line with this view, an elegant study demonstrated a significant reduction in cardiac ACE2 expression and activity along with elevated circulating levels of AngII and reduced Ang-(1-7) concentration in the heart in streptozotocin-induced diabetic mice. The changes in RAS components in response to diabetes induction were associated with

a significant cardiovascular damage, which included thinning of the LV wall, mild ventricular dilatation, increased cardiomyocyte apoptosis and compensatory heart hypertrophy [90]. Interestingly, the induction of diabetes by streptozotocin in mice genetically deficient for ACE2 did not change Ang II and Ang-(1-7) concentrations; neither led to cardiovascular dysfunction. Moreover, the absence of ACE2 also prevented the accelerated atherosclerosis found in diabetic apolipoprotein E-deficient mice. Altogether, these findings suggest that ACE2 might be a key factor in RAS activation in diabetic CVD, mainly by regulating cardiac levels of Ang II and of Ang-(1-7) [91]. Accordingly, in a model of human diabetes by employing the Akita mice with the loss of ACE2 expression increased plasma and heart tissue levels of Ang II, leading to systolic dysfunction on a background of impaired diastolic function [91]. The cardiovascular systolic alterations were associated with increased oxidative stress, degradation of the extracellular matrix activation of protein kinase C and loss of Akt and endothelial nitric oxide synthase phosphorylation, all of which prevented by the administration of the AT_1 receptor blocker, irbesartan [90]. Similarly, diabetes induction by streptozotocin in male Wistar rats resulted in diastolic dysfunction, cardiac hypertrophy and fibrosis along withACE2/ACE ratios imbalance, ERK1/2 phosphorylation and changes in the AMP-activated protein kinases, AMPK-α and AMPK-β1 expression. All these changes were prevented by the oral administration of the ACE2 activator XNT, suggesting that increase in ACE2 activity might be a promise therapy for diabetic CVD [50]. This hypothesis was supported by further studies showing that ACE2 over expression induced by a gene therapy with adenovirus was superior to losartan in attenuating diabetic cardiomyopathyas indicated by a decrease in myocyte hypertrophy, myocardial fibrosis, and LV remodeling and an improvement in LV systolic and diastolic function [92]. A protective effect was also found following an oral administration of the ACE2 activator, diminazene aceturate (DIZE), reflected by the improvement in cardiac electrical function in streptozotocin-induced diabetic rats [93].

Emerging evidence have been supported the idea that the beneficial effects of ACE2 is related with its capacity to convert AngII into Ang-(1-7). For instance, increased plasma levels of Ang-(1-7) were independently associated with a protection of left ventricular function in patients with type 2 diabetes mellitus [94]. Moreover, a growing body of experimental studies showed that the administration of Ang-(1-7) or of the Mas receptor oral agonist, AVE0991, significantly protects against diabetes-induced cardiovascular dysfunction [95–99]. Importantly, the opposite effect was observed with the administration of the Mas receptor antagonist, A779 [95, 98]. In this scenario, the elevation of Ang-(1-7) levels might also represent a promise therapeutic strategy for diabetic CVD.

The mechanisms underlying Ang-(1-7) cardiac protection might rely on the inhibition of inflammation and of oxidative stress by decreasing the transcript factor NF-kB activity and the NADPH oxidase activation, by restoring lipid profile alterations, and by reducing collagen and fibronectin-1 production, and TGF-β1 expression [95, 98, 99]. More recent studies, by employing the *db/db* mice, a well-established model of type 2 diabetic cardiomyopathy, showed that Ang-(1-7) improves myocardial hypertrophy and fibrosis by decreasing the lipotoxicity and

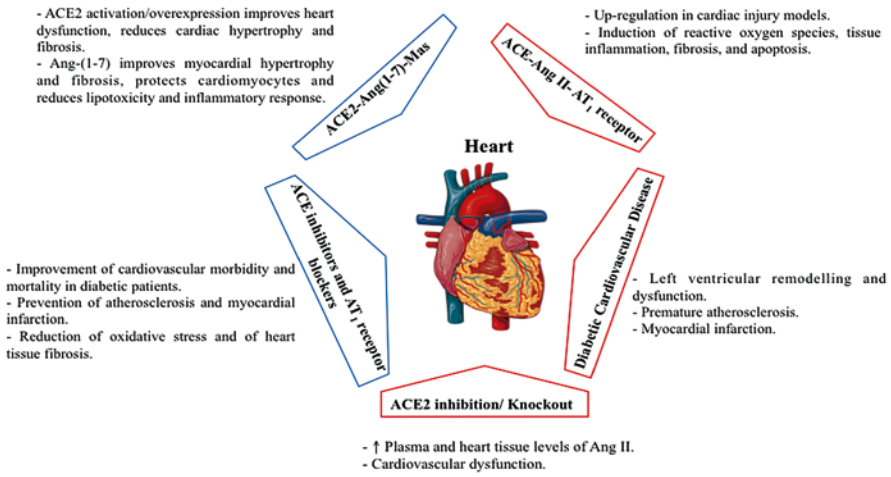

Fig. 11.3 The role of components of the classical and the counter regulatory renin-angiotensisn system axes in heart alterations in diabetes

the inflammatory response [100, 101]. Similar findings were reported by an in vitro study showing that Ang-(1-7) protects cardiomyocytes against high glucose-induced injuries by inhibiting the activation of the reactive oxygen species-activated leptin-p38 MAPK/ERK1/2 pathways [102].

It has been also reported that the cardioprotective effects of Ang-(1-7) may result from a complex interaction between AT2 and Mas receptors with a subsequent down-regulation of ACE expression and activity and of AT_1receptor expression, as well as up-regulation of ACE2 expression and activity [98, 103]. In addition, an increase in AT2 expression was associated with higher apoptosis rate of cardiomyocytes in diabetic rats [104]. In fact, the exogenous Ang-(1-7) significantly increased myocardial ACE2 activity and Ang-(1–9) levels, possibly via its effect on AT2 receptor. The increased activity of ACE2 leads to higher conversion rate of Ang II into Ang-(1-7), thus forming a positive feedback that elevates Ang-(1-7) levels, which, in turn, produce protective effects in diabetes-induced CVD [98].

Figure 11.3 shows the role of the classical and the counter-regulatory RAS axes in heart alterations of diabetes.

11.5 Conclusion

Despite available treatments for diabetes, a substantial population is still suffering from renal injury, cardiovascular alterations and other associated comorbidities. The inhibition of the classical RAS axis with angiotensin receptor blockers and/or ACE inhibitors is not effective for all cases and, in such conditions, we may speculate the usefulness of therapies to activate the counter-regulatory RAS axis.

Therefore, different ways to activate ACE2-Ang-(1-7)-Mas receptor axis emerge as a promise therapeutic strategy for diabetes and its co-morbidities.

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Conflict of Interest None declared

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