Angiotensin-Converting Enzyme II in the Heart and the Kidney

Ursula Danilczyk, Josef M. Penninger

Abstract—The renin-angiotensin system (RAS) has been recognized for many years as critical pathway for blood pressure control and kidney functions. Although most of the well-known cardiovascular and renal effects of RAS are attributed to angiotensin-converting enzyme (ACE), much less is known about the function of ACE2. Experiments using genetically modified mice and inhibitor studies have shown that ACE2 counterbalances the functions of ACE and that the balance between these two proteases determines local and systemic levels of RAS peptides such as angiotensin II and angiotensin1–7. Ace2 mutant mice exhibit progressive impairment of heart contractility at advanced ages, a phenotype that can be reverted by loss of ACE, suggesting that these enzymes directly control heart function. Moreover, ACE2 is also found to be upregulated in failing hearts. In the kidney, ACE2 protein levels are significantly decreased in hypertensive rats, suggesting a negative regulatory role of ACE2 in blood pressure control. Moreover, ACE2 expression is downregulated in the kidneys of diabetic and pregnant rats and ACE2 mutant mice develop late onset glomerulonephritis resembling diabetic nephropathy. Importantly, ACE2 not only controls angiotensin II levels but functions as a protease on additional molecular targets that could contribute to the observed in vivo phenotypes of ACE2 mutant mice. Thus, ACE2 seems to be a molecule that has protective roles in heart and kidney. The development of drugs that could activate ACE2 function would allow extending our treatment options in diabetic nephropathy, heart failure, or hypertension. (Circ Res. 2006;98:463-471.)

Key Words: angiotensin-converting enzyme 2 ■ knockout mice ■ renin-angiotensin system
angiotensin-converting enzyme (ACE) and ACE2, began only recently to unravel. ACE functions primarily as a “peptidyl dipeptidase,” removing dipeptides from the C terminus of peptide substrates. Its primary substrate was identified as Ang I. ACE processes the decapetide Ang I to the 8-amino acid (aa) peptide Ang II (Figure). In contrast, ACE2 cleaves only a single amino acid from the C terminus of any given substrate. The role of ACE in regulation of cardiovascular function, fluid and electrolyte homeostasis is well established. Several small molecule inhibitors of human ACE are used for antihypertensive therapies, lowering the risk of coronary heart disease and stroke, and treatments of cardiac failure and diabetic nephropathy. Much less is known about the physiological function of ACE2.

ACE2 was initially found to be expressed in endothelia of the heart and in tubular epithelial cells of the kidney. Subsequent studies using quantitative polymerase chain reaction have shown that ACE2 gene expression also occurs in the gastrointestinal tract and, to a lesser extent, in other organs such as lungs. Experiments showing that old ACE2-deficient mice develop progressively impaired heart functions that can be rescued by the loss of ACE have provided evidence for the direct involvement of the RAS in the modulation of cardiac contractility. Additionally, the observation of ventricular trabeculcardia and heart block in ACE2 transgenic mice suggested a role of RAS in ventricular remodeling, supporting the clinical observations that ACE inhibitors have beneficial effects on cardiac remodeling and heart failure. In addition to the heart, the RAS plays an important role in the control of kidney function. For instance, ACE inhibitors and Ang II receptor antagonists can confer renoprotection in experimental and human diabetic nephropathy. High expression levels of ACE2 in the normal kidney, together with the observations of reduced levels of ACE2 in diabetic rats and in human kidney diseases, imply ACE2 involvement in kidney physiology and pathophysiology. In line with these observations, ACE2 functions may not be limited only to the RAS.

Balancing the RAS Pathway

In the classic pathway of RAS, Ang II is a product of a “peptidyl dipeptidase” ACE. In this process, the decapetide Ang I is converted by ACE to Ang II (Figure), Ang I is generated from the circulating precursor angiotensinogen (AGT) by the action of renin, an enzyme secreted from by juxtaglomerular cells at the renal afferent arterioles. Ang II plays a central role as a potent regulator of fluid volumes, blood pressure regulation, and cardiovascular remodeling by binding to the Ang II G-protein–coupled receptors type 1 (AT1) and type 2 (AT2). The majority of the cardiac and renal actions of Ang II are mediated by the AT1 receptor, including vascular smooth muscle contraction, aldosterone secretion, dipsogenic responses, adrenergic stimulation, renal sodium reabsorption, and pressor and chronotropic responses. Ang II also binds to AT2 receptors, inducing a counter-regulatory vasodilatation that is largely mediated by bradykinin and NO. The emerging picture of ACE2 function is of a key enzyme catalyzing the cleavage of both Ang I and Ang II. ACE2 cleaves the C-terminal amino acid of Ang I to the nonapeptide angiotensin1–9 (Ang1–9). Ang1–9 is thought to potenti ate Ang II–mediated vasoconstriction in isolated rat aortic rings and to have vasopressor effects in conscious rats. In rat and human plasma, Ang1–9 levels are twice those of Ang II, and Ang1–9 accumulates in animals treated with ACE inhibitors. Also, Ang1–9 was found to augment bradykinin action on its B2 receptor by probably inducing conformational changes in the ACE/B2 receptor complex via interaction with ACE. The biological function of Ang1–9 in heart and kidney is still not well defined. ACE2 also directly converts Ang II to Ang1–7. In animals, Ang1–7 has been proposed to be an important regulator of cardiovascular and renal function promoting vasodilatation, apoptosis, and growth arrest. It is important to note that ACE and ACE2 are not the only enzymes involved in the RAS pathway; for example, chymases convert Ang I to Ang II, and other angiotensinases are known to hydrolyze Ang I to Ang1–7 or Ang1–9. Still, the unique patterns of Ang I metabolism by ACE and ACE2 may represent the biochemical and physiological counter-regulatory arms of the RAS in the regulation of cardiovascular and renal function. ACE2 seems to regulate Ang II production by ACE either by stimulating an alternative pathway for Ang I degradation or by facilitating the degradation of Ang II into Ang1–7. However, according to the feed-forward node enzymatic pathway, ACE determines both the production of Ang II and the degradation of Ang1–7, whereas ACE2, by facilitating the conversion of Ang II into Ang1–7, can regulate the net level of Ang II present in the tissue. The peptide Ang1–7, through its recently identified receptor the mas oncoprotein product (MAS), may stimulate NO synthase and counteract the potentially detrimental actions of Ang II via the AT1 recep-
The cardiac and renal functions of ACE2 substrates or products are not always well defined.

Neurotensin

| pGlu-Leu Tyr Glu Asn Lys Pro Arg |

balances ACE function.

that ACE2 is a negative regulator of the RAS and counter-

levels while simultaneously reducing Ang II. Thus, it appears

ACE itself. Therefore, ACE inhibition can increase Ang1–7

whereby the peptide is converted to inactive fragments, is via

G-protein–coupled receptors

ventricular contractility, regulation of renin release, sodi-

output

ACE2 functions as a carboxyamidopeptidase with a preference for C-terminal Leu or Phe. The ACE2 substrates, products, and their receptors, if known, are indicated. The cardiac and renal functions of ACE2 substrates or products are not always well defined.

ACE2 Substrates and Products

<table>
<thead>
<tr>
<th>ACE2 Substrates/Products</th>
<th>Receptor</th>
<th>Cardiac and Renal Functions</th>
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<tbody>
<tr>
<td>Ang I</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Asp Arg Val Tyr Ile His Pro Phe Leu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang1–9</td>
<td>Unknown</td>
<td>Vasoconstriction?</td>
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<tr>
<td>Asp Arg Val Tyr Ile His Pro Phe</td>
<td></td>
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<tr>
<td>Ang II Asp Arg Val Tyr Ile His Pro Phe</td>
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<tr>
<td>Ang1–7 Asp Arg Val Tyr Ile His Pro</td>
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<tr>
<td>Apelin-36 c term-Ser His Lys Gly Pro Met Pro Phe Apelin-13 Gin Arg Pro Arg Leu Ser His Lys Gly Pro Met Pro Phe</td>
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<tr>
<td>des-Arg9-bradykinin</td>
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<td>Arg Pro Gly Phe Ser Pro Ph</td>
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<td>Lys des-Arg9-bradykinin Lys Arg Pro Gly Phe Ser Pro Phe</td>
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<tr>
<td>Dynorphin A Tyr Gly Phe Leu Arg Arg Ile Arg Pro Lys Leu Lys β casamorphin Tyr Pro Phe Val Glu Pro Ile</td>
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<tr>
<td>Neuropeptide Y-Glu-Leu Tyr Glu Asn Lys Pro Arg</td>
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ACE2 Substrates/Products

Ang I

Ang1–9

Ang II

Ang1–7

Apelin-36

Phe

G-protein–coupled AT1 and AT2 receptors

Vasoconstrictor, cardiomyocyte hypertrophy, fibroblasts proliferation, cardiac and cardiomyocyte contractility, regulation of glomerular hemodynamics, and proteinuria

Vasodilator, inhibition of cell growth, sodium and water flux, reduction in glomerular filtration

Vasoconstriction, vasodilation, water intake, myocardial contractility, regulation of stroke volume and cardiac output

Induced during inflammation and ischemia

Protective role in the development of hypertension and renal and cardiovascular complications

Pain perception, cardiomyocyte contractility, arterial pressure

Ventricular contractility, regulation of renin release, sodium excretion

ACE2 Substrates/Products

Ang I

Ang1–9

Ang II

Ang1–7

Apelin-36

Phe

Additional ACE2 Substrates

In addition to its activity as an enzyme converting Ang II to Ang1–7 or Ang I to Ang1–9, ACE2 can remove in vitro assays the C-terminal residue from apelin and other vasoactive peptides such as neurotensin, kinetensin (a neurotensin-related peptide), and des-Arg bradykinin (Table). Indeed, ACE2 acts on apelin-13 and apelin-36 peptides with high catalytic efficiency. These two forms of apelin were recently identified as endogenous ligands for the human APJ receptor, the homolog of the angiotensin receptor AT2. However, APJ knockout mice showed a rather minimal increase in their vasoressor response to Ang II, nevertheless, suggesting a counter-regulatory role in relation to the RAS. Apelin also induces an increase in myocardial contractility and a reduction of vasomotor tone. Although the increase in contractility seems to depend on an activation of Na+/H+ and Na+/Ca2+ exchangers, vasodilation is attributed to a release of NO from the vascular endothelial cells. When apelin is given acutely, the decrease in preload favors the reduction of stroke volume and cardiac output in spite of an increased contractility. Chronic administration of apelin significantly increases cardiac output without the occurrence of cardiac hypertrophy. However, potential chronic side effects of apelin administration need to be determined.

Two opioid peptides, dynorphin A and β-casamorphin, are also substrates of ACE2 (Table). These peptides activate κ and δ opioid G-protein–coupled receptors that regulate pain perception and, among other functions, may have negative effects on cardiomyocyte contractility. Opioid peptides and their receptors show broad distribution in the various brain areas but are also expressed at sites that control the cardiovascular system. Potent cardiovascular effects have been reported after central administration of opioid peptides. For instance, intracerebroventricular administration of β-endorphin decreases the lumber sympathetic nerve activity and mean arterial pressure in anesthetized rats. However, it should be noted that studies with various opioid agonists are conflicting.

The kinin metabolites, the nonapeptide bradykinin, and its biologically active metabolite exert their effects by selective activation of the two kinin receptor types: B1 and B2. The bradykinin B1 receptor is constitutively expressed in most human tissues and mediates the majority of the visceral and vascular actions of bradykinin, whereas the bradykinin B2 receptor is expressed mainly under pathological conditions such as inflammation and sepsis, being selectively activated by des-Arg9 metabolites of the kinins. ACE2 does not metabolize bradykinin but activates both des-Arg9-bradykinin and lys-des-Arg9-bradykinin. In various animal models and in humans, it has been shown that the stimulation of bradykinin B2 receptors is not only implicated in the pathogenesis of inflammation, pain and tissue injury, but also triggers cardioprotective and renoprotective func-
In conclusion, although the biological peptides Ang I and Ang II are principal ACE2 substrates, ACE2 can cleave multiple other target peptides such as apelin-13, dynorphin A, or des-Arg^8-bradykinin. Thus, although ACE2 functions have been primarily attributed to the regulation of the RAS, Ang II and Ang1–7 are probably only part of the ACE2 story, and other ACE2 substrates may contribute to the in vivo functions of ACE2.

Cardiac Functions

For a number of years, ACE and its main biologically active peptide Ang II have assumed a central position in the cardiac RAS. With the discovery of ACE2, a new regulator entered the established metabolic RAS pathways. Components of the local cardiac RAS are heterologously distributed on different cell types within the heart. For instance, AGT is primarily distributed in atrial muscle and the neuronal fibers of the conduction system, with small amounts in the subendocardial region of the ventricle. In contrast, ACE is primarily expressed by coronary endothelial cells and cardiac fibroblasts. Additionally, ACE expression can be detected in all four heart valves, coronary blood vessels, the aorta pulmonary arteries, endocardium, as well as epicardium. ACE2 is localized to the endothelium and smooth muscle cells of most intramyocardial vessels, including capillaries, venules, and medium-sized coronary arteries and arterioles. Furthermore, ACE2 protein expression was detected in cardiac myocytes from failing human hearts. It is important to note that although all the components of RAS are present in the heart, not all of them are believed to be synthesized in heart. For example, the question whether renin is synthesized in heart or is derived primarily from circulation remains still unresolved. Together, the final balance of biologically active peptides produced within local heart environment may depend on the coexpression and the relative levels of ACE and ACE2 within different cell types.

Cardiac Contractility

Although hearts from young ace2 mutant mice are functionally normal, hearts of old ace2-deficient mice in this particular mouse background display a reduction in cardiac contractility as demonstrated by 40% reduction in fractional shortening and velocity of circumferential shortening (heart rate corrected) with slight ventricular dilation. The significance of ACE2 in regulating cardiac function is further highlighted by the thinning of the left ventricular wall in aged ace2 mutant mice. This progressive cardiac dysfunction occurred without myocardial fibrosis or hypertrophy and in the absence of the myosin heavy chain isoform switches typically found in other animal models of heart failure. Thus, one may speculate that the observed phenotype closely resembles the defective heart found in patients with cardiac stunning/hibernation. Cardiac stunning and hibernation reflect adaptive responses to prolonged tissue hypoxia that occurs in coronary artery disease or after bypass surgery. In these human diseases and related animal models, chronic hypoxic conditions lead to compensatory changes in myocyte metabolism, upregulation of hypoxia-induced genes, and reduced heart function. Accordingly, the hearts of ace2 null mice show upregulation of mRNA expression of hypoxia-inducible genes such as BNIP3 and PAI-1. The magnitude of increased expression of these hypoxia-inducible genes resembles previously observed levels in other hypoxic models such as the myocyte-specific vascular endothelial growth factor mutant mice. However, the link between cardiac stunning/hibernation and the heart defect observed in ace2 knockout mice has to be investigated further. Whether ACE2 expression levels indeed change under conditions of hypoxia remains to be demonstrated.

ACE2 knockout mice show also increased local heart Ang II levels. Interestingly, both the cardiac phenotype and increased Ang II levels were completely reversed by additional deletion of ace gene (i.e., ablation of ACE expression on an ace2 mutant background abolished the cardiac dysfunction phenotype of ace2 single knockout mice). The heart function of ace/ace2 double mutant mice was similar to that in ace single mutant and wild-type littermates. The normal cardiac functions of ace/ace2 double mutant mice suggest that the catalytic products of ACE account for the observed contractile impairment of old ace2 single mutant mice. These observations for the first time demonstrated at the genetic level that ACE2 counterbalances the enzymatic actions of ACE. It seems that increased local cardiac Ang II might have been the cause for the cardiac abnormalities in ace2-deficient mice. However, it remains unclear why despite the elevated plasma and heart Ang II levels, the heart of the ace2-deficient mice did not show any evidence for cardiac hypertrophy. In fact, it is well established that cardiac myocytes express Ang II receptors and undergo hypertrophy in response to Ang II. However, in vivo, elevated cardiac Ang II levels alone do not directly induce cardiac hypertrophy but do increase interstitial fibrosis. Thus, it is important to note that Ang II–independent pathways could also play an important role in ACE/ACE2-regulated heart function.

ACE2 and Heart Conductivity

In several published studies, Ang II has also been implicated in conduction abnormalities, although some results appear contradictory. Slowed conduction was associated with increased myocardial and plasma ACE activity. Moreover, administration of an ACE inhibitor improved conduction velocities in cardiomyopathy using a Syrian hamster model. These observations suggest that Ang II slows cardiac conduction. This conclusion is further supported by the finding of slowed ventricular conduction in mice overexpressing the AT1 receptor. However, in contrast, in cardiac myocyte cultures, Ang II stimulated an increase in connexin43, a protein implicated in the upregulation of cardiac conduction, implying that Ang II may accelerate cardiac conduction. Interestingly, in ace2 null mice, elevated levels of Ang II did not affect normal conductivity, and the mice appear to have a normal life span, at least under nonstress laboratory conditions. However, overexpression of ACE2, under the control of the myosin promotor, caused conduction disturbances that in some animals degenerated into ventricular fibrillation with arrest and sudden death. The severity of this phenotype correlated with the ACE2 expression levels; mice with higher expression of ACE2 were dying by 5 weeks.
ACE2 expression may shift the balance from the production of the cardioprotective and anti-arrhythmic Ang1–7 to Ang1–9. Whether ACE2 plays indeed a role in cardiac conductance system should be assessed in mutant animals under conditions of stress or chronic injury.

ACE2 and the Failing Heart

Accumulating evidence indicates that the local cardiac RAS and myocardial Ang II production is activated in myocardial infarction.72–74 Indeed, increased cardiac expression of AGT, ACE, and AT1 receptor proteins, increased ACE activity, as well as elevated Ang II levels have been reported in infarcted hearts.73 Moreover, ACE2 expression increases in the infarct zone, followed by increased ACE2 expression in the myocardium surrounding the ischemic zone after coronary artery ligation in rats.73 Blockade of AT1 receptors by losartan or olmesartan for 28 days after occlusion of a coronary artery resulted in a significant increase in cardiac ACE2 mRNA expression as well as increased ACE2 activity.36 Furthermore, inhibition of Ang II synthesis by 12-day oral administration of lisinopril increased cardiac ACE2 gene transcription.36 Moreover, ACE2 gene expression and activity are also significantly increased in the failing human heart.75,76 The identification of ACE2 in the failing heart highlights its possible role in opposing the effects of Ang II.

The hypothesis that ACE2 and its product Ang1–7 may oppose the actions of Ang II was further supported by studies using normotensive Lewis rats.77 After coronary artery ligation, cardiac hypertrophy and left ventricular dysfunction were accompanied by increased plasma concentrations of Ang I, Ang II, and Ang1–7, and downregulation of cardiac AT1 receptor expression. Treatment with the AT1 receptor antagonists losartan and olmesartan reversed cardiac hypertrophy and improved ventricular contractility. Both AT1 receptor blockers further increased angiotensin peptide concentrations, returned AT1 receptor expression to normal, and increased ACE2 expression in the heart.77 It is important to note that in both studies in Lewis rats, cardiac ACE and ACE2 expression were unchanged in response to coronary artery ligation in the absence of drug treatment. Whether ACE2 expression has affected the severity or outcome of myocardial infarction remains contentious. However, what has emerged from recent studies appears to be the involvement of ACE2 in increasing the content of cardiac Ang1–7. Because Ang1–7 is formed within the heart after AT1 receptor blockade, ACE2 may be responsible for the beneficial actions observed on such a treatment on cardiac function. Furthermore, although ACE inhibitors were originally developed to suppress the formation of Ang II, recent studies suggest that part of their beneficial effect in cardiovascular diseases may be attributed to the elevation of plasma Ang1–7 levels.78–80 Whether Ang1–7 indeed contributes to heart disease or is simply a byproduct of the local RAS activation needs to be examined further (eg, in mice lacking the Ang1–7 receptor).

Renal Function of ACE2

A paradigm shift has occurred in recent years from an emphasis on the role of the systemic circulating RAS in the regulation of fluid and electrolyte balance and arterial pressure to focus on the local tissue RAS in kidneys. In the kidney, number of components of the RAS such as renin, AGT, and ACE mRNA are colocalized in a site-specific manner.81–84 Furthermore, the hypothesis that Ang II plays a tissue-specific role in the kidney is consistent with the finding that Ang II receptors are localized to renal arterioles, glomerular mesangial cells, and on the basolateral and apical membranes of proximal tubule cells.21,85

Within the kidney, ACE2 has a distribution similar to ACE. ACE2 is present in distal tubules, proximal tubules, and to a much lesser extent in glomeruli, as assessed by both gene and protein expression.21,85–88 Interestingly, most of the intrarenal AGT is localized in the proximal tubule,82–84,89–91 and AGT is secreted directly into the tubule lumen, where it serves as a substrate for renin or renin-like enzymes.89,91 Because ACE is located on the proximal tubule cell brush border, it can promptly convert Ang I to Ang II.92,93 Renal interstitial fluid contains a 1000-fold higher level of Ang II than plasma. However, as shown recently, ACE seems not to be the only enzyme contributing to Ang II formation in kidney, suggesting that besides other “angiotensinases,” the intrarenal levels of Ang II may be also regulated by ACE2. For instance, incubation of isolated proximal tubules with Ang I led to generation of Ang II as well as Ang1–7 and Ang1–9. Generation of Ang1–7 was blocked by the ACE2 inhibitor DX600. Although in vitro studies indicate that ACE2 has 400-fold greater efficacy to convert Ang II to Ang1–7 compared with the conversion of Ang I to Ang1–9,31,33 or the conversion of other peptide substrates, incubation of proximal tubules with Ang II or luminal perfusion of Ang II did not result in detection of Ang1–7.88 Nonetheless, ACE2-regulated Ang1–7 production in vivo may represent an important component of the proximal tubular RAS. Several studies have documented that Ang1–7 is a major biologically active peptide in kidneys.80,94–96 However, the role of Ang1–7 remains somewhat controversial. In most situations, Ang1–7 opposes the actions of Ang II. For instance, Ang1–7 infusion produced a marked natriuresis in the kidney of normotensive rats and dogs.34,96 Moreover, it has been reported that Ang1–7 causes afferent arteriolar vasodilation,97 and even if devoid of any vasodilator actions by itself, it antagonizes the renal vasoconstrictor effects of Ang II. Furthermore, treatment with either an Ang1–7 monoclonal antibody or with the selective Ang1–7 receptor antagonist 7-d-Ala-Ang1–7 elicited a dose-dependent rise in blood pressure and reversed to a significant degree the blood pressure–lowering effects of ACE inhibitors in hypertensive rats.34,98 In contrast to these experiments, it has been shown that Ang1–7 exhibits antiduretic actions in water-loaded rats and stimulates renal tubular sodium reabsorption in normotensive rats.99 Moreover, it has been reported that Ang1–7 does not exert vasodilator or Ang II, opposing actions in the renal circulation.97 That ACE2 may
be functionally linked to the tissue production of Ang1–7 is supported by the increased coexpression as well as colocalization of ACE2 protein and Ang1–7 in the renal proximal tubules of spontaneously hypertensive rats on treatment with the vasoconstrictor ACE inhibitor omapatrilat. Omapatrilat targets both ACE and nephrilysin but not ACE2. Furthermore, mRNA ACE2 levels in the kidney increased 75% after Omapatrilat treatment. Similar findings were reported in pregnant rats. Pregnancy increases the levels of both Ang1–7 and ACE2 in the renal tubules without affecting the overall pattern of ACE2 distribution. Increased levels of Ang1–7 in association with increased ACE2 expression support the notion that ACE2 may indeed play an important role in local kidney RAS. Together, these findings suggest that Ang 1–7 might be an important component of the RAS and a critical link in mediating the negative regulatory feedback between ACE and ACE2. To what extent ACE2 may contribute to these divergent functions of Ang1–7 in the kidney remains unclear.

Few data are available on the functional role of ACE2 in the kidney. The first reported data on ACE2 in kidneys showed that hypertension correlates with ACE2 expression. For example, ace2 mRNA levels in the kidneys of salt-sensitive Sabra hypertensive (SBH/γ) rats were lower then in the normotensive salt-resistant Sabra normotensive (SBN)/γ rats. In addition, ACE2 protein expression was also markedly reduced in SBH/γ animals that were fed a normal diet. Increase in blood pressure of SBH/γ rats after a 4-week diet of DOCA salt correlated with a further decrease in ACE2 protein expression. ACE2 protein levels were also significantly decreased in the kidneys of spontaneously hypertensive stroke-prone and spontaneously hypertensive rats compared with their Wistar Kyoto controls. Recently, it has been reported that ACE2 levels are reduced in experimental diabetic nephropathy. It is not yet known whether this reduction in ACE2 is of pathophysiological significance in diabetic nephropathy, but one could postulate that ACE2 deficiency leads to a local increase in tubular Ang II with subsequent effects such as promotion of interstitial fibrosis. For instance, local increases in Ang II have also been reported in damaged tubules in various experimental models of progressive renal disease such as in renal ablation, passive Heymann nephritis, anti-Thy1 glomerulonephritis, anti-GBM nephritis and also glomerulosclerosis. For instance, in glomerulosclerosis, it has been suggested that elevated Ang II levels might contribute to late development of glomerular injury and proteinuria. These studies support the view that local unopposed action of the ACE enzyme is generally associated with enhanced Ang II formation, resulting in increased renal damage. In line with this hypothesis, ACE inhibitors and AT1 receptor antagonist are known to reduce such renal injury and are used in the clinic for diabetic nephropathy. In humans, increased expression of ACE2 in glomerular and peritubular endothelium has been consistently observed in diseased kidneys across different diagnosis categories as well as renal transplants. Furthermore, mice at an early stage of diabetes exhibit increased ACE2 protein in renal cortical tubules coupled with profound reduction in renal expression of ACE. These data are consistent with the assumption that increased expression of ACE2 may reflect a protective mechanism. Because Ang II is thought to play an important role in the progression of diabetic nephropathy, decreased renal ACE activity tied with increased renal ACE2 expression may be protective for the kidneys in the early phases of diabetes by limiting the renal accumulation of Ang II and favoring Ang1–7 formation. Interestingly, the decrease in ACE activity associated with an increase in ACE2 protein expression resembles the pattern seen after administration of a renoprotective drug, ramipril, to diabetic rats. However, increased ACE2 protein expression in renal cortical tubules from the young diabetic mice does not exclude the possibility of an ACE2 reduction later during the development of nephropathy. In fact, decreased ACE2 expression in concert with increased ACE activity may foster kidney damage in diabetes. Importantly, it has been shown recently that old ace2 mutant mice, in particular males, develop Ang II–dependent glomerulosclerosis that resembles diabetic nephropathy in humans.

Concluding Remarks

The transmembrane protease ACE2 has emerged as a negative regulator of the RAS that counterbalances the multiple functions of ACE. Genetic data have shown that ACE2 plays a protective role in heart and kidney functions. In addition to the critical and multiple functions of Ang II, it is becoming clear that Ang1–7 and possibly Ang1–9 are additional major biologically active products of the RAS. ACE2 does not only function in the metabolism of RAS peptides but also in the catalysis of opioid peptides, apelin, neurotenisin, or kinetensin. Thus, enhancing ACE2 function might have effects and benefits that extend beyond the known functions of Ang II and its receptor. Understanding the physiological roles of ACE2 in myocardial function and its contribution to kidney damage may ultimately lead to the development of new therapeutic agents.

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