Angiotensin II revisited: new roles in inflammation, immunology and aging

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Introduction

To control body fluid volume homeostasis is essential to life and the complex system devoted to this task in humans is the result of an evolutionary process that was shaped by survival responses (Yun et al, 2006). To respond to trauma for example, activation of the sympathetic nervous system promotes the release of renin, angiotensin, aldosterone, catecholamine and natriuretic peptide whose effects maintain fluid pressure in the circulation despite volume loss due to haemorrhage (Helwig et al, 1956; Yun et al, 2006). The maintenance of volume homeostasis allowed animals to migrate from the sea’s salty water to fresh water and dry lands (Smith, 1953). In human evolution, the renin-angiotensin system (RAS) played an important role given its ability to control salt intake and stimulate thirst. The study of contemporary primitive tribes suggests that hunting–gathering ancestors survived on little salt possibly thanks to RAS activation without developing hypertension (Lev-Ran & Porta, 2005). As eating habits changed, salt intake also increased, turning blood pressure increase mediated by RAS activation into a negative factor. Thus, natural selection was strongly influenced by the development of hypertension, whose incidence varied widely among populations with different geographic and ethnic origins (Wooding, 2004). In ancient human populations residing in hot and humid areas like the tropics, the tendency to retain salt as an adaptation to low salt availability and the risk of electrolyte imbalance evolved (Gleibermann, 1973). By contrast, populations in cooler, drier climates such as the temperate zones, adapted to conditions of greater sodium availability and less sodium loss (Gleibermann, 1973). In this regard, variations in the human RAS genes might account for some of the regional differences in hypertension susceptibility (Nakajima et al, 2004). Beside salt retention and hypertension, recent studies have unravelled roles of RAS and particularly, its main effector molecule angiotensin II (Ang II) in inflammation, autoimmunity, oxidative stress and aging.

That the renin–angiotensin system (RAS) is involved in regulation of blood pressure, vasoconstriction, sodium intake and potassium excretion is well established. Studies in the last few years have however documented new roles for this molecule as a pro-inflammatory molecule and more recently as a possible pro-fibrotic agent that contributes to progressive deterioration of organ function in disease. Binding of Ang II to its receptors (in particular AT₁) mediates intracellular free radical generation that contributes to tissue damage by promoting mitochondrial dysfunction. Blocking Ang II signalling protects against neurodegenerative processes and promotes longevity in rodents. Altogether these findings open the unanticipated perspective for exploring Ang II signalling in therapeutic interventions in inflammatory diseases and aging-related tissue injury. This review extends from the discovery of Ang II and its implications in renal and cardiovascular physiology to cover the roles of the system in inflammation, tissue injury, autoimmunity, oxidative stress and aging.
The Effects of the Renin–Angiotensin System Components

In 1898, Robert Tigerstedt and his student Per Gunnar Bergman discovered the presence of a pressor compound in the renal cortex extracts of the rabbit that they named renin (Tigerstedt & Bergman, 1898). The interest in the nature of the pressor substance released by the kidney was renewed when in 1934, Henry Goldblatt demonstrated that constriction of dog renal arteries with silver clamps produced chronic hypertension (Goldblatt et al, 1934). Using the same technique, Braun-Męndez et al., as well as Page and Helmer later demonstrated the renal secretion of yet another compound with a quick pressor action of very short duration, angiotensin (Braun-Menéndez et al., 1940; Braun-Menéndez & Page, 1958; Page & Helmer, 1940). Since these early studies our understanding of Ang II in physiology and pathophysiology has improved considerably.

Angiotensin II is an octapeptide produced from the substrate angiotensinogen through sequential enzymatic cleavages by renin and angiotensin converting enzyme (ACE). Specifically, renin cleaves angiotensinogen, forming Ang I that in turn is converted to Ang II by ACE. The angiotensinogen substrate is produced in the liver, while renin is produced in the kidney and Ang II in the vascular tissue (Timmermans et al, 1993). ACE is a circulating enzyme that also degrades bradykinin to inactive fragments, reducing the serum levels of endogenous vasodilators (Brewster & Perazella, 2004; Fleming, 2006). The genetic analysis of ACE has revealed an important insertion (I)/deletion (D) polymorphism, a 287 bp DNA sequence in the intron 16 of chromosome 17 in the ACE gene, a major locus that accounts for approximately 50% of the total phenotypic variance of circulating and tissue ACE (Rigat et al, 1990). The ACE I/D polymorphism is a reliable tool to identify patients at risk to renal disease progression and to elect those who may benefit the

Glossary

Aldosterone
Aldosterone is a steroid hormone that acts on the distal tubules and collecting ducts of the nephron causing sodium retention, potassium secretion, water retention and blood pressure increase.

Alzheimer’s disease
Alzheimer’s disease is the most common form of dementia with advancing age. It is associated with a deterioration of memory and other cognitive domains.

Angiotensin II
Angiotensin II is the main effector molecule of the RAS. It causes increases in blood pressure, influences renal tubuli to retain sodium and water, and stimulates aldosterone release from adrenal gland. Besides being a potent vasoconstrictor, Ang II also exerts proliferative, pro-inflammatory and pro-fibrotic activities.

Bradykinin
Bradykinin is a potent endothelium-dependent vasodilator, causes dilation of non-vascular smooth cells, increases vascular permeability, promotes natriuresis and reduces blood pressure.

Catecholamine
Catecholamines are neuromodulators released by the adrenal glands in response to stress causing increases in heart rate, blood pressure and blood glucose levels.

Dendritic cells
Dendritic cells are “professional” antigen-presenting cells, which capture and present the antigen to the T cells.

Macrophage
Macrophages are white blood cells that phagocyte cellular debris and pathogens and stimulate lymphocytes and other immune cells to respond to the pathogen.

Multiple sclerosis
Multiple sclerosis is an autoimmune disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelization and scarring as well as a broad spectrum of signs and symptoms.

Natriuretic peptide
Natriuretic peptides (NPs) are peptide hormones that are synthesized by the heart, brain and other organs and are involved in the long-term regulation of sodium and water balance, blood volume and arterial pressure.

Pre-eclampsia
Pre-eclampsia is a pregnancy condition in which high blood pressure and proteinuria develop after the 20th week of pregnancy.

Regulatory T cells
A specialized subgroup of T cells that act to suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to antigens.

Renin
Renin is secreted by the kidney from specialized cells called granular cells of the juxtaglomerular apparatus. Renin activates the RAS by cleaving angiotensinogen, produced by the liver, to produce angiotensin I.

Sirtuins
Sirtuins are nicotinamide adenine dinucleotide (NAD)-dependent deacetylases associated with mitochondrial and cell cycle regulation, apoptosis, DNA damage repair and longevity.

Systemic lupus erythematosus
Systemic lupus erythematosus is an autoimmune disease with numerous immunological and clinical manifestations. In particular, acute or chronic renal impairment may develop with lupus nephritis leading to acute or end-stage renal failure.

Th1
A CD4+ helper T-cell that produces the cytokines IFN-γ and IL-2.

Th2
A CD4+ helper T-cell that produces the cytokines IL-4, IL-5 and IL-13.

Th17
A recently discovered helper T-cell that produces IL-17.

Toll-like receptors
Proteins that act as sensors for the presence of microorganisms and tissue damage and activate immune cell responses.
most from treatment with Ang II blockers (Ruggenenti et al., 2008a). It is conceivable that the same applies to patients with cardiovascular disease or progressive deterioration of brain function including senile dementia and Alzheimer, but studies of this kind are not available at the moment.

ACE2 is another carboxypeptidase that cleaves one aminoacid from Ang II leading to the production of the heptapeptide vasodilatory Ang 1–7 (Crackower et al., 2002; Ferrario & Chappell, 2004) and the balance between ACE and ACE2 is crucial for controlling Ang II levels (Danilczyk & Penninger, 2006). Ang II levels can also be regulated by chymase, an enzyme expressed in the heart by mast cells, endothelial and mesenchymal interstitial cells (Urata et al., 1993) and in the kidney by mesangial and vascular smooth muscle cells (Huang et al., 2003). Chymase-mediated Ang II production has emerged as an alternative pathway to ACE in cardiac, vascular and renal tissue, particularly in disease conditions (Bacani & Frishman, 2006; Huang et al., 2003; Miyazaki & Takai, 2006) (Fig 1). Finally, Ang II can also be cleaved in the circulation by other aminopeptidases generating Ang (2–8) (Ang III) and Ang (3–8) (Ang IV). Ang III has similar effects to Ang II, although with lower potency, of enhancing blood pressure and vasopressin release (Cesari et al., 2002; Reaux et al., 2001) and stimulating the expression of pro-inflammatory mediators in cultured renal cells (Ruiz-Ortega et al., 2000). Ang IV exerts a protective role by increasing blood flow in the kidney (Hamilton et al., 2001) and brain (Kramar et al., 1997).

Circulating Ang II contributes to increased blood pressure and influences renal tubuli to retain sodium and water (Brewster & Perazella, 2004; Kim & Hiroshi, 2003). One of the most significant advances in the field, in the past two decades has been the discovery of local or tissue RAS. The local system is characterized by the presence of RAS components in several organs including the heart (Van Kats et al., 1998), kidney (Kobori et al., 2004), brain (Moulid et al., 2002) and pancreas (Ghiani & Masini, 1995), as well as reproductive (Thomas & Sernia, 1990), lymphatic (Iwai et al., 1996) and adipose tissues (Karlsson et al., 1998). The local RAS exerts different functions in each organ and it can operate independently, as in the adrenal glands and brain, or in close interaction with circulating RAS as in the heart and kidney. In addition a functional intracellular RAS has been identified (De Mello, 2003; Re & Cook, 2006). The discovery of local and intracellular RAS highlights several prominent non-haemodynamic effects of Ang II including pro-inflammatory, proliferative and pro-fibrotic activities. Ang II promotes reactive oxygen species (ROS) production, cell growth, apoptosis, cell migration and differentiation, extracellular matrix remodelling, regulates gene expression and can activate multiple intracellular signalling pathways leading to tissue injury (Ruster & Wolf, 2006). In tissues such as kidney, heart and vasculature, Ang II induces an inflammatory response by fostering the expression of pro-inflammatory chemokines, responsible for tissue accumulation of immunocompetent cells (Suzuki et al., 2003). In

**Figure 1. The renin-angiotensin system (RAS).** Renin, a protease produced in the kidney, cleaves the AGT to produce the inactive decapeptide angiotensin I. Cleavage of angiotensin I by ACE or alternatively by chymase produces the active octapeptide Ang II that acts via AT₁ and AT₂ receptors. Ang II levels are also regulated by ACE2 that cleaves Ang II to produce the heptapeptide vasodilatory Ang 1–7. AGT, angiotensinogen; ACE, angiotensin converting enzyme; AT₁R, angiotensin type 1 receptor; AT₂R, angiotensin type 2 receptor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
hypertension, a noxious amplification mechanism occurs in the kidney, in which Ang II induces renal angiotensinogen expression and thereby its own synthesis (Kobori et al, 2001).

**Angiotensin receptors**

Angiotensin II acts through two pharmacologically distinct G protein-coupled receptors, angiotensin type 1 and the type 2 (AT$_1$ and AT$_2$) receptors (Hunyady & Catt, 2006; Porrello et al, 2009). Human cells express a single AT$_1$ receptor, while two isoforms, AT$_{1A}$ and AT$_{1B}$ with 95% of aminoacid sequence identity, can be found in rat and mouse. The AT$_{1A}$ receptor, the closest murine homologue to the human AT$_1$ receptor, is expressed in the kidney, heart, brain adrenal gland, vascular smooth muscle, liver and several other tissues (Burson et al, 1994). AT$_{1B}$ on the other hand is predominantly expressed in anterior pituitary gland and adrenal zona glomerulosa (Oliverio & Coffman, 2000). AT$_{1A}$ confers most of classical actions of Ang II such as blood pressure increase (Ito et al, 1995), aldosterone release from the adrenal zona glomerulosa (Aguilera, 1992), salt retention in proximal tubular cells (Thekkumkara et al, 1998) and stimulation of the sympathetic nervous system via receptors in the brain (Davison et al, 2000). AT$_{1B}$ regulates blood pressure when AT$_{1A}$ receptor is absent (Oliverio & Coffman, 2000). Angiotensin type II receptor is ubiquitously expressed in developing foetal tissues, it decreases after birth remaining low in various adult tissues including adrenal medulla, uterus, ovary, vascular endothelium and distinct brain areas (Steckelings et al, 2005). AT$_{1}$ and AT$_{2}$ receptor have counter-regulatory actions in the cardiovascular and renal system (reviewed by Schulman and Raij (2008)). Ang II binding to the AT$_2$ receptor induces vasodilation in resistance and conduit arteries and improves artery remodelling in humans and mice. The AT$_2$ receptor is upregulated in conditions associated with cardiovascular injury and it exerts a cardio-protective role against ischemia-reperfusion injury and acute myocardial infarction (Schulman & Raij, 2008). Furthermore, this receptor is protective against kidney fibrosis and ischemic renal injury as lack of AT$_2$ receptor aggravates renal injury and reduces survival in a mouse renal ablation model (Benndorf et al, 2009). A pro-inflammatory role of the AT$_2$ receptor, through activation of the NF-$\kappa$B pathway has also been proposed in response to Ang II (Esteban et al, 2004; Ruiz-Ortega et al, 2003; Wolf et al, 2002).

Finally, the AT$_{1}$ and AT$_{2}$ receptors are also binding site for Ang III, while the AT$_{4}$ receptor is specific for Ang IV and is expressed in brain, kidney, heart and vessels (de Gasparo et al, 2000).

**Beyond Blood Pressure Control, Angiotensin II Promotes Inflammation and Tissue Injury**

As discussed above, the roles of Ang II go well beyond controlling circulatory homeostasis. Recently, a large number of experimental studies have shown that Ang II mediates several key events of the inflammatory processes (Fig 2) (Marchesi et al, 2005).
Modulation of MCP-1/CCR2 via AT1 receptor blockade reduces renal inflammation in models of progressive nephropathies, interstitial accumulation of macrophages is accompanied by increased renal expression of MCP-1, and renoprotection afforded by the ACE inhibitor lisinopril limits interstitial inflammation and reduces MCP-1 expression (Donadelli et al, 2000). The pro-inflammatory activity of Ang II is also mediated by activation of dendritic cells (DCs), highly specialized antigen-presenting cells (APCs) responsible for inflammation defence and immune response. Cultured DCs express both Ang II receptors (Lapteva et al, 2001) and Ang II enhances DCs migration, maturation and antigen presenting ability (Lapteva et al, 2002; Muller et al, 2002; Nahmod et al, 2003). In rats with subtotal renal ablation, blockade of Ang II synthesis/biological activity reduces tubulointerstitial damage (Remuzzi et al, 1999; Wu et al, 2006). In models of progressive nephropathies, interstitial accumulation of macrophages is accompanied by increased renal expression of MCP-1, and renoprotection afforded by the ACE inhibitor lisinopril limits interstitial inflammation and reduces MCP-1 expression (Donadelli et al, 2000). The pro-inflammatory activity of Ang II is also mediated by activation of dendritic cells (DCs), highly specialized antigen-presenting cells (APCs) responsible for inflammation defence and immune response. Cultured DCs express both Ang II receptors (Lapteva et al, 2001) and Ang II enhances DCs migration, maturation and antigen presenting ability (Lapteva et al, 2002; Muller et al, 2002; Nahmod et al, 2003). In rats with subtotal renal ablation, blockade of Ang II synthesis/biological activity reduces tubulointerstitial damage (Remuzzi et al, 1999; Wu et al, 2006). The beneficial effect of Ang II blockers on tissue inflammation also relies on their ability to block Ang II-mediated activation of Toll-like receptors (TLRs). In cultured mesangial and vascular smooth muscle cells, Ang II via AT1 receptor signalling stimulates TLR-4 expression, which promotes cellular oxidative injury, apoptosis and inflammation (Ji et al, 2009; Lv et al, 2009). These in vitro observations are paralleled by in vivo studies showing protection against myocardial ischemia/reperfusion injury after AT1 blockade through suppression of TLR-4 expression and reduction of cytokine release (Yang et al, 2009). The pro-inflammatory effects of Ang II can also involve T cells. T cells possess an endogenous RAS that modulates T cell proliferation and migration (Jurewicz et al, 2007), NAD(P)H activity and ROS production (Hoch et al, 2009). During inflammation, Ang II acts via its AT1 receptor to stimulate cytoskeletal rearrangements in T cells and to trigger the release of specific cytokines and chemokines that favour T cell recruitment to the sites of inflammation (Crowley et al, 2008; Jurewicz et al, 2007; Kvakan et al, 2009). Tissue infiltration of T cells contributes to the genesis of hypertension as documented by the blunted blood pressure increase to both Ang II infusion and DOCA-salt hypertension in RAG1−/− mice, which lack T and B cells. Adoptive transfer of T, but not B cells, restores the hypertensive response to Ang II in this knockout mouse strain (Guzik et al, 2007). Among T cell subsets, IL-17-producing T cells are critical for the maintenance of Ang II-induced hypertension (Madhur et al, 2010). Ang II can also affect T cell responses in transplantation. In renal-transplant patients, the presence in the serum of activating antibodies targeting the AT1 receptor may contribute to steroid-refractory vascular allograft rejection, and treatment with AT1 receptor antagonist losartan significantly improved allograft survival as compared with untreated patients (Dragun et al, 2005). Furthermore, passive transfer of AT1 receptor activating antibodies in rats receiving kidney transplant promotes vascular rejection and hypertension (Dragun et al, 2005).

Angiotensin II and Autoimmunity

The recent observation that Ang II modulates T cell responses, suggests a possible role of the peptide in autoimmune diseases. RAS is critically involved in the development of Th1/Th17-mediated multiple sclerosis (MS) as shown in experimental autoimmune encephalomyelitis (EAE), a well-established mouse model for human MS (Platten et al, 2009). Peripheral CD4+ T cells from EAE mice show increased levels of Ang II which acting through the AT1 receptor promote the synthesis of Th1 and Th17 cytokines, specifically IFN-γ and IL-17. Drugs that limit Ang II synthesis and its biological activity, such as the angiotensin converting enzyme inhibitor (ACEI) lisinopril or angiotensin receptor blocker (ARB) candesartan, result in the suppression of Th1 and Th17 cytokine release and the induction of powerful antigen-specific regulatory T cells (Treg) through the modulation of the NF-κB pathway. Of note, the adoptive transfer of Treg protects mice from severe signs of EAE (Platten et al, 2009). AT1 is also involved in promoting experimental autoimmune uveitis (EAU) and myocarditis (EAM) through its influence on T cell function. Administration of ARB suppresses EAU (Okunuki et al, 2009) and reduces the severity of myocardial lesions in EAM by inhibiting antigen-specific T cell activation (Liu et al, 2009) and contributing to the shift of Th1–Th2 immune response (Liu et al, 2009). A recent study also highlighted the role of AT1 receptors in glomerular inflammation associated with autoimmune disease in rodents by studying AT1A receptor-deficient (AT1A−/−) MLR-Fas+/lpr (lpr) mice, which develop an autoimmune disease resembling human systemic lupus erythematosus (SLE) (Crowley et al, 2009). The Ang II type 1A receptor deficiency in lpr mice accelerates renal damage and mortality. Increased disease severity of AT1A−/−/lpr mice is not a direct effect of immune cells since transplantation of bone marrow from AT1A−/−/lpr donors does not affect survival of lpr wild-type recipient mice. Moreover, autoimmune injury in extrarenal tissues.
injected with purified AT1-autoantibodies from women with pre-eclampsia and followed up on this suggestion and showed that pregnant mice operating independently from the circulatory RAS has fostered the discovery of the existence of a paracrine, locally acting RAS. Accumulation of amyloid-(A-beta) peptide results in oxidative and inflammatory damage, which in turn leads to molecular oxygen species that trigger mitochondrial dysfunction (Griendling et al, 2004; Querfurth & LaFerla, 2010). Increased ACE activity has been observed in homogenates of post mortem brain tissue from Alzheimer’s disease patients and correlated with A-beta plaque load and the severity of amyloid angiopathy (Arregui et al, 1982). More recently, elevated neuronal and perivascular immunoreactivity of ACE and Ang II surrounding the parietal and frontal cortex vessels in the brain of Alzheimer’s disease patients has also been reported (Miners et al, 2008; Savaskan et al, 2004; Querfurth & LaFerla, 2010). Increased ACE activity would be expected to reduce brain perfusion, characteristic of Alzheimer’s disease possibly through elevated production of Ang II (Kehoe et al, 2009).

Several studies indicate that treatment with ARB and ACEi help to preserve cognitive functions through a mechanism that is independent from their antihypertensive effect (reviewed by Poon (2008) and Shah et al (2009)). In the Tg2576 Alzheimer’s disease mouse model, preventive treatment with an AT1 receptor blocker reduces Alzheimer’s disease-type neuropathology and attenuates the aggregation of A-beta peptide into extracellular amyloid plaque deposits in the brain (despite no detectable blood pressure-lowering activity) (Wang et al, 2007).

In Alzheimer’s disease patients, treatment with ACEi that cross the blood–brain barrier (BBB), such as perindopril and captopril, has a beneficial effect on the rate of cognitive decline, as compared to enalapril and imidapril that cannot cross the BBB or an antihypertensive calcium channel blocker (Ohnui et al, 2004). Results from a cohort analysis of 819,491 (mostly male) patients with Alzheimer’s disease or dementia show that ARB treatment reduces the incidence and progression of the disease—measured as admission to a nursing home—as compared to ACEi or other medications that control vascular disease or hypertension. Combined treatment with ARB and ACEi shows additive benefits as indicated by reduced risk of Alzheimer’s or dementia progression (Li et al, 2010). This protection is consistent with the mutual activity of the drugs on the AT1 receptor. The strength and the consistency of the protective effect of ARB clearly support the involvement of AT1 receptor in the pathogenesis of the disease (Lopez-Real et al, 2005; Munoz et al, 2006). Neuroprotective action of ARB against oxidative stress, a key player of the disease (Lopez-Real et al, 2005; Munoz et al, 2006). Neuroprotective action of ARB against ischemic injury has also been shown to prevent stroke in experimental and clinical studies (Schmieder et al, 2007; Turnbull, 2003).

Activation of brain RAS is also involved in the pathogenesis and progression of Parkinson’s disease (Mertens et al, 2010). Treatment with ACEi or ARB have neuroprotective effects in mice with Parkinson’s disease mainly due to the reduction of oxidative stress, a key player of the disease (Lopez-Real et al, 2005; Munoz et al, 2006). Neuroprotective action of ARB against oxidative stress, a key player of the disease (Lopez-Real et al, 2005; Munoz et al, 2006). Neuroprotective action of ARB against ischemic injury has also been shown to prevent stroke in experimental and clinical studies (Schmieder et al, 2007; Turnbull, 2003).

Angiotensin II: A Key Player In Oxidative Stress Toxicity and Aging

We have previously referred to the impact of Ang II in ROS generation. In fact, Ang II robustly stimulates the production of molecular oxygen species that trigger mitochondrial dysfunction and cellular injury (de Cavanagh et al, 2007; Wilson, 1990). Ang II via AT1 receptor stimulation can activate NAD(P)H oxidase to produce ROS, resulting in oxidative stress damage (Griendling et al, 1994). Harman has proposed that ROS are the most prominent molecular species involved in the aging process (Harman, 1956).

According to his theory, ROS contribute significantly to various age-associated organ failures, including hypertension, cardiovascular diseases and renal damage (de Cavanagh et al, 2007). Hence, Ang II could be involved in organ senescence given its...
ability to mediate the release of oxidant species. Supporting this hypothesis, Ang II-induced ROS production via AT₁ receptor promotes the onset of vascular senescence associated with functional and structural changes of blood vessels that contribute to age-related vascular diseases (Min et al, 2009). Interestingly, homozygous mice deficient for AT₁A grow-up normally and outlive their wild-type littermates by 26% (Benigni et al, 2009). These AT₁A−/− mice also develop fewer aortic atherosclerotic lesions and less cardiac injury during aging. Oxidative stress is reduced in cardiomyocytes, aortas and kidneys from mice lacking AT₁A receptor with respect to aged wild-type mice and ultrastructural analysis of mitochondria in proximal renal tubular cells show that AT₁A−/− mice have an increased number of mitochondria (Benigni et al, 2009). Extension of lifespan is associated with upregulation of pro-survival genes including nicotinamide phosphoribosyltransferase (Nampt) and Sirtuin 3 (Sirt3) in the kidney from these mice (Benigni et al, 2009). Importantly, candesartan prevents Ang II-induced Nampt and Sirt3 mRNA down-regulation in cultured tubular epithelial cells indicating a possible molecular link between Ang II, AT₁A and these survival genes. The effects in longevity observed in AT₁A-deficient mice are likely the consequence of reduced mitochondrial damage due to attenuation of oxidative stress and the increased expression of Nampt and Sirt3 survival genes (Fig 3). Our results shed light on early reports that showed favourable effects of chronic long-term Ang II inhibition by either ACEi or ARBs in protecting rats from the deleterious effects of aging on cardiovascular system and prolonging life span (Basso et al, 2007). Other studies implicate the AT₁ receptors in ROS-induced damage and aging; old mice lacking AT₁ receptors also do not develop age-related cerebral circulation damage caused by the accumulation of oxygen radicals (Modrick et al, 2009). The inhibition of RAS reverses age-related advanced myocardial hypertrophy and fibrosis in aged spontaneously hypertensive rats, and the protective effect presumably involves the attenuation of Ang II-mediated oxidative stress, as documented by reduced expression of NAD(P)H oxidative components in the hearts of aged animals (Ito et al, 2007). Chronic treatment with ACEi or ARB reduces kidney damage associated with age, and the beneficial effect of RAS inhibition involves the preservation of renal mitochondria (Feeder et al, 2002). Enalapril and losartan treatments prevent the age-associated decline in the renal mitochondrial capacity for energy production and attenuate the age-associated increase in mitochondrial oxidant production (de Cavanagh et al, 2003). RAS inhibition exerts a similar protective effect in the liver from old rats through the maintenance of an adequate mitochondrial function due to enhanced expression of genes responsible for mitochondrial respiration and biogenesis (de Cavanagh et al, 2008).

**Clinical Implications**

The synthesis of the first orally active ACEi, captopril (Ondetti et al, 1977) fostered the development of new therapeutic paradigms and opened a new era of research in the under-

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**Figure 3. Ang II signalling affects aging**. Ang II increases ROS generation and reduces the expression of the pro-survival gene Sirt3, affecting transcription of antioxidant enzymes. As depicted in red, the disruption of AT₁A receptor preserves mitochondrial and cellular wellness and promotes longevity by modulating ROS production and sirtuin expression.
standing of the clinical significance of RAS system. Despite the first warning of possible side effects of ACEi on the kidney, the efficacy of RAS blockers in treating hypertension, heart failure and renal diseases has gradually unfolded (Perico et al, 2008). Treatment of hypertension also benefited from the subsequent discovery of Ang II antagonists, selectively blocking AT1 receptor activation without influencing the vasodilatory kinins, which reduce blood pressure even in patients who do not have increased Ang II formation. The beneficial effect of inhibition of RAS activity by ACEi or ARB in patients with left ventricular dysfunction or systolic heart failure is now well established. Treatment with ACEi or ARB decreases mortality rate and reduces the risk for adverse cardiovascular outcome in high-risk patients with coronary artery disease, independently of the blood pressure control (Yusuf et al, 2000). Intensive treatment with ACEi of diabetic artery disease, independently of the blood pressure control function loss, possibly contribute to kidney repair (Benigni et al, 2010). While studying the beneficial effects of RAS blockade on heart and kidney, emerging evidence showed additional activities of RAS antagonists as anti-inflammatory and immunomodulatory agents and paved the way to new potential applications of these drugs in autoimmune diseases. The challenge for the next years is to establish whether these may translate in new medical applications of these drugs. Protection of brain blood vessels against damage by selective blockade of AT1 receptor alone, or even better in combination with ACEi, opens new perspectives to provide health benefits to patients with cognitive decline. Based on the recent studies on genetically modified animals and on aged rats chronically treated with ACEi or ARB, drugs that interfere with Ang II synthesis and/or biological activity may be promising candidates to regulate signalling cascades of senescence and extend lifespan. The excellent safety record of ACEi and ARB that have been administered chronically to millions of subjects with hypertension, cardiac and renal failure would indicate that long-term use of these medications might prove effective in preventing the progressive deterioration of organ function associated with aging without significant side-effects. Whether this would contribute to healthier aging and a longer live is a matter of intriguing speculation so far.

The authors declare that they have no conflict of interest.

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