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THE ACE2/ANGIOTENSIN-(1–7)/MAS AXIS OF THE RENIN-ANGIOTENSIN SYSTEM: FOCUS ON ANGIOTENSIN-(1–7)

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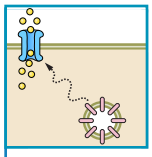


Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/Angiotensin-(1–7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1–7). *Physiol Rev* 98: 505–553, 2018. Published December 20, 2017; doi:10.1152/physrev.00023.2016.—The renin-angiotensin system (RAS) is a key player in the control of the cardiovascular system and hydroelectrolyte balance, with an influence on organs and functions throughout the body. The classical view of this system saw it as a sequence of many enzymatic steps that culminate in the production of a single biologically active metabolite, the octapeptide angiotensin (ANG) II, by the angiotensin converting enzyme (ACE). The past two decades have revealed new functions for some of the intermediate products, beyond their roles as substrates along the classical route. They may be processed in alternative ways by enzymes such as the ACE homolog ACE2. One effect is to establish a second axis through ACE2/ANG-(1–7)/MAS, whose end point is the metabolite ANG-(1–7). ACE2 and other enzymes can form ANG-(1–7) directly or indirectly from either the decapeptide ANG I or from ANG II. In many cases, this second axis appears to counteract or modulate the effects of the classical axis. ANG-(1–7) itself acts on the receptor MAS to influence a range of mechanisms in the heart, kidney, brain, and other tissues. This review highlights the current knowledge about the roles of ANG-(1–7) in physiology and disease, with particular emphasis on the brain.

I. INTRODUCTION

The renin-angiotensin system (RAS) is a key player in the control of blood pressure and the hydroelectrolyte balance. The first end product of this system associated with a biological activity was the octapeptide angiotensin (ANG) II, produced through the activity of the angiotensin converting enzyme (ACE) at the end of the pipeline. Years later it was discovered that the amino-terminal aspartate could be removed from ANG II to produce the heptapeptide ANG III, which had similar biological activities (67, 562). Finally, about three decades ago came the discovery that phenylalanine could be removed from the carboxy terminus of ANG II to produce another RAS peptide, ANG-(1–7) (45, 65, 85, 470, 492).

Originally the biological relevance of this finding was questioned because up to that point, ANG-(1–7) had been seen purely as a degradation product of ANG I and ANG II (221, 619). This perception has changed mainly through the discovery that the ACE homolog ACE2 is often involved in its formation and that ANG-(1–7) acts on the G protein-coupled receptor MAS (468). ANG-(1–7) and ANG II usually have opposing effects, stimulating high interest because it suggests that ANG-(1–7) or other MAS agonists might be useful in the development of therapeutic agents to counteract the negative role of ANG II in many diseases. This review will examine physiological aspects of the ACE2/ANG-(1–7)/MAS axis in different organs/systems, with special emphasis on the role of ANG-(1–7) in the brain.

II. THE DISCOVERY OF THE ACE2/ANGIOTENSIN-(1–7)/MAS AXIS

FIGURE 1 shows the main findings which contributed to the discovery of the ACE2/ANG-(1–7)/MAS axis as one of the main components of the RAS. In 1968, Yang, Erdos and Chiang (619) described the heptapeptide Des-Phe^{8}-Angiotensin II, generated from ANG II as a route for the inactivation of ANG II. Tonnaer et al. (544) came to the same conclusion when he found this heptapeptide in brain synaptosomes. In 1988, Santos and colleagues examined tissue taken from dogs that had been treated with enalapril to determine how this affected the RAS in the brain (470). They incubated brain micro-punch homogenates with ^{125}I-labeled ANG I and discovered a consistent formation of a radioactive peak they identified as ^{125}I-ANG-(1–7). The peptide continued to form when they added an ACE inhibitor to the incubation. This meant that the ANG-(1–7) peptide was being formed from ANG I, but along a different route that bypassed ACE (470). The formation of ^{125}I-ANG-(1–7) from ^{125}I-ANG I was in keeping with an early observation made by Greene et al. (221) in whole rodent brain homogenates, who had interpreted ANG-(1–7) as the end point of an angiotensin inactivation pathway. Santos et al. (470) suggested instead that ANG-(1–7) might be another biologically active product of the RAS, achieved along this enzymatic pathway. The same year, Schiavone et al. (492) delivered proof through experiments with hypothalamus/hypophysial explants. The function they found for ANG-(1–7) in this preparation was to trigger the release of vasopressin (AVP), through dose-dependent effects that were just as potent as those of ANG II. In vivo confirmation came 1 yr later, when Campagnole-Santos et al. reported the first biological action of ANG-(1–7) in vivo (65). Microinjection of femtomole amounts of ANG-(1–7) in the nucleus tractus solitarii (NTS) produced significant reductions in the blood pressure of urethane-anesthetized rats. This effect was similar to that produced by microinjection of ANG II in the same region. These exciting observations motivated Carlos Ferrario's group at Cleveland Clinic to produce an ANG-(1–7) antibody which was then used by Block et al. (45) to describe the localization of ANG-(1–7) immunoreactivity in the brain. In 1989, Chappell et al. (85) again using this antibody confirmed these findings. In 1994, we (473) and Ambühl et al. (17) described the first selective antagonist for ANG-(1–7), its analog D-Ala^{7}-ANG-(1–7), synthetized by Prof. Mahesch Khosla, which we named A-779. Having a selective antagonist was critical in uncovering many of the physiological actions of ANG-(1–7) including its role in baroreflex modulation (66) and in the

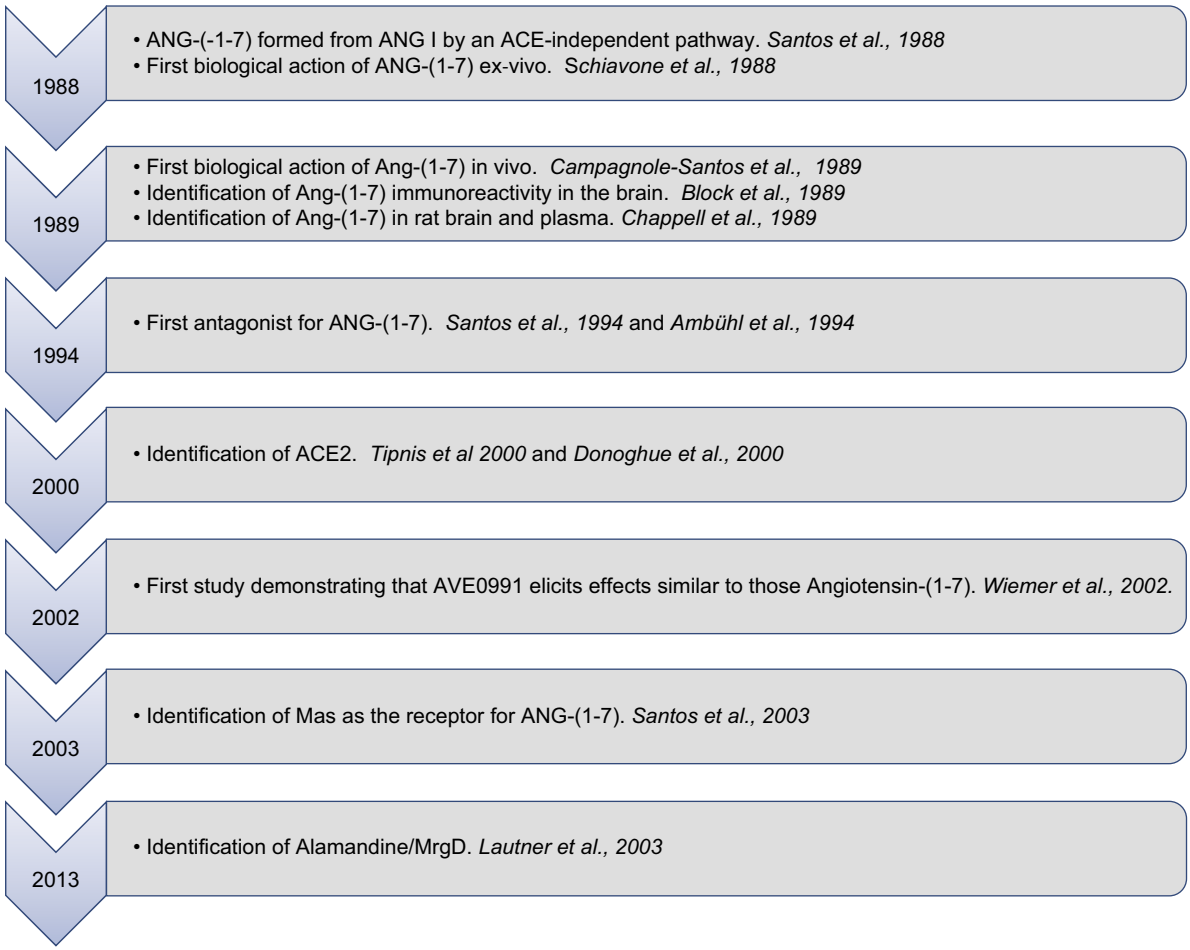


FIGURE 1. ACE2/angiotensin-(1–7)/Mas axis discovery timeline.

central control of blood pressure (183). The use of A-779 was also important in postulating that ANG-(1–7) had a specific receptor (183).

Despite the relatively large body of evidence that ANG-(1–7) was a biologically active component of the RAS, the idea only gained general acceptance with the discovery that ACE2 was the major enzyme involved in its formation (140, 543, 570, 647), followed by identifying MAS as its receptor years later (479). ACE2 is a membrane-anchored carboxypeptidase, which is the product of an ancient duplication of ACE that underwent a fusion with collectrin. Its discovery was reported in two papers which appeared almost simultaneously in 2000 (140, 543). The first, by Tipnis et al. (543) reported on the ability of ACE2 to convert ANG II to ANG-(1–7) and thus identified it as the key ANG-(1–7) forming enzyme. The Donoghue et al. article (140) did not test ANG II as a substrate for ACE2; they identified several other substrates, such as des-Arg^9-bradykinin, apelin, and neurotensin, and first reported ANG-(1–7) generation in a subsequent paper (570). Later the Turner group also discovered that the ectodomain of ACE2 can be shed from the membrane by ADAM17 (290). Interestingly, some years later it turned out that the carboxypeptidase activity is not the only function of the enzyme. Its collectrin domain serves as trafficking adaptor for the large amino acid transporter B(O)AT1, transferring it to the apical membrane of epithelial cells in the intestine (285). This translocation is essential for the uptake of several amino acids from food, and the absence of ACE2 leads to the depletion of some, particularly of tryptophan in the blood (242). Later ACE2 was also discovered to be the cellular receptor of the SARS coronavirus (309).

MAS is a G protein-coupled receptor (GPCR) that was first described in 1986 as mas oncogene (the name is the first 3 surname letters of the patient whose tumor cells were used to identify the gene)(624) and was initially thought to be a receptor of ANG II (263). However, this hypothesis was disproved through further studies on MAS signaling (15) and also cloning of the ANG II receptor AT1 in 1991 (382, 487). It was not until 2003 that we finally demonstrated the specific binding of ANG-(1–7) to *Mas*-transfected cells (479). The fact that this binding was abolished in kidney sections of *Mas*-deficient mice demonstrated that MAS is a receptor for the heptapeptide (479).

III. ANGIOTENSIN-(1–7) FORMATION AND METABOLISM

FIGURE 2 shows the main enzymatic pathways involved in the formation and catabolism of angiotensin peptides. In

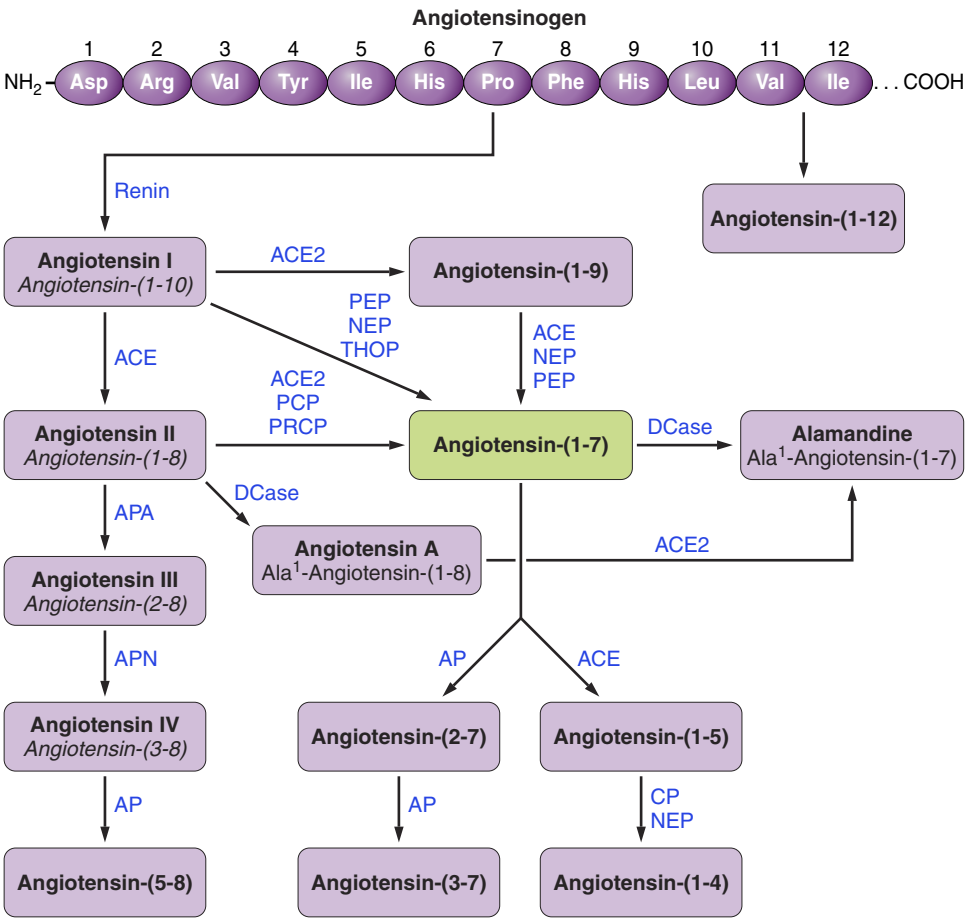


FIGURE 2. The renin-angiotensin system cascade: updated view. ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; APA, aminopeptidase A; APN, aminopeptidase N; PRCP, prolyl endopeptidase; PCP, prolylcarboxy-endopeptidase; NEP, neutral endopeptidase; PEP, prolyl endopeptidase; CP, carboxypeptidase; AP, aminopeptidase; Dcase, decarboxylase; THOP, thimet oligopeptidase.

the classical RAS, the enzyme renin cleaves its substrate angiotensinogen to form the decapeptide ANG I, which is in turn cleaved by ACE to produce ANG II, a key player in this system. As shown in **FIGURE 2**, ANG-(1–7) can be generated by the cleavage of ANG I by endopeptidases or ANG II by carboxypeptidases. The main enzymes involved in the production of ANG-(1–7) from ANG I are thimet oligopeptidase (THOP1; EC 3.4.24.15), neutral endopeptidase (NEP; EC 3.4.24.11) and prolyl oligopeptidase (PEP; EC 3.4.21.26). In addition, ACE2 (EC 3.4.17.23), carboxypeptidase A (EC 3.4.17.1), and prolyl carboxypeptidase (EC 3.4.16.2) can generate ANG-(1–7) from ANG II (72, 441, 468). The formation of ANG-(1–7) from ANG I by ACE2 involves the production of the intermediate ANG-(1–9) and its subsequent cleavage by ACE or NEP (444). However, the catalytic efficiency of this pathway is much lower than that of the ACE2-dependent conversion of ANG II to ANG-(1–7) (444).

A. Alamandine

Recently a new biologically active angiotensin, alamandine, was discovered (297) as seen in **FIGURE 2**. Alamandine has an Ala which replaces Asp at position 1 of ANG-(1–7). This peptide can be generated by either decarboxylation of the Asp residue or through the catalytic action of ACE2 on ANG A (264), Ala^1-ANG II. Functional studies in blood vessels (235, 297) and transfected cells (297) have provided evidence that the receptor for alamandine is the MAS-related G protein-coupled receptor D (MrgD). However, despite solid functional evidence that the effects of alamandine can be at least partially mediated through binding to MrgD, there is no direct radioligand binding data or other classical pharmacological data to fully demonstrate that MrgD has this function. Even so, alamandine has attracted attention as a potential mediator of the RAS.

IV. TOOLS FOR STUDYING ANG-(1–7)

A. Pharmacological Tools

The main pharmacological tools used to study the ACE2/ANG-(1–7)/MAS axis are shown in **FIGURE 3**. Many are MAS agonists that stimulate NO production/release [ANG-(1–7), AVE 0991, CGEN 861, CGEN 856, CGEN 856S, cyclic ANG-(1–7)] (3, 147, 163, 281, 424, 449, 489, 490, 509, 545, 594), NorLeu3-A(1–7) (2, 448). There are also two antagonists [D-Ala^7-ANG-(1–7) (A-779) and D-Pro^7-ANG-(1–7)]. Other MAS ligands, the non-peptides AR234960 (agonist) and AR244555 (inverse agonist) and neuropeptide FF (NPFF) appear to act through a different signaling pathway in which ANG-(1–7) is essentially ineffective (276, 633). Therefore, the possibility that some of the non-peptide or peptidic compounds are biased MAS agonists should be considered (522).

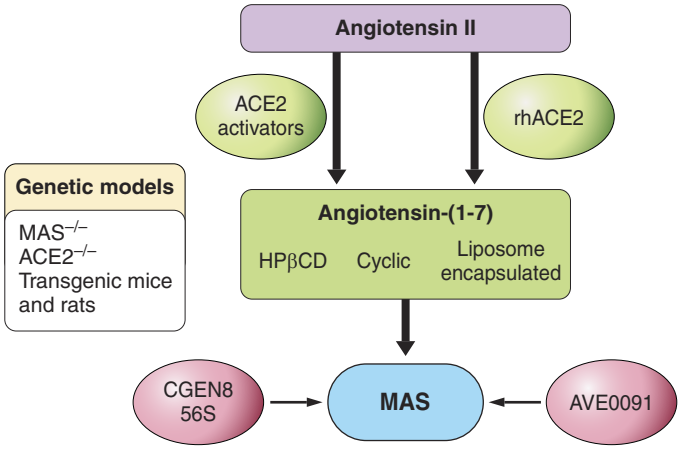


FIGURE 3. Pharmacological and genetic tools for the study of the ACE2/angiotensin-(1–7)/Mas axis.

One of the formulations for the chronic administration of ANG-(1–7) that has been well tested in animals is an inclusion compound, hydroxypropyl-β-cyclodextrin/ANG-(1–7) [HPβCD-ANG-(1–7)]. This compound protects ANG-(1–7) from inactivation by digestive tract enzymes and permits oral administration (188, 332). It should be emphasized that in this case, only ANG-(1–7) enters the bloodstream. The inclusion compound acts as a sustained-release system or, more properly, as a long-lasting releasing system. This approach has led to the description of many beneficial cardiovascular and metabolic effects of ANG-(1–7), including antithrombogenesis (185), an attenuation of cardiac remodeling induced by isoproterenol treatment (347), a reduction of the lesion area, and an attenuation of acute and chronic postinfarction cardiac dysfunction (348). There have also been reports of antihypertensive effects (37) and improvements in cases of erectile dysfunction (187), muscular dystrophy (5a, 455), and type II diabetes mellitus (486). Some of the effects in preclinical studies have been remarkable considering that the peptide was given orally once a day in doses ranging from 10 to 50 μg/kg, which are equivalent to 11 to 55 nmol·kg^{-1}·day^{-1}.

In addition to cyclodextrins, cyclic ANG-(1–7) is also undergoing preclinical testing (146, 281). It is more resistant to enzymatic hydrolysis than ANG-(1–7). Interestingly, the vasorelaxation produced by cyclic ANG-(1–7) in aortic rings from Sprague-Dawley rats is only partially blocked by the MAS antagonist A-779 (281), whereas this effect is completely blocked by the ANG-(1–7) analog D-Pro^7-ANG-(1–7), an ANG-(1–7)/alamandine antagonist (297). This pharmacological profile suggests that cyclic ANG-(1–7) could be a dual MAS/MrgD agonist sharing ANG-(1–7) and alamandine characteristics. This possibility awaits clarification.

In addition to MAS agonists, recombinant human ACE2 (hACE2) is currently being used in physiological/pharmacological studies and tests of its potential therapeutic use

(241). Prof. Raizada's group has suggested another interesting possibility: to use ACE2 activators to alter the balance between the ACE/ANG II/ AT1R and the ACE2/ANG-(1–7)/MAS axes. The group virtually screened its structure to identify small-molecule ACE2 activators (250). The first compound they found was the 1-[(2-dimethylamino)ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl)sulfonyloxy]-9H-xanthene-9-one, or XNT. Acute administration induced a dose-dependent hypotensive response in spontaneously hypertensive rats (SHR), while long-term treatment with XNT improved cardiac function and reversed the cardiac and renal fibrosis in these animals (250). Oral administration of XNT was able to attenuate diabetes-induced heart dysfunction (381). XNT adminstration also prevented the increase in right ventricular systolic pressure and hypertrophy in a monocrotaline-induced pulmonary hypertension model (169) and attenuated thrombus formation in SHR (190). Numerous protective effects have been reported with diminazene aceturate (DIZE), another putative ACE2 activator (102, 118, 119, 184, 186, 335, 341, 357, 429, 445, 511, 513, 535, 566). It should be pointed out, however, that the beneficial effects of these small-molecule activators might also depend on ACE2-independent mechanisms (234). And results obtained in rodents should be interpreted with caution considering the important differences between the biochemical properties of rodent and human ACE2 (622). Moreover, ACE2 can cleave other substrates (140), a fact which should be taken into account when interpreting results obtained with methods involving the gain or loss of ACE2 functions.

More recently, oral delivery of ACE2 and ANG-(1–7) bioencapsulated in plant cells has been reported to attenuate pulmonary hypertension (497). This is in keeping with early studies using a similar construct, developed by the Reudelhuber group (556), showing that transgenic rats and mice which overexpress an ANG-(1–7)-forming fusion protein presented reduced heart failure/remodeling following isoproterenol treatment or ANG II infusion (366, 466).

B. Genetic Models

1. ACE2 models

A) ACE2 KNOCKOUT MICE. Based on the pleiotropic actions of this protein, mice lacking ACE2 are expected to exhibit increased levels of ANG II, and decreased levels of ANG-(1–7) and tryptophan as well as alterations in other peptide levels, all of which may contribute to the phenotypes that are observed. The X-chromosomal localization of the ACE2 gene makes male mice with ACE2 gene deletion already deficient in the enzyme in the hemizygous state ($ACE2^{-/y}$). The first report on $ACE2^{-/y}$ mice described several cardiac abnormalities, particularly at older ages (104), which were later attributed to an increased effect of ANG II. However, other groups could not confirm these effects and the issue remained controversial (231, 232, 617). Notwithstanding, several studies report a higher susceptibility of $ACE2^{-/y}$ and heterozygous female $ACE2^{+/-}$ mice to cardiac injury induced by pressure overload or diabetes (410, 598, 617). Additional cardiovascular effects of ACE2 deletion remain under debate, including hypertension. Here the strain of mice that is used seems to be important. The 129 strain of mice lacking ACE2 is normotensive and C57BL/6 and FVB/N mice are hypertensive (232, 541) (our unpublished results). The hypertensive phenotype of ACE2-deficient mice on the C57BL/6 background is exacerbated in pregnancy, and they develop a preeclampsia-like syndrome (39). The main reason for increased blood pressure in $ACE2^{-/y}$ mice is probably endothelial dysfunction (327), but central effects including an increased sympathetic outflow cannot be excluded (605). Moreover, endothelial dysfunction may be involved in the aggravating effect of ACE2 deficiency in two models of atherosclerosis and aortic aneurysm, apolipoprotein E (ApoE)- and low-density lipoprotein receptor-deficient mice (397, 457, 537, 538), as well as in the increased neointima formation after vascular injury (457). ACE2-deficient mice also show a worse outcome in other inflammation and injury models, such as diabetic and shock-induced kidney injury (501, 598, 621), chronic hepatic injury (406), bleomycin- or influenza virus-induced lung injury (443, 648), and in models of acute respiratory distress syndrome (258). The lung injury phenotype could be rescued by infused mesenchymal stem cells overexpressing ACE2 (243). The unifying feature of most of the injury models is an increase in oxidative stress in $ACE2^{-/y}$ mice, which was recently confirmed for the kidney (603), liver (own unpublished results), and vessels (412, 431) of these animals.

Due to the trafficking function of ACE2 in the gut, mice lacking this protein show reduced tryptophan and other large amino acids in the blood, alterations in their gut microflora, and intestinal inflammation (242). These effects may contribute to the metabolic changes observed in these mice, mainly in insulin resistance and impaired glucose homeostasis (397, 406), which is aggravated under high-fat diets (328). The fact that ANG-(1–7) could rescue this phenotype in the liver seems again to indicate that the dysbalance between different angiotensin peptides is crucial.

B) HUMAN ACE2 OVEREXPRESSION IN MOUSE. In an effort to humanize mice regarding their susceptibility to the human severe acute respiratory syndrome (SARS) coronavirus, several transgenic mouse models have been generated expressing human ACE2 in a range of tissues using the ACE2 promoter itself (620), the ubiquitously active cytomegalovirus promoter (546, 623), or the airway-specific cytokeratin 18 promoter (355, 392). One of these mice was also used in a kidney injury model and showed a protected phenotype (621).

C) HUMAN ACE2 OVEREXPRESSION IN MOUSE HEART. Somewhat surprisingly, ventricular tachycardia and sudden death were observed in transgenic mice expressing human ACE2 in the heart (141). This was accompanied by a dysregulation of connexin expression. Peptides besides angiotensins are likely to be involved in this gain-of-function model, and apelin may be a candidate, since it has been shown to be important for cardiac function (287) and is also metabolized by ACE2 (570).

D) HUMAN ACE2 OVEREXPRESSION IN MOUSE PODOCYTES. In contrast to the heart, overexpression of human ACE2 in the kidney, particularly using the nephrin promoter in podocytes, turned out to be protective in diabetes-induced kidney injury (386). Again, the shifted balance between ANG II and ANG-(1–7) seemed to be critical through its regulation of the local expression of transforming growth factor β.

E) HUMAN ACE2 OVEREXPRESSION IN MOUSE BRAIN. ACE2 seems to be particularly important in the central nervous system for cardiovascular regulation. Transgenic mice expressing human ACE2 driven by the synapsin promoter exhibit protective phenotypes for cardiovascular diseases including hypertension induced by peripheral infusions of ANG II (154) and by DOCA-salt treatment (605), cardiac hypertrophy also induced by ANG II (154), chronic heart failure elicited by coronary ligation (606), and stroke triggered by middle cerebral artery occlusion (91, 637). The balance between ANG-(1–7) and ANG II in different brain regions, which determines local NO production and regulates the autonomic nervous system, seems to be critical in these effects.

F) HUMAN ACE2 OVEREXPRESSION IN RAT VASCULAR SMOOTH MUSCLE. ACE2 is a candidate gene for hypertension in the spontaneously hypertensive stroke-prone rat (SHRSP) strain. This is based on a linkage study and on the fact that very low levels of the enzyme are found in these animals (104). Therefore, we restored ACE2 expression specifically in the vascular smooth muscle cells (VSMC) of these rats by expressing human ACE2 from the smooth muscle myosin heavy chain promoter. This again shifted the balance between ANG II and ANG-(1–7) to the protective side, blunted oxidative stress, improved endothelial function, and markedly reduced blood pressure in the transgenic rats (439).

2. MAS models

A) *MAS* KNOCKOUT MICE. The first phenotypes analyzed in *Mas*-deficient ($Mas^{-/-}$) mice concerned brain function, since this is the most important MAS expressing organ (578). Male (but not female) (579) $Mas^{-/-}$ mice showed increased anxiety-like behavior and long-term potentiation (LTP) in the hippocampus. Unexpectedly, despite the improved LTP, object recognition memory was impaired (299).

The discovery of MAS as the receptor for ANG-(1–7) triggered extensive cardiovascular phenotyping. On the C57BL/6 mouse background, MAS deficiency leads to cardiac fibrosis and dysfunction both in vitro (78) and in vivo (416, 476). While oxidative stress and endothelial dysfunction were observed in the C57BL/6 and FVB/N genetic backgrounds (430, 611), it resulted only in significantly increased blood pressure in FVB/N mice. MAS seems to play a major role in regional hemodynamics since vascular resistance was significantly and differentially altered in the tissues of $Mas^{-/-}$ mice (48). Increased vascular resistance in the corpus cavernosum is also the most likely cause of the erectile dysfunction that occurs in these mice (107).

Renal function is also impaired in $Mas^{-/-}$ mice, which exhibit increased urinary volume and proteinuria (423). Surprisingly, however, the absence of MAS seems to be beneficial in one kidney injury model (149), while in others the outcome is worse, confirming the protective effects of the ACE2/ANG-(1–7)/MAS axis of the RAS (507). This discrepancy remains unresolved, but anti-inflammatory actions of MAS have repeatedly been described (267, 485, 514), most recently in an endotoxic shock model (515).

$Mas^{-/-}$ mice develop metabolic abnormalities such as type 2 diabetes mellitus and dyslipidemia (484), which together with their increased blood pressure renders them a valuable model for the metabolic syndrome. This is accompanied by decreased PPARγ expression in adipose tissue (346) and the development of liver steatosis when the animals are bred with apolipoprotein E (ApoE)-deficient mice (505).

B) MAS OVEREXPRESSION IN RETINA. MAS has a certain degree of constitutive, ligand-independent activity that may induce proliferative effects in cells when the gene is overexpressed. This may be the reason for the degeneration of photoreceptors in a transgenic mouse in which MAS is overexpressed in the retina under the control of the opsin promoter (612).

3. ANG-(1–7) models

A) TRANSGENIC RATS OVEREXPRESSING ANG-(1–7). Using an artificial protein which releases a predesigned peptide upon secretion from a cell (366, 368), ANG-(1–7) was overexpressed in transgenic rats using the cytomegalovirus promoter (166). Surprisingly the resulting strain, TGR(A1–7)3292, expressed the peptide mainly in the testis, which nevertheless led to significantly increased plasma levels. Despite a decrease in total peripheral resistance and increases in blood flow to several organs, the animals remained normotensive, which may be due to their improved cardiac function (48). These cardiac effects protect the heart from pressure and ischemia-induced damage (477). The high plasma levels of ANG-(1–7) also have effects in the kidney, such as a reduced urinary flow and increased urinary osmolality (166). Furthermore, the TGR(A1–7)3292 strain exhibits decreased levels of lipids in plasma, improved glucose toler-

ance, and less fat mass, confirming the beneficial metabolic actions of the peptide (44, 483).

B) TRANSGENIC MICE AND RATS OVEREXPRESSING ANG-(1–7) IN THE HEART. Transgenic mice and rats expressing the ANG-(1–7) release construct specifically in the heart with the alpha cardiac myosin heavy chain promoter show normal to slightly improved cardiac function at the baseline and are protected from cardiac hypertrophy (161, 366), but not from myocardial infarction (589).

V. ACTIONS OF ANGIOTENSIN-(1–7)

A. Brain

The brain expresses all the necessary components, precursor and enzymes, to produce the active peptides of the RAS known to date: ANG II, ANG III, ANG IV, ANG-(1–7), and alamandine. The effects elicited by angiotensins in the brain are complex, site-specific, and dependent on the pathophysiological condition. ANG II, ANG III, and ANG-(1–7) can be considered the main effectors of the RAS in the brain, since ANG IV presents more restricted actions (599). These peptides interact with a certain degree of selectivity to receptor proteins including AT1, AT2, MAS, or MrgD distributed within the central and peripheral nervous systems. Although there is still a debate on whether ANG II or ANG III is the true ligand of the AT1 receptor in the brain (195), the effects described for ANG-(1–7) appear to be related to MAS (479). It is well established that in the central nervous system (CNS), ANG II/ANG III function through AT_1 to induce thirst, release of AVP, an increase of sympathetic activity and blood pressure, and an impairment of the baroreflex function. In contrast, ANG-(1–7) facilitates the baroreflex and may lower or increase blood pressure depending on the specific brain area or the pathophysiological condition in which it occurs. Additional features not directly related to cardiovascular function have been described, including neuroprotection from brain ischemia or hemorrhage, improvements of memory, and an attenuation of epileptic seizures. The possibility that ANG II and ANG-(1–7) may exert opposite effects from each other in the brain, even if this only occurs under specific physiological situations, provides a more complete picture of the RAS mechanisms involved in the neural regulation of physiological functions.

1. ANG-(1–7) metabolism in the brain

The exact site at which angiotensins are generated in the brain, intracellular or extracellular, is still uncertain (269, 415, 592). Nor is it known whether the generation of ANG peptides is solely dependent on brain angiotensinogen (Angiotensinogen), ACE, ACE2 and renin, taking into account discrepancies in the location of RAS components (23, 45, 56, 160, 224, 415). However, increasing evidence suggests that RAS generation is intracellular and includes the expression of intracellular ANG II and ANG-(1–7), as well as their respective receptors (87, 233, 289, 379). Krob et al. (286) demonstrated intense ANG-(1–7) immunostaining in hypothalamic neurons of TGR(mREN2)27 transgenic rats, suggesting an intracellular localization of the peptide. Further experiments have demonstrated an intracellular expression of ACE2 based on immunohistochemistry in different areas of the brain (142) and ANG-(1–7) expression in primary neuronal cell cultures from the hypothalamic-brain stem areas (209, 211, 325). Interestingly, studies using double transgenic mice that overexpress both human Angiotensinogen and renin in either glial or neuronal cells suggest that the source of ANG II may be both cell types. Moreover, glia-derived angiotensin peptides are responsible for impairments in the baroreflex sensitivity (BRS) that controls heart rate (HR), whereas neuronal overexpression of angiotensin peptides resets the baroreceptor set point without altering BRS (458). Overexpression in both glial and neuronal cells contributes to increases in resting arterial pressure (379). On the other hand, rats that express an antisense RNA against Angiotensinogen under the control of the glial GFAP promoter indicates that the source of ANG-(1–7) is mainly non-glial cells (460).

More recently an interesting possibility has been raised: ANG-(1–12) could be a renin-independent precursor for angiotensin peptides in the rodent brain (158). ANG-(1–12) exhibits higher concentrations in the brain than ANG II and displays cardiovascular effects upon microinjection into discrete areas of the medulla and hypothalamus. These effects were partially antagonized by A-779, suggesting that ANG-(1–12) can be metabolized to ANG-(1–7) (158).

Nevertheless, ANG-(1–7) can be processed directly from ANG I by several endopeptidases including NEP, thimet oligopeptidase, and prolyl endopeptidase (84, 442, 592). Additionally, ANG-(1–7) is efficiently generated directly from ANG II by the monocarboxypeptidase, ACE2, and prolyl carboxypeptidase (136, 211). Accordingly, it has been shown that ANG-(1–7) attenuates the ANG II pressor response in the hypothalamus, and concomitant injections of ANG II and A-779 increased the response, suggesting that ANG-(1–7) may be formed from ANG II, at least in the hypothalamus (256). It is interesting to point out that although ACE constitutes the major ANG II-forming pathway, it also degrades ANG-(1–7) in a way that leads to ANG-(1–5) (89). However, so far not a single brain cell has been detected that expresses all components of the RAS; thus the formation of bioactive forms of angiotensin might require interactions between multiple cell types, or, the brain possesses enzymatic mechanisms different from the classical ones which are responsible for the formation of neuroactive forms of angiotensins (115, 116, 574).

Recently, sheep medulla and cerebrospinal fluid (351) have demonstrated a peptidase activity capable of metabolizing ANG-(1–7) to ANG-(1–4). This peptidase exhibits marked sensitivity to mercury-based inhibitors, chelating agents, and the metalloendopeptidase agent JMV-390. It also hydrolyzes ANG-(1–7) to a greater extent than ANG II and ANG I, while other bioactive peptides such as bradykinin, neurotensin, and apelin-13 are not cleaved. The peptidase appears to preferentially cleave the Tyr^4-Ile^5 bond of ANG-(1–7) generating ANG-(1–4). These data likely represent a novel pathway for the specific regulation of central ANG-(1–7) levels. The intracellular distribution of this ANG-(1–7) peptidase and the specific cell type that may express it within the brain (i.e., neuronal vs. glia) are not known. This peptidase may influence the local processing of ANG-(1–7) within cells or may be secreted or released from medullary tissue to degrade extracellular ANG-(1–7) or other peptides/substrates (87). The protein identity of this metalloendopeptidase-like activity, which converts ANG-(1–7) to ANG-(1–4) in the brain, has not yet been described, and its role in the physiological regulation of the brain RAS is similarly elusive.

ANG-(1–7) in the brain can also be converted to alamandine, through the decarboxylation of aspartate to alanine (297). Although a selective enzyme responsible for this decarboxylation has not yet been identified, the actions of alamandine and the receptor mediating its effects, MrgD, have been described in the brain (573).

2. ANG-(1–7) location in the brain

ANG-(1–7) immunoreactivity has been described in paraventricular, suprachiasmatic nuclei, the bed nucleus of the stria terminals, substantia innominata, median eminence, and neurohypophysial and other areas of the medulla oblongata and amygdala of normotensive rats (45). ANG-(1–7) was also identified in hypothalamic extracts (63, 85). Later, ANG-(1–7) immunoreactivity was described in neurons of the supraoptic nucleus (SON), and in the anterior (ap-), medial (mp-), and lateral (lp-) parvocellular, and posterior magnocellular (pm-) subdivisions of the paraventricular nucleus (PVN) in TGR(mREN2)27 transgenic hypertensive rats (286). Furthermore, cells immunoreactive for ANG-(1–7) were also stained for AVP, specifically in the SON and in the pmPVN, suggesting that ANG-(1–7) and AVP are colocalized, coreleased, and may carry out similar actions on common targets (286), possibly in combination. Interestingly, ANG-(1–7) levels were found to be fivefold higher in hypophysial-portal plasma than in jugular plasma of normotensive sheep, while no differences were observed for ANG II, renin, or angiotensinogen (298). In addition, it was shown that ACE2, the major enzyme involved in ANG-(1–7) formation, is present in the brain, predominantly in neurons (142). ACE2 immunostaining is in fact widespread throughout the brain, from the telencephalon to the medulla, at least in the mouse (142).

3. MAS location in the brain

The hypothesis of a receptor that selectively mediated the physiological effects of ANG-(1–7) in the brain developed from studies that showed that ANG-(1–7) and ANG II triggered distinct effects. The first antagonistic effect of ANG-(1–7) was described on the modulation of the baroreflex (66). ANG-(1–7), given intracerebroventricularly (ICV), facilitated baroflex control, while ANG II attenuated it (66). Further studies have strengthened this hypothesis by showing that ANG-(1–7) binds with low affinity to AT1 and AT2 receptors (452) and that its central and peripheral effects are different from those induced by ANG II (159, 473).

In 2003, with the identification of MAS as an ANG-(1–7) receptor (479), we showed that MAS expression was localized to specific areas of the brain (30) particularly related to cardiovascular control. There was a strong staining in the NTS, caudal and rostral ventrolateral medulla (CVLM and RVLM), inferior olive, parvo- and magnocellular portions of the PVN, SON, and lateral preoptic area (LPA) of normotensive Sprague-Dawley (SD) rats. However, other areas also stained for MAS, such as the hippocampal nucleus, different subregions of the frontal cortex, anterodorsal thalamic nucleus, basomedial and basolateral amygdaloid nucleus, and hypoglossal nucleus (nXII). In fact, MAS had already been recognized as an orphan receptor for some time and mRNA had been found in areas such as the hippocampus, the dentate gyrus, piriform cortex, and amygdala (58, 352, 369). In the murine brain, strong MAS protein expression was detected in the dentate gyrus of the hippocampus, within the piriform cortex, hippocampus, amygdala, basal ganglia, thalamus, and hypothalamus (192). Recently, Regenhardt et al. (433) have shown MAS immunostaining mainly in the soma of neurons and microglia of the adult rat cerebral cortex but not in astroglia, and in both nonnuclear and nuclear compartments. We still do not know whether AT1, AT2, and MAS may have a degree of overlapping localization or are expressed in distinct neuronal populations.

4. ANG-(1–7) actions in the brain

ANG-(1–7) acts as an important neuromodulator, especially in areas related to the tonic and reflex control of arterial pressure, in the hypothalamus, and in the dorsomedial and ventrolateral medulla **(FIGURE 4)**. At these sites, the cardiovascular effects induced by ANG-(1–7) are blocked by the MAS antagonist A-779 (133, 336), suggesting that in the brain, ANG-(1–7) actions are mainly mediated by its interaction with MAS.

Among its central actions, the more consistent effects of ANG-(1–7) are related to the modulation of the baroreflex, especially through improving the bradycardic component of the baroreflex control of heart rate in normotensive (46, 66) or hypertensive animals (249, 402). This effect was

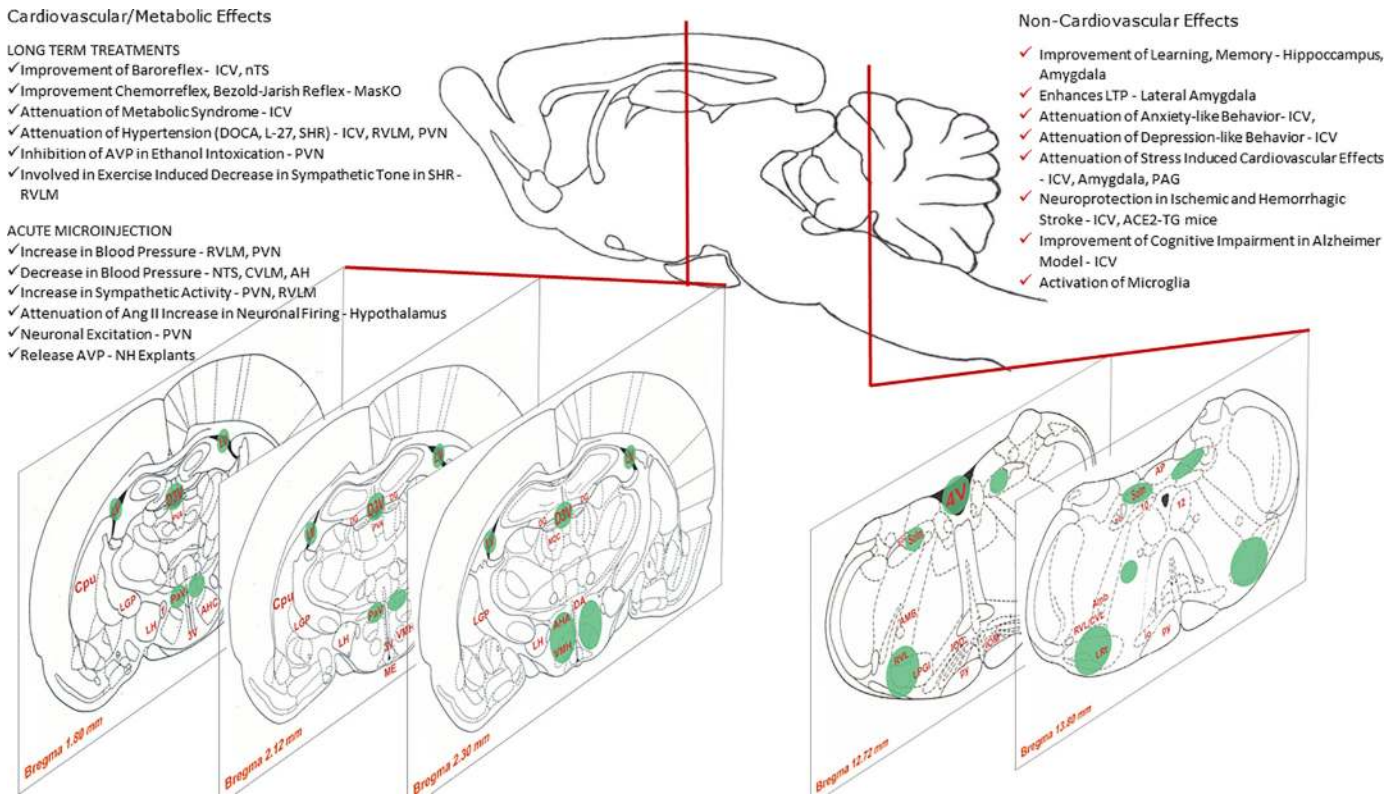


FIGURE 4. Localization of Mas in the central nervous system and main actions of angiotensin-(1–7) in the brain. See text for definitions.

initially investigated through short-term infusions of ANG-(1–7) into the lateral ventricle. On the other hand, infusion of A-779 attenuated the baroreflex sensitivity of normotensive rats but did not significantly alter the depressed baroreflex sensitivity of SHR (249, 402), suggesting an overall imbalance of ANG formation or MAS expression in SHR. However, when SHR received an ICV infusion of an ACE inhibitor, baroreflex experienced a significant increase in sensitivity that could be completely prevented by ICV A-779 (249). Moreover, the improvement in baroreflex after oral treatment with an ACE inhibitor in Goldblatt two kidney-one clip (2K1C) hypertensive rats was also reversed by ICV infusions of A-779 (52), showing that ANG-(1–7) may at least partly contribute to the beneficial effects on baroreflex from ACE inhibitor treatments. Because ACE inhibitors also affect bradykinin metabolism, we showed that ICV infusions of subeffective doses of ANG-(1–7), combined with equally subeffective doses of bradykinin, significantly facilitated baroreflex bradycardia, an effect which could be completely blocked by the bradykinin B2 receptor antagonist HOE-140 or by A-779, suggesting an interaction of both peptides in modulating baroreflex gain (46).

No alteration in blood pressure or drinking behavior was observed after short-term (up to few hours) infusions of ANG-(1–7) into the lateral ventricle (66) or microinjections into the PVN (427), in contrast to the classical stimulatory effect mediated by AT1 in the brain (339). However, when long-term infusions (14–28 days) were performed, a chronic increase in ANG-(1–7) levels in the CNS strongly attenuated the increase in arterial pressure that is observed in DOCA-salt rats (226), TGR(mREN2)27 hypertensive rats (390), or in female rats (614) subjected to DOCA-salt or ANG II hypertension (613). Similar data were observed after the delivery of an ANG-(1–7) fusion protein at the cisterna magna of TGR(mREN2)27 hypertensive rats (197). Furthermore, the blood pressure-lowering effect of ANG-(1–7) in DOCA-salt hypertensive rats was related to an improvement in baroreflex bradycardia, the restoration of the baroreflex control of renal sympathetic nerve activity (RSNA), and a regaining of the balance of cardiac autonomic tone (226). These effects were blocked by A-779, once again suggesting a mediation by MAS (273). An enhancement of the baroreflex control of the RSNA was also observed after 4 days of ICV infusion of ANG-(1–7) in rabbits subjected to chronic heart failure (274) and in transgenic mice overexpressing human ACE2 selectively in the brain (154). Additionally, mice lacking MAS presented a marked imbalance in the neural control of blood pressure, with a blunted sensitivity of not only the baroreflex but also the chemo- and Bezold-Jarisch reflexes (125). It is interesting to observe that in pathophysiological conditions, such as aortic coarctation (209), TGR(mREN2)27 hypertensive transgenic rats (493) exhibit an increase in concentrations of ANG-(1–7) in the brain.

Interestingly the facilitatory effect of ANG-(1–7) on the baroreflex control of heart rate is also consistently observed in the NTS, a key site in the brain stem which controls cardiovascular reflex functions (20, 90, 103, 135, 136, 459, 460). Microinjections of ANG-(1–7) induce facilitation, while injections of ANG II produce attenuation of the baroreflex bradycardia (90, 133). Accordingly, A-779 and losartan, selective MAS and AT1 receptor antagonists, produce opposite effects on the baroreflex in normotensive or hypertensive rats (90, 135, 460). At this site ANG-(1–7), which can be at least partially derived from ANG II through ACE2 (136), is degraded by ACE (259) and may have a preferential non-glial source (103, 460). Moreover, decreased levels of ANG-(1–7) at the NTS may be related to the attenuated baroreflex control that is observed in hypertension and aging (20, 90, 133, 249, 389, 459).

More recently studies in rats that develop metabolic syndrome after chronic fructose intake have shown that fructose-fed rats receiving ANG-(1–7) infusions into the lateral ventricle had normalized baseline mean arterial pressure, baroreflex control of heart rate (HR), and reduced cardiac sympathetic tone (225). More strikingly, alongside these cardiovascular improvements, the rats presented normalized glucose tolerance, glycemia, insulinemia, and HOMA score. Fructose-fed rats treated with ANG-(1–7) had increased HDL and normalized hepatic and muscle glycogen content (225). These data suggest that activation of ANG-(1–7)/MAS pathway in the brain may produce important benefits for cardiovascular and metabolic disorders.

Molecular analyses of the brains of fructose-fed rats treated with ANG-(1–7) ICV revealed a reduced mRNA expression of neuronal nitric oxide synthase (nNOS) and NR1/NMDAr in the hypothalamus and medullary areas of these animals (225). The major candidates for mediation of the central actions of ANG-(1–7)/MAS lie in these regions: the PVN, the RVLM, and the NTS, which are crucial for the sympathetic drive to the cardiovascular system and for baroreflex control. In agreement with this interpretation, a selective overexpression of ACE2 in the RVLM (618) or PVN (635) induces a significant decrease in blood pressure of SHR (618), attenuation of sympathetic activity, and improvement of the baroreflex function in animals with congestive heart failure (635).

Antagonizing the effect of ANG-(1–7) through ICV infusions of A-779 attenuated ethanol-induced activation of NOS in the PVN and restored hemorrhage-induced AVP in circulation (593). In congestive heart failure (CHF), restoring ACE2 induces an increase in NO and a decrease in sympathetic nerve activity (275, 605). In the ethanol-intoxicated hemorrhaged states, ICV A-779 administration decreased NOS activity and NO concentrations, partially restoring the rise in levels of circulating AVP, suggesting that MAS activation contributes to the NO-mediated inhibitory tone of AVP release (593).

5. Cardiovascular effects of angiotensin-(1–7) at specific medullary sites

At selective medullary sites, the acute stimulation of MAS induces effects similar to those triggered by ANG II (12, 14, 17, 26, 31, 64, 65, 103, 133, 170, 171, 180, 182, 183, 210, 297, 403, 425, 492, 506). In the NTS, ANG-(1–7) induces neuronal excitation (26) and decreases baseline blood pressure in normotensive (65) and hypertensive rats (90, 135). In the CVLM, an inhibitory area participating in the baroreflex arch (595), ANG-(1–7) induces decreases in mean arterial pressure similar to those observed for ANG II (13, 14, 69, 170, 581). However, the hypotensive effect of ANG-(1–7) was blocked by A-779, while ANG II was inhibited by losartan (475). Wang et al. (581) showed that the depressor response to ANG-(1–7) in the CVLM was accompanied by an increased release of glutamate and a decrease in taurine. More interestingly, we showed that the signaling mechanisms triggered by these peptides at the CVLM were distinct. ANG-(1–7) acts through a nitrergic pathway sensible to the NOS inhibitors, L-NAME and 7-NI, while ANG II acts preferably by decreasing the noradrenergic drive (14). Also in contrast to ANG II, microinjections of ANG-(1–7) into the CVLM attenuated the bradycardia and facilitated the baroreflex tachycardia (13). These effects were completely abolished by intravenous methyl-atropine, showing a dependence of a cholinergic/nitrergic peripheral mechanism (13). In SHR, the hypotensive effect of these peptides reaches a similar magnitude but involves the participation of different vascular beds (170). The hypotensive effect produced by ANG-(1–7) and ANG II at CVLM was caused by a decrease in renal vascular resistance, but did not alter femoral vascular resistance as shown for ANG-(1–7) in normotensive rats (170). This suggests a possible impairment of vasodilatory mechanisms triggered by ANG-(1–7) in the CVLM of SHR to the hindlimb. In 2K1C rats, the CVLM BP effect of ANG-(1–7) is mediated by MAS. However, A-779 at the CVLM of renovascular hypertensive rats induced a fall in BP and improved baroreflex bradycardia (69).

The RVLM represents the main relay for sympathetic output regulating cardiovascular homeostasis (112). MAS is expressed in the RVLM (29, 30) and microinjections of ANG-(1–7) induce a pressor response whose magnitude is similar to that of ANG II (172, 182, 183, 308, 316, 506, 640). Conversely, the selective blockade of endogenous ANG-(1–7) actions by A-779 results in a decrease in BP in normotensive (24, 180, 182, 315) and hypertensive rats (143, 172, 180, 307, 308, 388). The ANG-(1–7) pressor effect at the RVLM is increased after hemorrhage (316) and in hypertensive rats (172, 388). In keeping with the excitatory role of ANG-(1–7) after acute injections, A-779 or an inhibition of ACE2 with DX600 induces greater decreases

in blood pressure in SHR (388) and TGR(mREN2)27 rats (180). In addition, RVLM microinjections of ANG-(1–7) induce an increase in RSNA in normotensive (425, 640) and renovascular hypertensive rats (307). Although ANG-(1–7)/MAS at this site does not alter baroreflex (13), it increases the cardiac sympathetic afferent reflex (CSAR), which contributes to sympathetic excitation in hypertension (307, 388, 640). The facilitation of CSAR seems to be mediated by MAS activation of cAMP-protein kinase A and increases in NAD(P)H oxidase activity and the superoxide anion level (307, 308).

The pressor effect induced by acute injections of ANG-(1–7) into the RVLM may involve the release of glutamate and decreases in glycine, taurine, and GABA (582). Interestingly, in astrocytes from newborn SHRs, MAS mediates ANG-(1–7)-driven increases in Ca^{2+} signaling (228). On the other hand, A-779 but not the AT1 receptor antagonist losartan inhibited $[Ca^{2+}]_i$ elevations induced by ANG-(1–7), which could also be antagonized by blocking intracellular Ca^{2+} stores (228). ANG-(1–7) evoked no consistent changes in $[Ca^{2+}]_i$ or membrane excitability in catecholaminergic or noncatecholaminergic neurons of slice cultures containing the RVLM in either SHR or WKY (228). Recently, in an evaluation of the peripheral mechanism involved in the ANG-(1–7) effect at the RVLM, we showed that its pressor response may involve an increase in sympathetic tone, the release of AVP and possibly the inhibition of a vasodilatory peripheral mechanism (403).

All the excitatory effects described above counter the hypothesis that ANG-(1–7) plays a counterregulatory role to ANG II and mediates a decrease in blood pressure, improvement in baroreflex, decrease in sympathetic tone, and increase in vagal tone to the periphery. These effects were triggered by acute injections of ANG-(1–7) or antagonists into the RVLM. However, inducing a long-term alteration of RAS peptides at this site led to specific results which are informative. Stress-induced hypertension, for instance, induces increases in the expression of ACE and AT1, a decrease in ACE2, and a hyperresponsiveness of the RVLM to ANG II (143). Moderate physical exercise during SHR development (7–23 wk old) attenuates hypertension, prevents increases in tumor necrosis factor (TNF)-α, interleukin (IL)-1β, ACE, and AT1 expression in the RVLM and upregulates IL-10, ACE2, and MAS at this site (6). In addition, these changes are associated with reductions in plasma ANG II levels, neuronal activity, NADPH-oxidase subunit gp91(phox), and inducible NOS in trained SHRs, all of which indicate reduced oxidative stress (6). Accordingly, exercise rescues ACE2 expression in the RVLM of animals subjected to heart failure (275). Exercise training in normotensive rats, on the other hand, induces a pressor response to A-779, suggesting that in this condition, endogenous ANG-(1–7) triggers the inhibition of pressor neurons at the RVLM (31). Nevertheless, the most striking result was obtained with lentivirus-mediated long-term ACE2 expression in the RVLM, which induced a significant and long-term reduction in blood pressure in SHR (618). This suggests that increasing the level of ANG-(1–7) may contribute to the anti-hypertensive effects of exercise training, at least in the RVLM.

6. Cardiovascular effects of angiotensin- (1–7) at specific hypothalamic sites

Biological effects of ANG-(1–7) have been described in several nuclei of the hypothalamus (80, 108, 134, 137, 138, 213, 214, 252, 253, 349, 353, 414, 504, 547, 649). Diz et al. (134) used hypothalamic slice preparations of normotensive and hypertensive TGR(mREN2)27 rats to show that ANG-(1–7) produced a significant increase in the release of substance P from the hypothalamus of normotensive but not hypertensive rats. The physiological significance of these actions is still unclear. ANG-(1–7) does not, however, change the firing of cultured hypothalamic neurons; instead, it attenuates the action of ANG II in neurons of prehypertensive SHR through MAS and PTEN (phosphatase and tensin homolog deleted on chromosome 10) signaling (370).

Microinjections of ANG-(1–7) in the anterior hypothalamus (AH) had no effect in normal rats but induced a decrease in blood pressure in baroreceptor denervated rats (252). This effect, which was blocked by A-779, was in contrast to the excitatory effect induced by ANG II in control and pressoreceptor-denervated rats. More interesting, ACE inhibitors lower blood pressure after microinjections into the AH of denervated rats, an effect that is blocked by A-779 (252). This suggests that the effect of ACE inhibition is due to the formation of ANG-(1–7), which increases in this condition.

Felix and co-workers (16, 17, 152) used a microiontophoresis methodology to show that most neurons in the PVN are excited by ANG-(1–7). In fact, Qadri et al. (427) confirmed the first study performed in neurohypophysial explants by Schiavone et al. (492), showing that ANG-(1–7) microinjections into the PVN induce a release of AVP. However, in this study ANG-(1–7) was much less potent and its effect was abolished by losartan (AT1 antagonist) and PD123319 (antagonist for AT2 and MrgD). More recently, Whitaker and Molina (593) studied hemodynamic alterations after hemorrhagic shock in a model of acute ethanol intoxication. They found a reduction in the release of AVP mediated by a decrease in central NO inhibitory tone. The decrease in AVP release is considered the main factor in aggravating hemodynamic instability in animals with ethanol intoxication that suffer hemorrhages. These authors further showed an increase in ACE2 activity and ANG-(1–7) and substantial MAS-mediated upregulation of NOS in PVN of acute ethanol intoxicated hemorrhaged animals. A blockade of MAS ICV or in the PVN partially

restored circulatory levels of AVP, suggesting that NO upregulation mediated by ANG-(1–7) contributes to inhibitory tone upon AVP release during hemorrhaging in acute ethanol intoxication (593). Although these studies point to contrasting effects of ANG-(1–7) on the release of AVP, together they strengthen the concept that distinct ANG-(1–7) effects can be observed in specific brain areas depending on the existing pathophysiological condition.

In anesthetized normotensive rats, Fontes and colleagues (504) in our laboratory showed that bilateral microinjections of A-779 into the PVN decreased the RSNA, suggesting that endogenous ANG-(1–7) at the PVN contributes to the maintenance of the tonic activity of the sympathetic system and blood pressure. More recently, A-779 injections into the PVN have been shown to attenuate hypertension induced by a sleep apnea model in rats (108), which agrees with the sympathetic stimulatory effect of acute injections of ANG-(1–7) into the PVN. Nevertheless, ANG-(1–7) injections into the PVN effectively increased the RSNA, CSAR, and arterial pressure through an activation of MAS via the cAMP-PKA pathway (237, 307, 308, 527, 640). However, these studies were performed in anesthetized vagotomized and sinoaortic denervated rats, a condition that may introduce important changes in the activity of PVN neurons and their sensitivity to neuromodulators. For instance, others have reported opposite trends in other models (409, 413, 635)

7. Other angiotensin-(1–7) effects in the brain

A role for ANG-(1–7) has been reported in stress, learning, and memory processes that occur in central limbic regions such as the hippocampus and amygdala (7, 43, 246, 299, 404, 518, 607, 629). Hellner et al. (246) were the first to show that ANG-(1–7) enhances LTP in limbic structures, implicating a distinct function in learning and memory mechanisms via MAS. In 2007, Albrecht (7) showed that the LTP modulatory effect of ANG-(1–7) working through MAS in the lateral nucleus of the amygdala depended on cyclooxygenase-2 (COX-2) and NO. Moreover, Staschewski et al. (518) showed that there is a gender-dependent involvement of different isoforms of NOS in the effects of ANG-(1–7) on LTP in the amygdala. The ANG-(1–7)-induced increase in the magnitude of LTP involves nNOS in males and eNOS in females (518). In CA1 region of the hippocampus, Lazaroni et al. (299) showed that mice without MAS or subjected to MAS blockade present impaired object recognition memory (ORM). In addition, in $Mas^{-/-}$ mice, ANG-(1–7) concentrations are increased in the whole hippocampus, as well as in the CA1 area, suggesting the need for a functional ANG-(1–7)/MAS axis for normal ORM processing (299). Interestingly, it has been reported that in this brain region ANG-(1–7) can be formed independent of ANG II processing (417). Despite this evidence, the role of ANG-(1–7)/MAS axis in limbic-dependent memories remains poorly understood.

In 1998 Walther et al. (578) reported that Mas-deficient animals displayed an increase in anxiety-like behavior. Accordingly, years later Bild and Ciobica (43) showed an anxiolytic-like effect after chronic ICV infusions of ANG-(1–7), accompanied by a reduction in oxidative stress in the amygdala. More recently, using two different transgenic rat lines, we showed that ANG-(1–7) ICV infusions could attenuate anxiety-like behavior (11, 272). In addition, we showed that ANG-(1–7) was also effective in attenuating a depression-like phenotype (11). Interestingly, hypertensive patients who suffer from depression exhibit mood improvements after treatment with the ACE inhibitor captopril, which increases levels of ANG-(1–7) (50). Recently, we showed that the anxiety-like behavior of hypertensive rats was rescued in enalapril-treated animals after blockade, unveiling an anti-aversive role for endogenous ANG-(1–7), at least in hypertensive rats (11). More recently, similar findings have been obtained in mice by increasing ACE2 activity (583).

ANG-(1–7) is involved not only in modulating chronic stress-coping responses in psychiatric disorders, such as anxiety and depression, but can also participate in cardiovascular adjustments to acute responses to stress. Fontes and colleagues (181, 353, 404) have suggested that the ANG-(1–7)/MAS axis is a promising target to attenuate the physiological response to emotional stress and reduce the risk of cardiovascular diseases. ANG-(1–7) given in the lateral ventricle (353) or microinjected into the basolateral amygdala (404), an area of the limbic system that is involved in coordinating emotional responses, markedly attenuated the pressor and tachycardia responses evoked by air jet stress, a model to study cardiovascular changes to acute stress. Additionally, ANG-(1–7) injections into basolateral amygdala also attenuated the pressor response evoked by the cage-switch stress paradigm, another model of acute psychosocial stress (404). These effects were blocked by A-779, suggesting that they are MAS-mediated (353, 404). These findings reinforce the concept that ANG-(1–7)/MAS can modulate the cardiovascular responses evoked by emotional stress and point to the basolateral amygdala as an important site for mediating these actions.

Another area implicated in the integration of emotional behavior and sympathetic drive to the periphery is the periaqueductal gray (PAG). Xing et al. (608) showed that ANG-(1–7) interaction with MAS inhibits the neuronal activity of dorsolateral PAG which depends on a NO-dependent signaling pathway via MAS activation. More recently, these authors showed a decrease in ANG-(1–7) levels and an attenuation in MAS-nNOS pathways in the PAG of rats with chronic heart failure (609). Moreover, ANG-(1–7)'s ability to attenuate the neuronal activity of the dorsolateral PAG was significantly decreased in chronic heart failure animals (609). Whether the inhibitory effects of ANG-(1–7) at PAG are involved in modulating responses of emotional stress is an open question; however, it is very likely consid-

ering the role of the PAG in controlling sympathetic and cardiovascular system.

The ACE2/ANG-(1–7)/MAS axis also exerts a neuroprotective influence on ischemic and hemorrhagic strokes. In 2011, the Sumners group published the first (357) of a series of studies showing that ICV infusions of ANG-(1–7) or an ACE2 activator before and after endothelin-1-induced middle cerebral artery occlusion (MCAO) significantly attenuated the size of the cerebral infarct and the neurological deficits measured 72 h after the insult (32, 357, 433, 434, 526). These data were corroborated and extended by others, who showed an involvement of NO and different NOS isoforms, a decrease in cytokines, and a reduction in NFκB, COX-2, ROS, and neuronal apoptosis (267, 268, 421, 422, 637). The anti-inflammatory effects of central administrations of ANG-(1–7) were in accordance with the demonstration of a decrease in the activation of microglia both in ischemic stroke (433) and in hemorrhagic stroke induced in SHR-SP (434). All of these effects were attenuated by A-779, but were unaffected by the AT2 receptor antagonist PD123319, pointing to MAS as the receptor involved (526).

It has been reported that ischemic stroke increases ACE2 activity and MAS expression in the brain and ANG-(1–7) in the brain and circulation (329). Nevertheless, treatment with an ACE2 activator after stroke induces a decreased infarct volume and improves neurological functions without significant changes in cerebral blood flow (357). Accordingly, ACE2 overexpression in neurons of transgenic mice that overexpress human renin and Angiotensinogen (SARA, triple transgenic mice) induced neuroprotection, as demonstrated by a reduction in MCAO-induced infarct volume, an increase in cerebral blood flow, attenuation of neurological deficits, and increases in cerebral microvascular density in the peri-infarct area (636). These effects were MAS-related and independent of baseline arterial pressure. Moreover, there were increases in the ANG-(1–7)/ANG II ratio, angiogenic factors, eNOS expression, and NO production, whereas levels of NADPH oxidase subunits and ROS were decreased in the brain of SARA mice (636). The counterbalancing effect of ANG-(1–7) in the presence of high levels of ANG II was also observed in hemorrhagic stroke (42).

Other effects of ACE2/ANG-(1–7)/MAS in cerebroprotection are an attenuation of the loss of endothelial function of cerebral arteries that occurs with aging (421), increases in cerebral angiogenesis in ischemic stroke (268), and an attenuation of alterations in the integrity of the blood brain barrier after ischemia reperfusion injury (IRI), which induces deleterious alterations in brain permeability and edema (600). In this regard, ANG-(1–7) infusion restored the expression of tight junction proteins (claudin-5 and zonula occludens ZO-1) in IRI-induced blood-brain barrier damage by modulating the TIMP1-MMP9 pathway (600).

Imbalances of the two arms of the RAS in the brain favoring ANG II/AT1 activity are involved in the pathophysiology of diseases such as arterial hypertension, metabolic syndrome, heart failure, psychiatric disorders, and emotional stress. Strategies aimed at rescuing the RAS balance and inducing an increase in ANG-(1–7) in the brain can help ameliorate the problems that arise as these diseases develop. Physical exercise is an effective, nonpharmacological strategy to lower blood pressure in hypertensive patients, improving cognitive function, attenuating depression, and demonstrating other effects. Recent studies have shown that physical exercise induces changes in RAS components that lead to an increase in ACE2 activity and ANG-(1–7) in the brain in animals with heart failure or arterial hypertension (81, 275). Future studies will be necessary to reveal the mechanisms involved in exercise-triggered alteration in RAS components in the brain and their role in the beneficial effects of exercise.

8. Neurotransmitter/neuromodulator effects of ANG-(1–7)

Gironacci and colleagues have contributed to the understanding of the intracellular mechanisms triggered by ANG-(1–7) in neurons (80, 211–214, 325). These authors showed that ANG-(1–7) acting induces a decrease in presynaptic norepinephrine (NE) release in hypothalamus isolated from normotensive (214) and SHR (213) both by direct action or by blocking the release of ANG II-stimulated NE, thus balancing the stimulatory action of ANG II. They also showed that the decrease in NE release through ANG-(1–7)/MAS activation leads to bradykinin generation, which stimulates the B2 receptor and enhances NO release, activating the cGMP/PKG signaling pathway (215). In agreement, Feng and colleagues (154, 634) showed that the overexpression of ACE2 produces a significant increase in brain NO production, as do ICV administrations of ANG-(1–7). The activation of cGMP/PKG signaling in turn inhibits voltage-dependent calcium channels or induces the phosphorylation of proteins of the synaptic vesicle, decreasing the release of neurotransmitters and thus lowering their levels at the synaptic cleft. Additionally, it was shown that ANG-(1–7) decreases tyrosine hydroxylase (TH) activity and expression, the rate-limiting enzyme in catecholamine biosynthesis, in neurons from the hypothalamus and brain stem of WKY and SHR (325). This effect was unrelated to MAS, but blocked by PD123319, which led the authors to conclude that ANG-(1–7) acts via AT2 receptor activation, to stimulate the ubiquitin-proteasome system; this, in turn, induces increases in TH degradation. However, the recent finding that PD123319 also inhibits MrgD (297) means that the reduction in TH activity could be due to alamandine, a possibility yet to be explored.

Neuronal communication in the brain depends on neurotransmitter transporters in the cell membrane of neurons and/or glial cells which limit concentrations of neurotrans-

mitters in the synaptic cleft. ANG-(1–7) does not alter acute NE neuronal uptake in the hypothalamus of SHR (212). However, through MAS, ANG-(1–7) induces both MEK1/2-ERK1/2 and phosphatidylinositol 3-kinase/AKT pathways, resulting in increase in NE transporter transcription and translation (326). This suggests that ANG-(1–7) induces a long-term stimulatory effect on NE uptake by augmenting levels of the transporter. In addition to NE, Stragier et al. (523) showed that ANG-(1–7)/MAS stimulated the release of GABA and dopamine, but not of glutamate, in the rat striatum. In contrast, ANG-(1–7)/MAS stimulation in the CVLM induces an increase in the release of glutamate and a decrease in taurine (581). Thus a site-specific regulation of levels of synaptic neurotransmitters may be an alternative mechanism by which ANG-(1–7) contributes to the control of various functions in a range pathophysiological conditions through MAS.

B. Heart

Effects of ANG-(1–7) in the heart have been reported in a large number of studies (4, 9, 10, 21, 35, 78, 79, 82, 101, 120–124, 130, 145, 146, 161, 162, 164, 165, 167, 168, 175, 193, 203, 204, 206, 208, 216, 217, 222, 227, 239, 240, 260–262, 277, 303, 311, 313, 317–319, 321, 347, 354, 356, 358, 362, 366, 370, 377, 393, 394, 398, 408, 411, 413, 465, 476, 477, 489, 494, 498, 521, 531, 532, 561, 565, 576, 585–587, 589, 641, 646). Averill et al. (21) were the first to report ANG-(1–7) immunoreactivity within myocytes in the heart. This was in line with immunoreactivity in blood collected from the canine coronary sinus (472). More recently, ANG-(1–7) and MAS were identified in the sinoatrial node, providing the morphological basis for the ANG-(1–7) antiarrythmogenic effect (164). The presence of ACE2 in cardiomyocytes further supports a local formation of ANG-(1–7) in the heart of different species (164, 646). It should be pointed out that other enzymes capable of directly or indirectly forming ANG-(1–7) are also present in the heart, including prolyl-oligopeptidase (94) and cathepsin A (262).

1. Coronary vessels

ANG-(1–7) produces vasorelaxation in the coronary vessels of dogs (53, 54) and pigs (220, 426). In rodents, the peptide generally has no effects or produces vasoconstriction (288, 371, 393, 474). However, these observations were made using relatively high concentrations of ANG-(1–7) (nano- to micromolar range). Recently, using picomolar concentrations of ANG-(1–7), Souza et al. (516) were able to detect a significant vasodilator effect of ANG-(1–7) in isolated hearts from aorta-coarcted rat. Intriguingly, the blunted ANG-(1–7)-induced vasodilation in hypertensive animals was rescued by acute or chronic AT1 blockade using losartan. These observations are in keeping with an interaction of AT1 receptors with MAS (68, 79, 284), which still needs to be addressed in more detail.

2. Cardiomyocytes

In cardiomyocytes, acute exposure to ANG-(1–7) has no demonstrable effect on Ca^{2+} transients but promotes NO release by activating endothelial NO synthase (eNOS) and nNOS (101, 130). On the other hand, chronic exposure to ANG-(1–7) or genetic deletion of MAS has significant effects on Ca^{2+}-handling proteins (217, 476). Transgenic rats harboring an ANG-(1–7)-producing fusion protein in the heart show an increased Ca^{2+} transient amplitude, faster Ca^{2+} uptake, and increased expression of SERCA2 (217). Cardiomyocytes from $Mas^{-/-}$ mice have a smaller peak Ca^{2+} transient and a slower uptake of Ca^{2+}, probably due to the decreased expression of SERCA2 (217). These changes translated into impaired heart functions in $Mas^{-/-}$ mice (48, 198, 476). The changes in calcium-handling proteins were paralleled by changes in the NO production machinery (130). Cardiomyocytes from $Mas^{-/-}$ mice have normal eNOS protein levels, but a 70% increase in caveolin-3 expression and a decrease in heat shock protein 90 (117, 130). These two alterations may induce a decrease in eNOS activity because caveolin-3 prevents interactions between calmodulin and NOS, and heat shock protein 90 acts as a scaffold protein to recruit protein kinase B (AKT) to the eNOS complex (602).

3. ANG-(1–7) and cardioprotection

Most data related to ANG-(1–7) or other MAS agonists in the heart deal with its cardioprotective effects **(FIGURE 5)** (117, 168, 216, 223, 465, 477).

The first description of such an effect was made by Ferreira et al. (168). Low concentrations (220 pM) of ANG-(1–7) produced a significant reduction of ischemia/reperfusion-induced cardiac arrhythmias in isolated rat hearts. This was in contrast to the pro-arrhythmogenic effects of ANG-(1–7) at 10-fold higher concentrations (393). In keeping with these observations, De Mello et al. (124) reported a biphasic effect of ANG-(1–7) on impulse propagation and cardiac arrhythmias: at 10 nM, an anti-arrhythmogenic effect was observed (466), whereas at a 10-fold higher concentration, ANG-(1–7) was pro-arrhythmogenic (124). In transgenic TGR(A1–7)3292 rats which presented a moderate increase in circulating ANG-(1–7), a reduction in the duration of reperfusion cardiac arrhythmias and improved postischemic heart functions were observed (466). The mechanism of the anti-arrhythmogenic effect of ANG-(1–7) seems to involve, at least in part, the sodium pump (124).

In addition to influencing cardiac rhythm, ANG-(1–7) has a significant anti-remodeling effect in different models of cardiomyopathy. TGR(A1–7)3292 rats exhibit a marked attenuation of isoproterenol-induced cardiac fibrosis (466).

A number of later studies have described anti-remodeling effects of ANG-(1–7) (82, 117, 161, 177, 216, 223, 229,

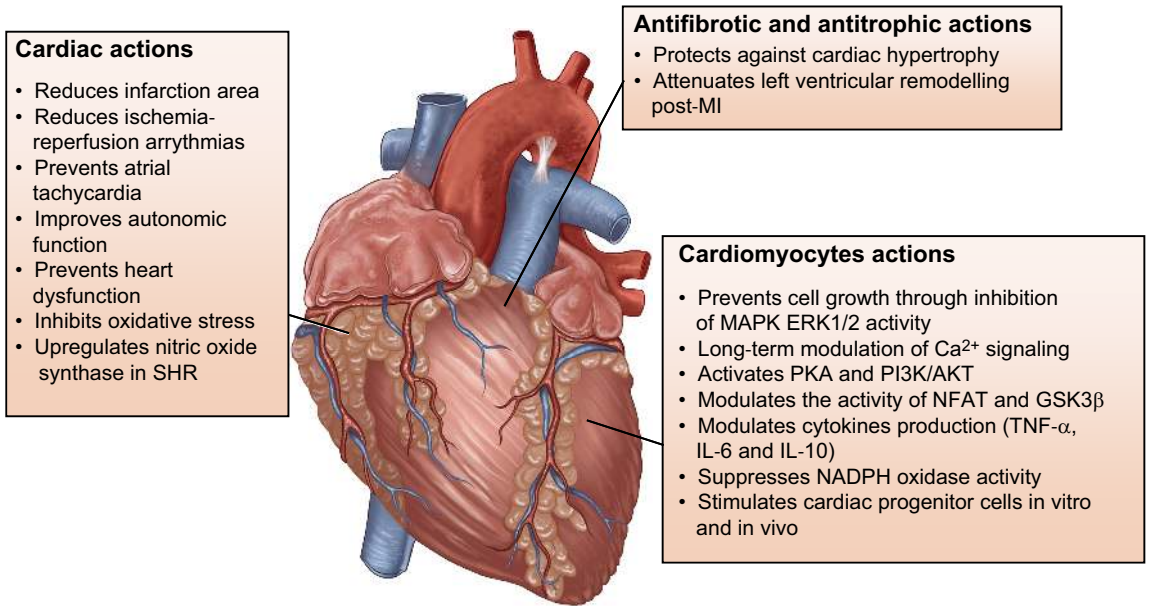


FIGURE 5. Effects of ANG-(1–7) in the heart. The effects illustrated in the figure include the ones produced in coronary vessels, fibroblasts, and cardiomyocytes.

311, 317, 348, 354, 366, 428, 440, 465, 585) and of other MAS agonists (AVE0991, CGEN-856S) (105, 165, 244, 334, 490, 628). These observations are in line with the deleterious cardiac effects of the genetic ablation of MAS in mice (48, 75, 78, 198, 476, 611). Interestingly, even an acute blockade of MAS with A-779 has been reported to produce a deterioration of function in isolated mouse hearts (78).

In contrast to the consistent antifibrotic effects of ANG-(1–7)/MAS, the picture is less clear for cardiomyocyte hypertrophy, although in general antihypertrophic effects have been described. The pro-hypertrophic effect of isoproterenol is attenuated in ANG-(1–7)- overexpressing TGR(A1–7)3292 rats (387). Similarly, treatments with ANG-(1–7) attenuated ANG II-induced cardiac hypertrophy (216). However, in the DOCA-salt model of hypertension, treatment with ANG-(1–7) attenuated cardiac fibrosis without interfering with blood pressure or cardiac hypertrophy (223), whereas the induction of DOCA-salt hypertension in TGR(A1–7)3292 rats (466) resulted in the attenuation of hypertension, myocardial fibrosis, and cardiac hypertrophy (465). An anti-hypertrophic effect of ANG-(1–7) was also observed in cultured cardiomyocytes treated with ANG II (177), AVP (177), and endothelin (193).

In contrast to several reports showing a cardioprotective effect of ANG-(1–7), Velkoska et al. (565) reported a dramatic deleterious effect of ANG-(1–7) infusions in SD rats after 5/6 nephrectomy. However, opposite effects were reported by Li et al. in the mouse (311) and, more recently, Xu et al. in the rat (610). In their studies, ANG-(1–7) prevented heart dysfunctions and left ventricular remodeling. Additional studies are needed to clarify this issue. It would be interesting, for example, to remove interfering factors such as the action of ANG-(1–7) on AT1 receptors in this condition (468). In a contrasting report, Zhang et al. (633) showed that the overexpression of human MAS in rat cardiomyocytes leads to hypertrophy. In addition to the possibility that the overexpressed receptors might be uncoupled from the usual signaling machinery activated by endogenous receptors, these data and other studies of ANG-(1–7) (393) indicate that important differences in signaling may arise in conditions where levels of MAS or ANG-(1–7) rise well above physiological concentrations.

C. Blood Vessels

The production of ANG-(1–7) in vascular endothelium was first described by Santos et al. (471). Its endothelium-dependent vasorelaxation has been reported by many authors. ANG-(1–7) relaxes the aortic rings of SD (300) and TGR(mREN2)27 (304) rats, canine (53) and porcine (426) coronary arteries, the canine middle cerebral artery (174), piglet pial arterioles (361), feline systemic vasculature (405), rabbit renal afferent arterioles (437), and mesenteric microvessels of normotensive (156) and hypertensive (155) rats. Moreover, ANG-(1–7) potentiates the vasodilator effect of bradykinin in several vascular beds, including dog (53) and rat (10) coronary vessels, rat kidney vessels (467), mesenteric arteries (156), and pancreatic microcirculation (625).

Although vasodilation is the most well-characterized action of ANG-(1–7), the ANG-(1–7)/MAS axis also induces antiproliferative (191, 530) and antithrombotic (185, 189) effects in vasculature. ANG-(1–7) and MAS are expressed

in VSMCs (530) and platelets (189). The antiproliferative action of ANG-(1–7) in the vasculature has been demonstrated in VSMCs, in which ANG-(1–7) reduces the ANG II-stimulated mitogen-activated protein kinase (MAPK) activities of ERK1/2 through an increase in prostacyclin (PGI_2) (530). A concurring result was observed in a rat stenting model, where ANG-(1–7) treatment produced a significant reduction in neointimal thickness, neointimal area, and stenosis (292). In rats with vascular calcification, ANG-(1–7) restored the decreased expression of lineage markers in VSMCs, including smooth muscle α-actin, SM22α, calponin, and smoothelin, and retarded the osteogenic transition of these cells by reducing the expression of bone-associated proteins (525). This antiproliferative potential was also observed in cardiac fibroblasts (354) and tumor cells (194).

As for antithrombotic effects, experiments performed in $Mas^{-/-}$ mice demonstrated an increased venous thrombus size and short bleeding times (189). Changes of an opposing nature were observed with the administration of an orally active form of ANG-(1–7), based on ANG-(1–7) inclusion in cyclodextrin [HPβCD-ANG-(1–7)]. The oral administration of HPβCD-ANG-(1–7) promotes an antithrombotic effect that has been associated with an increase in the plasma concentration of ANG-(1–7) (185). The antithrombotic effects of HPβCD-ANG-(1–7) were abolished in $Mas^{-/-}$ mice (185). This activity was also found in bradykinin B2 receptor-deleted mice ($Bdkrb2^{-/-}$), in which the MAS antagonist A-779 shortens the time leading up to arterial thrombosis and tail bleeding time (150). MAS-mediated NO release from platelets and increased prostacyclin seem to mediate these antithrombogenic actions (150, 189).

Most work on the hemodynamic actions of ANG-(1–7) over the years has been focused on clarifying its effects on vessels and blood pressure. **FIGURE 6** illustrates its main effects on blood vessels. Interestingly, the vasodilator effect of ANG-(1–7)/MAS is selective for specific vascular beds, contrasting with the more widespread vasoconstriction described for ANG II/AT1. In normotensive rats, ANG-(1–7) produced marked changes on regional blood flow, increasing vascular conductance in the mesenteric, cerebral, cutaneous, and renal territories. Furthermore, ANG-(1–7) simultaneously increases cardiac output (CO) by 30% and decreases total peripheral resistance (TPR) by 26%. These opposing changes lead to an absence of substantial changes in blood pressure (462). Similarly, transgenic rats with a slight increase in circulating ANG-(1–7) over their lifetime, TGR(A1–7)3292, present pronounced changes in regional blood flow, resulting in an increase in vascular conductance in the kidneys, lungs, adrenals, spleen, brain, testis, and brown fat tissue. In contrast, $Mas^{-/-}$ mice show a marked increase in vascular resistance in many territories such as the kidney, lung, adrenal gland, mesentery, spleen, and brown adipose tissue. This model also exhibited a parallel increase in TPR and decreased CO (48).

Many vascular actions of ANG-(1–7) have their effects through the release of NO. Human endothelial cells express MAS, through which ANG-(1–7) mediates an activation of eNOS and NO production via AKT-dependent pathways. ANG-(1–7) also promotes NO release in Mas-transfected Chinese hamster ovary cells via the phosphoinositide 3-kinase (PI3K)/AKT pathway (463). Recently, it has been demonstrated that ANG-(1–7) can also activate downstream components such as the FOXO1 transcription factor, a well-known negative modulator of the AKT signaling pathway (568). These results highlight the complex modulatory effects of ANG-(1–7), which probably involve downstream effectors that coordinate negative feedback loops through fine-tuned mechanisms.

Regarding its effects on NO generation, ANG-(1–7) regulates the phosphorylation of eNOS at Ser1177 and Thr495. In resting conditions, eNOS is phosphorylated on Thr495 and only weakly phosphorylated on Ser1177. The relative phosphorylation state of Ser1177 and Thr495 determines

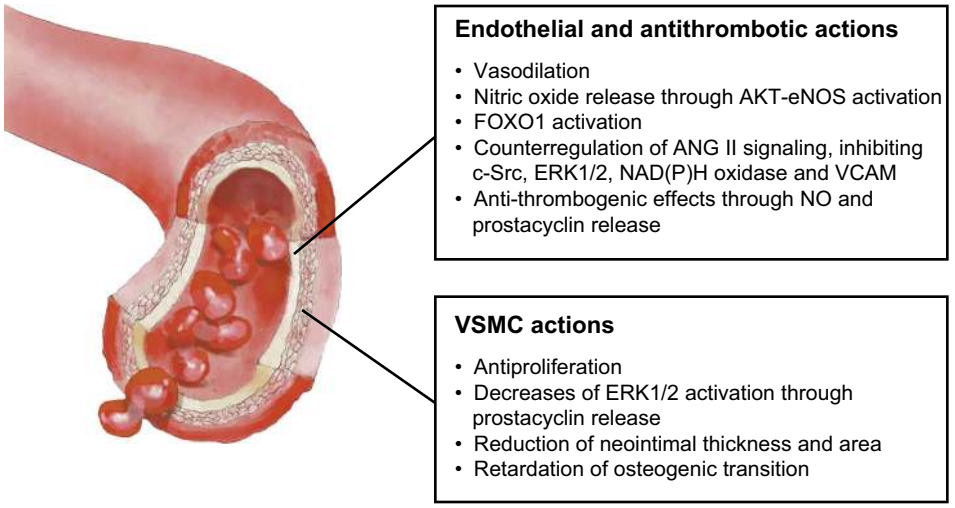


FIGURE 6. Main known effects of ANG-(1–7) in blood vessels.

the activity of eNOS in endothelial cells (176). ANG-(1–7) increases Ser1177 phosphorylation while simultaneously decreasing the phosphorylation of Thr495; both posttranslational effects are blocked by the MAS antagonist A-779 (461). Subsequently, it was demonstrated that the ANG-(1–7)-mediated activation of PI3K/AKT counteracts the negative effects of ANG II on insulin signaling in endothelial cells and is involved in the survival and proliferation of CD34(+) cells from diabetic individuals (536). In vivo, this pathway seems to mediate the improvement of insulin sensitivity induced by ANG-(1–7) in liver, skeletal muscle, and adipose tissue from fructose-fed rats (384).

In human endothelial cells, ANG-(1–7) also counterregulates ANG II signaling, blunting the phosphorylation of c-Src and ERK1/2 as well as the activation of NAD(P)H oxidase by ANG II. This modulatory effect is mediated by the phosphorylation of SHP-2, preventing ANG II-induced SHP-2 dephosphorylation and promoting interactions between SHP-2 and c-Src. A-779 inhibited these actions, demonstrating that these effects are mediated through MAS (463). In keeping with this concept, the impairment of endothelial function in two different genetic backgrounds with MAS deficiencies, C57Bl/6 and FVB/N, indicates a crucial role of MAS in endothelial functions through its effects on the generation and metabolism of NO and ROS (430, 611). In the FVB/N background, endothelial dysfunction is associated with an increase in blood pressure (611), whereas in C57BL/6 mice, no alteration of blood pressure has been reported (430). A worsening of 2K1C Goldblatt hypertension has also been observed in $Mas^{-/-}$ mice (432). Conversely, short-term infusions of ANG-(1–7) improve endothelial functions, significantly increasing the hypotensive effects of administering intra-arterial acetylcholine in normotensive rats (151). In diet-induced obesity mice, chronic treatments with ANG-(1–7) induced a significant improvement in endothelial functions and reversed the elevated aortic expression of the NAD(P)H oxidase subunits p22(phox) and p47(phox) and plasma TBARS (38). Similar results were obtained in diabetic rats, in which the carotid blood flow was restored by chronic treatment with ANG-(1–7), probably through the MAS-mediated antioxidant effects that oppose AT1-activated NAD(P)H oxidase (420). Moreover, ANG-(1–7) also negatively regulates the ANG II-induced expression of VCAM-1 by attenuating the nuclear translocation of NFκB in endothelial cells (630).

The actions of ANG-(1–7) in human vasculature still require investigation to determine whether the potent vasodilator effect described in rodents applies. Although an initial examination focused on human vessels led to some controversy, the conflicting results could be due to methodological divergences, or a racial or vascular territory selectivity of ANG-(1–7). The infusion of ANG-(1–7) in patients chronically treated with ACE inhibitors had no effect on forearm blood flow, whereas the infusion of bradykinin produced a noticeable vasodilation (114). This observation was taken as evidence that ANG-(1–7) played no role in the hemodynamic effects of ACE inhibitors. However, this did not consider the fact that ACE inhibition significantly increases circulating levels of ANG-(1–7), which means that using a MAS antagonist rather than ANG-(1–7) would have been more suitable to evaluate the peptide's effects on blood flow. Similar negative results were obtained in the forearm blood flow of normotensive patients, in which ANG-(1–7) did not alter vasodilation produced by bradykinin infusion (596). In contrast, Sasaki et al. (488) observed a dose-dependent vasodilation in the forearm circulation in normotensive subjects and patients with essential hypertension. Ueda et al. (548) similarly reported a dose-dependent potentiation of bradykinin vasodilation by ANG-(1–7) in normotensive forearm resistance vessels of normotensive healthy men, which is in keeping with the well-known bradykinin-potentiating activity of ANG-(1–7) described in animal models (10, 53, 156, 467). An attenuation of the vasoconstrictor effect of ANG II, but not of NE, by ANG-(1–7) was described in the forearm of normotensive patients as well as in mammary arteries in vitro (451, 488). ANG-(1–7) also antagonized ANG II in renal vessels in vitro, but does not appear to have a pronounced effect in normal physiological regulation of renal vascular function in vivo (450). More recently, Van Twist et al. (560) observed a significant dose-dependent increase in blood flow to the kidney during intrarenal infusions of ANG-(1–7) in hypertensive patients. Interestingly, like the observation made in rat renal vessels (555), this effect was weakened in patients on a low-salt diet, probably because this diet leads to an increase in circulating angiotensin peptides including ANG-(1–7) (282). The same authors (560) demonstrated that the effect of ANG-(1–7) infusion on renal blood flow was also reduced in stenotic kidneys. Mendonça et al. (359) have recently demonstrated that ANG-(1–7) significantly attenuates ANG II-induced vasoconstriction in human mammary arteries from patients submitted to coronary revascularization, probably through direct effects on smooth muscle cells, since this action was not abolished by A-779, PD123177, or endothelium removal.

As discussed here there are numerous MAS-mediated effects of ANG-(1–7) in blood vessels. Here the ANG-(1–7)/MAS axis clearly acts as an important counterregulatory arm within the RAS. However, further studies are required to elucidate the complex interactions between RAS receptors, peptides, and enzymes in the vasculature.

D. Kidney

ANG-(1–7) has many well-established effects in the kidney. Since the initial reports, the complexity of the vascular and nonvascular actions of ANG-(1–7) in this organ have been

recognized. They appear to be highly dependent on experimental conditions, gender, species, the nephron segment, and hydroelectrolyte status (83, 86, 131, 474, 508, 643). For example, in water-loaded rats, ANG-(1–7) produces a potent antidiuretic effect (469), while in baseline conditions, natriuresis or an absence of a clear effect has been reported (see **TABLE 1**). At least some of the controversial effects of ANG-(1–7) in the kidney may be due to an involvement of AT1 and AT2 in its actions (293, 295, 474). For instance, in water-loaded rats, the antidiuretic effects of ANG-(1–7) could be blocked by pretreatment with the AT1 antagonist losartan (25). An involvement of non-angiotensin receptors can also explain the variability of its kidney effects. For example, evidence for a participation of AVP V2 receptors in distal tubular cells was obtained by Magaldi et al. (337). In these cells, ANG-(1–7) produces a marked increase in cAMP. Interestingly, pretreatment with A-779 in this preparation abolished the effect of AVP on water absorption, while pretreatment with an AVP antagonist abolished the effects of ANG-(1–7). However, when the antagonist was added on top of the AVP or ANG-(1–7) effects, no cross-inhibition was observed. Yet as expected, A-779 reversed the effects of ANG-(1–7), and the AVP antagonist reversed the effects of AVP. Whether this phenomenon is due to a cross-internalization of MAS and AVP V2 receptors induced by the antagonists or crosstalk between the signaling mechanisms remains to be clarified.

TABLE 1 lists most of the known actions of ANG-(1–7) in the kidney, illustrating its complexity and unpredictability in this organ (28, 33, 34, 36, 40, 41, 59, 60, 76, 77, 128, 129, 132, 196, 202, 218, 238, 245, 251, 256, 257, 266, 271, 278, 294, 320, 342–344, 378, 391, 400, 408, 453, 478, 480, 495, 499, 512, 519, 520, 524, 534, 552–554, 557, 558, 564, 597, 615, 631, 638, 639, 644, 645).

1. Vascular effects of ANG-(1–7) in the kidney

The first direct demonstration of a vasoactive activity of ANG-(1–7) in the kidney was provided by Ren et al. using microperfused rabbit afferent arterioles (437). ANG-(1–7) produced a NO-dependent vasodilation that was abolished by A-779 but not by AT1 (L-158809) or AT2 (PD-123319) antagonists. The blockade of cyclooxygenase had no effect on ANG-(1–7) action (437). Evidence for vasodilator action in vivo was provided by Sampaio et al. using fluorescent microspheres (462). Other approaches did not lead to any direct effects of the heptapeptide on the renal vasculature in vivo despite in vitro activity **(TABLE 1)**. This latter observation has led to skepticism regarding the biological significance of ANG-(1–7) in vivo (57). However, more recent studies in humans clearly indicate that ANG-(1–7) promotes vasodilation in human kidneys, a phenomenon that is influenced by the Na^+ balance (560) or by the presence of renal artery stenosis (559).

E. Lung

Although little is known concerning the physiological roles of the ACE2/ANG-(1–7)/MAS axis in the lung, it appears to be critically involved in pathophysiological processes in this organ. ANG-(1–7) has been reported to reduce lung inflammation, fibrosis, and pulmonary arterial hypertension (92, 310, 333, 338, 364, 445, 449, 576). MAS has been detected in the epithelium and bronchial smooth muscle, suggesting sites where the beneficial actions of ANG-(1–7) may occur (148, 338). Anti-inflammatory actions of ANG-(1–7) were first described in a model of allergic asthma by El-Hashim et al. (148). The authors demonstrate that treatments with ANG-(1–7) resulted in the inhibition of the ovalbumin-induced increase in total cell counts, eosinophils, lymphocytes, and neutrophils as well as significantly reductions in ovalbumin-induced perivascular and peribronchial inflammation, fibrosis, and goblet cell hyper/metaplasia. These effects were mediated via MAS and blocked by A-779. ANG-(1–7) further reduced ovalbumin-induced increases in phosphorylation levels of ERK 1/2 and IκB-α and also inhibited the phytohemagglutinin-stimulated proliferation of human peripheral blood mononuclear cells (HPBMC). In chronic asthma, ANG-(1–7) triggered the beneficial attenuation of three major characteristics of this disease: lung inflammation, airway remodeling, and hyperresponsiveness (338). Similar effects were achieved in a model using the ANG-(1–7) mimetic compound AVE 0991 (449). The molecular mechanisms involved in these anti-inflammatory actions include a reduction of NFκB-related signaling, reductions of transforming growth factor (TGF)-β, and cytokine modulation (reducing IL-6 and IL-1β and increasing IL-10) (312, 363) (see **FIGURE 7**). The pulmonary activity of ACE and ACE2 activity becomes imbalanced in acute respiratory distress syndrome, which is characterized by an enhancement in ACE activity, the main pathway to ANG-(1–7) degradation, combined with a reduction in the activity of ACE2, which mainly generates it (598a). Experimental models of acute lung injury have highlighted an important protective role for ANG-(1–7). Infusions protected rats from acute lung lesions after oleic acid administration as seen through a decrease in lung edema, myeloperoxidase activity, histological lung injury score, and pulmonary vascular resistance (280). Similar results were observed in a pulmonary injury model based on lipopolysaccharide (LPS) (92). ANG-(1–7) treatment also decreases the severity of lung damage and inflammation induced by a combination of acid aspiration and high stretch ventilation. Moreover, continuous infusions of ANG-(1–7) reduced lung fibrosis 2 wk after acid aspiration injury, indicating its potential use in therapies for acute respiratory distress syndrome (ARDS) (626). The signaling mechanisms underlying the protective effects of the ACE2/ANG (1–7)/MAS axis against lung fibroblast migration and lung fibrosis seem to involve the inhibition of the NOX4-derived ROS-mediated RhoA/Rock pathway (363). In addition to its protective actions in pulmonary inflammatory progression, ANG-(1–7) also reg-

Table 1. *Renal actions of ANG-(1–7)*

Species	ANG-(1–7) Effects	Condition	Reference Nos.
Rat	Antidiuresis	Water loaded	469
Rat	Natriuresis/diuresis	SD isolated kidneys	128
Rat	*Biphasic dose-dependent effect on fluid absorption (↑ 1 pM) (↓ 10 nM)	Isolated rat proximal straight tubule	196
Rat	Natriuresis/diuresis	SD isolated kidneys	251
Rat	Transient natriuresis/diuresis	Hypertensive	33
Rat	Antidiuresis	Water loaded	480
Rat	Natriuresis/diuresis	Na-repleted anesthetized rats with denervated kidney and rat proximal tubules in vitro	238
Rat	*Biphasic dose-dependent effect on fluid absorption (↑ 10^{-8} M) (↓ 10^{-12} to 10^{-10} M)	Anesthetized Wistar rats	553
Rat	Antidiuresis	Water loaded	25
Rat	Natriuresis/diuresis	Anesthetized rat	552
Dog	Natriuresis/diuresis	Anesthetized dogs	245
Pig	Modulation of Na^+-ATPase ouabain-insensitive	Cortex homogenates and basolateral membranes from adult pig kidney	76, 294
Rabbit	Vasodilation	Isolated afferent arterioles	437
Rat	↑ Oxidative stress generation	Production of TBARS in rat kidneys	218
Rat	ANG II-mediated vasoconstriction	Interlobular arteries, afferent and efferent arterioles	557
Rat	Blunted the ANG II–induced decrease in Na^+ excretion	Normotensive anesthetized rats	59
Rat	↑ RBF	Urethane-anesthetized rats, using fluorescence microspheres	462
	↓ RVR		
Rat	Inhibition of ANG I and ANG II-mediated norepinephrine release in kidney	Isolated kidney	520
Mouse	MAS-dependent antidiuretic effect	Water loaded	479
Rat	↑ Water permeability involving vasopressin V2 receptors	Normotensive rat IMCD	337
Rat	↑ NE release and inhibition of ANG I and ANG II-mediated NE release in kidney	Isolated kidneys of SHR	519
Rat	No antiproteinuric effect	Adriamycin-induced proteinuria	554
Rat	↓ Proteinuria and ↓ histological indexes of renal damage	L-NAME-induced proteinuria in SHR	34
Rat	↓ TGF–β1	Proximal tubular cells	524
	↓ ANG II-stimulated phosphorylation of p38, ERK 1/2, and JNK		
Rat	↓ Urine flow	[TGR(A1–7)3292] rats with a chronic 2.5-fold increase in plasma ANG-(1–7)	166
	↑ Urinary osmolality compared with SD control		
Rat	↓ ANG-II-induced constriction of isolated renal arteries	Isolated perfused kidneys, intravital microscopy in vivo under anesthesia, electromagnetic flow probe in freely moving rats	555
	No effects on ANG-II-induced constriction of glomerular afferent and efferent arterioles in vivo		
	No effect on ANG-II-induced renal blood flow reduction in vivo		

Continued

Table 1.—*Continued*

Species	ANG-(1–7) Effects	Condition	Reference Nos.
Rat	Vasodilation and ↓ renal vascular responsiveness to ET-1, NE, and ANG II in SHR	SHR and diabetic SHR	30
	↑ Sodium excretion		
	↓ Proteinuria		
	↓ Renal NOX-mediated oxidative stress		
Rat	↑ Diuresis in late gestation	Pregnant and virgin rats	271
	↓ Diuresis in virgin rats		
	↑ AQP1 (virgin)		
	↓ AQP1 (pregnant)		
Rat	↓ Effects of ovariectomy on renal wrap-induced renal pathology (tubulointerstitial fibrosis and glomerulosclerosis)	Ovariectomized renal wrap model of hypertension	266
Rat	↓ Renal function	Streptozotocin (STZ) injection-induced diabetic rats	495
	↑ TGF-β1, ACE, and AT1 receptor		
Sheep	Minimal effects on basal GFR, renal plasma flow, and Na^+ excretion in males	Prenatal betamethasone-exposed ewes and rams	534
	↑ Na^+ excretion in vehicle-treated females when compared with betamethasone-exposed females		
Human	↑ Growth-stimulatory effects in human mesangial cells	Cultured human mesangial cells	643
Pig	↓ Profibrotic effects of high glucose	LLC-PK_1 proximal tubular cells	199
Mice	↓ Urine volume and fractional sodium excretion	Mas knockout mice	423
	↑ Microalbuminuria		
	↓ Renal blood flow in Mas-knockout mice		
Mice	↓ NF-κB activation and proinflammatory cytokines in Mas knockout	Unilateral ureteral obstruction (UUO) model in Mas knockout mice	149
Rat	A-779 infusion reduced RPF	2-Kidney-1-clip model in [TGR (A1–7)3292] rats	60
Rat	↓ Glomerulosclerosis	Monoclonal anti-Thy-1 antibody, OX-7 induced glomerulonephritis	630
Mice	Did not alter FITC-inulin clearance or urinary albumin excretion, increased relative mesangial area	Mouse model of chronic kidney disease (CKD)	132
Rat	↓ Proteinuria, renal collagen content, blood urea nitrogen, and dyslipidemia	STZ diabetic model	512
Rat	↓ NADPH oxidase activity	SHR-STZ combined model	129
	↑ Catalase and PPAR-gamma		
Rat	↓ Proteinuria, and structural alterations in the kidney (↑ glomerular nephrin, ↓ IL-6, TNF-α, and NF-κB)	Salt-loaded SHRSP	207
Rat	↑ Plasma ANG-(1–7) correlated with glomerular sclerosis and ↓ renal perivascular collagen deposition	SHR given an AT1 receptor blocker	257
Rat	↑ ERK1/2 in a MAS/cAMP/PKA/MEK-dependent way	SD mesangial cells	320

Continued

Table 1.—*Continued*

Species	ANG-(1–7) Effects	Condition	Reference Nos.
Rat	↓ α-SMA, vimentin, E-cadherin, TGF-β1, and fibronectin	High glucose-induced epithelial to mesenchymal transition (EMT) NRK-52E cells	637
	↓ ERK, p38 phosphorylation		
Mice	↓ Neutrophil influx and CXCL1/KC chemokine and renal damage	AVE0991 treatment in renal ischemia and reperfusion (I/R) injury in Mas knockout mice	28
	↓ Serum creatinine		
Rat	↓ Triglyceridemia	Zucker diabetic fatty rats (ZDF)	202
	↓ Proteinuria		
	↓ Renal fibrosis		
	↑ Creatinine clearance		
Rat	↓ ERK1/2 and TGF-β1 phosphorylation	Cultured rat renal mesangial cells (MCs)	615
Mice	↑ RVR and ↓ RBF in Mas-knockout mice	Mas knockout mice	48
Sheep	↓ RBF	ANG-(1–7)–treated adult, uninephrectomized rams exposed to betamethasone before birth	40
	↓ Basal sodium excretion		
Rat	↓ Basal sodium excretion	Normal, low and high salt intake rats	400
	↓ Diuresis and natriuresis in high-salt intake		
Rat	↓ $JHCO_3^-$ [endogenous ANG-(1–7)]	In vivo proximal tubules	77
	Biphasic dose-dependent effect on $JHCO_3^-$, mediated via NHE3		
Mice	AVE0991 treatment ↓ renal injury and proteinuria	Adriamycin (ADR)-induced nephropathy in Mas-KO mice	507
	No differences in adriamycin-induced nephropathy in Mas-knockout or wild-type mice		
	↓ Losartan reduction in renal injury in Mas knockout		
Mice	↓ Urinary albumin excretion	Diabetic nephropathy in *db/db* mice	378
	↓ NADPH oxidase activity		
	↓ Inflammation in perirenal adipose tissue		
Rat	↑ RBF in male and female, A-779 blocked this response only in female	Male and female Wistar rats	378
Human	↓ LDL-induced lipid deposition	Human mesangial cells (HMCs)	256
	↓ LDLr-SREBP2-SCAP		
	Dual effect on TGF-β1		
Human	↓ Podocyte injury	Podocytes incubated with serum from preeclamptic and normal pregnant women	539
	↓ MAPK (p38, ERK1/2, and JNK) phosphorylation		
Rat	No effect on glomerular damage	Uni-nephrectomized fawn-hooded hypertensive rat	564
Rat	A-779 blockage ↑ urine flow rate and sodium excretion in males, but not in females	Anesthetized male and female rats	344
Sheep	↓ 8-Isoprostane excretion	Male and female adult sheep preexposed to antenatal betamethasone	41

Continued

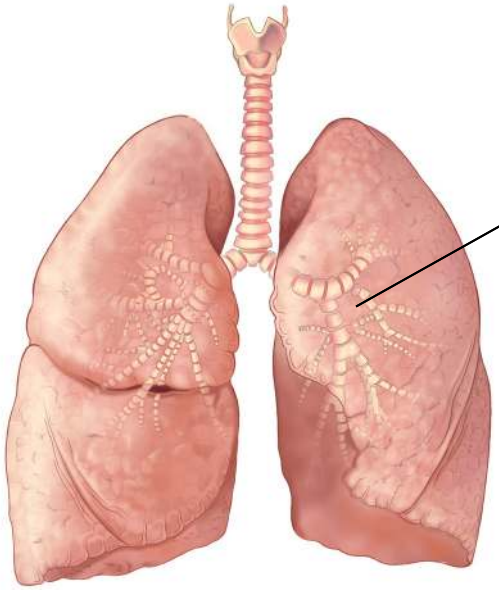
Table 1.—*Continued*

Species	ANG-(1–7) Effects	Condition	Reference Nos.
Human	Vasodilation in contralateral stenotic kidneys, but reduced in stenotic kidneys	Human kidneys with renal artery stenosis	559
Rat	↓ Glomeruli sclerosis	STZ rats	638
	↓ Oxidative stress	Rat mesangial HBZY-1 cell line exposed to high-glucose	
	↓ Cell proliferation,		
	↓ Collagen IV, TGF-β1, VEGF, NOX4, p47phox, PKCα, and PKCβ1		
	↓ Smad3 phosphorylation		
Mice	↓ Kidney injury	Type 1 diabetic Akita mice	499
	↓ Urinary albumin/creatinine ratio, glomerular hyperfiltration, renal hypertrophy, fibrosis, and tubular apoptosis		
	↓ Renal oxidative stress		
Mice	↑ Renal injury in Mas-knockout mice [endogenous ANG-(1–7) protection] and in high doses of ANG-(1–7)	Mice with unilateral ureteral obstruction	644
Mice	↓ Glomerular damage	*db/db* mice	408
	↓ Renal oxidative stress		
Rat	↓ Renal apoptosis and fibrosis	Unilateral ureteral obstruction in SD rats	278
	↓ TGF-β1/Smad		
Rat	Dose-dependent increase in RBF	Ovariectomized female Wistar-rats treated with ANG-(1–7)	453
Rat	In presence of AT1 and AT2 blockade, there was a tendency for an increase in RBF/kidney weight by A779 (P = 0.08)	Anesthetized male and female Wistar rats	343
Human	Intrarenal infusion of ANG-(1–7) ↑ RBF	Hypertensive patients with multifocal renal artery fibromuscular dysplasia	558
Rat	Significant increase in RBF	Hemorrhagic shock model in Wistar rats	342
Rat	↓ Renal injury (fibronectin and plasminogen activator inhibitor-1)	SD nephrectomized rats	610
	↓ Serum creatinine, ↓ proteinuria		

SD, Sprague-Dawley rats; IMCD, inner medullary collecting duct; SHR, spontaneously hypertensive rats; SHRSP, stroke-prone spontaneously hypertensive rats; STZ, streptozotocin-induced diabetic nephropathy; NE, norepinephrine; ET1, endothelin-1; AQP1, aquaporin 1; NRK-52E, rat renal cell line; α-SMA, α-smooth muscle actin; 2K1C, two-kidney one-clip Goldblatt hypertensive rats; RPF, renal plasma flow; RBF, renal blood flow; RVR, renal vascular resistance; $JHCO_3^-$, bicarbonate reabsorption; NHE3, Na^+/H^+ exchanger 3; LDLr-SREBP2-SCAP, low-density lipoprotein receptor-sterol regulatory element binding proteins 2-SREBP cleavage activating protein; LLC-PK_1, porcine kidney cells.

ulates cell survival, inhibiting alveolar epithelial cell (AEC) apoptosis, a critical event that initiates and propagates lung fibrotic disease. It decreases AEC apoptosis through pathways including the inhibition of JNK activation (312), reduction of endoplasmic reticulum (ER) stress-induced apoptosis (549), inhibition of LPS-induced ADAM17 shedding activity (333), and the upregulation of MAPK phosphatase-2 (219). Altogether, these findings indicate that this peptide may hold therapeutic potential in the treatment of lung fibrosis.

Since the demonstration of the beneficial effects of the ACE2/ANG-(1–7)/MAS axis in pulmonary arterial hypertension (PAH) by Shenoy et al. (497), emerging evidence has suggested that ANG-(1–7) has a protective role in this condition (498). Its importance in PAH comes from the observation that in patients with PAH from congenital heart disease, the peptide is reduced in plasma (110). The significant smaller response shown by TGR(mREN2)27 rats than SD to chronic hypoxia was related to the increased expression of ACE2 in the lung, leading to ACE2 activity and especially to markedly increased lung ANG-(1–7) concentrations and MAS expression in this strain (236). Interestingly, treatments with DIZE, a putative ACE2 activator, protect rats from monocrotaline (MCT)-induced PAH and reverse the imbalance in the autonomic nervous system



Pulmonary actions

- Decreases airway hyperresponsiveness
- Improves oxygenation and reduces cellular infiltrate in experimental Acute Respiratory Distress Syndrome (ARDS)
- Attenuates pulmonary hypertension immune system actions
- Reduces pro-inflammatory cytokines
- Increases anti-inflammatory cytokines

Lung signalling

- Decreases NF-kB and ERK phosphorylation
- Inhibits LPS-induced JNK activity and ADAM17 shedding activity
- Reduces lung fibrosis inhibiting the MAPK/NF-kB pathway
- Prevents JNK phosphorylation and apoptosis of alveolar epithelial cell (AEC)
- Activates JNK-selective phosphatase MKP-2
- Inhibits NOX4-derived ROS-mediated RhoA/Rock pathway

FIGURE 7. Effects of ANG-(1–7) in the lung. Most of the known effects of ANG-(1–7) in the lungs are related to inflammation.

modulation elicited by PAH, increasing parasympathetic and decreasing sympathetic cardiac activation (445). Although the administration of ANG-(1–7) and cyclic ANG-(1–7) immediately after induction of PAH in rats demonstrated no superiority of the MAS agonists compared with conventional treatments, the route of administration as well as the high doses used, which may have effects via AT1 receptors, suggest caution in interpreting the authors' conclusions (51). On the other hand, these results are important in designing future evaluations of the therapeutic potential of ANG-(1–7) for PAH treatment. Remarkable recent results from the Touyz group demonstrated that ANG-(1–7) negatively modulates the pro-inflammatory signaling of endothelin-1, a powerful pro-fibrotic mediator and vasoconstrictor that is elevated in PAH (255). This protective effect involves a crosstalk between MAS and the ETB receptor. These data identify the endothelin system as a novel molecular mechanism involved in the putative protective actions of ANG-(1–7) in PAH and illustrate the need for more studies to clarify the therapeutic usefulness of MAS agonists in this area.

F. Endocrine System

In addition to its actions directly related to the cardiovascular system, ANG-(1–7) has widespread effects in the endocrine system. The majority of these actions can also influence the role of the RAS in cardiovascular, metabolic, and electrolyte control. As discussed below, ANG-(1–7) has physiological actions in the major endocrine organs and plays a modulatory role in metabolic disorders such as diabetes and metabolic syndrome. **FIGURE 8** illustrates the beneficial effects of ANG-(1–7) in diabetes (35, 36, 47, 71, 129, 139, 147, 202, 345, 377, 438, 447, 481–483, 486, 510).

RAS components have been identified in both the endocrine and exocrine pancreas. Angiotensinogen, renin, AT1 and AT2 receptors, ACE, and ACE2 are all expressed in this organ (74, 88, 305, 306, 542). The pancreatic RAS appears to be important in pathological conditions such as pancreatitis, hypoxia, inflammation, and endocrine pancreatic tumors. The expression of both ANG-(1–7) (88) and ACE2 (542) has been established in the rat and canine endocrine pancreas as well as in the developing mouse pancreas, where ACE2 and MAS proteins were similarly localized in cytoplasm throughout the periods of gestation that were evaluated (E12.5 to E18.5) (580). ANG-(1–7) modulates islet function through the regulation of blood flow and inhibition of fibrosis by stimulating eNOS expression and NO release (625). Islet blood flow is critical for endocrine pancreas function, and it is important to note that pancreatic islets have a wide capillary network. Each β-cell neighbors at least one islet endothelial cell, which delivers signals for islet cell development and for adult β-cell proliferation (291). It has been reported that ANG-(1–7) attenuates palmitate-induced apoptosis in islet endothelial cells, decreasing phosphorylation levels of p38 MAPK and JNK and preventing palmitate-induced decreases in the PI3K/AKT/eNOS pathway (625). In islets isolated from neonatal mouse pancreas, treatment with ANG-(1–7) augmented mRNA levels of insulin and the pancreatic progenitor marker Ngn3 (584). These effects were attenuated by co-

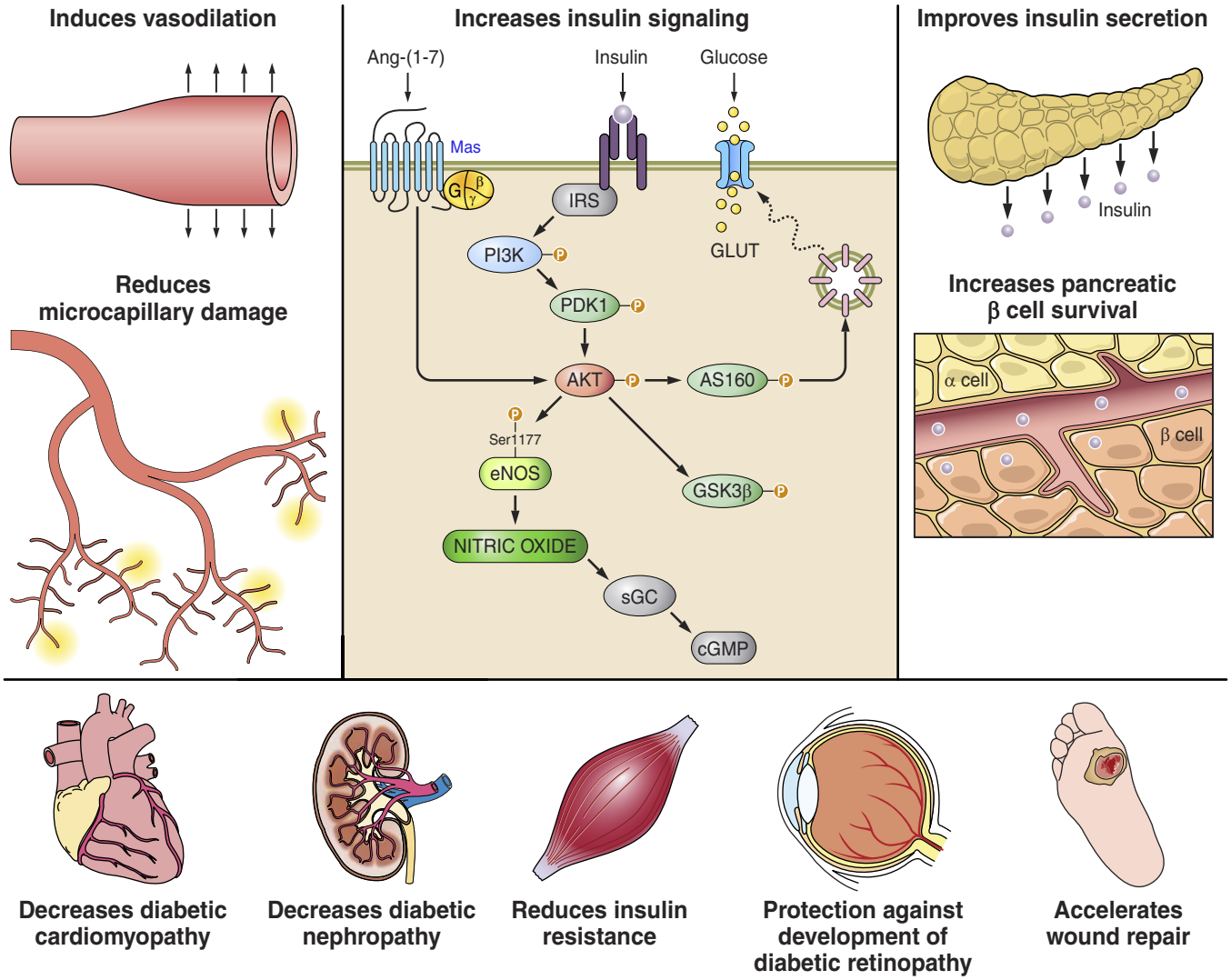


FIGURE 8. Protective effects of ANG-(1–7) on diabetes. ANG-(1–7) improves insulin signaling, increasing AKT phosphorylation, which is a key event for GLUT translocation to membrane and glucose uptake. This effect on AKT is also related to the increase in nitric oxide release and vasodilation. In addition to the anti-inflammatory and antioxidative properties, these effects lead to the reduction in microcapillary damage and in the vascular damage. Together, these actions result in clinical benefits, including reduction in cardiomyopathy and nephropathy, decrease in peripheral insulin resistance, protection against eye microcirculation damage, and retinopathy as well as acceleration in wound dermal repair.

treatment with A-779, suggesting that ANG-(1–7), via MAS, stimulates the differentiation of pancreatic progenitors into insulin-producing cells (584). Increased plasma and pancreatic levels of ANG-(1–7) and increased ACE2 expression were observed in a murine model of severe acute pancreatitis, suggesting that the ACE2/ANG-(1–7)/MAS axis participates in the pathogenesis of severe acute pancreatitis (322, 588). Endogenous ACE2 seems to have a key role in the adaptive β-cell hyperinsulinemic response, as seen in a diet-induced diabetes type 2 model, in which β-cell mass and proliferation were significantly reduced in ACE2$^{-/y}$ mice compared with controls (502).

In addition to its effects on acute pancreatic conditions, the protective axis of the RAS, ACE2/ANG-(1–7)/MAS also has beneficial modulatory effects in chronic metabolic diseases such as diabetes and metabolic syndrome. In these conditions, the triad insulin resistance/hyperglycemia/ANG II is intimately involved in the pathogenesis of target organ damage (49, 73). The main triggers for the development of vascular complications are endothelial dysfunction, inflammation, and proliferation of VSMC. High levels of ANG II and hyperglycemia form a self-reinforcing positive feedback loop that accelerates vascular damage. Like other growth factors, insulin stimulates the MAPK pathway, and the stimulatory cascade starts with the phosphorylation of IRS and/or Shc proteins that interact with the Grb2 protein. It is constitutively associated with the SOS protein, which sequentially activates Ras, a small G protein. In turn, Ras triggers the sequential phosphorylation of the MAPK cas-

cade, leading to cell proliferation and differentiation (350). The responses of ANG II in vascular cells are mediated by various and complex effector systems of the plasma membrane, such as phospholipases (A, C, and D), adenylyl cyclase, PKC, and ion channels, which are activated in conjunction with a number of microdomain proteins, mainly adapters. These proximal pathways lead to the activation of Ras/MAPK/ERK and JAK/STAT cascades which amplify the signal and extend it to the nucleus by regulating gene expression and stimulating cell proliferation (350). In addition, ANG II stimulates TGF-β, an important mediator of collagen formation, extracellular matrix (ECM) deposition and fibrosis, all of which are involved in nephropathy. Hyperglycemia enhances the vasoconstrictive and proliferative actions of ANG II, increasing vascular hyperplasia and the progression of diabetic nephropathy (49). On the other hand, ANG-(1–7) has protective actions on vascular functions, increasing the generation of NO and inhibiting both vascular proliferation and inflammation. Intracellular pathways activated by ANG-(1–7) are opposed to those stimulated by ANG II. The antiproliferative effects of ANG-(1–7) on VSMC are associated with inhibitory activity on MAPKs ERK1/2 (p44/42 MAPK) and p38 (530, 601).

An essential pathway in insulin signaling is PI3K/AKT. ANG II, via the AT1 receptor, inhibits the protective effects of insulin in the vasculature, interfering with the PI3K/AKT cascade and reducing NO availability while also reducing GLUT translocation and glucose transport (517). ANG-(1–7), on the other hand, induces the in vivo activation of GSK3β, the downstream target of AKT, in liver and skeletal muscle (385). It stimulates the phosphorylation of crucial insulin signaling mediators (AKT, GSK3β, and AS160) in liver, skeletal muscle, and adipose tissue (384). Chronic ANG-(1–7) treatment restored IR/IRS-1/PI3K/AKT activation, which was decreased in fructose-fed rats, a model of metabolic syndrome. Additionally, ANG-(1–7) ameliorates insulin resistance in this model (205). It was also demonstrated that a high sucrose intake in rats is associated with increased ACE2 and ANG-(1–7) levels in adipose tissue, suggesting a modulatory role of this axis under altered metabolic conditions (96). In TGR(A1–7)3292 rats, increased ANG-(1–7) levels enhanced glucose tolerance, insulin sensitivity, and insulin-stimulated glucose uptake and decreased levels of triglycerides, cholesterol, and abdominal fat mass, despite normal food intake (483). Moreover, the elevated levels of ANG-(1–7) protected the rats against metabolic stress induced by a high-fat diet by decreasing the proinflammatory molecules IL-1β and COX-2 in adipose tissue (485). Similar results were observed by Santos et al. (485) and Mario et al. (346), also suggesting crosstalk between ANG-(1–7) and sirtuins, particularly, SIRT1, whose levels rise in the adipose tissue of mice on a high-fat diet which are treated with ANG-(1–7) (346). In these mice, the oral administration of ANG-(1–7) improved insulin sensitivity and glucose tolerance and lowered plasma levels of fasting glucose and lipids (346). These effects were associated with an increase in GLUT4 and AMPK/FOXO1/peroxisome proliferator-activated receptor gamma (PPARγ) expression in adipose tissue (346). ANG-(1–7) and MAS are also essential in mediating the endothelium-dependent relaxation response induced by perivascular adipose tissue (302). MAS deficiency alters the response of adipocytes to insulin and decreases the expression of PPARγ in adipose tissue, which is accompanied by a lower expression of acetyl-CoA carboxylase and lower amounts of fatty acid synthase, which are the target enzymes of PPARγ (346). Oh et al. (401) showed that the effect of captopril in body weight decrease was partly related to ANG-(1–7)-stimulated NO release, since this action was attenuated by pretreatment with A-779 as well as by both PI3K and eNOS inhibitors. Interestingly, Gupte et al. (230) demonstrated that sex differences in the development of obesity-associated hypertension are related to the ACE2-mediated regulation of the ANG II/ANG-(1–7) balance. Male mice exhibited obesity hypertension associated with enhanced ANG II/AT1 effects, whereas the protection of female mice against obesity hypertension was abolished by the MAS antagonist A-779.

1. Female reproductive system

The presence of ANG-(1–7) in the ovary was initially described by Costa et al. in 2003 (100). These authors also were the first to suggest an involvement of the ANG-(1–7) peptide in pre- and postovulatory events, demonstrating higher levels of ANG-(1–7) in the proestrus and estrus as well as in equine chorionic gonadotropin (eCG)-treated rats (254). Later, the same group demonstrated that the ACE2/ANG-(1–7)/MAS axis is fully expressed in rat ovaries (419) and in all stages of follicular development in humans (436). ANG-(1–7) also plays a role in the ovulatory process, stimulating estradiol production and enhancing ovulatory efficiency. The specific ANG-(1–7) antagonist A-779 blocked these effects (569). Additionally, ANG-(1–7) promotes meiotic resumption in follicle-enclosed oocytes (FEOs), and gonadotropins upregulate the ACE2/ANG-(1–7)/MAS axis. A-779 reduced the percentage of germinal vesicle breakdown in luteinizing hormone (LH)-stimulated FEOs, suggesting that ANG-(1–7) participates in oocyte maturation as a gonadotropin intermediate (254). In addition to this action in ovaries, the expression of ANG-(1–7) in rat longitudinal myometrium and uterine serosa may indicate that the peptide is important for muscle physiology (563). Interestingly, ovarian steroids are not required for the endometrial expression of ANG-(1–7) in rats, since it remains abundant in ovariectomized animals. However, estrogen and progestin may modulate the distribution pattern of ANG-(1–7) in endometrial glands, where this peptide participates in the regulation of the endometrial response to ovarian steroids (563).

The ACE2/ANG-(1–7)/MAS axis is also differentially expressed during follicular development in cattle (27). ACE2 was upregulated in the granulosa cells of the largest follicles (F1) during and after the follicular deviation. MAS was upregulated in granulosa cells of the second-largest follicles (F2) after the establishment of follicular deviation, while its expression increased in F1 in which atresia had been induced, suggesting that MAS may be involved with the establishment of follicular dominance (27).

There is also evidence indicating that ANG-(1–7) plays an important role in pregnancy. In humans, ANG-(1–7) plasmatic and urinary levels increase during pregnancy, indicating that this peptide may have an important function in adaptations during gestation. Remarkably, lower concentrations of maternal and fetal ANG-(1–7) have been independently associated with preterm births (93). Moreover, in pregnant rats, ANG-(1–7)-induced vasodilation in mesentery resistance vessels increases, reinforcing the hypothesis that ANG-(1–7) may make an essential contribution to the regulation of blood pressure during pregnancy (55). Systemic infusions of ANG-(1–7) resulted in a greater increase in CO in normotensive pregnant women than in women who were not pregnant (616).

Merril et al. (367) were the first to demonstrate an increase in plasma ANG-(1–7) in normal pregnant women compared with nonpregnant women; they also found decreased levels of ANG-(1–7) in preeclamptic compared with normal pregnant women. Velloso et al. (567) also found a significant reduction in plasma ANG-(1–7) levels, as well as a significantly higher plasma ACE activity and a marked reduction in plasma renin activity in preeclamptic women, especially in patients presenting the ACE deletion polymorphism deletion/deletion (DD) genotype. In contrast, ANG II levels in the plasma of preeclamptic women did not differ from those of normotensive pregnant subjects (567). Pregnancy-induced increases of plasma ANG-(1–7) are also blunted in gestational diabetes (399). Following iontophoretic applications of ANG-(1–7), normotensive pregnant women exhibited a higher change in skin flow compared with preeclamptic women (616). Women who developed gestational hypertension or preeclampsia had increased ANG-(1–7) levels at 15 wk of gestation compared with women with normal pregnancies, suggesting that levels of ANG-(1–7) during early gestation could be useful indicators in predicting a woman's risk of developing hypertension during pregnancy (528).

Regarding the expression of ACE2/ANG-(1–7)/MAS axis components in human placentas of normal and pathological pregnancies, syncytial ANG-(1–7) expression in samples obtained from pathological placentas was higher than those from normal-term pregnancies. In the maternal stroma, ANG-(1–7) and ACE2 expression was found in the invading and intravascular trophoblast and in decidual cells. Furthermore, ANG-(1–7) and ACE2 are expressed in arterial and venous endothelium and smooth muscle of the umbilical cord. The expression of ACE2 is increased in umbilical arterial endothelium in preeclampsia (550). Preeclamptic women also exhibit an imbalance of local RAS in the chorionic villous in the placenta, where it is responsible for the regulation of fetal oxygen and nutrient transport. In association with the upregulation of angiotensinogen and the AT1 receptor, a significant increase in ANG II was observed, but there was no accompanying increase in ANG-(1–7) and a decrease in MAS (19). In the uteroplacental unit of pregnant rats, the distribution profile of ANG-(1–7) and ACE2 expression differs during early stages of pregnancy (decidua, luminal, and glandular epithelium, embryo, and ectoplacental cone) and late pregnancy (epithelial cells of the yolk sac and amnion). This pattern indicates that ANG-(1–7) participates in the initial events of a pregnancy, including angiogenesis, apoptosis, and growth, and it also plays a role in uteroplacental blood flow during the last phase of gestation (395). In guinea pigs, ANG-(1–7) and ACE2 have been detected in the endothelium and syncytiotrophoblast of the labyrinthine placenta, interlobium, subplacenta, giant cells, syncytial sprouts, syncytial streamers, and myometrium throughout pregnancy. Moreover, ANG-(1–7) and ACE2 expression were especially notable in giant cells, which also express kallikrein, the bradykinin B2 receptor, vascular endothelial growth factor (VEGF) and its type 2 receptor, and eNOS, which integrates ANG-(1–7) into the uteroplacental vasodilatory network (551). The expression of the ACE2/ANG-(1–7)/MAS axis was also found in two trophoblast cell lines (HTR-8/SVneo and BeWo cells), reinforcing the idea that ANG-(1–7) is involved in the early stages of pregnancy (588). ANG-(1–7) treatment attenuated podocyte injuries in cultured podocytes incubated with preeclamptic serum, which demonstrated a decrease in the expression of podocyte-specific proteins (nephrin and WT-1), a rearrangement of F-actin, and apoptosis. These protective effects of ANG-(1–7) are probably mediated through the downregulation of MAPK (p38, ERK1/2, and JNK) phosphorylation (539).

2. Male reproductive system

ANG-(1–7) also plays a role in the male reproductive system, regulating spermatogenesis and erection. The expression of MAS mRNA was detected in Leydig cells (8), and a specific binding of fluorescent-labeled ANG-(1–7) in testis occurred mainly in the intertubular compartment (likely also in Leydig cells), where ANG-(1–7) has regulatory actions on spermatogenesis (301). Studies in $Mas^{-/-}$ mice demonstrated that these animals exhibited a significant reduction in testis weight and a greater volume of apoptotic cells, giant cells, and vacuoles in the seminiferous epithelium (301). Moreover, $Mas^{-/-}$ mice also showed lower Sertoli efficiency, meiotic index, overall rate of spermatogenesis, and daily sperm production, indicating the overall importance of MAS in male reproduction (301). Neither

ANG-(1–7) nor MAS was detected in the seminiferous tubules of infertile men with nonobstructive azoospermia and severely impaired spermatogenesis. Furthermore, testicular samples from infertile men with impaired spermatogenesis (nonobstructive azoospermia) expressed MAS and ACE2 mRNA at lower concentrations than samples with normal spermatogenesis (obstructive azoospermia) (435).

ANG-(1–7) also mediates penile erection through the activation of MAS. Erectile functions of $Mas^{-/-}$ gene-deleted mice are substantially reduced and associated with a marked increase in fibrous tissue in the corpus cavernosum (107). In rats, the MAS agonist AVE 0991 potentiates the penile erectile response in a NO-dependent manner (106). Similarly, chronic treatment with HPβCD-ANG-(1–7), an oral formulation of ANG-(1–7), reduces penile fibrosis associated with an attenuation of oxidative stress in hypercholesterolemic $ApoE^{-/-}$ mice) (187).

G. Skeletal Muscle System

The identification of RAS components in skeletal muscle (590) indicates that the effects of angiotensins on metabolism and skeletal muscle blood flow can also be adjusted locally. In addition, due to their large presence throughout the body, skeletal muscle cells represent important modulators of the systemic effects of angiotensins.

The local production of ANG II and its effects on skeletal muscle have been widely studied (61, 111, 126, 157, 179, 200, 270). ACE inhibition and AT1 blockade represent novel strategies that are being pursued in the treatment of various skeletal muscle disorders and cachexia induced by CHF (97, 127, 144, 464, 491, 529, 575).

An example is Duchene Muscular Dystrophy (DMD), caused by mutations in the dystrophin gene, the most common muscular dystrophy in children. The primary animal model used to study this pathology is the MDX mouse (503). Recently, rodent studies have shown beneficial effects of ANG-(1–7) in this and other muscular dystrophy models (5a, 95, 360, 372, 374, 375, 446, 454, 456) **(FIGURE 9)**.

In a recent study, chronic infusion or oral treatment with ANG-(1–7) in MDX mice normalized skeletal muscle structure, drastically reducing the total amount of collagen and collagen III and improving muscle function "in vitro" and "in vivo" (5a). This study also demonstrated that MDX mice treated with A-779 or crossed with $Mas^{-/-}$ mice (mdxKOMas) presented a dramatic increase in damaged and inflamed tissue in comparison with MDX mice. These effects are mediated TGF-β/Smad signaling (5a).

Chronic ANG II treatment induced skeletal muscle wasting in a manner involving p38MAPK and Smad TGF-β1 signaling (376). The accompanying increases of fibronectin, collagen, TGF-β1, atrogin, and MURF1 induced by ANG II were attenuated by treatment with ANG-(1–7) (95).

Some patients with DMD carry mutations in genes that encode sarcoglycans (SGs). δ-Sarcoglycan-deficient mice ($Sgcd^{-/-}$) develop a DMD-like disease and exhibit higher levels of ANG I, ANG II, and AT1 expression in skeletal muscle, whereas the levels of ANG-(1–7) and MAS expression are reduced (454). Mice treated with HPβCD-ANG-(1–7) exhibited ameliorations in skeletal muscle pathology, a normalization of autonomic activity, and an increase in spontaneous locomotor activity (455). Skeletal muscle fi-

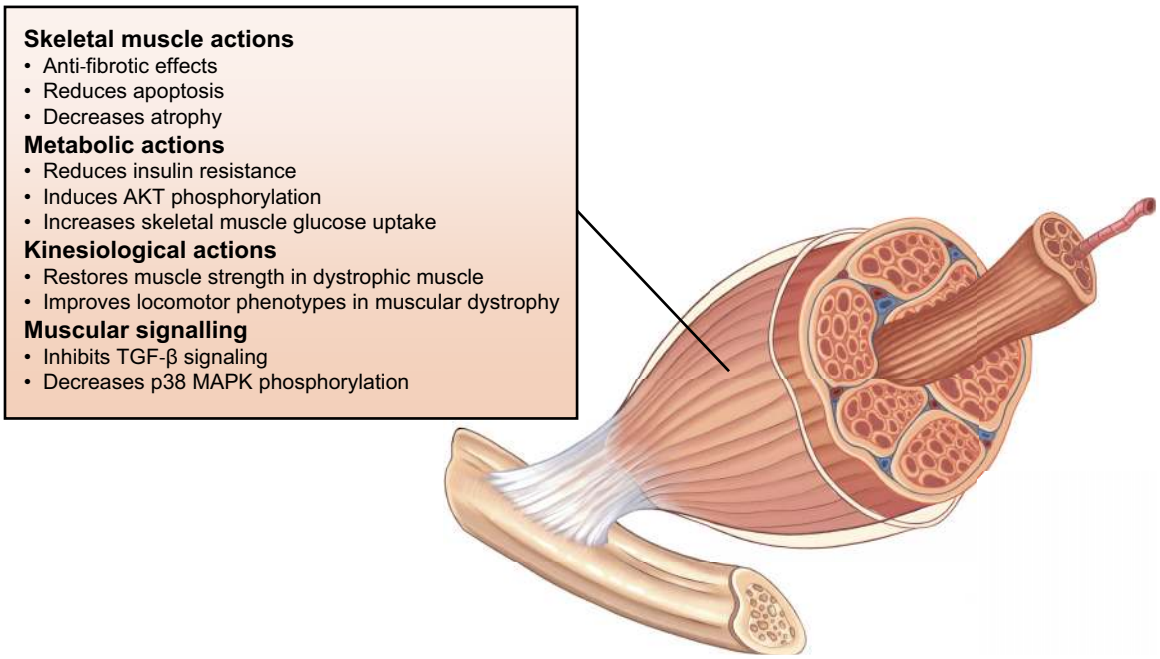


FIGURE 9. Actions of ANG-(1–7) in the skeletal muscle system.

brosis and oxidative stress were also markedly reduced in Sgcd$^{-/-}$ mice treated with HPβCD-ANG-(1–7).

Riquelme et al. (446) suggested that the expression of ACE2 regulates fibrosis in dystrophic muscle since muscle damage causes increased activity of ACE2, and ACE2 levels correlate with the degree of fibrosis. Recently it has been reported that ACE2$^{-/y}$ mice show reduced performance in voluntary running (380), but it is unknown whether this is a result of the genetic deletion of ACE2 in muscle cells, considering that this mouse exhibits an overall deficiency in ACE2.

MAS is also upregulated in skeletal muscle atrophies that have been induced by sepsis, immobilization, or ANG II (373). In these conditions, MAS expression in gastrocnemius and tibialis anterior muscles was upregulated, as were atrogin-1 and MURF-1. These data and the fact that ANG-(1–7) has protective effects against muscle atrophy suggest that MAS is involved in modulating the muscle wasting response (95, 360, 372–375). Mice who are submitted to a unilateral cast immobilization of the hindlimbs for a period of 14 days developed decreased muscle strength; pretreatment with ANG-(1–7) improved isometric strength and prevented the decreased fiber diameter of muscle. This also increased atrogin and MuRF1 expression, important markers of muscle atrophy (372). These anti-atrophic effects of ANG-(1–7) involve the IGF-1/IGFR-1/AKT pathway as shown by the fact that pretreatment with ANG-(1–7) prevents the decrease in AKT phosphorylation and FOXO3. All the effects of ANG-(1–7) were absent in Mas$^{-/-}$ mice, confirming the involvement of MAS in the actions of ANG-(1–7) in muscle tissue (372).

H. Liver

A number of reports document beneficial effects of the ACE2/ANG-(1–7)/MAS axis in the liver **(FIGURE 10)**. They include improvements in nonalcoholic steatosis and inflammation (70, 153, 533), liver fibrosis (331, 340, 406, 418, 591), and sensitivity to insulin (71, 205). These observations are in keeping with the increase in ACE2 in chronic liver injuries in rats and humans (247, 407) and with the liver steatosis associated with MAS-deficiencies in ApoE$^{-/-}$ mice (505). Other reports indicate that ANG-(1–7) suppresses the growth of hepatocellular carcinoma and angiogenesis via interactions of different angiotensin receptors (323).

The liver ACE/ANG II axis is mainly activated in patients with chronic liver disease and plays important roles in hepatic fibrosis and portal hypertension (279). On the other hand, as in other tissues, the axis also has a protective role, delaying the development of hepatic fibrosis (406, 571). Lubel et al. (330) demonstrated that human patients with cirrhosis exhibit markedly elevated levels of concentrations of both plasma ANG-(1–7) and ANG II. Furthermore, ANG-(1–7) levels were higher in non-cirrhotic patients with hepatitis C than in controls. This study also showed that ANG-(1–7) is upregulated in human liver disease and has antifibrotic actions in a rat model of cirrhosis (bile-duct ligation). Hepatic stellate cells (HSCs) expressed MAS and when treated with ANG-(1–7) or the MAS agonist AVE 0991 produced less α-SMA and hydroxyproline, which was blocked by the MAS antagonist A-779 (331). In cirrhotic rat liver, ANG-(1–7) significantly inhibits vasoconstriction induced by intrahepatic ANG II or the α1 agonist methox-

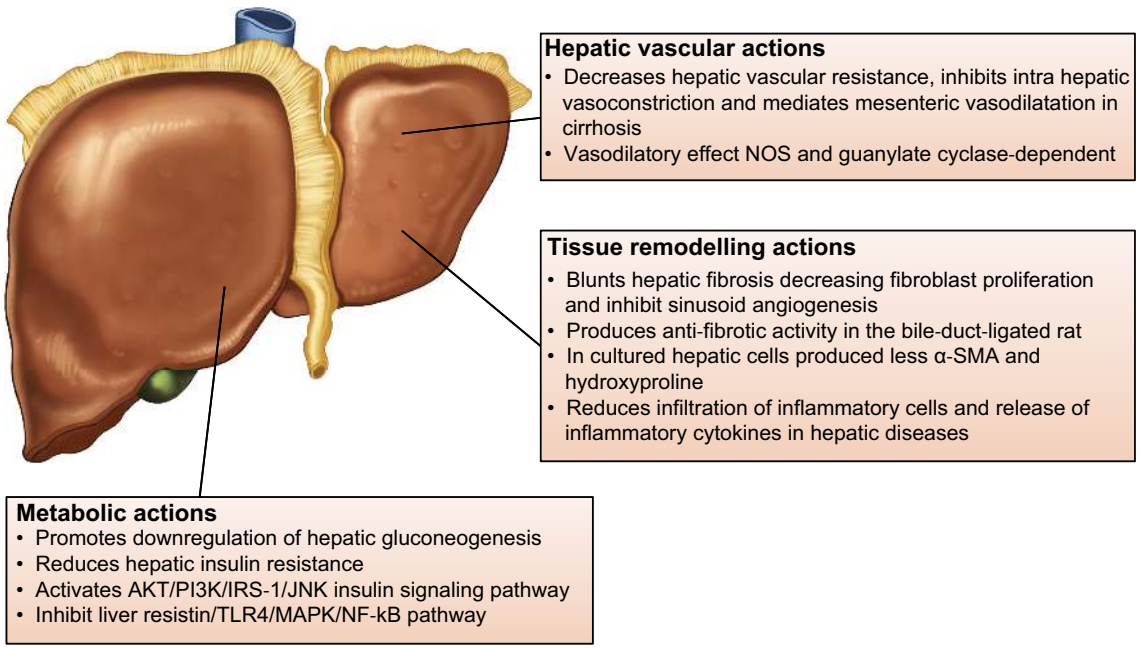


FIGURE 10. Effects of ANG-(1–7) in the liver.

amine (MTX) through eNOS and guanylate cyclase-dependent NO signaling pathways (248). Recently, it has also been demonstrated that ANG-(1–7) reduces bile duct ligation-induced hepatic fibrosis via redox balance modulation. ANG-(1–7) treatment decreased H_2O_2 as well as NOX4 and the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, which is activated by reactive oxygen species (ROS) and is involved in ANG II-stimulated collagen synthesis (62, 632). On the other hand, ANG-(1–7) increased glutathione and the nuclear erythroid 2-related factor 2 antioxidant response element (218).

VI. INTRACELLULAR SIGNALING PATHWAYS INDUCED BY ANGIOTENSIN-(1–7)

In recent decades several aspects of ANG-(1–7)-induced signaling have been clarified. The increase in NO release is the most classic event related to the protective role of ANG-(1–7) and includes calcium-independent pathways and the posttranslational regulation of eNOS (463). ANG-(1–7), via AKT-dependent pathways, stimulates eNOS activation (reciprocal phosphorylation/dephosphorylation at Ser1177/Thr495), which triggers NO production (463) and increases levels of cGMP (174, 216, 536). ANG-(1–7)-mediated AKT activation is also involved in its metabolic actions and participates in improvements in insulin resistance (205). In addition to the phosphorylation of AKT, ANG-(1–7) mediates the phosphorylation of GSK-3β and AS160, which are crucial insulin mediators (384). It has also been demonstrated that chronic oral administration of HPβCD-ANG-(1–7) attenuates hyperglycemia in an animal model of type 2 diabetes (486), indicating the potential of ANG-(1–7) as a hypoglycemic drug.

Although AKT is an important FOXO inactivator, ANG-(1–7) is able to dephosphorylate FOXO1 at Ser256, directly activating this transcription factor (568). This effect is probably involved in the antitumor actions of ANG-(1–7) since FOXO1 is a well-known tumor suppressor (99).

ANG-(1–7) increases arachidonic acid (AA) release, phospholipase A_2 (PLA_2) activity and prostaglandin E_2 (PGE_2)/prostacyclin (PGI_2) synthesis (18, 324, 383). It also counterregulates ANG II signaling, blunting the phosphorylation of c-Src and the activation of NAD(P)H oxidase by ANG II and reducing ROS generation (461). This modulatory effect is mediated by the phosphorylation of SHP-2, preventing ANG II-induced SHP-2 dephosphorylation and promoting the interaction between SHP-2 and c-Src (461). Additionally, ANG-(1–7) inhibits MAPKs (ERK1/2, p38, JNK), which are central mediators in cell proliferation, fibrosis, and remodeling. The inhibition of these pathways has been demonstrated in a number of cell types including VSMCs (642), lung cancer cells (194, 396), cardiac myocytes (531), endothelial cells (461), and kidney proximal tubule cells (LLC-PK) (199). In tumor cells (98) and myocytes (354), the inhibition of MAPK induced by ANG-(1–7) probably involves the MAPK phosphatase dual-specificity phosphatase (DUSP)-1.

ANG-(1–7) additionally decreases TGF-β/NFκB signaling (148, 267, 345, 482, 627), a key pathway in inflammation. Reductions in proinflammatory molecules such as TNF-α (5, 207, 482, 514), MCP-1, IL-8 (42), IL-1β (42, 485), and COX-2 (267, 365, 485) were observed. The anti-inflammatory role of ANG-(1–7) has been demonstrated in pathological conditions such as asthma (148, 338), arthritis (5, 109), angioplasty (627), cerebral ischemia (267), diabetes (486), and intracerebral hemorrhagic stroke (42). There is growing evidence for an activation of the G_S pathway by ANG-(1–7) (320), leading to increased cAMP formation and PKA activity (337).

The signaling pathways elicited by alamandine are being clarified and also involve NO release. In ventricular myocytes, alamandine leads to the phosphorylation of 3-phosphoinositide dependent protein kinase-1 (PDK1), which is crucial for the activation of AKT and interferes with GSK3β depending on the model. In cardiac myocytes from TGR(mREN2)27 rats, alamandine increases GSK3β phosphorylation but decreases it in myocytes from healthy animals (265). **FIGURE 11** summarizes the main signaling pathways involved in the ANG-(1–7) effects.

Besides MAS, other GPCRs have been implicated in mediating ANG-(1–7) actions. The blockade of some functions of ANG-(1–7) by the bradykinin B2 receptor antagonist HOE-140 has been taken as evidence that these receptors are linked (1, 178). This may indicate that some vascular actions of ANG-(1–7) depend on protein-protein interactions involved in eNOS activation (283). In addition to caveolin and calmodulin, which undergo reciprocal Ca^{2+}-dependent associations and dissociations with eNOS, the eNOS protein complex includes the B2 receptor and other proteins, including the AT1 receptor, the cationic amino acid transporter-1 arginine transporter, and the chaperone heat shock protein 90 (283). The direct heterodimerization of MAS with the B2 receptor is another possibility to explain the effect of HOE-140. However, the fact that ANG-(1–7), through MAS, is capable of producing strong actions in B2-deficient mice demonstrates that these actions of ANG-(1–7) are independent of B2 receptors (496).

The participation of the ANG II AT2 receptor in some of the ANG-(1–7) effects has also been suggested (79, 500, 572, 577). Part of the evidence for this has been derived from experiments using the putative AT2 antagonist PD123319 (572). The specificity of this compound has been challenged, however, because it can produce effects in AT2 knockout mice (113), and it can displace the binding of alamandine to human MrgD-transfected cells and the vas-

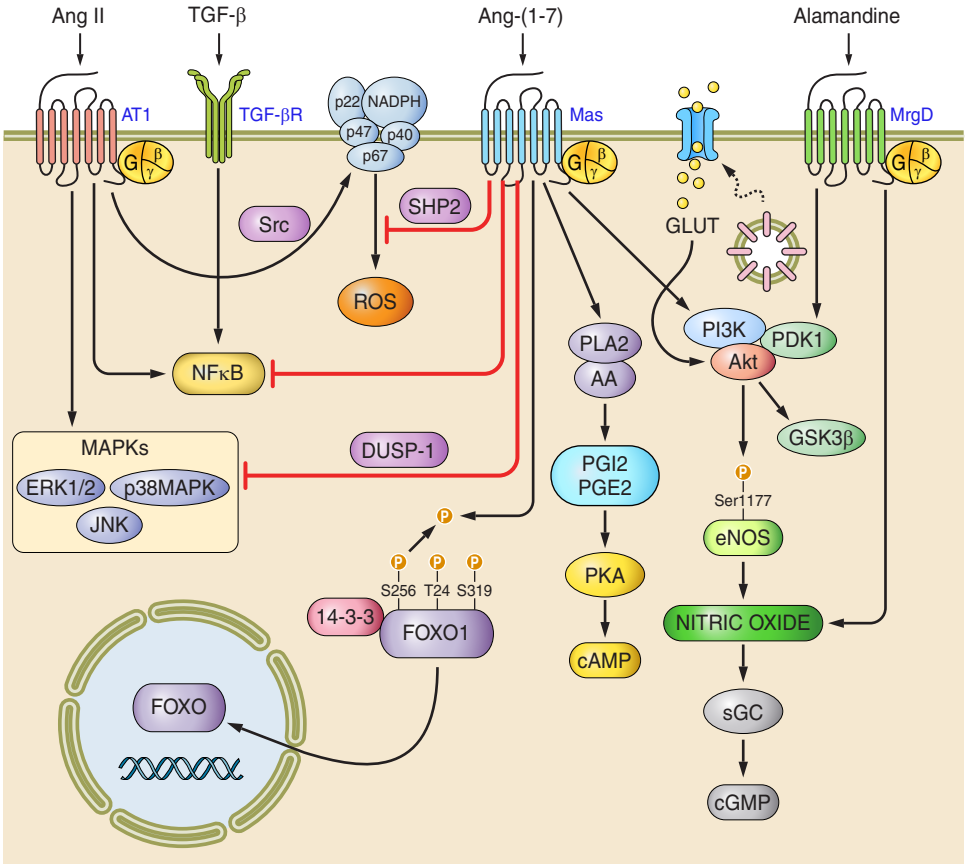


FIGURE 11. Intracellular signaling pathways induced by ANG-(1–7). ANG-(1–7) mediates, via AKT-dependent pathways, phosphorylation (Ser 1177) and activation of eNOS, stimulating nitric oxide (NO) production. ANG-(1–7)-mediated AKT activation is also involved in its metabolic actions, through GLUT phosphorylation and translocation to the membrane, enhancing glucose uptake. Although AKT is an important FOXO inactivator, ANG-(1–7) is able to dephosphorylate (Ser256) FOXO1, directly activating this transcription factor. ANG-(1–7) also counterregulates ANG II signaling, blunting phosphorylation of c-Src and the activation of NAD(P)H oxidase by ANG II, reducing reactive oxygen species (ROS) generation. This modulatory effect is mediated by phosphorylation of SHP-2, preventing ANG II-induced SHP-2 dephosphorylation and promoting interaction between SHP-2 and c-Src. Additionally, ANG-(1–7) inhibits MAPKs (ERK1/2, p38, JNK, and ERK5), central mediators in proliferation, fibrosis, and remodeling. Furthermore, ANG-(1–7) inhibits NF-κB, a key transcription factor in inflammation. The signaling pathways elicited by alamandine also involve NO release.

cular effects of alamandine. On the other hand, MAS appears to heterodimerize with AT2 (572). More reports include a ligand-induced heterodimerization of MAS with endothelin ETB receptors (255). Weak interactions of ANG-(1–7) with MrgD receptors have also been described (201). Finally, the heterodimerization of MAS with the AT1 receptor has been reported, and this inhibited the actions of ANG II. In this situation, MAS acts as a physiological antagonist of AT1 (284). These observations are in keeping with the well-known heterodimerization of other GPCRs (173).

VII. CONCLUDING REMARKS

Since the initial discovery of the RAS made by Tigerstedt and Bergmann by the end of the 19th century (540), studies by many laboratories have contributed to the establishment of this system as a key player in the physiology and pathophysiology of systems throughout the body. This review covers one of the most important recent chapters in the never-ending story of this system. The compelling evidence that the stimulation of the ACE2/ANG-(1–7)/MAS axis of the RAS may represent a powerful, novel therapeutic approach in the treatment of cardiometabolic diseases and other disorders has motivated many groups to evaluate the role of ANG-(1–7) in a range of conditions related to health. In this review we have attempted to highlight relevant aspects of the role of ANG-(1–7) in a broad range of physiological and pathophysiological contexts. Ongoing clinical trials based on ACE2- and ANG-(1–7)/MAS-related strategies may soon usher in a new chapter of the RAS saga.

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DISCLOSURES

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