The ANG-(1–7)/ACE2/mas axis in the regulation of nephron function

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Ferrario CM, Varagic J. The ANG-(1–7)/ACE2/mas axis in the regulation of nephron function. Am J Physiol Renal Physiol 298: F1297–F1305, 2010. First published April 7, 2010; doi:10.1152/ajprenal.00110.2010.—The study of experimental hypertension and the development of drugs with selective inhibitory effects on the enzymes and receptors constituting the components of the circulating and tissue renin-angiotensin systems have led to newer concepts of how this system participates in both physiology and pathology. Over the last decade, a renewed emphasis on understanding the role of angiotensin-(1–7) and angiotensin-converting enzyme 2 in the regulation of blood pressure and renal function has shed new light on the complexity of the mechanisms by which these components of the renin angiotensin system act in the heart and in the kidneys to exert a negative regulatory influence on angiotensin converting enzyme and angiotensin II. The vasodepressor axis composed of angiotensin-(1–7)/angiotensin-converting enzyme 2/mas receptor emerges as a site for therapeutic interventions within the renin-angiotensin system. This review summarizes the evolving knowledge of the counterregulatory arm of the renin-angiotensin system in the control of nephron function and renal disease.

FOR MORE THAN A CENTURY THE kidney has maintained a position of dominance as a primary suspect in the pathogenesis of arterial hypertension given its critical function in the regulation of body fluid volumes and its role in controlling arterial pressure through the regulation of fluid balance and as the predominant source for the synthesis and the secretion of renin. The demonstration by Goldblatt et al. (54) that the placement of a clamp at the level of the renal artery was associated with a blood pressure elevation that could persist for several months or even years became the definitive underpinning to the exploration of how the kidneys either cause or contribute to the pathogenesis of arterial hypertension. Sixty-eight years later, Cervenka et al. (24) would demonstrate the essentiality of intrarenal expression of receptors to angiotensin II (ANG II) in mediating the hypertensive response due to ischemia through their report that clipping of a renal artery failed to induce the development of two-kidney, one-clip hypertension in ANG II receptor knockout mice. Of the many regulatory mechanisms affecting nephron function, the influence of a kidney-borne renin-angiotensin system continues to gain acceptance (101, 102). Regulated independently from the circulating renin-angiotensin system, intrarenal formation of ANG II modulates solute and water transport across the renal tubules and the filtration of proteins through the glomerular barrier. In addition, ANG II trophic actions may contribute to renal pathology in part by increasing collagen deposition. On the opposite side of the story, Facsio (35), in the Andean city of Mendoza, Argentina, first articulated the concept that the kidneys possessed an antihypertensive action that could buffer the pressor actions mediated by the renin-dependent formation of ANG II in the circulation. While the pursuit of this concept by others met with relative success (97, 98), the recent characterization of the actions of angiotensin-(1–7) [ANG-(1–7)] and its further elaboration as a component of the now named angiotensin-converting enzyme 2 (ACE2)/ANG-(1–7)/mas axis (43), provides an alternate explanation as to how components within the intrarenal renin-angiotensin system function to counteract the hypertensive effects of ANG II in the long-term regulation of body fluids and arterial pressure. This review summarizes the evidence for the actions of the ANG-(1–7)/ACE2/mas axis in the regulation of renal function and its participation in renal disease.

The ANG-(1–7)/ACE2/mas Axis

General considerations. The heptapeptide ANG-(1–7), generated from either ANG I or ANG II, acts to oppose the vasoconstrictor, proliferative, and profibrotic actions of ANG II in the circulation, cardiac, vascular, and renal tissues (37, 43). ANG-(1–7) is generated from ANG I through the hydrolytic activity of the tissue endopeptidases nepriysin (neutral endopeptidase 24.11), prolyl-endopeptidase 24.26, and thimet oligopeptidase 24.15 (150). ACE2, acting as a monocarboxypeptidase to cleave the peptide bond between proline and a hydrophobic C-terminal residue (145), degrades ANG II into ANG-(1–7) (118, 135). ACE2 is found primarily in the luminal surface of the tubular epithelium (16, 134), a finding that contrasts with the more generalized distribution of ACE (148). The diversity of the enzymes contributing to ANG-(1–7) formation may be a function of tissue-specific localization and access to the corresponding substrates (either ANG I or ANG II) within either the

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extracellular or intracellular compartments. Therefore, the actions of ANG-(1–7) may be regulated in part through the control of when and where the dual substrates are expressed. Vascular endothelial cells having a rich content of both prolyl endopeptidase 24.26 and nephrin explain their predominant role for ANG-(1–7) formation from ANG I in the systemic and coronary vascular circulations while the abundant expression of nephrin in deep proximal renal tubules and brush border membranes (86, 125) catalyzes the formation of ANG-(1–7) from ANG I as well as its degradation into ANG-(1–4) (38). In experiments conducted in spontaneously hypertensive rat (SHR) urine, ANG-(1–7) hydrolysis into the inactive ANG-(1–4) fragment was suppressed in the presence of omapatrilat, a specific inhibitor of both ACE and nephrin (38).

ACE2 is an exopeptidase that catalyzes the conversion of ANG I to the nonapeptide ANG-(1–9) or the conversion of ANG II to the heptapeptide ANG-(1–7). Studies by Vickers et al. (145) and Rice et al. (118) demonstrated a primary role of ACE2 in converting ANG II into ANG-(1–7) with an efficacy >400-fold compared with the hydrolytic action of ACE2 in forming ANG-(1–9). ACE2 protein levels are significantly downregulated in the kidneys of hypertensive (28), diabetic (133), and pregnant rats (14, 16), suggesting a negative regulatory role of ACE2 in blood pressure control. In addition, ACE2 mutant mice develop late-onset glomerulonephritis resembling diabetic nephropathy (106).

The heptapeptide ANG-(1–7) binds to the mas receptor, a seven-transmembrane protein with domains containing sequences characteristic of G protein-coupled receptors (157). The mas receptor is expressed in renal cortical and proximal tubular cells and also afferent arterioles and the apical surface of the tubular epithelium (1, 130). In mutant mice lacking the mas receptor, the specific ANG-(1–7) binding to renal tissue was eliminated and this was associated with loss of the antidiuretic response to ANG-(1–7) after water loading as well as blunting of ANG-(1–7)-mediated vascular endothelial relaxation in aortic rings (124). We have confirmed that the mas receptor conveys the signaling actions of ANG-(1–7) in cardiac myocytes in culture (131) and further showed that ANG-(1–7) stimulates a MAPK phosphatase (48). The obtunding actions of ANG II as a negative regulator of ACE2 mRNA in neural and cardiac tissues suggests that ANG II has a direct effect on influencing the hydrolytic activity of ACE2 in ANG-(1–7) formation (47, 49). Although in our studies ANG-(1–7) showed no direct effect on the expression of ACE2 mRNA (48), the heptapeptide blocked the negative effect of ANG II in inhibiting cardiac ACE2 transcripts in cardiac myocytes and astrocytes in culture (47, 49).

**Effects of the ANG-(1–7)/ACE2/mas axis on renal hemodynamics.** As addressed by us elsewhere (37), the systemic vasodilator effects of ANG-(1–7) are not consistently observed in animals with intact baroreceptor reflexes or in conditions in which there is no activation of the renin-angiotensin system. In contrast, in rats made areflexic by spinal cord destruction (7), the SHR (8, 9), and canine renal hypertension (100), dose-dependent decreases in arterial pressure can be readily demonstrated. Similarly, a robust vasodilator response may be obtained in rat isolated blood vessels (103), piglet pial arteries (92), and rabbit afferent renal arterioles (117). The consistent demonstration of ANG-(1–7) vasodilator actions in isolated vessel preparations underscores the actions of ANG-(1–7) as a paracrine local regulator of vascular tone, as the concentrations of the ligand near its receptor site are always much higher than those found in the circulation. Because the importance of the prevailing level of renin-angiotensin system activity in unmasking the vasodilator actions of ANG-(1–7) has not been consistently recognized, it may account for a failure of others to uncover vasodilator properties of the peptide (141, 152).

Table 1 summarizes the hemodynamic and tubular actions of the ANG-(1–7)/ACE2/mas axis. ANG-(1–7)-mediated increases in renal blood flow are abolished by blockade of the mas receptor or inhibition of prostaglandin release and nitric oxide in SHR and Wistar-Kyoto (WKY) controls (31, 119, 120). As reviewed elsewhere, ANG-(1–7) growth-inhibitory properties (46) can be demonstrated in rat proximal tubular cells where the heptapeptide inhibits ANG II-stimulated phosphorylation of MAPK and transforming growth factor-β1 (130).

**ANG-(1–7) and tubuloglomerular balance.** In 1996 we first reported that “a constant intrarenal infusion of ANG-(1–7) at 0.1 and 1 nmol·min⁻¹·kg⁻¹ had minimal effects on renal blood flow and blood pressure and resulted in an elevated urinary excretion of Na and water compared with the time-control saline-infused group” (58). We further showed that ANG-(1–7) inhibition of the transport-dependent O₂ consumption was abolished by pretreatment with the Na⁺-K⁺-ATPase inhibitor ouabain in fresh suspensions of rat proximal tubules in a concentration-dependent fashion (58). These studies followed the report that the ANG-(1–7) increase in glomerular filtration rate was associated with a substantial natriuretic and diuretic response in isolated rat kidneys (30). The inhibitory effects of ANG-(1–7) on transcellular sodium transport is associated with activation of phospholipase A₂ (4), increased phosphatidylycholine (53), and release of cyclooxygenase products (27) (Table 1). Inhibition of Na⁺-K⁺-ATPase activity by ANG-(1–7) may be under dual regulation of both AT₁ and AT₂ receptors (29), although in the rat low ANG-(1–7) (10⁻¹² M) concentrations increase fluid reabsorption while the opposite is true at higher concentrations (10⁻⁸ M) (51). While natriuretic actions of ANG-(1–7) have been confirmed in experiments in which rats have been given ACE inhibitors (155) or ANG-(1–7) infusions (70, 121), the issue remains controversial since other studies in water-loaded animals demonstrated antiuretic actions of ANG-(1–7) that are blocked in the presence of the mas receptor antagonist [p-Ala³]-ANG-(1–7) (A-779) (123). As noted by Dilauro and Burns (32), differences in experimental designs, anesthesia, and site-specific effects along the nephron structures may account for reported variations of ANG-(1–7) effects on renal hemodynamics and salt and water excretion (Table 1).

In our opinion, additional factors need to be considered. Cross talk between the mas and AT₁ and AT₂ receptors provides alternate explanations since supraphysiological actions of ANG-(1–7) can be blocked by AT₁ receptor antagonists in Chinese hamster ovary cells transfected with AT₁ receptors (26). Moreover, Kostenis et al. (81) reported the occurrence of heterooligomerization between the mas and AT₁ receptors. Evidence that ANG-(1–7) may augment the vasodilator actions of bradykinin through binding to either AT₂ or mas receptors (13, 23, 36, 55, 88, 108, 122) is another indication of a complex regulation of the net signaling mechanisms determining the actions of ANG II and ANG-(1–7) at the receptor level. In this connection, the possibility we suggest is that ANG-(1–7) may...
Table 1. Summary of major actions of ANG-(1–7) in the nephron

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<th>Hemodynamic and Water Transport Actions</th>
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<td>Intrenaren infusion of ANG-(1–7) in normotensive rats reduces renal plasma flow and increases absolute and fractional sodium excretion without chages in glomerular filtration rate. Blockade of ANG-(1–7) receptors reverses these effects (19). Antiuretic effects of ANG-(1–7) are associated with increases in urinary Na⁺ concentration, urinary osmolality, and reduction in creatinine clearance. These effects are blocked by administration of A-779 or losartan (5). ANG-(1–7) stimulates substantial diuresis and natriuresis in the isolated rat kidney (30). Intrenaren infusions of ANG-(1–7) in the dog are followed by increases in water, sodium, and urea (but not potassium) excretion rates. This effect is not completely blocked by the AT₁ antagonists and not at all by the AT₂ receptor antagonist PD123319 (59). The aquaporin-1-mediated antiuretic effect of ANG-(1–7) in female virgin rats is reversed in the pregnant ones (62, 73). ANG-(1–7)-enhanced water transport in rat inner medullary collecting duct is abolished by both A-779 and a vasopressin V₂ receptor antagonist (90). The nonpeptide AVE 0991 is shown to mimic the effects of ANG-(1–7) binding on mas receptors while A-779 completely blocks the antiuretic effects of AVE 0991. In vitro receptor autoradiography in C57BL/6 mice showed that the specific binding of ¹²⁵I-ANG-(1–7) to mouse kidney slices was displaced by AVE while the nonpeptide AVE 0991 agonist displaced the binding of ¹²⁵I-ANG-(1–7) in mas-transfected monkey kidney cells and of rhodamine-ANG-(1–7) in mas-transfected Chinese hamster ovary cells (113).</td>
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<th>Actions on Electrolyte Transport Across Renal Tubules</th>
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<td>Regulation of kidney epithelial electrolyte transport by ANG-(1–7) may involve activation of PLA₂ (4). ANG-(1–7) selectively modulates the Na⁺-ATPase activity present in basolateral membranes of kidney proximal tubules through a losartan-sensitive receptor (22). Stimulatory effect of ANG II on the Na⁺-ATPase activity in proximal tubules is reversed, in a dose-dependent manner, by ANG-(1–7) through the mas receptor (82). Later studies from the same laboratory indicate that ANG-(1–7) stimulates Na⁺-ATPase activity through the AT₁R-G protein-PI-PLC-β-PKC pathway (83). Bradykinin counteracts the stimulatory effect of ANG-(1–7) on the proximal tubule Na⁺-ATPase activity (23). Basolateral membrane Na⁺-ATPase activity of inner cortex from pig kidney is comparably inhibited by both ANG II and ANG-(1–7) (29). At physiological levels ANG-(1–7) induces stimulation of bicarbonate transport in proximal straight renal tubules through an AT₁ receptor mechanism (51). In LLC-PK₁ cells, ANG-(1–7) inhibits high glucose stimulated p38 MAPK and increases Src homology 2-containing protein tyrosine phosphatase-1 in a dose-dependent fashion. Effects are blocked by the ANG-(1–7) antagonist A-779 (52). Enhanced phosphatidylincholine biosynthesis by ANG-(1–7) in the rat renal cortex is mediated by a non-AT₁/AT₂ receptor (53). The generation of ANG IV [ANG-(3–7)] (from the NH₂-terminal metabolism of ANG-(1–7) is implicated in eliciting a decrease in energy-dependent solute transport in proximal renal tubules (56). ANG-(1–7)-derived ANG IV binds with high affinity to AT₁ receptors in Madin-Darby bovine kidney (MDBK) epithelial cells (57). Infusion of ANG-(1–7) stimulates release of 6-keto-PGF₁α in both urine and perfusate of isolated rat kidneys. Concomitant treatment with indomethacin causes a robust decrease in ANG-(1–7)-mediated diuresis and natriuresis (62). ANG II-induced angiotensin-converting enzyme 2 downregulation in human kidney tubular cells is associated with ACE upregulation through activation of ERK1/2 or p38 MAPK (79). Immortalized mouse POD convert ANG I to ANG-(1–7) preferentially, and the conversion is blocked by a neprilysin inhibitor (142). Isolated rat glomeruli also generate ANG-(1–7) from ANG I (143). ANG-(1–7) inhibits ANG II-stimulated phosphorylation of MAPK in proximal tubular cells, while the peptide given alone has no effect (130). In inactin-anesthetized Munich-Wistar-Fromter rats, intratubular application of small doses of ANG-(1–7) has no effect on tubular reabsorption in proximal convoluted or distal tubule. Intratubular ANG-(1–7) at a concentration of 10⁻⁸ M increase reabsorption in Henle’s loop by an AT₁ receptor-mediated mechanism (139).</td>
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be acting as an endogenous allosteric modulator of either the AT₁ or AT₂ receptor. As reviewed by Christopoulos et al. (25, 91), allosteric modulators are defined as ligands that bind to a site on the receptor that is topographically distinct from the orthosteric binding site. Based on this consideration, ANG-(1–7) may act as an endogenous allosteric modulator of AT₁ or AT₂ receptors by changing their binding and functional responses. Contribution of ACE2 to nephron function. ACE2 within the kidneys colocalizes with ACE in proximal and distal tubules and in podocytes within the glomerulus (87, 133, 156). In mice, expression of ACE2 in the tunica media of renal arterioles contrasts with the expression of ACE in the vascular endothelium of these arterioles (129). As first shown by us in the heart (68) and the aorta (65, 66), administration of an ANG II receptor antagonist leads to an increase kidney arteriole ACE2 gene expression (129). In keeping with previous studies (28), renal expression of ACE2 was reduced by kidney disease and subtotal nephrectomy (78). Similar reductions in ACE2 activity were obtained in isolated glomeruli from streptozotocin-induced diabetic rats, and this was accompanied by increased content of glomerular angiotensinogen and ANG II (84). Neoexpression of ACE2 occurs in glomeruli and peritubular capillary endothelium of patients with primary and secondary renal disease, including transplanted kidneys (85). Interestingly, urinary ACE2 expression correlates with proteinuria in patients with diabetic nephropathy (147). Little is known about the expression of mas receptors in renal structures. However, a study by Velkoska et al. (144) reported increased cortical ACE binding and medullary mas receptor expression associated with reduced cortical and medullary ACE2 activity in the remnant kidney following subtotal nephrectomy. Measurements of ACE2 and ACE gene transcripts in renal biopsies obtained from type 2 diabetic patients provides insight into the opposing regulation of the enzymes involved in ANG II and ANG-(1–7) formation (116). In this study, the expression pattern of ACE2 and ACE mRNAs was measured by real-time PCR in laser microdissected renal biopsies from 13 diabetic and 8 control patients (116). A reduced expression of ACE2 mRNA was found in both the glomerular and proximal tubular compartments of diabetic subjects while the opposite was found for ACE mRNA (116). In agreement with these studies, the ANG II-mediated upregulation of ACE and downregulation of ACE2 in hypertensive nephropathy was shown to occur via activation of ERK1/2 and p38 MAPK (79).
The diverse nature of the structures composing the nephron, the functional unit of the kidney, provides a particular challenge in assessing the expression of renin-angiotensin system proteins and their effects. This is exemplified by the diverse well-characterized distribution of renin-angiotensin system components along the nephron by Navar and colleagues (75, 101, 102, 114, 115). Nevertheless, the current evidence suggests that the ACE2/ANG-(1–7)/mas axis is represented in the various components of the nephron, colocalizes with angiotensinogen, renin, ACE, ANG II, and AT1 receptors, and responds to stimuli and injury in a manner that agrees with a renoprotective role to buffer the actions of the ACE/ANG II/AT1 receptor axis. The demonstration of ACE2-dependent formation of ANG-(1–7) in sheep kidney, a species in which the organ closely resembles the human structure, provides further evidence for its role in the regulation of renal function (126). Importantly, our own studies first showed the presence of ANG-(1–7) in urine of both experimental animals (38, 40, 71, 76, 77, 109, 126, 155) and humans (41, 42, 89). In humans, ANG-(1–7) excretion exceeded those for ANG I and ANG II while in untreated essential hypertensive subjects the urinary content of ANG-(1–7) was markedly reduced compared with normal subjects (41, 42).

The ANG-(1–7)/ACE2/mas Axis in Human Disease

In advancing the proposal that ANG-(1–7) counteracts the vasoconstrictor, growth-promoting, and profibrotic actions of ANG II (39), there was an obvious need to investigate the role of this heptapeptide in contributing to diseases of the cardiovascular system. A first glimpse into this possibility was provided when the magnitude of the antihypertensive effects of ANG-(1–7) antagonist or an ACE2 inhibitor worsened the course of two-kidney, one-clip hypertension (20) are certainly in agreement with this possibility. As illustrated in Fig. 1, increased tissue expression of renin in mRen2.Lewis congenic hypertensive rats is associated with large decreases in renal ACE2 activity and ACE2 gene transcripts. In addition, the presence of a significant correlation between renal ACE2 activity and plasma ANG-(1–7) levels further documents the role of ACE2 in regulating the formation of ANG-(1–7) from ANG II. Protective effects of the ANG-(1–7)/ACE2/mas axis in renal disease (6, 21, 80, 85, 127, 128, 140, 144, 146, 147, 159) and experimental and human diabetic nephropathy (10, 11, 33, 95, 104, 116, 132, 133, 151, 153, 156, 158) have been demonstrated in several studies, and a therapeutic potential for recombinant ACE2 (rACE2) is derived by the recent finding that its administration in mice obtunds the pressor actions of ANG II while increasing plasma ANG-(1–7) levels (152). While several studies support a renoprotective role of the ANG-(1–7) axis in kidney disease (3, 6, 11, 17, 18, 20, 31, 45, 69, 80, 85, 96, 112, 128, 133, 144, 156, 159), Esteban et al. (34) found a proinflammatory effect of exogenously administered ANG-(1–7) in mas knockout mice. Their study contrasts with the recent finding by Zhang et al. (159), who showed that ANG-(1–7) administration reversed chemically induced glomerulonephritis in rats.

It should be stressed that additional findings in other disease states such as cirrhosis (2, 60, 61, 63, 64, 105, 107, 149, 154), systemic sclerosis (111), and even cancer (50, 93, 110) further underscore the possible participation of the ANG-(1–7)/ACE2/mas axis as a compensatory mechanism in these disorders. Novel exploratory research on the role of the ANG-(1–7)/ACE2/mas axis in pregnancy (12, 14–16, 138) and the developmen...
opment of eclampsia (94) is another indication of how the intrinsic regulatory mechanisms within the renin-angiotensin system govern homeostasis.

**Novel ANG I-Forming Peptides**

A brief review of renin-angiotensin system components within the kidney is amplified by the discovery of an alternate precursor for the formation of ANG II and ANG-(1–7) through the characterization of proangiotensin 12 by Nagata and collaborators (99). Proangiotensin 12 [ANG-(1–12)] is an upstream precursor to ANG I first isolated from the rat small intestine (99). ANG-(1–12) constricted aortic strips and, when infused intravenously, raised blood pressure in rats. The vasoconstrictor response to ANG-(1–12) was abolished by either captopril or the ANG II type I receptor blocker CV-11974 (99). From our laboratory has confirmed the existence of ANG-(1–12) in cardiac and renal tissues of WKY and SHR and further demonstrated increased cardiac content of ANG-(1–12) in the heart of SHR (72).

To date it has been generally accepted that angiotensinogen is the only known functional substrate for the generation of ANG peptides by renin. Because the level of angiotensinogen in humans and other species is close to the Km value for renin, changes in angiotensinogen levels have been shown to influence directly the activity of the renin-angiotensin system (101, 102). In the rat, the sequence of the dodecapeptide ANG-(1–12) is Asp1-Arg2-Val3-Tyr4-Ile5-His6-Pro7-Phe8-His9-Leu10-Leu11-Tyr12. Since renin specifically cleaves the Leu10-Leu11 bond of rat angiotensinogen to form ANG I, the cleavage between the two aromatic residues Tyr12-Tyr13 for the liberation of ANG-(1–12) may not be accounted for by the action of renin. We have confirmed this idea in several models of experimental hypertension in which cardiac metabolism of ANG-(1–12) into ANG II and ANG-(1–7) occurred through a non-renin-dependent pathway (137). In addition, content of ANG-(1–12) was increased in the heart of WKY rats in which renin was absent from the circulation and the heart 48 h postnephrectomy (44). The discovery of ANG-(1–12) and the studies conducted to date (67) suggest an alternate answer of how tissues process the primary precursor that gives rise to the tissue formation of ANG II and ANG-(1–7), independently from the circulation. While additional work is clearly necessary, the data reviewed here clearly suggest that the regulation of renin-angiotensin system influence in blood pressure control and tissue function is tissue selective and embodies multiple mechanisms for expression of the biologically active peptides.

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 Review

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