Interactions Between Angiotensin-(1-7), Kinins, and Angiotensin II in Kidney and Blood Vessels

Robson Augusto Souza dos Santos, Kátia Tomagnini Passaglio, João Bosco Pesquero, Michael Bader, Ana Cristina Simões e Silva

Abstract—The heptapeptide angiotensin (Ang)-(1-7) is currently considered one of the biologically active end products of the renin-angiotensin system. The formation of Ang-(1-7) by pathways independent of Ang II generation, the selectivity of its actions, and its peculiar property of exhibiting effects that are partially opposite of those of the parent compound, Ang II, confer a unique biochemical and functional profile to this peptide. In this article, we will review novel aspects of the biological actions of Ang-(1-7), dealing with its interaction with Ang II and kinins, especially in the kidney and blood vessels. **(*Hypertension*. 2001;38[part 2]:660-664.)**

Key Words: bradykinin ■ renin-angiotensin system ■ receptors, angiotensin

The heptapeptide angiotensin (Ang)-(1-7) is formed from Ang I and Ang II by tissue peptidases, including neutral endopeptidase (neprilysin), thimet oligopeptidase, prolyl-carboxypeptidase, and prolyl-endopeptidase.[1] In addition, the possibility should be considered that at least in the kidney and heart, Ang-(1-7) could be formed from Ang I or Ang II by a pathway involving the ACE-related enzyme ACE2[2,3] (Figure 1). Once formed, Ang-(1-7) is rapidly hydrolyzed, especially by ACE.[4] Therefore, in the presence of ACE inhibition, the levels of Ang-(1-7), which circulates in blood at concentrations close to those of Ang II, raises several-fold,[5] probably owing to both the increase in Ang I concentration and the decrease in Ang-(1-7) breakdown. The related observation that Ang-(1-7) can increase following long-term administration of angiotensin type 1 (AT_1) receptor blockers[1] raises the possibility that Ang-(1-7) contributes to the pharmacological effects of both ACE inhibitors and AT_1 receptor antagonists.

Interactions between Ang-(1-7) and Kinins in Blood Vessels

Most of the interactions between Ang-(1-7) and bradykinin (BK) have been reported to occur in blood vessels.[1,6–11] There are 2 major types of interaction: potentiation of BK by Ang-(1-7) and mediation of the vascular actions of Ang-(1-7) by kinins, although the latter does not exclude the former. Potentiation of BK by Ang-(1-7) has been observed in conscious normotensive and hypertensive rats in terms of the BK hypotensive effect in the whole animal[1,6] or the vasodilating action of BK in rat mesenteric microvessels in situ.[1,7] Brosnihan and colleagues[8,9] have shown that preincubation of isolated dog coronary arteries with Ang-(1-7) increased the relaxation produced by BK. Similarly, Almeida et al[10] have shown that Ang-(1-7) at 2 nmol/L concentration increased the vasodilation produced by BK in isolated rat hearts. Interestingly, the venoconstriction produced by BK in rabbit endothelium denuded femoral vein was also potentiated by Ang-(1-7),[11] indicating that the BK potentiating activity of Ang-(1-7) is not an exclusively endothelium-dependent phenomenon. Potentiation of bradykinin by Ang-(1-7) has also been described in other preparations. In Chinese hamster ovary cells co-transfected with the human cDNA for BK-B_2 receptors and ACE, Deddish et al[12] described a potentiating effect of Ang-(1-7) on the arachidonic acid release induced by BK. Bomtempo et al[13] observed that intracerebroventricular infusion of a combination of subeffective doses of BK and Ang-(1-7) increased baroreflex sensitivity. Furthermore intracerebroventricular infusion of the BK-B_2 receptor antagonist HOE 140 produced a marked attenuation of the facilitatory effect of Ang-(1-7) on baroreflex sensitivity. The mechanism of the BK potentiating activity of Ang-(1-7) is complex. It appears to involve receptor-mediated facilitation of NO release[9,10,14] and/or prostaglandins,[6,7,10] endothelium-derived hyperpolarizing factor,[7] binding to ACE facilitating the cross-talk between ACE and BK-B_2 receptors,[12] and ACE inhibition.[4,9] The relative contribution of each of these mechanisms appears to change from vascular bed to vascular bed, with species and probably with vessel diameter.[1]

Evidence that Ang-(1-7) actions can be kinin mediated has been obtained with several preparations.[8,9,13–15] In all studies aiming at clarifying the contribution of kinins to the action of

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From the Laboratório de Hipertensão, Instituto de Ciências Biológicas (R.A.S.d.S., K.T.P.) and Departamento de Pediatria, Fac. Medicina (C.S.S.), Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Departamento de Biofísica, Universidade Federal de São Paulo (J.B.P.), 04023-062, São Paulo, São Paulo; and Max-Delbrück-Center for Molecular Medicine (M.B.), Berlin-Buch, Germany.

Correspondence to Robson A.S. Santos, Departamento de Fisiologia e Biofísica, Av. Antonio Carlos, 6627-ICB-UFMG, 31270-901-Belo Horizonte, MG, Brazil. E-mail marrob@dedalus.lcc.ufmg.br

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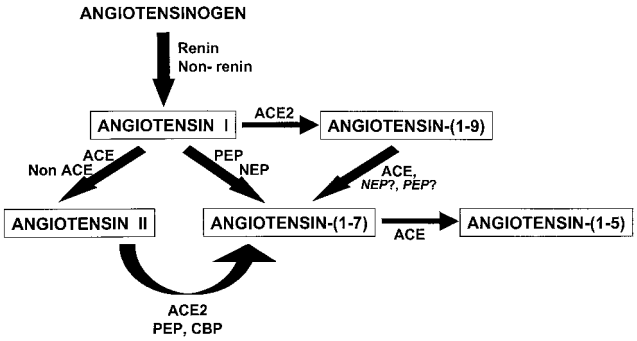

Figure 1. Simplified illustration of the proteolytic pathways for the formation of biologically active angiotensin peptides. ACE indicates angiotension-converting enzyme; ACE 2, ACE-related carboxypeptidase[2,3]; PEP, prolylendopeptidase; NEP, neutral endopeptidase; and CBP, carboxypeptidase.

Ang-(1-7), the BK-B_2 antagonist HOE 140 was used. This approach does not rule out the possibility that Ang-(1-7) could be acting by potentiating endogenous kinins or by a cross-talk mechanism dependent on unoccupied BK-B_2 receptors. Only a preliminary report is available concerning a possible direct effect of Ang-(1-7) on kinin release.[16] Particularly interesting, however, is the recent finding reported by Tsutsumi et al[17] about the kinin-releasing effect of AT_2 receptor activation, involving intracellular acidification which in turn activates kininogenases. Whether a similar mechanism is involved in some of the Ang-(1-7) actions remains to be elucidated.

The possible importance of the interaction of Ang-(1-7) with BK has been recently underscored. Fernandes et al[7] observed that in an in situ preparation of rat mesenteric microvessels, the Ang-(1-7) selective antagonist, the D-Ala[7]-Ang-(1-7) (A-779) analogue,[18] completely reversed the potentiation of the BK effect produced by acute or chronic treatment with the ACE inhibitor enalapril. In untreated rats, no effect of A-779 on the vasodilator activity of BK was observed. These observations open the intriguing possibility that Ang-(1-7) can play an important role in the mechanisms leading to potentiation of BK by ACE inhibitors at the arteriolar level. More important, these findings suggest that Ang-(1-7) may be importantly involved in the cardiovascular effects of ACE inhibitors, in which increased levels/actions of bradykinin may be implicated.[19]

Interactions Between Angiotensins and Kinins in the Kidney

As demonstrated for the renin-angiotensin (RAS), all the components of the kallikrein-kinin system (KKS) are expressed within the kidney, exerting a paracrine influence on local nephron function.[20,21] Furthermore, it is well known that renal KKS can produce local concentrations of BK much higher than those present in blood.[21] The major effects of the renal KKS, diuresis and natriuresis, involves BK-B_2 receptors and are caused by an increase in renal blood flow and by inhibition of sodium and water reabsorption in the distal nephron.[21,22] Indeed, this system is believed to play a pivotal role in the regulation of fluid and electrolyte balance, mostly through its renal actions.[22]

The interactions between the RAS and KKS at the renal level are only starting to be appreciated. An evidence for a possible interaction between the 2 systems is the simultaneous presence of KKS and RAS components and receptors along the nephron.[21,22]

Transgenic animals with various alterations of the KKS and RAS have been recently produced.[17,21,23,24] This approach has substantially increased the understanding of the physiological role of these peptidergic systems and the interaction between them.[23] Using AT_1 receptor–deficient mice, Tsuchida et al[24] showed that the BK-B_2 receptor system has a potent antihypertrophic effect on the renal vasculature in vivo. On the other hand, a number of studies have suggested that AT_2 receptors may interact with the KKS.[17,21,25] Siragy et al[25] postulated that Ang II tonically stimulates renal kinin peptide production by an AT_2 receptor–dependent mechanism. However, studies performed by Campbell and coworkers[21] do not support the hypothesis that the AT_2 receptor regulates kinin peptide production. Their results point to a role of the AT_1 receptor mechanism in the stimulation of kinin peptide production by Ang II, because losartan reduced kidney levels of BK and its metabolism.[21] These discrepancies may be caused by methodological limitations in the measurement of kinins.[21]

In our laboratory, we recently studied the interactions between Ang-(1-7) and BK in the kidney by examining the renal effects of Ang-(1-7) in transgenic rats harboring the human tissue kallikrein gene (TGR [hKLK1])[26] These animals present a significant increase in the bradykinin concentration in the kidney.[27] As shown in Figure 2, administration of a low dose of Ang-(1-7) to Sprague-Dawley rats submitted to acute volume expansion produced a significant attenuation of the increase in the diuresis and natriuresis produced by this maneuver. A striking difference in the response to Ang-(1-7) was observed in transgenic rats. In these animals, Ang-(1-7) produced an increase of the diuresis and natriuresis evoked by acute extracellular volume expansion. These results suggest that, more than mediating some of the Ang-(1-7) effects, kinins can act by modifying the actions of Ang-(1-7), at least in the kidney. Alternatively, TGR (hKLK1) could present low renal levels of Ang-(1-7), and this putative imbalance was corrected by the exogenous administration of the heptapeptide. The interaction of Ang-(1-7) with kinins appears not to be limited to BK. We have recently shown that in isolated perfused rat kidneys Ang-(1-7) potentiated the effect of the B_1 receptor agonist Des-Arg[9]-BK.[28]

Interactions of Ang-(1-7) With Ang II in the Kidney

The renal effects of the RAS are very complex, involving interactions between multiple mediators and angiotensin receptors.[29–31] As observed for KKS, the kidney is also an important source of RAS mediators. Regarding angiotensin receptors, AT_1 receptors are present in the whole kidney, mostly in cortical sites, and AT_2 receptors are present in glomeruli and distal tubules.[31] Moreover, there is evidence for the existence of other angiotensin receptors, which specifically mediate some of the renal effects of Ang-(1-7) and Ang IV.[1,29,30]

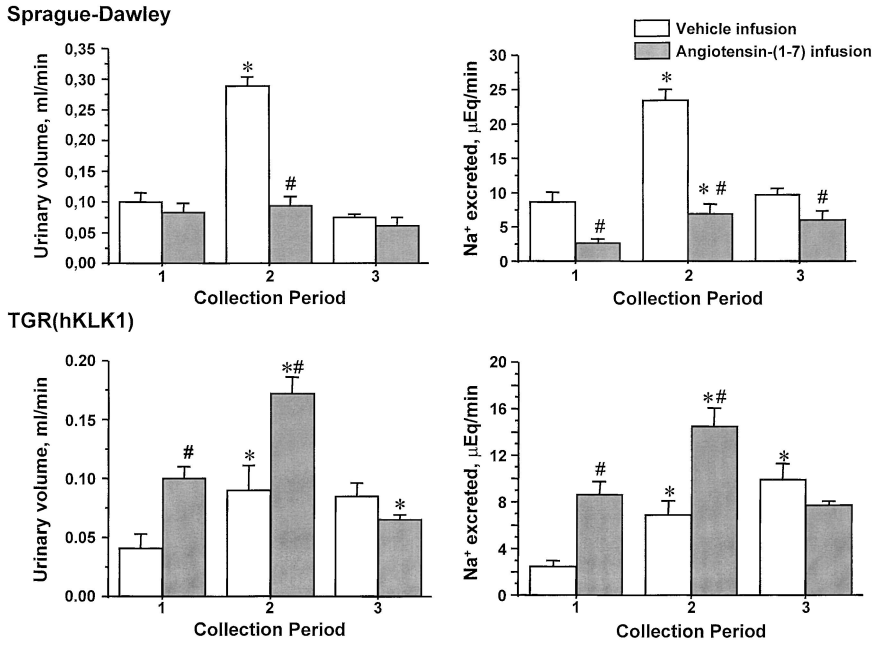

Figure 2. Effect of Ang-(1-7) on the renal response to acute volume expansion in TGR (hKLK1) and Sprague-Dawley rats. Arterial (femoral and carotid) and venous (jugular vein) catheters were implanted into TGR (hKLK1) (n=5) and Sprague-Dawley rats (n=6). Twenty-four hours after cannulation, the rats received an injection of 0.9% NaCl (3 mL/100g IV) followed by a continuous infusion of 0.9% NaCl (15 $\mu L \cdot 100\ g^{-1} \cdot min^{-1}$) into the descending aorta through the carotid catheter. Ang-(1-7) (30 $ng \cdot 100\ g^{-1} \cdot 15\ \mu L^{-1} \cdot min^{-1}$) or vehicle (0.9% NaCl, 15 μL/min) was continuously infused through the carotid artery catheter. After a control period (1) of 30 minutes, a volume expansion (2) was performed by intravenous injection of 0.9% NaCl (2 mL/100 g over 1 minute). After 30 minutes (3), an additional urine sample was collected (recovery). Data are expressed as mean±SEM. *$P<0.05$ vs control period (ANOVA for repeated measures). #$P<0.05$ vs vehicle-treated rats (unpaired t test).

The interactions between Ang-(1-7) and Ang II at the renal level are poorly understood. As suggested for vascular actions, it has been proposed that Ang-(1-7) could be a physiological antagonist of Ang II at the renal level.[30] So, Ang-(1-7) may produce natriuresis and diuresis, opposing the water and sodium retention produced by Ang II.[30] Several studies, mostly in vitro, substantiate this hypothesis (see Santos et al[1] and Chappell et al[30]). On the other hand, other reports also pointed out for a major role of this angiotensin in water transport.[32–35]

Despite the existence of considerable evidence for a specific renal receptor for Ang-(1-7), some of the actions of this heptapeptide are completely blocked by AT_1 receptor antagonists. For instance, the biphasic effect of Ang-(1-7) on straight proximal tubules[36] and the antidiuresis produced in water-loaded rats[35] are completely blocked by losartan. Recently, Caruso-Neves et al[37] found that Ang-(1-7) stimulated Na^+-ATPase activity in pig kidney proximal tubules, and this effect was abolished by losartan but not by A-779 or the AT_2 receptor antagonist PD 123,319. This stimulatory action of Ang-(1-7) was similar to the effect of Ang II alone. However, when the 2 angiotensin peptides were both present, Na^+-ATPase activity was restored to control values, suggesting that Ang-(1-7) modulates Na^+-ATPase activity through a losartan-sensitive receptor that is probably different from the receptor involved in the Ang II effect.[37] These findings raised at least 2 possibilities: (1) Ang-(1-7) may act through AT_1 receptors, or more likely, (2) losartan can block a subtype of Ang-(1-7) receptor, an AT_1-like receptor.[1] The first explanation is unlikely because Ang-(1-7) does not exert most of the actions of Ang II mediated through AT_1 receptors such as vasoconstriction[1] and Ang-(1-7) binds poorly to AT_1 receptors.[38] In keeping with the second possibility is the fact that losartan cannot be regarded as a highly specific ligand for Ang II AT_1 receptors because it can bind to other sites.[39] In addition to the data suggesting that the tubular actions of Ang-(1-7) are mediated at least in part by an AT_1-like receptor, other studies have pointed out that this receptor seems to be also present in the glomerulus.[40] These findings suggest that AT_1-like receptors, sensitive to both Ang-(1-7) and losartan, may play a role in the renal effects of Ang-(1-7) and possibly of Ang II.

Contrasting with the data obtained for mammals, Santos et al[32] reported that the stimulatory effect of Ang-(1-7) on water transport in the frog skin was not blocked by A-779 or losartan but was completely abolished by PD 123,319. On the other hand, the effect of Ang II was blocked by losartan. Thus, in this preparation, the effect of Ang-(1-7) on water transport can be completely dissociated from AT_1 receptors and appears to involve an atypical AT_2-like receptor.

It was recently suggested that some of the actions of Ang-(1-7) in the kidney might depend on the interaction of the peptide with AT_4 receptors through metabolism to Ang-(3-7).[29] Actually, according to these studies, Ang-(3-7) appears to be the more important endogenous ligand for the putative AT_4 receptors, because both Ang-(1-7) and Ang-(3–8) can be converted to it.[29] Handa[29] found that Ang-(3-7) produced a concentration-dependent inhibition of nystatin-stimulated proximal tubule O_2 consumption, interpreted as a reduced basolateral Na^+,K^+-ATPase activity. This effect was abolished by AT_4-receptor blockade. In contrast, Caruso-Neves et al[37] showed that in pig kidney proximal tubules, Ang-(1-7) did not change Na^+,K^+-ATPase activity. In this preparation, Ang-(1-7) selectively modulates Na^+-ATPase activity through a losartan-sensitive receptor.[37] Further studies are clearly needed to fully understand the physiological role of the interaction between Ang-(1-7) and renal angiotensin receptors.

Interactions of Ang-(1-7) With Ang II in Blood Vessels

The first evidence for an interaction between Ang-(1-7) and Ang II has been provided by Bovy et al[41] who described

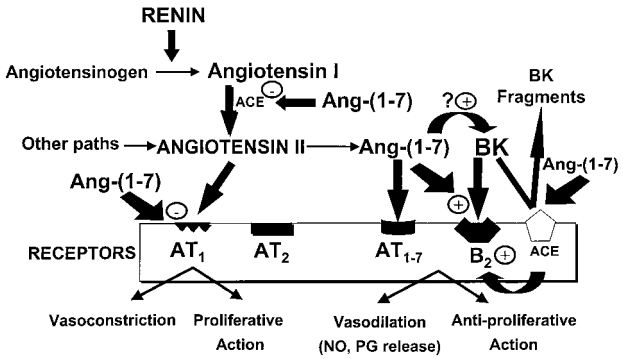

Figure 3. Putative mechanisms of the counter regulatory role of Ang-(1-7) within the RAS. − indicates inhibition; and +, stimulation.

inhibition of the contractile effect of Ang II in the rabbit aorta by the Ang-(1-7) analogue Sar[1]-Ang-(1-7). Further studies have confirmed the ability of Ang-(1-7) to antagonize the vascular effects of Ang II.[42–44]

Of special interest are the recent descriptions of antagonism by Ang-(1-7) of the vascular actions of Ang II in human isolated blood vessels[44] and in the forearm vascular bed.[43] Most of the evidence points to a direct interaction of Ang-(1-7) with AT_1 receptors in conveying this antagonistic action.[42,44] Indeed, when used at high concentrations, Ang-(1-7) can produce Ang II-like effects.[15,45] These actions can be explained by low affinity binding of Ang-(1-7) to AT_1 receptors.[38] Alternatively, Ang-(1-7), binding to its specific receptors and/or to AT_1 receptors, can interfere with extracellular Ca^{2+} influx into smooth muscle cells, as recently proposed for mesangial cells.[46]

Although Ang-(1-7) has been described as a peptide capable of releasing prostaglandins[47] and NO,[9,14] these mechanisms are less likely to contribute to its attenuating effect on the Ang II actions.[42–44] This reasoning is mostly based on the absence of an Ang-(1-7) effect on the vasoconstrictor action of α-adrenergic drugs in vitro[42] or in the human forearm.[43] Release of NO and/or prostaglandins would be expected to nonspecifically reduce vasoconstriction.

In addition to a direct or indirect interaction with AT_1 and perhaps AT_2 receptors,[1,14] Ang-(1-7) appears to be able to influence the synthesis of Ang II receptors at the mRNA level. A short-term infusion of Ang-(1-7) increased mRNA levels for AT_1 and AT_2 receptors in the kidney of ovine fetuses.[48] Similarly, Ang-(1-7) produced up-regulation of the AT_1 mRNA in cultured vascular smooth muscle cells from rat strains (spontaneously hypertensive rats [SHR] and Wistar-Kyoto) from the University of Akron but not from cells in Charles River SHR and Wistar-Kyoto rats, suggesting a strain-specific effect.[49]

Figure 3 illustrates the putative mechanisms for the counter regulatory role of Ang-(1-7) within the RAS. Ang-(1-7) can act at several levels, counterbalancing the expected vascular (and perhaps renal and cardiac) effects consequent to Ang I formation. Acting as an ACE inhibitor, Ang-(1-7) can decrease Ang II formation. In addition, as described above, Ang-(1-7) can antagonize the vasoconstrictor effect of Ang II by acting as a competitive antagonist for AT_1 receptors or by a cross-talk mechanism. Finally, Ang-(1-7) can counterbalance the effects of Ang II through its BK potentiating activity and through its kinin-mediated and/or receptor-mediated actions. The biological significance and the therapeutic potential of these Ang-(1-7) actions are strikingly appealing.

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Robson Augusto Souza dos Santos, Kátia Tomagnini Passaglio, João Bosco Pesquero, Michael Bader and Ana Cristina Simões e Silva

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