Hypertension
Volume 30, Issue 3, September 1997, Pages 535-541
https://doi.org/10.1161/01.HYP.30.3.535

ARTICLE

Counterregulatory Actions of Angiotensin-(1-7)

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ABSTRACT: *Abstract* Angiotensin (Ang)-(1-7) is a bioactive component of the renin-angiotensin system that is formed endogenously from either Ang I or Ang II. The first actions described for Ang-(1-7) indicated that the peptide mimicked some of the effects of Ang II, including the release of prostanoids and vasopressin. However, Ang-(1-7) is devoid of vasoconstrictor, central pressor, or thirst-stimulating actions. In fact, new findings reveal depressor, vasodilator, and antihypertensive actions that may be more apparent in hypertensive animals or humans. Thus, the accumulating evidence suggests that Ang-(1-7) may oppose the actions of Ang II either directly or by stimulation of prostaglandins and nitric oxide. These observations are significant because they may explain the effective antihypertensive action of converting enzyme inhibitors in a variety of non–renin-dependent models of experimental and genetic hypertension as well as most forms of human hypertension. In this context, studies in humans and animals showed that the antihypertensive action of converting enzyme inhibitors correlated with increases in plasma levels of Ang-(1-7). In this review, we summarize our knowledge of the mechanisms accounting for the counterregulatory actions of Ang-(1-7) and elaborate on the emerging concept that Ang-(1-7) functions as an antihypertensive peptide within the cascade of the renin-angiotensin system.

Key Words: angiotensin II ■ angiotensin receptors ■ blood pressure ■ hypertension, essential ■ rats, inbred SHR

It is well recognized that the renin-angiotensin system has an important role in cardiovascular physiology, fluid homeostasis, and cell function. Angiotensin (Ang) II has long been considered the main biologically active product of an endocrine system that contributes significantly to the pathogenesis of arterial hypertension, renal dysfunction, and congestive heart failure. Attesting to the importance of this function is the impressive clinical therapeutic benefits achieved by angiotensin-converting enzyme (ACE) inhibitors and a new class of Ang II receptor antagonists.[1] However, newer studies have revived the possibility that other peptide fragments of Ang I may either contribute to or actually oppose the pressor and proliferative actions of Ang II, endowing this hormonal system with greater capability for

the regulation of tissue perfusion. Earlier studies demonstrated selective actions of the heptapeptide Ang III [Ang-(2-8)] in the secretion of aldosterone;[2] more recent studies by Harding (Swanson et al[3]) suggest that a smaller carboxyl product of Ang II, Ang IV [Ang-(3-8)], is biologically active by virtue of recognizing a binding site that is not competed for by selective AT_1 or AT_2 Ang II receptor antagonists.

The characterization of Ang-(1-7)[4 5 6 7] as the first amino-terminal angiotensin peptide product possessing biological actions provided a foundation for the pursuit of a new concept regarding the regulation of cardiovascular function by the renin-angiotensin system. While prostacyclin, bradykinin, and nitric oxide (NO) act as vasodilator hormones limiting the pressor and proliferative actions of Ang II, it had not been considered that products of Ang I could also function to counterbalance the actions of Ang II. This review updates the progress that has been made in the development of this concept since its introduction in 1993[7 8] and also outlines the areas where further work will be necessary to attain a mechanistic understanding of how the opposing activities of Ang II and Ang-(1-7) contribute to the long-term regulation of blood pressure.

PRINCIPLES OF ANG-(1-7) FORMATION AND FUNCTION

Synthesis of Ang-(1-7)

Ang I is the ultimate precursor of both Ang II and Ang-(1-7). This readily indicates a common source for the generation of the two active and functionally opposing peptides. While ACE cleaves Ang II from Ang I, processing of Ang I into Ang-(1-7) requires the participation of tissue-specific endopeptidases found in the plasma membranes of neuroepithelial (prolyl-endopeptidase [EC 3.4.24.26]), epithelial (neprilysin [EC 3.4.24.11]), vascular endothelial (prolyl-endopeptidase and neprilysin), and smooth muscle cells (metalloendopeptidase [EC 3.4.24.15]).[9 10 11] The processing pathways in these various tissues have been reviewed recently.[10 11 12 13] The diversity of the enzymatic pathways by which Ang-(1-7) is cleaved from Ang I suggests that the production of the heptapeptide may be regulated at the tissue level, an interpretation which favors the possibility that Ang-(1-7) functions as a true paracrine hormone.

Little is known yet about the factors that determine the rate of conversion of Ang I into Ang II and Ang-(1-7). We know that any condition that augments plasma or tissue levels of Ang I is associated with increased formation of Ang-(1-7). In several experimental conditions, Ang-(1-7) is the primary peptide produced from Ang I.[9 14 15 16] These findings suggest that production of Ang-(1-7) may limit the amount of substrate that is available for the generation of Ang II. This theoretical possibility provides a glimpse into the mechanisms that may determine the balance of the opposing actions of Ang II and Ang-(1-7) in the control of cardiovascular and body fluid functions (see below). In keeping with this interpretation, studies in humans and animals[17 18 19 20 21 22] showed that increased concentrations of Ang I after inhibition of ACE are associated with increases in the

concentration of Ang-(1-7). While Ang I is a primary substrate for the formation of Ang-(1-7), the heptapeptide may be formed from Ang II by the cleavage of the Pro^7-Phe^8 bond by prolyl-endopeptidase[14] [23] and a postproline carboxypeptidase.[24] The physiological significance of this alternate pathway has not been characterized yet; conceivably, it provides an additional route for the inactivation of Ang II.

Fig 1 provides a schematic diagram of the active pathways involved in the production of Ang-(1-7) from both Ang I and Ang II. With a more complete understanding of the biochemical routes for the processing of Ang I, it becomes apparent that the potential involvement of the endopeptidase pathways in the pathogenesis of hypertension may be a fruitful area of inquiry. One of the Ang-(1-7)–forming enzymes, neprilysin, converts the atrial natriuretic peptide and bradykinin into inactive fragments.[25] Potential interactions of these enzymes with the various substrates have not been investigated yet, nor have studies been undertaken to assess whether polymorphisms in the genes encoding these enzymes might be linked to disorders of cardiovascular function.

Physiological Actions of Ang-(1-7)

The first studies of Ang-(1-7) revealed that the peptide stimulates the activity of hypothalamic-neurohypophysial neurons regulating vasopressin release with a potency equal to Ang II.[4] Subsequently, we found that Ang-(1-7) releases prostaglandins from astrocytes, VSMCs, and endothelial cells in culture.[26] [27] [28] [29] Prostaglandin release in human astrocytes and porcine smooth muscle cells was mediated by AT_2 receptors, whereas a non-AT_1, non-AT_2 receptor accounted for these actions in rat C6 glioma and porcine endothelial cells. Furthermore, Ang-(1-7) elicits prostaglandin production through calcium-independent mechanisms in cells in culture and in the vasculature.[30] Ang-(1-7) also causes a depressor effect when injected into the circulation of the pithed rat, and this action is blocked completely by indomethacin but only partially by an AT_1 receptor blocker.[31] The peptide induces relaxation of porcine and canine coronary artery,[32] [33] piglet arterioles,[34] and the feline mesenteric bed, possibly via release of NO through a non-AT_1, non-AT_2 angiotensin receptor.[35] Unlike Ang II, Ang-(1-7) does not elicit vasoconstriction, aldosterone release, or stimulation of thirst and salt appetite, nor does it produce a pressor response after intraventricular administration in normotensive rats. Indeed, Ang-(1-7) facilitates the baroreflex and displays depressor effects in sites within the dorsal medulla.[5] [36] These effects in the dorsal medulla are blocked by a selective antagonist to Ang-(1-7), [d-Ala^7]-Ang-(1-7).[37] Thus, increasing evidence supports the concept that Ang-(1-7) opposes the actions of Ang II and may do so through a novel receptor.

Actions That Oppose the Effects of Ang II Are Enhanced in Models of Hypertension

Ang-(1-7), similar to losartan and ACE inhibitors, counteracts the actions of Ang II.[7] Ang-(1-7) may contribute to the antihypertensive effects produced by ACE inhibitors, since

circulating levels of Ang-(1-7) increase 25-fold to 50-fold during ACE inhibition[19 21 22] and Ang-(1-7) alone can produce antihypertensive effects in hypertensive animals.[38] In the spontaneously hypertensive rat (SHR), chronic infusion of Ang-(1-7) produces significant increases in urinary excretion of prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$ accompanied by diuresis, natriuresis, and a decrease in blood pressure.[38] Systemic administration of Ang-(1-7) attenuates the vasoconstrictor actions of phenylephrine and Ang II in hypertensive but not normotensive rats,[39] in contrast with the potentiation of α-adrenoceptor-mediated pressor responses by Ang II. Moreover, intravenous infusions of Ang-(1-7) reverse the inhibitory effects of Ang II on the reflex control of heart rate in both SHR and Wistar-Kyoto rats[39] and improve the impaired slope of the reflex control of heart rate in SHR after either peripheral or central administration.[36 39]

A recent study in a genetic model of hypertension that is associated with heightened activity of the brain angiotensin system clearly demonstrated the opposing actions of Ang-(1-7).[40] In this important research, we evaluated the hemodynamic effects of delivering either a specific, affinity-purified Ang-(1-7) antibody or an Ang II monoclonal antibody (KAA8) into the brain of conscious homozygous mRen2(27) renin transgenic [Tg(+)] rats (Fig 2). Cerebroventricular administration of the affinity-purified Ang-(1-7) antibody in conscious Tg(+) hypertensive rats caused significant dose-related elevations in blood pressure and heart rate.[40] The hypertensive response was augmented in transgenic rats studied 7 to 10 days after cessation of lisinopril therapy. In contrast, all doses of the Ang II antibody produced hypotension and bradycardia. The magnitude of the depressor response was significantly augmented in transgenic rats weaned off lisinopril therapy. Central administration of either the Ang-(1-7) or Ang II antibodies had no effect on normotensive Sprague-Dawley rats. These data demonstrate that Ang-(1-7) opposes the action of Ang II on the central mechanisms that contribute to the maintenance of this model of hypertension. In addition, these studies showed an important contribution of the brain renin-angiotensin system to the maintenance of this form of monogenetic hypertension.

There is also evidence that Ang-(1-7) can act as an antagonist to the actions of Ang II in the vasculature.[41] Therefore, mechanisms other than activation of prostaglandins and NO may play a role in mediating the depressor effects of Ang-(1-7). It is not currently possible to determine the exact contribution of prostaglandins versus other mechanisms to the effects produced by Ang-(1-7) in the SHR or Tg(+) hypertensive rats from these initial studies. In addition, the mediators stimulated by Ang-(1-7) may differ, depending on the vascular bed and species studied. In recent studies we showed that the Ang-(1-7)–induced prostacyclin release from aortic VSMCs of Tg(+) rats was greater than that from VSMCs isolated from Sprague-Dawley control rats.[42] Similarly, in the renovascular hypertensive dog, the depressor component of the response to systemic Ang-(1-7) is exaggerated.[43] Thus, the degree of activation of these depressor systems is influenced by the state of activation of the renin-angiotensin system.

Evidence for Ang-(1-7) Vasodilator Actions in Canine Coronary Vessels and Interactions With Kinins

Ang-(1-7) relaxes canine or porcine coronary artery rings,[32] [33] as well as isolated feline mesenteric beds.[35] This effect is blocked in both canine and porcine rings by removal of the endothelium or pretreatment with an NO synthase inhibitor. Moreover, the vasorelaxant activity of Ang-(1-7) is markedly attenuated by the bradykinin B_2 receptor antagonist Hoe 140 and does not appear to be associated with the synthesis and release of prostaglandins.[33] Assessment of the angiotensin receptor subtypes mediating the responses to Ang-(1-7) revealed that these effects are not inhibited by subtype-selective AT_1 or AT_2 receptor antagonists but are markedly attenuated by prior exposure to the competitive nonselective Ang II peptide receptor antagonist [Sar^1, Thr^8]-Ang II. These results suggest that Ang-(1-7) has a direct effect on the endothelium, through the release of NO and kinins, mediated by an angiotensin receptor pharmacologically distinct from AT_1 and AT_2 receptor subtypes. Furthermore, Ang II and Ang-(1-7) at equivalent concentration ranges produced diametrically opposite changes in the contractile state of coronary artery rings (Fig 3).

Additionally, Ang-(1-7) potentiated synergistically bradykinin-induced vasodilation. These actions of Ang-(1-7) may contribute to the cardioprotective effects of chronic ACE inhibition. Ang-(1-7)'s potentiating effect on the response to bradykinin was first described by Paula et al,[44] who showed that low concentrations of Ang-(1-7) given intravenously augmented by 2-fold to 10-fold the vasodepressor response elicited by bradykinin. In isolated canine coronary arteries, Ang-(1-7) has a synergistic, concentration-dependent action on bradykinin-induced vasodilation that is dependent on the release of NO but not prostaglandins.[45] The response is specific for Ang-(1-7), since neither acetylcholine, sodium nitroprusside, nor prostaglandins were able to augment the bradykinin-induced relaxation.[45] This synergistic effect of Ang-(1-7) is not mediated by a known angiotensin receptor, since the effect persists in the presence of AT_1, AT_2, and [Sar^1, Thr^8]-Ang II receptor antagonists. In fact, in contrast to a receptor-mediated effect of Ang-(1-7),[33] the peptide may augment vasodilation in coronary arteries by acting as a local modulator of ACE activity. Li et al[45] found that Ang-(1-7) significantly inhibits the degradation of ^{125}I-[Tyr^0]-bradykinin and the appearance of the bradykinin-(1-7) and bradykinin-(1-5) metabolites in coronary vascular rings while it also inhibits purified canine ACE activity with an IC_{50} of 0.65 μmol/L. These findings indicate that Ang-(1-7) may inhibit ACE activity to elevate bradykinin levels as one mechanism of promoting vasodepressor actions.

Antiproliferative Actions of Ang-(1-7) in VSMCs

In previous studies in porcine and rat VSMCs, Ang II activates phospholipase C and D and releases prostaglandins, whereas Ang-(1-7) releases only prostaglandins.[29] [30] [46] [47] The activation of phospholipase C by Ang II in VSMCs is known to stimulate growth. Because prostaglandins inhibit vascular growth, we speculated that Ang-(1-7) might also prevent the

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