Circulating and Tissue Angiotensin Systems

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Angiotensin has many different actions, most of which relate, either directly or indirectly, to the regulation of blood pressure, fluid, and electrolyte homeostasis (1, 2). In addition to potent vasoconstrictor effects, actions of angiotensin on vasculature include the stimulation of prostaglandin release (3), the modulation of angiotensin receptor number (4), and the stimulation of angiogenesis (5). Angiotensin also has important actions on the central and peripheral nervous systems, the adrenal, kidney, intestine, and heart (6–11). Given these multiple diverse actions of angiotensin, two important questions are (*a*) which of these actions represent normal physiological events, and (*b*) whether such actions may assume a pathogenic role. These questions have recently been placed in sharper focus by the clinical application of inhibitors of the renin–angiotensin system (RAS),[1] and in particular, the use of converting enzyme inhibitors (CEIs) for the treatment of hypertension. Any attempt to answer these questions requires an accurate concept of the RAS. The purpose of this review is to discuss new concepts concerning angiotensin production by the circulating RAS, how these relate to angiotensin production within tissues, and the possible mechanisms by which CEIs lower blood pressure. The study of tissue angiotensin systems is still at an early stage. In this review I have attempted to synthesize a coherent model of the interaction between the circulating and tissue angiotensin systems, which might assist in the interpretation of new developments in this area.

Circulating RAS

At the present time, the prevailing view holds that the circulating RAS is primarily an endocrine system designed for the general mediation, through the systemic circulation, of the effects of renin on angiotensin production in plasma (12, 13). This concept can be summarized as follows: renin released by the kidney circulates in plasma, where it cleaves angiotensinogen to generate angiotensin I (AI). On passage through the pulmonary vasculature AI is converted to angiotensin II (AII), which is conveyed by arterial blood to the peripheral tissues, where it exerts its effects by interaction with specific AII receptors.

Recent evidence suggests that this classic concept of the circulating RAS requires revision (14, 15). Given the extensive conversion of AI to AII and clearance of both peptides across peripheral tissues, both AI and AII are present in venous blood in amounts far too high to be explained by their generation in blood alone. Rather, the evidence suggests that the major site of production of AI and AII is peripheral tissues (reviewed in reference 15). According to this revised concept, the primary function of the circulating RAS is not the systemic delivery of AII to tissues, but rather the delivery of renin and angiotensinogen to tissues; most AI and AII is generated locally within tissues by the action of plasma-derived renin on plasma-derived angiotensinogen and the action of tissue converting enzyme. Thus, this revised concept predicts that plasma levels of angiotensin largely represent a spillover from the tissue sites of production (15). That plasma angiotensins predominantly result from the action of kidney-derived renin on plasma (liver-derived) angiotensinogen is shown by the fall in plasma angiotensin levels that follows nephrectomy (16–19), and by the hypotensive effect of anti–angiotensinogen antibodies when injected into either sodium-replete or sodium-deplete rats (20). Given this local production of AI and AII by the circulating RAS, it is apparent that such local production may be subject to tissue-specific mechanisms of regulation, which cause changes in local AII concentration that are not reflected in the plasma concentrations of renin or AII. Such tissue-specific mechanisms may include the extent of tissue uptake of renin and angiotensinogen, and the local tissue concentration of converting enzyme.

Tissue angiotensin systems

An increasing number of studies suggest the existence of local angiotensin generating systems which operate, in whole or in part, independently of the circulating RAS. These have been described for brain (21–25), kidney (26–31), adrenal (32–34), testis (35), and arterial wall (36, 37). Angiotensinogen is the only known precursor of the angiotensin peptides; thus, definitive evidence for an independent tissue angiotensin system requires demonstration of local synthesis of angiotensinogen. Recently, angiotensinogen messenger RNA (mRNA) has been detected in 12 different extrahepatic tissues of the rat: kidney, brain, spinal cord, aorta, mesentery, adrenal, atria, lung, stomach, large intestine, spleen, and ovary (38, 39). Renin mRNA has also been detected in several extrarenal tissues: adrenal, heart, testes, and submaxillary gland (40–42). These data for extrarenal renin mRNA were obtained from studies of mice with two renin genes. These two renin genes have different patterns of tissue-specific expression, and for many tissues (adrenal, heart, testes) it is not known to which gene the renin mRNA corresponds; whether these data apply to man and other species with one renin gene remains to be determined.

The detection of mRNAs for angiotensinogen and renin in a tissue is strong evidence for their local synthesis in vivo. Evi-

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1. *Abbreviations used in this paper:* AI and AII, angiotensins I and II; CEI, converting enzyme inhibitor; RAS, renin–angiotensin system.

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dence for local renin production is also provided by studies demonstrating renin synthesis in vitro by chorionic cells (43, 44) and by vascular tissue (45, 46). However, given that the reninlike activity of aortic tissue falls to very low levels after nephrectomy (47, 48), local synthesis would appear to make little contribution to vascular reninlike activity in vivo. In contrast to the obligatory role for angiotensinogen as angiotensin precursor, many different enzymes are able to cleave angiotensinogen to release AI or AII. In addition to renin, enzymes that release AI include cathepsin D (49, 50), pepsin (51), and other aspartyl proteases (52–54) and reninlike enzymes (55–58). Enzymes that cleave angiotensinogen to release AII directly include tonin (59), cathepsin G (60), trypsin (61), and kallikrein (62). Thus, there would not appear to be an obligatory role for renin in local tissue angiotensin systems. Moreover, enzymes other than converting enzyme may convert AI to AII (59, 63, 64).

In man, as much as 90% of circulating renin is inactive (65), and this inactive renin has a plasma half-life approximately twice that of active renin (66). This inactive renin represents prorenin that was not completely processed by cleavage of the prosegment before secretion (67–69). Although the kidney is an important site of synthesis of inactive renin (66), the presence of nearly normal plasma levels of inactive renin in nephrectomized subjects (65, 66) emphasizes that extrarenal synthesis of renin is at least equal to, if not greater than, renal synthesis. At the present time, the kidney is the only known source of circulating active renin in normal man, although certain malignant tumors of nonrenal origin have been reported to secrete active renin (70). Whereas it is possible that local activation of circulating inactive renin may play a role in tissue angiotensin systems, definitive evidence for such a role is lacking.

Integration of circulating and tissue angiotensin systems

Fig. 1 describes how the circulating RAS and locally synthesized components may integrate in the generation of angiotensin. The generation of angiotensin within a tissue may be either intracellular or extracellular. Intracellular generation of angiotensin may result from cleavage of either locally synthesized angiotensinogen or angiotensinogen taken up by the cell; the enzyme responsible for cleavage may be either a cellular enzyme or an enzyme taken up by the cell. Angiotensinogen or enzyme taken up by a cell may be plasma derived, or may have been secreted into the interstitial space by neighboring cells. Plasma-derived and locally synthesized angiotensinogen may coexist in the interstitial space, where they may be cleaved by either plasma-derived renin, or locally synthesized renin or reninlike enzyme, to produce angiotensin.

For the brain, immunohistochemical studies (71) suggest that angiotensin is primarily produced within neurones from neuronally synthesized angiotensinogen. Studies of angiotensin-like immunoreactive neurones of the intestine (72) suggest a similar intracellular mechanism for local angiotensin production. However, these immunohistochemical studies need to be interpreted with caution because intracellular angiotensin-like immunoreactivity may represent any of several possible mechanisms: (*a*) Intracellular production of angiotensin from angiotensinogen synthesized within the same cell; (*b*) Intracellular production of angiotensin from angiotensinogen taken up by the cell; or (*c*) Angiotensin taken up by the cell. For the kidney, angiotensin-like immunoreactivity has been shown to coexist with reninlike immunoreactivity in juxtaglomerular cells (27, 28), and isolated renin granules have been reported to contain AI and AII (31). However, these renin granules may have been contaminated during isolation with angiotensinogen granules (30), which have been identified in cells of the proximal tubule (73). Immunohistochemical studies have not supported the proposal that juxtaglomerular cells synthesize angiotensinogen (29, 73), and studies of colchicine-treated rats suggest that angiotensinogen in cells of the proximal tubule is not locally synthesized but represents angiotensinogen reabsorbed from the glomerular ultrafiltrate (73). Given that immunohistochemical studies have yet to show co-localization of angiotensin and angiotensinogen,

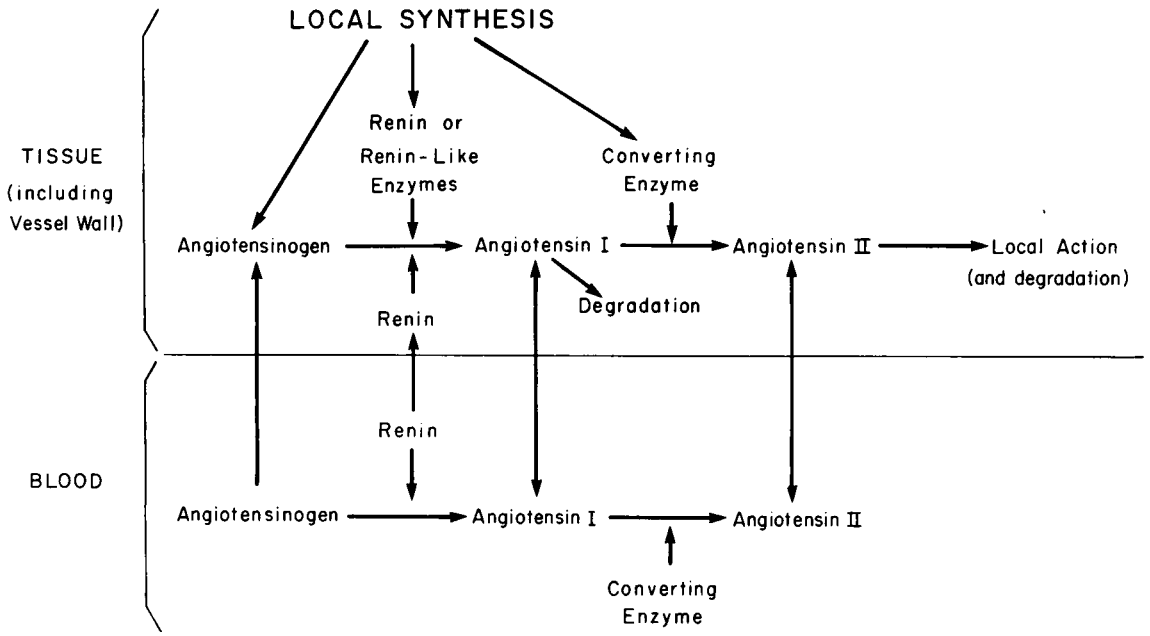

Figure 1. Proposed relationship of circulating RAS and local tissue angiotensin system in the generation of angiotensin within tissues.

the identification of intracellular angiotensin-like immunoreactivity cannot be considered strong evidence for cellular synthesis of angiotensinogen. For extrahepatic tissues that contain angiotensinogen mRNA, those cells that contain the mRNA, and therefore synthesize angiotensinogen, remain to be identified.

Given that locally produced angiotensin may be derived from the interaction of plasma-derived renin and angiotensinogen, and/or the interaction of locally synthesized components, an important question is the relative contribution of these two systems to local angiotensin production. For those areas of the brain and spinal cord within the blood–brain barrier, locally synthesized components are probably the major source of angiotensin. However, for other tissues, this question remains unanswered. Inasmuch as local production is the major source of plasma angiotensin, circulating renin and angiotensinogen are the major determinants of local production overall. This is shown by the response of plasma angiotensin to nephrectomy and the hypotensive effects of anti-angiotensinogen antibodies, cited above. However, the presence of reninlike activity and immunoreactive AI and AII in the plasma of anephric subjects (16, 18, 19, 66, 74–76), and the hypotensive response to the CEI, captopril, by a sodium-depleted anephric subject (77), suggest that renin or reninlike enzymes synthesized in extrarenal tissues may, in addition to local angiotensin production, also contribute to the generation of plasma angiotensin.

Estimates of angiotensinogen mRNA abundance in liver and other tissues (38, 39) suggest that extrahepatic synthesis of angiotensinogen is unlikely to make a significant contribution to circulating levels of angiotensinogen. However, synthesis of angiotensinogen by a tissue may cause a significant increase in the angiotensinogen concentration of interstitial fluid of that tissue. The concentration of angiotensinogen in interstitial fluid is similar to that of plasma (78), and approximates its Michaelis constant (K_m) for renin. Thus, any local increase in interstitial angiotensinogen concentration due to local synthesis would produce a parallel increase in local interstitial angiotensin concentration, given a constant amount of renin (or other appropriate enzyme) in the interstitial space. The secretion of angiotensin by cells that both synthesize and cleave angiotensinogen would produce a direct increase in the angiotensin concentration of interstitial fluid.

It is apparent, from what I have reviewed, that local angiotensin systems may assume a functional significance without a parallel change in the circulating RAS. Yet why have both the circulating RAS and independent tissue angiotensin systems evolved? The circulating RAS, in particular renin secretion by the kidney, provides an extremely rapid and efficient homeostatic response to acute changes in blood pressure and fluid and electrolyte status. In contrast, tissue angiotensin systems may provide a more tonic, and specifically local, influence in those tissues where they exist, for example the regulation of vascular tone, or renal, cardiac, adrenal, or intestinal function. I have previously reviewed evidence for the functional, and possibly pathogenic, significance of the local generation of angiotensin within vasculature (15). More recent studies (79, 80) support this concept.

Angiotensin, blood pressure, and CEIs

The RAS plays a significant role in the regulation of normal blood pressure, and blood pressure becomes increasingly dependent upon the RAS during dietary sodium restriction and sodium deficiency. This role of the RAS has been demonstrated using many different approaches, including the administration of angiotensin antagonists, and inhibitors of renin and converting enzyme. Moreover, the primary pathogenic role of renin in high-renin hypertension due to renin-secreting tumors and unilateral renal artery stenosis is established. However, the role of the RAS in essential hypertension is much less certain. The increasing interest in the role of angiotensin in essential hypertension has resulted from the development of increasingly specific inhibitors of the RAS, and their therapeutic efficacy in the treatment of essential hypertension. CEIs are effective antihypertensive agents in patients with essential hypertension who have normal or low levels of plasma renin (81), and this raises the question of whether the hypotensive effects of CEIs may be due, in part, to the inhibition of local tissue angiotensin production. However, the mechanisms by which CEIs exert their hypotensive effects are not clearly understood.

There has been considerable debate as to whether the hypotensive effects of CEIs necessarily reflect a reduction in AII formation. Since angiotensin converting enzyme is responsible, in part, for the inactivation of the potent vasodilator, bradykinin, it has been proposed that part of the hypotensive effect of CEIs may result from the accumulation of bradykinin (82). Moreover, some studies have suggested a role for vasodilator prostaglandins in the hypotensive response (83). However, several studies have found no increase in plasma bradykinin levels in response to the orally active CEIs captopril and enalapril (84–86), although there is some question as to the accuracy of the methods used to measure plasma bradykinin levels (87). Enalapril does not increase plasma prostaglandin E_2 metabolite levels (86).

Both the kallikrein–kinin and the prostaglandin systems are best regarded as local tissue endocrine (paracrine) systems, somewhat analogous to the model of the RAS presented here (Fig. 1). Indeed, CEIs do appear to modify kinin production at the local tissue level, as shown by the increase in urinary kinin excretion and also by the down-regulation of uterine bradykinin receptors during captopril administration, accompanied by normal levels of circulating bradykinin (88–90). The increase in renal kinin production may mediate the increase in renal production of prostaglandins that accompanies both captopril and enalapril administration (91–93).

The relative contribution of prostaglandins in mediating the effects of CEIs may be dependent upon the sodium status, and thus the degree of activation of the RAS. The hypotensive effects of captopril in normal subjects on a high sodium diet, or in rats with deoxycorticosterone acetate/salt hypertension, can be blocked with inhibitors of prostaglandin production (94, 95). In contrast, inhibitors of prostaglandin production do not modify the hypotensive effects of captopril in subjects on a low sodium diet, or in spontaneously hypertensive rats (94, 96).

Administration of CEIs does inhibit AII formation, and plasma AII falls to undetectable levels (97). Many studies have shown less marked falls in plasma AII (83–86, 98), but these results probably reflect methodological problems, including cross-reactivity by the elevated plasma levels of AI (99), and also a significant assay blank (98). The hypotensive effects of acute inhibition of AII production may be due to inhibition of any of several AII-dependent pressor mechanisms. These include the direct vasoconstrictor effects of AII, the facilitation of adrenergic transmission by AII (100), and the effects of AII on central sympathetic (101) and angiotensin (100) systems. Moreover, AII may potentiate the response of vasculature to other vasoconstrictors. When administered to normal subjects, captopril attenuated the pressor responses to norepinephrine and

pitressin infusions, and potentiated the baroreflex-mediated slowing of heart rate, effects that were abolished by concomitant infusion of a subpressor amount of AII (102). Thus, part of the hypotensive effect of CEIs may be mediated by inhibition of the actions of AII on sympathetic nervous system activity (102, 103). At present, the relative importance of these mechanisms is unknown. The hypotensive effects of chronic inhibition of angiotensin production may also be due to inhibition of the effects of AII on aldosterone secretion, and fluid and electrolyte transport in the intestine and kidney, in addition to inhibition of vasopressin secretion (104) and inhibition of the "slow pressor" effect of AII (105).

Attempts to directly demonstrate a nonangiotensin mechanism for the hypotensive actions of CEIs have met with mixed success. Textor et al. (106) observed no effect of captopril on the blood pressure of rats chronically infused with AII. Studies comparing the hypotensive responses to saralasin (an AII antagonist) and captopril have shown a greater response to captopril, and also an additional effect of captopril when given to saralasin-pretreated rats, thus suggesting a nonangiotensin mechanism for the effects of captopril (107, 108). However, interpretation of these studies is complicated by the partial agonist activity of saralasin. Subsequent studies comparing renin inhibitors with CEIs (109, 110) have, with one exception (111), not shown any discrepancy, and these data have been considered to indicate that the hypotensive response to CEIs is primarily mediated through inhibition of AII formation. These studies were performed in sodium-deplete subjects, however, and whether these results apply to sodium-replete subjects will require further investigation.

Given the complexity of AII-dependent mechanisms, it is not yet possible to fully interpret the effects of CEIs in hypertension. Evidence that the hypotensive actions of renin inhibitors and CEIs may be due, at least in part, to inhibition of local tissue angiotensin systems is reviewed elsewhere (15, 100). While the effects of CEIs on the function of a particular tissue may represent a reduction in local AII levels, they may also be indirect, resulting from the interruption of other, possibly multiple, AII-dependent processes, such as a decrease in sympathetic nerve activity; moreover, CEI effects independent of the RAS may also contribute.

Concluding comments

Accumulating evidence indicates that the major site of angiotensin production is not in blood but in tissues, and results from the action of plasma-derived renin on plasma-derived angiotensinogen, together with the interaction of locally synthesized components. Both the production of angiotensin in tissues and the regulation of its production may be, to a greater or lesser extent, independent of the circulating RAS. This new concept of the RAS indicates a need to revise previous concepts concerning the role of angiotensin in hypertension. The development of these concepts has been greatly accelerated by the availability of more specific inhibitors of AII production and their therapeutic effectiveness in hypertension.

Our increasing knowledge of the RAS has revealed it to be much more complex than previously thought. One immediate challenge is to obtain a clearer insight into the mechanisms and regulation of angiotensin production in vivo, in individual tissues, and within the multiple compartments of each tissue, including the brain. The application of hybridization in situ to monitor cellular levels of mRNA for renin and angiotensinogen will assist in this endeavor. However, there is also a need for the development of methodology able to measure the concentration of AII at the local receptor level, if the functional and pathogenic significance of local tissue angiotensin systems is to be established.

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