

# Mechanisms of Disease: local renin–angiotensin–aldosterone systems and the pathogenesis and treatment of cardiovascular disease

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## SUMMARY

Accumulating evidence has made it clear that not only does the renin–angiotensin–aldosterone system (RAAS) exist in the circulation where it is driven by renal renin, but it is also active in many tissues—and likely within cells as well. These systems might not be completely independent of each other, but rather interact. These local RAASs affect tissue and cellular angiotensin II concentrations and appear to be associated with clinically relevant physiologic and pathophysiologic actions in the cardiovascular system and elsewhere. Evidence in support of this possibility is reviewed here. In addition, direct (pro)renin action after binding to its specific receptor, the existence of renin transcripts, which apparently encode an intracellular renin, the discovery of an angiotensin-converting-enzyme homologue (ACE2), which leads to enhanced generation of angiotensin-(1–7) and the newly appreciated role of angiotensin-receptor dimerization in the regulation of angiotensin activity, all point to the conclusion that the RAASs are complexly regulated, multifunctional systems with important roles both within and outside the cardiovascular system.

**KEYWORDS** aldosterone, angiotensin, cardiovascular disease, intracrine, renin

## REVIEW CRITERIA

Relevant manuscripts were identified by searching MEDLINE, using the terms “renin”, “angiotensin”, “aldosterone” and “renin angiotensin aldosterone system” and by searching the reference lists of identified papers. They were all English-language papers published in the past 5 years.

## INTRODUCTION

The RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM (RAAS) is well established as an important regulator of blood pressure and intravascular volume (Figure 1).<sup>1</sup> The use of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) to interrupt this system has become an important element in the clinical armamentarium for hypertension. Over the years, however, the results of many clinical trials have suggested that the interruption of the RAAS could provide benefits not associated with blood-pressure lowering alone. For example, ACE inhibitor interruption of angiotensin-II generation is associated with a reduction in proteinuria and a slowing of renal-function decline in patients with type 1 diabetes. Blockade of angiotensin action with ARBs is associated with similar effects in type 2 diabetes. ACE inhibition provides survival benefits in patients with pre-existing vascular or coronary disease. In patients suffering from congestive heart failure, ACE inhibitors and ARBs similarly improve clinical status and decrease mortality.<sup>1–6</sup>

Beneficial effects of these agents on the progressive ventricular enlargement that can occur following myocardial infarction have also been demonstrated. Clinical benefit has also been shown when aldosterone-receptor blockers have been added to the therapeutic regimen of patients with congestive heart failure. Also, studies in humans have demonstrated that interrupting or blocking the RAAS can lead to reversal of cardiac fibrosis and the reduction of cardiac myocyte apoptosis in hypertensive left-ventricular hypertrophy, as well as reversal of hypertensive vascular remodeling. These benefits of RAAS interruption appear additive to, or independent of, lowering of blood pressure and are observed in cardiovascular conditions that are associated with both activation and suppression of the circulating RAAS.<sup>2–5</sup> This finding then lends support to the contention that local and even cellular RAASs play a role in cardiovascular physiology and pathophysiology.<sup>1–6</sup>

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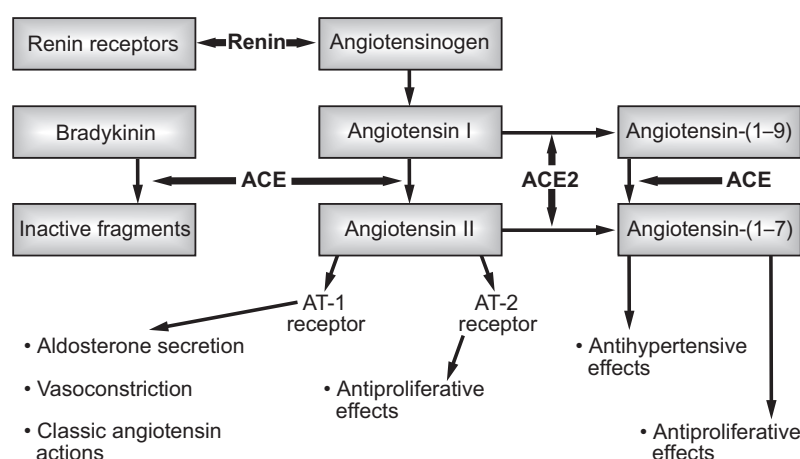
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## LOCAL RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEMS

By the late 1960s, enzymatic renin-like activity had been detected in vessels, brain and other noncardiovascular tissues, although the possibility remained that some or all of this activity could be the result of angiotensinogen cleavage by nonrenin proteases. The application of molecular biological techniques as northern blotting and amplification by reverse-transcriptase PCR only partly resolved the controversy surrounding extrarenal renin. Only some investigators detected (pro)RENIN expression in injured vessels, uninjured vessels or both, and in infarcted or normal hearts or both. More agreement surrounded the validity of (pro)renin expression in adrenal, uterus, endothelium, salivary gland and brain. In the case of the cardiovascular system, it was clear that components of the renin-angiotensin system could be taken up by tissues and that kidney-derived renin could drive the generation of angiotensin I in vessel walls. Thus, the contribution of any locally synthesized renin would be expected to be felt in the immediate locale of the synthesizing cell where relatively small increases in renin could be physiologically relevant.<sup>6,7</sup>

Several discoveries have further complicated this picture. A (pro)renin receptor has been described on mesangial cells and vascular myocytes. Binding of (pro)renin to this receptor is associated with: activation of the enzyme, leading to enhanced generation of angiotensin II in the vicinity of angiotensin-II receptors on the external cell membrane; generation of a second messenger leading to intracellular signaling; and biological effects.<sup>8,9</sup> Thus, (pro)renin must be considered a hormone in its own right. Glycosylated (pro)renin is also taken up by the insulin-like growth factor II or mannose receptor and is activated within cardiomyocytes. However, no physiologic effect of this uptake has been described and, therefore, the receptor is currently assumed to be a clearance receptor.<sup>10</sup> Finally, the existence of another cardiac renin receptor is inferred from studies of transgenic rats overexpressing nonglycosylated renin. The cardiomyocytes of these animals internalize the expressed renin and generate angiotensin II within their cytoplasm, leading to the development of myocardial pathology.<sup>11</sup> Thus the existence of functional cellular renin receptors further complicates any interpretation of the role of locally synthesized (pro)renin.



**Figure 1** The renin-angiotensin cascade. Renin cleaves the decapeptide angiotensin I from angiotensinogen; (pro)renin can also bind to specific cellular receptors. Angiotensin I is converted to angiotensin II by ACE, or to angiotensin-(1-7) by the sequential actions of the ACE homologue ACE2 and probably ACE. ACE2 also generates angiotensin-(1-7) from angiotensin II. In the postnatal state, angiotensin II binds to the AT-1 receptor to produce classical angiotensin actions, and to the AT-2 receptor to produce antiproliferative effects. Physiologically relevant AT-1/AT-2 HETERODIMERIZATION can also occur, as can heterodimerization involving AT-1 and the bradykinin B(2) receptor.

An alternative renin transcript is also synthesized in brain, adrenal, heart and other tissues.<sup>12-14</sup> This so-called renin exon 1-A lacks the sequences encoding the secretory signal, and thus the protein product of this transcript is expected to be retained in the intracellular space of the cell that synthesized it. Moreover, the product is expected to be synthesized in an active as opposed to a PRORENIN form. There is evidence to indicate that adrenal expression of this renin isoform supports aldosterone synthesis in the anephric rat.<sup>15</sup> In addition, upregulation of renin exon 1-A has been reported in the left ventricle following experimental myocardial infarction; if confirmed, this observation could have implications for the design of therapeutic strategies for preventing the sequelae of infarction.<sup>14</sup>

Thus, the physiologic role of (pro)renin expression and its participation in regulating tissue or intracellular angiotensin-II concentrations is unclear. On the other hand, the expression in cardiovascular tissues of other RAAS components, such as angiotensinogen, ACE and angiotensin receptors, is more consistently detected.<sup>6,7,16</sup> Because elevations in local concentration of angiotensinogen, and possibly of ACE, alter the rate of angiotensin-II production by renin, regulation of these components probably plays an important role in

## GLOSSARY

### RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

An enzyme-driven (i.e. renin-driven) cascade in the circulation that regulates blood pressure, intravascular volume etc.

### HETERODIMERIZATION

The binding of two different molecular moieties to form one, often functional, unit

### (PRO)RENIN

Refers to characteristics of prorenin or renin

### PRORENIN

Protein product of the renin gene (pro sequence intact); although with less enzymatic activity than renin, it can form renin on activation

determining tissue angiotensin-II concentrations. In many animal studies, local concentrations of angiotensin II in various tissues parallel the circulating levels, suggesting that renal renin is the determinant of both. For any given tissue, however, local angiotensin-II levels often vary widely from the circulating concentrations, and in some tissues, such as the adrenal, even the correlation with the circulating angiotensin-II level is relatively poor.<sup>17</sup> Thus, there is a role for local factors in determining tissue angiotensin-II concentrations.

Clinical studies have determined the cardiac angiotensin-II concentration gradient across the human heart. Of note, when healthy people were placed on a high-sodium diet, thereby suppressing the circulating RAAS, cardiac angiotensin-II production actually increased; conversely, cardiac angiotensin-II production decreased with a low-sodium diet.<sup>18</sup> This dissociation of the effect of sodium on the cardiac, as opposed to the renal, RAAS indicates local regulation. When these studies were extended to patients suffering from congestive heart failure, a similar result was obtained.<sup>19</sup> Although no renin message could be detected in biopsies of the ventricles of these patients, angiotensinogen and ACE were higher than in normal donor hearts. Moreover, cardiac angiotensin-II production paralleled high plasma renin activity but not in less-severe heart failure, in which plasma renin activity was lower. These data support the local regulation of tissue angiotensin in humans in health and disease.

Aldosterone is a steroid component of the RAAS secreted by the adrenal gland. In the past decade, synthesis of aldosterone by cardiac myocytes and vascular smooth-muscle cells has been reported.<sup>20</sup> This synthesis appears to be angiotensin-II driven and potentially participates in a positive feedback loop because aldosterone upregulates the angiotensin AT-1 receptor and ACE in cardiac cells.<sup>21</sup> Moreover, aldosterone probably participates in ventricular fibrosis. In rodent myocardial infarction studies, the administration of either an ARB or an aldosterone-receptor blocker ameliorated the reactive fibrosis usually seen in this model. Notably, in human catheterization studies, cardiac production of aldosterone is elevated in congestive heart failure<sup>22</sup> and hypertension.<sup>23</sup> These findings again suggest the clinically relevant participation of the local cardiac RAAS in human disease.

## CELLULAR RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEMS

As early as 1971, the internalization and nuclear/mitochondrial trafficking of angiotensin II by cardiac myocytes was described.<sup>24</sup> High-affinity nuclear and chromatin receptors were later reported, and these were subsequently shown to be AT-1-like, in that angiotensin-II binding was inhibited by losartan. Angiotensin binding to these receptors was associated with enhanced transcription (e.g. of platelet-derived growth factor and angiotensinogen) and with increased chromatin sensitivity to nuclease digestion.<sup>6,24,25</sup> In studies of cardiac myocytes, the enhanced generation of angiotensin in the intracellular space that resulted from the intracellular instillation of renin was associated with changes in calcium fluxes and conductance; this effect was abolished by co-introducing an ACE inhibitor into the intracellular space.<sup>26</sup> Similar changes in conductance and calcium fluxes were observed following the intracellular application of angiotensin.<sup>27,28</sup> Studies employing colloidal gold-tagged antibodies to angiotensin and electron microscopy confirmed the presence of angiotensin II in association with euchromatin, and several confocal microscopy studies have shown that upon angiotensin-II binding, AT-1 receptors translocate from the external cell membrane to nucleus.<sup>29,30</sup> Thus angiotensin II apparently can be internalized and probably acts in the intracellular space at sites such as the nucleus. In addition, in some cases, the peptide continues to signal in the endosome after internalization.<sup>31</sup>

Given these findings, it was natural to question whether angiotensin II can be made and act in the same cell. Two decades ago we suggested the term intracrine for peptide signaling either after peptide internalization or retention in the cell that synthesized it.<sup>25,32</sup> This intracrine action is common among signaling molecules, including hormones, growth factors and even some enzymes and transcription factors.<sup>31,33</sup> Angiotensin II can be considered an intracrine by virtue of its internalization and nuclear/mitochondrial localization. Although controversial, data also indicate that angiotensin II can also be made within the cell in which it acts. This theory has been challenged because angiotensinogen is rapidly secreted and does not appear to be stored in the cells that synthesize it. Moreover, angiotensinogen internalization has not been described. Therefore, in the absence of angiotensinogen, renin, whether internalized or synthesized in an intracellular

form, is argued to have no substrate from which to generate angiotensin I and, thus, angiotensin II. Renin and angiotensin II do, however, coexist in JUXTAGLOMERULAR CELLS (which do not express angiotensinogen), and the angiotensin II does not appear to have been internalized because losartan administration does not affect it.<sup>34</sup> It is most likely that angiotensinogen is internalized by these cells.

Cardiomyocytes of transgenic rats overexpressing nonglycosylated renin, take up that renin and generate intracellular angiotensin; this angiotensin is not internalized from the extracellular space because angiotensin II applied to cultured cardiac myocytes does not produce detectable intracellular concentrations of angiotensin.<sup>11</sup> Moreover, in the brain, the angiotensinogen gene is expressed in glial cells but not in neurons; nonetheless, neurons contain angiotensinogen protein as well as angiotensin II.<sup>35</sup> In addition, in transgenic animals bearing reporter genes, angiotensinogen and renin might be coexpressed in some brain neurons.<sup>36</sup>

As already noted, the intracellular instillation of renin into cardiac myocytes produces changes in conductance that are prevented by ACE inhibitors.<sup>26</sup> These observations suggest that, in at least some circumstances, angiotensinogen is available in the intracellular space and can serve as a substrate for intracellular angiotensin production. Moreover, the expression of angiotensinogen, ACE and renin in cells, such as human endothelial cells, keratinocytes and others, argues for autonomous cellular angiotensin synthesis, as does the upregulation of renin exon 1A in the nephrectomized rat adrenal gland and the apparent ability of that renin to act in the intracellular space to stimulate aldosterone synthesis.<sup>15,37-39</sup>

Finally, renin acts as an extracellular signaling molecule (i.e. a hormone). Some forms of extracellular renin can be internalized and act within the cell, although it is not yet clear if this action occurs in the course of normal physiology, as opposed to transgenic models.<sup>8,9,11</sup> In addition, an apparently intracellularly acting renin isoform has been identified.<sup>12-14</sup> This constellation of findings suggests that (pro)renin is an intracrine.<sup>31</sup>

#### **PATHOLOGICAL RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ACTIONS**

Despite important roles in circulatory homeostasis and normal fetal development, angiotensin and aldosterone can participate in the pathogenesis of cardiovascular disease.<sup>1,6,40</sup> For example,

angiotensin II can induce cardiac myocyte hypertrophy. The possible participation of the local cardiac system in left-ventricular hypertrophy is suggested by transgenic animal studies showing that overexpression of angiotensinogen restricted to the ventricles of normotensive animals is associated with the induction of left-ventricular hypertrophy in the absence of hypertension.<sup>16,40,41</sup> In addition, upregulation of ACE occurs at the shoulder of atherosclerotic plaques, suggesting that local angiotensin generation at those sites could activate metalloproteinases and facilitate plaque rupture.<sup>42</sup> Indeed, the insertion of the ACE gene in localized segments of rat carotid artery led to increased ACE expression and localized hypertrophy; conversely, local inhibition of ACE activity with antisense oligonucleotides inhibited proliferation.<sup>43</sup> This finding supports the concept that local upregulation of RAAS components can participate in the pathogenesis of vascular disease.

Infusion of C-reactive protein to achieve levels seen in vascular-disease patients increased the vascular hyperplasia that normally occurs following carotid injury. This effect was prevented by the ARB losartan, suggesting that low levels of C-reactive protein upregulate the AT-1 receptor and thereby enhance cellular proliferation.<sup>44</sup> Indeed, the ability of the AT-1 receptor to heterodimerize with the bradykinin B(2) receptor, leading to enhanced AT-1 signaling, and with the AT-2 receptor, leading to reduced AT-1 signaling, also highlight the potential for local regulation of the RAASs at the cellular receptor level.<sup>45,46</sup> Similarly, the upregulation of AT-1 receptors by oxidized LDL represents one of several synergistic interactions linking dyslipidemia, monocyte adhesion, inflammation and the RAAS in the development of atherosclerosis.<sup>47</sup>

Although considerable evidence links activation of the systemic and local RAASs with vascular pathology, it also appears that some system components tend to offset this pathologic action. For instance, angiotensin-(1-7) is a vasodilator that can be produced via the cleavage of angiotensin I by a newly described ACE homologue, ACE2, apparently acting in concert with ACE itself. Alternatively, ACE2 can directly generate angiotensin-(1-7) from angiotensin II.<sup>48,49</sup> Thus, the net effect of blockade or interruption of the RAASs is likely to result from the interactions of a variety of system components.

#### **GLOSSARY**

##### **JUXTAGLOMERULAR CELLS**

Cells in the renal corpuscle, close to the renal glomerulus, that secrete renin



## CONCLUSIONS

Local regulation of angiotensin-II production and action at the tissue level has been demonstrated. Indirect evidence suggests that this local production participates in the pathogenesis of vascular disease, but the relative roles of the systemic and local RAASs remain to be determined. Angiotensin II can act within cells, and evidence suggests that this activity is also physiologically relevant. Renin acts as both a component of the RAAS and as a signaling molecule in its own right. The implications of this dual action remain to be determined, but given the hyper-reninemia that accompanies ACE inhibitor and ARB therapy, they could be important. This conclusion is reinforced by the finding of a high prorenin concentration in the diabetic eye.<sup>50</sup> Also, antisense inhibition of local angiotensinogen synthesis markedly blunts the growth of human neuroblastoma cells possessing an autonomous renin-angiotensin system, but only lipophilic renin inhibitors suppress the growth of human glioblastoma cells.<sup>51,52</sup> This raises the possibility that intracellular renin systems, a direct receptor-mediated renin action or both participate in the growth of these tumors, thereby exemplifying the potential application of an understanding of the RAASs to disorders other than those of the cardiovascular system. Similarly, the potential for local RAASs to operate in noncardiovascular tissues is illustrated by the demonstration of angiotensinogen, renin, ACE, AT-1 and AT-2 gene expression in bone-marrow cells.<sup>53</sup>

Thus, the RAASs collectively are powerful, but not fully understood, regulators of cardiovascular biology. Determining the modes in which they function and designing therapies based on that knowledge represents an important opportunity to expand the therapeutic armamentarium.

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**Competing interests**

The author declared he has no competing interests.