



# Clinical relevance of local renin angiotensin systems

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The concept of a “local” renin angiotensin system (RAS) can mean different things to different people. Its main purpose is to differentiate the “local” RAS operating in tissues from the classical “circulating” RAS, but it is difficult to differentiate between the two systems because of their extensive overlap. The circulating RAS comprises kidney-derived renin acting on liver-derived angiotensinogen to generate angiotensin (Ang) I that is converted to Ang II by angiotensin converting enzyme (ACE). However, tissues are the main site of production of angiotensin peptides by the circulating RAS, whereby plasma-derived renin acts on plasma-derived angiotensinogen to generate Ang I, which is converted to Ang II by endothelial ACE (1–4).

Local RAS refers to tissue-based mechanisms of Ang peptide formation that operate separately from the circulating RAS. Although many different concepts of local RAS have been described, a key feature is the local synthesis of RAS components including angiotensinogen and enzymes such as renin that cleave angiotensinogen to produce Ang peptides independently of the circulating RAS. ACE and Ang II type 1 (AT1) and type 2 (AT2) receptors are invariably locally synthesized, but these are also components of the circulating RAS. Many other potential components of local RAS have been described that may contribute to tissue-specific mechanisms of Ang peptide formation, and that may either participate in disease processes or contribute to mechanisms that protect from tissue injury. These include the (pro)renin receptor (5), renin-independent mechanisms of

Ang peptide generation from Ang- (1–12) (6), intracellular (or intracrine) RAS that may contribute to cardiovascular disease (7, 8), and AT2 receptors (7) and the ACE2/Ang-(1–7)/Mas receptor pathway (6–8) that may mediate therapeutic benefit in cardiovascular disease. In addition, novel Ang peptides with novel pharmacology, including Ang IV, Ang A, alamandine, and angiotensin (6, 8), have the potential to contribute to disease or to protective mechanisms. Moreover, the brain RAS, including the ACE2/Ang-(1–7)/Mas receptor and the Ang IV/insulin regulated aminopeptidase pathways may play a role in Alzheimer's and Parkinson's diseases (9). Local production of aldosterone may have a pathogenic role (7, 10), ACE, AT2 receptors, Ang-(1–7) and acetyl-Ser-Asp-Lys-Pro may have a role in hematopoiesis (11), and the ACE2/Ang-(1–7)/Mas receptor pathway may contribute to fetal programming, reproduction, and cancer (6, 12).

This short opinion piece discusses the potential clinical relevance of local RAS. The challenge in demonstrating the independence of local from circulating RAS, and the potential interaction of ACE inhibitor and AT1 receptor blocker (ARB) therapies with local RAS are discussed. Attempts to define local RAS that are independent of the circulating RAS have been primarily based on animal models and the clinical relevance of local RAS is uncertain. However, this area of research continues to evolve, and today's opinions may change as we gain better understanding of how these novel components and mechanisms impact on clinical medicine.

## HOW CAN LOCAL RAS BE SHOWN TO BE INDEPENDENT OF THE CIRCULATING RAS?

As reviewed elsewhere (5–12), many lines of evidence suggest the possibility of local RAS that may operate independently of the circulating RAS and play a pathogenic or protective role. This evidence includes the widespread tissue expression of angiotensinogen, the only known precursor of the Ang peptides and an essential requirement for an independent local RAS (13–16). However, local production of RAS components does not prove their functional significance, and proving their clinical relevance presents many challenges. One approach to study of the role of locally synthesized RAS components is their targeted deletion from specific tissues. This approach has been applied to the kidney.

Both clinical experiences with ACE inhibitor and ARB therapies during pregnancy, and ACE, renin, angiotensinogen, and AT1 receptor gene mutation and knockout models demonstrate a critical role for the RAS in renal development and function in animals and humans (17–23). Moreover, ACE inhibition demonstrates a differential regulation of Ang II levels in kidney and blood (24). However, these data do not prove a specific role for the local RAS in the kidney. Matsusaka et al. investigated the role of the local RAS in renal development and function by producing mice with genetic deletion of angiotensinogen synthesis in the kidney. In contrast to the morphological and functional consequences of whole body or liver specific deletion of angiotensinogen gene expression, deletion of angiotensinogen production in the

kidney had no effect on renal morphology or function (25). Moreover, contrary to the expectation that locally produced angiotensinogen was the main contributor to renal Ang II levels, Matsusaka et al. showed deletion of renal angiotensinogen production had no effect on renal Ang II levels, and that liver angiotensinogen is the primary source of Ang II in the kidney (25). With the caveat that the studies of Matsusaka et al. were not in pathophysiological models (25), these data show that evidence for local synthesis of a RAS component is not sufficient to establish a role for the locally synthesized component in physiology or pathology, whether by an intracellular (intracrine) or extracellular mechanism. Proof that a locally synthesized RAS component contributes to physiology or pathology requires demonstration that deletion of the locally synthesized component impacts on physiology and/or pathology.

Similar to the case for angiotensinogen, mice with reduced renal expression of ACE had normal histology and urine concentrating ability (26), suggesting that locally synthesized ACE does not play an essential role in normal renal development and function. Moreover, the marked reduction in Ang II levels in kidney, heart, and other organs caused by global ACE gene deletion, despite near-normal Ang I levels (27, 28), indicates that an intracellular (intracrine) ACE-independent mechanism of Ang II formation is unlikely to exist in these tissues.

Evidence for a pathogenic role of renal ACE is the demonstration that genetic deletion of renal ACE expression prevented hypertension produced by subcutaneous administration of Ang II (26), suggesting a specific renal ACE-dependent mechanism of hypertension in this model. However, the significance of this finding is uncertain because ACE inhibition does not modify hypertension produced by intravenous Ang II administration in either animal or human studies (29–33), and it is questionable whether the subcutaneous Ang II model of hypertension has any physiological or pathological relevance (34).

An alternative approach to defining a local tissue RAS was to use recombinant technology to express ACE as a reporter gene on the cardiomyocyte membrane (35). In this model, ACE expression on the

cardiomyocyte membrane (where it is not normally expressed) would be expected to increase cardiac Ang II levels if Ang I were also present in this tissue compartment. Expression of ACE on the cardiomyocyte membrane increased cardiac Ang II levels in mice without endothelial expression of ACE, but not in rats or mice with endothelial ACE expression (35, 36). These studies do not therefore provide evidence in support of Ang I formation in the extravascular compartment of the heart of animals with endothelial ACE expression. By contrast, deletion of testicular ACE reduced male fertility (37), indicating a specific role for testicular ACE. However, ACE has many substrates (38) and the reduction in male fertility may reflect an action of testicular ACE that is independent of Ang peptides.

Part of the challenge in identifying a local RAS that is independent of the circulating RAS is the difficulty in measuring *in vivo* levels of Ang peptides in tissues. For example, initial reports of substantial amounts of Ang II and Ang-(1-7) in the brain (39, 40) were not confirmed when more rigorous methodology was applied (41, 42).

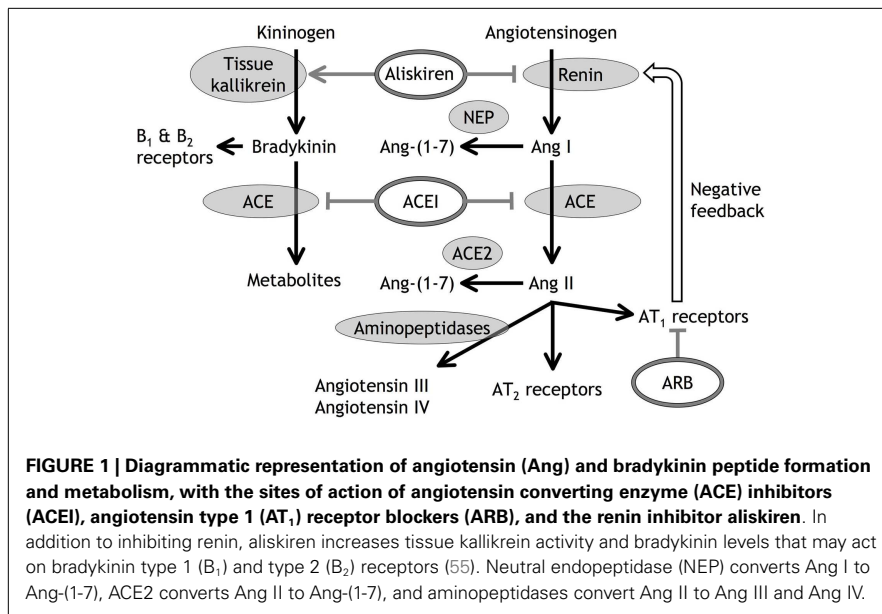
### DO THE THERAPEUTIC BENEFITS OF ACE INHIBITOR AND ARB THERAPIES ESTABLISH THE CLINICAL RELEVANCE OF LOCAL RAS?

A key argument in support of the clinical relevance of the RAS, whether local or circulating, is the therapeutic benefit from inhibition of this system. De Mello and Frohlich proposed that the local RAS mediates in part the therapeutic benefits of ACE inhibitor and ARB therapies (7), but there are difficulties in establishing such a role for local RAS. For example, the claim that the beneficial effects of these therapies occurred independently of blood pressure (7) suggests, but does not prove, a role for local RAS. The complexity of blood pressure regulation means that alternative explanations are possible and ambulatory blood pressure monitoring may be necessary to demonstrate an effect of therapy on blood pressure not detected by office blood pressure measurement (43). Furthermore, the different benefits of ACE inhibitor and ARB therapies in comparison with antihypertensive agents that act independently of the RAS (7) do not prove that these benefits

were due to inhibition of local rather than the circulating RAS.

Ang II administration is a well-recognized model of cardiovascular and renal disease (44–46), and the therapeutic benefits of RAS inhibition are almost certainly in large part a consequence of reduced Ang II stimulation of the AT1 receptor in high renin, high Ang II conditions such as renal artery stenosis and heart failure. Reduced AT1 receptor stimulation may also play an important role in the renal effects of RAS inhibition, including the side effects of these therapies (47, 48). Many studies investigating the combination of ACE inhibitor, ARB, and renin inhibitor therapies were based on the assumption that the therapeutic benefits of these agents are the consequence of reduced AT1 receptor stimulation, and that combination of these therapies would produce greater therapeutic benefit by producing greater reduction in AT1 receptor stimulation (47–53). What may not have been appreciated was the large body of preclinical and clinical data indicating that these drugs also produce benefits by mechanisms separate from reduced AT1 receptor stimulation. Moreover, many of these mechanisms separate from reduced AT1 receptor stimulation involve novel RAS components implicated in local tissue RAS (Figure 1). For example, ARB therapies, by blocking the negative feedback control of renin secretion, also increase Ang II levels that stimulate the AT2 receptor, leading to cardioprotection (54, 55). Moreover, both ACE inhibitor and ARB therapies increased Ang-(1-7) levels (56) that may produce therapeutic effects mediated by the Ang-(1-7)/Mas receptor pathway (6). In addition, ACE inhibitor, ARB, and renin inhibitor therapies increase bradykinin levels that may contribute to their antihypertensive and cardioprotective actions (54, 55, 57–63). Consequently, therapeutic benefit from ACE inhibitor, ARB, and renin inhibitor therapies does not prove a pathogenic role for the RAS, either local or circulating.

An important aspect of these additional mechanisms of therapeutic benefit from RAS inhibition is that combination of ACE inhibitor, ARB, and/or renin inhibitor therapies may block some of these mechanisms of benefit, thereby explaining the many clinical studies, apart from heart failure (49), that showed no additional benefit



from combination of ACE inhibitor, ARB, and renin inhibitor therapies (47, 48, 50–53). For example, the benefits of ARB therapy produced by increased Ang II levels and AT<sub>2</sub> receptor stimulation will be blocked if combined with renin inhibitor or ACE inhibitor therapies, because renin inhibitor and ACE inhibitor therapies attenuate the increase in Ang II levels produced by ARB therapy (55, 56, 64, 65). Moreover, the benefits of ACE inhibitor and ARB therapies produced by increased Ang-(1-7) levels and Mas receptor stimulation will be blocked if combined with renin inhibitor or neutral endopeptidase inhibitor therapies because renin inhibitor and neutral endopeptidase inhibitor therapies attenuate the increase in Ang-(1-7) levels produced by ACE inhibitor and ARB therapies (66). In addition, neutral endopeptidase inhibitor therapy may increase Ang II levels by reducing Ang II metabolism (66, 67).

## CONCLUSION

Current concepts of the local RAS have expanded to include the (pro)renin receptor, renin-independent mechanisms of Ang peptide generation from Ang-(1-12), AT<sub>2</sub> receptors, the ACE2/Ang-(1-7)/Mas receptor and Ang IV/insulin regulated aminopeptidase pathways, an intracellular (intracrine) RAS, and novel Ang peptides (5–9, 11, 12). Much of the evidence for these new RAS components is based

on animal studies and further research is required to establish that local RAS contribute to physiology and disease. Consequently, the clinical relevance of local RAS remains speculative. Nevertheless, the expanding repertoire of local RAS components offers new therapeutic targets and the prospect of new therapies.

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