SUMMARY

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure and body fluid homeostasis. Traditionally, the RAS has been viewed as a circulating system ("circulating" RAS). However, it is now well-established that angiotensin (Ang) generation also occurs at tissue sites ("tissue" RAS).

The complexity of the system has increased even further now that we know that Ang II activates more than one receptor, that Ang II has metabolites which activate their own receptors, and that there may even be receptors for renin and prorenin.

As soon as it was realized that angiotensin production at tissue sites is of greater importance than angiotensin generation in the circulation, many investigators started to unravel how and where such local angiotensin production might occur. Initially, it was thought that all components required for local Ang II production (i.e., renin, angiotensinogen and ACE) would be produced at tissue sites. Infusions of radiolabeled angiotensins, allowing the quantification of uptake of blood-derived angiotensin in tissues, confirmed that the majority of tissue Ang I and II is produced at tissue sites, and not derived from blood .

ACE is well-known to be abundantly expressed in virtually every tissue of the body, its main site being the surface of endothelial cells. Thus, its local synthesis is beyond doubt.

Although angiotensinogen mRNA has been detected outside the liver, direct proof for actual angiotensinogen synthesis at important sites of local angiotensin production (e.g., heart and vessel wall) is lacking.

For instance, the isolated perfused heart does not release angiotensinogen .Therefore, the majority of tissue angiotensinogen is probably of hepatic origin.

The fact that angiotensinogen is neither internalized, nor binds to membranes, combined with the observation that angiotensinogen-synthesizing cells release angiotensinogen to the extracellular space rather than storing it intracellularly, indicates that angiotensin generation must occurs extracellularly.

Thus, tissue angiotensin generation is restricted to the interstitial space and/or the cell surface.

Ang II generated at tissue sites stimulates both AT1 and AT2 receptors. This local generation depends largely on angiotensinogen and renin and/or prorenin taken up from blood, the latter uptake possibly involving the recently discovered (pro)renin receptor.

ACE is generated locally, and appears to be the main, if not the only, Ang II-generating enzyme. Ang II has a whole range of metabolites, the most important of which are Ang (1-7), Ang III and Ang IV.

The enzymes generating these metabolites, including ACE2, have recently been characterized, as well as their putative (non-AT1/AT2) receptors, like the Mas and AT4 receptor. Stimulation of AT2 receptors most likely contributes to the beneficial effect of RAS blockers, in particular during AT1 receptor antagonism. These receptors are upregulated under pathophysiological conditions, and are generally believed to counteract the effects of AT1 receptor stimulation. However, not all studies agree on this aspect, and thus it remains to be seen how the effect of drugs that completely suppress the RAS, i.e., renin inhibitors, compare to those that allow/require AT2 receptor stimulation,like ACE inhibitors and AT1 receptor antagonists.

A local RAS may be suggested by evidence of gene expression of RAS components within the tissue as well as physiological responsiveness of this gene expression.

Local generation of angiotensin II and the demonstration of physiologically active angiotensin II receptors within the tissue are also key features.

Local RAS have been described in the pancreas , heart , lung, brain and in adipose tissue .

As has been suggested local angiotensin II production may depend either on in-situ synthesis of all RAS components or uptake of various constituents from the circulation. Or, as in the case of the skeletal muscle RAS, a combination of in-situ synthesis and uptake.