The renin angiotensin system plays an important role on the regulation of arterial pressure, blood volume and cardiac function. Both a circulating and several tissue-localized systems have been identified and able to cleave angiotensinogen by renin to form angiotensin I which is converted to angiotensin II (Ang II) by angiotensin converting enzyme. The presence of local Ang II generation, which has been supported by the beneficial effects of Ang II AT$_1$ receptor blockers and ACE inhibitors independently of their effects on arterial blood pressure, certainly requires that renin, angiotensinogen and ACE be synthesized locally or taken from the plasma.

Concerning the presence of the different components of the RAS in different tissues evidence is available that in nephrectomized rats, the renin levels in the heart, for instance, are extremely low what indicates that intracellular renin in cardiac myocytes of normal animals, would need to come from plasma.

However, rats transgenic for the mouse ren-2d renin gene developed severe hypertension and cardiac remodeling and incubation of cardiac myocytes from these animals with prorenin (the precursor of renin) leads to intracellular appearance of angiotensin I and II what suggests prorenin internalization. Moreover, an alternative transcript for a nonsecreted renin has been described in brain and heart. The transfection of a nonsecreted form of angiotensinogen into hepatoma cells that expressed this renin transcript, increased proliferation by a process that is sensitive to renin antisense, indicating that the renin transcript has functional properties. Indeed, the alternative renin transcript is upregulated in adult rats with MI suggesting its functional effects. Both a circulating and several tissue-localized systems have been identified and able to cleave angiotensinogen by renin to form angiotensin I which is converted to angiotensin II (Ang II) by angiotensin converting enzyme. The presence of local Ang II generation, which has been supported by the beneficial effects of Ang II AT$_1$ receptor blockers and ACE inhibitors independently of their effects on arterial blood pressure, certainly requires that renin, angiotensinogen and ACE be synthesized locally or taken from the plasma.

E-mail: wmello@rcm.upr.edu

School of Medicine, PO Box 36–5067, San Juan, PR 00936-5067, USA.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the School of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan.

Correspondence to Walmor C. De Mello, Medical Sciences Campus, School of Medicine, PO Box 36–5067, San Juan, PR 00936-5067, USA. E-mail: wmello@rcm.upr.edu

(Circ Res. 2006;99:1285–1286.)

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*Circulation Research* is available at [http://circres.ahajournals.org](http://circres.ahajournals.org) DOI: 10.1161/01.RES.0000253141.65450.fc

On the Pathophysiological Implications of an Intracellular Renin Receptor

Walmor C. De Mello

The question remains whether renin is able to work by itself or depends on the formation of Ang II. Tissue accumulation of plasma prorenin results in angiotensin generation but could also, through binding to a recently cloned prorenin/renin receptor, lead to angiotensin-independent effects including p42/p44 mitogen-activated protein kinase (MAPK) activation and plasminogen-activator inhibitor (PAI-1) release. In mesangial cells, renin increases transforming growth factor-β 1 and matrix proteins also independently of Ang II mechanisms whereas in cardiomyocytes isolated from the failing heart, intracellular renin increments the inward calcium current, an effect suppressed by intracellular losartan. These apparent discrepant results lead us to think that the activation of RER has multiple functions some related to the activation of the RAS and other not (see Figure). Here caution must be exercised because variations of species or type of preparations used in the experiments might influence the results.

The intracellular localization of the renin receptor described in Schefè’s article certainly reactivates the tantalized question whether an intracellular renin angiotensin system is involved on the regulation of tissue function in different pathophysiological conditions. Activation of this receptor by enhanced expression of renin gene elicited by cell stretch for instance, might be in part responsible for cardiac remodeling and changes in electrical properties. On the other hand, increased internalization of

See related article, pages 1355–1366
Renin internalization

Diagram illustrating the activation of RER by intracellular renin and the displacement of the transcription factor (PLZF) to the nucleus with regulation of target genes (see Schefe et al10). Possible sources of intracellular renin include renin internalization, a nonsecreted isoform of renin or the enhanced expression of the renin gene elicited by different pathological conditions involving stretch. The diagram also shows the possible generation of Ang II inside the cell and its effect decreasing gap junctional communication and increasing the inward calcium current.

renin can result in intracellular degradation18 or intracellular angiotensin generation.1,38

The clinical implications of these findings are several: 1) inhibition of prorenin binding attenuates the development and progression of cardiac fibrosis19 and inhibits the development of diabetic nephropathy in animal models20; 2) RER messenger RNA can be detected in human glioblastomas and renin inhibitors decreases the number of cells in glioblastoma cell lines21; 3) a mutation of the renin receptor gene causes the X-linked mental retardation and epilepsy in humans22; and 4) intracellular renin reduces cell communication in the heart, an effect drastically reduced by intracellular enalaprilat.23 It is, then, conceivable that stimulation of RER by overexpression of the renin gene might impair impulse propagation and facilitates the generation of cardiac arrhythmias.

As it can be seen, the intricacies of the RER activation and possible consequences are barely realized. The widespread implications of RER in different pathological conditions as described above, support the view that the biological relevance of this receptor goes beyond the RAS. Cytoplasmic compartmentalization and the activation of a variety of intracellular signal pathways as well positive or negative regulation of target genes might be responsible for the diverse pathophysiological implications related to the activation of RER. Future research in this area promises to bring far more penetrating insights into the intracellular renin receptor and it will help to develop specific RER inhibitors.

Sources of Funding

This work was supported by grants HL 34148 and G2RR-03051 from NIH.

Disclosures

None.

References


KEY WORDS: intracellular renin receptor pathophysiological implications

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Circ Res. 2006;99:1285-1286
doi: 10.1161/01.RES.0000253141.65450.fc
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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