ACTA MEDICA SALINIANA

ISSN 0350-364X

Acta Med Sal 2009; 38 (1): 8-12

REVIEW PAPER

A SHORT HISTORY OF THE RENIN-ANGIOTENSIN SYSTEM

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Received: 07.11.2008
Accepted: 15.01.2009

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ABSTRACT

The renin-angiotensin system (RAS) was initially recognized as the body's most powerful hormone system for controlling body fluid volumes and arterial pressure. Then, it was shown that the RAS operates at both systemic (endocrine) and tissue (local) level. Development of angiotensin converting enzyme (ACE) inhibitors proved that the RAS is effective in controlling hypertension and heart failure, and in preventing the vascular injury in chronic diseases. The success of ACE inhibitors stimulated research into inhibitors of other components of this system. Major challenge in the future will be to utilize the technological advances for better understanding the physiology and pathophysiology of the RAS, and to develop new therapeutic paradigms. This article briefly reviews the research in this area, and points out the seventieth anniversary of angiotensin.

Keywords: *renin-angiotensin system, history*

During the period of the 110 last years, science has accumulated rich information, and scientists have tried to understand the role of renin and various peptides that are created by this and some other enzymes involved in the renin-angiotensin cascade. This knowledge has produced many useful drugs for treatment of cardiovascular disease and some other conditions.

The discovery of renin in 1898,[1] as a hypertensive factor in extracts of rabbit kidney, was appreciated many years later when it was shown that it had an important role in the experimental models of hypertension (Table 1). In 1956, Skeggs and coworkers[2] discovered angiotensin converting enzyme (ACE), an enzyme that converts angiotensin (Ang) I to Ang II, and they published the amino acid sequence of Ang II. On the basis of collected information, the classic concept on the RAS came out: Renin is released from renal juxtaglomerular cells into the blood where it converts angiotensinogen to Ang I. This peptide is hydrolyzed by a dipeptidyl carboxypeptidase, ACE, from plasma and lung to Ang II which acts on the Ang receptors.

However, the concept of the RAS as an endocrine system had to be modified when it was found that Ang II levels were much higher in tissue than in plasma and that the treatment with ACE inhibitors was effective even when concentrations of renin and Ang II in the circulation were normal. Thus, after a lengthy history, a new concept emerged: The RAS operates at both systemic (endocrine) and tissue (local, paracrine/autocrine) level.[3, 4]

In addition to hypertension, the RAS contributes to a multitude of functions, including pathophysiologic changes associated with cell hypertrophy and mitogenesis, normal organ development, and reproduction. Rapid progress in understanding the physiology of the RAS (Fig. 1) again forced basic and clinical scientists to make several conceptual changes.

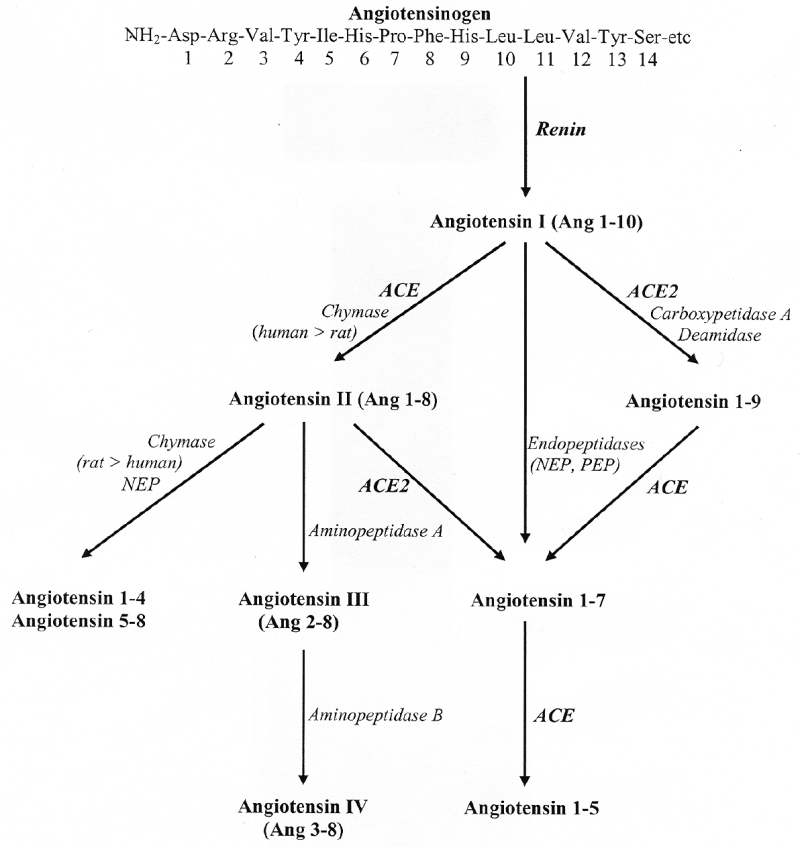

Figure 1. *Classic and Alternative Pathways of Angiotensin I Metabolism.*[9]
All peptides presented are subject to further hydrolysis by various angiotensinases.
Ang-angiotensin; ACE-angiotensin converting enzyme;
NEP-neutral endopeptidase 24.11 (neprilysin); PEP-prolyl endopeptidase

First, the discovery of ACEH, or ACE2,[5, 6] a homologue of ACE capable of producing vasodilator Ang 1-7, demonstrated that ACE and ACE2 might ultimately have opposing physiological effects. Then, a renin receptor was described[7] and a novel function of ACE as a key signal molecule was revealed.[8]

Considering so many surprises in such a short period of time, we may soon come close to the point of understanding the physiology and pathophysiology of the RAS and utilize this knowledge to discover the best way to correct malfunctions of this complex system.

SOME HISTORIC DETAILS

In 1965, Ferreira and Rocha e Silva[10] described the 'bradykinin-potentiating factor' (BPF) in the extract prepared from venom of the Brazilian pit snake, *Bothrops jararaca*. These scientists studied the venom because the workers in the banana plantations of Brazil, right after being bitten by a pit snake, were known to collapse due to a drastic drop in blood pressure. When Ferreira joined the pharmacologists at the Royal College of Surgeons, he brought some extracts of this snake venom to London. The head of the department, sir John Vane, suggested to one of his associates to test the venom for potential inhibition of ACE. When the result was positive,[11] Vane as a consultant of the Squibb Company suggested to the company to further investigate this venom extract.[12] Inventive Squibb scientists developed a project that enabled them to discover captopril, the first orally active ACE inhibitor, in less than a decade.[13] Now, we have numerous ACE inhibitors and several Ang receptor blockers that are in wide clinical usage. Also, a highly potent, selective inhibitor of renin, aliskiren was discovered by the Ciba-Geigy (today Novartis Pharmaceuticals) in cooperation with Speedel, and it is in wide clinical usage under following names: Enviage, Rasilez, Riprazo, Sprimeo, and Tekturna.[14, 15, 40]

SEMANTICS AND TWO SCIENTIFIC GROUPS

Fusion of two names, angiotonin and hypertensin, into angiotensin deserves a short explanation. In 1939, the pressor substance that was released from underperfused kidney[35] was named as hypertensin[36] by the Argentine scientists working with Braun-Menendez in Buenos Aires. The same year, the US group of scientists working with Page in Indianapolis and later in the Cleveland Clinic, identified the pressor substance angiotonin.[37] These two research groups a great geographical distance apart independently discovered

Table 1. *Historical Perspective of the Renin-Angiotensin System (RAS)*

Major Discoveries That Helped to Make Various Concepts on the RAS	
1898	*Discovery of renin in an extract from rabbit kidney cortex – Tigerstedt and Bergman.[1]*
1934	*Renal artery stenosis causes hypertension --Goldblatt et al.[16]*
1939	*Discovery that hyper**tensin** or **angio**tonin is a substance formed by the interaction of renin and blood "protein substrate" (Braun-Menendez et al.) [17] or 'renin activator' (Page et al.).[18] In 1958, the pressor substance was named **angiotensin**.*
1956	*Discovery of Ang I and Ang II, and ACE - Skeggs et al. [2]*
1957	*Ang II was synthesized by Bumpus et al.[19].*
1958-1960	*Ang II regulates aldosterone secretion.[20, 21]*
1967-1972	*ACE also inactivates bradykinin and kallidin; it is identical with kininase II - Erdos and colleagues.[22, 23]*
1969	*The lungs are vital organ for metabolism of circulating Ang II and bradykinin, indicating that this component of the RAS also operates locally.[23, 24]*
1969-1971	*Development of peptide antagonists to Ang II.[25, 26]*
1970	*Angiotensin receptors were identified by Lin and Goodfriend.[27]*
1988	*The concept that RAS operates at both systemic and tissue level was developed by Dzau.[3] Molecular cloning of ACE gene.[28]*
1991	*Ang 1-7 opposes Ang II activity - Ferrario et al.[29]*
2000	*A homologue of human ACE was discovered, and named ACEH by Tipnis et al. [5] and ACE2 by Donoghue et al.[6]*
2002	*Receptor that binds renin was described by Nguyen et al.[7]*
2003	*Crystal structure of the human ACE-lisinopril complex was determined by Natesh et al.[30]*
2004	*ACE is a key signal molecule - Kohldtedt et al.[8]*
Development of RAS Inhibitors	
1965-1968	*Bradykinin-potentiating factor (BPF), described by Fereira and Rochae Silva,[10] inhibits conversion of Ang I to Ang II - Bakhle.[11]*
1971	*Bradykinin-potentiating peptide (teprotide) was synthesized - Ondetti et al.[31]*
1977	*The first orally active ACE inhibitor, captopril was synthesized at Squibb - Ondetti et al.[13]*
1982-1988	*Non-peptide orally active Ang II blocking agents that selectively block the AT_1-type receptors were developed.[32, 33]*
2003-2007	*Aliskiren, an orally active renin inhibitor was developed.[14, 34]*

a novel pressor agent that was released from a blood protein by renin. The detailed studies on the generated substances were published in 1940.[38-40] Soon, it was established that hypertensin and angiotonin were the same substance and for many years both terms were used in the scientific literature. Finally, the leaders of the two groups, Braun Menendez and Irvine Page, agreed to name the pressor substance angiotensin, and correspondingly the renin substrate angiotensinogen.[41] Despite some scientific advantage of the Argentine group, Braun-Menendez accepted this combined name in order to overcome lasting linguistic confusion. However, even for some time after the eclectic name was anounced, several researchers used the old names—especially hypertensin, a peptide that was marketed under the same name by the Ciba Company.

SEVENTIETH ANIVERSARY OF ANGIOTENSIN (1939-2009)

The 70th anniversary of angiotensin should be observed not only in Buenos Aires, where the 60th birthday of this peptide was celebrated.[42, 43] Let us all take notice of this important joint discovery because research scientists and physicians today accknowledge that the discoveries of both renin and angiotensin greatly improved our understanding of several diseases. Certainly medical practice profited significantly from the synthesis and application of numerous pharmacological responses of endogenously generated angiotensin II. Ultimately, discovery of the renin-angiotensin system enabled many studies that resulted in successful control of vascular disease. Certainly, nei-

ther of these outstanding clinical scientists, Eduardo Braun-Menendez, Irvine H. Page, and their teams, would have imagined the significance of findings that were developed by numerous scientists over the years from their mutual discovery.

EPILOGUE

To enhance the antihypertensive effect and increase end-organ protection, ongoing research is directed towards domain-selective ACE inhibitors, orally active inhibitors of renin, and inhibitors of the enzymes that are not considered as part of the classic RAS but have an impact on the level of physiologically active Ang peptides (such as, chymase and neprilysin). Some of the RAS components could be targeted for long-lasting suppression by antibodies via active immunization and by gene-restraint (angiotensinogen, renin, ACE, AT1 receptor) or gene-activation (ACE2, endopeptidases, aminopeptidases) utilizing a gene therapy approach. Also, usage of the biphasic antibodies (e.g., anti ACE/ anti-adenoviral antibodies) could be used for systemic delivery of adenoviral encoding endothelial protecting enzymes or proteins to prevent elevation of blood pressure and end-organ damage.[44]

The role of the RAS contributing to vascular pathogenic conditions is quite clear, but our challenge in the future will be to effectively utilize the technological advances to translate them into better understanding of the patophysiology and treatment of vascular disease. Thus, more studies are needed to exploit new opportunities of targeting this system, and confirm that existing and new drugs confer vascular protection.[45-49] Regardless the advancement in this area of research, the global approaches to hypertension and cardiovascular disease need to focus on lifestyle changes that may be initiated as preventive measures, while approaches for individual patients should be associated with drug therapy.

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