A Centennial of Renin Discovery

A Memorial to Robert Tiegerstedt
The Centennial of Renin Discovery

Tadashi Inagami

One hundred years have passed since the first discovery of renin as a “pressor substance” in 1898 by Robert Tiegerstedt at Karolinska Institute. Since then, we have undergone long and difficult but highly productive years of renin-angiotensin research.

This work was an important breakthrough in the context of the new concept of the endocrine mechanism “milieu interieur” initiated by Claude Bernard. The 48-page publication “Niere und Kreislauf” in Skandinavisches Archiv für Physiologie in 1898 by Tiegerstedt and Bergman detailed their meticulous approaches, even including the design of a flow-meter to measure blood pressure changes and documentation of long-lasting pressor effects of renin and tachyphylaxis.1 Curiously, however, no sequel study was published. According to Professor Mattias Aurell, this was because of the rather poor reproducibility of renin activity measurement, a well-known feature that has troubled many renin investigators since then. The choice of the kidney as the source of renin had an important implication because it coincided with the long-standing recognition that high blood pressure goes hand in hand with kidney diseases.

The kidney became the target of studies again 30 some years later in independently conducted studies by Goldblatt, a pathologist who succeeded in making a dog model of renovascular hypertension by constricting the renal artery with silver clips. This work is based on Goldblatt’s repeated observations that renal arterial stenosis frequently accompanies hypertension. He also found that venous plasma of ipsilateral kidney contains a vasopressor substance.

Angiotensins

Study of renin-angiotensin was given a solid base when renin was found to be a peptidase that produces the pressor peptide angiotensin (a hybrid of angiotonin and hypertensin), demonstrated by Page and Braun-Menendez and their associates in the late 1930s. Angiotensin I (Ang I) was isolated by Skeggs et al, and the structure of Ang II was determined by Lentz et al, Elliot, and Peart. Its synthesis was reported by Bumpus’ and Schwyzer’s groups in 1950. Skeggs et al discovered 2 forms of angiotensin and 2 steps of Ang II formation from angiotensinogen by way of Ang I; Skeggs’ group also discovered angiotensin-converting enzyme (ACE). Later, ACE was identified as kininase II by Erdős. This discovery by Erdős demonstrated an intimate relationship between angiotensin formation and bradykinin destruction (see Reference 2 for a review of the early history).

Renin Purification and Identification of Specific Renin

During this accelerated phase of research, the entity and nature of renin remained elusive because of its instability, the very small amount present in the kidney and the lack of a readily available assay method, and confusion created by the presence of several reninlike enzymes such as isorenins and pseudorenins in greater quantities in various tissues.

We were fortunate to collaborate with Stanley Cohen in determination of the structure of epidermal growth factor (EGF), which he isolated from the submandibular gland of male mice, and to begin isolation of proteases from the same tissues. Reports from Werle’s and Bing’s laboratories indicated the possible presence of reninlike activity in this gland, and synthesis of fluorogenic renin substrate by Roth and Reinharz allowed us to completely purify renin in a stable form in a milligram quantity, which had not been dreamed of until then.3 Isolation of the submandibular gland renin also provided evidence for production of renin in extrarenal tissues. This allowed us to determine its complete amino acid sequence 10 years later and to show that it is a unique peptidase possessing a structural homology with acid protease such as pepsin.4 Whether the submandibular gland renin is identical with renal renin had to be examined by comparison with purified renal renin. Convergence of 4 major technical developments—radioimmunoassay of renin activity by Haber et al, new affinity chromatography techniques, discovery of bacterial peptide pepstatin, and use of inhibitor cocktails for proteolytic destruction of renin—permitted us to isolate pure renal renin in the 1970s from hog kidney,5 which was followed by isolation of rat and human kidney renin. Utility of affinity chromatographic approaches was also recognized by Corvol et al, Dzau et al, and McIntire et al, who obtained pure renin from pigs, dogs, and human kidneys (see Reference 6 for review). Characterization of their active sites with type-specific covalently reacting inactivators of proteases showed that renin is a relatively simple protease belonging to the family of aspartyl (acid) proteases such as pepsin and cathepsin D, and it has a singularly limited substrate specificity dedicated only to the production of Ang I from

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From the Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.
Correspondence to Tadashi Inagami, PhD, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37232-0164. E-mail inagami@ctrvax.vanderbilt.edu
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angiotensinogen without a general protein digestive activity, thus fulfilling the requirement for a specific peptide hormone–generating enzyme.\(^7\) The finding of a hormone-specific peptidase was also an important discovery that later found support in many other mechanisms generating peptide hormone from their prohormones, which are mediated by a specific peptidase dedicated for each prohormone. The molecular mechanism for the unique substrate specificity was investigated by Murakami and Brundell’s group with molecular mutagenesis and x-ray crystallographic studies (see Reference 6 for review).

Purified renin allowed us and Hackenthal to produce well-defined monospecific antibodies to renin. Using these antibodies, we and Hackenthal’s group were able to produce definitive evidence that the dense granules in juxtaglomerular cells contain renin, supporting the earlier hypotheses by Goormaghtigh and Dunihue. Furthermore, these cells and other renin-containing cells in pituitary and testis were also found to contain Ang II, indicating possible intracellular generation of Ang II by renin (see Reference 8 for review).

**Early Contributions of Molecular Biology**

Since the early 1980s, molecular biological techniques have played an increasingly important role. Corvol’s group (Rougeon et al\(^9\)) cloned a cDNA fragment for mouse renin (a Ren-2 product) by an ingenious differential cloning method. Gross’s group (Piccini et al\(^10\)) and Mullins et al\(^11\) showed that the mouse has 2 closely homologous renin genes, Ren-1 and Ren-2, the former being typical renal renin and the latter the salivary gland renin. Corvol et al\(^12\) also cloned Ren-2 cDNA and determined the complete structures of preprorenin and active renin.

Ohkubo and Nakanishi’s group cloned rat and human angiotensinogen gene, and Nakanishi and Murakami cloned human renin cDNA.\(^13\) Later in the 1980s, the groups of Soubrier, Alhenc-Gelas, Corvol, Bernstein, and Riordan cloned 2 alternatively spliced ACE cDNAs with 1 and 2 active sites, the former being expressed in the testis, and the latter shown to be the somatic form (see Reference 14 for review). These techniques provided a powerful method that led to the uncovering of many new important facts and concepts, such as the structure of prorenin, 2 active forms of ACE, and detection of gene polymorphisms, that allowed geneticists to pursue the genetic analysis of the renin-angiotensin system (RAS) in relation to cardiovascular abnormalities. cDNA cloning was also essential for Ang II receptor studies as discussed later.

**Pathophysiology of Renin Release**

Physiological studies on the control of renin release from juxtaglomerular cells by Vander, Malvin, Churchill, Nishimura, Kotchen, and many others revealed very intricate mechanisms. Adrenergic stimulation was found to suppress renin release, whereas high salt diet (the macula densa mechanism), high blood pressure (the baroreceptor mechanism), and the direct action of Ang II (short-loop negative feedback) were shown to regulate renin release in response to minute-to-minute changes in these physiological conditions to maintain blood pressure homeostasis (see Reference 15 for review).

One of the most important discoveries in studies on the possible pathophysiological roles of RAS came from the laboratories of Gross, Davis, Laragh, Genest, Ganong, Mulrow, and Denton, published from 1959 to 1961. Using various approaches these investigators reached the conclusion that Ang II stimulates aldosterone release and that high salt loading reduces renal renin content but markedly sensitizes pressor response to Ang II. These unique features, as well as other important properties, placed Ang II at the center of hypertension research among other pressor substances such as norepinephrine and vasopressin (see Reference 16 for review). Chronic administration of Ang II results in increased salt and water retention, with a decreasing amount of Ang II needed for other pressor substances such as norepinephrine. This observation by Laragh\(^17\) suggested that Ang II possesses a unique ability to retain NaCl in addition to its vasopressor action. Later, Ang II was recognized to be an important factor for vascular and cardiac remodeling.\(^18\) These multiple adverse effects made Ang II a central factor in the etiology of hypertension and cardiovascular degenerative diseases.

The realization of the interplay of plasma RAS and salt load led Laragh\(^17\) to develop an ingenious concept that the plasma renin level is strongly affected by NaCl load. This concept led further to a rational classification of human hypertension into at least 2 major types, high renin and low renin. Thus, from this brief review through the 1980s, one can see that recognition of the importance of RAS in hypertension has been developed as a result of multidisciplinary research involving clinical scientists, physiologists, pathologists, biochemists, molecular biologists, and more recently, geneticists.

**Pharmaceutical Development of RAS Inhibitors and Reevaluation of Etiology of Cardiovascular Diseases**

Pharmaceutical and pharmacological studies also made very important contributions. The ACE inhibitor was designed by Ondetti, Rubin, and Cushman on the assumption that ACE is a dipeptidyl carboxypeptidase and it may have an active site structure similar to pancreatic carboxypeptidase A, whose 3-dimensional structure was already available. Its inhibitor was invented with a limited but well-focused objective of treating diseases elicited by an elevated plasma RAS in renovascular hypertensive subjects, who comprise <10% of the human hypertensive population in industrialized nations.\(^19\) The first effective drug, captoril, turned out to be a great success, although these secondary hypertensive patients have a better prognosis when treated by revascularization than by vascular surgery. To our great surprise, however, Gavras et al\(^20\) realized that the peptidic ACE inhibitor teprotide is effective in normalizing blood pressure of essential hypertensives. Captoril and other ACE inhibitors also were found to be effective in normalizing the blood pressure of a large population of essential hypertensive subjects, as well as spontaneously hypertensive rats (SHR), which have subnormal plasma renin levels and are considered to be an animal model of essential hypertension. Furthermore, all types of inhibitors of RAS developed in more recent years,
for example, renin inhibitors and Ang II type 1 receptor (AT₁) blockers such as losartan and candesartan, were found to be effective in the treatment of essential hypertension.

The extended efficacy of RAS inhibitors from renovascular hypertension to essential hypertension was a big boon to a large hypertensive population. The area of application seems to extend to cardiac ventricular hypertrophy, congestive heart failure, prevention of stroke, atherosclerosis, and renal degenerative diseases.

The consistent success in normalizing the high blood pressure in much of the essential hypertensive population also establishes RAS as a key factor in hypertension. However, given the relatively normal plasma renin levels of the subjects, these successes also presented a major challenge to researchers to reevaluate the role of RAS in the etiology of hypertension and degenerative diseases of the cardiovascular and renal system.

**New Hypotheses**

Three new hypotheses were developed: (1) The efficacy of RAS inhibitors in blood pressure normalization could indicate that Ang II is merely a permissive factor. (2) This efficacy could also suggest that circulating plasma renin may play a minor role. It could very well be the local tissue RAS that regulates local Ang II production. (3) Receptor signaling in cardiovascular tissues is more sensitive in hypertensives. This hypersensitization may include reduced endogenous vasodilator activity, overexpression of receptor, or hypersensitive signaling downstream of the receptor.

If this efficacy is due to the permissive nature of RAS, then it indicates that some other systems are involved that are functional only when Ang II is produced, which may reduce the problem to an abnormal receptor signaling that transactivates another pressor system.

We, 21, 22 Ganten and Speck, 23 Bunneman et al, 24 Dzau, 25 and many other researchers investigated local production of Ang II by local RAS (see Reference 22 for review). There is no question that several tissues produce the specific renin rather than isorenin or cathepsin D, which were the subject of heated discussions. We and Ganten’s group showed that the brain contains endogenous renin capable of producing Ang II. The adrenals, vascular cells, renal tubule, cardiac myocytes (particularly under stress), pituitary, testis, and uterus were shown to express renin mRNA and endogenous renin. The question is whether locally produced renin makes a contribution comparable to that of renin of renal origin, which is transported to various cells and tissues. It is important to bear in mind that the probability of reaction of freely circulating enzyme and substrate in solution is much (2 orders of magnitude) less than that of renin associated to the luminal surface. 26 There is accumulating evidence that renin is associated to the luminal surface of the vasculature. For example, we showed that after bilateral nephrectomy of SHR, washout of the associated renin takes 8 to 12 hours. 27 Ang I produced by membrane-associated renin can be transferred to membrane-bound ACE to be converted to Ang II, which then finds its receptor on the luminal or medial surface. During tests of renin inhibitors, it was often noted that the inhibitor is effective even if plasma renin activity increases, an observation that free plasma renin itself does not contribute significantly to blood pressure regulation as much as bound renin, although plasma renin is a good index of how much is bound to the vascular wall, as in the case of ACE.

Significant to this concept is the finding of widespread distribution of angiotensinogen-producing cells and tissues outside of the liver and articulate regulation of ACE expression in growing vascular smooth muscle layers in neointima as discovered by Pratt and Dzau. 18 Note that both renin and ACE play roles in the regulation of Ang II production.

Thus, cell surface–bound renin, as originally noted by Swales, 28 and ACE expressed on the surface of neointima may also play significant roles. 18 At the same time, hypertension induced by overexpression of renin by transgenic rats 29 is clear-cut evidence that tissue renin in adrenal cortex 30 can still be a significant factor.

**Angiotensin Receptors**

The most plausible explanation for elevated sensitivity to RAS including aldosterone can be attributed to high receptor expression density or hypersensitive cellular signaling responses downstream of the receptor. The exaggerated responses may also be secondary to structural remodeling of the cardiovascular system. We owe a great deal to pioneers of Ang II receptor studies: T. Goodfriend for its discovery; M. Peach, K. Catt, W.A. Alexander, B. Berk, J. Exton, G. Owens, and J. Garrison for analyzing receptor signaling; and F.A.O. Mendelsohn, J. Saavedra, and R. Speth for autoradiographic distribution studies.

Research on Ang II receptors began to appear as the subtype-specific receptor blockers were invented in 1988. Timmerman’s group produced the AT₁-specific blocker losartan; the Parkes-Davis group produced the AT₂-specific blockers PD123177 and PD123319, and the Ciba-Geigy group produced CGP24112 (see Reference 31 for review). Expression cloning of AT₁ and AT₂ by us, Bernstein’s group, and Dzau’s group have resolved the long-standing difficulties and more recent confusion caused by the claim by Hanley that the mas oncogene product is an Ang II receptor. We and others also showed that AT₁ of rodents consists of closely homologous AT₁α and AT₁β. In addition, Ang[1-7] and Ang IV (Ang [3-8]) seem to have their own receptors according to C. Ferrario and J. Harding, respectively (for review see Reference 32).

Most of the traditionally recognized Ang II actions can be ascribed to Gq₁₁-coupled phospholipase Cβ action, which increases intracellular Ca²⁺ concentration and stimulates protein kinase C. 31 However, there are several signaling mechanisms that lead to cellular hypertrophy or mitogenesis in response to Ang II through activation of mitogen-activated protein (MAP) kinases and NAD(P) oxidases to produce reactive oxidative species. These processes involve tyrosine kinases. Cross talk between the Gq₁₁-mediated G protein–coupled receptor (GPCR) and tyrosine kinase did not seem to be explained by the traditional mechanism involving phospholipase C activation and intracellular Ca²⁺ release as protein kinase C activation (for review see Reference 33).

Morrero, Bernstein, and Bakers’ groups found evidence that the first step is the activation of c-Src, an oncogene product, and also JAK-2 (Jauns kinase), which initiates the subsequent...
activation of the transcription factor Sis (or STAT). However, how c-Src and JAK-2 are activated is not clear. We found that AT\textsubscript{1}-mediated elevation of cytoplasmic Ca\textsuperscript{2+} is sufficient to stimulate MAP kinase and that a mechanism of this activation is mediated by tyrosine phosphorylation of EGF receptor (EGF-R) in cultured rat aortic smooth muscle cells (VSMCs), which in turn activates Sox, p21 Ras, and eventually MAP kinase.\textsuperscript{35} This activation of EGF-R kinase proceeds without generating the autocrine growth factor EGF. Yet EGF-R tyrosine kinase is activated as the MAP kinase activation is blocked by the EGF-R kinase–specific inhibitor tyrphostin AG1478. This transactivation of the growth factor receptor by Ca\textsubscript{2+} generated by the GPCR AT\textsubscript{1} indicates the functional coupling between these 2 types of receptors. Increased Ca\textsubscript{2+} could activate a Ca\textsubscript{2+}-dependent protein kinase such as Pyk2, as well as Src, which form an activating complex.

By contrast, according to us, Dzau, Nahmis, and Sumners, the second isoform of Ang II receptor AT\textsubscript{2} seems to activate protein phosphatases, which include tyrosine phosphatase PTP-1C (SHP-1), MAP kinase phosphatase (MKP-1), and even Ser/Thr phosphatase PP2A. Thus, overall, AT\textsubscript{1} counteracts the growth-promoting action of AT\textsubscript{2}, AT\textsubscript{1} also seems to suppress the vasopressor activity of AT\textsubscript{2}, because the AT\textsubscript{2}-specific blocker PD123177 or PD123319 can increase the vascular strip tension developed by Ang II/AT\textsubscript{1}.\textsuperscript{36}

These effects are more clearly seen in AT\textsubscript{1} or AT\textsubscript{2} gene-deleted mice. The mouse contains 2 types of AT\textsubscript{1} receptors: AT\textsubscript{1A} and AT\textsubscript{1B}. AT\textsubscript{1A} null mice show a slight pressor response to infused Ang II due to intact AT\textsubscript{1B}.\textsuperscript{37,38} However, AT\textsubscript{1A}/AT\textsubscript{1B} dual gene-deleted mice show no detectable pressor response.\textsuperscript{39} It was noted that AT\textsubscript{1A} and AT\textsubscript{1B} mice do not exhibit mutually compensatory changes; they were completely independent of each other. By contrast, AT\textsubscript{2} gene null mice showed markedly elevated pressor sensitivity to infused Ang II compared with control mice.\textsuperscript{40,41} Also, as discussed above, AT\textsubscript{1} supports cellular growth or hypertrophic changes, whereas AT\textsubscript{2} suppresses it and in extreme situations induces apoptosis as reported from Dzau’s laboratory (Yamada et al\textsuperscript{42}). Detailed mechanisms of AT\textsubscript{2} signaling leading to the growth-suppressive and vasorelaxant actions of AT\textsubscript{2} are not known. Likewise, vasorelaxants such as nitric oxide and cGMP are known to be important counterbalances to AT\textsubscript{1}.

AT\textsubscript{1} seems to play important roles in renal morphogenesis. Angiotensinogen nullizygotes show delayed glomerular maturation, hyperplasia of extraglomerular mesangial cells, and most curiously, gross hypertrophy of small renal arteries.\textsuperscript{43-44} Because very similar nephrogenic defects are seen in AT\textsubscript{1A} and AT\textsubscript{1B} dual nullizygotes,\textsuperscript{39} but milder defects are seen in AT\textsubscript{1A} null mice\textsuperscript{38} and none in AT\textsubscript{2} null mice,\textsuperscript{40} both AT\textsubscript{1A} and AT\textsubscript{1B} should be important in renal development.

Effects of AT\textsubscript{1} and AT\textsubscript{2} in renal hemodynamic and tubular function and cardiac functions are not yet clear. Even though both AT\textsubscript{1} and AT\textsubscript{2} are expressed in given organs, they may or may not be expressed in the same type of cells. Although AT\textsubscript{2} is expressed at high levels in various fetal tissues, these levels plummet after birth. Yet, AT\textsubscript{2} contains to be expressed at clearly detectable levels in various vital organs, such as heart, blood vessels, kidney, adrenals, brain, and pancreas.

### Current and Future Issues

Consistent successes of blood pressure normalization by inhibitors and blockers of RAS strongly indicate central roles of the RAS in hypertension. Genetic studies to identify a mutation in the human RAS identified a mutated angiotensinogen allele that carries a methionine-to-threonine mutation and additional nucleotide mutation at positions 5’-noncoding region. Although this mutation seems to account for <10 mm Hg elevation among white populations, its identification is an encouraging start. However, there should be other hypertensive alleles in other candidate genes. A deletion/insertion (DD/II) mutation in the ACE gene was found to have little effect on hypertension, but the DD allele is a significant risk factor in cardiac hypertrophy and subsequent cardiac failure. Renal mechanisms of hypertension by possible defects in salt retention (eg, defective pressure natriuresis), possible vascular remodeling in resistance vessels, endothelial dysfunction leading to inefficient suppression of contractility, neural adrenergic hyperactivity and many more mechanisms are subjects of intensive studies in many laboratories. In many of these mechanisms, RAS or Ang II signaling seems to be a significant factor.

It has long been recognized that numerous adverse effects of Ang II are not limited to blood pressure regulation. Intensive studies are in progress as to whether or how Ang II mediates ventricular and vascular remodeling and further degenerative transformation of these tissues, such as atherosclerosis and neointima formation, renal glomerulopathy, and interstitial fibrosis. In many of these changes, the involvement of MAP kinase activation through the generation of reactive oxygen species, activation of c-Src, and participation of EGF-R are considered as a possible mechanism. Interactions with eicosanoid and nitric oxide synthetases are important factors. Thus, our recognition of the areas of RAS involvement in normal and abnormal cardiovascular neuronal and renal functions is still expanding.

Ang II breakdown products such as Ang IV (Ang[3-8]) have been demonstrated to stimulate specific endothelial proteases, such as plasminogen activator inhibitor. Ang[1-7] also seems to have its unique functions in the generation of prostaglandins.

RAS research has seen many ups and downs in its tortuous progress. Nevertheless, reflecting the pivotal roles of Ang II in cardiovascular diseases, studies on RAS have occupied a central position in research on vasoactive substances and will continue to do so. Concerted efforts of multidisciplinary investigators have led to a spectacular success in the highly efficacious and high quality-of-life therapeutic modality for hypertension in a purely empirical manner, without understanding of the precise underlying mechanism. We must guard against premature curtailment of research efforts and funding, because much can be accomplished via RAS and related studies in the fight against cardiac and renal disease. Genetic studies are one of the key factors, along with cell and molecular biological approaches, and will be of great value for prevention of degenerative diseases. Although the last decade was very productive in these types of research, it must be emphasized that studies on the pathophysiology of the
cardiovascular system are not complete unless we go back to
in vivo systems for their validation.

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