History About the Discovery of the Renin-Angiotensin System

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Abstract—The history of the discovery of the renin-angiotensin system began in 1898 with the studies made by Tigerstedt and Bergman, who reported the pressor effect of renal extracts; they named the renal substance renin based on its origin. In 1934, Harry Goldblatt induced experimental hypertension in dogs by clamping a renal artery. About 1936, simultaneously in the Medical School of the University of Buenos Aires, Argentina, and in the Eli-Lilly Laboratories in Indianapolis, 2 independent groups of researchers, using the Goldblatt technique to produce experimental hypertension, demonstrated renal secretion of a pressor agent similar to renin. In the following years, both teams described the presence of a new compound in the renal vein blood of ischemic kidneys. This agent was extracted from blood with 70% acetone and had a short pressor effect. The final conclusion was that renin acted enzymatically on a plasma protein to produce the new substance. In Buenos Aires, it was called hypertensin; in the United States, angiotensin. In 1958, Eduardo Braun Menéndez from Argentina and Irving H. Page from the United States agreed to name it angiotensin. (Hypertension. 2001;38:1246-1249.)

Key Words: renin ■ angiotensin ■ angiotensin ■ renin substrate ■ renin activator

The first observation linking renal disease to left ventricle hypertrophy was reported by Richard Bright in 1835. He related hypertrophy to an increased resistance to blood flow in the small vessels due to the altered condition of the blood. In 1868, George Johnson, reporting studies on nephritis, suggested that hyaline-fibroid alterations in the renal vessels were due to an impure condition of the blood, which was also responsible for left ventricular hypertrophy. F.A. Mahomed, using a primitive sphygmonograph for the first time, described high blood pressure in 1872. He also linked left ventricular hypertrophy to hypertension due to nephritis and reported the presence of high blood pressure in patients without renal disease. Finally, Riva-Rocci, in 1896, described the first indirect sphygmomanometer to measure arterial pressure in humans, and in 1905, Korotkoff defined the sounds that are named after him.

The relationship between pathological alterations in the kidney and the development of systemic arterial hypertension had been postulated for many years. In this sense, Franz Volhard suggested the existence of a circulating vasoressor substance. He classified the hypertensive patients: those with slight vascular damage as reds, and those with important vascular lesions—mostly in the kidney, pale skin, and cerebral damage (malignant hypertension)—as white.

On the other hand, by the end of the nineteenth century, Tigerstedt, a Finnish professor of physiology working at the Karolinska Institute, and his assistant Bergman analyzed the effect of renal extracts on arterial pressure. They discovered the presence of a pressor compound in the renal tissue of the rabbit, and based on its origin, they named it renin. The pressor activity could be extracted with glycerin, did not dialyze, and was stable at 56°C and was destroyed by boiling. Moreover, they showed that the renal vein blood increased blood pressure when injected into nephrectomized animals. They also detected the potentiation and protraction of the pressor response to renin in the nephrectomized recipient. They explained that the association between renal disease and cardiac hypertrophy was due to the kidney release of a vasoactive substance that induced contraction of the blood vessels through a direct action.

Based on these facts, many attempts were performed to develop an experimental model of arterial hypertension by manipulation of the renal function. Reduction of the renal mass, X irradiation of the kidney, renal artery occlusion, renal vein constriction, and wrapping of the kidney with a membrane were tested. Results were unreliable, probably as a consequence of inappropriate techniques and/or inadequate methods to measure blood pressure. The first successful experiment was performed by Goldblatt et al in 1934, and their technique led to the discovery of the active polypeptide. These researchers linked the ischemic characteristic of the renal disease with hypertension. They induced the experimental hypertension in the dog by the partial constriction of the renal artery using a silver clip. Their results were confirmed by several groups, and the search for the mechanisms involved for the increase in blood pressure began. The section

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of the sympathetic nervous system that regulates the vaso-

motor mechanisms did not prevent or abolish the develop-

ment of hypertension.

Goldblatt had already proposed the existence of a humoral

mechanism due to the release of a pressor substance by the

kidney, even though he recognized that this possibility was

only sustained by indirect evidences. This concept was not

new, Volhard had suggested the presence of a vasoconstrictor

factor causing malignant, or “pale,” hypertension. Nonethe-

less, neither he nor his collaborators could establish the nature

of such an agent in the circulation of patients suffering from

this pathology. Lack of its detection was probably due to

inadequate methods for analysis.

Two research groups, working independently, simulta-

neously reached similar conclusions on this matter. One of

them was investigating at the University of Buenos Aires,

Argentina, under the leadership of Dr Bernardo Houssay at

the Physiology Institute of the School of Medicine. The other

group pursued their studies at the Eli Lilly Research Labora-

tories in Indianapolis, under the leadership of Dr Irvine H.

Page.

The discovery of the renin-angiotensin system in Buenos

Aires began with the arrival of Dr Juan C. Fasciolo, a young

physician, at the Institute chaired by Dr Houssay. He was

interested in performing his doctoral thesis in physiology

under the direction of Prof Houssay. The subject, selected by

Houssay, was to repeat the experiment described by Goldblatt

in the dog to find out the nature of the mechanisms involved

in the development of high blood pressure. The interest of Dr

Houssay in this problem was related to the fact that one of his

young disciples, 32-year-old Dr J. Guggiarmetti, had recently

died of malignant hypertension.

They faced all kind of problems, but finally the develop-

ment of an adequate silver clip resulted in a number of

hypertensive dogs. This first stage was followed by the

detection of a vasoactive agent. The presence of a pressor

compound in the ischemic kidney had been analyzed by

several investigators injecting renal extracts, obtained from

hypertensive animals, into the circulation of dogs or rat,

while recording changes in blood pressure at the same time.

However, the results were not conclusive, even though these

preparations produced higher pressures than those obtained

from normal animals. In contrast, the presence of a pressor

substance in the circulation of hypertensive animals had

always been negative. Finally, only 1 experiment, using a

cross circulation between a donor hypertensive dog and a

nephrectomized recipient dog, revealed a significant increase

in the blood pressure of the recipient dog. Thus, the

recipient dog had to be nephrectomized.

Based on these findings, an experiment was designed to

search for the presence of a pressor agent in the venous blood

of the ischemic kidney. Grafting of an ischemic kidney into

the neck of a recently nephrectomized dog was chosen. Blood

pressure of the dog began to rise shortly after the grafting, and

it remained elevated even after the graft was eliminated,

supporting the presence of a true pressor secretion. Moreover,

grafting a kidney from a normal dog did not show a pressor

action. These results were later confirmed by other au-

thors. Further support for the release of a pressor sub-

stance was afforded by the experiments of Dr Alberto C.

Taquini, head of research at the Physiology Institute. He

added strong evidence supporting the secretion of a vasoac-

tive agent from the ischemic kidney. Indeed, plasma

obtained from the renal vein blood of the ischemic kidney,

diluted with saline and injected in the well-known preparation

of Lawen-Trendelenburg, produced a strong constrictor effect

on the isolated vascular bed of the hind-leg of the toad. The

venous plasma from numerous ischemic kidneys of hyperten-

sive dogs always induced a significant and immediate vaso-

constrictor effect. To the contrary, venous plasma from

normal kidneys had little or no pressor action.

Experimental results had demonstrated that in the acute

period, the ischemic kidney of the hypertensive dog released

a vasoconstrictor agent. It became necessary to establish the

nature of this compound and to characterize, purify, and

isolate it to identify its chemical structure.

In 1938, Taquini went to the United States with a 2-year

fellowship. And, at the same time, Eduardo Braun Menéndez

returned from his stay in England, where he had studied the

metabolism of the heart with Dr Lovatt Evans. He planned to

continue his work on this subject after returning to Buenos

Aires. However, when he returned he had to replace Taquini

as head of research, he learned of the promising experiments

that were being developed in the field of arterial hyperten-

sion. He decided to lead a team that also included Drs Juan

C. Fasciolo, Luis F. Leloir, and Juan M. Muñoz. Leloir and

Muñoz were already involved in studies related to the

chemical nature of physiological enzymatic processes.

Some authors had previously described a significant

increase in arterial blood pressure, a few minutes after

inducing renal ischemia in the dog. This increase was

probably due to the secretion of the same vasoactive sub-

stance under their study. Therefore, the next step was to

perfuse dog kidneys after a short period of ischemia. Braun

Menéndez and Fasciolo demonstrated that in acute ischemia,

the blood coming from the renal vein induced a strong pressor

effect when injected in the circulation of nephrectomized

dogs. The pharmacological characteristics of this pressor

agent indicated that its effect was not modified by the action

of atropine, cocaine, or sympatholytic agents and that it was

potentiated after bilateral nephrectomy of the recipient

animal.

The following goal now was to isolate the active substance

from the blood. Extraction of the active principle was

accomplished with acetone (70%). This compound produced

a quick pressor action of very short duration, thus completely

different from renin. On the other hand, the agent was

thermostable and soluble in acetone, and it was not detected

in the venous blood of an intact kidney. It had a strong

vasoconstrictor action on the vascular bed of the toad. These

chemical and pharmacological characteristics were different

from those of all the known substances at that time. The logic

conclusion was that a new compound had been isolated from

the blood coming from the ischemic kidney. Based on its

properties and effects, it was named hypertensin.

Renin, the pressor principle obtained from renal extracts by

Tigerstedt and Bergman in 1898, was thermolabile and had a

prolonged pressor effect. This action was recorded when
studying renal grafts from hypertensive dogs and also when injecting blood coming from acute ischemic kidneys. Previous observations, therefore, linked renin with the newly discovered agent. However, the nature of the relationship between the 2 compounds remained unknown.

The first studies designed to clarify this matter were unsuccessful. Kidney slices were incubated with plasma (under hypoxic conditions). The release of the active principle could not be detected, probably because of the enzymatic destruction of the formed angiotensin. Then, they incubated a semipurified kidney extract with plasma and were able to isolate a vasoconstrictor substance similar to hypertensin. The compound was soluble in 75% acetone and in glacial acetic acid, was insoluble in ether and amyl alcohol, and was resistant to acid hydrolysis and dialyzable. These characteristics were different from those of renin, epinephrine, tyramine, vasopressin, and urohiptensin.32

Based on these results, the Argentine group described, for the first time, renin as an enzyme similar to papain (protease), which could act on a protein present in the plasma to release hypertensin as the final product of the enzymatic reaction. Through subsequent experiments, these researchers demonstrated that renin was secreted by the kidney, and hypertensin was formed in the plasma from a proteic substrate that was named hypertensinogen because it was the actual origin of the active principle. Blood, as well as kidney, was able to inactivate hypertensin through the action of other enzymes that were called hypertensinasises.33 Inactivation of hypertensin was avoided by purifying preparations containing either renin or hypertensinogen.

The fact that bilateral nephrectomy increased considerably the plasma concentration of hypertensinogen was also demonstrated.33 At the same time, the specificity of the enzymatic system was described. Hog renin could not release hypertensin from the human plasma substrate, whereas human renin system was described. Hog renin could not release hypertensin when incubated with human plasma. Therefore, this plasma enzyme, belonging to the kinase group, that was present in the proteic fraction of plasma and blood. Thus, the plasma concentration of hypertensinogen was also demonstrated.

The hepatic origin of renin substrate was suggested by Page et al.34 However, conclusive experiments were performed later by LeLoir et al35 in nephrectomized dogs with and without hepatectomy.

All the research performed on the renin-angiotensin system by the Argentine group were published in a book in 1943.36 Simultaneously, Page, working with Helmer and Kohlstaedt, was investigating the mechanism of action of renin.37 They had observed that when the purified protein was injected in the dog isolated tail preparation and perfused with Ringer solution, it was barely active compared with the strong constrictor and pressor effect obtained after intravenous injection. They postulated the existence of a blood component that was necessary for the vasoactive action of renin. They had observed that the addition of small amounts of plasma to the Ringer’s solution containing purified renin induced a strong vasoconstrictor effect in the perfused dog tail preparation. They concluded that renin was an inactive enzyme that was activated by yet another enzyme, belonging to the kinase group, that was present in the proteic fraction of plasma and blood. Therefore, this plasma protein compound was named renin activator. The final product, a pressor substance formed through the interaction of renin and its activator, was named angiotensin38–41 and was, probably, the actual effector of the renin pressor action.

The similarity between renin substrate and renin activator was immediately accepted, as was the identity of the final product. Moreover, the enzymatic nature of the renin system and the pepptic nature of the hypertensin was also confirmed. Renin acted as a hormone and as an enzyme with a pressor effect that was due to angiotensin release. Shortly after, Page et al42 changed the name of renin activator to renin substrate to emphasize the enzymatic nature of the system. During the following years, both nomenclatures were used, generating a certain degree of confusion.

Synthesis of the octapeptide was successfully accomplished, for the first time, by the group led by Dr Page, then in Cleveland,43 and by Dr Schwyzer in Basil, Switzerland.44,45 The Basil group, working at the CIBA laboratories, marketed the octapeptide under the name Hypertensin4.46

To commemorate the 25-year anniversary of Goldblatt’s first successful experiment to induce arterial hypertension by renal ischemia in the dog, the University of Michigan Regional Conference on the Basic Mechanisms of Arterial Hypertension was held in Ann Arbor, Mich, in 1957 under the organizing Committee of Drs Sibley W. Hoobler and David F. Bohr. (Under the direction of these 2 distinguished investigators, several Argentine physicians were trained.) Back in Argentina, they continued to work on the mechanisms of arterial hypertension and on the renin-angiotensin system. Among them were Dr. Alberto Agrest, Pedro C. Blaquier, Alberto C. Taquini, Jr, and Ignacio J. de la Riva. All returned to work at the Instituto de Investigaciones Cardiológicas of the School of Medicine of the University of Buenos Aires, where they had begun their research studies. Dr Braun Menéndez et al47 and Dr Alberto C. Taquini et al48 presented their experimental results at the University of Michigan conference, and the results were published in a supplement to Circulation. Also at this meeting, Dr Braun Menéndez (for the Argentine team) and Dr Page (for the American group) arrived at a single nomenclature for the components of the enzymatic system.49 Even though there was already a marketed name of Hypertensin, Braun Menéndez agreed to name the active final compound angiotensin, taking half of each original name. Similarly, the renin substrate was named hypertensinogen, and the enzymes that metabolize the peptide were termed hypertensinasises.

A few years were needed for the general acceptance of the new nomenclature. The leading groups in the United States, like those of Goldblatt and Skeggs, and in Europe continued using the Argentine name. In 1959, Dr Braun Menéndez died, and in 1961, Taquini et al50 insisted on the necessity of using the unified nomenclature.

Those involved in the discovery of the renin-angiotensin system probably did not imagine the importance and transcendent significance of their findings as well as the enormous flow of information added to the knowledge of the enzymatic system. In spite of the fact that >50 years have elapsed, the role of the full implications of the renin-angiotensin system on the development of renal arterial hypertension has not been completely elucidated. Notwithstanding, there are no doubts about the beneficial effect of inhibition of...
the enzymatic system in a group of essential hypertensive patients. In this sense, drugs that are able to block the effect of angiotensin II have contributed to modify the evolution of arterial hypertension and to increase the lifespan of the hypertensive patients.

References


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