Chapter 1

The Angiotensin Affair: How Great Minds Thinking Alike Came to a Historical Agreement

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Abstract

In 1934, J. C. Fasciolo had to submit a thesis and Dr. Houssay suggested he investigate about nephrogenic hypertension. E. Braun-Menéndez showed interest in helping and Drs. L.F. Leloir and J.M. Muñoz from the Institute of Physiology joined them in their attempt to isolate and purify the pressor substance. In 1939, they extracted the substance "hypertension" from the venous blood from the ischemic kidneys. They proposed an enzyme-substrate reaction. They named hypertensinogen the substrate and hypertensinases the enzymes that break down the hypertension. Two months following the Argentine publication, the team in the United States, formed by I.H. Page and O.M. Helmer, published their findings, which were in agreement with those reported by the Argentine team. By 1940, they isolated angiotonin, the equivalent of hypertension, and called the renin substrate hypertensinogen. In 1957, in the conference held in Ann Arbor, Braun-Menéndez and Page agreed on a new nomenclature. As a result, the words angiotensinogen and angiotensin were born from the combination of the names originally set by both teams. The discovery of the renin-angiotensin system is an example that science should follow: Value the progress made by colleagues, collaborate side by side, and pursue the ultimate truth.

Keywords: angiotensin discovery, hypertension, renal disease, renin-angiotensin system, vasoconstriction, blood pressure, kidney ischemia, renal grafting

1. Introduction

A systematic review of both autobiographical and biographical documentation is provided, concerning with original experiments that change the course of hypertension treatment, along with a chronology of the major events which led to angiotensin discovery. This historical hit marked the evolution of antihypertensive treatment and later on gave rise to the development

of a whole new family of drugs, the angiotensin receptor blockers (ARBs). At present, their main uses are in the treatment of hypertension, diabetic nephropathy, and congestive heart failure. By now, annual global sales of renin-angiotensin inhibitor drugs are estimated around US$ 27.3 billion, 24% in Europe. Actually, much of these come from single-sourced angiotensin receptor blockers (ARBs).

2. Discovery of angiotensin

Using relatively unsophisticated methods (in light of present technology), laboring hard and carrying out keen experiments, two teams of prestigious scientists identified the precise peptide called angiotensin, which induced experimental renal hypertension [1]. The discovery of the renin-angiotensin-aldosterone system (RAAS) was relevant in understanding a key mechanism involved in the maintenance and control of arterial blood pressure. As it would be revealed in time, this system indeed participates in other processes such as inflammation and oxidative stress as well. Years later, the characterization of the RAAS would render the synthesis of the presently used antihypertensive drugs. The development of angiotensin-converting enzyme (ACE) inhibitors proved that the RAAS is effective in controlling hypertension and heart failure, and in preventing vascular injury in chronic diseases.

2.1. Early investigation that led to the discovery of angiotensin

The nineteenth century was the seeding period where evidence and theories linking renal perfusion and blood pressure control in both physiological and pathological conditions were put forward [2]. It was not until 1936 when R Bright first reported evidence supporting the functional link between cardiac hypertrophy and renal disease [3]. He associated hypertrophy with an increase in small vessels resistance to blood flow as a result of an altered condition in blood. In 1868, G. George Johnson had indeed shared the outcome of his studies on nephritis and suggested that some kind of abnormal condition of the blood induced the hyaline-fibroid modifications he observed in renal vessels. Moreover, such particular condition of the blood was responsible for left ventricular hypertrophy as well [4]. Only 4 years later, FA Mahomed succeeded in measuring blood pressure using an interesting "ultramodern" device at the time, namely a sphygmograph [5]. He also reported the relationship between left ventricular hypertrophy and hypertension due to nephritis in patients not affected by renal disease [6, 7]. Later on, Riva-Rocci explained and depicted in detail the characteristics of another device, the sphygmomanometer which made possible to measure arterial pressure in humans. At the beginnings of the new century, the Russian physician Nikolai Korotkoff, at the time of his work at the Imperial Medical Academy in St. Petersburg, described the characteristic sounds which took his name in his honor [8, 9].

In 1898, the medical scientist and physiologist Professor Robert Tigerstedt (1853–1923) and Gunnar Bergman, one of his fellows at the Karolinska Institute (Stockholm), reported a dramatic rise in blood pressure following the injection of kidney extracts to rabbits, suggesting the presence of a vasoconstrictor substance which they called "renin" in renal cortex [10]. As to why Tigerstedt paid attention to the subject, inconclusive guesses had been put forward.

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Perhaps the intertwining pathophysiology linking hypertension and renal disease established by Bright (1789–1859) or the discovery of an adrenal hormone by Séquard (1817–1894) awakened his interest. Yet, he abandoned the subject on his return to Finland later [11] and published no follow-up. Reproducibility of renin activity posed high technical difficulties. Tigerstedt may have felt discouraged and gave up trying any longer, as suggested by Professor Aurell [12].

The cardiovascular, renal, and central nervous systems are targets for hypertensive damage. In 1923, Franz Volhard (1872–1950) put forward the idea of a vasospastic substance causing malignant "pale" hypertension which characteristic symptoms as pale skin, decreased or blurred vision and headaches (ocular and central changes, respectively) [13]. Contradictory reports appeared regarding whether this vasoconstrictor substance was actually found in the blood of hypertensive patients or it was not [14]. Unsuccessfully, Volhard and his collaborators attempted to measure and characterize a circulating vasoconstrictive substance in hypertensive patients with acute glomerulonephritis [13], most probably due to technical issues and defective analysis techniques [15].

Many attempts were made to create an experimental model of hypertension, such as irradiating the renal parenchyma, reducing its mass by ablations, and occlusion of branches of the renal artery. These were not successful. In 1909, Theodore Caldwell Janeway (1872–1917) described an increase in blood pressure after occlusion of the renal artery branches and excision of the contralateral kidney [16]. However, it was not until 1934 that Harry Goldblatt (1891–1977) developed an experimental canine model of hypertension, known as "Goldblatt kidney." He reported that permanent hypertension induced by renal artery blockage that was neither prevented nor abolished by section of the vasomotor branch of the sympathetic nervous system in dogs [17].

2.2. Work performed by the Argentine team

In the 1930s, the lab of physiology at the Faculty of Medicine of the University of Buenos Aires, led by the Nobel Prize winner Bernardo Houssay (1887–1971), was about to live one of its most prolific periods. In 1934, J. C. Fasciolo (1911–1993), a student of the School of Medicine at the University of Buenos Aires, had to submit a thesis to complete his undergraduate degree. Dr. Houssay suggested he investigate about nephrogenic hypertension, a suggestion brought by the premature death of one of his most brilliant fellows called Juan Guglielmetti (1891–1922). He died at the age of 33 years from a malignant hypertension [18].

Carlos Alberto Taquini (1905–1998) was a member of the Department of Physiology who had the privilege of listening to F. Volhard in 1931. He proposed and discussed with Fasciolo and Houssay the humoral theory of vasospasm involved in hypertension. This theory considered the possibility that the substance released by the kidneys might act directly on the blood vessels. Taquini reported that following kidney ischemia, a vasoconstrictor substance appeared in the renal vein of dogs. Actually, perfusion with a blood of hypertensive animals induced strong vasoconstriction, while blood from normotensive dogs did not [19]. In the same line of work, he perfused the hind legs of toads with diluted plasma in the experimental condition known as Lawen-Trendelenburg preparation [20, 21]. During the same year, Taquini proved

that the increase in blood pressure observed after restoring blood flow in ischemic kidneys was caused by the same vasopressor substance involved in the previous studies [22].

Fasciolo initially sought to destroy the renal cortex of rats to develop a model of experimental hypertension. However, he encountered methodological difficulties, and the results were not consistent. He came across the article published by Goldblatt, and after reading it, he began to apply the method described by him [23]. Being instructed in renal grafting by Houssay, now without failures and disappointments in the beginning, Fasciolo succeeded in inducing hypertension in dogs as shown by Goldblatt [24, 25]. Unequivocally, when the grafted kidneys were perfused, hypertension slowly and gradually developed [23]. This experiment confirmed that a pressor substance was actually secreted by the kidneys. Pharmacologically, induced hypertension was refractory to an administration of sympatholytic drugs, atropine or cocaine, while it was potentiated following bilateral nephrectomy [26].

Of course, they had to characterize, purify, and learn much more about the physiological role of this pressor substance to study its physiological activity [23]. Eduardo Braun-Menéndez (1903–1959) showed himself interested in helping, just after his return from England where he had obtained a grant and studied myocardial metabolism with Dr. Charles Arthur Lovatt Evans (1884–1968). Using a heart-lung preparation and perfusion of an isolated kidney, they observed that flow interruption for just a few minutes was enough to induce the presence of the vasopressor substance in the renal venous blood. This was checked by injecting the venous blood from that preparation into nephrectomized dogs. This finding would later become of huge importance. The preparation of hypertensive dogs was not simple, and large amounts of venous blood would be required to isolate the hypertensive agent [23, 27]. At that time, Drs. L.F. Leloir (1906–1987) and J.M. Muñoz were working at the Institute of Physiology and accompanied Fasciolo and Braun-Menéndez in their attempt to isolate and purify the pressor substance. Leloir and Muñoz worked mainly on the chemical aspects, and Braun-Menéndez and Fasciolo worked on the pharmacological aspects [23]. This group, perhaps one of the most brilliant that Argentine science has had, functioned in total harmony. In the words of Leloir: Good spirit reigned in the laboratory. Fasciolo pointed out the importance of the diversity in viewpoints of him and his colleagues stating that "Leloir and Muñoz are well versed in biochemistry, while Braun-Menéndez and I are better versed to physiology" [28]. Dr. Houssay was aware of the progress of their research and helped them with his advice and his constant support [23].

The group first tried working with the toad preparation successfully used earlier by Taquini in the characterization of various extracts. Later on, they decided to perform their research using the most reliable, though more expensive, dog model [23]. In 1939, they extracted the vasopressor substance with acetone from the venous blood from the kidneys that were subjected to periods of ischemia. This substance produced an increase in arterial pressure when it was injected in animals, although this effect only lasted a few minutes. A very different scenario occurred when ischemic kidneys were implanted to the cervical circulation, where the increase in arterial pressure was of a prolonged nature. The isolated substance was heat stable, dialyzable and had a brief hypertensive effect, characteristics that differentiated it from renin. The Argentine team named this substance hypertension. The next step was to elucidate

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the existing relationship between renin and hypertension. In the first instance, fragments of renal cortex were incubated with plasma in anoxic conditions. This, however, did not yield hypertension. It was explained by the possible presence of enzymes that metabolize it. In a second attempt, the extracts of renin were incubated at 37°C with plasma, obtaining through this method the vasopressor in vitro. Basing themselves on their findings, they proposed an enzyme-substrate reaction for the formation of hypertension. They named hypertensinogen the substrate, the enzyme renin, and hypertensinases the enzymes that break down the hypertension [29, 30]. The sustained hypertensive effect achieved through the implantation of ischemic kidneys would be caused by renin release of renin and continuous generation of hypertension in plasma, as they reported in the "Revista de la Sociedad Argentina de Biología" (Journal of the Society of Argentine Biology) in 1939 [23].

It is important to note that Taquini was not in Argentina exactly when hypertension was isolated. He had left to the United States to work at the Fatigue Laboratory at Harvard University alongside Dr. David B. Dill (1891–1986) and Dr. Paul Dudley White (1886–1973) within the frame of a fellowship in 1938 [31]. After 1 year working in Boston, Dr Taquini returned to Argentina and went on working as part of the team again, though he was not included in the work where the discovery was published [23].

2.3. The team in the United States arrives at the same conclusions

Only 2 months following the Argentine publication, Drs Irvine H. Page and O M. Helmer (Eli Lilly Research Laboratories, Indianapolis) published a full-scale study showing experimental evidence of the existence of a pressor substance, renin [32]. Their findings were in agreement with those reported by the Argentine team The Americans followed an entirely different approach: They dedicated themselves to concentrating renin from extracts of renal parenchyma and to study its vasoconstrictory function in dog tail and rabbit ear. These experiences showed that vasoconstriction was only observed when the animal tissue was perfused with plasma and did not happen when Ringer Lactate was utilized. In 1938, this led to the conclusion that there should be an activating substance for renin in plasma [33]. In 1939, this conclusion was presented by Page et al. at a reunion of the American Heart Association. Taquini, having been present in the auditorium and being aware of the progress of the Argentine team, refutes the arguments presented by Page saying it was not activated renin substance that caused vasoconstriction but an entirely different substance [20]. Page said that he was widely criticized for using the word activator of renin, but that he did so wanting to be wise, seeing as how the enzymatic reaction catalyzed by renin had not been demonstrated by that time [32]. By 1940, the team isolated angiotonin, the equivalent of hypertension that the Argentine team had obtained, through the interaction between the renin activator and renin [34]. Later, Page et al. reviewed the denomination called renin activator, hypertensinogen, or renin substrate [35].

2.4. Treaty between gentlemen

Braun-Menéndez et al. must have been very disappointed when a few months after their publication, Page and his team reached the same results utilizing another route. In 1957, 25 years

after Goldblatt' successfully raised blood pressure by inducing renal ischemia in dogs, the Regional Conference on Basic Mechanisms of Arterial Hypertension of the University of Michigan was held in Ann Arbor in his honor. The Organizing Committee was chaired by Drs Sibley W. Hoobler and David F. Bohr [15]. It was then that, beyond and far from conflict, Braun-Menéndez and Page agreed on a new nomenclature. As the result, the words angiotensinogen and angiotensin were born from the combination of the names originally set by both teams [32, 36].

Edward D. Frohlich (Alton Ochsner Distinguished Scientist at the Alton Ochsner Medical Foundation and Editor in Chief of the *Hypertension* journal) commented that Page had pointed out to him, while he was drinking martinis with Braun-Menéndez at a lunch during the Michigan meeting. It was by then that the compromised to solve the differences getting to a common nomenclature for their findings. Then, a very short and concise report was published in Science and was the very proof of their settled agreement [1, 36]. Actually, as Page recognized, cooperation was so close that claiming priority from any part would have been nonsense and they should share either the blame of the congratulations [32]. In 1985, Page sent a letter to Fasciolo expressing his hope that their resolve on the nomenclature issue would serve as an example for future generations of scientists to come. He shared an interesting message for the future generations of scientists saying that they could not possibly leave unsolved a historical puzzle so anyone might speculate on an imaginary dispute which had never occurred. In his letter, he clearly stated that the hypertension story should well serve as a model to follow when dealing with difficult situations, for example, with gentleness and making alliances [23].

The following years were strange, in the sense that Goldblatt and Skeggs in the United States, and leading groups in Europe went on using the Argentine name [15]. In contrast, Taquini et al. emphasized on the need of accepting unified names [37]. In one of his publications, Leonard T. Skeggs Jr. (1918–2002, biochemist in Case Western Reserve University, Cleveland, Ohio) mentioned: "I must explain, parenthetically that angiotensin was known to us, being followers of Harry Goldblatt and Eduardo Braun-Menéndez, as hypertension. Merlin Bumpus knew angiotensin as angiotonin. This was natural because Merlin worked with Irvine Page, who had coined the name angiotonin. It was a number of years later that Page and Braun-Menéndez agreed on the name angiotensin, and all the rest of us used the new name" [38].

Both teams shared the merit of the discovery, proving that beyond being great investigators they were essentially remarkable persons.

2.5. What comes after this great discovery

Following angiotensin discovery, the Argentine team focused on studying the enzymatic origin and release of angiotensin from angiotensinogen, the peptidic nature of angiotensin, renin secretion from kidneys, hepatic synthesis of angiotensinogen, pharmacological profile of angiotensin, and so [39–41]. Researchers like Alberto Agrest, Pedro C. Blaquier, Alberto C. Taquini, Jr and Ignacio J. de la Riva, who had begun their scientific career working at the *Instituto de Investigaciones Cardiológicas* (School of Medicine, University of Buenos Aires) years ago, returned to work there [15]. Leloir et al. conclusively confirmed the hepatic origin of renin studying nephrectomized dogs with and without liver ablation [42]. This had been proposed earlier by Page et al. showing no convincing evidence though [43].

In the 1940s, a powerful mineralocorticoid called electrocortin was described by Grundy. In 1953, Russian-born English Sylvia Agnes Sophia Tait (1917–2003) et al. identified electrocortin by means of chromatography. This hormone was then renamed aldosterone. In 1955, Jerome W. Conn (1907–1994) described primary hyperaldosteronism, as a result of a single adrenal adenoma [44].

Skeggs et al. succeeded in the isolation of Angiotensin I (Ang I). Others like Lentz et al., Elliot, and Peart could elucidate the structure of Angiotensin II (Ang II). In 1950, Bumpu's and Schwyzer's groups reported the synthetic pathway of angiotensin. Skeggs and his group recognized the existence of two different forms of angiotensin and also identified the angiotensin-converting enzyme (ACE) which was later revealed as a kininase II enzyme by Erdös. Then, an intimate relationship between angiotensin generation and bradykinin destruction was demonstrated [45].

The contribution of another Argentine scientist the chemist Miguel Angel Ondetti (1930–2004) is also important. He synthesized captopril in 1975, the first of the ACE inhibitors, the same as the enalapril precursor and others of substantial therapeutic importance, showing the pathophysiological relevance of angiotensin [46].

The discovery of the renin-angiotensin system is much more than theoretical knowledge required for any physiology book. It undoubtedly represents one of the highlights of Argentine physiological discoveries, and what is even more important, an example that science should follow: Value the progress made by colleagues, collaborate side by side, and pursue the ultimate truth.

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