The Renin-Angiotensin System and Progression of Renal Diseases
The Renin-Angiotensin System and Progression of Renal Diseases

Volume Editor

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46 figures, 7 in color, and 5 tables, 2001
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Fifteen years ago, it was assumed that almost everything about the renin-angiotensin system was known. Angiotensin II (ANG II) was thought to be a systemic circulating hormone. The paradigm that served well for decades was that renin is produced in juxtaglomerular cells of the kidney and acts as an enzyme in the circulation to form angiotensin I from angiotensinogen. Angiotensinogen in turn is produced in the liver. Angiotensin I is subsequently converted to ANG II, primarily by high angiotensin-converting enzyme (ACE) activity of the lungs. ANG II was viewed as a peripheral vasoconstrictor, a regulator of glomerular filtration, and a secretagogue for aldosterone. The efficacy of ACE-inhibitor therapy, in terms of lowering blood pressure, has been known since the mid 1970s. However, the drugs were considered at least nephrotoxic if not down right dangerous and were commonly administered when everything else had failed. The scientific input that changed this simple view of ANG II forever, comes from two different sources. First, it was recognized that specific organ tissues exhibit their own local renin-angiotensin systems (RASs). Such tissue-specific RASs function mainly independent from their systemic counterparts. Local RASs have been detected in many organs including the kidney, brain, vascular wall, heart, and adrenal glands, among others. The cloning of genes for the diverse RAS components and the generation-specific reagents to detect their protein and mRNA expression on a cellular level have greatly facilitated the characterization of these local systems.

Today, it is known that even specific cell populations, such as renal proximal tubular cells for example, exhibit all components of active RASs including angiotensinogen, the ANG II receptors, and ANG II-degrading enzymes. The second
A major breakthrough in the study of RASs came with the characterization of ANG II receptors. Although it has been known since the early 1980s that there is heterogeneity in ANG II-receptor expression and affinity using classical binding assays, many investigators tried unsuccessfully to isolate ANG II receptors by applying classical protein purification techniques. In 1988, the properties of specific competitive nonpeptide ANG II-receptor antagonists of the imidazole-5-acetic acid compound group provided an investigative breakthrough. The specific ANG II-receptor antagonists were influential in the cloning of the first ANG II receptor in 1991 by two groups. In parallel, it became clear that ANG II has many additional properties above and beyond being a simple vasoconstrictor. Landmark discoveries were ANG II’s function in tubular transport, and its role as a growth factor. The profibrogenic role of ANG II was appreciated. More recently, the function of the ANG II as an immune regulator has been identified.

In addition, it has gradually become clear that not only ANG II, but also related peptides such as angiotensin III, angiotensin IV, and angiotensin (1–7) have specific effects independent of the parent substance. These ‘other’ angiotensins partly act through receptors other than AT1 and AT2. The enormous deluge of novel information regarding the RAS is also mirrored in the submission of abstracts to the annual meeting of the American Society of Nephrology. ANG II-related abstracts rose from 26 in 1988 to more than 70 in 2000.

Sharon Anderson and co-workers published their landmark study in 1985 demonstrating that an ACE inhibitor reduced proteinuria and limited glomerular injury in rats with an experimentally induced reduction in renal mass. It took almost a decade until ACE inhibitors were also validated as providing protection against the progression of renal insufficiency in humans with various renal diseases. It is now clear that part of these protective effects are independent of a reduction in blood pressure and may likely involve antagonizing ANG II’s growth-promoting, profibrogenic, and proinflammatory effects. There is also evidence that ACE inhibitor treatment may induce regression of renal disease under certain circumstances or protect renal structure, even in patients without proteinuria. AT1-receptor antagonists may have similar salutary effects. However, this notion must first be proved in still ongoing studies. Such studies must show that the drugs are at least equal to, or perhaps even better than ACE inhibitors, in slowing the progression of chronic renal disease.

This volume of Contributions to Nephrology is timely and deals with an important topic of today’s nephrology research. This truly international endeavor to summarize current knowledge in the rapidly developing field was undertaken by experts who made many of the key discoveries that constitute our contemporary understanding of ANG II as a central factor in the progression of renal disease. Basic concepts of the RASs, ANG II’s profibrogenic and proinflammatory actions as well as specific disease entities are reviewed. We have
come a long way from the cold Helsinki winter more than 100 years ago when Tigerstedt and Bergmann first prepared a saline extract from rabbit kidney and found an increase in blood pressure when this extract was intravenously injected into a bilaterally nephrectomized rabbit. Today, ANG II is considered a multifarious peptide with many properties. However, the great German clinician Franz Volhard (1872–1950), who predicted the existence of ANG II based almost exclusively on clinical observations, said concerning medicine: ‘The truth of today is the error of tomorrow’. It will be interesting to see whether or not he was correct regarding the current understanding of ANG II in the progression of renal disease.

Gunter Wolf