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Renin Angiotensin System and Cardiovascular Disease

Humana Press

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Preface

Experimental and clinical evidence supports the view that the activation of the renin angiotensin aldosterone system is involved in cardiovascular pathology including hypertension, heart failure, myocardial ischemia, and atherosclerosis. The present volume describes the intricacies involved in these processes, including the influence of prorenin/renin, angiotensin II, angiotensin (1-7), and aldosterone on cardiac and vascular functions as well as their involvement in the generation of cardiovascular diseases. Fundamental aspects like intracellular signaling, regulation of cell volume in the failing heart, and the presence of an intracrine renin angiotensin system are discussed. Moreover, the role of the mineralocorticoid receptor as an important component of the intracrine renin angiotensin system and as a regulator of extracellular action of angiotensin II is described, reinforcing the view that aldosterone inhibitors are helpful in the treatment of heart failure and hypertension. Let us hope the important topics included here motivate basic and clinical investigators and contribute to the development of new therapeutic approaches for cardiovascular diseases.

We want to thank the distinguished authors and Humana Press for the opportunity to publish this important book.

Walmor C. DeMello
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Chapter 1
Systemic Versus Local Renin Angiotensin Systems. An Overview

Walmor C. DeMello and Richard N. Re

Abstract The concept of local renin angiotensin systems in the cardiovascular system is discussed, and evidence is presented that these systems work independently of the systemic one.

Particular attention was given to the presence of an intracrine renin angiotensin aldosterone system in the heart and the novel role of the mineralocorticoid receptor. Furthermore, the influence of the renin angiotensin system on cell volume regulation is briefly discussed.

This chapter includes an overview of these important biological concepts and provides an introduction to the topics that are discussed in detail by different authors throughout the book.

The renin angiotensin system (RAS) is an enzymatic cascade in which renin derived from the juxtaglomerular cells (JG) of the kidney acts on an hepatically synthesized substrate, angiotensinogen, to generate the decapeptide angiotensin I. This peptide is cleaved by angiotensin-converting enzyme (ACE), primarily in the pulmonary circulation, to the vasoconstrictor and aldosterone secretagogue, angiotensin II. The blood pressure-elevating action of angiotensin II, together with its direct suppressive action on JG cells and the volume expansion produced by enhanced aldosterone-driven sodium retention, leads to the suppression of JG renin secretion, thereby forming a negative feedback loop. Volume depletion or lowered blood pressure stimulates renin release, leading to pressure elevation and volume retention. Elevated blood pressure or hypervolemia suppresses renin release and tends to lower blood pressure and intravascular volume. However, as powerful as this construct is, accumulating evidence indicates that it is incomplete in that it focuses solely on angiotensin synthesis in the circulation. For example, the blood pressure response to ACE inhibitors, which block ACE-driven angiotensin I generation, is not predicted by circulating renin activity, suggesting that RAS activity in tissues may be relevant [1]. Indeed, early on it was shown that most angiotensin II generation takes place in the arterial wall where angiotensin II is generated from RAS components taken

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up from the circulation [2]. In the follow-up to these observations, it was then noted that components of RAS were taken up by many tissues [3], leading to the possibility that angiotensin II synthesis could be locally influenced by the relative uptake of components at those sites [4] and the synthesis of the various components can be detected in various tissues under various conditions [3]. Together, these observations made the concept of local RASs in tissues compelling. It must be recalled that renin in the circulation is not strictly rate-limiting for angiotensin I production. That is, angiotensinogen circulates at a concentration close to the K_m for the generation of AI by renin. Therefore, an increase in angiotensinogen will lead to an increased production of angiotensin I [3, 5]. Thus, if a tissue were to augment tissue concentration of angiotensinogen by local production, more angiotensin I and likely angiotensin II would be generated in that tissue as compared to a tissue that did not augment the concentration of angiotensinogen with local synthesis. Also, it must be noted that the alteration of JG renin secretion cannot possibly equalize the angiotensin concentrations in the two tissues, which clearly indicates local regulation of local angiotensin II [5]. This, in turn, is particularly important because, of all the components of the RAS, the synthesis of renin in tissues (with a few exceptions) is the most contentious. Indeed, in many tissues the reported renin secretion is very low, suggesting that this renin could influence angiotensin production in only a small area [4]. Nonetheless, renin upregulation has been reported in the adrenal gland following nephrectomy where it helps maintain aldosterone secretion, as well as in the left ventricle and other tissues such as the heart in specific circumstances [6]. But it is clear from the arguments presented above that even in the absence of local renin synthesis, local regulation of angiotensin production can occur through local synthesis of other RAS cascade components [3]. Differential uptake of renin into tissues provides another mechanism for local RAS regulation. Although in normal heart cardiac renin seems to be related to its uptake from plasma [5], evidence is available that renin expression is increased after myocardial infarction [7] and after stretch of the cardiomyocytes [8]. On the other hand, a renin transcript that does not encode a secretory signal [9] and remains inside the cell is overexpressed during myocardial infarction – suggesting that intracellular renin has functional properties.

Indeed, previous studies showed that intracellular renin and Ang II administration impairs cell coupling in the heart [10, 11] and intracellular Ang II reduces the inward calcium current in the failing heart [12], supporting the view that there is a functional intracrine renin angiotensin system [13–17]. This intracrine angiotensin II must properly also be considered an aspect of the tissue RASs, and it may well play an important role in such pathological processes as left ventricular hypertrophy, cardiac arrhythmias and cardiac myocyte apoptosis [13, 17] (see also Chapters 4 and 7).

Other studies have demonstrated upregulation of angiotensinogen and angiotensin-converting enzyme (ACE) in tissues under normal or pathological conditions. The enzyme chymase, which can substitute for ACE in the conversion of angiotensin I to angiotesnin II, is also expressed in multiple tissues and upregulated in some circumstances [17]. Even more telling is the recent demonstration of a (pro)renin receptor in mesangial and other cells, which signals using classical

second messengers following the binding of prorenin or renin [18, 19]. This reveals the hormonal nature of (pro)renin. At the same time, binding of prorenin to the receptor activates its binding site so that the prohormone becomes enzymatically active, generating angiotensin I in the vicinity of cell surface receptors [19]. Similarly, renin bound to the receptor becomes more enzymatically active [4, 20]. These observations make clear that the biological activity of the RAS in a tissue can be powerfully influenced by the level of expression of the (pro)renin receptor in the tissue – a variable totally hidden from any analysis of the concentrations of circulating RAS components. The potential importance of this finding is suggested by the fact that prorenin levels are elevated in diabetic patients, and high concentrations of circulating prorenin are a predictor of retinopathy – a finding made all the more compelling by the observation that prorenin can be synthesized locally in the Mueller cells of the retina [19]. In addition, it now appears that there exist countervailing systems which while not influencing angiotensin II action at the receptor nonetheless offset some of its effect. For example, an ACE homologue, ACE2, has recently been described and studied [21]. ACE2, unlike ACE, does not convert angiotensin I to angiotensin II, but rather its principal action seems to be the conversion of angiotensin II to the hepatapeptide angiotenin (1–7), which operating through its own receptor offsets many of the vasoconstrictive and growth-promoting actions of angiotensin II [22, 23], improving impulse propagation during ischemia reperfusion through activation of the sodium pump, reducing the incidence of slow conduction and the generation of cardiac arrhythmias [24] (see also Chapter 10).

Recently, it was found that chronic administration of eplerenone, a mineralocorticoid receptor blocker, reduces the expression of AT1 receptors at surface cell membrane as well as intracellularly inhibiting the intracrine and extracellular actions of Ang II on the inward calcium current in the failing heart [25]. These findings indicate that the mineralocorticoid receptor is involved in the regulation of intracellular and extracellular actions of Ang II and lead to the concept that there is an intracrine renin angiotensin aldosterone system (see also Chapter 7). It is possible to conclude that the beneficial effects of eplerenone in patients with heart failure are in part explained by the suppression of fibrosis, hypertrophy and electrophysiological abnormalities elicited by Ang II [26].

It is well known that regulation of cell volume is essential for normal cellular function. Recent evidence is available that the renin angiotensin system is involved in the regulation of heart cell volume [27] because extracellular Ang II increases cell volume through inhibition of the sodium pump and activation of the Na-K-2Cl cotransporter, while intracellular Ang II reduces the cell volume by activating the Na-K pump [27]. These findings are relevant particularly to myocardial ischemia which by itself causes cell swelling. According to these observations, the activation of the circulating renin angiotensin system is particularly harmful during myocardial ischemia while the activation of the intracrine renin angiotensin system might be beneficial by decreasing the cell volume (see Chapter 7).

In conclusion, evidence is available that there are local renin angiotensin systems in the cardiovascular system, and that a functional intracrine renin angiotensin aldosterone system contributes to cardiovascular pathology [13, 25, 28, 29].

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Chapter 2
Clinical Import of the Local Renin Angiotensin Aldosterone Systems

Edward D. Frohlich

Abstract The concept of local renin angiotensin (and possibly aldosterone) systems has been a relatively recent interjection to the investigative milieu. Much interest and important studies have resulted, and reference to applicability to disease and disease mechanisms is still of innovative and imaginative clinical and experimental studies. To this end, there are several areas of pertinence which have evolved including the underlying causations, mechanisms, and treatment of a number of diseases. Among those fascinating and provocative study areas is the need for additional motivated investigation related to ventricular and vascular hypertrophy, remodeling, and cardiac and renal failure and new thinking related to lifestyle modifications (including those related to salt excess, obesity, and responses to various drugs, clinically useful or otherwise). We have much confidence that these and other areas for study will be productive and useful and will lead to important clinical approaches and contributions on the issue of existing local RAAS.

Much of the present-day clinical and investigative considerations of the renin angiotensin aldosterone system (RAAS) as well as this monograph concern the classically accepted endocrine RAAS system. The overall concepts involved have been extremely important in understanding the biology, physiology, and clinical relevance of this system as it pertains to cardiovascular and renal diseases, and they have led to the synthesis of new classes of therapeutic agents which have changed dramatically approaches to disease. Consequently, these changes have resulted in remarkable reductions in the morbidity and mortality of cardiovascular, renal, brain, and other diseases.

2.1 The Classical System

The framework of this classically understood system embodies the synthesis of the enzyme renin in the kidney, the variety of mechanisms that promote and stimulate its release by the renal juxtaglomerular apparatus, and its action on the complex

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protein angiotensinogen which is synthesized in the liver. The consequence of this action is the production of the decapeptide angiotensin I which, as it passes through the pulmonary circulation, loses its terminal two peptides by virtue of the proteolytic action of the angiotensin-converting enzyme. The resultant octapeptide angiotensin II is the potent vasopressor agent which is responsible for vasoconstriction; release of aldosterone by the adrenal cortex and consequent retention of sodium and water by the kidney; stimulation of specific brain centers responsible for increased cardiovascular adrenergic outflow and thirst; and local endothelial actions that promote mitogenesis, hypertrophy, collagen synthesis and tissue fibrosis, apoptosis, inflammation, and, no doubt, other intracellular signaling and other biological and pathophysiological effects [1]. Already, many of these latter actions have been incorporated in our consideration of the clinical diagnosis used clinically with respect to "endothelial dysfunction" [2, 3]. Although relatively recently described, there have been several additional components to the RAAS which have intriguing biological actions that have the potential for developing new physiological and pathological implications [4].

2.2 The Local Systems

Although several of the foregoing actions of angiotensin II are relatively new, they have already been inculcated into a new dimension of the classical RAAS. This then relates to the overall concept of this monograph. It therefore concerns the concept of local RAAS (hereafter to be considered in plurality) that affect the structure and function of specific target organs of disease, including heart, blood vessels, kidney, and, no doubt, other organs [5]. To this end, although to some extent considered by some to be controversial, each of the components of these local RAAS has been identified within these foregoing organs although certain specific components (e.g., the putative synthesis of the enzyme renin within the heart) of the system. Indeed, these local systems already have important clinical and even therapeutic considerations and implications in health and disease [6]. In this respect, we also have deliberately included the hormone aldosterone in this local system since this hormone has already been identified to be present in some of these systems as for vital consideration of the existence of local RAAS [7]. Thus, although perhaps still in the realm of speculation, consideration of these local systems and newer components and metabolites of the system is neither premature, irrelevant, nor speculative for present-day consideration in this monograph. This monograph has been conceived and organized to stimulate further fundamental and clinical investigations dealing with the impact of the RAAS in disease. Thus, the participants of this workshop are of the unanimous opinion that these local RAAS are no longer a subject of debate; indeed, this is an important area of fundamental and clinical study, which is the intellectual commitment of this entire volume.

To this end, the existence of these local systems in certain organs and the information derived from recent and current investigations provide the substance of

tentative (but appealing) and exciting information which relates to specific clinical problems. Thus, this rather selective and speculative discussion of local RAAS in disease is included to tantalize the interested reader, student, and investigator in certain specific clinical situations including the pathogenesis and pathophysiology of ventricular hypertrophy in hypertension; ventricular and vascular remodeling in hypertensive and ischemic cardiovascular diseases; secondary (e.g., renal) therapeutic responses to disease; structural and functional responses of organs and in toxemias of pregnancy, to certain lifestyle and other interventions (e.g., salt excess) in hypertension. Ever since the Framingham Heart Study demonstrated that left ventricular hypertrophy (LVH) was a major risk factor predisposing the hypertensive patient to increased morbidity and mortality associated with coronary heart disease [8], we have been intrigued about the fundamental pathophysiological mechanisms of LVH that account for this risk. Thus, soon after this landmark epidemiological study, we initiated our earliest clinical and pathophysiological studies of this problem in which we elucidated the clinical correlates associated with the development of LVH [9]. We perceived the well-recognized concept that arterial pressure increased as an adaptive response of the left ventricle to the progressive increase in afterload in response to the increasing total peripheral resistance imposed by arteriolar constriction imposed.

Our subsequent studies introduced the feasibility of the new noninvasive technology of M-mode echocardiography in order to identify the pathophysiological sequence in the clinical development of LVH [10]. We confirmed that coincident with the developing increased left ventricular (LV) mass and wall thicknesses, the earlier events associated with electrocardiographic evidence of left atrial abnormality were also identified with increased left ventricular mass and LVH. Moreover, these structural changes were associated with functional changes of LV functional impairment early in LVH [10]. These early findings suggested to us our ongoing concern that the development of LVH in hypertension were not solely the consequence of "adaptive hypertrophy". We soon focused our attention on the functional events associated with antihypertensive therapy and whether it reversed the increased LV mass [11–14]. These studies indicated that certain agents decreased LV mass and impaired the ventricular functional responses. However, other agents decreased LV mass and were associated with normal ventricular function following reversal. We also showed some of those therapeutic agents that reduced LV mass also maintained normal function when the ventricular afterload was abruptly increased to pretreatment levels; other agents did not maintain that normal function [15–23]. These findings suggested to us that associated with treatment were intrinsic biological and physiological alterations which were related to the "reversal of hypertrophy" and were also responsible for these disparate functional changes.

Our ensuing hypothesis was supported by our subsequent reports that the reduction of LA mass was achieved within only 3 weeks of therapy at a time when arterial pressure had not been reduced. In some studies, this was achieved with doses of some of these agents that had not even reduced arterial pressure [18, 20]. We therefore restated our concept to the development and reversal of the increased LV mass in hypertension, which were associated with nonhemodyanamic as well

as hemodynamic factors [24, 25]. These provocative findings permitted a further assessment of the issue concerning whether there were additional comorbid pathophysiological alterations associated with LVH. This concept was soon supported by our studies in untreated naturally developing spontaneously hypertensive rats (SHR) and their normotensive (control) Wistar-Kyoto (WKY) rats, matched for gender and age. In these studies we learned that they developed progressive ventricular ischemia not only in the hypertrophied LV but also in the nonhypertrophied right ventricles and in the LV of the WKY rats. Furthermore, this progressive ischemia with aging was closely related to increased hydroxyproline deposition and histological evidence of fibrosis in the extracellular matrix of the ventricle as well as surrounding the intramural arterioles in the chamber [26]. These findings were supported further by additional reports demonstrating pathological changes of apoptosis [27] and inflammatory changes [25]. Hence, we concluded that the underlying mechanisms of risk associated with LVH in hypertension related to ischemia, fibrosis, apoptosis, and inflammatory changes [23, 25]. More recently, we added yet another factor that complicates risk associated with LV – certain environment factors including excessive dietary salt-loading (*vide infra*) (28–30].

In this chapter, I shall not discuss the important experimental and clinical evidence that provides abundant clinical and experimental data demonstrating that angiotensin II contributes importantly to the development of LVH as well as the remodeling of the LV and the arterioles in clinical and experimental hypertension. This is the subject of separate chapters in this monograph [31, 32]. The evidence is abundant with reference to the numerous well-designed placebo-controlled multicenter pharmacological clinical trials involving administration of either angiotensin-converting enzyme agents or angiotensin II type 1 receptor blocking agents to patients following myocardial infarction. These trials demonstrated the efficacy of these drugs in reducing not only arterial pressure but cardiovascular morbidity and mortality, cardiac failure, and even a second myocardial infarction [6].

2.3 Structural and Function Response of Organs to Salt-Loading

Abundant clinical and experimental evidence has accumulated in recent years to the response of various organs (i.e., heart, vessels, kidney) to excessive salt-loading [28–30, 33*).* Until relatively recently, much evidence of risk with salt-loading has been ascribed to increase in arterial pressure; however, more recent reports have demonstrated clearly that salt-loading (experimentally as well as clinically) was associated with increased cardiovascular morbidity and mortality as well as structural and functional alterations of heart, aorta, and kidney [34–36*).* Recent data have shown that co-treatment with angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors along with the salt-loading will prevent the structural and functional end-organ damage [30, 33, 35]. The reader is referred to those specific references that provide abundant data and references to support the foregoing statements. Moreover, sodium-restricted diets in prehypertension patients will significantly reduce cardiovascular morbidity and mortality as compared with

control group patients whose daily sodium diet was not reduced [36]. These findings provide important data that relates the data derived from chronic salt-loading diets in the earlier epidemiological studies that demonstrated a close relationship between salt-loading and the prevalence of hypertension in large population groups [37–39].

2.4 Secondary Organ Responses of Therapy to Certain Treatment

Over the past five or more decades of antihypertensive therapy and the well-documented evidence of associated reduction in cardiovascular morbidity and mortality, a disturbing conundrum has complicated this therapeutic effort [33]. Thus, each national and international report has attested to the remarkable reduction in morbidity and mortality of such disease endpoints in hypertensive emergencies, stroke, and coronary heart disease [40, 41]. However, over the years, the successive publications of these very same reports have continued to provide an ever-increasing prevalence, morbidity and mortality resulting from end-stage renal disease and of cardiac failure [40, 41]. How can we reconcile these startling data? In response to this shocking and as yet unresolved conundrum, we have suggested that this may be the result of long-term stimulation or ineffective inhibition of the local cardiac and renal renin angiotensin systems. Indeed, there are abundant experimental data which have demonstrated that prolonged diuretic treatment promotes structural and functional renal abnormalities which can be prevented by co-existent treatment with an angiotensin-converting enzyme agent or an angiotensin II type 1 angiotensin receptor blocker [42, 43]. This led to our suggestion resulting from long-term diuretic therapy, there is a secondary increase of renin generation in the kidney that promotes the local synthesis of angiotensin II and its attendant pathophysiological alterations from secondary renal renin generation [34]. These latter studies have demonstrated that in addition to promoting renin release from the juxtaglomerular apparatus of the kidney, a second source of renin production occurs in renal tubular cells [44, 45]. In addition, salt-loading without adequate treatment with either an ACE inhibitor or an angiotensin II type 1 receptor blocker may not protect or prevent stimulation of the local cardiac RAAS. These salt/pharmacological stimuli or inhibition of local renal and cardiac RAAS may be analogous to the multiplicity of Yin/Yang biological systems in the body. Therefore, unless the consequent events stimulating the increased renin synthesis and angiotensin II generation are prevented, the adverse structural and functional cardiac and renal biological events may result.

2.5 Toxemias of Pregnancy

Finally, a word or two may be in order concerning yet another clinical expression of pathological stimulation of a local RAAS in the uterus or other female genital organs. Several recent reports have suggested that the utero-placental unit may be the source of stimulated synthesis of components of the RAAS [46, 47]. In part, this

may be related to inadequate perfusion of the utero-placental unit and/or a consequent relative hypoxemia stimulation, endothelial dysfunction of that unit, upregulation of specific genes, generation of autoantibodies, and generation of certain humoral or hormonal factors, inflammatory changes and production of an increased arterial pressure and proteinuria that are characteristic of pre-eclampsia or eclampsia [48, 49]. Each of these possible pathophysiological changes may be responsible for the establishment of toxemia alone or in association with preexisting or otherwise predisposed underlying mechanisms of hypertensive disease. Although these provocative findings are of great significance, what is most important is that this much neglected area for study has now captured much needed interest and work.

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Chapter 3
Renin, Prorenin, and the (Pro)Renin Receptor

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Abstract The discovery of a receptor for renin and for its inactive precursor prorenin, and the introduction of renin inhibitors in therapeutic, has renewed the interest for the physiology of the renin angiotensin system (RAS) and has brought prorenin back in the spotlight. The receptor known as renin for (*P*ro)*R*enin *R*eceptor binds both renin and prorenin, and binding triggers intracellular signaling involving the MAP kinases ERK1/2 and p38. The MAP kinases activation in turn upregulates the expression of profibrotic genes, potentially leading to fibrosis, growth, and remodeling. Simultaneously, binding of renin to (P)RR increases its angiotensin I-generating activity, whereas binding of prorenin induces the inactive prorenin to become enzymatically active. These biochemical characteristics of (pro)renin binding to (P)RR allow to distinguish two aspects for the new (pro)renin/(P)RR system, an angiotensin-independent function related to the intracellular signaling and its downstream effects and an angiotensin-dependent aspect related to the increased generation of angiotensin I on the cell surface. Ongoing experimental studies should now determine which of the two aspects is the most important in pathological situations.

List of Abbreviations

(pro)renin:	designate renin and prorenin
AOG:	angiotensinogen
Ang I and Ang II:	angiotensin I and angiotensin II
ACE:	angiotensin-converting enzyme
HRP:	handle region peptide
(P)RRB:	(pro)renin receptor blocker

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3.1 Introduction

The discovery of a specific receptor for renin and for its precursor, prorenin, has modified our conception of renin being just an enzyme responsible for the cleavage of angiotensinogen and of prorenin being just an "inactive" proenzyme. The receptor named (P)RR binds with similar affinity to renin and prorenin. Binding to the receptor allows these enzymes to display increased enzymatic activity on the cell surface and trigger intracellular signaling that in turn modifies gene expression. This implies that renin may also be considered as a hormone and that a function was finally found for prorenin. Information on the role of the (P)RR in organ damage was obtained only recently, and experimental models suggest that (P)RR may play a role in the development of high blood pressure and of glomerulosclerosis, in cardiac fibrosis, in diabetic nephropathy and retinopathy by "non-proteolytically" activating prorenin. Importantly, blocking prorenin/(P)RR interaction with a putative (P)RR blocker called "handle region peptide" (HRP) was claimed to not only prevent diabetic nephropathy but also reverse the glomerulosclerosis of diabetic nephropathy. If this is true, then it would make (P)RR a major therapeutic goal.

3.2 Renin and Prorenin

The term "renin" is used to cover two entities:

– renin, the mature enzyme which is catalytically active in solution and
– prorenin, the proenzyme form of renin which is virtually inactive in solution.

Prorenin is synthesized in many organs, the kidney of course, and also the eye, the brain, the adrenal gland, the submandibular gland, the glands of the reproductive system and the adipose tissue. All these tissues are able to secrete inactive prorenin in the surrounding milieu and in plasma, but the only tissue able to mature and secrete active renin is the kidney. Indeed, prorenin, but not renin, is still detectable in blood after bilateral nephrectomy, although prorenin levels are lower than in normal subjects indicating that, although kidney is the main if not the only source of renin in the body, other tissues are able to release prorenin in the circulation [1, 2].

3.2.1 Renin

Renin is an aspartyl protease with a typical structure made of two lobes. The cleft in between the lobes contains the active site characterized by two catalytic aspartic residues. Renin is a highly specific enzyme and has only one known substrate, angiotensinogen (AOG). Renin cleaves AOG to generate angiotensin (Ang) I that is converted into Ang II by the angiotensin-converting enzyme. In addition to its substrate specificity, renin catalytic activity is species-specific and renin can only

cleave AOG of the same species. Renin is synthesized by the renin-producing cells of the juxtaglomerular apparatus (JGA) and is stored as active enzyme in secretory granules from which it is released upon acute stimulation of the JGA. Renin has also been called "active" renin in opposition to the enzymatically "inactive" form of renin, prorenin [3].

3.2.2 Prorenin

Being the precursor of renin, prorenin was assumed to have no function of its own, and yet it represents 70–90% of total renin in human plasma. The absence of enzymatic activity of prorenin is due to the fact that a 43-amino acid N-terminal prosegment covers the cleft of the active site. Unlike for the proenzymes of trypsin and of cathepsin D, prorenin does not undergo auto-activation in the plasma ant its activation takes place under two circumstances: a proteolytic activation by a proconvertase which identity is still not established and that removes the prosegment, an irreversible process that occurs in physiology in the renin- producing cells of the juxtaglomerular apparatus exclusively; and non-proteolytic activation in a test tube by exposure to low pH (pH < 3.0) or cold (4°C) and which can be imagined as a reversible unfolding of the prosegment. In plasma and in physiological conditions, however, approximately 2% of prorenin is in the open, active form and can display enzymatic activity, whereas 98% is in closed and inactive form [3].

In contrast to renin, prorenin is released constitutively and renin and prorenin levels are usually well correlated. However, under some physiopathological circumstances such as pregnancy and diabetes, prorenin levels exceed by far those of renin. In diabetes mellitus complicated by retinopathy and nephropathy, prorenin is increased out of proportion to renin and this increase starts before the occurrence of microalbuminuria, so that prorenin level was suggested to be a marker of microvascular complications in diabetic patients [4, 5]. Pregnant women also have high plasma prorenin levels, likely derived from the ovaries. The reason for the elevated prorenin levels in diabetes and pregnancy is unknown.

3.3 The (Pro)Renin Receptor

Interestingly, the renal vasodilator response to captopril in diabetic subjects correlated better with plasma prorenin than plasma renin [6]. Possibly therefore, prorenin rather than renin is responsible for tissue angiotensin generation despite the absence of prorenin–renin conversion that cannot occur elsewhere than in the JGA cells [7]. In support of this concept, transgenic rodents with inducible prorenin expression in the liver display increased cardiac Ang I levels, cardiac hypertrophy, hypertension, and/or vascular damage without evidence for increased circulating renin or angiotensin [8–10]. Even more surprising, increased tissue Ang I formation occurred even when expressing a non-activatable prorenin variant mutated in the