# PARADOXICALLY EFFECTS OF RENIN-ANGIOTENSIN SYSTEM SUPPRESSION

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***Abstract***

*Is any specific organ protection by blocking the renin-angiotensin system?*

*What is the role of the renin-angiotensin system (RAS) in progressive renal disease?*

*The renoprotective effect of ACE-inhibitors and angiotensin II (Ang II) receptor blockers is not only mediated via their renal hemodynamic effects, but also through non-hemodynamic mechanisms?*

*What is the clinical evidence for the importance of local renin-angiotensin system (RAS)?*

*These are several questions of a medical reality: that pharmacological blockade of renin-angiotensin system (RAS) is paradoxically effective although circulating plasma renin activity (PRA) is low. An overview of the normal function of the system, as well as ramifications of its dysfunction (overactivity) and potentials for therapeutic blockade, is provided below.*

***Keywords:*** *renin-angiotensin system, plasma renin activity, ACE-inhibitors, angiotensin II (Ang II) receptor blockers, microalbuminuria.*

***Rezumat***

*Se poate obține vreun efect de protecție specifică a organelor prin blocarea sistemului renină-angiotensină?*

*Care este rolul sistemului renină-angiotensină (RAS) în boala renală progresivă?*

*Efectul renoprotector al inhibitorilor ECA și al blocanților receptorilor angiotensinei II (Ang II) nu este mediat numai prin efectele lor hemodinamice renale, ci și prin mecanisme non-hemodinamice?*

*Care sunt dovezile clinice pentru importanța sistemului renină-angiotensină (RAS)local?*

*Acestea sunt câteva întrebări ale unei realități medicale: că blocarea farmacologică a sistemului renină-angiotensină (RAS) este paradoxal de eficientă, deși activitatea reninei plasmatice circulante (PRA) este scăzută. O privire de ansamblu asupra funcției normale a sistemului, precum și a ramificațiilor disfuncției acestuia (supraactivitate) și potențialelor de blocare terapeutică este oferită mai jos.*

***Cuvinte cheie:*** *sistem renină-angiotensină, activitate renină plasmatică, inhibitori ECA, blocanți ai receptorilor angiotensinei II (Ang II), microalbuminurie.*



# Internal Medicine

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### The role of the renin-angiotensin system in progressive renal disease

The renin-angiotensin system (RAS) plays a crucial role in the regulation of renal, cardiac, and vascular physiology, and its activation is central to many common pathologic conditions including hypertension, heart failure, and renal disease. The classical (historical) view of the RAS pathway begins with renin cleaving its substrate, angiotensinogen (AGT), to produce the inactive peptide, angiotensin I, which is then converted to angiotensin II by endothelial angiotensin-converting enzyme (ACE). ACE activation of angiotensin II occurs most extensively in the lung. Angiotensin II mediates vasoconstriction as well as aldosterone release from the adrenal gland, resulting in sodium retention and increased blood pressure[1].

The main components of the renin-angiotensin system (RAS) are:

- **Renin** is synthesized from the precursor, prorenin, in juxtaglomerular cells Active renin is stored in and released from secretory granules and then cleaves the decapeptide, angiotensin I, from renin substrate (AGT). Renal hypoperfusion, caused by hypotension or volume depletion, and increased sympathetic activity are the major physiologic stimuli to renin secretion. Circulating renin can be measured indirectly or, less often, directly; such measurements are often used in the context of adrenal disease.
- **Prorenin,** the precursor of renin, is constitutively expressed and is also secreted into the systemic circulation. Despite its abundance, the physiological role of prorenin remains unclear.
- **The (pro)renin receptor (PRR)** is a receptor for both prorenin and renin. When bound to the PRR, the ability of renin to catalyze the conversion of AGT to angiotensin I is increased fourfold. When prorenin binds to the PRR, it undergoes a conformational change that uncovers its active catalytic site, permitting prorenin to function as enzymatically active renin. In addition, binding of prorenin or renin to the PRR activates various signaling pathways. However, an important physiologic role for the PRR in blood pressure regulation is uncertain.
- **AGT** is the sole substrate for renin. The liver is the main source of AGT production.
- **ACE** catalyzes the conversion of the decapeptide, angiotensin I, to the octapeptide, angiotensin II. This conversion occurs most extensively in the lung by ACE generated in vascular endothelial cells; ACE is also located in the glomerulus as well as other tissues. Thus, the pleiotropic effects of

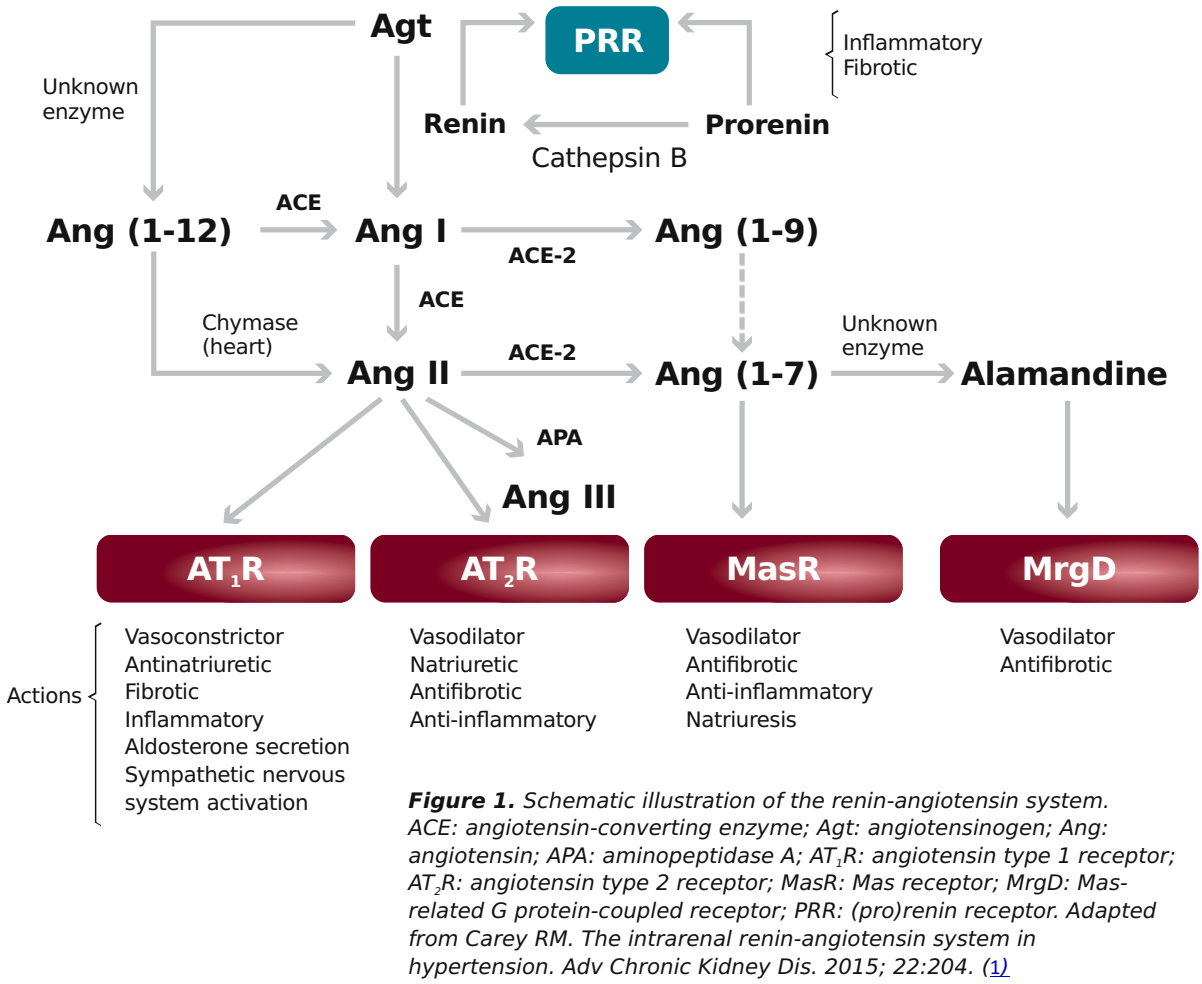


***Figure 1.*** *Schematic illustration of the renin-angiotensin system. ACE: angiotensin-converting enzyme; Agt: angiotensinogen; Ang: angiotensin; APA: aminopeptidase A; $AT_1R$: angiotensin type 1 receptor; $AT_2R$: angiotensin type 2 receptor; MasR: Mas receptor; MrgD: Mas-related G protein-coupled receptor; PRR: (pro)renin receptor. Adapted from Carey RM. The intrarenal renin-angiotensin system in hypertension. Adv Chronic Kidney Dis. 2015; 22:204. (1)*

pharmacologic ACE inhibition may be due in part to inhibition of local, tissue ACE, in addition to inhibition of ACE in the lung. A homolog to ACE has been identified and named angiotensin-converting enzyme 2 (ACE2). ACE2 cleaves an amino acid from angiotensin II, forming angiotensin$^{(2\text{-}8)}$ which regulates a pathway that has opposing physiology to ACE and angiotensin II.

- **Angiotensin II** effects include arteriolar vasoconstriction and sodium reabsorption by the kidney. Both actions tend to reverse the hypotension or hypovolemia that is usually responsible for the stimulation of renin secretion. Beyond these effects, however, angiotensin II has a host of important and mostly deleterious actions. Most of these effects are mediated by the angiotensin II type 1 receptor (AT1R). Angiotensin II and angiotensin III binding to the sparsely expressed angiotensin II type 2 receptor (AT2R) have effects that generally counteract its classical actions, producing vasodilation and natriuresis.
- **Aldosterone**, an adrenal steroid hormone, binds to the mineralocorticoid receptor in various tissues, inducing pleiotropic effects in the kidney (where it increases sodium **and water reabsorption and potassium**



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**secretion, the heart, and elsewhere.**

- **Extrarenal renin-angiotensin systems** exist and are likely to have important functions. Angiotensin II can be synthesized at a variety of sites, such as the kidney, vascular endothelium, adrenal gland, and heart. These local renin-angiotensin systems are likely involved in renal sodium handling, cardiovascular regulation, and other functions ranging from cognition to ovulation.

However, it is widely recognized that this classical view of the endocrine RAS pathway represents an incomplete description of the system. Instead of one simple circulating RAS, it is recognized that there are also several tissue (local) renin-angiotensin systems that function independently of each other and of the circulating RAS.

Angiotensin II generation at the tissue level by these local systems appears to have physiologic effects that are as important as circulating angiotensin II and, under some circumstances, **more** important than circulating angiotensin II.

Thus, the RAS includes local systems with autocrine (cell-to-same cell) and paracrine (cell-to-different cell) effects in addition to the classical circulating RAS with endocrine effects. Physiology of the RAS is proving far more complex than a simple circulating pathway controlling blood volume and blood pressure. In these local systems, activation of angiotensin II results in harmful effects and target-organ damage that extend beyond vascular and renal hemodynamics to direct tissue actions, including tissue remodeling, endothelial dysfunction, and fibrosis.

While protective in its purpose, activation of the system in many patients today is maladaptive and leads to disease, with heart failure being a classic example. Sodium retention, coupled with hyperaldosteronism, results in vascular remodeling of the heart and disease progression[2].

Blockade of the RAS has represented a groundbreaking development in the prevention and treatment of heart failure, chronic kidney disease, myocardial infarction, and hypertension[3-8]. There are several steps at which the RAS can be interrupted.

Beta-adrenergic blocking agents reduce renin release. ACE inhibitors block the conversion of angiotensin I to angiotensin II downstream from the renin step, and angiotensin receptor blockers (ARBs) interfere with the interaction of angiotensin II with its receptor. Another class of antihypertensive drugs, renin inhibitors, interfere with the first step in the cascade, which is the interaction of renin with its substrate, AGT.

Whether or not to block the RAS is no longer the appropriate question in the clinical scenarios of diabetic nephropathy, chronic kidney disease, and heart failure. Efforts are dedicated to answering how best to optimize blockade. Discoveries of new peptides, enzymes, receptors, and cell-signaling targets of the system are changing our understanding of physiology and providing potential new therapeutic targets.

Since renal disease is characterized by sodium/volume retention and elevated blood pressure one would expect suppression of the renin-angiotensin system (RAS) in renal patients, but inappropriate activity of the RAS has been documented even in early stages of renal diseases: i.e., when glomerular filtration rate (GFR) and blood pressure are in the normal range. The activation of RAS has been attributed to a faulty sensing by the baroreceptor because of luminal narrowing and altered wall texture of afferent glomerular arterioles.

Consequently, despite hypertension, the juxtaglomerular apparatus senses low blood pressure and secretes inappropriate amounts of renin. It has become evident that is not the only mechanism of inappropriate activation of the RAS. In several studies renin production outside of juxtaglomerular apparatus could be demonstrated. Activation of RAS has been documented by measurements of plasma renin activity (PRA), which is inappropriately high in relation to blood pressure and sodium status.

Plasma renin activity (PRA) is mostly normal or slightly elevated. Low PRA is common in elderly diabetic patients. The most convincing evidence for a pathogenic role of the RAS in progression has come from intervention studies following the report of Anderson et al[9] that the ACE-inhibitor enalapril abrogates proteinuria and glomerulosclerosis more than equipotent lowering of BP by alternative hypertensive agents. This has been confirmed in many models of renal disease and in clinical trials[10-12]. It is evident that the nephroprotective effect of ACE-inhibitors and angiotensin II (Ang II) receptor blockers is not only mediated via their renal hemodynamic effects, but also through non-hemodynamic mechanisms.

## The effects of involvement of local versus systemic renin-angiotensin system in renal disease

Pharmacological blockade of the RAS is paradoxically effective although circulating PRA is low: this is the conclusion of experimental and human studies[10,24]. Price and colab.[25] looked at the increment in renal plasma flow (RPF) after administration of the Ang II receptor antagonist irbesartan in patients with type 2 diabetes.

They noted that although PRA was lower than in healthy subjects RPF increased more in response to irbesartan in type 2 diabetes than in normal subjects. The author's conclusion was that there was activation of the local RAS, which would explain the paradoxical contrast between suppressed renin in the circulation and the exaggerated renal vasodilator response to irbesartan, as well as therapeutic effectiveness of pharmacological blockade of the RAS[10]. The question arises is: which signal activates the local RAS?

The evolution of RPF after losartan to normo- and hyperglycemic subjects indicated that losartan is responsible to increase the RPF only in hyperglycemic subjects. It is possible that hyperglycemia per se activates the RAS possibly in sites outside of the juxtaglomerular apparatus. There is study that documents





local synthesis of angiotensinogen and other components of RAS in proximal tubular epithelial cells.

The idea that local activation of the RAS in the proximal tubular cells may be generalized to apply to non-diabetic renal disease as well is illustrated by the study of Gilbert and al.[26]. They found marked expression of renin and Ang II (predominantly in tubular epithelial cells) by in -situ hybridization and immuno-staining in the sub totally nephrectomized rat.

Upon administration of the ACE-inhibitor perindopril renin expression in the juxtaglomerular apparatus increased (as one would anticipate because of interruption of the short feed-back loop), while expression of renin and Ang II in the proximal tubular cells decreased. This illustrated that the juxtaglomerular and extra-juxtaglomerular systems are not controlled by the same regulatory mechanisms.

**Clinical evidence and consequences of local renin-angiotensin system**

Today there is no good clinical evidence available that clearly documents blood pressure -independent effects of ACE-inhibitors on progression of renal damage, despite some tantalizing findings pointing towards this direction, particularly the dissociation between the blood pressure -lowering and the antiproteinuric effect[13].In HOPE clinical study Ramipril caused a remarkable reduction of death from cardiovascular causes (-26%), myocardial infarction (-20%), stroke (-32%) , death from any cause (-16%) revascularization procedures (-15%), cardiac arrest (-38%), heart failure (-23%), and complications related to diabetes (-16%). In parallel, progression of microalbuminuria to more advanced stages of diabetic nephropathy were also reduced[14].

What is the explanation for this blood pressure -independent cardiovascular benefit from ACE-inhibition? There have been many recent reports on accumulation of ACE within coronary artery plaques in humans, specifically in macrophages.

Ang II presumably enhances the expression of IL-6, stimulates the NADPH/NADH dehydrogenases, increases reactive oxygen species and acts as a signal to induce an inflammatory phenotype. Due to space limitation, we cannot discuss other potential mechanisms of Ang II-induced vascular/renal damage, particularly activation of TGF-alpha, which undoubtedly also plays an important role. It is logical to assume that the beneficial effect of ACE-inhibition in cardiovascular protection studies is mediated via such non-hemodynamic mechanisms.

One clinical consequence of the existence of tissue RAS is that measurement of the systemic

RAS (i.e., PRA or circulating angiotensin II) can provide a misleading estimate of the tissue RAS activity. Circulating renin measures may correlate poorly with the activity of tissue renin-angiotensin systems. In some patients with primary (formerly, "essential") hypertension, for example, angiotensin II appears to be responsible for persistent renal vasoconstriction and sodium retention, even though plasma levels of renin and angiotensin II are like those in hypertensive patients with normal renal perfusion[15].

These findings suggest that there can be a selective increase in the activity of the tissue RAS in the kidney. A similar selective activation of the tissue RAS in the kidney may occur in stable heart failure[16], in diabetic nephropathy, and may explain racial differences in renal hemodynamics[17]. There is no known way to obtain direct measures of tissue renin (or angiotensin II) in humans. Alternative (indirect) approaches to assessing tissue RAS are therefore required.

ACE-inhibitors and Ang II receptor blockers have been dosed according to their antihypertensive action. If needed local RAS are involved the question arises whether the antihypertensive dose is identical with the dose conferring maximal benefit from blockade of these non-classical systems. As to the kidney, there are suggestions that when blood pressure is maximally lowered by ACE-inhibitors or Ang II receptor blockers, a further increase of dose may reduce proteinuria despite no further change in blood pressure.

Increasing doses of losartan and enalapril, which were clearly higher than those required to control blood pressure in rats with mesangioproliferative glomerulopathy, caused progressively more marked reduction in glomerulosclerosis and transcription of TGF-α despite no further lowering of blood pressure. As a practical consequence of the above considerations, it follows that urinary protein excretion should be routinely monitored in renal patients receiving ACE-inhibitors or Ang II receptor blockers. If no satisfactory decrease of proteinuria is noted, more rigorous sodium depletion and increase of dose of the ACE-inhibitor are indicated.

Indirect measurement of tissue RAS in the kidney is possible because there is substantial variation in angiotensin-mediated control of the renal circulation, and this can be ascertained by identifying variations in the renal vasodilator responses to captopril or vasoconstrictor responses to angiotensin II[18]. As an example, healthy Black individuals compared with White individuals have a blunted increase in renal plasma flow when switching from a low-salt to high-salt diet, have a blunted decrease in renal plasma flow when administered angiotensin II, and have a marked increase in renal plasma flow when given an ACE inhibitor; this phenotype suggests that angiotensin II levels in the kidneys of these individuals are increased[17]. This activated tissue RAS in the kidneys could sequentially produce increased sodium and water reabsorption, expansion of the extracellular fluid volume, and reduced circulating plasma renin levels (i.e., a "low-renin" state).

As with diabetes, the apparent low-renin state in Black individuals may indeed be paradoxical, reflecting activation of the RAS locally in the kidney as well as other tissues[19].

The interaction between the RAS and prostaglandins may seem confusing since each stimulates the secretion of the other[20,22-24] and since they induce opposing vascular actions (vasoconstriction with angiotensin II and vasodilation with most prostaglandins). However, angiotensin II is a systemic vasoconstrictor, whereas the prostaglandins





act locally because they are rapidly metabolized when they enter the systemic circulation. Thus, the net effect of simultaneous renal secretion of angiotensin II and prostaglandins is that angiotensin II can cause systemic vasoconstriction and raise the blood pressure, while the prostaglandins minimize the degree of renal vasoconstriction, thereby maintaining renal blood flow and glomerular filtration rate (GFR)[22].

Finally, in addition to support for a local RAS active within tissues, accumulating data support the existence of an intracellular RAS and for "intracrine" (within-cell) actions of angiotensin II.

The existence and biological importance of intracellular RAS within humans remains to be proven. Intracrine systems are proposed to work within multiple tissues and to be involved in the pathophysiology of conditions ranging from cardiac myocyte apoptosis to diabetic kidney disease[24].

***References***

*1. Carey RM. The intrarenal renin-angiotensin system in hypertension. Adv Chronic Kidney Dis 2015; 22:204.*

*2. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001; 345:1689.*

*3. Dzau VJ, Colucci WS, Williams GH, et al. Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. N Engl J Med 1980; 302:1373.*

*4. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327:669.*

*5. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345:851.*

*6. Rigatto C, Parfrey P, Foley R, et al. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. J Am Soc Nephrol 2002; 13:1084.*

*7. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342:145.*

*8. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345:861.*

*9. Anderson S, Renke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in therat. J Clin Invest 1986; 1993-2000.*

*10. Price DA, Porter LE, Gordon M.The paradox of the low-renin state in diabetic nephropathy. J Am Soc Nephrol 1999; 10:2382-2391.*

*11. Lewis EJ et al. The effect of angiotensin-converting - enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;*

*329:1456-1462.*

*12. Maschio G, Alberti D. Effect of yje angiotensin-converting-enzyme inhibitor benazepril on progression of chronic renal insufficiency. The Angiotensin-Converting- Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med 1996; 334:939-945.*

*13. Ruggenenti P, Perna A, Gherardi G et al. Renoprotective proprieties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999; 354:359-364.*

*14. Effects of Ramipril on cardiovascular and micro-vascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE sub study. Heartly Outcomes Prevention. Evaluation Study Investigators. Lancet 2000; 355:253-259.*

*15. Redgrave J, Rabinowe S, Hollenberg NK, Williams GH. Correction of abnormal renal blood flow response to angiotensin II by converting enzyme inhibition in essential hypertensives. J Clin Invest 1985; 75:1285.*

*16. Schunkert H, Ingelfinger JR, Hirsch AT, et al. Evidence for tissue-specific activation of renal angiotensinogen mRNA expression in chronic stable experimental heart failure. J Clin Invest 1992; 90:1523.*

*17. Price DA, Fisher ND, Osei SY, et al. Renal perfusion and function in healthy African Americans. Kidney Int 2001; 59:1037.*

*18. Fisher ND, Price DA, Litchfield WR, et al. Renal response to captopril reflects state of local renin system in healthy humans. Kidney Int 1999; 56:635.*

*19. Price DA, Porter LE, Gordon M, et al. The paradox of the low-renin state in diabetic nephropathy. J Am Soc Nephrol 1999; 10:2382.*

*20. Freeman RH, Davis JO, Villarreal D. Role of renal prostaglandins in the control of renin release. Circ Res 1984; 54:1.*

*21. Stahl RA, Paravicini M, Schollmeyer P. Angiotensin II stimulation of prostaglandin E2 and 6-keto-F1 alpha formation by isolated human glomeruli. Kidney Int 1984; 26:30.*

*22. Oliver JA, Pinto J, Sciacca RR, Cannon PJ. Increased renal secretion of norepinephrine and prostaglandin E2 during sodium depletion in the dog. J Clin Invest 1980; 66:748.*

*23. Data JL, Gerber JG, Crump WJ, et al. The prostaglandin system. A role in canine baroreceptor control of renin release. Circ Res 1978; 42:454.*

*24. Kumar R, Thomas CM, Yong QC, et al. The intracrine renin-angiotensin system. Clin Sci (Lond) 2012; 123:273.*

*25. Weidmann P, Scheiner M.Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy; an update meta-analysis. Nephrpl Dial Transoalnt 1995; 10 (Suppl 9): S39-S426.*

*26. Gilbert RE, Wu LL, Kelly DJ ei al.Patholpgical expression of renin and angiotensin II in the renal tubule after subtotal nephrectomy.Implications for the pathogenesis of tubule -inyerstitial fibrosis. Am J Pathol 1999; 155: 429-440.*