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Intrarenal angiotensin II levels in normal and hypertensive states

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Introduction

The contributions of the renin-angiotensin-aldosterone system (RAAS) to the regulation of arterial pressure and the physiopathology of hypertension has long been recognised. Plasma renin is derived primarily from the juxtaglomerular cells on the afferent arterioles of the kidney, [1] while angiotensinogen is primarily formed and constitutively secreted by liver cells into the circulation,[2] thus allowing systemic formation of angiotensin I (Ang I) within the vascular compartment.[2-4] It is important to recognise that the circulating concentrations of angiotensinogen are generally quite high, being more than 1000 times greater than the plasma Ang I and II concentrations.[2,5,6] Figure 1 shows the representative plasma angiotensinogen concentrations measured in rats, expressed as pmol/ml while the Ang I and Ang II concentrations are expressed as fmol/ml, indicating that the active Ang II concentration in the plasma is a small fraction of the available Ang II in the form of angiotensinogen.[5,6] Therefore, even small relative changes in the rates of Ang I and Ang II generation may make large absolute differences in the circulating concentrations. Because renin is synthesised and stored in the granules of juxtaglomerular cells, release mechanisms are rapid and can elicit large changes in plasma renin levels, leading to rapid changes in Ang I generation. However, the concentrations of angiotensinogen in the plasma are close to the Km value of the proteolytic activity of renin, so that changes in substrate concentration can also influence the Ang I generation rate. Nevertheless, changes in angiotensinogen synthesis and release occur slowly, so the effects of changes in angiotensinogen are not as dynamic as the effects of changes in plasma renin concentration.[2,7] Once Ang I has been formed through the action of renin, it is rapidly converted to Ang II owing to the widespread localisation of angiotensin-converting enzyme (ACE) on the endothelial cells of many vascular beds, including the lung.[8-10] Several angiotensinases and peptidases are then able to metabolise Ang II further.[11] While other pathways for Ang II formation have been identified in certain tissues, the circulating levels of Ang II reflect primarily the consequences of the renin and ACE enzymatic cascade on angiotensinogen.[5,12]

Recent attention has been focused on findings from several laboratories that local tissue Ang II levels are differentially regulated and cannot be explained on the basis of circulating

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concentrations. This has led to a greater interest in Ang II acting as a paracrine factor.[5,13-15] In particular, the Ang II contents of renal and adrenal tissues are much higher than can be explained on the basis of equilibration with the circulating concentrations.[5,6,16,17] Furthermore, the demonstration of much higher concentrations of Ang II in specific regions and compartments within the kidney indicates selective local regulation of Ang II levels within the kidney.[18,19] Thus, it is now apparent that the mechanisms regulating intrarenal Ang II levels are distinct from those responsible for regulating circulating Ang II concentrations.

Intrarenal levels of angiotensin II

Ang II is a dynamically-regulated peptide that is formed and degraded rapidly, thus making it difficult to obtain accurate indices of intrarenal Ang II activity that appropriately reflect the levels existing *in vivo*. Total tissue contents have been assessed by rapidly harvesting and processing tissue samples in solutions that arrest further formation and metabolism.[20-22] While this approach provides a value for overall tissue content that is reproducible, it does not allow assessment of the concentrations within specific compartments or domains in the kidney. Other approaches include measurements of concentrations in samples taken from the renal vein, the interstitial fluid, the tubular fluid or the urine, but each has advantages and disadvantages.[17-19]

The limitations of total content measurements not withstanding, this approach provides a useful method to determine the effects of various dietary and experimental procedures on overall intrarenal Ang II levels.[5,21,23] When the absolute levels, expressed per gram of tissue, are compared with the corresponding plasma levels, the Ang II tissue contents are higher than can be explained on the basis of non-specific equilibration between plasma and the intrarenal extracellular fluid.[5,21,24] The differences between plasma concentrations and tissue contents are maintained during variations in dietary NaCl intake. For each level of NaCl intake, the total kidney contents, expressed as fmol/g kidney weight (fm/g) are higher than the plasma concentrations expressed as fmol/ml.[5,21,23,25-27] Campbell *et al*.[5] used HPLC separation techniques and found that kidney Ang II content was about 340 fmol/g, compared with 50 fmol/ml for plasma concentrations. Likewise, kidney Ang I concentrations were 2−3 times higher than the plasma concentrations. Several experimental models of hypertension, such as the 2 kidney 1 clip (2K-1C) Goldblatt hypertension and Ang II-induced hypertension, also have intrarenal Ang II levels that can be dissociated from the circulating Ang II concentrations.[6,26,27] Collectively, the data show that the intrarenal levels of Ang II are regulated in a complex manner such that there is accumulation of Ang II from the amount delivered to the kidney and/or augmentation of intrarenally-formed Ang II. The kidney also metabolises and/or degrades most of the Ang II delivered in the arterial blood, such that the net intrarenal Ang II content is the consequence of several mechanisms.[17,28] Figure 2 depicts the multiple formative processes and metabolic pathways that are involved in the regulation of intrarenal Ang II content. In addition to intrarenal formation of Ang II there is also intrarenal conversion from systemically delivered Ang I and angiotensinogen and from intrarenally-formed Ang I, originating from either circulating or locally-formed angiotensinogen. There are species variations in the conversion rates by the kidney. Previous studies in dogs indicate that about 20% of the arterially-delivered Ang I is converted to Ang II.[28] In contrast, Danser *et al*.[29] infused ^{125}I-Ang I into the renal artery in humans and found less than 10% net conversion rate.

The intrarenal content of Ang II is not distributed in a homogeneous manner but is compartmentalised.[30] There is a marked difference in the distribution of Ang II content in medulla *vs.* cortex.[25,31] Within the cortex,there is distribution of Ang II among the interstitial fluid, tubular fluid and the intracellular compartments.The recognition that much of the Ang II that binds to receptors is internalised via receptor-mediated endocytosis has suggested that

some of the internalised Ang II remains intact and contributes to the total Ang II content measured in tissue homogenates.[23,32-36]

Ang II in the renal medulla is of interest because various studies have suggested that Ang II influences medullary haemodynamics to a greater extent than cortical haemodynamics.[14,37-42] In addition, receptor binding studies have demonstrated that the Ang II receptor density is much greater in the medulla than in the cortex.[43,44] Recent studies have shown that medullary Ang II levels are higher than cortical levels in both normal and Ang II-infused hypertensive rats.[25,31] The combination of high Ang II levels in the medulla, coupled with the high density of Ang II receptors, suggest that Ang II does indeed exert a powerful role in regulating haemodynamics and tubular function in the medulla. However, the total mass of the medulla is less than 1/10 that of the cortex so that the overall contribution of medullary Ang II levels to the total intrarenal Ang II content is relatively small. Nevertheless, these data suggest that there may be specialised Ang II-forming pathways or accumulation mechanisms in the medulla that are subject to localised regulation.

The interstitial compartment also contributes to the increased total Ang II levels. Earlier measurements of renal lymph, considered a reflection of renal interstitial fluid, suggested that interstitial fluid Ang II concentrations were much higher than plasma concentrations.[45-47] These results were consistent with the notion that Ang II is formed locally and added to the interstitial compartment. However, it was not clear how much of renal lymph Ang II concentrations were due to continued Ang II formation within the lymphatic compartment, since lymph also contains ample quantities of renin and renin substrate.[46,47] More recent studies have assessed interstitial fluid concentrations of Ang II using microdialysis probes implanted in the renal cortex.[48] The microdialysis tubing had a molecular weight cut-off of 5000,thus allowing equilibration of smaller molecules such as the angiotensin peptides. However, renin, angiotensinogen and various enzymes with higher molecular weights do not cross the membrane and thus there should be limited formation and/or metabolism of Ang II after it crosses the dialysis membrane. Using this procedure, Siragy *et al*.[48] found that interstitial fluid Ang II concentrations in the dog are in the range of 10−20 pmoles/ml, much higher than the plasma levels. These data indicate that interstitial fluid concentrations are substantially higher than plasma levels and contribute to the elevated intrarenal Ang II content.

Tubular compartmentalisation of angiotensin II

Micropuncture studies directly evaluating the proximal tubule fluid concentrations of Ang I and Ang II have demonstrated that these peptides are also present at concentrations much greater than the plasma concentrations.Seikaly *et al*.[18] reported that Ang II concentrations in the proximal tubule fluid of rats were in the nanomolar range (30−40 nM) and about 1000 times higher than the plasma concentrations. Braam *et al.*[19] also found nanomolar concentrations of Ang II in proximal tubule fluid and demonstrated further that similar concentrations were present in tubular fluid of microperfused proximal tubule segments. Fluid samples collected from downstream segments had Ang II concentrations similar to those measured from free-flow collections from non-perfused tubules. These findings provided definitive evidence that the tubular fluid Ang II concentrations are not derived from the filtrate, indicating that the proximal tubule secretes Ang II or a precursor into the proximal tubule fluid. Braam *et al.* 19 and Boer *et al*.[49] have also demonstrated a dissociation between circulating and intratubular Ang II concentrations, in that extracellular fluid volume expansion reduced plasma Ang II concentrations but did not reduce intratubular Ang II concentrations. Navar *et al.*[50] demonstrated that Ang I, as well as Ang II, was present at nanomolar concentrations in proximal tubular fluid, thus indicating that the Ang II could be secreted preformed or formed by the action of brush border ACE on Ang I. Figure 3 depicts the approximate values for intratubular Ang I and Ang II concentrations.

Origins of intrarenal angiotensin II

The evidence suggesting that renal interstitial fluid Ang II concentrations are much higher than the plasma levels has accrued for many years and it is well recognised that all of the components needed for Ang II generation are present within the renal interstitium.[3,51] Most of the renin is thought to be secreted by the juxtaglomerular cells into the interstitial compartment, where it acts on angiotensinogen that was thought to originate primarily by diffusion across the peritubular capillaries. The presence of abundant ACE and Ang II receptors on tubular basolateral membranes and vascular smooth muscle of arterioles provided ample support for the importance of interstitial Ang II in regulating both haemodynamic and transport function.[3,13,51,52] While these concepts remain valid, the findings that proximal tubule cells produce angiotensinogen has added substantial complexity to the mechanisms regulating intrarenal angiotensinogen levels.

The sources of intrarenally-formed Ang II have been explored in several ways. Studies utilising immunohistochemical techniques demonstrated that Ang I and Ang II are co-localised with renin in JGA cells and vascular smooth muscle cells of the afferent arteriole.[53-56] These studies suggested that Ang II could be formed or internalised into the smooth muscle cells.[32] Because there is no direct evidence for intracellular angiotensinogen in vascular smooth muscle cells, it is more likely that Ang I and/or Ang II are internalised via receptor-mediated endocytosis in smooth muscle cells.[32,33,53] In contrast to vascular smooth muscle cells, proximal tubular cells contain angiotensinogen mRNA and protein.[57-60] Immunohistochemical studies using antibodies to angiotensinogen have clearly localised angiotensinogen to the proximal tubule segment.[56,61] These results indicate that much of the intrarenally-produced angiotensinogen is derived from proximal tubule cells and suggest it is one source of the intratubular concentrations of Ang I and Ang II. It has been noted that the preponderance of immunoreactive angiotensinogen in proximal tubule cells is located along the luminal membrane of the proximal tubule cells thus supporting the notion that angiotensinogen could be secreted into the tubular lumen and/or producing its metabolites intracellularly and secreting them directly into the tubule lumen.[56,61,62]

To test for the presence of angiotensinogen in proximal tubule fluid, proximal tubule fluid samples were collected and incubated with excess renin, in order to determine total available Ang II from angiotensinogen or related precursors secreted into the lumen.[63] As shown in Figure 3, we found that the proximal tubule fluid angiotensinogen concentrations in rats were over 300 nM and greatly exceeded the free Ang I and Ang II tubular fluid concentrations. Because angiotensinogen is a 55−60 kD glycoprotein, it seems unlikely that much of the plasma angiotensinogen would filter across the glomerular membrane.[64,65] These data provide further support to the scheme, depicted in Figure 3, that proximal tubule cells secrete angiotensinogen directly into the tubule, as recently suggested.[31,61,62,65,66] Thus, Ang I could be formed either within the proximal cells or the tubular lumen if renin or other renin-like enzymes are present in the tubular fluid, on the brush border or inside the cells.[57,67,68] Several studies have reported that cultured proximal tubule cells do indeed produce renin and contain renin mRNA, thus suggesting that a low level of constitutive renin secretion may occur in proximal tubule cells.[57,67,69] In addition, Leyssac[70] reported low but measurable renin concentrations in proximal tubule fluid. It has also been shown that there are abundant amounts of ACE and its mRNA associated with the proximal tubule brush border.[71] ACE has also been measured in proximal and distal tubular fluid, but is more abundant in proximal tubular fluid.[72] It seems clear that Ang II would have to be continuously produced or added to the proximal tubule fluid in view of the abundant ACE and angiotensinases found in the brush border.[10,11,73,74] At present, however, it is not known how much of the peptides are formed intracellularly and how much are formed in the tubular fluid. It is also not clear if the angiotensinogen produced in proximal

tubule cells is secreted both at luminal and basolateral sites or primarily into the tubular lumen, as suggested by others.[62,66]

The Ang II concentration in tubular fluid from the other segments of the nephron remains unknown,owing to the problems of collecting sufficient volumes to detect the anticipated concentrations. However, there are several studies supporting an important role for Ang II in regulating reabsorptive function in the distal nephron and collecting duct segments as well as in proximal tubule segments, and Ang II receptors have been identified on the luminal border of distal nephron segments.[60,75-79] There have been efforts to use urinary Ang II concentrations or excretion rates as indices of intrarenal levels.[80-82] However, the reported urinary concentrations of Ang II have been as low as 1 fmol/ml to about 35 fmol/ml,[81,82] much lower than the proximal or interstitial concentrations reported. Recent data from our laboratory have indicated that urine Ang II concentrations in anaesthetised rats may be somewhat higher, in the range of about 0.8 pmol/ml.[83] If similar concentrations exist in the distal tubule or collecting duct fluid, they would be sufficient to exert an influence on transport function. Wang and Giebisch[75] found that Ang II concentrations as low as 10^{-11} M (10 fmol/ml) stimulated distal tubular sodium transport.Whatever the Ang II concentration in distal tubular fluid, it appears that it is not derived from plasma Ang II, since systemically-infused, tritiated Ang II could not be recovered in the urine.[82]

Angiotensinogen is also present in urine, suggesting that continued Ang I generation may occur throughout the tubule.[62,66,80,84] Recent studies have localised renin to the luminal side of cells from the connecting tubule of the distal nephron, suggesting that renin may also be secreted into the distal tubular fluid.[62] When coupled with the findings of angiotensinogen in urine, it now seems highly likely that intraluminal Ang II formation continues throughout the length of the nephron, with residual angiotensinogen appearing in the urine.[62,66,80] Ding *et al.*[66] demonstrated, in transgenic mice harbouring the gene for human angiotensinogen fused to the kidney androgen-protein promoter, that human angiotensinogen was localised primarily in proximal tubule cells. They found abundant human angiotensinogen in the urine but only slight traces in the systemic circulation. It was suggested that most of the angiotensinogen formed in proximal tubular cells is destined for secretion into the lumen. Rohrwasser *et al.*[62] emphasised the luminal localisation of angiotensinogen in proximal tubular cells *in vivo* and showed in monolayer proximal tubule cell cultures that most of the angiotensinogen was detected in the apical compartment. They also reported that angiotensinogen was detected at low (nanomolar) concentrations in urine from mice and human volunteers. Mice placed on low dietary salt intake showed increased urinary angiotensinogen levels. Thus, it seems possible that urinary angiotensinogen concentrations or excretion rates may be a useful marker of intrarenal angiotensinogen production.[80]

Intrarenal angiotensin II formation in hypertensive states

Several studies have demonstrated that intrarenal Ang II levels can be dissociated from circulating renin and Ang II concentrations in several forms of angiotensin-dependent hypertension.[6,25,85-87] Progressive increases in intrarenal Ang II content occur during the development of hypertension, leading to renal Ang II contents that are greater than can be explained from equilibration with the circulating concentrations. Interestingly, in 2K-1C Goldblatt hypertension, Ang II-induced hypertension and the TGR Ren2 rat model of hypertension, the increases in renal Ang II content occur even in kidneys that become renin-depleted owing to the elevations in arterial pressure.[6,85-87] In 2K-1C Goldblatt hypertensive rats, intrarenal Ang II increased not only in the clipped kidney but also in the non-clipped kidney, which had an elevated or sustained intrarenal Ang II content even in the face of elevated arterial pressures and renal renin depletion.[26,27]

To evaluate mechanisms responsible for the augmented intrarenal Ang II in renin-depleted kidneys, further experiments were performed using the Ang II-infused hypertension model that leads to marked suppression of both circulating and tissue renin activity.[6,26,88,89] Instead of renal arterial stenosis, an osmotic minipump containing Ang II was implanted, in order to raise the plasma Ang II concentrations to levels similar to those observed in 2K-1C rats. As shown in Figure 4, this procedure leads to a slowly-developing hypertension that mimics the development of hypertension in the 2K-1C model. The renal renin content and renin mRNA and the plasma renin activity are all markedly suppressed in this model.[88,90] Renal Ang II content increased significantly after 8−10 days of Ang II infusion to levels substantially greater than could be explained by the circulating Ang II concentrations.[6,26] While some of the intrarenal Ang II could be due to accumulation of circulating Ang II, continued intrarenal formation of Ang II was also likely, since both the renal angiotensinogen activity and kidney Ang I contents were not significantly reduced from control levels.[6]

These initial results led to the possibility that the Ang II infusions initiated an active accumulation process that could be mediated by activation of Ang II receptors and internalisation via the Ang II-receptor complex, such as has been shown in several cell systems.[32,35,36,91,92] As also shown in Figure 4, chronic treatment with the AT_1-receptor blocker, losartan, not only prevented the development of hypertension but also prevented the increases in intrarenal Ang II content caused by two weeks of Ang II infusion.[6,93] This finding indicates that AT_1-receptor activation either stimulates intrarenal Ang II formation or leads to internalisation and intracellular accumulation of the circulating Ang II into an intracellular compartment that protects the peptide from degradation.[34] This conclusion has received further support from recent studies using mice that have deletion of the AT_{1A} receptor.[94] Cervenka *et al*.[94] found that, although the circulating Ang II concentrations in AT_{1A} knockout mice are much higher than in the wild type controls, the kidney Ang II contents are lower in the AT_{1A} knockout mice.These findings suggest a role for the AT_{1A}-receptor in mediating the increases in intrarenal Ang II content during conditions of elevated plasma Ang II concentrations.

To determine the extent of intracellular accumulation of circulating Ang II, Zou *et al*.[89] infused Val^5-Ang II, which has essentially the same immunoreactivity and biological activity in the rat as the endogenous Ang II that has isoleucine in the five position. By separating the Ang II peptides using HPLC, it was possible to determine the amounts of each peptide present in tissues after two weeks of infusion. Val^5-Ang II elicited the slowly developing hypertension previously observed and increases in total intrarenal Ang II similar to those found with Ile^5-Ang II.[89] Analysis of the renal Ang II contents revealed levels of Val^5-Ang II that were much higher than the circulating levels, indicating that Val^5-Ang II had accumulated in the kidney. About two thirds of the intrarenal Figure 4, chronic treatment with the AT_1-receptor blocker, losartan, not only prevented the development of hypertension but also prevented the increases in intrarenal Ang II content caused by two weeks of Ang II infusion.[6,93] This finding indicates that AT_1-receptor activation either stimulates intrarenal Ang II formation or leads to internalisation and intracellular accumulation of the circulating Ang II into an intracellular compartment that protects the peptide from degradation.[34] This conclusion has received further support from recent studies using mice that have deletion of the AT_{1A} receptor.[94] Cervenka *et al*.[94] found that, although the circulating Ang II concentrations in AT_{1A} knockout mice are much higher than in the wild type controls, the kidney Ang II contents are lower in the AT_{1A} knockout mice.These findings suggest a role for the AT_{1A}-receptor in mediating the increases in intrarenal Ang II content during conditions of elevated plasma Ang II concentrations.

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It is also important to recognise that, in the Ang II infused model of hypertension, there is sustained production of endogenous Ang II. Endogenous production of Ang II can be due, in part, to Ang II-stimulated angiotensinogen production. *In vivo* and *in vitro* studies have shown that Ang II stimulates angiotensinogen mRNA levels in rats and in a murine proximal tubule cell line.[95-97] Kobori *et al*.[98] was also able to demonstrate that there were significant increases in intrarenal angiotensinogen protein as well as angiotensinogen mRNA levels in response to two weeks of Ang II infusion. This positive feedback system may be responsible for sustained or enhanced generation of angiotensinogen, leading to continued intrarenal production of Ang II under conditions of elevated circulating concentrations. The intrarenally-produced Ang II would be additive with the Ang II that is internalised by the AT_1-receptors, leading to the overall increased intrarenal Ang II content. It remains unclear whether the Ang II is recycled and secreted in order to exert further biological function by binding to Ang II receptors on the cell membrane.Ang II may also migrate to the nucleus to exert genomic effects.[32,36] Recently, Chen *et al*.[36] transfected Chinese hamster ovary cells with an AT_{1a}-receptor fused with green fluorescent protein (GFP),which allowed visualisation of trafficking of the internalised ligand-receptor complex. Ang II increased co-localisation of GFP fluorescence with nuclear markers, suggesting migration of the receptor complex to the nucleus.[36]

Until recently there was no direct evidence that Ang II was present in substantive concentrations in intracellular organelles. Endocytosis of the Ang II-AT_1-receptor complex has been demonstrated to be required for the full expression of functional responses.[99-102] In the proximal tubule, binding of Ang II to the AT_1-receptor and endocytosis of the AT_1-receptor-Ang II complex is coupled to the activation of signal transduction pathways and enhanced sodium transport.[103] Recent studies evaluated the presence of angiotensin peptides, ACE and Ang II receptors in renal endosomes.[23] It was found that renal intermicrovillar clefts and endosomes contain both Ang I and Ang II, with the Ang II content being greater than that of Ang I. In addition, both AT_1-receptors and ACE were found in these structures. ACE activity was important for the maintenance of Ang II content in the endosomes and microvillar clefts, as they were markedly reduced by acute ACE inhibition. These results demonstrate that Ang II is either formed or trafficked through intracellular endosomal compartments. In a recent preliminary report, the effects of Ang II infusions on Ang II content in intrarenal endosomes were evaluated.[104] Renal cortical endosomes were harvested after two weeks of Ang II infusion. As previously reported, overall kidney Ang II levels were increased. Ang II levels in both light and heavy endosomes were significantly increased. In agreement with previous studies showing the effects of AT_1-receptor blockade to prevent the increases in renal Ang II content, concurrent treatment with candesartan prevented the increases in endosomal Ang II levels. These data provide additional support to the concept that there is increased uptake and trafficking of Ang II into renal endosomes, which is mediated by AT_1-receptors. The prevention of these increases in intracellular levels of Ang II may be of importance, not only in reducing the hypertensive effects of Ang II but also in minimising the renal injury that occurs in Ang II-dependent hypertension.

Perspective

Collectively, the results of experiments evaluating Ang II-dependent hypertension have shown that elevated intrarenal Ang II levels can occur even when plasma renin levels and intrarenal renin content are reduced. The elevated intrarenal Ang II levels contribute to hypertension via multiple effects on the vasculature and the tubules, leading to sodium retention, vasoconstriction and long-term proliferative actions. Studies in Ang II-infused rats have demonstrated that intrarenal accumulation of Ang II is due, in part, to uptake of circulating Ang II via an AT_1-receptor-mediated mechanism; however, endogenous production of Ang II is sustained. Some of the internalised Ang II appears to be protected from degradation and therefore potentially available for intracellular actions. Circulating Ang II also exerts a positive feedback action by which the Ang II infusions lead to augmented intrarenal levels of angiotensinogen mRNA and protein, which contribute to the overall enhancement of intrarenal Ang II in hypertension. In addition, renal AT_1-receptor protein and mRNA levels are maintained, allowing increased Ang II levels to elicit progressive effects.While the systemic vascular effects of Ang II are important in maintaining elevated peripheral vascular resistance, it is the antinatriuretic consequences caused by the synergistic actions of the augmented intrarenal Ang II levels that are responsible for maintaining a chronic state of hypertension. As long as the renal effects are sustained, the hypertension can be maintained even after the circulating Ang II concentrations return to near normal levels.[105,106]

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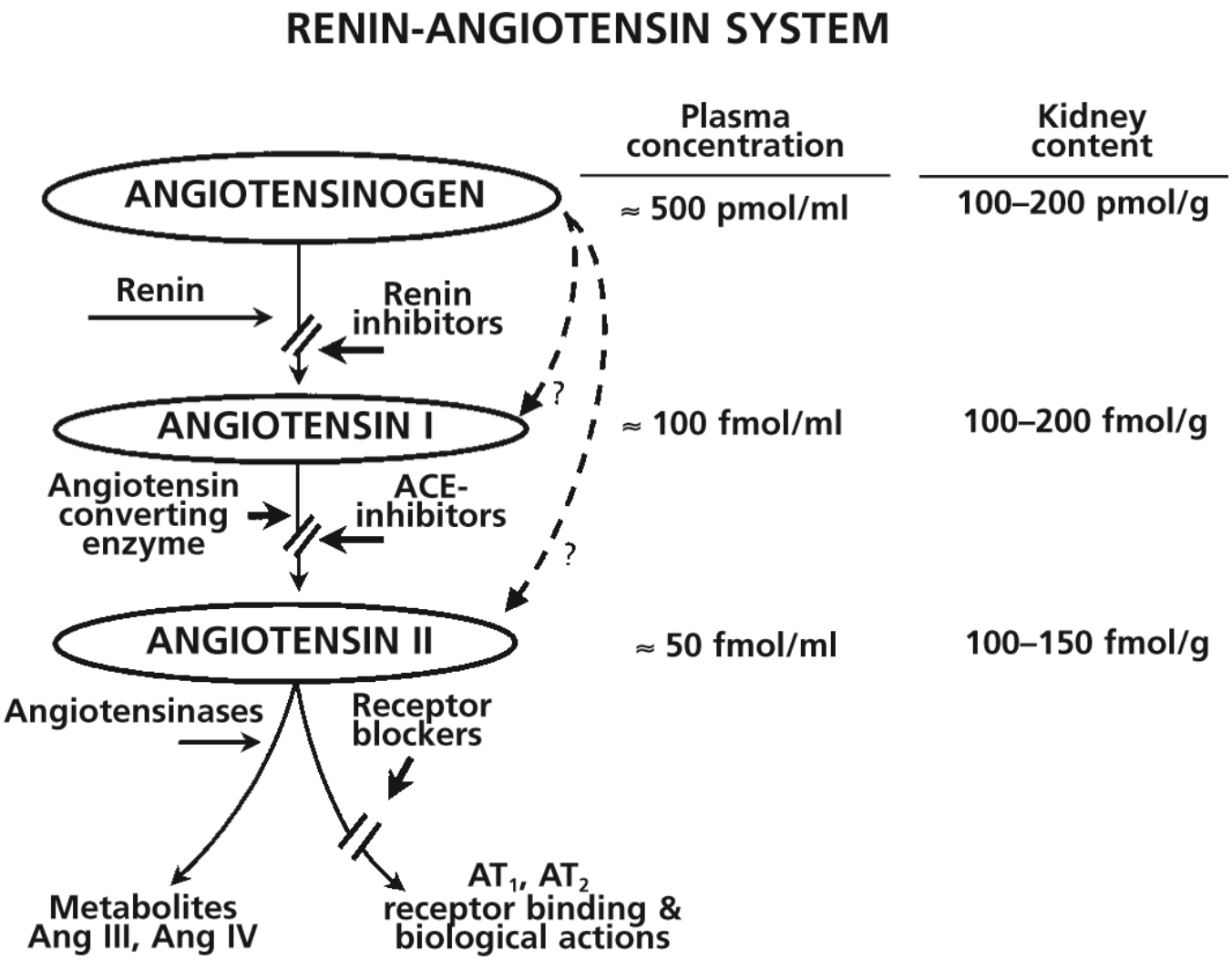

Figure 1.
The renin-angiotensin system cascade with representative plasma concentrations and kidney contents for angiotensinogen, angiotensin I and angiotensin II. The dashed arrows represent alternative pathways for formation of angiotensin I and II.

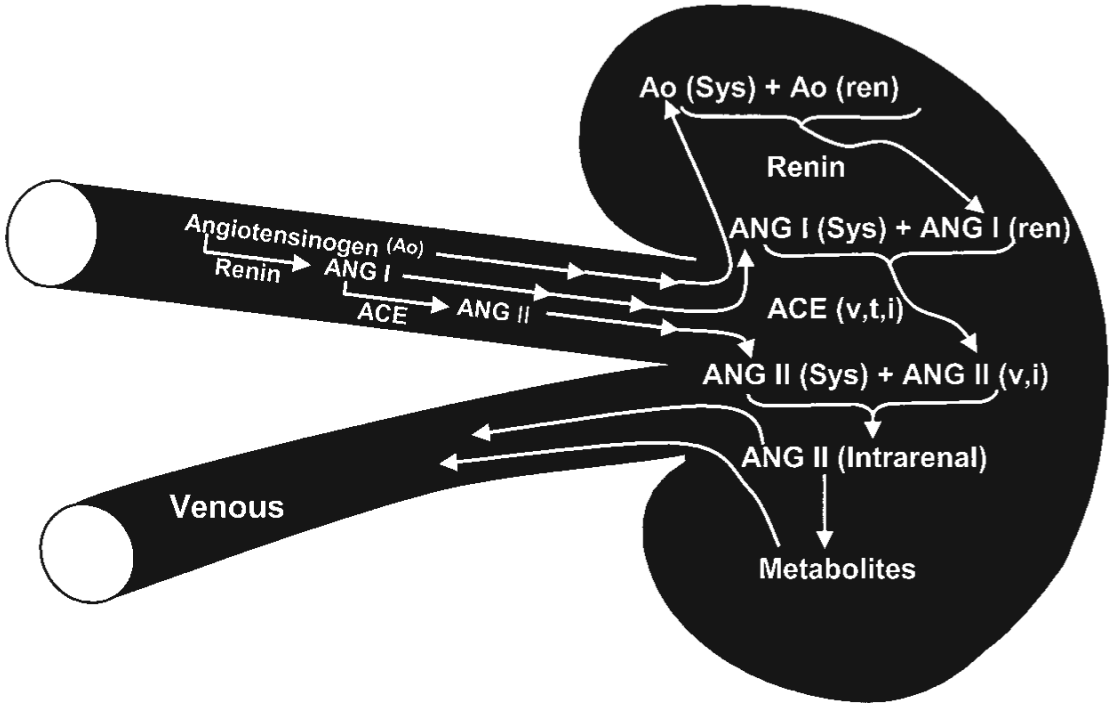

Figure 2.
Mechanisms of intrarenal formation of angiotensin II. See text for detailed explanation.

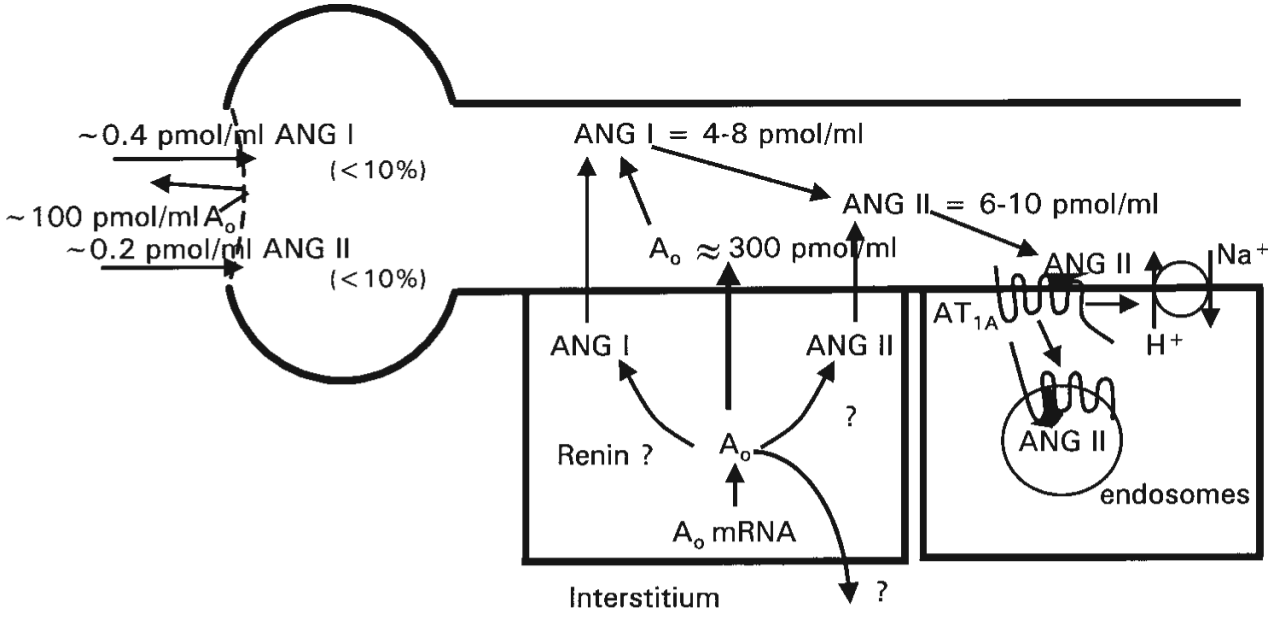

Figure 3.

Concentrations and sources of proximal tubule angiotensinogen, angiotensin I and angiotensin II and AT_1-receptor mediated uptake of angiotensin II into endosomal compartments. Angiotensinogen and peptides may be secreted only into the tubular lumen or possibly also into the interstitium.

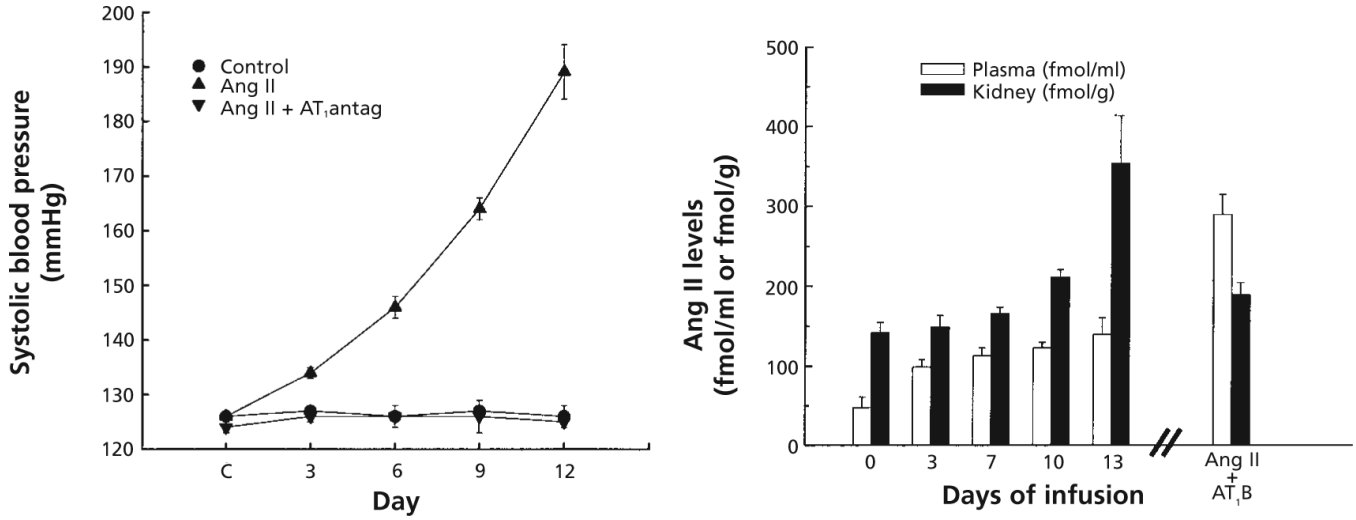

Figure 4.

Increases in systolic arterial pressure (left), and plasma and intrarenal angiotensin II levels (right) in rats infused with angiotensin II for two weeks. Treatment with AT_1-receptor blockers (AT_1B) prevented the increases in arterial pressure and intrarenal angiotensin II even though plasma angiotensin II concentrations increased further.