Intrarenal Angiotensin II Augmentation in Angiotensin II Dependent Hypertension

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In several models of angiotensin II (ANG II) dependent hypertension, intrarenal ANG II levels increase to a much greater extent than the circulating levels even though the renal renin levels are decreased. The 2-kidney-1-clip (2K1C) Goldblatt rat model is particularly intriguing because hypertension develops in the presence of an intact kidney which would be expected to maintain sodium balance and protect against hypertension. Although the non-clipped kidney becomes renin depleted, it exhibits enhanced microvascular reactivity and increased tubular fractional sodium reabsorption. The non-clipped kidney ANG II content is either elevated or unchanged and proximal tubular fluid ANG II concentrations are not suppressed compared to the nanomolar concentrations found in normal rats. These results suggest that intrarenal ANG II content can be regulated independently of renal renin content. A similar hypertensive process occurs in rats infused chronically with low doses of ANG II. Renal ANG II content increases over 14 days to a greater extent than the circulating concentrations. Functionally, ANG II infused rats demonstrate reduced sodium excretion and marked suppression of pressure natriuresis. These ANG II dependent influences on kidney function contribute to the maintenance of hypertension. Renal augmentation of ANG II, hypotension, and suppressed sodium excretion are blocked by AT1 receptor blockers. To study the mechanisms responsible for intrarenal ANG II augmentation, we infused a different form of ANG II (Val15 ANG II), that can be separated from endogenous ANG II by HPLC. These results indicated that the increased renal ANG II content was due to accumulation of circulating ANG II in addition to continued production of endogenous ANG II. The renal accumulation of Val15-ANG II was markedly reduced by concomitant treatment with the AT1 receptor blocker, losartan. In addition, we found an unchanged overall ANG II-AT1 receptor protein which probably contributes to the maintained ANG II dependent influences. Collectively, the data support the concept that there is internalization of ANG II through an AT1 receptor mediated process and that some of the internalized ANG II is protected from degradation. The augmented intrarenal ANG II coupled with sustained levels of AT1 receptors contribute to the continued ANG II dependent suppression of renal function and sodium excretion thereby maintaining the hypertension. (Hypertens Res 2000; 23: 291-301)

Key Words: renin-angiotensin system, intrarenal ANG II, angiotensin receptors, tubular angiotensin II

Introduction

While it is well accepted that progressive renal injury is a serious consequence of uncontrolled hypertension, there is increased recognition that sustained hypertension involves either a primary or secondary derangement in renal microcirculatory and/or tubular transport function that limits the capability of the kidney to maintain sodium balance at normal arterial pressures. Even when there is not
a primary intrarenal derangement, there may exist alterations in renal function secondary to inappropriate humoral or neural stimulation to the kidney. Under these conditions, increases in arterial pressure become necessary in order to re-establish normal balance. Thus, a widely held premise is that hypertension can not be sustained unless there is an impairment in kidney function (1-5). This premise is supported by the findings of varying degrees of reduced renal function in hypertensive patients. Often, the reduced renal function is associated with inappropriate activation of the renin-angiotensin system as reflected by a greater responsiveness to ACE inhibitors or ANG II receptor blockers (5-8). Experimental models of hypertension also support the important role of an overactive renin-angiotensin system in the development and maintenance of hypertension (9-13). However, the precise mechanisms responsible for the sustained actions of ANG II on intrarenal function remain unclear since often there is not clear evidence for markedly elevated circulating renin or ANG II concentrations.

**Intrarenal ANG II Receptors**

The complex and powerful actions of ANG II on renal function are due to the widespread distribution of ANG II receptors in various regions and cell types in the kidney. As shown in Fig. 1, there are two major categories of ANG II receptors, AT1 and AT2 but most of the hypertensinogenic actions of ANG II are generally attributed to the AT1 receptor. Studies utilizing polyclonal and monoclonal antibodies to the AT1 receptor have identified abundant AT1 receptors widely distributed throughout the kidney. AT1 receptor protein has been localized to afferent and efferent arteriolar smooth muscle cells, thick ascending limb epithelia, proximal tubular brush border, and mesangial cells (14, 15). AT1 receptors are also present on proximal tubule luminal and basolateral membranes, distal tubules, collecting ducts, glomerular podocytes and macula densa cells (15). As illustrated in Fig. 2, extensive luminal localization of AT1 receptors in both proximal and distal nephron segments has been observed. More recent studies using an AT1A specific polyclonal antibody (16) and a polyclonal AT1 receptor antibody (17) have reported a similar renal distribution of AT1 receptors. AT1 and AT2 receptors have also been found on glomerular epithelial cells (18, 19). Moderate AT2 receptor immunostaining has been found in proximal tubules, collecting ducts and some of the vasculature (17).

**Fig. 1.** The renin-angiotensin system and the major ANG II receptor types. Their main actions on renal and vascular function are listed. Some rodents have two AT1 subtypes, AT1A and AT1b.
localize the AT₁ mRNA in various segments of the kidney. AT₁ mRNA has been localized to tubule cells of the outer medulla, proximal tubules, thick ascending limb of the loop of Henle (20), glomeruli, arterial vasculature, vasa recta (21) and juxtaglomerular cells (22). AT₁ transcripts have been localized on microdissected glomeruli, proximal convoluted and straight tubules, medullary thick ascending limbs, medullary collecting ducts, cortical collecting ducts, vasa recta bundles and arcuate arteries (23). High levels of AT₁ mRNA have also been shown in proximal tubule primary cultures, freshly isolated proximal tubule segments (24, 25) and immortalized rabbit cortical collecting duct cells (26). AT₁A and AT₁B mRNAs have been demonstrated in the glomerulus and all nephron segments including the proximal tubule, distal tubule, thick ascending limb and collecting ducts (17, 25, 27). The AT₁A mRNA is the predominant subtype in all nephron segments, while the AT₁B is more abundant than AT₁A only in the glomerulus (25, 28).

Responses to Unilateral Renal Arterial Stenosis

Although many experimental models of hypertension have been used to evaluate renal function in hypertension, one intriguing experimental model is the 2-kidney 1-clip (2K1C) Goldblatt model (9, 29-32). In the 2K1C model of renovascular hypertension, hypertension is induced by unilateral stenosis of the renal artery, usually by application of a silver clip. In general, the stenosis is not so severe to cause ischemia and the normal autoregulatory mechanism helps maintain renal blood flow and GFR near normal levels (33). However, the reduced renal perfusion pressure stimulates renin release from the stenotic kidney. The increased renin stimulates the formation of ANG I from angiotensinogen. Because of the abundance of angiotensin converting enzyme (ACE), ANG I is promptly converted to ANG II. Circulating ANG II, via its direct vascular effects, acutely increases total peripheral resistance and raises blood pressure. In addition, ANG II exerts multiple actions on almost every organ system (10). With the progressive increases in arterial pressure, perfusion pressure and flow to the clipped kidney are restored, and the non-clipped contralateral kidney becomes subjected to elevated arterial pressure which would be expected to lead to increased sodium excretion due to pressure natriuresis (34).

Since one normal kidney is sufficient to maintain fluid and sodium balance at normal arterial pressures, it would be expected that the normal kidney would prevent the development of hypertension. Nevertheless, the normal non-clipped kidney, although not the initial causative factor fails to respond sufficiently with the predicted natriuresis. Within one to two weeks after unilateral renal arterial constriction, the non-clipped kidney develops impaired renal autoregulatory capability, altered microvascular reactivity to various stimuli, enhanced tubular sodium reabsorption and a rightward shift in the pressure natriuresis relationship (9, 10, 33, 35-37). These alterations prevent the nonclipped kidney from re-establishing sodium balance without an increase in arterial pressure. The effects of elevated ANG II are powerful. Multiple direct and indirect effects of the increased circulating ANG II concentrations along with the resultant increases in aldosterone production and the ANG II dependent in-
creases in the activity of the sympathetic nervous system all contribute to the impaired excretory capability of the non-clipped kidney (9, 10). While the increases in circulating ANG II concentrations during the early developmental stages of hypertension exert major effects; it has been shown that after a few weeks of stenosis renal perfusion pressure to the clipped kidney is re-established and plasma renin activity and circulating ANG II concentrations return toward the normal range even though the arterial pressure remains elevated or increases further (38). Even during this maintenance stage, however, ANG II continues to exert powerful actions on function of the non-clipped kidney.

The cascade of events initiated by the increase in renin secretion following unilateral arterial stenosis leads to increased circulating ANG II and arterial pressure, which inhibit renin production by the non-stenotic kidney (39, 40). The reduced renin synthesizing ability of the non-clipped kidney is clearly reflected by the markedly reduced renin mRNA levels (41, 42). Renin depletion and reduced renin mRNA levels in the non-clipped kidney have previously been considered as evidence that the activity of the intrarenal renin-angiotensin is greatly diminished in the non-clipped kidney (43, 44). However, functional data have demonstrated that the non-clipped kidney is still highly responsive to pharmacological blockade of the renin-angiotensin system with ACE inhibitors or ANG II receptor antagonists (29, 31, 33, 45, 46). The non-clipped kidney responds to acute ANG II receptor blockade by increasing sodium excretion, RBF and GFR (33, 47).

Another indication that intrarenal ANG II activity is not suppressed is that the reactivity of the tubuloglomerular feedback mechanism (TGF) which responds to flow dependent changes in tubular fluid composition at the level of the macula densa is either normal or enhanced in the non-clipped kidney (37, 48). As shown in Fig. 3, TGF sensitivity is markedly influenced by the prevailing activity of intrarenal ANG II and is decreased by ACE inhibition and ANG II receptor blockade (37, 48). If ACE inhibitors or ANG II receptor antagonists are given chronically to 2K1C Goldblatt rats the hypertension is prevented and the ANG II induced decreases in renal function of the non-clipped kidney are prevented (46). This responsiveness of the non-clipped kidney to blockade of the renin-angiotensin system persists even during the maintenance phase of hypertension when the plasma renin and ANG II concentrations have returned to near normal levels (36, 38). The continued influence of ANG II on the non-clipped kidney after circulating levels return towards normal is of critical importance to the hypertensinogenic process (31, 33, 37, 47, 49, 50).

Intrarenal ANG II Levels in Hypertensive Rats

The findings that ANG II continues to exert powerful actions on the non-clipped renin-depleted kidney even after the circulating ANG II levels have returned to normal suggested that intrarenal ANG II levels remain elevated and thus do not parallel intrarenal renin activity. Earlier studies indicated that ANG II content in non-clipped kidneys is not suppressed as would be expected from the reduced renin content (51). To explore this in greater detail and to determine if the intrarenal ANG II contents of the
non-clipped kidney were dissociated from the circulating ANG II levels, a detailed evaluation of the intrarenal contents of the ANG peptides was undertaken (38, 52). As shown in Fig. 4, the plasma ANG II levels were elevated at 7 days after renal artery clipping but were close to control values at 25 days after clipping. However, the intrarenal ANG II levels in both the clipped and non-clipped kidneys were elevated during the early developmental stages of hypertension. Even after the hypertension was well established, the ANG II content in the non-clipped kidney remained slightly above or at the control levels even though renin content was markedly suppressed (38). Furthermore, the ANG II levels in the non-clipped kidneys, expressed as fmol/g were substantially greater than the circulating plasma ANG II concentrations expressed as fmol/ml indicating that the elevated renal ANG II levels were not likely to be due simply to the ANG II present in the plasma and interstitial fluid within the kidney. Elevated intrarenal ANG II contents were also associated with increased ACE activity indicating more efficient conversion of ANG II from ANG I (38, 52).

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The data obtained from the 2K1C Goldblatt hypertensive rats demonstrated that renal renin depletion is not necessarily indicative of renal ANG II depletion. These findings raise the possibility that other "low renin" models of hypertension may also have high intrarenal ANG II levels that are not predictable from renin measurements. This may help explain why ACE inhibitors and ANG II-AT1 receptor antagonists exert an antihypertensive action in essential hypertension and in several experimental models where plasma renins are normal or near normal. It was also clear that the intrarenal ANG II levels in the non-clipped kidney were much greater than could be explained simply by passive sequestration. This indicated that either the kidney was accumulating circulating ANG II into a protected compartment, or the kidney was able to sustain ANG II production through a mechanism not dependent on renin. As also shown in Fig. 4, similar results have been obtained by Mitchell et al. (53) in transgenic rats with an extra renin gene. The hypertensive TGR (Ren 2) rats show a reduced renal renin content but elevated intrarenal ANG II levels that are much higher than the plasma ANG II concentrations.

The findings that intrarenal ANG II levels expressed per gram of tissue are higher than plasma ANG II concentrations suggests that intrarenal ANG II is compartmentalized and maintained at elevated concentrations in some of these compartments. Micropuncture experiments have shown that proximal tubular fluid contains very high concentrations of the ANG peptides and angiotensinogen (54-56). Indeed, both proximal tubule ANG I and ANG II concentrations have been shown to be in the range of 3-10 pmol/ml which are from 10 to 100 times higher than the corresponding plasma ANG I and ANG II concentrations. To determine the source of the tubular ANG II, Braam et al. (55) perfused proximal tubular segments with artificial solutions and found similar ANG II concentrations in samples collected from downstream proximal convolutions indicating that ANG II and/or precursors of ANG II are secreted into the proximal tubule. Additional studies have demonstrated that angiotensinogen is also present in very high concentrations in proximal tubule fluid (57) and are supported by the earlier studies showing that angiotensinogen protein and its mRNA in the kidney are found primarily in proximal tubular cells (58-60). As illustrated in Fig. 5, these results have led to the hypothesis that ANG II and/or its precursors, ANG I and angiotensinogen, are secreted into the tubular fluid at rates sufficient to maintain very high intratubular concentrations.

Similarly high concentrations of ANG II have been found in proximal tubular fluid from the non-clipped kidneys of 2K1C Goldblatt hypertensive rats and in TGR (Ren 2) rats (47, 53). In both cases, the kidneys were renin depleted and exposed to elevated systemic arterial pressures. Yet, the proximal tubule ANG II concentrations were similar to the levels found in normotensive rats with normal renal renin content. Luminal ANG II has shown to stimulate Na/H exchange activity on the brush border so the sustained proximal tubule ANG II concentrations in these hypertensive models may be responsible for maintained proximal tubule sodium reabsorption rates and thus contribute to the continued ANG II dependent actions on proximal tubule reabsorption rate. A recent study by Rohrwasser et al. (61) demonstrated localization of angiotensinogen mRNA and protein in proximal tubules of mice and detected angiotensinogen from the apical side of mouse proximal tubule monolayers. These investigators also detected angiotensinogen in the urine and renin in connecting tubule cells of the distal nephron. Collectively, the data suggest that intra-

Fig. 4. Comparison of plasma and kidney ANG II levels in control rats, in 2K1C Goldblatt hypertensive rats at 7 days and 25 days after clipping, in TGR Ren 2 rats, and in ANG II infused rats without and with concomitant treatment with AT1 receptor blocker.
tubular ANG II formation may occur throughout various parts of the nephron and thus influence tubular reabsorption via actions on luminal ANG II receptors.

**ANG II Infused Hypertension**

To evaluate mechanisms responsible for the augmented intrarenal ANG II in renin depleted kidneys, further experiments were performed using a model of ANG II infused hypertension that leads to marked suppression of both circulating and tissue renin activity (42, 52, 62, 63). Instead of renal arterial stenosis, an osmotic minipump containing ANG II was implanted. As shown in Fig. 4, the ANG II infusions raise the plasma ANG II concentrations to levels similar to those observed after unilateral arterial stenosis. At the infusion rate selected, ANG II does not cause immediate increases in systemic arterial pressure, but rather leads to a slowly developing hypertension that mimics the development of hypertension in the 2K1C model. The renal renin content and renin mRNA and the plasma renin activity are all markedly suppressed in this model (42). The critical new observation from these experiments was that renal ANG II content increased significantly after 8 to 10 days of ANG II infusion to levels substantially greater than could be explained by the circulating ANG II (52, 63). These data support the presence of a positive amplification mechanism by which modest increases in circulating ANG II elicit more substantive increases in renal ANG II content. Because plasma renin activity, renal renin content and renin mRNA levels are markedly suppressed, it can be concluded that the intrarenal ANG II amplification mechanism is not dependent on renin. While some of the intrarenal ANG II could be due to accumulation of circulating ANG II, there was also evidence for intrarenal formation of ANG II because both the renal angiotensinogen activity and kidney ANG I contents were not significantly reduced from control levels (63). In addition to the elevated intrarenal ANG II levels, it has also been shown that the renal AT1 receptor mRNA and protein levels are maintained in ANG II induced hypertension and do not show signs of downregulation (64).

These results uncovered important questions regarding the mechanisms responsible for the increases in intrarenal ANG II levels in the ANG II infused hypertensive rats. ANG II measurements in other tissues such as heart, aorta, and adrenal gland did not show disproportionate increases in ANG II levels so the changes observed seemed to be specific to the kidney (63). In addition, the increases in renal ANG II could not simply represent nonspecific accumulation because the levels expressed per gram of total kidney weight were much greater than the plasma concentrations. These considerations raised the likelihood of an active accumulation process perhaps dependent on activation of ANG II receptors. One possibility was that the ANG II was bound and perhaps internalized by the ANG II-receptor complex such as has been shown in cultured vascular smooth muscle cells. Anderson and Peach (65) characterized the intracellular pathway of ANG II using an ANG II-colloidal gold conjugate and observed that the conjugate is internalized by AT1 receptors via small receptosomes and accumulates in large vesicles deep within the cell. It was suggested that not all of the internalized peptide was degraded by lysosomes and that part of the intracellularly delivered ANG II or an active metabolite could have unique intracellular functions.

Fig. 5. Potential sources of intratubular ANG II. Because the filtered concentrations of ANG I and ANG II are much lower than the proximal tubule concentrations and very limited amounts of angiotensinogen can permeate the glomerular membrane, most of the ANG II and angiotensinogen in the tubules are thought to be a consequence of secretion by the proximal tubule cells. Luminal ANG II binds to ANG II receptors to stimulate transport and is also internalized into the endosomal compartment.
and perhaps influence transcriptional processes.

Further experiments were performed by Zou et al. (63) to determine if the intrarenal ANG II augmentation process required AT₁ receptor activation as was shown for vascular smooth muscle cells. The AT₁ receptor blocker, losartan, was given chronically to one group of ANG II infused rats. As expected, the rats drinking losartan did not develop hypertension. The critical finding, however, was that losartan markedly reduced the intrarenal ANG II content of kidneys harvested after 2 weeks of ANG II infusion (63). The decrease in intrarenal ANG II content occurred even though losartan markedly stimulated renin production and increased circulating ANG II concentrations to much higher levels than elicited by the ANG II infusion alone. The decrease in intrarenal ANG II content occurred even though losartan markedly stimulated renin production and increased circulating ANG II concentrations to much higher levels than elicited by the ANG II infusion alone. This finding indicated that ANG II binds to AT₁ receptors and leads to increases in intrarenal ANG II levels. Thus, either AT₁ receptor activation stimulates further intrarenal ANG II formation or AT₁ receptor activation leads to internalization and intracellular accumulation of the circulating ANG II. This conclusion has received further support from recent studies using mice that have deletion of the AT₁A receptor (66). Cervenka et al. (66) found that although the circulating ANG II concentrations in AT₁A knockout mice are much higher than in the wild type controls, the kidney ANG II contents are lower in the AT₁A knockout mice. These findings suggest a role for the AT₁A receptor in mediating the increases in intrarenal ANG II contents during conditions of elevated plasma ANG II concentrations. As shown for the ANG II infused rats receiving losartan, the AT₁A knockout mice did not exhibit intrarenal ANG II levels greater than could be explained from the circulating concentrations.

Fig. 6. Plasma and kidney levels of Val⁵-ANG II and Ile⁵-ANG II in rats infused with Val⁵-ANG II and the effects of chronic treatment with losartan. Rats were infused with Val⁵-ANG II and plasma and kidney samples were assessed for both Val⁵-ANG II and Ile⁵-ANG II content.

Infusions of Val⁵ ANG II

One interesting variant of ANG II is Val⁵-ANG II which has essentially the same immunoreactivity and biological activity in the rat as the endogenous form of rat ANG II that has isoleucine in the 5 position (67). Because these two ANG II peptides can be separated by HPLC, we were able to determine how much of each peptide was present in plasma and tissues after infusing into rats for 2 weeks. As expected from previous studies, Val⁵-ANG II elicited the slowly developing hypertension previously seen with Ile⁵-ANG II. Furthermore, the increases in total intrarenal ANG II were similar to those found in previous studies (62). By using this experimental design, we determined how much of the ANG II came from the minipump and how much of the ANG II was formed endogenously. As shown in Fig. 6, analysis of the plasma ANG II levels, demonstrated that only about half of the circulating ANG II was from the minipump and that endogenous ANG II constituted half of the total ANG II even though circulating plasma renin activity was markedly suppressed. Analysis of the renal ANG II levels revealed levels of Val⁵-ANG II that were proportionately much higher than the circulating levels indicating that Val⁵-ANG II had accumulated in the kidney. About 2/3 of the intrarenal ANG II content was Val⁵-ANG II; however, the native form of ANG II (Ile⁵-ANG II) content was not reduced from that seen in control rats.

To determine if the accumulation of the Val⁵-ANG II was mediated via AT₁ receptors, one group of rats infused with Val⁵-ANG II was also given losartan chronically. The renal content of Val⁵-ANG II was markedly reduced in the losartan treated group demonstrating that the accumulation process involves AT₁ receptor activation (68). These results are consistent with the results from the AT₁A knockout experiments and indicate that the augmentation of intrarenal ANG II involves receptor mediated accumulation of circulating ANG II as well as sustained production of endogenous ANG II. The endoge-
nously formed ANG II may be formed intrarenally or may be due to internalization of endogenous circulating ANG II formed systemically. Endogenous production of ANG II may be due to ANG II stimulated angiotensinogen production. In vitro studies have shown that ANG II can stimulate local production of angiotensinogen mRNA levels in a murine proximal tubule cell line (69). This positive feedback system may be responsible for the continued endogenous production of ANG II in high ANG II states.

These results demonstrate a mechanism by which elevated intrarenal ANG II levels can occur in renin depleted kidneys. They also suggest that some of the circulating ANG II that binds to its receptor is internalized and protected from degradation. The functional role and subsequent trafficking of the internalized ANG II remains unclear. Haller et al. (70) microinjected ANG II into vascular smooth muscle cells and demonstrated increases in intracellular Ca ++ concentration and inositol trisphosphate activity. It is also possible that 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 as suggested by Anderson and Peach (65). Until recently, however, there was no direct evidence that ANG II was present in substantive concentrations in intracellular organelles.

**Direct Evidence for Intact ANG II in Intracellular Endosomes**

The ANG II infusion studies indicate that an AT1 receptor mediated internalization process may be responsible for the intracellular accumulation of ANG II. Endocytosis of the ANG II-AT1 receptor complex has been demonstrated to be required for the full expression of functional responses (71, 72). In the proximal tubule, binding of ANG II to the AT1 receptor and endocytosis of the AT1 receptor-ANG II complex is coupled to the activation of signal transduction pathways and enhanced sodium transport. Recent studies by Imig et al. (73) evaluated the presence of angiotensin peptides, angiotensin converting enzyme and ANG II receptors in renal endosomes. It was found that renal intermicrovillar clefts and endosomes contain both ANG I and ANG II but the ANG II contents were greater than ANG I. In addition, both AT1 receptors and angiotensin converting enzyme were found in these structures. It was found that ACE activity was important for the maintenance of ANG II contents in the endosomes and microvillus clefts as they were markedly reduced by ACE inhibitors. These results demonstrate that ANG II is either formed or trafficked through intracellular endosomal compartments. Further studies are needed to determine if the amount of ANG II in the endosomes is augmented in ANG II dependent hyperten-

**Summary**

Collectively, the results of experiments evaluating ANG II dependent hypertension have shown that elevated intrarenal ANG II levels can occur in the presence of reduced plasma renin and normal plasma ANG II concentrations and that intrarenal ANG II levels may be increased even when intrarenal renin content is 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 AT1 receptor mechanism; however, endogenous production of ANG II is sustained. Some of the internalized ANG II appears to be protected from degradation and therefore potentially available for intracellular actions. In addition, renal AT1 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 of elevated renal ANG II are sustained, the hypertension can be maintained even after the circulating ANG II concentrations return to near normal levels (1, 34).

**References**

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