Converting Enzyme Inhibition and the Kidney

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SUMMARY We review information on the renal response to converting enzyme inhibition, and attempt to evaluate the evidence that a reduction in angiotensin II formation is responsible for the renal response. There is little response to converting enzyme inhibitors in animals or man when the renin-angiotensin system is suppressed by a liberal sodium intake. With restriction of sodium intake, an increase in renal blood flow occurs; because a quantitatively similar response occurs to the angiotensin II analogs it is likely that the response reflects reversal of the local action of angiotensin II. In other settings it is not yet clear whether the renal response to converting enzyme inhibitor reflects only a reduction in angiotensin II formation or an additional action such as potentiation of the local actions of bradykinin or enhanced prostaglandin formation. Because these agents induce a potentiated increase in renal blood flow in the patient with essential hypertension, and with it an increase in glomerular filtration rate and sodium excretion in some patients, despite a fall in arterial pressure these questions have considerable importance. (Hypertension 2: 551-557, 1980)

KEY WORDS • sodium excretion • glomerular filtration rate • renal blood flow • angiotensin II antagonists

MULTIPLE observations over the years have suggested that angiotensin, in addition to its systemic effect on blood pressure (BP) and on sodium homeostasis through control of aldosterone secretion, may have a direct action on the renal blood supply. The important conceptual role played by ablation in defining the action of a hormone in an effector system was pointed out by Haber. In the special case of the interaction of the renin-angiotensin system and the kidney, the kidney is both the source of the hormone and the responding organ. The ablation experiment, therefore, has clearly been impossible. For that reason, the development of several classes of agent that have made it possible to interrupt the renin-angiotensin system pharmacologically has made a major contribution to the evolution of our ideas.

Before we convert pharmacologic responses to a physiologic interpretation, it is important that we assess the specificity of the available agents. The two classes of pharmacologic agents that have made the major contribution have been the angiotensin analogs (AII A), which act as competitive antagonists or partial agonists, and the converting enzyme inhibitors (CEI). In the case of the angiotensin analogs, the major problem has involved not their specificity — for it appears they have no action in addition to those anticipated from an angiotensin analog — but as partial agonists their angiotensin-like activity may well have led to an underestimate of angiotensin's role in specific situations.

In the case of the converting enzyme inhibitors, a host of actions in addition to their well-documented impact on angiotension II generation have been uncovered: under some circumstances, inhibition of kininase II has led to bradykinin accumulation, and bradykinin is a renal vasodilator. More circumstantial evidence suggests that activation of prostaglandin synthetase, at least under some circumstances, may have led to the generation of yet another potent endogenous vasodilator. Whether these actions apply to the kidney has often been unclear from available information. In the special circumstance when an angiotensin analog and a converting enzyme inhibitor have produced a quantitatively identical result, the results are very likely to have been due to pharmacologic interruption of the renin-angiotensin system, in view of the clear differences in structure, mechanism of action, and potentially misleading influences between these two classes of agent.
appear to differ or have not been clearly documented, and it is by no means clear at this time by which mechanism renal perfusion and function have been altered. We will attempt to make clear, in this review, where such evidence is available and where it is still lacking.

Renal Response to Pharmacologic Interruption in the Normal State

In healthy, recumbent animals and man, in the absence of a deficit of extracellular fluid volume and while ingesting a typical, liberal salt intake, the administration of neither angiotensin analogs nor CEI influences renal perfusion or glomerular filtration rate.10 Even the modest challenge to extracellular fluid volume engendered by a diet restricted in sodium content, however, results in a striking change in the renal response to CEI and AII A.

It has long been known that restriction of sodium intake not only activates the renin-angiotensin system, but also reduces renal perfusion and glomerular filtration rate.11 In addition, as renal blood flow fell, the renal vascular response to angiotensin II was also reduced.12 Circumstantial evidence, which raised the interesting possibility that the renal response was due to the direct action of angiotensin on the renal blood supply, was quickly tested in a number of species when pharmacologic antagonists became available. Many studies have documented an increase in renal blood flow in the dog and the rabbit when either class of agents was employed,11 but the interpretation of the functional response to the pharmacologic agents was complicated by the drop in arterial blood pressure when these agents were administered to animals in balance on a low salt diet.

Perhaps the least equivocal study among the many reported was that performed by Kimbrough et al.,13 in which the converting enzyme inhibitor was infused directly to the renal artery, raised interesting questions concerning the locus of the converting enzyme being altered by the inhibitor. Because the highest concentration and the largest total amount of converting enzyme is found in the lung, it would have been reasonable to assume that the converting enzyme inhibitors operate at this level.14 Multiple observations in the interim have suggested that angiotensin II formation within the kidney may be very important in the renal response. First, while the total amount of converting enzyme in the kidney is small, it is sharply localized to the juxtaglomerular apparatus where its action on the afferent and efferent arteriole would be maximal.25 Second, the concentration of angiotensin II of lymph draining the kidney is substantially higher than in the arterial or renal venous plasma, again suggesting local generation.24 Third, converting enzyme inhibition with the nonapeptide, SQ 20,881, blocked the action of angiotensin I on the canine renal blood supply, suggesting that angiotensin I had to undergo hydrolysis to angiotensin II for activity, and that conversion happened within the kidney.24, 26 More recent evidence that at least part of the action of converting enzyme inhibitors on the renal blood supply is due to enzyme within the kidney is presented below.

Two approaches have been used for localization of the converting enzyme. Microdissection and assay have revealed quantitatively important converting enzyme in the juxtaglomerular apparatus.25, 26 As a second approach, fluorescent antibody has shown the...
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FIGURE 1. Influence of converting enzyme inhibition (SQ 20,881) and an angiotensin antagonist (P 113) on glomerular filtration rate (GFR) studied in unaneslhetized dogs in balance on a restricted sodium intake. Note the parallel increase in GFR induced by the two agents. Not shown is a similar increase in renal blood flow and a brisk natriuresis. Reproduced from Kimbrough et al. (ref. 15) by permission of the author and publisher.

The highest concentration of the converting enzyme to lie at the level of proximal tubule. Whether the enzyme, a dipeptidyl peptide hydrolase, functions as “converting enzyme” at this site is, of course, not known. If it does it would be reasonable to conclude that angiotensin formation had an important tubular action.

Considerably less is known about the renal blood supply in man. Saralasin and SQ 20,881 both failed to increase renal blood flow in normal subjects ingesting sodium and potassium sufficient to depress the renin-angiotensin system. Conversely, both classes of agent increased renal blood flow (fig. 2) to a quantitatively similar extent, in normal subjects ingesting a sodium-restricted intake, sufficient to induce a documented activation of the renin-angiotensin system. Moreover, the dose of converting enzyme inhibitor that induced a threshold increase in renal blood flow was the same as that which induced a sharp drop in plasma angiotensin II concentration; plasma bradykinin concentration was not modified. Taken in all, this evidence suggests that in normal man, as in the dog, the entire renal vascular response to a modest volume stimulus can be accounted for on the basis of a direct action of angiotensin II on renal blood supply.

As mentioned above, restriction of sodium intake results in a reduced vascular response to angiotensin II in many systems, including that of the renal blood supply. The development of converting enzyme inhibitors has made it possible to assess the role played directly by angiotensin, as opposed to the other possible influences of sodium, on the blunted response. Converting enzyme inhibition in the dog, in which a reduction in the extracellular fluid volume had been induced, resulted in a striking potentiation in the renal vascular response to angiotensin II, but not nor-epinephrine, suggesting that occupation of receptors by endogenous angiotensin II played a role. Recent evidence that angiotensin may down-regulate receptors in other tissues makes it possible that such a phenomenon rather than receptor occupation played a role, although the time involved in the experiments with converting enzyme inhibition was much shorter than usually associated with receptor down and up regulation. Additional substances potentially relevant as determinants of renal vascular reactivity to angiotensin II include prostaglandins and other endogenous vasoactive substances, but a discussion of these is beyond the scope of this review.
Documentation of the renal vascular response to SQ 20,881 infused intravenously in normal man on a restricted sodium intake provided access to the solution of the problem raised above: Was any of the converting enzyme being inhibited by CEI within the kidney? If all of the converting enzyme had been in lung, one would have anticipated that infusion of the peptide directly into the renal artery would have resulted in either an identical response, as the agent circulated through the kidney and reached the lung, or a reduced response — to the extent that some of the agent was lost or degraded in its prolonged transit. On the other hand, a potentiated response would have indicated that, at least in part, the response was due to enzyme within the kidney. The latter was found (fig. 2): an unequivocal potentiation of the renal vascular response occurred to infusion directly into the renal artery.28

The Renal Circulation in Hypertensive Disease

The possibility that the renal blood supply participates not only in the pathogenesis of renovascular hypertension, but also of essential hypertension, has been the subject of continuing interest. Reduced renal blood flow and glomerular filtration rate are certainly common in essential hypertension. The mechanisms responsible for these derangements are incompletely delineated, with possibilities including fixed changes due to the organic influence of arteriolonephrosclerosis in the afferent arterioles and glomeruli; a functional change in the reactivity of the intrarenal vessels; or an increase in the intrarenal action of local vasoconstrictors such as angiotensin II. Some years ago we reported a reciprocal relationship between renal blood flow and renin release from the same kidney in patients with essential hypertension.4 In brief, as renal blood flow fell, renin secretion calculated from renal blood flow and the renin activity in arterial and renal venous plasma rose (fig. 3). At that time it seemed reasonable to attribute both the reduction in blood flow and the increasing renin release to advancing arteriolonephrosclerosis. In view of the evidence presented below, the alternative possibility — that the reduction in renal blood flow was a consequence of and not a cause of the increased renin release — had to be considered.

A characteristic that would distinguish, at least in part, the influence of an organic lesion from that due to a functional abnormality is the reversibility of the latter. Several lines of evidence now suggest that a functional abnormality often makes a substantial contribution to the reduction in renal perfusion: the intrarenal infusion of vasodilators, such as acetylcholine and dopamine, resulted in a potentiated increase in renal blood flow in about two-thirds of patients with essential hypertension in association with normalization of the renal arteriogram.28 The renal response in patients with advanced arteriolonephrosclerosis, chronic pyelonephritis, and polycystic kidney disease, all settings in which fixed organic lesions would be expected to contribute to abnormalities in renal perfu-

![Image of figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Relationships between degree of small vessel disease, evaluated from the arteriogram in patients with essential hypertension, and both the character of renal perfusion and the rate of renin secretion. The original interpretation was that both the reduction in renal blood flow and increased renal secretion rate reflected an influence of organic, fixed microvascular disease. The possibility that angiotensin formation, due to increasing renal release, resulted in the reduction in renal blood flow must now be considered. Reproduced by permission of the publisher from Hollenberg et al. (ref. 34).
— at least in part —for the reduction in renal perfusion.

Renal Response to Converting Enzyme Inhibition in Essential Hypertension

On the premise that angiotensin is a major intra-renal hormone, and that essential hypertension is a process in which disordered volume control could lead to excessive local formation of this hormone, we undertook a study of the renal responses to CEI.

Infusion of the nonapeptide, SQ 20,881, in patients with essential hypertension led to an enhanced renal vascular response, with renal blood flow increasing at lower doses of the pharmacologic agent and to a greater extent than in normal subjects (fig. 4). Moreover, as opposed to virtually every other antihypertensive agent studied to date, the peptide converting enzyme inhibitor, SQ 20,881, increased glomerular filtration rates in patients with essential hypertension with the increase in filtration rate being most striking in the patients in whom an initial reduction in filtration rate was evident and in whom hypertension was most severe (fig. 5). To our knowledge, no other antihypertensive agent has led to an increase in glomerular filtration rate as perfusion pressure fell.

The antihypertensive efficacy of CEI has often been striking in patients with accelerated hypertension, but little has been reported on its renal action in this setting — which is often characterized by important abnormalities in renal perfusion and function. We have had the opportunity to assess the renal response to SQ 20,881 in one such patient who presented with a brief history of severe hypertension (arterial blood pressure as high as 240/150), hypertensive neuro-retinopathy (hemorrhage, exudates, and papilledema), early azotemia (recent rise in serum creatinine to 2.0 mg/dl), and reduced renal perfusion (fig. 6). Administration of SQ 20,881 in graded dosage led to a large increase in renal perfusion at doses well below those required to reverse the hypertension. Moreover, when increasing SQ 20,881 dosage led to control of the hypertension, the increase in renal perfusion was well-sustained. Control of hypertension with this agent for several days was associated with gradual improvement of renal function. Could there be a functional component in the renal abnormality, at least early in accelerated hypertension?

Before concluding that, by inference from the studies of normal man, that the renal response reflected a reduction in the influence of angiotensin II on the renal blood supply in essential hypertension, the caveat raised in the introduction must be remembered: responses to these agents are complex. In a series of studies from this laboratory, differences in the endocrine response of normal subjects and patients with essential hypertension have been documented: plasma bradykinin, for example, rose in the latter, and the rise in plasma bradykinin concentration was most striking in those in whom blood pressure fell. The reduction in plasma angiotensin II concentration was also potentiated in the patients with essential hypertension, suggesting that perhaps more than one mechanism was operative. More recently, a rise in PGE has been documented in response to CEI, and the cyclo-oxygenase inhibitor, indomethacin, has been shown to blunt the BP-lowering effect of CEI in essential hypertension. In support of these studies, Vinci et al. have recently reported that the vasodepressor response to converting enzyme inhibition in patients with hypertension correlated more closely with increased urinary kinins and plasma PGE than changes in the plasma angiotensin II concentration.

Only preliminary information is available on the renal response to the oral CEI, SQ 14,225. As was the case for the peptide, SQ 20,881, the agent induces an increase in renal perfusion in normal subjects when in balance on a restricted sodium intake, and a potentiated response in patients with essential hypertension. In nine normal subjects, a single 10 mg dose taken by mouth led within 20 minutes to an increase of 0.83 ± 0.07 ml/g/min, whereas the increase was 1.28 ± 0.17 ml/g/min in four patients with essential hypertension. There are differences already apparent, however, in

![Figure 4. Changes in renal blood flow (Δ RBF) and mean arterial blood pressure (Δ BP) induced by graded doses of SQ 20,881 in normal subjects and patients with essential hypertension, studied when in balance on a restricted sodium intake. Note the enhanced renal blood flow response in patients with essential hypertension despite the larger fall in blood pressure. Reproduced by permission of the publisher from Williams and Hollenberg (ref. 37).](http://hyper.ahajournals.org/)

FIGURE 4. Changes in renal blood flow (Δ RBF) and mean arterial blood pressure (Δ BP) induced by graded doses of SQ 20,881 in normal subjects and patients with essential hypertension, studied when in balance on a restricted sodium intake. Note the enhanced renal blood flow response in patients with essential hypertension despite the larger fall in blood pressure. Reproduced by permission of the publisher from Williams and Hollenberg (ref. 37).
the renal response to SQ 20,881 and SQ 14,225. SQ 20,881 never led to an increase in renal perfusion in normal subjects in whom a liberal sodium intake suppressed the renin-angiotensin system. Preliminary studies on SQ 14,225 in our laboratory have revealed an increase in renal perfusion in seven normal subjects despite a substantial sodium intake (0.41 ± 0.11 ml/g/min), and a potentiated renal vascular response in patients with essential hypertension (1.4 ± 0.36 ml/g/min) despite suppression of the renin-angiotensin system — at least as evidenced by low plasma levels of renin and angiotensin. The possibility that plasma and intrarenal concentrations of these hormones do not parallel each other must be considered.

Perhaps germane to the problem of the renal response to converting enzyme inhibition, Zusman and Keiser have shown that bradykinin increases prostaglandin synthesis by renal medullary interstitial cells, and Gimbrone and Alexander have documented a similar phenomenon in cultured endothelial cells. Obika and Mills have shown that intrarenal PGE infusion resulted in an increase in urinary kallikrein activity. The possible role played by the complex interaction of kinins, prostaglandins, or other vasoactive hormones in the salutary renal response to converting enzyme inhibition in patients with essential hypertension requires assessment.

**Conclusions**

Taken in all, the available information suggests that the renal vascular response to a modest but not necessarily large volume stimulus is mediated entirely by the direct action of angiotensin II on intrarenal arterioles. On this basis, the renal response to converting enzyme inhibition probably reflects reversal of this action. When the stimulus is larger, additional effector mechanisms are probably recruited, and it may well be that the renal response to converting enzyme inhibition reflects additional actions. In patients with essential hypertension, a potentiated response to converting enzyme inhibition may reflect an increased action of angiotensin II on the renal blood supply, due either to increased local formation or to an enhanced renal response to a normal concentration, but the direct evidence required to rule out other actions of the converting enzyme inhibitors on other systems is not yet available. Evidence is appearing that the kidney plays a role in the antihypertensive action of converting enzyme inhibition, and here, too, the mechanism of that renal contribution is unclear.

The development of more specific antagonists to the known prostaglandins, an effective antagonist to bradykinin, and improved assays for these hormones would help us to elucidate the mechanism of action of
the converting enzyme inhibitors on the kidney in essential hypertension. If, indeed, the kidney plays a key role in sustaining hypertension — as has been suggested — the answers to the questions raised here may well be relevant to pathogenesis as well as for effective therapy.

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