The introduction of agents capable of blocking the function of the renin-angiotensin system has had a profound impact on our knowledge of the physiology of the renin-angiotensin system and its role in various pathophysiological conditions, including hypertension. Saralasin and other angiotensin antagonists, peptides similar in chemical structure to angiotensin II itself, have been used since the early 1970s. Because saralasin and other angiotensin antagonists were found to lower systemic arterial pressure in conditions characterized by high renin levels (e.g., renovascular hypertension and sodium restriction) and to cause changes in renal hemodynamics and function, there was a renewed interest in the potential role that angiotensin II plays in hypertension. Later the realization that the venom of Bothrops jararaca possessed a substance capable of inhibiting the angiotensin converting enzyme (ACE) led to the design of synthetic ACE inhibitors, of which captopril is the prototype.

For the past 2 decades, angiotensin antagonists (and more recently the ACE and renin inhibitors) have provided powerful tools for investigators to learn more about the renin-angiotensin system and its role in blood pressure and volume regulation. However, as is true for drugs in general, these pharmacological agents have undesirable actions that complicate interpretation of many of the findings made during their use. Because of the structural similarity of saralasin and other peptide angiotensin antagonists to angiotensin II, the antagonists possess agonistic properties.

Although the use of peptide angiotensin II antagonists has stimulated the field greatly, they are far from ideal blocking agents. The ACE inhibitors can also cause effects through actions other than blockade of the renin-angiotensin system. ACE and kininase II are identical, and thus kinin potentiation and inhibition of the metabolism of other peptides may enter into the effects of these agents. Even the most recently introduced group of compounds, the renin inhibitors, which were designed specifically to inhibit human renin, have a profound hypotensive action in higher doses that is evidently unrelated to renin inhibition. As a result of these undesirable actions and also because of an apparent distinction between the circulating and tissue renin-angiotensin systems, the search has continued for more effective drugs to block these systems. A means of discriminating between the physiological actions of circulating and locally generated angiotensin II is a goal that is highly sought. P.C. Wong and his colleagues have reported the development of a very promising nonpeptide angiotensin antagonist1-2 and, in this issue of Hypertension, report on a monoclonal angiotensin II antibody3 as new approaches to blocking renin-angiotensin function.

By binding angiotensin II, the monoclonal angiotensin II antibody KAA8 antagonizes the pressor response to angiotensin II in vivo as well as inhibits contractile responses of isolated vascular smooth muscle.4 This is a specific action because the effect of norepinephrine and vasopressin is unchanged by KAA8. Intravenous administration of the antibody decreased systemic arterial pressure in the conscious renal-ligated hypertensive rat, a high renin hypertensive model. In these animals, the high circulating angiotensin II was completely bound by the antibody and undetectable by radioimmunoassay. Prevention of circulating angiotensin II from reaching its receptor sites is the presumed mechanism of antihypertensive action. Interestingly, after blockade with KAA8, captopril no longer exerted any effect on the blood pressure. Wong et al.6 have not reported whether KAA8 is hypotensive in normal animals but have shown that a control immunoglobulin G antibody exerted no effect on the blood pressure of hypertensive rats. KAA8 also has no effect on the blood pressure of spontaneously hypertensive rats. It is important, however, to demonstrate that KAA8 also has no effect in normal rats.

The nonpeptide angiotensin antagonists developed by this group offer other advantages and may be used along with the antibody. These imidazole
derivatives lack the nonspecific actions that might occur because of the protein nature of an antibody, and thus they do not cause immunologic reactions. The compounds reported so far, designated S-8307 and EXP 6803, exert a specific blockade of the pressor and contractile responses to angiotensin II and decrease blood pressure in high renin hypertensive rats.\(^2\)\(^-\)\(^7\) Captopril had no effect on blood pressure of the hypertensive rats after blockade with these nonpeptide angiotensin antagonists. Therefore, a common mechanism of antihypertensive action, namely, blockade of the renin-angiotensin system, seems to exist for the antibody, the angiotensin antagonists, and captopril. Because furosemide treatment enhanced the hypertensive effect induced by this compound, the ability of the angiotensin antagonist S-8307 to decrease blood pressure in the anesthetized normal rat is attributed to blockade of the vasoconstrictor tone due to endogenous angiotensin II. However, these imidazole derivatives may possess some additional hypertensive properties. Captopril or saralasin treatment reduced, but failed to eliminate, the hypertensive response to S-8307 in the anesthetized rat. It would be of interest to compare the effects of the antibody KA\(\text{A}8\) and the nonpeptide antagonist on the blood pressure of conscious low renin animals to rule out any nonspecific actions of these agents.

Another interesting facet of the action of KA\(\text{A}8\) that is emphasized in the current report is the absence of interference with vasomotor responses to sympathetic nervous activation. It is well known that angiotensin II potentiates vasoconstrictor and vascular contractile responses to adrenergic nerve stimulation. There also have been numerous publications demonstrating that the angiotensin antagonist saralasin and ACE inhibitors attenuate these responses. The blocking effect has been attributed to antagonism of both a prejunctional and postjunctional adrenergic potentiating action of angiotensin II. Wong and colleagues\(^5\) found depression of the adrenergically mediated pressor response to spinal cord stimulation in the pithed rat by saralasin and captopril but showed no such effect of KA\(\text{A}8\). Based on these findings, the antibody differs from saralasin and captopril in the capability of blocking responses to sympathetic stimulation. Thurston and Swales\(^8\) have also reported a difference in the blocking capability of angiotensin antibody and an angiotensin antagonist. Because the antibody is a large protein (whereas both saralasin and captopril are smaller molecules), it has been hypothesized that KA\(\text{A}8\) fails to gain access to the site of adrenergic potentiation by endogenous angiotensin II. Wong and coworkers\(^5\) suggest that tissue-derived angiotensin II rather than circulating angiotensin II is responsible for adrenergic potentiation in the pithed rat and that KA\(\text{A}8\) does not block this effect. Previous workers have implied that angiotensin II synthesized in the vascular wall is responsible for its adrenergic potentiating effect, and the present results would agree with this postulate.

The interesting proposal set forth by Wong et al\(^3\) is that, with use of a combination of drugs, it may be possible to determine whether tissue or circulating angiotensin II is the causative agent in pathophysiological states. Such a proposition has merit and may offer investigators a tool to dissect the respective roles of the circulating and tissue renin-angiotensin system. Comparison of the results derived with a specific angiotensin antagonist that blocks the effects of both circulating and locally released angiotensin II with those obtained with the monoclonal antibody affecting only circulating angiotensin II would provide leads to the roles played by these renin-angiotensin systems. There have been many suggestions concerning the possible contributions of the tissue renin-angiotensin system to blood pressure and vascular regulation but few approaches to define the functional role of this system.

The ultimate aim is to apply nonpeptide angiotensin antagonists in the treatment of essential hypertension, and this seems advantageous. Like the ACE inhibitors, these compounds offer efficacy by the oral route of administration; they appear to have minimal side effects, and their sole pharmacological action to date is to antagonize the effects of angiotensin II. Much additional work will have to be done to determine the advantages and disadvantages of these compounds, but regardless of their potential clinical applicability, they represent, along with the monoclonal antibody, powerful pharmacological tools. Clarification of the pathophysiological and physiological roles of the renin-angiotensin system, as well as definition of the structure of the angiotensin receptor, is anticipated through the use of these agents.

References


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