Editorial Comment

Renin System Inhibition
Beginning the Fourth Epoch

Robert J. Cody, MD

It is difficult to divide an area of research endeavor into arbitrary stages of development. However, investigation of the role of the renin system in cardiovascular disease has ostensibly passed through three epochs. The first epoch was the identification of the renin system as an important endocrine system in pathophysiological disorders such as hypertension and congestive heart failure. The second epoch was the preliminary attempt to inhibit the renin system to identify both the physiological and pharmacological implications of inhibition. The initial endeavors in this regard included nonspecific agents such as β-adrenergic blockade and preliminary studies with angiotensin II antagonists, renin inhibitors, anti-renin antibodies, and converting enzyme inhibitors. The third epoch was the emergence and application of converting enzyme inhibitors. This class of agents has provided 15 years of valuable physiological information and clinical insight regarding not only the renin system but also the fundamental abnormalities of cardiovascular disorders such as hypertension and heart failure.

The article by Kiowski and coworkers1 in this issue of Circulation is one of several recent articles that heralds the fourth epoch. The authors address an important and controversial area regarding converting enzyme inhibitors; namely, the mechanism for the reduction of blood pressure that occurs following administration of a converting enzyme inhibitor in sodium-replete normotensive subjects. There are several key features of the article. First, the study demonstrates that the renin and non-renin effects of a converting enzyme inhibitor can be segregated in a clinical study. Second, the study provides powerful evidence that the reduction of blood pressure, produced by an angiotensin converting enzyme (ACE) inhibitor in normotensive sodium-replete subjects, is mediated by bradykinin. Third, the study raises important issues regarding the non-angiotensin II effects of ACE, a carboxypeptidase that may have other independent physiological roles, particularly at the cellular level. Fourth, and not least important, the study demonstrates the power of using discrete inhibitors of the renin system to characterize angiotensin-independent and angiotensin-independent vascular responses. In experimental animals and in humans, it is well known that the state of sodium balance determines the magnitude of renin system activation and the subsequent hypotensive response to inhibitors of the renin system.2-4 In sodium-depleted subjects, converting enzyme inhibitors produce a marked reduction of blood pressure, at times to the point of syncope. In the sodium-replete state, reductions in blood pressure are of a much smaller magnitude and have been attributed to either the lesser presence of angiotensin II or to nonspecific effects of converting enzyme inhibitors. The inhibition of bradykinin degradation by converting enzyme inhibition, producing an increased circulating level of the vasodilator bradykinin, had been postulated as one explanation. The article by Kiowski and coworkers may have finally resolved this issue in normal sodium-replete subjects. Inferences as to the magnitude of such a response in disease states cannot be established. To place these observations in the context of implications for future research requires an understanding of the pharmacological inhibition of the renin system, the concept of the angiotensin converting enzyme, and the impact and promise of newer approaches to renin system inhibition.

The Renin System: Sites of Inhibition and Implications

The rate at which angiotensin is converted to the vasoactive angiotensin II is determined by renin. Renin is the rate-limiting enzyme for the renin system, cleaving four amino acids from angiotensinogen to form angiotensin I. Angiotensin I is then converted to the vasoactive angiotensin II by converting enzyme, a carboxypeptidase. In general, angiotensin I does not have the vasoactive or pathologically important role of angiotensin II. In addition to other important roles within the body, angiotensin II is also the most important secretagogue of aldosterone. Together, these effects are mediated by the angiotensin II receptor, which appears to have at least two subgroups.
Pragmatically, there are three sites of renin system inhibition. One is to provide a "pseudosubstrate" for renin to inhibit its binding to angiotensinogen. This has lead to the development of renin-inhibitory peptides such as that studied by Kiowski and coworkers. The second class of agents is the angiotensin converting enzyme inhibitors, or ACE inhibitors. The third class of inhibitors of the renin system is angiotensin II antagonists. The studies of renin inhibitory peptides have extended over 25 years, and from the initial in vivo studies of renin inhibitory peptides, there was a debate as to whether inhibiting the rate-limiting step of the pathway would hold greater promise than the already well-established use of converting enzyme inhibitors. However, several limitations of the early renin inhibitory peptides stifled this approach: These compounds had low solubility in physiological solutions, and they required intravenous administration. The concept of converting enzyme inhibitors is also approaching 25 years of development, and the initial discovery and development of these compounds could be considered a historic landmark in medicinal chemistry. When first described, the initial compound derived from the snake venom B jararoca was initially labeled a "bradykinin potentiating substance" that was the template for development of an intravenous peptide converting enzyme inhibitor, teatropide, and subsequent development of an oral dipeptide form, captopril. This converting enzyme inhibitor and the compounds that followed in its path have made a major impact in cardiovascular disease states, as confirmed again in recent clinical trials of heart failure. Angiotensin II antagonists, like other inhibitors of the renin system, have also spanned 20 years of development. These peptides, like the initial renin inhibitory peptides, also required intravenous administration. Of greater concern with these sarcosine-modified peptides was the potential for either an antagonist or agonist hemodynamic response. In high renin conditions, they functioned as antagonists. In low renin conditions such as the sodium-replete normal subject, these compounds acted as agonists, with characteristics not unlike endogenous angiotensin II. This was a flaw of these compounds that lead to their demise.

**ACE: What Is It?**

Early in development, the converting enzyme was characterized as a carboxypeptidase of the kininase II group, an enzyme that cleaves two amino acids from angiotensin I, producing angiotensin II. In addition, this enzyme inhibited the degradation of bradykinin, with implications also for prostaglandin biosynthetic pathways. Initially, substances that inhibited this enzyme were referred to as "CEIs," converting enzyme inhibitors. This was partially in deference to the multiple actions of this enzyme. Despite the demonstration that a converting enzyme inhibitor would increase circulating bradykinin, CEIs became "ACE inhibitors," emphasizing the angiotensin mechanism. It is now virtually impossible to attend a clinical meeting without the question being raised: "What about tissue ACE?" In fact, converting enzyme has always been tissue. Initially identified in pulmonary tissue, converting enzyme was later identified in vascular tissue and subsequently in many organ systems. However, assay of tissue converting enzyme continues to demonstrate that its presence in the lung exceeds other tissue sites by orders of magnitude. In contrast, the importance of serum converting enzyme levels has not been established. Furthermore, converting enzyme, or carboxypeptidase, may have specific cellular effects. Rather than the question "What about tissue ACE?" it might be more important to ask the question "What about carboxypeptidase?" This enzyme, and the changes produced by its manipulation, may be of importance beyond the renin-specific effects of the enzyme. In this regard, a better question might be: "Are ACE inhibitors the current best non-specific inhibitors of carboxypeptidase?" These questions may be relevant in view of recent clinical congestive heart failure trials. Unlike severe heart failure, in early left ventricular dysfunction and early congestive heart failure, the endocrine-renin system is often within normal limits. Under these conditions, what mechanisms produce the beneficial response? In this regard, the fourth epoch of renin system inhibition may prove to be the most important.

**The Fourth Epoch: Specific Renin System Probes**

The clinical impact of the converting enzyme inhibitors, particularly in disorders such as congestive heart failure, cannot be overstated. In an attempt to delineate endocrine, paracrine, autocrine, and intercrine effects of angiotensin II, the role of this seemingly ubiquitous substance defies such arbitrary classification and exerts major cardiovascular morbidity. The non-renin effects of converting enzyme inhibitors require better definition. These effects likely go beyond changes in circulating bradykinin. In the study by Kiowski and coworkers, the observed blood pressure reduction may have resulted from increased circulating bradykinin. Like angiotensin II, bradykinin also has specific tissue effects within the kidney, and it may be an important regulator of endothelium-dependent vasodilation. Furthermore, there may be undescribed effects of carboxypeptidase, particularly within the cell, that are not explained by any of the above phenomena. This is the larger implication of studies such as that by Kiowski and coworkers. We now have renin system inhibitors, presumably specific, to block the rate-limiting renin step of the pathway. These substances have been carefully developed in the last decade and are now a reality. Yet some doubts linger regarding the feasibility of this approach. Furthermore, specific non-peptide angiotensin II antagonists are now available. These substances have a high binding affinity for the angiotensin II receptor, are orally effective, and most importantly, do not have the agonist effects of their predecessors. It will require at least the remainder of this decade to segregate the precise mechanisms that account for
the clinical outcome that we have attributed to ACE inhibitors. There will also be a continued debate as to whether it is better to inhibit the rate-limiting renin step, or to antagonize the angiotensin II receptor. Use of combined probes of the renin system should have considerable impact on the design and outcome of future studies that assess the physiological, cellular, and molecular mechanisms of circulatory control in normal subjects and abnormalities of the circulation in hypertension and congestive heart failure.

References

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R J Cody

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