It is remarkable how the medical community’s view of the renin-angiotensin system has changed in less than a decade. Before 1978, the determination of plasma renin activity, along with other tests, appeared useful in the diagnosis of two rather uncommon causes of hypertension: renal artery stenosis and tumor or hyperplasia of the adrenal cortex. Saralasin, a competitive inhibitor of the angiotensin II receptor, was at that time the only inhibitor of the renin-angiotensin system available for clinical use. Because this compound can be administered only by intravenous injection and has a very short half-life, its sole application was in the recognition of "angiotensinogenic" hypertension. Even though blockade of the renin-angiotensin system by direct inhibition of renin (renin-specific antibodies) or by the angiotensin converting enzyme teprotide (a snake venom peptide) could be effected in experimental models of hypertension and in short-term clinical studies, evaluations of long-term therapy could not be carried out with these very limited agents. In 1978, Gavras et al. reported the first clinical trial of an oral converting enzyme inhibitor, captopril. It soon became apparent that inhibition of the renin-angiotensin system was an effective treatment for essential hypertension regardless of the patient’s plasma renin concentration and a means of ameliorating advanced heart failure by reducing afterload.

While the clinical use of converting enzyme inhibitors flowered, the development of agents that directly blocked the action of renin was considerably slower. Monoclonal antibodies are excellent experimental tools, but the necessity of parenteral administration and potential immunogenicity prevent their use in clinical trials. A small organic compound that was a specific renin inhibitor had to be found. The first low-molecular-weight inhibitor to block renin’s action effectively in vivo was an analogue of an octapeptide that Skeggs et al. had shown many years before to be the minimal substrate for renin. This compound was not very potent (with reported inhibitory constants between 1.0 and 2.3 μM) and at higher doses exhibited some lack of specificity. More potent inhibitors were then constructed by substituting various nonhydrolyzable transition-state analogues for the scissile bond (the peptide bond cleaved by renin). These analogues included a secondary amine, the hydroxyethylene moiety, the amino alcohol linkage, and the amino acid statine, which is a constituent of the nonspecific, bacterial acid protease inhibitor pepstatin. The transition-state analogue compounds proved to be very potent, with inhibitory constants in the nanomolar range, and were shown to be effective in experimental animals and in humans.

The development of these compounds has progressed rapidly over the past several years. Incorporation of the statine analogues cyclohexyl statine, difluorostatine, and difluorostatone into the substrate sequence further increased potency. Several substitutions for the carboxy group at the carboxy terminus have had a significant impact on the inhibitory constant. The placement of an amino acid aldehyde at the carboxy terminus surprisingly reduced the required size of a renin inhibitor to that of a dipeptide or tripeptide. Reducing the carboxy-terminal carboxylic acid amide to an amine also appears to increase potency, but not in the presence of plasma. Dipeptide glycols, another carboxy-terminal change, result in moderately effective inhibition.

Although promising with respect to specificity and potency, all these compounds are poorly absorbed by the gastrointestinal tract and are thus of no use in investigations of the chronic illness for which they were designed — essential hypertension. There is no
general method, as yet, for converting a pharmacologically active peptide into an equivalent compound that can be administered orally.

In this issue of the journal, Pals and collaborators describe a modified peptide renin inhibitor that has a rather lipophilic structure and is characterized by limited oral efficacy. They demonstrate absorption of approximately 10% of the oral dose. While this limited degree of absorption has certainly not solved the problem of creating an orally active drug, the observation offers encouragement that it will one day be possible to synthesize a more useful structure. As yet, our understanding of renin inhibitors has not reached a point equivalent to that of the masterful insight of Ondetti, Rubin and Cushman, which generalized the principles of converting enzyme inhibition and led to the commonly used antihypertensive drugs captopril and enalapril. A detailed study of renin's catalytic site, either by building models based on the structure of related molecules or by the direct determination of human renin's three-dimensional structure by x-ray crystallography (which will be facilitated when the enzyme becomes available through recombinant DNA techniques), may be required before the general principles of renin inhibition can emerge.

Although effective oral renin inhibitors may offer a more selective means of blocking the renin-angiotensin system, it is not certain whether they will offer significant clinical advantages over converting enzyme inhibitors. One potential advantage of any new class of drugs is that they may eliminate adverse reactions associated with agents in current use. It remains to be determined, however, whether the adverse reactions common to both captopril and enalapril are the result of blockade of one of the two target enzymes (both kininase II and angiotensin converting enzyme are inhibited) or whether they are the consequence of a general inhibition of the renin-angiotensin system and would be a feature of any class of drugs used to block it.

EDGAR HABER

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