CHAP TER 19

THE EFFECTS OF CONVERTING ENZYME INHIBITION

Several compounds have been discovered or created that inhibit angiotensin converting enzyme and thereby dramatically slow the conversion of angiotensin I to angiotensin II. One of these, captopril, has been widely used as an experimental tool and is currently being evaluated for routine clinical use because it can be administered orally.

Acute inhibition of angiotensin formation produces large decreases in blood pressure only when plasma renin activity is grossly elevated, as in malignant hypertension or salt deprivation; in other instances acute inhibition has only a small hypotensive effect. With continuing or chronic inhibition, on the other hand, the acute effect is supplemented with a further, progressive decline in arterial pressure. Chronic treatment with captopril has been shown to lower blood pressure in hypertensives not associated with high levels of plasma renin, such as essential hypertension in humans and genetic hypertension in the Okamoto strain of rats. The cause of this potent antihypertensive effect is not clear. It has been postulated that bradykinin is responsible; converting enzyme is an enzyme that also controls bradykinin degradation and converting enzyme inhibition might lead to important increases in bradykinin levels. A renal factor may also be important, since inhibition often produces natriuresis and since arterial pressure falls gradually with chronic treatment as if a slow, cumulative process was at work. Acute studies have shown that converting enzyme inhibition increases renal blood flow, increases (but sometimes decreases) glomerular filtration rate, increases salt and water excretion and stimulates renin release. Diuretics in general have been observed to stimulate renin release and the renin in turn appears to blunt the antihypertensive effectiveness of the diuretic. Converting enzyme inhibition, in addition to providing a diuresis, will prevent the additional renin from being translated into more angiotensin II. Therefore, chronic inhibition might lower pressure via diuresis but without the hinderance usually produced by
compensatory renin release.

The function of the renin-angiotensin system can also be interrupted using analogs of angiotensin II. Substitution of amino acids at the ends of the octapeptide sequence has produced variations of angiotensin with affinity for the angiotensin receptor but with attenuated activity. Use of these analogs has produced results that are qualitatively very similar to the results of converting enzyme inhibition. Synthesis of angiotensin analogs preceded the development of converting enzyme inhibitors; however, the use of analogs has been overshadowed by converting enzyme inhibition because analogs must be continuously infused to produce effective blockade and are not orally active.

THE RENIN-ANGIOTENSIN SYSTEM

Renin is an enzyme with a molecular weight of slightly greater than 40,000. It is synthetized primarily in the kidney and released into the circulating blood. Larger and less active proteins, called big renin and inactive renin, have been described and these may be the precursors of the active enzyme. Renin releases angiotensin I from a circulating alpha-2-globulin called renin substrate or angiotensinogen.

Angiotensin I is a decapeptide with the structure Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu. Angiotensin I has minimal biological activity. Angiotensin II is a biologically active decapeptide that is formed when angiotensin converting enzyme splits the carboxy-terminal histidylleucine (His-Leu) from angiotensin I. The structure and activity of angiotensin varies among the biological genera. A phylogenic review has been presented by Khosla and colleagues (510).

Angiotensin converting enzyme is actually one or more non-specific dipeptide carboxypeptidases found in the circulation and particularly in the lungs. Therefore, this enzyme also inactivates bradykinin by cleaving carboxy-terminal dipeptides. Bradykinin is a nonapeptide with the structure Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg.

There are several ways to interfere with the formation and action of angiotensin (623).

1. Decrease the activity of renin. Phospholipid inhibitors decrease the release and activity of renin. Pepstatin, a pentapeptide, decreases renin's enzymatic