Brief Reviews

Angiotensin I Converting Enzyme

By Ervin G. Erdös

Interest in particular biologically active substances waxes and wanes. Investigators rush into a newly opened field, solve a few problems, and frequently raise more; then they rush out to follow more promising developments elsewhere. However, interest in angiotensins generally has persisted and increased. Observation of the actions of angiotensins has led to the study of enzymes involved in the metabolism of the liberated peptides, including the angiotensin I converting enzyme.

The angiotensin I converting enzyme was discovered by Skeggs and his associates in the mid 1950's (1-3) when they noticed that horse plasma contains an enzyme that converts angiotensin I to angiotensin II. Renin releases the decapeptide angiotensin I from angiotensinogen. This decapeptide is in turn converted to the octapeptide angiotensin II when the converting enzyme cleaves a histidyl-leucine dipeptide from the C-terminal end of angiotensin I. The enzyme requires chloride ions and is inhibited by ethylenediaminetetraacetic acid (EDTA). Around the same time Helmer (4, 5) also observed the existence of a factor in plasma that activated his angiotensin preparation.

After these discoveries, the matter lay dormant for a long time, no doubt because angiotensin I was not available in pure or synthetic form in substantial quantities. The issue of conversion was kept alive, however, because of the difference between the effects of angiotensin I and angiotensin II on isolated smooth muscle preparations. It was observed that angiotensin I must be converted enzymatically to angiotensin II before it becomes active in most biological systems in vitro (2, 5, 7). (The need for such conversion in vivo is not that noticeable, because the two peptides have similar effects on systemic blood pressure after intravenous injection due to the rapid conversion of angiotensin I in the body.) It has been difficult to measure the conversion of angiotensin I to angiotensin II by bioassay, because tissues which contain the converting enzyme also inactivate the released peptide. Estimation of conversion in vitro gave only semiquantitative data (8), until radioactive and other synthetic substrates became available.

Independent of the investigation of angiotensin conversion, the enzymatic inactivation of bradykinin was studied between 1961 and 1967. It was observed that a partially purified collagenase preparation from Clostridium histolyticum inactivated the peptide by cleavage of the Pro^Phe bond and release of C-terminal phenylalanylarginine (6, 9). Later, a kininase that split the same bond in bradykinin and released Phe^Arg was concentrated from a microsomal fraction of the hog kidney cortex (10); this enzyme was named peptidase P. The same enzyme was also detected in human plasma (11). Because the first plasma kininase characterized was called carboxypeptidase N (E.C. 3.4.12.7) (6), to distinguish the second enzyme, carboxypeptidase N was renamed kininase I and peptidase P was termed kininase II (E.C. 3.4.15.1). Partially purified kininase II is inhibited by metal-binding agents, by some heavy metals, and by Phe^Arg (the split product of the reaction) (11). That kininase II and angiotensin I converting enzyme are identical could not be established, however, until synthetic angiotensin I became available and the enzyme had been purified.

Presence in Tissues

Research on angiotensin was stimulated when solid-phase synthesis of angiotensin I made appreciable quantities of the peptide available (12, 13). Vane and his associates (14-16) began studying the fate of angiotensin I by using the purified peptide and the isolated superfused organ technique to separate the effects of angiotensin I and angiotensin II in the circulating blood. They found that conversion in plasma was too low for the formation of angiotensin II in vivo but, when they injected angiotensin I intravenously into the dog, they recovered angiotensin II after pulmonary passage. Little or no angiotensin II was recovered from venous blood when angiotensin I was injected into the renal or femoral artery. They concluded that...
the pulmonary circulation is the site of conversion of angiotensin I. Centrifugation of homogenized lung tissue yielded a particulate fraction that converted angiotensin I and inactivated bradykinin (17, 18), although it was initially assumed that the two activities were due to two different enzymes (17). Isolated pulmonary arteries converted angiotensin I more readily than did vessels taken from other vascular beds (19). Other workers confirmed the importance of the lung in the conversion of angiotensin I, but they found greater conversion by the lung tissue than by other vascular beds (19). Other workers (23, 29) found about the same percent conversion in the two activities; the more esoteric sources of the enzyme are the mesenteric circulation (24, 25) and splanchnic (26) circulation. 

Although the converting enzyme was detected in the lung and the kidney contains so much of the enzyme, they are the suspected source of the plasma activity. Antibody to purified hog kidney enzyme inhibits the lung, kidney, or plasma enzyme similarly (41).

The existence of different types of angiotensin I converting enzyme has been indicated recently. One enzyme termed tonin forms angiotensin II from either angiotensin I or synthetic tetradecapeptide substrate. Tonin has a much lower molecular weight than does the converting enzyme discussed in this review, and its pH optimum is below neutrality. It is not inhibited by inhibitors of the converting enzyme, and it occurs in the submaxillary gland and other organs such as the kidney (47). An enzyme that has a higher molecular weight than the converting enzyme has been found in hog and guinea pig plasma; its action becomes apparent only in the presence of added Co²⁺. This enzyme releases angiotensin I and angiotensin II, but has no kininase activity (48).

**Purification**

The converting enzyme from the plasma, kidney, and lung of man and animals has been purified to various degrees. Erdös and Yang (10) extracted and concentrated the enzyme first as kininase II from the microsomal fraction of the kidney and then as converting enzyme from the lung (18); they later purified it from plasma (11, 18, 36-38). Eliseeva et al. (49) purified the renal enzyme and probably obtained a homogeneous protein, but they did not report the details of their preparation techniques. They (49) also stated that the converting enzyme was identical to a "carboxycathepsin" that they had described previously in the Russian literature. Cushman and Cheung (50) purified the
enzyme from rabbit lung, and simultaneously Igic et al. (28, 51) prepared a homogeneous protein from hog lung. Dorer et al. (52) also used the hog lung as a source of the enzyme. The enzyme has been obtained in homogeneous form from human lung, hog kidney, and human kidney as well (41, 43). Other investigators (53–58) have also reported the purification of plasma and lung enzyme from man and animals. The converting enzyme prepared from hog lung in my laboratory has a molecular weight of 206,000; it contains subunits of 70,000 molecular weight (43). Other published estimates for the molecular weight of converting enzyme vary from 140,000 to 480,000 (53–58).

These discrepancies may be due to differences in the sources of the enzymes and the techniques used to solubilize them. However, they may also be due to the fact that some estimates of molecular weight have been based on only partially purified enzyme preparations. Finally, another possibility is that some fractions of partially purified enzyme preparations contain a converting enzyme that is not identical to the peptidyl dipeptide hydrolase discussed in this review. (The conversion of angiotensin I is obviously just one of the functions of the enzyme discussed in this review. Because the converting enzyme breaks peptidyl dipeptide bonds in substrates other than angiotensin I, it is referred to in the literature as peptidyl dipeptide hydrolase [E.C. 3.4.15.1]. The term dipeptidyl carboxypeptidase, although incorrect, has also been used to describe this enzyme. I have referred to peptidyl dipeptidase as the converting enzyme throughout this review. This enzyme is not to be confused with other enzymes that may form angiotensin II but are different from this peptidyl dipeptide hydrolase.)

The enzyme requires a divalent cation cofactor for activity (18, 59). In addition to the monomeric form of the hog lung enzyme, we have detected a dimer and an aggregate of even larger molecular weight (43). The converting enzyme purified from human lung or hog kidney also has a molecular weight of about 200,000, but, in contrast to the hog lung enzyme, it does not dissociate into subunits (41, 43). The kidney enzyme contains carbohydrate as neutral sugar (41).

Antibody induced by injecting purified renal enzyme into rabbits cross-reacts with the lung and plasma enzyme from the hog. The conversion of angiotensin I and the inactivation of bradykinin by hog lung, kidney, and plasma enzyme are blocked to a similar extent by the antibody (41). Antibody to hog kidney enzyme does not cross-react with the human enzyme, indicating that there is a species specificity. The inhibition of the enzyme by antibody depends, however, on the structure of the substrate used. The hydrolysis of bulkier synthetic substrates by renal converting enzyme is inhibited by purified antibody, although that of smaller ones is not. This finding indicates that the antigenic and hydrolytic sites of the enzyme protein differ. Presumably, attachment of antibody to the antigenic site partially blocks the hydrolytic center by a steric effect.

**SUBSTRATES**

The synthesis of radioactive angiotensin I and the chromatographic or electrophoretic separation of the enzymatic reaction products (12, 28, 29, 60) have allowed researchers to assay converting activity at a low substrate concentration by nonbiological means. The first peptide substrates shorter than angiotensin I represented the protected C-terminal sequence of angiotensin I, such as Z-Pro-Phe-His-Leu (61) or Hip-His-Leu (62). These peptides were used in chemical assays of the enzyme. When the converting enzyme was found to cleave peptide bonds of a wide variety of amino acids (18, 28, 38, 49), other peptide substrates were synthesized. The simplest were protected tripeptides of glycine, such as Hip-Gly-Gly (18, 38). Other substrates had chromophor groups, such as p(NO₂) phenylalanine [t-BOC-p(NO₂)Phe-Phe-Gly] (18, 38) and Z-Phe(NO₂) Gly-Gly (55). Hydrolysis of these substrates was assayed with ultraviolet spectrophotometric or fluorometric techniques (Table 1).

The rate of hydrolysis of two of these substrates (Hip-His-Leu and Hip-Gly-Gly) has been compared with that of angiotensin I during purification (50, 52). The relative rates of cleavage of the short peptide substrate and angiotensin I do not change during purification, indicating that a single enzyme cleaves all of these substrates. However, the Km of the substrates varies when they are hydrolyzed by converting enzyme from the different sources. The Km of the shorter optically active substrates, such as the hippuryl derivatives, is about 10⁻²M (18, 35, 63). Km values for angiotensin I and bradykinin are much lower. Angiotensin I has a Km on the order of 10⁻⁶M (64, 65). The Km of bradykinin is 9 × 10⁻⁷M in the presence of chloride ions and 4 × 10⁻⁷M in the absence of these ions (65). A slightly different figure has been obtained by radioimmunoassay using plasma as a source of the converting enzyme; in these experiments, bradykinin has a Km of 10⁻⁷M (66).

Although partially or completely purified converting enzyme preparations from human and animal tissues cleave bradykinin (18, 28, 38, 41, 43,
TABLE 1

Peptide Bonds Cleaved by Converting Enzyme

<table>
<thead>
<tr>
<th>Representative substrates</th>
<th>Sources of enzyme</th>
<th>Lung, kidney</th>
<th>Plasma</th>
<th>Name of substrate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>-R&lt;sub&gt;1&lt;/sub&gt;-R&lt;sub&gt;2&lt;/sub&gt;-R&lt;sub&gt;3&lt;/sub&gt;-OH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Pro&lt;sup&gt;a&lt;/sup&gt;-Phe&lt;sup&gt;b&lt;/sup&gt;-Arg&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>+</td>
<td>+</td>
<td>Bradykinin</td>
<td>10, 11, 18, 28</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38, 49, 62, 65</td>
</tr>
<tr>
<td>-Phe&lt;sup&gt;a&lt;/sup&gt;-His&lt;sup&gt;b&lt;/sup&gt;-Leu&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>+</td>
<td>+</td>
<td>Angiotensin I</td>
<td>2, 12, 18, 38, 43, 49, 53, 56, 59, 60, 64, 66</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Pro&lt;sup&gt;a&lt;/sup&gt;-Lys&lt;sup&gt;b&lt;/sup&gt;-Ala&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>+</td>
<td>+</td>
<td>B chain of insulin</td>
<td>28</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Trp&lt;sup&gt;a&lt;/sup&gt;-Ala&lt;sup&gt;b&lt;/sup&gt;-Pro&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>+</td>
<td>+</td>
<td>BPF&lt;sub&gt;5α&lt;/sub&gt; (SQ 20475)</td>
<td>18, 69</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip-Gly-Gly</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>18, 28, 38</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18, 62</td>
</tr>
<tr>
<td>Hip-His-Leu</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-Phe-His-Leu</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>18, 38</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cbo-Pro-Leu-Gly</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>18, 38</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-BOC-Phe(NO&lt;sub&gt;2&lt;/sub&gt;)&lt;sup&gt;a&lt;/sup&gt;-Phe-Gly</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>18, 28, 38</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-Phe(NO&lt;sub&gt;2&lt;/sub&gt;)&lt;sup&gt;a&lt;/sup&gt;-Gly-Gly</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14&lt;sup&gt;C&lt;/sup&gt;-DNS-Gly-Gly-Gly</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cbz-Gly-Phe-Phe-Tyr</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

Arrows indicate the site of cleavage. Hip = hippuryl, Cho, Cbz, and Z = benzyloxycarbonyl, t-BOC = t-butyloxycarbonyl, and DNS = 1-dimethylaminonaphtalene-5-sulfonyl.

49, 58, 62, 65), the identity of the converting enzyme with kininase II has been questioned by some. The major discrepancy is that angiotensin I is converted in vitro only when the incubation medium of the enzyme contains chloride ions, although kininase II inactivates bradykinin in a chloride-free medium as well. Thus, inactivation of bradykinin and conversion of angiotensin I were attributed to two different enzymes. In addition, some inhibitors affect the inactivation of bradykinin and the conversion of angiotensin I differently (67, 68). The effect of chloride ions on the rate of hydrolysis, however, depends on the structure of the substrate. Although the hydrolysis of Hip-Gly-Gly or angiotensin I stops almost entirely in chloride-free medium, that of bradykinin continues at about 30-50% of the optimum rate (35, 65). The cleavage of another pentapeptide substrate does not require the presence of chloride ions at all. Chloride has been described as an allosteric modifier of the enzyme (69) and chloride ions lower the $K_m$ of bradykinin hydrolysis by the converting enzyme (65). Study of the ultraviolet spectrum of purified renal converting enzyme indicates that chloride ions induce a spectral shift toward the red in the conformation of renal converting enzyme (41). Based on this observation, it has been hypothesized that bradykinin can combine with the enzyme protein in both configurations, whereas angiotensin I can be cleaved only when the tyrosine and tryptophan residues are exposed. However, angiotensin I can inhibit hydrolysis of bradykinin by converting enzyme even in a chloride-free medium (70); when the enzyme is immobilized by coupling it to Sepharose 4B, it still cleaves angiotensin I at an appreciable rate in the absence of chloride ions (35, 43).

Because cleavage of any bond in bradykinin inactivates the peptide (6), hydrolysis by the converting enzyme is not the only route of inactivation of bradykinin, although it is a major one. In contrast, cleavage of the Phe<sup>a</sup>-His<sup>b</sup> bond in angi-
tensin I is the only effective way to convert angiotensin I in the body. In addition to the converting enzyme (peptidyldepeptide hydrolase), which has an intrinsic kininase activity (18, 28, 38, 41, 43, 49, 58, 62, 65), other different types of enzymes which can release angiotensin II (71) but have no kininase II activity may exist in the body.

Table 1 summarizes the information on the structure of substrates (28): the general structure is \( R_1-R_2-R_3-OH \). The enzyme cleaves \( R_3 \) from \( R_2; R_1 \) can be a protected amino acid or a peptide. \( R_2 \) should be an amino acid with a free carboxyl terminal but not glutamic acid (49). \( R_3 \) can be any amino acid except proline, because peptides having proline in the \( R_3 \) position are not cleaved. This fact explains why liberated angiotensin II is not broken down further by the converting enzyme (38).

A highly sensitive assay uses \(^{14}C\)-Dansyl-Gly-Gly-Gly (28), which is a fluorescent, radioactive substance. Additional substrates and inhibitors of the enzyme have been listed in a recent review (7).

**INHIBITORS**

When the angiotensin I converting enzyme was discovered it was also observed that EDTA inhibited the plasma enzyme (2). Other inhibitors were found in studies on the metabolism of bradykinin (6, 9, 11). Among in vitro inhibitors of the enzyme are metal-binding agents such as o-phenanthroline (6, 9, 11) or 8-OH-quinoline (7) which sequester the metal cofactor of the enzyme (Table 2). An inhibitor present in the plasma of man and animals also blocks the converting enzyme activity (18, 41, and Oshima, Kato, and Erdős, unpublished observations).

Split products of the enzymatic cleavage of bradykinin and angiotensin I such as Phe-Arg or His-Leu inhibit the reaction (11, 18). As expected, competitive substrates such as bradykinin or Hip-His-Leu block the conversion of angiotensin I (18, 28, 68). Although insulin and the B chain of insulin inhibit the enzyme in vitro and in the lung perfused in situ (18, 28), it is not known whether these peptides also inhibit the enzyme in vivo. In these aforementioned experiments, the substrates, bradykinin and angiotensin I, and the inhibitors were used in higher than physiological concentrations.

Gladner and associates (72) noticed that a derivative of a fibrinopeptide potentiated the action of bradykinin on the isolated uterus. Other "bradykinin potentiators" have been detected in various extracts ranging from snake venoms (73) to proteolytic enzymes (74). Although their action is still not completely understood, some of them potentiate by inhibiting the hydrolysis of bradykinin by kininase II. Work on the potentiating peptides extracted from Bothrops jararaca and other snakes has yielded interesting compounds (75-78) that inhibit the conversion of angiotensin I (17) as well. A number of the peptides that occur in snake venoms have been synthesized (Table 2); the first one was the pentapeptide BPF\( _{5a} \) (75) which has

---

**TABLE 2**

*Representative Inhibitors of Converting Enzyme*

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>In vitro</th>
<th>In situ</th>
<th>In vivo</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products of hydrolysis of substrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>His-Leu</td>
<td>+</td>
<td></td>
<td>18, 68</td>
<td></td>
</tr>
<tr>
<td>Phe-Arg</td>
<td>+</td>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Arg-Pro-Pro</td>
<td>+</td>
<td></td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Endogenous peptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td>+</td>
<td>+</td>
<td>28, 68</td>
<td></td>
</tr>
<tr>
<td>Insulin, B-chain</td>
<td>+</td>
<td>+</td>
<td>18, 28</td>
<td></td>
</tr>
<tr>
<td>Glutathione</td>
<td>+</td>
<td>+</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Snake venom peptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 20861 (BPF( _{9a} ))</td>
<td>+</td>
<td>+</td>
<td>16-19, 28, 32, 69, 75-78, 79-87</td>
<td></td>
</tr>
<tr>
<td>SQ 20475 (BPF( _{5a} ))</td>
<td>+</td>
<td>+</td>
<td>79-87</td>
<td></td>
</tr>
<tr>
<td>Potentiator C</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma factor (man, animals)</td>
<td>+</td>
<td></td>
<td>18, 41</td>
<td></td>
</tr>
<tr>
<td>Heavy metal ions (Hg(^{2+}), etc.)</td>
<td>+</td>
<td></td>
<td>11, 18, 59</td>
<td></td>
</tr>
<tr>
<td>Sequestering agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDTA</td>
<td>+</td>
<td>+</td>
<td>2, 7, 28, 32</td>
<td></td>
</tr>
<tr>
<td>o-phenanthroline</td>
<td>+</td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>8-OH-quinoline</td>
<td>+</td>
<td></td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
proved to be a good inhibitor in vitro (18, 19, 62), possibly because it is also a substrate of the enzyme (18, 69). This peptide is a less effective inhibitor in vivo (75). The nonapeptide SQ 20881 (BPF9a) (Table 2) and the undecapeptide "Potentiator C" (77) contain a C-terminal Pro-Pro sequence that is not cleaved by the converting enzyme. Thus, they inhibit the hydrolysis of bradykinin, angiotensin I, the B chain of insulin, and shorter substrates without being substrates of the enzyme themselves (28, 69). The I<sub>50</sub> values of the peptide inhibitors are low: in concentrations ranging from 10<sup>-5</sup>M to 10<sup>-4</sup>M (28, 69), they block 50% of the activity of the converting enzyme extracted from various sources.

The C-terminal end of the most potent synthetic inhibitors is Pro-Pro. Because the N-terminal end of bradykinin also contains this sequence, Arg-Pro-Pro, representing the first three amino acids in bradykinin, has been tested as an inhibitor of the converting enzyme. This tripeptide inhibits the enzyme competitively (63). Among other peptides that occur in the body, insulin, the B chain of insulin, and glutathione are also converting enzyme inhibitors (28) (Table 2).

Many investigators have recognized the potential usefulness of inhibitors. These compounds have been employed to probe the identity of kininase II with the converting enzyme (28, 79), to block the conversion of angiotensin I during perfusion of various tissues (28, 32) or after intravenous injection into animals (80, 81), to determine whether elevated blood pressure is due to increased renin release in man (82) and animals (81, 83-85), to establish the role of renin in shock (86), etc.

When the pentapeptide is given to rats with renovascular hypertension, it lowers the elevated arterial blood pressure during the period of infusion (84). The nonapeptide SQ 20881 has a longer-lasting effect (80, 81, 83). The elevated blood pressure induced by renal arterial stenosis in the dog is prevented by intravenous injection of SQ 20881 (85). SQ 20881 blocks the conversion of angiotensin I in anesthetized rats and in unanesthetized rats and dogs similarly (81-83). Because SQ 20881 blocks the rise in systemic blood pressure in rats when angiotensin I is injected into the aorta (81), it may inhibit the extrapulmonary conversion of angiotensin I as well (71). The inhibitor also blocks or attenuates the compensatory rise in systemic arterial blood pressure in response to hypotension induced by endotoxin or hemorrhagic shock (86).

Intravenous injection of SQ 20881 in the rat potentiates the vasodepressor effect of bradykinin. The concentrations required for this effect are lower than those required to block the vasopressor action of angiotensin I (80, 83). Interestingly, application of the inhibitor in vivo increases the level of the circulating renin in rats, possibly by eliminating the feedback inhibition of renin release by circulating angiotensin II (87).

Clinical studies have not yet determined whether the administration of the nonapeptide will be useful in elucidating the cause of hypertension or whether it can be employed therapeutically. SQ 20881 has a relatively long-lasting effect (hours) in experimental animals (80, 81), which is much longer than that indicated by the generally short half-life of peptides in the circulation (minutes) (6, 88).

CONCLUSIONS AND SPECULATIONS

The angiotensin I converting enzyme discussed in this review converts angiotensin I to angiotensin II and inactivates bradykinin when it is prepared from human and animal tissues in highly purified or homogeneous form (18, 28, 38, 41, 43, 49, 58, 62, 65). Thus, the same enzyme can inactivate hypotensive kinins and activate hypertensive angiotensin. Since it occurs in many different tissues, it probably has multiple functions. Presumably in the lung the enzyme is located in the vascular endothelium (89). Pulmonary arteries contain more converting enzyme than do other vessels (19). Here the converting enzyme may be important in regulating the systemic blood pressure by metabolizing circulating vasoactive peptides, by releasing angiotensin II, by inactivating bradykinin, and, hypothetically, by cleaving accessible bonds in other circulating peptides. Because the enzyme is relatively easily inhibited by peptides that occur in blood, such as the competitive substrates bradykinin (18, 28) or insulin (28) and their fragments, these inhibitors may influence the action of the enzyme. We do not know how the converting enzyme functions in the diseased lung. Histamine liberators and histamine itself release the enzyme from the blood-free perfused lung (35); this phenomenon may influence the course of shock.

In the brain and the pituitary gland, it may be important to convert angiotensin I (42), because of the effect of angiotensin II on sympathetic centers and on the drinking reflex (90). The presence of the enzyme in the choroid plexus suggests the importance of conversion of angiotensin I for the drinking reflex. The subfornical body, the site where angiotensin II can elicit drinking, is in proximity to the choroid plexus (91).
ANGIOTENSIN I CONVERTING ENZYME

We can also speculate about the role of the plasma enzyme. The guinea pig (18), for example, has a high level of plasma enzyme; it may protect the animal by inactivating bradykinin rapidly. The guinea pig is highly sensitive to bronchoconstriction, and bradykinin is a potent bronchoconstrictor. In addition, the rapid conversion of angiotensin I to angiotensin II in guinea pig blood may cause catecholamine release, which also protects against bronchoconstriction.

Because the kidney has such a high concentration of converting enzyme (10, 41, 49), it has been hypothesized that, in contrast to the lung, the renal role. If renin is a local hormone of the kidney have no kininase activity.

It is necessary for this function. In that case, it may not be localized in renal vascular endothelium alone but also in other types of cells such as tubular cells.

Finally, some experiments have suggested (47, 48, 71, 95) the existence of other different enzymes in the body that can release angiotensin II but have no kininase activity.

References
65. LEE HJ, LARUE JN, WILSON IB: Dipeptidyl carboxypeptidase from Corynebacterium equi. Biochim Biophys Acta 250:608-613, 1971

Circulation Research, Vol. 36, February 1975
ANGIOTENSIN I CONVERTING ENZYME


81. Collier JG, Robinson BF, Vane JR: Reduction of pressor effects of angiotensin I in man by synthetic nonapeptide (BFP1, or SQ 20881) which inhibits converting enzyme. Lancet 1:72-74, 1973


84. Miller ED, Samuels AI, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 177:1108-1109, 1972


87. Miller ED, Samuels AI, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 177:1108-1109, 1972


Angiotensin I converting enzyme.
E G Erdős

doi: 10.1161/01.RES.36.2.247

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/36/2/247.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/