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A Review of Angiotensin Converting Enzyme in Health and Disease

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Abstract. ACE, a carboxypeptidase that hydrolyses angiotensin–1 to angiotensin–2, is widely found in human tissues including vascular endothelium. It is also produced by epithelioid cells of sarcoid granulomata which elevate serum ACE, a useful test of active sarcoidosis, despite its less than optimal sensitivity and specificity. It is not known why ACE production is increased in only certain granulomatous disorders. The explanation may assist our understanding of the pathogenesis of sarcoidosis.

Key Words. Angiotensin Converting Enzyme. Biochemical properties. Tissue localisation. ACE assay.

History

Angiotensin–converting enzyme (kininase II, EC 3.4.15.1) was first isolated from equine plasma [1,2]. It is a chloride ion–dependent dipeptidyl carboxypeptidase which converts the decapeptide, angiotensin–1 to the pressor octapeptide, angiotensin–2 by the removal of the C–terminal dipeptide, histidyl–leucine (*Fig.1*).

ACE is readily inactivated by chelating agents such as EDTA [2], since it requires zinc at its active site [3]. Many specific inhibitors have now been identified, the first being a nonapeptide found in the venom of the South American pit viper, *Bothrops jararaca* [4]. The discovery of this inhibitor (teprotide) led to the subsequent synthesis of a large number of specific ACE inhibitors. The first compound, captopril [5] was synthesised as a result of a detailed knowledge of the structure of a related enzyme, carboxypeptidase A. Converting enzyme inhibitors are now widely used in the treatment of hypertension and cardiac failure [6–8]. One of these compounds, lisinopril [9] was the parent compound of an analogue which was radio–iodinated to demonstrate ACE in sarcoid tissue by autoradiography [10].

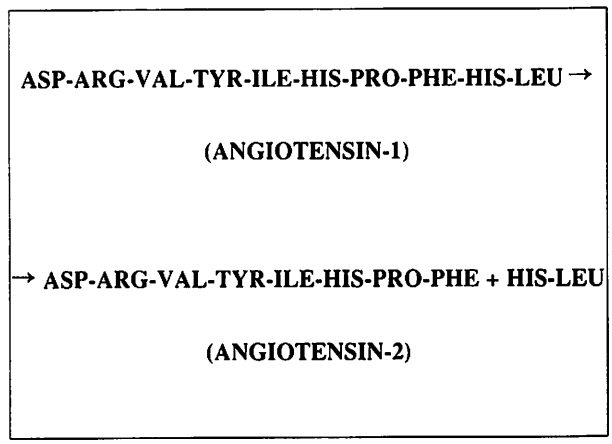

Fig. 1.

Biochemical Properties

The pulmonary vasculature contains much higher ACE activity than plasma [11] and a single passage of angiotensin–1 through the pulmonary circulation leads to its rapid conversion to the potent vasopressor peptide, angiotensin–2 [13]. As the enzyme which was isolated was in a particulate cell fraction, it was correctly proposed that

it was located in the endothelial cell wall. Bradykinin, an important vasodepressor nonapeptide, is rapidly inactivated in its passage through the lung by ACE [13]. This occurs by the sequential catalysis of Phe–Arg and Ser–Pro from its C–terminal. ACE is responsible for the hydrolysis of both these vasoactive peptides [14–16]. Angiotensin–converting enzyme also hydrolyses the C–terminal tripeptide and dipeptide of substance P, neurotensin and various other peptides [17].

Rabbit lung ACE has an oligosaccharide content of approximately 26 percent, consisting of galactose, N–acetyl–glucosamine, mannose, N–acetyl–neuraminic acid and fucose. The Michaelis–Menton constants for the hydrolysis of hippuryl–L–histidyl–L–leucine and angiotensin–1 are 2.3 and 0.07 mM respectively [3]. Chloride ion activation varies with the reaction conditions and the nature of the substrate and is essential for the hydrolysis of angiotensin–1 but not for bradykinin [18]. With increasing anion concentration at alkaline pH, the Km decreases, unlike Kcat which does not change. Under physiological conditions (pH 7.4 and 100 mM chloride), ACE exhibits only 50 percent of its maximal hydrolytic activity towards angiotensin–1 while being maximally active towards bradykinin [19]. In organs such as the kidney and brain where chloride concentrations vary, this may locally modulate enzyme activity.

The NH_2 and COOH–terminal sequences of ACE from rabbit lung and testis have been determined [20]. An 82 kDa fragment from the NH_2–terminal sequence contains the catalytic site. Cleavage of the two fragments from native ACE (140 kDa Mr) by 1N NH_4OH was unexpected and specific for rabbit lung ACE, rabbit testis ACE being resistant to this treatment [21]. The smaller fragment's resistance to tryptic digestion and tendency to aggregate suggest that ACE has a hydrophobic COOH–terminal region buried in the cell membrane, with the larger hydrophylic glycoprotein–containing fragment exposed on the cell surface.

The cDNA of mouse kidney ACE [22] and human vascular ACE mRNA have been sequenced [23]. The human ACE gene contains two very hydrophobic amino acid sequences [23] which probably encode the hydrophobic portion that secures ACE to the plasma membrane. Internal homology exists in two large domains, suggesting gene reduplication. These domains contain small repeated amino acid sequences identical to those around the critical residues of the active sites of other metallopeptidases (thermolysin, neutral endopeptidase and collagenase) [23]. In the mouse, ACE mRNA of kidney and lung are the same size [22]; suggesting they are both encoded by the same gene. Similarly, in man, endothelial and epithelial ACE share a single gene [23].

The catalytic action of ACE is similar to that of other zinc–containing carboxypeptidases, which cleave amino acids rather than dipeptides. In common with carboxypeptidase A [24], ACE will not hydrolyse otherwise susceptible substrates which lack a free C–terminal carboxyl group (Bz–Gly–Phe–Phe–NH_2), those with penultimate proline residues (angiotensin–2, SQ 20881, Bz–Gly–Pro–Gly) or those with C–terminal dicarboxylic amino acids (Bz–Gly–Phe–Glu), nor hydrolyse substrates smaller than tripeptides [25]. However, peptides with an amidated C–terminus such as substance–P are hydrolysed by ACE [17]. Isozymes of ACE have been isolated from rat brain corpus striatum and rat lung with molecular weights of 165 and 175 kDa respectively [26]. They demonstrated different hydrolytic properties, the brain isoenzyme being unique in its pattern of cleavage of substance P and substance K [27, 28].

Serum ACE appears to be shed from endothelial cell membrane, possibly through the action of sialic acid transferase, as the serum enzyme has a higher content of sialyl terminal residues than that in the lung [29]. The loss of sialic acid content on purification of the enzyme causes the isoelectric point to change from pH 4.3 to 4.6 [30].

Circulating ACE is probably inactivated initially by desialylation [31], followed by hepatic uptake [32] and lysosomal catabolism [31]. The elevated levels of serum ACE seen in patients with liver disease [33–35] is probably due to reduced hepatic uptake or degradation.

Tissue Localisation

Although the lung contains the highest ACE activity, the enzyme occurs in all mammalian organs and tissues. In the lung it is found on the luminal surface of endothelial cells [36] and has a molecular weight of between 129 and 480 kDa [37]. It is found on the brush–border of the renal tubules [38, 39], brain [40, 41], gut and testis [42, 43], urine [44], pleural fluid [45], amniotic fluid [46], the eye [47], tears [48] and semen [49]. Although produced by the choroid plexus in large quantities [50], little ACE is released by the epithelial cells. As a result, only small quantities are found normally in the cerebrospinal fluid [51]. It is also produced by the pulmonary macrophages [52, 53] and peripheral blood monocytes [54] with only a slight difference in molecular weight and catalytic properties from serum ACE [55]. Its presence in bronchoalveolar lavage fluid in both health and disease reflects the local production by alveolar macrophages [52, 53].

ACE Assay

The action of ACE to hydrolyse angiotensin–1 to yield angiotensin–2 has been used to assay the enzyme but it is more convenient to use synthetic substrates. A spectrophotometric method [56] measured hippuric acid generated from the hydrolysis of L–Hip–His–Leu. The same substrate was used in a spectrofluorimetric method which assayed the liberation of His–Leu [57]. A variety of radiochemical methods such as carbon–14 [58], iodine–125 [59] and tritium [60] have also been used.

ACE and Disease

Sarcoidosis

Serum ACE was found to be elevated in active sarcoidosis in 1974 by Lieberman [61] who was studying the renin–angiotensin system in a group of patients with chronic airflow obstruction, including a few with sarcoidosis. Sarcoid granulomata have subsequently been found to contain large quantities of ACE, mainly in the epithelioid cells [62, 10]. From these cells ACE is released into the circulation. Angiotensin–2 has also been found in sarcoid granulomata indicating that local hydrolysis of angiotensin–1 occurs [63]. ACE may modulate cell traffic in granulomata via local production of angiotensin–2 which is chemotactic for macrophages [64]. Angiotensin–2 may also enhance macrophage phagocytosis by the polymerisation of intracellular actin [65].

Many studies have demonstrated the clinical value of ACE as a marker of disease activity in sarcoidosis [66–68]. However, its usefulness as a marker of disease activity is limited in patients taking corticosteroids which suppress ACE activity independently of the clinical status [69–71]. Serum ACE in normal subjects is generally unaffected by corticosteroids [72], suggesting that the fall in serum ACE in sarcoidosis is related to the serum component derived from the granulomata. The enzyme is not a sensitive marker of *high intensity* sarcoid alveolitis [73]. This is not unexpected if the level of serum ACE activity is the product of all the sarcoid granulomata in the body. Serum ACE in sarcoidosis is inversely related to the degree of fibrosis in sarcoid lymph nodes [10]. In bronchoalveolar lavage fluid ACE is elevated in active pulmonary sarcoidosis and falls as the lung disease becomes less active [74].

Other Diseases

Many conditions may produce abnormal levels of serum ACE [75]. However, most conditions which can be confused clinically with sarcoidosis such as extrinsic allergic alveolitis, tuberculosis and lymphoma do not usually produce elevations in serum ACE [66, 75]. Berylliosis [76], asbestosis [77] and silicosis [78] which have all been reported to cause elevations in serum ACE can usually be distinguished from sarcoidosis on clinical grounds. Histoplasmosis may cause a transient elevation in serum ACE at the onset of the illness in a minority of cases [79, 80], and is

probably produced by the epithelioid cells of the granulomata.

Acute pulmonary endothelial injury induced experimentally in animals causes a transient rise in serum ACE [81]. In man, serum ACE is depressed in acute respiratory distress syndrome of either septic or non–septic causes [82, 83]. Serum ACE falls rapidly within five minutes after the lung ceases to be perfused in patients undergoing cardiopulmonary bypass [84]. It is also reduced in patients with lung cancer possibly due to destruction of the pulmonary vascular bed [85].

Gaucher's Disease

Gaucher's disease consistently produces the highest levels of serum ACE of any disease known, probably through the release of the enzyme by Gaucher cells which are histiocytic in origin [86, 87]. This rarely causes diagnostic confusion with sarcoidosis because of the different clinical features of the two diseases.

Leprosy

There have been conflicting reports of the levels of serum ACE in leprosy. One study [88] found that half their patients had raised levels, regardless of the type of leprosy, while another [89] reported that all their patients had normal levels.

Liver Disease

Serum ACE has been reported to be elevated in primary biliary cirrhosis [89], alcoholic liver disease [33], chronic hepatitis with cirrhosis and viral hepatitis [34, 35]. In extra–hepatic cholestasis, serum ACE was subnormal in contrast to intrahepatic cholestasis where elevated levels were common [34]. Although the mechanism for this is unclear, it is probably due to impaired hepatic clearance of ACE.

Pneumoconiosis

Silicosis and asbestosis may cause an elevation in serum ACE in a minority of cases [77, 78].

Diabetes Mellitus

Diabetes mellitus has been reported to elevate serum ACE, especially in the presence of retinopathy [90]. However, this observation has not been confirmed in a large group of patients with diabetic retinopathy studied in the Department of Medicine, Austin Hospital, Melbourne (personal communications). A more detailed study showed that 32 percent of diabetics had sporadic elevations in serum ACE and 14 percent had persistent elevations [91]. Although mean serum ACE was higher in patients with diabetic retinopathy, nevertheless, 18/24 of these had normal serum ACE. They found that the duration of disease and degree of metabolic control bore no correlation with serum ACE. More recently, a significant correlation between serum ACE and vascular complications were reported in a group of over one thousand patients [92].

Hyperthyroidism

Mild elevations of serum ACE occur in thyrotoxicosis, probably due to the effect of thyroxine on enzyme induction [93].

Conclusion

Of the large number of granulomatous diseases both in man and animals, sarcoidosis, leprosy, silicosis and murine schistosomiasis [94–96], are among the few which produce ACE in increased amounts. Kveim and B.C.G.–induced granulomata produce no change in serum ACE in

animals [97]. Therefore granulomata can be grouped into the ACE–producers and the non–ACE–producers.

The reason for this difference is unclear and highlights our incomplete understanding of granuloma formation. The elucidation of the role of this enzyme in certain granulomatous conditions should reveal more of the pathogenesis of sarcoidosis.

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