Review

Serum Angiotensin Converting Enzyme in Pulmonary Disease

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Abstract. Synthetic acylated tripeptides, which may or may not be radiolabelled, are generally used as substrates for measuring serum angiotensin converting enzyme (SACE) activity. The capillary endothelial cells are the major source of SACE in normals and certain diseased states, however Gaucher's cells in Gaucher's disease and epithelioid cells in granulomatous disorders, including sarcoidosis, are the major source of enzyme in these disorders. SACE is generally elevated in active sarcoidosis and is normal when the disease is dormant or resolved. Sequential measurement of SACE are helpful in monitoring activity of sarcoidosis, both off and on corticosteroids. SACE may also be elevated in certain non-granulomatous pulmonary and systemic diseases.

Key words: Sarcoidosis – Chronic granulomatous disease – Angiotensin converting enzyme – Lung diseases – Neoplasms.

Introduction

In humans, angiotensin converting enzyme (ACE) is found in several tissue extracts and fluids. The largest amounts of this enzyme are found within the brush border of epithelial cells lining the proximal convoluted tubules of the kidney, and on the luminal surface of endothelial cells of most capillaries, venules and some arteries [7]. Since the lungs have the largest capillary bed of any organ in the body, it is here that ACE acts on circulating substrates. ACE is a dipeptidyl carboxypeptidase, which cleaves C-terminal dipeptides of several oligopeptides including angiotensin I and bradykinin. It catalyzes conversion of angiotensin I to angiotensin II, a potent vasopressor, and produces inactivation of bradykinin, a powerful vasodepressor [27]. While evaluating the effect of various lung diseases on serum angiotensin converting enzyme (SACE), and trying to determine whether the low blood pressure in patients with chronic lung disease was associated with low levels of SACE [21], Lieberman found elevated SACE levels in untreated patients with sarcoidosis. This ob-
servation of elevated SACE activity in patients with sarcoidosis provided a strong impetus to evaluate serum and tissue ACE activity in various granulomatous and nongranulomatous pulmonary diseases. This paper will review the common methods of measuring ACE activity, the clinical significance of measuring ACE activity in sarcoidosis, and the changes in SACE activity in other chronic pulmonary as well as systemic diseases.

Methods of Measuring Angiotensin Converting Enzyme Activity

ACE is a dipeptidyl carboxypeptidase, which cleaves C-terminal dipeptide of its substrate. It cleaves C-terminal dipeptide histidyl-leucine of angiotensin I, a decapeptide, to form angiotensin II, an octapeptide [27].

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu
ANGIOTENSIN CONVERTING ENZYME
↓
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe + His-Leu.

Similarly it cleaves C-terminal dipeptide (Phe-Arg) of bradykinin, followed by removal of another C-terminal dipeptide (Ser-Pro) of the molecule as illustrated below [10]:

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
ANGIOTENSIN CONVERTING ENZYME
↓
Arg-Pro-Pro-Gly-Phe-Ser-Pro + Phe-Arg
ANGIOTENSIN CONVERTING ENZYME
↓
Arg-Pro-Pro-Gly-Phe + Ser-Pro.

ACE activity can be measured in terms of the rate of conversion of a known amount of angiotensin I into angiotensin II [27]. However, serum and other biological fluids contain other enzymes which will degrade both angiotensin I and angiotensin II, and thereby interfere with the assay. To obviate these limitations, a number of small synthetic peptides have been used as substrates for the converting enzyme. Synthetic acylated tripeptides such as hippuryl-histidyl-leucine and hippurylglycyl-glycine have been found to be the most suitable substrates for determining the activity of ACE, because they are resistant to other circulating dipeptidyl carboxypeptidase. Hippuryl-histidyl-leucine has been used most commonly as substrate to measure ACE activity. The enzyme hydrolyzes hippuryl-histidyl-leucine to yield hippuric acid and histidyl-leucine. The enzyme activity can be measured in terms of the formation of hippuric acid, which can be measured spectrophotometrically (SP) [5], or in the terms of the released dipeptide, which can be measured spectrofluorometrically (SF), after reaction with O-phthalaldehyde [13].

The above methods require tedious preparations. The SP method requires the extraction of hippuric acid with ethyl acetate from the reaction mixture, followed by