Acta Scientific Biotechnology (ASBT)

Volume 1 Issue 1 January 2020

Review Article

Association of *ACE* Gene with Human Performance

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Received: December 09, 2019

Published: December 30, 2019

Abstract

The *ACE* gene provides instructions for making the angiotensin-converting enzyme. The aim of this project is to check the association of *ACE* gene with human performance. The *ACE* gene encodes an enzyme involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II. Angiotensin II causes blood vessels to narrow (constrict), which results in increased blood pressure. This protein also increases the production of the hormone aldosterone levels, which triggers the absorption of water and salts by the kidneys. ACE is a zinc metalloenzyme. The zinc ion is essential to its activity, since it directly participates in the catalysis of the peptide hydrolysis. Therefore, ACE can be inhibied by metal-chelating agents.

Keywords: *ACE* Gene; Enzyme; Kidney

Introduction

The *ACE* gene provides instructions for making the angiotensin-converting enzyme. This enzyme is able to cleave (cut) proteins. It is important part of the renin-angiotensin system, which regulates the blood pressure and the balance of salts and fluids in the body. By cleaving a protein called angiotensin I at a particular location, the angiotensin-converting enzyme converts this protein to angiotensin II. Angiotensin II causes blood vessels to narrow (constrict), which results in increased blood pressure. This protein also increase the production of the hormone aldosterone levels, which triggers the absorption of water and salts by the kidneys [1].

The increased amount of fluid and salts in the body also increases the blood pressure. Proper blood pressure during fetal growth, which delivers oxygen to the developing tissues, is required for normal development of the kidneys, particularly of structures called the proximal tubules, and other tissues. The angiotensin-converting enzyme (ACE) can cut the other proteins, including bradykinin. Bradykinin causes blood vessels to dilate, which decreases the blood pressure. Cleavage by the (ACE) angiotensin-converting enzyme inactivates bradykinin, helping to increase blood pressure growth factors contribute in the development of kidney structures [2].

ACE or Angiotensin-converting enzyme, is a main and important component of the renin–angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids and salts in the body. It converts the angiotensin I hormone to the active vasoconstrictor angiotensin II. Therefore, ACE indirectly increasesthe hypertention by causing blood vessels to constrict. ACE inhibitors are mainly used as pharmaceutical drugs for treatment of cardiovascular diseases [3]. It is located mainly in the capillaries of the lungs but can also be found in kidney epithelial cells and endothelial. Some other less known functions of ACE are degradation of amyloid beta-protein and bradykinin [4]. ACE is a zinc metalloenzyme. The zinc ion is essential to its activity, since it directly participates in the catalysis of the peptide hydrolysis. Therefore, ACE can be inhibited by metal-chelating agents. The E384 residue was found to have a dual function. First it acts as a general base to activate water as a nucleophile. Then it acts as a general acid to cleave the C-N bond. The function of the chloride ion is very complex and is highly debated. The anion activation by chloride is a characteristic feature of ACE [5]. It was experimentally determined that the activation of hydrolysis by chloride is highly dependent on the substrate. While it increases hydrolysis rates for e.g. Hip-His-Leu it inhibits hydrolysis of other substrates like Hip-Ala-Pro. Under physiological conditions the enzyme reaches about 60% of its maximal activity toward angiotensin I while it reaches its full activity toward bradykinin [6].

It is therefore assumed that the function of the anion activation in ACE provides high substrate specificity. Other theories say that the chloride might simply stabilize the overall structure of the enzyme. ACE hydrolyzes peptides by the removal of a dipeptide from the C-terminus. Likewise it converts the inactive decapeptide angiotensin I to the octapeptide angiotensin II by removing the dipeptide His-Leu.Angiotensin-1 converting enzyme (ACE) is the rate limiting enzyme of the renin [7] angiotensin system and is known to be involved in vascular remodelling1 and atherosclerosis. A single copy gene encoding ACE lies on human chromosome 17q and has two polymorphic alleles depending on the insertion I, or the deletion D, of a 287 bpalu sequence within intron 16. 47% of the variance of plasma ACE is known to be determined by this allelic variation [8]. Angiotensin II is potent vasoconstrictor in a substrate concentration-dependent manner. Angiotensin II binds to the type

1 angiotensin II receptor (AT1), which sets off a number of actions that result in vasoconstriction and therefore increased blood pressure [9]. ACE is also part of the kinin-kallikrein system where it degrades bradykinin, a potent vasodilator, and other vasoactive peptides. Kininase II is the same as angiotensin-converting enzyme. Thus, the same enzyme (ACE) that generates a vasoconstrictor (ANG II) also disposes of vasodilators (bradykinin). The level of serum angiotensin-converting enzyme (ACE) was elevated in 15 of 17 patients with active sarcoidosis. Serum ACE was studied to determine the effect of chronic lung disease upon the blood level of an enzyme believed to originate from the lungs [10].

The assay was performed in approximately 200 control subjects and 200 patients with chronic lung disease using hippuryl-L-histidyl-L-leucine as substrate. Enzyme activity greater in male control subjects than in female subjects of comparable age and greater in children than in adults. Serum ACE was significantly reduced in patients with chronic obstructive lung disease, lung cancer, tuberculosis and cystic fibrosis, as compared to control subjects, and was even lower in those receiving corticosteroids. Of greatest interest, however, was that levels in patients with active sarcoidosis not receiving steroids were greater than 2 standard deviations above the mean for the adult control subjects (greater than 11.6 units) whereas levels in patients with sarcoidosis receiving steroids and in those with resolved disease were normal [11]. Increased ACE activity in the myocardium of rats significantly increases local angiotensin II production. This effect is replicated in human right atrial appendages and in DD subjects who show increased conversion of angiotensin I to angiotensin II. The classical pressor actions of angiotensin II are mediated directly through vasoconstriction, and indirectly through renal salt and water retention via aldosterone. Other effects that may influence the human training-response include the stimulatory effect of angiotensin II on endothelial, cardiac, and smooth muscle cell growth (hypertrophic and hyperplastic). These effects may contribute to a potential hypertrophic training response that may then confer an advantage in power sports [3].

A survey of subjects with other granulomatous diseases failed to reveal any other condition that was significantly associated with a similar elevation of serum ACE levels. Elevation of ACE levels in sarcoidosis appears to be associated with the active disease process and does not appear to be a familial inherited enzyme abnormality. An assay of serum ACE is a useful tool for regulating therapy in sarcoidosis and for confirming the diagnosis, since it readily distinguishes these patients from others with tuberculosis, lung cancer or lymphoma [12]. Angiotensin-converting enzyme (ACE) inhibitors have become a cornerstone in the management of patients with cardiovascular disorders. A large number of trials have demonstrated important clinical benefits for this class of drugs in patients with arterial hypertension, heart failure, diabetic and non-diabetic nephropathy and in patients who have undergone renal transplantation [13].

Cytogenetic Location: 17q23.3, which is the long (q) arm of chromosome 17 at position 23.3 Molecular Location: base pairs 63,477,061 to 63,498,380 on chromosome 17. Whilst the ACE genotype is associated with overall performance ability, at a single organ level, the ACE genotype and related polymorphism have significant associations. In cardiac muscle, ACE genotype has associations with left ventricular mass changes in response to stimulus, in both the health and diseased states. The D allele is associated with an exaggerated response to training, and the I allele with the lowest cardiac growth response [8]. In light of the I-allele association with endurance performance, it seems likely that other regulatory mechanisms exist. Similarly in skeletal muscle, the D allele is associated with greater strength gains in response to training, in both healthy individuals and chronic disease states. As in overall performance, those genetic polymorphisms related to the ACE genotype, such as the bradykinin 2 gene, also influence skeletal muscle strength.

Finally, the ACE genotype may influence metabolic efficiency, and elite mountaineers have demonstrated an excess of I alleles and I/I genotype frequency in comparison to controls. Interestingly, this was not seen in amateur climbers [14]. Corroboratory evidence exists among high-altitude settlements in both South America and India, where the I allele exists in greater frequency in those who migrated from the lowlands. Unfortunately, if the ACE genotype does influence metabolic efficiency, associations with peak maximal oxygen consumption have yet to be rigorously demonstrated. A polymorphism in intron 16 of the human angiotensin I converting enzyme (ACE) gene has been identified in which the presence (insertion, I allele) rather than the absence (deletion, D allele) of a 287 bpAlu-sequence insertion fragment is associated with lower serum and tissue ACE activity [15].

An excess of the I allele has been associated with some aspects of endurance performance, being identified in elite British distance runners and mountaineers. In addition, an excess of the I allele is present in Australian and Croatian rowers as well as Spanish elite athletes. Conversely, an excess of the D allele has been reported amongst elite athletes in more power-oriented events such as short distance swimming and sprinting. However, there has been debate as to the reproducibility of such associations. Several studies have failed to identify any association with elite endurance performance. examined hockey players, cyclists, skiers, track and field athletes, swimmers, rowers, gymnasts and `others'. Similarly, the mixed cohort examined by Karjalainen included diverse sports such as long distance running, orienteering, cross country skiing and triathlon [16]. The 192 athletes studied also included skiers, long and middle distance runners, cyclists and biathletes (the latter would also have to demonstrate more than a proficiency. Such studies thus comprise individuals selected from diverse sporting disciplines, with potential variation in standard, with events of varying duration and skill mix. In general, therefore, the association of ACE genotype with sporting prowess is recognized in studies of elite athletes drawn from a single sporting discipline, in whom the I and D alleles seems to associate with some aspects of endurance and power performance respectively [13]. The use of subjects from mixed disciplines might thus account for the lack of association reported in such study groups. We have tested this hypothesis in

the study of a mixed cohort of Russian athletes. *ACE* gene I/D allele frequencies for the cohort overall were first compared to those in a control sample. Subsequently, allele frequency was compared across event duration in individual sporting disciplines, for those performing at the highest level. As an essential substrate for the renin-angiotensin system, angiotensinogen (AGT) plays an important role in hydromineral balance and the control of blood pressure. A highly significant correlation was observed between plasma AGT concentration and blood pressure in a large cross-sectional epidemiological study [17].

Within the context of a family study, Watt and coinvestigators reported higher plasma AGT levels in young adults with an elevated blood pressure whose parents also had high blood pressure compared with young adults with low blood pressure whose parents also had low blood pressure [18]. Plasma AGT is also reported to be higher in hypertensive subjects and in the offspring of hypertensive parents. In addition, overexpression of the *ACE* gene causes elevated blood pressure in transgenic mice carrying the rat AGT gene. A recent collaborative investigation of the *ACE* gene in siblings from Utah and Paris sharpened these findings by reporting both linkage and association of AGT molecular variants (235T and 174M) with hypertension, suggesting that these AGT polymorphisms may represent markers of an inherited predisposition to essential hypertension in humans [19].

These findings have recently been extended to a Japanese population, where a significant association was also noted between hypertension and the 235T allele, along with a substantial increase in the population frequency of the 235T allele. ACE is also able to hydrolyze the vasodilator peptide bradykinin. The wide distribution of ACE in many body tissues suggests that, in addition to its major role in the metabolism of vasoactive peptides, ACE is probably involved in the metabolism of other peptides, such as neurotransmitters (Erdos and Skidgel,1987). The structures of the two forms of the human enzyme have been determined by molecular cloning of their respective cDNAs. A large form (M, = 170,000) is present in endothelial cells and in the brush border of epithelial cells. A smaller form (Mr = 90,000) is present in the germinal cells of the testis and is encoded by a shorter mRNA (3 instead of 4.3 kb). The large form of the enzyme has a 2-fold internal homology, and each of the homologous domains bears a putative active site, suggesting gene duplication [20]. The small form contains only one of these domains and has a different amino terminal region. Although the specific substrate of the fully active ACE in germinal cells is not known, it must be important as this peculiar form is highly conserved, being found in all the mammalian species studied to date, including humans. The expressions of the two forms are also under different hormonal regulations; the endothelial enzyme is induced by glucocorticoids, whereas the testicular form is stimulated by androgens The *ACE* gene is constitutively expressed in several types of somatic cells, including vascular cells [21]. A soluble form of the enzyme is secreted in plasma by proteolytic cleavage of the membrane anchor. The inter individual variability in plasma ACE levels is very large, and a family study has indicated that it was under the influence of a major gene polymorphism. An insertion (I) deletion (D) polymorphism in intron 16 of the *ACE* gene was then found to be associated with plasma and cellular ACE levels [22].

The D allele, which is associated with higher plasma ACE levels, and the level of ACE in plasma, were found in case control studies to be associated with an increased risk of myocardial infarction, an increased risk of diabetic nephropathy in type I diabetic patients, and a faster rate of renal function degradation in glomerular diseases. Although these findings should be confirmed in prospective studies, they can support the concept that ACE level is a critical factor in the determinism of angiotensins and kinins (and perhaps also other peptide substrates) levels in peripheral circulations and in tissue interstitium, especially in the heart and kidney [23-35].

Conclusion

The *ACE* gene provides instructions for making the angiotensin-converting enzyme. This enzyme is able to cleave (cut) proteins. It is important part of the renin-angiotensin system, which regulates the blood pressure and the balance of salts and fluids in the body. By cleaving a protein called angiotensin I at a particular location, the angiotensin-converting enzyme converts this protein to angiotensin II. The increased amount of fluid and salts in the body also increases the blood pressure. Proper blood pressure during fetal growth, which delivers oxygen to the developing tissues, is required for normal development of the kidneys, particularly of structures called the proximal tubules, and other tissues. The angiotensin-converting enzyme (ACE) can cut the other proteins, including bradykinin. Bradykinin causes blood vessels to dilate, which decreases the blood pressure. Cleavage by the (ACE) angiotensin-converting enzyme inactivates bradykinin, helping to increase blood pressure growth factors contribute in the development of kidney structures.

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