**The ACE I/D Polymorphism and Human Physical Performance**

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The D allele of the angiotensin-converting enzyme (ACE) I/D polymorphism is associated with elevated levels of serum and tissue ACE, increased production of the vasopressor angiotensin II and a reduction in the half-life of the vasodilator bradykinin. Several cardiac and renal conditions appear to have a worse prognosis in subjects homozygous for the D allele, whereas the I allele has been associated with enhanced endurance performance in elite distance runners, rowers and mountaineers. The nature of the gene–environment interaction between ACE I/D polymorphisms and physical training, an overview of recent findings and a discussion of possible underlying mechanisms is the subject of this review.

The aspartyl protease renin is released from cells of the juxtaglomerular apparatus under conditions of salt or volume loss or sympathetic activation. Renin cleaves the α2 globulin angiotensinogen (synthesized in the liver) to generate the non-pressor decapetide angiotensin I. The octapeptide angiotensin II (Ang II) is then derived primarily by the action of the dipeptidyl-carboxypeptidase, angiotensin-converting enzyme (ACE), which is responsible for the hydrolytic cleavage of dipeptides from the C-terminal His-Leu dipeptide. ACE also catalyses the inactivation of the nonapeptide bradykinin by two sequential dipeptide hydrolytic steps and, in this context, is also known as kininase II.

ACE, a zinc metalloprotease, is released from the cell membrane by a carboxypeptidase that cleaves the protein between Arg663 and Ser664 to generate circulating ACE (Ref. 1). Large interindividual differences in plasma ACE levels exist but are similar within families, suggesting a strong genetic influence. The human ACE gene* is found on Chromosome 17 and contains a restriction fragment length polymorphism consisting of the presence (insertion, I) or absence (deletion, D) of a 287 base pair Alu repeat sequence in Intron 16 (Ref. 2). The association of the I allele with lower ACE activity in both serum and tissues has ramifications throughout the renin–angiotensin system (RAS) and the kallikrein–kinin system, and has stimulated much fascinating work with regard to various pathological and physiological states.

Recent studies have suggested that the I allele might be associated with some aspects of endurance performance, being found with increased frequency in elite distance runners, rowers and mountaineers. In addition,

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*D The official symbol for the gene encoding ACE is now DCP1 and the two alleles are designated DCP1*I and DCP1*D.

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the increase with training of the duration of loaded repetitive biceps flexion is 11-fold greater among those with the II genotype compared with those homozygotic for the D allele.

In one study, 78 British Army recruits completed an identical ten-week general physical training programme. The maximum duration (in seconds) for which they could perform repetitive elbow flexion while holding a 15 kg barbell was assessed both before and after the training period. Pretraining performance was independent of genotype, and duration of exercise improved significantly for those with the II and ID genotypes (79.4 ± 25.2 and 24.7 ± 8.8 sec; mean ± SEM, respectively), but not for the DD subjects (7.1 ± 14.9 sec; mean ± SEM). Thus, the improvement was 11-fold greater for those subjects homozygotic for the I rather than for the D allele.

Genotype distribution and allele frequency differ significantly between elite climbers with a history of ascents beyond 7000 m (without the use of supplemental inspired oxygen) and controls, with a relative excess of the II genotype and a deficiency of the DD genotype (Fig. 1). Among the 15 climbers who had ascended beyond 8000 m without oxygen, none was of the DD genotype and, ranked by the number of such ascents, the top performer had the II genotype (five ascents, compared to a mean of 2.4 ± 0.3). This is a small population association study, and not all elite mountaineers identified by the British Mountaineering Council participated (25 from a total of 33 identified). Nevertheless, it suggests a performance advantage conferred by the I allele among elite endurance athletes exercising at a very high altitude where calorie intake is low, calorie expenditure high and oxygen supply low.

One might anticipate a similar gene skew at sea level among endurance athletes. In 64 Australian national rowers attending their pre-Olympics selection trial, there was an excess of the I allele and the II genotype reported compared with matched healthy controls. Furthermore, analysis of 91 British Olympic-standard runners revealed an excess of both the I allele and the II genotype compared with controls, following a significant linear trend of increasing I allele frequency with the distance run (Fig. 2).

Other workers have failed to find an association between the I allele and elite endurance performance. The common denominator among these studies has been the selection of athletes from mixed sporting disciplines, albeit all with an element of endurance. Population association studies test whether a genetic marker (the polymorphism/allele) occurs more frequently in specified groups than in controls, a significant association suggesting that the allele being studied is itself responsible, or is at least in the locus, or that this allele is in linkage disequilibrium with the ‘real’ locus. Several confounding factors, including subtle phenotypic differences, make comparison between investigations difficult. What exactly is an elite endurance athlete? Olympic runners and Australian national rowers might represent a slightly different endurance phenotype from the skiers and swimmers forming part of the cohorts in the studies with negative findings. Certainly, if one combines different sporting disciplines, one combines several slightly different phenotypes and confuses the issue being evaluated. The positive findings regarding the ACE genotype and endurance have compared individuals within one sporting discipline with a control group, and as such, are more acceptable. Eliminating variables that might influence the ‘elite athlete’ phenotype (as opposed to the ‘endurance’ phenotype) might require the examination of the gene frequency within a sporting discipline that has an increasing element of endurance. This increases phenotypic homogeneity, focuses on the effect of the ACE genotype with regard to endurance within a discipline and has previously produced positive findings.

• Potential Mechanisms

Are there ACE Genotype-dependent Alterations in Cardiorespiratory Fitness with Training?

A high level of aerobic fitness, for which maximum oxygen utilization (VO2 max) has been used as a marker, is an essential requirement for prowess in endurance activity. VO2 max is a multifactorial phenotype influenced by genetic and environmental factors, the most important of the environmental factors being regular physical activity. There are marked interindividual differences in the trainability of the VO2 max phenotype and identical training.

Figure 1. Distribution of ACE II/D genotypes in 25 elite British mountaineers (black bars) and 1906 healthy British men (white bars). The ACE genotype distribution in the control population is 0.24, 0.50 and 0.26 for II, ID and DD genotypes, respectively, (I allele frequency = 0.49). Both II genotype and I allele frequency differed significantly between climbers and controls. Abbreviation: ACE, angiotensin-converting enzyme.

Figure 2. Relative I allele frequency of 91 Olympic-standard runners. Relative I allele frequency in controls was 0.49. The proportion of I alleles showed a significant linear trend and increased from 0.35 to 0.53 and 0.62 among those running ≤200 m (n = 20), 400–3000 m (n = 37) and ≥5000 m (n = 34), respectively. A similar, although non-significant, trend was seen among the 79 Caucasian athletes.
ACE inhibitors, which reduce serum ACE and therefore have an effect analogous to that of the I allele, can improve peak Vo2 max in heart failure through enhanced alveolar–capillary gas transfer and ventilation-perfusion. Indeed, Losartan (an Ang II type 1 receptor blocker) and Enalapril can increase peak Vo2 by approximately 16% in heart failure patients and are synergistic when combined. Unfortunately, there appears to be no similar effect in health.

These effects might suggest that reducing serum ACE can affect cardiorespiratory performance through central cardiopulmonary changes, albeit only in disease states such as heart failure, where there is an upregulated RAS. The relationship between the ACE genotype and Vo2 max has been examined and has provided conflicting evidence. Hagberg and colleagues found that, among postmenopausal women homozygous for the I allele, a significantly greater Vo2 max (6.3 ml kg\(^{-1}\)min\(^{-1}\), or 23%) exists than in DD homozygotes, which was due entirely to increased maximal arteriovenous oxygen difference and not to cardiac output index. Differing habitual physical activity levels accounted for 71% of the interindividual variation in Vo2 max in these women, but the ACE genotype accounted for a further 12%.

In the HERITAGE study reported by Rankinen and colleagues, there was no difference in Vo2 max by genotype at baseline, but a significant increase after 20 weeks training for DD homozygotes of Caucasian offspring, but not their parents.

Findings relating endurance performance to the ACE genotype have always been either in military recruits or in elite athletes and mountaineers, where a prolonged period of training and, therefore, gene–environment interaction, has taken place. In determining factors that might enhance endurance performance, we should ideally examine the change in a parameter, with training as an environmental stimulus. If attempting to investigate a gene–environment interaction (in this case the interaction of the ACE gene I/D polymorphism with exercise training), then it is crucial that as many other environmental factors as possible are kept constant. British military recruits are particularly suitable for these studies because they are all sleeping in the same location, eating the same diet, sleeping the same hours and exercising to identical supervised targets at identical times. They are also often of one sex, from a very narrow age band and from a similar racial background.

Are there Factors other than Cardiorespiratory Fitness that Might Influence the ACE Genotype Response to Training?

The findings of Rankinen and colleagues from a well-designed longitudinal study, with strictly supervised training and a large number of subjects, showed no evidence to support a hypothesis that the enhanced endurance characteristics conferred by the ACE I allele result from improvements in cardiorespiratory fitness. However, endurance performance can vary greatly among individuals with an equal Vo2 max (Refs 18, 19), suggesting that other factors might play a significant role. Vo2 max is limited primarily by the ability of the cardiorespiratory system to deliver oxygen to the exercising muscles, and the increase in Vo2 max with training is mainly the result of an increase in maximal cardiac output, rather than an increased arteriovenous oxygen difference. Vo2 max might set the upper limit for energy production in endurance activities but it does not determine the final performance. The apparent benefit conferred by the I allele in elite climbers might also be the result of mechanisms other than improved cardiorespiratory fitness. Their static and dynamic lung volumes and echocardiographic measurements are similar to sedentary controls and their Vo2 max is between that of sedentary controls and long distance runners. The reduction in muscle fibre cross-sectional area and increased ratio of capillaries – which therefore facilitates oxygen delivery to muscle mitochondria – might explain their adaptation, as well as their increased arteriovenous oxygen difference despite a lower Vo2 max after exposure to high altitude. The improvement with training in repetitive biceps flexion for II subjects also suggests that the endurance of a fairly small muscle group might be influenced in an ACE genotype-dependent manner owing to local muscle effects, rather than to significant changes in the cardiovascular system.

In competitive cyclists with a similar Vo2 max, those reaching their lactate threshold at a lower workload, fatigue quicker than those with a lactate threshold occurring at a higher work intensity (29.1 versus 60.8 min, respectively) when both groups exercise at the same work rate (80–88% Vo2 max). These groups were similar in terms of mitochondrial enzyme activity in their vastus lateralis muscle but the group with a higher lactate threshold and greater endurance had a greater percentage of type I fibres. Interestingly, the proportion of type I fibres falls in patients with heart failure, a condition associated with reduced metabolic efficiency, but is preserved by medication such as ACE inhibitors. Furthermore, the metabolic efficiency of skeletal muscle can be increased in response to the environmental challenge of lactation, dietary energy deficiency and exercise training.

Fifty-eight army recruits underwent a bicycle ergometer submaximal exercise protocol at three fixed workloads both before and after an 11-week programme of physical training. Delta efficiency (DE, the ratio of the change in work performed min\(^{-1}\) to the change in energy expended min\(^{-1}\)) was calculated for each subject and expressed as a percentage. Baseline DE was independent of genotype (24.5% and 24.9%, respectively) but after training was strongly genotype dependent, with DE rising significantly only among those with the II genotype (absolute change of \(-0.26%\) for those with the DD genotype).
and 1.87% for those with the II genotype). The absolute improvement in DE of 1.87% among those with the II genotype represents a proportional increase in efficiency of 8.62% relative to baseline and −0.39% for DD subjects (Fig. 3).

It is this difference in muscular efficiency and not cardiorespiratory fitness that might account for part of the enhanced endurance characteristics associated with the ACE I allele.

If this is true then one might expect a relative sparing of energy stores over time with a period of training. Of 123 male army recruits studied before and after training32 those with the II genotype had a greater anabolic response than did ID or DD subjects for fat mass (0.55 versus −0.20 kg) and non-fat mass (1.31 versus −0.15 kg) by bioimpedance. Magnetic resonance imaging (MRI) of the mid-thigh showed a significant increase in total mass and non-fat mass in the II group compared with the ID or DD subjects. The insertion polymorphism of the human ACE gene is therefore associated with a relative sparing of fat stores and a relative anabolic effect on non-fat mass in the thigh during a structured training programme.

**Is there a Possible Physiological Explanation?**

ACE is a key component of the circulating RAS, influencing circulatory homeostasis through the degradation of vasodilator kinins and the formation of the vasopressor Ang II. However, local tissue-based RASs also exist in various tissues such as human myocardium33, adipose tissue34 and skeletal muscle35. ACE levels are raised in serum2 and myocardial tissue3 during a structured training programme.

**• Summary and Future Directions**

The I allele does seem to be associated with enhanced endurance performance, probably via a local muscle effect rather than a central cardiorespiratory mechanism. Future research might clarify the exact relationship between the ACE I/D polymorphism and ACE expression in skeletal muscle and the interaction of this with training on muscle fibre type and size, mitochondrial and capillary density and substrate utilization. If future work demonstrates that low ACE levels mediate the benefit of the I allele and confirm that this improves muscle efficiency, this may allow us to manipulate situations where whole body oxygen and substrate delivery are compromised, such as in heart failure or malignant disease. If we develop new insights into improving cellular efficiency, then in conditions such as myocardial or cerebral infarction we might be able to develop new therapeutic strategies or increase indications for existing drugs to counteract the sudden reduction in cellular delivery of metabolic substrates and oxygen associated with these states. Consistent with this hypothesis, ACE inhibition improves myocardial cell survival in the face of...
ischaemia and patient survival in cases of cardiac dysfunction.

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