The renin–angiotensin system and physical performance

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Abstract
Many of us recognize that some individuals seem ‘gifted’ in sporting ability. We may also have noted the association of such elite performance with past parental success, recognizing intuitively the role of inherited traits. With the expansion of molecular biology and associated technologies, we now find ourselves better able to explore these genetic influences. This article examines the role of the renin–angiotensin system in regulating physical performance, based on data arising from candidate gene-association studies. In particular, the association of angiotensin-converting enzyme genotype with performance-related phenotypes will be addressed. Finally, we will briefly discuss the applicability of this data to disease states such as heart failure.

Genetic diversity and performance phenotypes

Genetic diversity
As humans, we all share up to 40,000 genes. What then makes us all different as individuals? The basic human genetic code contains small variations, there being about 40 points of difference in any one gene. If common (by convention, found in >1% of individuals) such a difference is described as a polymorphism or gene variant. Often, polymorphisms are small, comprising the substitution of one single base pair for another – a single nucleotide polymorphism or SNP. Such genetic variation interacts with environmental conditions to determine phenotype; a genetic predisposition to tallness is unlikely to be evident in an individual who was malnourished during childhood. The many different combinations of ≈40 small differences in each of 40,000 genes, and their interaction with environmental influences, make us all different from one another. This genetic diversity, and associated gene–environment interactions, explains much of the variation seen in human physical performance.

Performance phenotypes
Elite sporting performance represents a composite of elite physical performance characteristics which, in turn, may depend upon a variety of biological and mechanical tissue properties. Such properties may be metabolic (choice of substrate and efficiency of use) or anatomical/structural (bone mass and structure, tendon lengths, hinge and limb lengths, skeletal muscle mass, tendon elasticity, muscle tension properties and fibre types). Further, such diverse structural and functional variation may relate to skeletal, muscular, cardiac, respiratory, circulatory or even neurological and psychological function. To determine phenotype, all of these will depend upon the interaction of genetic and environmental factors ranging from lifelong diet, to factors including infection and injury, the use of tobacco products and exercise.

Only a few of these intermediate phenotypes have been studied in any great detail, possibly because the motivation driving such studies is the need to understand disease of the bone and heart. However, the overwhelming conclusion is that genetic diversity accounts for much of the variation seen in those intermediate phenotypes studied. Twin studies have shown that heritable factors account for 60–80% of the variance in human skeletal muscle mass [1], 60–90% of the variance of human bone mass at the femoral neck and lumbar spine [2] and greater than 50% of the variance of human left ventricular mass [3].

The ACE (angiotensin-converting enzyme) gene polymorphism and physical performance

The ACE (angiotensin-converting enzyme)
Produced in the kidney, renin cleaves angiotensinogen to yield angiotensin I. Acted upon by ACE, angiotensin I is converted into Ang II (angiotensin II), whose effects are mediated predominantly through two specific human receptors (AT₁ and AT₂). Stimulation of the AT₁ receptor by Ang II mediates a hypertensive response through primary vasoconstriction, and salt and water retention secondary to adrenal aldosterone release. ACE also degrades bradykinin, whose action on the type 2 (BK₂) receptor results in vasodilatation. This is the circulating or endocrine RAS. In addition to endocrine RAS, local tissue RAS are now well-described existing in tissues such as the human myocardium [4], adipose tissue [5] and skeletal muscle [6].
Ang II has effects which might alter performance. In the heart Ang II is a powerful cellular growth factor [7]; local synthesis in response to mechanical loading (both in vivo [8] and in vitro [9]) may drive cardiomyocyte growth. Conversely, infusion of Ang II into rats causes weight loss [10] due to a reduction in skeletal muscle mass [11] with such changes being associated with altered oxygen consumption. These and other data [12] have led to the suggestion that Ang II plays an important metabolic role [6]. Alternatively, such effects may be mediated through alterations in bradykinin levels. Bradykinin acts upon BK1 and BK2 receptors. ACE is a potent kininase, and bradykinin levels are thus dependent on ACE activity [13]. Bradykinin alters energy-rich phosphate and glycogen levels, reduces lactate concentration [14] and changes glucose-free fatty-acid substrate availability [15]. This indirect evidence implicates bradykinin receptors in metabolic regulation.

The ACE gene I/D polymorphism

A polymorphism of the ACE gene has been described in which the absence (deletion or ‘D’ allele) rather than the presence (insertion or ‘I’ allele) of a 287-base-pair marker in intron 16 is associated with significantly higher ACE levels in the circulation [16], as well as in tissue systems [17] including the human myocardium [18].

The ACE I/D polymorphism and left ventricular hypertrophy

There are ample data to suggest that exercise is a potent stimulus for LV (left ventricular) growth (hypertrophy), with increases in LV mass noted in response to both endurance [19] and isometric training [20].

Given the trophic effects of Ang II on the myocardium, we might anticipate the D allele (higher ACE activity) of the ACE gene to be associated with increased exercise-related cardiac growth. This hypothesis was tested by examining 460 consecutive males recruited to an army training regiment over a 9-month period [21]. Subjects were assessed before and after 10 weeks of intensive upper body strength and lower limb endurance training. Left ventricular growth was measured using echocardiography; paired echocardiograms suitable for analysis were obtained in 140 subjects, amongst whom echocardiographic LV growth with training was found to be strongly associated with ACE genotype. LV mass altered by +2.0, +38.5 and +42.3 g for II, ID and DD genotypes respectively (P < 0.0001). This association was later confirmed using the same model, but assessing LV mass change using the far more reproducible method of cardiac magnetic resonance imaging [22].

The LV growth response to exercise is thus ACE genotype-dependent [21], a finding since confirmed in other studies [22–24].

Does ACE genotype influence other performance phenotypes?

Given that variation in myocardial ACE activity (as marked by ACE I/D genotype) is associated with an altered LV growth response to exercise, and that a local skeletal muscle RAS exists, Folland et al. [25] examined the effect of ACE genotype upon changes in strength of the quadriceps muscle in response to 9 weeks of strength training in 33 healthy male volunteers. Greater strength gains were associated with the D allele (means ± S.E.M.; II, 9.0 ± 1.7%; ID, 17.6 ± 2.2%; DD, 14.9 ± 1.3%; ANOVA, P < 0.05). In contrast, Woods et al. [26] showed the I allele to be associated with greater gains in strength response of the adductor pollicis muscle to hormone-replacement therapy in post-menopausal women. Such disparity may be understandable given the different subjects used (post-menopausal women versus young fit men), the different muscle groups examined (small hand muscle versus large leg muscle), stimulus applied (hormone-replacement therapy versus strength training) and the small number of subjects in each genotype group. Nevertheless, both studies were prospective and suggest that ACE plays an active role in regulating skeletal muscle strength.

The ability of skeletal muscle to withstand fatigue has also been examined [27]. ACE genotype was determined in 123 Caucasian males recruited to the British army consecutively. A total of 78 completed an identical 10-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. Pre-training performance was independent of genotype (mean; 119.8 ± 6.2 s). Duration of exercise improved significantly for those (66 individuals) of II and ID genotype (79.4 ± 25.2 and 24.7 ± 8.8 s; P = 0.005 and 0.007 respectively) but not for the 12 of DD genotype (7.1 ± 14.9 s; P = 0.642). Improvement was thus 11-fold greater (P = 0.001) for those of II than for those of the DD genotype.

Studies examining the effect of ACE genotype on muscle fibre type may provide a clue as to how such associations with muscle performance come about. Skeletal muscle is composed of a variety of muscle fibre types with varying metabolic and contractile properties. They are classified as being either slow-twitch (type I) or fast-twitch (type IIa or IIb) based on their histochemical staining for myosin ATPase activity. Slow-twitch fibres are more efficient than fast-twitch fibres during low-velocity contraction. On this basis, Zhang et al. [28] hypothesized that the ACE polymorphism I allele would be associated with increased number of slow-twitch fibres by examining the association between the ACE genotype and skeletal muscle fibre types in 41 untrained healthy young volunteers. Skeletal muscle samples were taken from the left vastus lateralis using the needle-biopsy method. II subjects had significantly higher percentages of type I fibres (50.1 ± 13.9% versus 30.5 ± 13.3%) and lower percentages of type IIb fibres (16.2 ± 6.6% versus 32.9 ± 7.4%) than DD subjects.

ACE genotype and ME (metabolic efficiency)

The association of ACE genotype with the metabolic properties of muscle fibres and the theoretical role of Ang II in metabolism has led to the suggestion that RAS have an important role in ME. Data from Williams et al. [29] have added
strength to this suggestion. They measured the ‘delta efficiency’ (the ratio of the change in muscle work performed/min to the change in energy expended/min: the most valid measure of the ME of muscular contraction) in young male army recruits, and its response to a 10-week exercise training programme. This response was found to be strongly ACE genotype-dependent, with delta efficiency rising by 8.62% in those of II genotype, and falling slightly (−0.39%) amongst those of DD genotype [29]. These data support a role for lower ACE activity interacting with physical training in the regulation of metabolic efficiency. They suggest that increased RAS activity is associated with reduced ME. Meanwhile, the reduced RAS activity associated with ACE inhibition may lead to increased ME.

**ACE genotype and $\dot{V}O_{2\text{max}}$**

$\dot{V}O_{2\text{max}}$ has long been thought to be a useful marker of performance ability, although this may not be so, since many endurance athletes limit the intensity of their training based on their $\dot{V}O_{2\text{max}}$. Also, $\dot{V}O_{2\text{max}}$ is a complex phenotype, being dependent upon integrated cardiopulmonary, vascular and skeletal muscle metabolic function, all of which ACE may influence.

Linkage studies have failed to associate the chromosomal region in which the ACE gene lies with $\dot{V}O_{2\text{max}}$ [30]. However, this strategy has limited power [31], and more targeted candidate gene approaches have provided greater success. Change in $\dot{V}O_{2\text{max}}$ in response to training has been examined in at least two studies. One such study [32] was blighted by the use of a racially heterogeneous and mixed-sex population [33], rendering the negative result in trying to associate $\dot{V}O_{2\text{max}}$ with ACE genotype inconclusive. A second study in male Caucasian army recruits [34] also concluded there was no association between the training response of $\dot{V}O_{2\text{max}}$ and ACE genotype, concluding that any links between performance and ACE to be independent of changes in $\dot{V}O_{2\text{max}}$.

Using a less favourable cross-sectional study design that included 60 post-menopausal women with a broad range of athletic ability, Hagberg et al. [35] showed the I allele of the ACE gene polymorphism to be associated with greater $\dot{V}O_{2\text{max}}$, possibly highlighting the importance of age and sex on how gene variants alter phenotype.

**ACE genotype and elite athlete status**

Thus a strong case can be made to support the existence of an association between ACE genotype and human physical performance. On this sound basis, several investigators have hypothesized that the I allele is likely to be more frequent amongst successful endurance athletes, because of the advantages conferred by it on metabolic efficiency. Such a hypothesis is supported by a study of Olympic-standard runners (79 Caucasians) where I allele frequency increased with distance run (0.35, 0.53 and 0.62 for £200 m, 400–3000 m and ≥5000 m respectively; $P = 0.009$ for linear trend) [36]. These data have since been confirmed amongst Russian runners [37] and rowers [38]. Conversely, these studies also suggest that the D allele frequency was greater than might be expected amongst sprinters; a finding also noted amongst swimmers [39].

A putative association of the I allele with endurance and ‘fatigue-resistant’ phenotypes, and the D allele with sprint or ‘power’ might account for the conflicting findings of studies in which mixed sporting disciplines are examined [32,40–42]. For example, one of these studies included 81 men and 39 women who excelled in a variety of sports: hockey, 26; cycling, 25; skiing, 21; track and field, 15; swimming, 13; rowing, 7; gymnastics, 5; other, 8 [40].

**ACE is associated with performance: what is the underlying mechanism?**

We have already suggested that angiotensin II may underlie the effect of ACE on performance. However, rather than acting through increased angiotensin II synthesis, ACE may mediate its effects through alterations in bradykinin metabolism. ACE degrades bradykinin, and bradykinin levels are thus dependent on ACE activity [43] and ACE insertion/deletion genotype [44]. The BK$_2$ receptor is likely to have a role in growth inhibition, and thus in preventing LV growth [45,46]. Further investigation is open to the application of a genetic strategy, similar to that described above for the ACE gene. A variant in exon 1 of the BK$_2$ receptor gene has now been identified in which the absence (−9) rather than the presence (+9) of a 9 base-pair segment is associated with higher gene transcriptional activity, receptor mRNA expression, and receptor agonist response. If kinins do modulate the human LV growth response, then we might expect BK$_2$ receptor genotype to influence such growth. We investigated this possibility. Subjects were recruited from a British Army Training Regiment [22], and genotyping performed in 109 of the 141 who completed training. The growth response was strongly dependent on BK$_2$ receptor genotype (4.6 ± 2.6, 8.3 ± 1.7 and 13.7 ± 2.4 g for the 16, 60 and 33 individuals of −9/−9, −9/+9 and +9/+9 genotypes respectively; $P < 0.01$ for linear trend). ACE and BK$_2$ receptor genotypes interacted additively, with growth being greatest amongst those with lowest kinin and BK$_2$ receptor activity (of DD/+9/+9 genotype), and least amongst those with highest kinin and BK$_2$ receptor levels (II/−9−9 genotype). Growth was 15.71 ± 3.5 versus −1.43 ± 4.1 g respectively; $P = 0.009$ for comparison of homozygote groups; $P = 0.003$ for trend across all genotypes. These data strongly support a role for the modulation of bradykinin activity in the regulation of human cardiac growth, with ACE and BK$_2$ receptor genotype interacting additively to influence such growth.

Thus the effect of ACE on LV growth appears to be mediated at least partly by bradykinin. A similar mechanism may underlie the association of ACE with other performance phenotypes, although this hypothesis is as yet unproven.

**Do such data extrapolate to disease states?**

Does the association of the I allele of the ACE I/D polymorphism with improved physical performance give insight into human pathophysiology?
Heart failure is associated with a detrimental increase in circulating RAS activity. A class of drugs known as ACE inhibitors have now become a mainstay in the treatment of heart failure, and an effect of ACE inhibition on ME has been postulated to partially account for the dramatic beneficial effects of treatment with ACE inhibitors in patients with heart failure [47]. Research to date supports this concept. Intrinsic defects in metabolic function of skeletal muscle may be responsible for limiting physical performance in heart failure [48], making muscles less resistant to fatigue. Part of this metabolic failure may relate to reductions in the ME of skeletal muscle with increasing amounts of evidence supporting this notion [49]. So the benefits of ACE inhibition in heart failure may well be mediated, at least in part, through such peripheral (skeletal muscle) metabolic effects rather than through central (cardio-respiratory) effects [50].

Summary
It appears that genetic diversity makes significant contributions to performance-related phenotypes. By presenting the data associating the ACE I/D polymorphism with these phenotypes, we hope firstly to have shown a role for the RAS in regulating performance, and secondly demonstrate the usefulness of a candidate gene environment strategy in undoing some of the complex mechanisms that human physiology encompasses.

References