INTRODUCTION

Exercise performance results from the complex interaction among physiologic, biochemical, and psychological factors, among many others. Years of research have enhanced our understanding of how the body responds to exercise training from the level of the whole human to cellular, subcellular, and molecular mechanisms, and nutritional intake has been established as a primary factor affecting human performance. In addition, a growing body of research has provided support for the notion that response to exercise training may be influenced by genetic variation. Evidence that DNA sequence variation exists within human populations can be seen in the variety of sizes, shapes, and faces that can be observed in any group of individuals. The challenge is to determine how variation in genes and how the interaction between genes and environments, such as dietary intake, may influence the variability that is seen in physiologic changes resulting from exercise. With the completion of the Human Genome Project, a myriad of approaches has been used to study the effects of genes and gene–environment interactions on exercise performance. Although the effects of exercise and nutrition on gene function and expression have been fairly well studied, how the two influence each other or interact with genetic variation to produce alterations in exercise outcomes is not well understood. This review briefly summarizes strategies currently being used to elucidate genetic effects that may influence or be mediated by physical activity and nutritional intake.

GENETIC FACTORS IN EXERCISE AND PHYSICAL ACTIVITY

Family-based studies have indicated that the propensity to engage in physical activity, particularly in the form of organized athletics, to some extent may be rooted in our genes. Heritability (the amount of variation in a trait that can be accounted for by variation in genes) estimates for physical activity measured by self-report or by observation range from 0.29 to 0.62, with the wide span in estimates likely due to differences in the age and type of the subject samples and in the physical activity assessment instruments. Gottschaldt studied the concordance or similarity of various mental and physical activity traits in monozygotic twins over the span of 30 y and found that, although cognitive skills remained highly concordant throughout a lifetime, physical activity level did not, suggesting that environmental factors rather than genetic factors are more important in determining an individual’s propensity to be active in later life. Recently, Maia et al. studied 411 Portuguese twins of different zygosity to determine the heritability of the amount and type (sports or leisure) of participation in physical activity. The researchers estimated that up to 68% of total variation in sports participation was due to genetic factors in males and 40% in females. Using data from the Quebec Family Study, maximal heritability was found to be 16% to 25% for physical activity. It is likely that a genetic predisposition for exercise and physical activity improves athletic performance in part by influencing an individual to begin sports participation early in life. Although family-based research has provided support for the role of genes in human performance, the identification and detection of genes and gene–environment interactions that influence exercise performance is difficult due to a number of factors. First, the response to exercise training is highly heterogeneous and can be influenced by multiple components in addition to genetic factors. Second, several to many genes are likely to influence performance and response to exercise, each with small to moderate effects. Third, expression of the genetic variation influencing performance may be context dependent (e.g., a genetic predisposition for muscle hypertrophy may only be evident after a specific type of resistance training). Fourth, complex physiologic functions such as the regulation of blood pressure or vasoconstriction during exercise will have multiple pathways and redundancy to ensure survival of the organism. Many association studies of candidate gene polymorphisms for exercise performance have been conducted often with conflicting results due, at least in part, to the context dependency of the genetic effects. Fifth, genes and environments...
may act independently and in concert to influence the exercise outcomes of interest. Figure 1 illustrates the interrelation among nutritional intake, genetic variation, and exercise. In this diagram, genes and nutritional intake may influence exercise outcomes directly, jointly, or via their effects on each other. In turn, exercise can alter gene expression and fuel use.

GENES FOR HUMAN PERFORMANCE

One of the first genes identified as a putative factor in response to exercise training was the angiotensin-converting enzyme (ACE) gene. ACE is part of the renin-angiotensin pathway, and an insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene has been well studied for its association to hypertension and left ventricular hypertrophy in multiple study populations. The deletion (D) allele has been associated with higher protein activity level compared with the insertion (I) allele, and the I/D polymorphism accounts for up to 47% of the variation in plasma ACE levels.6-7 Although many association studies of this gene variant and exercise-related outcomes have been conducted, there is still conflicting evidence as to the role the ACE I/D polymorphism plays in athletic performance. Montgomery et al.8 analyzed genotype at the I/D locus within the ACE gene for association to exercise response and reported that individuals with one or two I alleles showed significantly greater duration in repetitive arm flexion time after exercise training than did D/D homozygotes. The frequency of the I allele has also been shown to be elevated among elite Australian rowers, British mountaineers, and elite distance runners compared with the population at large.8-10 In addition, the individuals with one or two I alleles were found to have better exercise heat tolerance compared with D/D homozygotes.11

Although the I allele has been found with greater frequency among elite athletes, other studies have indicated that the ACE D allele is associated with exercised-induced left ventricular hypertrophy in young and middle-age males.12-14 Paradoxical findings for associations with the ACE I and D alleles may be the result of genetic effects interacting with specific types of training. The D allele is associated most strongly in athletes who perform in the short-duration, power-oriented events, whereas the I allele has been associated with performance in longer-duration events.15 Other studies, primarily in non-athlete or multiple sport athlete groups, have reported no association between the ACE I/D polymorphism and cardiovascular changes after exercise training.16,17

Although many other genes have been identified as putative factors in determining exercise response, the ACE gene is one of the few that has a large body of data accumulated, and the conflicting findings for this gene exemplify the complexity of genetic studies of physical activity and exercise-related outcomes. Table 1 presents a fraction of genes that have been shown to influence metabolic response to exercise, and there are countless others that regulate cardiac, respiratory, and body composition changes after exercise. A recent review of genes that have been linked to performance phenotypes associated more than 90 autosomal genes or quantitative trait loci (QTLs), two X-linked genes, and 14 mitochondrial genes with exercise response or performance.19

EXERCISE-INDUCED ALTERATIONS IN GENE ACTION

The body’s response to exercise may be regulated at the level of DNA sequence variation, gene transcription, and/or translation of proteins. The multitude of changes brought about by a single exercise bout and by repeated training are the result of activation of many and varied genes. As with as the study of genetic variation on exercise outcomes, the effects of short- and long-term exercise training on gene expression and function are just beginning to be understood. Gene expression is highly regulated, involving many proteins and activated by multiple signals. In addition, gene expression and protein assembly are not completely correlated, and measures of gene expression are merely the first step to understand the genes’ effect on the cell.

### Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein transcription after exercise</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT/CD36</td>
<td>Increase</td>
<td>Enhancement of fat oxidation</td>
<td>Tunstall et al.25</td>
</tr>
<tr>
<td>CPT-1</td>
<td>Increase</td>
<td>Enhancement of fat oxidation</td>
<td>Tunstall et al.25</td>
</tr>
<tr>
<td>PPARG</td>
<td>Decrease</td>
<td>Transcriptional activator</td>
<td>Tunstall et al.25</td>
</tr>
<tr>
<td>AMPK</td>
<td>Increase</td>
<td>Regulatory role in fatty acid oxidation and</td>
<td>Nielsen et al.2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glucose metabolism</td>
<td></td>
</tr>
<tr>
<td>SREBP-1c</td>
<td>Increase</td>
<td>Transcription factor that regulates lipid</td>
<td>Ikeda et al.2002</td>
</tr>
<tr>
<td>ACC2</td>
<td>Increase</td>
<td>Controls the rate of fatty acid oxidation and</td>
<td>Schrauwen et al.2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>triacylglycerol storage</td>
<td></td>
</tr>
<tr>
<td>LPL</td>
<td>Increase</td>
<td>Hydrolysis of plasma triacylglycerols</td>
<td>Schrauwen et al.2002</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Increase</td>
<td>Stimulates lipolysis from adipocytes</td>
<td>Fujii et al.1997</td>
</tr>
<tr>
<td>UCP3</td>
<td>Decrease</td>
<td>Uncouple respiration, releasing heat</td>
<td>Schrauwen et al.2003</td>
</tr>
<tr>
<td>HKII</td>
<td>Increase</td>
<td>Catalyzes the phosphorylation of glucose</td>
<td>Koval et al.27</td>
</tr>
<tr>
<td>PDH</td>
<td>Increase</td>
<td>Regulates rate of carbohydrate oxidation</td>
<td>Peters 2003</td>
</tr>
<tr>
<td>GLUT-4</td>
<td>Increase</td>
<td>Responsible for glucose transport into the</td>
<td>Greiwe et al.2000</td>
</tr>
</tbody>
</table>

FIG. 1. Interrelation between nutritional intake, genetic variation, and exercise. In this diagram, genes and nutritional intake may influence exercise response directly, jointly, or via their effects on each other. In turn, exercise can alter gene expression and fuel use.
It has long been known that an individual who regularly exercises may experience improvements in insulin sensitivity, glucose metabolism, muscle hypertrophy, changes in mitochondrial content and fiber type of muscle cells, and an increase in the use of fat as fuel during exercise.20,22 Expression of numerous genes associated with these changes has been shown to be induced or upregulated in exercising skeletal muscle. Richter et al.23 reported that a single exercise bout can alter glucose transport and insulin sensitivity in skeletal muscle of rats, and subsequent work has confirmed these findings in humans.26 Use of specific fuel types can be enhanced by exercise, and the effect may be short and long term. Exercise training has been shown to increase basal and exercise fat oxidation. In a recent study, a single (1-h) bout of cycle ergometer exercise produced no increase in expression of the fatty acid transporter (FAT/CD36) or the carnitine palmitoyltransferase-1 (CPT1) genes, key regulators of fatty acid metabolism; nevertheless, after 9 d of such exercise, expressions of FAT/CD36 and CPT1 had increased significantly above baseline, and expression of the peroxisome proliferative activated receptor-γ (PPARG) gene, an important factor in adipocyte differentiation, was markedly reduced.25 These findings provide evidence that habitual exercise may specifically improve use of stored lipids and inhibit the proliferation of adipose tissue.

Gene expression studies often follow discoveries of increased protein activity after exercise and in many instances shed some light as to the time course and regulation of these changes. Exercise has been shown to increase translocation of glutamate transporter-4 (GLUT4), activities of hexokinase, glycogen synthase, and phosphatidlyinositol-3 kinase, and levels of insulin receptor and insulin receptor substrate-1.25 In healthy subjects undergoing moderate exercise, hexokinase levels increased after 5 d of physical training; however, increases in insulin sensitivity and glucose uptake in muscle cells occurred within 24 h, and mRNA levels of hexokinase II doubled within 3 h after completing the exercise bout.26 Levels of GLUT-4 mRNA have been shown to increase in trained subjects over sedentary controls.27 After a single exercise bout of 60 min on a cycle ergometer at a power output requiring 73 ± 4% peak oxygen consumption, GLUT-4 gene expression was increased immediately after exercise and remained significantly higher than baseline 3 h after completion of the exercise.28

Adenosine monophosphate–activated protein kinase (AMPK) is activated by the rapid decreases in the ratio of adenosine triphosphate to adenosine monophosphate and of phosphocreatine to creatine in contracting muscle. In this way AMPK is an “energy-sensing enzyme” and provides a direct link for the exercising state of the muscle cell with gene transcription. AMPK increases after exercise29 and activates numerous metabolic genes, such as GLUT4 and PGC-1, in exercising rodents.30 Two isoforms of AMPK in humans, AMPKα-1 and AMPKα-2, have been shown to be differentially expressed after the same exercise bout. Low- to moderate-intensity exercise (40% to 70% of maximum oxygen capacity) resulted in an increase in the transcription of the AMPKα-2 isoform, whereas the AMPKα-1 isoform was expressed after maximal sprint exercise in untrained individuals.31 Basal AMPKα-1 was increased in response to 4 wk of endurance training, but no such increases were observed in the AMPKα-2 isoform.31

The genes described above provide a brief glimpse of studies currently being undertaken to understand the complexity of gene expression in response to exercise. Gene expression is modified differentially based on exercise type, intensity, duration, and frequency. In addition, the expression of many genes, such as AMPK, is dependent on the nutritional status of the individual and, thus, gene expression studies may be altered by the physiologic state of the organism being studied. As shown by the number of genes listed in Table I, further research designed to elucidate the factors underlying genetic response to exercise is urgently needed.

**EXERCISE PERFORMANCE AND NUTRITION**

An athlete’s food choices influence that athlete’s biochemical responses during exercise training, recovery from exercise training, and, most importantly, exercise performance.32 Carbohydrate (CHO) is a primary source of fuel for the human body, and when muscle glycogen stores are depleted (e.g., during prolonged exercise) and circulating blood glucose levels are not sufficiently maintained, exercise intensity and time to exhaustion decrease.33 Consumption of a high-CHO diet in trained individuals results in increased glycogen storage in skeletal muscle and rapid replenishment of depleted glycogen stores after exercise and has been shown to increase endurance exercise performance.34-36 In addition, several studies have examined the effects of a high-CHO diet on metabolic parameters during exercise. Athletes, consuming a high-CHO, low-fat diet, experienced decreased total fat oxidation and non-plasma fatty acid oxidation during exercise (for 2 h/d at 70% maximum oxygen capacity) in the fasted state.37 Subjects in the very low-fat diet group (2% of energy from fat) had lower intramuscular triacylglycerol stores and higher muscle glycogen content at rest. Fat oxidation during exercise was reduced by 27% compared with those who consumed 22% of energy from fat.38 Dietary fat provides a rich source of energy during exercise, and studies have shown that chronic exposure to high-fat diets increases use of fat as a fuel source at rest and during exercise. This is due to an increase in intramuscular triacylglycerol stores and induction of metabolic genes involved in fat oxidation.39,40 The increase in fat oxidation after exercise results in a decreased use of stored glycogen for fuel, which may play a role in improving exercise performance. However, muscle and liver glycogen stores are often lower than in individuals consuming a high-CHO diet, which may adversely affect exercise performance during exercise at an intensity of 65% to 85% of maximum oxygen capacity, when muscle glycogen is thought to play a critical role in fatigue. Performance outcomes after a high-fat diet can be influenced not only by exercise intensity but also by the duration of the exercise regime, length of dietary intervention, amount of fat in the diet, and the type of fat (polyunsaturated, saturated, etc.). Even with all of the performance variables mentioned above, many studies have found no improvement in performance after a high-fat diet.41

The nourishment needs of an athlete depend on the total amount of daily energy expenditure, type, duration, and frequency of sport activity, body mass and composition, sex, food preferences, and environmental circumstances.42 Hence, key nutritional aspects in athletic performance are energy needs, macronutrient requirements, intake of vitamins and minerals, and hydration. Similar to the general adult population, energy balance is the primary nutritional goal for athletes.43 Increased physical activity augments energy expenditure; hence, athletes have higher than normal energy requirements. Overall, athletes require sufficient energy intake to maintain body weight and body composition, and insufficient energy intake may lead to loss of lean muscle mass,43 loss or failure to gain bone density,44,45 menstrual amenorrhea,46 increased risk of fatigue, injury, and illness,47,48 and diminished performance.49

**NUTRIENT-INDUCED ALTERATIONS IN GENE ACTION**

A large body of evidence has determined that macronutrients (CHO, fats, and proteins) regulate gene transcription. After a single meal, the body must break down CHO and fat for immediate energy and for storage. The role of hormones such as insulin in maintaining homeostasis after a meal has been well characterized,51 as have nutrient-sensing mechanisms that activate appropriate behavioral and metabolic responses after a meal. However, the immediate regulation of gene expression by CHO, protein, and fat is not well characterized. The body adapts to differences in
macronutrient intake by regulating genes that play a role in the breakdown or storage of those nutrients. Hence, fatty acids up-regulate genes responsible for their oxidation (removal) or for adipose differentiation (storage). Macronutrients may affect gene expression by acting as ligands for transcription factor receptors, by altering concentrations of substrates or intermediates, or by affecting signaling pathways. Fatty acids induce expression of αP2, a transcription factor that aids in fatty acid use and storage in the adipocyte. Polynsaturated fatty acids directly stimulate the production of phosphoenolpyruvate carboxykinase (PEPCK) mRNA in 3T3-F442A adipocytes, and the induction of this gene is physiologically relevant because PEPCK is crucial in the formation of triacylglycerols in adipose tissue for storage. In addition, different genes involved in transport of fatty acids into the cell and mitochondria for use as energy are upregulated by dietary fatty acids. There are many exhaustive reviews of the effect of fatty acid intake on gene expression. The mechanisms behind fatty acid regulation are beyond the scope of this review, but in mammals fatty acids directly activate several transcription factors including peroxisome proliferator-activated receptors (α, β, and γ), HNF4-α, nuclear factor-κB, and SREBP1c.

Glucose and products derived from its breakdown can directly regulate gene expression through gene regions called glucose response elements and CHO response elements. The gene encoding L-pyruvate kinase contains a glucose response element and is expressed with glucose activation. Pyruvate kinase is a key enzyme in glycolysis in generating adenosine triphosphate from pyruvate. Glucose also influences the activity of transcription factors. Although not as much is known about CHO regulation of transcription factors as for fatty acids, it is known that glucose acts on the transcription factor Sp1 and related family members. Glucose acts by increasing protein phosphatase-1 activity, which dephosphorylates Sp1, increasing its DNA binding affinity for a number of metabolic genes, including acetyl COA carboxylase-1 (ACC), lepton, fatty acid synthase, and adenosine triphosphate citrate-lyase. The effect of CHO on gene expression is important in the context of exercise.

The role of amino acids on gene regulation is currently not very well understood. Several studies have examined the effects of a deficiency of certain essential amino acids on gene expression and found that certain genes are increased in transcription rate in the absence of key protein components. One such gene is the C/EBP homologous protein (CHOP), a member of the C/EBP family of transcription factors. It contains an amino acid response element that facilitates transcription of the gene in the absence of several amino acids. The absence of certain amino acids also upregulates the expression of insulin-like growth factor binding protein-1 and asparagine synthetase.

GENE–NUTRITION INTERACTION IN EXERCISE PERFORMANCE

The interaction of nutrition, genes, and exercise, visually illustrated in Figure 1, is highly complex. Many studies measuring gene expression in response to exercise control for the effects of diet, requiring subjects to ingest the same postexercise meal, with an identical “normalizing diet” for up to 2 wk before the training experiment. In most research designed to determine the optimum macronutrient content of the athletic diet, researchers rarely look at gene expression or the molecular mechanism behind performance benefits that may be seen. However, the interaction among genes, nutrition, and exercise is becoming an active field, and the remainder of this review outlines recent findings.

After exercise, the muscle works to replenish depleted glycogen through increased glucose uptake, glycogen synthase activity, and sensitivity to insulin. These changes have been inversely correlated to muscle glycogen concentration after exercise, and the genes responsible have been demonstrated to increase transcription after an exercise bout. One study tested the hypothesis that interleukin-6 (IL-6), a cytokine involved in hepatic gluconeogenesis, is altered by diet and exercise. Six male subjects underwent a dietary intervention of a normal (control) diet or a low-CHO diet to induce a muscle glycogen level of 60% of those on the normal diet. The day after the initiation of the diet, subjects performed 180 min of two-legged dynamic knee-extensor exercise, and plasma IL-6 levels were measured before and throughout the exercise bout. Plasma IL-6 increased in both groups; however, after 120 min, the low-glycogen group experienced an increase of two-fold higher than the controls, which remained significantly higher throughout the exercise. To determine whether this difference was due to increased gene transcription and mRNA levels of IL-6, muscle biopsies of the vastus lateralis were taken before exercise and after 30, 90, and 180 min. IL-6 transcription rate and mRNA content were significantly higher in the low-glycogen group at 90 and 180 min than in controls. This increase in IL-6 expression in response to low glycogen levels is thought to be one mechanism by which the body regulates muscle glycogen levels, a key component to endurance performance.

The relation between the amount of glycogen stores brought about dietary CHO and exercise on gene transcription was also examined by Pilegaard et al. who used cycling exercise to directly compare the effects of exercise on one leg that had been depleted of muscle glycogen with one control leg. Glycogen stores were first built up in both legs by a diet consisting of 500 g of CHO for 2 d preceding the experiment. Glycogen stores were then depleted in one leg by one-legged cycling to exhaustion, followed by 30 min of two-arm cycling exercise to lower liver glycogen stores the day before the test, with CHO intake restricted until the beginning of the test. Muscle biopsies were obtained from the vastus lateralis before the exercise bout, immediately after, and after 2 and 5 h of recovery. Subjects consumed high-CHO meals immediately after exercise and at 1 and 3 h of recovery. Muscle glycogen content was significantly lower at all time points in the glycogen-depleted leg than in the control leg.

Before exercise, transcription levels of UCP3, PKD4, HKII, and LPL genes were similar in the control and low-glycogen legs. However, only transcription of UCP3 increased significantly after exercise in the low-glycogen leg. The mRNA levels for PKD4, HKII, and LPL were significantly higher in the low-glycogen leg before the exercise; moreover, although exercise did not further increase these levels, exercise induced increasing mRNA levels to those similar to the low-glycogen leg, indicating that the genes could be induced by a change in glycogen content of the muscle cell.

In another study, six subjects underwent two trials of two-legged knee-extensor exercise for 3 h at approximately 60% of their maximum 2-min workload. Muscle glycogen stores were further depleted in one group by combining exercise to exhaustion with a low-CHO diet, whereas the control normal muscle glycogen group ate a high-CHO meal to replenish the muscle glycogen stores. The time points for muscle biopsies in this study were pre-exercise, after 1.5 and 3 h of exercise, and after 2 h of recovery. Transcription of PKD4, HKII, UCP3, and LPL increased after exercise, but this increase was more dramatic in the low-glycogen group. These studies demonstrate that the physiologic alterations induced by diet and exercise may be manifested at the molecular level.

CONCLUSIONS

The profound effect of nutrition on exercise performance is well documented. However, each individual athlete is unique and nutritional requirements depend on age, sex, body size, lean tissue mass, previous nutritional status, and the duration, frequency, intensity, and type of physical activity performed. In addition,
References

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