Exercise, diet, and skeletal muscle gene expression

MARK HARGREAVES and DAVID CAMERON-SMITH

School of Health Sciences, Deakin University, Burwood, AUSTRALIA

ABSTRACT

HARGREAVES, M., and D. CAMERON-SMITH. Exercise, diet, and skeletal muscle gene expression. Med. Sci. Sports Exerc., Vol. 34, No. 9, pp. 1505–1508, 2002. Skeletal muscle, as a consequence of its mass and great capacity for altered metabolism, has a major impact on whole-body metabolic homeostasis and is capable of remarkable adaptation in response to various physiological stimuli, including exercise and dietary intervention. Exercise-induced increases in skeletal muscle mRNA levels of a number of genes have been reported, due to transcriptional activation and/or increased mRNA stability. The cellular adaptations to exercise training appear to be due to the cumulative effects of transient increases in gene transcription after repeated exercise bouts. The relative importance of transcriptional (mRNA synthesis) and translational (mRNA stability or translational efficiency) mechanisms for the training-induced increases in skeletal muscle protein abundance remains to be fully elucidated. Dietary manipulation, and the associated alterations in nutrient availability and hormone levels, can also modify skeletal muscle gene expression, although fewer studies have been reported. A major challenge is to understand how exercise and diet exert their effects on gene and protein expression in skeletal muscle. In relation to exercise, potential stimuli include stretch and muscle tension, the pattern of motor nerve activity and the resultant calcium transients, the energy charge of the cell and substrate availability, oxygen tension and circulating hormones. These are detected by various cellular signaling mechanisms, acting on a range of downstream targets and a wide range of putative transcription factors. A key goal in the years ahead is to identify how alterations at the level of gene expression are coupled to the changes in skeletal muscle phenotype. It is clear that gene expression, although representing a specific site of regulation, is only one step in a complex cascade from the initial stimulus to the final phenotypic adaptation and integrated physiological response. Key Words: PHYSICAL ACTIVITY, NUTRIENTS, TRANSCRIPTION, TRANSLATION

Skeletal muscle, as a consequence of its mass and great capacity for altered metabolism, has a major impact on whole-body metabolic homeostasis. It is the predominant site of glucose and lipid disposal under various physiological conditions, most notably exercise, and is a significant reservoir of protein. Furthermore, reduced muscle mass and defects in metabolic pathways within skeletal muscle are associated with various clinical disorders, including insulin resistance, dyslipidemia, obesity, and hypertension (2). Mature skeletal muscle is capable of remarkable adaptation in response to various physiological stimuli that result in regeneration, hypertrophy, and enhanced metabolic potential. Perhaps one of the most powerful stimuli for inducing changes in the skeletal muscle phenotype is physical exercise, both acute and chronic. Numerous studies, over many years, have characterized the changes in skeletal muscle composition, and metabolic potential and function in response to exercise stimulation (see 15). Dietary modification, resulting in altered carbohydrate and lipid substrate availability and utilization, has also been studied. The potential of the powerful tools of molecular and cellular biology to better elucidate the basic mechanisms underpinning the integrated physiological adaptations to exercise, and dietary manipulation, has been recognized for some time (3). In recent years, there has been a rapid increase in the number of studies examining the effects of these stimuli on gene regulation in skeletal muscle. This review briefly summarizes some of the recent work in this area, with a primary focus on studies in human volunteers.

EXERCISE AND GENE EXPRESSION

The molecular mechanisms responsible for the cellular adaptations to acute and chronic exercise remain to be fully elucidated. Exercise-induced increases in skeletal muscle mRNA levels of a number of genes have been reported including those encoding the immediate early genes c-fos and c-jun (31), the glucose transporter GLUT-4 (Fig. 1, 22, 31), hexokinase II (21,22,31), glycogenin (22), glycogen synthase (31), insulin-signaling intermediates (40), lipoprotein lipase (31,36), heat shock proteins (8), interleukin-6 (30), and various putative regulators of angiogenesis (12,33,34). Because the steady-state skeletal muscle mRNA levels reflect the balance between rates of production and degradation, it is likely that the above-mentioned exercise-induced increases in mRNA are a consequence of transcriptional activation and/or increased mRNA stability. It has been demonstrated that after chronic electrical stimulation of rat skeletal muscle, increased cytochrome c mRNA stability preceded the increase in transcriptional activation (9). On the other hand, using a novel protocol to measure nu-
clear mRNA abundance, Neufer and colleagues (20,31) have demonstrated rapid exercise-induced increases in transcription of a number of genes in human skeletal muscle. Although it has been demonstrated that transcriptional activation can occur during exercise (8,22,32), several studies have observed greater increases in gene expression during the postexercise recovery period (22,31). Furthermore, exercise has been shown to attenuate fasting-induced transcriptional activation in rat skeletal muscle (14). Thus, the dominant transcriptional response to exercise may be present during recovery; however, the increases in gene transcription may be transient, with mRNA levels returning to baseline within 24 h after exercise (26).

It appears that the cellular adaptations to exercise training may be due to the cumulative effects of transient increases in gene transcription after repeated exercise bouts (43). The relative importance of transcriptional (mRNA synthesis) and translational (mRNA stability or translational efficiency) mechanisms for the training-induced increases in skeletal muscle protein abundance remains to be fully elucidated. The effects of repeated bouts of exercise on transcriptional activation have not been widely studied and variable results have been obtained. An attenuated exercise-induced transcriptional activation of certain genes after training has been observed in some studies (34,40). A recent study from our laboratory demonstrated that the expression of genes involved in skeletal muscle fatty acid transport (FAT/CD36) and oxidation (CPT-1) was not altered after a single exercise bout but was increased at rest and after exercise after 9 d of exercise training (38). Similarly, whereas a single exercise bout had no effect on myosin heavy chain (MHC) IIx gene expression, 7 d of exercise training resulted in reduced mRNA levels after the last exercise session (27). It is possible that immediate early genes, and genes encoding growth factors and signaling intermediates, are more responsive to exercise in the untrained state, whereas other genes, such as those encoding metabolic enzymes and transporters, may be more influenced in the trained state. Clearly, the interactive effects of exercise and training status on the skeletal muscle expression of various genes are likely to be complex and further studies are required to determine their functional significance for increased protein synthesis.

It is also important to elucidate the effects of exercise on downstream targets involved in protein synthesis. The important first step in protein synthesis involves an initiation step in which the mRNA transcript is coupled to the ribosomal machinery and several proteins, including the 70-kDa ribosomal protein S6 kinase (p70S6k) and eukaryotic initiation factor (4E-BP1, also known as PHAS-I), are involved. The phosphorylation of p70S6k appears to be specific to the mode of exercise (25). Less information is available on the regulation of protein elongation and termination, or on the role of direct interaction of regulatory factors with mRNA, but these steps represent potential sites of regulation and targets for further study. Readers are directed to a recent review on translational control in skeletal muscle for a more detailed discussion of this topic (37).

Finally, skeletal muscle remodelling with exercise requires activation of protein degradation, the major mechanism being via the ubiquitin-proteasome pathway. Chronic electrical stimulation of rabbit muscle for 28 d markedly increased total proteasome activity of muscle extracts, with increased abundance of the 20S proteasome subunit and two regulatory proteins PA28 and PA700 (29).

**DIET AND GENE EXPRESSION**

Variations in dietary intake of macronutrients are associated with marked changes in substrate availability and oxidation and energy metabolism. For example, significant alterations in substrate oxidation during exercise have been reported after several days on either a high-carbohydrate or high-fat diet (4). Alterations in plasma glucose (39) and fatty acid (7) levels can influence gene transcription and the availability of these substrates, and their effects on gene expression, may be involved in the adaptive response to dietary manipulation. Having said that, we are aware of very few studies that have examined the effects of diet on gene expression in human skeletal muscle. Recently, it was reported that consumption of a high-fat diet increased uncoupling protein-2 and -3 mRNA expression in human skeletal muscle in a fiber-type dependent manner (35). We have observed that the increased fat and decreased carbohydrate oxidation during exercise after dietary manipulation (4) were associated with increased FAT/CD36 gene and protein expression in human skeletal muscle (Cameron-Smith et al., unpublished observations). Hyperinsulinemia has been shown to decrease MHC IIx mRNA in human skeletal muscle (19) but increase gene expression of GLUT-4, glycogen synthase, and the p85 subunit of phosphatidylinositols-3-kinase (23), as well as enhancing p70S6k phosphorylation (11). Ingestion of an amino acid-carbohydrate supplement enhanced muscle protein synthesis after resistance exercise, and this may be partly due to effects on gene expression, as well as the stimulatory effect of leucine and insulin on p70S6k phosphorylation (11). Dietary creatine ingestion, in
combination with resistance exercise, stimulated muscle hypertrophy (13) and increased skeletal muscle GLUT-4 protein expression (28) during recovery from a period of immobilization that resulted in loss of muscle mass. The underlying mechanisms have yet to be elucidated but may involve effects on gene expression and the protein abundance of various myogenic transcription factors (13). Clearly, the effects of diet and potential interactions with exercise on skeletal muscle gene expression are fruitful areas for further work.

TRANSCRIPTIONAL REGULATION

A major challenge is to understand how exercise and diet exert their effects on gene and protein expression in skeletal muscle. In relation to exercise, potential stimuli include stretch and muscle tension, the pattern of motor nerve activity and the resultant calcium transients (6), the energy charge of the cell and substrate availability, oxygen tension, and circulating hormones (43). These are potentially detected by various cellular signaling mechanisms such as the mitogen-activated protein kinase family (1,25), protein kinase C (10), Ca²⁺/calmodulin dependent protein kinase, and the AMP-activated protein kinase, to mention just a few. In relation to this latter kinase, it has been demonstrated that its chronic pharmacological activation is associated with increased mitochondrial (44) and GLUT-4 (16) protein expression in rat skeletal muscle. Indeed, the GLUT-4 promoter region has a binding site for AMP-activated protein kinase (46). Finally, the various transcription factors involved in the activation of gene transcription after exercise and dietary manipulation must be identified and their regulation defined. Putative factors include those involved in mitochondrial biogenesis (17), such as mitochondrial transcription factor A (Tfam) and nuclear respiratory factor-1 (NRF-1), those belonging to the basic-helix-loop-helix family including MyoD, myogenin, myf-5 and MRF-4, peroxisome proliferator-activated receptors-α and -γ (PPAR-α and PPAR-γ; 18), coactivator of PPAR-γ (PGC-1), sterol response element-binding protein (SREBP), and myocyte enhancer factor 2, which has been implicated in downstream calcium signaling (45) and regulation of GLUT-4 expression (24). There are likely to be many more, all subject to complex regulation determined by factors including the mode, intensity, and duration of exercise and nutrient availability.

REFERENCES


