INTRODUCTION

The capacity of human skeletal muscle to adapt to repeated bouts of physical activity over time so that exercise capacity is improved is termed physical training. For the competitive endurance athlete, the goal of such training is to increase the ability to sustain the highest average power output or speed of movement for a given distance or time. This, in turn, depends on the rate and efficiency at which chemical energy can be converted into mechanical energy for skeletal muscle contraction. Therefore, training for enhancement of endurance performance should aim to induce multiple physiological and metabolic adaptations that enable an individual to: (i) increase the rate of energy production from both aerobic and oxygen-independent pathways; (ii) maintain tighter metabolic control (i.e. match ATP production with ATP hydrolysis); (iii) minimize cellular disturbances; (iv) increase economy of motion; and (v) improve the resistance of the working muscles to fatigue during exercise.

This brief review summarizes some of the major molecular and cellular adaptations that occur in skeletal muscle as a result of prolonged, intense endurance training: such adaptations are likely to exert a major influence on the performance capacity of highly trained athletes.

SUMMARY

1. Endurance exercise induces a variety of metabolic and morphological responses/adaptations in skeletal muscle that function to minimize cellular disturbances during subsequent training sessions.
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   - The key components of a training programme are the volume (duration, intensity and frequency of exercise sessions. The sum of these inputs can be termed the training stimulus or training impulse that either enhance (fitness) or decrease (fatigue) performance capacity. Modifications in muscle cells that persist for extended periods as a consequence of training are termed ‘chronic’ exercise adaptations, whereas cellular alterations that occur in response to a single training session are said to be ‘acute’ responses. Although chronic adaptations in skeletal muscle are likely to be the result of the cumulative effect of repeated bouts of exercise, the initial signalling responses that lead to these chronic adaptations are likely to occur after each training session.

2. Chronic adaptations in skeletal muscle are likely to be the result of the cumulative effect of repeated bouts of exercise, with the initial signalling responses leading to such adaptations occurring after each training session.
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3. Recently, activation of the mitogen-activated protein kinase signalling cascade has been proposed as a possible mechanism involved in the regulation of many of the exercise-induced adaptations in skeletal muscle.
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4. The protein targets of AMP-activated protein kinase also appear to be involved in both the regulation of acute metabolic responses and chronic adaptations to exercise.
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5. Endurance training is associated with an increase in the activities of key enzymes of the mitochondrial electron transport chain and a concomitant increase in mitochondrial protein concentration. These morphological changes, along with increased capillary supply, result in a shift in trained muscle to a greater reliance on fat as a fuel with a concomitant reduction in glycolytic flux and tighter control of acid–base status. Taken collectively, these adaptations result in an enhanced performance capacity.
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Key words: AMP-activated protein kinase, carbohydrate, fat, mitogen-activated protein kinase.
activity (i.e. cytochrome c) to those observed after more prolonged, submaximal exercise training. However, from a performance perspective, an increase in training intensity may result in a change in the pattern of muscle recruitment from predominantly slow twitch (type I) oxidative fibres to fast twitch (type II) glycolytic fibres. Accordingly, while more intense training may elicit similar mitochondrial concentrations per g whole muscle, there may be a loss of adaptation in the type I fibres and a resultant decline in endurance performance capacity.

With regard to the exercise stimulus/impulse, training responses/adaptations are highly specific to the type, frequency and duration of exercise performed and to the corresponding patterns of muscle recruitment. For example, increases in mitochondrial density and oxidative enzyme activity are greatest in the muscles engaged directly in training, with little or no adaptation in untrained limbs. This implies that the signal for mitochondrial adaptation is local rather than systemic.

**ACUTE RESPONSES OF SKELETAL MUSCLE TO EXERCISE**

**The mitogen-activated protein kinase signalling pathway**

Several possible mechanisms could potentially mediate the training-induced adaptation in skeletal muscle. These include: (i) increased blood flow leading to increased delivery of hormonal factors to muscle and activation of receptor-mediated signalling; (ii) the release of autocrine and paracrine factors from muscle that would stimulate cell surface receptors and activate signalling cascades; and (iii) muscle contraction (concentric or eccentric) per se. In turn, many interdependent factors (both local and systemic) may elicit signal transduction in skeletal muscle, including (but not limited to) energy depletion (ATP, glycogen), increased muscle lactate concentration, decreased muscle (and blood) pH and impaired oxygen flux. Because exercise induces numerous metabolic and morphological responses/adaptations (discussed subsequently), it is highly likely that such responses would depend on the integration of multiple local/systemic factors rather than a single mechanism. Although the major disruptions to cellular homeostasis occur during a training bout, the time-course responses of several signalling pathways during recovery from exercise are likely to be of major significance for the activation of many of the stress-activated protein kinases and upregulation of gene transcription. These postexercise events may ultimately be the stimulus for the chronic intracellular adaptations.

Recently, activation of the mitogen-activated protein kinase (MAPK) signalling cascade has been proposed as a possible mechanism involved in the regulation of many of the exercise-induced adaptations in skeletal muscle. Important MAPK are the extracellular signal-regulated kinases 1 and 2 (ERK 1/2) and p38 MAPK. These kinases are general mediators of the stress response to exercise and may be intracellular messengers linking muscle activity to adaptation. In addition to cytoplasmic proteins, which are activated by exercise and undergo subsequent translocation to the nucleus, nuclear proteins can also be phosphorylated by MAPK.

In human skeletal muscle, moderate-intensity (70–75% of maximal O2 uptake; VO2max) cycling increases ERK 1/2 phosphorylation, with the greatest effect observed after approximately 30 min of exercise. The exercise-induced MAPK phosphorylation declines rapidly when exercise is terminated, such that it is restored to pre-exercise levels after 1 h. The ERK 1/2 phosphorylation is only observed in the exercised muscle, indicating that local rather than systemic factors mediate this effect. Recently, Widgren et al. reported that exercise effects on MAPK signalling were intensity dependent, with ERK 1/2 phosphorylation greater in high- versus low-intensity cycling. In contrast with ERK 1/2 phosphorylation, p38 MAPK phosphorylation is mediated by both local and systemic factors, with the magnitude of the exercise-induced increase being less than observed for ERK 1/2. Thus, exercise seems to favour ERK 1/2 over p38 signalling.

Recently, the first evidence that chronic exercise training may be associated with differential protein expression of the MAPK pathways was reported by Yu et al. These workers obtained resting muscle samples from untrained and moderately trained humans and found that expression of total ERK 1/2 was 90% greater in muscle from trained subjects. In contrast, p38 MAPK expression was 32% higher in untrained individuals. These data suggest that at least some of the training-induced responses of skeletal muscle may be mediated by MAPK activation. Because an acute bout of exercise induces transient increases in skeletal muscle gene transcription, even in highly trained athletes with a prolonged history of endurance training, the activation of various signalling pathways in response to exercise would appear to be central to the upregulation of a variety of metabolic and mitogenic responses that are likely to induce the adaptations seen in skeletal muscle after repeated bouts of exercise.

**The AMP-activated protein kinase pathway**

In addition to MAPK cascades, AMP-activated protein kinase (AMPK) has recently been identified as a candidate signal transducer involved in transcriptional regulation by repressing genes involved in the glucose-signalling system in hepatocytes and upregulating genes involved in glucose uptake and substrate metabolism in skeletal muscle. AMPK is activated by cellular stress associated with ATP depletion and appears to be designed to monitor the energy charge of the muscle fibre and to initiate responses that prevent high-energy phosphate depletion. Low- to moderate-intensity aerobic exercise (≤ 70% of VO2max) induces an isoform-specific and intensity dependent increase in AMPKα2 but not AMPKα1 activity in moderately trained subjects. Conversely, activity of both AMPKα1 and α2 is increased in response to a 30 s ‘all-out’ sprint requiring power outputs two- to threefold greater than attained during maximal aerobic exercise. The protein targets of AMPK appear to be involved in both the regulation of acute metabolic responses and chronic adaptation to exercise. AMPK may play a role in the acute postexercise increase in GLUT-4 translocation, whereas increases in mitochondrial oxidative enzyme activity have been hypothesized to be due, in part, to chronic activation of AMPK.

**CHRONIC RESPONSES OF SKELETAL MUSCLE TO EXERCISE**

**Morphological**

During recent years, it has been popular to determine the muscle fibre composition of elite athletes in different types of events. The most interesting findings are that sprint-trained athletes have a...
marked predominance of type II fibres in their leg muscles and endurance-trained athletes have a high proportion of type I fibres. Because type I fibres possess a higher capillary density and oxidative potential than type II fibres, it is not surprising to find that a high proportion of type I fibres in the vastus lateralis muscle is associated with a lower submaximal oxygen cost (i.e. a greater gross efficiency) during exercise, possibly because of a lower ATP turnover during contraction shortening. Furthermore, the energy cost per unit force per cross-sectional area is greater in type II than type I muscle.

Cross-sectional data reveal that the number of type I fibres in the trained musculature is related to the numbers of years of prior endurance training. This would imply that either those individuals who have a predominance of type I fibres advance into elite endurance sport via a ‘natural selection’ process or that there is a training-induced interconversion between the fibre types. While there is evidence to suggest that there is a change in the ratio of type Ia to type Ib fibres with endurance training, there are no longitudinal data to support type II to type I interconversion in already well-trained endurance athletes. Such studies are warranted because small improvements in gross mechanical efficiency have the potential to result in large enhancements in performance power output.

In athletes of both genders, endurance training increases the capillary supply to skeletal muscle. Furthermore, in individuals with a range of aerobic powers there is a close correlation between VO$_{2max}$ and the mean number of capillaries per fibre in the trained musculature. Accordingly, in highly trained muscle, diffusion distances for substrates and gas exchange are reduced.

Endurance training is also associated with an increase in the activities of the enzymes of the mitochondrial electron transport chain and a concomitant increase in mitochondrial protein concentration. While there is a minimum duration of daily training required to increase mitochondrial density, there is a threshold at which further increments in duration or frequency of training will not induce further adaptation. This threshold volume is not currently known for humans, but is likely to be close to the upper limits of endurance training currently undertaken by elite endurance athletes. In contrast with the impressive training-induced increases in aerobic enzymes, endurance training results in a decreased glycolytic flux in skeletal muscle that function to minimize cellular disturbances during submaximal standardized exercise compared with untrained individuals. Endurance training reduces the production, uptake and oxidation of plasma glucose during both moderate and intense exercise. The decreased carbohydrate utilization during submaximal exercise in the trained state is compensated for by a proportional increase in fat oxidation, reflected by a lower respiratory control sensitivity that results from increased mitochondrial density.

The training-induced shift in substrate selection at the same absolute power output or speed has been attributed to the improved respiratory control sensitivity that results from increased mitochondrial density. However, this phenomenon can only partially explain the glycogen ‘sparing’ effect of endurance training. For example, Coyle et al. reported that, in well-trained cyclists with similar (high) VO$_{2max}$ values (66–68 mL/kg per min), mitochondrial enzyme activity and capillary density, the utilization of muscle glycogen during 30 min of cycling at 79% of VO$_{2max}$ was twofold higher (65 vs 28 mmol/kg) in those individuals with a high power output at lactate threshold. Similarly, Westgarth-Taylor et al. have reported that 3 weeks of intensified training in already well-trained cyclists significantly decreased rates of carbohydrate oxidation over a range of exercise intensities (60–80% of VO$_{2max}$) despite no changes in muscle oxidative capacity. Thus, although the early training-induced shifts in substrate selection (from carbohydrate to fat) are likely caused by improved muscle respiratory capacity, other factors must be important for the subsequent shifts in the patterns of fuel metabolism seen after a period of intensified training in already well-trained individuals. Such factors could include a greater supply of fat due to an increase in intramuscular triglyceride concentration and/or morphological adaptations, such as a greater recruitment of active muscle mass. Whatever the precise mechanism, the training-induced shift in substrate selection by working muscles plays a major role in the increases in endurance capacity that occur after training.

**Acid–base status**

An individual’s maximal sustainable power output or speed is highly related to their lactate threshold. Accordingly, the rate of lactate disposal or disappearance must be greater than or equal to its rate of appearance or production for steady state blood/plasma lactate concentrations to prevail. In this regard, the capacity to transport lactate across the sarcolemma is significantly higher in endurance-trained athletes compared with untrained individuals. Furthermore, the highest lactate transporter values are observed in those endurance athletes who incorporate high-intensity anaerobic workouts into their training regimen. Such workouts undertaken twice a week for as little as 3 weeks have been reported to increase muscle buffering capacity in already well-trained athletes. These results strongly suggest that a large volume of endurance training alone may be insufficient stimulus to improve the ability to transport lactate and may explain why a short-term (3 week) supramaximal training programme (six sessions of $12 \times 30 \text{ s}$ work bouts at 650 W) was just as effective at improving 40 km cycle time (lasting approximately 1 h) as longer aerobic interval sets.

Finally, individuals with a high proportion of type I fibres in their active musculature have higher monocarboxylate transporters (MCT), particularly the isofrom MCT1, than untrained individuals. Because a muscle with predominantly type II fibres has approximately 50% of the lactate transport capacity compared with a muscle composed mainly of type I fibres and because endurance athletes have a predominance of type I fibres, the functional significance of these membrane-bound transporters for prolonged, intense submaximal endurance performance is obvious.

**CONCLUSIONS**

Regularly performed endurance training induces a variety of metabolic and morphological responses/adaptations in skeletal muscle that function to minimize cellular disturbances during subsequent training sessions. Chronic adaptations in skeletal muscle are likely to be the result of the cumulative effect of repeated bouts
of exercise, with the initial signalling responses leading to such adaptations occurring after each training session. The activation of several MAPK signalling cascades act as signalling mechanisms involved in the regulation of exercise-induced adaptations in skeletal muscle. The protein targets of AMPK also appear to be involved in the regulation of both the acute metabolic response to exercise and chronic adaptations to prolonged training. Endurance training is associated with an increase in the activities of key enzymes of the mitochondrial electron transport chain and a concomitant increase in mitochondrial protein concentration. These morphological changes, along with increased capillary supply, result in a shift in trained muscle to a greater reliance on fat as a fuel with a concomitant reduction in glycolytic flux and tighter control of acid-base status. Taken collectively, these adaptations result in an enhanced performance capacity.

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REFERENCES