

Adaptations of skeletal muscle to endurance exercise and their metabolic consequences

HOLLOSZY, JOHN O., AND EDWARD F. COYLE. *Adaptations of skeletal muscle to endurance exercise and their metabolic consequences*. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 56(4): 831–838, 1984.—Regularly performed endurance exercise induces major adaptations in skeletal muscle. These include increases in the mitochondrial content and respiratory capacity of the muscle fibers. As a consequence of the increase in mitochondria, exercise of the same intensity results in a disturbance in homeostasis that is smaller in trained than in untrained muscles. The major metabolic consequences of the adaptations of muscle to endurance exercise are a slower utilization of muscle glycogen and blood glucose, a greater reliance on fat oxidation, and less lactate production during exercise of a given intensity. These adaptations play an important role in the large increase in the ability to perform prolonged strenuous exercise that occurs in response to endurance exercise training.

lactate; mitochondria; oxygen uptake; substrate utilization

SEDENTARY INDIVIDUALS can markedly increase their endurance by means of regularly performed exercise. After a few weeks of endurance training, such as long-distance running, it is often possible for individuals to exercise comfortably for prolonged periods at exercise intensities that they could maintain for only a few minutes prior to training. For many years it was thought that this increase in the capacity for endurance exercise was exclusively the result of the cardiovascular adaptations to endurance training which, by increasing the capacity to deliver O_2 to the working muscles, are primarily responsible for the large increase in maximal O_2 uptake capacity ($\dot{V}O_{2\max}$) that can occur in response to training.

Central to this concept was the belief that the working muscles become hypoxic during exercise of relatively moderate intensity and that, as a result of improved O_2 delivery, the same exercise results in less hypoxia after training. The major evidence cited in support of this belief, which still persists in the “anaerobic threshold” concept (57), was that lactate concentration increases during submaximal exercise and that this increase is less after training. This interpretation was based on the assumption that because lactate is the end product of what has been termed “anaerobic glycolysis,” lactate appearance must reflect an O_2 deficiency. This is a misconception. Lactate formation will occur when NADH and pyruvate are available to lactate dehydrogenase regardless of how much O_2 is present.

O_2 consumption ($\dot{V}O_2$) at the same “submaximal” work rate (the term submaximal exercise is used in this review

to mean exercise that requires less than $\dot{V}O_{2\max}$) is the same in the trained and untrained states (22, 27). If muscles were hypoxic during exercise requiring 50–70% of $\dot{V}O_{2\max}$ in the untrained state and if the lower lactate production and improved endurance at the same absolute work rates after training were due to improved O_2 delivery, it would seem reasonable that aerobic metabolism, as reflected in $\dot{V}O_2$, should be higher at the same work rate after training. Because this is not the case, it seemed probable that the lower lactate production and increased endurance in the trained state might in large part be due to metabolic consequences of biochemical adaptations in the muscles rather than to improved delivery of O_2 . This line of reasoning led to the research in this laboratory on the adaptations of skeletal muscle to endurance exercise.

Mitochondrial Adaptations to Endurance Exercise in Skeletal Muscle

The first study to show that endurance exercise training induces an increase in the mitochondrial content of skeletal muscle was performed on young rats trained by means of treadmill running 5 days/wk (29). To induce a progressive training effect, running speed and duration were gradually increased until after 3 mo the rats were running for 120 min/day up an 8° incline at 31 m/min with 12 intervals at 42 m/min lasting 30 s interspersed at 10-min intervals through the exercise session. This program resulted in a major training effect as evidenced by a large increase in endurance.

The run time to exhaustion for the trained group averaged 186 ± 18 min compared with 29 ± 3 min for control rats that had been maintained on a program of 10 min of running 5 days/wk (29). Similar increases in endurance have been found in subsequent studies on rats adapted to comparable training programs (10, 16, 17). This large difference in endurance illustrates the simple but important point that in order for major adaptations to occur the training stimulus must be progressively increased until it exceeds the capacity for endurance exercise in the untrained state. If a training program is well within the capacity of the untrained organism it cannot be expected to provide a major adaptive stimulus. Lack of an adequate training stimulus is why earlier studies that employed mild exercise, and did not increase training intensity or duration, failed to show adaptive changes in muscle (cf. Ref. 29).

Evidence for an increase in muscle mitochondria. The capacity of the mitochondrial fraction from gastrocnemius muscle to oxidize pyruvate doubled in rats that had adapted to the 2-h/day running program (29). Succinate dehydrogenase, NADH dehydrogenase, NADH-cytochrome *c* reductase, and cytochrome oxidase activities per gram muscle increased approximately twofold in hindlimb muscles in response to the training. Cytochrome *c* concentration was also increased twofold, providing evidence that the increases in respiratory chain enzyme activities were due to an increase in mitochondrial enzyme protein. The total protein content of the mitochondrial fraction increased ~60%. Mitochondria from muscles of the trained animals exhibited a high level of respiratory control and tightly coupled oxidative phosphorylation, providing evidence that the increase in electron transport capacity was associated with a concomitant rise in the capacity to generate ATP via oxidative phosphorylation (29).

This finding of an increase in respiratory capacity and mitochondrial enzyme levels in muscle in response to endurance training was soon confirmed by other investigators (4, 20, 47). Of particular importance was the study of Morgan and co-workers (47), who showed that human skeletal muscle also undergoes an adaptive increase in mitochondrial respiratory enzyme levels and the ability to oxidize pyruvate in response to endurance training. Electron-microscopic studies by Gollnick and King (21) with rats and by Morgan et al. (47) and Hoppeler et al. (36) with humans have shown that increases in both size and number of mitochondria are responsible for this increase in the mitochondrial content of muscle.

Mitochondrial enzyme adaptations to exercise. Subsequent studies using isolated mitochondria and whole muscle homogenates showed that rat skeletal muscle undergoes adaptive increases in the capacities to oxidize fatty acids (2, 46) and ketones (58) in addition to pyruvate (2). Underlying these increases in respiratory capacity are increases in the levels of the enzymes responsible for the activation, transport, and β -oxidation of long-chain fatty acids (2, 46), the enzymes involved in ketone oxidation (58), the enzymes of the citric acid cycle (33), the components of the respiratory chain involved in oxidation of NADH and succinate (29, 33), and mito-

chondrial coupling factor 1 (49). Increased levels of marker enzymes of the pathway for fatty acid oxidation (6, 8, 39, 48, 54), the citrate cycle (6, 48, 54), and the respiratory chain (8, 18, 39, 47) have also been demonstrated in muscles of endurance-trained people.

Mitochondrial composition. Skeletal muscle mitochondria undergo an alteration in composition in response to endurance training, with some enzymes increasing two- to threefold, others increasing 30–60%, and some not increasing at all (cf. Ref. 30). The enzymes that do not increase include mitochondrial creatine kinase and adenylate kinase (49) and mitochondrial α -glycerophosphate dehydrogenase (32, 48). The absence of an increase in α -glycerophosphate dehydrogenase, and therefore in the capacity of the α -glycerophosphate shuttle, is of considerable interest, as the ability of muscles to oxidize α -glycerophosphate parallels their glycolytic capacity and is inversely related to respiratory capacity (cf. Ref. 30). As a consequence of the increase in mitochondrial protein, the specific activities of mitochondrial creatine kinase, adenylate kinase, and α -glycerophosphate dehydrogenase expressed per milligram protein decrease, making skeletal muscle mitochondria more like heart mitochondria in their enzyme pattern (cf. Ref. 30).

Malate-aspartate shuttle. Normal mitochondria are impermeable to NADH. The major pathways for transferring the reducing equivalents from cytoplasmic NADH formed during glycolysis into the mitochondria in muscle are the α -glycerophosphate and the malate-aspartate shuttles (cf. Ref. 31). In contrast to α -glycerophosphate dehydrogenase, which does not increase (32, 48), large increases occur in the enzymes of the malate-aspartate shuttle in both the mitochondria and cytoplasm in muscle in response to training (31).

Muscle fiber types. Detailed studies of the enzymatic adaptations of the different skeletal muscle fiber types in rodents have provided some insights regarding the plasticity of mitochondrial composition. However, although the mitochondrial enzyme adaptations in mixed muscles follow the same general pattern and have similar physiological consequences in rodents and humans, it has become evident that information from detailed studies of the different fiber types in rodents is not directly applicable to humans. In the rat the capacity to oxidize pyruvate and fatty acids and the levels of the majority of mitochondrial enzymes [except those involved in ketone metabolism (58)] are roughly twice as high in the fast-twitch red fibers as in the slow-twitch red fibers, and four to eight times as great in fast-twitch red fibers as in the fast-twitch white fibers (30, 31). In contrast, in humans it is the slow-twitch red (type I) fibers that have the highest content of mitochondria, with mitochondrial enzyme levels approximately twice as high as in the fast-twitch (type II) fibers in untrained individuals (6, 13, 45). Furthermore, the difference between the fast-twitch red (type IIa) and fast-twitch white fibers (type IIb) is very much smaller in humans than in rats. Although it is convenient to classify the muscle fibers into three, or in the case of humans sometimes two, types, it must be realized that there is a wide spectrum of enzyme activities in fibers classified as belonging to the same type in muscles of the same individual (45).

Although the majority of people have roughly 50% type I and 50% type II fibers, competitive endurance athletes tend to have a higher percentage of type I fibers, while sprinters have a high percentage of type II fibers (19). These differences appear to be the result of selection for different types of athletic ability, i.e., a high percentage of slow-twitch fibers may confer an advantage for endurance activities, rather than a training phenomenon. There is no evidence that fast-twitch (type II) fibers can be converted to slow-twitch (type I) fibers, or vice versa, by means of normal exercise training.

In rats, endurance training programs such as the treadmill running protocol used in this laboratory do not appear to result in a conversion of fast-twitch white into fast-twitch red fibers, as the large (4- to 8-fold) differences in mitochondrial enzyme activities between these fiber types are still present in the trained state (2, 58). In contrast, in men who have adapted to strenuous endurance training it is often impossible to detect type IIb fibers, and it appears that there may be a complete conversion of type IIb to type IIa fibers in response to endurance training (6, 39). Furthermore, the mitochondrial content of the type II fibers tends to increase to a greater extent than that of type I fibers in response to very strenuous endurance training, so that the difference in mitochondrial enzyme levels between type I and II fibers is largely, or even completely, eliminated in highly trained individuals (6, 39).

Time course of decrease in mitochondrial enzymes after cessation of training. The effect of stopping training on mitochondrial enzymes in muscle has been studied in detail in rats (5). A number of mitochondrial marker enzymes increased approximately twofold in leg muscles in response to a 15-wk-long program of treadmill running. After training was stopped the concentration of cytochrome *c* and the levels of activity of citrate synthase and 3-ketoacid CoA-transferase decreased exponentially toward sedentary control values with a half life of about 7 days were back to base line between 28 and 35 days.

The decrease in mitochondrial enzyme levels after cessation of exercise has also been studied in humans (6, 25, 41). In individuals who have trained for only 8–12 wk, the increase in mitochondrial enzyme levels appears to be reversed within 6–8 wk after cessation of exercise (25, 41). The basis for this somewhat slower reversal in humans than in rats is unknown; it could be due to either a longer half-life of mitochondrial enzymes in human than in rat skeletal muscle or a more severe restriction of activity in rats housed in individual cages than in people going about their normal daily activities.

In contrast to the rapid loss (6–8 wk) of the mitochondrial adaptations in muscles of individuals who have trained for only 2–3 mo, people who have been training hard for many years appear to have a more persistent increase in mitochondria. In a study on the effects of cessation of training in subjects who had been training for 6–20 yr, citrate synthase, β -hydroxyacyl-CoA dehydrogenase, and malate dehydrogenase declined significantly over a 12-wk period but were still about 40% above control values in mixed muscle (6). Single muscle fiber analyses revealed that this persistent elevation of mitochondrial enzyme levels above control values was much

more marked in the fast-twitch (type II) fibers than in the slow-twitch (type I) fibers after 12 wk of inactivity (6). This finding suggests the possibility that many years of endurance training may result in long-lasting adaptations, such as changes in the firing frequency of the nerves innervating the type II fibers or in the recruitment pattern of these fibers.

Mechanisms responsible for increase in muscle mitochondria. The increase in muscle mitochondria with endurance training appears to be mediated by contractile activity per se rather than by exogenous stimuli such as alterations in hormonal milieu. This is evidenced by the observation that the mitochondrial adaptations are limited to the muscle fibers that are recruited to contract. For example, in runners and cyclists the increase in mitochondria is limited to the muscles of the lower extremities (19); when only one lower extremity is trained, the adaptations are limited to the exercised leg (24, 47, 53). It has also been shown that an adaptive increase in muscle mitochondria can be induced by exercise despite the absence of thyroid and/or pituitary hormones (20) and that administration of large doses of epinephrine does not induce an increase in mitochondria in sedentary rats (15).

Because the type II fibers are generally recruited only during strenuous exercise, interval training appears to be necessary to induce a large increase in their mitochondrial content. Within limits, the magnitude of the increase in mitochondria appears to be a function of the total amount of contractile activity, which can be increased either by performing more contractions in a given time period or by maintaining the same frequency of contraction for a longer period of time (11, 16, 23).

Little is known regarding the series of events initiated by repeated muscle contraction that lead to the increase in muscle mitochondria. Available evidence indicates that increased synthesis, rather than decreased degradation, is primarily responsible for the increase in mitochondrial proteins (5). The first enzymatic adaptation to occur in response to exercise appears to be an increase in δ -aminolevulinic acid synthase, which occurs within 17 h after a single bout of exercise (35). δ -Aminolevulinic acid synthase is the rate-limiting enzyme in heme synthesis, and it has been hypothesized that this enzyme plays a key role in the increase in mitochondrial enzymes in response to endurance exercise (35).

Glycolytic enzymes. Endurance training appears to result in rather minor changes in glycolytic enzyme activities in skeletal muscle (3, 19, 47, 54). The only important adaptations appear to be an increase in hexokinase activity (3, 43, 47) and a decrease, in some individuals, in total lactate dehydrogenase activity (6, 55) with an increase in the proportion of the heart-specific isozyme and a decrease in the skeletal muscle-specific isozyme of lactate dehydrogenase (55).

Physiological Consequences of Biochemical Adaptations of Skeletal Muscle to Endurance Exercise Training

When previously sedentary individuals adapt to endurance training, $\dot{V}O_{2\text{ max}}$ increases and endurance at

exercise intensities requiring less than $\dot{V}O_{2\max}$ is improved. There is considerable interest regarding the roles that the biochemical adaptations in muscle may play in determining $\dot{V}O_{2\max}$ and endurance.

Maximum O_2 uptake. The factors that determine $\dot{V}O_{2\max}$ have not been completely elucidated. However, it seems clear that the great capacity of their cardiovascular system to deliver O_2 to the muscles (12), rather than their elevated muscle respiratory capacity, is the primary factor responsible for the extremely high $\dot{V}O_{2\max}$ in elite endurance athletes.

Individuals who perform strenuous endurance training for 1 h/day or more over prolonged periods of time can have very similar elevations in skeletal muscle mitochondrial content but markedly different $\dot{V}O_{2\max}$ capacities (Fig. 1). Conversely, muscle mitochondrial enzyme levels can differ as much as twofold among elite middle and long distance runners with similar, extremely high $\dot{V}O_{2\max}$ values (9). Furthermore, a number of studies have provided evidence that small changes in muscle respiratory capacity can occur without a change in $\dot{V}O_{2\max}$, and vice versa, during periods of training and detraining (25, 41, 48).

Questions that remain to be answered are 1) does increased muscle mitochondrial content play a permissive role in individuals with a high $\dot{V}O_{2\max}$, i.e., is it possible to have a very high $\dot{V}O_{2\max}$ without a marked elevation in muscle mitochondrial content? and 2) does the increase in muscle mitochondria play a role in making possible the greater extraction of O_2 from the blood by the working muscles and thus contribute to the increase in $\dot{V}O_{2\max}$ in response to training? With regard to the first question, it is of interest that the lowest value for succinate dehydrogenase activity in gastrocnemius muscles of the elite runners studied by Costill et al. (9) was approximately 2.5-fold greater than the value found in untrained individuals in the same study. Relative to the second question, a number of investigators have reported that the adaptive increase in $\dot{V}O_{2\max}$ in response to endurance training is partly accounted for by an increase in arteriovenous O_2 difference (cf. Refs. 12, 30).

Response to exercise that requires less than $\dot{V}O_{2\max}$. While there seems little doubt that increased O_2 delivery is the major factor responsible for large increases in maximum aerobic power induced by strenuous prolonged endurance training, it seems unlikely that improved O_2 delivery is responsible for the increased endurance and lower muscle and blood lactate levels seen at the same absolute exercise intensity after training. If, as was once thought, the working muscles were hypoxic because of inadequate O_2 delivery during submaximal exercise that results in lactate production and if O_2 supply was improved by training, $\dot{V}O_2$ at a given submaximal work rate should be higher after training. However, it is well documented that $\dot{V}O_2$ at a given submaximal work rate is not increased by training (22, 27, 40). Furthermore, blood flow to the working muscles is either unchanged or decreased (cf. Ref. 30) at the same submaximal exercise intensity after training.

Endurance training results in marked alterations in the metabolic response to exercise that requires less than $\dot{V}O_{2\max}$. These include smaller increases in muscle and

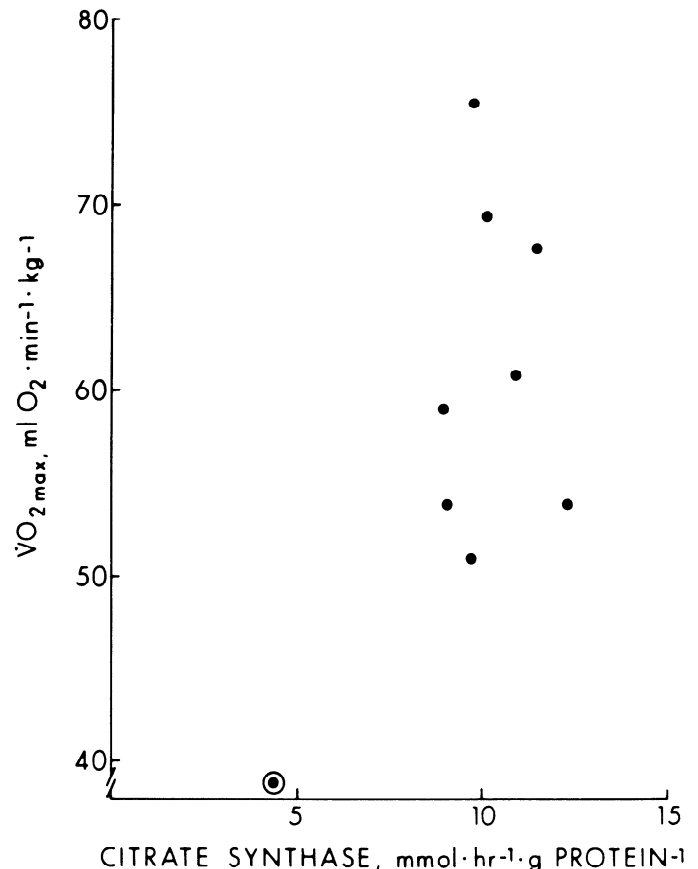


FIG. 1. Relationship between citrate synthase activity in gastrocnemius (runners) or quadriceps (cyclists) muscle and maximum O_2 uptake ($\dot{V}O_{2\max}$). Individual values are given for 8 highly trained people (●), and the average value is given for 8 untrained individuals (○). Data are from Ref. 6 and unpublished results.

blood lactate concentrations, a slower utilization of carbohydrate, and an increased reliance on fat oxidation as a source of energy. It seems probable that these interrelated metabolic adaptations to endurance training are largely responsible for the increased endurance in the trained state.

Lower lactate levels. The same relative exercise intensity (i.e., the same percent of $\dot{V}O_{2\max}$) results in a smaller increase in blood lactate concentration, and a considerably higher relative work rate is required to attain a given lactate level in the 1.5–4 mM range in the well-trained than in the untrained state (37). It has long been suspected that lactate accumulation plays a role in the development of fatigue. Although the mechanism by which such an effect may be mediated remains elusive, it does seem clear from a number of studies that there is good correlation between endurance performance and the exercise intensity required to elicit a given lactate concentration in the 1.5–4 mM range (14, 42, 56). In this context the adaptations to endurance training that are responsible for the lower lactate production during exercise may play a major role in accounting for 1) the greater endurance at the same relative exercise intensity in the trained compared with the untrained state (cf. Ref. 1) and 2) the ability of highly trained individuals to exercise at a higher relative exercise intensity for a given time period (in the activity in which they are trained)

than untrained individuals.

Karlsson et al. (40) have provided evidence that the lower blood lactate concentration during submaximal exercise in the trained state is secondary to a lower lactate concentration in the exercising muscles. Studies in which the subjects trained only one lower extremity have clearly shown that decreased lactate production by the muscles is the primary factor responsible for the lower blood lactate levels during submaximal exercise following endurance training (24, 53). In these studies lactate production by the trained leg was markedly lower even though the training programs used were mild (24, 53).

Glycogen depletion. Studies employing serial muscle biopsies have shown that men deplete their muscle glycogen stores less rapidly during standardized exercise when trained than when untrained (26). Studies on rats have given similar results and in addition have shown that liver glycogen is depleted less rapidly in the trained state (16). In rats at various levels of training (ranging from 10 to 120 min running/day), there was an inverse relationship between the respiratory capacity of the leg muscles and the total amount of glycogen utilized during a bout of exercise (16).

Fat oxidation. The decreased utilization of carbohydrate during submaximal exercise in the trained state is compensated for by a proportional increase in fat oxidation. This is reflected in a lower respiratory exchange ratio (R) at both the same absolute and the same relative exercise intensities when individuals are restudied after adapting to endurance exercise training (cf. Ref. 30). There is evidence that depletion of glycogen stores can play a role in the development of fatigue during prolonged strenuous exercise (cf. Ref. 30). The glycogen-sparing effect of increased fat oxidation probably plays a major role in the increase in endurance that occurs with training.

Some Hypotheses Regarding Mechanisms That Mediate the Altered Metabolic Response to Submaximal Exercise in the Endurance-Trained State

Although we are still a long way from a complete understanding of the mechanisms responsible for the altered metabolic response to exercise of muscles that have adapted to endurance training, sufficient information is available to suggest a number of possibilities. The following section reviews some of the possible mechanisms that we think best explain the slower utilization of carbohydrate, the slower lactate production, and greater utilization of fat during submaximal exercise in the trained state.

When the concentrations of substrate and O_2 are not limiting, the rates of substrate flux through the citrate cycle and the fatty acid oxidation pathway, and the rate of electron transport down the respiratory chain, are determined by the cell's need for energy. During exercise, the major factor determining the energy requirement is, of course, the rate of ATP hydrolysis at the cross bridges formed between actin and myosin in the contracting muscles. The levels, i.e., the total amounts, of the enzymes in these pathways of aerobic metabolism become

limiting only when the energy need of the cell requires a rate of substrate catabolism that exceeds the maximum catalytic ability of the rate-limiting enzymes.

In this context one probable consequence of the adaptive increase in mitochondria is that work rates that exceeded the capacity of some of the muscle fibers for the aerobic generation of energy in the untrained state become "submaximal" for these muscle fibers after prolonged intense training. This is particularly likely to be true for those type II fibers that have the lowest capacity for aerobic metabolism in the untrained state and that may undergo a fourfold or greater increase in mitochondria in response to strenuous endurance training. Exercise intensities that exceeded the respiratory capacity of these type II fibers and resulted in rapid lactate accumulation and fatigue in the untrained state may be well within the capacity of these fibers for aerobic metabolism when they are highly trained. Thus the adaptations to endurance training may make possible prolonged steady-state contractile activity, during which ATP hydrolysis is balanced by ATP resynthesis via oxidative phosphorylation, at work rates that could be maintained for only short bursts by some type II fibers that have a low oxidative capacity when untrained.

When the energy requirement of a given work rate is below a muscle cell's capacity for generating ATP via aerobic metabolism, the rates of substrate oxidation are controlled not by enzyme quantity but by a variety of regulatory mechanisms. The simplest level of regulation involves the concentrations of substrates, products, and cofactors, which determine the rate of flux through each enzymatic step. A second level of control is via regulation of the activities of rate-limiting enzymes, which are influenced by a wide range of activators and inhibitors. The primary factor determining the extent to which rate-limiting enzymes in the pathways of carbohydrate and fat catabolism are activated is the need for energy; i.e., enzyme activity is regulated so that substrate catabolism balances the rate of energy utilization.

In this context it seems probable that the altered metabolic response of trained muscle cells to submaximal exercise is largely mediated by the smaller disturbance in intracellular homeostasis needed to activate substrate catabolism sufficiently to balance a given rate of ATP hydrolysis. With more molecules of each of the mitochondrial respiratory enzymes per gram of muscle, the rate of substrate flux per enzyme molecule must be less at any given rate of energy utilization. As a consequence, substrate, cofactor, and/or activator concentrations must change less in order to achieve a given rate of ATP formation.

Currently available evidence favors the interpretation that the primary factor regulating mitochondrial respiration, when O_2 and substrate availability are not limiting, is the concentration of ADP, rather than the ratio of $[ATP]/[ADP] \times [P_i]$ (where P_i is inorganic phosphate) as was once thought (38). Electron transport is tightly coupled to oxidative phosphorylation of ADP, and this is the mechanism responsible for the close gearing of $\dot{V}O_2$ to the rate of ATP hydrolysis. With the onset of muscle contractile activity, ATP is hydrolyzed, the concentrations of ATP and phosphocreatine decline, and the levels

of ADP and P_i increase progressively, resulting in a progressive increase in respiration. If the ATP requirement of the contractile activity is below the muscle cell's maximal capacity for aerobic metabolism, a steady-state concentration of ADP is attained at which the rate of oxidative phosphorylation balances the rate of ATP hydrolysis (cf. Ref. 30). Concomitantly, ATP and PC concentrations fall, until a steady-state level of respiration is attained, resulting in the muscle " O_2 deficit."

The energy requirement and rate of $\dot{V}O_2$ are the same in the trained and untrained states at the same submaximal work rate. Therefore the increase in ADP concentration required to attain the same rate of O_2 utilization at a given submaximal work rate must be lower in trained muscle with a high mitochondrial content than in untrained muscle with a lower respiratory capacity. The reason for this is that with more respiratory chains per gram muscle, O_2 uptake per respiratory chain must be less in order to maintain a given rate of O_2 utilization per gram muscle. In this context it seems reasonable that at the same submaximal work rate ATP and phosphocreatine concentrations must decrease less (40), and ADP, P_i , and creatine concentrations must increase less in trained than in untrained muscle.

Adenylate kinase activity in muscle results in conversion of some of the ADP formed during muscle contraction to AMP, part of which is deaminated by adenylate deaminase to form IMP and ammonia (44). With a smaller rise in ADP it seems likely that AMP, IMP, and ammonia levels are lower in trained muscle during submaximal exercise; however, no information regarding this point is yet available. The intracellular concentrations of ATP, P_i , AMP, ADP, and ammonia play important roles in controlling the rate of glycolysis. ATP inhibits phosphofructokinase, and this inhibition is countered by P_i , ADP, AMP, and ammonia (cf. Ref. 30). Therefore as a consequence of a higher steady-state concentration of ATP and lower levels of P_i , ADP, and possibly of AMP and ammonia, glycolysis should be activated to a smaller extent at a given work rate in trained than in untrained muscle. This mechanism could play a role in accounting for the slower rates of carbohydrate utilization and of lactate production during submaximal exercise in the trained than in the untrained state.

Additional factors that may contribute to the slower lactate production are the adaptive decrease in total lactate dehydrogenase activity, with a shift in isoenzyme pattern toward the heart-specific form of lactate dehydrogenase (55), and the increase in the capacity of the malate-aspartate shuttle (31) in muscle in response to endurance training. These adaptations should, together with the increase in mitochondria, increase the ability of the mitochondria to compete with lactate dehydrogenase for pyruvate.

The factor that plays the key role in making possible the slower utilization of muscle glycogen and blood glu-

cose during submaximal exercise after training is, of course, the greater oxidation of fat (24, 26, 30, 31). The concentration of plasma free fatty acids (FFA) available to muscle, which plays an extremely important role in determining the rate of FFA utilization during exercise (7, 28, 50), is similar in the trained and untrained states (cf. Ref. 34, 59). However, the intracellular concentration of FFA available to the mitochondria is unknown, and the possibility that the intracellular FFA concentration is different in trained and untrained muscle during submaximal exercise has not been ruled out.

If it is assumed that, like the plasma FFA level, intracellular FFA concentration in muscle is similar in the trained and untrained states, the difference in FFA oxidation must be a consequence of the adaptations induced by exercise. The overall rate of substrate oxidation is determined by the rate of ATP hydrolysis, which is a function of the work rate. However, the relative proportions of carbohydrate and fat oxidized are determined by substrate (i.e., FFA and pyruvate) availability, the relative activities of the rate-limiting enzymes in the pathways for generating acetyl-CoA from carbohydrate and fatty acids, and by a number of regulatory mechanisms. Of these regulatory mechanisms, the most important probably are 1) less activation of glycolysis as a consequence of smaller changes in the levels of the high-energy phosphate compounds and P_i at the same submaximal work rate after muscle has adapted to training with an increase in mitochondria and 2) the inhibitory effects of FFA oxidation on glucose uptake and glycolysis (7, 28, 51, 52). The increases in the levels of the enzymes of the fatty acid oxidation pathway make possible the provision of a larger proportion of the energy required during strenuous exercise by means of fat oxidation, with a proportional reduction in carbohydrate utilization.

In conclusion, endurance exercise training induces a number of adaptations in skeletal muscle. Probably the most important of these is an increase in mitochondria with an increase in respiratory capacity. One consequence of the adaptations induced in muscle by endurance exercise is that the same work rate requires a smaller percentage of the muscles' maximum respiratory capacity and therefore results in less disturbance in homeostasis. A second consequence is increased utilization of fat, with a proportional decrease in carbohydrate utilization, during submaximal exercise. These metabolic consequences of these adaptations of muscle to endurance training could play important roles in 1) the increase in endurance and 2) the ability to exercise at a higher percent of $\dot{V}O_{2\max}$ in the trained state, by slowing glycogen depletion and reducing lactate production (i.e., raising "lactate threshold").

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John O. Holloszy and Edward F. Coyle

Section of Applied Physiology, Department of Medicine

Washington University School of Medicine, St. Louis, Missouri 63110

