REVIEW ARTICLE

Effect of Endurance Training on Muscle Fat Metabolism During Prolonged Exercise: Agreements and Disagreements

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INTRODUCTION

Endogenous triacylglycerols (TGs) represent a major fuel source for skeletal muscle (SM) energy availability during prolonged submaximal exercise. Lipids as fuel for energy conversion originate from fat stored as TG within the adipocytes (mobilized as free fatty acids [FFA]) and from intramuscular triacylglycerols (IMTG). Circulating very low-density lipoproteins rich in TGs (VLDL-TGs; chylomicrons) also serve as an energy source during exercise. Energy from TG is produced at a relatively low rate as compared with carbohydrates (CHOs) even when fully activated. CHOs are necessary to provide energy demands during vigorous exercise requiring energy release above levels supplied by fat metabolism. The capacity of the human body to store CHO is limited. When glycogen stores become depleted, the energy disposal rate from CHO is diminished, and the exercise intensity must be reduced because adenosine triphosphate cannot be generated at a sufficient rate. With these considerations in mind, the advantage of an increased capacity to oxidize fats in working muscles is advantageous. The relative use of lipids and CHOs for energy conversion in exercising muscle depends on a variety of factors (exercise mode, exercise intensity, duration, dietary status, hormonal milieu, type of skeletal muscle cell used, training status, etc.). The complexity of the regulatory mechanism is not fully understood. However, many previous studies have established a marked adaptive response to endurance training by shifting metabolism to a greater use of fat and sparing of limited glycogen stores at the same exercise intensity. These adaptive responses of muscles to endurance training include a number of structural and metabolic adaptations in the SM. The foci of this review paper are on lipid metabolism during prolonged exercise and on the influence of endurance training on these physiologic processes.

EXERCISE-INDUCED CHANGES IN FAT METABOLISM

Mobilization of Fatty Acids From Adipose Tissue

During aerobic exercise, non-esterified fatty acids are released into circulation as a product of TG hydrolysis in the adipose tissue. The rate of lipolysis in the adipose tissue is influenced by a number of factors, the most important being the level of neurohormonal stimulation or inhibition[1–7] and the rate of adipose blood flow.[7–11] During exercise, plasma epinephrine and norepinephrine are elevated several times above resting values.[3,4,6] The modulatory effects of physiologic catecholamines on fat cell function involve various adrenergic receptor subtypes,[12] which are lipolytic through β_1-, β_2-, and β_3-adrenergic receptors and anti-lipolytic through the α_2-adrenergic receptor.[1,7,13–16]

The effect of endurance training on the ability to mobilize endogenous TG is controversial because of conflicting results originating from different investigations. Several investigators have reported that aerobic exercise training increases catecholamine-stimulated lipolysis.[13,15,17–21] This induced sensitization of adipose tissue to catecholamine stimulation has been demonstrated in in vitro studies using isolated adipocytes in nonobese[17–20] and obese[13] human subjects. In in vitro methods, the physiologic value of these techniques has been evaluated differently. There is evidence that lipolysis assay with isolated adipocytes in vitro and microdialysis studies in vivo provide concordant information regarding adipose tissue metabolism in the same individual.[22] Previous studies also have indicated that endurance training increases in vivo lipolytic activity in male obese subjects.[15,21]

The suggestion of an increased lipolytic activity of trained versus untrained individuals has been contradicted by several studies. Horowitz et al.[23] found an unchanged lipolytic sensitivity to epinephrine in vivo after 16 wk of endurance exercise training. They reported that, within the physiologic range of epinephrine levels in vivo, lipolytic response of adipose tissue is similar in trained and untrained persons and that it is only at high epinephrine concentrations ($\geq 10^{-6}$ M) that lipolysis in adipocytes is enhanced through endurance training.[17,20] Stallknecht et al.[9] found that the lipolytic response of abdominal subcutaneous adipose tissue to epinephrine infusion is the same in trained and untrained subjects when using microdialysis probes to measure regional glycerol release in vivo. Sial et al.[24] found no significant change in lipolysis after a 16-wk period of endurance training in elderly subjects.

An assessment of fat mobilization by the FFA rate of appearance (R_a) in plasma has yielded conflicting results. $FFAR_a$ was found to be higher,[25,26] the same,[27,28] and lower[29–31] in trained compared with untrained subjects at the same relative intensity. In in vivo training studies using C-labeled isotopic measures, Turcotte et al.[32] and Kiens et al.[33] found that endurance training enhances the $FFAR_a$ in the blood during prolonged single-leg knee extensor exercise. These findings are contradicted by other data from longitudinal training studies.[29–31,34] Numerous investigators have demonstrated that training results in a reduction of $FFAR_a$ in plasma as a function of larger muscle mass (cycling versus running) involved in exercise.[29–31] These results were attributed to a slower rate of adipose tissue lipolysis in the trained state resulting

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from a reduction in sympathetic nervous activity,[31] thus confirming previous findings.[35–37] Horowitz et al.[34] used the microdialysis technique for direct measurement of lipolysis and found that training increases total fatty acid oxidation but does not alter regional abdominal and femoral subcutaneous adipose tissue R_as (determined via microdialysis) and whole-body palmitate R_a.

When analyzing and comparing the literature findings, it is difficult to ascertain the degree to which endurance training enhances lipolysis from adipose tissue during exercise and when lipolysis might even be reduced if the exercise involves a large muscle mass. Further longitudinal training studies combining in vivo microdialysis technique (which allows measurement of extracellular concentrations of various substances that diffuse from the interstitium of adipose tissue in different anatomic locations) with other recent techniques (tracer technology, dual-energy x-ray absorptiometry, measurement of adrenergic receptor subtypes, measurement of hormonal and enzymatic responses to training, measurement of sympathetic nerve activity, and measurement of local blood flow) may clarify the different research results cited in the literature. The peroxisome proliferator-activated receptors (isotypes α, β, and γ: NR1C1, NR1C2, and NR1C3) seem to play an important role in systemic lipid use. Their functions involve control systems that are sensitive to stimuli such as available nutrients, physical activity, stress, light, and temperature. Undoubtedly, studies of these peroxisome proliferator-activated receptors will offer new insights to the network of the catabolic and anabolic aspects of lipid metabolism during exercise.

From a review of the literature, it seems unlikely that lipolysis is the limiting step of fat oxidation during exercise because various studies have suggested that $FFAR_a$ during exercise exceeds the rate of whole-body fat oxidation.[26,30–33]

Plasma Fatty Acid Uptake Into the Plasma Myocytes

The transmembrane long-chain fatty acid (LCFA) transport into plasma myocytes often has been suggested to be involved in determining the rate of overall fatty acid oxidation during exercise. This notion was supported by the finding of fatty acid saturation uptake in the SM during exercise at relatively high plasma fatty acid concentrations,[38] which was more evident in untrained than in trained muscles.[33]

In the past it was postulated that the entry of LCFA across the plasma membrane of myocytes was regulated via simple diffusion. This view is no longer tenable considering the recent reports in the literature. There is evidence supporting the existence of an LCFA protein-mediated process, suggesting that a significant part of LCFA uptake during exercise occurs via plasma membrane-associated proteins.[39–44] Recent research interest has focused on the transport proteins fatty acid translocase identified as the rat homolog of human glycoprotein CD36 (FAT/C36), fatty acid transport protein (especially the isoform FATP1), plasma membrane-bound fatty acid-binding protein (FABPpm), and FACS1, an isoform of fatty acid acetyl CoA synthetase (FACS). Previous investigations have been conducted mostly on rat muscles. However, most of the transport protein transcripts are also present in human SM.[39] An experiment by Bonen et al.[40] provided evidence that LCFA uptake is regulated by a protein-mediated mechanism, showing that it is possible to block the contraction-induced increase in LCFA uptake with sulfo-N-succinimidyl oleate, a known inhibitor of FAT/C36. Cumulative data have indicated that CD36 facilitates a major fraction of fatty acid uptake by muscle and fat, and that CD36 deficiency is associated with a large defect in fatty acid uptake by those tissues.[41,45]

There are direct and indirect evidence that training influences the protein-mediated LCFA uptake into SM cells. Several studies conducted on rat muscles have demonstrated an increase of mRNA expression of LCFA transport proteins[39,41,42,44,46,47] after chronic muscle activity. Specifically, FAT/C36 and FSCS1 mRNAs have been demonstrably upregulated after increased muscle activity resulting in higher fatty acid uptake rates of muscles.[39–42,44,46] In addition, FABPpm expression was increased after endurance training in human SM,[47] resulting in increased uptake and oxidation of LCFA.[32,33] Increased transmembrane LCFA transport capacity of trained muscles have been indirectly supported by the findings of significantly higher fatty acid transport protein saturation kinetics in rat red as compared with white muscles.[42–44,48] Differences in the ability among red and white muscles to oxidize LCFA may be attributed in part to a greater rate of protein-mediated fatty acid uptake. There is also evidence that fatty acid transport proteins may play a significant role in intramuscular TG depots. This idea is supported by previous reports indicating that IMTG depots are doubled in muscles of transgenetic FAT/C36 mice.[43] Dyck et al.[49] found that LCFA uptake of electrically stimulated isolated muscles is higher in a trained group than in an untrained group of rats. This increase in LCFA observed in trained muscles was not accompanied by an enhanced activity of LCFA transport proteins (FAT/C36, FABPpm, FACS, and FABPc), suggesting that an increase in transport proteins may not be responsible for modest increases in LCFA uptake.

In additional, previous in vivo training studies may offer partial explanations with regard to plasma fatty acid turnover during prolonged exercise. Friedlander et al.[50] found increased working-leg net FFA uptake after training. Similarly, Coggan et al.[26] reported higher rates of disappearance from plasma ($FFAR_a$) in trained than in untrained subjects, thus affirming that trained subjects must have oxidized a higher percentage of fatty acids released during lipolysis. These findings are contrasted by those of Martin et al.[30] who found a reduction in plasma fatty acid oxidation (and a decline of plasma glycerol concentration) when subjects exercised at a similar exercise intensity of 75% to 80% after 12 wk of physical conditioning. In addition, Phillips et al.[31] and Sial et al.[24] found no evidence for effects of training on the FFA uptake during exercise.

From these reports, we can only speculate on possible differences in the uptake of LCFA into the plasma of myocytes between endurance-trained and untrained individuals. Data obtained from isolated muscles (removed from normal circulatory and neural influences) clearly demonstrate a training-induced increase in the capacity of SM to transport LCFA into the plasma of myocytes. However, data from in vivo studies are inconsistent with regard to plasma LCFA uptake during exercise and the influence of training. This inconsistency is complicated by the fact that LCFA delivery seems to be lowered during exercise in trained individuals due to a blunted sympathoadrenal response[35,36] and a reduction in adipocyte lipolysis and circulating LCFA. The transport of LCFA into the plasma of myocytes may be facilitated by transport proteins as represented by saturation kinetics; this in itself does not corroborate that transport is rate determining for LCFA use. It has been speculated that LCFA uptake into the plasma of myocytes follows the rate of mitochondrial LCFA oxidation.[51]

Additional studies have to be conducted on the molecular biology of membrane transporters because several important transporters have not yet been identified via gene encoding. To identify membrane transporters with an impact on fat metabolism, the role of molecules must be more precise. A major task finding will need to occur in the field of transgenetic animals, in which the transporters are overexpressed, and in the field of in vivo longitudinal training studies based on the determination of gene expression of the transporter molecules.

Plasma TG Use

Plasma TGs represent a rich source of circulating energy substrates. There are two major TG-rich plasma lipoproteins: TG produced in the liver and released into the circulation as VLDL-TG and chylomicrons, which are produced in the intestinal

tract after ingestion of a meal containing lipids. Human TG-rich lipoprotein (TRL) kinetics has been difficult to determine directly due to technical limitations. Despite poor data assessing the quantitative involvement of circulating TRL metabolism during exercise, there is evidence that TRL can serve as an energy source for exercising SM.

Direct evidence for the contribution of TRL to the energy supply of SM during exercise has been published by Kiens et al.[33] who found a net uptake of VLDL-TG from total serum during knee extension exercise when isolating VLDL-TG from the total serum TG. Recently, Helge et al.[52] documented the use of circulating VLDL-TG after adaptation to a 7-wk fat-rich diet when participants were subjected to a 60-min exercise bout of 68% of maximum oxygen consumption ($V_{O_{2max}}$). In this investigation, VLDL-TG use after a fat-rich diet was greater than that after a carbohydrate-rich diet, indicating glycogen sparing. Interestingly, this higher VLDL-TG use after the fat-rich diet was not related to a higher arterial VLDL-TG concentration but, more likely, to a higher activity of muscle lipoprotein lipase.[53] There is also indirect evidence that TRL as a fuel for exercising SM may lead to a decrease in plasma VLDL-TG persisting for 1 to 5 d.[54,55]

Muscular endothelium is virtually impermeable to circulating TRLs. Therefore, the initial step in TRL plasma clearance requires TG hydrolysis at the endothelial surface by lipoprotein lipase (LPL). Mackie et al.[56] investigated the influence of muscle stimulation on the uptake of exogenously administered chylomicrons ^{14}C-labeled TG in rats and found a strong correlation between LPL activity and the uptake of plasma chylomicrons. Transgenic mice that overexpressed human muscle LPL showed higher content of muscle mitochondria,[57,58] decreased plasma TG levels, and elevated FFA uptake by muscle tissue.[58]

It is also well known that endurance training increases the capillarization of SM.[59–80] This increase in capillarization may enhance the lipolytic capacity of muscle LPL, thus providing more space for LPL enzymes.[81] Thus, the activity of muscular LPL (mLPL) has been suggested as a determining factor for TRL use during exercise. Indeed, the LPL activity of trained subjects is significantly higher in the trained than in the untrained state.[82–85] Borensztajn et al.[81] found a significant increase in mLPL activity in sedentary rats after 12 wk of endurance training. Svedenhagen et al.[84] reported an approximately 47% increase in mLPL activity in human muscles after a period of endurance training. Kiens and Lithell[81] investigated the influence of 8 wk of dynamic exercise training on the knee extensors of human subjects. The knee extensors of one leg were trained, and the other leg served as the control. They found an approximately 70% increase in mLPL in muscles of the trained as compared with the untrained leg. The increased mLPL was correlated with an increase in capillary density. While investigating human SM, Simsolo et al.[86] found that a 2-wk detraining of endurance-trained athletes resulted in a decrease in mLPL in addition to an increase in adipose LPL, yielding a redirection of circulating TRL from oxidation to storage in adipose tissue. Further, there is evidence that LPL activity is different in the three muscle fiber types, with the greatest LPL activity in slow twitch fibers.[56,82,87–89] However, exercise training seems to reduce the production and release of VLDL-TG by hepatocytes,[90] which suggests that during exercise the availability of circulating VLDL is decreased rather than increased through endurance training.[91]

Despite training adaptations, the contribution of plasma lipoprotein-derived fatty acids to muscle total lipid energy use during exercise has been estimated to be not more than 3% to 10%.[52,54,91–93] It has been proposed that the resulting increased clearance of TG from circulation, as observed after exercise[54,55] and during exercise,[33] may provide fatty acids for the restoration of reduced IMTG stores induced by exercise.[33,52,54,56,89,91,92]

Technical limitations (e.g., the lack of commercially available tracers and a high blood flow, which makes it difficult to detect modest rates of VLDL uptake) have impeded the quantification of VLDL use during exercise. Further investigations (e.g., isotopic VLDL tracer studies) are needed to evaluate the role of VLDL as an energy source to develop a more precise model of fat oxidation during exercise.

Use of SM Intramuscular Fat Stores

Four decades ago, studies with radiolabeled tracers suggested that plasma FFAs derived from IMTG stores may be an important source for oxidation during submaximal work. This suggestion was based on the finding that a significant portion of an infused tracer was not immediately oxidized and that, even if complete oxidation had occurred, the turnover rate of plasma FFA would have been insufficient during a 1- to 2-h bout of moderate exercise to account for the total rate of fatty acid oxidation.[94,95]

IMTG is supposed to contribute to the energy supply of working muscles and is stored mainly in the form of lipid droplets in the cytoplasm of muscle cells. Because these intramyocellular (IMCL) droplets are in proximity to muscle mitochondria,[96–98] the transit time of fatty acids hydrolyzed from droplets to the outer mitochondrial membrane is very short; therefore, these fatty acids seem to be readily available for oxidation during exercise.

There is evidence that IMTGs play an important role in substrate delivery during recovery from exercise. In this context it has been shown[99,100] that a significant breakdown in IMTG occurs during recovery from exercise, with no breakdown during exercise. In a different study, Larson-Meyer et al.[101] demonstrated that IMTG content does not recover even 3 d postexercise when subjects consume a recovery diet of only 10% fat. It appears that, in the recovery period after long glycogen-depleting exercise, the resynthesis of CHO stores has a metabolic priority leading to IMTG (and possibly VLDL) breakdown to supply lipid fuel for oxidative muscle metabolism.[100] These data are also supported by studies demonstrating that use of fat for energy is elevated after different types of exercise.[102–105]

There is also direct evidence of availability of IMCL as an energy source based on muscle biopsies and electron microscopy. Several investigators have reported a greater than 20% decrease in IMCL content in exercising SM after prolonged submaximal exercise.[29,106–114] In contrast, numerous investigators have documented smaller decrements[27,33,115,116] or no decline[100,116,117] in IMCL. There are also recent studies[118,119] that found no significant decrease in IMCL content in male but did in female subjects. These data suggest the fat used during exercise might be recruited from different sources in females and males.

The discrepancy in results may be due to differences in exercise mode, intensity, and duration; differences in muscle mass and hormonal response[33,120]; differences in pre-exercise intramuscular concentrations[27,53,115,121]; and differences in use among muscle groups or muscle fibers.[122–126] In addition, methodologic difficulties in measuring IMCL content in muscle tissue[33,64,127,128] may have contributed to inconsistent results reported in the literature.

Further, there is evidence that plasma FFAs are incorporated into the IMTG pool during exercise.[129–131] Guo et al.[131] used a dual-tracer pulse-chase technique to measure IMTG oxidation in muscle biopsies to determine turnover of IMTG and indirect calorimetry (^{14}C excretion) to calculate fatty acid oxidation. The dual-tracer pulse-chase technique approach combined with prelabeled IMTG by a ^{14}C-FFA tracer infusion before exercise and an infusion of ^{3}H-FFA tracer during exercise allowed determination and incorporation of plasma FFA into the IMTG pool of muscles during exercise. The finding that plasma FFAs are incorporated into the IMTG pool during exercise suggests that a lack of change in IMCL content does not necessarily negate findings that IMCLs are oxidized during exercise.

^{1}H nuclear magnetic resonance spectroscopy is used increasingly for investigations of IMCL use during exercise. This method allows non-invasive measurement of the content of IMCL (with

high temporal resolution) and has been validated in recent studies.[128,132–134] When using ^{1}H nuclear magnetic resonance spectroscopy, previous investigations found a decrease in IMCL content after prolonged submaximal exercise.[101,135,136] Krssak et al.[135] determined the IMCL content before and after an exhausting treadmill run and found a significant decrease in IMCL content in human gastrocnemius and soleus muscles after 2 to 3 h at 65% to 70% of the athletes' predetermined peak oxygen uptake (45-min bouts with rest intervals of approximately 30 min including ^{1}H nuclear magnetic resonance spectroscopy measurement). Brechtel et al.[136] investigated IMCL content in the soleus and tibialis anterior muscles of six subjects participating in a non-competitive run, with three runners in a competitive half marathon and another three runners in a competitive marathon, and found significant (10% to 56%) decreases in IMCL depending on the group of runners and muscles investigated. These results are in agreement with data reported by Larson-Meyer et al.[101] who found a decrease in IMCL content of soleus muscle of seven female runners after a 2-h treadmill run at 67% of $V_{O_{2max}}$.

Other studies have estimated in vivo IMTG use during exercise by indirect calorimetry to quantify whole-body lipid oxidation and isotopic labeling of the carbon source of fatty acids, thus determining the contribution of circulating LCFA to energy requirements of muscles. The findings obtained from most of these studies support the assumption that IMTG contributes to energy delivery to SM during prolonged submaximal exercising.[4,24,26,29,30,31,137,138] It should be noted that use of IMCL seems to be substantially influenced by the intensity of exercise and the concomitant glycolytic flux.[4,137,138]

There is indirect evidence that training has a positive effect on IMTG turnover during exercise. It has been frequently noted that endurance-trained SMs possess considerably larger IMCL content[64,96,98,125,128,139,140] and that IMCL content in SM increases after a period of endurance training.[33,64,96,141–143] Other investigators have suggested that oxidative muscle fibers (type II fibers) are supplied with higher volume density of IMCL than are type I fibers.[125,126,139] Further, it has been demonstrated in animals that the absolute and relative contact surface areas between the intracellular lipid droplets and the outer mitochondrial membrane are significantly increased in muscles with higher oxygen uptake (Labrador dogs) when compared with muscles with lower oxygen uptake (goats).[98] This observation seems to support the importance of close proximity of intracellular lipid droplets to the mitochondrial membrane of muscle cells (thus circumventing a long diffusion process).

Several cross-sectional studies have examined the contribution of substrate delivery during prolonged submaximal exercise by comparing endurance-trained with untrained subjects. Jansson and Kaijser[27] compared a group of five endurance-trained cyclists and five untrained volunteers and found a lower-leg respiratory exchange ratio when subjects exercised at 65% $V_{O_{2max}}$ on a cycle ergometer, suggesting a greater contribution of fat to oxidative metabolism. In this study, the higher relative contribution of fats to substrate oxidation could not be explained by a difference in plasma FFA use. The investigators concluded that this occurred as the result of a greater turnover rate of IMTG. Klein et al.[144] arrived at a similar conclusion in an isotopic tracer study demonstrating that 4 h of treadmill exercise elicits an oxygen uptake of 20 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} of fat oxidation and is higher in trained subjects, whereas the lipolytic response (expressed as average glycerol and $FFAR_a$ in the plasma) is similar in trained and untrained subjects. The findings presented by Coggan et al.[26] are somewhat different. They investigated endurance-trained and untrained subjects during exercise at 75% to 80% of $V_{O_{2max}}$ and found that the contribution of $FFAR_d$ was greater in trained subjects when expressed as the relative percentage of total energy expenditure. Even if one assumes that 100% of $FFAR_d$ was oxidized, this could not account for the difference in fat oxidation between groups. They concluded that trained individuals rely more heavily than untrained individuals on non-adipose tissue-derived FA during exercise.

The results derived from muscle biopsy studies and cross-sectional studies are in agreement with data obtained from longitudinal training studies using isotopic tracer techniques. Hurley et al.[29] investigated the influence of a strenuous 12-wk program of endurance training on substrate use. They found that, during cycle exercise at the same submaximal workload, the respiratory exchange ratio is lower during exercise in the trained state than in the untrained state, indicating a shift of energy provision from CHO to fat stores. This assumption was supported by muscle biopsies showing marked changes in the proportion of glycogen and TG stores in the quadriceps muscle (two-fold higher glycogen concentration and approximately two-fold greater decrease in ICML content in muscles after training). In addition, they found lower levels of plasma FFA and blood glycerol concentrations in the trained state. Based on these data, the investigators suggested that the increase in fat oxidation observed after training was not fueled by a higher availability of FFA for adipose tissue but rather by increased lipolysis from IMTG. These findings are in agreement with data reported by other isotopic tracer studies.[24,30,31] Martin et al.[30] found 41% higher fat oxidation after 6 wk of training in the trained state, with a concomitant significant decline of 1-13 palmitate oxidation, plasma free fatty acids, and plasma glycerol levels. Phillips et al.[31] found an increase in total fat oxidation during 90 min of submaximal excise (60% pretraining $V_{O_{2max}}$) after 31 d of endurance training. In this case, fat use demonstrated a reduced reliance on plasma FFA ($FFAR_a$ and $FFAR_d$). Sial et al.[24] reported a significant increase in fat oxidation after 16 wk of endurance training in elderly men, with no changes in the rate of glycerol and FFA appearance. Horowitz et al.[34] found that 12 wk of endurance training increases total fatty acid oxidation but does not alter abdominal and femoral subcutaneous adipose tissue (measured via microdialysis), whole-body palmitate, R_a and plasma fatty acid oxidation.

The discussion about the role of IMTG as energy has been accompanied by methodologic concerns. This is especially true for studies using indirect calorimetry, and isotopic tracer techniques (calculating the IMTG use by subtracting plasma FFA oxidation from total fatty acid oxidation) have been repeatedly contested.[49,52,117,129–131] The major concern with this approach is that these indirect measures depend on several factors: 1) LCFAs entering muscle cells during exercise are not stored in the IMCL pools, as reported in the recent literature,[129–131] 2) labeling is not lost in metabolic pathways,[145] 3) circulating VLDL-TG,[33,52–55] and 4) the fat from adipocytes dispersed between the muscle cells do not contribute as a quantitative fuel for muscle during exercise. Further, the whole-body measurement does not reflect exclusively the metabolic activity in the working muscle.[99] Studies based on the needle biopsy methodology have been challenged because their findings represent only small samples and do not allow for repetitive measures in the same muscle.

Building a better model of IMTG use during exercise requires a more precise determination of the amount of plasma FFA that is incorporated into the IMTG pool, the amount of VLDL-TG contributing to energy demands, and the contribution of fats stored between the myocytes. Further studies based on ^{1}H nuclear magnetic resonance spectroscopy measures may provide more precise data concerning IMTG breakdown during exercise and recovery.

Despite the uncertainty reflected in the literature, it appears that IMTGs function as fuel for SMs during prolonged submaximal exercise, but to what extent is not clear. In addition, considering the literature, it appears that endurance training enhances the ability to oxidize IMTG during prolonged exercise of moderate intensity; however, new data and new methods may be necessary to ascertain results that are more precise.

Transport of LCFA Into the Mitochondria and Mitochondrial Fat Use

Another adaptation of SM to endurance training has been speculated to occur via an elevation of LCFA through the mitochondrial membranes. The so-called carnitine shuttle system seems to play a significant role in this transmembrane transport. LCFAs, after entering the muscle cell, are activated to acyl coenzyme (CoA) by acyl-CoA synthase. The long-chain acyl-CoA cannot diffuse freely across the inner mitochondrial membrane[146–150] for subsequent β-oxidation in the mitochondria. Therefore, the acyl-CoA ester is converted into acyl-carnitine. This transfer of acyl groups from CoA to carnitine is catalyzed by carnitine palmitoyltransferase I (CPT-I), which spans the outer mitochondrial membrane. The acyl-carnitines can permeate the inner mitochondrial membrane in exchange with a molecular-free carnitine (acylcarnitine-translocase)[138,146,147,149,150,151] that is coupled to CPT-II. CPT-I is considered a rate-limiting step in the oxidation of long-chain fatty acids[152–154] and is reversibly inhibited by malonyl-CoA.[138,146,147,149–151,153,155,156]

Endurance training increases the activity of muscle CPT-I (muscle isoform CPT-Iβ) in the rat.[152,154,157–159] Berthon et al.[152] reported a parallel increase in CPT-I activity with increasing $V_{O_{2max}}$. In a different study, they found that training attenuates the exercise-induced decline in malonyl-CoA levels observed in rat SM,[160] suggesting that training may result in a greater decrease in muscle malonyl-CoA concentration during exercise, thereby relieving inhibition of CPT-I and enhancing fatty acid oxidation.[146,147] This mechanism has been contested by recent observations of no change in human SM malonyl-CoA concentration at a variety of exercise power outputs.[161,162] Starritt et al.[154] reported that sensitivity of trained human SM to malonyl-CoA increases in comparison with untrained muscles. Interestingly, despite this increase in CPT-I sensitivity to the inhibitory effect of malonyl-CoA, the CPT-I activity remained higher in trained muscles.

These data suggest that the role of malonyl-CoA as a regulator of CPT-I activity in human as opposed to rat muscle may be more complicated than originally proposed.[152,159] Malonyl-CoA paradoxically should completely inhibit CPT-I activity in human muscle cells in concentrations measured in SM.[154,159,163] It would be interesting to discover why fatty acid oxidation actually proceeds in working muscles under these conditions. It has been hypothesized that compounds structurally related to malonyl-CoA such as acetyl-CoA and CoA-SH (coenzyme A) may compete with malonyl-CoA for a binding site on CPT-I. It also has been demonstrated that these compounds can inhibit CPT-I activity.[164,165] In the presence of malonyl-CoA, acetyl-CoA and CoA-SH have been shown to act as partial agonists because they are less potent inhibitors than malonyl-CoA.[154]

There may be another mechanism of increased activity of the carnitine shuttle system induced by endurance training. It has been reported that a significant portion of CPT-I activity measured in muscle mitochondria is not inhibited by malonyl-CoA.[146,154,163] Jong-Yeon et al.[159] recently provided evidence of a malonyl-CoA–insensitive fraction of muscle cells that is predominantly active in red muscles and that this malonyl-CoA resistance correlates positively with the capacity of SM cells to oxidize LCFA. They also found differences in gene expression across muscle fiber types, which were consistent with similar fatty acid oxidation rates. These differences suggested that red muscle may expresses a novel CPT-I isoform that confers a modified (malonyl-CoA-resistance) regulatory site, a theory that would help to explain the higher CPT-I activity and fat oxidation rates observed in endurance-trained muscles.

When addressing the transport of fatty acids into the mitochondria, we should be cognizant that fatty acid metabolism is closely linked to metabolism of CHO during exercise. It has been reported that fatty acid oxidation rates decline during high-intensity exercise.[4,137,138] Findings from studies using indirect calorimetry and isotope tracers are supported by a ^{1}H nuclear magnetic resonance spectroscopy study[136] showing that one bout of moderate intensity (60% to 70% $V_{O_{2max}}$) markedly reduces IMCL content in tibialis anterior and soleus muscles, whereas an exercise of similar duration but higher workload (>80% $V_{O_{2max}}$) does not. Kiens et al.[51] investigated the regulation of fatty acid use in SMs at rest and during exercise. They estimated the intracellular content of LCFA by using a muscle biopsy technique at rest and during two exercise bouts at different intensities on a cycle ergometer (40 min at 65% $V_{O_{2max}}$ continuing with 15 min at 90% $V_{O_{2max}}$ separated by 5 to 15 s for muscle biopsy). The finding of this study was that LCFA content in muscle tissue declines substantially by 43% after exercise at 65% $V_{O_{2max}}$ when compared with resting values and increases after exercise at 90% $V_{O_{2max}}$. This result suggested that the decrease in fat oxidation observed during heavy exercise cannot be due to a decrease in cellular LCFA availability but rather to a decrease in mitochondrial oxidation. However, it is not completely understood which mechanism is responsible for this phenomenon.

Strong glycolytic flux that occurs during high-intensity work leads to the accumulation of muscle citrate and muscle acetyl-CoA[166–168] and an increased activation of the pyruvate dehydrogenase complex.[138] If the flux through glycolytic pathways and pyruvate dehydrogenase complex reaction markedly exceeds the flux through the citrate cycle muscle (as it occurs during high-intensity exercise), then citrate diffuses out of the mitochondria and is cleaved to acetyl-CoA and oxaloacetate by citrate lyase.[156] The decreased fat oxidation observed during prolonged high-intensity exercise may be caused by an increased malonyl-CoA level (and inhibited CPT-I-activity) in muscle cells.[156,168] This suggestion was based on the premise that acetyl-CoA (accumulated during high-intensity exercise) becomes a substrate for malonyl-CoA synthesis (catalyzed by acetyl-CoA-carboxylase) and therefore inhibits CPT-I activity.[156,168] However, this is unlikely to occur because several studies have found no changes in malonyl-CoA concentration after exercise at different power outputs.[161,162]

A more recent attempt to explain the decrease in fatty acid oxidation during high-intensity exercise is the theory of decreased free carnitine availability. This theory is based on the assumption that an increase in acetyl-CoA (occurring during high-intensity exercise) may result in enhanced acetylation of the carnitine pool by forming acetyl-carnitine, thereby decreasing the pool of free carnitine in muscles. Van Loon et al.[138] recently reported that the increase of muscle acetyl-carnitine is accompanied by the reduction of free carnitine and a reduction in fat oxidation. Therefore, the investigators postulated that the decrease in free carnitine might be directly responsible for a decreased LCFA entry into the mitochondria. In addition, a decline in muscle pH during heavy exercise may diminish CPT-I activity and thus may be responsible for the decrease in LCFA oxidation.[4,51,154,169,170] However, endurance training diminishes the glycolytic flux at a given workload of prolonged intense exercise, thereby preventing the blockage of carnitine shuttle system.

In summary, there is no question that endurance training increases the capacity of muscles to transport LCFA into mitochondria. However, the greater supply of fatty acids available in the mitochondria of trained SMs has to be oxidized there. This scrutiny supports a model of a greater pull by the mitochondria[26] in endurance-trained SMs as opposed to their untrained counterparts.

From the late 1960s, a wealth of data on exercise-induced ultrastructural changes in SM became available.[96,142,171,172] Since then it has been frequently demonstrated that endurance training increases the size and number of mitochondria.[64,65,70,71,97,143,173–181] This increase in mitochondrial surface area observed in trained SM seems to represent an increased capacity to exchange substrates, adenosine diphosphate, oxygen, and carbon dioxide between the mitochondrion and the cytoplasm.[64,96,98,147,182]

Training adaptations of the mitochondrial system has been shown to include increases in mitochondrial enzyme activities.[29,63,70,148,174,178,181,183–193] The observation that a training-induced increase in mitochondrial enzyme activity is accompanied by an increase in total fat oxidation during exercise[27,29,31] and the finding of a coincidental increase of mitochondrial adenosine triphosphate production rates and mitochondrial enzyme activity after longer periods of endurance training[185,192] support the suggestion that the mitochondrial enzymes are decisively involved in the shift from CHOs to fatty acids during submaximal exercise observed in trained SM.[181] This assumption is also indirectly supported by the observation that oxidative type I fibers contain considerably greater mitochondrial activity of oxidative enzymes than do type II fibers.[63,194,195]

However, the findings of a higher fat flux to the mitochondrion (caused by an increased mitochondrial surface area) and a higher fat-use rate (caused by an increased mitochondrial activity of oxidative enzymes in mitochondria) in SMs are in agreement with the observation of larger IMCL stores of endurance-trained muscle cells.[64,96,98,125,128,139,140–143] In this regard, the relatively larger contact surface area between the intracellular lipid droplets and the outer mitochondrial membrane of trained SMs[98] and the higher volume density of oxidative muscle fibers (type II fibers have a greater volume density of IMCL than do type I fibers)[125,126,139,196] also have been interpreted as an adaptive mechanism of trained SMs to increase fatty acid turnover.

One needs to be cognizant that fat use is an oxidative process and therefore dependent on the microvascular supply of SMs.[197] Based on available data, it has been hypothesized that the capillary surface per muscle fiber (capillary-to-fiber ratio) is linked to the mitochondrial volume.[70,172,198] This notion suggests that differences in oxygen (and substrate) supply to SM seem to be matched by differences in the amount of mitochondrial structure.[198] However, there is a preponderance of evidence indicating that capillarization of human and animal SMs increases as a result of training[59–80,199] prolonging the transit time of red blood cells that pass through the capillaries into the mitochondria of muscle cells.[200,201]

There is common agreement in the literature about the importance of mitochondrial ultrastructural and metabolic adaptations for a training-induced increase in fat use by SM during prolonged submaximal exercise. Recent investigations conducted in isolated mitochondria of SMs support this suggestion by clearly demonstrating an increase in mitochondrial adenosine triphosphate production rates, mitochondrial fat oxidation rates, and muscle oxidative power as a result of training.[186,193,202–204]

The prospects for future research concerning the transport of FFA through the mitochondrial membrane are similar and comparable to processes mediated by transporters of other membranes. The suggestion that 40% of the inner mitochondrial surface is made up of proteins involved in energy transduction, relevant structural parameters, and the topography of the outer surface of contact sites must be identified to evaluate the limits of oxidative use of fats in muscle cells. New gene-encoding transporters must be found, and the function and interaction of known transporters will have to be investigated. Further, experiments using transgenetic animals (with overexpressed transporters) and in vivo longitudinal training studies may contribute to novel findings in this field.

The mitochondrial biogenesis in response to physiologic stimuli requires an appropriate expression of gene-encoding mitochondrial products. Several transcription factors have been identified that encode these mitochondrial products and as such are involved in the coordinated expression of nuclear and mitochondrial genomes. However, the process of regulation remains unclear. Future studies may yield new insights into the molecular mechanism involved in altering mitochondrial properties in response to physical stress.

CONCLUSION

During prolonged moderate exercise, it is apparent that lipid oxidation is a trainable process in humans, as reported by numerous investigators.[24,29–34,49,100,117,189,205–207] The available data suggest that fatty acids oxidized after a longer period of endurance training are not derived from adipose tissue and rather marginally from circulation of TGs. In contrast, there is considerable evidence that endurance training enhances the ability of muscle cells to transport FFAs into the mitochondria and the ability of mitochondria to combust fatty acids and, hence, accelerating the removal of fatty acyl moieties from the cytoplasmic space. It cannot be ignored that enhanced mitochondrial oxidation of FFA has to be accompanied by a quantitatively similar increase in the supply of fatty acids to mitochondria. Lipids represent a major source of energy for exercising muscles, but their relative contribution depends on the mode, duration, and intensity of exercise. From moderate to intense exercise, lipid use declines despite the increase in available FFA concentrations in the cytoplasm of muscle cells. This finding supports the assumption that, during intense exercise, the total fat oxidation is limited by the transport capacity into the mitochondria. The capacity of mitochondria to oxidize fats is due to limitations in fatty acid mobilization from endogenous stores and their transport from vascular compartments to the cytosol. Nevertheless, training-induced adaptations in several important steps of fat metabolism await further exploration to ascertain the complex mechanisms of whole-body fat oxidation during prolonged submaximal exercise in humans.

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