Regulation of skeletal muscle fat oxidation during exercise in humans

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ABSTRACT

SPRIET, L. L. Regulation of skeletal muscle fat oxidation during exercise in humans. *Med. Sci. Sports Exerc.*, Vol. 34, No. 9, pp. 1477–1484, 2002. Fat and carbohydrate are the major energy substrates during aerobic exercise in well-fed humans. The regulation of fat metabolism during exercise has not been as thoroughly studied as carbohydrate metabolism, especially in human skeletal muscle. Traditionally, it was believed that the regulation of skeletal muscle fat metabolism was mainly at the level of the delivery of free fatty acids to the muscle (adipose tissue lipolysis) and transport of the long chain fatty acids into the mitochondria. It is now known that the transport of fatty acids into the muscle cell and the regulation of muscle triacylglycerol lipase activity are also important sites of regulation. New lines of research are currently underway examining the regulation of fat metabolism in skeletal muscle at the level of fat transport across the sarcolemmal and mitochondrial membranes and regulation of TG lipase activity in both rodent and human models. A major goal of this research is to determine the regulatory signals that control the up-regulation of fat metabolism during the transition from rest to low and moderate aerobic exercise (30-65% $\dot{V}O_{2max}$) and the down-regulation that occurs when exercising at intense aerobic exercise (~85% $\dot{V}O_{2max}$). Although it is expected that the signals that activate carbohydrate metabolism during exercise (Ca^{2+} and free ADP, AMP, and P_i) would also play a role in fat metabolism, this has not been demonstrated to date. **Key Words:** METABOLIC REGULATION, ADIPOSE TISSUE LIPOLYSIS, MUSCLE MEMBRANE FAT TRANSPORT, MUSCLE TRIACYLGLYCEROL LIPASE ACTIVITY, MUSCLE CARNITINE PALMITOYLTRANSFERASE I ACTIVITY

Fat and carbohydrate are the dominant substrates for the production of ATP (oxidative phosphorylation) in skeletal muscle during aerobic exercise in well-fed humans. The absolute contribution of fat to the total energy production during exercise increases from low power outputs to a maximum between ~50 and 65% $\dot{V}O_{2max}$ and then decreases as the exercise intensity increases to ~85% $\dot{V}O_{2max}$ and above (18,34,36). Fat is often depicted as the less important of the two fuels, as carbohydrate becomes the dominant substrate during intense aerobic exercise and fat cannot be used to generate ATP via "anaerobic" metabolism (substrate phosphorylation) during sprint exercise. However, it does have some advantages over carbohydrate. Fat is an energy-dense fuel with a high energy yield per unit mass and is also stored in large quantities in the body as compared with carbohydrate. Therefore, fat can provide a substantial amount of substrate for oxidative phosphorylation during prolonged exercise at low to moderate intensities. Aerobic training also increases the absolute rate of energy production from fat oxidation in skeletal muscle. Increasing fat and decreasing carbohydrate use during aerobic exercise increases the power output and/or time that aerobic exercise can be maintained before the carbohydrate store in the body is consumed. Surprisingly, the regulation of fat metabolism has not been studied as thoroughly as carbohydrate metabolism in skeletal muscle. Although this is changing, there is still little known regarding the regulation of fat metabolism in human skeletal muscle during exercise.

The purpose of this paper is to briefly review the regulation of fat oxidation in human skeletal muscle during exercise, with an emphasis on the key regulatory sites believed to determine the rate of fat provision and oxidation. Processes that are not directly involved in the oxidation of fat, such as esterification of triacylglycerol, are not examined. Several detailed reviews of various aspects of fat metabolism during exercise already exist (8,27,28,39,42,44,50). This article attempts to provide the metabolic bases for the papers that follow in this symposium.

OVERVIEW OF SKELETAL MUSCLE FAT METABOLISM AND REGULATION

A major source of fat for the working muscle during exercise is the delivery of long-chain free fatty acids (FFAs) to the muscle from adipose tissue (Fig. 1). It now appears that the majority of the FFAs are transported or assisted across the muscle membrane by transport proteins whereas a smaller portion diffuses across the membrane. A second major source of fat is the release of FFAs from triacylglycerol (TG) stored directly in the muscle, although the quantitative importance of this source remains controversial (Fig. 1). All FFAs released or moved into the cytoplasm must be chaperoned by fatty acid binding proteins (FABP) and if destined for oxidation are transported to the surface of the outer mitochondria membrane. The FFAs are then activated via binding with coenzyme A (CoA), converted to a fatty acyl carnitine compound, and moved across the mitochondrial membranes while bound to carnitine. Inside the mito-

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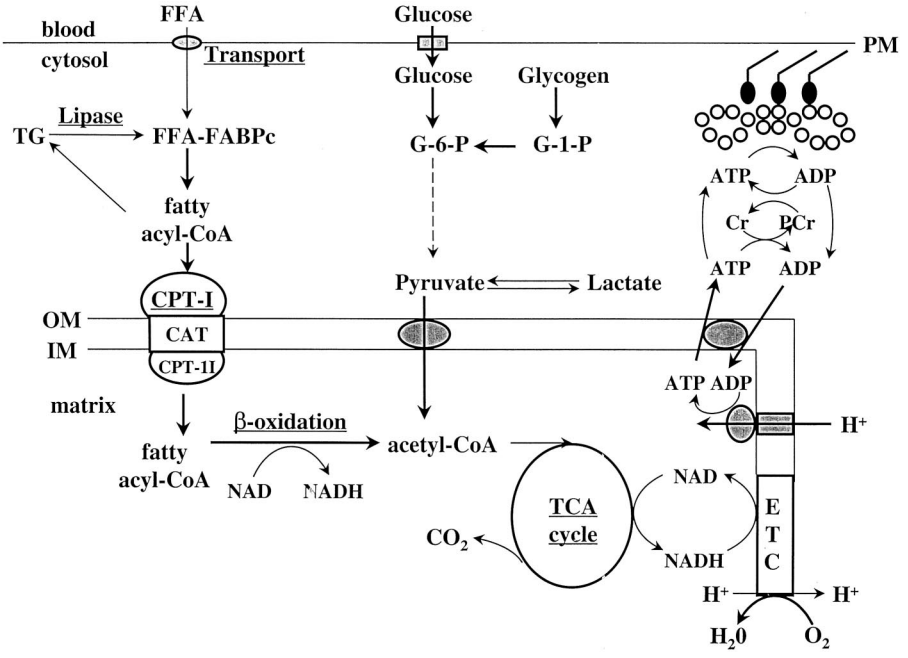

FIGURE 1—Schematic overview of energy production in skeletal muscle. PM, plasma membrane; OM, IM, outer and inner mitochondrial membranes; FFA, free fatty acid; FABPc, cytoplasmic fatty acid binding protein; TG, triacylglycerol; CoA, coenzyme A; CPT I, II, carnitine palmitoyltransferase I and II; CAT, carnitine-acylcarnitine translocase; NAD, NADH, oxidized and reduced nicotinamide adenine dinucleotide; G-6-P, G-1-P, glucose 6- and 1-phosphate; PCr, phosphocreatine; Cr, creatine; TCA, tricarboxylic acid; ETC, electron transport chain.

chondria, the carnitine is removed, the CoA is rebound, and the fatty acyl-CoA molecules are metabolized in the β-oxidation pathway with the production of reducing equivalents (NADH, $FADH_2$) and acetyl-CoA (Fig. 1). The acetyl-CoA is further metabolized in the tricarboxylic (TCA) pathway with the production of additional reducing equivalents. The electron transport chain, including oxygen, accepts the reducing equivalents to generate the proton motive force, which provides the chemical energy used to synthesize ATP from inorganic phosphate (P_i) and ADP in the process of oxidative phosphorylation.

The potential sites that control skeletal muscle fat metabolism and oxidation during exercise appear to include: 1) adipose tissue lipolysis and FFA delivery to the muscle, 2) FFA movement across the muscle membrane, 3) regulation of muscle TG lipase (or hormone sensitive lipase) activity, and 4) regulation of FFA movement across the mitochondrial membranes (carnitine palmitoyltransferase I activity). It would be expected that the final three sites of regulation would be controlled at least in part by events occurring in the cytoplasm of the muscle. As such, three major classes of regulators are generally believed to be important for activating the metabolic pathways that lead to the generation of energy during exercise: 1) early warning signals from the release of Ca^{2+} as muscle contraction is initiated; 2) feedback from factors related to the use of ATP in the muscle ("energy state"), such as free ADP, AMP, and P_i; and 3) feedback from the involvement of the redox couple (NAD/NADH) at many sites of metabolism (Fig. 2).

Closer examination, however, reveals that these regulators have only been well studied and heavily implicated in controlling the cytoplasmic and mitochondrial pathways involved in the metabolism of carbohydrate. There has not been the same research interest or success in linking these putative regulators with the important control sites of fat metabolism. The same regulators are also important in activating the TCA cycle during exercise, a shared pathway for the metabolism of both carbohydrate- and fat-derived acetyl-CoA. There does not appear to be external regulation of the β-oxidation pathway in the mitochondria and the shared TCA cycle is activated as a function of the power output during exercise. Therefore, major sites of unexplained regulation of fat metabolism lie at the level of TG lipase and the movement of fat across the muscle and mitochondrial membranes.

ADIPOSE TISSUE LIPOLYSIS AND FFA DELIVERY TO MUSCLE

The ability of adipose tissue to respond to exercise by activating TG lipolysis and release FFAs into the blood is important for increasing or maintaining the delivery of FFAs to the working muscle. The regulation of adipose tissue lipol-

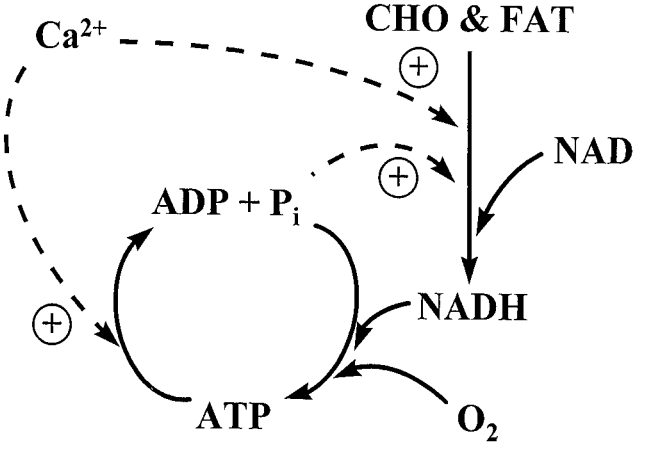

FIGURE 2—Schematic diagram demonstrating the importance of Ca^{2+}, by-products associated with the energy state of the cell (ADP + P_i) and the redox couple (NAD/NADH) in the activation of the pathways that synthesize ATP.

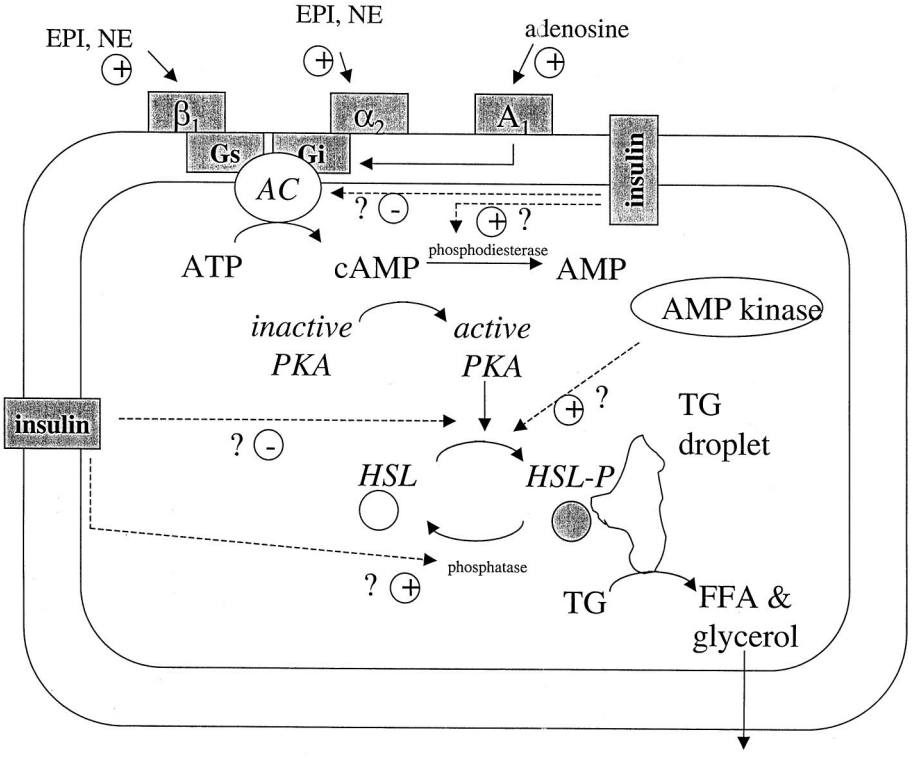

FIGURE 3—Schematic diagram outlining the major regulation of adipose tissue lipolysis during exercise. EPI, epinephrine; NE, norepinephrine; Gs and Gi, stimulatory and inhibitory G proteins; cAMP, cyclic AMP; PKA, protein kinase A; TG, triacylglycerol, HSL, hormone sensitive lipase; FFA, free fatty acid.

ysis has been well studied and reviewed previously (15,17,44) and will not be discussed in detail here. Briefly, it appears that increases in plasma norepinephrine and epinephrine during exercise succeed in overriding the inhibition of lipolysis by these same hormones at lower concentrations and the inhibition by adenosine and a constant or decreasing insulin concentration (Fig. 3). The net result is the activation of hormone sensitive lipase (HSL) and ultimately TG degradation to FFAs and glycerol. The FFAs must then be released from the adipose tissue into the blood.

The delivery of FFAs to working muscle is a function of the plasma [FFA] and muscle blood flow. Because muscle blood flow increases as a function of the power output, even the maintenance of a constant blood [FFA] means that FFA delivery to muscle increases severalfold during exercise. During prolonged low- to moderate-intensity exercise, the blood [FFA] often increases and also contributes to increased FFA delivery, as FFA release from adipose tissue slightly exceeds its removal from the blood. Although there is not a linear relationship between muscle FFA delivery and plasma FFA uptake and oxidation during all exercise situations, the FFA delivery to the muscle does influence FFA oxidation.

Romijn et al. (34) measured plasma [FFA] and tracer based estimates of adipose tissue lipolysis and plasma FFA oxidation during 30 min of whole-body exercise at 25, 65, and 85% $\dot{V}O_{2max}$ on three separate days in well-trained cyclists. Lipolysis increased as a function of the power output at 25 and 65% $\dot{V}O_{2max}$, and the plasma [FFA] remained high during exercise at these two intensities (pre-exercise FFAs were already high at ~0.8–10 mM due to an overnight fast). Therefore, FFA delivery to the working muscles increased from rest to exercise at 25% $\dot{V}O_{2max}$ and again from 25 to 65% $\dot{V}O_{2max}$ and presumably contributed to the maintenance of high plasma FFA uptake and oxidation rates at these two intensities.

These same relationships did not hold during exercise at 85% $\dot{V}O_{2max}$ (34). Adipose tissue lipolysis was not decreased during 30 min of exercise at 85% $\dot{V}O_{2max}$ but maintained at the 65% $\dot{V}O_{2max}$ rate, yet the [FFA] decreased by ~50%. The authors speculated that in spite of the maintained lipolysis at the high power output, decreasing adipose tissue blood flow prevented much of the released FFA from reaching the blood, thereby accounting for the lower blood [FFA]. It is likely that the large fall in [FFA] outweighed the increase in muscle blood flow from 65 to 85% $\dot{V}O_{2max}$, resulting in a decrease in FFA delivery to the working muscles at 85% $\dot{V}O_{2max}$. This corresponded with a large decrease in plasma FFA uptake and oxidation at 85% $\dot{V}O_{2max}$. To assess the importance of FFA delivery during exercise, Romijn et al. (35) artificially maintained the plasma [FFA] at the 65% $\dot{V}O_{2max}$ level during exercise at 85% $\dot{V}O_{2max}$. The plasma FFA uptake and oxidation rate was higher when the FFA delivery was maintained but did not return to the rate at 65% $\dot{V}O_{2max}$. This suggests that other factors, related to intramuscular events also play an important role in determining the rate of plasma FFA uptake and oxidation at higher exercise intensities.

FFA TRANSPORT ACROSS THE MUSCLE MEMBRANE

Until recently, it was believed that FFAs simply diffused through the bilipid layer of the muscle membrane into the bilipid muscle cell. The plasma [FFA] and/or the rate of

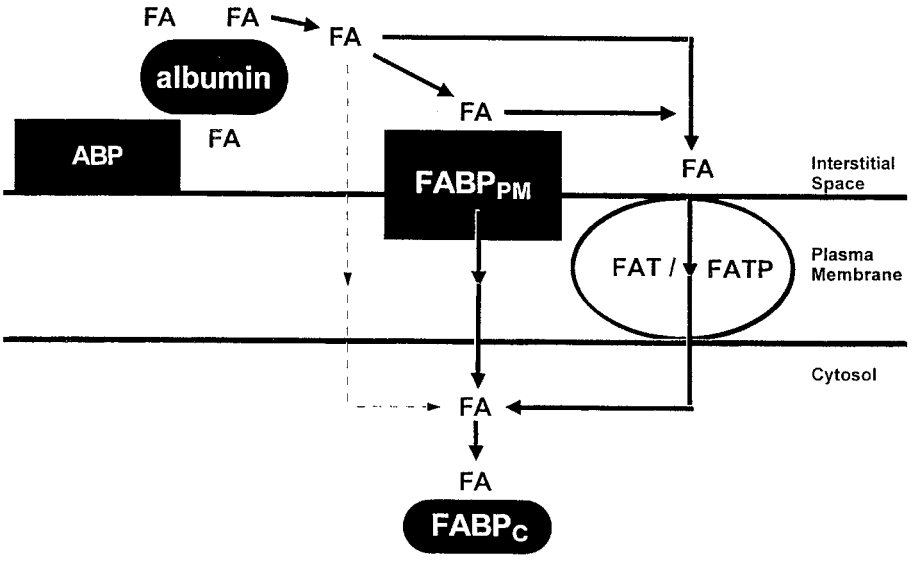

FIGURE 4—Schematic diagram of possible molecular mechanisms for long chain fatty acid uptake across the muscle plasma membrane. *Bold lines* represent possible carrier-mediated transport systems. FA, fatty acid; ABP, albumin binding protein; FABPpm, plasma membrane fatty acid binding protein; FAT, fatty acid translocase; FATP, fatty acid transport protein; FABPc, cytoplasmic fatty acid binding protein. Reproduced with permission from ref. 42.

FFA delivery to the muscles were believed to control their uptake into muscle. Although it still remains controversial (14), there is now strong evidence that a major portion of the FFAs enter muscle cells via protein-mediated mechanisms (28,42,51). This may involve actual transport of FFAs across the muscle membrane by carrier proteins or facilitation of their movement across the membrane by initial binding to transport proteins. The discovery of proteins that transport or assist the movement of fat into muscle cells is exciting for the field of muscle metabolism as it carries the implication that this is a major site of regulation for fat metabolism (Fig. 4).

Work in the last 10 years has identified and cloned three potential fat transport proteins: the fatty acid binding protein in the plasma membrane (FABPpm), the fatty acid translocase (FAT/CD36), and the fatty acid transport protein (FATP) (28,42). Although studies have confirmed that transcripts (mRNA) of these putative transporters are present in human and rodent skeletal muscle (4,20), much of the work has been done with red and white rodent skeletal muscle. Several lines of evidence support the importance of transport proteins in assisting fat movement across the muscle membrane and the work in this area has been greatly aided by the use of giant sarcolemmal vesicles derived from white and red skeletal muscle (28). The prepared vesicles are entirely right side out and contain ample cytoplasmic FABP to sequester incoming FFAs during the uptake measurements. Pure measurements of FFA uptake are therefore possible, without the confounding influence of ongoing metabolism, as all the FFA moved into the vesicle are accounted for and bound to cytoplasmic FABP. Measurements of the abundance of muscle membrane transporter protein can also be made on the vesicles. It has been reported that mRNA abundance and protein content of the fat transporters in the plasma membrane and FFA transport capacity were several fold higher in red, oxidative muscle (high capacity for fat metabolism) versus white, glycolytic muscle (6). The transport of fat also appeared to be a saturable process in both isolated perfused rat hindlimb muscle (43) and sarcolemmal vesicles prepared from red and white rat muscles (6).

From an exercise point of view, contractions acutely increased the maximal rate of fatty acid uptake and oxidation in perfused skeletal muscle (42). Chronic electrical stimulation increased the expression of FAT/CD36 mRNA and protein, vesicle fatty acid transport, and fatty acid oxidation in both red and white rodent muscle (3). Aerobic training in humans has also been reported to increase muscle FATPpm protein content (20). The most startling finding, however, was the recent report that the FAT/CD36 protein is acutely translocated from an intracellular pool to the muscle membrane during muscle contractions (5), in a similar manner to that reported for the GLUT 4 transporter. This correlated with increased fatty acid transport into vesicles prepared from the contracted muscle. These data strongly suggest that the FAT/CD36 transporter acutely translocated to the muscle membrane and promoted the uptake of FFAs during exercise.

Studies examining the regulation of fat transporter activity and translocation in various physiological situations are currently underway. For example, recent studies have reported that insulin also translocates FAT/CD36 to the muscle membrane (2) and that FAT/CD36 transport protein migrates to the muscle membrane without an increase in total protein expression in obese rats (29). This underlines the importance of measuring fatty acid transporter abundance directly in the muscle plasma membrane and not simply in the whole muscle homogenate. However, there appears to be no work to date identifying the factors that activate fat transporter activation/translocation during exercise. It might be expected that Ca^{2+} and the factors related to the energy status of the cell (e.g., free ADP, AMP, and P_i) would be involved as they play a large role in activating the pathways that metabolize carbohydrate in the cytoplasm. Certainly the activation of AMP kinase, secondary to increases in free AMP, would be a likely candidate, as it has been demonstrated to correlate with increased fat oxidation in resting and contracting skeletal muscle (47).

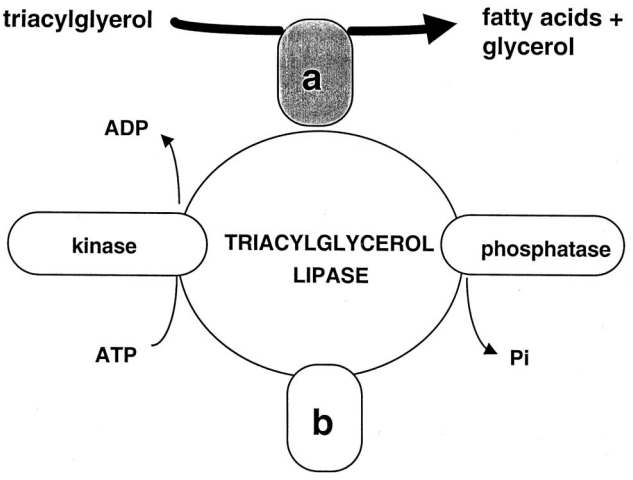

FIGURE 5—Proposed covalent regulation of muscle triacylglycerol lipase activity. The kinase is thought to be activated by cyclic AMP and unknown contraction factors.

REGULATION OF MUSCLE TRIACYLGLYCEROL LIPASE ACTIVITY

A significant amount of fat is stored in human skeletal muscle, usually in the range of 20–40 mmol·kg^{-1} dry muscle (19,21,40,45,46) or enough energy to account for ~70–100% of the energy stored as glycogen in a well-fed person (44). There are many metabolic pathways leading to storage of FFAs as TG and degradation of TG to FFAs and glycerol. However, the reaction catalyzed by TG lipase appears to be the only site of external regulation in these pathways and determines the rate of TG degradation to diacylglycerol and ultimately FFA during exercise. The additional enzymes responsible for removing the final two FFAs are near-equilibrium in nature and continue to degrade the di- and mono-acylglycerol as a function of increasing substrate concentrations. TG lipase, or the muscle version of hormone sensitive lipase (HSL), has been identified in skeletal muscle and is distinct from the other lipases that exist in muscle (16). It has a neutral pH optimum and is covalently activated by the action of a kinase that adds a phosphate and deactivated by a phosphatase that removes a phosphate as described for adipose tissue HSL (Fig. 5).

Very little is known regarding the regulation of this important enzyme as several factors have contributed to a general lack of research in this area. The first problem with studying muscle TG lipase has been the possibility of contamination with two other lipases that exist in skeletal muscle, a lysosomal lipase with an acidic pH optimum and lipoprotein lipase with an alkaline pH optimum. Lipoprotein lipase is produced in vesicles and secreted to the outside of the muscle cell to ultimately reside on the endothelial surface of the muscle blood vessels. It is important in regulating the degradation of circulating TGs in the blood during rest.

A second problem has been the controversy regarding whether muscle TG is actually utilized during aerobic exercise. Most studies that have measured pre and post exercise [TG] in needle muscle biopsy samples have not reported significant decreases (<20% of total TG) after 90–120 min of exercise at 50–65% $\dot{V}O_{2max}$ (13,19,21,40,46). When exercise is prolonged from 4–8 h, studies generally reported significant decreases (>40% of total TG) in the intramuscular lipid store (7,12). On the other hand, most studies that have estimated the use of intramuscular TG from measurements of the whole-body respiratory exchange ratio and plasma FFA oxidation have concluded that muscle TG is a major contributor of substrate during low- to moderate-intensity aerobic exercise (34,36). More recent direct measurements of muscle TG using a ^{1}H magnetic resonance spectroscopy technique also generally report significant muscle TG use during aerobic exercise, although absolute calibrations are difficult (11,24). Although all TG measurement techniques suffer from various limitations and assumptions, one concern with directly measuring intramuscular fat use in muscle biopsies over the shorter term is the energy density of TG. For example, estimations of the fat that would be required from the muscle TG store during exercise at 50–65% $\dot{V}O_{2max}$ for 90–120 min is only ~2–4 mmol·kg^{-1} dm or only 10–15% of the total TG store. A second concern with the direct measurements of muscle TG is the large variability that has been reported between biopsies from the same person (20–24%) in untrained subjects (46). These problems suggest that the biopsy technique may not be sensitive enough to detect the expected magnitude of change in many studies, whereas the other measurement/estimation techniques are. However, a recent study reported a much lower between biopsy variability with aerobically trained subjects (12%) and a significant decrease in muscle TG during 120 min of cycling at 55% $\dot{V}O_{2max}$ (45). Taken together, these recent results and those of the other techniques suggest that muscle TG is a significant fuel for oxidation during prolonged moderate-intensity exercise.

A third problem delaying work on the regulation of muscle TG has been the lack of a viable analytical technique for trapping and measuring the activity of the enzyme in the inactive and active fractions during exercise. These techniques exist for other covalently regulated enzymes that metabolize carbohydrate, such as glycogen phosphorylase and pyruvate dehydrogenase. Recently, Langfort and colleagues (23,25–27) reported activities of the inactive and active fractions of muscle TG lipase in rodent and human skeletal muscle in a variety of conditions. Their findings represent the first work examining the regulation of this important enzyme. Incubation of rat soleus muscles with epinephrine increased the activity of the enzyme in the active form (25). The conversion to the active form was mediated by the B-adrenergic second messenger cyclic AMP, via activation of protein kinase A. Presentation of the antiserum to HSL removed the effects of epinephrine (25). The activity of TG lipase in the active form was also increased in isolated soleus muscles after 1 and 5 min of electrical stimulation but returned to control levels after 10 and 60 min of contractions (26). Total TG activity was unaffected during the entire 60 min of stimulation. Neither prior removal of the sympathoadrenal organs nor the addi-

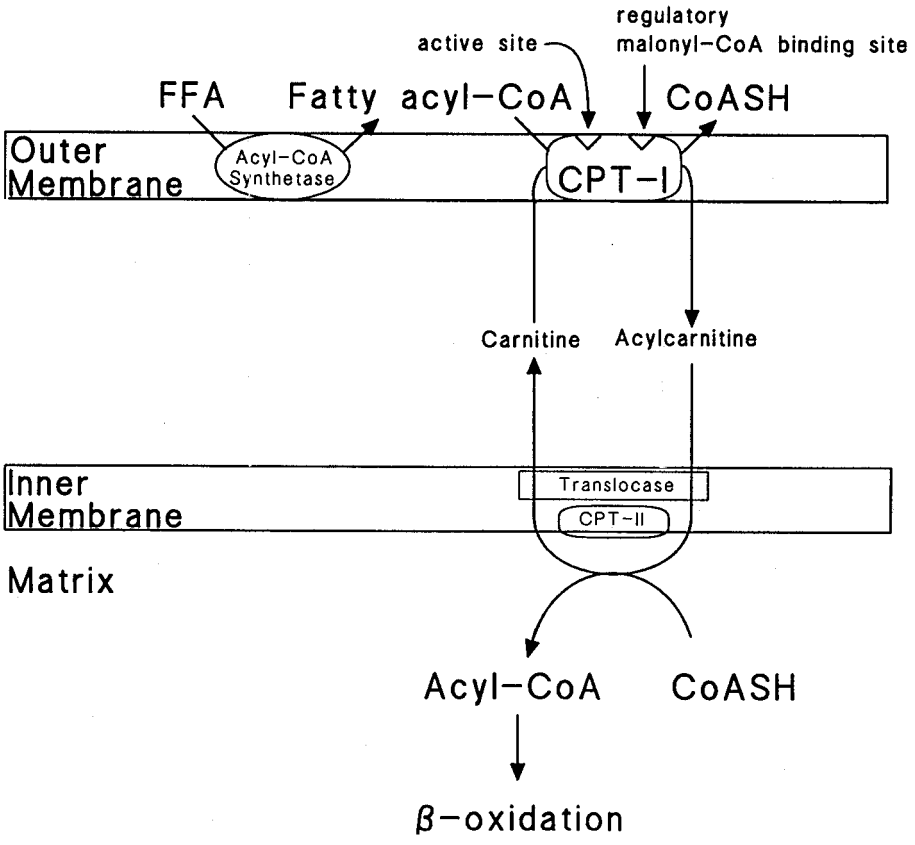

FIGURE 6—Schematic diagram of proposed regulation of long chain free fatty acid transport into the mitochondria. CPT I and II, carnitine palmitoyltransferase I and II.

tion of propanolol to the incubation medium impaired the contraction-induced activation of TG lipase (26).

One study has examined the effect of exercise on the activity of TG lipase in the active form in human subjects. Control and adrenalectomized (ADR) subjects cycled at ~70% $\dot{V}O_{2max}$ for 45 min and at ~86% $\dot{V}O_{2max}$ for 15 min (23). As the ADR subjects had no increase in catecholamines during exercise, they repeated the protocol a second time with the infusion of epinephrine to mimic the situation in the control subjects. The activation of TG lipase increased at the end of the exercise at 70% $\dot{V}O_{2max}$, with no further increase at 86% $\dot{V}O_{2max}$ in the control subjects. However, no activation of TG lipase occurred in the ADR subjects in the absence of increases in plasma epinephrine, whereas the infusion of epinephrine increased TG lipase activation at both power outputs (23).

These experiments demonstrated for the first time that TG lipase is activated during aerobic exercise in humans. However, the regulatory factors that govern this activation during exercise are unknown. Again, it might be predicted that increases in Ca^{2+} and free ADP, AMP (AMP kinase) and P_i may be involved, but this has not been examined. The results also demonstrate that the presence of plasma epinephrine was necessary for TG lipase activation in ADR subjects. However, it is not known whether this is the case for normal subjects with functioning adrenal glands and whether events in the cell alone are sufficient to activate TG lipase as demonstrated in the isolated rat soleus preparation.

TRANSPORT ACROSS THE MITOCHONDRIAL MEMBRANES

The carnitine palmitoyltransferase (CPT) complex, consisting of CPT I, acylcarnitine translocase and CPT II, plays a regulatory role in the transport of long chain fatty acids into the mitochondria for subsequent β-oxidation in skeletal muscle (Fig. 6) (31). CPT I, located on the outer surface of the outer mitochondrial membrane, catalyzes the transfer of a variety of long chain fatty acyl groups from CoA to carnitine. The generated acylcarnitine can then permeate the inner membrane, via the acylcarnitine/carnitine translocase. The acyl-CoA is then reformed in the matrix of the mitochondria by CPT II. This enzyme is located on the inner mitochondrial membrane and catalyzes the transfer of the acyl group from carnitine to CoA and the re-formed acyl-CoA enters the β-oxidation pathway (31).

CPT I is considered the rate limiting step in the oxidation of long chain fatty acids and is reversibly inhibited by malonyl-CoA (M-CoA), the first committed intermediate in fatty acid synthesis (1,30). Thus, there has been considerable interest in the potential role of M-CoA in regulating mitochondrial FFA uptake and oxidation in skeletal muscle. Work in rodent skeletal muscle suggests that muscle M-CoA levels are highest at rest to inhibit CPT I activity and maintain low rates of fatty acid transport. During exercise, when increased fat transport and oxidation are needed, M-CoA levels decrease and release the inhibition of CPT I (48,49).

Another line of work also proposed that fat metabolism is regulated by the level of glycolytic activity occurring in the muscle (9,37,38). Increases in glycolytic flux rates as the aerobic exercise intensity increases correlated with decreasing rates of fat oxidation. It was proposed that signals related to the increased glycolytic flux down-regulate fat metabolism inside the muscle cell and that increases in [M-CoA] could be the regulator inhibiting fat uptake and oxidation during intense aerobic exercise.

However, recent studies have demonstrated that M-CoA levels did not change during low to moderate aerobic exercise of varying durations in human skeletal muscle despite large increases in fatty acid oxidation rates (10,32,33). In addition, increasing the exercise intensity from 65 to 90% $\dot{V}O_{2max}$ was not associated with an increase in muscle [M-CoA] despite large decreases in fat oxidation (33). Therefore, the conclusion at the present time must be that M-CoA is not involved in the up-regulation of fat metabolism from rest to low- and moderate-intensity exercise and also not responsible for down-regulating fat metabolism when aerobic exercise becomes intense.

These findings in human muscle suggested that the regulation of CPT I activity is more complex than simple changes in [M-CoA]. Starritt et al. (41) used an isolated, intact mitochondrial preparation from human skeletal muscle (1) to study CPT I regulation *in vitro* and determined that CPT I is also inhibited by decreases in pH (7.0 to 6.8) but unaffected by other metabolites that accumulate (acetyl-CoA, acetylcarnitine) or decrease (CoA) during exercise. This suggests that substrate-enzyme interactions, structural changes in the binding of M-CoA to CPT I, and/or the presence of additional regulators may be important for increased fat transport during exercise. The sensitivity to pH may also explain the decrease in fat metabolism that occurs when moving from moderate to intense aerobic exercise. An interesting recent development has been the report that an M-CoA insensitive CPT I exists in rodent skeletal muscle, suggesting that a control system independent of M-CoA may account for the up-regulation of fat transport and oxidation during exercise (22). However, no studies to date have examined whether CPT I activity is sensitive to increases in cytoplasmic [Ca^{2+}] or free ADP, AMP (AMP kinase), or P_i, as might be expected for an enzyme that must up-regulate at the onset of exercise. If this type of control did exist, an explanation for how the enzyme becomes less sensitive to these signals during intense aerobic exercise would be needed to explain the decrease in mitochondrial fat transport and oxidation that occurs.

SUMMARY

Fat and carbohydrate are the major fuels metabolized to provide substrate for the aerobic production of energy during exercise in well-fed humans. Unlike carbohydrate metabolism, the regulation of fat metabolism in human skeletal muscle during exercise has not been well studied. Traditionally, it was believed that the regulation of fat metabolism was mainly at the level of fatty acid provision to the muscle (adipose tissue lipolysis) and transport of long chain fatty acids into the mitochondria (CPT I activity). It is now known that the transport of fatty acids into the muscle cell and the regulation of muscle triacylglycerol lipase activity within the cell are also important sites of regulation. Consequently, new lines of research are examining the coordinated regulation of skeletal muscle fat metabolism at the level of fat transport across the muscle and mitochondrial membranes, and regulation of TG lipase activity in both rodent and human models.

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