REVIEW ARTICLE

Optimizing Fat Oxidation Through Exercise and Diet

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Interventions aimed at increasing fat metabolism could potentially reduce the symptoms of metabolic diseases such as obesity and type 2 diabetes and may have tremendous clinical relevance. Hence, an understanding of the factors that increase or decrease fat oxidation is important. Exercise intensity and duration are important determinants of fat oxidation. Fat oxidation rates increase from low to moderate intensities and then decrease when the intensity becomes high. Maximal rates of fat oxidation have been shown to be reached at intensities between 59% and 64% of maximum oxygen consumption in trained individuals and between 47% and 52% of maximum oxygen consumption in a large sample of the general population. The mode of exercise can also affect fat oxidation, with fat oxidation being higher during running than cycling. Endurance training induces a multitude of adaptations that result in increased fat oxidation. The duration and intensity of exercise training required to induce changes in fat oxidation is currently unknown. Ingestion of carbohydrate in the hours before or on commencement of exercise reduces the rate of fat oxidation significantly compared with fasted conditions, whereas fasting longer than 6 h optimizes fat oxidation. Fat oxidation rates have been shown to decrease after ingestion of high-fat diets, partly as a result of decreased glycogen stores and partly because of adaptations at the muscle level. *Nutrition* 2004;20:716–727. ©Elsevier Inc. 2004

KEY WORDS: substrate utilization, exercise intensity, training, dietary CHO intake

INTRODUCTION

An inability to oxidize lipids appears to be an important factor in the etiology of obesity and type 2 diabetes. An elevated 24-h respiratory quotient in Pima Indians has been associated with a high rate of weight gain.[1] It has also been reported that individuals with obesity and non–insulin-dependent diabetes mellitus have a decreased capacity to oxidize fatty acids (FAs) and this is related to increased insulin resistance.[2] Further, some of the benefits of performing regular exercise, such as decreased insulin resistance, reduced hypertension, and reduced plasma low-density lipoprotein (LDL) concentration, are likely to be related to enhanced fat oxidation. This effect could be direct by adaptations in the fat metabolism pathways or indirect by reducing fat mass.[3,4] Exercise training and regular physical activity have been shown to increase fat oxidation in healthy individuals[5,6] and in obese populations.[7] Having a better understanding of the factors that influence the rate of fat oxidation at rest and during exercise is therefore important. Interventions aimed at increasing fat metabolism could potentially reduce the symptoms of the disease in these groups of patients and might have tremendous clinical relevance.

One of the main training adaptations observed in endurance athletes is increased fat oxidation, and it has been suggested that an increased capacity to oxidize fat is related to endurance capacity and exercise performance.[8] Training or diet interventions that optimize fat metabolism could therefore, at least in theory, also benefit endurance athletes.

Understanding the mechanisms behind the changes in fat metabolism that might occur as a result of various interventions and knowledge of the different sources of fat that may be utilized is important. Long-chain fatty acids (LCFAs) are a major source of energy at rest and during low- to moderate-intensity exercise. The source of FA utilized during exercise (FA from adipose tissue, FA in circulating lipoproteins (plasma triacylglycerol [TAG]) or muscle TAG, may vary depending on the conditions. Several sites have been suggested at which FA oxidation can be regulated: 1) adipose tissue lipolysis and FA delivery to the muscle, 2) FA movement across the muscle membrane, 3) hydrolysis of intramuscular TAGs (IMTAG), and 4) FA movement across the mitochondrial membranes. In Figure 1 these sites have been graphically displayed.

This review focuses on several interventions that influence fat oxidation, including the selection of the exercise intensity or the type of exercise, exercise training, and the influence of diet. In addition, the mechanisms behind the effects of these interventions on fat metabolism are discussed. This discussion is structured around the sites, displayed in Figure 1, where regulation of FA metabolism is believed to take place. For a more detailed discussion of these mechanisms, the reader is referred to several recent reviews.[9–14] This review is based predominantly on human studies in healthy individuals.

FAT OXIDATION AND EXERCISE

Acute Exercise and Fat Oxidation

An important question from a practical point of view is: At what exercise intensity can the highest rates of fat oxidation be found? In 1932, Christensen[15] showed, using respiratory exchange ratios (RERs), that changes in exercise intensity induce changes in substrate utilization. It was also observed that, with increasing exercise duration, fat oxidation progressively increased.[16] Later this was attributed to a reduction in muscle glycogen breakdown and total carbohydrate (CHO) oxidation.

The percentage of energy derived from CHO oxidation increases with increasing intensities, whereas the relative contribution of fat oxidation to total energy expenditure decreases. Few

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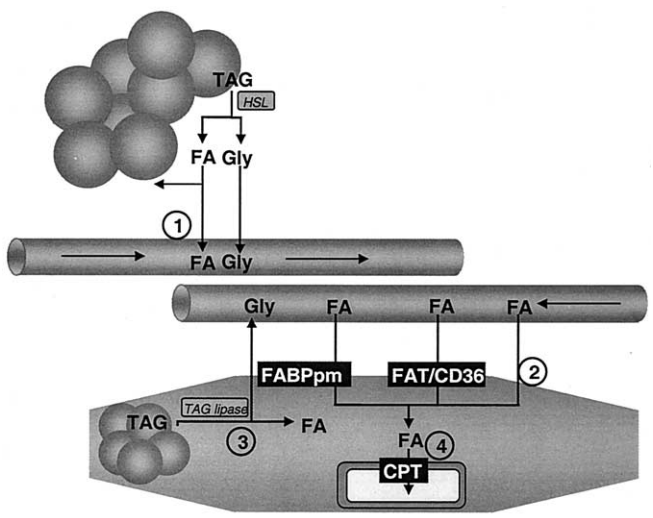

Fig. 1. Schematic representation of pathway of FAs from TAG stores to myocyte mitochondria and the sites where fat oxidation may be limited. HSL hydrolyses TGs into FAs and GLY. FAs will be re-esterified or appear in the circulation. 1, The availability of FA depends on the rate of lipolysis, rate of re-esterification, and the adipose tissue blood flow. 2, Several FA binding proteins have been identified in the plasma membrane of muscle cells, which facilitate the transport of FA into the myocyte. 3, A second pool of FA available for oxidation are FAs stored in IMTAG. 4, Hydrolysis of these IMTAGs is mediated by TG lipase (intramuscular HSL), which has been shown to be regulated by a number of factors. 5, After FAs are inside the myocyte, the CPT-I complex is necessary to transport the FA into the mitochondria, where they can undergo β-oxidation. CPT, carnitine palmitoyl transferace; FA, fatty acid; GLY, glycerol; HSL, hormone-sensitive lipase; IMTG, intramuscular triacylglycerol; TAG, triacylglycerol; TG, triglyceride.

studies have measured absolute rates of fat oxidation at different exercise intensities. In an often cited study, Romijn et al.[17] measured substrate utilization using indirect calorimetry and stable isotopes in male subjects exercising at 25%, 65%, and 85% of maximum oxygen consumption (Vo_{2max}). In absolute terms, CHO oxidation increased gradually with increasing exercise intensity, whereas fat oxidation increased from 25% of Vo_{2max} to 65% of Vo_{2max} and then decreased at 85% of Vo_{2max}. In this study, only three exercise intensities were investigated, and the precise intensity at which peak fat oxidation rates were found may not have been identified very accurately (the differences between 25%, 65%, and 85% of Vo_{2max} are very large). To more accurately determine the intensity that elicits maximal fat oxidation rates, we developed an exercise protocol that allowed us to study a larger number of exercise intensities with smaller increments.[18] On average, fat oxidation rates peaked around 64% of Vo_{2max}, with maximum rates of 0.60 ± 0.07 g · min^{-1} (Figure 2A).

In a follow-up study in a larger group of moderately and highly trained individuals (Vo_{2max} range 45 to 83 mL · kg^{-1} · min^{-1}) maximal fat oxidation rates were found at 63% of Vo_{2max}[19] (Figure 2B). At exercise intensities above approximately 65% to 70% of Vo_{2max}, fat oxidation rates decreased markedly. When the group was divided into a moderately trained group with moderate Vo_{2max} and a highly trained group with high Vo_{2max} (58 and 72 mL · kg^{-1} · min^{-1}, respectively), maximal fat oxidation rates were 0.48 and 0.56 g · min^{-1} ($P < 0.05$), respectively[19] (Figure 2C). Interestingly the exercise intensity at which peak fat oxidation rates were observed did not differ between the two groups, suggesting that the difference was caused predominantly by differences in energy expenditure, rather than differences in the relative contribution of fat. More recently, the protocol used in the above studies was modified for use on a treadmill and a larger group of volunteers was investigated with a wider range of Vo_{2max} and physical activity level. Venables et al.[20] studied fat oxidation (measured by gas exchange measurements) in 300 volunteers (157 men and 143 women) and observed that on average maximal fat oxidation was 0.46 ± 0.01 g · min^{-1} and this occurred at an exercise intensity of $48 \pm 1\%$ of Vo_{2max}. Women had higher peak fat oxidation rates than did men (8.18 ± 0.13 versus 7.14 ± 0.16 mg · kg^{-1} · min, respectively) and this occurred at a slightly higher exercise intensity (52 ± 1 versus $45 \pm 1\%$ Vo_{2max}, respectively, Figure 2F). From this study[20] and others[19,21–24] it is obvious that large interindividual differences exist in the ability to oxidize fat during exercise. Although sex, estimated physical activity level, and Vo_{2max} were good predictors of fat oxidation, a large percentage of the variation remained unexplained. This is discussed later in this review.

In conclusion, fat oxidation seems to peak at moderate exercise intensities (45% to 65% of Vo_{2max}) and the intensity at which this occurs may depend on sex, training status, Vo_{2max}, and diet. At higher intensities, however, fat oxidation will be downregulated. The possible mechanisms for this upregulation from low to moderate intensities and the downregulation from moderate to high intensities have been discussed in detail by other reviews[9–14] and is discussed briefly below.

ADIPOSE TISSUE LIPOLYSIS AND FA DELIVERY TO THE MUSCLE. The increase in fat oxidation from rest to moderate exercise intensities is mainly the result of increased FA availability. The rate of appearance (Ra) of FA is increased[17] as a consequence of increased lipolysis and a reduced rate of re-esterification of FA. Wolfe et al.[25] reported that the re-esterification percentage dropped from approximately 70% at rest to approximately 25% during 30 min of low- to moderate-intensity exercise. This decrease in combination with a three-fold increase in FA release from TAG hydrolysis resulted in a six-fold increase in the availability of FA for oxidation. In addition to the increased availability of FA, the transport of FA away from the adipose tissue and toward the exercising muscle was increased.[17]

The results of the study by Wolfe et al.[25] were based on measurements of the rate of appearance of glycerol as a measure for whole-body lipolysis. This method is based on a number of assumptions, including the fact that all lipolysis should be complete (so only complete hydrolysis of the TAG and no formation of diacylglycerols [DAG] and mono-acylglycerols) and that the main lipolytic tissues (muscle and adipose tissue) lack the capacity to reutilize glycerol. Recent studies have shown that it is likely that both these assumptions are violated to some extent, leading to an underestimation of the rate of lipolysis.[26–29] All studies using Ra glycerol as a measure of whole-body lipolysis may have to be interpreted with caution.

Nevertheless, when the exercise intensity increases to high intensities, there was no concomitant increase in Ra glycerol.[17] Romijn et al.[17] suggested that the lipolytic rate during exercise at 85% of Vo_{2max} was equal to the rate at 65% of Vo_{2max}. It has been suggested that part of the FA becomes trapped within adipose tissue as a result of a reduced adipose tissue blood flow.[30] It is a common observation that plasma FA concentrations do not change[31] or even decrease[17,32] when the exercise intensity is increased from moderate to high, and it has been suggested that reduced FA availability (the product of blood FA concentration and muscle blood flow) could be the reason for the lower fat oxidation rates at high intensities. To investigate whether reduced concentration of FA could be responsible for the decrease in fat oxidation, intralipid and heparin were infused in subjects cycling at 85% of Vo_{2max}[33] to establish plasma FA concentrations normally observed at 65% of Vo_{2max}. The increased FA availability resulted in a 27% increase in fat oxidation compared with the control trial (saline infusion), indicating that a lowered FA availability is causing the decrease in fat oxidation. However, the decrease in fat

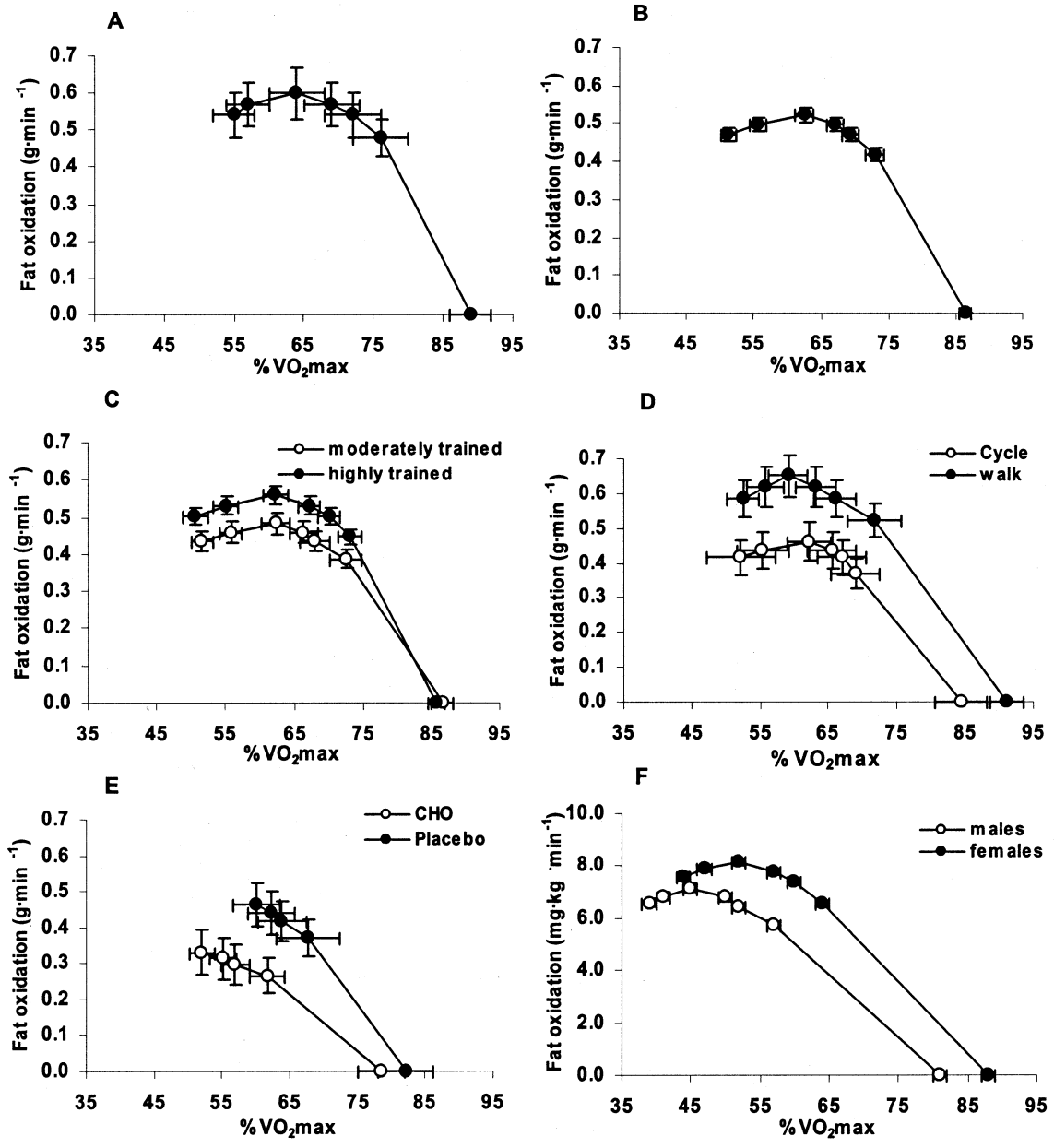

Fig. 2. Fat oxidation rates versus exercise intensity expressed as percentage of Vo_{2max} determined in (A) moderately trained men ($n = 11$)[18] (B) a large group of trained male cyclists with wide range of Vo_{2max} values ($n = 53$)[19] (C) moderately ($n = 26$) and highly ($n = 27$) trained male cyclists (Vo_{2max}, 59 versus 72 mL · kg^{-1} · min^{-1})[19] (D) cycle-ergometer-based and treadmill-based tests in moderately trained triathletes ($n = 12$),[85] (E) moderately trained cyclists after overnight fast and 45 min after ingestion of 75 g of glucose ($n = 11$),[108] and (F) large group of individuals on the treadmill-based test (157 men and 143 women).[20] CHO, carbohydrate; Vo_{2max}, maximum oxygen consumption.

oxidation seen when the intensity is increased from 65% to 85% of Vo_{2max} was almost 50%.[17] This suggests that fat oxidation at 85% of Vo_{2max} is only partly limited by plasma FA availability and that additional mechanisms are responsible for the decrease in fat oxidation.

HYDROLYSIS OF INTRAMUSCULAR TRIACYLGLYCEROLS. Whether IMTAGs are used during exercise and whether they contribute to a significant degree to energy provision have been points of discussion for many years. Measuring IMTAG use is difficult and it is possible that the outcomes of studies are somewhat affected by the limitations of the techniques used. It has been repeatedly shown that there is large interbiopsy variation in the determination of IMTAG content.[34] One of the main limitations of determining IMTAG breakdown using stable isotope tracers is the inability to distinguish between FA oxidation from TAGs originating from the circulation and TAGs originating from inside the muscle cells. Whereas isotope tracer and ^1H magnetic resonance spectroscopy studies have demonstrated IMTAG use during exercise, muscle biopsy studies often have found no statistical differences between pre- and postexercise IMTAG concentrations.[34] However, in a recent review evaluating all the literature regarding IMTAG use, it was concluded that the majority of studies suggest a significant and energetically important oxidation of FA derived from IMTAG in trained individuals regardless of the method used to determine or estimate IMTAG utilization.[34]

Romijn et al.[17] and van Loon et al.[31] determined the contributions of different fat sources to fat oxidation during exercise at different intensities. From these studies it becomes clear that at very low intensities (25% of $V_{O_{2max}}$), most of the energy is generated from the oxidation of plasma FA[17] and only a small portion is derived from other fat sources (plasma TAG and IMTAG) and CHO. During moderate-intensity exercise approximately half of the total energy is derived from the oxidation of fat and half from the oxidation of CHO. At these intensities, the contribution of non-plasma–derived FA and plasma FA to total fat oxidation is equal. Van Loon et al.[31] reported that at 57% of $V_{O_{2max}}$, 52% of the FA oxidized originated from adipose tissue. The contribution of non-plasma–derived FA decreased when the intensity was increased further. At 72% and 85% of $V_{O_{2max}}$ it was shown that only one-third of FA oxidized was from non-plasma sources. Because total fat oxidation was markedly decreased at these intensities, the overall contribution of non-plasma–derived FA oxidation total energy expenditure was only 10%.

One could speculate that the blunted hydrolysis of IMTAG at high-intensity exercise is the result of decreased activation of TAG lipase. It has been shown that the enzyme works optimal at neutral pH.[35] The low pH associated with high-intensity exercise could potentially decrease lipolysis of IMTAGs, depriving the cell of this fuel and causing the decrease in fat oxidation. However, in a recent study by Watt et al.[36] this theory was not confirmed. No difference in TAG lipase activity was detected in muscle biopsy samples after 10 min of exercise at 31%, 59%, and 90% of $V_{O_{2max}}$. It was suggested by the investigators that TAG lipase activation is not likely to be a regulatory factor in IMTAG hydrolysis.[36] It remains to be determined which factors govern the rate at which IMTAG are hydrolyzed at different exercise intensities.

FA MOVEMENT ACROSS THE MITOCHONDRIAL MEMBRANES. The transport of FA into the mitochondria is a potential limiting step for LCFA oxidation. It has been shown that, during conditions of high glycolytic flux, the oxidation of medium-chain fatty acids (MCFAs) is less inhibited than the oxidation of LCFAs. The main difference in the oxidation pathway of LCFA and MCFA is the transport into the mitochondria. LCFAs require the carnitine palmitoyl transferase (CPT) complex, whereas MCFAs use a different enzyme complex (carnitine octanoyl transferase), which appears to be less regulated, and part of the MCFAs can freely diffuse into the mitochondria.[37] It has therefore been suggested that the inhibition of the LCFA oxidation occurs at the CPT complex.[38,39] In Figure 3 the possible factors involved in the reduced activity of CPT-I have been displayed.

Malonyl coenzyme A (CoA) is an intermediate of FA synthesis and has been shown to inhibit CPT-I activity at rest.[40] Results from a study in which rats ran at different exercise intensities suggested a role for malonyl-CoA in the reduction of fat oxidation at higher exercise intensities,[41] although its role in human skeletal muscle is less clear. Odland et al.[42] studied eight subjects during three 10-min exercise bouts at intensities eliciting 35%, 65%, and 90% of $V_{O_{2max}}$. Muscle biopsies were collected at rest and at the end of the exercise bout. No marked changes in malonyl-CoA were found between the rest and exercise samples at any of the intensities. Although this study did not indicate a role for malonyl-CoA *concentration* in FA metabolism in skeletal muscle, it does not rule out a role for malonyl-CoA completely. It has been suggested that, under certain conditions, the sensitivity of CPT-I to malonyl-CoA is altered.[42] A cross-sectional study showed that CPT-I found in skeletal muscle of trained individuals is more sensitive to malonyl-CoA than is CPT-I from untrained muscle tissue.[43] Further, it has been shown in rodent muscle that the sensitivity of CPT-I to malonyl-CoA is pH dependent.[44] At pH 6.8, CPT-I binds to malonyl-CoA more efficiently than at a more neutral pH, which is present in the muscle at rest or during low-intensity exercise. Because high-intensity exercise is associated with increased muscle acidity, the reduction of fat oxidation at high exercise intensities could be the result of a pH-induced increased sensitivity of CPT-I to malonyl-CoA. The effect of pH on CPT-I sensitivity to malonyl-CoA in human muscle has not been established.

Apart from an indirect regulatory effect via malonyl-CoA, decreased muscle pH has been proposed as one direct mechanism causing the decrease in fat oxidation at high exercise intensities. In vitro studies performed in rat[45] and human[43] skeletal muscles have shown that even very small decreases in pH can reduce the activity of CPT-I substantially.[43] With the techniques presently available, it has not been possible to determine the effects of muscle pH on CPT-I activity or fat oxidation rates in vivo.

Several studies have reported that the availability of free carnitine is decreased with increasing exercise intensities when glycolytic flux and acetyl-CoA formation are high.[31,42,46–48] More recently, it was shown that, when exercise is performed with high muscle glycogen levels, significantly lower free carnitine levels are found compared with exercising in a glycogen-depleted state. Van Loon et al.[31] measured free carnitine and acetylcarnitine concentrations in vastus lateralis muscle in eight endurance-trained male subjects after 30 min of exercise at 40%, 55%, and 75% of $V_{O_{2max}}$. Whereas the total amount of carnitine measured in the muscle was the same at the three intensities, a shift occurred from mainly free carnitine at the lower intensity to mainly acetylcarnitine at high intensity. It was speculated that the decreased concentration of free carnitine observed at high exercise intensities could have limited CPT-I activity.[31]

In summary, when increasing exercise intensity from low to moderate, increases are seen in lipolysis, adipose tissue blood flow, and muscle blood flow, all of which increase the availability of FA for the muscles. This increased availability is accompanied by an increase in the absolute rates of fat oxidation. However, when the intensity is increased to high work rates, glycolytic flux and therefore CHO oxidation are markedly increased, whereas a decrease in fat oxidation is observed. Apart from reduced FA availability, reduced activity of CPT-I has been indicated as the main candidate responsible for the downregulation of fat oxidation at higher exercise intensity.

Training and Fat Oxidation

ENDURANCE TRAINING AND FAT OXIDATION. Endurance training can markedly increase fat oxidation during submaximal exercise. Data from cross-sectional[23,49–53] and longitudinal[22,54–60] studies have supported the notion that training reduces the reliance on CHO as an energy source, thereby increasing fat oxidation during submaximal exercise. Most training studies have been performed in young lean males, but the observed increase in fat oxidation is not confined to this specific group. Similar observations have been made in women,[6,60] elderly persons,[54,57,61] and obese individuals.[7] Further, increases in fat oxidation with training have been reported when trained and untrained individuals were compared at the same absolute and relative exercise intensities. This was shown in an elegant study by Friedlander et al.[6] who measured substrate use in a group of eight untrained women before and after a 12-wk training program. Subjects $V_{O_{2max}}$ was increased by 20% after training. Before training, subjects performed a trial at 65% of $V_{O_{2max}}$, after training, the subjects performed two additional trials, one at the same absolute workload as the pretraining trial and one at the same relative intensity. RER decreased significantly from 0.91 to 0.86 at the same absolute intensity and decreased to 0.88 at the same relative intensity.[6]

Differences found in fat oxidation at the same relative exercise intensity can be partly explained by the fact that the trained individuals are exercising at a higher absolute work rate. When cycling at 62% of $V_{O_{2max}}$, moderately-trained cyclists had fat oxidation rates of 0.48 ± 0.15 g · min^{-1}, and this rate was 0.56 ± 0.14 g · min^{-1} in well-trained cyclists[19] (Figure 2C). Despite this

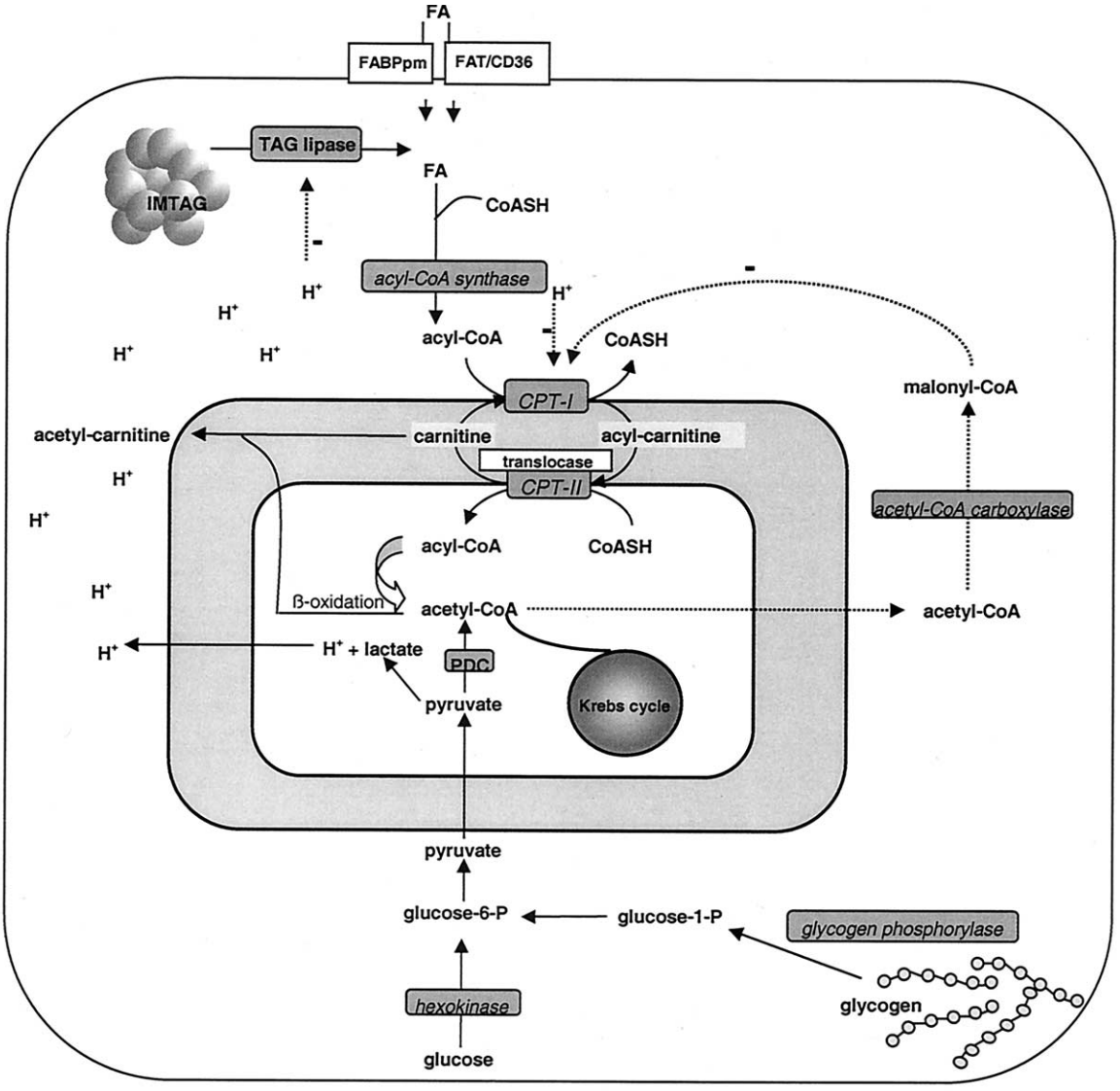

Fig. 3. Schematic representation of pathway of transport of glucose and FA into the mitochondria and subsequent oxidation. The uptake of FA is partly mediated by carrier proteins, FABPpm and FAT/CD36. FAs taken up from the plasma or released from TAG droplets stored inside the muscle cell are activated to acyl-CoA. Acyl-CoA is translocated across the mitochondrial membrane by the CPT complex. Once inside the mitochondria, acyl-CoA undergoes β-oxidation and acetyl-CoA is formed. Acetyl-CoA is also formed from pyruvate, a reaction catalyzed by the PDC. During high-intensity exercise, fat oxidation rates are diminished. It has been suggested that the decreased oxidation of FA is the result of increased glycolytic flux. Enhanced activation of PDC will increase the concentration of acetyl-CoA originating from glucose and glycogen. Several mechanisms have been proposed linking decreased rates of fat oxidation to an increase in glycolytic flux. 1) An increased concentration of acetyl-CoA can enhance the production of malonyl-CoA, which is the first intermediate in FA synthesis. Malonyl-CoA has been shown to have an inhibitory effect on CPT-I, inducing a reduction in FA transport into the mitochondria. 2) When the production of acetyl-CoA is larger than utilization by the Krebs cycle, part of the acetyl group will bind to carnitine. Carnitine will act as a temporary storage place for acetyl groups. However, the formation of acetyl-carnitine will result in a lower concentration of free carnitine. Because free carnitine is essential for optimal operation of the CPT complex, a reduction in free carnitine might be responsible for the reduced fat oxidation rates. 3) Increased glycolytic flux is accompained by an increased formation of lactic acid. The hydrogen ions, which are released when lactic acid disassociates, will reduce the pH in the muscle. Reduced muscle pH has been shown to directly decrease the activity of CPT. Further, it decreases the activity of intramuscular hormone-sensitive lipase and may increase the sensitivity of CPT-I to malonyl-CoA. CoA, coenzyme A; CoASH, free coenzyme-A; CPT, carnitine palmitoyl transferase; FA, fatty acid; PDC, pyruvate dehydrogenase complex; TAG, triacylglycerol.

relatively large difference in the absolute rate of fat oxidation, the relative contribution of fat oxidation to total energy expenditure was 30% in both groups.

To the best of our knowledge no studies have investigated which training is most effective in inducing changes in fat metabolism. The effects of intensity and duration of training programs on fat oxidation should be investigated to predict such changes. Also, it would be important from a practical point of view to know what the minimum amount of daily activity or training required to induce a measurable change in fat oxidation.

Nevertheless, it is clear that endurance training can induce adaptations that result in increased fat oxidation. One of the key adaptations that take place in skeletal muscle after training is an increase in mitochondrial protein and, as a consequence, activities of the enzymes of the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation. In addition, there is an increase in the cap-

illarization of the muscle.[62] Research investigating the effect of endurance training on fat oxidation has focused on many different sites that have been identified as potentially rate limiting in the fat oxidation process.

Adipose tissue lipolysis and FA delivery to the muscle. Although it is attractive to think that endurance training would increase lipolysis, whole-body or regional lipolysis does not appear to be affected to a great extent. This has been shown for young[55,56,60] and elderly[54,63] individuals. In cross-sectional studies, no difference in lipolytic activity was detected between trained and untrained subjects.[64]

FA movement across the muscle membrane. Until recently it was generally accepted that FA uptake into myocytes was through passive diffusion and was not one of the rate-limiting steps in FA oxidation. Turcotte et al.[65] however, recently showed that palmitate uptake and binding are saturable processes, thereby indicating a possible limitation at this stage of the fat oxidation process. No such saturation kinetics were observed in trained rat muscle, indicating that endurance training may facilitate the transport of FA across the sarcolemma. Endurance training results in increases in FA transport proteins because increases in mRNA and protein content have been found. Turcotte et al.[66] showed that the fatty acid binding protein plasma membrane (FABPpm) content increased significantly in rat red muscles after training. In accordance with an increase in transport proteins, an increased uptake of palmitate was reported.[66] Similar adaptations as a result of training were reported in human muscle. It was recently shown that after 3 wk of intense one-legged endurance training FABPpm content increased by 49%.[67] Tunstall et al.,[68] however, was unable to detect any change in FABPpm gene expression or protein content after 9 d of training. It is possible that 9 d of training is not sufficient to induce changes in gene expression. Few studies have investigated the effect of endurance training on FAT/CD36. When rat tibialis anterior muscles were constantly stimulated for 1 wk increases of three to seven-fold in FAT/CD36 mRNA were detected. The protein content of FAT/CD36 increased to a similar extent as the mRNA, which was associated with a two-fold increase in palmitate uptake.[69] When lean untrained human subjects exercised for 60 min at 63% of Vo_{2max} for 9 consecutive days, FAT/CD36 gene expression increased by 36%,[68] and this was accompanied by an increased FAT/CD36 protein content and FA uptake in the cells.[68]

Hydrolysis of intramuscular triacylglycerols. The effect of endurance training on the use of IMTAG is a controversial issue. Kiens and colleagues[59] measured IMTAGs use in seven male volunteers during exercise before and after a 9-wk endurance training program with one leg while keeping the other leg untrained. No difference in IMTAG use was detected during exercise between the trained and untrained legs. These data were confirmed in longitudinal[5,58] and cross-sectional studies.[70] Interestingly, in all of these studies, no net decrease in IMTAG could be detected during exercise. An equal number of studies has shown that the use of IMTAG during exercise is higher in the trained state than in the untrained state. Schrauwen et al.[71] trained six lean men for 3 mo and found that the increase in fat oxidation was completely accounted for by a increase in IMTAG utilization. IMTAG and/or very LDL-derived FA oxidation were 159% higher after the training period. Hurley et al.[22] reported a doubling in the decrease in IMTAG content during exercise after 12 wk of training. These findings were confirmed by Phillips et al.[72] and Martin et al.[56] There is a lot of uncertainty regarding the adaptations that trigger a possible increase in IMTAG use with endurance training. It has been shown on many occasions that the catecholamine response during exercise in the trained state is blunted and that skeletal muscle β-adrenergic receptor density remains the same. These data indicate that adaptation to other factors must occur with endurance training. In 2001, Enevoldsen and colleagues[73] examined the enzyme regulation of IMTAG breakdown changed before and after training in rat skeletal muscle. They found that the amount of TAG lipase protein did not change and the activity of the adrenaline-stimulated TAG lipase decreased after training. Because TAG lipase is under the regulation of adrenaline and contractions, the researchers speculated that the training-induced enhancement of IMTAG breakdown was probably due to an increased contraction-mediated hormone-sensitive lipose activity.[73]

FA movement across the mitochondrial membranes. CPT-1 activity has been shown to be significantly higher in the trained state than in the untrained state.[68,74,75] Tunstall et al.[68] recently investigated whether short-term training had an effect on the regulation of the genes involved in fat metabolism. Nine consecutive days of training resulted in a 57% increase in CPT-1 gene expression at rest and immediately after exercise. Whether the increase in CPT-1 mRNA was the net result of increased mRNA synthesis or increased stability remains to be determined.

To summarize, it has been consistently shown that fat oxidation rates increase with endurance training. Whole-body and regional lipolysis do not seem to be affected, which may rule out increased FA availability as a cause for the increased fat oxidation rates. Some evidence has been presented to show an increase in gene expression and protein content of protein transporters embedded in the myocyte membrane and this may increase FA transport. Some controversy exists regarding increased oxidation of FA from IMTAGs. The main adaptation that occurs in the body during endurance training is an increase in the activity of CPT-1, the enzyme identified as rate limiting in the process of fat oxidation.

RESISTANCE TRAINING AND FAT OXIDATION. The effect of resistance training on substrate use has not been extensively studied. Whereas studies investigating the effect of endurance training measured fat oxidation rates during the exercise bout, resistance training studies focused mainly on oxidation rates in the hours immediately after exercise or over 24 h. Numerous studies have investigated the effect of one strength training session on the rate of fat oxidation after exercise. Most of these studies reported a significant decrease in RER immediately[76,77] and 15 to 40 h[77–79] after the exercise bout. For example, Shuenke et al.[77] found that RERs were 0.89 24 h before the exercise bout and 0.79 immediately after the 31 min period of resistance exercise. The RER was still significantly lower 43 h after exercise, when the ratio was 0.84 (all measurements were taken after a 4-h fast).

The results regarding the effect of regular resistance exercise sessions are less consistent. Poehlman et al.[80] studied 16 young, lean, sedentary women before and after a 6-mo resistance training program. Measurements of O_2 uptake and CO_2 production were measured for 60 min using the ventilated hood technique several days after the last exercise session. The data showed that RER was 0.85 before and after the training program. Similar findings were reported in a group of young men after 3 mo of strength training.[81] Pratley et al.[82] were also unable to detect a difference in RER after 16 wk of resistance training in 13 elderly men. However, resistance training significantly decreased RER from 0.86 to 0.83 in a group of men and women ages 61 to 77 y.[83] The RER was measured using a ventilated hood system for 3 h in the morning after a 12-h fast, and 96 h after last exercise bout. Trueth et al.[84]

showed even larger decreases in a group of women after 16 wk of resistance training, from 0.87 to 0.81. Further research is necessary to specifically investigate the effects of resistance training program of varying durations on fat metabolism. Further, as far as we are aware, no studies have determined what mechanisms are behind the reported changes in fat metabolism, although it is likely that this is at least partly caused by a decreased muscle glycogen content.

Mode of Exercise and Fat Oxidation

Substrate oxidation may be different during different modes of exercise. Comparisons between running and cycling have generally shown higher rates of fat oxidation during running. However, comparing running with cycling may be problematic, and there has been debate about the best way to compare these different exercise modalities. $V_{O_{2max}}$ is higher during running than during cycling[85–88]; therefore, exercise at the same relative exercise intensity results in greater total energy expenditure during running. RER data provide an indication of the proportion of fat and CHO used but do not provide a good reflection of the absolute amount of fat oxidized (because this is also dependent on energy expenditure). Substrate metabolism has been compared in running and cycling at the same V_{O_2},[85] relative intensity,[87–90] intensity related to lactate threshold,[91] and over a wide range of intensities.[85] Nieman et al.[88] studied 10 triathletes during 2.5 h of running and cycling at 75% of the respective $V_{O_{2max}}$. Values RERs were only marginally different between the two exercise modalities (0.85 versus 0.87 for running and cycling, respectively); however, absolute fat oxidation rates were approximately 18% higher during running than during cycling. In our laboratory, an attempt was made to overcome these problems by measuring fat oxidation rates during walking and cycling over a wide range of absolute and relative exercise intensities.[85] In a group of 12 moderately trained triathletes, fat oxidation rates were between 10% and 40% higher at oxygen uptakes between 2.75 and 3.75 $L \cdot min^{-1}$. In Figure 2D, the fat oxidation rates during the treadmill and cycle ergometer tests are plotted against the exercise intensity (percentage of $V_{O_{2max}}$). Between 50% and 70% of $V_{O_{2max}}$, fat oxidation rates were significantly higher during the walking test than during the cycle test, with maximal rates of fat oxidation being 0.65 and 0.47 $g \cdot min^{-1}$, respectively.[85] This is agreement with data by Snyder et al.[92] who showed that, over a wide range of intensities, fat oxidation rates were significantly higher during the treadmill test than during the cycle ergometer test. It has been argued by Arkinstall and colleagues[91] that exercise intensity needs to be normalized relative to the individual's lactate threshold for each exercise mode. No differences were detected in RER or absolute fat oxidation rates between running and cycling when CHO was consumed during exercise. However, after 60 min of fasted exercise at lactate threshold, fat oxidation rates were significantly higher in the running trial than in the cycling trial.[91] This is in agreement with results from our laboratory,[85] which indicated fat oxidation rates of 0.28 $g \cdot min^{-1}$ at lactate threshold during cycling compared with 0.54 $g \cdot min^{-1}$ during walking. Thus, it appears that fat oxidation rates were higher during running or walking exercise than during cycling exercise, regardless of the way exercise intensity was matched between exercise modalities.

It remains to be determined whether the additional oxidized FA originate from adipose tissue, circulating TAG, or IMTAG. The mechanisms responsible for these differences are also unknown. It has been suggested that a lower catecholamine response as a result of the recruitment of a smaller muscle mass during cycling can lead to reduced activation of lipolysis.[85] Further, the number of muscle fibers recruited during cycling is smaller, thereby increasing the metabolic stress placed on the individual fibers, which potentially can only be met by increased CHO oxidation.

FAT OXIDATION AND DIET

Short-term CHO Intake and Fat Oxidation

Fatty meals have been suggested as a way to increase fat oxidation and the ingestion of medium-chain triacylglycerols (MCTs). The effectiveness of these nutritional interventions have been discussed elsewhere in this issue.[93] Here we discuss the effects of CHO intake before and during exercise.

It has been demonstrated that the ingestion of CHO before or during exercise can result in a marked reduction in FA oxidation. The magnitude of the effect that CHO intake has depends on several factors including the type and amount of CHO. Another important factor is the timing of intake, i.e., whether CHO is ingested in the hours before exercise, from the start of exercise, or at any point during exercise. When CHO is ingested before the start of exercise, RER is significantly higher than during fasted conditions in most studies.[94–107] Recently, it was shown that the suppression of fat oxidation is apparent over a wide range of exercise intensities. In 11 moderately trained men, fat oxidation rates were decreased by almost 30% from 50% until 70% of $V_{O_{2max}}$[108] (Figure 2E). The effect of ingestion of CHO after the start of exercise on fat oxidation depends on the exercise intensity. During low- and moderate-intensity exercise, CHO ingestion has been reported to reduce fat oxidation compared with fasting conditions almost to the same extent as when CHO is ingested before exercise.[109,110] During high-intensity exercise, however, most studies reported no differences in fat oxidation between the fasted and fed states.[111–113] The reported changes in fat oxidation as a result of CHO intake before and during exercise are caused by a number of mechanisms.

ADIPOSE TISSUE LIPOLYSIS AND FA DELIVERY TO THE MUSCLE. It has been shown repeatedly that plasma FA concentration is reduced after ingestion of CHO, which has been ascribed in part to a lower rate of lipolysis induced by increased insulin concentrations. In vivo studies at rest have demonstrated that even very small increases in insulin have a marked effect on lipolysis.[114,115] Horowitz et al.[107] studied lipolysis and fat oxidation rates in six male subjects during 60 min of exercise at 44% of $V_{O_{2max}}$ after an overnight fast and after ingestion of a bolus of CHO. It is generally accepted that in fasted conditions FA availability is significantly greater than fat oxidation during exercise. It was found that FA oxidation during fed conditions equaled FA liberation from lipolysis.[107] The suppressive effect of CHO intake on lipolysis during exercise can last at least 6 h. Montain *et al.*[116] showed that the glycerol concentration during exercise, which has been used as a very rough measure of lipolysis, remained lower after 2, 4, and 6 h of fasting compared with a 12-h fast. To investigate whether the decrease in lipolysis was responsible for the reported decrease in fat oxidation, Horowitz et al.[107] elevated increased plasma FA concentration from 0.15 to 0.48 $mmol \cdot L^{-1}$ after pre-exercise CHO feedings by infusing a TAG emulsion (Intralipid) and heparin. This resulted in an increase of fat oxidation of 22%, indicating that decreased FA availability was contributing to the decrease in fat oxidation. However, because the rate of fat oxidation with elevated plasma FA concentrations remained lower than fat oxidation in the fasted state, it was concluded that this was not the only mechanism responsible for the reduction in fat oxidation.

When CHOs are provided to subjects from the onset of low- to moderate-intensity exercise, the lipolytic response resembles the response seen after the ingestion of CHO in the hour(s) before exercise. When the ingestion of CHO is delayed until after the start of exercise, the effect on fat oxidation is altered. In trials where CHO was ingested 60 min before exercise, insulin concentration peaked at 53 μU/mL and decreased to 40 $\mu U \cdot mL^{-1}$ at the start of exercise. Horowitz et al.[113] performed a study with six trained

men who cycled for 2 h at 25% $V_{O_{2max}}$ while consuming CHO after 30, 60, and 90 min. Ingestion of CHO after 30 min of low-intensity exercise resulted in a peak insulin concentration of 27 $\mu U \cdot mL^{-1}$, far lower than when the CHO was ingested before exercise. Because the antilipolytic effect of insulin is strong even at low concentrations, a blunting of lipolysis was observed. However, because lipolysis had been stimulated during the first 30 min of exercise, lipolysis was decreased only to a limited extent and fat oxidation was not decreased until after 90 min of exercise. Interestingly, lipolysis was in excess of fat oxidation during the entire trial. This suggests that, under these circumstances, plasma FA availability was not limiting fat oxidation.

When the same experiment was repeated at a higher exercise intensity, a different response was observed.[113] The insulin concentration increased only marginally, albeit significantly, as a result of the CHO ingestion. Lower lipolytic rates were observed during the final 20 min of exercise in the CHO trial compared with the fasted trial, resulting in a lower plasma FA concentration. Despite this reduced availability of FA, total fat oxidation rates appeared not to be lower in the CHO trial. Coyle et al.[111] reported that when CHO ingestion was started after 20 min of even higher intensity exercise (74% of $V_{O_{2max}}$), the insulin response was completely prevented. Insulin has been shown to affect not only lipolysis but also FA re-esterification. In mice and rats, the rate at which FAs are being re-incorporated in TAGs is increased with increasing insulin concentrations at rest[117,118] and during exercise.[119] Sidossis et al.[120] studied FA uptake and oxidation over the leg and splanchnic area under hyperglycemic and hyperinsulinemic conditions in five healthy human volunteers. Fat oxidation appeared to be decreased in both areas compared with basal conditions, whereas no change was detected in the uptake of the FA. These results suggest that the FA have an alternate fate, e.g., (re)esterification into TAG.

HYDROLYSIS OF INTRAMUSCULAR TRIACYLGLYCEROLS. CHO ingestion 30 min after the onset of a 2-h exercise bout at 68% of $V_{O_{2max}}$ resulted in a 25% lower lipolytic rate compared with the same exercise bout in fasted conditions. At the same time, a 30% to 40% reduction in plasma FA concentration was seen in an attempt to determine the effect of CHO intake during exercise on TAG lipase. Watt et al.[121] had seven men cycling for 2 h at 60% of $V_{O_{2max}}$ while ingesting a glucose or a placebo drink. CHO ingestion resulted in elevated insulin and decreased epinephrine concentrations, but failed to reduce fat oxidation. TAG lipase activity was measured in muscle biopsies taken before and immediately after exercise. Enzyme activity increased significantly from rest to the end of exercise in the fasted trial; however, the exercise-induced increase was blunted in the CHO trial. Despite this change in the activity of the key enzyme in the process of IMTAG use, no difference in non-plasma FA oxidation was detected between the two trials.[121]

FA MOVEMENT ACROSS THE MITOCHONDRIAL MEMBRANES. In a study by Coyle and colleagues[38] it was shown that the reduction in fat oxidation seen after CHO ingestion is partly caused by a reduced entrance of LCFA in the mitochondria. This study was also based on the fact that MCFAs do not require CPT-I to be transported into the mitochondria, whereas LCFAs do. Six endurance-trained men cycled for 40 min at 50% of $V_{O_{2max}}$ after an overnight fast and after ingestion of a CHO bolus 60 and 10 min before the start of exercise. During the exercise bout tracer amounts of isotopically labelled octanoate (MCFA) and palmitate (LCFA) were infused and their respective oxidation rates were measured. The oxidation of LCFA was reduced in the CHO trial, whereas MCFA oxidation was not affected by the intake of CHO. The basis for the decreased CPT-I activity has not been firmly identified, although several suggestions have been brought forward (as discussed above).

In summary, the effects of CHO intake on fat oxidation depend on a number of factors, including timing of CHO intake and exercise intensity. However, under most conditions, CHO intake decreases fat oxidation. When CHOs are consumed before exercise, large increases in insulin are seen, which affect the rate of lipolysis, thereby decreasing the availability of FA for oxidation. In addition, the effect of CHO intake is lower when the CHOs are taken just before or 20 to 30 min after the start of exercise. When CHOs are taken during high-intensity exercise, they appear to have no effect on fat oxidation.

Long-Term Diets and Fat Oxidation

In addition to the acute dietary manipulation described above, chronic dietary interventions have been shown to affect fat oxidation. The effect of high-fat diets and high-CHO diets on substrate utilization has been studied extensively. It is important to note that if, in a situation of energy balance, one of the macronutrients is present in abundance, this automatically lowers the contribution of the others, i.e., a high-fat diet can also be seen as a low-CHO diet (and vice versa). This suggests that the metabolic characteristics of a high-fat diet might be due to the relatively low dietary CHO intake.

After 3 to 49 d on a high-fat, low-CHO diet, fat oxidation usually increased compared with a control diet.[122–127] For example, Stepto et al.[127] showed that after only 3 d of consuming a diet containing 65% fat, RER values dropped from 0.89 to 0.79 in a group of trained cyclists who exercised daily. However, a decrease has not always been observed.[128,129] The diets in studies in which no effect on substrate utilization was found had a relatively low dietary fat content (55% to 60%) and no exercise was performed during the diet period. It could be speculated that changes reported in substrate utilization after ingestion of high-fat diets with a relatively high-fat content in combination with regular exercise are partly driven by a lowering of glycogen content. Depletion of glycogen stores has been reported when CHO intake is low and/or exercise is performed regularly.[130,131] Achten et al.[130] provided seven trained runners with a diet containing 45% CHO, 40% fat, and 15% protein for 11 d, during which the subjects performed daily intense exercise. After 11 d, fat oxidation rates were significantly increased, whereas muscle glycogenolysis was decreased. This effect was most likely caused by reduced muscle glycogen stores.[131]

In addition to decreased glycogen stores while following high-fat, low-CHO diets, some adaptations may occur at the muscle level as a result of the high dietary fat intake. In rats it has been consistently shown that ingestion of high quantities of dietary fat increases the activity of β-hydroxyacyl CoA dehydrogenase (β-HAD), one of the key enzymes in the β-oxidation pathway.[132–135] An increased β-HAD activity was also shown in humans,[136] in some cases after only 5 d after changing to a high-fat diet.[137] In addition, increases in CPT-1 activity have been reported after 10 d of consuming a high-fat diet.[124] Cameron-Smith et al.[137] reported another interesting finding: after 5 d of a high-fat diet, the gene expression of FAT/CD36 increased. This suggests an upregulation of the transport of FA into the muscle cell as a result of ingestion of high-fat diet.

To separate any changes in substrate utilization occurring due to enzymatic adaptations from partial glycogen depletion, a high-fat diet needs to be combined with a glycogen refueling intervention. The effects of consumption of a CHO-rich diet for a short period after adaptation to a high-fat diet (i.e., CHO store "restoration") has been investigated on several occasions. Burke et al.[138] and Carey et al.[123] investigated substrate utilization and performance in trained cyclists/triathletes who consumed a high-fat diet for 5 d (days 1 to 5) followed by 1 d (day 6) of a high-CHO diet. In both studies, it was shown that RER during exercise at 70% of $V_{O_{2max}}$ decreased significantly from day 1 to day 6. Subjects were

allowed to consume a high-CHO breakfast before the start of the exercise bout on day 7, which makes a direct comparison of fat oxidation rates after a control diet and a high-fat, high-CHO diet impossible. Not surprisingly, no difference was detected between the RERs on day 1 and day 7. With a similar protocol (6 d high fat, 1 d high CHO) without a pre-exercise meal on day 7, despite the complete restoration of muscle glycogen stores, the blunted RER values as a result of the high-fat diet remained.[122] This indicates that metabolic adaptations take place in the body that are independent of muscle glycogen concentrations. However, when the duration of the high-CHO period is prolonged, the differences in fat oxidation between high-CHO and high-fat diets disappeared.[139] Helge et al.[139] performed a study in which 13 untrained men consumed a high-fat diet for 7 wk or a high-CHO diet followed by 1 wk of a high-CHO diet. Fat oxidation rates were significantly lower after 7 wk of the high-fat diet, but these differences were no longer apparent after the week of high-CHO feeding.

There remains some controversy regarding the sources of the additional fat oxidized after consuming a high-fat diet. Schrauwen et al.[129] reported similar plasma FA oxidation after consumption of the high-fat diet compared with a low-fat diet. In this study the increased rate of fat oxidation was completely accounted for by increased TAG oxidation (plasma very LDL-TAG and/or IMTAG). Conversely Helge et al.[140] found whole-body plasma FA oxidation to be significantly higher after a 7-wk consumption of a high-fat than after a high-CHO diet. No significant breakdown of IMTAG could be detected during exercise, so the researchers concluded that IMTAGs were not a prime contributor to the increased fat oxidation. It was argued by Helge et al.[141] that the difference between the two studies might have been caused by the duration of the diet (7 d versus 7 wk). In two recent short-term fat diet studies,[142,143] one using muscle biopsies and one using stable isotopes to investigate the source of increased fat oxidation, increased IMTAG breakdown was found. Six well-trained cyclists consumed a diet consisting 65% fat or CHO for 2 d followed by a 3-h exercise bout at 70% of $V_{O_{2max}}$ on day 3.[142] A greater decrement in IMTAG content was found during exercise after the high-fat diet. Zderic et al.[143] suggested that elevated hydrolysis of TAGs stored intramuscularly were mainly responsible for the increased fat oxidation after short-term ingestion of a high-fat diet. The importance of IMTAG in the determination of substrate selection was further shown by Coyle and colleagues.[144] Depletion of IMTAG stores, induced by a very low-fat diet (2%), decreased fat oxidation rates by 27%. Using stable isotopes showed that the plasma FA oxidation rates were not altered, indicating that the entire reduction in fat oxidation was accounted for by lowered IMTAG stores.

To summarize, consumption of high-fat diets in which more than 60% of the energy is derived from fat has been shown to decrease fat oxidation rates during exercise, even if the diet is consumed for only 2 to 3 d. It is likely that part of the change in substrate selection is caused by reduced muscle glycogen stores. However, increased activity of β-HAD and CPT-I and gene expression of FAT/CD36 have been reported.

LARGE VARIATION IN FAT OXIDATION STILL UNEXPLAINED

Although a number of important factors regulating fat oxidation have been identified, It is apparent from many studies that a considerable degree of intersubject variability in substrate utilization persists. This is especially apparent in a study by Venables et al.[20] in which fat oxidation was measured in a large group of healthy individuals. Peak fat oxidation rates ranged from 0.18 to 1.01 g/min. This variation still exists (although to a lesser degree) when all factors such as training status and diet have been controlled for. For example, Helge et al.[145] found RERs to range between 0.83 and 0.95 in a group of untrained men exercising at 55% of $V_{O_{2max}}$. Goedecke et al.[21] studied 61 trained cyclists and measured RER at rest and during exercise at three different intensities (25%, 50%, and 70% of peak power output), and found that resting RER ranged between 0.72 and 0.93 and that this degree of variability remained throughout all exercise intensities. When testing a fairly homogeneous group of moderately to highly trained males, we observed maximal fat oxidation rates of 0.23 g/min in some subjects, whereas others were able to oxidize FA at four times that rate (0.91 g/min).[19] Measurements of fat oxidation seem fairly reproducible within one person,[19] but a large degree of interindividual variation exists. Venables et al.[20] demonstrated that lean body mass, estimated physical activity level, $V_{O_{2max}}$, sex, and fat mass together could only account for 34% of the variance in peak fat oxidation rates. This means that 66% of the variance could not be accounted for. Dietary factors are likely to explain some of the remaining variances, but there is still a large part of the variance unexplained and this is likely to be genetically determined.

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