

## CHAPTER 20

# Fat Oxidation During Exercise: Role of Lipolysis, FFA Availability, and Glycolytic Flux

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Although it long has been recognized that fat and carbohydrate are the two primary substrates oxidized during exercise, much remains to be learned about the factors that regulate fat oxidation. Fat oxidation by skeletal muscle during exercise is derived predominantly from either the vast store of triglyceride in adipose tissue or from triglyceride contained directly within muscle fibers (i.e., intramuscular triglyceride; IMTG) (11). Another potential source of fat, plasma triglyceride seem to contribute little to fat oxidation during exercise because chylomicron triglyceride hydrolysis by lipoprotein lipase and uptake by muscle during exercise appears relatively low (24, 26). However, plasma triglyceride probably serve primarily to replenish IMTG after exercise.

This review will discuss the conditions during which the delivery of fatty acids (FA) into the mitochondria of skeletal muscle may limit fat oxidation during exercise. The amount of FA in plasma or in the sarcoplasm is small, and thus their turnover must be high in order to deliver significant FA to the mitochondria for oxidation. Therefore, triglyceride hydrolysis (i.e., lipolysis) theoretically establishes the upper limit for fat oxidation during exercise. Not all of the FA liberated in lipolysis is oxidized due to re-esterification or limitations at various steps in transporting FA. This includes the transport of FA out of adipose tissue, through the circulation of plasma or from capillary to mitochondria (38). Finally, the transport of FA through the mitochondrial membrane can limit fat oxidation (8). Evidence is accumulating that this latter process is sensitive to carbohydrate metabolism in general and glycolytic flux in particular (8).

This review supports the idea that fat oxidation in skeletal muscle during exercise is largely regulated by carbohydrate metabolism. It is interesting that situations that shift substrate oxidation from fat toward carbohydrate, such as pre-exercise carbohydrate meals and increasing exercise intensity, appear to exert well-coordinated effects both on adipose tissue and skeletal muscle (8, 21, 18, 29, 34). It seems that the various systems of the body coordinate to minimize the appearance of FA that cannot be oxidized by skeletal muscle during exercise.

### Substrate Mobilization and Oxidation During Exercise of Increasing Intensity

Figure 20.1 describes the pattern with which endurance-trained subjects oxidize carbohydrate and fat during exercise of increasing intensity, performed after an overnight fast (29). Constant rate infusion of stable isotopes and determination of isotopic enrichment, allowed calculation of the rates of plasma FFA appearance (RaFFA) and disappearance (RdFFA). The FA oxidation in excess of plasma FFA disappearance is calculated to be that derived from IMTG with the assumption that oxidation of other triglyceride stores during exercise (i.e., plasma triglyceride) is relatively small and that RdFFA is fully oxidized. As shown (figure 20.1), the turnover (Rd) of FFA in plasma declines as the intensity of exercise increases from low (i.e., 25%  $\dot{V}O_{2\max}$ , comparable to walking), to moderate (i.e., 65%  $\dot{V}O_{2\max}$ , comparable to a running pace for 2–4 hours), to high intensity (i.e., 85%  $\dot{V}O_{2\max}$ , the highest pace maintained for 30–60 min) (figure 20.1). Furthermore, this decline in plasma FFA turnover (i.e., both Ra and Rd) was directly reflected in plasma FFA concentrations after 30 min of exercise (figure 20.2). Measurements were not made at 45%  $\dot{V}O_{2\max}$  for comparison to 25%  $\dot{V}O_{2\max}$  to identify the exercise intensity with the highest rate of RdFFA. Interestingly, RaFFA and plasma FFA concentrations increased abruptly with the cessation of exercise at 85%  $\dot{V}O_{2\max}$  and to a lesser extent after 65%  $\dot{V}O_{2\max}$  with little perturbation after 25%  $\dot{V}O_{2\max}$  (figure 20.2). In that this influx of FFA into plasma upon exercise cessation was not associated with increased lipolysis, it would seem to reflect entry into plasma of FA trapped in adipose tissue during exercise, possibly due to inadequate adipose tissue blood flow (2, 33). If indeed the magnitude of the post-exercise increase in plasma FFA concentration reflects the relative FA trapping, it appears to be directly related to exercise intensity. The assumed greater trapping of FA in adipose tissue during high-intensity compared with low-intensity exercise (i.e., 85% vs. 25%  $\dot{V}O_{2\max}$ ), despite higher rates of lipolysis during high-intensity exercise (29), seems to prevent the mobilization into plasma of FA under conditions during which their oxidation by skeletal muscle is reduced, as discussed below.

Figure 20.1 indicates that the increase in total fat oxidation when intensity is increased from 25% to 65%  $\dot{V}O_{2\max}$  appears to be derived from increased IMTG oxidation in these endurance-trained subjects. At 25%  $\dot{V}O_{2\max}$ , total FA oxidation is matched to RdFFA, whereas at 65%  $\dot{V}O_{2\max}$ , RdFFA can account for approximately one-half of total FA oxidation, with IMTG presumably providing the remainder. Total fat oxidation is reduced at 85% compared to 65%  $\dot{V}O_{2\max}$  in association with large increases in glycolytic flux, which, as discussed below, may be a mechanism by which carbohydrate metabolism actively regulates FA oxidation.

### Lipolysis During Exercise

At rest the "triglyceride-FA substrate cycle" is high, with only about 30% of the FA resulting from lipolysis appearing in plasma, whereas the remainder is re-esterified

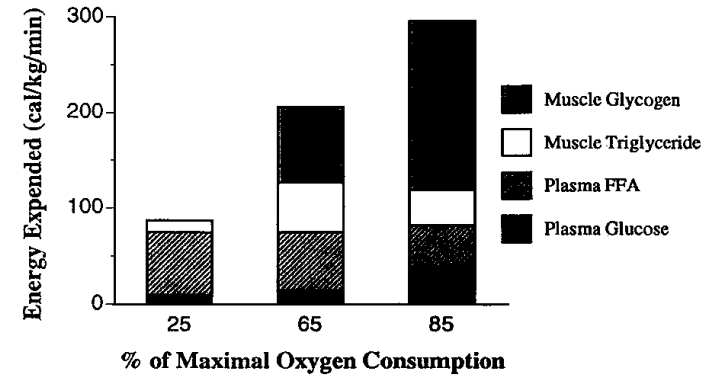


Figure 20.1. Contribution of the four major substrates to energy expenditure after 30 min of exercise at 25%, 65%, and 85% of maximal oxygen uptake when fasted. Reprinted, by permission, from Romijn et al. 1993.

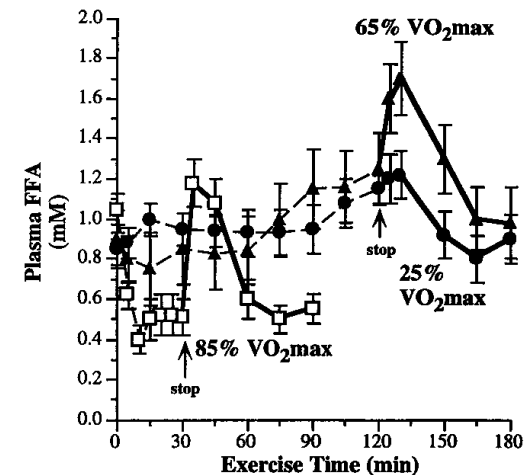


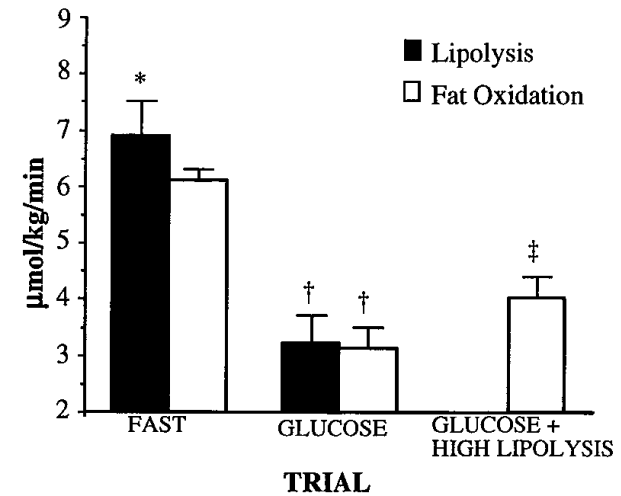
Figure 20.2. Plasma FFA concentration during and following exercise at 25%, 65%, and 85% of maximal oxygen uptake when fasted. Note the magnitude of increase in plasma FFA when exercise is stopped, especially after exercise at 85% and 65% of maximal oxygen uptake.

(40). Therefore, resting lipolysis greatly exceeds RaFFA and total FA oxidation (3, 20, 40). However, re-esterification is reduced markedly during exercise, and thus the difference between lipolysis and fat oxidation is reduced (40). During exercise in the fasted state, lipolysis exceeds fat oxidation by 10–30% depending upon the intensity of exercise and oxidative ability of the subjects (18, 22).

Lipolysis in adipose tissue as well as IMTG is controlled by hormone sensitive lipase, which is activated by beta-adrenergic receptor stimulation during exercise, largely via the action catecholamines in general, particularly epinephrine (1, 6). Lipolysis of IMTG also may be influenced by metabolic processes within the contracting muscle fibers (26, 36). These processes may be responsible for the apparent increase in IMTG oxidation during exercise at 65% compared to 25%  $\dot{V}O_{2\max}$  (figure 20.1). Insulin is by far the most potent antilipolytic hormone (4, 6). The lowering of insulin below resting basal levels during exercise may serve to further release inhibition of lipolysis. At rest, alpha-adrenergic receptor stimulation inhibits adipose tissue lipolysis, but this system exerts little influence on lipolysis during exercise (1). Therefore, in a simplistic sense, lipolysis during exercise appears to be activated largely through catecholamines and intramuscular metabolism and inhibited by the action of insulin.

### Lipolysis Can Limit Fat Oxidation During Exercise

During exercise in the fasted state, which is accompanied by low insulin levels, whole-body lipolysis exceeds and thus does not appear to limit fat oxidation. Studies that have given subjects nicotinic acid, an antilipolytic agent in adipose tissue, have observed reduced fat oxidation during exercise (15). This observation indicates that reductions in lipolysis are associated with reduced fat oxidation, but it did not establish quantitatively that fat oxidation was reduced to the level of lipolysis (15). Until recently, studies have not directly measured lipolysis during exercise following administration of antilipolytic agents to quantitatively compare lipolysis and fat oxidation. Recognizing that lipolysis is very sensitive to insulin, Horowitz et al. (18) recently directly determined that lipolysis is reduced markedly during exercise after a carbohydrate meal to a level where it appears to equal and thus limits fat oxidation. As shown in figure 20.3, during exercise (44%  $\dot{V}O_{2\text{peak}}$ ) in the fasted state, lipolysis exceeded fat oxidation by 13%. However, when exercise was performed 60 min after ingesting glucose to increase insulin, fat oxidation was suppressed to the point where it equaled lipolysis (figure 20.3). During a third trial, also performed after glucose ingestion (i.e., GLUCOSE + HIGH LIPOLYSIS), lipolysis was exogenously increased by intravenous infusion of triglycerides and heparin; the latter releases LPL to hydrolyze the infused triglyceride in plasma. Interestingly, this stimulation of lipolysis increased fat oxidation by 30% during exercise after carbohydrate ingestion (figure 20.3), suggesting that lipolysis did indeed limit fat oxidation. However, it should be noted that the increase in lipolysis did not restore fat oxidation to the levels observed during exercise in the fasted state. This implies that carbohydrate ingestion has additional effects on skeletal muscle that directly reduce its ability to oxidize fat. As discussed below, one factor appears to be a reduction in the transport of FA into the mitochondrial



**Figure 20.3.** Comparison of fat oxidation relative to lipolysis after 20–30 min of exercise at 44% of peak oxygen consumption. During exercise in the fasted state, lipolysis exceeded fat oxidation (\* indicates  $P < 0.05$ ). During exercise after ingesting glucose 60 min. before exercise, both lipolysis and fat oxidation are significantly reduced († indicates  $P < 0.05$ ). The increase in lipolysis via intravenous infusion of Intralipid and heparin, after glucose ingestion, resulted in a significant increase in fat oxidation compared to glucose (‡ indicates  $P < 0.05$ ), but not a restoration to the fasted levels. Reprinted, by permission, from Horowitz et al. 1997.

### Plasma FFA Availability

Under conditions when lipolysis exceeds fat oxidation during exercise, fat oxidation still might be limited by impaired entry of the liberated FA to the mitochondria. As discussed above, high-intensity exercise seems to be a good example of this situation with high lipolysis but very low RaFFA and plasma FFA concentrations (9, 21, 30). We have found well-trained cyclists to oxidize FA at 43  $\mu\text{mol/kg/min}$  after 30 min at 65%  $\dot{V}O_{2\max}$  compared with only 27–30  $\mu\text{mol/kg/min}$  when exercising at 85%  $\dot{V}O_{2\max}$  (29, 30). In that the restoration of plasma FFA concentration to 1–2 mM during exercise at 85%  $\dot{V}O_{2\max}$  increased fat oxidation to 34  $\mu\text{mol/kg/min}$  during exercise at 85%  $\dot{V}O_{2\max}$ , it seems that approximately one-half of the normal decline in fat oxidation when intensity is increased from 65% to 85%  $\dot{V}O_{2\max}$  is due to limited availability of plasma FFA for oxidation by muscle. However, the failure of fat oxidation to reach the higher levels capable by muscle (i.e., 43  $\mu\text{mol/kg/min}$  at 65%  $\dot{V}O_{2\max}$ ), indicates that fat oxidation at 85%

$\dot{V}O_{2\max}$  is not merely limited by plasma FFA supply. As discussed below, intracellular factors such as increased glycolytic flux may directly impair FA oxidation in muscle.

During exercise at both 85%  $\dot{V}O_{2\max}$  and at 44%  $\dot{V}O_{2\max}$  (after glucose ingestion), we have seen that the restoration of plasma FFA concentration to 1–2 mM reduced carbohydrate oxidation due solely to a sparing of muscle glycogen utilization, with no apparent reduction in blood glucose disappearance (18, 30). This glycogen sparing effect agrees with the original findings of Costill et al. (7), who had subjects run at 70%  $\dot{V}O_{2\max}$ , 5–6 hours after a carbohydrate meal, which resulted in a very low plasma FFA concentration during the control trial (i.e., 0.2 mM). Ingestion of heavy cream and heparin injection raised fat oxidation 32% and reduced muscle glycogen use by 40%. Therefore, it seems that fat oxidation is somewhat impaired and muscle glycogen use increased during moderate- to high-intensity exercise when plasma FFA concentration is only 0.2–0.3 mM and that total fat oxidation can be increased somewhat by raising plasma FFA concentration (7, 9, 30). However, in studies with plasma FFA during the control trial in the range of 0.5–1.0 mM, it seems that further elevation does not raise fat oxidation or spare muscle glycogen use (16, 28, 30). This is probably because plasma FFA availability did not limit total fat oxidation in the control conditions.

### Mitochondrial Factors and Endurance Training

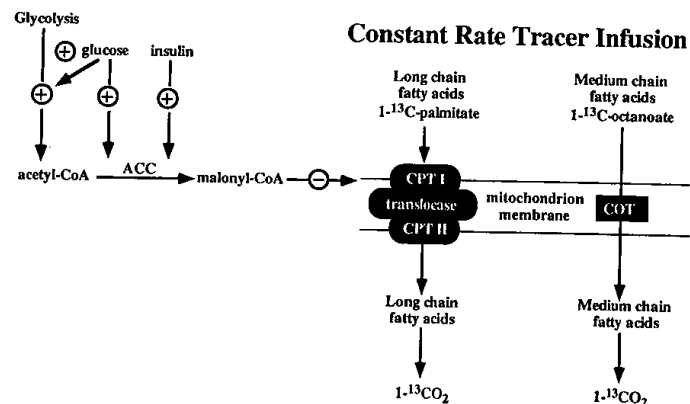
Fat oxidation occurs in mitochondria, which, of course, have great potential to influence fat oxidation during exercise. The increased mitochondrial density characteristic of endurance training results in increased fat oxidation and reduced glycolytic flux from both muscle glycogen and blood glucose (5, 17, 19, 35). The reduction in glycogenolysis during exercise at a given absolute intensity is associated with a lesser disturbance of cellular homeostasis (i.e., lesser increase in AMP and ADP) and increased oxidation of IMTG (17, 19, 25). The extent to which endurance training increases fat oxidation directly by increasing mitochondrial density, as opposed to the indirect effect of increased mitochondrial density on reducing glycolytic flux, is not clear.

During low-intensity exercise eliciting an oxygen consumption of 20 ml/kg/min, endurance-trained and untrained subjects have comparable levels of whole-body lipolysis as well as plasma FFA Ra and Rd (22). Despite this comparable stimulation of FA mobilization, the untrained subjects display lower fat oxidation. Thus, during exercise at this low intensity, the endurance-trained subjects show a close matching between RdFFA and total fat oxidation, whereas the untrained subjects display reduced fat oxidation despite high plasma FFA Rd as well as a higher plasma FFA concentration. This suggests that during low-intensity exercise in untrained subjects, FA availability does not limit fat oxidation. It is likely that mitochondrial factors limit fat oxidation. In contrast to low-intensity exercise at a given absolute intensity, exercise at 70%  $\dot{V}O_{2\max}$  in endurance-trained compared to untrained subjects elicits higher rates of lipolysis and total fat oxidation (23). The higher lipolytic rate probably is due, for the most part, to greater IMTG lipolysis (19, 25,

29), and it is not surprising that total fat oxidation is increased because total oxidative metabolism is increased.

### Glycolytic Flux and Fat Oxidation

We tested the hypothesis that fat oxidation is regulated by carbohydrate metabolism in general and muscular glycolytic flux in particular (8). Pre-exercise carbohydrate feedings were used as a tool to produce hyperglycemia and hyperinsulinemia and thus to increase glycolytic flux during exercise (8). As shown in figure 20.4, FA oxidation rates were measured during constant rate intravenous infusion of trace amounts of a long-chain fatty acid ( $1\text{-}^{13}\text{C}$ -palmitate) vs. a medium-chain fatty acid ( $1\text{-}^{13}\text{C}$ -octanoate). Octanoate oxidation is not as limited by transport into mitochondria as is palmitate oxidation (14, 32). We observed that the increased glycolytic flux from glucose ingestion significantly reduced palmitate oxidation, whereas it had no effect on octanoate oxidation. This suggests that glycolytic flux regulates long-chain fatty acid oxidation in skeletal muscle during exercise, possibly by inhibiting its transport into the mitochondria. A similar experimental approach, using increased exercise intensity to raise glycolytic flux, found similar results (34).



**Figure 20.4.** Scheme of the experimental approach used by Coyle et al. (8) to determine if long-chain fatty acid oxidation (i.e., palmitate) is reduced more than medium-chain fatty acid oxidation (i.e., octanoate) by elevations in plasma glucose and insulin. It is hypothesized that the formation of malonyl-CoA from acetyl-CoA through the activity of acetyl-CoA carboxylase (ACC) is a potent inhibitor of carnitine palmitoyltransferase (CPT) with much less of an effect on carnitine octanoyltransferase.

Glycolytic flux may regulate fat oxidation within exercising skeletal muscle via the formation of malonyl-CoA (10, 39). Malonyl-CoA is formed from acetyl-CoA through the activity of acetyl-CoA carboxylase (ACC), and it is a potent inhibitor of carnitine palmitoyltransferase (CPT) with much less of an effect on carnitine octanoyltransferase (COT) (31, 32) (figure 20.4). It is hypothesized that malonyl-CoA concentration can reflect the availability of carbohydrate as a substrate with increased glycolytic flux producing more pyruvate and thus increasing acetyl-CoA/CoA and malonyl-CoA, which then reduces fatty acid oxidation by reducing transport of long-chain fatty acids into mitochondria via inhibition of CPT.

It seems that increases in glycolytic flux increase carbohydrate oxidation while directly and actively reducing FA oxidation. If the reduction in FA oxidation following glucose ingestion were simply a passive phenomenon from increased glycolytic flux and acetyl-CoA production from glucose, the oxidation of palmitate versus octanoate should have been equal in response to increased glycolytic flux. This did not occur. Therefore, it seems that the preference for carbohydrate oxidation when both carbohydrate and fat are made available to muscle is mediated, in part, by the active inhibition of fat oxidation via a process that appears to involve transport of FA into the mitochondria.

## Summary

Situations that shift substrate oxidation from fat toward carbohydrate, such as pre-exercise carbohydrate meals, and increasing exercise intensity, appear to exert well-coordinated effects both on adipose tissue and skeletal muscle. High-intensity exercise (85% vs. 65%  $\dot{V}O_{2,max}$ ) reduces plasma FFA mobilization in concert with a direct reduction in FA oxidation within skeletal muscle (figures 20.1 and 20.2) (29). Furthermore, lipolysis appears to limit fat oxidation when exercise is performed following a pre-exercise meal, most likely from the inhibition of lipolysis by insulin (18). However, increased lipolysis (via intralipid and heparin infusion) after pre-exercise carbohydrate ingestion only partially restores fat oxidation toward fasting conditions (figure 20.3) (18). Increased glycolytic flux from pre-exercise carbohydrate ingestion also appears to actively and directly inhibit the oxidation of FA in skeletal muscle, possibly by inhibiting FA transport into mitochondria (figure 20.4) (8). It appears that various systems of the body somehow act in concert to minimize the appearance of FA that cannot be oxidized by skeletal muscle during exercise when glycolytic flux is increased.

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