



Fatty acid mobilization from adipose tissue during exercise

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By far the largest energy reserve in the human body is adipose tissue triglycerides, and these reserves are an important source of fuel during prolonged endurance exercise. To use this rich source of potential energy during exercise, adipose tissue triglycerides must first be hydrolyzed and the resultant fatty acids delivered to the working muscles. The aims of this review are to describe how exercise alters lipid mobilization from adipose tissue, to identify alternative sources of lipids and to discuss some of the key factors regulating fatty acid mobilization, uptake and oxidation during exercise. The impact of understanding factors involved in the coordinated regulation of lipid mobilization and oxidation during exercise goes far beyond its relevance for endurance exercise performance. A better understanding of the regulation of these processes will facilitate the development of more effective treatment modalities for obesity-related metabolic disorders.

Most energy reserves in the human body are stored as adipose tissue triglycerides. Even most lean adults have >80 000 kcal of potential energy stored as triglyceride in adipose tissue. This is enough energy to complete >25 marathon races and is >40 times more than the amount of energy stored as glycogen in skeletal muscle and liver. As a result, oxidation of these triglycerides enables sustained physical activity and can delay the onset of glycogen depletion and hypoglycemia. To use this abundant energy resource, triglycerides must first be hydrolyzed, and the resultant fatty acids must then be exported from adipose tissue and delivered to the tissues where they will be oxidized. Therefore use of adipose tissue triglycerides as a fuel during exercise requires the coordinated regulation of lipolysis, blood flow and fatty acid transport in skeletal muscle to enhance the delivery of released fatty acids from adipose tissue to the mitochondria of working muscle. The aims of this review are to describe how exercise alters lipid mobilization from adipose tissue, identify alternative sources of lipids and discuss some of the key factors regulating fatty acid mobilization, uptake and oxidation during exercise.

Mobilization of adipose tissue triglycerides during endurance exercise

The increased energy demands during exercise are met in part by an enhanced rate of triglyceride hydrolysis

(i.e. lipolysis). Even during low-intensity exercise (25% maximal oxygen consumption; $\text{VO}_{2\text{max}}$), adipose tissue lipolysis [measured as the rate of appearance of glycerol in the circulation (Ra glycerol)] increases two- to fivefold above resting levels [1–3] (Fig. 1). At the same time, the rate of fatty acid re-esterification decreases, resulting in a greater proportion of released fatty acids being delivered to skeletal muscle for oxidation [2]. The lipolytic rate remains relatively stable with increasing exercise intensity [4] (Fig. 1), but increases progressively during prolonged exercise at low to moderate intensity, reaching rates as high as $20 \mu\text{mol kg}^{-1} \text{min}^{-1}$ after 4 hours (tenfold greater than resting levels) [2]. Although the lipolytic rate remains relatively high with increasing exercise intensity, the release of fatty acids into the circulation declines (measured as the rate of appearance of fatty acids in plasma) (Fig. 2) [4]. This might seem counterproductive, reducing the availability of an energy-rich source of fuel at a time when energy demands are reaching their maximum but, during high-intensity exercise, muscles rely predominantly on intramuscular stores of carbohydrate and fat. In fact, even when lipids were infused intravenously during high-intensity exercise to increase plasma fatty acid concentrations to very high levels (1–2 mM), the rate of fat oxidation was still less than that seen at lower exercise intensities [5]. The mechanism responsible for this reduction in fatty acid mobilization is not known. However, because plasma fatty acid concentrations increase dramatically immediately after intense exercise, it has been hypothesized that the reduction in fatty acid release into the circulation might result from a restriction

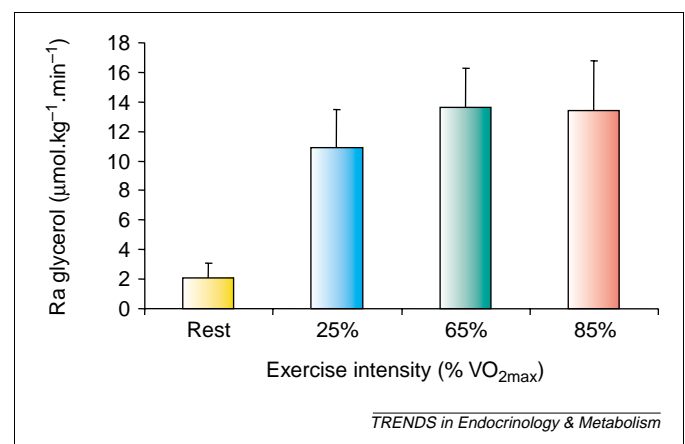


Fig. 1. Whole-body lipolytic rate (Ra glycerol) at rest and during 30 min of exercise at 25%, 65% and 85% $\text{VO}_{2\text{max}}$. Values represented as mean \pm SE. Data from [2,4].

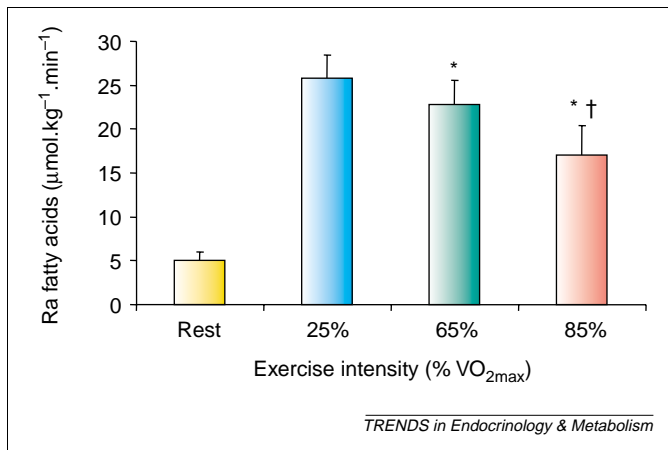


Fig. 2. Fatty acid mobilization in the circulation (Ra fatty acids) at rest and during 30 min of exercise at 25%, 65% and 85% VO_{2max}. *Significantly different from value at 25% VO_{2max}, $P < 0.05$. †Significantly different from value at 65% VO_{2max}, $P < 0.05$. Values represented as mean \pm SE. Data from [2,4].

in adipose tissue blood flow [6], mediated by catecholamine-stimulated vasoconstriction in adipose tissue blood vessels.

Sources of fatty acids during exercise

Lipolytic activity is heterogeneous in different adipose tissue beds [7,8]. Intra-abdominal adipose tissue is the most lipolytically active adipose tissue depot [9], linking the accumulation of fat in this region to a range of clinical complications [10]. However, in spite of the high rate of lipolysis of intra-abdominal adipocytes, it is unlikely that this fat source is an important contributor to fatty acid oxidation by skeletal muscle during exercise. Fatty acid release from the splanchnic region contributes little to whole-body fatty acid flux [8], suggesting that most fatty acids released from intra-abdominal adipose tissue are cleared by the liver and never enter the systemic circulation. In addition, even in obese humans this depot constitutes a small proportion of total body fat mass. Therefore, most fatty acids delivered to the systemic circulation (i.e. most of the fatty acids that skeletal muscle is exposed to during exercise) are derived from subcutaneous adipose tissue.

Lipolytic activity is also heterogeneous in different subcutaneous adipose tissue regions. Most studies have subdivided subcutaneous adipose tissue beds into two general categories; upper body (abdominal subcutaneous) and lower body (femoral or gluteal subcutaneous) adipose tissue. Although certainly an oversimplification, I use this broad distinction here to describe differing regulation between subcutaneous adipose tissue beds. During endurance exercise, the lipolytic rate is much greater in upper body than in lower body subcutaneous adipose tissue [11]. In fact, in lean and obese humans, lower body adipose tissue contributes only very little to whole-body lipolytic rate [12]. Therefore, most of the plasma fatty acids available to working muscle are probably derived from abdominal subcutaneous fat.

Lipid sources other than triglycerides stored in adipose tissue also contribute to fatty acid oxidation during endurance exercise (Fig. 3). Intramuscular triglycerides (IMTGs) are lipid droplets stored within muscle cells.

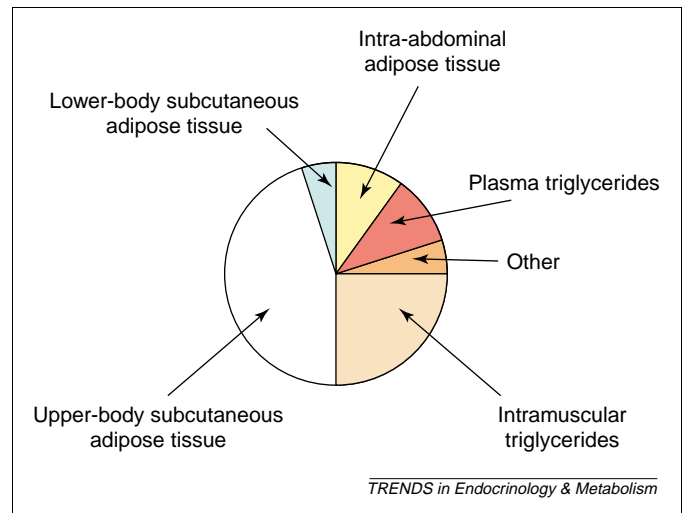


Fig. 3. Estimate of the relative proportion of fatty acid availability from different lipid stores for oxidation during moderate-intensity exercise.

Although the use of IMTG during exercise is disputed [13–17], a large amount of evidence suggests that IMTG provides as much as 10–50% of total fat oxidation during exercise [18–23]. IMTGs release fatty acids directly into the cytosol of working muscles [24], avoiding having to traverse the muscle plasma membrane, making them a very attractive potential energy source during exercise. Lipid droplets can also accumulate between muscle fibres (extramyocellular triglyceride; EMTG). The contribution of EMTG to energy production during exercise is largely unknown, but certainly the liberated fatty acids from EMTG are not as readily available as IMTG because they must still be transported inside the muscle cell. Plasma triglycerides are another potential source of fuel for exercise. Circulating triglycerides are hydrolyzed by lipoprotein lipase (LPL), which resides on the capillary endothelium of skeletal muscle and releases fatty acids that can be taken up by muscle tissue. However, many of these released fatty acids are not taken up directly at the site of the LPL activity [25,26]. Although fatty acids derived from plasma triglycerides have not been considered to be an important fuel source during exercise [27], more recent evidence suggests that plasma triglycerides might contribute more to energy production during exercise than originally believed [28]. Further study is required to gain a more complete understanding of the contribution of circulating triglycerides to energy metabolism during exercise in humans.

Regulation of adipose tissue lipolysis

The rate-limiting step for the liberation of fatty acids from adipose tissue triglycerides into the circulation and ultimately for use as fuel during exercise is the activation of the enzyme hormone-sensitive lipase (HSL), via a cascade of cellular signals. Phosphorylated HSL moves from the cytosol of the adipocyte to the surface of the lipid droplet within the cell [29]. The phosphorylation of a family of proteins located on the surface of the lipid droplet (perilipins) is also required before HSL can catalyze the

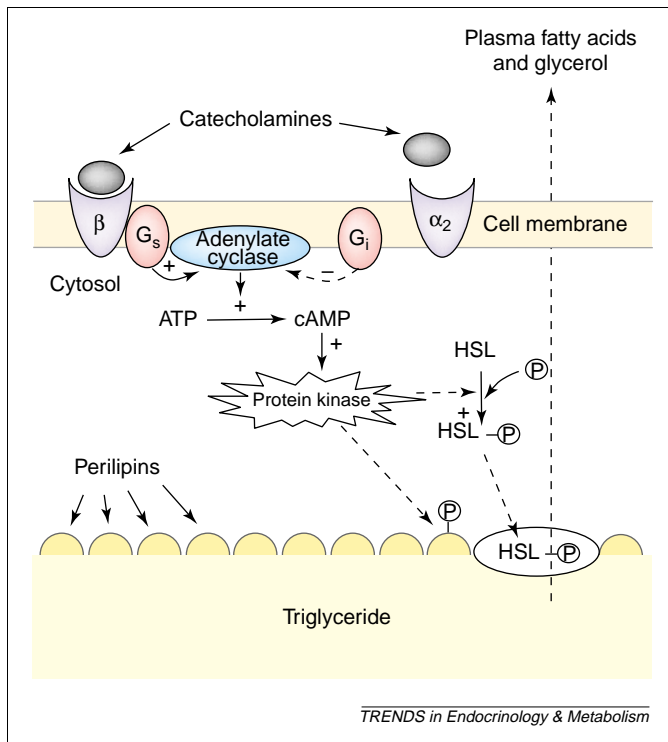


Fig. 4. The lipolytic cascade. Abbreviations: α_2 , α_2 -adrenoceptor; β , β -adrenoceptor; Catecholamines, epinephrine and/or norepinephrine; G_i , inhibitory G protein; G_s , stimulatory G protein; HSL, hormone-sensitive lipase; P, phosphate group. See text for details.

hydrolysis of the triglyceride inside the lipid droplet [30–32] (Fig. 4). Unphosphorylated perilipins create a barrier between HSL and cellular lipids, and prevent lipolysis [30]. Phosphorylation of perilipin by protein kinase A enables HSL to gain access to intracellular triglycerides, possibly by modifying the surface of the lipid droplet [33]. The action of HSL on triglyceride yields two moles of unesterified fatty acids and one mole of monoglyceride. Hydrolysis of this remaining monoglyceride to one glycerol and one fatty acid moiety occurs readily through the action of monoglycerol lipase, which is presumably not under direct hormonal control *in vivo*. Catecholamines (epinephrine and norepinephrine) and insulin are the major plasma hormones that regulate lipolysis in humans.

Influence of catecholamines on adipose tissue lipolysis

Catecholamines activate the lipolytic cascade by binding to β -adrenoceptors (β_1 , β_2 and β_3) on the plasma membrane of adipocytes, whereas catecholamine binding to α_2 -adrenoceptors inhibits lipolytic activity. These adrenoceptors interact with membrane-bound GTP-binding regulatory proteins (G proteins), which modulate the activity of the enzyme adenylate cyclase (Fig. 4). All β -adrenoceptors are coupled with a stimulatory G protein (G_s), and α_2 -receptors are coupled with inhibitory G proteins (G_i). Activation of adenylate cyclase by β -adrenergic stimulation catalyzes the conversion of ATP to cAMP, which serves as a second messenger to activate cAMP-dependent protein kinase, which then phosphorylates HSL and perilipins [30,31].

Because catecholamines act through both α - and β -adrenoceptors, they can either increase or decrease lipolysis, depending on their concentration in plasma and their receptor-binding affinity [34]. At rest, the plasma catecholamine concentration is relatively low and the lipolytic rate is largely regulated through the inhibitory action of α_2 -adrenoceptors [11] (i.e. lipolytic rate is prevented from increasing at rest owing to α_2 -adrenergic inhibition). During exercise, however, the increase in circulating catecholamines and the resultant increase in β -adrenoceptor stimulation overrides the α_2 -mediated inhibition and whole-body lipolytic rate increases [11]. The role of the three different adipocyte β -receptors in lipolytic regulation is not well understood. The affinity for catecholamines differs among the three β -adrenoceptors; $\beta_2 > \beta_1 > \beta_3$ for epinephrine and $\beta_1 \geq \beta_2 > \beta_3$ for norepinephrine [34,35]. After prolonged exposure to catecholamines, β -adrenoceptors become desensitized to catecholamine binding. However, each class of β -receptors differs in resistance to desensitization ($\beta_3 > \beta_2 \geq \beta_1$) [36]. The receptor with the lowest affinity for catecholamines (β_3) remains active in response to prolonged catecholamine exposure and, therefore, might provide for more prolonged stimulation of lipolysis after the higher-affinity receptors have become desensitized. In addition, heterogeneous distribution of β_1 -, β_2 - and β_3 -receptors in various adipose tissue beds [9,37] might reflect an important role for the different receptors in the regional regulation of lipolysis.

Influence of insulin on adipose tissue lipolysis

Adipose tissue lipolysis is very sensitive to changes in plasma insulin concentration [38]. Even a very small increase in plasma insulin concentration (i.e. 10–30 $\mu\text{U ml}^{-1}$) can suppress the lipolytic rate to >50% below basal levels [38]. Conversely, a decrease in plasma insulin concentration, as occurs during exercise, increases lipolysis [39]. Most of the antilipolytic action of insulin has been attributed to stimulating the activity of cellular phosphodiesterase-3 [40,41], which degrades cAMP, thereby reducing the signaling cascade responsible for activating HSL. Insulin phosphorylates and subsequently activates phosphodiesterase through activation of phosphatidylinositol 3-kinase (PI3-K) [42], which also plays a key role in mediating insulin-stimulated glucose uptake. Therefore, much of the effect of insulin on substrate metabolism (i.e. increase in carbohydrate metabolism and decrease in fat metabolism) appears to be through activation of PI3-K.

Alternative regulators of lipolysis

Although catecholamines and insulin are the primary factors regulating adipose tissue lipolysis, other hormones and metabolites can also influence lipolytic rate (Table 1). In general, the effects of these factors are not as profound as those of catecholamines and insulin. The response to these agents is often much slower and, in many cases, they act through modulating the effects of catecholamines and/or insulin. In addition, the direct effect of many of these factors on the lipolytic rate is controversial. For example, cortisol has been reported to be both a lipolytic stimulator [43,44] and inhibitor [45]. The reason(s) for these

Table 1. Alternative regulators of lipolysis (other than catecholamines and insulin)

Lipolytic activators	Refs
Growth hormone	[45,78,79]
Cortisol	[43,44]
Thyroid hormones	[80]
Tumor necrosis factor	[81]
Leptin	[82,83]
Testosterone	[84,85]
Lipolytic inhibitors	
Insulin-like growth factor-1	[86]
Adenosine	[87,88]
Prostaglandin	[87,88]
Neuropeptide Y	[89]

discrepancies are unclear, but might be a consequence of the fact that many of these agents regulate lipolysis indirectly and, therefore, the specific conditions or environment might result in vastly different outcomes.

Many factors, conditions or environments can differentially influence the regulation of lipolysis and fatty acid mobilization during exercise. These factors include: sex [46], aging [47], diet [1,48], obesity [49] and weight-loss [49]. A detailed discussion of the influence of these factors on lipid metabolism during exercise is beyond the scope of this review.

Regional lipolysis

The variability in lipolytic rate in different adipose tissue beds is related to regional differences in adrenergic and insulin receptor density and function. Lipolytic sensitivity to catecholamines is greater in fat cells obtained from intra-abdominal adipose tissue than in those from subcutaneous adipose tissue [9,50]. In addition, the antilipolytic effect of insulin is greater in fat cells obtained from subcutaneous adipose tissue than in fat cells from intra-abdominal adipose tissue [51]. However, in spite of this enhanced lipolytic activity, intra-abdominal fat is not a major contributor to muscle energy production. Abdominal subcutaneous adipocytes are more sensitive to β -receptor agonists [50,52,53] and less sensitive to α_2 -receptor agonists [52,54] than are adipocytes obtained from either femoral or gluteal subcutaneous adipose tissue. These differences in adipocyte β - and α -adrenergic sensitivity observed *in vitro* help explain region-specific differences in lipolytic sensitivity to catecholamines observed *in vivo*. For example, the increase in lipolytic rate that occurs during systemic epinephrine infusion *in vivo* is blunted in femoral compared with abdominal subcutaneous fat depots [55]. Differences in local adipose tissue α_2 - and β -adrenoceptor affinity, density and function [53] are probably responsible for regional heterogeneity in exercise-induced lipolytic rate.

The regulation of IMTG lipolysis during exercise is less clear, but similarities have been found between IMTG and adipose tissue triglyceride lipolysis. For example, HSL has been isolated in skeletal muscle [56], and stimulation of β_2 -adrenergic receptors is associated with an increase in HSL activity [57] and a decrease in IMTG content [58]. An exercise-induced increase in epinephrine and the resultant β_2 -adrenergic stimulation might increase HSL activity through

phosphorylation of extracellular-regulated kinase [58]. However, muscle HSL activity can also increase independently of adrenergic stimulation [59]. This increase in muscular HSL activity involves HSL phosphorylation, perhaps mediated by Ca^{2+} release during muscle contraction [58].

Endurance exercise training and lipid mobilization

Endurance exercise training increases the use of fat as a fuel during exercise [60]. However, this increase in fat oxidation is not the result of increased availability of fatty acids coming from adipose tissue triglycerides. Lipolytic rates are similar in endurance-trained athletes and untrained volunteers during exercise performed at the same absolute intensity [3]. In addition, data from longitudinal studies indicate that plasma fatty acid mobilization during exercise does not increase [61] and can even decrease [62] after several weeks of endurance training, probably because of a suppressed catecholamine response to exercise after training. However, even with similar catecholamine responses, lipolysis is not enhanced after training [63]. Although data from several studies have found the maximal lipolytic response to epinephrine (concentrations between 10^{-6} and 10^{-4} mol l⁻¹) is greater in isolated adipocytes obtained from endurance-trained than in those from untrained subjects [64,65], at physiological epinephrine concentrations (between 10^{-10} and 10^{-8} mol l⁻¹), lipolytic activity was the same or slightly lower in adipocytes from endurance-trained subjects than in those from untrained subjects [64]. Similarly, Stallknecht *et al.* [66] found that the lipolytic response of abdominal subcutaneous adipose tissue to epinephrine infusion *in vivo* was the same in trained and untrained subjects. Moreover, in longitudinal studies, whole-body lipolytic sensitivity to a physiological range of catecholamine concentrations was not affected by endurance training [63,67]. Therefore, although the maximal lipolytic response to catecholamines *in vitro* is enhanced by endurance training, lipolytic sensitivity to catecholamines, across a physiological range of plasma epinephrine concentrations *in vivo*, remains unchanged.

The lack of an increase in lipolysis during exercise after training does not compromise fat oxidation because, in the post-absorptive state, lipolytic rate exceeds fat oxidation both before and after training. In fact, this increase in fat oxidation without an increase in lipolytic rate improves the coordination between fatty acid availability and oxidation, limiting the amount of fatty acids that are released into the circulation but are not oxidized. The source of the additional fat oxidized after training remains controversial. Data from one cross-sectional study suggest that endurance-trained athletes oxidize more circulating fatty acids than their untrained counterparts [68]. However, this observation might reflect differences between the subject populations studied rather than an adaptation to training, because several longitudinal studies have shown that the uptake and oxidation of plasma fatty acids does not increase after several weeks of endurance training [20,61,62,69]. These data suggest that the increase in fatty acid oxidation seen after training is derived from a source other than circulating fatty acids;

perhaps an increase in IMTG oxidation. However, the precise source of the additional oxidized fatty acids remains uncertain because of the technical difficulties in directly assessing the oxidation of IMTG [70].

During exercise performed at the same relative intensity (i.e. same %VO_{2max} before and after training), whole-body lipolytic rate (glycerol Ra) is greater in endurance trained than in untrained subjects [71,72]. The mechanism responsible for the higher rate of lipolysis in trained subjects is not clear, but might be related to both the greater absolute intensity of exercise being performed in the trained state and enhanced contraction-mediated IMTG lipolysis. In addition, endurance-trained athletes have a greater adipose tissue blood flow in response to epinephrine infusion compared with sedentary control subjects [66], so that catecholamine delivery to adipose tissue might be greater during exercise.

Fatty acid uptake and oxidation in skeletal muscle

Although mobilizing fatty acids from their triglyceride storage sites is the first crucial step for using fat as a fuel during exercise, these fatty acids must still be transported into skeletal muscle and then to the mitochondria before being oxidized. Our understanding of this process has increased tremendously in only the past few years, but still much remains unknown. Until recently, it was believed that all plasma fatty acids traverse the lipid bilayer of the muscle cell membrane by simple diffusion. However, the entry of fatty acids into muscle is much more complex, involving a series of protein carriers to facilitate fatty acid entry into the cells and solubility within the aqueous cytosol. At least three putative fatty acid transporter proteins have been identified; plasma membrane fatty acid-binding protein, fatty acid translocase (FAT/CD36) and fatty acid transport protein. The exact mechanisms of facilitated fatty acid transport in skeletal muscle are still unclear. It has been proposed that at least one of these transporters, FAT/CD36, might translocate from an intracellular storage site to the plasma membrane during muscle contraction [73]. Furthermore, it is possible that some of these proteins might interact with each other to aid fatty acid entry into the cell. Once the fatty acids enter the muscle cell they still must traverse the mitochondrial membrane before they can be oxidized. Carnitine palmitoyltransferase-I, which is the key regulator of this process, is considered the rate-limiting step for the regulation of whole-body fat oxidation [74]. Specifics describing these processes will not be discussed in detail here. Other recent reviews provide excellent overviews detailing the regulation of fatty acid transport in skeletal muscle [74–76].

Clinical implications and future directions

Exercise is often prescribed in the prevention and/or treatment of obesity-related disorders, such as type II diabetes and cardiovascular disease. Although exercise is an important part of a successful weight-loss program for these patients, it is the negative energy balance associated with exercise and a low-calorie diet that leads to the weight loss, not alterations in lipid metabolism. Although not directly responsible for reductions in body weight or body

fat, alterations in lipid metabolism with exercise can reduce the health risk associated with obesity, independently of a negative caloric balance or weight loss. For example, when fatty acid availability to muscle exceeds the rate of fat oxidation, which is typical for someone with abdominal obesity, fatty acid intermediates (e.g. fatty acyl-CoA, ceramide and diacylglycerol) can accumulate within the cytosol of the muscle cell. This lipid accumulation interferes with the insulin-signaling pathway and impairs glucose uptake [77], which is the primary sign of type II diabetes and those at risk for the disease. Endurance exercise and exercise training can improve the coordination between fatty acid mobilization, uptake and oxidation, and therefore reduce the potential for lipid accumulation in muscle. Future research exploring the influence of exercise, and the resultant changes in cellular energetics (e.g. ADP, AMP, Pi, Ca²⁺ kinetics and AMP-activated protein kinase) on the coordinated regulation of fatty acid availability, transport and oxidation might pave the way for improved treatment modalities for diabetes and other obesity-related disorders.

Conclusion

Adipose tissue triglycerides are a very important source of fuel to meet energy demands during exercise. Increases in lipolytic rate and availability of fatty acids that occur during exercise require the coordination of neural, hormonal and circulatory events, which facilitate delivery of fatty acids from adipose tissue to the working muscle for oxidation. Lipolysis of adipose tissue triglycerides is heterogeneous, and much of the fat used during exercise is derived from abdominal subcutaneous adipose tissue. Not only do these fatty acids have to be liberated from their adipose tissue storage sites and delivered to the muscle, but they must also be transported to the muscle mitochondria for oxidation. Exciting new research is shedding light on the complex mechanisms that facilitate the delivery and transport of these fatty acids in skeletal muscle. Understanding the factors involved in the regulation of lipid availability and oxidation is an important step towards the clarification of how exercise can best be implemented as a first line for prevention and/or treatment of obesity-related disorders.

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