

Adipose Tissue Lipid Mobilization During Exercise

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The vast majority of the energy reserves in the human body are the triglycerides stored in adipose tissue. Even most lean adults have more than 100,000 kcal of potential energy in their adipose tissue, an amount which is 50-fold greater than the energy stored as glycogen in skeletal muscle and liver. Oxidation of triglycerides permits sustained physical activity and delays the onset of glycogen depletion and hypoglycemia. Before this rich energy resource can be used, triglycerides must be hydrolyzed and the resultant fatty acids must be exported from adipose tissue and transported to the tissues where they will be oxidized. Therefore, using triglycerides from adipose tissue during exercise requires the coordinated regulation of lipolysis, adipose tissue blood flow (ATBF), and skeletal muscle blood flow to enhance the delivery of fatty acids to working muscles. This chapter reviews the regulation of mobilizing fatty acids from adipose tissue and discusses the effects of carbohydrate ingestion, obesity, aging, gender, and endurance training on the availability and use of endogenous triglycerides during exercise.

Regulation of Lipolysis in Adipose Tissue

A cascade of cellular signals stimulates lipolysis of triglycerides in adipose tissue, phosphorylating and activating hormone-sensitive lipase (HSL). Once phosphorylated, HSL moves from the cytosol of the adipocyte to the surface of the lipid droplet within the cell (1). Perilipins, proteins located on the surface of the lipid droplet, may also require phosphorylation before HSL can initiate lipolysis within the lipid droplet (2) (see figure 6.1). Unphosphorylated perilipins prevent lipolysis by creating a barrier between HSL and cellular lipid (2). Phosphorylated perilipins allow HSL access to intracellular triglycerides, possibly by modifying the

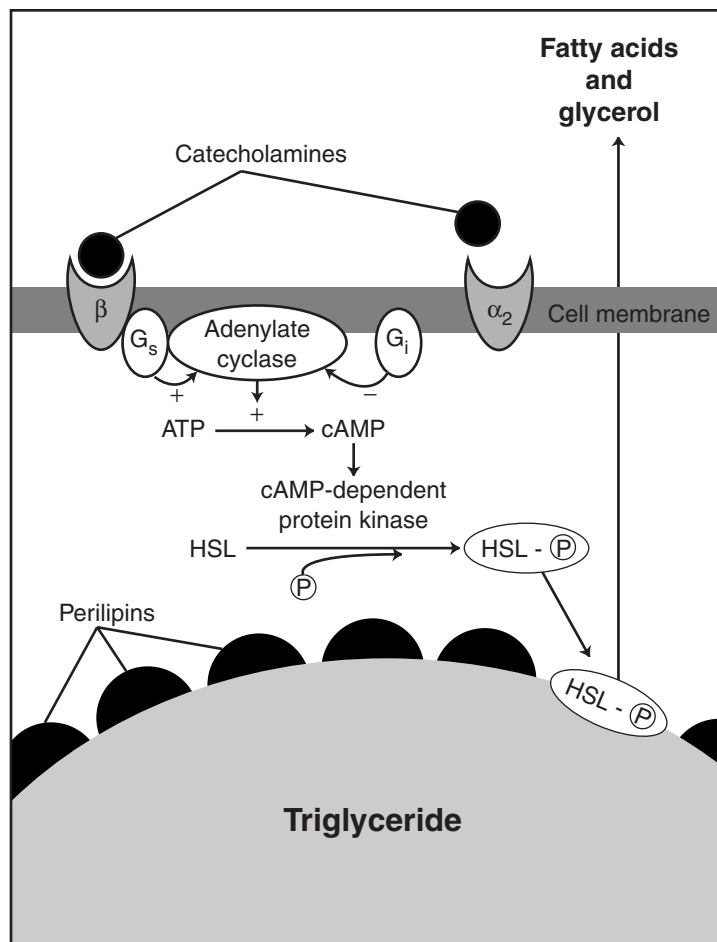


Figure 6.1 Schematic diagram of the lipolytic cascade.

α_2 = α_2 -adrenergic receptor; ATP = adenosine triphosphate; β = beta adrenergic receptor; cAMP = cyclic adenosine monophosphate; Catecholamines = epinephrine and norepinephrine; G_i = inhibitory G protein; G_s = stimulatory G protein; HSL = hormone sensitive lipase; P = phosphate group.

surface of the lipid droplet (3). HSL lipolysis yields 2 mol of unesterified fatty acid and 1 mol of monoglyceride. The monoglyceride is hydrolyzed to 1 glycerol and 1 fatty acid moiety by monoglycerol lipase, which is not under direct hormonal control. Catecholamines (epinephrine and norepinephrine) and insulin are the major plasma hormones regulating lipolysis in humans.

Regulation of Lipolysis by Catecholamines

Catecholamines activate the lipolytic cascade by binding to β -adrenergic receptors (β_1 , β_2 , and β_3) on the plasma membrane of adipocytes and inhibit the cascade by binding to α_2 -adrenergic receptors. These adrenergic receptors interact with membrane-bound guanosine triphosphate-binding regulatory proteins (G proteins), which modulate the activity of adenylate cyclase (see figure 6.1). All β -adrenergic receptors are coupled with stimulatory G proteins (G_s), and α_2 receptors are coupled with inhibitory G proteins (G_i). Stimulating the β -adrenergic receptors activates adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). The cAMP acts as a second messenger to activate cAMP-dependent protein kinase, which then phosphorylates HSL and perilipins (2).

Because catecholamines regulate lipolysis by stimulating both α - and β -adrenergic receptors, they increase or decrease lipolysis depending on their plasma concentrations and their binding affinities for the different receptors (4). At rest, when the concentration of plasma catecholamines is relatively low, the lipolytic rate is largely regulated through the inhibitory action of α_2 -adrenergic receptors (5). During exercise, however, circulating catecholamines increase and stimulate lipolysis by activating β -adrenergic receptors (5). The role of the three different β -receptors in lipolytic regulation is not well understood. The affinity for catecholamines differs among the three β -adrenergic receptors; $\beta_2 > \beta_1 > \beta_3$ for epinephrine and $\beta_1 \geq \beta_2 > \beta_3$ for norepinephrine (4, 6). After prolonged exposure to catecholamines, β -adrenergic receptors become desensitized to catecholamine binding. However, each class of β -receptors differs in resistance to desensitization (i.e., $\beta_3 > \beta_2 \geq \beta_1$) (7). The receptor with the lowest affinity for catecholamines (i.e., β_3) remains active in response to prolonged catecholamine exposure and, therefore, may 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 (8-10) may reflect an important role for the different receptors in the regional regulation of lipolysis.

Regulation of Lipolysis by Insulin

Adipose tissue lipolysis is very sensitive to changes in the concentration of plasma insulin (11). A very small increase in plasma insulin (i.e., 10-30 $\mu\text{U/ml}$) can suppress the lipolytic rate more than 50% below basal levels (11-13). Conversely, a decrease in plasma insulin, which occurs during exercise, increases lipolysis (14). Most of the antilipolytic action of insulin

has been attributed to its stimulation of cellular phosphodiesterase-3 (15-18), which degrades cAMP and reduces the signaling cascade responsible for activating HSL. Insulin activates phosphatidylinositol 3-kinase (PI3K) (19), which phosphorylates and subsequently activates phosphodiesterase-3. PI3K 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) occurs through PI3K.

Other Lipolytic Regulators

Although catecholamines and insulin are the primary regulators of lipolysis in adipose tissue, other factors can also influence the lipolytic rate (see table 6.1). Generally the effects of alternative lipolytic regulators are not as profound as those of catecholamines and insulin. These agents often elicit a much slower response, and in many cases they act by modulating the effects of catecholamines or insulin. The effects of many of these factors on lipolytic rate are controversial. For example, cortisol has been reported to both stimulate (20-22) and inhibit (23) lipolysis. The reasons for these discrepancies are unclear, but they may occur because the alternative factors often regulate lipolysis indirectly, and therefore differing conditions may result in vastly different outcomes.

Regional Lipolysis

Lipolytic activity is heterogeneous among different adipose tissue beds (41, 42). This variability relates to regional differences in adrenergic and insulin receptor density and function. Lipolytic sensitivity to catecholamines is greater in fat cells obtained from intraabdominal adipose tissue than in cells obtained from subcutaneous tissue (8, 44). The reverse is true of the antilipolytic effect of insulin (45). These data suggest that lipolytic activity is enhanced in adipocytes from intraabdominal fat. Despite this enhanced activity, it is unlikely that intraabdominal fat is an important contributor to fatty acid oxidation in skeletal muscle during exercise. Fatty acid release from the splanchnic region contributes little to whole-body fatty acid flux (42, 43), suggesting that most of the fatty acids released from intraabdominal tissue are cleared by the liver and never enter systemic circulation. Even in obese subjects, the intraabdominal depot constitutes only a small portion of total fat mass. Therefore, most of the fatty acids delivered to the systemic circulation (i.e., most of the fatty acids reaching skeletal muscle during exercise) originate from subcutaneous adipose tissue.

Table 6.1 Lipolytic Regulators and Their Putative Mechanisms of Action

Factor	Putative mechanism of action	Reference
Lipolytic Stimulators		
Catecholamines (epinephrine and norepinephrine)	<ul style="list-style-type: none"> • Stimulate β-adrenergic receptors and interact with G_s proteins on plasma membrane • Activate adenylate cyclase, initiating a cascade of signals culminating in the activation of HSL 	24
Growth hormone (GH)	<ul style="list-style-type: none"> • Increases catecholamine-stimulated lipolysis • Increases in secretion overnight, and thus may be important for regulating nocturnal lipolysis • Apparently modifies lipolytic rate over several hours and thus may have little or no acute effect on lipolysis during acute exercise 	23, 25-27
Cortisol	<ul style="list-style-type: none"> • Increases posttranscriptional β-adrenergic receptor expression • Increases the lipolytic response to catecholamines 	20-22
Thyroid hormones	<ul style="list-style-type: none"> • Upregulate adipocyte β-adrenergic receptor expression • Decrease phosphodiesterase 	28, 29
Cytokines	<ul style="list-style-type: none"> • Tumor necrosis factor α (TNFα) increases lipolysis by downregulating G_i proteins 	30, 31
Leptin	<ul style="list-style-type: none"> • Stimulates lipolysis independently of the adenylate cyclase cascade • Perhaps acts through inhibition of phosphodiesterase • May involve NO₂ • Enhances glycerol release without a proportional increase in fatty acids 	32, 33

(continued)

Table 6.1 (continued)

Factor	Putative mechanism of action	Reference
Testosterone	<ul style="list-style-type: none"> Increases catecholamine-stimulated lipolysis via increased β-receptor expression and enhanced adenylate cyclase activity May require GH for action 	34, 35
Lipolytic Inhibitors		
Insulin	<ul style="list-style-type: none"> Increases phosphodiesterase activity, which leads to a reduction in cAMP 	15-18
Catecholamines (epinephrine and norepinephrine)	<ul style="list-style-type: none"> Stimulate α_2-adrenergic receptors and interact with G_i proteins on plasma membrane, which inhibits adenylate cyclase 	24
Insulin-like growth factor-1 (IGF-1)	<ul style="list-style-type: none"> Likely inhibits lipolysis in a manner similar to insulin (via phosphorylation of phosphodiesterase) May interfere with lipolysis induced by growth hormone 	36
Adenosine	<ul style="list-style-type: none"> Stimulates adenosine receptors, which inhibit adenylate cyclase by interacting with G_i proteins on the plasma membrane (similar to α_2-adrenergic receptors) 	37, 38
Prostaglandin	<ul style="list-style-type: none"> Prostaglandin E_1 and E_2 inhibits lipolysis via interaction with G_i proteins 	37-39
Neuropeptide Y (NPY)	<ul style="list-style-type: none"> Inhibits adenylate cyclase through interaction with G_i proteins 	40

Within different subcutaneous adipose depots, lipolytic regulation is also heterogeneous. Abdominal subcutaneous adipocytes are more sensitive to β -receptor agonists (46-49) and less sensitive to α_2 -receptor agonists (48, 50) than adipocytes obtained from either femoral or gluteal subcutaneous tissue. These differences in adipocyte β - and α -adrenergic sensitivity, observed in vitro, help explain region-specific differences in sensitivity to catecholamines observed in vivo. For example, the increase

in lipolytic rate that occurs *in vivo* during systemic epinephrine infusion is blunted in femoral fat depots when they are compared with abdominal fat depots (51). Moreover, during endurance exercise at moderate intensity, triglyceride lipolysis is greater in upper-body than in lower-body subcutaneous adipose tissue (52). Therefore, upper-body subcutaneous tissue provides most of the fatty acids delivered to working muscles during exercise.

Measuring Lipolysis In Vivo

Because lipolysis results in the release of glycerol from triglycerides, glycerol is often used as a marker for lipolytic rate. However, simply measuring glycerol concentration in blood does not provide a very accurate assessment of lipolysis. Several different methods can be used to determine whole-body and regional lipolytic rates with reasonable accuracy.

Measurement of Whole-Body Lipolysis

The rate of appearance (R_a) of glycerol into the bloodstream, which is assessed by measuring the dilution of infused, tracer-labeled glycerol in plasma, provides the most reliable method for evaluating whole-body lipolytic rate. This procedure assumes that 1) the breakdown of 1 mol of triglyceride releases 1 mol of glycerol into the bloodstream and that 2) all endogenous glycerol released into the plasma is detected by sampling blood from the systemic circulation during intravenous tracer infusion. However, these assumptions are not completely correct, and the strengths and limitations of tracer methods must be understood to properly interpret data from isotope dilution. The hydrolysis of adipose tissue triglycerides should release 1 mol of glycerol and 3 mol of fatty acid because partial hydrolysis is minimal (53). Nearly all glycerol released during lipolysis enters the bloodstream because glycerol kinase, the enzyme that metabolizes glycerol, is virtually absent in adipose tissue (54). Glycerol serves as a better marker than fatty acids because the latter can be reesterified within adipose tissue without entering the bloodstream (and thus lipolytic rate would be underestimated). The glycerol R_a in plasma measured by isotopic dilution represents the total lipolysis occurring in all tissues throughout the body. These lipolytic events include lipolysis of adipose tissue, intramuscular triglyceride stores, and plasma lipoproteins. The contribution from each source may vary under different physiological conditions. In contrast, glycerol released from visceral adipose tissue enters the portal circulation, where it is predominantly cleared by the liver. Therefore, very little of the glycerol released by lipolysis of intraabdominal adipose tissue

enters the systemic circulation and is not detected by peripherally infused tracers. However, as discussed previously, these triglycerides represent only a small portion of whole-body lipolytic activity.

The concentration (or change in concentration) of glycerol in plasma is often used to index whole-body lipolysis during exercise. However, this indirect marker should be interpreted with caution because changes in plasma concentrations may not necessarily reflect changes in lipolytic rates. The concentration of plasma glycerol represents a balance between glycerol delivery into plasma and glycerol uptake by tissues (primarily liver). The relationship between glycerol concentration and lipolysis can vary markedly with physiological state (55). For example, because exercise intensity can greatly impact blood flow to the liver (the greater the intensity, the lower the splanchnic blood flow), it can also affect the rate at which glycerol is cleared from the circulation. Therefore, measuring the increase in the concentration of plasma glycerol during the exercise transition from low intensity to high intensity overestimates the whole-body lipolytic rate because the concentration does not simply represent an increase in adipose tissue lipolysis but reflects a reduction in glycerol clearance from the liver as well.

Measurement of Regional Lipolysis

Lipolytic activity in individual tissues can be assessed *in vivo* by using standard arteriovenous methods, which evaluate the balance between the delivery (from an artery) and release (into a vein) of glycerol across an adipose tissue bed. This approach measures arterial and venous glycerol concentrations and adipose tissue blood flow (ATBF). Subcutaneous ATBF can be determined by analyzing the clearance of ^{133}Xe , an inert and lipophilic radioisotope that is injected locally into an adipose tissue bed (56). Blood flow is quantified as the product of the fractional decline of ^{133}Xe radioactivity measured at the site of injection and of the partition coefficient for adipose tissue (57). Combined with the measurement of ATBF, abdominal vein catheterization and microdialysis probe techniques evaluate regional fatty acid or glycerol released from adipose tissue.

Glycerol released into veins draining blood from subcutaneous adipose tissue can be measured directly by sampling blood from an abdominal vein. This technique involves positioning a small (22-gauge) catheter into an abdominal vein so that the tip is superior to the inguinal ligament as judged by surface anatomy (58). With the catheter in this position, the sampled blood represents drainage from adipose tissue and overlying skin without contribution from underlying muscle, because a sheet of avascular fibrous tissue completely separates the muscle from the fat (59). The concentration of venous glycerol from a specific tissue bed also

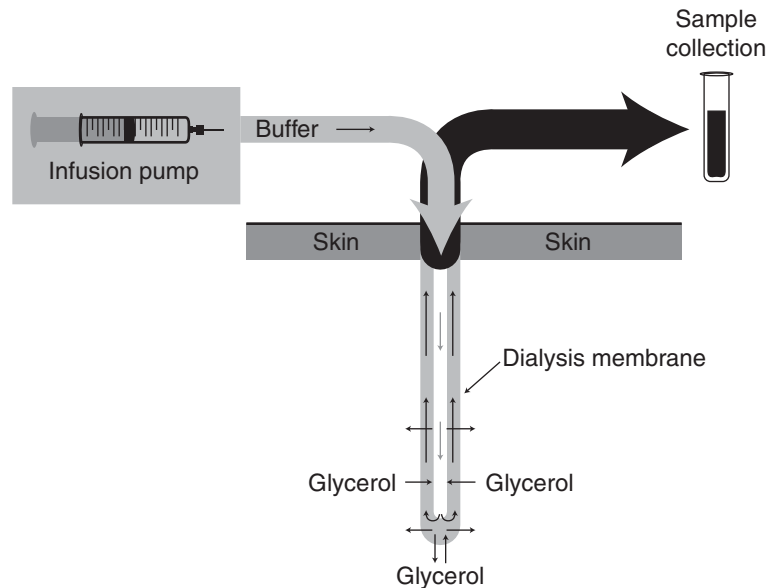


Figure 6.2 Schematic diagram of the microdialysis probe and the process of collecting samples from a probe placed below the skin and into adipose tissue.

can be calculated from interstitial glycerol concentration measured by microdialysis. Microdialysis probes can be placed percutaneously into subcutaneous abdominal adipose tissue. Each probe consists of a dialysis membrane glued to the end of a double cannula (see figure 6.2). Perfusion of a buffer solution, or perfusate, through the inner cannula delivers perfusate into the space between the inner cannula and the outer dialysis membrane. The perfusate equilibrates with the fluid in the interstitial space surrounding the dialysis membrane before exiting through the outer cannula, where it is collected in small vials. Slow perfusion (0.03 ml/min) of Ringer's solution through the probe allows the perfusate to completely equilibrate with interstitial glycerol (60). Fick's law of diffusion for a thin membrane (61) can be used to convert concentrations of interstitial glycerol (measured in the microdialysis samples) to venous concentrations in order to calculate regional glycerol R_a .

Regulation of Adipose Tissue Blood Flow

Adipose tissue blood flow (ATBF) helps regulate fatty acid release from adipose tissue by delivering lipolytic hormones and fatty acid carrier proteins (albumin) and exporting albumin-bound fatty acids. Catecholamines

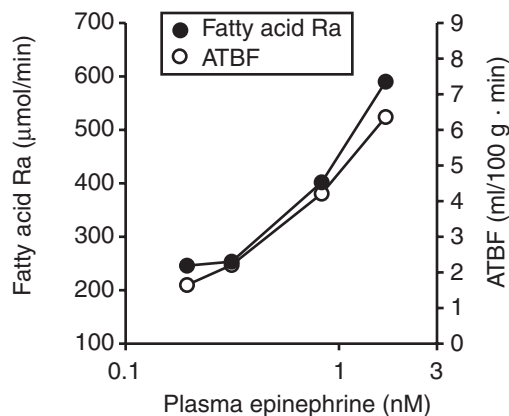


Figure 6.3 Coordinated increase in fatty acid rate of appearance in plasma (fatty acid Ra) and in adipose tissue blood flow (ATBF) in response to a physiological increase in the concentration of plasma epinephrine in lean men ($n = 5$).

Data from 62.

stimulate β -adrenergic receptors in vascular smooth muscle within adipose and skeletal muscle, reducing vascular tone and increasing vascular conductance and blood flow. Therefore, lipolysis and ATBF are stimulated by similar mechanisms. In fact, when plasma epinephrine concentrations are between 0.3 and 1.6 nM, fatty acid mobilization (fatty acid Ra) and ATBF increase in parallel (see figure 6.3) (62). Therefore, during endurance exercise at low to moderate intensities (i.e., 25%-65% $\dot{V}O_2$ max), when plasma epinephrine concentrations are less than 1.6 nM, the coordinated increase of lipolysis and ATBF by catecholamines enhances the release of newly liberated fatty acids into the circulation, where they can be delivered to muscle for oxidation. Exercise at moderate intensity increases ATBF by twofold (63, 64) and muscle blood flow by more than 10-fold.

Other Triglyceride Sources

Lipid sources other than adipose tissue triglycerides contribute to fatty acid oxidation during endurance exercise. A large amount of evidence suggests that intramuscular triglycerides (IMTG), lipid droplets stored within muscle cells, provide a considerable amount of fuel to muscle during exercise (70-75), although this hypothesis has been disputed (65-69). IMTG releases fatty acids directly into the cytosol of working muscles (76). Similarities have been found between the regulation of IMTG and the regulation of lipolysis in adipose tissue. For example, HSL has been

isolated in skeletal muscle (77, 78), and stimulating β_2 -adrenergic receptors decreases IMTG content (73). However, HSL activity in muscle can also increase independently of adrenergic stimulation (78). This increase involves HSL phosphorylation, which is perhaps mediated by calcium (Ca^{++}) release during muscle contraction (73). Plasma triglycerides are another potential source of fuel. Lipoprotein lipase hydrolyzes circulating triglycerides in the capillary endothelium of skeletal muscle and thus releases fatty acids that can be taken up by muscle tissue. Although fatty acids derived from plasma triglycerides are not considered important fuels for exercise (79), their contribution to energy metabolism during exercise has not been carefully studied in humans.

Lipolytic Response During Endurance Exercise

The greater energy demands of exercise are met by an increased mobilization of available fuel. The increase in triglyceride hydrolysis helps supply some of this energy.

Whole-Body Lipolysis During Exercise

Even during exercise at low intensity (25% $\dot{V}\text{O}_2\text{max}$), lipolysis of adipose tissue triglycerides increases two- to threefold above resting levels (80-82) (see figure 6.4). At the same time, fatty acid reesterification within adipose tissue decreases, so that a greater proportion of released fatty acids are delivered to skeletal muscle for oxidation (81). Although the whole-body lipolytic rate (measured as glycerol R_a) remains relatively high as exercise intensity increases, fatty acid release into the circulation (measured as fatty acid R_a) and whole-body fat oxidation decline with high-intensity exercise ($\geq 85\%$ $\dot{V}\text{O}_2\text{max}$) (83). The mechanism reducing the availability of fatty acid is not known but may relate to vasoconstriction in adipose tissue mediated by α_2 -adrenergic receptors at high plasma catecholamine concentrations. The resultant suppression of ATBF may reduce the release of fatty acid into the systemic circulation (84). The lowered availability of fatty acid may help explain the suppression in fat oxidation observed during exercise at high intensities. One finding supporting this hypothesis is that preventing the decline in plasma fatty acid concentration during high-intensity exercise by infusing lipid and heparin increased total fat oxidation by about 30% (85-87). However, fat oxidation was not completely restored to the rate observed during moderate exercise (83, 85). Therefore, fat oxidation during high-intensity exercise is limited by both a reduction in plasma fatty acid availability and altered fatty acid metabolism within muscle (88).

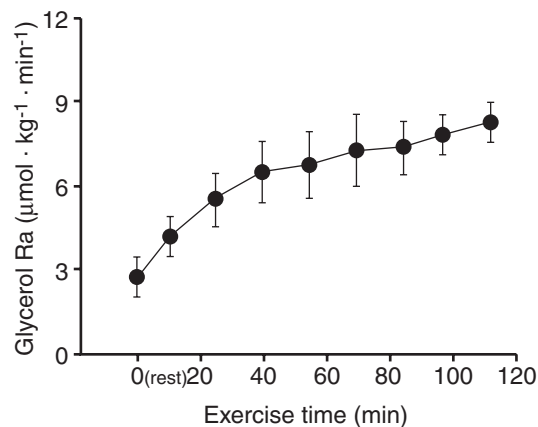


Figure 6.4 The increase in lipolytic rate (glycerol Ra) during exercise at low intensity (25% $\dot{V}O_{2\text{max}}$) in lean men ($n = 6$).

Data from 92.

Regional Lipolysis During Exercise

During endurance exercise, lipolytic rate progressively increases in abdominal but not in lower-body (i.e., femoral/gluteal) subcutaneous adipose tissue (5, 52). Therefore, most of the plasma fatty acids available to working muscle are likely derived from upper-body rather than lower-body subcutaneous fat. This hypothesis is consistent with studies demonstrating regional differences in lipolytic sensitivity to catecholamines *in vivo* (47) and *in vitro* (49). Differences in local α_2 - and β -adrenergic receptor affinity, density, and function (49) are probably responsible for regional heterogeneity in exercise-induced lipolysis.

Effect of CHO Ingestion on Exercise

The elevation in plasma insulin after preexercise carbohydrate (CHO) intake has a potent antilipolytic effect (80). Ingesting only a small amount of CHO (~60 g) during the hour before exercise sufficiently reduces lipolysis to limit fatty acid oxidation during subsequent exercise (80). Consequently, muscle glycogen oxidation increases during early exercise to compensate for the loss in energy derived from fat (80, 89). Lipolysis of adipose tissue is even sensitive to the small insulin response caused by low-glycemic CHO such as fructose (80). Although the duration of influence from the insulin is not known, the increase in fat oxidation normally observed during exercise can be blunted up to 6 h after a meal

(90). Therefore, in daily living, the lipolytic rate during exercise is often under the influence of our insulin response to our most recent meal.

CHO ingestion during endurance exercise can delay fatigue by providing exogenous glucose late in exercise when endogenous glycogen stores are very low (91). However, CHO ingestion also decreases endogenous substrate availability by suppressing the lipolytic rate. Despite a lower rate of lipolysis, CHO ingestion during exercise does not sufficiently reduce availability of fatty acids to limit fat oxidation (92).

Regulation of Lipolysis and ATBF During Exercise and Obesity

The lipolytic response to exercise is suppressed in persons with abdominal obesity, despite having higher basal lipolytic rates than persons with lower-body obesity or lean persons (42). Suppression of the lipolytic response is largely a consequence of a blunted lipolytic sensitivity to catecholamines (41, 51, 93, 94). This lower sensitivity is attributed to a low density of β_2 -adrenergic receptors (95) and to an increased activation of α_2 -adrenergic receptors (96) in adipocytes from subcutaneous abdominal adipose tissue of persons with abdominal obesity. Moreover, a blunted lipolytic response to catecholamines in subcutaneous fat of the abdomen but not fat of the femoral region has been demonstrated in vivo (51). Despite the blunted lipolytic rate in abdominally obese subjects, the absolute rate of fatty acid mobilization is similar in lean and obese subjects during exercise (97, 98).

Although fatty acid release into plasma is similar in lean and obese subjects, the source of fatty acids used during exercise differs. We recently found that uptake and oxidation of circulating plasma fatty acids were similar in lean and obese exercising subjects matched for aerobic capacity (98). However, total fat oxidation was 25% greater in the obese subjects (98). Therefore, abdominally obese subjects must oxidize more of an alternative source of fatty acids, presumably IMTG.

Basal subcutaneous abdominal ATBF is lower in obese than in lean persons (99). Although the effect of exercise on ATBF in obese subjects is not known, the increase in ATBF in response to β -adrenergic stimulation at rest is less in obese than in lean persons (51). Therefore, it is likely that during exercise ATBF is lower in obese persons as well. The mechanism suppressing ATBF in obesity is unclear. The reduced ATBF may simply be a function of the anatomical relationship between capillaries and adipocytes. Because each adipocyte is located near a capillary, blood flow per fat cell remains constant regardless of the size of the fat cell. So, blood flow per unit of adipose tissue decreases as the volume of the fat

cell increases. Conversely, a reduction in adipose tissue with weight loss can increase ATBF.

Although it may seem counterintuitive, the lower lipolytic sensitivity to catecholamines and lower ATBF in persons with abdominal obesity may provide metabolic benefits. A blunted increase in fatty acid flux in response to adrenergic stimulation helps maintain a more reasonable balance between fatty acid availability and oxidation. Excessive fatty acid availability in the circulation in conjunction with high rates of fatty acid uptake (by liver and muscle) relative to the amount oxidized may be a principal contributor to some of the metabolic disorders found in persons with abdominal obesity (e.g., insulin resistance, hypertriglyceridemia). Therefore, better coordination between fatty acid availability and oxidation minimizes triglyceride reesterification in muscle and liver, possibly increasing insulin sensitivity and improving the lipid profile of the blood.

Lipolytic Regulation With Advancing Age

Although advancing age has been found to suppress lipolytic sensitivity to adrenergic stimulation (100, 101), the rate of lipolysis and of fatty acid release into plasma is greater in older (>70 y) than in younger (<35 y) adults exercising at the same absolute intensity (102). Despite enhanced fatty acid availability, fat oxidation is lower in older subjects (102), presumably due to alterations in fatty acid metabolism in skeletal muscle. Consistent with this notion, mitochondrial oxidative capacity is reduced in muscle homogenates from older subjects (103). Skeletal muscle from elderly subjects adapts to endurance exercise training by increasing oxidative capacity and fat oxidation without increasing fatty acid uptake (102). Therefore, poor aerobic fitness, which impairs the capacity for fatty acid oxidation in muscle, slows fat oxidation and contributes to the disparity between fatty acid uptake and oxidation observed with advancing age.

Gender Differences in Lipolytic Response

Most (5, 104-107) but not all (108) studies have reported that the lipolytic rate during exercise is greater in women than in men. Because both aerobic fitness and body composition independently affect lipolytic rate during exercise (52, 98), it is attractive to hypothesize that the gender differences relate to differences in fitness levels and to the well-described differences in the proportion of body fat between men and women. However, it was recently reported that even when matched for aerobic fitness and body composition, women exhibited a greater lipolytic rate during exercise than men (107). These differences may be a consequence

of gender-related alterations in the activity of α -adrenergic receptors. It has been found that α -adrenergic blockade increases lipolytic response during exercise in men but not in women (106), indicating that activity in α -adrenergic receptors inhibits lipolysis during exercise in males but not in females. Enhanced lipolysis during exercise in women may lead to an increase in plasma fatty acid uptake and oxidation so that they are greater in women than in men.

Endurance Exercise Training

It is well established that endurance training increases the use of fat as a fuel during exercise (109). However, this increase in fat oxidation is not due to an increased availability of fatty acids coming from adipose tissue triglycerides. Lipolytic rates are similar in endurance-trained athletes and untrained volunteers exercising at the same absolute intensity (82). Additionally, data from longitudinal studies indicate that the mobilization of plasma fatty acid during exercise does not increase (52) but may even decrease (110, 111) after several weeks of training. The observed decrease is due to a suppressed catecholamine response to exercise after training. However, even when the catecholamine response is not lower, lipolysis is not enhanced after training. Although data from several studies have found that the maximal lipolytic response to epinephrine (at concentrations between 10^{-6} and 10^{-4} mol/L) is greater in isolated adipocytes from trained subjects than in those from untrained subjects (112-115), at physiologic epinephrine concentrations (between 10^{-10} and 10^{-8} mol/L), lipolytic activity was the same or slightly lower in adipocytes from trained subjects (113, 114). Similarly, Stallknecht and colleagues (116) found that abdominal subcutaneous adipose tissue lipolytic response to epinephrine infusion was the same in trained and untrained subjects. Moreover, longitudinal studies have shown that whole-body lipolytic sensitivity to a physiological range of catecholamine concentrations is not affected by endurance training (62, 117). Therefore, although endurance training enhances the maximal lipolytic response to catecholamines *in vitro*, it does not change lipolytic sensitivity to catecholamines across a physiological range of plasma epinephrine concentrations *in vivo*.

Although training does not accelerate lipolysis during exercise, fat oxidation is not compromised because the lipolytic rate in the postabsorptive state exceeds fat oxidation both before and after training. In fact, increasing fat oxidation without increasing lipolytic rate improves the coordination between fatty acid availability and oxidation, limiting the amount of fatty acids that is released into the circulation but not oxidized. If these effects of exercise training also apply to persons with

abdominal obesity, then this may have important clinical implications by reducing the amount of fatty acids being taken up and reesterified in tissues like skeletal muscle and liver. Additionally, these data suggest that the increased fatty acid oxidation observed after training uses a source of fat other than circulating fatty acids. The results from several studies suggest that fat oxidation induced by training may be due to an increase in IMTG oxidation (52, 72, 110, 111). However, the precise source of the additional oxidized fatty acids is controversial because of the technical difficulties in directly assessing the oxidation of IMTG.

During exercise performed at the same relative intensity (same % $\dot{V}O_{2\max}$ before and after training), the whole-body lipolytic rate (glycerol Ra) is greater in trained than in untrained persons (118-120). The mechanism that elevates the rate of lipolysis in trained subjects is not clear, but it may relate to both the greater absolute intensity of exercise performed in the trained state and the enhanced contraction-mediated IMTG lipolysis. Additionally, because endurance-trained athletes have a greater ATBF in response to epinephrine infusion than sedentary control subjects (116), catecholamine delivery to adipose tissue may be greater during exercise in trained subjects.

Summary

Adipose tissue triglycerides are an essential source of fuel for meeting energy demands during exercise. The increases in lipolytic rate and availability of fatty acids that occur during exercise require the integration of neural, hormonal, and circulatory events that deliver fatty acids from adipose tissue to skeletal muscle for oxidation. The lipolysis of adipose tissue is heterogeneous. Although intraabdominal adipose tissue is the most sensitive to lipolytic stimulators (and the least sensitive to lipolytic inhibitors), its relative contribution of fat for oxidation during exercise is likely very small. Most of the fatty acids oxidized during exercise originate from subcutaneous adipose tissue and intramuscular triglycerides. The regulation of lipolysis in subcutaneous adipose tissue is also heterogeneous; lipolytic rate is greater in subcutaneous fat depots from the upper body than from lower-body fat stores. Nutrition, fat content, age, gender, and fitness level can all affect the mobilization and oxidation of triglycerides from adipose tissue, and therefore these factors can greatly impact the mix of fuels that provides energy for working muscles during exercise.