Regulation of Lipid Mobilization and Oxidation during Exercise in Obesity

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INTRODUCTION

Obesity is a major public health problem in the United States and other industrialized countries. Although all obesity phenotypes are associated with a substantial health risk, persons with abdominal obesity (waist circumference > 100 cm) are especially prone to obesity-related metabolic disorders. Dysregulation of lipid mobilization and oxidation in persons with abdominal obesity may be central to many of their medical complications. Excessive release of fatty acids from adipose tissue relative to the rate of fat oxidation may lead to disorders such as skeletal muscle insulin resistance, hyperlipidemia, and cardiovascular disease. Although endurance exercise is often prescribed in the treatment of obesity and obesity-related disorders, the regulation of fatty acid mobilization and oxidation during exercise in obese persons is poorly understood. Therefore, further research into the effects of exercise on lipid metabolism in obesity is necessary to identify regulatory factors that may improve the therapeutic approach to obesity. This review provides an overview of the mechanisms known to regulate triglyceride lipolysis, adipose tissue blood flow (ATBF), fatty acid uptake, and fat oxidation during exercise in lean and obese persons. Furthermore, possible benefits of exercise and endurance exercise training in obesity are discussed.

FATTY ACID RELEASE FROM ADIPOSE TISSUE

In the fasted state, the majority of fat used for fuel at rest and during exercise is derived from adipose tissue triglycerides. For fatty acids to be delivered from adipose tissue to skeletal muscle and other tissues for oxidation, they must first be liberated from triglycerides and then exported into the systemic circulation. Therefore, the release of fatty acids from adipose tissue depends primarily on the rate of triglyceride lipolysis and ATBF.

Lipolytic Regulation

Catecholamines (epinephrine and norepinephrine) and insulin are the major hormones that regulate lipolytic activity. Adipose tissue lipolysis is stimulated through a cascade of cellular signals, resulting in the phosphorylation and subsequent activation of the enzyme hormone-sensitive lipase (HSL) (Fig. 1). Catecholamines initiate this cascade by binding to and activating β-adrenergic receptors (β_1, β_2, and β_3) on the fat cell surface, whereas catecholamine stimulation of α_2-adrenergic receptors inhibits HSL activity. Insulin is also a potent inhibitor of lipolysis. Only a very small increase in plasma insulin concentration (i.e., 10–30 μU/mL) is necessary to dramatically suppress lipolytic rate. Furthermore, insulin has a persistent influence on fat metabolism, lasting several hours after a meal and even well after plasma insulin concentration returns to baseline values. Therefore, throughout the day, lipolytic rate is primarily under the influence of both circulating insulin and catecholamines.

The regulation of lipolysis can vary depending on the anatomic site of the adipose tissue bed. The variation in
lipolytic rate is largely attributed to regional differences in adrenergic and insulin receptor density and function. In vitro evidence indicates that lipolytic sensitivity to catecholamines is highest in fat cells from intra-abdominal adipose tissue, followed by subcutaneous fat of the abdomen and then gluteal/femoral subcutaneous fat (Table 1). In addition, the antilipolytic effect of insulin is greater in fat cells from subcutaneous than from intra-abdominal adipose tissue. Therefore, these data suggest that fatty acid release from intra-abdominal stores may be very high. Fatty acids from intra-abdominal adipose tissue are primarily taken up by the liver, and fatty acid flux from this depot into the portal circulation has been hypothesized to be responsible for many of the cardiovascular and metabolic disorders associated with abdominal obesity. However, the causality of this relationship is uncertain (14) and requires further investigation. Intra-abdominal adipose tissue represents only a very small portion of whole-body fat mass. Moreover, although an elevated hepatic fatty acid flux and a resultant increase in very low density lipoprotein (VLDL)-triglyceride (VLDL-TG) production may indirectly alter substrate metabolism, the direct effect of intra-abdominal adipose tissue on abnormalities in peripheral tissues, such as skeletal muscle insulin resistance, is unclear. In contrast, the majority of fatty acids delivered to skeletal muscle are derived from subcutaneous adipose tissue (Fig. 2). More specifically, most of these fatty acids are derived from abdominal subcutaneous adipose tissue (5), which itself may be divided into functionally distinct compartments (7). Therefore, fatty acids released from subcutaneous adipose tissue are more likely to have a direct effect on skeletal muscle metabolism.

At rest, fatty acid mobilization in the systemic circulation is more than 50% greater in persons with abdominal obesity than in persons with lower-body obesity (waist-to-hip ratio < 0.76) or lean persons (6,10). Basal lipolytic rate is primarily regulated by inhibition through α2-adrenergic stimulation (1), and subcutaneous fat cells from abdominal region are less responsive to the inhibitory effects of α2-agonists than lower-body fat (13). In the postprandial state, despite a greater insulin response to a meal, the normal suppression in fatty acid flux is attenuated in abdominally obese compared with lean and lower-body obese persons. Moreover, HSL activity is dependent on fat cell size, which is typically larger in abdominal than in femoral subcutaneous adipose tissue. Therefore, high basal and postprandial fatty acid mobilization into the circulation in persons with abdominal obesity appears to be a direct consequence of their excessive abdominal subcutaneous fat mass.

Although persons with abdominal obesity have a high basal lipolytic rate, the increase in lipolysis during exercise is blunted compared with lean persons and persons with lower-body obesity (6). β-Adrenergic stimulation is responsible for much of the increase in lipolytic rate during exercise (1), and lipolytic sensitivity to β-agonists is suppressed in persons with abdominal obesity (12). Moreover, we recently found that the blunted lipolytic sensitivity to catecholamines occurs in subcutaneous fat of the abdomen but not of the femoral region (5). Lipolytic resistance to catecholamines in persons with abdominal obesity has been attributed to a low density of β2-adrenergic receptors in adipocytes from abdominal subcutaneous adipose tissue (12). Because basal lipolysis is elevated in persons with abdominal obesity, the blunted increase in lipolysis during exercise results in similar lipolytic rates during exercise in abdominally obese, lower-body obese, and lean subjects (6).

Adipose Tissue Blood Flow

ATBF is important for regulating fatty acid release from adipose tissue by delivering lipolytic hormones and fatty acid carrier proteins (albumin) to adipose tissue and by exporting albumin-bound fatty acids from adipose tissue. In addition to increasing lipolytic rate, catecholamines stimulate β-adrenergic receptors in vascular smooth muscle, reducing vascular tone and thereby increasing ATBF. At low and moderate catecholamine concentrations, the increases in lipolysis and ATBF are coordinated. Therefore, with an increase in catecholamine concentration during low-to-moderate in-

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**Figure 1** Lipolytic regulation cascade. Catecholamines (epinephrine and norepinephrine) binding to β-adrenergic receptors activate stimulatory G-proteins (Gβγ), which in turn activate the enzyme adenylate cyclase. Adenylate cyclase catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP activates a specific protein kinase that phosphorylates (P) and thus activates HSL, which hydrolyzes triglyceride into fatty acids and glycerol. Catecholamine binding to α2-adrenergic receptors activates inhibitory G protein (Gi), which inhibits this cascade.

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**Figure 2** Schematic demonstrating that most fatty acids in the systemic circulation are derived from subcutaneous adipose tissue. Most of the fatty acids derived from the relatively small pool of intra-abdominal triglycerides are taken up by the liver before entering the circulation.
tensity endurance exercise (25–65% maximal oxygen consumption \(\text{VO}_{2\text{max}}\)), this coordination enhances the release of the newly liberated fatty acids from adipose tissue into the circulation, where they may be taken up and oxidized by muscle.

Basal ATBF is lower in obese than in lean persons. Although the effect of exercise on ATBF in obese subjects is not known, the increase in ATBF in response to \(\beta\)-adrenergic stimulation at rest is suppressed in obese compared with lean persons. Therefore, it is likely that ATBF during exercise may be lower in obese than in lean persons as well. The mechanism responsible for the suppression in ATBF in obesity is unclear. It is possible that the reduced ATBF may simply be a function of the anatomic relationship between capillaries and adipocytes. Because each adipocyte is located in proximity to a capillary, blood flow per fat cell remains constant, independent of fat cell size. Therefore, blood flow per unit of adipose tissue decreases with increasing fat cell volume. Along these lines, a reduction in adipose tissue mass 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 compared with lean people may provide metabolic benefits. A blunted increase in fatty acid flux in abdominally obese persons in response to adrenergic stimulation helps to maintain a more reasonable match between fatty acid availability and oxidation. Excessive fatty acid mobilization in the circulation, in conjunction with liver and muscle uptake of fatty acids that are not 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 will result in less triglyceride reesterification in muscle and liver, which may increase insulin sensitivity and improve the blood lipid profile.

**FATTY ACID METABOLISM IN SKELETAL MUSCLE**

**Fatty Acid Uptake**

At rest, whole-body fatty acid disposal is greater in persons with abdominal obesity than in lean persons (10). This may be due in part to their increased availability of plasma fatty acids (6,10) and a greater capacity for fatty acid uptake by muscle (15). During exercise, however, the blunted increase in fatty acid availability in the circulation in abdominally obese subjects may reduce the drive for fatty acid uptake, because fatty acid disposal is similar in lean and obese subjects during exercise (6). In addition to fatty acid availability, alterations in protein-mediated transport and variations in intracellular fatty acid metabolism can regulate fatty acid uptake by muscle at rest and during exercise.

Because fatty acids are hydrophobic, they can freely diffuse through the plasma membrane of muscle cells, down a concentration gradient. Until recently, this passive diffusion of fatty acids through the plasma membrane was thought to be unimpeded. However, evidence indicating that unbound fatty acid uptake plateaus at high plasma fatty acid concentrations and the discovery of at least three transmembrane proteins that bind fatty acids with high affinity suggest that fatty acid uptake by muscle is also mediated by membrane-bound transporter proteins. This facilitated transport of fatty acids may provide regulation for fatty acid uptake to match the energy demands of the muscle, which may be especially important during exercise.

The proteins allegedly involved in fatty acid transport across the plasma membrane include fatty acid translocase (FAT/CD36), fatty acid transport protein (FATP), and plasma membrane fatty acid binding protein (FABPpm). The exact mechanisms of facilitated fatty acid transport are not known. However, it has been proposed that the FAT/CD36 transporter may translocate from an intracellular storage site to the cell surface during muscle contraction (2). Furthermore, it is possible that these proteins may interact to aid fatty acid entry into the cell. Few studies have measured these putative transporters in human skeletal muscle from lean and obese subjects. However, FABPpm protein content has been found to be about 30% greater in muscle from obese compared with lean subjects (15). This greater FABPpm content may increase the capacity for fatty acid uptake by muscle in obesity.

**Intramuscular Triglycerides**

Fatty acids taken up by muscle that are not oxidized are primarily reesterified and stored within muscle cells. Although the storage of these “intramuscular triglycerides” (IMTGs) is limited compared with the vast supply of fatty acids available from adipose tissue triglycerides, there is approximately 500 mmol of IMTGs stored within skeletal muscle, and they are often found in close proximity to mitochondria. Therefore, IMTGs represent a locally available source of fuel with potential to supply a substantial amount of energy during exercise. However, the reliance on IMTGs for fuel during exercise is controversial; IMTG concentration has been found to increase, decrease, or remain the same during

| TABLE 1 |
| Lipolytic regulation |

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<th>Activating hormones</th>
<th>Effect on lipolysis</th>
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<td>(\beta_1), (\beta_3), (\beta_4)</td>
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<td>+</td>
<td>Intra-abdominal &gt; abdominal subcutaneous &gt; femoral subcutaneous</td>
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<tr>
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<td>Insulin</td>
<td>insulin</td>
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Epi, epinephrine; NE, norepinephrine.
exercise. These differences may be due in part to the high variability of the assay used to measure IMTGs in muscle samples. In contrast, studies that have indirectly calculated IMTG oxidation as the difference between total fat oxidation (indirect calorimetry) and plasma fatty acid oxidation (isotope tracer methods) have consistently found that a considerable proportion of total fat oxidation during moderate-intensity endurance exercise may be derived from IMTGs.

The use of IMTGs during exercise in persons with abdominal obesity may provide metabolic and clinical benefits not previously realized. Abdominal obesity is associated with a high concentration of IMTGs, which is directly related to insulin-resistant glucose metabolism (3). Therefore, an exercise-induced decrease in IMTG content in obese persons may be beneficial by contributing to the enhancement of insulin sensitivity associated with acute exercise (Fig. 3) and the decreased risk of diabetes associated with chronic aerobic exercise training.

**Fatty Acid Oxidation**

Regulation of fatty acid entry into the mitochondria by the enzyme carnitine palmitoyl transferase-I (CPT-I) is considered to be a rate-limiting step in the oxidation of fatty acids. Once inside the mitochondria, the fatty acids (or fatty acyl-CoAs) proceed through a sequence of metabolic processes to synthesize adenosine triphosphate (ATP) for energy. Impairment in any of these processes could reduce fat oxidation. Along these lines, persons with abdominal obesity have been found to have a low skeletal muscle CPT-I activity as well as a reduced activity of some key mitochondrial oxidative enzymes (15). These data suggest that alterations in skeletal muscle of persons with abdominal obesity may result in a reduced capacity to use fat as a fuel, despite a greater uptake of fatty acids. This disparity between fatty acid uptake and oxidation may help explain the accumulation of IMTG in persons with abdominal obesity, which may contribute to their insulin resistance (3). Although some studies have found fatty acid oxidative capacity to be reduced in persons with abdominal obesity and this reduction in fat oxidation can persist even after weight loss, it is difficult to remove the effect of physical inactivity that is usually superimposed on obesity. Physical inactivity is associated with reductions in the very same fatty acid oxidative enzymes found to be low in persons with abdominal obesity. Moreover, when lean and obese subjects are matched for aerobic fitness relative to fat-free mass, fat oxidation during exercise has been found to be similar or even higher in obese subjects (6). Therefore, although it is possible that an innate reduction in factors that regulate fatty acid oxidation in skeletal muscle may predispose some obese people to a reduced capacity to oxidize fat, much of this response may be due in large part to their level of physical activity and fitness.

**EFFECT OF ENDURANCE EXERCISE TRAINING**

Exercise training is a key component of the clinical management of obesity. Although weight loss due to exercise without caloric restriction is very small, exercise is one of the major factors in determining the success of a weight loss program. In addition, aerobic fitness itself, independent of weight loss, is associated with a reduced incidence of diabetes and cardiovascular mortality rate. Therefore, aerobic exercise training may be particularly beneficial for persons with abdominal obesity because of their increased risk of diabetes and cardiovascular disease.

The addition of an endurance exercise regimen to a dietary intervention attenuates the reduction in fat-free mass that occurs after several weeks of caloric restriction alone. Several studies suggest that this maintenance of fat-free mass with exercise training prevents the reduction in resting fat oxidation that accompanies diet-induced weight loss and may increase fat oxidation during exercise (8). However, the effect of endurance training on substrate metabolism in obesity is controversial because other studies have reported no change or even a decrease in resting fat oxidation after endurance training in formerly obese subjects (11). Differences in these findings may be related to diet, magnitude of weight loss, magnitude of fitness improvements, complexities involved in measuring resting substrate oxidation, and the confounding effects of weight loss and exercise training.

Unfortunately, few studies have examined the effect of endurance exercise training on fat metabolism in obesity without the confounding influence of weight loss. Therefore, most of what is known about the effect of endurance exercise training per se on fat metabolism is derived from studies performed on lean subjects and may not directly apply to obesity. The effect of endurance training on resting fat oxidation is equivocal in both lean and obese subjects. However, it is well known that endurance exercise training increases fat oxidation during exercise in lean subjects. This increase in fat oxidation is largely attributed to an increase in mitochondrial density. Despite the increased capacity to oxidize fat after training, endurance training does not alter plasma fatty acid availability during exercise performed at the same absolute submaximal exercise intensity (9). Furthermore, although maximal lipolytic response to catecholamines is increased after training, lipolytic sensitivity to catecholamines is not affected when careful control is made to prevent changes in body weight and body composition (4). The lack of an increase in lipolysis during exercise after training does not compromise fat oxidation because in the postabsorbptive state,
lipolysarate exceeds fat oxidation. In fact, this increase in fat oxidation without an increase in lipolysarate 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 (Fig. 4). If these effects of exercise training also apply to persons with abdominal obesity, then this may have clinical implications by reducing the amount of fatty acids being taken up and reesterified in tissues like skeletal muscle and liver.

**SUMMARY**

The high incidence of metabolic disorders in persons with abdominal obesity may be associated with alterations in fatty acid mobilization and oxidation. Excessive fatty acid availability relative to fat oxidation results in an increased uptake, esterification, and storage of fatty acids, which may contribute to the development of insulin resistance, hyperlipidemia, and cardiovascular disease. Increasing energy expenditure and fat oxidation during exercise together with a blunted increase in the lipolysarate response to exercise in persons with abdominal obesity improves the relationship between fatty acid availability and oxidation. Furthermore, IMTG use during exercise and a subsequent reduction in IMTG concentration may help increase insulin sensitivity for several hours after an exercise bout.

In addition to these benefits of a single exercise session, improved aerobic fitness due to increased daily physical activity is associated with a decreased incidence of diabetes and cardiovascular disease. Although several studies have re-

![Fatty acid availability and oxidation](image)

**Figure 4** Hypothetical data demonstrating that endurance exercise training increases fat oxidation without an increase in systemic fatty acid availability. After training, a reduction in the amount of fatty acids that are released into the circulation but are not oxidized ("nonoxidized fatty acids") may have metabolic benefits.

- Fatty acid availability
- Fatty acid oxidation

µmol/min

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<tr>
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References