

LIPOLYSIS: Contribution from Regional Fat

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ABSTRACT

In vitro studies of adipocytes taken from different body fat regions suggest substantial differences in lipolysis between intra-abdominal, lower-body subcutaneous, and abdominal subcutaneous regions. Gender and obesity appear to influence these regional differences. In situ measurements of glycerol release from adipose tissue provided further evidence that regional heterogeneity of lipolysis occurs in humans. In vivo studies of regional free fatty acid (FFA) release have confirmed that adipose tissue lipolysis varies between upper- and lower-body fat. Release of FFA from lower-body adipose tissue is less than that from upper-body adipose tissue in both obese and non-obese men and women. In non-obese men and women, meal ingestion suppresses FFA release from all adipose tissue regions, and adrenergic stimulation activated FFA release from different sites in a gender-specific fashion. Significant regional and gender differences in adipose tissue lipolysis occur in humans, and this could contribute to differences in the health effects of adipose tissue and could theoretically influence body fat distribution.

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INTRODUCTION

The primary function of adipose tissue is to store (triglycerides) and release [free fatty acids (FFA) and glycerol] lipid fuel. Adipose tissue triglyceride is an efficient storage form of energy. For example, an adult with 15 kg of body fat has more than 110,000 kcal of lipid fuel stores, which could provide 2,000 kcal daily for ~2 months. Because body fat is such an enormous energy depot, appropriate regulation of fuel release is critical. Fortunately, adipose tissue lipolysis is a highly regulated process, generally allowing appropriate delivery of FFA to meet lipid fuel energy needs.

Following the ingestion of a carbohydrate-containing meal, adipose tissue FFA release can be suppressed (primarily by insulin) by at least 90% from overnight postabsorptive rates. In contrast, the combination of falling plasma insulin concentrations and increasing catecholamines during exercise can increase FFA release by as much as 400%. Thus, at times of reduced lipid fuel needs, FFA availability is suppressed, whereas at times of high lipid fuel demand, the supply can increase dramatically.

Appropriate regulation of FFA availability is important for optimal human health. Excess FFA can induce insulin resistance with respect to muscle glucose uptake (19) and can induce resistance to insulin's ability to suppress endogenous glucose production (37). Other associations with increased FFA include hypertriglyceridemia (20), reduced hepatic insulin clearance (10), and impaired β -cell insulin secretion (41). These abnormalities are the same as those associated with obesity. Thus, abnormalities of FFA flux, which are present in some forms of obesity, may be responsible for some of the metabolic complications of obesity.

Upper-body obesity is associated with increased risk of insulin resistance, hyperlipidemia, type II diabetes mellitus (21), and increased FFA flux relative to lean-tissue mass (16). Understanding whether generalized, as opposed to regional, abnormalities of adipose tissue lipolysis are present in upper-body obesity could have important implications for understanding the pathophysiology and treatment of obesity. Regional differences in adipose tissue lipolysis could also contribute to differences in body fat distribution. The net balance between fatty acid uptake and FFA release determines whether a given body fat depot will have greater or lesser amounts of triglyceride stores. Increased regional

fat accumulation could result either from alterations in triglyceride uptake or from FFA release. Thus, understanding regional differences in the regulation of lipolysis has implications for both the pathophysiology of obesity-related metabolic abnormalities and the physiology of body fat distribution in humans.

IN VITRO STUDIES

Much insight has been gained from the in vitro study of lipolysis in adipocytes taken from different body regions. Following the adipose tissue biopsy, fat cells are isolated and added to reaction mixtures that permit measurement of glycerol concentrations. The change in concentration over time allows one to calculate glycerol production rates. Lipolysis (glycerol release rates) relative to adipocyte mass, number, or surface area can be studied under a variety of conditions. These types of studies provided the first data suggesting that regional differences in lipolysis are present in humans.

Basal Lipolysis

Basal lipolytic rates are measured in the absence of known regulators of lipolysis (e.g. catecholamines, insulin, growth hormone, etc). This may not simulate the in vivo situation, in which adipocytes are exposed to a variety of lipolytic and antilipolytic hormones even under "basal" conditions. Nonetheless, several important observations have been made. In general, basal lipolysis correlates positively with fat cell size (11, 30, 36), so that larger adipocytes have greater basal lipolytic activity per cell. This may explain why some investigators find regional differences in basal adipocyte lipolysis and others fail to. Gluteal adipocytes from women tend to be larger than those from men, and when they are, higher basal lipolytic rates are found (27, 35, 40). Investigators who include in their studies men and women with lower-body and abdominal subcutaneous adipocytes of equal size report that basal lipolysis is also equal between sites and genders (24). In contrast, abdominal subcutaneous adipocytes are reported to have greater basal lipolysis rates than are found in omental adipocytes of equal size (9). Visceral (omental and mesenteric) adipocytes are larger in men than in women (31), and in men visceral adipocyte lipolysis is greater than is abdominal subcutaneous lipolysis, whereas the reverse is true in premenopausal women (31). Studies that report basal lipolytic rates of adipocytes obtained from uncharacterized obese men and women are difficult to interpret. The lack of characterization regarding body fat distribution may explain some of the contradictory findings.

Catecholamine-Regulated Lipolysis

Human adipocytes contain a number of different adrenergic receptors. These include the β_1 , β_2 , and β_3 -adrenoreceptors, as well as the α_2 -adrenoreceptors.

Activation of β -receptors stimulates lipolysis, whereas activation of α_2 -receptors inhibits lipolysis. β_1 -Receptors are the most abundant (4) of the stimulatory adrenergic receptors, and significant regional variations in the effects of catecholamine on the different receptor subtypes have been reported (4, 9).

Several confounding variables make it difficult to compare studies of regional differences in catecholamine-regulated lipolysis. Local adipocyte production of adenosine, an antilipolytic compound, may affect the results of in vitro studies of lipolysis (18). Some investigators add adenosine deaminase to the system to avoid this problem (36), whereas others do not (31). Using adipocytes from obese and non-obese individuals without characterizing the obesity phenotype, or combining data from men and women, will also limit the ability to compare study results from different reports.

In general, endogenous catecholamines (norepinephrine and epinephrine) stimulate lipolysis in abdominal subcutaneous adipocytes from both men and women. Omental adipocytes are more sensitive to β -adrenergic stimulants than subcutaneous adipocytes are (9, 27, 31, 36), except in premenopausal women (31). In men, abdominal subcutaneous adipocytes appear to be more sensitive to β -adrenergic stimulation than gluteal adipocytes are (40). Many investigators report a decreased response of gluteal adipocytes to endogenous catecholamines in women (23, 24, 27, 35), possibly because of greater expression of α_2 -adrenergic receptors in lower-body adipocytes in women (35).

Although β_1 -adrenergic receptors are more numerous than are β_2 -adrenergic receptors (4), abdominal subcutaneous adipocytes from men with the insulin-resistance syndrome have a reduced lipolytic response because of fewer β_2 -adrenergic receptors and reduced activity of hormone-sensitive lipase (33). In women with upper-body obesity, decreased β_2 -adrenergic sensitivity in abdominal subcutaneous adipocytes accounts for reduced β -adrenergic lipolytic response (34).

The β_3 -adrenergic system also may play role in the regulation of lipolysis. β_3 -Adrenoreceptors are more prominent in omental adipocytes (22), and increased β_3 -adrenergic lipolytic sensitivity of abdominal adipocytes from obese subjects has been reported (25). Reduced sensitivity of α_2 -adrenergic receptors on omental adipocytes from obese individuals may also contribute to enhanced catecholamine-stimulated lipolysis (25).

In summary, the concept that upper-body adipocytes are more sensitive to the lipolytic effects of catecholamines than are lower-body adipocytes originated from in vitro studies. Lower-body adipocytes may have increased α_2 -adrenergic or decreased β -adrenergic receptor sensitivity. These findings are more consistent in women than in men. In contrast, omental adipocytes from men, but not from premenopausal women, appear to be more responsive to β -adrenergic stimuli (31). Improper regulation of catecholamine-mediated lipolysis in vitro

has been reported in several disease states (22, 25, 34), although a pathogenic role has not been proven.

Insulin-Regulated Lipolysis

Few studies have been conducted to examine insulin regulation of regional lipolysis in vitro (3, 36). Some investigators find that lower-body adipocytes are unresponsive to the antilipolytic effects of insulin (32), whereas others do not (36). One author concluded that gluteal adipocytes were the most responsive to insulin (a 73% decrease), whereas omental adipocytes were least responsive (a 20% decrease), and abdominal subcutaneous adipocytes were intermediately sensitive (36). It has been suggested that regional differences in the suppression of lipolysis are present in lean, but not obese, individuals (2) and that this may affect regional fat distribution (2).

IN SITU MEASUREMENTS OF REGIONAL LIPOLYSIS

Microdialysis catheters temporarily implanted into subcutaneous adipose tissue have been used to sample interstitial glycerol concentrations as an index of local lipolysis. Dialysis tubing, which allows the passage of small-molecular-weight compounds, is passed through an adipose tissue depot using a needle. The catheter is perfused with a solvent, which is collected and assayed for glycerol content. The system is calibrated by perfusing the fibers with isotonic solutions containing a known range of glycerol concentrations. This allows one to predict interstitial glycerol concentrations in that region of adipose tissue.

Adipose tissue interstitial glycerol concentrations are determined by both the rate of lipolysis and blood flow. Although it is possible to assess changes in local adipose tissue blood flow by measuring the escape of ethanol from the microdialysis perfusate (7), it is not possible to measure blood flow directly using microdialysis methods alone (38). Thus, differences in interstitial glycerol concentrations between two different adipose tissue beds, or changes in interstitial glycerol subsequent to an intervention, could be due to differences in lipolysis or differences in regional blood flow. Direct measurements of blood flow (e.g. xenon washout) are required to determine whether regional differences in glycerol concentrations are due to differences in lipolysis or differences in blood flow (38). Without measures of the change in blood flow, such as the ethanol escape technique, one cannot assume that changes in interstitial glycerol concentration are due solely to changes in lipolysis.

Regional Differences in Lean and Obese Humans

Interstitial glycerol concentrations have been measured by using microdialysis techniques in abdominal subcutaneous and femoral fat in lean and obese men

and women (12). Interstitial glycerol concentrations were greater in obese than in lean subjects in both abdominal and femoral interstitial fluid, before and after glucose ingestion (12). Greater interstitial glycerol concentrations were found in abdominal than in femoral sites in obese, but not non-obese, subjects (12). The investigators suggested that lipolysis is enhanced in the abdominal subcutaneous as compared with the femoral site in obese subjects, and that it was exaggerated in both regions in obese compared with lean individuals (12). Unfortunately, without direct measures of blood flow, it is difficult to be confident of this interpretation (38).

Regional Lipolysis During Exercise

The microdialysis technique also has been used to examine the lipolytic activity and adrenergic regulation of abdominal and gluteal adipose tissue at rest and during exercise in men and women (5). At rest, the glycerol concentration in adipose tissue increased rapidly when the catheters were perfused with phentolamine (an α_2 blocking agent) but did not change in response to propranolol (5). Glycerol concentrations in adipose tissue increased during exercise, more so in the abdominal than in the gluteal adipose tissue, and more so in women than in men (5). Propranolol perfused through the catheter blunted the exercise-induced increase of glycerol concentrations in adipose tissue. Although measurements of blood flow are lacking, these data would suggest that regional differences in adipose tissue lipolysis may be present during exercise, and that lower-body lipolysis may increase to a lesser degree in women compared with men (5).

IN VIVO LIPOLYSIS

Most in vivo studies of regional lipolysis have examined regional FFA release as an index of effective adipose tissue lipolysis. We have used the combination of isotope dilution, arterio-venous difference, and regional body composition techniques to develop a model of regional FFA release relative to regional fat mass. This model requires the placement of blood-sampling catheters in the femoral artery, femoral vein, and hepatic vein, together with FFA isotope dilution techniques and plasma flow measurements using indocyanine green (26). Regional fat mass is determined by dual energy X-ray absorptiometry with (29) or without (13, 17, 26) abdominal computed tomography scanning. This model allows measurement of adipose tissue FFA release from lower-body (leg), splanchnic, and nonsplanchnic upper-body regions. Leg and splanchnic FFA uptake and release are measured by using isotope dilution techniques and plasma flow (26). Upper-body, nonsplanchnic FFA release is calculated by subtracting the sum of splanchnic FFA release and leg FFA release ($\times 2$) from systemic FFA release.

These values can then be expressed relative to regional fat mass to determine the relative lipolytic rates of different adipose tissue beds. The exception is visceral lipolysis, because splanchnic FFA release is a minimum estimate of visceral FFA release (26). Some of the FFA released by visceral adipose tissue depots are taken up by the liver; thus, net splanchnic FFA release is less than visceral lipolysis to the extent that hepatic FFA uptake by liver occurs (6).

This approach to measuring kinetics of FFA in different regions of the body can be applied only to steady state conditions. Rapid changes in plasma substrate concentrations will result in apparent changes in substrate uptake across the tissue bed because of the delay in the equilibration between arterial and venous concentrations (42). The kinetics of this process are such that calculated tissue uptake will be overestimated if plasma concentrations increase and underestimated if plasma concentrations decrease. Thus, measures of regional FFA uptake and release must be made either during steady state conditions or under circumstances in which any changes in concentration are allowed to return to baseline before the completion of the experiment. This will allow calculation of an area under the curve, which should accurately predict the total substrate uptake and release.

Regional Differences in Basal FFA Release

Using the model outlined above, we have examined regional, basal FFA release in upper-body obese, lower-body obese, and non-obese women (26), and in non-obese men and women (17). As expected, systemic palmitate flux was greater in upper-body obese than in lower-body obese or non-obese women (26). Leg fat was less lipolytically active than was upper-body fat (relative to fat mass) in non-obese, upper-body obese, and lower-body obese women (26) (Figure 1). Leg FFA release (micromoles per minute) was similar between these three groups despite substantial differences in leg fat mass (26). Despite increased upper-body fat mass in lower-body obese women compared with non-obese women, FFA release from upper-body fat release was not elevated in lower-body obese women (Figure 1), thus preventing excess availability relative to lean tissue needs (26). Upper-body subcutaneous fat, not visceral fat, was the source of the increased systemic FFA rate of appearance in upper-body obese women. FFA release per kilogram of upper-body fat was nearly identical in non-obese and upper-body obese women (Figure 1). Thus, FFA flux in upper-body obese women increases in proportion to the increased mass of upper-body adipose tissue, but not lower-body regions. This suggests that nonsplanchnic upper-body fat is down-regulated in lower-body obese women, and that this fails to occur in upper-body obese women.

The finding that overnight postabsorptive FFA release from lower-body fat was significantly less than that from upper-body fat in lean women suggested

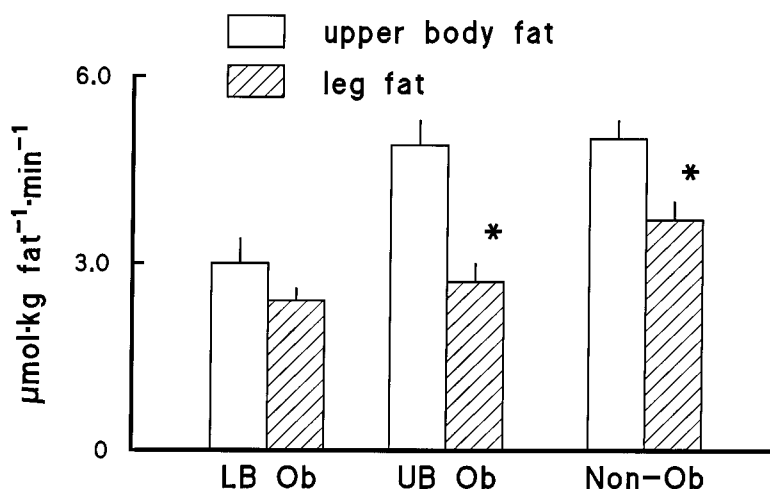


Figure 1 Palmitate release per kilogram of upper-body fat and leg fat in lower-body obese (LB Ob), upper-body obese (UB Ob), and non-obese (Non Ob) women is shown. * = $P < 0.05$. (Adapted from Reference 26.)

that regional differences in basal lipolysis could account for the lower-body fat distribution in women compared with men. FFA release rates from adipose tissue beds from the upper-body, lower-body, and the splanchnic area were therefore compared in non-obese men and women (17). We wished to determine whether lipolytic rates in upper-body and lower-body regions were equivalent in men, and whether splanchnic FFA release would be greater in men than in women, considering men's greater visceral fat mass (8).

Adipose tissue FFA release from upper-body fat was greater than from lower-body fat in both men and women (Figure 2), and the relationship between regional FFA release and systemic FFA release was similar in both groups (Figure 3) (17). These findings strongly support the concept of regional heterogeneity of adipose tissue lipolysis in adult humans but suggest that regional differences in postabsorptive lipolytic rates do not contribute significantly to the differences in body fat distribution between non-obese adult men and women.

Regional Differences in Postprandial FFA Release

Some studies have reported greater suppression of plasma FFA concentrations in women than in men following glucose ingestion (28). This could be related to regional or generalized resistance of adipose tissue to postprandial hyperinsulinemia. If regional differences in postprandial suppression of FFA

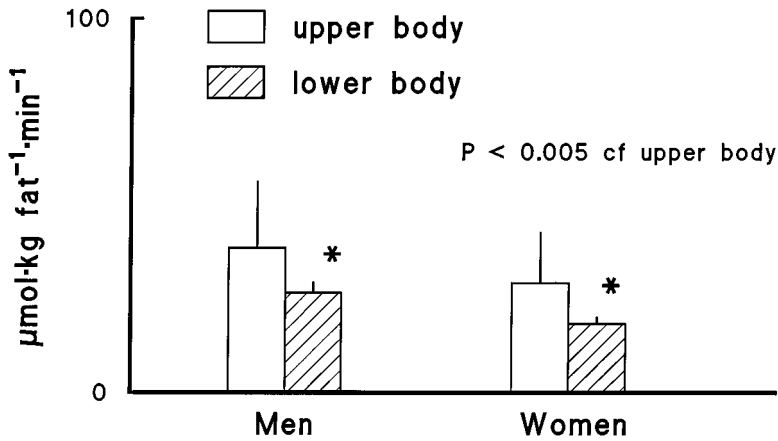


Figure 2 FFA release per kilogram of upper-body and lower-body fat in non-obese men and women. (Adapted from Reference 17.)

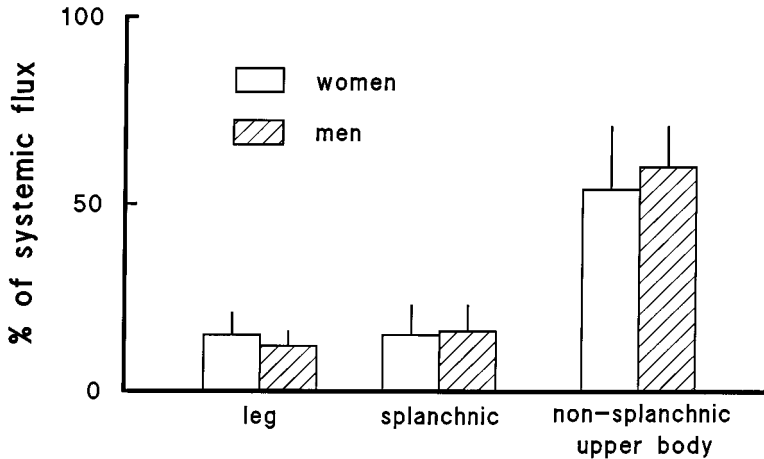


Figure 3 The percentage contribution of FFA release from leg, splanchnic, and nonsplanchnic upper body in non-obese women and men is shown. There were no significant differences between men and women. (Adapted from References 17.)

release occur, this could contribute to differences in regional fat distribution. For example, if postprandial fatty acid uptake of the leg was similar in men and women but men failed to suppress lipolysis following meal ingestion, lesser net fatty acid storage would occur in men compared with women.

Studies were therefore conducted to test the hypothesis that non-obese men and women would differ in regard to the regional suppression of FFA release following meal ingestion. Consistent with previous observations, the postprandial suppression of FFA flux was less in men than in women (14). By measuring regional (leg, splanchnic, and nonsplanchnic upper body) FFA release, it was possible to determine that nonsplanchnic upper-body fat accounted for the greater FFA availability in men compared with women (14). Marked suppression of FFA release from leg, splanchnic, and nonsplanchnic upper-body FFA release was observed in both men and women, which suggests that each adipose tissue region was sensitive to antilipolytic effects of insulin. To our surprise, leg FFA release in men following meal ingestion was suppressed to equal to or greater than that observed in women (14). This observation has been confirmed by subsequent studies (29), which have also allowed us to assess the net balance of meal triglyceride uptake versus FFA release in the leg and splanchnic bed of non-obese men and women (29). The major difference between men and women was the greater chylomicron uptake in the splanchnic bed of non-obese men (29).

Thus, although there are regional differences in postprandial FFA release between non-obese men and women, these small differences do not appear to be of sufficient magnitude that they could completely account for gender-related differences in body fat distribution. The finding of greater splanchnic chylomicron uptake in non-obese men (29) suggests that gender-related differences in regional disposal of meal triglycerides may be a significant determinant of body fat distribution in non-obese adults.

Regional Difference in Catecholamine-Stimulated FFA Release

We have conducted studies to examine whether non-obese men and women differ in regard to regional responses of FFA release to epinephrine in vivo (15). In response to intravenous epinephrine, FFA release increased ($P < 0.01$) by approximately 30% in both men and women. Although basal FFA release in the leg was similar in women and men, it doubled during the epinephrine infusion in men and was virtually unchanged in women. In contrast, release of splanchnic palmitate increased in response to epinephrine in men ($P < 0.05$) but not in women. Release of nonsplanchnic upper-body palmitate increased more in women than in men in response to epinephrine. Thus, release of FFA from lower-body adipose tissue increases in response to epinephrine in men but not in women, whereas palmitate release from upper-body fat increases in both groups. These findings are consistent with some in vitro studies and suggest that catecholamine-mediated lipolysis may play a role in determining gender-based differences in the distribution of body fat. It is not known whether the failure of epinephrine to increase lower-body lipolysis in women was due to

regional differences in responses of β -adrenergic receptors or α_2 (antilipolytic)-adrenergic receptors.

Regional FFA Release During Exercise

A few studies have examined regional FFA release in humans in response to exercise (1, 39). In a group of healthy, young male volunteers, FFA release from the leg and splanchnic region was measured at rest and during 240 min of bicycle exercise (1). FFA release from both leg and splanchnic areas increased throughout the 240 min of exercise; however, the fractional contribution of each region to systemic FFA release did not change significantly throughout the study. Thus, it appears that the combination of falling plasma insulin concentrations and increasing catecholamines increase FFA mobilization from these two adipose tissue beds in proportion to nonsplanchnic upper-body fat.

In the second study, FFA release from the leg and splanchnic areas was measured in type I diabetic and non-diabetic men (39). Although FFA flux increased in both non-diabetic and diabetic volunteers, splanchnic FFA release did not increase in diabetic volunteers, but leg FFA release did increase. The diabetic volunteers started exercise with much greater FFA flux rates than controls did, and it is likely that the plasma insulin concentrations in diabetics did not decrease during exercise to the same extent as in non-diabetics. Plasma catecholamine concentrations increased to a greater degree in diabetic than in non-diabetic subjects during exercise (39). These differences in basal flux, the likely insulin response to exercise, and the catecholamine response to exercise may have been responsible for the regional variations in FFA release. No studies of regional lipolysis during exercise in women or obese humans have been reported.

SUMMARY

Different adipose tissue beds have significantly different fatty acid uptake and mobilization properties. These differences vary between men and women and between obese and non-obese individuals. Body fat distribution is strongly associated with regional differences in lipolysis, and differences in FFA release between different body fat depots (e.g. visceral fat) can potentially mediate the health consequences of body fat distribution. Although much needs to be learned about the regulation of lipolysis, there is little evidence from in vivo studies that regional differences in lipolysis play a major role in determining body fat distribution.

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