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PHYSIOLOGIC BASIS FOR THE CONTROL OF BODY FAT DISTRIBUTION IN HUMANS

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But although a bearer of a rather prominent belly, I still have the bottom of my leg lean and the nerve salient as an Arab horse's.

Brillat-Savarin: *Physiologie de goût* (Quoted by 146)

INTRODUCTION

The association between obesity and important medical morbidity is now widely appreciated (55). This correlation is the basis for campaigns designed to convince the public of the health benefits of weight control. Careful

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inspection of clinical data (51, 145) and subsequent formal epidemiologic studies (40, 41, 83, 84, 138) suggest, however, that a major factor in this correlation is not obesity per se, but the anatomic distribution of the adipose tissue. Thus, at equal degrees of relative (percentage of body fat) or absolute (mass of body fat) adiposity, individuals with a predominantly central ("android" or "apple") distribution of fat will experience higher rates of atherosclerotic heart disease, stroke, hypertension, hyperlipidemia, and diabetes mellitus than will similarly obese individuals whose adipose tissue is distributed in a peripheral pattern ("gynoid" or "pear"). Despite the growing number of advocates of the "distribution effect" on adiposity-related morbidity and mortality, however, several respected investigators have found only small or nonexistent contributions of fat distribution to these parameters (especially blood pressure) (10, 58, 126, 136).

Our aim in this review is to examine current understanding of the mechanisms that ultimately determine the anatomic distribution of adipose tissue in humans and of some proposed physiologic bases for the apparent contribution of relative fat distribution to human disease. This area of clinical investigation is one in which conflicting data abound. We have endeavored to provide a cross-section of the more recent literature, leaving the controversies intact.

INFLUENCE OF BODY FAT DISTRIBUTION ON HEALTH

Measurement of Body Shape

Various parameters have been used to quantify body shape. Vague et al (146) originally proposed that a line drawn between the L_4-L_5 lumbar disc space and the umbilicus be considered the clinical dividing point between these depots, and they noted that adrenergic innervation to these regions originates above and below the thoracic 10, 11 spinal nerves (146). Skinfolds (subscapular, triceps, abdominal, thigh) and body circumferences ("waist," that is, the narrowest region between bottom of rib cage and superior iliac spine; abdomen at umbilicus; pelvis at pubic symphysis; thigh; arm) have been used most widely, but x-rays (both conventional and computed tomography), ultrasound, and magnetic resonance imaging have also been employed. The use by different investigators of various anatomic landmarks for the definition of "hip" or "waist" explains some of the differences in reported measurements. Various ratios of these measures are used to define the relative quantities of central and peripheral, or upper and lower, body fat, which are then related to available measures of morbidity or mortality. Studies by Sjöström and his collaborators (129) of regional adipose tissue distribution using computed tomography (CT) indicate that the L_4-L_5 landmark produces optimal male-female separation for upper and lower body fat. Using this as a

border, the investigators found adult men to have 53% of their fat in the upper body, while women have 46% in this region. These same techniques indicate that there is wide interindividual variability in the relative amount of adipose tissue located in the intraabdominal ("visceral") depots and that men have proportionately more of their adipose tissue mass in this compartment (see Table 1).

Because of their more direct access to the liver via the portal circulation, the intraabdominal depots have been proposed as likely mediators for some of the apparent effects of abdominal adiposity on glucose and lipid metabolism (75). Abdominal CT scanning has indeed demonstrated a relationship between such metabolic disturbances and the ratio of visceral to total adipose tissue (125, 134).

Cardiovascular risk appears to be closely related to relative amounts of visceral adipose tissue (i.e. percentage of total) but not to the absolute amount of visceral tissue. Likewise, the waist:hip (W:H) circumference ratio is a better prospective indicator of cardiovascular risk than is waist circumference alone (129). Using CT in 28 women and 16 men, Ashwell et al (9) found a significant correlation ($r = 0.61$, $p < 0.001$) between waist:hip ratio and intraabdominal:subcutaneous fat ratio. No significant correlation was found between body mass index (BMI) [weight in kg/(height in m)^2] and the intraabdominal fat:subcutaneous fat ratio, despite the fact that BMI and W:H ratio were correlated ($r = 0.44$, $p < 0.01$). Thus, the W:H ratio appears to be a useful indirect measure of the relative amount of visceral adipose tissue, and this ratio in turn correlates well with many obesity-related morbidities. These relationships suggest, but certainly do not prove, that the W:H ratio's correlative relationship to morbidity derives from its sensitivity to relative visceral adiposity. The apparent relationship of other anthropometric measures (e.g. subscapular skinfold thickness) to clinical outcome variables may reflect the high intercorrelation of anthropometric variables, or it may be due to causal links not yet appreciated.

Table 1 Percent fat in subcutaneous vs visceral depots (mean ± SD)[a]

Site	Men (N = 24)	Women (N = 19)
Subcutaneous	79.1 ± 7.1	91.9 ± 3.1
Visceral	20.9 ± 7.1	8.1 ± 3.1
Visceral range	9.1 – 33.5	3.7 – 14.4

[a]This table summarizes work by H. Kvist and L. Sjöström in which computed tomography was used to assess the distribution of adipose tissue in men and women. From Sjöström (see 129).

Whatever is reflected in the W:H ratio appears to be more closely related to adiposity-related morbidities than to the BMI itself. Thus, in several of the epidemiologic studies cited earlier, within each BMI category, increasing W:H ratio was associated with increased risk of morbidity or death. In both of the studies from Sweden (83, 44), lean individuals with the lowest BMI and highest W:H ratio were at greatest risk.

In light of these considerations, from a therapeutic perspective, absolute decrements in adipose tissue mass might appear less important than changing the relative anatomic distribution of adipose tissue. No medical intervention project looking specifically at changes in adipose tissue distribution and morbidities has yet been reported, and few data are available concerning changes in fat distribution with weight gain or loss. Poehlman et al (108) overfed adult male monozygotic twin pairs by 1000 kcal/day for 22 days and noted (in addition to genetic susceptibility to amount and site of weight gain) slightly greater increases in trunk skinfold thicknesses than in the extremities. Sims et al (127) overfed nine men for 200 days and used photographs to calculate changes in body shape; they reported a tendency to centripetal distribution of newly acquired fat. As Himes has emphasized (66), the few studies examining changes in body shape following weight loss in normal-weight (25) and obese (148) subjects suggest that the relative distribution of body fat changes only modestly, if at all. That is, the response of each depot appears to be proportional to the mass of its initial stores.

Mechanisms of Interaction: Body Shape and Medical Morbidity

The biologic explanation(s) for the epidemiologic associations between adipose tissue distribution and morbidity/mortality are unknown. Most investigators have looked for mechanisms whereby intraabdominal fat depots might perturb glucose/lipid homeostasis and blood pressure. Peiris et al (106) reported simultaneous measures of insulin and C-peptide turnover in humans that indicate that, while total adiposity correlates directly with insulin production rate, the W:H circumference ratio correlates inversely with the fraction of insulin extracted by the liver. These investigators and others (131) have suggested that high concentrations of hepatic free fatty acids (FFA) (due to large intraabdominal fat depots draining into the portal vein) may interfere with hepatic catabolism of insulin and provide substrate for oversynthesis of very low density lipoproteins. The resulting increase in circulating insulin concentration may lead to peripheral insulin resistance (type II diabetes) (46), as well as hypertension due to insulin's effects on renal sodium clearance (34) and sympathetic nervous system activation (19, 82). In addition, Smith (132) has raised the interesting possibility that high W:H ratio may, possibly through an effect of ambient FFA on hepatic metabolism, influence levels of

circulating clotting factors so as to increase the coagulability of blood in the coronary arteries and cerebral vessels. In these models, the topographic differences in adipose tissue distribution are variously attributed to effects of sex steroids (45, 106), genetics (24), and ethnic background (100). Presumably, each of these factors in turn influences aspects of adipocyte development (cell number) and metabolism (cell size) differentially in specific adipose tissue depots.

Björntorp and his collaborators (85) have recently turned the shape → disease hypothesis on its head by proposing that body shape and various of its associated morbidities are *both* caused by a neuroendocrine "hypothalamic arousal syndrome" that results from response to environmental stress. They suggest that the stress response, by activating the hypothalamic-pituitary-adrenal axis, results in persistent mild hypercortisolism with secondary shifts in adipose tissue distribution ("Cushingoid" or centripetal), and characteristic derangements in glucose homeostasis. The salt-retaining effects of the adrenal steroids may lead to hypertension, which is exacerbated by coexisting stress-induced activation of the sympathetic autonomic nervous system.

SEX– AND SITE–RELATED DIFFERENCES IN BODY FAT DISTRIBUTION

The amount of lipid stored within the adipose tissue of any specific region of the body is dictated by the number of adipocytes and their respective volumes. Adipocyte number, in general, reflects long-term processes of multiplication and differentiation of adipocyte precursor cells dependent upon complex—and as yet poorly understood—genetic and environmental factors. Adipocyte volume is a more rapidly changeable parameter that responds at any one time to the net impact of biochemical processes controlling the storage and release of triglyceride (TG) in the adipocyte. There appears to be a maximal fat cell size of approximately 1 μg lipid per cell. Proliferation of new fat cells is apparently stimulated after this critical fat cell size is achieved (48).

The number of morphologically identifiable, lipid-filled fat cells can increase even in adult humans (67). Since mature adipocytes do not appear to divide in vivo (98), the ability of adipose tissue to grow by increases in fat cell number depends on the recruitment of adipocyte precursors (61, 65, 76). Precisely which type of cell constitutes the adipocyte precursor is uncertain. At present, we have no morphologic or biochemical marker for a cell that has the potential to differentiate into an adipocyte.

At equal amounts of total body fat, women have greater subcutaneous adipose tissue thickness in the femoral-gluteal region, while men have greater adipose thickness in the abdominal region (14, 80, 128). Women have larger femoral-gluteal fat cells than do men, while abdominal fat cell size is similar

in men and women (56, 80). Despite these sex-related differences in femoral-gluteal cell size, most of the difference in the size of subcutaneous fat depots between men and women at specific sites is explained by differences in the number of fat cells (14, 80, 128).

Site-related differences in fat deposition are also apparent within each sex. In women, gluteal and femoral fat cells are significantly larger than abdominal fat cells, but again differences in the adipose tissue thickness are due mainly to differences in the number of fat cells. Similarly, the abdominal adipose tissue preponderance of men is due mainly to increased fat cell number. The fat distribution typical of each sex is apparent as early as four years of age and diverges further during adolescence as girls gain fat in the hip region and boys tend to lose fat from peripheral depots, resulting in the relative predominance of abdominal fat depots in males (23, 71). Increases in local cellularity during puberty occur in the femoral-gluteal region of girls and in the epigastric region of boys (23).

The ontogenesis of internal (omental, mesenteric, and retroperitoneal) adipose depots in humans has not yet been described. Sex-related differences in the size of intraabdominal fat stores have been reported, however. Men have more visceral fat than women on both a relative and an absolute basis, although the percentage of internal fat is increased in women with upper body fat distribution (129). CT scanning reveals that with increasing fatness, men deposit internal fat proportionately so that it continues to comprise approximately 21% of total body fat. In contrast, at low levels of body fat, women deposit little internal fat. As total body fat exceeds 30 liters, however, women deposit visceral fat in the same proportion as men (129). This relative protection against the deposition of visceral adipose tissue may explain the observation that women in a cross-sectional study ($N = 100$) were able to tolerate about 30 kg more body fat than men before experiencing comparable degrees of metabolic compromise (80).

The increases in the size of mesenteric and omental fat stores in obese men, compared with those of obese women of equal body fat, are at least in part due to increased fat cell size in these depots (56). No data are available comparing lean men and women. In addition, omental fat cells in obese women are smaller than those in subcutaneous gluteal, femoral, and abdominal depots and those in the mesenteric depot. In contrast, in obese men, omental fat cells are equal in size to fat cells in other subcutaneous depots, and mesenteric fat cells are larger than those in all other sites (56).

The relative distribution of fat between various internal adipose depots in humans is uncertain. Even cadaver studies (31) have failed to distinguish between two major sites: omental and mesenteric. CT scan examinations indicate that approximately one third of the intraabdominal fat in both sexes is in the retroperitoneal region. At the midabdomen, men have significantly more retroperitoneal (RP) fat than women do (11).

CONTROL OF BODY FAT DISTRIBUTION

Regulation of Regional Fat Cell Number

Although centripetal fat deposition occurring with specific endocrine derangements—Cushing's disease (77), androgen excess (47), and growth hormone (GH) deficiency (22)—is well known, the mechanisms involved are uncertain. Methods of determining regional fat cell number are not sufficiently accurate to establish whether increases in fat cell number occur in specific fat depots with modest degrees of weight gain or endocrine-mediated adipose tissue redistribution.

In the rat, responsiveness of fat cell number to nutritional influences varies among adipose depots (13, 48). Regional differences in the control of adipose tissue growth—i.e. the proliferation and differentiation of adipocyte precursor cells—probably contribute to site-specific variations in adipose tissue deposition. Progress in this field has been limited, however, by the lack of in vitro systems appropriate to the examination of these processes in human adipose tissues. The factors regulating fat cell differentiation in established adipose cell lines (1, 147) are fairly well understood. The most commonly studied preadipocyte cell lines were derived from mouse embryo fibroblasts (3T3-L1) or dedifferentiated epididymal fat cells from the obese mouse (ob/ob). These cell lines have been serially passaged and have stable phenotypic properties. They provide an excellent in vitro model system for the study of adipocyte differentiation. There is as yet no adipose cell line of human origin. Unfortunately, studies of rodent cell lines provide little insight into possible depot-related differences in adipocyte growth or possible influences of genetic or nutritional factors. In addition, applicability of these results to human preadipocyte differentiation is uncertain (36). Insight into mechanisms regulating regional adipose tissue growth in humans must be pursued by using primary cultures of preadipocytes as described below.

STUDIES OF ADIPOCYTE PRECURSORS IN CULTURE Observations made in vivo on the developing rodent adipocyte led to the hypothesis that both stem cells, or adipoblasts (cells not yet committed to a differentiation program), and preadipocytes (cells already committed to differentiate but not yet identifiable as such) exist within adipose tissue. During normal growth or overfeeding, preadipocyte differentiation and adipoblast stem cell proliferation are stimulated in rodents (2, 42, 76).

The stromal-vascular fraction of adipose tissue of rats can be obtained by collagenase digestion and grown in culture (15–17). When the stromal-vascular fraction of adipose tissue from young rats is cultured, approximately half of the cells spontaneously acquire multi- or unilocular fat droplets and exhibit the biochemical characteristics of mature adipocytes. Substantially fewer cells differentiate spontaneously in stromal-vascular preparations of

adipose tissue taken from older rats (18). In contrast, a maximum of 6.5% of stromal-vascular cells derived from human subcutaneous or abdominal adipose tissues achieves adipocyte morphology (107); values as low as 0% or 1% have been reported (64, 107). Recent studies using serum-free medium (35, 36) indicate that substantially greater numbers of potential adipocyte precursors are present in both rat and human adipose tissue than was previously supposed. Differentiation occurred in more than 90% of the cells derived from the stromal-vascular fraction of adipose tissue from young rats (36) and in 20% of cells derived from human adipose tissues (35). These results suggest that factors present in serum may inhibit differentiation. Growth arrest is thought to be a prerequisite for terminal differentiation (2). The high mitogenic potency of most serum may inhibit differentiation by stimulating rapid growth. Differences in the adipogenic activity of sera obtained from overfed or genetically obese rodents and humans have been sought, but results thus far are inconclusive (63, 140).

No systematic studies have examined the effects of anatomic site or age on the number of human adipocyte precursors. Before such studies can be fruitfully pursued, further work is needed to establish optimal conditions for inducing the differentiation of human adipose cells.

In the rat, fat depots in different anatomic sites display striking differences in their capacity to generate new adipocytes. The RP fat depot, for example, can greatly increase fat cell numbers in response to overconsumption of a high-fat diet, while the epididymal fat depot does not (48, 50). In tissue culture, precursor clones derived from the RP depot, compared with the epididymal, show increases in replication rate and capacity for differentiation into fat cells (37, 38). Sztalryd & Faust (141) have also found substantial differences in the capacity for differentiation between primary cultures of preadipocytes derived from the epididymal and RP fat depots. Epididymal preadipocytes may be more sensitive to as-yet-unidentified serum factors that influence differentiation (141).

Differences between fat depots in the potential for hypertrophic and hyperplastic growth could result from differences in metabolic or growth capacities of adipocyte precursor cells (38, 49). Some precursor clones may exhibit higher lipoprotein lipase (LPL) activity or responsiveness to lipogenic hormones; this variability may reflect intrinsic differences among fat depots in the distribution of receptors for specific hormones that regulate adipose tissue metabolism and growth. For instance, glucocorticoid receptors, which may be important in the differentiation of human adipocyte precursors (29, 64), are present in greater numbers in omental than in subcutaneous adipose tissues. In rat adipose tissues there are marked sex- and depot-related variations in receptors for estrogen and progestins (60). Xu & Björntorp (152) have recently shown that the addition of progesterone to culture medium

stimulates the differentiation of preadipocytes from immature male or ovariectomized female rats. However, when progesterone was administered to rats, although depot-specific effects on fat-cell size were observed, no short-term effects on fat-cell number were noted. Progesterone increased fat-cell size more in parametrium than in other fat depots (78).

Paracrine factors may also be important in controlling local recruitment and maturation of preadipocytes (39). Thus, when fat cells in a given depot reach a certain size, local hyperplasia may be stimulated by signals emanating from the enlarged adipocytes themselves. The "critical" cell size may vary among depots (48). Factors such as blood flow or innervation may contribute to depot differences in the number of fat-cell precursors. As a result of increased supply of substrates, hormones, or neural factors, precursor multiplication in some fat depots may be stimulated, or more precursor cells in a given depot may reach a late stage of differentiation. An increase in the number of preadipocytes that have reached a late stage of differentiation would be reflected by an increase in the number of cells that spontaneously differentiate in primary culture, while the number of cells at earlier stages in the differentiation program would be revealed if such cells are allowed to grow and are then induced to differentiate under proper conditions (141).

In summary, susceptibility to increases in adipocyte cell number is likely to vary among adipose tissue depots in humans as it does in the rat. Further research is needed to define the factors that influence the proliferation and differentiation of human adipocyte precursors, the manner in which these processes are regulated by hormones, and the possible sex- and depot-related differences in responsiveness to specific hormones.

Regulation of Fat Cell Size

The synthesis of lipid by adipocytes is favored by high ambient levels of LPL, insulin, glucose, FFA, and TG (as lipoproteins). Hydrolysis of stored TG is favored by circumstances tending to lower the availability of the above fuels and hormones and to activate the enzyme hormone sensitive lipase (HSL), which catalyzes the breakdown of the TG molecule into its constituent three molecules of FFA and one molecule of glycerol. The activation of HSL is ultimately controlled by phosphorylation-dephosphorylation events, which are regulated, to a large extent, by the respective activities of protein kinase A (via adenylate cyclase generated cAMP) and an insulin-activated protein phosphatase (12).

LIPOLYSIS: ENDOCRINE AND PARACRINE REGULATORS OF LIPOLYSIS

Adrenoreceptors The plasma membrane of human adipocytes contains catecholamine receptors capable of activating (β-1) and deactivating (α-2) hormone-sensitive lipase (HSL) via effects on adenylate cyclase (AC) (89).

Although α-2 receptors are readily demonstrated in adipocytes of humans, hamsters, rabbits, and dogs, the consensus seems to be that rat adipocytes do not contain functionally significant α-2 receptors (27, 28). Recent studies performed with the highly selective α-2 agonist UK14304, however, suggest that rat adipocytes do, in fact, contain functionally significant α-2 receptors (112). The naturally occurring catecholamines—norepinephrine (NE) and epinephrine (EPI)—are capable of activating both of these receptors (i.e. they are "mixed agonists"), although EPI's affinity for the α-2 receptor is somewhat greater than that of NE. Most of the NE in the circulation is released from nerve terminals abutting the vasculature; EPI derives mainly from the adrenal medulla.

In the catecholamine response cascade, both stimulatory and inhibitory signals are transduced by so-called G proteins (or N proteins)—trimeric peptides with the ability to either activate (G_s) or inactivate (G_i) AC (59). AC, in turn, modulates the generation of the "second messenger" cAMP, and thereby protein phosphorylation, the means by which cAMP exerts metabolic control. Of particular interest is the fact that many other stimulatory (prostaglandin E_1) and inhibitory (adenosine, prostaglandin E_2) modifiers of lipolysis act via unique membrane receptors that are, in turn, coupled to the appropriate G protein. Several distinct receptors, therefore, share the same G protein.

Insulin Insulin decreases both the activity of HSL (lipolysis) and blood flow to adipose tissue (109), and it is an important regulator of synthetic processes (LPL, glucose transport, acylglyceride synthesis) in the adipocyte. The mechanisms by which the insulin receptor conveys its signal to the interior of the cell are the topic of intense investigation and may involve phosphorylation of proteins (135) as well as the release of second messengers, such as inositol glycans, from the plasma membrane (93).

The role of insulin in determining body fat distribution has been investigated only to a limited extent. In postabsorptive men and women, adipocytes from the abdominal subcutaneous site are more sensitive to the antilipolytic effect of insulin than are those derived from the femoral (130) or omental (21) sites. This difference in response occurs despite the fact that insulin binding is increased in femoral depots (130), but the difference is consistent with an increased affinity of the insulin receptor for its ligand in abdominal subcutaneous adipocytes, as compared with that of omental adipocytes (21).

Adenosine Adenosine, a product of the dephosphorylation of cAMP, has potent effects on lipolysis (inhibition) and blood flow (vasodilation). Adenosine release by adipose tissue appears to decline during fasting, and some

investigators have suggested that this phenomenon is largely responsible for the increase in lipolysis rate that occurs during caloric restriction (72). This view of adenosine as an autocrine regulator of both lipolysis and insulin sensitivity is widely held but has recently been questioned by one of its major proponents. Kather (74) has reported that most of the adenosine accumulating in vitro in the extracellular space of isolated human adipocytes is not released as such from adipocytes but is, rather, an artifact of the action of extracellular ectophosphatases (e.g. ecto-S_1-nucleotidase) on adenine nucleotides released by leaking adipocytes. Although virtually no adenosine escapes from intact adipocytes, inosine and hypoxanthine, which are also products of nucleotide catabolism (deamination), are released from human adipocytes. The rate of release is increased upon catecholamine stimulation of lipolysis (74). The roles, if any, of inosine and hypoxanthine in regulation of lipolysis are not yet clear, but Gaion et al (57) reported that inosine stimulates lipolysis in rat fat cells.

The plasma concentration of adenosine in humans is approximately 200 nM (92). Comparison of adenosine concentrations in serum and interstitial fluid, as measured by microdialysis, reveals only slightly lower adenosine concentrations in the interstitium (92). The concentration of adenosine found in the interstitium (150 nM) is potently antilipolytic in vitro, which suggests that lipolysis may be tonically inhibited in vivo by ambient adenosine.

Adenosine inhibits lipolysis in fat cells by binding to specific receptors. The Ri receptor (specific for the ribose moiety) is most abundant and inhibits adenylate cyclase via G_i. Adenosine also enhances sensitivity to insulin stimulation of glucose metabolism (124) and decreases sensitivity to the lipolytic effects of a number of hormones (68). Although nutrition-induced changes in adipocyte sensitivity to adenosine have been reported in rats, no such changes have been found in human adipocytes (73).

Regional variations in adenosine concentration, perhaps controlled by blood flow, may modulate regional adipose tissue metabolism. The adenosine content of whole adipose tissue is higher in the femoral than in the abdominal region of nonobese women. The situation is reversed in lactating women. Sensitivity to the antilipolytic effect of N^6-phenylisopropyladenosine (PIA), a nonhydrolyzable analog of adenosine, does not differ between the two sites (139). These findings are consistent with the female tendency to accumulate fat in the femoral depot and to mobilize it from that site during lactation.

Growth hormone The centripetal distribution of adipose tissue in GH-deficient children, and the preferential depletion of abdominal adipose depots upon GH replacement therapy, suggest site-specific differences in adipose tissue responses to GH (22, 52). The human growth hormone receptor does not appear either to be a tyrosine kinase (such as insulin) or to act via G

proteins (88). The effects of GH on lipolysis, both in vivo and in vitro, are variable and highly dependent upon GH concentration, duration of exposure, and hormonal and substrate milieu (54). In general, GH appears to increase rates of FFA release by increasing lipolytic rate and by decreasing the reesterification of FFA (62, 111).

Prostaglandins High-affinity antilipolytic prostaglandin E_2 (PGE_2) receptors have been found on intact human adipocytes obtained from the gluteal region. No sex differences were apparent; possible site differences have not been examined (120).

LIPOLYSIS: CATECHOLAMINE–MEDIATED EFFECTS Many in vitro studies suggest that the catecholamines are important in the regulation of body fat by virtue of their effects on the rate of lipolysis, as distinguished from their effects on oxidative metabolism. Consequently, more detailed information is available about site- and sex-related variations in the response to adrenergic agonists and antagonists than to any other agents.

Anatomic Site–Related Differences in Adrenoreceptor Number and Response Based upon Scatchard analysis of radioligand binding isotherms [^{3}H-dihydroalprenolol (β) and ^{3}H-yohimbine (α-2)], Östman et al (103) estimated that there were 90×10^3 β and 840×10^3 α-2 receptors on both hypogastric and femoral adipocytes of obese female subjects. A seven-day fast was associated—in femoral adipose tissue—with concomitant declines in β receptor number ($90 \times 10^3 \rightarrow 30 \times 10^3$ per cell) and lipolytic sensitivity (30-fold) to a pure beta agonist (isoproterenol). In hypogastric tissue, such changes did not occur. In both regions, α-2 receptor number decreased in association with a decrease in sensitivity (10-fold) to inhibition of lipolysis by clonidine (α-2 agonist). The large decline in femoral β responsiveness and sensitivity was concordant with the diminished lipolytic response to NE in this region. In fasting subjects, NE had an antilipolytic effect at NE concentrations greater than 10^{-9}M. Prior to fasting, however, lipolytic responses to the mixed agonist NE were not predicted by relative α-2 and β receptor number in the two sites. The authors report approximately equivalent dose-response curves to NE in both sites. Other investigators (86, 130) report higher lipolysis rates in hypogastric than in femoral tissue; they attribute these higher rates to higher α-2 receptor activity in the femoral region. The frequent discordance in such studies, between apparent receptor number and affinity and the actual response to a mixed agonist, suggests that other aspects of the lipolytic response cascade—e.g. receptor "coupling" to G

protein or G protein interaction with cyclase—may also be important modulators of cellular response (81).

In a study of 35 nonobese subjects one month to 45 years old, Arner et al (7) demonstrated a positive correlation between fat cell size (FCS) and lipolytic response in abdominal subcutaneous adipocytes. FCS showed a negative correlation with the α-2 effect of NE but no correlation with the β-1 effect of this agent. These findings suggest that the α-2 receptor may be important in regulating adipocyte size in humans; the α-2 receptor may tend to oppose substantial increases or decreases in cell size by affecting response to NE.

Intraabdominal adipose tissues have not been examined as extensively but are obviously important because of their contribution to abdominal girth and their more direct access to the hepatic portal circulation. Östman et al (102) reported (and we have confirmed; R. Leibel, N. Edens, S. Fried, J. Kral unpublished observations) that omental adipose tissue had a lower basal rate of lipolysis and an enhanced lipolytic response to NE (compared with abdominal or femoral subcutaneous) and that these differences could be attributed both to diminished α-2 and augmented β-1 response. More recently, Mauriege et al (97) reported an α-2:β ratio of 3:2 in abdominal and femoral subcutaneous tissue and 0.9:1 in omental tissue due to a relative increase of beta receptors in the omental site.

Sex-related differences in lipolysis Leibel & Hirsch (86) reported enhanced α-2 receptor activity in abdominal subcutaneous adipocytes of men, as compared with women, and they suggested that such a situation might contribute to the greater tendency of men to accumulate fat in this region. Richelsen (118) found greater α-2 receptor number and response in the gluteal adipocytes of women as compared with men; these findings are also consistent with sex-related differences in adipose tissue distribution.

Endocrine modulation of lipolysis The lipolytic response to NE is greater in abdominal than in femoral adipocytes in premenopausal women; this response is equal in the two sites in postmenopausal women (116). The response to 10^{-6}M NE was examined in adipose tissue obtained from healthy women during the early or late portion of the menstrual cycle and during pregnancy and lactation. Lactation (with an attendant increase in circulating prolactin levels) was associated with an enhanced lipolytic response in femoral adipose tissue. Whether this enhancement was due to increased β or decreased α-2 activity was not determined (113). Evans et al (45) reported a correlation between abdominal FCS and the plasma concentration of free testosterone in premenopausal women, a correlation suggesting that testosterone may en-

hance abdominal α-2 receptor activity. Cortisol and thyroid hormones are also reported to have conditioning effects on adipocyte responses to adrenoreceptor agonists (137, 149). Triiodothyronine (T_3) binding sites in the nuclei of human adipocytes have been identified (33). They may be important in modulating the lipolytic response to adrenergic agonists and antagonists (119). Again, depot- and sex-related differences in T_3 binding have yet to be reported. Women exposed to exogenous corticosteroids for therapeutic purposes have smaller gluteal adipocytes than untreated, age-matched controls. No difference in femoral or abdominal subcutaneous adipocyte size was noted in this study (77).

Age effects on lipolysis Infants in the first year of life show enhanced α-2 activity in abdominal subcutaneous adipocytes over that of adults, a phenomenon believed to "protect" the adipocyte and enhance lipid accretion (94). Some data suggest that aging is accompanied by stable β-1 performance but increased α-2 activity (possibly predisposing to obesity) (94).

ACYLGLYCERIDE SYNTHESIS Adipose tissue synthesizes TG by esterifying fatty acids to glycerol-3-phosphate. The rate at which TG is synthesized is determined both by substrate (glycerol-3-phosphate and FFA) supply and by the activity of the enzymes of TG biosynthesis. The final enzyme in the pathway, diacylglycerol acyltransferase, may catalyze the rate-controlling step (133), but no direct evidence on this point is available for human adipose tissue. Substrate (glucose and FFA) supply may also be rate-limiting for TG synthesis. Lipid synthesis in human adipose tissue increases with increasing glucose concentration in the physiologic range (1–10mM) (8), which suggests that the supply of glucose may, in part, determine the rate of lipid deposition in normal human adipose tissue. Extensive work has been done to characterize the mechanisms and control of glucose transport across the adipocyte plasma membrane. At physiologic glucose concentrations, however, glucose transport is not rate limiting for lipid synthesis (105) in human adipose tissue.

Adipocyte glucose metabolism and insulin effects Site-related differences in adipocyte metabolism occur in vivo. When a ^{14}C-glucose load was administered to obese and lean women, more label was converted to acylglyceride by abdominal than by femoral adipocytes of the obese but not the lean women when label in acylglyceride was measured at four hours and at one week after ingestion of the radioisotope. The half-life of the label in acylglyceride, measured over seven months, was shorter in abdominal than in femoral adipose tissue, a result suggesting that turnover of lipids was more rapid in the abdominal depot (95).

Insulin binding (105) in femoral adipocytes and glucose transport (53, 105) in both femoral and abdominal adipocytes are higher per fat cell in women than men, but when the increased size of adipocytes obtained from women is taken into account, there is no difference between the sexes. Basal and insulin-stimulated glucose oxidation and conversion to lipid are higher in femoral adipocytes from women than in those from men, however, even when the larger size of women's fat cells is taken into account (105). Exercise training increases basal and maximally insulin-stimulated glucose conversion to lipids in men, but not in women, despite the fact that physical training decreased cell size in men but not in women (123). Several studies have attempted to document site-specific effects of exercise on subcutaneous body fat, as measured by skinfold thickness (144). Aerobic exercise decreases subcutaneous fat slightly more in the trunk than in the extremities but not to a statistically significant degree. Exercise does not cause differential mobilization of fat from the exercised limb (79).

Fatty acids In normal adult human adipose tissue, fatty acids for esterification are not derived to any significant extent from de novo fatty acid synthesis in the adipocyte (104). Adipocytes may obtain FFA directly from plasma, where they circulate bound to albumin, or from hydrolysis of circulating TG by LPL. LPL is synthesized and secreted by adipocytes and is activated within capillaries by apolipoprotein CII. Adipose tissue LPL activity is rapidly increased by feeding and decreased by caloric deprivation (90). Insulin and glucocorticoids are thought to be the primary mediators of these changes (30). The relative proportion of FFA derived from circulating FFA and TG is unknown. Very limited data, obtained from perfusion of rat fat pads with labelled chylomicra or FFA, suggest that the two processes may yield approximately equal amounts of FFA for esterification within adipose tissue (121).

1. *Lipoprotein lipase*. A role for LPL in controlling lipid deposition in adipose tissue is suggested by the fact that LPL activity varies markedly with changes in nutritional status (90) and is positively correlated with fat cell size (6). Adipose tissues from the gluteal and femoral sites of premenopausal women have significantly higher LPL activity than does adipose tissue from the abdominal subcutaneous site. This difference remains whether the data are expressed per fat cell or per unit fat cell surface area. These variations in LPL activity parallel differences in fat cell size, suggesting a role for LPL in control of local fat accumulation (56, 91, 113, 116). Site-specific variations in LPL activity occur with changes in physiologic state such as pregnancy and lactation. LPL activity increases during pregnancy and decreases during lactation in femoral but not abdominal adipose tissue. The femoral fat depot may be important in supplying energy needed for lactation (113).

There are significant sex-related differences in LPL activity expressed per

cell or per unit cell surface area. Femoral and gluteal LPL activity is greater in premenopausal women than in men (56, 142). This high gluteal-femoral LPL activity disappears with menopause (115, 116). Administration of estrogen plus levonorgestrel or medroxyprogesterone specifically increases femoral LPL activity in postmenopausal women (116).

The cellular bases for these regional and sex-related variations in LPL activity are unknown but are likely due to effects of reproductive hormones. Site- and sex-related differences in LPL activity may be due to the distribution of receptors for sex steroids evident in studies of estrogen and progestin receptors in rat adipose tissue (60), although efforts to measure these receptors in human adipose tissue have thus far been unsuccessful (117). A very high negative correlation between plasma estradiol and gluteal LPL activity has recently been reported, however (69).

Glucocorticoids in the presence of insulin markedly increase LPL activity (30) in vitro in human adipose tissue. Glucocorticoid receptor number is greater in omental than in abdominal subcutaneous adipose tissue (99, 114), and this difference may in part mediate the changes in fat distribution that occur when plasma corticosteroid concentrations are chronically elevated. Differential effects of hormones on the regulation of LPL in different fat depots have yet to be demonstrated in vitro, however.

2. *Reesterification*. FFA newly hydrolyzed from adipocyte TG stores are another source of FFA substrate for TG synthesis. During lipolysis, both glycerol and FFA are liberated by hydrolysis of TG. Adipocytes cannot reutilize glycerol, but FFA may be reactivated to acyl CoA and reesterified with glycerol-3-phosphate derived from glycolysis. This cycle of TG hydrolysis and reesterification of resulting FFA (the triglyceride/fatty acid cycle) has been extensively studied (101). Although no net TG is gained in this cycle, the pathway may represent a mechanism by which adipose tissue conserves FFA, rather than releasing them into the circulation for oxidation.

Recent data suggest that some portion, perhaps all, of the reesterification pathway occurs by an extracellular route, as FFA are cycled through the interstitial space around adipocytes (87). FFA hydrolyzed from TG during lipolysis may leave the adipocyte and be taken up again to be reesterified either by the same adipocyte or by those adjacent (43). The temporary appearance of newly hydrolyzed FFA in the extracellular space renders them susceptible to changes in tissue perfusion (26). The rate of adipose tissue blood flow may thus determine, to some extent, whether hydrolyzed FFA are removed from the tissue to the general circulation or are taken up again by adipocytes and reesterified.

3. *Blood flow*. Adipose tissue blood flow is decreased by sympathetic nerve stimulation because norepinephrine acts at vascular α receptors to

increase vasoconstriction and to reduce blood flow (122). As stimulation is prolonged, FFA from lipolysis are released and accumulate within the tissue. Adenosine also accumulates within adipose tissue, although, as noted earlier, its cell of origin is unclear. Both FFA and adenosine exert feedback inhibition on lipolysis. In addition, adenosine is a vasodilator, and its accumulation mediates vasodilatory escape, despite continuing neural stimulation (96). When stimulation ceases, blood flow rebounds above prestimulation levels, and FFA and adenosine are flushed from the tissue. Adipose tissue blood flow is decreased by a 100-g oral glucose load in humans (110) and by a meal or insulin infusion in the rat (109, 150). As mentioned above, adipose tissue blood flow may play an important role in determining rates of FFA reesterification. Adipose tissues with low blood flow may preserve, through reesterification, stores of lipid more efficiently than do tissues with higher rates of blood flow. Significant site-related differences in blood flow have been observed in rat adipose tissues (32). Site-related differences in adipose tissue blood flow have not been explored in humans but represent a very important subject for future investigation.

SITE–SPECIFIC CHANGES IN ADIPOSE TISSUE DURING PERIODS OF ALTERED NUTRITION

Many investigators have examined the biochemistry and receptor physiology of human adipose tissue in different anatomic sites under circumstances of changed nutrition or metabolic status. The purpose of these studies has been to understand possible unique contributions of specific depots to circumscribed clinical events. In one of the earliest such studies, Arner & Ostman (3) reported that fasting increases levels of cAMP in thigh adipose tissue while blunting the tissue's lipolytic response to NE. The latter effect was attributed to enhanced α-2 receptor activity in the fasted tissue, because the effect could be blocked with phentolamine. These findings were extended in a study by the same investigators that demonstrated that fasting in women was associated with greater increases in α-2 adrenoreceptor response in gluteal and femoral depots than in abdominal subcutaneous fat (102). Basal lipolysis rate was lower, and LPL activity higher, in femoral versus abdominal subcutaneous fat of postabsorptive women. During fasting, femoral LPL fell and basal lipolysis rates rose to levels similar to those found in the abdominal subcutaneous tissue after fasting. Rates of acylglyceride synthesis were comparable in the two depots before fasting but decreased to a lower level in abdominal than in gluteal tissue during fasting (6). In the aggregate, such changes might be expected to modulate rates of lipid evacuation in vivo to favor relatively greater loss from abdominal than gluteal depots. And, in fact, adipocyte size

decreased in the abdominal but not in the gluteal depots. A one-week fast in women was reported to produce a reduction in both β receptor density (specific binding of ^{3}H-dihydropranolol and/or ^{125}I-cyanopindolol) and sensitivity to β receptor–induced lipolysis (isoproterenol) in femoral but not in abdominal adipocytes. In both sites, a rightward shift in dose-response (decreased sensitivity) to the antilipolytic effects of the α-2 agonist clonidine was found in association with an $\sim$ 20% decrease in receptor number (by ^{3}H-yohimbine binding) (103). The decline in abdominal α-2 receptor activity, in conjunction with a relatively greater decrease in β than α-2 activity in the femoral region, may explain the observed pattern of in vitro response to mixed agonists such as epinephrine and norepinephrine (abdominal lipolysis $>$ femoral or gluteal) under these circumstances.

During caloric restriction, LPL activity has been reported by some to decrease proportionately in femoral, gluteal, and abdominal adipose tissue of women (143), while others have found a slightly greater decrease in the femoral compared with the gluteal region (6). Depot-specific differences in basal and postprandial LPL activity, as well as the stimulation of LPL activity after a meal, persist during refeeding (143). Thus, no disproportionate change in site-specific relative rates of TG turnover (to the extent that this turnover is controlled by LPL) would be expected during caloric restriction, and the pattern of fat distribution would be expected to remain constant with weight loss and gain. Whether the same is true in men remains to be investigated.

In vitro glucose oxidation was 60% higher in femoral than in abdominal adipocytes (pooled results from men and women in the postabsorptive state). The ability of insulin to stimulate glucose oxidation did not vary between sites in absolute terms, although the percentage of stimulation was higher in abdominal than in femoral adipocytes. Seven days of fasting decreased basal glucose oxidation 44% in abdominal adipocytes, and 50% in femoral adipocytes. More interestingly, the ability of insulin to stimulate glucose oxidation, while blunted by fasting in femoral adipocytes, was completely abolished in abdominal adipocytes (44).

Insulin receptor number was reported to be twofold higher in femoral than in abdominal adipocytes in women. This difference was associated with enhanced insulin responsiveness in the region (20). One week of fasting was associated with enhanced sensitivity to insulin-mediated antilipolysis in femoral but not in abdominal fat (5). Femoral adipocytes from fasted female subjects showed increased insulin binding and enhanced sensitivity and responsiveness to the antilipolytic effect of insulin, while sensitivity and responsiveness to insulin stimulation of glucose transport and lipogenesis were decreased because of changes in insulin effects at the postreceptor level (8).

RELATIONSHIP OF IN VITRO RESPONSES OF ADIPOSE TISSUE TO IN VIVO CHANGES DURING CALORIC DEPRIVATION

The broad array of hormone-mediated responses in human adipose tissue in vitro, discussed above, might reasonably be taken as evidence that these processes have an important role in vivo. A clear relationship is difficult to demonstrate between such in vitro measures of adipocyte metabolism and measures of in vivo function, particularly with respect to lipolysis. Systemic infusion of norepinephrine into obese subjects after 15 days of fasting is associated with significantly greater increments of plasma concentrations of FFA and glycerol than occur when the infusion is performed during the fed state. This effect is apparently due both to an absolute increase in adipose-tissue sensitivity to the lipolytic effects of NE and to a pancreatic α-receptor–mediated decrease in circulating insulin concentration (4). EPI infusion has a similar effect on rates of appearance of FFA and glycerol in obese subjects who have fasted for 87 hr (151). Conversely, fasting reduces systemic sensitivity to the antilipolytic effects of infused insulin (70), in contrast to in vitro results (5).

The precise reasons for the increases in basal and stimulated lipolysis rate that occur with fasting are unknown. Likely candidates include, of course, the decline in plasma insulin, changes in circulating catecholamines, and shifts in receptor and postreceptor processes which control the adipocyte's response to lipolytic and antilipolytic agonists. Studies of organ turnover rates of NE in animals, and urinary excretion rates of NE and EPI in humans, suggest that fasting is accompanied by a decline in sympathetic autonomic tone (NE) and an increase in adrenal medullary activity (EPI). Thus, EPI, and not NE, appears to be the major catecholamine modulator of fuel flux during fasting. Among the consequences of such elevations in ambient EPI would be suppression of pancreatic insulin release and site-specific effects on lipolysis rate (dependent upon the status of relevant receptor and subreceptor systems). Given the rather striking site-related differences in in vitro α-2 and β-1 adrenoreceptor status between sites during fasting, one would anticipate catechol-mediated suppression of lipid evacuation from gluteal and femoral depots and stimulation of such evacuation from adbominal (subcutaneous and intraabdominal) depots. Such differential effects, if the sole or major mediators of fuel mobilization, would generate increasing pelvic preponderance of fat location with each episode of weight loss, culminating in the achievement of extreme gynoid body habitus. Similar shape changes would be expected on the basis of differential sensitivity of these depots to the antilipolytic effect of insulin. Although there have been reports of subtle enhancements in pelvic preponderance in women undergoing weight re-

duction (148), for the most part, relative body proportions are not much altered by weight reduction (66). Thus, either the in vitro experiments do not reflect with fidelity what is occurring in vivo, or the adipocyte receptors studied do not play an important role in mediating alterations in fuel mobilization during fasting.

In contrast to these findings during caloric restriction, the degree of fat cell hypertrophy in the gluteal compared with the abdominal region of women undergoing weight gain agrees well with the in vitro results (both LPL and α-2 activity are higher in the gluteal region). Thus, depot differences in the regulation of lipid storage may be important in determining the body fat pattern, but only to the extent that fat cell enlargement is affected.

CONCLUSIONS

The anatomic distribution of adipose tissue appears to play a role in some of the medical morbidity that accompanies obesity. The biologic mechanisms for the association between central adiposity and these morbidities are not known, but high concentrations of FFA in the portal venous circulation may play a role. Most of the variation in fat distribution among humans is probably due to anatomic site-specific differences in number of adipocytes; subtler variations are due to differences in adipocyte size. Control of adipocyte precursor production, recruitment, and differentiation—and possible regional variations in these processes—is poorly understood but is apparently influenced by genetic, endocrine, and nutritional factors as well as clonal differences between adipocytes in different anatomic sites. Sensitivity and responsiveness to insulin, catecholamines, and adenosine as well as the enzymes controlling the synthesis (e.g. LPL) and hydrolysis (HSL) of triglyceride are influenced by anatomic site, nutritional status, and other endocrines (e.g. T_3, gonadal and adrenal steroids). The fact that body proportions remain more or less constant despite substantial increases or decreases in body fat suggests that between-site differences in the in vitro status of these receptors and biochemical processes may not fully reflect events in vivo. In vivo regulation of fat-cell size in different fat depots reflects a complex interplay of the effects of many hormones, autocrine regulators, and other local factors such as blood flow. Whatever the local mechanisms involved, the "first order" character of triglyceride loss from specific depots indicates that, in vivo, depot mobilization is proportional to regional adipocyte number and size.

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