Obesity is responsible for the mounting incidence of metabolic disease in adult and pediatric populations. Understanding of the pathogenesis and maintenance of the obese state has advanced rapidly over the past 10 years. Bodily energy reserves are managed actively by complex systems that regulate food intake, substrate partitioning, and energy expenditure. An underlying assumption that circulating factors released from storage organs were able to signal bodily energy reserves was confirmed with the discovery of the leptin system. This proof of concept has spurred on the discovery of a multitude of other adipocyte-generated factors. These circulating factors signal to the brain and other organs of metabolic importance, including adipose tissue, liver, muscle, and the immune system. Adipose-derived factors have numerous implications for the basic biology of obesity and provide prospective targets for the amelioration of obesity and its adverse metabolic consequences. In this review we detail the current understanding of leptin as a prototypical adipose tissue–derived hormone related to appetite and obesity. We also describe other important adipose-derived factors in relation to their metabolic effect.

Regulation of Energy Balance

It is now widely understood that an intricate system exists to regulate bodily energy balance. Because such mechanisms are vital for multicellular life they are deep seated, necessarily complex, and include sensing and effector arms that respond to multiple metabolic cues. Metabolic regulation relies on sensing and signaling of nutrient intake, circulating fuels, energy stores, and likely energetic demands. As such, these signals may be generated from short-term events such as ingestion of a meal or longer-term states such as degree of adiposity. Effector arms alter behavior, fuel availability, and energy expenditure via basal metabolic rate and physical activity, growth, and reproductive ability. Such complex interactions require a high degree of integration, which for the most part occurs in the central nervous system; a number of different centers are involved in forebrain and hindbrain. Overall, the hypothalamus is a key center for integration and control of energy balance, although there is significant communication with effector areas in the forebrain and hindbrain centers controlling the autonomic nervous system. The importance of the hypothalamus was made apparent by early lesioning studies. However, the discovery of leptin revealed some of the

Abbreviations used in this paper: adipoR, adiponectin receptor; AgRP, agouti-related peptide; ANGPTL4, angiopoietin-like peptide 4; HSD, hydroxysteroid dehydrogenase; IL, interleukin; JAK2, Janus activating kinase 2; PAI1, plasminogen activator inhibitor 1; POMC, pro-opiolanocortin; PPAR, peroxisome proliferator activated receptor; RBP4, retinol binding protein 4; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3; TNFα, tumor necrosis factor α.
The hormone leptin is produced in adipose tissue and has peripheral and central targets. Leptin is the best characterized of all secreted products of adipose tissue. It is secreted in proportion to adipose stores and immediate nutritional state. Leptin is transported across the blood-brain barrier and gains access to central nervous system targets. These include neurons within the hypothalamus and the ventral tegmental area. Resulting effects of central leptin action include changes in food intake, energy expenditure, and peripheral metabolic actions on glucose and lipid metabolism and neuroendocrine effects. Direct peripheral targets include pancreatic islet β-cells, immune cells, and other cell types. In addition to leptin, an increasing number of other adipocyte-secreted products have been identified.

**Subtlets of Hormonal Regulation of Hypothalamic Circuitry Not Previously Appreciated.**

**Leptin as an Adipose Tissue-Derived Hormone**

Characterization of the ob gene product, leptin, revealed that absence of this 16-kilodalton hormone is responsible for severe obesity in the mouse model. The importance of leptin in energy homeostasis is further anchored by other loss-of-function experiments of nature. Most notably, the discovery that distinct rodent models of obesity were caused by defects in the leptin receptor. More recently, human beings with obesity mediated by leptin deficiency were identified and treated successfully with recombinant leptin. The initial impression from mouse studies was that leptin was an inducer of thinness; the name *leptin* derived from the Greek “leptos,” for thin. Leptin-deficient mice have defects in body temperature regulation and fecundity. Similar effects are evoked by fasting and these effects may be ameliorated by leptin replacement in vivo. Hence, leptin is a hormone more responsible for signaling of energy sufficiency rather than a signal to lose weight. Because they decrease soon after the onset of fasting. The precise manner by which leptin expression is controlled is unclear, although insulin-stimulated glucose metabolism and peroxisome proliferator-activated receptor (PPAR) γ agonists play a role. In common with many hormonal signals, leptin has both circadian rhythmicity and short-term pulsatility in circulating levels. Interestingly, the chronicity of leptin pulses are distinct from those of fellow adipose tissue product adiponectin, and asynchronous with those of the hunger hormone ghrelin. Generation of the leptin signal may be regulated at multiple posttranscriptional levels, including synthesis, tissue storage, turnover, and secretion. Recent in vitro studies have suggested that insulin stimulates leptin release from intracellular stores and leads to postprandial increases in circulating leptin. However, interpretation of the dynamics of leptin regulation in vivo should be performed with caution because paracrine, endocrine, and neural control of adipose tissue is well described. Indeed, the latter routes may be of importance for suppression of leptin levels during cold exposure. Furthermore, differences in function of the distinct adipose depots is suggested by differences in leptin secretion by subcutaneous and visceral fat, a theme that recurs with many other adipose tissue products.

**Leptin Action at the Hypothalamus**

Leptin has actions in the brain and a number of peripheral tissues including cells of the pancreas, liver, adipose tissue, and immune system. However, the central action of leptin in the brain and in particular the hypothalamus has been best characterized with regards to energy homeostasis and is of importance for reproductive function. Brain-specific deletion of the leptin receptor leads to obesity; conversely the phenotype of *db/db* mice, which lack functional leptin receptors, is rescued by brain-specific re-expression of leptin receptors. In normal animals the leptin receptor is highly expressed in the arcuate nucleus of the hypothalamus, which contains 2 distinct populations of leptin-responsive neurons that express neuropeptide Y (NPY)/agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (Figure 2). Neurons containing POMC/cocaine and amphetamine-regulated transcript promote energy expenditure and weight loss and are activated by leptin, whereas neuropeptide Y (NPY)/AGRP neurons promote food intake and weight gain and are inhibited by leptin. The importance of these circuits has been reinforced by conditional leptin-receptor deletion on POMC neurons, which results in an obese phenotype. Moreover, arcuate-specific re-activation of leptin receptors under universal control of a transcription blocker leads to reduced body weight and food intake. It is entirely possible, given the relatively modest phenotypic changes engendered by these manipulations in comparison with...
those of *db/db* mice, that there are additional areas of leptin action within the brain. A number of areas expressing the leptin receptor have been detailed and may be of importance for energy homeostasis are the ventral medial hypothalamus and the ventral tegmental area. Syndromes of Deficient Leptin Signaling in Human Beings

Obesity syndromes resulting either from loss-of-function mutations in leptin or its receptor have been reported in human subjects. Leptin deficiency was first observed in a consanguineous kindred including 2 severely obese children lacking leptin owing to a frameshift mutation in the ob gene. Further studies have revealed others with the same mutation, and affected individuals with a missense mutation. Leptin deficiency in human beings manifests as severe early onset obesity, hyperphagia, hyperinsulinemia, hypogonadism, and impaired T-cell-mediated immunity; features that are remediable with recombinant leptin treatment. A dramatic response in body weight as a result of preferential loss of fat mass and reduced hyperphagia has been noted in patients treated with recombinant leptin. Administration of leptin also allows appropriately timed puberty in children, induces pubertal development in adults, and corrects defects in the hypothalamo-pituitary-thyroid axis. For the most part the syndrome of leptin deficiency is similar in human beings and mice, yet there are some informative differences across the species divide. Notably, gross deficits in energy expenditure commonly noted in leptin-deficient mice are not shown in human beings. Moreover, circulating glucocorticoid levels are not increased in human subjects in contrast to mouse models. Indeed, increased cortisol levels in murine leptin deficiency has been implicated in defects in linear growth, which also are absent in human beings. To date, there are too few subjects available to fully assess the effect of leptin replacement on fecundity.

Appreciation of the effect of leptin-receptor mutations also is progressing. Initial studies described a single consanguineous kindred with a mutant leptin receptor lacking intracellular and transmembrane domains responsible for severe obesity in 3 homozygous subjects. More recently, screening of a highly selected cohort of subjects resulted in the identification of 5 nonsense and 4 missense mutations. As with leptin deficiency, individuals with leptin-receptor defects show severe obesity, hyperphagia, hypogonadotrophic hypogonadism, and T-cell function. These features are present in those with leptin deficiency, yet several features of the syndrome of leptin-receptor deficiency appear less severe; notably body mass index and ad libitum energy intake. These differences could be ascribed to differences in age and ethnicity, but raise the possibility of alternative pathways of leptin action independent of its one identified receptor. Outright deficiency of leptin signaling is not a common cause for obesity; in the majority of human beings, leptin production is up-regulated in obesity and there is diminished end-organ response to the leptin signal, or leptin resistance.

**Leptin Resistance**

Diseases resulting at least in part from hormone resistance have long been recognized; type II diabetes mellitus is probably the most common. It has been suggested that leptin increases hepatic C-reactive protein production and that circulating C-reactive protein interacts with leptin and prevents it from binding to receptors. This initial observation has been challenged at molecular, cellular, and physiologic levels in mice and human beings. Methodologic variance has been put
forward to explain some vital inconsistencies at the level of molecular and murine studies. Interestingly, leptin administration does not alter C-reactive protein levels in leptin-deficient individuals, although there have been calls for further well-controlled clinical studies of the effect of leptin administration to healthy, nonobese, normoinsulinemic individuals.40

Leptin signaling via the Janus activating kinase (JAK)–signal transducer and activator of transcription (STAT) pathway (Figure 3). The leptin receptor lacks intrinsic kinase activity, but associates noncovalently with JAK2. When leptin binds to the long form of its cognate receptor JAK2 mediates phosphorylation of 3 groups of tyrosine molecules. These groups include autophosphorylation of sites on JAK2 itself, and Tyr985 and Tyr1138 of the leptin receptor that trigger 3 different downstream signaling cascades (Figure 3). Autophosphorylation of JAK2 allows interaction with insulin receptor substrate (IRS) proteins, which may mediate activation of phosphoinositide-3 kinase signaling cascades. Phosphorylation of Tyr985 enhances association of the tyrosine phosphatase src homology 2-domain-containing tyrosine phosphatase 2, which activates the p21ras-extra cellular signal-related kinase (ERK) signaling pathway. Phosphorylation of Tyr1138 recruits the transcription factor STAT3, which subsequently is tyrosine phosphorylated itself. Subsequent dimerization of Tyr705 phosphorylated STAT3 facilitates binding in promoters of relevant genes. The majority of leptin actions are mediated in this fashion by induction of gene expression.

Of interest, there is a well-characterized system of intracellular feedback whereby phosphorylated STAT3 induces expression of a key intracellular regulator suppressor of cytokine signaling (SOCS3), a potential mediator of neuronal leptin resistance.42 Homozygous loss of SOCS3 is embryonically lethal, however, SOCS3-haploinsufficient mice display attenuated diet-induced obesity and improved leptin and insulin sensitivity.43 These findings are recapitulated by mice lacking SOCS3 in the brain.44 Importantly, mice with selective deletion of SOCS3 within POMC-expressing cells alone have enhanced leptin sensitivity, improved glucose homeostasis, and are resistant to the weight gain on a high-fat diet because of increased energy expenditure.44 Thus, improvement in central leptin signaling may provide a target for pharmacologic intervention for weight-loss therapies. One attractive target is an endogenous regulator of tyrosine phosphorylation, protein-tyrosine phosphatase 1b, as evidenced by the metabolically advantageous effect of knockdown of this gene.45,46

**Figure 3.** Intracellular signaling cascades activated by leptin. When leptin binds to the long-form receptor JAK2 is activated and autophosphorylates a number of sites, which allows interaction with IRS proteins and subsequent activation of phosphoinositide-3 kinase signaling cascades. Phosphorylation of Tyr985 of the leptin receptor enhances association of the tyrosine phosphatase src homology 2 domain containing tyrosine phosphatase 2, which activates the p21ras-ERK signaling pathway. Phosphorylation of Tyr1138 of the leptin receptor recruits the transcription factor STAT3, which subsequently is tyrosine phosphorylated. Tyr705 phosphorylated STAT3 dimerizes and translocates to the nucleus to induce a number of genes including those encoding target neuropeptides and SOCS3. A negative regulatory loop is mediated by SOCS3, which binds phosphorylated moieties on the leptin receptor. Similarly, the intracellular inhibitor protein-tyrosine phosphatase 1b effects a reduction of leptin signaling in the cell.

**Other Secreted Adipose Tissue Products**

**Adiponectin**

Adiponectin is secreted primarily from mature adipocytes and was identified almost simultaneously by 4 independent groups. The biology of adiponectin is of interest for a number of reasons. First, adiponectin circulates at extremely high concentrations, approximately 1000 times that of other polypeptide hormones. The implications of such high circulating levels have yet to be determined. Second, adiponectin resembles a number of other molecules. Mature adiponectin has a calculated molecular mass of 30 kilodaltons and has primary structural elements that closely resemble C1q and types VIII and X collagen with a C-terminal globular head and a collagen-like tail. Crystal structure analysis suggests that despite an absence of direct sequence homology, the tertiary structure of the globular head may somewhat resemble tumor necrosis factor α (TNFα). Third, adiponectin self-associates to form higher-order structures that impact directly on its function. Biologically, adiponectin rarely is found as a monomer.
In nonhuman primates there is a strong relation between low circulating adiponectin levels and development of the metabolic syndrome. In human beings, circulating adiponectin is reduced in obesity but can be increased by weight loss, or treatment with thiazolidinediones, the latter increasing both total and higher molecular weight forms of adiponectin. In common with rodent studies, low adiponectin states are associated with insulin resistance, dyslipidemia, and atherosclerosis.

How are the effects of adiponectin mediated? Two putative adiponectin receptors (adipoR1 and adipoR2) exist; adipo1 has higher affinity for high molecular weight forms of adiponectin whereas adipoR2 has equal affinity for full-length and higher molecular weight forms. Each contains 7-transmembrane domains and are expressed in a number of peripheral tissues and also in the brain. In mice, adipoR1 is located predominantly in muscle whereas adipoR2 is expressed in the liver; in human beings both adipoR1 and adipoR2 are found in muscle. Both AdipoR1 and adipoR2 cause phosphorylation of adenosine monophosphate (AMP)-activated protein kinase, leading to further phosphorylation of acetyl CoA carboxylase. Thus, adiponectin is a strong candidate as a peripheral insulin-sensitizing signal.

Does adiponectin input signals to the brain in the same manner as leptin? Certainly adipoR1 and adipoR2 are expressed in the brain, particularly in the paraventricular nucleus (PVN), amygdala, area postrema, and also diffusely in periventricular areas. However, the potential for peripheral adiponectin to act centrally still is contentious. Adiponectin can gain access to the brain after peripheral injection. Other studies with radiolabeled adiponectin suggest that high molecular weight forms do not cross the blood-brain barrier, and that central nervous system actions are mediated through endothelial receptors, possibly by induction of a local immunologic cascade. Nevertheless, direct intracerebroventricular injection of adiponectin leads to weight loss as a result of increased energy expenditure and is more potent than peripheral administration. The fact that ob/ob mice are particularly sensitive to adiponectin whereas agouti mice that overexpress AgRP do not respond suggest a common final pathway that involves the melanocortin system. More recently, Fry et al detected receptors for and specific activity of adiponectin in the area postrema, a medullary circumventricular organ. Thus, in addition to greater understanding of the diverse physiologic roles of adiponectin in the periphery, elucidation of specific sites and actions of adiponectin within the brain remains an exciting prospect.

Resistin

Resistin is a 12-kilodalton peptide hormone expressed by adipocytes in rodents and by macrophages in human beings, and is secreted as a trimer of disulfide-linked dimers. Resistin was first identified as a transcript induced during in vitro adipocyte differentiation
and down-regulated by treatment by thiazoladinediones. At first believed to be a link between adiposity and insulin resistance, study of resistin biology is informative inasmuch as it shows that orthologous proteins may serve different roles across species barriers.

In rodents, resistin is expressed particularly in visceral depots and is down-regulated by thiazoladinediones and increased in rodent obesity. Resistin impairs insulin action on cultured adipocytes, an effect that can be immunoneutralized with antiresistin antibodies. Although the mechanism by which insulin resistance is induced is not understood fully, at least in the adipocyte induction of SOCS3 may play a part. Administration of resistin to mice leads to insulin resistance. Resistin null mice are similar in bodily composition to wild-type mice when fed regular or high-fat diets. Intriguingly, resistin null mice display improved glycemic parameters when either fed chow or a high-fat diet, yet insulin sensitivity was unaffected. This seeming paradox is owing to decreased hepatic gluconeogenesis in resistin null mice, an effect mediated at least in part via increased activity of AMP-activated protein kinase and decreased expression of gluconeogenic enzymes in the liver. Similar findings also have been shown with dominant-negative resistin mutants, although targeted deletion of resistin in ob/ob mice improves glucose tolerance and insulin sensitivity by enhancing insulin-mediated glucose disposal in muscle and adipose tissue. This reinforces the importance of resistin in rodent physiology.

Human resistin shares only 53% identity with murine resistin at the protein level and is expressed sparingly in adipocytes. A number of epidemiologic studies in human beings have failed to provide a clear and consistent link between resistin expression in adipose tissue or circulating resistin levels and adiposity or insulin resistance. The induction of resistin by cytokines may be a link between obesity and inflammatory states resulting in insulin resistance. However, the role of resistin in human beings remains uncertain.

**Retinoid Binding Protein 4**

Beyond signaling energy stores, mouse studies suggest that adipocytes can sense glucose and regulate metabolism by the release of circulating factors. The seminal observation supporting this hypothesis is that mice lacking glucose transporter 4 specifically in adipose tissue are also insulin resistant in muscle and liver. The suggested adipose-derived circulating factor responsible for this systemic insulin resistance has been identified as the 21-kilodalton retinoid binding protein 4 (RBP4). Increased circulating RBP4 is seen in adipose-specific glucose transporter 4 null mice and increased RBP4 increases hepatic gluconeogenesis.

In human beings RBP4 levels correlate with bodily adiposity, abdominal obesity, and insulin levels and are correlated inversely with insulin sensitivity. Hence, it is not surprising that circulating RBP4 is increased in human beings with impaired glucose tolerance or diabetes. Notably, serum RBP4 levels decrease after weight loss. Is RBP4 a marker or effecter of insulin resistance? In obese mice fenretinide, a synthetic retinoid that reduces serum RBP4, improves insulin sensitivity and glucose tolerance. Moreover, mice overexpressing RBP4 or injected with synthetic RBP4 are more insulin resistant; transgenic mice lacking RBP4 are more insulin sensitive. The role of RBP4 in human beings has not been supported by all studies. However, the validity of a number of commercially available assays has been questioned. Moreover, genetic studies in Caucasians show that noncoding variants located close to RBP4 may contribute to impaired insulin sensitivity and insulin secretion, and hence increase the risk of type 2 diabetes.

**Visfatin**

Visfatin recently was identified as a secreted molecule released from visceral adipocytes. This 52-kilodalton protein is identical to a lymphocyte-derived cytokine identified as pre–B-cell colony–enhancing factor more than a decade ago. Pre–B-cell colony–enhancing factor inhibits apoptosis of activated neutrophils and has been linked to inflammatory disease states including acute lung injury. Surprisingly, visfatin has been shown to bind and activate the insulin receptor through a site distinct from that where insulin binds. Insulin-mimetic activity has been shown in vitro and administration of visfatin to mice decreases blood glucose levels. Moreover, mice lacking one allele as a result of targeted mutation have slightly increased plasma glucose levels. Although further studies are required to clarify its mechanism of action, recent studies have suggested that visfatin may be an important immune regulator with potential proinflammatory properties.

**Visceral Adipose-Tissue–Derived Serine Protease Inhibitor**

Hida et al used differential screening to identify visceral adipose factors differentially regulated in the obesity and diabetes-prone Otsuka Long-Evans Tokushima fatty rats and nonobese, diabetes-resistant Long-Evans Tokushima Otsuka rats. Their search revealed a visceral adipose-tissue–derived serine protease inhibitor, vasin, a novel 45- to 50-kilodalton member of the serpin superfamily. Serpins are a group of structurally related molecules named as a result of their serine protease-inhibitor activity. More than 500 different serpins have been identified, the best characterized being α1-antitrypsin. Among other functions, serpins have been implicated as regulators of hormone conversion and transport, inhibitors of inflammatory cascades, complement activation, coagulation fibrinolysis, and angiogenesis.
Expression of vaspin is adipose specific and PPARγ regulated. The administration of recombinant human vaspin improves insulin sensitivity and glucose tolerance and normalizes adipose tissue gene expression in a mouse model of dietary-induced obesity. Tantalizingly, effects of vaspin on adipocyte insulin sensitivity have not been replicated in vitro, raising the possibility that this agent modulates the local inflammatory milieu within adipose tissue.93 In human beings, vaspin expression is not limited to visceral adipose tissue because messenger RNA also is detectable in subcutaneous tissue. Vaspin expression is correlated most strongly with measures of adiposity and rarely is detected in lean individuals, suggestive of a beneficial or compensatory role for this polypeptide.95 Recent proteomic analysis of molecules secreted by human adipocytes revealed that vaspin is not the only serpin that is up-regulated after adipogenesis.96 Indeed, given the pleiotropic and broadly anti-inflammatory nature of serpins it may be that other members of this class of proteins may be discovered that combat features of the metabolic syndrome.

**Plasminogen Activator Inhibitor 1**

Another member of the serpin superfamily, secreted at least in part by adipocytes, is the 85-kilodalton plasminogen activator inhibitor 1 (PAI1). Functionally, PAI1 is the primary inhibitor of fibrinolysis and inactivates urokinase-type and tissue-type plasminogen activators. However, PAI1 may also be involved in angiogenesis and atherogenesis and is expressed by many cell types within adipose tissue.19,97 As with many adipose factors, PAI1 expression and secretion is greatest in visceral adipose depots.19 Indeed, circulating PAI1 levels are increased in the metabolic syndrome and are associated strongly with visceral adiposity. PAI1 null mice have increased energy expenditure, improved glucose tolerance, enhanced insulin sensitivity, and are resistant to diet- or genotypically induced obesity.98,99 Improvement in insulin sensitivity by weight loss or treatment with insulin sensitizers such as metformin or thiazolidinediones significantly reduces circulating PAI1 levels.100 Hence, PAI1 is more than a biomarker for the metabolic syndrome and, in contrast to vaspin, has negative effects that may contribute to the procoagulant inflammatory state in obesity.

**Adipsin**

Further interaction between adipose tissue and circulating proteolytic cascades is exemplified by adipsin, also known as complement factor D.101 Adipsin is a 28-kilodalton enzyme that mediates the rate-limiting step in the alternative pathway of complement activation. In a parallel manner to resistin, adipsin is expressed predominantly by adipocytes in mice, whereas in human beings this molecule together with other components of the complement pathway are expressed mainly in resident cells of monocytic lineage that reside within adipose tissue.101,102 A novel pathway has been delineated whereby adipin generates acylation-stimulating protein, an agent that increases triglyceride synthesis in fat-storing cells. Adipsin levels are low in murine models of obesity and acylation-stimulating protein levels also vary according to dietary or genetic obesity models. However, the relation of the adipsin pathway to human obesity has yet to be determined.103

**Angiopoietin-Like Peptide 4/Fasting Induced Adipose Factor**

Angiopoietin-like peptide 4 (ANGPTL4); also known as fasting induced adipocyte factor, is a recently described 35-kilodalton molecule that is part of the large family of fibrinogen/angiopoietin-like proteins. Although predominantly expressed in adipose tissue, ANGPTL4 initially was identified simultaneously by 2 groups analyzing liver transcripts.104,105 At the same time another group identified ANGPTL4 as a transcript up-regulated in adipose tissue by treatment with the PPARγ agonist troglitazone.106 Hence, ANGPTL4 is induced by activation of PPARγ in adipose tissue and PPARα in the liver.107 Functionally, ANGPTL4 associates with circulating lipoproteins.108 Injection of exogenous ANGPTL4 causes an increase in plasma triglyceride levels.109 Adenoviral and transgenic overexpression of ANGPTL4 in the liver increases circulating triglyceride levels, possibly owing to altered mitochondrial properties at the cellular level.110 A receptor for ANGPTL4 has yet to be defined properly; however, in vitro studies have shown direct inhibition of lipoprotein lipase by this peptide. ANGPTL4 also has been detected in cardiac and skeletal muscle,105,106 and novel regulation of ANGPTL4 also has been described by gut microbionta.111,112 In addition, 2 similar molecules, ANGPTL3 and ANGPTL6, are also produced in nonadipose tissues. Thus, although it is expressed at highest levels in the adipocyte, ANGPTL4 represents a signal from multiple sites including adipose tissue, liver, and the gut, and is integrated at the adipocyte to prevent fat storage and increase lipid mobilization.108 Identification of molecular targets or receptors for this group of molecules may provide significant advances in the understanding of fatty acid metabolism.

**Cytokines and Chemokines**

A number of cytokines and chemokines are generated by adipocytes. The association between an increase of proinflammatory cytokines, obesity, and diabetes has long been recognized, although a causative role only recently has been addressed. The contribution of adipocyte cytokines to the inflammatory milieu of the metabolic syndrome is addressed elsewhere in this issue (see article by Shoelson in this issue on p 2069). Nevertheless, TNFα and interleukin 6 (IL-6) represent the most widely studied cytokines produced by adipose tissue. The key obser-
vation that ignited this field was that adipose tissue production of TNFα actually caused insulin resistance. This concept was quickly applied to other cytokines. The expression of both TNFα and IL-6 are increased in adipose depots and circulating levels are increased in obese subjects, and these findings are remediable by weight loss. Indeed, adipose tissue has been estimated to yield approximately a third of circulating IL-6, with visceral fat contributing more than subcutaneous adipose tissue. As with resistin in human beings, IL-6 may originate from adipocytes and stromovascular components within adipose tissue, however, the ultimate signal that up-regulates expression in obesity still is uncertain. Disappointingly, direct suppression of circulating TNFα levels by immunoneutralization fails to ameliorate insulin-resistant states.

Adipose tissue is also the site of expression of numerous other cytokines, including IL-1 and IL-18, which may provide future targets to ameliorate the inflammatory state. Indeed, the chemokine monocyte chemoattractant protein 1 is released from adipocytes and circulating levels are increased in obesity. This has been implicated in the infiltration of macrophages into adipose depots in obesity. Recent transgenic mouse studies revealed that adipose-specific overexpression of monocyte chemoattractant protein 1 leads to macrophage accumulation, whereas loss of function either in transgenic null animals or by acute expression of a dominant-negative monocyte chemoattractant protein 1 lead to improvement in the metabolic milieu. Another link between nutrition, lipids, and inflammation and the innate immune system is provided by the Toll-like receptor 4. In particular, it has been shown that nutritional fatty acids activate Toll-like receptor 4 signaling in adipocytes and macrophages. In the absence of Toll-like receptor 4 the capacity of fatty acids to induce inflammatory signals in adipose cells or tissue and macrophages is reduced. Moreover, mice lacking Toll-like receptor 4 are protected from insulin resistance induced by systemic lipid infusion or dietary-induced obesity. This presents the possibility that many arms of the obesity-inflammation axis may be amenable to pharmacologic intervention.

**Adipose Production of Corticosteroids**

The classic sites of steroid hormone production include the adrenal cortex and the gonad. However, it is increasingly clear that adipose tissue, especially when present in excess, is capable of generating significant amounts of steroid hormones. Adipose tissue expresses enzymes of steroid synthesis including cytochrome P450–dependent aromatase, 3β-hydroxysteroid dehydrogenase (HSD), 3αHSD, 11βHSD type 1, 17βHSD, 7α-hydroxylase, 17α-hydroxylase, 5α-reductase, and UDP-glucuronosyltransferase.

With regard to glucocorticoid production, the oxidoreductase 11βHSD1 catalyzes conversion of inactive 11β-ketoglucocorticoid metabolites to active 11β-hydroxylated metabolites. In human beings this results in production of cortisol from cortisone and in rodents corticosterone from 11-dehydrocorticosterone (Figure 5). Of note 11βHSD1 is expressed abundantly in visceral adipose depots where it increases local production of cortisol or corticosterone without affecting circulating levels. Studies in rodents have linked increased 11β-HSD1 activity in adipose tissue to the metabolic syndrome. Obese Zucker rats overexpress 11βHSD1 in adipose depots, presenting the possibility of “Cushing’s disease of the omentum” resulting from local overproduction of cortisol. Moreover, transgenic mice that overexpress 11β-HSD1 specifically in adipose tissue have increased local corticosterone levels resulting in hyperphagia, visceral obesity, insulin resistance, dyslipidemia, hypertension, and hepatic steatosis. Conversely, 11βHSD1 null mice are protected from diet-induced obesity. Indeed, fat deposition is predominantly subcutaneous rather than visceral in these animals and is associated with improved glucose and lipid parameters and reduced incidence of atherosclerosis. Consistent with visceral adipose depot being a key metabolic regulator, 11βHSD1 null mice have low circulating leptin and re-
sistin levels and increased adiponectin levels. Moreover, expression of uncoupling protein 2 is induced in visceral adipose depots of the 11βHSD1 null mice. This is consistent with decreased local glucocorticoid levels because uncoupling protein 2 normally is suppressed by cortisol. Importantly, mitochondrial uncoupling performed by uncoupling protein 2 predisposes to substrate oxidation to yield heat rather than chemical energy in the form of adenosine triphosphate. Measurement of 11βHSD1 activity in human beings is complicated by tissue-specific differences in expression and activity. Hence, in obese human subjects, 11βHSD1 activity is decreased in the liver whereas increased expression and activity has been reported in adipose tissue in some but not all studies. It may well be that depot-specific expression of 11βHSD1 is a key confounding factor. However, 11βHSD1 expression and activity has yet to be determined in situ within visceral depots of obese subjects. Genetic studies assessing the impact of 11βHSD1 genotype on body habitus have not yet revealed a linkage. Nevertheless, inhibitors of 11βHSD1 exist as pharmacologic entities and are being developed for use in the metabolic syndrome.

**Summary**

Body habitus is an expression of the interaction between heritable genetic factors and environment. Although our genes have not altered demonstrably of late there have been substantial changes in our environment pertaining to food availability and energy expenditure. It is clear that adipose tissue should no longer be regarded as a passive store for surplus energy but instead constitutes a number of separate depots that contribute dynamically to energy homeostasis. Thus, signals secreted from different adipose depots differ in terms of specific signaling molecules, the stimuli for their release and potential systemic targets including the brain, liver, muscle, pancreas, and the immune system. The ongoing epidemic of obesity is making us increasingly aware that these systems are intricately balanced and that in the current environment physiology signals can all too readily develop pathologic consequences. However, the obesity epidemic has spurred a mammoth effort to understand the basic biology that underlies the regulation of weight and energy expenditure. It is a hopeful prospect that this push to grasp the molecular mechanisms that lead to obesity eventually may provide useful pharmacologic agents for safe and effective weight control.

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