Clinical Chemistry 50:9
1511–1525 (2004)

Review

Endocrine Regulation of Energy Metabolism: Review of Pathobiochemical and Clinical Chemical Aspects of Leptin, Ghrelin, Adiponectin, and Resistin

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Background: **Recent studies point to the adipose tissue as a highly active endocrine organ secreting a range of hormones. Leptin, ghrelin, adiponectin, and resistin are considered to take part in the regulation of energy metabolism.**

Approach: **This review summarizes recent knowledge on leptin and its receptor and on ghrelin, adiponectin, and resistin, and emphasizes their roles in pathobiochemistry and clinical chemistry.**

Content: **Leptin, adiponectin, and resistin are produced by the adipose tissue. The protein leptin, a satiety hormone, regulates appetite and energy balance of the body. Adiponectin could suppress the development of atherosclerosis and liver fibrosis and might play a role as an antiinflammatory hormone. Increased resistin concentrations might cause insulin resistance and thus could link obesity with type II diabetes. Ghrelin is produced in the stomach. In addition to its role in long-term regulation of energy metabolism, it is involved in the short-term regulation of feeding. These hormones have important roles in energy homeostasis, glucose and lipid metabolism, reproduction, cardiovascular function, and immunity. They directly influence other organ systems, including the brain, liver, and skeletal muscle, and are significantly regulated by nutritional status. This newly discovered secretory function has extended the biological relevance of adipose tissue, which is no longer considered as only an energy storage site.**

Summary: **The functional roles, structures, synthesis, analytical aspects, and clinical significance of leptin, ghrelin, adiponectin, and resistin are summarized.**

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Received February 10, 2004; accepted June 28, 2004.
Previously published online at DOI: 10.1373/clinchem.2004.032482

Leptin

STRUCTURE AND SYNTHESIS

Leptin, the product of the *ob* gene, is a recently discovered single-chain proteohormone with a molecular mass of 16 kDa that is thought to play a key role in the regulation of body weight *(1)*. Its amino acid sequence exhibits no major homologies to other proteins *(2)*. This product of the *ob* gene (obesity mice) is named leptin from the Greek word "leptos", meaning thin. Leptin is produced by differentiated adipocytes, although production has been demonstrated in other tissues, such as the fundus of the stomach, the skeletal muscle, the liver, and the placenta *(3)*. Leptin acts on the central nervous system, in particular the hypothalamus, suppressing food intake and stimulating energy expenditure *(4)*.

Leptin receptors belong to the cytokine class I receptor family *(5)* and are found ubiquitously in the body *(6)*, indicating a general role of leptin that is currently not fully understood. A circulating form of the leptin receptor exists, which acts as one of several leptin-binding proteins *(7)*. Abnormalities in db/db mice (diabetic mice) include severe leptin resistance caused by leptin receptor mutation.

Several alternatively spliced isoforms of the leptin receptor have been identified (Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, and Ob-Re) *(8)*. Ob-Ra is thought to be a leptin transporter, and Ob-Re is the soluble form of the transmembrane leptin receptor. Ob-Rb is a long form containing an intracellular signaling domain and shows high peak concentrations in the feeding centers of the hypothalamus *(9)*, consistent with leptin being the afferent signal informing the central nervous system of the body fat status. This concept is further supported by the obser-

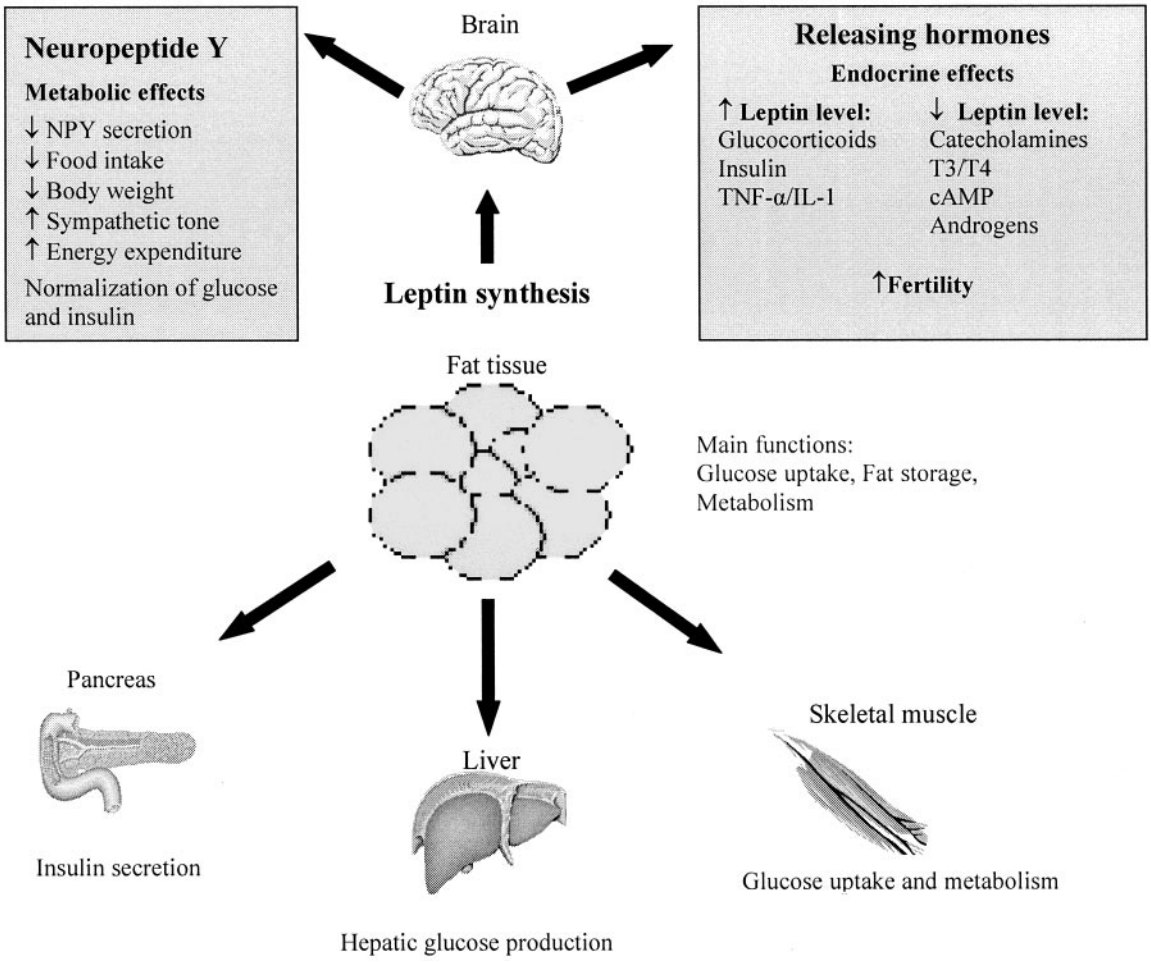

Fig. 1. Action of leptin on the hypothalamus and peripheral organs (pancreas, liver. and skeletal muscle).
IL-1, interleukin-1; *T3*, triiodothyronine; *T4*, thyroxin.

vation that leptin-deficient (ob/ob) mice and humans can be successfully treated with leptin. Leptin was therefore initially considered for treatment of obesity.

Obese individuals, however, often have increased leptin concentrations *(10)*, and leptin administration shows only very limited effects *(11)*. Recent data have indicated that this is likely the result of desensitization for the leptin signal, a phenomenon now often referred to as leptin resistance. This may occur on at least two distinct levels: saturable transport of leptin across the blood–brain barrier and abnormalities in the extent of leptin receptor activation and/or signal transduction *(12)*. In addition to its role via the central nervous system, leptin also has direct effects on a series of peripheral tissues, implying a much more complex leptin axis than was originally hypothesized *(13)*.

FUNCTIONS

In addition to its metabolic effects, leptin has been shown to have a strong influence on several endocrine axes (Fig. 1).

It was shown recently in humans that decreasing leptin concentrations in response to food deprivation are responsible for the starvation-induced suppression of the hypothalamic-pituitary-gonadal axes *(14)* as well as the malfunction of several other neuroendocrine axes. Thus it seems that leptin may act as the critical link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system, indicating whether adequate energy reserves are present for normal reproductive function *(15)*.

These actions may, at least in part, be explained by the suppressive effect of leptin on neuropeptide Y (NPY)[1] production and secretion by neurons in the arcuate nucleus *(16)*. NPY is a strong stimulator of appetite *(17)* and is known to be involved in the regulation of various pituitary hormones: suppression of growth hormone

[1] Nonstandard abbreviations: NPY, neuropeptide Y; GH, growth hormone; BMI, body mass index; TNF, tumor necrosis factor; GHS-R, growth hormone secretagogue receptor; AGRP, agouti-related peptide; IGF, insulin-like growth factor; PPAR, peroxisome proliferator-activated receptor; FIZZ, found in inflammatory zone; and RELM, resistin-like molecule.

(GH) through stimulation of somatostatin *(18)*, suppression of gonadotropins *(19)*, or stimulation of the pituitary–adrenal axis *(20)*.

Orexins (orexin-A and -B; also known as hypocretin-1 and -2) were recently discovered in the hypothalamus. Orexins were initially thought to function in the hypothalamic regulation of feeding behavior, but orexin-containing fibers and their receptors are also distributed in parts of the brain closely associated with the regulation of cardiovascular and autonomic functions. Functional studies have shown that these peptides are involved in cardiovascular and sympathetic regulation *(21)*. Although the pathophysiologic role of the sympathoexcitatory effects of leptin and orexins is not yet clear, the close relationship between obesity, hypertension, and altered cardiovascular responses has been documented *(22)*. Leptin and orexins may therefore be the chemical mediators in the brain responsible for the generation and maintenance of hypertension, which is associated with conditions of energy imbalance, such as obesity.

The most important variable that determines circulating leptin concentrations is body fat mass *(23)*. Obviously, under conditions of regular eating cycles, leptin reflects the proportion of adipose tissue *(24)*, showing an exponential relationship. This constitutive synthesis of leptin is modulated by several nonhormonal and hormonal variables. Stimulators in both rodents and humans are overfeeding, insulin, and glucocorticoids *(25)*. Suppression has been shown for fasting *(26)*, cAMP, and β_3-adrenoreceptor agonists *(27)*. It has been demonstrated that leptin production occurs after increases in insulin in response to feeding, and a decrease in leptin concentrations follows decreases in insulin during fasting. Early studies reported no acute effect of eating on leptin concentrations, but later studies demonstrated that meals and insulin acutely affect leptin concentrations *(28)*.

Patients with lipodystrophy have significantly reduced plasma leptin concentrations. The administration of leptin reduces hepatic fat mass and improves insulin sensitivity in humans suffering from this condition *(29)*. Suppression of the fatty-acid-synthesizing enzyme stearyl-CoA desaturase-1 can correct the hypometabolic phenotype of leptin deficiency, implying that leptin not only works via central anorectic effects but also by increasing hepatic fatty acid oxygenation *(30)*. The main functions of leptin and the other hormones of the energy metabolism are summarized in Table 1.

Soluble leptin receptor. The long isoform of the leptin receptor, or Ob-Rb, consists of 1162 amino acids and is the only isoform with clearly demonstrated signaling capability. Circulating leptin crosses the blood–brain barrier and binds to its receptor in the hypothalamus where it activates the JAK-STAT3 pathway *(31)*. Neuronal-specific ablation of Ob-Rb leads to obesity, clearly indicating that the weight-reducing properties of leptin are exerted centrally *(32)*.

High concentrations of the short isoforms Ob-Ra and Ob-Rc can be found in choroid plexus and brain microvessels *(33)*, suggesting their role in blood–brain barrier transport. This idea is further supported by observations in mouse models for obesity *(34)* and by the use of an in vitro leptin transport assay *(35)*. The secreted isoform can be generated either by alternative splicing (Ob-Re) or by ectodomain shedding and may be involved in modulating leptin activity *(36)*. Because the soluble leptin receptor affects the effect of leptin on food intake and body weight in ob/ob mice, regulated ectodomain shedding of membrane-spanning leptin receptors may represent a novel mechanism for regulating the biological activity of leptin *(37)*.

ANALYTICAL ASPECTS

For clinical purposes, it is important to note that serum leptin concentrations show a moderate circadian variation with a peak during the night at ~0200 *(38)*. The leptin

Table 1. Molecular properties, synthesis, and main functions of leptin and the other hormones of the energy metabolism.

Molecule	Molecular mass, kDa	Location of main synthesis	Function
Leptin	16	Adipose tissue	• Conveys information to the hypothalamus on the amount of energy stored in fat • Suppresses appetite • Affects energy expenditure
Soluble leptin receptor	90	Blood	• Soluble form of the transmembrane leptin receptor • Leptin-binding protein that transports leptin to the blood–brain barrier in the hypothalamus
Ghrelin	3.3	Stomach	• Conveys information to the hypothalamus and stimulates appetite, enhances use of carbohydrates and reduces fat utilization, increases gastric motility and acid secretion
Adiponectin	30	Adipose tissue	• Decreases insulin resistance • Decreases blood glucose concentrations
Resistin	12.5	Adipose tissue	• In rodents, causes tissues to become less sensitive to insulin (increases insulin resistance) • Actions in humans not established

concentrations at this time are ~30–100% higher than the concentrations measured in the morning or early afternoon. This variation, together with the influence of food intake, needs to be taken into account when blood samples are collected. Under fairly standardized conditions, i.e., normal eating cycles and blood sampling in the morning or early afternoon, a single leptin measurement is informative.

Leptin in serum is stable for at least five freeze–thaw cycles. There is no alteration in measured leptin concentrations in samples stored at −20 °C over a 2-year period. Samples are stable for at least 2 months when stored at 4 °C *(8)*. The stability properties of leptin and the other hormones *(39)* of energy metabolism are summarized in Table 2.

Some manufacturers have developed a sensitive RIA suitable for the measurement of leptin in fluids such as cerebrospinal fluid or in serum from patients with anorexia nervosa, which have much lower leptin concentrations *(40)*. ELISA procedures are now also commercially available: serum concentrations of leptin and soluble leptin receptor in female patients with anorexia nervosa were evaluated by use of commercially available ELISAs. For the measurement of leptin, there was a good correlation ($r = 0.95$) between the sensitive RIA from Mediagnost (lower limit of detection, 0.04 μg/L; linear range, 0–16 μg/L; intraassay CV <5%; interassay CV = 7.6%) and the ELISA from Biovendor (lower limit of detection, 0.5 μg/L; linear range, 1–50 μg/L; intraassay CV = 3%; interassay CV = 7%).

Soluble leptin receptor concentrations in human serum are measurable with a sandwich ELISA from Biovendor (lower limit of detection, 0.4 kilounits/L; linear range, 2–100 kilounits/L; intraassay CV = 3%; interassay CV = 3.5%; 2 ng of the recombinant calibrators are equivalent to 1 unit). Soluble leptin receptor concentrations in patients with anorexia nervosa were higher than in healthy individuals and were not affected by partial refeeding. In contrast, body mass index (BMI), body fat content, and serum leptin concentrations in patients with anorexia nervosa increased after partial refeeding. Other studies showed that opposite modifications occur in circulating concentrations of leptin and soluble leptin receptor across the eating-disorder spectrum (anorexia nervosa, bulimia nervosa, and binge-eating disorder) *(41)*.

Table 2. Stability properties of leptin and its receptor, ghrelin, adiponectin, and resistin.

Molecule	Stability
Leptin	• Stable over five freeze–thaw cycles • Stable at −20 °C over 2 years • Stable at 4 °C for 2 months
Soluble leptin receptor	• Stable over repeated freeze–thaw cycles
Active ghrelin	• Very unstable and labile in serum because of the nature of the octanoyl group on serine-3 • Samples and assay reagents should be kept on ice
Adiponectin	• Possibility of long-term storage at −20 °C • Stable over repeated freeze/thaw cycles
Resistin	• Stable over repeated freeze/thaw cycles

For the appropriate interpretation of leptin concentrations, reference intervals are required. Because body fat mass is the major confounding variable, these ranges should be referred to measures of the percentage body fat such as BMI *(42)*. Leptin concentrations are higher in females than in males, and an age dependence was shown in children and adolescents *(43)*. Reference intervals referring to measures of body fat should therefore be stratified according to gender and pubertal development.

Developmental changes in circulating concentrations of the soluble leptin receptor and leptin have been shown in humans *(10)*. In both sexes, the increase in leptin concentration with age was associated with a decrease in the concentration of soluble leptin receptor, and age-related changes in the concentrations of both leptin and its soluble receptor preceded the pubertal increase in gonadal hormones. Leptin concentrations >10 μg/L were a strong predictor of soluble leptin receptor concentrations, but this predictive value decreased as leptin concentrations decreased. In young individuals, there were no gender differences in serum leptin, but boys had higher soluble leptin receptor concentrations. In adults, neither leptin nor soluble leptin receptor changed with age, but serum leptin was higher and soluble leptin receptor was lower in women than men. In women, there is a significant negative correlation between soluble leptin receptor and leptin.

CLINICAL SIGNIFICANCE OF LEPTIN AND ITS SOLUBLE RECEPTOR

Hyperleptinemia is an essential feature of human obesity. The BMI is the best predictor of circulating leptin concentrations. Although the *ob* gene is differentially expressed in different fat compartments, apart from total body fat, upper or lower body adiposity and visceral fat do not influence basal leptin concentrations. Similarly, age, basal glucose concentrations, and ethnicity do not influence circulating leptin concentrations. Only in insulin-sensitive individuals do basal concentrations of insulin and leptin correlate positively even after factoring in body fat. Diabetes does not influence leptin secretion in both lean and obese individuals. In the eating disorders anorexia nervosa and bulimia nervosa, leptin concentrations are not up-regulated but simply reflect BMI and, probably, body fat *(44)*. In spite of a strong correlation between body fat and leptin concentrations, there is great heterogeneity in leptin concentrations at any given index of body fat. Approximately 5% of obese populations can be regarded as "relatively" leptin deficient and could benefit from leptin therapy.

Leptin has dual regulation in human physiology. During periods of weight maintenance, when energy intake

and energy output are equal, leptin concentrations reflect total body fat mass. However, in conditions of negative (weight-loss programs) and positive (weight-gain programs) energy balances, the changes in leptin concentrations function as a sensor of energy imbalance. This latter phenomenon is best illustrated by short-term fasting and overfeeding experiments. Within 24 h of fasting, leptin concentrations decrease to ~30% of initial basal values. Massive overfeeding over a 12-h period increases leptin concentrations by ~50% of initial basal values. Meal ingestion does not acutely regulate serum leptin concentrations. A few studies have shown a modest increase in leptin secretion at supraphysiologic insulin concentrations 4–6 h after insulin infusion *(45, 46)*. Similar to other hormones, leptin secretion shows circadian rhythm and oscillatory pattern. The nocturnal increase of leptin secretion is entrained by mealtime, probably as a result of the cumulative hyperinsulinemia that occurs over the entire day.

Like other growth factors and cytokines, leptin-binding proteins, including soluble leptin receptor, are present in human serum. In lean individuals, the majority of leptin circulates in the bound form, whereas in obese individuals, the majority of leptin is present in the free form. When free-leptin concentrations are compared between lean and obese individuals, even more pronounced hyperleptinemia in obesity is observed than that reported by measuring total leptin concentrations. During short-term fasting, free-leptin concentrations in lean individuals decrease in much greater proportion than those in obese individuals. In lean individuals with a relatively small energy store and particularly during food deprivation, leptin circulating predominantly in the bound form could be the mechanism that restricts its availability to hypothalamic leptin receptors to produce the inhibiting effect of leptin on food intake and/or energy metabolism. Unlike marked changes in serum leptin, leptin in cerebrospinal fluid is only modestly increased in obese individuals, and the ratio of leptin in the cerebrospinal fluid to that in serum decreases logarithmically with increasing BMI. If leptin concentrations in the cerebrospinal fluid are any indication of brain interstitial fluid concentrations, then hypothalami of obese individuals are not exposed to abnormally increased leptin concentrations *(47)*.

In a small percentage of patients, however, leptin concentrations have been found to be inappropriately low with respect to fat mass. It remains for future studies to confirm that these patients represent a new pathophysiologic entity: leptin deficiency *(48)*. In addition to the well-known consequences of absolute leptin deficiency, individuals with heterozygous leptin gene mutations have low circulating concentrations of leptin and increased body adiposity. Leptin treatment dramatically improves metabolic abnormalities (insulin resistance and hyperlipidemia) in patients with relative leptin deficiency attributable to lipoatrophy. Leptin production is primarily regulated by insulin-induced changes of adipocyte metabolism. Dietary fat and fructose, which do not increase insulin secretion, lead to reduced leptin production, suggesting a mechanism for high-fat/high-sugar diets to increase energy intake and weight gain *(49)*.

Because leptin has also been shown to be of great importance for reproductive functions, possible new pathophysiologic mechanisms may be discovered relating infertility to insufficient leptin production *(48)*.

Insulin resistance and abdominal obesity are associated with low soluble leptin receptor concentrations and a low ratio of bound to free leptin independent of fat mass. Low soluble receptor concentrations and low bound/free leptin ratios segregate with components of the metabolic syndrome. Low soluble receptor concentrations and a low fraction of specifically bound leptin are markers of leptin resistance, which is independently associated with insulin resistance and abdominal obesity and may constitute an additional component of the metabolic syndrome *(50)*.

Patients with advanced chronic heart failure have increased serum concentrations of leptin and its soluble receptor. Leptin may participate in the catabolic state leading to the development of cardiac cachexia in the course of chronic heart failure *(51)*.

In patients with chronic hepatitis C and higher BMI and blood glucose concentrations, the severity of liver fibrosis is associated with serum leptin. Tumor necrosis factor-α (TNF-α) is a putative candidate involved in the mechanism *(52)*. Increasing concentrations of leptin are detected in fibrotic and cirrhotic livers, whereas concentrations of the receptor protein remained unchanged *(53)*.

Ghrelin

Ghrelin was discovered as the peptide hormone that potently stimulates release of GH from the anterior pituitary. It was subsequently determined that ghrelin, along with several other hormones, has significant effects on appetite and energy balance.

STRUCTURE

Ghrelin is synthesized as a preprohormone, which is proteolytically processed to a 28-amino acid peptide (3.3 kDa). A postsynthetic modification takes place in which an *n*-octanoic acid residue is bound to one of the amino acids; this modification is necessary for biological activity *(54)*. Synthesis occurs predominantly in epithelial cells lining the fundus of the stomach; only small amounts are produced in the placenta, kidney, pituitary, and hypothalamus.

The ghrelin receptor was known well before ghrelin was discovered. Cells within the anterior pituitary have a receptor that, when activated, potently stimulates secretion of GH; that receptor was named the growth hormone secretagogue receptor (GHS-R). The natural ligand for the GHS-R was announced in 1999 as ghrelin and was named for its ability to provoke GH secretion (the suffix "ghre" means grow) *(55)*.

Ghrelin receptors are present on the cells in the pitu-

itary that secrete GH and have also been identified in the hypothalamus, heart, and adipose tissue *(56)*.

FUNCTIONS

The discovery of ghrelin contributed considerably to the understanding of the regulation of GH secretion (Fig. 2).

Ghrelin activates GHS-Rs located on the pituitary and GH-releasing hormone-containing neurons in the hypothalamic arcuate nucleus, stimulating GH release *(57)*. The activation of GHS-Rs by ghrelin on NPY/agouti-related peptide (AGRP)-producing neurons located in the arcuate nucleus stimulates food intake *(58)*. Ghrelin increases fat tissue by decreasing fat oxidation. Stimulation of motility and gastric emptying induced by ghrelin may involve a local effect as well as central mechanisms *(59)*.

Ghrelin is much more than simply a natural GH secretagogue, however. It also acts on other central and peripheral receptors and exhibits other actions, including stimulation of lactotroph and corticotroph secretion; it also influences gastroenteropancreatic functions and has orexigenic, metabolic, cardiovascular, and antiproliferative effects *(60–62)*.

Studies established that ghrelin stimulates food intake in rodents as well as in humans *(63)* and is strongly involved in the regulation of energy homeostasis *(64)*. Although several other potent orexigenic peptides, including NPY, AGRP, and melanin-concentrating hormone, have previously been characterized in the brain, ghrelin is the first food-intake-stimulating signal originating from the stomach.

In adult humans, plasma ghrelin concentrations increase twofold before a meal and decrease to trough concentrations within 1 h after eating. In cases in which negative energy balance is typically observed, such as low-calorie diets, chronic exercise, cancer anorexia, anorexia nervosa, and Prader–Willi syndrome, the most common form of human syndromic obesity, ghrelin concentrations were reported to be increased *(65)*. In human obesity, the ghrelin concentration is low, which may be related to the high caloric intake, whereas a reduction in body weight in obese patients brings the ghrelin concentration up. Interestingly, although ghrelin concentrations are reported to be high in patients undergoing diets, stomach-bypass surgery decreased ghrelin concentrations, suggesting that the size of the stomach may be directly correlated to ghrelin concentrations *(66)*. Several

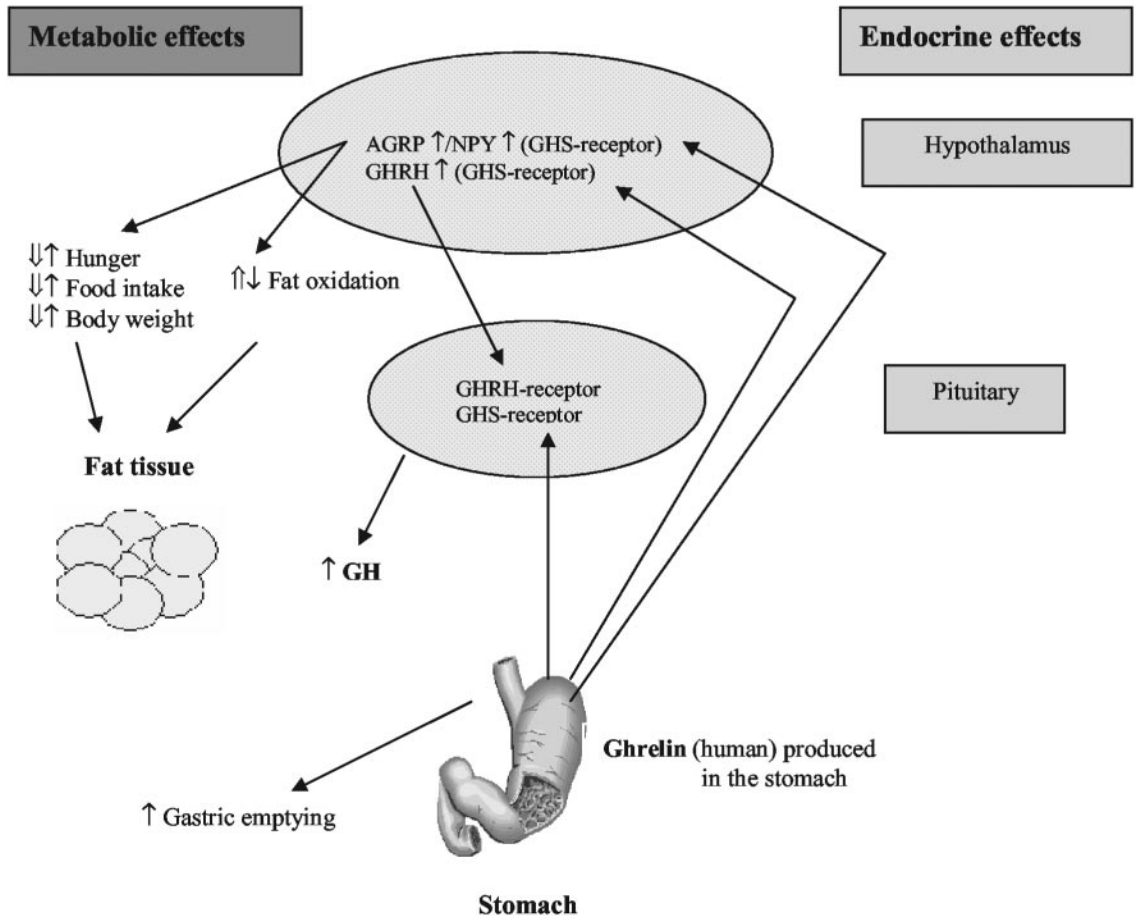

Fig. 2. Action of ghrelin on adipose tissue and the brain.

Leptin as indicated in this figure has effects opposite to those of ghrelin (↑ ↓ ghrelin; ⇓ ⇑ leptin). *GHRH*, growth hormone-releasing hormone; *GHS*, growth hormone secretagogue.

experimental observations have suggested that the ghrelin is a strong gastrokinetic agent *(67)*.

Endocrine signal to the hypothalamus. The arcuate nucleus is a major hypothalamic site regulating food intake and body weight through the presence of neurons containing orexigenic (NPY and AGRP) and anorexic (pro-opiomelanocortin and cocaine amphetamine-regulated transcript) peptides. In the brain, the GHS-R gene is abundantly expressed in the hypothalamic arcuate nucleus and ventromedial nucleus. Existing evidence supports a key role of the Arc nucleus in the orexigenic effects of ghrelin *(68)*, but its regulatory effect on appetite is not essentially related to GH release *(69)*.

The pathways through which gastric ghrelin released into the bloodstream signals the hypothalamus are not clearly understood. There is anatomic evidence derived from studies on the capillary network in the Arc nucleus that part of the parenchyma in this nucleus can be exposed to circulating neuroactive substances. Pharmacokinetic studies in mice also showed that human ghrelin crosses the blood–brain barrier as an intact molecule by saturable transport. Although passage for des-octanoyl mouse ghrelin was observed in the blood-to-brain direction, the octanoylated (bioactive) mouse ghrelin crosses the mouse barrier predominantly in the brain-to-blood direction. The extent and direction in which ghrelin can cross the blood–brain barrier is therefore influenced by at least two features of its primary structure: its posttranslationally added fatty acid side chain and its amino acid sequence *(70)*.

analytical aspects

Several assays are available to measure human ghrelin. Linco Research, Inc. *(71)* introduced a system for analyzing the so-called "active" human ghrelin (lower limit of detection, 10 ng/L; linear range, 10–2000 ng/L; intraassay CV = 7.4%; interassay CV = 13.5%). The antibody was raised against a human ghrelin epitope carrying an octanoyl group on the serine-3 position, which determines the biological function of the hormone by enabling binding to the receptor. To perform this analysis, however, special precautions must be taken, such as acidification of the sample to stabilize the labile side chain. Because a majority of studies performed at present refer to samples that have been collected and stored without fulfilling these requisites, the investigations are focused on those assays designed for the analysis of total ghrelin in human serum. It is likely, however, that measurement of the physiologically active ghrelin portion may be more relevant.

Serum ghrelin concentrations change in opposite directions in obesity and anorexia nervosa after dietary intervention, suggesting that ghrelin is a good marker of nutritional status *(72)*.

The concentration is reduced in states of obesity. Insulin resistance and hyperinsulinemia are inversely associated with ghrelin concentrations, which may constitute part of a feedback mechanism by which body weight is regulated in humans *(73)*.

Anorexia nervosa is associated with high concentrations of GH and low concentrations of insulin-like growth factor-1 (IGF-1), suggestive of a nutritionally acquired lack of GH action or GH resistance. Although ghrelin values are higher in patients with anorexia nervosa than in controls, there is no relationship between ghrelin and GH values. The inability of healthy girls to uniformly suppress GH concentrations to 1 μg/L or less, a "normal concentration" defined for adults may be related to higher GH secretion in pubertal years compared with adult life *(74)*.

The decrease in ghrelin over childhood and with puberty does not suggest that it is a direct growth-promoting hormone. However, in view of the relationship with IGF-1 and the positive relationship with IGF-binding protein-1, this decrease in ghrelin could facilitate growth acceleration over puberty *(75)*.

There is a possible link between glucose concentrations and ghrelin; hence, the persisting low ghrelin concentrations in diabetic children may suggest a defensive mechanism against hyperglycemia *(76)*.

The observation that ghrelin is further decreased in cases of abnormal energy profit adds new evidence to the relationship between ghrelin activity and energy balance in obesity *(77)*. Circulating ghrelin concentrations are influenced by body fat distribution, but not by concentrations of either GH or IGF-1. However, given that obesity is associated with reduced ghrelin concentrations and that GH deficiency is commonly associated with increased body fat, it is possible that these two opposing influences on circulating ghrelin concentrations produce normal concentrations in individuals with GH deficiency *(78)*.

clinical significance

Ghrelin has profound orexigenic, adipogenic, and somatotropic properties, increasing food intake and body weight. Secreted predominantly from the stomach, ghrelin is the natural ligand for the GHS-R in the pituitary gland, thus fulfilling the criteria of a brain–gut peptide. The brain–gut axis is the effector of anabolism by regulating growth, feeding, and metabolism via vagal afferent-mediating ghrelin signaling. However, the wide tissue distribution of ghrelin suggests that it may have other functions as well. It also enhances immune responses and potentially down-regulates antiinflammatory molecules. The role of ghrelin as a brain–gut peptide emphasizes the significance of afferent vagal fibers as a major pathway to the brain, serving the purpose of maintaining physiologic homeostasis. The discovery of ghrelin has increased our understanding of feeding regulation, nutritional homeostasis, and metabolic processes. Further characterization of the functions of ghrelin will likely generate new approaches to the diagnosis and treatment of different disease entities, including those related to the overnutri-

tion of obesity and the catabolic response to surgical trauma *(79–81)*.

Ghrelin may have also cardioprotective effects, serve as a diagnostic or therapeutic tool in GH deficiency, and function as a marker for neuroendocrine tumors. Theoretically, ghrelin is a promising candidate for treating catabolic states and enhancing immune function in cachexia or AIDS, as well as for treating eating disorders such as obesity and anorexia nervosa *(82)*.

Adiponectin

STRUCTURE AND SYNTHESIS

Adiponectin, also known as adipocyte complement-related protein of 30 kDa (ACRP30), adipoQ, adipose most abundant gene transcript 1 (apM1), and gelatin-binding protein of 28 kDa (GBP28), is an adipocyte-specific, secreted protein with roles in glucose and lipid homeostasis. Circulating adiponectin concentrations are high (500–30000 μg/L), accounting for ~0.01% of total plasma protein *(83)*. Adiponectin contains a modular structure that includes an N-terminal collagen-like domain and a C-terminal globular domain with significant sequence and structural similarities to the complement factor C1q. Although they share little sequence identity, similar three-dimensional structure and certain conserved amino acid residues suggest an evolutionary link between the C1q-like domain of adiponectin and members of the TNF superfamily. Adiponectin assembles into homotrimers, and higher-order oligomeric structures are formed by interactions between the collagen-like regions *(84)*. Adiponectin is induced during adipocyte differentiation, and its secretion is stimulated by insulin. Two receptors for adiponectin, termed AdipoR1 and AdipoR2, have been cloned *(85)*. Although functionally distinct from G-protein-coupled receptors, the genes encode predicted proteins containing seven transmembrane domains. AdipoR1 is produced primarily in skeletal muscle, whereas AdipoR2 is primarily found in hepatic tissues. Recently, T-cadherin was identified as a receptor for the hexameric and high-molecular-weight species of adiponectin. It may act as a coreceptor for a signaling receptor through which adiponectin transmits metabolic signals *(86)*.

FUNCTIONS

Metabolic effects. Injection of adiponectin into nonobese diabetic mice leads to an insulin-independent decrease in glucose concentrations. This is likely attributable to insulin-sensitizing effects involving adiponectin regulation of triglyceride metabolism *(87)*. A truncated form of adiponectin (gAdiponectin) containing only the C-terminal globular domain has been identified in the blood, and recombinant gAdiponectin has been shown to regulate weight reduction as well as free fatty acid oxidation in mouse muscle and liver. The full-length recombinant adiponectin protein is apparently less potent at mediating these effects. The mechanism underlying the role of adiponectin in lipid oxidation may involve the regulation of production or activity of proteins associated with triglyceride metabolism, including CD36, acyl CoA oxidase, 5′-activated protein kinase, and peroxisome proliferator-activated receptor γ (PPARγ) *(88)*.

A negative correlation between obesity and circulating adiponectin has been well established, and adiponectin concentrations increase concomitantly with weight loss *(89)*. Decreased adiponectin concentrations are associated with insulin resistance and hyperinsulinemia, and patients with type II diabetes are reported to have decreased circulating adiponectin. Thiazolidinediones, a class of insulin-sensitizing antidiabetic drugs, increase adiponectin in insulin-resistant patients. In addition, high adiponectin concentrations are associated with a reduced risk of type II diabetes *(90)*. Magnetic resonance spectroscopy has demonstrated that intracellular lipid content in human muscle negatively correlates with adiponectin concentrations, potentially because of adiponectin-induced fatty acid oxidation *(91)*.

The synthesis and secretion of adiponectin is regulated by several mechanisms (Fig. 3). Small adipocytes secrete insulin-sensitizing hormone, adiponectin, leptin, and other hormone-like peptides. Adipocyte hypertrophy (large adipocytes), induced by a high-fat diet, causes decreases in the production and secretion of insulin-sensitizing hormone and increases in insulin-resistant hormone, leading to insulin resistance in obesity. Reduction in the activity of PPARγ, which belongs to the nuclear hormone receptor superfamily, leads to protection against obesity and type II diabetes induced by a high-fat diet. Adiponectin decreases lipid synthesis and glucose production in the liver and causes decreases in glucose and free fatty acid concentrations in the blood. In addition, triglyceride production is decreased and fat oxidation and energy dissipation in the muscle are increased.

Both insulin and IGF-1 increase adiponectin synthesis in white adipose tissue. The synthesis and secretion of adiponectin are decreased in the presence of caloric excess, presumably associated with leptin deficiency or resistance *(92)*. The protein can also increase the sensitivity of the hepatocyte to insulin, either through direct action or indirectly by lowering circulating lipids concentrations via its action on muscle. Thus, administration of adiponectin can lead to improved insulin sensitivity and glucose tolerance and can correct the hyperglycemia associated with obesity.

Pharmacologic effects. Chronic treatment with the PPARα agonist rosiglitazone reduces adiponectin production in obese db/db mice, which lack functional leptin receptors *(93)*. In contrast, Maeda et al. *(94)* observed that thiazolidinediones, which are PPARγ agonists, stimulate adiponectin gene expression and increase circulating adiponectin concentrations in obese mice and insulin-resistant obese humans. Because adiponectin improves glucose tolerance by increasing insulin sensitivity, the effect of thiazolidinediones on adiponectin secretion may

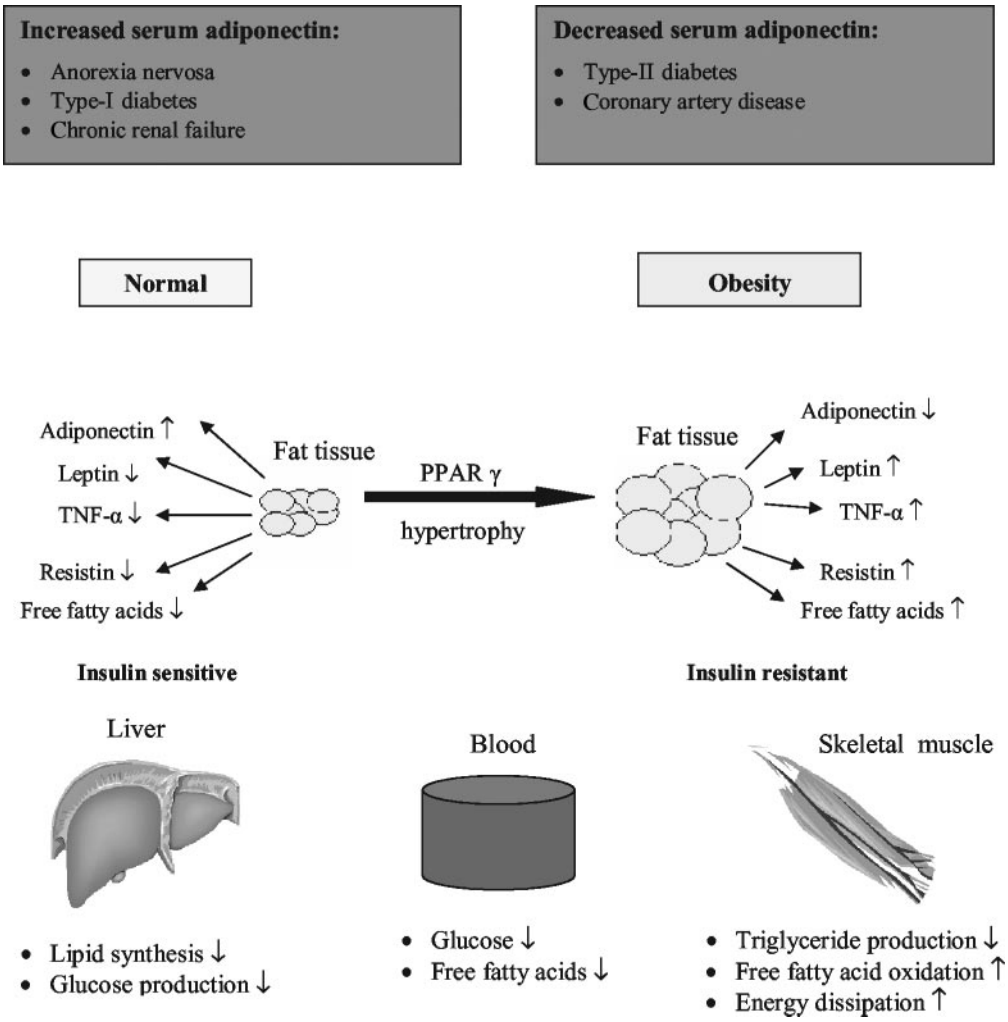

Fig. 3. Action of adiponectin on adipose tissue and peripheral organs (liver, blood, and skeletal muscle).

explain, at least partially, the hypoglycemic effect of these drugs in patients with type II diabetes mellitus.

TNF-α produced by white adipose tissue is markedly up-regulated in obesity and contributes to insulin resistance by interfering with insulin receptor signaling *(95)*. This cytokine suppresses adiponectin production in adipose tissue, whereas thiazolidinediones prevent this inhibitory effect of TNF-α *(96)*. The pharmacologic effect of adiponectin in reducing insulin resistance has been related to a decrease in plasma fatty acid concentrations and in triglyceride content in mice models of obesity, but also in human hyperlipidemia. Adiponectin can improve fatty acid catabolism either directly or by stimulating the production of PPARα, which regulates the enzymes involved in lipid metabolism *(97–99)*.

Atherosclerotic effects and adhesion. Adiponectin may also play antiatherogenic and antiinflammatory roles. Plasma adiponectin concentrations are decreased in patients with coronary artery disease *(100)*. Furthermore, neointimal thickening of damaged arteries is exacerbated in adiponectin-deficient mice and is inhibited by exogenous adiponectin *(101)*. Adiponectin inhibits endothelial cell production of adhesion molecules in vitro, suppressing the attachment of monocytes. In addition, adiponectin negatively regulates myelomonocytic progenitor cell growth and TNF-α production in macrophages *(102)*. Recent investigations of Kamada et al. *(103)* demonstrated that carbon tetrachloride induces extensive liver fibrosis in adiponectin knockout mice. Conversely, injection of an adenovirus that produces adiponectin before carbon tetrachloride treatment prevented liver fibrosis, and in cultured profibrogenic hepatic stellate cells, adiponectin suppressed platelet-derived growth factor-induced proliferation and attenuated the effect of TGF-β1 and connective tissue growth factor.

Low plasma adiponectin concentrations have been reported in coronary artery disease as well as associated with some risk factors of cardiovascular disease, such as male sex, high blood pressure, obesity, and type II diabetes mellitus. Adiponectin has been shown to reduce the secretion of TNF-α from monocyte/macrophages and

foam cells and also to attenuate the biological effects induced by TNF-α. In fact, this protein suppresses the secretion of TNF-α *(104–106)*.

Taken together, these data suggest that this adipocyte-derived cytokine may exert antiinflammatory, antifibrotic, and antiatherogenic effects, particularly in endothelial cells and macrophages; it therefore seems to play a protective role in experimental models of vascular injury as well as in the early events in the atherosclerotic process.

ANALYTICAL ASPECTS

Competitive RIAs and sandwich ELISAs are available to measure human adiponectin: the RIA (Linco Research, Inc.) has a lower limit of detection of 1 μg/L and a linear range of 0.78–200 μg/L (intraassay CV = 4%; interassay CV = 8%); the ELISA (R&D Systems) has lower limits of detection of 0.079–0.891 μg/L and a linear range of 3.9–250 μg/L (intraassay CV = 3.5%; interassay CV = 6.5%) *(107)*. Serum adiponectin concentrations were high in constitutionally thin individuals and low in obese individuals. The insulin resistance was significantly lower in anorexia nervosa and high in obese individuals. The concentrations of adiponectin after weight recovery increased to within reference values despite a relatively small increase in BMI. These findings suggest that abnormal feeding behavior in patients with eating disorders may lead to a decrease in circulating adiponectin concentration and that weight recovery can restore it *(108)*.

In humans, the plasma adiponectin concentration negatively correlates with BMI, percentage of body fat, fasting insulin concentration, and plasma triglycerides but positively with the plasma cholesterol contained in HDL *(109)*. Moreover, surgical treatment of morbid obesity by gastric partition surgery leads to an increase in plasma adiponectin concentration, which is significantly correlated with body weight reduction. Weight reduction achieved by low-calorie diet also increases plasma adiponectin in both nondiabetic and diabetic patients *(110)*. The adiponectin concentration is lower in patients with impaired glucose tolerance or type II diabetes mellitus than in age- and BMI-matched individuals with normal glucose tolerance and correlates negatively with plasma glucose measured at 2 h in the oral glucose tolerance test *(111)*.

CLINICAL SIGNIFICANCE

Increased serum adiponectin concentrations are associated with increased insulin sensitivity and glucose tolerance *(112)*. It can therefore be speculated that adiponectin, or drugs that stimulate adiponectin secretion or action, could play a role in disease states combined with insulin resistance, mainly type II diabetes mellitus, metabolic syndrome, and obesity. Low concentrations of adiponectin have also been implicated in the severe insulin resistance that accompanies lipoatrophy in both animal models and humans *(113)*. Therapy with adiponectin may be advantageous in reversing insulin resistance in lipodystrophic disorders and metabolic syndrome *(114)*.

The antiinflammatory effects of adiponectin indicate that it is an interesting protective factor for atherosclerosis development, particularly in those clinical situations associated with low plasma concentrations of adiponectin. It is conceivable that the use of recombinant adiponectin may become beneficial in the prevention of cardiovascular disease in selected patients.

Data suggest that increasing plasma adiponectin might be useful in preventing vascular restenosis after vascular intervention *(115)*. Further investigations in patients with the above-mentioned states and other hypoadiponectinemic conditions are required to clarify these aspects of the potential therapeutic applications of this adipocytokine.

Resistin

STRUCTURE AND SYNTHESIS

Human resistin, a 12.5-kDa protein, contains 108 amino acids as a prepeptide, and its hydrophobic signal peptide is cleaved before its secretion. Resistin circulates in human blood as a dimeric protein consisting of two 92-amino acid polypeptides that are linked by a disulfide bridge *(116)* at Cys-26. Holcomb et al. *(117)* first described the gene family and its tissue-specific distribution. By comparison of bronchoalveolar lavages from control mice with lavages from mice subjected to experimentally induced asthma, they identified, by microsequencing, a protein that was up-regulated in the asthmatic lung. This novel protein, FIZZ1 (found in inflammatory zone 1) is also known as resistin-like molecule α (RELMα). One of two additional homologs, FIZZ2, also known as RELMβ, was found to be localize in proliferating epithelia at the base of the crypts in the intestinal tract. Steppan et al. *(118)* later provided supporting data that FIZZ2/RELMβ is also present in rapidly dividing epithelia by demonstrating a marked increase in intestinal tumors compared with control epithelia. RELM, originally described as lung specific, is also produced in adipose tissue.

The third homolog, FIZZ3, is known as resistin or adipocyte-specific secretory factor and is identical to the fat specific homolog *(119)*. Steppan et al. *(120)* have subsequently proposed that resistin is increased in type II diabetes and suggested that it is a potential link between obesity and insulin resistance. The injection of recombinant resistin into mice reduces glucose tolerance and insulin action, whereas neutralization with anti-resistin antibodies improves insulin action.

FUNCTIONS

Very little is known about the potential function of resistin or its homologs *(121)*. As fat cells (adipocytes) store more fat molecules and enlarge, they release several products that can modify the body's sensitivity to insulin. Free fatty acids and TNF-α cause insulin resistance, and leptin, which regulates energy balance, probably causes insulin sensitivity. Thiazoladinedione drugs reduce insu-

lin resistance and are used to treat type II diabetes. These drugs suppress the production of resistin by adipocytes, and their antidiabetes effects may, at least in part, be achieved through this mechanism (Fig. 3).

Initial studies have demonstrated that obesity induced by a high-fat diet, mutation of the leptin gene (ob/ob mice), or mutation in the leptin receptor gene (db/db mice) is associated with increased circulating resistin concentrations. Resistin increases blood glucose and insulin concentrations in mice and impairs hypoglycemic response to insulin infusion. In addition, anti-resistin antibodies decrease blood glucose and improve insulin sensitivity in obese mice *(122)*. Resistin suppresses insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes, and this effect is prevented by anti-resistin antibodies. These data suggest that resistin induces insulin resistance and that hyperresistinemia contributes to impaired insulin sensitivity in obese rodents *(123)*. The suppressive effect of thiazolidinediones on resistin secretion found in some studies may contribute to the insulin-sensitizing effect of this class of drugs. However, other data do not confirm these results. Way et al. *(124)*, Moore et al. *(125)*, and Le Lay et al. *(126)* observed lower resistin mRNA in adipose tissue in different models of mouse obesity, such as diet-induced obesity, and in rat models characterized by hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and hypertension.

The physiologic role of resistin in humans remains unknown. Given the incomplete homology between human and mouse resistin and the absence in humans of one of the three murine resistin isoforms, resistin in humans may have a different physiologic role than that in mice. Studies of genetic variations in the resistin gene, including single-nucleotide polymorphisms, are controversial regarding the role of resistin in obesity and insulin sensitivity. Moreover, resistin mRNA expression is very low in isolated human adipocytes and does not correlate consistently with insulin resistance or obesity, making the role of human resistin in insulin resistance unclear *(127, 128)*.

There is no correlation between body weight, adiposity, and insulin resistance and resistin mRNA concentration. Resistin is produced in the stromovascular fraction of adipose tissue and in peripheral blood monocytes. Species differences in cellular resistin distribution may be partially explained by recent observation that in humans, in contrast to rodents, resistin is produced in high concentrations in cultured preadipocytes but barely detectable in mature fat cells *(129)*. Thus, the role of resistin and other members of the FIZZ/RELM family in humans remains to be established. These proteins may be involved in the regulation of cell proliferation and differentiation. Given the production of FIZZ1/RELMα in inflammatory regions and of resistin in inflammatory cells, another possibility is their involvement in chronic inflammatory reactions associated with obesity *(130)*.

Rajala et al. *(131)* provided clarification of the biological functions of the FIZZ/RELM family. Administration of recombinant resistin and RELMβ to rats led to acutely impaired hepatic insulin sensitivity and glucose metabolism. The primary pathway underlying changes in hepatic glucose metabolism appears to be increased glucose production. Interestingly, no effect was observed on peripheral glucose disposal under the clamp conditions, effectively ruling out a role for resistin in this part of the insulin action, at least under the experimental paradigms used in the study. This was a straightforward examination of the acute effects of resistin and RELMβ on insulin action, and the results are quite clear. The findings also suggest that resistin, and the closely related RELMβ, may act to establish links among adipose tissue, the intestine, and the liver. It now remains to be determined whether these pathways are operational under physiologic or pathophysiologic conditions.

analytical aspects

Some sandwich ELISAs are available to measure human resistin: the Biovendor assay has a lower limit of detection of 0.2 μg/L and a linear range of 1–50 μg/L (intraassay CV = 4.7%; interassay CV = 8%) *(132)*, and the R&D Systems assay has lower limits of detection of 0.01–0.055 μg/L and a linear range of 0.16–100 μg/L (intraassay CV = 4.7%; interassay CV = 8.4%). Plasma leptin and, probably, resistin concentrations are decreased in anorectic patients, whereas plasma adiponectin concentrations are increased. These alterations may have potential repercussions in the pathophysiology of anorexia nervosa. Thus, low leptin and high adiponectin may separately or in concert contribute to altered hematopoiesis and immunity, enhanced insulin sensitivity, neuroendocrine disturbances, or osteopenia in anorexia nervosa *(133)*.

In healthy populations, a correlation was found between leptin and resistin concentrations in serum. In patients with severe inflammatory disease, a correlation between resistin concentration and laboratory markers of inflammation was shown; however, no correlation was found between leptin and resistin. Serum resistin concentrations in these patients were significantly higher than in healthy individuals and persons with well-controlled type 2 diabetes mellitus with signs of insulin resistance. This may be attributable to a direct effect of inflammatory cytokines on resistin production. In persons with type 2 diabetes mellitus, no significant correlations were found between resistin and other individual characteristics (insulin sensitivity markers, BMI, or leptin). Resistin concentrations in persons with type 2 diabetes mellitus do not differ from concentrations in the general population *(131)*.

clinical significance

The role of resistin in obesity and insulin resistance in humans is controversial. There is more serum resistin protein in obese than lean individuals, with a significant positive correlation between resistin and BMI. BMI is a significant predictor of insulin resistance, but resistin adjusted for BMI is not. These data demonstrate that

resistin protein is present in human adipose tissue and blood and that there is significantly more resistin in the serum of obese individuals. Serum resistin is not a significant predictor of insulin resistance in humans *(132, 133)*.

Summary

The newly discovered secretory function of the adipocytes has shifted the view of the white adipose tissue from a simple energy storage tissue to a major endocrine system, the hormones of which influence energy homeostasis, glucose and lipid metabolism, vascular homeostasis, immune response, and even reproduction and fibrotic diseases.

The adipocyte-derived hormone leptin regulates food intake and systemic fuel metabolism. Leptin receptors are produced most abundantly in the brain but are also present in several peripheral tissues. Studies on the role of leptin in controlling energy homeostasis have to date focused on brain receptors and neuroendocrine pathways that regulate feeding behavior and sympathetic nervous system activity.

Ghrelin, produced predominantly in the stomach, displays strong GH-releasing activity mediated by the hypothalamus–pituitary GHS-Rs, which were found to be specific for a family of synthetic, orally active GH secretagogues. Ghrelin also acts on other central and peripheral receptors and exhibits other actions, including stimulation of lactotroph and corticotroph secretion; it also influences gastroenteropancreatic functions and has orexigenic, metabolic, cardiovascular, and antiproliferative effects.

Adiponectin is an adipose-tissue-derived protein with important metabolic effects. Its production and/or secretion is increased by IGF-1 and by activators of PPARγ. Its concentrations are decreased by TNF-α, glucocorticoids, β-adrenergic agonists, and cAMP. In addition to inhibiting inflammatory pathways, recombinant adiponectin increases insulin sensitivity and improves glucose tolerance in animal models. In humans, plasma adiponectin concentrations exceed those of any other hormones; they decrease with obesity and are positively associated with whole-body insulin sensitivity. Genetic variants in the adiponectin gene itself and/or in genes encoding adiponectin-regulatory proteins may be associated with hypoadiponectinemia, insulin resistance, and type II diabetes.

Resistin (FIZZ3) is a member of the newly discovered cysteine-rich secretory protein family referred to as RELM or FIZZ. FIZZ3 is produced in adipose tissue and was shown to antagonize insulin action. Resistin concentrations are increased in diet-induced obesity as well as in genetic models of obesity and insulin resistance. Furthermore, resistin gene expression is markedly down-regulated by treatment with antidiabetic drugs called thiazolidinediones, which improve target-tissue sensitivity to insulin. A possible role in inflammatory processes is suggested.

Several assays (competitive RIA and sandwich ELISA) have been developed by many manufacturers to measure leptin, its receptor, ghrelin, adiponectin, and resistin. All assays have good performance regarding detection limits, linearity, and precision. Leptin, its receptor, adiponectin, and resistin are stable, in contrast to ghrelin, which is labile and measured under difficult conditions. The concentrations of all of these hormones depend of the BMI.

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