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FAT CELLS: Afferent and Efferent Messages Define New Approaches to Treat Obesity

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■ **Abstract** For a long time neural and endocrine messages were studied for their impact on adipocyte metabolism and control of storage/release of fatty acids. In fact, bidirectional communication exists between adipocytes and other tissues. Several molecules secreted from adipocytes are involved in fat cell signaling to other tissues. Adipocyte products could initiate antagonistic effects on target tissues. Fat cells produce peptides that can elicit insulin resistance, such as tumor necrosis factor-α and resistin, as well as hormones that can improve insulin resistance, such as leptin and adiponectin. Secretion of complement proteins, proinflammatory cytokines, procoagulant, and acute phase reactant proteins have also been observed in adipocytes. There is much to learn about how these signals function. It is unlikely that all the adipocyte's endocrine and paracrine signals have been identified. Putative pharmacological strategies aiming at modulation of afferent and efferent fat cell messages are reviewed and discussed.

INTRODUCTION

Obesity can be viewed as an energy storage disorder where weight gain results from an energy imbalance (i.e., energy input exceeding output), with most of the excess calories stored as triglyceride in adipose tissue (AT). A strong correlation exists between the prevalence of obesity and the prevalence of type 2 diabetes. Excessive AT accumulation is a key pathological contributor to the "metabolic syndrome" characterized by insulin resistance and dyslipidemia that leads to type 2 diabetes and an increased risk for cardiovascular diseases (1). What causes this association between obesity, insulin resistance, and the development of type 2 diabetes? Although skeletal muscle, liver, and pancreas dysfunctions have been implicated as the major sites for development of insulin resistance, a number of recent results focus attention on AT as being a primary site (2, 3).

ATs represent complex organs, and a preliminary definition is useful to delineate the topic covered in the present review. The major distinctive characteristics that distinguish white AT (WAT) and brown AT (BAT) are detailed in a number of

reviews (4–6). BAT is specialized in adaptative thermogenesis; its thermogenic capacity is related to an original mitochondrial function related to the expression of the uncoupling protein-1 (UCP-1) (7).

Our knowledge about the biology of the adipocyte, the physiology of AT, and its involvement in obesity-related diseases has undergone major expansion during the past decade. The striking point is that the adipocyte has gained the status of an endocrine cell with the ability to regulate production of numerous secreted products of various natures.

In this review, attention is focused on afferent messages converging on the white fat cell and contributing to its functional control. Efferent messages originating in the fat cell and directed toward other organs and cells also are considered. Putative pharmacological strategies aiming at modulation of afferent and efferent fat cell messages are reviewed and discussed.

GENERAL CONSIDERATIONS ABOUT THE FUNCTIONAL ROLES OF ADIPOCYTES

Adipocytes allow surplus fuel to be stored as triacylglycerol (TAG) during caloric abundance for retrieval during periods of food shortage and calorie debt (e.g., fasting, starvation, long-term exercise). Nonesterified fatty acids (NEFAs) appearing as a result of lipolysis of TAG stores are released into the circulation and mainly oxidized in skeletal muscle to provide energy. This fat-storing capacity remains an important function of the fat cells, one that suffers some striking alterations in physically inactive and overfed persons. In normal conditions, the adipocyte is able to fine-tune a number of nervous and hormonal signals to precisely adapt the balance between the pathways of synthesis (TAG synthesis) and catabolism (lipolysis) of TAG to physiological needs. Through its TAG-storing capacity, involving a balanced lipogenic/lipolytic drive, the adipocyte could limit an abnormal increase in plasma NEFAs. NEFAs are widely viewed as an important etiologic factor in the initiation of insulin resistance and metabolic syndrome in the obese. They are elevated in obesity and represent a risk factor for the development of type 2 diabetes (8).

The major physiological importance of the fat-storage capacity of the adipocytes is evident when considering some situations when fat mass is reduced or lacking (lipoatrophy) (9). In lipoatrophic mice, a lack of fat is associated with insulin resistance, hyperglycemia, and liver steatosis (10). Adipocytes exert, through their fat-storing capabilities, a protective action against the occurrence of lipotoxic damage to lean tissues, which is referred to as lipotoxicity (lipid-induced dysfunction) or as lipoapoptosis (lipid-induced programmed cell death) (11).

One of the major features in adipocyte biology is the discovery of its complex secretory activities. A number of peptide hormones and proinflammatory cytokines, termed adipokines, secreted by the adipocyte exert endocrine effects (12–15). These adipokines allow the adipocyte to initiate potent feedback actions

in the regulation of appetite, food intake, glucose disposal, and energy expenditure. They are able to protect against the establishment of insulin resistance by actions on liver, skeletal muscle, and pancreatic function. They also contribute to the prevention or worsening of atherogenic processes. In addition, some of the factors secreted by the adipocyte exert local autocrine and paracrine actions mainly affecting AT remodeling, adipogenesis, and angiogenesis and are not found in the circulation.

The topography of fat distribution plays an important role in the appearance of health risks. Abdominal visceral fat extent is an important link between the many facets of the metabolic syndrome: glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other features such as hypertension and altered HDL and VLDL levels (16–18). Although it is quite well accepted that upper body obesity, with increased visceral fat, should be considered as a factor that initiates or exacerbates an individual's susceptibility to the components of the metabolic syndrome, the causality is poorly understood. What causes this consistent association between obesity and the development of type 2 diabetes? What are the factors interfering with the adipocytes from various depots that could explain the appearance of metabolic disorders? What is the contribution of adipocyte secretions to the generation of diseases related to the development of obesity?

AFFERENT MESSAGES CONTROLING WHITE FAT CELL FUNCTION

Physiological Features of White Adipose Tissue Innervation

The fat cell is under multiple influences, including that of the autonomous sympathetic nervous system [sympathetic (SNS) and parasympathetic (PSNS)], local blood flow variations and various hormones, and factors delivered from the plasma or produced locally by the various cell types existing in the fat pad (19). WAT is innervated by the nerve endings of the autonomic nervous system. Nerve terminals run along blood vessels and a limited number of adipocytes seem to be in direct contact with nerve varicosities. The direct links existing between SNS and WAT deposits have been revealed by experimental interventions. Surgical sympathectomy reduces lipolysis in the denervated WAT depot, whereas electrical stimulation of SNS nerve endings stimulates lipolysis in animals (20) and also in humans (21). PSNS innervation has been shown in WAT in rats (22). PSNS stimulation increases insulin sensitivity in peritoneal fat. The physiological relevance of these observations has been recently discussed (20, 23).

Adrenergic Regulation of Lipolysis and Human Fat Cell Function

Following SNS stimulation, norepinephrine and neuropeptide Y (NPY) are released from sympathetic nerve terminals, whereas adrenal medulla cells secrete epinephrine. The major elements involved in the regulation of the lipolytic

pathways are depicted in Figure 1. Rodents possess abundant β_3-adrenergic receptors (β_3-ARs) in the white fat cells, whereas in human fat cells, the role of the β_3-AR remains quite puzzling and controversial (24). In human fat cells, both β_1- and β_2-ARs initiate the activation of the lipolytic cascade by stimulation of cyclic AMP (cAMP) production, activation of cAMP-dependent protein kinase A (PKA) leading to phosphorylation of perilipin and hormone-sensitive lipase (HSL), and promotion of lipolysis in vitro. The originality of the human fat cell is related to the presence of abundant α_2-adrenergic receptors (α_2-ARs): their stimulation inhibits cAMP production and lipolysis (24, 25).

Differences exist in the adrenergic regulation of lipolysis in AT from different sites in normal-weight subjects and in obese subjects (18, 26, 27). The lipolytic response of isolated fat cells to catecholamines is weaker in the subcutaneous gluteal/femoral and abdominal AT than in visceral AT. Lipolytic defects are explainable by the reduced expression or function of HSL and/or of proteins that interact with HSL [e.g., adipocyte lipid binding protein (ALBP)] or the lipid droplet, such as perilipin. Alterations of the signaling pathways, such as reduced β_{1-2}-AR responsiveness or increased α_2-AR responsiveness (and a possible association or combination of defects), are also important. These site-related differences are more noticeable in women than in men (24, 27–29). An enhanced α_2-AR responsiveness associated with a concomitant decrease in β-AR responsiveness explains the lower lipolytic effect of catecholamines in gluteal/femoral fat cells of normal and obese women and abdominal fat cells of obese men. Reduced lipid mobilization occurs during exercise in subcutaneous AT of obese subjects (30). Functional changes in β_{1-2}/α_2-AR balance appear with the extent of the fat mass and are related to fat cell hypertrophy. Hypertrophic subcutaneous (abdominal, femoral) fat cells are known to be the least responsive to the lipolytic action of catecholamines; they exhibit the highest amount of α_2-ARs and the lowest amount of β_{1-2}-ARs. Increased expression of the α_2-AR (and the concomitant decrease of β-responsiveness) with fat cell hypertrophy could be a physiological adaptation leading to a reduction of the lipolytic responsiveness of the hypertrophied adipocytes of some fat deposits. The mechanisms leading to the opposite regulation of the expression of β_{1-2}- and α_2-ARs as cells become hypertrophied are unknown.

Whatever the mechanism controlling AR expression, limitation of basal and SNS-dependent lipolysis avoids excessive NEFA release from some fat deposits. A recent study aimed at the direct assessment of fasting AT metabolism using arterio-venous differences in defined depots has shown that the buttock is metabolically silent in terms of fatty acid release compared with the abdomen (31). The "buffering" action of NEFAs by AT is an important phenomenon (32). When the NEFA buffering system is inadequate, other tissues are exposed to elevated NEFA concentrations. A role for the α_2-AR gene in determining the propensity to store fat in the abdominal area, independent of total body fatness, has recently been reported (33).

Profound unresponsiveness of the subcutaneous AT to neurally stimulated lipolysis has been described in obese subjects (34). Reduced β_2-adrenergic lipolytic responsiveness has been reported in fat cells from obese subjects or subjects with

a reduced isoproterenol sensitivity (35). In addition, an increased antilipolytic responsiveness linked to α_2-AR stimulation has also been found in subcutaneous adipocytes of obese individuals of both sexes. The lipolytic defects revealed in fat cells have been confirmed during in vivo studies (36, 37). Using in situ microdialysis, a specific impairment in the capacity of β_2-AR agonists to promote lipolysis has been reported in the subcutaneous abdominal AT of obese adolescent girls (38). Moreover, when selective β_1- and β_2-AR-agonists are administered intravenously, the increase in lipolysis and thermogenesis promoted by selective β_2-adrenergic stimulation (salbutamol) was reduced in obese subjects. Conversely, β_1-AR-mediated (dobutamine) metabolic processes (i.e., lipolysis, thermogenesis, and lipid oxidation) were similar in obese and lean men. In conclusion, β_2-adrenergic-mediated increases in thermogenesis and lipid oxidation are impaired in the obese (39).

The putative role of β_2- and β_3-AR polymorphisms in the etiology of lipolysis disturbances and obesity has recently been reviewed (35, 40). To summarize, polymorphisms in the coding and noncoding sequences in the human β_2-AR gene could be of major importance for obesity, energy expenditure, and β_2-AR-dependent lipolytic function. Full β-adrenergic activation of the human fat cell usually requires synergistic activation of β_1- and β_2-ARs. A β_2-adrenergic defect could be sufficient to alter normal β-adrenergic responsiveness. In addition, in human fat cells, any reduction of β_2-AR-mediated lipolytic response will disturb the normal functional balance existing between α_2- and β-AR-mediated effects and amplify the reduction of the lipolytic responsiveness initiated by the physiological amines in stressful situations. All the discussions related to the adrenergic regulation of lipolysis must be expanded in terms of regulation to all cAMP-related events existing in fat cells.

Insulin Signaling in the Adipocyte: Heterogeneity of Responses

Insulin plays a major role in the control of AT development and function. Conditional ablation of the insulin receptor in adipocytes (FIRKO mice) has shown how insulin affects the development of the common metabolic alterations arising from obesity (41). Insulin not only regulates lipogenesis but also the rate of lipolysis and NEFA efflux. Insulin controls glucose uptake and causes fatty acid transport protein translocation and enhanced fatty acid uptake in adipocytes (42). The cascade of signaling events initiated by insulin binding to its receptor are conserved across tissues and species (43). In fat cells, the Ser/Thr protein kinase B (PKB/Akt) mediates the metabolic effects of insulin (44). Insulin inhibits basal and catecholamine-stimulated lipolysis through phosphorylation (via PKB/Akt-dependent action) and activation of type 3-B phosphodiesterase (PDE-3B), leading to decreased cAMP levels that prevent HSL activation. Insulin-induced antilipolysis and activation of NEFA reesterification are blunted in omental compared with subcutaneous fat cells. Various functional differences have been identified at the insulin receptor level and the postreceptor level of the insulin-signaling cascade (45). Other partners such as PDE-3B, which is responsible for the antilipolytic action,

and protein-tyrosine phosphatases, which are involved in the dephosphorylation of the insulin receptor, could also play a role. Endogenous PTPase1B (PTP1B) is increased in omental AT and may contribute to the relatively high insulin resistance of this fat depot (46). The role and regulation of this enzyme merit deeper investigations in human fat cells. Clinical studies have confirmed the regional heterogeneity of insulin-regulated NEFA release in vivo. Visceral AT is more resistant to insulin's antilipolytic effects than are leg and nonsplanchnic body fat. Nevertheless, visceral fat may be a marker for, but not the source of, excess postprandial NEFAs in obesity because the increased postprandial NEFA release observed in upper body obese women and type 2 diabetics originates from the nonsplanchnic upper body fat, not visceral fat (47).

Other Afferent Signals and Lipolytic Pathways

ATRIAL NATRIURETIC PEPTIDES Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) stimulate lipolysis as much as a nonselective β-AR agonist in isolated human fat cells (48). High levels of ANP receptors (NPR-A and NPR-C subtypes) are found in human adipocytes. Natriuretic peptides operate via a cyclic GMP (cGMP)-dependent pathway that does not involve PDE-3B inhibition or cAMP production. ANP stimulation of human fat cells activates a cGMP-dependent protein kinase (cGK-I type), which phosphorylates perilipin and HSL, thus explaining the lipolytic action (49). Intravenous administration of h-ANP in humans promotes a striking increment in plasma levels of NEFAs and glycerol (50). ANP is a relevant physiological activator of fat mobilization that contributes significantly to exercise-induced lipid mobilization (51).

GROWTH HORMONE Although growth hormone (GH) treatments in adults reduce abdominal obesity and affect insulin sensitivity, the physiological contribution of GH to the control of human AT lipid mobilization has remained elusive. GH stimulates lipolysis in human adipocytes; the effect is delayed (2–3 h) when compared with that of catecholamines. Contribution of cAMP-/PKA-dependent pathways as those used by catecholamines is suspected. GH-dependent modification of the relationships between adenylyl cyclase and Giα_2 protein removes inhibition of cAMP production and consequently increases lipolysis (52). GH administration promotes a significant increase in NEFA after 2–3 h, reflecting stimulation of lipolysis and ketogenesis (53). Small physiological GH pulses increase interstitial glycerol concentrations in both femoral and abdominal AT (54). Normal nocturnal rise in plasma GH concentrations also leads to site-specific regulation of lipolysis in AT (55). A small synthetic peptide sequence of human GH (AOD-9041) has been shown to increase human and rodent fat cell lipolysis in vitro and lipid mobilization in rodents (56).

OTHER LIPOLYTIC PEPTIDES AND CORTISOL In humans, the lipolytic peptides (adrenocorticotropic hormone, α-melanocyte-stimulating hormone, lipotropin)

commonly acting in rodent fat cells have no effect on human fat cells. Glucagon and glucagon-like peptide-1 (GLP-1) do not stimulate in vitro lipolysis. Moreover, no significant effect of either GLP-1 or glucagon on either lipolysis rate or blood flow was detected in muscle or AT during local or experimental i.v. hyperglucagonemia (57, 58). Parathyroid hormone (59) stimulates lipolysis in human fat cells at rather high extraphysiological concentrations. Human adipocytes express both IL-6 and its receptor system consisting of the IL-6 receptor and the signal transducing protein gp130. IL-6 administered in the normal physiological concentration range elicits lipolytic effects in human subcutaneous AT in vivo (60, 61). IL-6 stimulates lipolysis in human adipocytes and exerts anti-insulin actions (62). IL-6 also induces the expression of SOCS-3, a potential inhibitor of insulin signaling (63, 64). Whatever the results, it could be premature to include IL-6 inside a physiological loop of lipid mobilization regulation. Leptin induces a novel form of lipolysis in which glycerol is released without proportional release of NEFA and increase in peroxisome proliferator-activated receptor-α (PPAR-α) and NEFA oxidation in rat fat cells (65). It is unknown if the same leptin-dependent action operates in human fat cells.

Cortisol is less potent than catecholamines in the stimulation of lipolysis; the lipolytic effect is delayed and in vivo action is counteracted by corticoid-promoted insulin release (66). Cortisol-induced lipid mobilization is observed when cortisol-induced insulin increment is prevented (67). Short-term treatment with a standard dose of corticosteroids (i.e., prednisolone) induces increased abdominal adipose tissue lipolysis, hyperglucagonemia and insulin resistance, whereas GH levels are unaffected (68).

TUMOR NECROSIS FACTOR-α Stimulation of lipolysis by tumor necrosis factor-α (TNF-α) is not direct because it becomes apparent only after long-lasting exposure of human and rodent adipocytes to the cytokine (69). TNF-α-induced lipolysis, as well as inhibition of insulin-stimulated glucose transport, is predominantly mediated by the receptor TNFR1 (70, 71). TNF-α could regulate lipolysis, in part, by decreasing perilipin protein levels at the lipid droplet surface and activating the extracellular signal-related kinase (ERK) pathway (72). Blunting the endogenous inhibition of lipolysis through Gi protein downregulation is also another possible mechanism (73). In human fat cells, TNF-α activates the three mammalian mitogen activated protein kinases (MAPK) in a distinct time- and concentration-dependent manner. TNF-α-induced lipolysis is mediated by only p44/42 and Jun kinase but not by p38 kinase (74).

MISCELLANEOUS AGENTS Nitric oxide (NO) or related redox species such as NO^+/NO^- have been proposed as potential regulators of lipolysis in rodent and human fat cells (75, 76). Cachexia-inducing tumors produce a lipid-mobilizing factor (LMF) that causes immediate release of glycerol when incubated with murine adipocytes. Induction of lipolysis by LMF was associated with an increase in intracellular cAMP levels (77). Zinc-α_2-glycoprotein (ZAG), a protein of 43-kDa and a

tumor-related LMF, was detected in the major fat deposits of mice and in 3T3-L1 cells. ZAG expression and protein was also found in human fat cells (visceral and subcutaneous AT). ZAG is a new adipose tissue protein factor that may be involved in the modulation of lipolysis in adipocytes (78).

ADENYLYL CYCLASE INHIBITORS—ANTILIPOLYTIC AGENTS Various hormones and autacoid agents are known to negatively control adenylyl cyclase activity and inhibit cAMP production and lipolysis in fat cells. The effects are mediated by plasma membrane receptors, the stimulation of which inhibits adenylyl cyclase and cAMP production (Figure 1). In addition, the stimulation of leptin secretion was also observed with various agonists (A1-adenosine, α_2-AR, and NPY-Y_1 receptor agonists) (79, 80). The receptor of nicotinic acid (niacin), a well-known lipid-lowering drug, has recently been discovered. The orphan G protein–coupled receptor "protein up-regulated in macrophages by interferon γ" (mouse PUMA-G, human HM74), which is highly expressed in adipose tissue, is a nicotinic acid receptor that mediates the antilipolytic and lipid-lowering effect of nicotinic acid in vivo (81). Agonists leading to activation of Gi protein-coupled receptors of the adipocytes limit NEFA release and represent putative antihyperlipidemic drugs. All these antilipolytic agents will also exert leptin-secreting effects. Antagonists of such receptors, relieving inhibition of cAMP production promoted by the endogenous ligands, enhance the lipolytic activity of the fat cell. The physiological relevance of all these in vitro investigations is yet to be established.

ADIPOCYTE SECRETIONS AND EFFERENT ENDOCRINE MESSAGES

In addition to the metabolic disturbances resulting from altered NEFA handling (8, 32), AT can exert a substantial impact on systemic glucose homeostasis, insulin resistance, and initiation of cardiovascular disorders through production and release of adipokines, the bioactive molecules originating from adipocytes. Some of these molecules are secreted in the bloodstream in an AT deposit-related manner. Leptin, adiponectin (also called Acrp30, AdipoQ, and apM1), interleukin-6 (IL-6), TNF-α, and resistin are candidates of great interest among the growing number of factors found to be secreted by the adipocyte (14, 15).

Leptin

It is clear that leptin is an important part of the lipostatic system because it signals the size of the energy reserves existing in the body and controls fuel mobilization and utilization (82). Leptin crosses the blood-brain barrier, enters the central nervous system (CNS), and stimulates the long form of its receptor (Ob-Rb) located in the arcuate nucleus of the hypothalamus. A complex set of leptin receptor isoforms exist (83). Results in rodents fit with the "lipostatic paradigm," postulating that the adipocyte, through leptin, is able to provide a peripheral message of fat

mass repletion to the CNS areas involved in the regulation of energy balance to regulate energy intake and energy expenditure and limit fat deposition (82, 84). Leptin is a pleiotropic molecule that may regulate a number of other biological processes, as recently reviewed (15, 85, 86). Understanding of metabolic effects of leptin expanded after the discovery of its mechanism of action in liver and muscle. Leptin directly stimulates 5′-AMP-activated protein kinase (AMPK), which increases ATP-producing catabolic pathways, such as beta-oxidation, glycolysis, and mitochondrial biogenesis, and concomitantly decreases ATP-consuming anabolic pathways (87).

Under experimental adenovirus-induced hyperleptinemia in rats, the fatty acids inside the white adipocytes appear to be oxidized (88, 89). Leptin confines storage of excess calories to adipocytes and spares the appearance of chronic steatosis in nonadipocyte cells. It was proposed that in humans the metabolic syndrome might be the equivalent of the lipotoxic syndrome described in rodents (90). It will be essential to evaluate whether these novel effects appear at leptin concentrations that are found in a physiological context in humans. Some actions of leptin at high concentrations could be associated to effects independent of Ob-Rb and recruit additional transducing pathways. Cross talk of leptin pathways with other cytokine-related pathways cannot be excluded because leptin has similarities to the family of long-chain helical cytokines that includes IL-6, IL-11, ciliary neurotrophic factor, and leukemia inhibitory factor.

The subcutaneous fat depot is the major source of leptin, owing to the combination of a mass effect (subcutaneous fat being the major depot in men and women) and the higher secretion rate in the subcutaneous than in the visceral depots (91). Adipocyte size and anatomical location appear to be the major determinants of leptin mRNA expression. In vivo, overfeeding and obesity, glucocorticoid treatments, glucose, and insulin administration increase circulating leptin levels, whereas fasting, sustained exercise, cold exposure, and SNS activation reduce leptin levels. In vitro, positive effectors of leptin production include glucose, insulin, glucocorticoids, TNF-α, estrogens, IL-1, agents acting through Gi protein-dependent pathways, and melanin concentrating hormone. Conversely, catecholamines and cAMP agonists, β-adrenergic agonists, androgens, polyunsaturated fatty acids, peroxisome proliferator-activated receptor γ agonists, and phorbol esters negatively regulate leptin production. Insulin and glucocorticoids affect transcriptional mechanisms that increase leptin mRNA levels but also increase the traffic out of the adipocyte, which involves constitutive and regulated secretory pathways (14, 86, 92).

Interleukin-6

Plasma IL-6 levels are increased in obese subjects and correlate with fat mass and body mass index (BMI). High levels of plasma IL-6 are found in type 2 diabetes and also correlate with fasting insulin levels. The capacity of human adipocytes to release IL-6 was observed in AT explants and freshly isolated fat cells (93) and

human adipocytes differentiated in vitro (62). In vivo studies have shown that the cytokine IL-6 is secreted by subcutaneous fat in humans (94). In subcutaneous AT, IL-6 secretion increases tenfold during the postexercise rest period following a one-hour endurance exercise, and a concomitant increment of NEFA output was observed; this suggests a postexercise lipid mobilizing contribution of the cytokine (95). The IL-6 receptor and the gp-130 protein of cytokine pathways are expressed in human fat cells, suggesting that a direct paracrine action of IL-6 on the human fat cell is possible (96). IL-6 secretion is strongly stimulated by β-AR activation and mildly suppressed by glucocorticoids. To conclude, a hormonally regulated IL-6 secretion occurs in mature human fat cells and it is probable that a local paracrine action of IL-6 on adipocytes exists.

Adiponectin: An Adipocyte-Derived Insulin-Sensitizing Hormone

Adiponectin (Acrp30) is an abundant 30-kDa adipocyte-specific protein secreted in high concentrations in the serum. Adiponectin serum concentrations are reduced in a variety of obese and insulin-resistant states. Detailed information is provided in recent reviews (97–99). Genetic data has provided arguments showing that polymorphism within the adiponectin locus is linked to increased risk of type 2 diabetes (100). Altered multimerization of adiponectin and/or consequently impaired secretion could be among the causes of the hypoadiponectinemia described in subjects affected by mutations of the adiponectin gene (101, 102). Moreover, oligomerization of adiponectin is important for at least some of its biological activities. Hexameric and larger isoforms of adiponectin activate the nuclear factor-κB (NF-κB) pathway, whereas trimeric or globular forms could not activate NF-κB. Changes in the relative abundance of each oligomeric isoform in plasma may regulate adiponectin activity.

Globular adiponectin protects ob/ob mice from diabetes and apolipoprotein E (ApoE)-deficient mice from atherosclerosis (103). Adiponectin knockout mice exhibit severe diet-induced insulin resistance, glucose intolerance, and vascular defects such as neointimal formation (104, 105). Conversely, adiponectin expression in transgenic mice ameliorates insulin resistance and diabetes as well as vascular defects, even in ApoE-deficient mice that have a propensity to develop atherosclerosis. In nonalcoholic steato-hepatitis, adiponectin ameliorates hepatomegaly, steatosis, and alanine aminotransferase abnormality in ob/ob mice (106). Relationships between plasma adiponectin and insulin sensitivity for glucose disposal suggest that adiponectin also exerts pleiotropic insulin-sensitizing effects in humans (107). Hypoadiponectinemia is closely linked to impaired vasoreactivity and endothelial dysfunction in man. Adiponectin may play a protective role against atherosclerotic vascular change in humans (108–110).

Adiponectin administration enhanced hepatic insulin action and reduced liver gluconeogenesis and lipid accumulation in nonadipose tissues (97, 111). Glucose uptake and fatty acid oxidation were increased, whereas lipid accumulation was

decreased in skeletal muscle (112). Adiponectin effects are mediated by AMPK, which has been reported to increase fatty acid oxidation during muscle contraction and repress key enzymes of gluconeogenesis in hepatocytes. AMPK is known to mediate the insulin sensitizing action of exercise, some antidiabetic effects of metformin, and leptin action on skeletal muscle (113). Adiponectin most likely exerts its actions on muscle fatty acid oxidation by inactivating acetyl-CoA carboxylase-1 (ACC-1) via activation of AMPK and perhaps other signal transduction proteins (114). The effects of adiponectin are mediated by two receptor isoforms (AdipoR1 and AdipoR2) that have recently been cloned (115). The nature of the transducing elements linking receptors and AMPK activation has not been clarified. AdipoR1, which is mainly expressed in skeletal muscle but which is also expressed in many other tissues, has a higher affinity for the globular form of adiponectin. AdipoR2 predominates in liver and is less selective for adiponectin isoforms. The discovery of the receptors and of their distribution will help in the understanding of the molecular mechanisms of adiponectin action on various target cells. A number of hormones (insulin, catecholamines, and glucocorticoids) and other factors and pharmacological agents (pharmacological stimulators or inhibitors of cAMP production, TNF-α, ionomycine, and thiazolidinediones) have been shown to modulate adiponectin expression and secretion in vitro (116, 117). Nevertheless, the mechanisms of the secretory processes in the adipocyte have not been investigated in depth. Unlike other adipokines, adiponectin is decreased in adiposity and increases after weight reduction. The mechanisms that determine interindividual variability of adiponectin secretion, hence affecting body fatness, remain to be clarified.

Resistin

Resistin, for resistance to insulin, is 10-kDa adipocyte-secreted protein that possesses hormonal properties and has been claimed to represent an important link between obesity and insulin resistance. In the original paper, resistin administration was reported to cause glucose intolerance and insulin resistance in mice, whereas resistin antibody administration improved glucose intolerance. Moreover, serum levels of resistin were higher in mouse models of obesity and decreased after peroxisome proliferator-activated receptor γ (PPARγ) agonist (e.g., thiazolidinedione) treatment. WAT resistin mRNA and serum protein levels dropped during fasting and increased during refeeding (118). Other groups using different methods have confirmed the existence of resistin (119–121). Resistin has a rapid effect on hepatic, but not peripheral, insulin sensitivity (119). Mice lacking resistin (rstn$-/-$) exhibit low blood glucose levels after fasting owing to reduced hepatic glucose production. This is partly mediated by AMPK activation and decreased expression of gluconeogenic enzymes in the liver (122). The original concept is still open to discussion after major controversial results concerning resistin expression in obese rodents and thiazolidinedione effects. The role of resistin in human insulin resistance remains quite controversial. Very low levels of resistin mRNA were found in

human adipocytes, whereas it is expressed at higher levels in macrophages (123–125). Are there divergences in the major sites of resistin production in humans (e.g., macrophages) and rodents (e.g., adipocytes)?

Proinflammatory, Procoagulant, and Acute Phase Molecules

AT of the obese expresses several proinflammatory cytokines, such as TNF-α, IL-1, IL-6, inducible nitric oxide synthase (iNOS), transforming growth factor-β1, and monocyte chemotactic protein (MCP-1) (126). Biologically active procoagulant molecules, such as plasminogen activator inhibitor-1 (PAI-1), Factor VII, and tissue factor, are also produced in direct proportion to adiposity (127). AT also expresses a number of acute phase reactants at high levels, including serum amyloid A3 (SAA3), α1-acid glycoprotein, and the lipocalin 24p3. SAA3 expression is highly expressed in the diabetic state. Pro-inflammatory stimuli and high glucose can lead to the induction of SAA3 in adipose tissue in vivo as well as in the 3T3-L1 adipocytes (128). Cytokines within adipose tissue could originate from adipocytes, preadipocytes, and other cell types such as macrophages and endothelial cells of the stroma-vascular fraction. Expression studies with mRNA determinations have shown that the adipocyte is able to synthesize several interleukins (IL-6, IL-1β, and IL-8), TNF-α, macrophage colony-stimulating factor, various proteins of the complement system, and molecules of the acute phase reactants (129–131). Fat cell isolation procedures per se trigger the induction of many genes encoding inflammatory mediators, including TNF-α, IL-1α, IL-6, multiple chemokines, cell adhesion molecules, acute phase proteins, Type-I IL-1 receptors, and transcription factors involved in the inflammatory response (132). TNF-α has been considered as a key component in the obesity-diabetes link, at least in rodents (133, 134). TNF-α secretion has been correlated with insulin resistance measured in vitro and in vivo in humans (94, 135). However, the relation between AT TNF-α and insulin resistance remains an open question in humans. Its mechanisms of action have been extensively analyzed in recent reviews (136, 137). TNF-α-deficient obese mice have lower levels of circulating free fatty acids and are protected from the obesity-related reduction in insulin receptor signaling in muscle and fat tissues (138). Expression and secretion of TNF-α is increased in fat cells of obese subjects. However, there is no clear agreement as to which cytokines derived from adipose tissue act as hormonal regulators. IL-6 is systemically released, whereas TNF-α is not (94). To sum up recent literature, TNF-α is increased in adipocytes in obesity and β-adrenergic receptor stimulation is a positive regulator of TNF-α expression, whereas GH and PPARγ activators (e.g., thiazolidinediones) suppress its expression. Regulators of TNF-α production in fat cells might modulate insulin sensitivity via this cytokine.

Two recent studies have led to a major breakthrough in our understanding of the origin and the role of TNF-α and other cytokines in obesity. They have shown that macrophages accumulate in the adipose tissue of obese mouse strains

and in human adipose tissue. Macrophage accumulation occurs in proportion to adipocyte size. This adipocyte size–related accumulation probably increases the capacity for production of proinflammatory and acute phase molecules that contribute to obesity-related disorders. Thus the AT macrophages could be largely responsible for the major part of adipose tissue TNF-α, IL-1, IL-6, MCP-1, and iNOS expression. Release of macrophage TNF-α and IL-6 may contribute to the local decrease in insulin sensitivity of fat cells and to all the other TNF-α/IL-6-related disturbances (139, 140). What could attract macrophages to the adipose tissue, as opposed to other locations in obesity? It is proposed that an influx of bone-marrow-derived precursors into adipose tissue occurs, followed by their subsequent differentiation into macrophages. Adipocytes secrete MCP-1, which is considered a specific chemoattractant for monocytes and macrophages (141, 142), and colony stimulating factor-1 (CSF-1), a regulator of macrophage differentiation and survival (130). Leptin, released by the hypertrophied adipocyte, could also play a role in the process of chemoattraction because it has been shown to promote MCP-1 expression and secretion by endothelial cells (143, 144). Resistin upregulates adhesion molecules and chemokines. It also downregulates TRAF3 (tumor necrosis factor receptor-associated factor 3), an inhibitor of CD40 ligand signaling (145). It is of interest to establish if leptin, resistin, and other cytokines and active molecules secreted by the fat cell are capable of initiating the homing of various bone-marrow-derived precursors/progenitors toward the microvascular endothelial cells of adipose tissue to create permissive sites for the monocytes to enter adipose tissue and differentiate.

Miscellaneous Adipocyte Productions

As shown in Figure 2, some adipocyte products cannot be easily classified inside a functional box. In addition to the various factors cited previously, adipocytes secrete many other bioactive molecules, the roles of which are not fully delineated. Acylation stimulating protein (ASP) production, which results from the conversion of complement C3 into C3adesArg, involves three proteins of the alternate complement system synthesized and secreted by the adipocyte: C3, factor B, and adipsin (e.g., factor D). The ASP protein increases triglyceride synthesis in fat-storing cells (i.e., it increases glucose transport and fatty acid incorporation into TAG). ASP also inhibits hormone-sensitive lipase-mediated lipolysis (146). PAI-1 is a fibrinolytic inhibitor whose increased plasma concentrations are thought to contribute to the increased susceptibility to atherogenesis described in obese insulin-resistant patients. PAI-1 has been reported to be upregulated in AT from obese mice and humans concomitantly with increased plasma PAI-1 levels (147). Metalloproteases (148), metallothionein (149), and autotaxin, a phospholipase D secreted by the adipocytes that controls lysophosphatidic acid production in the adipose tissue (150, 151), have been clearly identified in fat cells. They are all secreted products. Angiotensinogen is expressed and released by mature white fat cells from rodents and humans and is involved in AT growth and blood pressure regulation (152).

WAT and adipocytes contain the components of the renin-angiotensin system, giving rise to angiotensin II (Ang. II) from angiotensinogen. Ang. II–stimulated adipocytes release prostacyclin, which is able to favor adipocyte formation. Ang. II could be considered as a trophic factor involved locally in AT development (153, 154). It is likely that many other secreted proteins have yet to be identified and their hormonal or local actions delineated. Genomic approaches reveal genes encoding newly discovered factors. For example, a factor regulated by fasting and insulin [fasting-induced adipose factor (FIAF)] (155) and activated by PPARγ agonists (PGAR for PPARγ angiopoietin related) (156) has been shown to be angiopoietin-like 4, in that it promotes angiogenesis and is produced during ischemia (157). Proteomic approaches will certainly be expanded for identification of secreted proteins in a high throughput and automatable fashion. Several new molecules involved in AT function have been identified using such methods (121).

Cortisol has been proposed to be involved in the development of visceral adiposity. Enhanced reactivation of cortisone to cortisol in AT may exacerbate obesity (158). An 11β-hydroxysteroid dehydrogenase1 (11β-HSD1) is synthesized in AT (in stromal preadipocytes and adipocytes) and exerts bidirectional effects; it has both dehydrogenase (cortisol to corticosterone) and reductase (cortisone to cortisol) potencies. The enzyme could contribute to local cortisol production in AT and exert differentiating effects on preadipocytes. Increased adipocyte 11β-HSD1 activities may be a common molecular etiology for visceral obesity and the metabolic syndrome (159).

NEW APPROACHES TO TREAT OBESITY

The history of obesity treatment is tarnished by limited long-lasting success, rebound recovery of weight after cessation of treatment, and some therapeutic disasters. Cure of obesity is rare and obesity is not, as previously discussed, a single entity. Nevertheless, palliation of obesity-related disorders remains a realistic clinical goal. Pharmacological treatment of obesity is still a matter of debate. In view of the evidence linking obesity to increased morbidity and mortality, recent recommendations suggest that safe and effective therapeutics must be employed to treat those overweight patients exhibiting symptoms of the metabolic syndrome to reduce their risk of type 2 diabetes, hypertension, and dyslipidemias.

Currently, orlistat is the only drug acting peripherally to limit fat absorption. Some beneficial effects have been reported in the prevention and management of diabetes mellitus. Discoveries in the neurosciences have been oriented toward drugs expected to modify the monoaminergic and peptidergic control of food intake (160). The strategies and drugs targeting fat cell responsiveness and secretion as well as some of the agents secreted by the fat cell, which could represent future therapeutic agents, are briefly considered.

Drugs Affecting NEFA Handling by the Fat Cell and Energy Expenditure

Obesity in humans is related to reduced energy expenditure and lipid mobilizing defects in some fat deposits. Owing to the lack of brown fat (6), skeletal muscle is the essential site of thermogenesis and NEFA utilization in humans. Stimulation of lipolysis in WAT without use of released fatty acids might be detrimental owing to the incidence of NEFA excess (8); energy expenditure must be activated in parallel. Sympathomimetic agents, by their ability to increase lipolysis and energy expenditure, have been considered as possible tools to treat human obesity. A marked thermogenic response to selective β_3-adrenergic agonists, leading to antidiabetic and antiobesity effects, was found in rodents (161). Selective β_3-adrenergic agonists were expected to limit adverse reactions, such as tremor and tachycardia, observed with early and less-selective β-agonists. Nevertheless, results concerning the action on body weight and energy expenditure of orally utilizable β_3-adrenoceptor agonists are rather disappointing in humans and likely explained by insufficient levels of expression and recruitment of β_3-ARs in β_3-responsive tissues in humans (162, 163). In the absence of any new and convincing input, this pharmacological strategy will become highly questionable in humans.

Blockade of fat cell α_2-ARs, which are abundant and exceed $\beta_{1/2}$-ARs in human fat cells, could promote lipid mobilization in fat deposits resistant to lipid mobilization and increase energy expenditure by activation of the SNS. The antilipolytic drive of α_2-ARs in the fat cell could be enhanced in patients with altered β-adrenergic responsiveness (18). Sustained lipid mobilization and increment of energy expenditure was observed after α_2-antagonist administration in dogs and humans. The interest in and limitations of α_2-antagonist use in obesity treatment has already been extensively discussed. However, reliable clinical studies have never been performed owing to the lack of suitable selective agents in humans (24, 164, 165).

Among possible agents, although GH is recognized to possess lipid-mobilizing properties, its undesirable effects on glucose metabolism (i.e., a diabetogenic effect) limit its potential use as a weight loss–inducing agent (166, 167). A domain of human GH (hGH177-191), which appears to act through a site distinct from the hGH receptor, promoted lipolysis in rodent and human fat cells. It also increased fat oxidation and decreased body weight in ob/ob mice. This active GH fragment has not been identified in human plasma; it is unknown if its administration would have an effect on lipid mobilization and weight loss in humans. Atrial natriuretic peptides exert potent lipid-mobilizing effects that are apparently independent of SNS stimulation and insulin effect modulation (50). It remains to be established whether the plasma NEFA increase promoted by the natriuretic peptides enhances fat oxidation and energy expenditure in humans. Because the action of natriuretic peptides is completely independent of that of insulin, it could be of interest to verify if such compounds and related agents are usable in weight loss management in obese subjects with lipid mobilizing defects and alterations of the adrenergic regulation of lipid mobilization.

NEFA release by fat cells is also under the control of all the antilipolytic agents, including insulin, but also hormones and agents acting via Gi protein-coupled receptors. Enhancement of antilipolytic effects will reduce plasma NEFA levels in subjects with increased NEFA (e.g., insulin-resistant subjects and patients with type 2 diabetes). Antilipolytic strategies based on nicotinic acid derivatives and adenosine A1-receptor agonists have been proposed to reduce plasma NEFA and TAG. Insulin sensitization of fat cells contributes to reducing the release of NEFAs by fat cells. Insulin sensitizers that enhance insulin action by modulating the events following the binding of insulin to its receptor and/or by activating transcription factors affecting the expression of the genes involved in the action of insulin in insulin-sensitive tissues are of interest to improve insulin action in the obese. Inhibitors of the protein tyrosine phosphatase 1B activity as well as of other putative negative regulators of insulin signaling are candidates to reduce insulin resistance and improve insulin action and may have potential in the future as antiobesity agents (168). Several agonists active at both PPARγ and PPARα represent promising tools with potential antidiabetic and lipid-lowering properties (3, 169). PPARs, widely distributed in tissues and cell types, constitute multiple therapeutic targets (168). Ideally, drugs possessing both PPARα/γ agonist potencies are expected to provide the best means to decrease multiple risk factors for morbidity and mortality existing in diabetic patients by acting on fat cells and liver (170). PPARγ is predominantly expressed in adipocytes, and the various beneficial metabolic effects reported for PPARγ agonists are thought to result from direct actions on AT along with secondary impact in skeletal muscle and liver. The beneficial actions of PPARγ agonists on muscle, liver, and vessels (i.e., atherosclerosis risk) are mediated by their ability (*a*) to improve insulin-mediated uptake and metabolism of glucose and NEFA in the adipocyte; (*b*) to induce the production of adiponectin by adipocytes (e.g., adiponectin is a relatively early and specific response to activation of PPARγ); and (*c*) to reduce production of adipocyte-derived factors leading to insulin resistance, such as resistin, inflammatory molecules, and TNF-α. The insulin-sensitizing potency of PPARγ agonists could be related to their antiinflammatory action because they inhibit TNF-α action on adipocytes and limit production of inflammatory molecules by fat cells and monocytes/macrophages, which have been found to be abundant in obese AT. In view of the multiple metabolic and vascular actions of adiponectin, it is possible that a number of ameliorations of metabolic disturbances related to the metabolic syndrome attributable to the effects of PPARγ agonists could be related to their action on adiponectin production and release by fat cells. Investigations in adiponectin-deficient mice will facilitate the answer to the question.

Role of Major Adipocyte Hormones in the Partitioning of Fat

Defective leptin production and action have been proposed to be an important element of the metabolic syndrome (90). Hyperleptinemia in the obese is considered to protect non-ATs from lipotoxicity (171). Leptin treatment of severely

diabetic lipodystrophic rodents and humans improves insulin-stimulated hepatic and peripheral glucose metabolism and promotes a reversal of insulin resistance and hepatic and muscle triglyceride content (172, 173). Leptin operates through activation of AMPK, which improves fatty acid oxidation in muscle and downregulates sterol regulatory element binding protein-1c (SREBP-1c) that reduces lipogenesis in liver. Recombinant leptin derivatives could be envisaged as new therapeutic agents. Therapeutic use of leptin could be proposed in hypoleptinemic patients with metabolic syndrome when its normal production by fat cells is defective. However, interference of various pathways [e.g., suppressor of cytokine signaling (SOCS)-3 protein, PTP-1B activity, protein inhibitor of activated signal transducer and activator of transcription-3 (STAT-3), and 11-β-HSD-1 activity] has been proposed to explain impairment of leptin action (e.g., leptin resistance) and could oppose the therapeutic action. Adenovirus-induced hyperleptinemia promotes a dramatic reduction of white fat cell size in rats, and the fatty acids are oxidized directly inside the white adipocytes that become able to burn fat. Because high circulating levels of leptin are obtained in such conditions, it is highly questionable if this provocative observation could have some kind of physiological or therapeutic relevance (89).

Adiponectin is an adipocyte product of major therapeutic interest with protective actions on the major tissues affected by the metabolic syndrome. Like leptin, it plays a major role in fat partitioning because it also prevents steatosis in various nonadipose tissues. Its production exhibits regulation opposite to that of leptin. Although plasma leptin levels increase with accumulation of fat and adipocyte hypertrophy, plasma adiponectin levels decrease with fat cell size increment and obesity. The physiological significance of the opposite regulation of two major adipocyte hormones involved in the control of lipid deposition/utilization balance requires further studies to be fully understood. Like leptin, adiponectin, via its receptors, stimulates AMPK-related metabolic pathways. AMPK activation and consequent ACC-1 inactivation will result in reduced lipid synthesis and increased fat oxidation. Does leptin become operative when major adiponectin effects have been reduced in the obese owing to a lack of adiponectin? It seems reasonable to propose that either recombinant adiponectin derivatives or adiponectin-mimetic compounds acting less or more specifically on adiponectin receptor subtypes could be suggested as new therapeutic approaches. Owing to the size of the protein and its various circulating forms, it would probably be better to use strategies aimed at the promotion of adiponectin production by the adipocyte. PPARγ agonists might play a key role in such an enterprise because they have been shown to promote adiponectin production in fat cells of humans and rodents (174, 175).

Control of Adipose Tissue Development and Remodeling-Interconversion of White Adipocytes into Fat Burning Cells

As is well known by investigators working on fat differentiation, nuclear receptors, such as PPARγ, play a crucial role in the regulation of adipocyte differentiation.

Although they are on the market and of interest for the treatment of type 2 diabetes, PPARγ agonists, such as thiazolidinediones, are not effective against obesity because they are known to promote recruitment/differentiation of new fat cells while improving insulin sensitivity. Moreover, adipogenesis could be induced in bone marrow stromal cells. It is a major negative side effect; PPARγ agonists might promote weight gain in patients still having serious metabolic disorders, and their short-term benefits could be reduced in the long term. Important efforts are being made to identify new PPARγ modulators having antidiabetic action without promoting fat cell differentiation and weight increase. In addition to adipogenesis, angiogenic processes play an important role in the development of AT mass (176). Adipocyte productions, such as leptin and vascular endothelial growth factor (VEGF), are known to exert proangiogenic effects and contribute to vascular development in AT. The extent of AT mass is sensitive to angiogenesis inhibitors (177); strategies aimed at the limitation of vascular supply in fat are opening new perspectives that merit future attention.

In humans, in whom there are no BAT depots in adults, conversion of white adipocytes into brown-like fat cells could be a great challenge. Appearance of brown adipocytes is possible in certain conditions in adults with pheochromocytoma. In a recent study using adenovirus expressing human PGC-1α, a PPARγ coactivator has demonstrated that it is possible to promote a metabolic shift in human white fat cells from lipid storage to fatty acid utilization with a concomitant induction of UCP-1, mitochondria respiratory chain proteins, and fatty acid oxidation enzymes. Palmitate oxidation was indeed elevated in such modified adipocytes (178). Such a study suggests that future strategies aimed at altering the phenotype of human white adipocytes could be envisaged for the treatment of obesity.

ISSUES AND TRENDS

The remarkable progress in our understanding of the regulation of fat cell function and the identification of a large number of hormonal and paracrine agents secreted by the adipocyte has prepared the ground for important reconsiderations of the role of this underestimated cell type. Although it is well recognized that abnormalities of fatty acid metabolism represent key components of the metabolic syndrome and type 2 diabetes, a number of adipocyte-secreted hormones considered in the present review are major contributors to the diseases affecting a large part of the obese population. Moreover, the discovery of such products has revealed original regulatory processes and offered new putative drug targets for pharmacological intervention. Nevertheless, a number of secreted compounds do not as yet have a clear functional status and will gain validation in the future.

Intensive DNA microarray utilization and gene knockouts will probably enable the identification of components that will lead to a wider array of potential interventions. Obesity-related diseases are of a multifactorial nature with a number of genetic and environmental factors leading to the final outcome. It is expected that human genomic studies will identify subpopulations of patients and allow

early and better targeting. Tailored treatment, adapted to a given pathophysiology, is certainly important in complex metabolic diseases. The search for antiobesity agents remains inherently difficult. The ultimate therapeutic goal is not necessarily weight loss but reduction of related cardiovascular and metabolic morbidities. It must be noted that only a very small number of effective compounds results from the large number tested in preclinical research. It is difficult to know which of the centrally or peripherally acting agents will be the most efficient and safe. Whatever the research outcomes and discoveries, it is probable that the "magic bullet" that promotes slimming despite excessive food intake and inactivity will never exist. Antiobesity drugs should only be prescribed as adjuncts to dieting and exercise; prevention remains the major goal.

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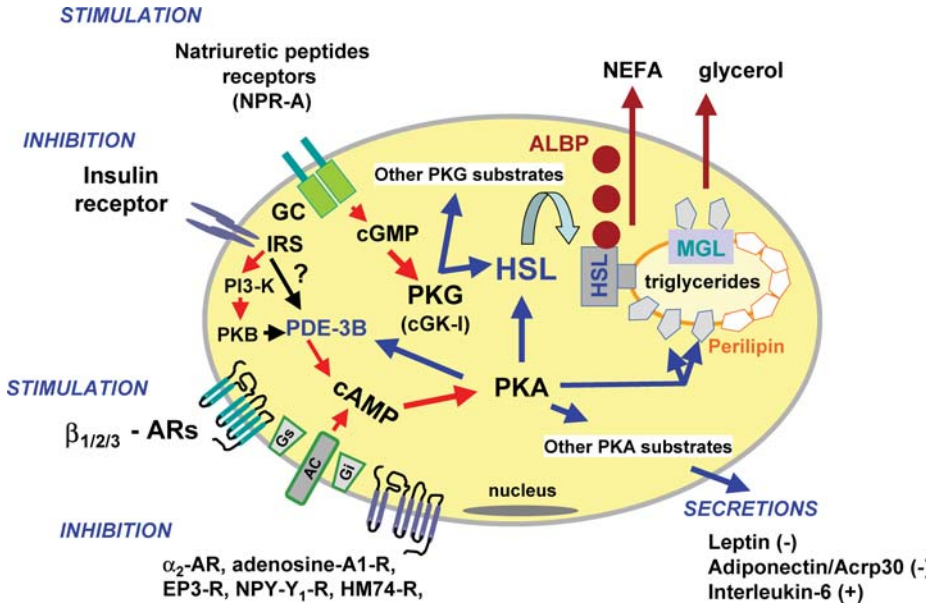

Figure 1 Control of human fat cell lipolysis: signal transduction pathways for catecholamines via β- and α_2-adrenergic receptors, atrial natriuretic peptide via type A receptor (NPR-A), and insulin. Catecholamines, insulin, and various inhibitory receptors negatively coupled to adenylyl cyclase control cAMP production, whereas atrial and brain natriuretic peptides (ANP and BNP, respectively) control cGMP production. cAMP and cGMP both contribute to the protein-kinase [PKA and PKG (cGK-I)]-dependent phosphorylation of HSL and perilipin. Perilipin phosphorylation induces an important physical alteration of the droplet surface that facilitates the action of HSL on triglyceride lipolysis. HSL phosphorylation promotes its translocation from the cytosol to the surface of the lipid droplet. Docking of ALBP to HSL favors the efflux of NEFA released by the hydrolysis of triglycerides. PKA and PKG (cGK-I) phosphorylate a number of other substrates that are not shown in the diagram and can influence the secretion of various adipocyte products such as leptin, adiponectin, and interleukin-6. Question marks show pathways that are still hypothetical or the relevance of which has not been fully demonstrated. AC, adenylyl cyclase; ALBP, adipocyte lipid binding protein; AR, adrenergic receptor; EP3-R, EP3-prostaglandin receptor; adenosine-A1-R, type A1 adenosine receptor; NPY-Y_1-R, type Y1 neuropeptide Y receptor; GC, guanylyl cyclase; Gi, inhibitory GTP-binding protein; Gs, stimulatory GTP-binding protein; HSL, hormone-sensitive lipase; IRS, insulin receptor substrate; PDE-3B, phosphodiesterase 3B; PI3-K, phosphatidylinositol-3-phosphate kinase; PKA, protein kinase A; PKB, protein kinase B/Akt; PKG (cGK-I), protein kinase G; NEFA, nonesterified fatty acid; ALBP, adipocyte lipid binding protein; (−), inhibition; (+), stimulation.

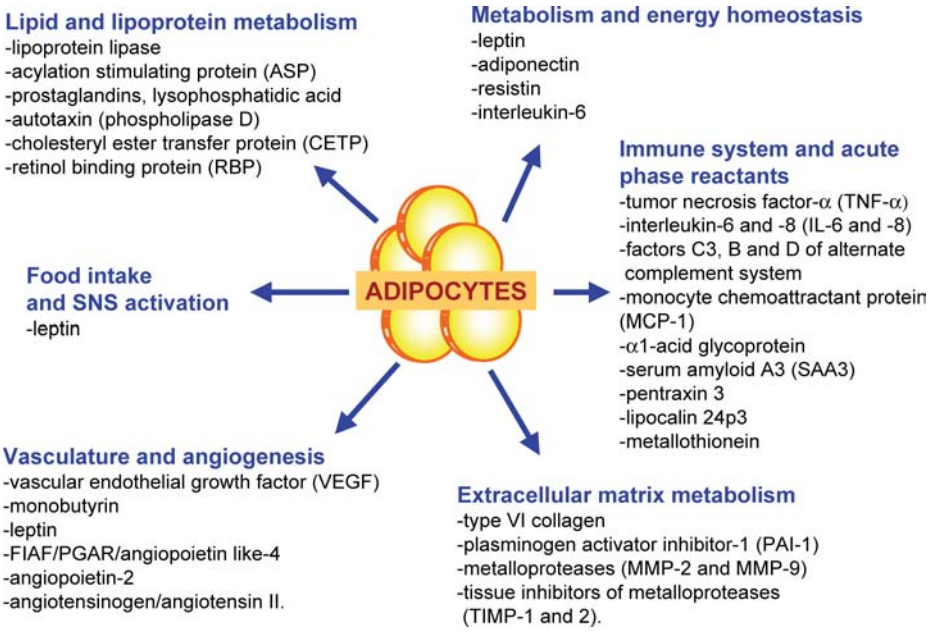

Figure 2 Overview of the major functions under the control of products secreted by the adipocyte. All the hormones and secretions (and abbreviations) are defined in the text.

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