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Adipose Tissue as an Endocrine Organ

Rexford S. Ahima and Jeffery S. Flier

The discovery of leptin in the mid-1990s has focused attention on the role of proteins secreted by adipose tissue. Leptin has profound effects on appetite and energy balance, and is also involved in the regulation of neuroendocrine and immune function. Sex steroid and glucocorticoid metabolism in adipose tissue has been implicated as a determinant of body fat distribution and cardiovascular risk. Other adipose products, for example, proinflammatory cytokines, complement factors and components of the coagulation/fibrinolytic cascade, may mediate the metabolic and cardiovascular complications associated with obesity.

Energy stores are depleted intermittently during sleep–wake cycles and over prolonged periods during famine or illness. To maintain vital cellular functions, humans and other mammals consume more calories than is required for immediate metabolic needs and store excess calories as glycogen, protein and lipids. Adipose tissue, commonly called 'fat', is a type of loose connective tissue comprised of lipid-filled cells (adipocytes) surrounded by a matrix of collagen fibers, blood vessels, fibroblasts and immune cells. In certain areas, for example, subcutaneous and mesentery regions, adipose tissue is organized into large lobular structures. White adipose tissue, the predominant type of adipose tissue in humans, is characterized by adipocytes with a single lipid inclusion and eccentrically located nucleus. Adipose tissue provides a virtually limitless storage site for triglycerides.

Fat metabolism is dependent on energy requirements, and is regulated by nutrient, neural and hormonal signals (reviewed in Ref. 1). For example, the fall in glucose levels during fasting stimulates lipolysis, leading to release of fatty acids for use by a variety of tissues, for example, muscle, liver and kidney. This switch from carbohydrate- to fat-based metabolism is mediated by a reduction in insulin and an increase in so-called 'counter-regulatory' hormones, for example epinephrine, growth hormone (GH) and glucocorticoids. Partial oxidation of fatty acids also generates ketones, which serve as an alternate fuel source for the brain and other organs. Conversely, the postprandial increase in glucose and lipids results in increased adipose fatty acid transport and lipogenesis under the influence of insulin.

There is considerable metabolic heterogeneity among various adipose depots. Furthermore, proteins secreted by adipose tissue are actively involved in energy homeostasis and regulation of neuroendocrine, autonomic and immune function[1–3]. The endocrine role of

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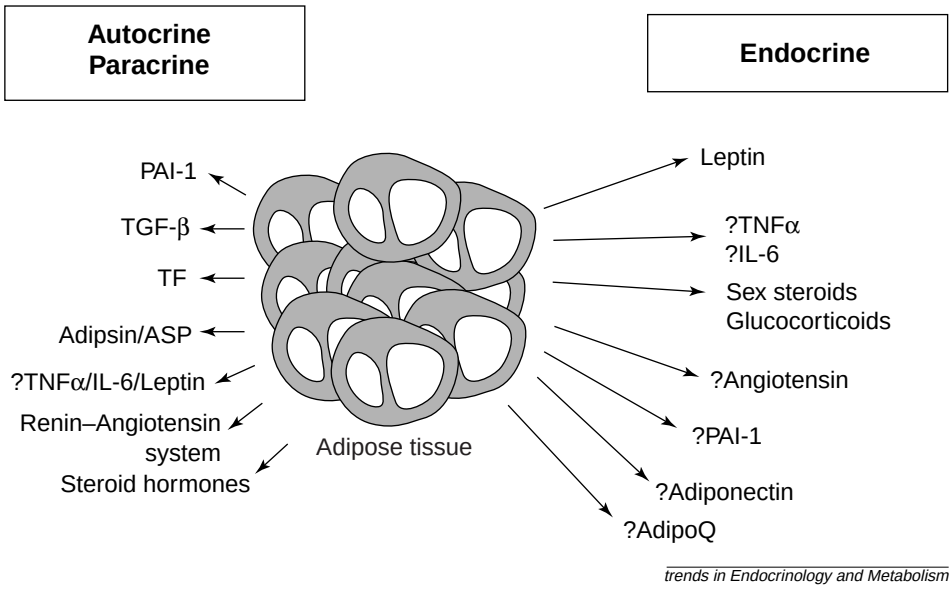

Figure 1. Hormones and other products secreted by adipose tissue. Leptin, angiotensinogen, inflammatory cytokines, complement factors (e.g. adipsin), steroids and components of the coagulation/fibrinolytic pathways have been implicated in metabolic, neuroendocrine, immune and cardiovascular regulation. Adiponectin and Adipo Q (adipocyte complement-related protein) are structurally similar to complement C1q and very abundant in human and murine serum respectively. Abbreviations: ASP, acylation stimulating protein; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor type 1; TF, tissue factor; TGF-β, transforming growth factor β; TNFα, tumor necrosis factor α.

adipose tissue is best characterized by leptin[3]. Total leptin deficiency or insensitivity causes hyperphagia, morbid obesity, diabetes, a variety of neuroendocrine abnormalities and autonomic and immune dysfunction[3]. Other products secreted by adipose tissue include sex steroids and glucocorticoids, peptide hormone precursors (e.g. angiotensinogen), complement factors (e.g. adipsin/acylation-stimulating protein), proinflammatory cytokines [e.g. tumor necrosis factor α (TNFα), interleukin 6 (IL-6)], transforming growth factor-β (TGF-β), tissue factor, plasminogen activator inhibitor-1 (PAI-1), Adipo Q and adiponectin (Fig. 1). While it is likely that most of these products act through paracrine or autocrine mechanisms, others, such as leptin and PAI-1, circulate in amounts that are capable of influencing distant targets. Here, we review the current understanding of the endocrine actions of products secreted by adipose tissue and their potential roles in disease.

• Leptin

The existence of a circulating factor that increases with energy stores and acts in the brain to inhibit feeding and adiposity was predicted more than four decades ago[4,5]. Subsequently, recessive mutations named *obese (ob)* and *diabetes (db)*, both of which caused marked obesity and diabetes in mice, were identified[6]. Based on parabiosis studies, it was suggested that the *ob* locus was associated with the production of a circulating satiety factor, while the *db* locus was required for response to the satiety factor. This hypothesis was confirmed by the cloning of the *ob* and *db* genes in the mid-1990s[7,8]. The product of the *ob* gene was named 'leptin' (from the Greek root 'leptos', meaning thin) because it decreased body weight and fat mass when injected into mice[9].

Leptin is expressed mainly by adipose tissue, although low levels have been detected in the placenta, skeletal muscle, gastric and mammary epithelium and the brain (reviewed in Refs 3,10,11). It has a relative mass of 16 kDa, a helical structure similar to cytokines and is highly conserved among mammals. The mechanism of leptin secretion is not well understood, although secretion via a constitutive pathway is very likely. Leptin circulates as both free and bound hormone and is cleared mainly by the kidneys. Adipose tissue and plasma leptin concentrations are dependent on the amount of energy stored as fat as well as the status of energy balance. Therefore, leptin levels are higher in obese individuals and increase with overfeeding. Conversely, lean individuals have lower leptin levels, and fasting results in reduction of circulating leptin. Nutritional regulation of leptin is mediated at least in part by insulin, as leptin decreases in response to low insulin levels and increases with feeding or in response to insulin stimulation.

Leptin is regulated by other factors (Fig. 2), some of which are likely to affect leptin synthesis directly, as regulatory elements for various transcription factors have been located in the *ob* gene promoter (reviewed in Refs 3,10,11). For example, leptin is increased by glucocorticoids, acute infection and proinflammatory cytokines. In contrast, cold exposure, adrenergic stimulation, GH, thyroid hormone, melatonin, smoking and thiazolidinediones decrease leptin. Leptin levels are higher in females than males, partly as a result of inhibition by androgens, stimulation by estrogen and depot-related differences in leptin expression (reviewed in Ref. 12). Leptin synthesis is greater in subcutaneous than in visceral adipose tissue, and the higher circulating concentration of leptin in females is likely to be due, in part, to a higher proportion of subcutaneous fat.

Diurnal and ultradian leptin rhythms have been identified[13–15]. In humans, leptin peaks at night and reaches a nadir in the morning. The diurnal leptin rhythm is reciprocal to glucocorticoids, is entrained by the timing of feeding and does not appear to be affected by obesity[13,15]. Leptin is secreted in a pulsatile manner, positively correlated with female sex hormones and blunted in patients with exercise-induced amenorrhea[14]. Although there is an inverse correlation between leptin pulses, adrenocorticotropin (ACTH) and cortisol, the physiological significance of this association is as yet unknown[13].

Physiological Role of Leptin: Anti-obesity Hormone vs Starvation Signal

The prevailing view of leptin as an anti-obesity hormone whose primary

role is to decrease appetite and increase energy expenditure through action in the brain (Fig. 2), was based on the following observations: (1) total leptin deficiency or insensitivity as a result of *ob* or *db* mutation leads to marked hyperphagia, decreased energy expenditure and morbid obesity, that is, features consistent with lack of negative-feedback regulation of adiposity[3,9]; (2) peripheral and, more potently, intracerebroventricular (icv) leptin injection reduces body weight and fat mass through inhibition of food intake and increased energy expenditure in rodents[3]; (3) a saturable transport system for leptin has been demonstrated in the rodent brain[16]; and (4) the long leptin receptor isoform (Ob–Rb) [which mediates Janus kinase-signal transducers and activators of transcription (JAK-STAT) activation] is localized in the hypothalamus and other brain regions involved in feeding and energy balance[17]. Leptin is likely to inhibit appetite and weight gain by decreasing the expression of orexigenic peptides, for example neuropeptide Y (NPY) and increasing anorexigenic peptides, for example α-melanocyte-stimulating hormone (α-MSH), corticotropin-releasing hormone (CRH) and cocaine- and amphetamine-regulated transcript (CART)[3,10,11,17].

However, the concept of leptin as an anti-obesity hormone must be reconciled with the inability of high endogenous leptin levels to prevent most obesities[10]. Although the rise in leptin with obesity is thought to indicate 'leptin resistance', this process is poorly understood. Potential mechanisms for leptin resistance include defective brain leptin transport and/or impaired leptin signaling. The cerebrospinal fluid : plasma leptin ratio is decreased in obese individuals[18]. New Zealand obese (NZO) and diet-induced obese mice are resistant to peripheral leptin administration, but respond to leptin injection into cerebrospinal fluid[19,20]. This suggests that leptin resistance could result from decreased transport to brain targets. Recent studies have also suggested that leptin resistance may be mediated by inhibition of leptin signaling. For example, a member of the suppressors of cytokine signaling family, SOCS-3, is induced by leptin via STAT3 activation and inhibits leptin signaling[21]. Leptin resistance may also be mediated by SH2-containing tyrosine phosphatase (SHP-2), as shown by enhancement of leptin signaling when the SHP-2 binding site on the long leptin isoform is mutated[22].

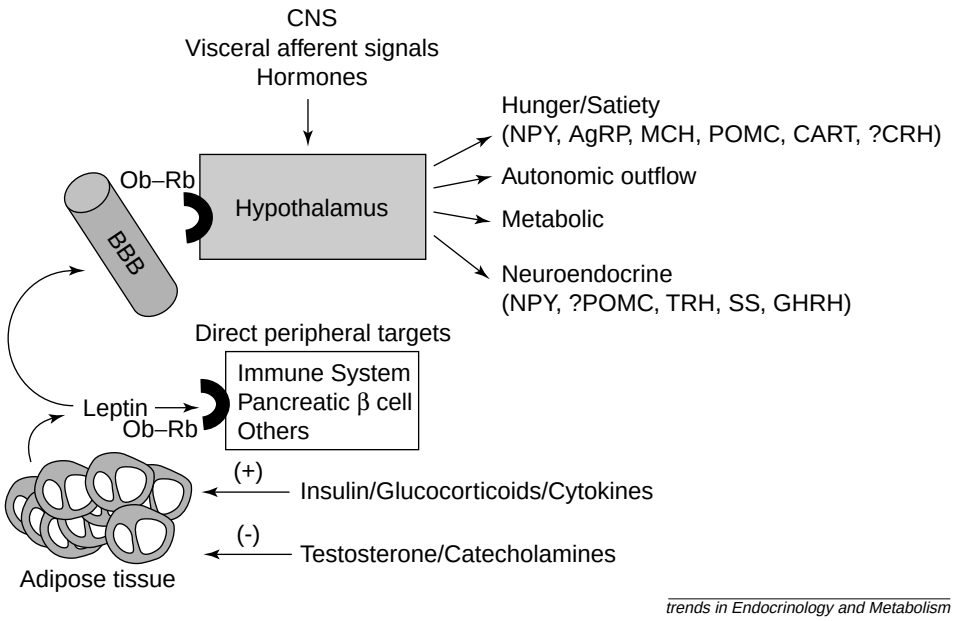

Figure 2. Regulation of leptin and sites of leptin action. Leptin is stimulated by insulin and glucocorticoids, and decreased by androgens and β-adrenergic stimulation. Leptin is transported to neuronal targets in the hypothalamus across the BBB and regulates the expression of orexigenic peptides, for example, NPY, AgRP and MCH and anorexigenic peptides, for example, POMC (precursor of α-MSH), CART, and CRH. Other leptin targets, for example, TRH, GHRH and SS are involved in neuroendocrine regulation. Leptin has direct effects on the immune system and pancreatic β cells. Abbreviations: AgRP, agouti related peptide; BBB, blood–brain barrier; CART, cocaine- and amphetamine-regulated transcript; CNS, central nervous system; CRH, corticotropin-releasing hormone; GHRH, growth hormone-releasing hormone; MCH, melanin-concentrating hormone; α-MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; Ob–Rb, long form leptin receptor; POMC, proopiomelanocortin; SS, somatostatin; TRH, thyrotropin-releasing hormone.

It has been suggested that the dominant physiological role of leptin is as a signal for the switch between fed and fasted states[10,23]. The reduction in leptin during fasting triggers profound metabolic and neuroendocrine responses in rodents, for example suppression of GH, thyroid and reproductive hormones, and activation of the hypothalamic–pituitary–adrenal axis. Furthermore, hypothalamic neuropeptide targets, for example NPY, proopiomelanocortin (POMC), and CART are more responsive to leptin during fasting than in the overfed or mildly obese state[24]. In addition, leptin is likely to mediate responses to chronic reduction in energy stores in fat[25]. Leptin is a potent mediator of immune suppression during fasting through direct regulation of T lymphocytes and cytokine production[26].

• Other Roles of Leptin

Leptin has been implicated in other roles, including modulation of the reward circuitry for feeding, glucose metabolism, lipid oxidation, substrate partitioning and adipocyte apoptosis (reviewed in Refs 3,11). A critical role of leptin in reproduction is manifested by the failure of pubertal maturation in humans and rodents with total leptin deficiency or insensitivity[3,27]. Leptin treatment restores puberty and fertility in *ob/ob* mice, and accelerates puberty when administered to wild-type rodents[27,28]. Other actions of leptin on the endocrine system include regulation of the hypothalamic–pituitary–adrenal axis, GH, prolactin and other anterior pituitary hormones, insulin production by

pancreatic β cells and steroid secretion by ovarian granulosa cells[3,10,11]. The dose requirement of leptin for normal development of the neuroendocrine axis may be lower than is required for suppression of appetite and adiposity.

Leptin activates the sympathetic nervous system, and is involved in regulation of blood pressure, hematopoiesis, angiogenesis, brain and bone development, and wound healing[3,10,11]. As often happens when a new protein is discovered, the original view of leptin as a metabolic hormone has been replaced by a more complex one. Leptin has multisystemic actions, and it is likely that leptin action or leptin resistance could mediate the metabolic, endocrine and cardiovascular complications associated with obesity.

• Steroid Hormones

The ability of adipose tissue to metabolize sex steroids and glucocorticoids is well known[29,30]. Adipose stromal cells are involved in the interconversion of steroids. For example, 17 β-hydroxysteroid oxidoreductase converts androstenedione (an adrenal androgen) to testosterone, and estrone to estradiol. Cytochrome P-450-dependent aromatase mediates the conversion of androgens to estrogens. The local production of sex steroids may be an important determinant of fat distribution. Estrogens stimulate adipogenesis in the breast and subcutaneous tissue, while androgens promote central obesity. Central obesity has been associated with insulin resistance, type 2 diabetes, dyslipidemia, hypertension and coronary artery disease[31,32]. Furthermore, alteration of the balance between androgens and estrogens may predispose individual to reproductive disorders and certain cancers[30].

As with sex steroids, adipose tissue does not synthesize glucocorticoids *de novo*. Instead, the active : inactive glucocorticoids ratio (i.e. cortisol : cortisone) in various fat depots is regulated by type 1 11-β hydroxysteroid dehydrogenase (11-βHSD-1)[33]. 11-βSD-1 is highly expressed by omental stromal cells, and stimulated by insulin and cortisol, and determines the ratio of cortisol : cortisone in subcutaneous abdominal adipose tissue in humans[34]. Cortisol increases aromatase activity, thereby affecting sex-steroid interconversion. Although fat redistribution as a result of glucocorticoid excess is well characterized in Cushing's disease[35], it is unclear as to what extent local/regional glucocorticoid production contributes to fat distribution and cardiovascular complications associated with common diet-induced obesity.

• Proinflammatory Cytokines

Adipose tissue produces and secretes inflammatory cytokines, for example TNFα and IL-6 (reviewed in Refs 2,36). Cytokine expression and plasma levels increase in proportion to adiposity and as a result of changes in energy balance. TNFα is synthesized as a 25-kDa transmembrane protein and cleaved to a 17-kDa protein that is present in the circulation. Two types of TNF receptors, that is, type 1 (p55) and type 2 (p75), have been described[36]. Both receptors are localized in the plasma membrane in most tissues and interact with major signal transduction pathways. TNF receptors are also secreted and could alter the pharmacokinetics and activity of TNFα.

TNFα regulates key components of fat metabolism, and has a net effect to prevent obesity through inhibition of lipogenesis, increased lipolysis and facilitation of adipocyte death via apoptosis[36]. TNFα has been suggested as a mediator of insulin resistance in obesity[36,37], although there is controversy surrounding the exact nature of this proposed role. Infusion of TNFα antibody did not improve insulin sensitivity in humans or rodents[36]. Targeted disruption of TNFα resulted in a reduction in insulin and glucose levels in lean or older obese mice, but did not prevent insulin resistance in gold-thioglucose-induced obesity[38]. Mutagenesis of TNFα receptors did not affect glucose levels and insulin sensitivity in wild-type and *db/db* mice[39]. These findings are at variance with other studies in which insulin sensitivity improved in mice with TNFα deficiency or with mutation of TNF receptors[40].

The effects of TNFα and other proinflammatory cytokines on feeding, energy balance, neuroendocrine and immune function during infection and inflammation are well recognized[41,42]. Interestingly, C-reactive protein is stimulated by IL-6, and is positively correlated with obesity, insulin resistance, elevated TNFα and endothelial dysfunction[43]. It remains to be determined whether IL-6 is a link between adipose tissue and thromboembolic complications of obesity.

• Coagulation and Complement Factors

Obesity is associated with increased cardiovascular risk[30,32]. Proteins involved in the coagulation and fibrinolytic pathways, for example fibrinogen and PAI-1 are altered in obesity and are likely to be involved in cardiovascular disease (CVD). High levels of PAI-1 have been detected following myocardial infarction[44] and although the liver is the major site of PAI-1 production, significant amounts are synthesized by adipose tissue[45]. Plasma PAI-1 levels increase in proportion to visceral adiposity, raising the possibility that PAI-1 serves as the link between abdominal/central obesity and CVD (Ref. 45).

Proteins of the alternate complement pathway are secreted by adipose tissue. Adipsin (complement D) was the first to be cloned from an adipocyte cell line, and subsequently shown to be synthesized and secreted by adipose tissue[46,47]. Adipsin is markedly suppressed in *ob/ob*, *db/db*, monosodium glutamate-induced obese mice and cafeteria-fed rats, and is regulated by glucocorticoids and insulin[46,47]. In contrast to rodents, adipsin increases with adiposity in humans and in response to feeding[48]. Adipsin is decreased during fasting, cachexia and lipoatrophy[48] and it is unclear whether the difference in adipsin response to adiposity between rodents and humans is because of higher levels of glucocorticoids that characterize rodent obesity[46,47]. Adipsin is required for the synthesis of acylation stimulating protein (ASP), a protein implicated in fat metabolism (reviewed in Ref. 49). ASP is produced by the cleavage of C3a by carboxypeptidase and is highly expressed by mature adipocytes. The synthesis of C3a from C3 requires complement factor B and adipsin. Plasma ASP increases with meals and facilitates the

synthesis and storage of triglycerides. Consistent with its role as a mediator of lipogenesis, ASP deficiency increases postprandial fatty acid levels and decreases weight gain and triglyceride synthesis in mice[50].

Adipocyte complement-related protein (Acrp30) (also known as AdipoQ) is a 30-kDa protein which is structurally similar to complement factor C1q, and is secreted by adipocytes[51,52]. Acrp30 also shares structural homology with the brain-specific protein cerebellin, and a hibernation protein isolated from Siberian chipmunk plasma[51]. In rodents, Acrp30 is increased in response to insulin[51] and is decreased in response to obesity in rodents and humans[52]. Although the functional role of Acrp30 is not known, these findings suggest that it may be involved in metabolism. Adiponectin is a collagen-like protein produced and secreted exclusively by adipocytes[53]. Plasma adiponectin concentration is decreased in obesity, type 2 diabetes and coronary artery disease[53,54]. Adiponectin inhibits vascular smooth muscle proliferation and could modulate coronary artery disease risk by altering the expression of various adhesion molecules[54,55].

• Renin–Angiotensin System

Proteins of the renin–angiotensin system (RAS), for example angiotensinogen, renin, nonrenin-angiotensin enzymes (chymase, cathepsins D and G and tonin), angiotensin-converting enzyme, as well as angiotensin II receptors are expressed by adipose tissue[56]. Moreover, adipose tissue angiotensinogen mRNA and protein levels are regulated by nutrition, leading to decreased levels with fasting and to increased levels with refeeding[57]. Angiotensin II stimulates prostacyclin synthesis, adipocyte differentiation and lipogenesis[58]. Based on these findings, it is suggested that adipose tissue-derived angiotensin may regulate adipocyte differentiation and growth, as is the case in other tissues. It is also possible that RAS peptides secreted by adipose tissue act on the vasculature and distant targets to regulate blood pressure and cardiovascular responses in obese individuals.

• Lessons from Lipoatrophy

Our understanding of the endocrine and metabolic function of adipose tissue has been enhanced by the recent generation of transgenic mice devoid of white adipose tissue (WAT)[59,60]. A research team headed by Brown and Goldstein[59] engineered WAT-free mice by forced expression of a constitutively active truncated form of sterol regulatory element-binding protein (SREBP)-1c, a transcription factor involved in the regulation of cholesterol and fatty-acid biosynthesis. There was significant reduction in the expression of several gene products required for normal maturation and function of WAT, for example peroxisome proliferator-activator receptor γ (PPARγ), CCAAT/enhancer binding protein (C/EBP) α, insulin receptor, insulin receptor substrate 1 (IRS-1), IRS-2 and glucose transporter 4 (GLUT4). Moreover, leptin was decreased while TNFα was increased. A research team at the National Institutes of Health (NIH) led by Vinson[60] generated WAT-free mice by inhibiting the function of the transcription factors Jun and C/EBP in adipose tissue by the expression of an artificial transcription factor A-ZIF/F-1. These mice were also insulin resistant, diabetic and had enlarged fatty livers[60]. Free fatty-acid levels were normal in SREBP-1c-overexpressing mice in the fed state, but were elevated in A-ZIF/F-1 mice[60].

The phenotypes displayed by WAT-free mice, that is, hypermetabolism, increased appetite, hyperinsulinemia, diabetes and hepatomegaly, are remarkably similar to those seen in humans with generalized lipodystrophy[61]. Contrary to the notion that type 2 diabetes develops as a result of excess adiposity, these lipoatrophic mouse models highlight the fact that WAT deficiency can also lead to type 2 diabetes. Possible mediators of insulin resistance in lipoatrophy include increased TNFα and free fatty acid, and low leptin concentration. Where leptin concentrations are low, leptin treatment has been shown to decrease insulin and improve hyperglycemia in lipoatrophic mice derived from overexpression of SREBP-1c and, to a lesser extent, in those expressing A-ZIF/F-1 (Refs 62,63). Transplantation of WAT from wild-type mice lowered insulin levels, enhanced insulin sensitivity and glucose tolerance, and reversed hyperphagia, fatty liver and organomegaly in A-ZIF/F-1 mice[64]. These findings are consistent with the notion that products secreted by adipose tissue are critical mediators of feeding and metabolism.

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