0013-7227/08/$15.00/0
Printed in U.S.A.

Endocrinology 149(3):925–934

doi: 10.1210/en.2007-1355

Minireview: Obesity and LipOdystrophy—Where Do the Circles Intersect?

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Adipose tissue is unique in that it can undergo significant hypertrophy and atrophy, resulting in wide ranges of obesities and lipodystrophies. At the base of this elasticity is the lipid-filled adipocyte, which can either overfill by storing large amounts of triglycerides or shrink to a tiny cell by depleting its lipids and as such is remarkable in sustaining insults. As a major energy reservoir, the adipocyte may hold considerable calories necessary for survival and reproduction, two functions that are essential for the survival of the species. This review will summarize some of the recent studies that have advanced our understanding of the central and peripheral mechanisms that are initiated by adipocyte-secreted factors such as leptin, adiponectin, resistin, and retinol-binding protein 4. The intersection of obesity and lipodystrophy results in insulin resistance, which may be unlocked by elucidating the roles of these factors in pathways that control insulin sensitivity and glucose uptake. (*Endocrinology* 149: 925–934, 2008)

NEITHER OBESITY NOR lipodystrophy is a simple disorder, whether defined by clinical or biological criteria. In fact, they are distinct disorders with, however, a common characteristic in that they both involve adipose tissue insults. These alterations in the adipose tissue mass are in turn influenced by common factors such as genetics, environment, and behavior. A great deal of our present knowledge of obesity and lipodystrophy originates from mouse models and the characterization of mutations in the monogenic form of either disease. Thus, this review will concentrate on the relevant pathways that have emerged from animal models and human studies and are most relevant to human biology.

Obesity: The First Circle

The increasing rate of the obesity epidemic argues against rapid genetic drift, thus reinforcing the notion that although genetics are pivotal in rare forms of obesity, the interaction of genes and the environment remains the most plausible explanation for the alarming steep rise in overweight disorders. The uncovering of multiple genes and their encoded proteins have come to light in recent years and have contributed to the understanding and regulation of central and peripheral pathways that govern energy metabolism. Some of these pathways are reviewed here.

First Published Online January 17, 2008

Abbreviations: AGPAT2, 1-Acylglycerol-3-phosphate-*O*-acyltransferase 2; AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CGL, congenital generalized lipodystrophy; FoxO1, forkhead transcription factor 1; FPLD, familial partial lipodystrophy; GLUT4, glucose transporter 4; 5HT2C-R, serotonin 2c receptor; IRS, insulin receptor substrate; MC4R, melanocortin 4 receptor; POMC, proopiomelanocortin; PPARγ, peroxisome proliferator-activated receptor-γ; RBP4, retinol (vitamin A)-binding protein 4; SF1, steroidogenic factor 1; STAT3, signal transducer and activator of transcription 3.

***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

Central pathways

Although positional cloning successes and the Human Genome Project were at the helm of late 20th century research, the tide is currently turning toward functional genomics, aimed at delineating pathways encoded by new genes. In the years that followed cloning of the *obese* gene from the morbidly obese *ob/ob* mouse and the discovery of its secreted hormone, leptin (1), the presence and consolidation of a neuronal circuit that regulates food intake came into light (Fig. 1). The role of this pathway in human obesity was justified by undertaking a wide search for mutations in genes governing this pathway among obese individuals. Although only a couple of leptin mutations were uncovered (2, 3), they vindicated the *ob/ob* animal model and suggested that leptin could trigger and orchestrate a series of events leading to body weight regulation. In fact, the central action of leptin is initiated by the binding to its signaling-competent long-form receptor in the hypothalamus to stimulate and inhibit anorexigenic and orexigenic pathways, respectively, leading overall to the suppression of food intake. Mutations of the leptin receptor and inactivation of the leptin pathway in its early steps led to obesity as shown by the obese animal models, the *db/db* mouse and *fa/fa* rat, and in a few obese individuals (4), demonstrating the critical roles of leptin and its receptor in the regulation of body weight.

Leptin-binding neurons. In the anorexigenic arm of the central leptin pathway, the binding of leptin to its receptor on proopiomelanocortin (POMC) neurons led to the finding that obesity is associated with rare human mutations in the prohormone convertase PC1/PC3 gene (5, 6), which encodes a serine endoprotease that cleaves prohormones such as insulin, glucagon, and POMC into their mature forms. Obesity-causing mutations are also present in the POMC (7–9) and cocaine- and amphetamine-regulated transcript (CART) genes (10) substantiating the physiological relevance of the POMC pathway to human obesity. Furthermore, deletion of the leptin receptor from POMC neurons in a mouse model

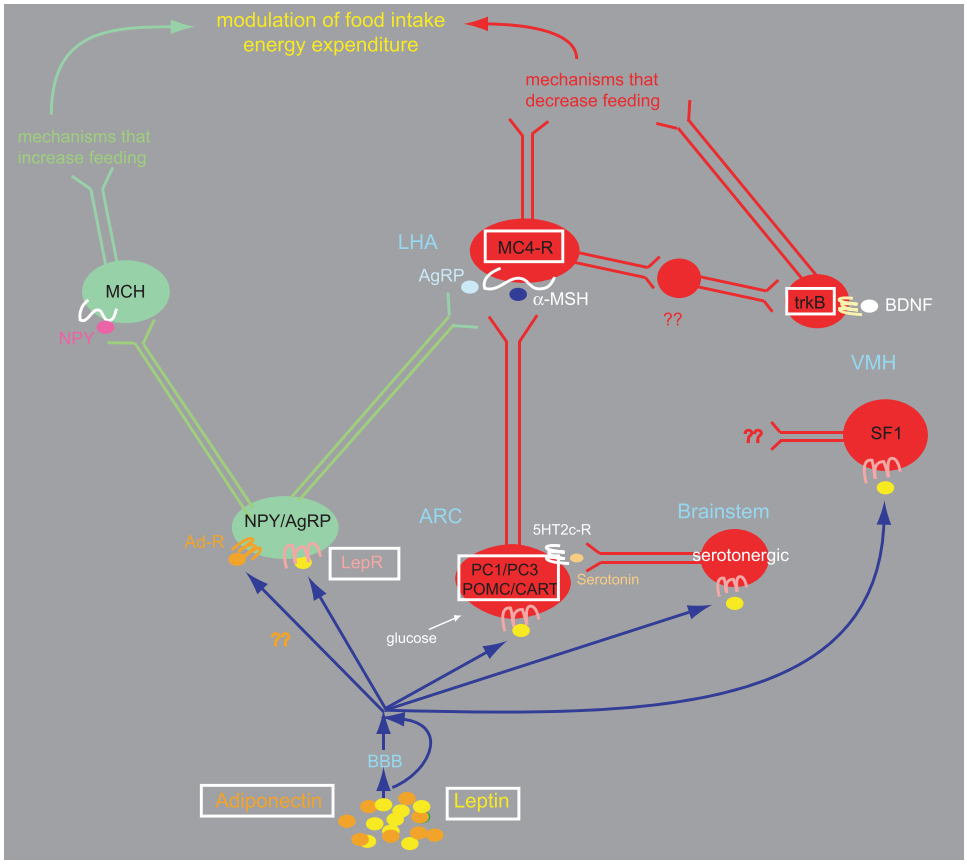

FIG. 1. Diagram showing activation of the neuronal circuit initiated by the binding of leptin and adiponectin to their respective receptors on hypothalamic neurons. Neurons in *green* and *red* represent those that act as stimulatory or inhibitory nodes for food intake, respectively. Leptin crosses or bypasses the blood-brain barrier (BBB) to bind neuropeptide Y (NPY)/AgRP-expressing neurons in the arcuate nucleus (ARC) to stimulate pathways that inhibit food intake. Leptin performs this function by suppressing, via STAT3-induced abrogation of FoxO1, the expression of the orexigenic peptide AgRP that would otherwise antagonize α-MSH at the MC4R-receptor. Conversely, the binding of adiponectin to its receptor on leptin-responsive neurons to stimulate food intake (30) is presumed to result from activation of the orexigenic NPY/AgRP neuronal node. Leptin also binds to POMC neurons in the ARC, to serotonergic neurons in the brainstem, and to SF1-expressing neurons in the ventromedial hypothalamus (VMH), which also contains neurons that bind BDNF on trkB receptors. POMC, MC4, serotonergic, SF1, and BDNF neurons activate anorexigenic pathways that inhibit food intake. In the orexigenic arm of this neurocircuit, which is inhibited by leptin but stimulated by adiponectin, the melanin-concentrating hormone (MCH) neurons are located in the lateral hypothalamic area (LHA) and are activated by NPY. The *boxes* around some factors represent those that are mutated or have been found to be associated with obesity in humans.

yielded only a mild obesity, alluding to the presence of other neurons that are critical for body weight regulation (11). The importance of POMC neurons in obesity and insulin resistance was even more strengthened by recent data showing that POMC neurons are critical for glucose sensing. In these studies, disruption of glucose sensing on mouse POMC neurons impaired whole-body glucose disposal, demonstrating yet another role for POMC neurons in the control of blood glucose (12) and their involvement in insulin resistance.

Proximal and distal neurons. Downstream of POMC neurons are the melanocortin 4 receptor (MC4R) neurons, which play an important role in body weight regulation. In humans, various mutations in the MC4R gene have been delineated and account for approximately 6% of severely obese individuals (13–15), demonstrating that they represent the most common form of monogenic obesity. The cross-talk between the MC4R and other neurons was further delineated by the finding that a mutation in trkB, a receptor for the brain-derived growth factor (BDNF) was detected in an obese individual (16), adding credence to the previous finding in mice that trkB regulates energy balance downstream of the MC4R (17). Furthermore, conditional deletion of BDNF in mice leads to obesity (18). Thus, trkB neurons, which are located in the ventromedial hypothalamus, an area that has long been known to be associated with body weight regulation, represent a new set of neurons that regulate body weight. Also in the hypothalamus are neurons expressing the steroidogenic factor 1 (SF1), a transcription factor that plays a prominent role on the reproductive axis (19). SF1 knockout mice unexpectedly revealed an obesity, thus interjecting SF1 as a putative factor linking the reproductive axis to obesity (20). Combining the leptin axis with SF1, Dhillon *et al.* (21) demonstrated that mice lacking the leptin receptor on SF1 neurons have increased body weight and fat stores but normal fertility. Thus, SF1 neurons represent a new class of first-order leptin-responsive neurons, and because SF1 plays a role in reproduction as does leptin (22, 23), it was disappointing that SF1 did not turn out to be the long-sought leptin link to the reproductive system, thus leaving this question open-ended.

On another level, pharmacological studies have stressed the importance of the serotonergic system in food intake and energy balance. Even though the serotonin 2c receptor (5HT2c-R) is expressed on POMC neurons (24), no mutations were found in the 5HT2c-R gene among a cohort of human obese patients, making it an unlikely candidate for an obesity gene (25). Consistently, deletion of the 5HT2c-R from lean leptin-overexpressing mice failed to reverse their skinny phenotype, showing that at least in experimental mouse models, the 5HT2c-R is not directly impacted by leptin (26).

New pathways. The mechanisms that allow leptin to exert its anorexigenic role through the hypothalamus are continuously emerging. Leptin has been known for quite some time to activate signal transducer and activator of transcription 3

(STAT3) signaling in leptin-responsive neurons in the hypothalamus (27). Recently, the forkhead transcription factor 1 (FoxO1), which is known for its peripheral effects, was shown to have a central role in the hypothalamus and to antagonize the effects of leptin on food intake and body weight by preventing leptin via STAT3 from suppressing the expression of the orexigenic peptide agouti-related peptide (AgRP). Thus, the transcription factors FoxO1 and STAT3 compete for activation of the AgRP promoter (28). Consistent with its anorexigenic role, leptin inhibits hypothalamic AMP-activated protein kinase (AMPK), which is stimulated by AgRP (29).

An exciting and recent finding was the demonstration that adiponectin, an adipocyte-secreted factor that acts peripherally, can also bind centrally on leptin-responsive neurons in the hypothalamus to stimulate food intake by activating AMPK (30). Thus, adiponectin antagonizes the effects of leptin on AMPK and food intake. This finding is important not only because it establishes adiponectin as a central regulator of food intake but also because it implies that leptin and adiponectin together modulate the firing of the same set of neurons and must be intimately involved in their differential regulation. New challenges will be aimed at pinpointing the nature and the balance of this modulation in different feeding states.

A recent study in knockout mice established a critical role for AMPK in the hypothalamus by demonstrating that deletion of AMPK from either AgRP or POMC neurons resulted in increased or decreased body weight, respectively, thus establishing AMPK as a leptin and insulin-independent central regulator of energy balance, (31). Thus, AMPK responds to different stimuli and integrates multiple pathways that regulate food intake, energy balance, and adiposity.

Deceptively, the orexigenic arm of the leptin pathway has failed to demonstrate that it is associated with a human mutation causing obesity. In a systematic search, the melanin-concentrating hormone (MCH) receptor was not mutated in a cohort of obese individuals (32). Teleologically, it is conceivable that mutations, which result in reduction of food intake, are detrimental for survival and have been eliminated by natural selection, thus favoring those mutations that convey a selective advantage for the accumulation of energy reserves and ensuring survival of the organism.

Peripheral pathways

New findings regulating energy metabolism in peripheral organs have emerged in the past few years and significantly contributed to our understanding of regulatory mechanisms.

AMPK. The contribution of AMPK as a regulator of energy balance and a gauge of anabolic and catabolic pathways using ATP, is primordial and well recognized (33, 34). AMPK is activated by an increase in AMP/ATP ratio within the cell and acts as an efficient metabolic sensor. Binding of AMP to the γ-subunit activates AMPK allosterically and stimulates the phosphorylation of its α-subunit at threonine residue 172 by the LKB1 kinase (35, 36). In addition, phosphorylation of AMPK is sustained by an inhibitory effect of AMP on protein phosphatases (37). Furthermore, and independently of the AMP/ATP ratio, calmodulin-dependent protein kinase kinase (CaMKK) also phosphorylates AMPK in response to an increase in intracellular calcium ions (38, 39). Thus, AMPK is intimately implicated in various cellular functions and is activated by exercise, hypoxia, and oxidative stress (40). Most relevant to this review is the fact that AMPK is also activated by peripheral leptin action (41) to stimulate fatty acids oxidation and glucose transport in muscle (42) via glucose transporter 4 (GLUT4) translocation (43) and the myocytes-enhancing factor 2 (MEF2), which transcriptionally activates GLUT4 expression (44). In non-GLUT4-expressing cell types, AMPK stimulates glucose uptake by activating membrane-bound GLUT1 (45) via an undefined mechanism. Overall, due to its wide role, especially in energy metabolism, AMPK activation has been the target of the insulin-sensitizing type II diabetes drugs metformin (46) and the thiazolidinediones (47).

Adipocyte-secreted factors. The role of factors secreted from adipocytes continues to unveil networks of glucose uptake and insulin signaling regulation (Fig. 2). Although the peripheral role of leptin has so far been unveiled by its activation of AMPK (41), the mechanisms of other factors remain at large. Adiponectin, a highly abundant plasma protein secreted from adipose tissue circulates as low, medium, and high molecular weight forms (48). Its high molecular weight complex appears to be the active form, and its levels are reduced in patients with type II diabetes (49), although earlier reports have shown that the total serum levels were reduced in diabetic individuals (50). Similar to the effect of leptin on skeletal muscle (41), adiponectin stimulates glucose uptake and fatty acid oxidation by activating AMPK (51). Recently, adiponectin overexpression in the leptin-deficient *ob/ob* mouse was shown to rescue its diabetic phenotype while paradoxically exacerbating its obesity (52), thus offering a mechanism to explain the heterogeneity of diabetes among obese individuals and for its potential use in the treatment of hyperglycemia. Although the mechanisms by which adiponectin acts as an insulin-sensitizing agent are largely unknown, it activates the LKB1-AMPK pathway, which alleviates negative regulation of insulin signaling via p70 S6 kinase (53).

The role of resistin, a 108-amino-acid plasma protein, first identified as being secreted from adipose tissue in rodents (54), was later found to be expressed in humans from macrophages, mononuclear cells, and adipose tissue (55–57). The association of resistin with obesity and diabetes in mice is tightly involved with the impairment of glucose homeostasis (58, 59). However, such an association in humans is blurred, disparate, and controversial. In some studies, resistin expression levels were elevated in human abdominal adipose tissue (56) and its plasma levels correlated with obesity (60), insulin resistance (61), and atherosclerosis (62). Yet in other studies, circulating resistin levels were associated with neither obesity nor insulin resistance (63–65). The discrepancy in the role of resistin between rodent and human studies underscores the differential regulation of energy metabolism between these species, especially in light of the fact that rodents also regulate their energy metabolism via brown fat, a pathway that is largely confined to the neonatal period in humans. Recently, resistin emerged as another hypothalamic

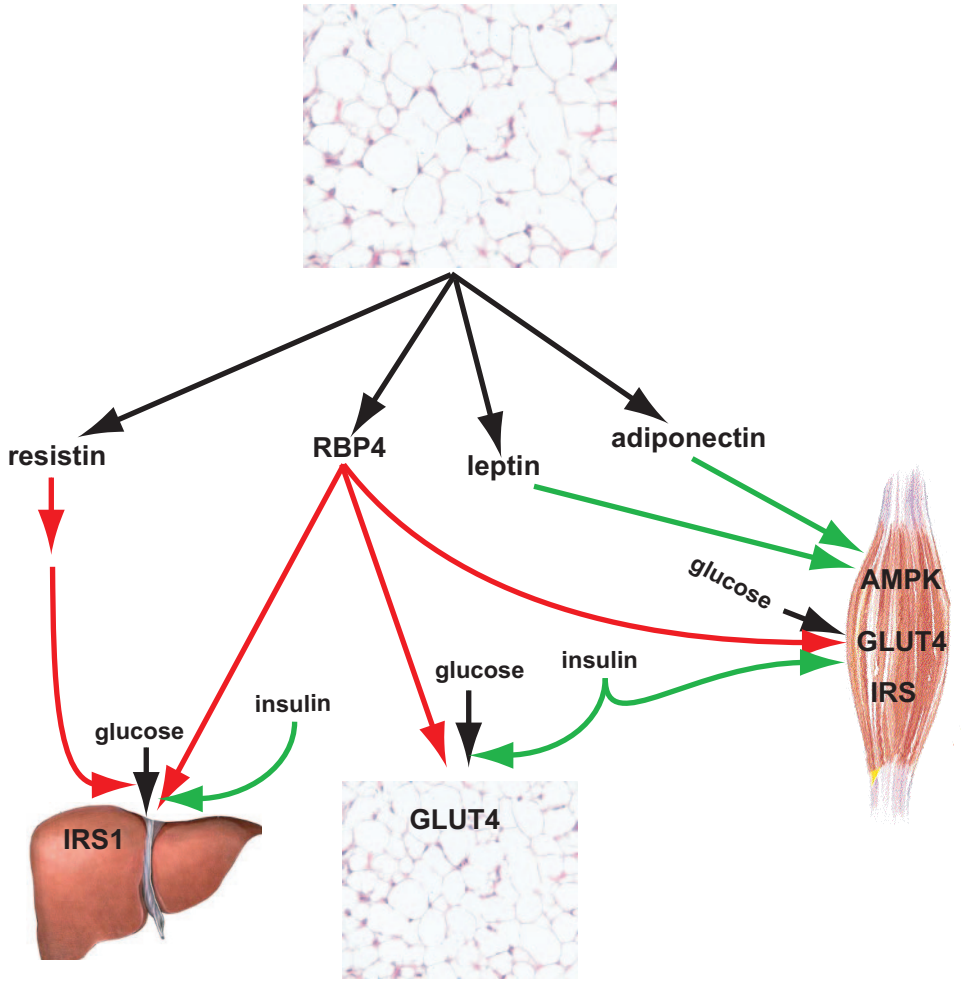

FIG. 2. Peripheral actions of adipocyte-secreted factors leptin, adiponectin, resistin, and RBP4 on the uptake of glucose in muscle, adipose, and liver cells. *Green* and *red arrows* denote stimulatory or inhibitory actions. Both leptin and adiponectin activate AMPK in muscle, resulting in increased insulin sensitivity and glucose uptake. RBP4 antagonizes glucose uptake in muscle and liver and performs the same action in adipose tissue via decreased expression of GLUT4 in adipocytes. Resistin also antagonizes the uptake of glucose in liver, either directly and/or via the hypothalamus. The net effect of these targeted actions of leptin, adiponectin, RBP4, and resistin is the modulation of glucose uptake in insulin-sensitive peripheral tissues.

factor (66) that when infused into the brain of rats led to hepatic insulin resistance (67). Overall, the contrasting findings linking resistin levels to energy balance in humans suggest that perhaps the heterogeneity found in various studies arises from different genetic backgrounds and environmental factors, both of which could significantly influence resistin expression levels. Hopefully, the latest findings linking central resistin to hepatic glucose production (67) might further bring the picture of resistin into focus.

Retinol (vitamin A)-binding protein 4 (RBP4), a plasma glycoprotein secreted from adipose tissue and liver, was unexpectedly found to be associated with insulin resistance (68). Remarkably, elevated RBP4 levels correlated with body mass index, insulin resistance, and impaired glucose homeostasis and were inversely correlated with the levels of GLUT4 in adipocytes, suggesting that its plasma levels could serve as a marker before the onset of diabetes (69). Although variability in RBP4 associations was noted in different populations and in obese individuals, they reinforce the effects of dietary factors, lifestyle, genetics, and even methodology on circulatory RBP4 levels (70–74). Thus, the correlation of RBP4 with the suppression of glucose uptake in muscle and the stimulation of glucose release from liver, classifies it as an insulin antagonizer. It remains to be determined whether agents that decrease circulatory RBP4 levels could serve as insulin sensitizers and ameliorate hyperglycemia in prediabetic or diabetic states.

Overall it can be concluded that the adipocyte-secreted proteins leptin, adiponectin, resistin, and RBP4 chiefly regulate glucose uptake and insulin signaling via the AMPK pathway. As such, these factors serve a central system that tightly regulates energy intake and responds to fluctuations of energy metabolism.

Impact of adipocyte-secreted factors on insulin signaling. It is well established that the binding of insulin to its receptor kinase induces the phosphorylation of insulin receptor substrates (IRS), which activate the phosphatidylinositol 3-kinase (PI3K) signaling cascade. Knockout mice for IRS1 or IRS2 revealed that either model exhibited insulin resistance; however, only IRS2 knockout mice developed overt diabetes (75–77). Furthermore, double-knockout mice for IRS1 and IRS3 resulted in a lipoatrophy caused by defective adipogenesis and an insulin resistance that could be rescued with leptin overexpression (78). Thus, the complementary roles of IRS1 and IRS3 on glucose homeostasis are in part mediated by leptin. Because a functional IRS3 allele is not found in humans, it is possible that a closer association between the functions of IRS1 and leptin may be even more pronounced in humans than in rodents (78).

A coculture model of myocytes and adipocytes suggested that factors secreted by adipocytes block the insulin-stimulated tyrosine phosphorylation of IRS1 in myocytes (79). Whereas the insulin-sensitizing effects of leptin have been demonstrated in lipoatrophic mouse models (see section below), the role of leptin in the disruption of insulin signaling is less clear (80). Nonetheless, leptin was shown to inhibit insulin signaling by its ability to phosphorylate IRS1 at serine 318 in a protein kinase C manner, which resulted in reduced association of IRS1 with the insulin receptor (81, 82) and, thus, decreased insulin signaling. Furthermore, the attenuation of insulin signaling by resistin and RBP4 were recently demonstrated. First, resistin treatment of rat skeletal muscle cells decreased IRS1 levels, suggesting that resistin could mediate a yet unknown mechanism that leads to IRS1 degradation (83). Second, RBP4 blocked the insulin-stimulated phosphorylation of IRS1 at serine 307 and concurrently increased by 4-fold the concentration of insulin that is required for stimulation of IRS1 tyrosine phosphorylation (84). On the other hand, the insulin-sensitizing effects of adiponectin were recently shown to induce IRS1 tyrosine phosphorylation in the presence of active AMPK (53).

Hence, the emerging pathways by which adipocyte-secreted factors have the potential to increase or decrease insulin signaling at the IRS level demonstrate their critical roles in the treatment of diabetes and obesity.

Unknown pathways. Although the majority of obesity-causing lesions remain at large, it is clear by now that single monogenic disorders are not at the root of human obesity. Complex phenotypes, arising from polygenic disorders that include obesity in their presentation, may provide further clues into additional pathways that have significant impact on energy balance. For example, the association of a missense mutation in the neutrophin receptor trkB in a hyperphagic obese individual resulting in impaired MAPK signaling (16), has opened yet another pathway that regulates energy intake. It is likely that multiple redundant pathways control food intake because these pathways are responsible for one of the most important survival functions of the organism. The complexities and heterogeneities of such pathways are exemplified by the 12 genes that underlie the Bardet-Biedl syndrome, which presents with obesity among most affected individuals. Most of the gene products encoded by the Bardet-Biedl syndrome genes are located in the basal body and cilia of the cell causing cilium dysfunction (85). How these proteins and this pathway affect energy metabolism is enigmatic and remains to be defined.

In another yet different level of complexity are reproductive and imprinted disorders, best exemplified in human by the polycystic ovary and Prader-Willi syndromes, respectively. In polycystic ovary syndrome, reproductive abnormalities in women are frequently accompanied by insulin resistance, which may or may not be manifested with obesity. Thus, another axis that remains to be elucidated is the triumvirate of reproduction-insulin resistance-obesity. Most interestingly, are Prader-Willi syndrome individuals who exhibit a hyperphagic obesity and frequently carry a microdeletion in an actively expressed region of their paternal chromosome 15, thus alluding to the presence of a dominant gene in this region of the genome. The possible involvement of imprinting mechanisms on energy metabolism is still unexplored, and it is conceivable that imprinted human and mouse genes encompassed by the multiple imprinted regions of their respective genomes may play a key role in obesity and lipodystrophy. Although the identity of the genes encompassed by the Prader-Willi microdeletion remain to be defined, it is very likely that their characterization will uncover new pathways regulating food intake. Thus, a continuous search for the underlying molecular lesions in obese individuals with complex and unusual phenotypes will chart the map for additional pathways that are relevant to energy metabolism and food intake regulation.

LipOdystrophy: The Second Circle

Lipodystrophies are characterized by selective loss of adipose tissue, which extends from simple cosmetic problems to severe metabolic complications. Lipodystrophy has gained less attention than obesity, namely because of its lower prevalence, as most forms of genetic lipodystrophies are quite rare. Research into acquired and genetic lipodystrophy is becoming increasingly significant mostly because the incidence of the former is rising and studies of the latter may provide new clues to decipher the biology of adipocytes. Thus, the study of lipodystrophy may be the backdoor to further understanding mechanisms leading to obesity.

A form of localized adipose tissue reduction, known as lipoatrophy, is most prevalent in individuals undergoing HIV treatment. Although quite a bit is to be learned about the mechanisms by which protease inhibitors cause fat reduction, whether through inhibition of adipocyte differentiation (86) or apoptosis (87), this review will not expand on this aspect of lipodystrophy but rather concentrate on its genetic aspects and animal models.

Clinical and molecular basis of human lipodystrophies

The clinical features of inherited lipodystrophies are generally classified as congenital generalized lipodystrophy (CGL) or familial partial lipodystrophy (FPLD), and genetic diseases affecting these conditions are autosomal dominant or recessive (88). Diabetes is a very common trait in CGL and HIV-related lipodystrophy but less common in FPLD. If biology were one-dimensional, then one would hypothesize that the genes associated with lipodystrophy are identical to the ones associated with obesity, with the exception that loss- or gain-of-function mutations might differentiate these two disorders. Although this is obviously not the case, except for the known role of peroxisome proliferator-activated receptor-γ (PPARγ) in adipocyte differentiation and in its mutation in one form of lipodystrophy (89), a new set of genes and associated complex pathways have turned out to be the cause of genetic lipodystrophy.

Generalized lipodystrophy. Cloning of the genes underlying two forms of CGL (CGL1 and CGL2) have revealed the culprits of these disorders. The molecular basis of CGL1 is caused by mutations in the gene encoding the acyltransferase 1-acylglycerol-3-phosphate-*O*-acyltransferase 2 (AGPAT2) (90), which catalyzes the formation of lysophosphatidic acid

to phosphatidic acid during triacylglycerol and glycerophospholipid synthesis. Although a family of six different AGPAT proteins is known (91), each of which could mediate this biosynthetic step, the selectivity for AGPAT2 and the lack of compensation from other AGPATs remain puzzling, especially in light of the AGPAT6 knockout mice, which exhibit subdermal lipodystrophy (92). In CGL2 or Berardinelli-Seip syndrome, null mutations were found in the BSCL2 gene, which codes for a 398-amino-acid protein termed seipin that is expressed diffusely in many tissues but predominantly in testis and brain (93). The mechanism by which seipin leads to lipodystrophy and insulin resistance remains unknown and does not appear to be connected to AGPAT either. Interestingly, missense heterozygous mutations in seipin were found in an autosomal dominant form of hereditary motor neuropathy (Silver syndrome) (94), suggesting that perhaps the lack of seipin expression (as in Berardinelli-Seip syndrome) leads to lipodystrophy, whereas alterations in its conformation (as in Silver syndrome) could result in a dominant-negative effect, leading to autosomal dominant neurological disorders. Due to the main expression of seipin in brain and testis, the elucidation of its effect on adipose tissue ought to unveil new mechanisms of adipocyte biology, perhaps through the reproductive axis because it is also expressed in reproductive organs.

Partial lipodystrophy. In the partial forms of lipodystrophy, FPLD1, -2, and -3 that are differentiated from each other by clinical criteria, the molecular basis of FPLD2 and FPLD3 have been reported. In FPLD2, the LMNA gene, which encodes the two isoforms of nuclear lamins A and C, was mutated in multiple families (95, 96). The ubiquitous expression of lamin and the fact that it is also mutated in other types of dystrophies, such as Emery-Dreifuss (97) and limb girdle muscular dystrophy type 1B (98) highlights the complexity of this system and our weak understanding of how it could lead not only to lipodystrophy but also to a wide group of disorders referred to as the laminopathies (99). FPLD3 is caused by mutations in PPARγ (89, 100). Because PPARγ is a well-known master regulator of adipocyte differentiation (101), its mutation in lipodystrophy did not reveal new pathways but reaffirmed its importance by showing that disruption of its expression via haploinsufficiency (102, 103) or of its activity by a dominant-negative effect (104) perturbs adipocyte differentiation. In another vein, protein kinase B/*Akt*, recognized for its multiple roles in cell signaling, promotes cell survival, regulates the cell cycle, glycogen synthesis, cell growth, and insulin-stimulated glucose transport (105). The critical role of *akt2* in insulin-sensitive tissues was physiologically vindicated by the findings that a missense mutation in the human gene abrogates its ability to phosphorylate downstream targets, resulting in insulin resistance and lipodystrophy of an affected individual (106).

Mouse models of lipodystrophy

Consistent with the *akt2* mutation described above, homozygous *akt2* knockout mice are insulin resistant and have reduced adipose tissue mass (107), adding more weight to the critical role of *akt2* in metabolism. Other mouse models of lipodystrophy were also generated in known and novel pathways, leading to clues into lipodystrophy-associated metabolic complications. Foremost was the overexpression of a dominant-negative transcription factor that blocks adipocyte differentiation (108) and that of a constitutive active form of the sterol-regulating binding protein SREBP1c (109). Both of these models revealed a similar phenotype, namely a drastic reduction in adipose tissue mass, hepatic steatosis, and an insulin resistance that could largely be rescued with leptin treatment either exogenously (110), via fat transplantation (111) or transgenic overexpression (112).

More striking are those animal models that have shed light into pathways not previously anticipated. For example, the *fld* (fatty liver dystrophy) mouse mutation was cloned and found to encode a nuclear protein termed lipin, which is expressed at high levels in testis (reminiscent of seipin expression), liver, and adipocytes (113). Overexpression of lipin in muscle and adipose tissue has yielded the opposite phenotype, namely increased adiposity, suggesting that its absence causes lipodystrophy and its overexpression causes obesity (114). Even though a mutation in human lipin has not yet been described in either lipodystrophic or obese subjects, it appears that lipin plays a role in human metabolism because its adipose tissue gene expression is decreased in obese and insulin-resistant subjects and increases with pioglitazone treatment (115, 116). The mechanisms of action of lipin are just starting to emerge, and recent studies in the mouse have shown that its expression is induced in the liver after fasting and that it interacts with the PPARγ coactivator PGC1α to stimulate the expression of genes involved in fatty acid oxidation (117).

Another mouse model of lipodystrophy resulted from adipocyte-induced apoptosis. The inducible activation of caspase-8 in adipocytes resulted in adipose tissue apoptosis and a lipodystrophy that was associated with impaired glucose homeostasis but surprisingly not steatosis (118), raising the question as to the fate and disposal of lipids in nonadipose tissues. Transfer of the caspase-8 transgene onto morbidly obese *ob/ob* mice resulted in fatless *ob/ob* mice that exhibited an exacerbation of their metabolic parameters compared with their obese *ob/ob* counterparts (118). Thus, ablation of fat from an obese mouse does not necessarily ameliorate its diabetic phenotype. Other mouse models with absence or significant reductions of the adipose tissue mass were generated through the overexpression of leptin either from adipose tissue (119) or liver (120). Contrary to lipodystrophic mice but consistent with lipodystrophic mice treated with leptin or fat transplants (110–112), leptin-overexpressing mice exhibited a marked insulin sensitivity (119, 120), demonstrating that reduction of the fat mass in the presence of leptin has beneficial effects on the glucose-insulin axis.

Intersection of the Circles

Obesities and lipodystrophies, representing stretches and shrinks of the adipose tissue, find common grounds in insulin resistance (Fig. 3A). Although the molecular basis of lipodystrophy has remarkably revealed a wide heterogeneity with respect to the underlying genes and their biological pathways, a common characteristic in the majority of lipodystrophies is that of insulin resistance. Because the absence

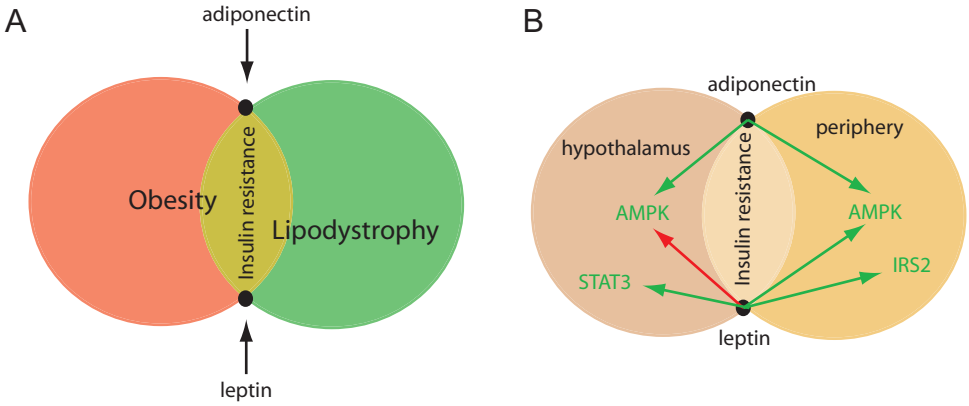

FIG. 3. A, Schematic diagram showing that insulin resistance is the common area that represents the intersection of lipodystrophy and obesity. The adipocyte-secreted factors adiponectin and leptin, represented by the *intersection points of the two circles*, obesity and lipodystrophy, are depicted as modulators of glucose uptake and insulin sensitivity. B, Mechanisms by which adiponectin and leptin regulate food intake in the hypothalamus and glucose uptake in peripheral tissues via their actions on intracellular signaling proteins that mediate glucose uptake and insulin signaling. *Green* and *red arrows* represent stimulatory and inhibitory effects, respectively.

or great reduction of adipose mass in the lipodystrophies also signifies that secreted factors from adipocytes are absent or low, the culprit of insulin resistance may be found in the pathways governed by those factors secreted exclusively from adipocytes, namely leptin and adiponectin.

Leptin

In obesity, the dysregulation of leptin and adiponectin leading, respectively, to hyperleptinemia and hypoadiponectinemia, emphasizes again their importance in insulin resistance. Thus, leptin and adiponectin are the common denominators of insulin resistance in lipodystrophy and obesity. Although leptin treatment was largely ineffective in obese individuals (121), who already have a hyperleptinemia and a natural state of leptin resistance, leptin significantly ameliorated insulin resistance in lipodystrophy (122, 123) and may even improve the amenorrhea associated with lipodystrophy (124). The mechanisms by which leptin and adiponectin ameliorate insulin resistance and improve our understanding of insulin sensitivity are intertwined because they both act on common targets in the periphery and the central nervous system (Fig. 3B). In lipodystrophic SREBP1c-overexpressing mice, leptin treatment ameliorated diabetes by enhancing insulin signaling transduction via IRS-2 and *akt* in the liver (125). Other insulin-independent pathways mediated by leptin include the stimulation of mouse fatty acid oxidation in skeletal muscle via the stimulation of AMPK activity, which in turn inhibits acetyl coenzyme A carboxylase activity (42). Fatty acid oxidation via the leptin-AMPK axis also helps in relieving the lipotoxicity induced by the accumulation of lipid droplets in skeletal muscle and liver in lipodystrophy and obesity (126). Centrally, a leptin-mediated decrease in AMPK activity in the hypothalamus of mice resulted in decreased food intake and reduced body weight, both of which are contributory factors for improving insulin resistance (127). Thus, leptin lies at the interphase of lipodystrophy and obesity and, although providing a significant improvement of insulin resistance in lipodystrophy, has the potential of exerting similar effects in obesity provided the leptin resistance block can be overcome. Therefore, unlocking leptin resistance in obesity will allow leptin to perform its insulin-sensitizing function. Although the latter is easier said than done, an area of research that could provide significant and additional input into leptin resistance but that has been relatively underexplored is the transport of leptin through the blood-brain barrier. Studies have shown that the transport of leptin through the blood-brain barrier is saturable (128) and that the physiological defect in the New Zealand obese (NZO) mouse, which exhibits a polygenic obesity associated with hyperinsulinemia and hyperglycemia, appears to be insensitive to peripheral leptin administrations but responsive to its intracerebroventricular infusions. Thus, the phenotype of the NZO mouse results at least in part from decreased leptin transport to the brain (129).

Adiponectin

The role of adiponectin as a peripheral factor and its promising role as a hypothalamic factor parallel those of leptin in terms of sites of action even though leptin, unlike adiponectin, performs its role predominantly in the hypothalamus and to a lesser extent in the periphery. In addition, both leptin and adiponectin find common ground in their targeted actions on AMPK, whether centrally or in peripheral target tissues. Whereas leptin inhibits AMPK in the hypothalamus and activates it in the periphery, adiponectin mimics leptin in the periphery but antagonizes it in the hypothalamus. The interplay of leptin and adiponectin both in the hypothalamus and the periphery, along with the modulation of glucose uptake into peripheral tissues by RBP4 and resistin, should allow us to further our understanding of the control of energy metabolism by providing an adequate armament to unlock the mechanisms underlying insulin resistance in obesity and lipodystrophy.

Acknowledgments

I thank Jun Zhu and Robert Lustig for help and critical reading of the manuscript.

Received October 3, 2007. Accepted December 6, 2007.

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Disclosure Statement: The author has nothing to disclose.

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