

Role of leptin resistance in the development of obesity in older patients

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Abstract: Obesity is a global epidemic associated with aging-like cellular processes; in both aging and obesity, resistance to hormones such as insulin and leptin can be observed. Leptin is a circulating hormone/cytokine with central and peripheral effects that is released mainly by subcutaneous white adipose tissue. Centrally, leptin controls food intake, energy expenditure, and fat distribution, whereas it controls (among several others) insulin sensitivity, free fatty acids (FFAs) oxidation, and lipolysis in the periphery. Aging is associated with important changes in both the distribution and the composition of adipose tissue. Fat is redistributed from the subcutaneous to the visceral depot and increased inflammation participates in adipocyte dysfunction. This redistribution of adipose tissue in favor of visceral fat influences negatively both longevity and healthy aging as shown in numerous animal models. These modifications observed during aging are also associated with leptin resistance. This resistance blunts normal central and peripheral functions of leptin, which leads to a decrease in neuroendocrine function and insulin sensitivity, an imbalance in energy regulation, and disturbances in lipid metabolism. Here, we review how age-related leptin resistance triggers metabolic disturbances and affects the longevity of obese patients. Furthermore, we discuss the potential impacts of leptin resistance on the decline of brown adipose tissue thermogenesis observed in elderly individuals.

Keywords: leptin, obesity, aging, insulin sensitivity, brown adipose tissue

Introduction

Obesity is a worldwide socioeconomic concern. In 2013, the World Health Organization estimated that more than 1.4 billion adults are overweight and that more than 500 million are obese.¹ This poses major economic and public health issues as some of the leading causes of mortality (ie, cardiovascular diseases and cancer) are strongly associated with obesity.² Obesity also leads to a reduced lifespan and accelerates cellular processes similar to aging such as oxidative stress and disturbance in homeostatic pathways.³⁻⁵ One important feature of obesity and aging in relation to morbidity and mortality is the dysregulation of both white adipose tissue (WAT) and brown adipose tissue (BAT).^{6,7} Adipose tissue has the capacity to secrete a large number of bioactive substances named adipokines.⁸ These adipokines, such as leptin, adiponectin, tumor necrosis factor alpha (TNF α) and interleukin 6 (IL-6) have paracrine and/or endocrine functions and their dysregulation is a common ground for the development of insulin resistance, hypertension, and dyslipidemia.⁹ Another important common feature of obesity and aging is the development of resistance to certain hormones such as insulin and leptin, which triggers metabolic dysregulations such as type 2 diabetes and failure to regulate food intake as well as fat distribution.¹⁰ Since obese patients will make up

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an important proportion of the elderly population in the near future, it is important to determine the causes and effects of leptin resistance in age-related diseases.

Physiological role of leptin

Leptin, from the Greek “leptos” (thin), is a 16-kDa circulating protein with hormone/cytokine activities released by WAT, mainly subcutaneous fat.¹¹ However, other tissues such as ovaries, skeletal muscles, stomach, and BAT also secrete leptin.¹² There is a clear sexual dimorphism; women have higher circulating levels of leptin than men.¹³ Although some studies have postulated that these increased circulating levels of leptin in women were associated with their higher percentage of body fat when compared to men, others have demonstrated that higher leptin levels in women were independent of fat mass.¹⁴ These sex differences may be associated with a stimulating role of estrogen or a suppressing role of androgens on leptin production.^{15,16} Leptin circulates in the plasma as a free adipokine or bound to leptin-binding proteins, mainly its soluble receptor. In lean individuals, the great majority of leptin circulates in the bound form whereas it circulates in the free form in obese individuals.^{17,18} Physiologically, leptin is involved in regulating energy balance through central

actions, which is of importance particularly in a context of fat accumulation and metabolic disorders. Leptin also has many peripheral actions, mainly on the circulatory and respiratory systems, glucose homeostasis, and reproduction (Table 1).¹²

Leptin is a key regulator of energy balance^{19,20} as it acts in the brain to decrease food intake and increase energy expenditure (Figure 1).^{21–23} The actions of leptin in neurons are mediated by the long isoform of the leptin receptor (LEPR-B), a splicing variant member of the class I cytokine receptor family.²⁴ This variant is characterized by a long cytoplasmic region²⁵ allowing the activation of the Jak-Stat signal transduction pathway, which is crucial for leptin action.²⁴ LEPR-B is predominantly located in hypothalamic nuclei known to be involved in the regulation of energy balance, including the arcuate nucleus (ARC).^{26–29} LEPR-B is expressed in at least two distinct neuronal populations of the ARC. One population cosynthesizes the orexigenic (appetite-stimulating) neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the other synthesizes pro-opiomelanocortin (POMC).^{30–32} In addition to being an orexigenic peptide, NPY suppresses the central leptin-mediated growth and reproductive axes.³³ In turn, POMC is processed to produce α -melanocyte-stimulating hormone

Table 1 Summary of the main central and peripheral actions of leptin

Site of action	Specific effects	References
Immunity	Chemoattractant for macrophages Induce the production of proinflammatory mediators by macrophages and T-lymphocytes Proliferation and differentiation of hemopoietic precursors	59
Circulatory system	Platelet aggregation Angiogenesis Wound repair Increase blood pressure Increase heart rate	60–65
Lungs	Lung capacity and compliance Predictor of lung function	66–68
Skeletal muscle	Triggers β -oxidation Attenuates insulin-mediated lipogenic effects	69,70
Liver	Inhibits insulin binding Inhibits glucagon-activated cAMP production Profibrotic effect in hepatic stellate cells Increase the sensitivity to hepatic inflammation	71–75
WAT	Inhibits insulin binding Inhibits insulin-mediated effects on glucose transport, glycogen synthase activity and lipogenesis Stimulates lipolysis Pro-inflammatory cytokine	77–82
BAT	Increases the insulin-stimulated utilization of glucose	47,89
Reproduction	Inhibits insulin-induced estradiol production Follicular growth and maturation	91,92
Brain	Neuroendocrine/neuroprotective functions Decreases food intake Increases energy expenditure SNS activation Stimulates lipolysis	21–23,41,42,46,48,49

Abbreviations: WAT, white adipose tissue; BAT, brown adipose tissue; cAMP, cyclic AMP; SNS, sympathetic nervous system.

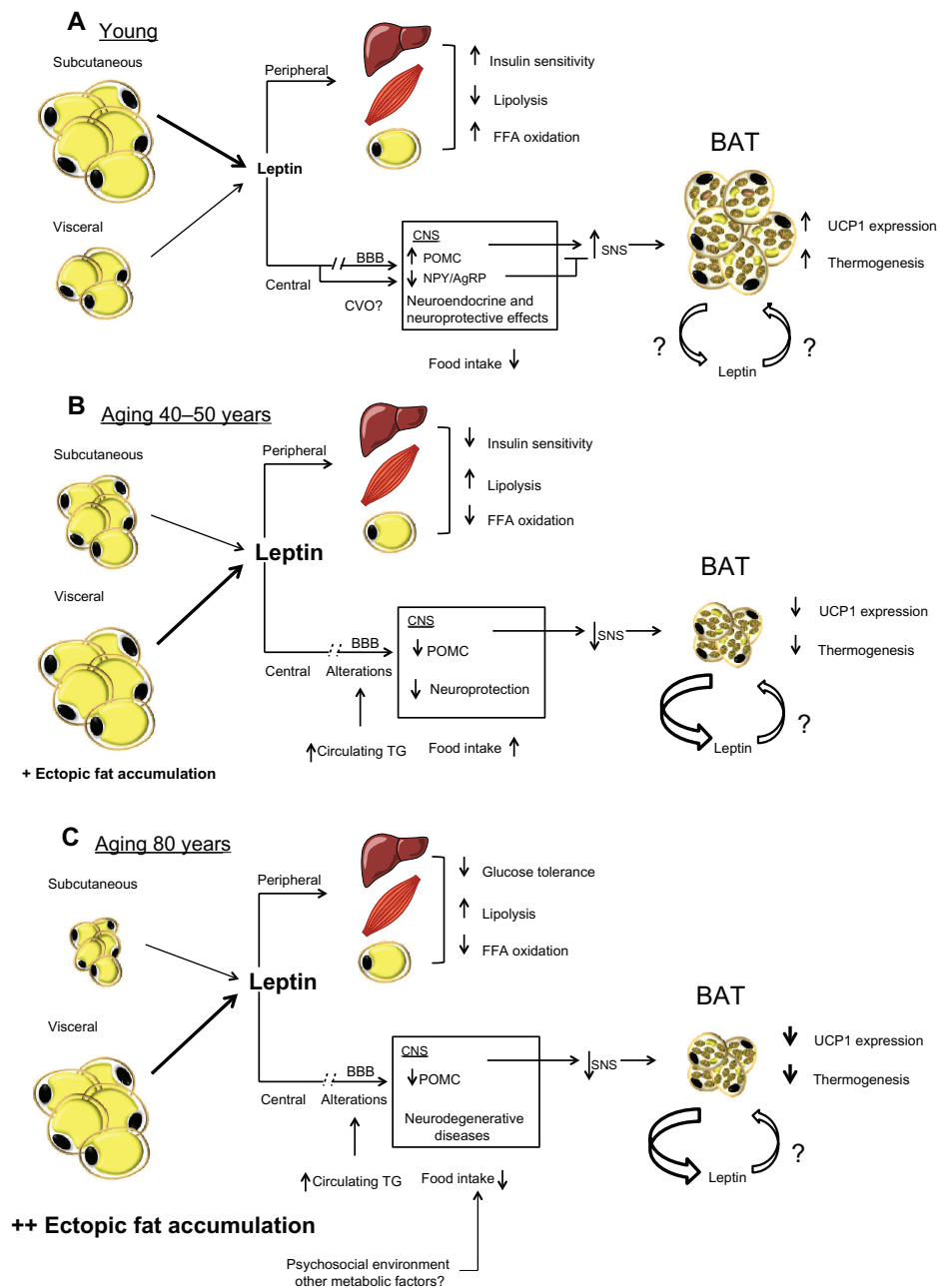


Figure 1 (A) Effects of leptin production in a young state. White adipocytes, mostly subcutaneous, secrete normal levels of leptin. Peripherally, leptin contributes to insulin sensitivity and free fatty acids oxidation in liver, muscle, and adipose tissue. Centrally, leptin reach its targets through its transport across the blood brain barrier provided by an active saturable transport system. Leptin is also transported through the circumventricular organs. Its binding to LEPRs expressed in the arcuate nucleus of the hypothalamus leads to an increase of POMC and a decrease of NPY/AgRP levels. This modulation of specific neuronal populations triggers SNS activation, which leads to an increase of UCP1 transcription and thermogenesis in BAT. (B) Effects of leptin production in middle-age condition. Subcutaneous fat begins to be redistributed and white adipocytes, mostly visceral, produce a high amount of leptin. Peripherally, leptin resistance develops in the liver, muscle, and adipose tissue and causes a decrease in insulin sensitivity and FFAs oxidation and an increase in lipolysis. Centrally, alterations in the blood brain barrier decrease leptin transport to the CNS, which leads to a reduction in the production of POMC. This diminution blunts SNS signaling and induces BAT atrophy and leads to a decrease in both UCP1 levels and thermogenesis. This BAT atrophy also contributes to an increase in leptin secretion. (C) Effects of old age on leptin secretion. The subcutaneous depot is atrophied and fat accumulates viscally and mostly in ectopic depots. High levels of leptin are secreted by visceral adipose tissue, concomitantly with an increase in glucose intolerance peripherally probably attributed to a loss of leptin signaling. Centrally, levels of POMC are still decreased, which leads to a more important atrophy of BAT and quiescent thermogenesis. Since BAT is inactive, levels of secreted leptin by this tissue are increased.

Abbreviations: BAT, brown adipose tissue; BBB, blood-brain barrier; FFA, free fatty acids; CNS, central nervous system; POMC, proopiomelanocortin; NPY/AgRP, neuropeptide Y/agouti-related peptide; UCP1, uncoupling protein 1; SNS, sympathetic nervous system; TG, triglycerides; CVO, circumventricular organs.

(α MSH), which leads to hypophagia by primarily activating the melanocortin-4 receptor (MC4R).^{34,35} AgRP is an antagonist of α MSH/MC4R signaling as well as an inverse agonist of MC4R activity itself.³⁶ NPY/AgRP neurons also

release γ -aminobutyric acid (GABA) and thus, can also negatively modulate POMC by a direct GABAergic synaptic mechanism.³⁷ Leptin modulates energy balance by promoting several neuronal responses involving inhibition of the

expression and secretion of NPY^{28,38} and stimulation of POMC synthesis.^{39,40} Consequently, microinjection of leptin into the ARC inhibits food intake.⁴¹ The involvement of leptin in the control of energy balance goes beyond food intake since leptin is also involved in energy expenditure by promoting BAT thermogenesis.²¹ A recent study showed a critical role for LEPR-B in the ARC in mediating the sympathetic nervous system (SNS) response to leptin.⁴² The role of leptin-induced activation of SNS-mediated BAT thermogenesis will be discussed in a later section.

Until recently and as described above, strong evidence suggested that the actions of leptin on energy balance were only due to its binding to LEPRs on AgRP/NPY and POMC neurons. However, since mice lacking LEPRs on either or both POMC and AgRP neurons develop very mild obesity,^{43,44} there are likely other leptin-responding neurons that contribute importantly to leptin's effects on energy balance. It has been shown that the effects of leptin on food intake and energy expenditure are also mediated by GABAergic neurons, raising the possibility that modulation of GABAergic output is a key aspect of leptin actions.⁴⁵ Moreover, leptin action on presynaptic GABAergic neurons decreases the inhibitory tone to postsynaptic POMC neurons, explaining in part the orexigenic and thermogenic POMC-dependent effects of leptin.⁴⁵ LEPRs-expressing GABAergic neurons are located in the ARC, where a small fraction are AgRP neurons, as well as in other hypothalamic nuclei known to be involved in energy balance regulation. However, although the investigation of these new first-order leptin-responsive neurons undoubtedly represents research perspectives, current knowledge mainly revolves around ARC NPY/AgRP and POMC neurons, which will be the focus of the present review. In addition to its effect on energy balance, central leptin is also involved in regulating peripheral lipid and glucose metabolism.⁴⁶ Indeed, it has been shown that intracerebroventricular administration of leptin significantly increases insulin sensitivity, glucose utilization, and glucose uptake in peripheral tissue including BAT.⁴⁷ Leptin also has neuroendocrine/neuroprotective functions; LEPRs are highly expressed in brain areas involved in learning and memory and leptin levels are associated with lower risk of dementia.^{48,49}

Initial knowledge with regards to leptin effects on energy balance derived from cross-circulation experiments called parabiosis in *ob/ob* and *db/db* mice, which showed that the *ob* gene was responsible for the generation of a circulating factor that regulates energy balance, and that the *db* gene encodes the receptor for this factor.⁵⁰ These mice weight up to three times more than normal mice and show remarkably

high levels of body fat, an obese phenotype now known to be attributed to a deficiency in leptin production or its receptor respectively.^{50,51} Although human leptin gene mutations are relatively rare, some cases result in morbid obesity.⁵² Administration of leptin either peripherally or centrally to *ob/ob* mice greatly reduces food intake and body weight.^{53,54} Moreover, a morbidly obese child who was found to have a mutation in the leptin gene was successfully treated with recombinant human leptin.⁵⁵ Therefore, in a context in which leptin is circulating at physiological levels, leptin-sensitive patients should have a normal body weight. Consequently, leptin acts as a feedback signal from body energy stores to the brain; circulating levels diminish during starvation, when fat depots are depleted to support the energy need of the organism, and increase during refeeding, when fat depots are replenished.⁵⁶ However, although absence of leptin leads to obesity, an excess of this hormone does not lead to a phenotype of leanness as theoretically expected. Indeed, leptin levels are found to be increased in obese humans and in several genetic and environmentally induced forms of rodent obesity,^{57,58} a state now commonly called leptin resistance, similar to the insulin resistance found in type 2 diabetes.

LEPR is also expressed in hemopoietic cells and studies showed that leptin could be linked to the proliferation and differentiation of hemopoietic precursors such as granulocyte-macrophage.⁵⁹ These effects of leptin have also been suggested to synergize with those of stem-cell factor (SCF) at least in primitive and progenitor cells.⁵⁹ Other reports propose a role for leptin in platelet aggregation, angiogenesis, and wound repair.^{60–62} Moreover, SNS activation by leptin goes beyond BAT thermogenesis, since leptin administration can increase heart rate and blood pressure in a dose-dependent manner.^{63,64} Elevated plasma leptin levels increase blood pressure in mice and plasma leptin concentration positively correlates with the sympathetic renal activation in humans, thus contributing to the development of hypertension.⁶⁵

Leptin is also implicated in respiratory control. The combination of leptin deficiency and profound weight gain in adult *ob/ob* mice can produce marked changes in the mechanics of respiration. In *ob/ob* mice, total lung capacity and lung compliance are 50% less than those of their wild-type counterparts.⁶⁶ *Ob/ob* mice develop a rapid breathing pattern when compared to age-matched wild-type mice and exhibit a depressed hypercapnic ventilatory response (HCVR).⁶⁷ These effects of leptin on ventilation were shown to be independent of obesity.⁶⁷ In humans, clinical studies provided some

evidence supporting these animal data. For example, leptin is a predictor of lung function in various conditions, including asthma and heart failure and correlates negatively with lung volume in chronic obstructive pulmonary disease patients.⁶⁸ However, the pathophysiological implications of leptin in the respiratory function in humans remain to be clarified. In rodent skeletal muscle, both leptin mRNA and leptin receptor have been identified. Leptin triggers skeletal muscle FFAs oxidation by selectively activating 5'-AMP-activated protein kinase and attenuates insulin-mediated lipogenic effects by 50%.^{69,70} Additional studies are needed to specify the role of leptin on immune cells development and angiogenesis considering that these two processes are implicated in the metabolic dysregulations associated with obesity. Importantly, the effects of the high circulating levels of leptin found in leptin resistant states on immune cells differentiation and the implications of this process on low-grade inflammation should be determined.

In the liver, leptin inhibits both insulin binding and glucagon-activated cAMP production.^{71–73} Additionally, leptin was shown to have a profibrotic effect in hepatic stellate cells.⁷⁴ This profibrotic effect was also described in a mouse model of hepatic steatosis where leptin was associated with an increase of CD-14+ Kupffer cell content.⁷⁵ However, in leptin-deficient lipodystrophic patients suffering from nonalcoholic fatty liver disease (NAFLD), administration of leptin improved their condition dramatically.⁷⁶ Taken together, these data suggest that the positive effects of leptin on triglycerides oxidation in the liver may overcome the effects of stellate and immune cells activation in the context of NAFLD. Since ectopic lipid storage is an important feature of aging, further studies are needed to better describe the effects of leptin on NAFLD. One important basic issue will be to determine whether mouse models of NAFLD are representative of an ectopic lipid storage disease and if findings can be translated to humans.

In WAT, leptin inhibits insulin binding and insulin-mediated effects on glucose transport, glycogen synthase activity, and lipogenesis.^{77,78} These effects can be observed when treating isolated rat adipocytes with recombinant leptin as it affects insulin sensitivity and alters important metabolic effects of insulin.⁷⁹ Leptin can stimulate lipolysis as well; these effects have been demonstrated both in vitro and in vivo in mouse models.^{80,81} In WAT, leptin also functions as a proinflammatory adipokine by acting as a chemoattractant for macrophages⁸² and by inducing the production of proinflammatory mediators from macrophages and T lymphocytes such as TNF α and IL-6.⁸³ TNF α interferes with preadipocyte differentiation and causes lipolysis, decreases size, and reduces insulin responsiveness

in adipocytes.⁸⁴ Considering the similarity between some of their responses, differentiating between central and peripheral effect of leptin on adipose tissue can be difficult. Consistently, this subject is still a matter of debate. Some studies showed that leptin's actions on lipolysis and insulin sensitivity in WAT are not mediated by the central nervous system since leptin can act on denervated fat.⁸⁵ Others have determined that leptin also regulates WAT via the central nervous system considering that intracerebroventricular leptin infusion leads to lipolysis in WAT, as shown by a decrease of stearyl-coenzyme A-desaturase-1 expression and an increase in hormone-sensitive lipase expression.^{86,87} At the whole-body level, leptin has a strong, positive influence on glycemia; this subject was recently thoroughly reviewed elsewhere.⁸⁸ Interestingly, leptin actions on lowering glycemia were suggested to be partly mediated via insulin-like growth factor (IGF)-binding protein 2, an established modulator of the IGF-1 pathway. Leptin also exerts peripheral effects on BAT since peripheral, but not central, administration of leptin in rats increases the insulin-stimulated utilization of glucose in BAT.⁸⁹

Finally leptin plays an important role in reproduction.⁹⁰ LEPR is expressed in both ovary and prostate and leptin can inhibit insulin-induced estradiol production by granulosa cells from bovine follicles.⁹¹ Moreover, a significant increase of circulating leptin levels is observed during ovarian hyperstimulation, which suggests that leptin plays a role in follicular growth and maturation.⁹² These observations can also be translated to animal models since infertility is a phenotype observed in both male and female leptin-deficient *ob/ob* mice. In this model, circulating reproductive hormones are decreased in females, but it is possible to restore fertility with repeated injections of human leptin.^{93,94} Further studies will be necessary to determine the exact role of leptin in male fertility and the role of androgens in the control of leptin expression.

Aging and inflammation in adipose tissue

Aging is associated with an important redistribution of fat among the different depots. Body weight usually increases until middle age (30–50 years old) and declines thereafter.⁹⁵ In contrast, total fat mass peaks in early and middle old age (40–70 years old), which results in an increased percentage of body fat (Figure 2).⁹⁶ This increased percentage of body fat is the consequence of both the increase in fat mass and the loss of fat-free mass encountered in the elderly, mainly in skeletal muscle and bone. Aging-associated redistribution of adipose tissue from the subcutaneous depot to the visceral compartment and ectopic sites namely muscle, liver, and

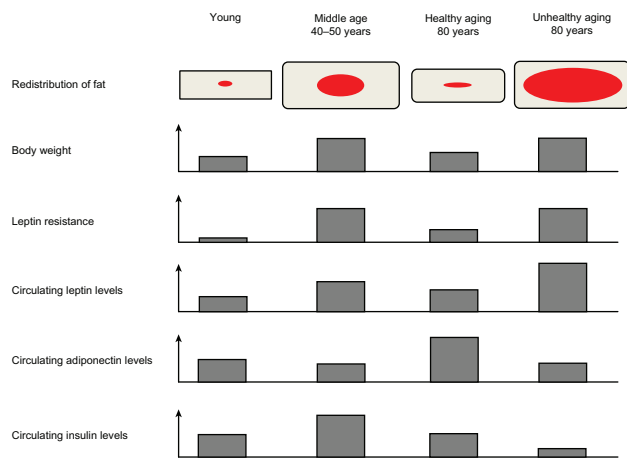


Figure 2 Representation of the different modifications regarding the redistribution of body fat, body weight, leptin resistance, and circulating levels of leptin, adiponectin, and insulin in conditions of youth, middle age, healthy aging, and unhealthy aging. Red and grey represent visceral and subcutaneous adipose tissue, respectively.

bone marrow has been shown to happen in subjects over 85 years old.⁹⁷ This redistribution may potentially contribute to age-related dysfunction of these tissues^{98,99} but also has strong metabolic implications, since visceral adiposity and intramuscular lipid accumulation are markers of impaired glucose metabolism independently of adiposity.¹⁰⁰ Aging is also associated with loss of BAT activity and brown preadipocyte dysfunction in rodents and humans.^{101–103} This process may contribute to energy imbalance since BAT is a thermoregulatory organ. Interestingly, leptin is also expressed in brown adipocytes. This expression seems to be only under conditions of inactivity and atrophy¹⁰⁴ considering that cold and activation of β_3 adrenoreceptors both decrease leptin gene expression.¹⁰⁵ Ueno et al showed that BAT thermogenic capacity and activity are diminished in both lean and obese old mice, but particularly in the

obese ones. These observations suggest a synergy between aging and obesity in the context of leptin secretion and BAT thermogenesis.¹⁰⁶

The different fat compartments undergo changes at different rates during aging (Table 2).¹⁰⁷ Retro-orbital and peripheral subcutaneous adipose tissue tend to be lost first during aging whereas visceral fat tends to be preserved.¹⁰⁸ Since subcutaneous adipose tissue is the principal source of leptin,¹⁰⁹ its loss reduces leptin's capacity for β -oxidation of FFAs, which contributes to the increase of circulating FFAs upon aging. In turn, increased levels of circulating FFAs favor visceral and ectopic fat redistribution.¹¹⁰ Age-associated decline in fat depot size appears to be the result of a decrease in cell size as opposed to a decline in cell number.⁹⁶ However, other reports have also noted a negative association between age and proliferation of subcutaneous preadipocytes, which may explain selective loss of subcutaneous adipose tissue with aging.¹¹¹ Adipogenesis is likely to occur throughout the lifespan since adipocyte numbers remain constant or even increase in old age.^{107,112} However, during aging, preadipocytes experience a decrease in their potential to differentiate and replicate.¹¹³ Preadipocytes are precursor cells found in adipose tissue; they have the potential to differentiate, store triglycerides, respond to insulin, and secrete adipokines.¹⁰⁷ In normal adipose tissue, fat mass is regulated by apoptosis and differentiation of preadipocytes.¹¹⁴ However, differentiation of preadipocytes isolated from aged rats and humans leads to a decrease of lipid accumulation and smaller fat cells when compared to preadipocytes from younger individuals.^{115,116} Since control for lipolysis is altered in fat cells upon aging,^{117,118} a decrease in lipid accumulation capacity could be a particularly important contributing factor for reduced adipocyte size. Thus, these age-related

Table 2 Modifications observed in different adipose tissue depot during aging

Characteristics	Subcutaneous WAT	Visceral WAT	BAT
Adipocyte size	Young: – Middle age: ++ Old age: +	Young: – Middle age: ++ Old age: +	Young: + Middle age: +/- Old age: –
Proportion of the depot	Young: + Middle age: ++ Old age: –	Young: – Middle age: + Old age: ++	Young: ++ Middle age: + Old age: –
Leptin secretion	Young: + Middle age: + to ++ Old age: ++	Young: +/- Middle age: + Old age: ++	Young: – (?) Middle age: +/- (?) Old age: + (?)
Relative contribution to circulating leptin levels	Young: ++ Middle age: + Old age: –	Young: – Middle age: + Old age: ++	Young: – Middle age: – Old age: +/- (?)

Note: Question marks indicate that these subjects need to be further investigated. The minus signs represent a small size or amount whereas the plus signs indicate an important (+) to very important (++) size or amount.

Abbreviations: WAT, white adipose tissue; BAT, brown adipose tissue.

intrinsic factors could affect fat mass by influencing both preadipocytes and adipocytes.

Changes in fat distribution associated with aging also lead to a modification of the secretion profile of adipokines. Circulating levels of inflammatory cytokines such as TNF α , C-reactive protein, and IL-6 are elevated in both aging and obesity.¹¹⁹ High plasma leptin levels are observed in aging rodent models^{120,121} as well as in humans^{122,123} suggesting that aging is a leptin-resistant state. Although normal aging involves a decline in appetite,¹²⁴ hyperleptinemia observed in the elderly may serve to counterbalance the decrease in hypothalamic responsiveness found in both animal and human models of aging.¹²⁵ This decrease leads to a poor response to fasting and plays a causative role in the intolerance to catabolic situations.¹²⁴ Increased fat mass may also contribute to elevated leptin in aging, but the increase is often disproportionate to the amount of fat. Consistently, leptin resistance during aging has been shown to be independent of fat mass in rats.¹²⁶ Via its proinflammatory adipokine function, leptin also plays an important role in adipose tissue inflammation through preadipocytes activation. When preadipocytes are activated, they likely make a greater contribution to age-related adipose tissue dysfunction because of their number (15%–50% of cells in fat).¹²⁷ They have full innate immune response capability, considering that they constitutively express toll-like receptor (TLR) 4 as adipocytes, but express TLR2 in a specific manner. This may contribute in part for the greater inflammatory responsiveness of preadipocytes compared to that of fat cells.¹²⁸ Consistent with those findings, other reports suggest that cytokines and chemokines are expressed predominantly in preadipocytes rather than in adipocytes.^{128,129} Activated preadipocytes can even acquire a macrophage-like phenotype.¹³⁰ This plasticity predisposes them to contribute to adipose tissue inflammation and dysfunction.¹³⁰ Stressed preadipocytes may promote an inflammatory response leading to dysfunctionalities in adipose tissue as well as metabolic abnormalities.

The release of various cytokines and chemokines in adipose tissue attracts immune cells such as proinflammatory T lymphocytes and macrophages. Infiltration of visceral adipose tissue by macrophages is increased in both obese and lipodystrophic subjects.^{131,132} The macrophages also experience a shift of their activation: anti-inflammatory IL-10-producing M2 macrophages are replaced by proinflammatory M1 macrophages.¹³³ Macrophage infiltration is preceded by the infiltration of proinflammatory T lymphocytes and mast cells, and the decrease of anti-inflammatory T lymphocytes subtypes. This infiltration of immune cells also contributes

to the production of proinflammatory cytokines, leading to a vicious circle. Although adipose tissue modifications caused by aging and obesity lead to highly similar metabolic abnormalities, the underlying mechanisms differ between the two conditions.^{134,135} Age-related metabolic dysfunctions cannot be explained completely by either the lipotoxicity associated with impaired lipid storage or by the increase in immune effectors. A combination of different mechanisms including, but not limited to, lipotoxicity caused by FFAs, inflammation and incapacity to store lipids may be responsible for the dysfunction of adipose tissue during aging.

Association of leptin, insulin sensitivity, and longevity

Adipokines from centenarians have been investigated and, in general, the subjects studied were lean (body mass index [BMI] of 19.4 ± 3.3) and exhibited low levels of plasma leptin which was an indicator of their low adipose tissue mass.¹³⁶ However, the lowest tertile of circulating leptin was surprisingly associated with higher all-cause mortality and, remarkably, these effects of low leptin levels on mortality were emphasized in patients with higher BMI.¹³⁶ Thus, maintaining adipose tissue mass and function, mainly by keeping a functional leptin signaling, seems to be essential for normal physiological functions under energy-deprived conditions associated with aging.¹³⁷ The role of leptin in sexual maturation makes associations between circulating leptin levels and longevity difficult since there is a positive correlation between age of reproduction and lifespan.¹³⁸ In rodents, caloric restriction delays both sexual maturity and aging.¹³⁹ Consistently, delayed sexual maturity and aging are observed in most animal models carrying a genetic mutation in the genes of the IGF1 pathway.¹⁴⁰ These studies suggest that genes implicated in the regulation of sexual maturation include a subset of pleiotropic genes that mediate the trade-off between development and aging.¹⁴¹ The expression of other adipokines, like adiponectin, has also been associated with healthy aging and increased lifespan. Adiponectin, a hormone secreted exclusively by WAT, has circulating levels inversely associated with percent body fat in adults.¹⁴² Centenarians have higher plasma adiponectin concentration than BMI-matched younger adults.¹⁴³ This hyperadiponectinemia in centenarians is also associated with a positive metabolic profile.¹⁴³ Furthermore, two common variants of the adiponectin gene have been associated with higher adiponectin levels and longevity.¹⁴³ Adiponectin levels were also inversely correlated with BMI, waist circumference, the percentage of body fat and with the homeostasis model assessment for insulin resistance, a marker of insulin resistance.^{143,144}

In addition to adiponectin levels, insulin sensitivity has also been identified as an important component of longevity and healthy aging.

Several studies have been conducted on centenarians to better characterize the healthy aging phenotype.^{145,146} Numerous pathways have been identified and insulin sensitivity has been considered a key factor for healthy aging.¹⁴⁷ In humans, insulin sensitivity decreases with advancing age and, accordingly, prevalence of type 2 diabetes increases with aging.¹⁴⁸ When compared to elderly individuals over 75 years of age, centenarians have better preserved glucose tolerance and insulin sensitivity.¹⁴⁹ Certain epidemiological evidence may provide a mechanistic insight into insulin sensitivity in centenarians: healthy centenarians with preserved insulin sensitivity have been shown to have a lower waist-to-hip ratio and a more favorable body fat content than their elderly controls.¹⁵⁰ To test this hypothesis, numerous models have shown that improving insulin sensitivity leads to an increased longevity. Modifying adipose tissue either genetically, surgically or by caloric restriction has important effects on lifespan and age-associated diseases onset. Mice with fat-specific disruption of the insulin receptor gene (FIRKO mice) have decreased adiposity and lower fasting insulin levels, which lead to an extended lifespan. Concomitantly, FIRKO mice also have elevated serum adiponectin levels.¹⁵¹

Modification of adiposity is also possible without genetic modifications through caloric restriction. For more than 75 years, caloric restriction without malnutrition has been noted to prolong lifespan.¹⁵² This modification of caloric intake leads to an important loss of adipose tissue, especially visceral fat.¹⁵³ The Barzilai group showed that surgical removal of visceral adipose tissue in rats increased lifespan and improved both insulin resistance and glucose intolerance.^{154,155} Comparatively, genetic interventions aimed at reducing fat mass are also associated with increased lifespan. For example, replacing the adipogenic transcription factor CCAAT/enhancer-binding protein α (C/EBP α) with C/EBP β in mice results in an increase in FFAs oxidation and reduced fat mass which leads to an extension of mean and maximal lifespan.¹⁵⁶ These animal models reveal that lifespan is closely related to adiposity. Taken together, these data show that reduced adiposity combined with hyperadiponectinemia and insulin sensitivity constitutes an important conserved pathway implicated in prolonged lifespan (Figure 2). However, aging has often been associated with leptin and insulin resistance. These

conditions have been linked to metabolic disorders and associated with age-related diseases, which increase morbidity and mortality.

Leptin resistance and development of disease in old age

The discovery of leptin has brought the long-awaited dream for a potential cure, which could induce satiety and weight loss in obese humans. This hope faded after the first observations of leptin resistance.^{157–159} Indeed, the magnitude of the weight loss achieved with leptin therapy in most obese individuals was modest compared to expectations, as most obese patients already exhibited elevated circulating levels of leptin as a consequence of their increased fat mass.⁵⁶ Generally, leptin resistance is described as a reduced sensitivity with respect to the anorectic response to exogenously administered leptin,¹⁶⁰ but a universally accepted definition of this condition is currently under consideration by the National Institutes of Health.¹⁶¹ The identity of the underlying mechanisms of leptin resistance still remains unclear, but at least three possibilities have been postulated to underlie it: (1) a failure of circulating leptin to reach its targets in the brain; (2) a decrease in the expression of LEPR; and/or (3) an inhibition of the signaling events within selected neurons in specific brain regions.^{33,56,162,163} The former hypothesis in itself establishes a debate, as the mechanisms by which leptin achieves its targets in the brain are controversial. Leptin is transported across the blood–brain barrier (BBB) by an active saturable transport system, but some suggest an action also attributed to the BBB-exempted circumventricular organs.^{164,165} Decreased leptin transport across the BBB has been demonstrated in diet-induced obesity rodents¹⁶⁶ and leptin resistance may be partly overcome by bypassing the BBB with intracerebroventricular injection of leptin.¹⁶⁷ Moreover, cerebrospinal fluid levels of leptin are lower in obese individuals, in spite of high serum leptin levels, reinforcing the view of an impaired transport into the brain.¹⁶⁸ Triglycerides have also been shown to mediate resistance to leptin by impairing the transport across the BBB.¹⁶⁹ In addition to the contribution of a defective leptin transport, it is also suggested that a decreased number of LEPR-B, impaired signal transduction with old age, as well as a decrease in POMC with aging could also contribute to leptin resistance.^{170–172}

Aged obese rats exhibit little or no anorectic or weight loss responses to peripherally infused leptin whereas young rats respond more robustly to leptin administration.^{121,172,173} Moreover, plasma leptin levels are high in aged animals and humans, thus suggesting that a failure in leptin action

may represent one of the primary defects in the metabolic dysfunctions observed in aging.^{10,126} Failure of action of leptin with aging is also evidenced in the transgenic mouse model that overexpressed leptin since despite continuous secretion of leptin, aged mice showed an increase in body weight.¹⁷⁴ Furthermore, a decreased number of LEPR-B has been demonstrated in the hypothalamic nuclei of old rats.^{170,172} Consistently, leptin injections failed to decrease body weight and hyperglycemia adequately in middle-aged obese and diabetic subjects.^{175,176} This suggests that leptin resistance also affects glycemic control. One other interesting way to determine the effects of leptin resistance during aging is to study the leptin receptor deficient *db/db* mice longitudinally. In this model, young animals (5–6 weeks) are normoglycemic because their peripheral insulin resistance is overcome by an increase in insulin secretion. This hyperinsulinemia usually occurs for 2 to 3 months and is then followed by a rapid increase in glycemia, reflecting a defect in β -cells secretion.¹⁷⁷ Aging in *db/db* mice is also characterized by an important increase in plasma FFAs,¹⁷⁸ higher mean arterial pressure,¹⁷⁹ and lower hepatic insulin-binding capacity.¹⁸⁰ Associated with the already well described important weight gain of *db/db* mice, these metabolic factors contribute to the alteration of cardiac metabolism in favor of fatty acid oxidation and the progressive development of a cardiomyopathy.¹⁷⁸ Whether these important age-related metabolic effects are directly mediated by leptin resistance or triggered by the consequent WAT accumulation still needs to be determined. Taken together, these data suggest that youth is associated with leptin sensitivity and that resistance to leptin occurs with aging. Aging is thus associated with failure in leptin's action, independent of obesity or changes in body fat distribution.¹²⁶ The failure of leptin to regulate food intake, body fat and its distribution, and insulin action suggests that leptin resistance plays a major role in the metabolic syndrome that is typical to aging.

Leptin also regulates the excitability of inter alia hippocampal neurons as well as synaptic plasticity,⁴⁹ demonstrating its involvement in neuroendocrine functions. Moreover, LEPR-B has been identified in neurons of the hippocampus, which are particularly vulnerable in Alzheimer disease (AD).¹⁸¹ AD is a progressive neurodegenerative disease that involves a variety of symptoms such as progressive impairment of cognitive function, and impaired orientation and attention.¹⁸² Several reports from various clinical studies support the idea of a negative correlation between obesity and cognitive function, as well as a positive association between reduced levels of circulating leptin and

risk for AD.^{182,183} Moreover, higher leptin levels are associated with lower risk of dementia and AD and less cognitive decline.^{184,185} Mice with targeted disruption of LEPR-B show a decreased synaptic plasticity associated with a poorer performance on spatial memory tasks,¹⁸⁶ reinforcing the view that leptin has an undoubted neuroprotective implication. Since obesity worsens cognitive functions and leptin protects against neurodegeneration, higher prevalence of AD in obese elderly patients¹⁸⁷ might be explained, in addition to low-grade inflammation and factors contributing to amyloidogenesis, by the presence of leptin resistance. Indeed, a large prospective study showed that aged individuals with the lowest leptin levels had a greater decline in their cognitive ability than those with the highest levels.¹⁸⁵ Moreover, central obesity in midlife increases the risk of dementia later in life independently of comorbidities such as type 2 diabetes or cardiovascular diseases, indicating that leptin deficiency is commonly observed in AD and is somehow associated with obesity characterized by leptin resistance.¹⁸³ Leptin also raises many research interests regarding its possible involvement in Parkinson's disease, epilepsy, and ischemia.¹⁸¹ All these lines of evidence suggest that leptin protects, at least indirectly, against age-related neuroendocrine/cognitive functions decline.¹⁸²

Leptin resistance and the loss of BAT activity upon aging

BAT is a specialized fat depot with incredible thermogenic potential.^{188,189} It is found in relative abundance in small eutherian mammals, allowing them to live in cold environments without relying on the shivering process to produce heat.¹⁹⁰ Brown adipocytes are characterized by multilocular lipid droplets and a high density of mitochondria, which contain uncoupling protein 1 (UCP1). UCP1 is located in the inner membrane of the mitochondria and uncouples substrate oxidation from adenosine triphosphate (ATP) synthesis, thereby providing the BAT capacity for nonshivering thermogenesis by dissipating energy as heat instead of generating ATP.¹⁸⁸

Until recently, BAT was thought to disappear rapidly after birth in humans and play only a minimal physiological role in adults.^{191,192} However, recent evidence involving imaging procedures has brought a whole new perspective to the involvement of BAT in adults.^{193,194} In nuclear medicine, since fat and tumors capture the radioisotope ¹⁸fluorodeoxyglucose in the same way, brown fat has long eluded researchers.¹⁹⁵ The use of combined positron emission tomography and computed tomography scanning has revealed the presence

of a metabolically active fat depot in adult humans.¹⁹⁵ BAT presence and activity are prevalent at a young age and remain present throughout adulthood, before declining robustly at an older age.^{196,197} Accordingly, BAT prevalence is higher in people younger than 50 years of age compared to patients older than 64 years.¹⁹⁴ A prospective study also showed that adolescents exhibit a higher prevalence of BAT (40%) compared to adults (5%–10%).¹⁹⁸ Thereby, all these lines of evidence suggest a protective role of BAT against age-related obesity. This age-related decline in BAT is thought to be the result of a gradual reduction of the amount of active BAT, followed by a reduction in the function and sensitivity at older age.¹⁹⁹ Unfortunately, the exact timing of the age-related decline in BAT is still undetermined as well as the possible impact that age-related leptin resistance could exert on it. Different assumptions suggesting that age-related leptin resistance could affect the decline of BAT observed in elderly individuals are discussed below.

The age-associated decline in thermoregulation (Figure 1)^{195,200} has been related to BAT atrophy associated with a loss of UCP1 activity and has been shown to be influenced by sex, as females show a more important loss of thermogenic capacity with advancing age than males.²⁰⁰ In this view, *ob/ob* mice have lower metabolic rate and a lower body temperature than their lean counterparts and are unable to survive for more than a few hours when exposed to cold due to a failure in thermogenesis.²⁰¹ BAT of the *ob/ob* mouse is usually thermogenically inactive, relatively atrophied, and has little UCP1, indicating that leptin deficiency leads to reduced BAT activity.¹⁰⁶ Furthermore, BAT thermogenesis is triggered by the activation of the SNS, which abundantly innervates BAT.^{188,202} SNS nerve endings in BAT release noradrenaline, which activates β -adrenergic receptors and a downstream cascade of events leading to BAT cell proliferation, mitochondrial biogenesis, and increased expression and activation of UCP1.¹⁸⁸ In addition, BAT-mediated thermogenesis induced by noradrenaline is significantly decreased in old rats compared to their younger controls¹⁰³ and impairment of brown adipocytes function with increasing age appears to be mediated, at least in part, by a disturbance in the intracellular adrenergic signaling.^{203,204} It is possible that a selective reduction in the SNS activity/sensitivity of BAT occurs with aging, even if paradoxically human SNS activity is generally increased in older individuals, at least in specific context such as at the cardiovascular level.²⁰⁵ The hypothesis of a selective reduction in SNS–BAT activity comes from the observations that selective neuronal circuits control SNS-mediated BAT thermogenesis in rodents.²⁰⁶

However, although it remains unclear whether such selectivity in SNS–BAT activity also exists in humans, it is known that leptin regulates SNS outflow to peripheral organs including BAT, suggesting that age-related leptin resistance could be related to this SNS–BAT activity reduction.²⁰⁷

In addition to stimulating food intake, NPY is known to suppress thermogenesis in BAT.^{208,209} Leptin increases energy expenditure through increasing thermogenesis in BAT and inhibits NPY, suggesting that age-related decrease in BAT activity could be the result of the inability of leptin to inhibit NPY-suppressed BAT thermogenesis. Moreover, aging is characterized by a significant decrease in POMC,¹⁷¹ which is activated by leptin and implicated in the activation of BAT thermogenesis mainly through α MSH/MC4R signaling, suggesting another plausible mechanism that can attribute the decline of BAT activity to leptin resistance. Absence of MC4R has also been shown to compromise the ability of leptin to increase UCP1 expression in BAT.²¹⁰ Several studies have demonstrated that changes in circulating levels of sex and thyroid hormones may contribute to age-related decline in BAT.^{211,212} Indeed, thyroid hormones have direct stimulatory effects on UCP-1 expression and enhance the adrenergic signaling to BAT.²¹³ However, the possible involvement of age-related leptin resistance in thyroid receptor hormone-mediated BAT activity needs further studies. This avenue represents a promising future for a better comprehension of the effect of leptin resistance associated with age-induced reduction of BAT thermogenesis. Age-related leptin resistance could selectively affect the SNS-BAT activity, as well as the NPY and/or POMC/ α MSH/MC4R modulation of BAT thermogenesis.

Conclusion

Leptin resistance and aging seem to be strongly intertwined. Both in the brain and in the periphery, the physiological actions of leptin experience a decrease during advancing age. The redistribution of adipose tissue and increased percent body fat observed during middle and old age contribute however to an increase in circulating leptin. This suggests that leptin resistance in aging is not overcome by an increase in leptin levels. Once established, leptin resistance increases adipose tissue inflammation through preadipocytes activation and seems to negatively impact cognitive function. When comparing the effects of leptin resistance to the metabolic dysfunctions observed in aging, leptin resistance appears to be an early contributor to the development of metabolic abnormalities in old age. Leptin resistance also exerts important functional impairment on

BAT; this decrease in thermogenesis may act in synergy with the robust age-associated decline of BAT prevalence to contribute to the negative metabolic changes associated with unhealthy aging.

Studies on leptin show that this hormone is central to the dysregulations observed in aging and obesity. Whether leptin plays an important role in longevity is still to be determined, but since leptin resistance and aging share common metabolic alterations, its role in morbidity is very likely. Taking into account the important fat redistribution associated with aging, numerous questions are still unanswered considering leptin secretion and autocrine actions, particularly in BAT. Although it is now recognized that BAT remains present during adulthood, available data do not allow a causal relationship between BAT atrophy and increasing body weight with aging. A role for leptin resistance has not yet been defined in this weight-gain process. Preventing leptin resistance and/or counteracting the effects of aging on BAT decline represent a plausible therapeutic approach to prevent age-related metabolic alterations. To our knowledge, no drug is currently available for these applications. However, exercise could be a large-scale and affordable manner of maintaining leptin signaling and BAT functionality. Importantly, understanding the mechanisms underlying age-related leptin resistance and involved in modulating BAT activity is an unavoidable prerequisite before trying to treat metabolic disorders that life reserves.

Acknowledgments

Research related to the subject of this paper in F Picard laboratory was funded by grants from the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research. F Picard holds a Senior Scholar Award from the Fond de recherche du Québec-Santé (FRQ-S). S Carter holds a FRQ-S PhD studentship. A Caron holds a Canadian Institutes of Health Research training program PhD studentship.

Disclosure

The authors declare no conflicts of interest in this work.

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