



Lipid overload and overflow: metabolic trauma and the metabolic syndrome

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Approximately two-thirds of the US population are overweight, which means that insulin resistance is probably the most common metabolic abnormality in the USA. I propose three novel concepts concerning the causes and consequences of insulin resistance that challenge current thinking. First, there is the evidence that resistance to insulin-stimulated glucose metabolism is not a primary event in obesity, but is secondary to lipid accumulation resulting from full responsiveness to insulin-stimulated lipogenic activity. Second, resistance to insulin-stimulated glucose metabolism, now considered detrimental to health, might be a protective mechanism that reduces lipid-induced damage to tissue by excluding glucose from cells, thus decreasing glucose-derived lipogenesis. Third, I suggest that lipid-induced insulin resistance and the accompanying metabolic syndrome are secondary to leptin resistance, resulting in breakdown in the normal partitioning of surplus lipids in the adipocyte compartment.

Researchers working on insulin resistance and its syndrome [1], more commonly referred to as 'metabolic syndrome' or 'syndrome X', have generated 17 000 published papers, >6000 of which have been published since 2000. This profusion of publications parallels the alarming increase in the prevalence of this obesity-associated disease complex (Box 1), reported to afflict 47 million people in the U.S.A [2].

Here, three issues relating to insulin resistance are addressed. First, I argue that the phrase 'insulin resistance of obesity' is an oxymoron given that resistance to insulin-stimulated lipogenesis would prevent the development of obesity. Second, I suggest that resistance to insulin-stimulated uptake of surplus glucose, widely considered to be the cause of the syndrome, might be a defense against lipid overaccumulation in lean tissues, protecting against or delaying the onset of severe features of the insulin resistance syndrome. Third, I propose that the underlying cause of the metabolic syndrome is loss of leptin action (i.e. that the insulin-resistance syndrome is a leptin-resistance syndrome).

Insulin resistance of obesity as an oxymoron

The term 'insulin resistance of obesity', as used currently, refers to resistance to insulin-stimulated glucose disposal, not to the many other actions of this

hormone. The development and maintenance of obesity requires the lipogenic action of insulin, which makes the term 'insulin resistance' oxymoronic, unless it is modified by the adjective 'glucometabolic' to emphasize that the resistance refers to insulin-stimulated glucose metabolism, and does not include insulin-stimulated lipogenesis [3].

Binding of insulin to its receptors in skeletal muscle and adipose cells normally initiates a phosphorylation cascade culminating with the translocation of the glucose transporter, GLUT-4, from intracytoplasmic vesicles to plasma membrane [3], thereby facilitating glucose entry into the cell (Fig. 1a). After phosphorylation to form glucose-6-phosphate, glucose is either stored as glycogen or enters the glycolytic pathway to form pyruvate. Pyruvate is irreversibly decarboxylated to acetyl CoA (See glossary) and enters the mitochondria for oxidation in the citric acid cycle forming CO₂ and H₂O. Any unoxidized surplus is returned to the cytosol via the acetyl-group shuttle and carboxylated to malonyl CoA, the first intermediate in the pathway of fatty acid (FA) synthesis. In addition to being a lipogenic substrate, malonyl CoA inhibits the mitochondrial enzyme, CPT-1 [4]. This reduction of FA oxidation by malonyl CoA is referred to as the McGarry effect (Fig. 1a).

In addition to stimulating the uptake of glucose, insulin induces expression of the enzymes of lipogenesis through upregulation of the lipogenic transcription factor, SREBP-1c [5,6], thereby providing the enzymatic machinery

Glossary

- 11-β-HSD:** 11β-hydroxysteroid-dehydrogenase.
- ACC:** acetyl CoA carboxylase.
- Akt1:** protein kinase.
- AMPK:** adenosine monophosphate activated kinase.
- Bcl2:** β cell leukemia.
- CGL:** congenital generalized lipodystrophy.
- CoA:** coenzyme A.
- CPT-1:** carnitine palmitoyl transferase-1.
- DIO:** diet-induced obesity.
- GLUT-4:** glucose transporter-4.
- HAART:** highly active antiretroviral therapy for AIDS.
- IRS:** insulin receptor substrate.
- LP:** lipoproteins.
- PI-3-kinase:** phosphoinositide 3-kinase.
- PPAR:** peroxisome proliferation-activated receptor.
- PTP-1B:** protein tyrosine phosphatase-1B.
- SOCS-3:** suppressor of cytokine signaling-3.
- SREBP-1c:** sterol regulatory element binding protein-1c.
- TG:** triglycerides.
- ZDF:** Zucker Diabetic Fatty.

Box 1. Components of the metabolic syndrome

- (1) Obesity
- (2) Hyperlipidemia
- (3) Coronary artery disease
- (4) Fatty heart
- (5) Hypertension
- (6) Insulin resistance
- (7) Diabetes (type 2)

for *de novo* synthesis of fat. Ironically, insulin-responsive SREBP-1c and its lipogenic target enzymes are expressed at higher levels in tissues of so-called 'insulin-resistant' obese rats with defective leptin receptors than in tissues of the 'insulin-sensitive' control animals [7]. This implies that the tissues of insulin-resistant animals are not resistant to insulin-stimulated lipogenesis and fits with the idea that glucometabolic insulin resistance is secondary to the overaccumulation of lipids [8].

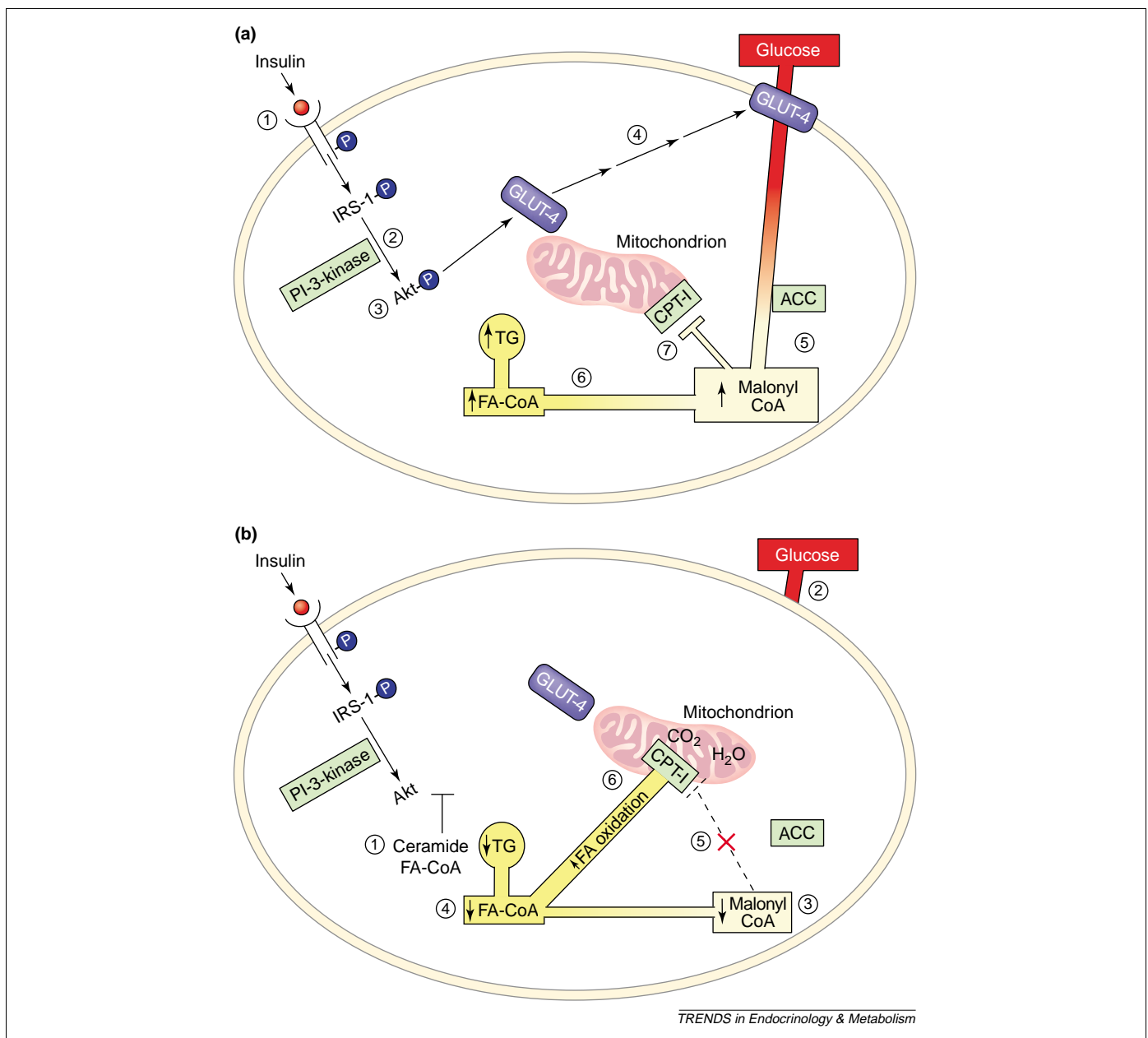


Fig. 1. (a) Glucometabolic insulin resistance development through increased insulin-stimulated lipogenesis. Insulin action begins when it binds to its receptor (1). This initiates a tyrosine phosphorylation cascade in which Insulin receptor substrate-1 (IRS-1)-associated phosphoinositide 3-kinase (PI-3-kinase) activity (2) and phosphorylation of Akt1 (3) are crucial for the translocation of the glucose transporter, GLUT-4, to the plasma membrane (4), which allows glucose to enter the cell. Surplus glucose not consumed in oxidative metabolism or stored as glycogen enters the lipogenic pathway (5) as acetyl CoA. Acetyl CoA carboxylase (ACC) catalyzes formation of malonyl CoA, the first step in the synthetic pathway of long-chain FAs (FA-CoA) (6) triacylglycerols (TGs) and their lipotoxic derivatives, such as ceramide (not shown). The increase in malonyl CoA inhibits the mitochondrial enzyme carnitine palmitoyl transferase 1 (CPT-1) (7) (McGarry effect), blocking oxidation of long-chain fatty acids (FAs). The resulting increase in intracellular FA-CoA and/or its derivatives, TG and/or ceramide, interferes with the phosphorylation of Akt (3). (b) Model showing how glucometabolic insulin resistance might protect against severe lipotoxicity. FAs or a lipid derivative such as ceramide (1) block the translocation of GLUT-4 to the cell membrane, excluding extracellular glucose from the cell (2). Although the precise mechanism of the translocation blockade is still being studied, it reduces malonyl CoA formation (3), which lowers FA-CoA synthesis (4) and eliminates the inhibition of CPT-1 (5). FA oxidation to CO₂ and H₂O by mitochondria therefore increases (6). This will limit the accumulation of intracellular lipids, including ceramide.

How sensitivity to insulin action can co-exist with insulin resistance

As insulin-stimulated lipogenesis increases, generating obesity, resistance to insulin-stimulated glucose disposal increases proportionately. The basis for this paradox of concomitant sensitivity to insulin-stimulated lipogenesis and glucometabolic resistance is being elucidated at the molecular level [9]. Insulin-stimulated glucose uptake in skeletal muscle involves phosphorylation of IRS, particularly IRS-1, and activation of the 85 kDa regulatory subunit of phosphoinositide-3-kinase (PI-3-kinase). Phosphorylation of the enzyme AKT1 by the products of phosphatidylinositol (3,4,5)-triphosphate is required for translocation of GLUT-4 to the plasma membrane [10,11] (Fig. 1a). Increased intracellular levels of long-chain fatty acyl CoA or derivatives of palmitoyl CoA, such as ceramide, block GLUT-4 translocation, possibly by

interference with Akt1 activation [12] (Fig. 1b). This would explain resistance to insulin-stimulated glucose uptake in myocytes [13]. However, a recent study also indicates that FAs impair protein kinase C λ or ζ activity [14]. Thus, in muscle, FAs interfere with glucose translocation by reducing phosphorylation of key enzymes at sites distal to PI-3-kinase.

In the fat-laden liver, the same paradox of glucometabolic insulin resistance (inappropriately high gluconeogenesis) and sensitivity to insulin-stimulated lipogenesis (inappropriately high lipogenesis) might also exist, perhaps explained by downregulation of IRS-2 by insulin [9]. SREBP-1c synthesis is increased in IRS-2 knockout mice [15], suggesting that downregulation of IRS-2 by hyperinsulinemia [9] could contribute to the upregulation of SREBP-1c. However, the increased SREBP-1c expression could also be a consequence of leptin resistance because SREBP-1c mRNA is lowered by leptin [16] (Box 2) and is abnormally high in the liver of both leptin-resistant [7] and leptin-deficient [17] rodents.

Box 2. The sequence of events postulated to occur during the development of diet-induced obesity and metabolic syndrome

- (1) Hyperinsulinemia, stimulated by overnutrition, upregulates SREBP-1c, the lipogenic transcription factor (2).
- (3) *De novo* lipogenesis increases.
- (4) Newly synthesized fatty acids (FA) and FA from dietary fat are transported as very low-density lipoproteins and stored as triacylglycerol (TG) in adipocytes, resulting in obesity.
- (5) Leptin secretion by adipocytes increases in proportion to the increase in fat accumulation.
- (6) The hyperleptinemia downregulates SREBP-1c in liver and activates AMP-kinase. This increases FA oxidation in peripheral tissues, thus limiting ectopic deposition of fat.
- (7) Despite this, insulin resistance and glucose intolerance result from the small increase in unoxidized FA accumulating in skeletal muscle, but serious lipotoxicity is prevented.
- (8) Later in the course of the disorder, leptin-mediated protection against the lipotoxic metabolic syndrome diminishes, in part because of leptin resistance factors that prevent leptin inhibition of SREBP-1c expression and block the compensatory increase in FA oxidation induced by hyperleptinemia. Unoxidized FA increases and lipid derivatives such as TG and ceramide accumulate in nonadipose tissues, compromising their functions and promoting apoptosis. I postulate that this is the basis of the metabolic syndrome (Fig. 1).

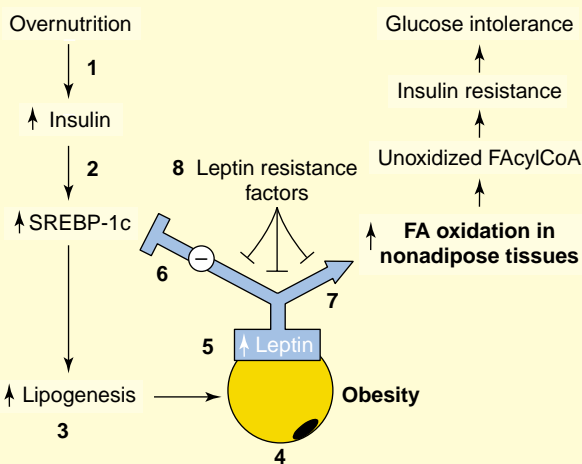


Fig. 1.

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Could the insulin-resistance syndrome be because of leptin resistance?

Loss of the suppressive effect of leptin on SREBP-1c mRNA expression [7] (Box 2) could be a proximal, if not primary, abnormality in the lipid overaccumulation associated with the metabolic syndrome of DIO [18]. This, and at least three other facts suggest that insufficient leptin action could be the underlying cause of the metabolic syndrome.

First, there is compelling evidence that the physiological role of the hyperleptinemia of diet-induced obesity is to protect nonadipose tissues from lipotoxicity [19–21]. When the hyperleptinemia of obesity fails to maintain normal lipid homeostasis in cells, lipotoxicity, the rodent equivalent of the metabolic syndrome ensues.

Second, there are several clinical states that share the phenotype of the metabolic syndrome (Box 3), and they all exhibit presumptive evidence of either leptin deficiency or resistance. Three of these eight states are genetic diseases in which leptin is either absent or inactive and all eight are characterized by ectopic lipid deposition appearing early in life. The liver of ZDF rats and of *db/db* mice, in which leptin is inactive, and of *ob/ob* mice, in which leptin is deficient, are all steatotic (fatty) [19]. In ZDF rats, the islets [21], heart [22] and skeletal muscle

Box 3. Disorders with features in common with the metabolic syndrome

Rare genetic causes

- (a) Obesity (leptin receptor mutation)
- (b) Obesity (leptin deficiency)
- (c) Generalized lipodystrophy

Non-genetic causes

- (a) Diet-induced visceral obesity
- (b) Cushing's syndrome
- (c) HAART in AIDS patients
- (d) Polycystic ovarian disease
- (e) Old age

[23,24] are steatotic. In leptin deficiency caused by generalized lipodystrophy, the liver is markedly steatotic [16], but the lipid content of other organs has not been reported.

The features of the metabolic syndrome can occur in at least four acquired nongenetic conditions: diet-induced obesity (DIO), glucocorticoid excess, aging and the lipodystrophy associated with HAART of AIDS patients [25]. The onset of the acquired forms of the metabolic syndrome is later in life and is far more variable in severity than the monogenic form. Leptin resistance has been identified in DIO, glucocorticoid excess and aging (Box 3). Although the lipid content of tissues has not been studied by direct biochemical measurement in humans with these conditions, excess triglycerides (TG) have been reported by magnetic-resonance spectroscopy in the skeletal muscle [24] and in the heart of obese humans studied to date [26].

The most important argument for insufficient leptin action being a cause of metabolic syndrome is based on the dramatic reversal of hepatic steatosis and insulin resistance by leptin treatment of lipodystrophic rodents [16] and humans [27]. The improvement in insulin-stimulated glucose disposal is attributed to the reduction of tissue lipids through leptin-induced downregulation of SREBP-1c, and activation of AMP-kinase [28]. Lipogenesis is thereby decreased and FA oxidation rises. These findings are consistent with the proposed mechanism for the metabolic syndrome as described in Box 2.

Is insulin resistance protective?

The disease cluster that includes the metabolic syndrome (Box 1) has long been attributed to resistance to insulin-stimulated glucose uptake. However, exclusion of surplus glucose from lipid-laden cells might protect these tissues from lipotoxic damage. What better protection against lipotoxicity and lipoapoptosis than a reduction in the intracellular availability of surplus glucose, the substrate for *de novo* lipogenesis (Fig. 1b). This protection comes at the relatively modest cost of impaired glucose tolerance, the most benign component in the metabolic syndrome cluster. By contrast, the alternative – severe lipotoxicity – might lead rapidly to premature morbidity and mortality; for example, in CGL, damage to nonadipose tissues causes hepatic steatosis and cirrhosis, severe type 2 diabetes mellitus and cardiomyopathy [29].

Adipocyte hormones determine partitioning of surplus dietary fat

When diet-induced obesity is induced in normal, leptin-sensitive rodents by feeding them a 60% fat diet, 96% of the increase in body fat is deposited in an enlarging adipose tissue mass, in which leptin gene expression [30] increases proportionally. Plasma leptin levels increase with adipocyte volume, and accumulation of fat in the lean body mass is minimal [18]. By contrast, in leptin-resistant rodents, even on a low-fat diet, a much larger fraction of triglycerides is deposited ectopically in nonadipose tissue

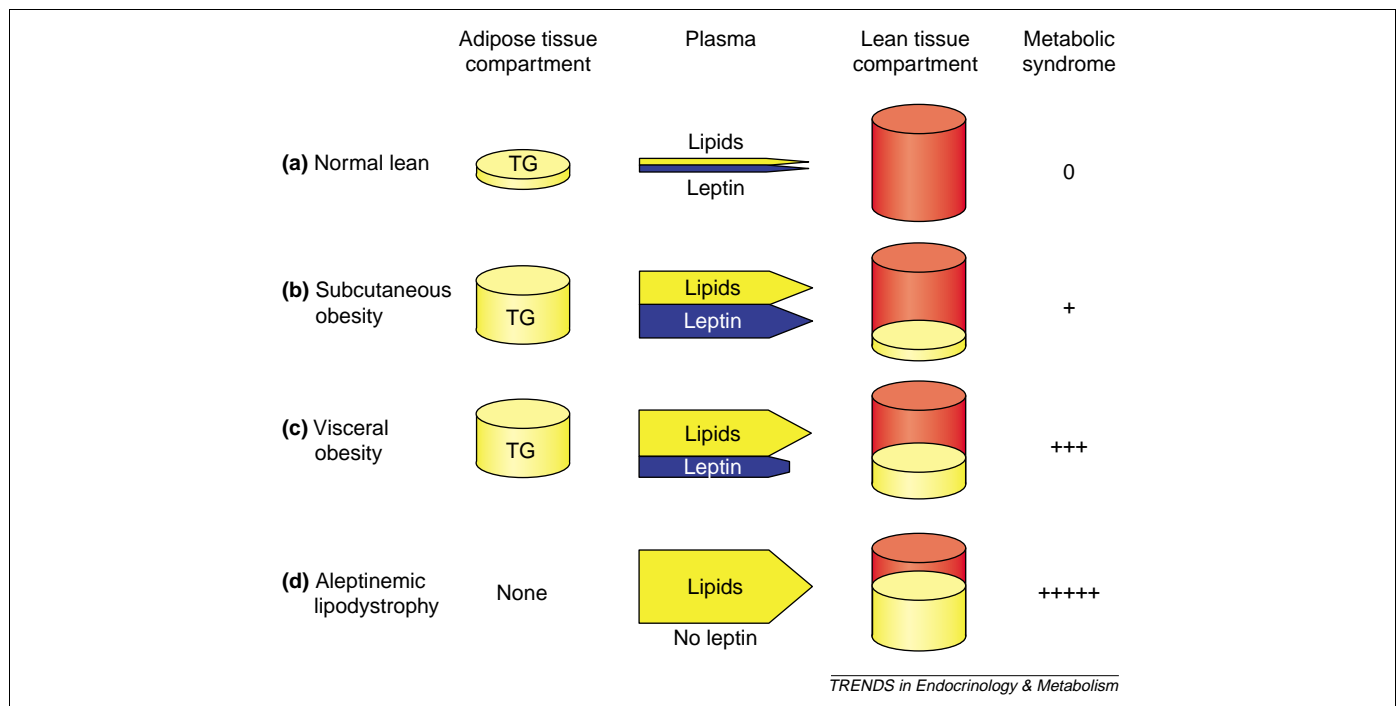


Fig. 2. Partitioning of caloric surplus between adipose tissue (yellow) and lean tissues (red). (a) In normal, lean subjects, the adipose tissue compartment is small, leptin is in its normal low range. Free fatty acids (FFAs) rise and fall in accordance with need for the fuel. Consequently lipid accumulation in lean tissues is negligible. (b) In subcutaneous obesity, the expanded adipose tissue compartment releases FFAs in excess of oxidative requirements and overnutrition increases circulating lipoproteins (LPs). The excess lipid load reaching the lean tissues causes glucometabolic insulin resistance, but a proportional increase in plasma leptin prevents more severe lipid accumulation and the more serious features of the metabolic syndrome are avoided. (c) In visceral obesity, visceral adipocytes underproduce leptin relative to FFA release. Because of this mismatch between leptin and lipids reaching the lean tissues, the hyperleptinemia is not sufficient to provide adequate antisteatotic action, particularly if there is leptin resistance (blunted leptin arrow) in target tissues. Lipids therefore accumulate and the severe components of the metabolic syndrome appear. (d) Aleptinemic lipodystrophy, this includes any congenital and acquired lipodystrophy with leptin deficiency. Lean tissues are completely unprotected from fatty acids (FA) delivered via the high LP levels. The resulting metabolic syndrome is the most severe.

[19], consistent with the idea that leptin action determines the partitioning of surplus dietary fat. Fig. 2 shows the putative spectrum of nonadipose tissue 'fat tolerance', ranging from the virtual absence of TG deposition in the lean mass of overnourished normals, to the near-total deposition of unused lipids in the lean tissues of patients with generalized aleptinemic lipodystrophy. However, another potential antisteatotic adipocyte hormone, adiponectin [31], might also play an important role in liporegulation [32]. Like leptin, it activates AMPK [33], and seems to protect against the serious components of the metabolic syndrome [34–37] (Box 1). Moreover, the antilipotoxic actions of PPAR γ agonists, such as rosiglitazone, might be mediated by adiponectin action on AMPK [37].

However, lipid-induced damage to tissues is probably not caused by the elevated intracellular TG content [33], but rather by derivatives of unoxidized palmitoyl CoA (Fig. 1b). For example, ceramide plays a role in the lipotoxicity of the islets [38] and of the heart [22] that occurs in the unleptinized tissues of ZDF rats and in transgenic mice with myocardial overexpression of acyl CoA synthase [39]. Ceramide-induced inhibition of AKT activity has been implicated in the impaired translocation of GLUT-4 in muscle [12] and might also play an important role in lipoapoptosis, which results in the tissue loss. AKT-mediated phosphorylation of proapoptotic BCL-2 family members, such as BAD, inhibits the pro-apoptotic factors [40]. Restoration of leptin action dramatically reduces the lipoapoptosis that otherwise occurs in unleptinized islets [38], while reversing the insulin resistance [16,27].

Leptin resistance

If impaired partitioning of dietary fat into the adipose tissue compartment is the cause of the metabolic syndrome in human obesity, the mechanism of impairment in leptin action needs to be determined. Candidate leptin-resistance factors include SOCS-3 [41], PTP-1B [42,43] (originally implicated in insulin resistance) [44], 11- β -HSD-1 [45] (which converts inactive glucocorticoids into more active forms), and various other factors [46,47]. In particular, there is extensive evidence linking glucocorticoids to obesity [48,49], raising the possibility that a high local level of the steroid hormone can cause leptin resistance in a given tissue [50].

Relative hypoleptinemia

There is now evidence linking visceral obesity, which is commonly associated with metabolic syndrome, to 'relative hypoleptinemia' [51]. Leptin levels in patients with the visceral type of obesity, although higher than those of normal, lean persons, are lower than in subcutaneous obesity. This suggests that the hyperleptinemia of visceral obesity is not high enough to cope with the elevated lipid levels accumulating in their lean body mass (Fig. 2). If the now well-accepted leptin resistance of obesity [52] is accompanied by relative hypoleptinemia, it would provide a powerful pathophysiologic explanation for the lean tissue complications of obesity that make up the metabolic syndrome.

Summary

There is evidence to support a revised perspective of the metabolic syndrome that accompanies obesity, including resistance to insulin action on glucose metabolism. I suggest that glucometabolic insulin resistance is, ironically, secondary to full sensitivity to insulin-stimulated lipogenesis, and that ectopic lipid overload causes the resistance. There is a possibility that by reducing glucose overaccumulation in cells, insulin resistance might protect against the more severe components of the syndrome by reducing glucose-derived lipogenic damage to cells. Lipid overaccumulation secondary to inadequate leptin and/or adiponectin action might underly the so-called insulin resistance syndrome. Evidence for this has been obtained from lipotoxic rodents with the equivalent of the human metabolic syndrome. To confirm validity of these hypotheses in humans will require the use of noninvasive techniques for measuring tissue lipids.

Afterthought

The evolution of adipocytes – cells that can stockpile calories during periods of nutritional abundance to sustain life during famine – was a transforming adaptive event. However, this capability required a liporegulatory system to protect the lean body compartment from the adverse effects of overnutrition. Until the 20th century, overnutrition was a transient condition for most humans and life was characterized by cycles of feast and famine. During the past century uninterrupted overnutrition coupled with life-long underexertion became widespread in some US and Western European populations, creating a calorie imbalance that has exceeded the compensatory capabilities of the existing liporegulatory system of most individuals. The result is the obesity-associated metabolic syndrome – the end-stage of uninterrupted calorie mismatch, and a major threat to the health of populations in developed nations.

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