Longevity, lipotoxicity and leptin: the adipocyte defense against feasting and famine

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Abstract

In this review, we propose that actions of the lipid-lowering, apoptosis-inhibiting effects of certain “longevity genes” oppose the life-shortening consequences of lipotoxicity and lipoapoptosis. We note that lipotoxicity occurs whenever leptin action is deficient, or whenever satiety is overridden, as in forced or voluntary overfeeding (“supersizing”). The role of hyperleptinemia, we suggest, is to extend survival during famine by permitting the storage of surplus calories in adipocytes without concomitant injury to nonadipose tissues from ectopic lipid deposits. It achieves this lipid partitioning by (1) restraining the level of overnutrition so as not to exceed the available adipocyte storage space and (2) enhancing oxidation of any ectopic lipid overflow: The mechanisms of lipoapoptosis are discussed, and the possibility that metabolic syndrome is the human equivalent of rodent lipotoxicity is suggested.

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1. Introduction

1.1. Lipids and longevity

The life span of several different species, ranging from yeast [1] to humans [2], can be prolonged by limiting the nutrients that are essential for life. The mechanisms by which caloric restriction seems to extend longevity have not been fully elucidated, but interacting genetic and metabolic factors seem likely to be involved [1,3–8]. For example, a highly conserved family of genes encoding NAD(+)−dependent protein deacetylases called sirtuins appear to mediate the life-prolonging effects of caloric restriction by promoting fat mobilization and inhibiting apoptosis [1,4,5]. This fits well with in vitro and in vivo [6–13] evidence that implicate unutilized lipids in the functional impairment and death of certain cells, processes referred to as “lipotoxicity” and “lipoapoptosis”. Both are prevented by eliminating the lipid surplus or by blocking the formation of potentially harmful fatty acid derivatives, such as ceramide [7] and reactive oxygen species (ROS). Furthermore, lipid depletion appears to protect cer-

tain cells against the apoptotic actions of cytokines [14] and cytotoxins (Park and Unger, unpublished data). Taken together, these reports raise the possibility that unoxidized nutrients may adversely affect the ability of a cell to withstand the various perturbations that can reduce its life span.

1.2. Balancing the risks of feast and famine

The length of survival in time of famine depends on supply of stored calories in adipocytes. To assure survival of a species nature has been obliged to balance the beneficial effect of overnutrition during its reproductive life with the ultimately harmful effects in its later life. This is in keeping with the theory of “antagonistic pleiotropy” [15]: favorable early-life effects with deleterious late-life effects. By permitting the intake and storage of surplus calories necessary to survive starvation, the early-life system protects from famine, while preventing the lipotoxicity of lipid overload in nonadipose tissues. In addition to providing storage space for surplus calories, white adipocytes minimize lipid accumulation in nonadipose tissues in two ways, by regulating food intake and enhancing the oxidation of lipids that may spill into nonadipose tissues. A specific adipocyte hormone, leptin, carries
out both of these roles. In addition, adiponectin may, like leptin, increase fatty acid oxidation [16].

Leptin secretion by adipocytes increases during overnutrition to act on appetite centers in the hypothalamus [17] and directly on various peripheral tissues [18]. The former action tailors the level of overnutrition to the available adipocyte storage space; the latter action reduces surplus lipids in nonadipose tissues by upregulating fatty acid oxidation and inhibiting lipogenesis [19,20]. This arrangement places the adipocytes in command of both the intake and partitioning of surplus calories. The life-shortening effects of caloric overload on peripheral tissues can thus be reduced without impeding the storage in adipocytes of the surplus calories required to survive famine (Fig. 1).

2. The roles of diet-induced hyperleptinemia

2.1. Hypothalamic action

A decade after the cloning of leptin [21] the function of the hyperleptinemia of diet-induced obesity (DIO) remains unsettled. Inasmuch as DIO is the only known cause of endogenous hyperleptinemia, one would predict that the hypersecretion is in response to greater physiologic need for the hormone. Initially it was thought that its physiologic role is to prevent obesity, but the coexistence of hyperleptinemia and DIO [17,22] excludes this possibility.

An alternative concept holds that the role of endogenous hyperleptinemia is not to prevent the storage of surplus calories, but rather to regulate the level of the surplus so that it does not exceed the available storage space for calories as the adipocyte mass expands to store the surplus calories. The latter action reduces surplus lipids in nonadipose tissues by upregulating fatty acid oxidation and inhibiting lipogenesis [19,20]. This arrangement places the adipocytes in command of both the intake and partitioning of surplus calories. The life-shortening effects of caloric overload on peripheral tissues can thus be reduced without impeding the storage in adipocytes of the surplus calories required to survive famine (Fig. 1).
2.2. The peripheral action

A second function of hyperleptinemia is to induce compensatory oxidation of surplus fatty acids (FA) in nonadipose tissues through direct leptin action on these tissues [24] so as to prevent collateral metabolic damage to nonadipose tissues from unoxidized long-chain fatty acids. Failure of the leptin system to protect the lean nonadipose tissues from lipid-induced metabolic trauma (lipotoxicity) is postulated to underlie the metabolic syndrome of Reaven [25]. In addition to leptin, a second adipocyte hormone, adiponectin, may also be involved in protecting against lipotoxicity [16]; polymorphisms in the adiponectin gene are associated with components of the metabolic syndrome [26].

3. Causes of failure of the antilipotoxic system and metabolic syndrome

3.1. Supersizing

“Supersizing,” i.e., extreme hyperalimentation, lies at one extreme of the spectrum of failure of the lipotoxic system. It is possible to force-feed normal individuals a quantity of food that far exceeds, not only their caloric needs, but also the caloric storage capacity of their adipose tissue mass. Normally a disparity of such magnitude is prevented by hypothalamic and gastric constraints on appetite and meal capacity. However, in geese the force-feeding of 6 pounds per day of salted maize for 30 days increases the weight of their livers from 120 to 1300 g and produces excellent paté de foie gras. In humans, the famous Vermont prison study of Sims and colleagues was the first study of experimental supersizing [27,28]. In 2004, the movie “Supersize Me” provided a visual record of the consequences of supersizing. A healthy, slim young filmmaker consumed 5000 calories of fast food per day for 30 days and developed acute hepatic steatosis of alarming proportions.

We hypothesize that in the foregoing geese and in humans, the massive influx of food outstripped the rate at which adipocytes can undergo the hypertrophy and hyperplasia necessary to accommodate the sudden influx of excess calories (Fig. 2A). Without sufficient time for expansion of the adipocyte mass, the leptin levels will be low relative to the caloric excess, thereby providing less than the full antilipotoxic protection and less than the full appetite constraint that occurs in gradual unforced ad lib overnutrition leading gradually to DIO. Indeed, when a 60% fat diet is fed ad lib to normal rats, their leptin levels rise fourfold within 24 h of overfeeding and then continue to rise in parallel with the increase in body fat [22]. These ad lib overfed rats become extremely obese but without the severe steatosis of liver, heart, pancreatic islets, and skeletal muscle that occurs in the absence of leptin action [22]. Perhaps the aggressively promoted and ubiquitously distributed high fat and carbohydrate intake of Americans constitutes a low-grade form of “supersizing”. If so, this could be responsible for the unprecedented outbreak of fatty liver and type 2 diabetes in our juvenile population [29,30]. In both supersizing and generalized lipodystrophic syndromes, the liver bears the brunt of the nutrient flood; the
hyperinsulinemia induced by the high carbohydrate content of the diets upregulates the lipogenic transcription factors in the liver, sterol regulatory element binding protein-1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP) [31,32], increasing the expression of their lipogenic target enzymes. This raises the hepatic production of very low-density lipoproteins (VLDL), which deliver FA to lipoprotein lipase-bearing tissues throughout the body.

3.2. Generalized congenital lipodystrophy

At the other extreme of the spectrum of failure of the antilipotoxic protection system is congenital generalized lipodystrophy (CGL), in which adipocytes are absent (Fig. 2B). Such patients lack all three crucial adipocyte functions, normal lipid storage capacity, leptin-mediated appetite modulation and leptin-mediated antilipotoxic protection of nonadipose tissues. They overeat, sometimes voraciously, but lack white adipocytes in which to store the surplus. The predicament is further amplified by the lack of adipocyte-derived leptin to minimize ectopic lipid deposition and restrain appetite. The result is generalized lipotoxicity that can be ameliorated by leptin replacement therapy or transplantation of normal fat tissue [33–35].

3.3. Common causes of failure of antilipotoxic protection

The foregoing two extremes in the spectrum of causes of failure of antilipotoxic protection, supersizing and generalized lipodystrophy are obviously extraordinarily rare. The acquired causes that lie between the extremes are far more common (Fig. 3). By far the most common cause of antilipotoxic failure is DIO, which is usually characterized by a variable period of relatively effective compensation that may continue for many years. However, at some time point, a substantial subset of DIO patients will undergo decompensation, particularly if the obesity is visceral. This takes the familiar form of the metabolic syndrome of Reaven [25] with insulin resistance, type 2 diabetes, fatty liver, hypertension, coronary artery disease and fatty heart. The mechanisms for decompensation of antilipotoxic protection in DIO are probably a combination of decreasing leptin sensitivity together with a level of hyperleptinemia that is insufficient relative to the increased leptin need (relative hypoleptinemia) (Fig. 2C).

Aging may be the most common cause of impaired leptin sensitivity at both the hypothalamic and peripheral levels [36]. Aging rats exhibit only a small fraction of the anorexic response to intense adenovirally induced hyperleptinemia as young rats and they lose less than 10% as much body fat as young rats (Fig. 4). A leptin resistance factor, suppressor of cytokine signaling (SOCS)-3, is increased in the leptin-unresponsive fat cells of aged rats [36] and is a prime suspect in age-related failure of antilipotoxicity.

However, the level of hyperleptinemia in long-standing DIO with antilipotoxic failure may not be high enough to overcome the leptin resistance of the metabolic syndrome. In visceral obesity, the most common fat distributional pattern in metabolic syndrome [37–39], visceral adipocytes express leptin at lower levels than subcutaneous adipocytes [39], possibly accounting for the higher prevalence of antilipotoxic failure. It is noteworthy that a paucity of subcutaneous fat relative to visceral fat is a feature of several of the causes of antilipotoxic failure listed in Fig. 3. Patients with Ruderman syndrome (normal weight, metabolically obese syndrome) [40], Cushing syndrome, polycystic ovarian syndrome, AIDS patients with protease inhibitor-induced lipodystrophy, and hyperalimented patients with extensive loss of subcutaneous fat...
fat due to third degree burns all have a preponderance of abdominal fat tissue relative to subcutaneous fat. It will be important to determine if these conditions are characterized by an increase in ectopic lipid deposition, as is the case in the equivalent rodent syndromes. It has been reported in Cush- ing’s syndrome that hepatic steatosis is related to the area of visceral and abdominal fat [41].

While complete studies of ectopic lipid deposition in organs of humans with the metabolic syndrome are not available, the rodent equivalent is characterized by an excess of ectopic lipid deposition in skeletal muscle, pancreatic islets, liver and heart (Fig. 5) [22,42–44]. The few indirect measurements of tissue lipids that are available in humans tend to support the lipotoxic concept. For example, in HIV protease inhibitor-induced lipodystrophy [45] and in obese children [46] altered myocellular and abdominal fat partitioning has been identified by magnetic resonance spectroscopy (MRS). A relationship between body mass index and intracardiomyo-
cellular fat has also been reported [47] and ectopic lipids have been identified in skeletal muscle [48] and liver [49] by MRS.

The possibility that failure of antilipotoxic protection is a common cause of the metabolic syndrome has become an important public health issue because of the likelihood that certain of its morbid components can be prevented by treatment with currently available agents that reduce ectopic lip-
ids [50–54].

4. Consequences of antilipoxic failure

4.1. The lipoapoptotic pathways

The leptin-unresponsive ZDF rat provides an excellent example of antilipotoxic failure. As shown in Fig. 5, virtually every tissue examined has a high level of triglycerides [22]. While triglycerides provide a convenient means to assess the magnitude of the lipid overload, they are probably the least toxic form in which the lipid surplus can be sequestered, and may not necessarily reflect the level of lipid derivatives responsible for the metabolic trauma.

The lipid derivatives that damage nonadipocytes may be generated via more than one pathway. In the pancreatic islets [7] and in the hearts of ZDF rats [44], lipotoxicity involves an increase in ceramide formation via condensation of unoxi-
dized palmitoyl CoA and serine, catalyzed by the enzyme serine palmitoyl transferase (SPT) (Fig. 6) [55]. Maneuvers that reduce palmitoyl CoA or block SPT reduce ceramide formation prevent the fatty acid-induced apoptosis that other-
wise occurs. In islets of ZDF rats, the increased ceramide is accompanied by upregulation of inducible nitric oxide syn-
thalase (iNOS), thereby enhancing nitric oxide and peroxyni-
trite formation. The iNOS blockers, aminoguanidine and nico-
tinamide, also prevent fatty acid-induced apoptosis of
β-cells in the islets of ZDF rats [56].

Other pathways almost certainly are involved. For example, while cardiac lipoapoptosis in the heart also appears to involve ceramide [51,57], the nitric oxide pathway has not been impli-
cated. The role of ROS has not been carefully delineated but is thought to play an important role. Thus, alternative path-
ways of lipotoxicity exist and their relative importance in inflicting damage to tissues may vary with the tissue, the stage of the process and the prevailing clinical conditions.

4.2. Anti-apoptotic factors

A potentially important influence on the vulnerability of a cell to noxious lipid derivatives may be the balance of apop-
totic and anti-apoptotic members of the Bcl-2 family. Nor-
mal, when islets are exposed to fatty acids, Bcl-2 expres-
sion falls precipitously, but this suppression can be prevented by leptin [58]. By contrast, in the ZDF rats, which are unre-
sponsive to leptin action, the fatty acid-induced decline in
Bcl-2 cannot be blocked by leptin, and the β-cells undergo apoptosis. However, adenoviral transfer of a normal leptin receptor gene (Lepr) restores the ability of leptin to block
fatty acid-induced suppression of Bcl-2 expression and, in doing so, reduces apoptosis in the islets [58]. It is thus likely that direct anti-apoptotic action of leptin on the pancreatic islets is mediated, at least in part, by reducing the fatty acid-induced suppression of Bcl-2.

Whatever the biochemical pathways to lipotoxicity, the end stage of the pathological process is lipid-induced apoptosis. This has been identified in the β-cells of the pancreatic islets of leptin-unresponsive Zucker diabetic fatty (fa/fa) rats (Fig. 7). Electron microscopic studies by Orci’s group in Geneva have demonstrated in β-cells of these rats the nuclear alterations of apoptosis, together with severe alterations of 85% of the mitochondria [43]. In another unrelated form of lipotoxicity in the heart caused by cardiomyocyte-specific transgenic overexpression of acyl CoA synthase (ACS), morphologic and biochemical evidence of apoptosis has also been identified [57]. The clinical consequences of this cellular loss will obviously vary greatly, but will be most apparent in organs that are unable to compensate for cellular loss. The fact that cardiomyocytes are terminal cells may explain why transgenic mice with cardiomyocyte-specific overexpression of ACS and leptin-unresponsive ZDF rats both develop severe lipotoxic cardiomyopathy.

The good news is that these forms of lipotoxicity are prevented by measures that lower the lipid excess. These include caloric restriction and exercise [50], and various AMP-activated protein kinase (AMPK)-activating agents such as leptin [50], thiazolidinediones [51,52], metformin [53] and AICAR [54]. If lipotoxicity of rodents models is equivalent to the human metabolic syndrome, we may already possess the means to prevent the most prevalent health threat to overweight Americans, of whom 47 million are already afflicted with this disease cluster [59].

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References


