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Minireview: Weapons of Lean Body Mass Destruction: The Role of Ectopic Lipids in the Metabolic Syndrome

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The obesity crisis in the United States has been associated with an alarming increase in the prevalence of the metabolic syndrome (MSX) disease cluster. Here we review evidence that the MSX reflects a failure of a system of intracellular lipid homeostasis that prevents lipotoxicity in the organs of overnourished individuals by confining the lipid overload to cells specifically designed to store large quantities of surplus calories, the white adipocytes. Normally, early in obesity, adipocytes increase leptin and adiponectin secretion, hormones that enhance oxidation of surplus liquids in nonadipose tissues by activating AMP-activated protein kinase and reducing the activity and expression of lipogenic enzymes. These events combine to lower malonyl coenzyme A. Deficiency of and/or unresponsiveness to leptin prevents these protective events and results in ectopic accumulation of lipids. Increased *de novo* ceramide formation is probably the most damaging lipid and is a cause of lipoapoptosis, abetted by a decline in tissue Bcl-2. Pancreatic β-cells and myocardiocytes are cellular victims of the process, leading to non-insulin-dependent diabetes and lipotoxic cardiomyopathy. The MSX is particularly prevalent in visceral obesity, probably because visceral adipocytes make less leptin than sc adipocytes. Cushing's syndrome, the lipodystrophy associated with protease inhibitor therapy of AIDS, polycystic ovarian disease, as well as diet-induced visceral obesity, all have a high waist/hip ratio, and all exhibit MSX. Increased lipid content in the heart and skeletal muscle organs of such patients is now under study. (*Endocrinology* 144: 5159–5165, 2003)

SHORTLY AFTER THE end of World War II, an unprecedented environmental change took place in the United States. For the first time in human experience, the eating habits of an entire nation were altered by the marketing of processed food having in common a high carbohydrate and fat content, very low cost, and easy availability in supermarkets and fast-food restaurants. The aggressive promotion of these foods, coupled with a reduction in caloric expenditure resulting from new immobilizing technologies, changed the caloric balance of at least two generations of Americans. Now, after a half-century of this nutritional revolution, less than 40% of the American population has a normal body mass index (BMI).

The health consequences of the physical transformation of an entire population have become all too apparent. A recent estimate places the number of Americans with the metabolic syndrome (MSX), a cluster of obesity-related diseases, at 47 million (1). This number is sure to increase, as a new generation of overweight children reaches adulthood with a longer duration of excess weight than any of their overweight predecessors. Current approaches to the obesity problem have failed to reverse or prevent it, creating a health care challenge unlike any encountered previously. In this review, we examine the molecular pathophysiology that we believe to be responsible for this clinical crisis.

Abbreviations: ACC, Acetyl coenzyme A carboxylase; AMPK, AMP-activated protein kinase; BMI, body mass index; CoA, coenzyme A; CPT-1, carnitine palmityl transferase-1; iNOS, inducible nitric oxide synthase; MCD, malonyl CoA decarboxylase; MSX, metabolic syndrome; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; SOCS, suppressor of cytokine signaling; SPT, serine palmitoyl transferase; STAT, signal transducer and activator of transcription; TG, triglyceride; ZDF, Zucker diabetic fatty.

Functional Roles of Adipocytes

Fuel storage

The evolution of adipocytes served the purpose of extending survival during the recurrent cycles of famine (2) by allowing surplus fuel to be stored as triglycerides (TG) during caloric abundance for subsequent retrieval during periods of caloric need. Dedicated fat-storing cells were necessary, because the tissues of the lean body mass lack the storage capacity to meet the fuel demands imposed by famine. Storage of even a modest caloric surplus in lean tissue would ultimately be manifested clinically by fatty liver, lipid cardiomyopathy, non-insulin-dependent diabetes mellitus, and insulin resistance. These abnormalities are precisely those observed in fatless rodents and in humans with generalized lipoatrophy. The lipid-induced dysfunction in the lean tissues is referred to as lipotoxicity (3), and lipid-induced programmed cell death is called lipoapoptosis (4).

Antilipotoxic action

In addition to storing surplus calories, adipocytes appear to protect against the lipotoxic damage to lean tissues that occurs in the lipoatrophic states. This protection is mediated by adipocyte hormones such as leptin (5) and, quite probably, adiponectin (6, 7). The antisteatotic role of adipocytes has been established by the demonstration that transplantation of normal fat tissue into fatless mice reverses the manifestations of lipotoxicity (8), whereas fat tissue from *ob/ob* mice, which do not secrete leptin, does not (9). Furthermore, rodents that lack leptin or leptin action develop the full syndrome of lean tissue steatosis and lipotoxicity (10). This strongly supports the contention that secretory products of

adipocytes, in particular leptin, are required to protect nonadipocytes from lipid-induced damage.

The mechanism of the protective effect of leptin is disputed. Although mediation via hypothalamic centers is well established for leptin's control of feeding behavior through autonomic outflow, particularly sympathetic outflow, much evidence points to a direct antisteatotic effect of leptin on tissues to reduce their lipid content by enhancing oxidation and blocking lipogenesis. For example, when isolated pancreatic islets from normal rats are cultured in a 1 mM mixture of long-chain fatty acids, the presence of 20 ng/ml leptin to simulate its concentration in the plasma of obese animals completely prevents the TG accumulation that otherwise occurs (11). However, the most compelling evidence for a direct antisteatotic effect of leptin has been obtained *in vivo* by infusing recombinant adenovirus containing the cDNA of the normal leptin receptor (OB-Rb) into obese Zucker diabetic fatty (ZDF) rats (10), which are completely unresponsive to leptin because of a loss-of-function mutation in their leptin receptors (12). Virtually all of the infused adenovirus-receptor construct is taken up by hepatocytes, making the liver their only leptin-responsive tissue. Any reduction in hepatic lipid content resulting from infection with the normal leptin receptor must, therefore, be due to direct action of endogenous hyperleptinemia on the now leptin-responsive liver, because the hypothalamus remains devoid of normal OB-Rb. As shown in Fig. 1, both hepatic and plasma TG levels are substantially reduced by the expression in liver of normal OB-Rb (10), evidence of a direct antisteatotic effect of endogenous hyperleptinemia.

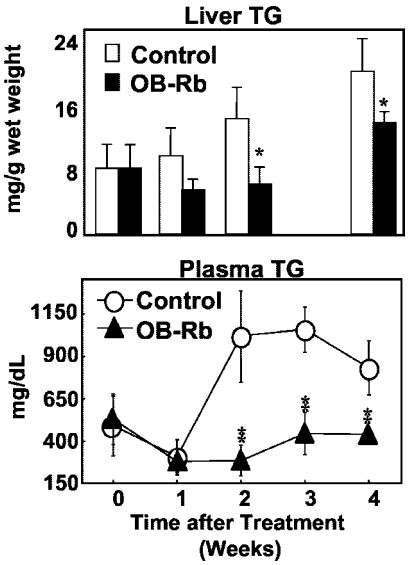

FIG. 1. The effect of adenoviral transfer of the wild-type leptin receptor (Ob-RB) gene by iv injection into previously leptin-unresponsive ZDF (*fa/fa*) rats on their hepatic TG content and plasma TG levels. The injected recombinant adenovirus containing the Ob-RB cDNA localizes almost exclusively in liver. *, $P < 0.05$; **, $P < 0.001$.

Normal Liporegulation

When normal, healthy individuals are in caloric balance, their liporegulatory system is at rest (Fig. 2A), *i.e.* their leptin levels are low. However, if such a person chronically consumes more calories than are needed to meet the caloric

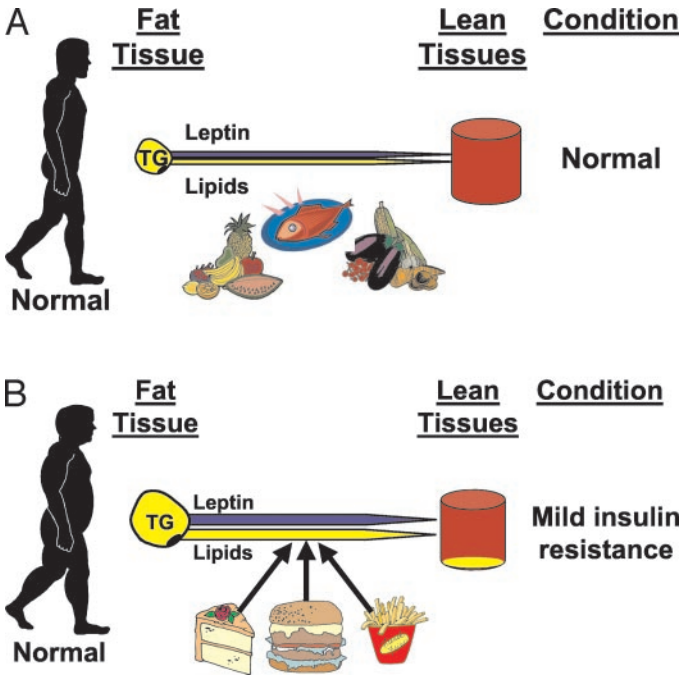

FIG. 2. A concept of the liporegulatory system and lipid partitioning in normal, healthy subjects. A, When caloric intake is equal to caloric expenditure, the liporegulatory system is at rest, and the lean tissues contain little or no unmetabolized lipids. B, During overnutrition, the adipocyte pool expands, and leptin levels rise proportionately. This up-regulates oxidative metabolism of long-chain fatty acids in the lean tissues (*cf.* Fig. 3A). Thus, ectopic accumulation of surplus lipids is minimal, and partitioning of body fat is well maintained. Nevertheless, there may be modest reduction in insulin sensitivity and glucose tolerance within the normal range.

expenditure, adipocytes will expand and leptin levels will rise in proportion to the degree of lipid overload (Fig. 2B). By promoting fatty acid oxidation and deterring lipogenesis, the hyperleptinemia maintains the lean tissue content of lipids at a near-normal level.

The molecular mechanism of this effect is not completely understood. Leptin signal transduction involves the phosphorylation of signal transducer and activator of transcription (STAT)-3 (13) and ERK (14) pathways, but how this translates into the observed changes in lipid metabolism is not clear. One likely mechanism is via increased phosphorylation activation of AMP kinase (15), which phosphorylates acetyl coenzyme A (CoA) carboxylase (ACC) (16) and malonyl CoA decarboxylase (MCD) (17) (Fig. 3A). Phosphorylation inactivates ACC (18), but activates MCD. Because ACC catalyzes malonyl CoA formation, and MCD catalyzes its decarboxylation, the net effect of AMP-activated protein kinase (AMPK) activation on these target enzymes is to lower malonyl CoA. Malonyl CoA is the first committed step in lipogenesis and a powerful inhibitor of carnitine palmityl transferase-1 (CPT-1)-mediated fatty acid oxidation via the McGarry effect (19, 20) (Fig. 3A). The combination of an increase in fatty acid oxidation and a decrease in fatty acid synthesis could account for the reduction in the lipid content of a cell. At present, however, we do not understand how leptin activates AMP kinase.

The antisteatotic action of leptin also involves transcriptional effects. It down-regulates sterol regulatory element

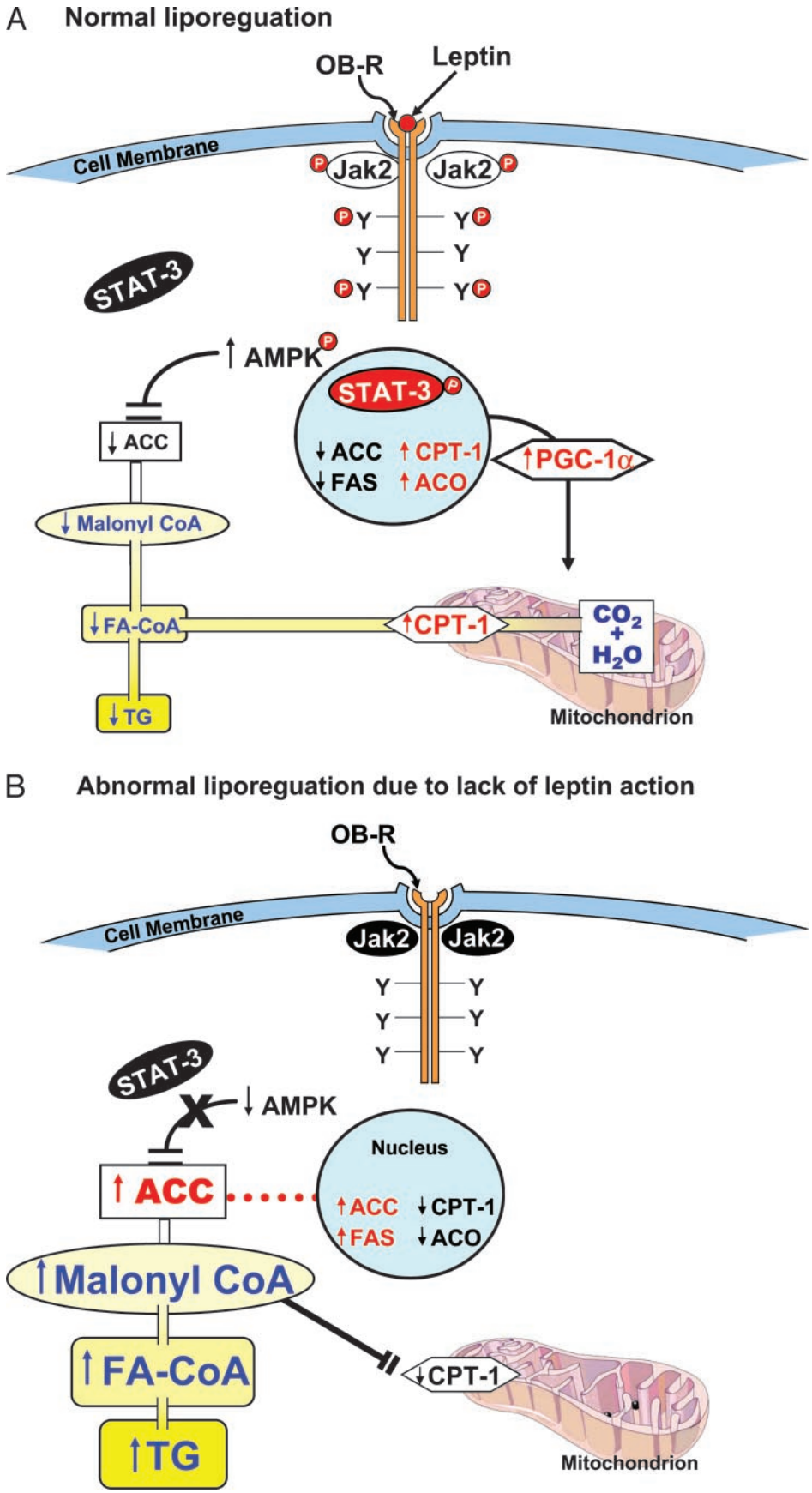

FIG. 3. Molecular physiology (A) and pathophysiology (B) of liporegulation. A, Normally during overnutrition (Fig. 2B), the increased plasma leptin will, by binding to its receptor, OB-Rb, initiate a phosphorylation cascade via the Janus kinase (Jak)/STAT pathway. Phosphorylated STAT-3 enters the nucleus and regulates transcriptional activity of its target genes. Its effects include up-regulation of PGC-1α, which is involved in mitochondrial biogenesis and the enzymes of fatty acid oxidation, CPT-1 and acyl-CoA oxidase (ACO). It also down-regulates lipogenic enzymes, such as ACC and fatty acid synthase (FAS). Another important action is to phosphorylate AMPK, which activates it. AMPK phosphorylates ACC, which blocks malonyl CoA formation. Not only is malonyl CoA the first committed substrate for fatty acid synthesis, but it also inhibits CPT-1 and mitochondrial oxidation of fatty acids. By lowering malonyl CoA, leptin maintains fatty acid oxidation at an appropriate level and prevents lipotoxicity. B, When leptin action is lacking, the Jak/STAT pathway is not activated during chronic overnutrition. The high level of ACC expression and activity generates malonyl CoA, the lipogenic precursor and inhibitor of fatty acid oxidation. More fatty acids and TG are synthesized and less are oxidized, raising the TG and FA-CoA (fatty acyl CoA) content of lean tissues.

binding protein-1c (21), a lipogenic transcription factor (22), thereby reducing the expression of lipogenic enzymes such as ACC, fatty acid synthase (Fig. 3A), and glycerol-3-phosphate acyl transferase (23), all of which are expressed at high levels in unleptinized tissues (24). It also up-regulates peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) (25), a powerful inducer of mitochondrial biogenesis (26) that probably plays an important role in the antisteatotic effects of leptin (Fig. 3A). Because the leptin-mediated up-regulation of PGC-1α requires the presence of peroxisome proliferator-activated receptor-α (27), it must be also assumed that this nuclear receptor is somehow involved in leptin action. The molecular consequences of loss of leptin action are depicted in Fig. 3B.

Failure of Liporegulation

The leptin-unresponsive ZDF rat provides an excellent example of defective liporegulation. As shown in Fig. 4, virtually every tissue examined has a high level of TG. However, TG are probably the least toxic form in which the lipid surplus can be sequestered and may, at least in the short term, actually protect against severe metabolic trauma (28). They also provide a useful measure by which to assess the lipid overload. However, the harmful lipids are quite probably not in the form of neutral fat.

Lipid-induced damage to cells may involve more than one pathway (29). In the pancreatic islets of ZDF rats, the determinant pathway involves ceramide formation via condensation of unoxidized palmitoyl CoA and serine (4) catalyzed by the enzyme serine palmitoyl transferase (SPT) (30) (Fig. 5). Maneuvers that block ceramide formation appear to prevent the fatty acid-induced apoptosis that otherwise occurs. In islets of ZDF rats, ceramide increases the expression of inducible nitric oxide synthase (iNOS), thereby enhancing nitric oxide and peroxynitrite formation (31). Peroxynitrite may mediate the apoptosis, because the iNOS blockers, aminoguanidine and nicotinamide, also prevent fatty acid-induced apoptosis of β-cells in the islets of ZDF rats.

Other pathways may be involved in other tissues. For example, lipoapoptosis in the heart also appears to involve ceramide, but the nitric oxide pathway has not been implicated (32). Thus, alternative pathways exist and may vary in importance in certain tissues at certain times under certain conditions (Fig. 5).

The deleterious end-effects of lipid excess on the viability of a cell may be strongly influenced by the balance of apoptotic and antiapoptotic members of the Bcl-2 family. In lipid-laden unleptinized islet cells, for example, antiapoptotic Bcl-2 is expressed at extremely low levels compared with wild-type ZDF controls (Fig. 6) (4). Normally, when islets are exposed to fatty acids, Bcl-2 expression falls precipitously, but this fall can be prevented by leptin. By contrast, in the ZDF rats, which are unresponsive 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 (OB-Rb) gene restores the ability of leptin to block fatty acid-induced suppression of Bcl-2 expression and, in doing so, reduces apoptosis in the islets (Fig. 6). It is thus likely that direct leptin action on the pancreatic islets has an antiapoptotic action mediated, at least in part, by blocking fatty acid-induced suppression of Bcl-2 (33).

Causes of Liporegulatory Failure

Aleptinemic disorders

Profound reduction of plasma leptin occurs in two rare conditions, congenital generalized lipodystrophy (34) and

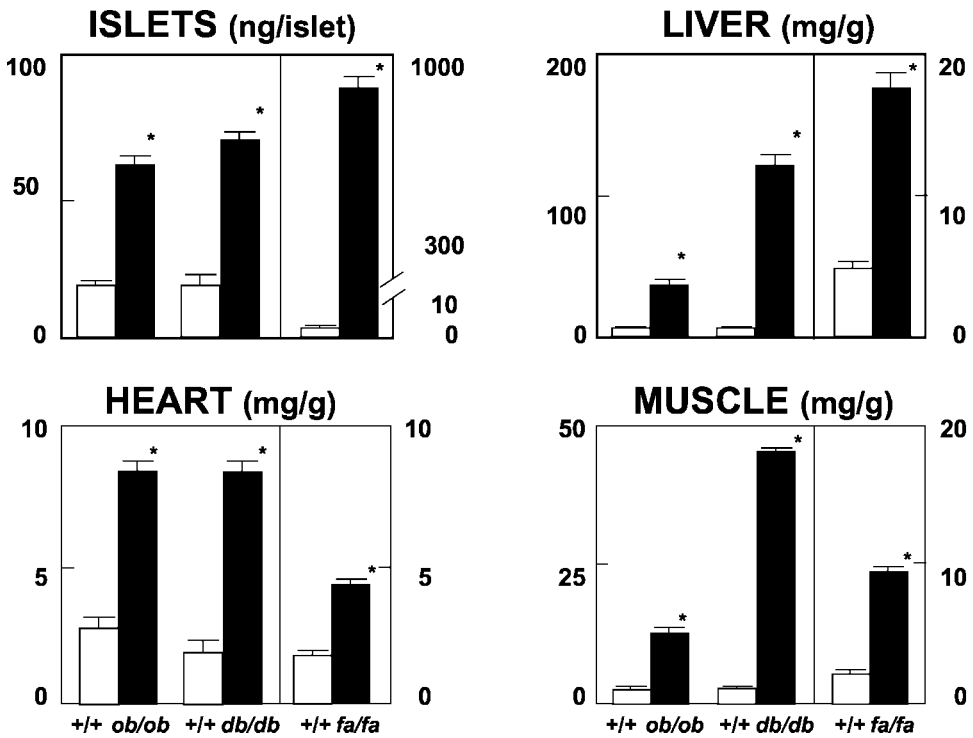

FIG. 4. TG content in nonadipose tissues of rodents with aleptinemia (*ob/ob* mice) or leptin unresponsiveness (*db/db* mice and *fa/fa* rats). Wild-type rodents (+/+) were used as controls. *, $P < 0.001$.

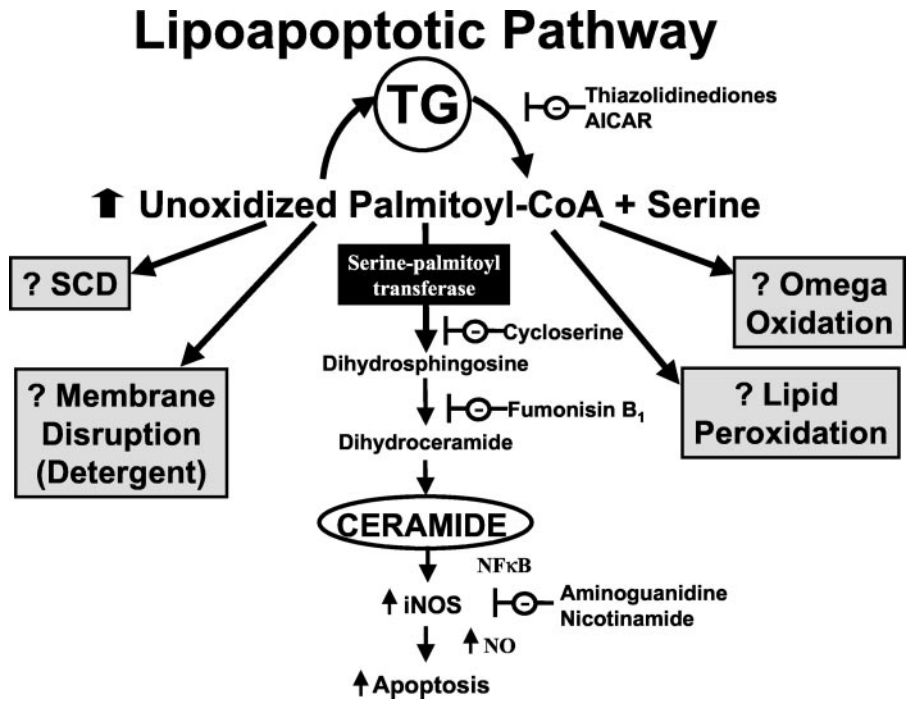

FIG. 5. Pathways believed to be involved in lipoapoptosis of β-cells in ZDF rats. The SPT/ceramide pathway is thought to be the principal one in ZDF islets, because inhibitors of ceramide formation, such as cycloserine and fumonisin B-1, completely prevent the apoptosis. Nitric oxide (NO) is believed to play a role in the islets, because aminoguanidine and nicotinamide inhibit the apoptosis. The role of other pathways through which lipid excess causes death of cells has not been adequately studied yet. Note that AMP kinase activators such as the thiazolidines, 5-amino-imidiazole carboxamide riboside (AICAR), and diet restriction all reduce the fatty acid overload and prevent loss of β-cells. NFκB, Nuclear factor-κB; SCD, stearoyl-CoA desaturase.

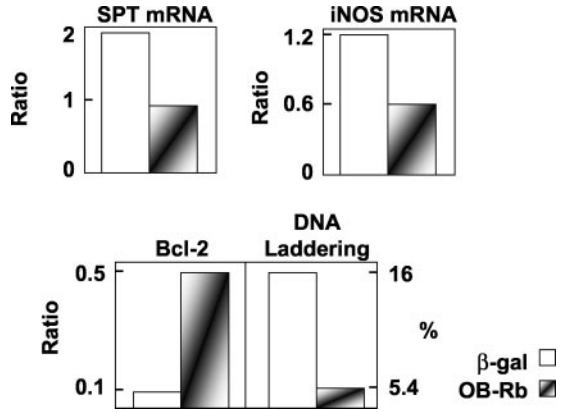

FIG. 6. Restoration of leptin action by adenoviral transfer of the leptin receptor gene OB-Rb into islets of ZDF (*fa/fa*) rats lowers SPT mRNA and iNOS mRNA and up-regulates Bcl-2 mRNA. DNA laddering, an index of apoptosis, is markedly reduced. β-gal, β-Galactosidase.

leptin gene mutations (5). Hyperphagia is prominent in both conditions because of lack of leptin action on hypothalamic feeding centers. In both conditions, the antisteatotic effect of leptin is absent, and fat accumulates in peripheral tissues. The ectopic lipid accumulation is greater in generalized lipodystrophy, perhaps because of concomitant adiponectin deficiency (35).

Relative hypoleptinemia

Relative hypoleptinemia is probably a common, currently unrecognized condition that occurs in visceral obesity (Table 1). In visceral obesity, the circulating level of leptin, although higher than normal, may not be high enough to provide effective antisteatosis (Fig. 7A). By contrast, leptin levels are higher in sc obesity and may therefore provide better antisteatotic protection (Fig. 7B). Visceral adipocytes underexpress and undersecrete leptin (36). They also express more 11-β-hydroxysteroid dehydrogenase-1, the enzyme that converts inactive cortisol to cortisol (37), which may also contribute to features of the MSX (38).

TABLE 1. Diseases with MSX-like features

- Diet-induced visceral obesity, especially in males
- Metabolically obese, normal weight (MONW) [Ruderman's syndrome (35)]
- Cushing's syndrome
- Protease inhibitor lipodystrophy in AIDS
- Polycystic ovary syndrome
- Extensive third-degree burns treated with hyperalimentation

Leptin unresponsiveness

Leptin resistance is probably the most common cause of liporegulatory failure and MSX. Although the mechanism has not been firmly established, it appears that everyone becomes leptin resistant, if they live long enough (39). Normal rodents lose virtually all responsiveness to leptin after a certain age (40) (Fig. 8). In humans, hyperleptinemia occurs with aging (41) and tissue fat increases, which implies leptin resistance. The cause of age-related leptin resistance could well be the increase in suppressor of cytokine signaling (SOCS)-3 observed in the unresponsive tissues of aging rodents (Fig. 8), but this has not been proven.

Manifestations of Lipotoxicity

Type 2 diabetes

Lipotoxicity in rodents is believed to cause insulin resistance and ultimately failure of pancreatic β-cells (42). The insulin resistance may be the result of lipid accumulation in skeletal muscle and liver (43). Initially β-cells undergo hy-

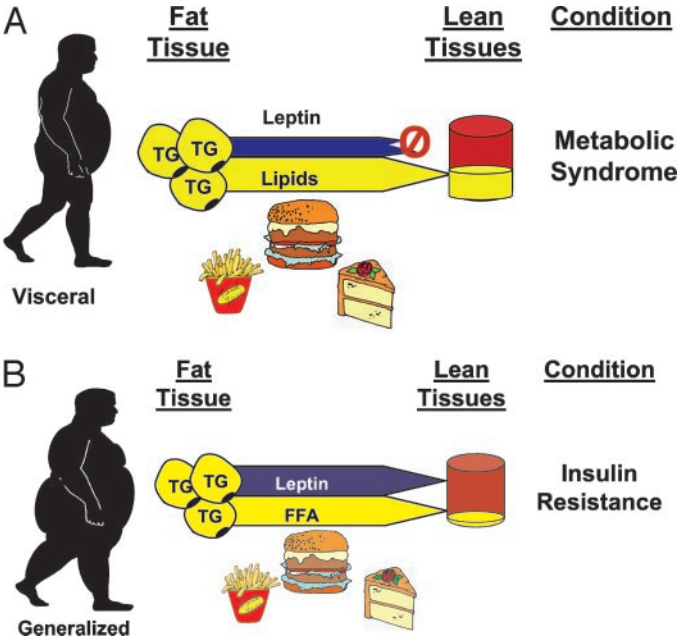

FIG. 7. Lipid partitioning in diet-induced obesity. A, Diet-induced visceral obesity is most commonly associated with features of the MSX. Some such patients may have a normal BMI, as emphasized by Ruderman's group (35). We suspect that, in visceral obesity, leptin levels, although elevated above those of normal lean subjects, may not be elevated sufficiently to prevent the accumulation of lipids in lean tissues. In addition, there may be resistance (ø) to leptin in its target tissues. In any case, the MSX is more prevalent. B, In generalized obesity, the hyperleptinemia is greater and is presumably better able to limit ectopic lipid accumulation. Although insulin resistance still occurs, most other features of the MSX may be absent. FFA, Free fatty acid.

perplasia (42) and compensate for the peripheral insulin resistance resulting from skeletal muscle and hepatic steatosis. However, they then lose glucose transporter-2 and glucokinase (44), which attenuates their glucose responsiveness, and diabetes begins. Ultimately, approximately 50% of the β-cells disappear through a process of lipoapoptosis (30). This reduces insulin production below the level required to meet the increased insulin demand.

Fatty heart

Studies in ZDF rats indicate that cardiac steatosis can lead to so-called lipotoxic cardiomyopathy (45). As in the case of β-cells, hyperplasia of cardiomyocytes may precede their loss; however, in time, the gradual loss through lipoapoptosis of irreplaceable cardiomyocytes leads to impaired cardiac function. It is of obvious importance to determine whether fatty heart occurs in humans. Estimates of myocardial fat made by magnetic resonance spectroscopy suggest that individuals with a BMI in excess of 30 may have abnormally high levels of TG in their heart and evidence of impaired contractile function (46). If this is true, it would mean that two thirds of the American population is at risk for, or actually now has, lipotoxic heart disease.

Clinical expression of liporegulatory failure

Table 1 lists conditions in which disease components of the MSX cluster are manifest. Interestingly, all of these conditions have one thing in common: a predominance of visceral adipocytes relative to sc adipocytes. Unfortunately, careful monitoring of leptin levels as a function of body fat distribution and tissue TG levels has not been conducted in these various syndromes. However, based on observations in animals and on the clinical configuration of the human conditions (Table 1), one could hypothesize that sc adipocytes provide much, if not most, of the protective function, perhaps by producing most of the hyperleptinemia (36). The visceral adipocytes, by contrast, provide less of the hyperleptinemia and are more active metabolically. In addition, they may activate inactive glucocorticoids and thus contribute to hepatic insulin resistance and hyperglycemia (38).

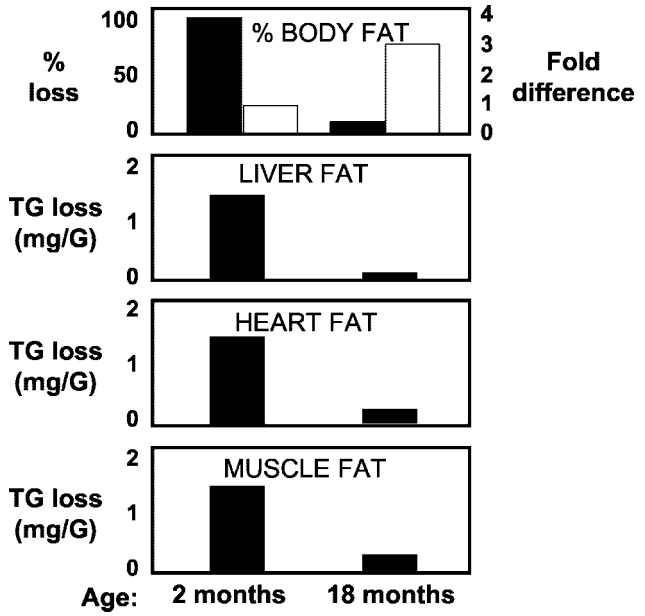

FIG. 8. Effect of aging on the response of TG content (■) to adenoviral transfer of the leptin gene in normal rats. Despite intense and equivalent hyperleptinemia in both groups, TG loss was negligible in the older rats. The mRNA of SOCS-3 (□), a SOCS, was several times higher in the old rats and could be involved in resistance to leptin.

Thus, the preponderance of truncal fat tissue observed in conditions such as Cushing's syndrome, the lipodystrophy associated with protease inhibitor treatment of patients with AIDS, polycystic ovarian disease, aging, and the diet-induced visceral obesity most common in males all share a truncal body fat configuration together with features of the MSX. One might, therefore, predict that they will also share relative hypoleptinemia (plasma leptin normalized for total body fat) and increased lipid content in the affected organs.

Adiponectin in liporegulation

The adipocyte hormone, adiponectin, may also play an important role in liporegulation. Like leptin, it activates AMPK (47) and seems to protect against various components of the MSX (48, 49). In fact, the antilipotoxic action of rosiglitazone may be mediated by adiponectin activation of AMPK (50).

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