

ADIPOBIOLOGY-BASED PHARMACOLOGY

Adnan Erol

Department of Internal Medicine, Faculty of Medicine, Celal Bayar University, İzmir Caddesi, Manisa, Turkey

*Adipose tissue has pleiotropic functions beyond lipid and energy metabolism. Adipose tissue secretes bioactive proteins, termed adipokines, which act through auto-, para- and endocrine pathways. These ensure multidirectional communications between the adipose and other tissues and organs. In obesity, an increased production of various adipokines leads to dysfunctions in food intake, immunity, insulin sensitivity, angiogenesis, hemostasis, and glucose and lipid metabolism, all of which linked to the pathogenesis of cardiometabolic diseases, including atherosclerosis, type 2 diabetes mellitus, and metabolic syndrome. Notable exceptions are adiponectin, nerve growth factor and interleukin-10, which circulating levels are decreased in these diseases. Here, we highlight some areas of adipobiology that may be implicated in the development of therapeutic progress through adipopharmacological studies on adipokines and other adipose tissue-derived molecules. **Biomed Rev 2006; 17: 73-87.***

Key words: adipokines, adiponectin, adipopharmacology, AMPK, PPAR γ , TNF- α

INTRODUCTION

Our knowledge of adipobiology of obesity and related cardiometabolic diseases (CMD), such as atherosclerosis, hypertension, type 2 diabetes mellitus (T2DM) and the metabolic syndrome, has undergone major expansion during the past decade. The striking point is that adipocytes and nonfat cells of the adipose tissue have gained the status of endocrine cells of numerous signaling proteins termed adipokines (1-3). Consequently, "adipopharmacology" was introduced as a field of adipotargeting research aimed at drug discovery, also in CMD (2).

This review outlines the adipopharmacology of adipokines, with special reference to adiponectin, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1/CCL2), angiotensin II (AngII), leptin, and resistin. An adipocentric view is also addressed to (i) currently-used drugs such thiazolidinediones (TZDs) and statins, and (ii) 5'-AMP-activated protein kinase (AMPK) and sirtuin 1 as novel adipopharmacological targets.

Received 5 October 2006, received revised 18 November 2006, accepted 21 November 2006.

Correspondence and reprint request to Dr Adnan Erol, Department of Internal Medicine, Faculty of Medicine, Celal Bayar University, İzmir Caddesi, Manisa, Turkey. Tel.: 9023623 2313, Fax: 90212728 3216, E-mail: adnan.erol@bayar.edu.tr

ADIPOBIOLOGY

“Adipobiology” connotes the study of the molecular and cellular biology of the adipose tissue in health and disease (1). Adipose tissue is represented by white and brown subtypes. Here we focus on the biology of white adipose tissue (“white” adipobiology). The main cellular components of this tissue are mature, lipid-filled adipocytes, lipid-free preadipocytes, stromovascular cells and associated immune cells (macrophages, mast cells, and lymphocytes) (1,3). Adipocytes (fat cells) from lean humans have an average cell diameter of approximately 70 μm , whereas fat cells from obese subjects can amount to a mean diameter of about 120 μm (4). There is continuing debate on the extent to which there is inter-convertibility between white and brown adipose tissue (5). Marked regional differences in adipose metabolism have been reported (6).

The cellular development associated with adipocyte growth involves both hypertrophy and hyperplasia. Hyperplasia including adipogenesis results from the recruitment of new adipocytes from precursor cells in adipose tissue and involves the proliferation and differentiation of preadipocytes. Both adipocyte hypertrophy and hyperplasia occur in association with positive energy balance (energy intake in excess of energy expenditure) during normal growth and during the development of obesity, with hypertrophy often preceding hyperplasia (4-6). However, the adipocyte has not an unlimited capacity for size expansion, and increases in fat cell number occur even during adulthood. When adipose tissue development in genetic or diet-induced obese animals is monitored over time, it is generally observed that increases in the adipocyte size precede increases in adipocyte number (7). It was suggested that there might be a “maximum cell size”. According to “critical fat cell size hypothesis”, enlarged adipocytes produce and release paracrine factors which control preadipocyte proliferation involved in the development of obesity (8).

It is traditionally known that adipose tissue serves as a lipid storage organ in the form of triglycerides (TG), which is the most efficient way to store calories. The functional idea was that in case of a chronic positive energy balance, the excess calories are converted into TG mainly under the control of insulin, while in case of undernutrition and higher energy demand, TG are rapidly mobilized upon increased secretion of catecholamines and other lipolytic hormones (9).

Because more than 90% of the adipocyte volume consists of TG, changes in adipocyte volume depend on the balance between synthesis (lipogenesis) and breakdown (lipolysis) of

TG (10). There are distinct age-dependent variations in adiposity, which are measured by body mass index (BMI) and other anthropometric criteria (11).

A SIMILARITY AT EXTREMITY: LIPODYSTROPHY VERSUS OBESITY

Presence of average amount and functionally active adipose tissue is crucially important for good health, including the regulation of lipid and energy metabolism. From the study of sterol response element-binding protein-1c (SREBP-1c)-deficient mice “we learned that too much fat is bad and so is not enough fat. The punch line here is that a little fat is good”, quoting Charles Vinson, a co-author of this study (12). Extreme ends of adipose mass growth, obesity and lipodystrophy, result in almost similar clinical metabolic disorders (12-15).

Lipodystrophies

Lipodystrophies are rare acquired and genetic disorders characterized by the selective loss of adipose tissue. Despite marked phenotypic heterogeneity among the different types of lipodystrophies, most of them predispose to metabolic complications seen in patients with obesity, such as insulin resistance, T2DM, hepatic steatosis, and dyslipidemia (12).

The underlying mechanisms that cause insulin resistance and the metabolic syndrome in patients with obesity and lipodystrophies may be similar. For example, in patients with severe forms of obesity and lipodystrophies, there may be limitation in further storage of TG in adipose tissue, which results in diversion of TG to aberrant sites such as the liver and skeletal muscles and results in insulin resistance (11).

Currently, an acquired form of lipodystrophy occurs in HIV infected patients treated with highly active antiretroviral therapy that contains HIV-1 protease inhibitors (HIV-1-PI). The latter have been reported to inhibit adipogenesis, increase lipolysis, and decrease glucose uptake, thus resulting in HIV-related adipose tissue redistribution syndrome (15-15a). Importantly, SREBP-1 levels may be altered in both the liver and adipose tissue of animals treated with HIV-1-PI, and may be a pathogenetic mechanism of this kind lipodystrophy, because SREBP-1c overexpression in adipose tissue has been reported to cause lipodystrophy (15).

Obesity

Generally, obesity can develop when energy intake is in excess of energy expenditure, differences in input and output being

buffered primarily by changes in the fat stores (16). Today, (i) obesity may be defined as a tumor-like expansion of adipose tissue (16), (ii) obese adipose tissue is a human body's largest source of endocrine protein and steroid signals (3), and (iii) upregulation of some of these signals being of pro-inflammatory nature is increasingly implicated in the pathogenesis of obesity-related, low-graded inflammatory disorders, including CMD (2,3).

With TG constituting $\geq 85\%$ of the tissue weight, there being only a thin area of cytoplasm between the fat droplet and the plasma membrane of the adipocyte. There are some 14 members of the facilitative glucose transporter gene family (gene name SLC2A), and white adipocytes appear to express as many as eight members: GLUT1, GLUT3, GLUT4, GLUT5, GLUT8, GLUT10, GLUT12, H⁺-coupled myoinositol transporter (17-19). These glucose transporters are highly important for glucose buffering and *de novo* lipid synthesis from carbohydrates. Moreover, direct measurements in humans by isotopic techniques under conditions of energy balance revealed that the contribution of hepatic *de novo* lipid synthesis to new TG is rather low comparing to adipose tissue. Thus, even this example is enough to stress the importance of adipose tissue

in the development of pandemics of diet-induced obesity due to glucose rich nutrition.

REGIONAL DIFFERENCES IN ADIPOKINE SECRETION

Clinical observations suggest that an abdominal pattern of fat distribution with increased visceral fat mass is closely associated with the adverse cardiometabolic consequences of obesity (Fig. 1). There is accumulating evidence that substantial differences may also exist for the secretory profile in subcutaneous and omental adipose tissue (3,20).

Recent studies have shown that not only is lower-body fat accumulation less deleterious than upper-body fat, it may actually be protective. Lower-body or peripheral subcutaneous fat is negatively associated with cardiometabolic risk factors, including insulin resistance, LDL cholesterol, TG, and blood pressure, and is associated with protection against atherosclerosis (21). It has been suggested that this might reflect the ability of lower-body adipose tissue to sequester fatty acids (FA) and thus protect other insulin-sensitive tissues from the adverse effects of TG accumulation (so-called ectopic fat deposition) (22).

Moreover, the paracrine secretion by the small, organ-as-

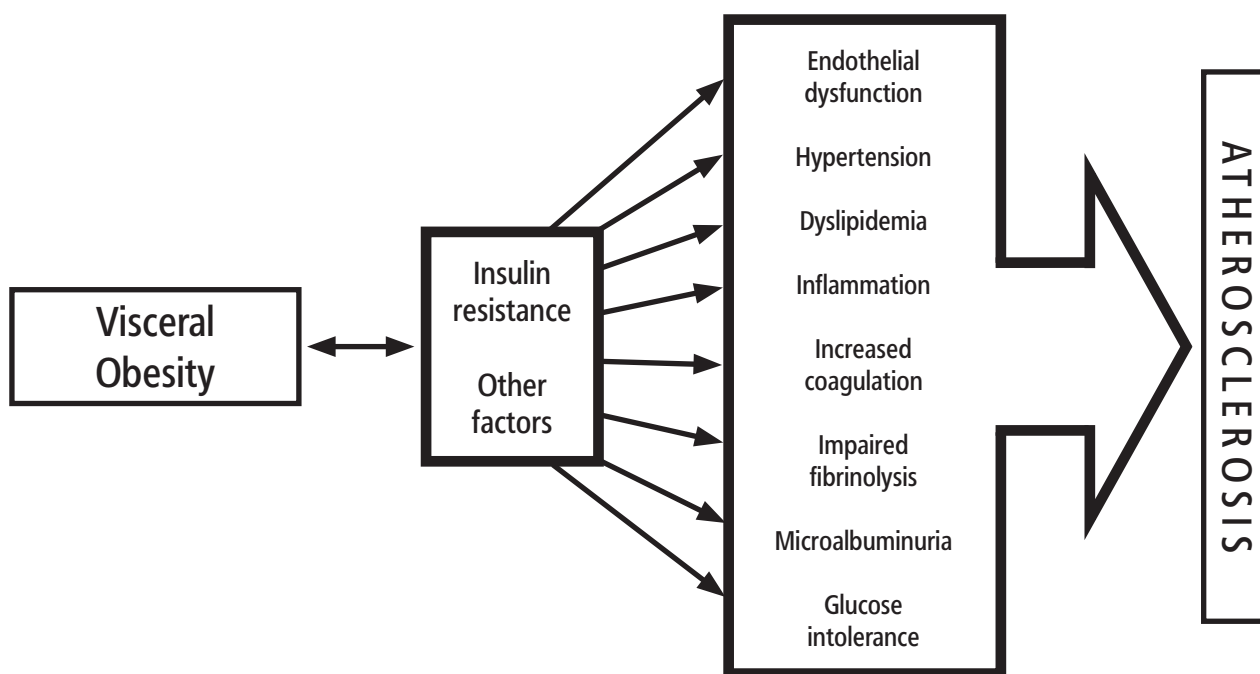


Figure 1. Visceral adiposity and atherosclerosis. Depicted is the significance of visceral obesity as a cause of important cardiometabolic risk factors.

sociated adipose depots have become a focus in the adipobiology of inflammation (23), including a possible link between epicardial adipose tissue and coronary atherosclerosis (23,24). It was found that “atherosclerotic” epicardial adipose tissue produces an increased amount of nerve growth factor (NGF) (2,23 and references therein) and of pro-inflammatory adipokines, whereas a decreased amount of adiponectin (24), a potential anti-inflammatory adipokine.

Japanese Sumo wrestlers are very good example to elucidate the significance of regional fat distribution in obesity. They eat a high energy diet to gain weight but, at same time, they are forced to perform strenuous physical training daily. Although they showed marked obesity, visceral fat ratio was comparable to subcutaneous fat obesity. Their glucose and lipid levels are normal. A computer tomograph scan imaging at the level of umbilicus demonstrated fat accumulation only in the subcutaneous fat obesity and showed marked muscularity. The incidence of diabetes increases markedly among retired wrestlers who do not continue physical exercise, but remain heavy eaters (25,26).

ADIPOSE TISSUE AND INFLAMMATION

An interesting phenomenon is that not all the molecules released from adipose tissue are produced by adipocytes (3,27-30). Recent studies suggest that obesity is characterized by an accumulation of macrophages in adipose tissue. Adipose tissue infiltration by macrophage (3,30, also see Permana in this volume of *Biomedical Reviews*) and mast cell (1) appears to substantially contribute to the inflamed adipose tissue-triggered release of pro-inflammatory adipokines in obesity and related CMD (31-36).

Like macrophages, the adipocyte is exquisitely sensitive to infectious disease agents and cytokine-mediated inflammatory signals. Adipocytes express a host of receptors, enabling them to sense the presence of pathogens and inflammatory signals. This activates multiple inflammatory signal transduction cascades, and secretes a number of potent inflammatory adipokines. Adipocytes and resident macrophages contribute independently to the local adipose inflammatory output.

The systemic inflammation observed in obesity is derived not only from adipose tissue but also from the liver and other important inflammatory tissues. However, even for some of the proteins derived from the liver, it is believed that adipose tissue is the initial driving force for their upregulation. Recent

studies have led to a major breakthrough in our understanding of the origin and the role of tumor necrosis factor- α (TNF- α) and other cytokines in obesity. Macrophage accumulation occurs in proportion to adipocyte size (32). This adipocyte size-related accumulation probably increases the capacity for production of proinflammatory and acute phase molecules that contribute to obesity-related disorders. Thus the obesity related increase in macrophages could be largely responsible for the major part of TNF- α , IL-1, IL-6, MCP-1 (CCL2), and iNOS expression in adipose tissue. Release of macrophage TNF- α and IL-6 may contribute to the local decrease in insulin sensitivity of adipocytes and to all the other TNF- α - and IL-6-related disturbances (33-36).

Adipocytes as well as nonfat cells of adipose tissue are now recognized as *bona fide* secretory cell types (1,3,20,27-30). Quantitatively, the most important secretion is FA, of which there is a net release at periods of negative energy balance, particularly fasting and during acute cold exposure. In addition to FA, several other lipid moieties are released by fat cells; these include prostanoids, which are synthesized by the tissue, and cholesterol and retinol, which are not synthesized but rather are stored and subsequently released (35). In addition, certain steroid hormone conversions can take place within white adipocytes, such as the activation of 11-dehydrocorticosterone (cortisone in humans) into active corticosterone (cortisol) catalysed by 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) (36). When overexpressed in adipocytes of transgenic mice, this enzyme induces the complete clinical picture of the metabolic syndrome (37), suggesting that the inhibition of the activity of 11 β HSD-1 may be of a potential therapeutic benefit for CMD.

After the identification of leptin as a specific adipocyte-derived cytokine/hormone, numerous reports have been published which clearly established that adipose tissue is a multifunctional organ that produces and secretes dozens of factors that act either in an auto-, para- and/or endocrine fashion (1-3,20,31,35,36).

NON-ADIPOKINE ADIOPHARMACOLOGY

Fatty acids

The release of free fatty acids (FFA) from adipose tissue regulates systemic FFA concentrations. Under physiological conditions, FFA concentrations fluctuate and this is regulated by the balance between lipolytic and antilipolytic effects in

adipose tissue. Antilipolysis as a pharmacological means of regulating FFA concentrations is effectively implemented by nicotinic acid. The recent demonstration of a G-protein-coupled receptor through which nicotinic acid signals give new and mechanistic insight to the action of an old drug (38). The expression of the receptor gene in adipose tissue gives the mechanistic framework for the antilipolytic action of nicotinic acid. In addition, efflux of cholesterol from macrophages is mediated by the ATP-binding cassette protein A1 (ABCA1) transporter; of note, nicotinic acid appears to upregulate the ABCA1 gene through cAMP/PKA-dependent pathway (39). It is therefore entirely possible that nicotinic acid increases the entry of macrophage-derived cholesterol into the HDL pool and that this is an antiatherogenic property of nicotinic acid which is independent of the TG-lowering effect of the drug (38,39).

Based on findings in rodents it has been postulated that insulin sensitization by the peroxisomal proliferator-activated receptor- γ agonists (PPAR- γ) thiazolidinediones (TZDs) depends on lowering of systemic concentrations of FFA. As these compounds promote lipogenesis, it is thought that they would also promote fat storage in adipose tissue. In humans, however, fasting FFA concentrations are not significantly reduced by rosiglitazone or pioglitazone in patients with T2DM, despite a clear insulin-sensitizing effect of these drugs (40).

Clearly, TZDs have a range of effects other than reducing systemic concentrations of FFA that contribute to insulin sensitization. These include stimulation of adiponectin secretion and receptors, downregulation of inflammatory mediators derived from adipose tissue and, most probably, exerting direct effects on skeletal muscle that are independent of lipid transport (41).

Free fatty acids are a normal physiological fuel. Like cholesterol, they are necessary for life and only harmful to the organism when present in excessive amounts. Interfering with FFA metabolism pharmacologically needs some caution because reduction of fasting FFA concentrations is not a desirable goal. It seems likely that suppressing FFA release in the fasting state with the nicotinic acid analogue acipimox distresses to body's energy regulation. A better strategy may be to modulate postprandial FFA metabolism (42).

C-reactive protein

One of the best examples of the clinical marker of systemic inflammation is C-reactive protein (CRP). The regulation of

CRP in the liver is believed to be driven by IL-6. It may be IL-6 derived from visceral adipose tissue draining directly into the portal system that causes the obesity-associated rise of liver CRP production (43). In addition to liver-derived CRP, newer data show that adipose tissue itself may contribute to obesity-associated increased CRP levels (44).

Elevated CRP levels in obesity and the decreases associated with weight loss provide another suggestive link between CRP and obesity-associated risks for CMD. There is *in vitro* evidence demonstrating that CRP also may be an active mediator of inflammatory vasculopathy. It was proposed that the complement-activating and opsonizing activities of CRP actually participate in the postinfarction pathology (45). Elevated CRP levels have been associated with endothelial dysfunction and the activation of endothelial nuclear factor kappa-beta (NF- κ B). Moreover, a number of pharmacological interventions aimed at improving insulin sensitivity (with TZDs or metformin), hypertension (angiotensin converting enzyme inhibitors), or cholesterol biosynthesis (statins) have also been shown to cause significant reductions in CRP levels (45,46) (Fig. 2).

ADIPOKINES AS PHARMACOLOGICAL TARGETS

Plasminogen activator inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1), although it usually derived from platelets and endothelium, is also synthesized in both liver and in adipose tissue. Messenger RNA^{PAI-1} concentrations increase up to 10-fold in visceral adipose tissue during development of fat accumulation while remains unchanged in subcutaneous adipose tissue (48).

It is not yet known why adipocytes secrete a large amount of PAI-1. Adipocytes change their cell size dramatically in response to nutritional signals. Although not directly demonstrated, it is possible to assume that adipose PAI-1 overexpression may contribute to the elevated risk of obese subjects to suffer from thromboembolic complications. Recent studies indicate that compounds with anti-inflammatory activity such as TZDs, metformin and angiotensin II-receptor antagonists may reduce adipose PAI-1 production (48).

Tumor necrosis factor- α

Tumor necrosis factor- α (TNF- α) is a proinflammatory cytokine that is involved in the pathogenesis of septic shock, autoimmune inflammatory disease, and host defense against tumors. Hotamisligil *et al* (49) were the first to describe adipose

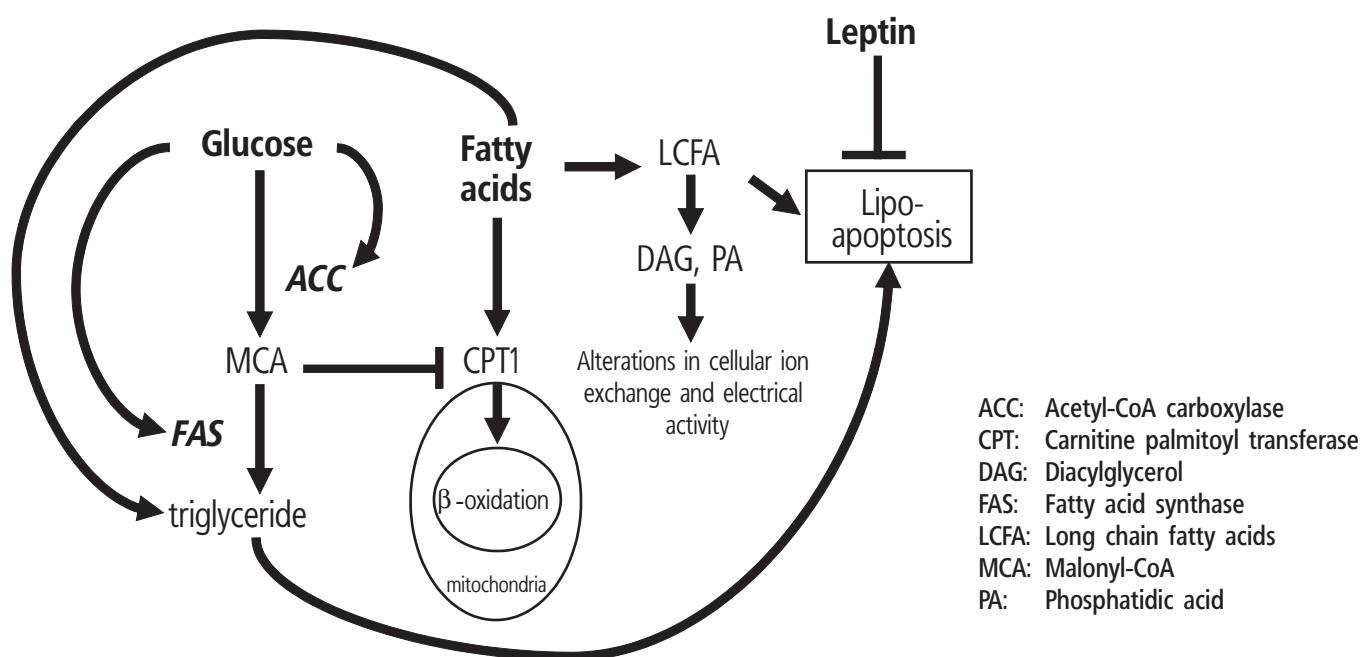


Figure 2. Hyperglycemia associated lipoapoptosis in the nonadipose cell. Excessive glucose intake stimulates de novo lipogenesis producing increased malonyl-CoA, which inhibits the enzyme carnitine palmitoyl transferase 1. Consequently, accumulated unoxidized long chain fatty acids in the cytosol cause lipoapoptosis.

tissue expression of TNF- α and its upregulation in rodent models of obesity and insulin resistance. Some of the contribution of TNF- α to vasculopathic processes may be mostly through its involvement in the development of insulin-resistant in T2DM (50). Tumor necrosis factor- α is a potent inhibitor of adiponectin synthesis, and increased secretion from accumulated visceral adipose tissue may be one of the reasons for the reduction of adiponectin in visceral obesity (51).

The animal studies on TNF- α and development of atherosclerosis have produced mixed results. Insulin sensitizers, TZDs, lower serum TNF- α in human and block TNF- α -mediated inhibition of insulin signaling (52). Neutralization of TNF- α had no effect on insulin sensitivity in obese, insulin-resistant subjects (53). More recent observations with the TNF- α antibody infliximab, a currently prescribed biological to treat rheumatoid arthritis, Crohn's disease and psoriasis, point to a possible benefit also for insulin sensitivity. These studies suggest that a chronic treatment rather than a single administration with TNF- α blocking agent is required to affect insulin sensitivity (54). Of note, TNF- α is thought to play a role in the progression of ischemia-related congestive heart

failure; however anti-TNF therapy has shown no benefits for congestive heart failure progression in patients (55). Whether this may be the case for adipose-derived TNF- α -related disorders, remains to be evaluated.

Interleukin-6

Interleukin-6 (IL-6) is long known as a multipotent cytokine. Clinical observations suggest that IL-6 may act as a central mediator of inflammation in obesity and may be the link to the increased risk of atherosclerosis (56). Adipose tissue has been shown to synthesize and secrete IL-6; it is estimated that approximately 25% of the circulating IL-6 originates from the adipose tissue. Omental adipose tissue secretes three times as much IL-6 as does its subcutaneous counterpart. The direct contribution of the adipocytes is only 10%, whereas stromal tissue accounts for 90% of the total IL-6 that is released from adipose tissue (57). The high levels of IL-6 are likely responsible for the increase in acute-phase proteins, such as CRP, observed in obese subjects. Although only minor autocrine/paracrine effects of IL-6 have been demonstrated in adipose tissue, it appears likely that the elevated adipose

expression of IL-6 in the obese state is of substantial physiological importance for the crosstalk between adipose tissue and distant organs and remains potentially important targets for prevention of inflammation-induced insulin resistance and vasculopathy (58). Further, it was analyzed differentiated adipocytes *in vitro* after statin treatment and found a reduction of IL-6 secretion (58).

Monocyte chemoattractant protein-1

The chemokine monocyte chemoattractant protein-1 (MCP-1), also named CCL2 (cysteine-cysteine motif chemokine ligand 2), has recently been added to the growing list of adipokines (59-63). It recruits monocytes, leukocytes and other inflammatory cells in response to inflammatory challenges. Circulating MCP-1 has been found to be increased in obesity and reduced after weight loss. This chemokine and its receptor, CCR2, have a negative role in adipogenesis and insulin sensitivity (61,62). Further, perivascular adipose tissue (23,24) also produces various chemokines, suggestive of their paracrine involvement in the process of atherogenesis (63).

Current understanding would suggest that treatments that prevent macrophage infiltration into obese adipose tissue will have beneficial effects on the inflammatory response and the abnormal metabolic state. Moreover, the finding that MCP-1 is approximately 7-8 fold higher in the stromovascular fraction of adipose tissue (3) and the attenuation of MCP-1 release by the anti-diabetic compounds metformin and TZDs supports the hypothesis that these drugs exert anti-inflammatory effects and thus improve low-grade inflammation in obesity (64).

Angiotensinogen and angiotensin II

Recent studies showed that adipose tissue may indeed function as a jugstglomerular-like apparatus, secreting all known components of renin-angiotensin system. Accordingly, the expression of angiotensinogen is significantly higher in adipose tissue from obese as compared to lean subjects. In addition, adipose cells from the omental depot produce more angiotensinogen than adipocytes from the subcutaneous depot (65).

In humans, angiotensin II (Ang II) was demonstrated to act as an inhibitor of adipose tissue differentiation, whereas the presence of a selective Ang II receptor antagonist induces adipocyte formation (66). Angiotensin II is also a potent inducer of PAI-1 production in human adipocytes and this effect is completely abolished by blockade of the Ang II receptor. Thus

elevated secretion of Ang-II in obesity may contribute to the development of hypertension and atherosclerosis (66).

Leptin

In 1994 (67), the paradigm-shifting discovery of adipocyte-derived leptin fundamentally changed our perspective of adipose tissue from that of an inert lipid and energy store to an active endocrine and metabolic organ that secretes numerous adipokines. Leptin was identified as an adipokine whose absence resulted in morbid obesity in *ob/ob* mouse (68-74). Although initially hopes were high that leptin would prove important in the pathophysiology and thus treatment of human obesity, early studies quickly showed that human obesity is generally not associated with leptin deficiency (69).

The effect of leptin on lipid metabolism may be mediated both through central and peripheral actions of leptin. For example, central administration of leptin increased resting metabolic rates, resulting in reduced TG content in adipose and nonadipose tissues, as well as reduced plasma FFA and TG levels (70).

Leptin may also exert autocrine and paracrine effects on adipocyte fat metabolism: incubation of mouse adipocytes with leptin stimulates lipolysis of intracellular TG. Overexpression of leptin in adipocytes also reduced gene expression of acetyl CoA carboxylase, which is the rate limiting enzyme in *de novo* lipogenesis. In other tissues, leptin also appears to inhibit lipogenesis and stimulate FA oxidation (71).

Leptin directly stimulates 5'-AMP-activated protein kinase (AMPK), which increases ATP-producing catabolic pathways, such as beta oxidation of FA, glycolysis, and mitochondrial biogenesis, and concomitantly decreases ATP consuming anabolic pathways including the phosphorylation and thereby inhibition of the acetyl CoA carboxylase activity and lipogenesis. Leptin also can inhibit the expression of lipogenic transcription factor SREBP-1c in liver, pancreatic islets, and adipose tissue, thereby inhibiting lipogenesis in those tissues (70,71).

Leptin confines storage of excess calories to adipocytes and spares the appearance of chronic steatosis in nonadipocyte cells. Defective leptin production and action have been proposed to be an important element of the metabolic syndrome. Hyperleptinemia in the obese is considered to protect nonadipocytes from lipotoxicity (72).

Some actions of leptin in high concentrations could be associated to effects independent of leptin receptor. Crosstalk of leptin pathways with other cytokine-related pathways is

important in the obesity-related pathologies because of the similarities of leptin to the some inflammatory cytokines including IL-6. Further, a large prospective study – the West of Scotland Coronary Prevention Study (WOSCOPS) – showed, for the first time, that leptin might be an independent risk factor for coronary heart disease (73).

Leptin plays a physiological role but leptin resistance may be of pathophysiological significance for cardiometabolic dysfunctions in obesity. Lipoapoptosis is a metabolic cause of tissue injury and death in obesity (74,75). Leptin is capable of oxidizing excessive long-chain FA to improve cardiac function. However, the leptin-induced FA oxidation may become inefficient under hyperleptinemia or leptin resistance, allowing unoxidized FA to enter nonoxidative pathways, eventually leading to cellular injury. Leptin-induced liporegulation serves to prevent lipid accumulation and lipoapoptosis (Fig. 3). Disruption of liporegulation in response to leptin is hypothesized to be essential under hyperleptinemia and may attribute to the metabolic syndrome in obesity (72).

Leptin supplementation is currently used clinically to treat patients with congenital leptin deficiency. Leptin deficiency is also found in acquired and inherited lipodystrophies, which are associated with severe insulin resistance, dyslipidemia and hepatic steatosis as stated above. Leptin-replacement therapy in these patients leads to a correction of the hyperglycemia and a reduction in plasma lipids, thus helping to minimize the risk of metabolic complications (76).

Adenovirus-induced hyperleptinemia promotes a dramatic reduction of white adipocyte size in rats, and the FA are oxidized directly inside the adipocytes that become able to burn fat (77). Physiological and therapeutic importance of this observation needs further studies.

Adiponectin

Adiponectin is thus far the best-studied adipokine until now. Although there are extra-adipose sources of adiponectin, the adipocytes are the most important producer of this multipotential adipokine. Today, adiponectin is promising a large number of therapeutic benefits, including many “anti-” effects, such as anti-inflammatory, anti-atherogenic, anti-diabetic, anti-obesity, and anti-cancer effects (25,78-84).

Very strong negative correlation is found between the adiponectin level and visceral adiposity. The mechanism for the reduction of plasma adiponectin levels in individuals with visceral fat accumulation has not yet been clarified.

However, some findings suggest that some inhibiting factors for adiponectin synthesis or secretion are secreted from visceral adipose tissue. Most probably, the increased secretion of TNF- α from accumulated visceral fat is responsible for this negative correlation (79).

Plasma adiponectin concentrations are lower in people with T2DM, and high adiponectin concentration was a notable protective factor against development of this disease. Likewise, plasma concentrations of adiponectin are lower in patients with coronary heart disease and with the metabolic syndrome (80). In a prospective study it is confirmed that high adiponectin concentrations are associated with reduced risk of acute myocardial infarction in men (81).

Adiponectin administration enhanced hepatic insulin action and reduced liver gluconeogenesis and lipid accumulation in nonadipose tissues. Glucose uptake and FA oxidation were increased, whereas lipid accumulation was decreased in skeletal muscle. Adiponectin effects are mediated by AMPK, which has been reported to increase FA oxidation during muscle contraction and repress key enzymes of gluconeogenesis in hepatocytes. AMPK is known to mediate the insulin sensitizing action of exercise, some antidiabetic effects of metformin, and leptin action on skeletal muscle (82).

The clinical and experimental evidence of adiponectin's multibeneficial effects might lead to the development of new therapeutic strategies for CMD (1,2,23,24,31,78-81,83,84). For instance, human recombinant adiponectin and/or adiponectin-mimetic compounds acting less or more specifically on adiponectin receptor subtypes might be new therapeutic approaches. Likewise, boosting adiponectin secretion in adipocyte and extra-adipose sources by small molecules appears to be a promising pharmacological strategy (84 for PPAR γ agonists). For more information about adiponectin biology and pharmacotherapy, see Shimomura *et al* and Cheng *et al* in this volume of *Biomedical Reviews*.

Resistin

Resistin (FIZZ-3, found in inflammatory zone-3) received its name from the original observation that it induced insulin resistance in mice. In humans, the role of resistin is even less certain. Some investigators reported low to undetectable expression of resistin in adipose tissue, whereas it is expressed at higher levels in macrophages (85). The role of resistin in human insulin resistance remains quite controversial. However, in humans, resistin seems to act as a critical mediator

of the insulin resistance associated with sepsis and possibly other inflammatory conditions (86).

ADIOPHARMACOLOGY OF CURRENTLY USED DRUGS

Thiazolidinediones

The most prominent examples of drugs favoring a healthy adipokine profile are the TZDs represented by PPAR- γ agonists. Various beneficial cardiometabolic effects reported for PPAR γ agonists are thought to result from direct actions on adipose tissue, along with secondary impact on skeletal muscle and liver. The beneficial actions of PPAR γ agonists on muscle, liver, and blood vessels are mediated by their ability to (i) improve the insulin-mediated uptake and metabolism of glucose and FFA in the adipocyte, (ii) increase the secretion of adiponectin, and (iii) reduce the production of factors leading to insulin resistance, such as TNF- α and resistin (87,88). The role of the TZDs rosiglitazone and pioglitazone in the treatment of T2DM is well established. The anti-inflammatory effects of TZDs may partly be mediated by their beneficial effects on dyslipidemia, but there is also evidence that TZDs may directly modulate inflammation via transcription factors such as NF- κ B (89).

Statins

Statins were introduced and then widely used for the management of plasma cholesterol levels in patients with atherosclerotic cardiovascular disease. This class of drugs comprises inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis primarily in the liver. Importantly, statins may affect therapeutically not only cholesterol levels, but many other processes such as various cellular events in atherogenesis and inflammation (90) and even T2DM-linked cognitive dysfunction (91,92).

As outlined above, the reduction of general inflammatory markers is advisable for the reduction of cardiovascular events along with an improvement of the lipoprotein profile. C-reactive protein is expressed in adipose tissue, but this tissue is unlikely to be a major systemic source for this protein. An alternative explanation is that statins might achieve some of their beneficial effects by altering the composition of adipocyte plasma membranes and/or the secretion of adipokines (58). In the context of obesity and adipose-derived inflammation, it was reported that statins may have direct anti-inflammatory

actions on adipocytes themselves (93) (Fig. 2). Treatment of cultured adipocytes with cerivastatin decreased expression and secretion of the pro-inflammatory adipokine IL-6 (58). Further studies may clarify the possible statin-adiponectin interactions and their implications for the therapy of adiponectin-associated diseases.

Adipocytes have very important functions in cholesterol homeostasis. Adipose tissue contains the largest pool of free cholesterol in the body. Adipocytes can uptake and degrade oxidized LDL (Ox-LDL) while such an ability was impaired under hypercholesterolemic condition (94). Speculatively, statins might increase uptake of ox-LDL by reducing cholesterol level and changing the transcriptional ability of adipocytes (95).

NEW TARGETS FOR ADIOPHARMACOLOGY

5'-AMP-activated protein kinase

5'-AMP-activated protein kinase (AMPK) is a heterotrimeric enzyme that is conserved from yeast to humans and function as a "fuel gauge" to monitor cellular energy status. AMPK stimulates pathways which increase energy production (glucose transport, FA oxidation) and switches off pathways which consume energy (lipogenesis, protein synthesis, gluconeogenesis). Activation of AMPK leads to phosphorylation, and thus inhibition of CoA carboxylase (82). The latter is the regulated step in malonyl-CoA production and subsequent FA biosynthesis. Malonyl-CoA is also a potent inhibitor of carnitine palmitoyl transferase-1, the rate-limiting enzyme of FA uptake into the mitochondria. Therefore, a reduction in malonyl-CoA removes inhibition of mitochondrial FA uptake and stimulates FA oxidation, as well as reduces lipid biosynthesis (22) (Fig. 3).

Adipose tissue is a major component of energy homeostasis and a key player in the regulation of insulin sensitivity through FA release and hormone secretion. Thus, it is clear that the function of AMPK in adipocytes should be crucial for the regulation of energy metabolism through the release of substrates and hormones involved in metabolism. While activation of adipose AMPK can be achieved through fasting and exercise (96), no pharmacological agents for treating obesity and obesity-associated diseases have been reported in targeting AMPK until now. Of note, two compounds that are widely used in the therapy of T2DM, metformin and rosiglitazone, have been demonstrated to activate AMPK (97).

ADIPOSE TISSUE AND LONGEVITY

Aging is a multiplex phenomenon characterized by the decay of biological function over time, eventually leading to the development of various disease. Adipose tissue seems to be a pivotal organ in aging processes and in determination of lifespan (98). Calorie restriction (CR) is the most robust, nongenetic intervention that increases lifespan and reduces the rate of aging in a variety of species (99-101). Mechanisms responsible for the anti-aging effects of CR remain uncertain, but reduction of reactive oxygen species (ROS) within mitochondria remains a major focus of research. Specifically, both *in vivo* and *in vitro* analyses have demonstrated that CR attenuates ROS-mediated damages (102), also stimulates mitochondrial biogenesis through induction of endothelial nitric oxide synthase expression in various tissues of mice (103, also *via* sirtuin-1 upregulation). In effect, mitochondria may play a pivotal role in the life of cells, controlling diverse processes ranging from energy production to

apoptosis (104). Further, small molecules including xenohormetics (105-107) may provide a benefit to aging and related diseases including Alzheimer's disease (106,107). Fat-specific disruption of the insulin receptor gene mice demonstrates the important role of reduced adiposity and suggests a special role for the insulin signaling pathway in adipose tissue in the longevity process (108). The effect of adipose tissue reduction on lifespan could be due to the production of adipokines acting on target tissues, or due to the indirect prevention of age-related metabolic disorders like T2DM or atherosclerosis (see 91,92).

Sirtuin 1, an ortholog protein encoded by the life-extending yeast gene silent information regulator 2 (*Sir2*), is involved in the molecular mechanisms linking lifespan to adipose tissue. In mature adipocytes, stimulation of sirtuin 1 activity by a small molecule, resveratrol (found in red grapes and red wine), promotes lipolysis and a reduction in adipose tissue mass (105-107).

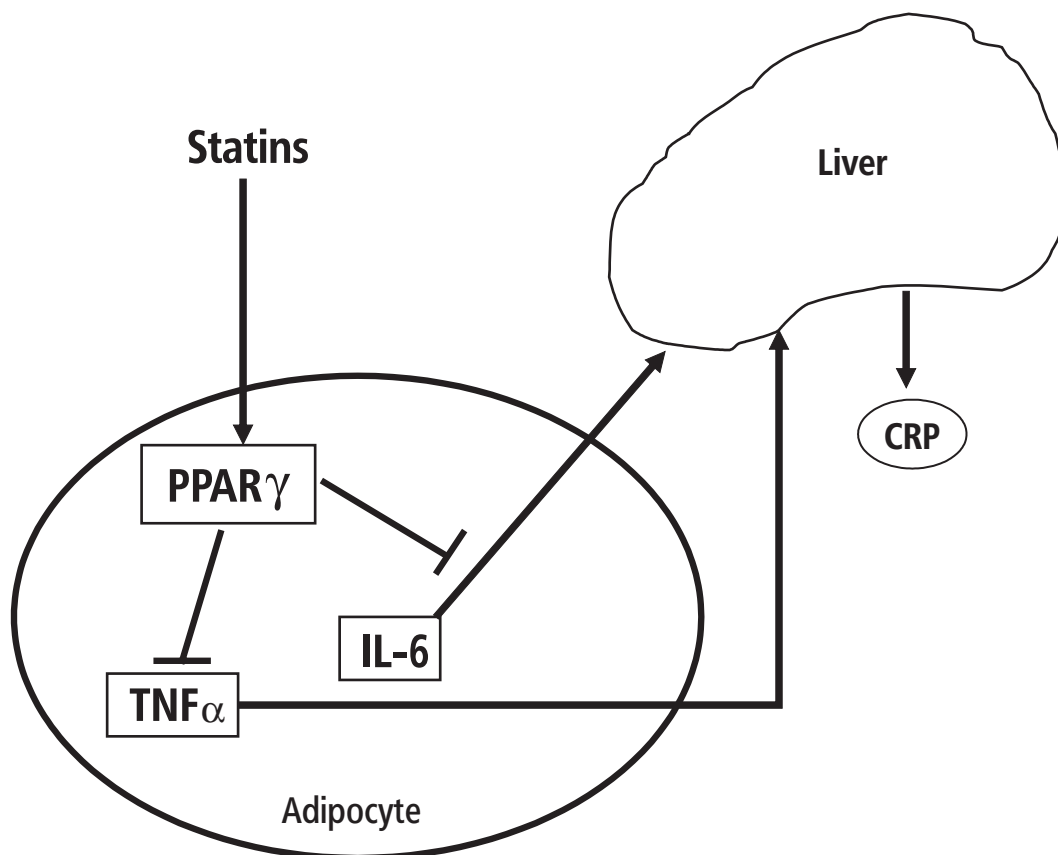


Figure 3. Anti-inflammatory action of statins. Inflammatory molecules, IL-6 and TNF- α , are under the inhibitory control of adipocyte transcription factor PPAR γ . Statins stimulate the activity of PPAR γ and suppress the production of these proinflammatory adipokines. CRP, C-reactive protein.

CONCLUSION AND A DREAM

The adipose tissue is now increasingly recognized not solely as lipid and energy storage but also as an active endocrine and paracrine organ, secreting a large number of adipokines, and also steroid hormones, fatty acids, and prostaglandins. There is overwhelming evidence that adipose tissue is at the center of dysfunctional regulatory cascades in many diseased states, ranging from CMD, fatty liver diseases, polycystic ovary syndrome, cancer, and Alzheimer's disease (type 3 diabetes?). Today, it is also extremely important to understand if this adipose dysfunction can be restored by dietary intervention and/or by pharmacological treatment. Whatever the research outcomes and possible discoveries, Paul Ehrlich's "magic bullets" in the adipopharmacology of disease will continue to be a dream of *Homo obesus* and his accompanying diseases.

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