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Metabolism and secretory function of white adipose tissue: effect of dietary fat

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ABSTRACT

Approximately 40% of the total energy consumed by western populations is represented by lipids, most of them being ingested as triacylglycerols and phospholipids. The focus of this review is to analyze the effect of the type of dietary fat on white adipose tissue metabolism and secretory function, particularly on haptoglobin, TNF-α, plasminogen activator inhibitor-1 and adiponectin secretion. Previous studies have demonstrated that the duration of the exposure to the high-fat feeding, amount of fatty acid present in the diet and the type of fatty acid may or may not have a significant effect on adipose tissue metabolism. However, the long-term or short-term high fat diets, especially rich in saturated fatty acids, probably by activation of toll-like receptors, stimulated the expression of proinflammatory adipokines and inhibited adiponectin expression. Further studies are needed to investigate the cellular mechanisms by which dietary fatty acids affect white adipose tissue metabolism and secretory functions.

Key words: adipokines, high fat diets, metabolism, white adipose tissue.

INTRODUCTION

White adipose tissue (WAT) plays a role in energy storage and insulation from environmental temperature and trauma. Paleontological evidence indicates that the rapid brain evolution, observed with the emergence of *Homo erectus* at approximately 1.6–1.8 million years ago, was likely associated with increased body fatness as well as diet quality (Leonard et al. 2003). In the long run, white fat mass reflects the net balance between energy expenditure and energy intake. Fat storage occurs both by the direct uptake of circulating lipoprotein triacylglycerols, which are hydrolyzed by lipoprotein lipase to non-esterified free fatty acids, and also by local lipogenic pathways, i.e. the *de novo* synthesis from glucose and other precursors (Pénicaud et al. 2000). On the other hand, this tissue can release both free fatty acids and glycerol, providing circulating substrates for other tissues, according to their energy needs.

Currently, it has been recognized that white adipose tissue acts also as an endocrine organ. This tissue secretes pro and anti-inflammatory protein factors, known as adipokines. These adipokines include hormones implicated in energy balance (e.g., leptin, adiponectin), glucose tolerance and insulin sensitivity (adiponectin, resistin), classical cytokines (e.g., TNF-α, interleukin-6), and proteins involved in lipid metabolism (e.g., lipoprotein lipase, retinol binding protein), vascular haemostasis (e.g., plasminogen activator inhibitor-1 and angiotensinogen) and in inflammation and stress responses (such as haptoglobin and metallothionein) (Trayhurn and Beattie 2001, Mohamed-Ali et al. 1998, Frühbeck et al. 2001).

In commemoration of the 75th anniversary of
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This review analyses the impact of dietary fatty acid composition on adipose metabolism and secretory function.

METABOLISM OF WHITE ADIPOSE TISSUE

Lipoprotein Lipase and Triacylglycerol Metabolism

Lipoprotein lipase (LPL) has its physiological site of action at the luminal surface of capillary endothelial cells, where the enzyme hydrolyses the triacylglycerol (TAG) component of circulating lipoprotein particles, chylomicrons and very low density lipoproteins to provide free fatty acids and 2-monoacylglycerol for tissue utilization. LPL is distributed in wide range of tissues (Cryer 1981).

Most of the plasma triacylglycerols are provided by dietary lipids, secreted from the intestine in the form of chylomicron or from the liver in the form of VLDL. Released into circulation as non-esterified fatty acids by lipoprotein lipase, those are taken up by WAT via specific plasma fatty acid transporters (CD36, FATP, FABPpm) and used for triacylglycerol synthesis (Large et al. 2004).

LPL activity can be altered in a tissue-specific manner, which is physiologically important because it directs fatty acid utilization, according to the metabolic demands, of individual tissues, so that the degradation of triacylglycerol-rich lipoproteins can be targeted to specific sites. For example, we observed a dramatic increase in mammary gland LPL activity with a corresponding decrease in WAT LPL activity during lactation to provide lipid for milk synthesis (Oller do Nascimento and Williamson 1986). On the other hand, after the removal of the pups, the activity of LPL in WAT is increased considerably compared with lactating mammary gland, which play a role in the replenishment of adipose tissue stores.

Starvation and malnutrition decreased LPL activity in mammary gland and WAT and increased it in muscle (Oller do Nascimento and Williamson 1988, do Carmo et al. 1996, Doolittle et al. 1990, Braun and Severson 1992). On the other hand, in the fed state, the LPL activity is increased in WAT and decreased in muscle. The physiological results are a preferential deposition of lipid in the adipose tissue after a meal, and supply energy to skeletal muscle during food deprivation.

The plasma insulin concentration seems to be more important than prolactin in controlling LPL activity and lipid deposition in WAT during lactation and after weaning (Oller do Nascimento et al. 1989).

Insulin increases LPL gene expression and activity in WAT via activation of phosphatidylinositol 3-kinase (PI3K) pathway (Kraemer et al. 1998). Glucocorticoids also increased LPL mRNA and LPL activity. Taking together, these hormones have a synergistic effect at the level of LPL gene expression, as well as posttranslationally (Fried et al. 1993).

In the monosodium glutamate model of obesity (MSG-obese), it has been demonstrated hyperinsulinemia (Sartin et al. 1985) and hypercorticosteronemia (Ribeiro et al. 1997, Dolnikoff et al. 1988) accompanied by an increase in WAT LPL activity (Nascimento Curi et al. 1991).

Lipogenesis *de novo*

The lipogenesis *de novo* is an important pathway to convert the excess of carbohydrate ingested to triacylglycerol to be stored into the WAT. Physiological factors such as dieting/fasting regulate this metabolic pathway, which is also modified in pathological conditions e.g. obesity. Several tissues (e.g. white and brown adipose tissue, liver, mammary gland) possess the complement of enzymes necessary for the active synthesis of triacylglycerol.

In humans, the liver is responsible for the conversion of excess dietary carbohydrates into fatty acids, through lipogenesis *de novo* (Denechaud et al. 2008a). A small part of triacylglycerols is synthesized into adipocytes from carbohydrates, but its regulation is still debated in humans. On the other hand, in rodents, the WAT lipogenesis *de novo* is higher than in humans and also could be regulated by nutritional and hormonal conditions. Iritani et al. (1996) demonstrated that the mRNA concentrations of acetyl-CoA carboxylase, fatty acid synthase (FAS) and ATP citrate-lyase increased after the refeeding in WAT and liver in rats.

MSG-obese rats have a high WAT and liver lipogenesis *de novo* rate as compared to lean ones (Nascimento Curi et al. 1991). In this obese model, partial removal of retroperitoneal and epididymal WAT caused an increase in the lipogenesis *de novo* in the carcass, epididymal and retroperitoneal WAT, which could have contributed

for observed fat mass replenishment and new adipocytes differentiation (Bueno et al. 2005).

The effect of glucocorticoid on the lipogenesis *de novo* is controversial. A previous study showed that, *in vivo*, this hormone causes a decrease in lipogenic enzymes activity in white adipose tissue (Volpe and Marasa 1975); conversely, dexamethasone increased the action of insulin on acetil-CoA carboxilase gene expression in adipocytes (Travers and Barber 1999). It is well known that insulin is the most important lipogenic hormone. Insulin increases FAS expression and activity in humans and in rodent adipocytes in primary culture (Moustaïd et al. 1996, Claycombe et al 1998). Evidences suggest that the regulation of lipogenic genes expression by insulin is mediated by sterol responsive element binding protein 1c (SREBP-1c) (Denechaud et al. 2008b).

Lipolysis and Triacylglycerol Fatty Acid Cycling

Adipose tissue is considered as the body's largest storage organ for energy in the form of triacylglycerols, which are mobilized through lipolysis pathway to provide fuel to other organs. Release of non-esterified fatty acids (NEFA) is a specific function for the adipose tissue; in fact, no other tissue in the mammalian body is known to mobilize NEFA and release them to the circulation to be taken up by other tissues.

The first evidence of a lipolytic enzyme sensitive to hormone, in adipose tissue with different characteristic of LPL, was observed in the 1960's decade. It was verified that this enzyme was stimulated by adrenalin and adrenocorticotrophic hormone and inhibited by insulin (Hollenberg et al. 1961, Björntorp and Furman 1962, Rodbell and Jones 1966, Goodridge and Ball 1965). Vaughan et al. (1964) denominated this enzyme as a hormone-sensitive lipase (HSL).

The HSL exists in two forms: an active phosphorylated form and an inactive (or less active) non-phosphorylated form, and this interconversion is regulated by hormonal action (Strälfors and Honnor 1989). Phosphorylation of HSL results in increased hydrolytic activity, translocation of HSL from cytosol to the lipid droplet surface, and enhanced TAG breakdown in the cell. The hydrolytic action of HSL is regulated by perilipin A, a lipid droplet-associated protein. Phosphorylation of perilipin by cAMP-dependent protein kinase (PKA) facilitate the translocation of HSL to the lipid droplet (Carmen and Víctor 2006).

Opposing regulation of lipolysis in WAT by catecholamines and insulin has been well documented. During fasting or exercise, catecholamines are the major hormones to stimulate lipolysis. Hormone binding to adrenergic receptors (β-adrenergic) and stimulating adenylate cyclase activity leads to an increase in intracellular cAMP concentrations activating PKA. In the fed state, insulin inhibits lipolysis by dephosphorylation of HSL and activation of phosphodiesterase that reduces cAMP levels (Jaworski et al. 2007).

Along with insulin and catecholamines, lipolysis is stimulated, under tight regulation, by catecholamines, glucagon, adrenocorticotrophic hormone (ACTH), growth hormone, testosterone, atrial natriuretic peptide and leptin (Slavin et al. 1994, Steinberg et al. 2002, Sengenes et al. 2002). Autocrine/paracrine factors may also participate in the precise regulation of lipolysis in adipocytes to meet the physiologic and metabolic changes.

NEFA can also be oxidized or used for reesterification in adipocytes to produce TAG. High rates of FA re-esterification in TAG have been shown to occur in WAT during fasting, both in rats and humans (Reshef et al. 2003). Esterification of FAs requires glycerol 3-phosphate formation which, under lipolytic situations, does not arise from glycolysis since glucose utilization is strongly reduced under such circumstances.

In 1967, Ballard et al. firstly demonstrated the activity of phosphoenolpyruvate carboxykinase (PEPCK) and the glycerol 3-phosphate synthesis from pyruvate in white adipose tissue. In 1969, this pathway was named glyceroneogenesis by Gorin et al., Olswang et al. (2002) reported that a selective ablation of PEPCK expression in WAT of homozygous mutant mice caused a reduction on triglyceride deposition, with 25% of the animals displaying lipodystrophy. These results demonstrated the physiological role of glyceroneogenesis to maintain fat homeostasis in adipose tissue. Aminoacids, lactate and pyruvate could be utilized as a substrate to *de novo* glycerol 3-phosphate synthesis. It has been shown that rats treated with hyperproteic carbohydrate free diet have an increase in the white adipose tissue glyceroneogenesis (Botion et al. 1995).

EFFECT OF DIETARY FAT ON WHITE ADIPOSE TISSUE METABOLISM

The prevalence of obesity is increasing worldwide, and data from the literature indicate that environmental and behavioral aspects play an important causal role. Among the environmental influences, the percentage of fat energy in the everyday diet and the lack of physical activity are two important factors (Jéquier 2002).

Obesity is often accompanied by abnormalities in carbohydrate and lipid metabolism and in insulin and leptin secretion and action (Buettner et al. 2000, Zhou et al. 1998). Exposure to high-fat diets for prolonged periods results in positive energy balance and obesity in certain rodent models that can be considered an adequate model of human obesity (Gaíva et al. 2001, Lin et al. 2000a). The hyperlipidic diet induced a more pronounced body weight gain accompanied by an increase in the adiposity, carcass lipogenesis rate and serum triacylglycerols, regardless of the regimen of administration, i.e., either continuous or cycled with chow (Estadella et al. 2004).

It has been shown that dietetic manipulations, hormones, and cytokines induce distinct metabolic responses at different fat depots (Pond 1999). High-fat diets reduced the activity of lipogenic enzymes and lipogenesis rate in retroperitoneal and inguinal fat depots (Gaíva et al. 2001, Rothwell et al. 1983), but increased lipoprotein lipase activity in visceral fat (Roberts et al. 2002).

The type of dietary fat has been shown to influence hepatic and WAT metabolism. Although it is well documented that the consumption of high-fat diets can induce obesity, the impact of dietary fatty acid composition on adipose tissue lipid metabolism has been examined by some authors, with conflicting results.

We have previously shown that feeding young rats for 8 weeks on diets containing either n-6 polyunsaturated fatty acid (PUFA) or long-chain saturated fatty acids, as 33% of total energy, produced similar elevations in body-weight gain and carcass fat content (da Silva et al. 1996). Similar results were obtained by Awad et al. (1990). In contrast, Shimomura et al. (1990) reported that a safflower oil diet produced a lower body-fat gain in young rats than a tallow diet, both at 45% of total energy. However, rats that were fed with a maize oil diet for 9 months were heavier and fatter than those that received a lard diet (Hill et al. 1993). The n-3 PUFA found in fish oils have received considerable interest, since they have been shown to exert beneficial health effects (Calder 1998). Tsuboyama-Kasaoka et al. (1999) have demonstrated that mice receiving 60% of dietary energy as n-3 fatty acids, during 5 months, did not develop obesity. Contrarily, a fish oil diet elevated body fat and lowered body protein content, compared with a safflower oil diet (Dulloo et al. 1995), while no difference in body-weight gain was observed between rats which were fed with lard or an n-3 fatty acid-supplemented lard diet (Rustan et al. 1993).

No effect on lipolysis and lipogenesis rates was reported by Awad et al. (1990) when comparing n-6 PUFA, n-3 PUFA and saturated diets, while Fickova et al. (1998) found higher noradrenaline-stimulated lipolysis in rats which were fed with n-3 PUFA than in those with n-6 PUFA. On the other hand, we have shown that rats that were fed with n-3 PUFA or n-3 plus n-6 PUFA diets had a lower WAT lipolysis rate as compared to control diet (Gaíva et al. 2001). The reduction of WAT lipolysis rate by n-3 PUFA has been shown by others (Singer et al. 1990, Dagnelie et al. 1994). This observation is consistent with the reported fish oil-induced reduction in plasma free fatty acids (Otto et al. 1992) and elevation of insulin sensitivity (Hill et al. 1993).

Diets enriched with n-6 PUFA have been shown to decrease FAS mRNA in liver and WAT and, thus, lipogenesis capacity in rats (Tsuboyama-Kasaoka et al. 1999).

Fernández-Quintela et al. (2007) postulated that suppression of lipogenic enzyme gene expression induced by PUFA is related to changes in the expression and nuclear localization of the transcription factor, sterol-regulatory element-binding protein-1 (SREBP-1), rather than to a direct effect on peroxisome proliferator-activated receptors PPARs, a family of transcription factors that regulate energy balance by promoting either energy deposition or energy dissipation.

Regional differences in the sensitivity of WAT depots to dietary manipulations have been found (Belzung et al. 1993). We also observed some differences between retroperitoneal and epididymal WAT metabolic responses to the fatty diets. Diet enriched with soyabean oil (rich in PUFA n-6) significantly increased retroperi-

toneal WAT weight and ^{14}C-labelled lipid accumulation, while the same variables were affected in epididymal WAT by diet enriched with fish oil (rich in PUFA n-3 and saturated fatty acid). All PUFA-rich diets increased the lipogenesis *de novo* rate (Gaíva et al. 2001). Increased retroperitoneal WAT lipogenesis rate after n-3- and n-6-rich diets has been reported previously (Raclot and Groscolas 1994, Fickova et al. 1998).

The consumption of industrialized food has led to an increased intake of hydrogenated vegetable oils, which have substantial amounts of saturated and *trans*-fatty acids (TFAs) (Allison et al. 1999, Popkin 1998). Recently, we have shown that the ingestion of TFA during gestation and lactation increases the carcass lipid content in 21-day-old and 90-day-old offspring (Pisani et al. 2008a, b). Similar findings were described by Takeuchi et al. (1995) in animals treated with a diet rich in saturated fatty acids. Furthermore, Shillabeer and Lau (1994) demonstrated that diets rich in saturated fatty acids promote the replication of adipocytes. It is possible that this mechanism has contributed to the high carcass lipid content found in the TFA feeding groups.

Silva et al. (2006), studying the effects of TFA ingestion just during lactation, verified increased lipogenesis *de novo* rates and lipid contents in the epididymal WAT of offspring aged 45 days. The same study observed more monounsaturated and saturated fatty acids in the WAT of the TFA-exposed offspring. Because those fatty acids have been shown to be mobilized at a lower rate than PUFA (Raclot 2003), a decreased lipolysis rate could also be present in the TFA-exposed rats.

SECRETORY FUNCTION OF WHITE ADIPOSE TISSUE

Obesity is associated with a chronic low grade inflammation, and it has been suggested that inflammation may be the link between obesity, type 2 diabetes and cardiovascular disease (Bullo et al. 2003). In this regard, it has recently been demonstrated that diabetes is associated with raised inflammation-sensitive plasma protein levels in overweight and obese men, but not in men of normal weight (Engstrom et al. 2003).

Cardiovascular and metabolic diseases are associated with obesity and with alterations in the production of adipokynes, e.g., leptin, resistin, adiponectin, TNF-α, plasminogen activator inhibitor- 1 (PAI-1) and haptoglobin (Trayhurn and Beattie 2001, Friedrichs et al. 1995, Nascimento et al. 2004).

As stated before, this review focuses on haptoglobin, TNF-α, plasminogen activator inhibitor-1 and adiponectin.

The liver is regarded as the main site of the synthesis of haptoglobin, as of other acute phase proteins. Hepatic expression of the haptoglobin gene is regulated by IL-1, IL-6, glucocorticoids and TNF-α in the case of rodents, but mainly by IL-6 and dexamethasone in humans (Baumann et al. 1990, Mackiewicz et al. 1991). IL-6 is, however, the common inflammatory cytokine mediator for haptoglobin gene regulation in the liver of all studied species (Pajovic et al. 1994).

The identification of haptoglobin, in particular, as a putative secreted factor from WAT (Friedrichs et al. 1995, Kratchmarova et al. 2002, Chiellini et al. 2002) is consistent with the concept that obesity and diabetes are states of chronic mild inflammation. Expression of the haptoglobin gene in epididymal WAT was first reported in normal mice, with increases in expression being observed following induction of an inflammatory response with lipopolysaccharide (Friedrichs et al. 1995). The level of haptoglobin mRNA has been shown to be elevated in WAT of several obese models, including ob/ob and db/db mice (Chiellini et al. 2002).

We have demonstrated that the gene encoding the acute phase reactant haptoglobin is higher in epididymal WAT from obese (ob/ob) mice relative to their lean siblings, and also haptoglobin is expressed in each of the main WAT depots of mice, both internal and subcutaneous, as well as in interscapular brown adipose tissue. Haptoglobin expression occurs in the adipocytes themselves rather than in the cells of the stromal-vascular fraction (Nascimento et al. 2004).

The increased haptoglobin expression in the epididymal WAT of obese animals suggests that WAT could be a source of the increase in plasma haptoglobin level observed in obese subjects (Engstrom et al. 2003, Scriba et al. 1979). Increased production of this acute phase reactant by WAT in the obese state could contribute to the mild inflammation that accompanies obesity.

Haptoglobin is a tetrameric glycoprotein which binds haemoglobin, preventing both iron loss and kidney damage during haemolysis. It has an antioxidant

function and has been reported to be angiogenic, stimulating endothelial cell differentiation and vascularisation (Cid et al. 1993). Within adipose tissue, haptoglobin could play a role as an antioxidant or in angiogenesis. Alternatively, haptoglobin synthesized in the tissue may not have a local role but instead may contribute primarily to the circulating pool of the protein and the general inflammatory response.

In 3T3-L1 adipocytes, haptoglobin mRNA was reduced by the PPARγ agonist, rosiglitazone. In contrast, it was stimulated by dexamethasone, IL-6, TNF-α, and LPS (Nascimento et al. 2004). In *in vivo* studies, Friedrichs et al. (1995) found that the injection of LPS in mice resulted in a several fold increase in haptoglobin mRNA level in adipose tissue. Since LPS receptors (Toll-like receptor) are present in white adipose tissue (Lin et al. 2000b), the effect of the inflammatory agent on haptoglobin expression in the tissue *in vivo* may reflect, at least in part, a direct interaction with the adipocyte. The most powerful effect on haptoglobin gene expression in our study was with the addition of TNF-α.

TNF-α also stimulates the production of other adipokines, such as leptin. Earlier studies have shown that TNF-α increases both leptin gene expression and leptin secretion in WAT and in 3T3-L1 adipocytes, while leptin mRNA levels have been reported to be lower in TNF-α deficient mice (Kirchgessner et al. 1997, Faggioni et al. 1998, Langhans and Hrupka 1999). Moreover, WAT expression of TNF-α also appears to be related to the circulating level of other inflammatory markers, such as C-reactive protein, fibrinogen, alkaline phosphatase and albumin.

TNF-α has been associated with obesity-related type 2 diabetes. This was first demonstrated by Hotamisligil et al. (1996). They showed that TNF-α is elevated in WAT from obese diabetic rodents and it is a mediator of obesity-related insulin resistance and type 2 diabetes.

Evidences from literature clearly established a correlation between TNF-α and insulin resistance in rodents (Ventre et al. 1997, Uysal et al. 1997). However, there are disagreements about the role of TNF-α in insulin resistance in humans; some researchers do not find association among them (Rush et al. 2007, Zavaroni et al. 2003), while others do (Behre et al. 2005, Hivert et al. 2008).

Initially, adipocytes were considered the predominant source of adipose tissue TNF-α. However, recent studies have demonstrated that preadipocytes, endothelial cells, smooth muscle cells, fibroblasts, leukocytes and macrophages, which are present in WAT as a stromavascular fraction, can produce substantially more TNF-α than adipocytes (Fain et al. 2004, Weisberg et al. 2003). It is well known that obesity is associated with an increased infiltration of macrophages into WAT (Coenen et al. 2007, Cawthorn and Sethi 2008), especially in visceral fat pad, which may participate in the inflammatory reaction that links central adiposity to insulin resistance (Curat et al. 2006).

The molecular mechanism for TNF-α-induced insulin resistance involves excessive phosphorylation of extracellular signal-regulated kinase-1/2 (ERK-1/2) and c-Jun NH_2-terminal kinase (JNK), concomitant with increased serine and reduced tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), and also TNF-α-induced transcription factor, NF-kβ (Cawthorn and Sethi 2008).

TNF-α upregulates PAI-1 expression in adipocytes and WAT, which is likely to contribute to obesity associated with cardiovascular complications of metabolic syndrome. Plasminogen activator inhibitor-1 (PAI-1) has traditionally been linked to the pathogenesis of atherosclerosis, although evidence suggests that it is also involved in the development of obesity and insulin resistance (Ma et al. 2004).

Plasma PAI-1 is derived from several sources, including the vascular endothelium, WAT and liver (De Taeye et al. 2005). Even though, WAT is a site of abundant PAI-1 synthesis (Allessi et al. 1997, Sawdey and Loskutoff 1991).

PAI-1 is a procoagulative agent and fibrinolysis inhibitor. Therefore, high circulating plasma PAI-1 concentration is a strong risk factor of thrombotic disease and independent predictor of coronary artery disease (Segarra et al. 2001). Several studies showed that adipose visceral tissue mass in humans was positively correlated with plasma PAI-1 concentration (Cigolini et al. 1996, Rega et al. 2005).

Recently, Sakamoto et al. (2008) showed that insulin and triacylglycerols, in combination with high concentration of insulin, enhanced PAI-1 production but

decreased adiponectin production by adipocytes. These two adipokines have opposing effects on the pathogenesis of coronary artery disease.

Adiponectin is the transcriptional product of the apM1 gene and is the most abundantly secreted protein from adipose tissue in humans (Maeda et al. 1996, Arita et al. 1999). Transcriptional regulation of the adiponectin gene involves a number of transcription factors. The adiponectin promoters contain binding sites for sterol regulatory elements (SREs), peroxisome proliferator-activated receptor (PPAR)-response elements, C/EBP sites, and E-boxes (Seo et al. 2004). Recently, it has been shown that Id3, the inhibitor of differentiation of the family of proteins, inhibits SREBP-1c-mediated adiponectin promoter activation (Doran et al. 2008).

This adipokine increases insulin sensitivity and has anti-inflammatory and antiatherogenic effects (Diez and Iglesias 2003). Decreased serum adiponectin levels have been observed in subjects with insulin resistance, obesity, type 2 diabetes and heart disease (Diez and Iglesias 2003, Hotta et al. 2000). Serum adiponectin levels are inversely correlated with body mass index, central adiposity, blood pressure, fasting glycemia, insulin resistance, serum insulin levels and uric acid levels (Yamamoto et al. 2002). It has been demonstrated that adiponectin reduces hepatic production of glucose and the concentration of triacylglycerols in the muscles, thus ameliorating insulin sensitivity (Prins 2002).

Salmenniemi et al. (2005) verified that hypoadiponectinemia is related to several features of metabolic syndrome (increased fasting glycemia, triglyceridemia, central obesity and decreased HDL cholesterol) and to high levels of inflammatory cytokines (IL-6, IL-1, and C-reactive protein).

EFFECT OF DIETARY FAT ON WHITE ADIPOSE TISSUE SECRETORY FUNCTION

Over the past few decades, epidemiological and clinical studies have indicated many relations between nutrition and health. In the last decade, studies have established that dietary signals could influence gene and protein expression, which further modulates markers of inflammation by producing both positive and negative effects depending on the net changes in gene expression.

Studies have proved that the incidence of insulin resistance and heart disease is positively related to the ingestion of saturated fatty acids, and negatively related to the ingestion of PUFA (Hu 2003, Sacks and Katan 2002).

High-fat diets reportedly impair glucose metabolism, stimulate abnormal glucose production, cause hyperinsulinemia and insulin resistance (Reaven 1988). Recently, Tsukumo et al. (2007) showed that C3H/HeJ mice, which have a loss-of-function mutation in Toll-like receptor 4 (TLR4), are protected against the development of obesity and insulin resistance induced by high fatty diet accompanied by a less pronounced increase in adipocyte size than the wild mice.

TLR2 and TLR4 are expressed in adipose tissue and other tissues (e.g. macrophages, and muscle), and play a critical role in inducing innate immune responses in mammals. TLR4 is activated by lipopolysaccharide and saturated fatty acids, which are inducers of insulin resistance. Since that, Tsukumo et al. (2007) suggested that TLR4 may be a candidate for participation in insulin resistance induced by saturated fatty acid rich diet.

It has been observed that saturated fatty acids can directly interact with the immune modulation and inflammation response through the activation of TLRs in macrophages (Lee et al. 2001). TLR is also expressed in 3T3-L1 cells, mouse cultured adipocytes and mouse and human WAT (Shi et al. 2006, Creely et al. 2007). This reinforces the findings in which inflammation and the composition of fatty acids in the diet, particularly diets rich in saturated fat, are closely related to metabolic disorders.

We have shown that lard enriched diet ingestion, for 2 or 60 days, increased haptoglobin gene expression in mice WAT. It was also found that 3T3-L1 adipocyte responds to palmitic acid in a dose dependent manner, in which the haptoglobin gene expression is increased in doses higher than 100μM (Oyama et al. 2005).

Treatment with palmitate induces the NF-kβ and the expression of IL-6 and TNF-α mRNA in 3T3-L1 adipocytes (Ajuwon and Spurlock 2005). *In vivo* study showed that WAT TNF-α gene expression was significantly increased by the cafeteria diet, rich in saturated fatty acid, while eicosapentaenoic acid (EPA) treatment was able to prevent the rise in this inflammatory cytokine (Pérez-Matute et al. 2007).

Ibrahim et al. (2005) demonstrated that treatment with TFA has a much greater effect in decreasing adipocyte insulin sensitivity than treatment with saturated fatty acids.

Recently, we have shown that maternal ingestion of hydrogenated vegetable fat rich in TFAs, during gestation and lactation, altered the blood lipid profiles and decreased serum adiponectin level, together with a decrease in adiponectin mRNA and an increase in TNF-α and PAI-1 mRNA levels in the WAT of their 21-day-old offspring (Pisani et al. 2008b). We also have found an increased levels of insulin, adiponectin, body fat and epididymal WAT PAI-1 mRNA in 90-day-old offspring of rats which were fed with a diet containing TFA during gestation and lactation (Pisani et al. 2008a). These results suggested that early exposure to TFA caused an increase in WAT PAI-1 gene expression and that this alteration became programmed.

Long-term diet-fed rats or short-term diet-fed rats (2 days) with fat-enriched, glucose-enriched diet showed lower adiponectin mRNA in epididymal WAT and plasma concentration, accompanied by an increase in plasma triacyglycerol and NEFA levels (Naderali et al. 2003).

We have shown that adiponectin gene expression was lower in retroperitoneal WAT after acute treatment (2 days) with diets enriched with soybean, coconut and fish oils, or lard. The same reduction in levels of adiponectin gene expression was observed in epididymal WAT of animals chronically (60 days) fed only with soybean and coconut diets and in 3T3-L1 adipocytes treated with palmitic, linoleic, EPA acids. Moreover, in the present study, adiponectin gene expression in subcutaneous WAT was less affected by the high-fat diet than in the retroperitoneal and epididymal depots. Acute treatment with high-fat diets decreased the serum adiponectin levels in all groups, although fish oil diet did not affect serum adiponectin concentration, in contrast to the other high-fat diet chronic treatments (Bueno et al. 2008).

It has previously been described that EPA increased serum adiponectin levels but did not alter adiponectin gene expression, either in subcutaneous, dorsolumbar, or epididymal fat pads, in mice treated with high-fat diet (Flachs et al. 2006). In another study, db/db mice treated with n-6 and n-3 PUFA-enriched diet had similar serum adiponectin levels and gonadal WAT adiponectin gene expression, as compared to animals treated with a low-fat diet (Todoric et al. 2006). Recently, it was reported that mice treated with a fish oil-enriched diet had increased serum adiponectin levels and raised adiponectin gene expression in retroperitoneal but not in epididymal WAT, compared to animals which were fed with the control diet or sunflower oil (rich in n-6 PUFA) diet (Neschen et al. 2006). The differences among these results may be partly explained by the duration of treatment and the diet composition, suggesting that the amount of n-3 PUFA in the diet might be an important factor for the stimulation of adiponectin gene expression.

CONCLUSION

The present review showed that, depending on the outcome being analyzed, the duration of the exposure to the high-fat feeding, amount of fatty acid present in the diet and the type of fatty acid may or may not have a significant effect on adipose tissue metabolism. However, the long-term or short-term-high fat diets, especially rich in saturated fatty acids, stimulated the expression of pro-inflammatory adipokines and inhibit the expression of adiponectin, an anti-inflammatory adipokine.

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RESUMO

Aproximadamente 40% do total de energia consumida pela população ocidental é representada pelos lipídios, a maioria dela sendo ingerida na forma de triglicerídeos e fosfolipídios. O foco desta revisão foi analisar o efeito dos tipos de gordura da dieta sobre o metabolismo e função secretora do tecido adiposo branco, principalmente, sobre a secreção de haptoglobina, TNF-α, inibidor do ativador de plasminogênio-1 e adiponectina. Estudos prévios demonstraram que durante a exposição de dietas hiperlipídicas, a quantidade e o tipo de ácidos graxos presentes na dieta podem ou não ter um efeito significante

sobre o metabolismo do tecido adiposo. Entretanto, o tratamento a curto ou longo prazo com dieta hiperlipídica, especialmente rica em ácidos graxos saturados, provavelmente por ativar receptores *toll-like*, estimula a expressão de adipocinas pró-inflamatórias e inibe a expressão de adiponectina. Estudos adicionais são necessários para investigar os mecanismos celulares pelos quais os ácidos graxos da dieta afetam a função secretória e metabólica do tecido adiposo branco.

Palavras-chave: adipocinas, dietas hiperlipídicas, metabolismo, tecido adiposo branco.

REFERENCES

AJUWON KM AND SPURLOCK ME. 2005. Palmitate activates the NF-kβ transcription factor and induces IL-6 and TNF-α expression in 3T3-L1 adipocytes. J Nutr 135: 1841–1846.

ALLESSI MC, PEIRETTI F, MORANGE P, HENRY M, NALBONE G AND JUHAN-VAGUE I. 1997. Production of plasminogen activator inhibitor-1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease. Diabetes 46: 860–867.

ALLISON DB, EGAN SK, BARRAJ LM, CAUGHMAN C, INFANTE M AND HEIMBACH JT. 1999. Estimated intakes of trans fatty and other fatty acids in the US population. J Am Diet Assoc 99: 166–174.

ARITA Y ET AL. 1999. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257: 79–83.

AWAD AB, BERNARDIS LL AND FINK CS. 1990. Failure to demonstrate an effect of dietary fatty acid composition on body weight, body composition and parameters of lipid metabolism in mature rats. J Nutr 120: 1277–1282.

BALLARD FJ, HANSON RW AND LEVEILLE GA. 1967. Phosphoenolpyruvate carboxykinase and the synthesis of glyceride-glycerol from pyruvate in adipose tissue. J Biol Chem 242: 2746–2750.

BAUMANN H, MORELLA KK, JAHREIS GP AND MARINKOVIC S. 1990. Distinct regulation of the interleukin-1 and interleukin-6 response elements of the rat haptoglobin gene in rat and human hepatoma cells. Mol Cell Biol 10: 5967–5976.

BEHRE CJ, FAGERBERG B, HULTEN LM AND HULTHE J. 2005. The reciprocal association of adipocytokines with insulin resistance and C-reactive protein in clinically healthy men. Metabolism 54: 439–444.

BELZUNG F, RACLOT T AND GROSCOLAS R. 1993. Fish oil n-3 fatty acids selectively limit the hypertrophy of abdominal fat depots in growing rats fed high-fat diets. Am J Physiol 264: r1111–r1118.

BJÖRNTORP P AND FURMAN RH. 1962. Lipolytic activity in rat epididymal fat pads. Am J Physiol 203: 316–322.

BOTION LM, KETTELHUT IC AND MIGLIORINI RH. 1995. Increased adipose tissue glyceroneogenesis in rats adapted to a high protein, carbohydrate-free diet. Horm Metab Res 27: 310–313.

BRAUN JE AND SEVERSON DL. 1992. Lipoprotein lipase release from cardiac myocytes is increased by decavanadate but not insulin. Am J Physiol 262(5 Pt 1): E663–E670.

BUENO AA, OYAMA LM, ESTADELLA D, HABITANTE CA, BERNARDES BS, RIBEIRO EB AND OLLER DO NASCIMENTO CM. 2005. Lipid metabolism of monosodium glutamate obese rats after partial removal of adipose tissue. Physiol Res 54: 57–65.

BUENO AA, OYAMA LM, DE OLIVEIRA C, PISANI LP, RIBEIRO EB, SILVEIRA VL AND OLLER DO NASCIMENTO CM. 2008. Effects of different fatty acids and dietary lipids on adiponectin gene expression in 3T3-L1 cells and C57BL/6J mice adipose tissue. Pflugers Arch 455: 701–709.

BUETTNER R, NEWGARD CB, RHODES CJ AND O'DOHERTY RM. 2000. Correction of diet-induced hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance by moderate hyperleptinemia. Am J Physiol Endocrinol Metab 278: E563–E569.

BULLO M, GARCIA-LORDA P, MEGIAS I AND SALAS-SALVADO J. 2003. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. Obesity Res 11: 525–531.

CALDER PC. 1998. Immunoregulatory and anti-inflammatory effects of n-3 polyunsaturated fatty acids. Braz J Med Biol Res 31: 467–490.

CARMEN GY AND VÍCTOR SM. 2006. Signalling mechanisms regulating lipolysis. Cell Signal 18: 401–408.

CAWTHORN WP AND SETHI JK. 2008. TNF-α and adipocyte biology. FEBS Lett 582: 117–131.

CHIELLINI C ET AL. 2002. Obesity modulates the expression of haptoglobin in the white adipose tissue via TNF-α. J Cell Physiol 190: 251–258.

CID MC, GRANT DS, HOFFMAN GS, AUERBACH R, FAUCI AS AND KLEINMAN HK. 1993. Identification of haptoglobin as an angiogenic factor in sera from patients with systemic vasculitis. J Clin Invest 91: 977–985.

CIGOLINI M, TARGHER G, BERGAMO ANDREIS IA, TONOLI M, AGOSTINO G AND DE SANDRE G. 1996.

Visceral fat accumulation and its relation to plasma hemostatic factors in healthy men. Arterioscler Thromb Vasc Biol 16: 368–374.

CLAYCOMBE KJ, JONES BH, STANDRIDGE MK, GUO Y, CHUN JT, TAYLOR JW AND MOUSTAÏD-MOUSSA N. 1998. Insulin increases fatty acid synthase gene transcription in human adipocytes. Am J Physiol 274: R1253–R1259.

COENEN KR, GRUEN ML, CHAIT A AND HASTY AH. 2007. Diet-induced increases in adiposity, but not plasma lipids, promote macrophage infiltration into white adipose tissue. Diabetes 56: 564–573.

CREELY SJ, MCTERNAN PG, KUSMINSKI CM, FISHER M, DA SILVA NF, KHANOLKAR M, EVANS M, HARTE AL AND KUMAR S. 2007. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab 292: E740–E747.

CRYER A. 1981. Tissue lipoprotein lipase activity and its action in lipoprotein metabolism. Int J Biochem 13: 525–541.

CURAT CA, WEGNER V, SENGENES C, MIRANVILLE A, TONUS C, BUSSE R AND BOULOUMIE A. 2006. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 49: 744–747.

DA SILVA MH, PITHON TC AND DO NASCIMENTO CM. 1996. Effect of saturated and polyunsaturated fatty acids rich diets on hepatic and adipose tissue lipid metabolism in rats.Int J Vitam Nutr Res 66: 258–262.

DAGNELIE PC, RIETVELD T, SWART GR, STIJNEN T AND VAN DEN BERG JW. 1994. Effect of dietary fish oil on blood levels of free fatty acids, ketone bodies and triacylglycerol in humans Lipids 29: 41–45.

DE TAEYE B, SMITH LH AND VAUGHAN DE. 2005. Plasminogen activator inhibitor-1: a common denominator in obesity, diabetes and cardiovascular disease. Curr Opin Pharmacol 5: 149–154.

DENECHAUD PD, GIRARD J AND POSTIC C. 2008a. Carbohydrate responsive element binding protein and lipid homeostasis. Curr Opin Lipidol 19: 301–306.

DENECHAUD PD, DENTIN R, GIRARD J AND D POSTIC C. 2008b. Role of ChREBP in hepatic steatosis and insulin resistance. FEBS Lett 582: 68–73.

DIEZ JJ AND IGLESIAS P. 2003. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 148: 293–300.

DO CARMO MG, DO NASCIMENTO CM, MARTÍN-HIDALGO AM AND HERRERA E. 1996. Effects of ethanol intake on lipid metabolism in the lactating rat. Alcohol 13: 443–448.

DOLNIKOFF MS, KATER CE, EGAMI M, DE ANDRADE IS AND MARMO MR. 1988. Neonatal treatment with monosodium glutamate increases plasma corticosterone in the rat. Neuroendocrinology 48: 645–649.

DOOLITTLE MH, BEN-ZEEV O, ELOVSON J, MARTIN D AND KIRCHGESSNER TG. 1990. The response of lipoprotein lipase to feeding and fasting. Evidence for post-translational regulation. J Biol Chem 265: 4570–4577.

DORAN AC, MELLER N, CUTCHINS A, DELIRI H, SLAYTON RP, OLDHAM SN, KIM JB, KELLER SR AND MCNAMARA CA. 2008. The helix-loop-helix factors Id3 and E47 are novel regulators of adiponectin. Circ Res 103: 624–634.

DULLOO AG, MENSI N, SEYDOUX J AND GIRARDIER L. 1995. Differential effects of high-fat diets varying in fatty acid composition on the efficiency of lean and fat tissue deposition during weight recovery after low food intake. Metabolism 44: 273–279.

ENGSTROM G, STAVENOW L, HEDBLAD B, LIND P, ERIKSSON KF, JANZON L AND LINDGARDE F. 2003. Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke: a population-based study. Diabetes 52: 442–447.

ESTADELLA D, OYAMA LM, DÂMASO AR, RIBEIRO EB AND OLLER DO NASCIMENTO CM. 2004. Effect of palatable hyperlipidic diet on lipid metabolism of sedentary and exercised rats. nutrition 20: 218–224.

FAGGIONI R, FANTUZZI G, FULLER J, DINARELLO CA, FEINGOLD KR AND GRUNFELD C. 1998. IL-1 beta mediates leptin induction during inflammation. Am J Physiol 274: R204–R208.

FAIN JN, BAHOUTH SW AND MADAN AK. 2004. TNF-α release by the nonfat cells of human adipose tissue. Int J Obes Relat Metab Disord 28: 616–622.

FERNÁNDEZ-QUINTELA A, CHURRUCA I AND PORTILLO MP. 2007. The role of dietary fat in adipose tissue metabolism. Public Health Nutr 10: 1126–1131.

FICKOVA M, HUBERT P, CRÉMEL G AND LERAY C. 1998. Dietary (n-3) and (n-6) polyunsaturated fatty acids rapidly modify fatty acid composition and insulin effects in rat adipocytes. J Nutr 128: 512–519.

FLACHS P, MOHAMED-ALI V, HORAKOVA O, ROSSMEISL M, HOSSEINZADEH-ATTAR MJ, HENSLER M, RUZICKOVA J AND KOPECKY J. 2006. Polyunsaturated fatty acids of marine origin induce adiponectin in mice fed a high-fat diet. Diabetologia 49: 394–397.

FRIED SK, RUSSELL CD, GRAUSO NL AND BROLIN RE. 1993. Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. J Clin Invest 92: 2191–2198.

FRIEDRICHS WE, NAVARIJO-ASHBAUGH AL, BOWMAN BH AND YANG F. 1995. Expression and inflammatory regulation of haptoglobin gene in adipocytes. Biochem Biophys Res Commun 209: 250–256.

FRÜHBECK G, GÓMEZ-AMBROSI J, MURUZABAL FJ AND BURRELL MA. 2001. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol 280: E827–E847.

GAÍVA MH, COUTO RC, OYAMA LM, COUTO GE, SILVEIRA VL, RIBERIO EB AND NASCIMENTO CM. 2001. Polyunsaturated fatty acid-rich diets: effect on adipose tissue metabolism in rats. Br J Nutr 86: 371–377.

GOODRIDGE AG AND BALL EG. 1965. Studies on the metabolism of adipose tissue. 18. *In vitro* effects of insulin, epinephrine and glucagon on lipolysis and glycolysis in pigeon adipose tissue. Comp Biochem Physiol 16: 367–381.

GORIN E, TAL-OR Z AND SHAFRIR E. 1969. Glyceroneogenesis in adipose tissue of fasted, diabetic and triamcinolone treated rats. Eur J Biochem 8: 370–375.

HILL JO, PETERS JC, LIN D, YAKUBU F, GREENE H AND SWIFT L. 1993. Lipid accumulation and body fat distribution is influenced by type of dietary fat fed to rats. Int J Obes Relat Metab Disord 17: 223–236.

HIVERT MF, SULLIVAN LM, FOX CS, NATHAN DM, D'AGOSTINO RB SR, WILSON PW AND MEIGS JB. 2008. Associations of Adiponectin, Resistin, and TNF-α with Insulin Resistance. J Clin Endocrinol Metab May 20.

HOLLENBERG CH, RABEN MS AND ASTWOOD EB. 1961. The lipolytic response to corticotropin. Endocrinology 68: 589–598.

HOTAMISLIGIL GS, PERALDI P, BUDAVARI A, ELLIS R, WHITE MF AND SPIEGELMAN BM. 1996. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α and obesity-induced insulin resistance. Science 271: 665–668.

HOTTA K ET AL. 2000. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20: 1595–1599.

HU FB. 2003. Overweight and obesity in women: health risks and consequences. J Women's Health (Larchmt) 12: 163–172.

IBRAHIM A, NATRAJAN S AND GHAFOORUNISSA R. 2005. Dietary trans-fatty acids alter adipocyte plasma membrane fatty acid composition and insulin sensitivity in rats. Metab Clin Exp 54: 240–246.

IRITANI N, FUKUDA H AND TADA K. 1996. Nutritional regulation of lipogenic enzyme gene expression in rat epididimal adipose tissue. J Biochem 120: 242–248.

JAWORSKI K, SARKADI-NAGY E, DUNCAN RE, AHMADIAN M AND SUL HS. 2007. Regulation of triglyceride metabolism. IV. Hormonal regulation of lipolysis in adipose tissue. Am J Physiol Gastrointest Liver Physiol 293: G1–G4.

JÉQUIER E. 2002. Pathways to obesity. Int J Obes Relat Metab Disord Suppl 2: S12–S17.

KIRCHGESSNER TG, UYSAL KT, WIESBROCK SM, MARINO MW AND HOTAMISLIGIL GS. 1997. Tumor necrosis factor-alpha contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. J Clin Invest 100: 2777–2782.

KRAEMER FB, TAKEDA D, NATU V AND SZTALRYD C. 1998. Insulin regulates lipoprotein lipase activity in rat adipose cells via wortmannin- and rapamycin-sensitive pathways. Metabolism 47: 555–559.

KRATCHMAROVA L ET AL. 2002. A proteomic approach for identification of secreted proteins during the differentiation of 3T3-L1 preadipocytes to adipocytes. Mol Cell Proteom 1: 213–222.

LANGHANS W AND HRUPKA B. 1999. Interleukins and tumor necrosis factor as inhibitors of food intake. Neuropeptides 33: 415–424.

LARGE V, PERONI O, LETEXIER D, RAY H AND BEYLOT M. 2004. Metabolism of lipids in human white adipocyte. Diabetes Metab 30: 294–309.

LEE JY, SOHN KH, RHEE SH AND HWANG D. 2001. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 276: 16683–16689.

LEONARD WR, ROBERTSON ML, SNODGRASS JJ AND KUZAWA CW. 2003. Metabolic correlates of hominid brain evolution. Comp Biochem Physiol A Mol Integr Physiol 136: 5–15.

LIN S, THOMAS TC, STORLIEN LH AND HUANG XF. 2000a. Development of high fat diet-induced obesity and leptin resistance in C57Bl/6J mice. Int J Obes Relat Metab Disord 24: 639–646.

LIN Y, LEE H, BERG AH, LISANTI MP, SHAPIRO L AND SCHERER PE. 2000b. The lipopolysaccharide-activated toll-like receptor (TLR)-4 induces synthesis of the closely

related receptor TLR-2 in adipocytes. J Biol Chem 275: 24255–24263.

MA LJ ET AL. 2004. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes 53: 336–346.

MACKIEWICZ A, SPERO T, GANAPATHI MK AND KUSHNER I. 1991. Effects of cytokine combinations on acute phase protein production in two human hepatoma cell lines. J Immunol 146: 3032–3037.

MAEDA K, OKUBO K, SHIMOMURA I, FUNAHASHI T, MATSUZAWA Y AND MATSUBARA K. 1996. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (Adipose Most abundant Gene transcript 1). Biochem Biophys Res Commun 221: 286–289.

MOHAMED-ALI V, PINKNEY JH AND COPPACK SW. 1998. Adipose tissue as an endocrine and paracrine organ. Int J Obesity 22: 1145–1158.

MOUSTAÏD N, JONES BH AND TAYLOR JW. 1996. Insulin increases lipogenic enzyme activity in human adipocytes in primary culture. J Nutr 126: 865–870.

NADERALI EK, ESTADELLA D, ROCHA M, PICKAVANCE LC, FATANI S, DENIS RG AND WILLIAMS G. 2003. A fat-enriched, glucose-enriched diet markedly attenuates adiponectin mRNA levels in rat epididymal adipose tissue. Clin Sci (Lond) 105: 403–408.

NASCIMENTO CO, HUNTER L AND TRAYHURN P. 2004. Regulation of haptoglobin gene expression in 3T3-L1 adipocytes by cytokines, catecholamines, and PPARgamma. Biochem Biophys Res Commun 313: 702–708.

NASCIMENTO CURI CM, MARMO MR, EGAMI M, RIBEIRO EB, ANDRADE IS AND DOLNIKOFF MS. 1991. Effect of monosodium glutamate treatment during neonatal development on lipogenesis rate and lipoprotein lipase activity in adult rats. Biochem Int 24: 927–935.

NESCHEN S, MORINO K, ROSSBACHER JC, PONGRATZ RL, CLINE GW, SONO S, GILLUM M AND SHULMAN GI. 2006. Fish oil regulates adiponectin secretion by a peroxisome proliferator-activated receptor-gamma-dependent mechanism in mice. Diabetes 55: 924–928.

OLLER DO NASCIMENTO CM AND WILLIAMSON DH. 1986. Evidence for conservation of dietary lipid in the rat during lactation and the immediate period after removal of the litter. Decreased oxidation of oral [1-14C]triolein. Biochem J 239: 233–236.

OLLER DO NASCIMENTO CM AND WILLIAMSON DH. 1988. Tissue-specific effects of starvation and refeeding on the disposal of oral [1-14C]triolein in the rat during lactation and on removal of litter. Biochem J 254: 539–546.

OLLER DO NASCIMENTO CM, ILIC V AND WILLIAMSON DH. 1989. Re-examination of the putative roles of insulin and prolactin in the regulation of lipid deposition and lipogenesis *in vivo* in mammary gland and white and brown adipose tissue of lactating rats and litter-removed rats. Biochem J 258: 273–278.

OLSWANG Y, COHEN H, PAPO O, CASSUTO H, CRONIGER CM, HAKIMI P, TILGHMAN SM, HANSON RW AND RESHEF L. 2002. A mutation in the peroxisome proliferator-activated receptor gamma-binding site in the gene for the cytosolic form of phosphoenolpyruvate carboxykinase reduces adipose tissue size and fat content in mice. Proc Natl Acad Sci USA 99: 625–630.

OTTO DA, BALTZELL JK AND WOOTEN JT. 1992. Reduction in triacylglycerol levels by fish oil correlates with free fatty acid levels in ad libitum fed rats. Lipids. 27: 1013–1017.

OYAMA LM, BUENO AA, ESTADELLA D, MOTOYAMA CSM AND NASCIMENTO CO. 2005. regulation of haptoglobin gene expression in 3T3-L1 adipocytes by fatty acids. Obesity Review 6: 46.

PAJOVIC S, JONES VE, PROWSE KR, BERGER FG AND BAUMANN H. 1994. Species-specific changes in regulatory elements of mouse haptoglobin genes. J Biol Chem 269: 2215–2224.

PÉNICAUD L, COUSIN B, LELOUP C, LORSIGNOL A AND CASTEILLA L. 2000. The autonomic nervous system, adipose tissue plasticity, and energy balance. Nutrition 16: 903–908.

PÉREZ-MATUTE P, PÉREZ-ECHARRI N, MARTÍNEZ JA, MARTI A AND MORENO-ALIAGA MJ. 2007. Eicosapentaenoic acid actions on adiposity and insulin resistance in control and high-fat-fed rats: role of apoptosis, adiponectin and tumour necrosis factor-alpha. Br J Nutr 97: 389–398.

PISANI LP, OLLER DO NASCIMENTO CM, BUENO AA, BIZ C, ALBUQUERQUE KT, RIBEIRO EB AND OYAMA LM. 2008a. Hydrogenated fat diet intake during pregnancy and lactation modifies the PAI-1 gene expression in white adipose tissue of offspring in adult life. Lipids Health Dis 7: 13–22.

PISANI LP, OYAMA LM, BUENO AA, BIZ C, ALBUQUERQUE KT, RIBEIRO EB AND OLLER DO NASCIMENTO CM. 2008b. Hydrogenated fat intake during pregnancy and lactation modifies serum lipid profile and adipokine mRNA in 21-day-old rats. Nutrition 24: 255–261.

POND CM. 1999. Physiological specialisation of adipose tissue. Prog Lipid Res 38: 225–248.

POPKIN BM. 1998. The nutrition transition and its health implications in lower-income countries. Public Health Nutr 1: 5–21.

PRINS JB. 2002. Adipose tissue as an endocrine organ. Best Pract Res Clin Endocrinol Metab 16: 639–651.

RACLOT T. 2003. Selective mobilization of fatty acids from adipose tissue triacylglycerols. Prog Lipid Res 42: 257–288.

RACLOT T AND GROSCOLAS R. 1994. Individual fish-oil n-3 polyunsaturated fatty acid deposition and mobilization rates for adipose tissue of rats in a nutritional steady state. Am J Clin Nutr 60: 72–78.

REAVEN GM. 1988. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37: 1595–1607.

REGA G ET AL. 2005. Inflammatory cytokines interleukin-6 and oncostatin m induce plasminogen activator inhibitor-1 in human adipose tissue. Circulation 111: 1938–1945.

RESHEF L, OLSWANG Y, CASSUTO H, BLUM B, CRONIGER CM, KALHAN SC, TILGHMAN SM AND HANSON RW. 2003. Glyceroneogenesis and the triglyceride/fatty acid cycle. J Biol Chem 278: 30413–30416.

RIBEIRO EB, DO NASCIMENTO CM, ANDRADE IS, HIRATA AE AND DOLNIKOFF MS. 1997. Hormonal and metabolic adaptations to fasting in monosodium glutamate-obese rats. J Comp Physiol [B] 167: 430–437.

ROBERTS CK, BARNARD RJ, LIANG KH AND VAZIRI ND. 2002. Effect of diet on adipose tissue and skeletal muscle VLDL receptor and LPL: implications for obesity and hyperlipidemia. Atherosclerosis 161: 133–141.

RODBELL M AND JONES AB. 1966. Metabolism of isolated fat cells. 3. The similar inhibitory action of phospholipase C (Clostridium perfringens alpha toxin) and of insulin on lipolysis stimulated by lipolytic hormones and theophylline. J Biol Chem 241: 140–142.

ROTHWELL NJ, STOCK MJ AND TRAYHURN P. 1983. Reduced lipogenesis in cafeteria-fed rats exhibiting diet-induced thermogenesis. Biosci Rep 3: 217–224.

RUSH EC, PLANK LD AND YAJNIK CS. 2007. Interleukin-6, tumour necrosis factor-alpha and insulin relationships to body composition, metabolism and resting energy expenditure in a migrant Asian Indian population. Clin Endocrinol 66: 684–690.

RUSTAN AC, HUSTVEDT BE AND DREVON CA. 1993. Dietary supplementation of very long-chain n-3 fatty acids decreases whole body lipid utilization in the rat. J Lipid Res 34: 1299–1309.

SACKS FM AND KATAN M. 2002. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. Am J Med 113: 13S–24S.

SAKAMOTO K, SAKAMOTO T AND OGAWA H. 2008. Effects of metabolic risk factors on production of plasminogen activator inhibitor-1 and adiponectin by adipocytes. Circ J 72: 844–846.

SALMENNIEMI U, ZACHAROVA J, RUOTSALAINEN E, VAUHKONEN I, PIHLAJAMÄKI J, KAINULAINEN S, PUNNONEN K AND LAAKSO M. 2005. Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure, and cytokines in offspring of type 2 diabetic patients. J Clin Endocrinol Metab 90: 4216–4223.

SARTIN JL, LAMPERTI AA AND KEMPPAINEN RJ. 1985. Alterations in insulin and glucagon secretion by monosodium glutamate lesions of the hypothalamic arcuate nucleus. Endocr Res 11: 145–155.

SAWDEY MS AND LOSKUTOFF DJ. 1991. Regulation of murine type 1 plasminogen activator inhibitor gene expression *in vivo*: tissue specificity and induction by lipopolysaccharide, tumor necrosis factor-alpha, and transforming growth factor-beta. J Clin Invest 88: 1346–1353.

SCRIBA PC, BAUER M, EMMERT D, FATEH-MOGHADAM A, HOFMANN GG, HORN K AND PICKARDT CR. 1979. Effects of obesity, total fasting and re-alimentation on L-thyroxine (T4), 3,5,3'-L-triiodothyronine (T3), 3,3',5'-L-triiodothyronine (rT3), thyroxine binding globulin (TBG), cortisol, thyrotrophin, cortisol binding globulin (CBG), transferrin, alpha 2-haptoglobin and complement C'3 in serum. Acta Endocrinol (Copenh) 91: 629–643.

SEGARRA A ET AL. 2001. Circulating levels of plasminogen activator inhibitor type-1, tissue plasminogen activator, and thrombomodulin in hemodialysis patients: biochemical correlations and role as independent predictors of coronary artery stenosis. J Am Soc Nephrol 12: 1255–1263.

SENGENES C, STICH V, BERLAN M, HEJNOVA J, LAFONTAN M, PARISKOVA Z AND GALITZKY J. 2002. Increased lipolysis in adipose tissue and lipid mobilization to natriuretic peptides during low-calorie diet in obese women. Int J Obes Relat Metab Disord 26: 24–32.

SEO JB ET AL. 2004. Adipocyte determination- and differentiation-dependent factor 1/sterol regulatory element-binding protein 1c regulates mouse adiponectin expression. J Biol Chem 279: 22108–22117.

SHI H, KOKOEVA MV, INOUYE K, TZAMELI I, YIN H AND FLIER JS. 2006. TLR4 links innate immunity and fatty

acid-induced insulin resistance. J Clin Invest 116: 3015–3025.

SHILLABEER G AND LAU DC. 1994. Regulation of new fat cell formation in rats: the role of dietary fats. J Lipid Res 35: 592–600.

SHIMOMURA Y, TAMURA T AND SUZUKI M. 1990. Less body fat accumulation in rats fed a safflower oil diet than in rats fed a beef tallow diet. J Nutr 120: 1291–1296.

SILVA AP, GUIMARÃES DE, MIZURINI DM, MAIA IC, ORTIZ-COSTA S, SARDINHA FL AND DO CARMO MG. 2006. Dietary fatty acids early in life affect lipid metabolism and adiposity in young rats. Lipids 41: 535–541.

SINGER P, WIRTH M AND BERGER I. 1990. A possible contribution of decrease in fatty acids to low serum triglyceride levels after diets supplemented with n-6 and n-3 polyunsaturated fatty acids. Atherosclerosis 83: 167–175.

SLAVIN BG, ONG JM AND KERN PA. 1994. Hormonal regulation of hormone-sensitive lipase activity and mRNA levels in isolated rat adipocytes. J Lipid Res. 35: 1535–1541.

STEINBERG GR, BONEN A AND DYCK DJ. 2002. Fatty acid oxidation and triacylglycerol hydrolysis are enhanced after chronic leptin treatment in rats. Am J Physiol Endocrinol Metab 282: E593–E600.

STRÄLFORS P AND HONNOR RC. 1989. Insulin-induced dephosphorylation of hormone-sensitive lipase. Correlation with lipolysis and cAMP-dependent protein kinase activity. Eur J Biochem 182: 379–385.

TAKEUCHI H, MATSUO T, TOKUYAMA K, SHIMOMURA Y AND SUZUKI M. 1995. Diet induced thermogenesis is lower in rats fed a lard diet than in those fed a high oleic acid safflower oil diet, a safflower oil diet or a linseed oil diet. J Nutr 125: 920–925.

TODORIC J, LOFFLER M, HUBER J, BILBAN M, REIMERS M, KADL A, ZEYDA M, WALDHAUSL W AND STULNIG TM. 2006. Adipose tissue inflammation induced by high-fat diet in obese diabetic mice is prevented by n-3 polyunsaturated fatty acids. Diabetologia 49: 2109–2119.

TRAVERS MT AND BARBER MC. 1999. Insulin-glucocorticoid interactions in the regulation of acetyl-CoA carboxylase-alpha transcript diversity in ovine adipose tissue. J Mol Endocrinol 22: 71–79.

TRAYHURN P AND BEATTIE JH. 2001. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 60: 329–339.

TSUBOYAMA-KASAOKA N, TAKAHASHI M, KIM H AND EZAKI O. 1999. Up-regulation of liver uncoupling protein-2 mrna by either fish oil feeding or fibrate administration in mice. Biochem Biophys Res Commun 257: 879–885.

TSUKUMO DM ET AL. 2007. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. Diabetes 56: 1986–1998.

UYSAL KT, WIESBROCK SM, MARINO MW AND HOTAMISLIGIL GS. 1997. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. Nature 389: 610–614.

VAUGHAN M, BERGER JE AND STEINBERG D. 1964. Hormone-sensitive lipase and monoglyceride lipase activities in adipose tissue. J Biol Chem 239: 401–409.

VENTRE J, DOEBBER T, WU M, MACNAUL K, STEVENS K, PASPARAKIS M, KOLLIAS G AND MOLLER DE. 1997. Targeted disruption of the tumor necrosis factor-alpha gene: metabolic consequences in obese and nonobese mice. Diabetes 46: 1526–1531.

VOLPE JJ AND MARASA JC. 1975. Hormonal regulation of fatty acid synthetase, acetyl-CoA carboxylase and fatty acid synthesis in mammalian adipose tissue and liver. Biochim Biophys Acta 380: 454–472.

WEISBERG S, MCCANN D, DESAI M, ROSENBAUM M, LEIBEL RL AND FERRANTE JR AW. 2003. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796–1808.

YAMAMOTO Y, HIROSE H, SAITO I, TOMITA M, TANIYAMA M, MATSUBARA K, OKAZAKI Y, ISHII T, NISHIKAI K AND SARUTA T. 2002. Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. Clin Sci (Lond) 103: 137–142.

ZAVARONI I, NUMEROSO F, DONGIOVANNI P, ARDIGO D, VALENTI L, FRACANZANI A, VALTUENA S, DELSIGNORE R, FARGION S AND REAVEN GM. 2003. What is the contribution of differences in three measures of tumor necrosis factor-alpha activity to insulin resistance in healthy volunteers? Metabolism 52: 1593–1596.

ZHOU X, DE SCHEPPER J, DE CRAEMER D, DELHASE M, GYS G, SMITZ J AND HOOGHE-PETERS EL. 1998. Pituitary growth hormone release and gene expression in cafeteria-diet-induced obese rats. J Endocrinol 159: 165–172.