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OLLER DO NASCIMENTO, CLÁUDIA M.; RIBEIRO, ELIANE B.; OYAMA, LILA M.

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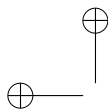
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Metabolism and secretory function of white adipose tissue: effect of dietary fat

CLÁUDIA M. OLLER DO NASCIMENTO¹, ELIANE B. RIBEIRO¹ and LILA M. OYAMA²

¹Departamento de Fisiologia, Universidade Federal de São Paulo, Campus São Paulo
Rua Botucatu, 862, 2º andar, 04023-060 São Paulo, SP, Brasil

²Departamento de Biociências, Universidade Federal de São Paulo, Campus Baixada Santista
Av. Ana Costa, 95, 11060-001 Santos, SP, Brasil

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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), 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 response.



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 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



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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 acetyl-CoA carboxylase 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 (Moustaid 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 (Strålfors and Honnor 1989). Phosphorylation of HSL results in increased hydrolytic activity, translocation of HSL from cytosol to the lipid droplet

perilipin by cAMP-dependent protein kinase (PKA) to 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 adenylyl 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. 1999, Sengenès et al. 2002). Autocrine/paracrine factors 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 re-esterification in adipocytes to produce TAG. High rates of re-esterification in TAG have been shown to occur in WAT during fasting, both in rats and humans (Sengenès et al. 2003). Esterification of FAs requires glycerol 3-phosphate formation which, under lipolytic situation, 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., Olszang et al. (1969). It was 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 developing lipodystrophy. These results demonstrated the physiological role of glyceroneogenesis to maintain 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



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

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 be-



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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 associ-

toglobulin (Trayhurn and Beattie 2001, Friedrich 1995, Nascimento et al. 2004).

As stated before, this review focuses on haptoglobin, TNF- α , plasminogen activator inhibitor 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 rodents, but mainly by IL-6 and dexamethasone in humans (Baumann et al. 1990, Mackiewicz et al. 1990). IL-6 is, however, the common inflammatory cytokine mediator for haptoglobin gene regulation in the all studied species (Pajovic et al. 1994).

The identification of haptoglobin, in particular a putative secreted factor from WAT (Friedrich 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 the lean siblings, and also haptoglobin is expressed in all the main WAT depots of mice, both internal and retroperitoneal, 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 may be a source of the increase in plasma haptoglobin observed in obese subjects (Engstrom et al. 2003, Trayhurn 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.



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 PPAR γ 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 as-

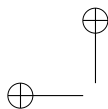
Initially, adipocytes were considered the predominant source of adipose tissue TNF- α . However, recent studies have demonstrated that preadipocytes, endothelial cells, smooth muscle cells, fibroblasts, leukocytes and macrophages, which are present in WAT as a stromavascular fraction, can produce substantially 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- κ B (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).



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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 inflamma-

resistance and heart disease is positively related to the ingestion of saturated fatty acids, and negatively to the ingestion of PUFA (Hu 2003, Sacks and 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 mice, which have a loss-of-function mutation in TLR4, are protected against the development of obesity and insulin resistance induced by a 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). They 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 directly interact with the immune modulation and inflammation response through the activation of TLR in macrophages (Lee et al. 2001). TLR is also expressed in 3T3-L1 cells, mouse cultured adipocytes and human WAT (Shi et al. 2006, Creely et al. 2006). This reinforces the findings in which inflammation is related to 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 ingested for 2 or 60 days, increased haptoglobin gene expression in mice WAT. It was also found that 3T3-L1 adipocytes responds to palmitic acid in a dose dependent manner in which the haptoglobin gene expression is increased at doses higher than 100 μ M (Oyama et al. 2005).

Treatment with palmitate induces the NF- κ B activation and the expression of IL-6 and TNF- α mRNA in 3T3-L1 adipocytes (Ajuwon and Spurlock 2005). *In vivo* studies showed that WAT TNF- α gene expression was significantly increased by the cafeteria diet, rich in



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 triacylglycerol 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

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

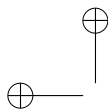
The present review showed that, depending on the outcome being analyzed, the duration of the exposure to the high-fat feeding, amount of fatty acid present in the diet and the type of fatty acid may or may not have a significant effect on adipose tissue metabolism. However, the long-term or short-term-high 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 adiponec-



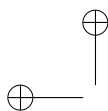
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sobre o metabolismo do tecido adiposo. Entretanto, o tratamento a curto ou longo prazo com dieta hiperlipídica, especialmente rica em ácidos graxos saturados, provavelmente por ativar receptores *toll-like*, estimula a expressão de adipocinas pró-inflamatórias 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.

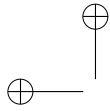
Palavras-chave: adipocinas, dietas hiperlipídicas, metabolismo, tecido adiposo branco.

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