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REVIEWS: CURRENT TOPICS

The role of dietary fatty acids in the pathology of metabolic syndrome

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Abstract

Dysfunctional lipid metabolism is a key component in the development of metabolic syndrome, a very frequent condition characterized by dyslipidemia, insulin resistance, abdominal obesity and hypertension, which are related to an elevated risk for type 2 diabetes mellitus. The prevalence of metabolic syndrome is strongly associated with the severity of obesity; its physiopathology is related to both genetics and food intake habits, especially the consumption of a high-caloric, high-fat and high-carbohydrate diet. With the progress of scientific knowledge in the field of nutrigenomics, it was possible to elucidate how the majority of dietary fatty acids influence plasma lipid metabolism and also the genes expression involved in lipolysis and lipogenesis within hepatocytes and adipocytes. The aim of this review is to examine the relevant mechanistic aspects of dietary fatty acids related to blood lipids, adipose tissue metabolism, hepatic fat storage and inflammatory process, all of them closely related to the genesis of metabolic syndrome.

Keywords: Dietary fatty acids; Metabolic syndrome; Inflammation; Steatosis; Adipose tissue metabolism; Lipid metabolism

1. Introduction

Metabolic syndrome is related to several cardiovascular risk factors such as insulin resistance, dyslipidemia, hypertension, nonalcoholic fatty liver disease, hyperuricemia, and prothrombotic and proinflammatory states [1]. Obesity is well recognized as the most important health problem related to the genesis of metabolic syndrome, and the rise of this disease all over the world has elicited interest in the underlying mechanisms involved in these pathologies [2]. The increase in the frequency of obesity and its comorbidities has been observed worldwide, not only in developed countries such as the United States but also in low-income populations; the World Health Organization estimates that there are 500 million obese people and 1.5 billion overweight individuals [3]. In the last decade, a strong association has been demonstrated between inflammatory mediators and insulin action, thus describing obesity as a state of chronic inflammation. Human obesity does not always result in disease, which means that the threshold for fat mass differs among individuals and may be determined by environmental and genetic variables [2].

Dietary interventions may induce changes in this metabolic and inflammatory state by modulating the expression of important genes involved in these chronic manifestations. The amount and the kind of dietary fatty acids can regulate complex intracellular signaling systems, thereby modulating cellular metabolism.

This review focuses on the relevant mechanisms involved in the influence of dietary fatty acids on plasma lipids and lipoproteins, hepatic steatosis, adipose tissue metabolism and inflammatory processes, which are all involved in metabolic syndrome.

2. Dietary fatty acids and plasma lipids

Abnormalities in lipid and lipoprotein metabolism in metabolic syndrome are mainly explained by increased adiposity, insulin resistance and alterations in transcription factors inherent to lipogenesis and lipolysis, both in the liver and in adipose tissue. Several of these conditions are a consequence of the amount and the quality of the alimentary fat.

Although similar patterns of the responses of blood lipids to alimentary fatty acids can be identified, a considerable individual variation is often observed, although this has yet to be explained. The recent advances in nutrigenomics are likely to explain the clinical and epidemiological findings involved in these individual dietary responses to fats.

Dietary fatty acids are generally classified according to parameters that have biological significance, such as the number and position of double bonds, carbon chain length and their position in the glycerol moiety. Despite the similarity among the fatty acids, subtle difference in their structure may induce relevant differences

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in the metabolic responses involved in plasma lipids and lipoprotein metabolism.

2.1. Saturated fatty acids

Saturated fatty acids (SAFAs) are a simple molecular structure with complex cellular function, and each SAFA has a specific role in the metabolic fate [4]. Although they harbor important physiological mechanisms, some SAFAs have also been associated with deleterious effects regarding several parameters involved in metabolic syndrome, especially due to their influence on plasma triacyglycerols (TAG), total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentration.

The major dietary saturated long-chain fatty acids, such as myristic acid (14:0), found in milk and its derivatives, and palmitic acid (16:0), the most abundant fatty acid in the diet, greatly influence plasma lipids. According to metabolic and epidemiological trials [5,6], myristic and palmitic acids increase plasma cholesterol and LDL-C compared to polyunsaturated fatty acids (PUFAs), and the LDL receptor is strongly involved in this outcome. LDL receptors are clustered in clathrin-coated pits that constitute <2% of the surface area of a cell [7]. Saturated fatty acids induce a reduction in mRNA abundance [8], protein content [9] and the activity of LDL receptors (receptor B–E) [10], and this is likely related to (a) changes in the cell membrane fatty acids content that decrease the plasma LDL catabolism rate [11]; (b) enrichment of cholesteryl ester in apolipoprotein B (apoB)-rich lipoproteins, which is related to an increase in activity of hepatic acyl-CoA:cholesterol acyltransferase (ACAT) (this enzyme catalyzes the cholesteryl esters synthesis from cholesterol and fatty acyl coenzyme A in endoplasmic reticulum) [12]; (c) increase in apoB-100 hepatic production, as shown in cultured HepG2 cells, resulting in increased LDL and very-low-density lipoprotein (VLDL) particle numbers, causing both cholesterol and triacylglycerols to increase [13]; (d) up-regulation of the sterol-regulatory element binding protein-1c (SREBP-1c) gene, a transcription factor involved in triacylglycerol synthesis; and (e) the fact that more lipid molecules can be accommodated by the apoprotein chain of the LDL containing SAFAs molecules due to their straight chain [14].

Palmitic acid is the predominant SAFA in the diet, which represents 56.3% of total SAFAs intake in the United States [15]. Although myristic acid has a higher impact in the cholesterolemia, palmitic acid has a higher deleterious effect because of its higher consumption.

Despite the fact that most of the SAFAs are related to an increase in blood cholesterol, such an effect is not observed with stearic acid (18:0), abundant in cocoa fat [5], because it is particularly sensitive to the liver stearoyl-CoA desaturase (SCD) 1, thus undergoing desaturation of SAFAs to monounsaturated fatty acids (MUFAs). Consequently, in contrast to palmitic and myristic acid, stearic acid does not modify LDL receptor expression [8]. The enzymes involved in both the elongation (Elovl) and desaturation (SCD) of fatty acids are regulated mainly at the transcriptional level rather than posttranslationally [16]. As observed in other steps involved in lipid homeostasis, the regulation of the expression of these enzymes is tightly controlled by hormones, circadian rhythms and food intake. Therefore, these enzymes are involved in a variety of synthetic pathways that may influence the levels of different fatty acid pools in response to multiple stimuli [16].

For instance, stearic acid is a substrate for elongation by Elovl1, Elovl3 and Elovl7, which, by promoting chain elongation, produce saturated arachidic acid [16]. However, the desaturases' (SCD-1, SCD-2 and SCD-4) actions on stearic acid are faster, and this fatty acid is a substrate for both palmitoyl- and stearoyl-CoA desaturases. This may explain why stearic acid did not induce all of the adverse effects attributed to plasma lipids and lipoproteins classically described for other SAFAs. Nonetheless, other potential deleterious effects of stearic acid involving parameters of metabolic syndrome should be investigated. Evidences from literature are not sufficient to determine whether it is superior to other SAFAs because multiple pathways may be involved and clear data on clinical endpoints are not available [17].

Myristic acid is more rapidly incorporated into cell triacylglycerols because it is faster elongated, and leads to the highest blood cholesterol when compared to the other fatty acids [18]. Despite that effect, a recent meta-analysis failed to relate dairy intake to increased cardiovascular risk, although a strong association has been reported between butter and cheese intake and an increase in LDL-C with a higher prevalence of metabolic syndrome [19]. One possibility is that subjects who maintained their milk consumption also maintained or acquired the habit of consuming other healthy foods. However, the properties of myristic acid have not been fully investigated because it is a rare molecule in cells and regularly represents only 0.5%–1% by weight of the total fatty acid content in animal tissues [4]. Nevertheless, several important cellular mechanisms have been described in the last few years, such as the myristoylation reaction [20], which occurs in 0.5 % of all the human genome [4]. Moreover, myristic acid activates Δ-6 desaturase and diΔ-4 desaturase activities in cellular models and regulates the PUFAs bioavailability *in vivo* [20].

2.2. Unsaturated fatty acids

Unsaturated fatty acids are classified by the number of double bonds as mono- or polyunsaturated. They are mainly found in the *cis* setting of double bond, where the two hydrogen atoms are positioned on the same side. Therefore, in double bond, the chain carbon axis forms a slightly bent angle in the opposite part to the two hydrogen atoms, and the higher the amount of double bonds is, the greater the bending is. Thus, in the phospholipids lipoprotein packing, PUFAs restrict the space for cholesterol molecules accommodation in the lipoprotein [14].

Polyunsaturated fatty acids belong to different series defined by the location of the first double bond in the carbon chain from the methyl terminal side and thus belong to the omega-3 (ω-3), omega-6 (ω-6) or omega-9 (ω-9) series. Oleic acid (C18:1), a member of the ω-9 series, is one of the most frequently found in nature, with olive and canola oil being the main dietary sources. In canola oil, which is extracted from rapeseed oil, erucic acid (C22:1) is eliminated. The latter very-long-chain fatty acid has an unpleasant flavor and is associated with myocardial function [22].

The most abundant PUFA belonging to the ω-6 series is linoleic acid (C18:2), followed by arachidonic acid (C20:4), which is mainly found in corn and sunflower oils. The main sources of α-linoleic acid, a member of the ω-3 series, are linseed, soy and canola oils. Linoleic and linolenic acids are essential to humans, as mammalian cells lack the capacity to insert a double bond (i.e., desaturate) before carbon 9 of the fatty acid chain. Eicosapentaenoic (C20:5; EPA) and docosahexaenoic (C22:6; DHA) acids, members of the ω-3 series, are found in the fat of cold and deep sea water fish. They are not essential to humans, as they can be synthesized from linolenic acid.

Several actions of PUFAs in the modulation of pathways that could influence blood cholesterol have been described. First, PUFAs reduce the hepatic production rate of VLDL concomitant to lesser expression of microsomal triacylglycerol transfer protein (MTP) which is involved in the assembly and secretion of this lipoprotein [13]. Second, PUFAs increase the membrane fluidity of hepatocytes, thus changing LDL receptor activity [21] and the amount of hepatic LDL receptors [13,23]; this is likely due to a high fatty acid affinity to the enzyme acyl-cholesterol-acyltransferase (ACAT), which esterifies cholesterol with oleic acid, lowering the unesterified cholesterol fraction and consequently stimulating the B/E receptor synthesis [24]. This investigation showed that PUFAs do not increase the mRNA for

the LDL receptor, indicating that the regulation occurred at the posttranslational level due to receptor protein abundance. However, a recent study reinforced that PUFAs induced an increase in the mRNA of LDL receptor [13]. Therefore, LDL removal rate increases, and its production is limited [25]. Third, changes in the spatial configuration of LDL occur because phospholipids and PUFAs exist in the *cis* conformation, thus occupying more space in lipoproteins and restricting the volume of this particle available to transport cholesterol [26]. Fourth, LDL formation with lower cholesteryl ester content is a consequence of the decreased cholesterol ester transfer protein (CETP)-mediated transfer rate from high-density lipoprotein cholesterol (HDL-C) to VLDL [27]. Lastly, reductions in HDL-C concentrations are a result of ATP-binding cassette transporter A-1 (ABCA-1) down-regulation induced by PUFAs. These fatty acids suppress the liver X receptor/retinoid X receptor (LXR/RXR) genes responsible for ABCA-1 synthesis [28], a transporter involved in the HDL formation.

Moreover, PUFAs modulate several genes involved in oxidative processes, such as PPAR-α, while impairing the SREBPs which are involved in lipogenesis. SREBPs are transcription factors bound to membranes that induce fatty acids synthesis whose expression is decreased with PUFAs, with the highest inhibitory effects being on SREBP-1a and SREBP-1c expression [29].

Some important trials have elucidated other actions related to ω-6 series PUFA and showed that, when consumed in large amounts, it can have some undesirable effects, such as lowering plasma HDL-C [30] and increasing LDL susceptibility to oxidation [31]. However, such results should be cautiously considered regarding dietary recommendation because it is known from several population studies [32] that ω-6 PUFAs are related to a reduction in prevalence of coronary disease. In a recent review from the American Heart Association Nutrition Commission, the authors showed evidence that ω-6 series fatty acids lower cardiovascular risk and reinforced that ω-6 consumption should be encouraged [33].

Regarding the ω-3 series PUFAs, EPA (20:5n-3) and DHA (22:6n-3) play important roles in several metabolic processes. Dietary intake of their precursor, α-linolenic acid (ALA, 18:3n-3), is essential because humans do not have the required Δ^{12}- and Δ^{15}-desaturase enzymes to synthesize ALA *de novo* from stearic acid [34]. Omega-3 fatty acids are mainly incorporated into phospholipids, sphingolipids and plasmalogens. These unsaturated long-chain ω-3 fatty acids influence the physical properties of membranes (e.g., fluidity, thickness and deformability) and, consequently, interfere with transmembrane protein activity [34]. They are related to the moderate reduction of triacylglycerols by impairing diacylglycerol acyltransferase activity, which is critical in hepatic triacylglycerol synthesis [35], thus decreasing hepatic VLDL secretion [36], but high doses may adversely decrease LDL receptor and produce small LDL, which is related to atherosclerosis [37]. In addition, as they are involved in important transcriptional regulatory pathways, they increase PPAR-α, which regulates lipoprotein lipase (LPL) synthesis [38]. They also modulate genes involved in lipogenesis, together with nuclear receptors and transcription factors, including PPAR-γ, hepatocyte nuclear factor 4α (HNF-4α), LXR and nuclear factor-kappa B (NF-κB) [46,37]. Therefore, they increase fatty acid oxidation by PPAR-α activation or by reducing SREBP activity, inhibiting lipogenesis [39,40]. Moreover, they suppress the carbohydrate regulatory element binding protein (ChREBP) which participates in the triglyceride production from glucose [41].

Among the prominent intervention trials with fatty acids ω-3, the Lyon Diet Heart Study, in which 200 subjects were instructed to increase their fiber and ω-3 fatty acid (ALA) consumption, should be highlighted. Although no change in blood cholesterol was shown, a decrease in cardiovascular events and mortality was reported. However, in that investigation, it was not possible to attribute that benefit only to ω-3 fatty acid consumption because the subjects changed their food habits in several beneficial ways [42].

About 1.0 g/day of ALA in the diet is recommended; an adequate supply of soy or canola oils provides the necessary amounts of this fatty acid, and in this situation, dietary supplementation is not necessary. Regarding the maintenance of the ω-6 to ω-3 ratio for cardiovascular disease prevention, the European study OPTLIP confirmed the importance of consuming ω-3 fatty acids and the irrelevance of establishing a requirement for an ideal ω-6 and ω-3 ratio in the diet [43]. The dietary ALA-to-linoleic acid ratio is not a determinant of ω-3 fatty acid conversion. An increase in EPA synthesis can be obtained by lowering the amount of linoleic acid in the diet, whereas an increase in DHA synthesis is achieved by increasing the amount of dietary ALA. Therefore, the amounts of ALA and linoleic acid in the diet, not their ratio, determine ALA conversion [44]. Furthermore, as not only do humans have a limited capacity to convert ALA to EPA, but likewise EPA to DHA, adequate amounts of fish consumption are recommended in the diet [45].

Regarding oleic acid, it was more resistant to LDL oxidation as compared to linoleic acid and also reduced plasma LDL concentrations [46], and these results are attributed to oleic acid being a better substrate for liver ACAT. Therefore, cholesterol excess in its free form is rapidly esterified and, so it does not induce LDL receptor suppression [47]. In addition, when compared to PUFAs, oleic acid lowers the endogenous cholesterol synthesis rate [48].

It is well documented that populations in the Mediterranean area, known for their high oleic acid intake, have lower prevalence of obesity, type 2 diabetes, cardiovascular events [49] and metabolic syndrome [50,51]. It is important to emphasize, however, that prevention of those diseases cannot be solely attributed to olive oil consumption [52] but also to other healthy foods included in the diet. Despite the absence of dietary standard due to cultural diversities, it is important to emphasize that some foods, such as whole grains, fruits, fishes and vegetables, are present in the diet of all populations in the Mediterranean region.

2.4. Trans fatty acids

Trans fatty acids are the geometric isomers of *cis* fatty acids, presenting the same molecular formulation with a different structure that can be synthesized from bacteria fermentation in ruminants (vaccenic acid) and found in small amounts in meat and milk [53]. However, their most important source is hydrogenated fat (elaidic acid), which is produced by a catalytic process that is widely employed in industrialized foods.

They have several implications in metabolic syndrome, as these fatty acids are strongly associated with a rise in inflammatory processes, plasma triacylglycerols and cholesterol, as well as a reduction in HDL [54].

Trans and saturated fatty acids increase cholesterol concentrations in similar ways; however, *trans* fatty acids adversely lower HDL, probably inducing apoA1 catabolism and increasing CETP activity [55]; an additional consequence is the reduction of HDL2, the subfraction most sensitive to dietary changes. Regarding the influence of *trans* fatty acids on the cholesterol efflux system from macrophages, it has been demonstrated that they do not differ from saturated or polyunsaturated fatty acids [56]. Therefore, *trans* fatty acids' harmful actions in atherosclerosis cannot be attributed to a role in the first step of the reverse cholesterol transport system. It is important to emphasize that this study was conducted with normal young subjects submitted to a normal total fat diet (30% of total calories) and that other parameters related to the pathology of atherosclerosis were not evaluated.

Trans fatty acids lower acylation stimulating protein (ASP) expression and raise the plasma free fatty acid concentration. ASPs are related to triacylglycerol uptake by the adipocytes. They interact with cell membranes, stimulating diacylglycerol, which regulates triacylglycerol synthesis by protein kinase C. In addition, ASPs relate to glucose uptake, regardless of insulin action. Therefore, the decrease in ASP expression in plasma caused by *trans* fatty acids could indirectly contribute to insulin resistance [57]. *Trans* fatty acids increase cardiovascular disease risk by influencing risk factors and also by direct actions on the endothelium, such as on its injury and death by inducing apoptosis in human cells via activation of the caspase pathway [58].

2.5. Interesterified fats

The importance of the types of fat that are used in the industrialized food is highly relevant, especially given the evidence that the *trans* fatty acid intake induces alterations that lead to metabolic syndrome [59]. The alternative to these products has been the use of interesterified fatty acids, which are obtained from the mixture of oil and a completely hydrogenated fat. Moreover, it can also be obtained from mixtures of solid fractions such as palm stearin and lauric acid from coconut oil [60]. They are prepared mainly by a chemical method, requiring sodium methoxide, which catalyzes a randomized process of the binding of fatty acids to glycerol, favoring the transference of the SAFA to the sn-2 position of the triacylglycerol molecule. In vegetable oils, this position is normally occupied by unsaturated fatty acids, and this change in position may lead to undesirable consequences for plasma lipid and lipoprotein metabolism [61,62]. About these parameters, the few relevant studies in the literature conducted in animals and humans have shown controversial results. It was demonstrated in healthy individuals that both partially hydrogenated and interesterified soybean oil led to increases in the LDL-C/HDL-C ratio and in fasting glycemia when compared to palm oil [63]. In another investigation performed in hypercholesterolemic subjects, the consumption of margarine containing interesterified fat did not induce alteration in plasma LDL concentration, despite the fatty acid alteration in the sn-2 position [64].

Regarding the influence of the type of interesterification, it was verified that the chemical method did not influence the lipoprotein profile in healthy [65] but did increase the postprandial triacylglycerol concentration (85%) in obese individuals [66], suggesting that the undesirable effects may depend on the presence of different risk factors for cardiovascular disease and type 2 diabetes.

In general, the high diversity of sources of interesterified fats (mainly palmitic and stearic acids), whose metabolic actions are completely different, makes it difficult to interpret their effects regarding plasma lipids and other alterations related to metabolic syndrome, reinforcing that more studies in this area are required.

3. Dietary fatty acids in nonalcoholic fatty liver disease

Hepatic steatosis, or nonalcoholic fatty liver disease (NAFLD), is a pathophysiological condition characterized by fat deposition in the liver in patients without a history of alcohol abuse [67]. NAFLD is currently identified as the hepatic manifestation of metabolic syndrome, which is associated with insulin resistance and central obesity. The presence of NAFLD has also been described in nonobese individuals, and in this situation, the metabolic changes are further exacerbated by marked insulin resistance [68]. Classically, NAFLD patients have slightly elevated values of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase and a higher prevalence of type 2 diabetes. Regarding the development of NAFLD, genetic susceptibility has also been reported [69]. NAFLD is associated with undesirable and detrimental changes in lifestyle and is frequently a consequence of high-fat, high-caloric diet consumption and physical inactivity as well [70], as demonstrated in insulin-resistant individuals. Steatosis was also observed in a long-term study conducted in LDLR knock-out (KO) mice submitted to a high-fat diet, and the liver fat accumulation was similar with polyunsaturated and saturated fatty acids [69]. In the latter study, we may conclude that independent of the type of fatty acids in the diet, a high-fat diet strongly induces fat deposition in the liver. It is important to note that steatosis can be successfully reversed as demonstrated in obese mice with metabolic syndrome after switching to a normal-fat diet [72].

Besides central obesity, type 2 diabetes and insulin resistance, NAFLD is also related to hyperuricemia, hypertriglyceridemia and decreased HDL-C concentration. These clinical manifestations observed in association with NAFLD can lead to premature atherosclerosis, as was reported in up to 80% of the patients [73,74]. Alone, hepatic steatosis has a benign course, whereas nonalcoholic steatohepatitis (NASH) is associated with fibrosis and the progression to cirrhosis and hepatocellular carcinoma [67]. The physiopathology of NASH is strongly associated with lipotoxicity, oxidative stress and inflammatory biomarkers, probably because of the greater ceramide contents in liver-infiltrated macrophages [75].

The main fatty acid sources of liver triacylglycerols and plasma lipoproteins in NAFLD patients are nonesterified fatty acids derived from adipose tissue lipolysis [76]. *De novo* lipogenesis (DNL) also contributes significantly to hepatic fat accumulation. In the fasting state, 26% of liver triacylglycerol in NAFLD patients was derived from DNL, which is several-fold greater than the 5% observed in healthy subjects. However, NAFLD patients failed to increase lipogenesis postprandially in response to a high-fat diet, suggesting that their lipogenic capacity has reached the threshold [76].

Westerbacka et al. [77] investigated the main genes that were significantly up-regulated in the fatty liver of insulin-resistant subjects with NAFLD. They found an increase in genes involved in fatty acid trafficking, synthesis and storage as well as inflammation, such as PPAR-γ2, the monocyte-attracting chemokines [i.e., monocyte chemotactic protein 1 (MCP-1)] and macrophage inflammatory protein-1 alpha (MIP-1α), and four genes associated with fatty acid metabolism: acyl-CoA synthetase long-chain family member 4 (ACSL4), fatty acid binding protein (FABP4 and FABP5) and LPL. Curiously, among these genes, PPAR-γ2, FABP and LPL are normally expressed, especially in adipose tissue. The implications of the dietary fatty acids regarding the majority of these genes will be discussed below and are presented in Fig. 1.

3.1. Saturated fatty acids

The consumption of diets rich in saturated fat and carbohydrates may trigger DNL. This fact was demonstrated in hamsters fed diets enriched with fructose (60% fructose) or SAFAs (30% beef tallow), which led to an increase in diacylglycerol acyltransferase-1 (DGAT1) expression and activity, eliciting lipid accumulation in hepatic and adipose tissues [78]. Another important factor that may play a role in hepatic damage is the composition of liver fatty acids. Animals submitted to a diet rich in sucrose, polyunsaturated fatty acids or saturated fatty acids showed TAG accumulation in the liver. However, the sucrose- and saturated-fat-fed groups had an increase in liver SAFA concentrations, which was associated with a higher expression of the unfolded protein response (UPR)-related components, such as X-box DNA binding protein-1 (XBP-1), glucose-regulated protein 78 (GRP78) and the proapoptotic C/EBP homologous protein (CHOP), all elicited by endoplasmic reticulum stress. Moreover, an increase in caspase 3 activity was also observed. Additionally, the sucrose- and saturated-fat-fed groups presented an increase in liver injury enzymes ALT and AST as well as caspase 3 activity (an ER stress marker) in

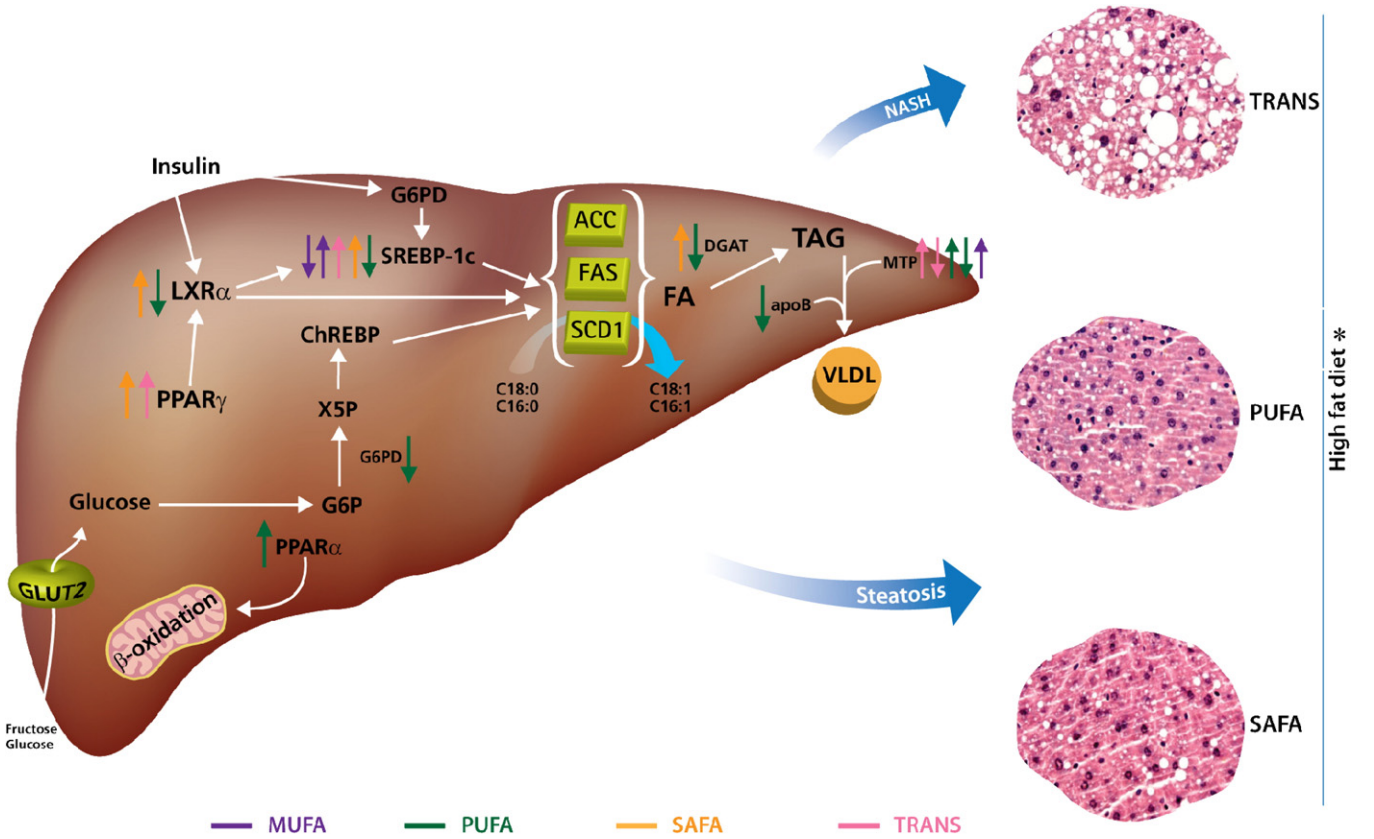

Fig. 1. Mechanisms of action of the alimentary fatty acids on the hepatic lipid metabolism. Fatty acids (SAFA, TRANS, MUFA and PUFA) modulate the expression of the FAS, ACC and SCD-1 enzymes via SREBP-1c (which is activated by the LXR). The activity of the LXR is influenced by the PPARγ2, a transcription factor activated by SAFA as well as by TRANS. The ACC, FAS and SCD-1 enzymes are related with the synthesis of triacylglycerols via DGAT, which is modulated by the action of SAFA, MUFA and PUFA. The release of endogenous triacylglycerols takes place via secretion of VLDL, whose formation is also dependent on apoB and MTP. The PUFAs increase the degradation of apoB; however, as has been observed with the TRANS, their action on MTP is still controversial. PUFA also takes part in β-oxidation as they activate PPARα. The MUFA action in SREBP1c is also controversial, but it seems to increase MTP expression. Apart from the fatty acids, carbohydrates play an important lipogenic role through ChREBP. In a diet rich in carbohydrates, PUFA is also involved in this lipogenic pathway by inhibiting both the activity and the expression of the G6PD enzyme. *Ref. 76.

response to lipopolysaccharide [79]. In primary mouse hepatocytes, SAFAs (e.g., stearic and palmitic acids) activated apoptosis via c-Jun N-terminal kinase (JNK), an effect not confirmed with oleic acid [80].

However, in a short-term high-SAFAs fat diet (mainly lauric and myristic acids), the authors observed an increase in hepatic lipogenesis without the development of hepatic steatosis in C57/Bl6J mice [81]. The action of the SAFAs on hepatic lipid metabolism is influenced by the PPAR-γ coactivator-1beta (PGC-1β). It has been demonstrated that the intake of a high-fat diet enriched with SAFAs stimulates liver PGC-1β, which coactivates SREBP-1c and enhances its transcriptional activity in lipogenic genes, such as SCD-1, fatty acid synthase (FAS) and DGAT, in the liver. However, although this coactivator increases lipogenic gene expression, there is no lipid accumulation in the hepatic tissue, probably due to the simultaneous increase in the nuclear receptor LXRα expression, which plays an important role in the cellular efflux of lipids [81]. It is worth noting that the greater efflux capacity found in the high-SAFAs-fed group led to hypertriglyceridemia and hypercholesterolemia [81]. This study was discussed by Sampath et al. [82], who mentioned that the lipogenic response elicited by SAFAs may be attributed to desaturation by SCD-1, an effect not evaluated in that study. This was further confirmed in SCD-1 knockout mice, which demonstrated that a stearic-acid-rich diet did not raise the expression of the SREBP-1c and PGC-1β genes to similar levels of those in wild-type mice [82]. However, oleic acid elicited a similar expression to that observed in wild-type mice, reinforcing that the SAFAs need to be desaturated to bring about their effects on lipogenesis [82].

The induction of the fatty acid synthesis by palmitic acid elongation into stearic acid, followed by desaturation to oleate by SCD-1, is more important than DNL as confirmed in C57BL/6J mice fed a diet rich in saturated fat [83]. In this study, it was also observed that, under such conditions, the VLDL–TG secretion remained unchanged, indicating a progressive steatosis in high-fat-fed mice [83]. ApoB and MTP are closely implicated in the VLDL–TG secretion, and PPAR-γ is involved in the transcription of these proteins [84].

A significant increase in PPAR-γ and in one of this target gene, fatty acid translocase FAT/CD36, has been observed in C57BL/6Ncrj mice submitted to a high-fat diet (82%) [85]. This mechanism fostered fatty acid uptake and therefore lipid accumulation in the hepatic tissue. However, it must be pointed out that, in this investigation, an excessive amount of fat was used, and the authors did not present the dietary fatty acid composition, making it difficult to conclude which fatty acid modulated such actions.

Regarding the effect of saturated fat on fatty acid oxidation, carnitine palmitoyltransferase-1 (CPT-1), acyl-CoA oxidase (AOX), PPAR-α and PGC-1α expressions were increased in mice fed a diet rich in stearic acid compared to mice fed an oleic-acid-rich diet [82].

In general, it is possible to observe that SAFAs induce hepatic lipogenesis. Moreover, hepatic steatosis characterized by increased SAFAs can promote liver injury, endoplasmic reticulum stress and a proapoptotic environment, which implies that they may be an important determinant of susceptibility for disease progression in NAFLD [79].

3.2. Polyunsaturated fatty acids

To better clarify the effects of PUFAs on the hepatic disease, several studies involving nutrigenomics have recently been conducted. Some of these effects relate to the induction of peroxisomal and mitochondrial oxidation and the reduction of the lipogenic enzymes expression, such as FAS, acetyl-CoA carboxylase (ACC) and SCD-1, mediated by SREBP-1c [29,86].

Opposing the effect of insulin [87], the suppressive action of PUFAs on the SREBP-1c transcription factor takes place not only by the reduction of the proteolytic process but also by the reduction of its mRNA concentration [29,88]. In addition, the suppression in SREBP-1c is LXR dependent because, in HEK293 cells, the deletion and mutation of the LXR response elements in the SREBP-1c promoter region eliminated the suppressive effect of PUFAs on SREBP-1c [89]. This may be explained by the removal of oxysterol from LXR by PUFAs [90]. An inhibitory effect of PUFAs on SREBP-1c has also been demonstrated and was mediated by the reduction in the activity of LXRα in rat hepatocytes treated with LXRα agonists or transfected with a synthetic promoter construct consisting of three LXRα response elements [91]. These PUFAs-related events are important because LXRα agonists were shown to reduce the formation of the atherosclerotic plaque in mice [92]. However, once activated in the liver, LXRα was also related to an increase in the transcription of genes involved in DNL (i.e., SREBP-1c, ChREBP, FAS, ACC, GPAT, L-PK, malic enzyme and SCD-1) [93]. However, it is important to emphasize that PUFAs are FXR agonists that, once stimulated, elicit a negative "feedback" on LXR, thereby suppressing its action [94,95]. Moreover, it has been demonstrated that FXR agonists reduce L-PK, ACC and SREBP-1c expression and increase PPAR-α; therefore, the effects of PUFAs on FXR are believed to be involved in the reduction of the development of steatosis [96,97]. FXR also has the capacity to induce the nuclear receptor small heterodimer partner by influencing SREBP-1c expression and finally inhibiting LXR activity [98].

Regarding SCD1, ω-3 and ω-6 fatty acids decrease its expression in animals, an effect that is shown to be dependent on the length of the carbon chain and on the amount of desaturation [99]. In that study, it was possible to observe that C18:1 only weakly suppressed the expression of hepatic SCD-1 mRNA, and this result was actually unexpected by the authors because oleoyl-CoA is a product of this enzyme that should exert a strong negative feedback.

In the postprandial period, the expression of hepatic lipogenic genes may be modulated by both an increase in the concentration of circulating insulin and the composition of lipoproteins originated from the diet. In rat hepatocytes, it has been observed that chylomicron remnants originating from animals fed a diet rich in PUFAs (linseed oil) were able to suppress insulin's action on the activation of SREBP-1c, SCD-1, FAS and ACC, a fact that was not observed with SAFAs [100]. In addition to the consumption of fat, carbohydrate-rich diets are directly implicated in hepatic lipogenesis through the involvement of ChREBP [101]. In the nucleus, this protein binds to a carbohydrate responsive element, which is present in the promoter regions of genes involved in the glycolytic pathways and in the promoter regions of lipogenic genes [102,103]. Thus, in the presence of carbohydrate-rich diets, ChREBP, which is normally present in its phosphorylated form in the cytosol, migrates into the nucleus by means of a phosphatase protein activation process mediated by xylulose 5-phosphate, which is an intermediate metabolite of the pentose phosphate cycle [104].

Because glucose-6-phosphate dehydrogenase (G6PD) is a limiting enzyme in the pentose phosphate pathway, it is believed that the action of the PUFAs might also be important in the reduction of ChREBP translocation into the nucleus, as they may reduce the activity and the expression of G6PD induced by a carbohydrate-rich diet [105]. The molecular mechanism of PUFAs involved in this process has been further explained in a study in mice submitted to a carbohydrate-rich diet, which induced an increase in the expression of genes related to both hepatic lipogenesis (SREBP-1c and FAS) and glycolysis (ChREBP and L-PK) [106]. In this study, the authors observed that the ω-6 (C18:2) and ω-3 (C20:5 a2d C22:6) fatty acids reversed this action. Moreover, in rat hepatocytes, arachidonic acid elicited a reduction in the expression of G6PD mediated by insulin, an action related to the inhibition of signal transduction via phosphatidylinositol 3 kinase [107].

Once PUFAs reduce the lipogenic pathway, they decrease the production of malonyl-CoA and promote an increase in CPT-1 activity, which facilitates the transport of fatty acid across the mitochondrial membrane to undergo beta oxidation, preventing the development of insulin resistance [102].

HNF-4α is another transcription factor modulated by long-chain fatty acids, especially in the form of fatty acyl-CoA thioesters, and this effect depends on the chain length and the degree of unsaturation [108]. In an assay with HeLa cells transfected with HNF-4α and HepG2 cells, the inhibition of glucose-6-phosphatase activity was observed in the presence of PUFAs ω-3 (C22:6) and ω-6 (C18:2 and C20:4), and these effects were probably mediated by HNF-4α. The investigators have observed that the mechanism whereby polyunsaturated fatty acyl-CoA suppresses the glucose-6-phosphatase gene transcription involves the inhibition of the HNF-4α binding to its cognate sites [109].

The fat liver content depends on triacylglycerol synthesis and on the mechanisms involved in the VLDL secretion rate as well. VLDL assembly and secretion depend on apoB and MTP levels. Oleic as well as palmitic, stearic and linoleic acids have shown to be strong stimulators of triacylglycerol synthesis and secretion by hepatocytes, whereas α-linolenic, γ-linolenic, arachidonic, docosahexaenoic and eicosapentaenoic acids seem to be less stimulatory [35]. However, in hamsters fed diets enriched with *cis* unsaturated fatty acids, present in soya oil or canola oil, an increase in MTP expression was observed compared to animals fed a SAFAs (butter)- or a *trans* fatty acids (margarine)-enriched diet [110]. Nevertheless, a limitation of this study recognized by the authors is that they did not determine the MTP content.

The suppression of VLDL secretion by fish oil has also been attributed to an increased apoB degradation mediated by oxidative stress [111], and recently, it was observed that DHA inhibits apoB secretion by stimulation of autophagy (LC3-II to LC3-I ratio) [112]. This isolated action could induce triacylglycerol accumulation in the hepatic tissue; however, it is worth noting that, prior to this, these fatty acids have a suppressive activity on the enzymes involved in triacylglycerol synthesis. Evidence of this fact is that the partial replacement of saturated fat with fish oil in C57Bl/6J mice was enough to normalize the lipogenic gene expression profiles and hepatic steatosis, even under conditions of inhibited VLDL–TG secretion [83]. It is also believed that the action of ω-3 PUFAs on the secretion of VLDL is modulated by the transcription factor HNF-4α, whose expression in rat hepatocytes was reduced in the presence of chylomicron remnants enriched with fish oil, simultaneously with the reduction of MTP and apoB [113].

In this context, ω-3 PUFA inhibit the secretion of VLDL because they reduce DNL and foster apoB degradation and fatty acid oxidation. Regarding this latter effect, it has been observed that PUFAs are able to reduce the expression of lipogenic enzymes (S14 and FAS) both in wild-type and PPAR-α-deficient mice. However, there was an increase in the enzymes of peroxisomal oxidation (e.g., AOX) and mitochondrial oxidation (cytochrome P450A2) only in the wild-type animals, thus confirming the important role of PPAR-α in the induction of PUFAs-mediated oxidation [86]. In animals submitted to a diet without methionine and choline (a model of hepatic

steatosis), though enriched with PUFAs, an increase in the expression of enzymes involved in the oxidation of fatty acids (e.g., PPAR-α and acyl-CoA oxidase) was observed [114].

It should be taken into account that obese subjects with NAFLD not only present an increase in the lipogenic enzymes expression and a reduction in the expression of enzymes related to the oxidation of fatty acids but also display a lower hepatic concentration of ω-3 when compared to the control group, which affirms the clinical importance of these fatty acids in hepatic disease [115]. Nevertheless, ω-3 fatty acids supplementation administered per gavage in a rat model brought on an improvement in NASH-related features since they increased antioxidative capacity as well as recuperation in hepatic uptake and excretory function, reversing severe hepatic macrovesicular steatosis [116].

In conclusion, in spite of some controversies mainly related to the secretion of VLDL, the beneficial effects of PUFAs have been confirmed, as they reduce lipogenesis and increase fatty acid oxidation in the hepatic tissue, reinforcing the importance of the consumption of the recommended PUFAs in a normal-fat diet.

3.3. Monounsaturated fatty acids

Studies involving the action of MUFA on liver fat deposition must be carefully interpreted, as it is very difficult to separate the oleic acid as a product of SCD1 from that provided by dietary fat. The majority of MUFAs produced endogenously are incorporated more efficiently into nonpolar lipids than are dietary MUFAs [16], likely due to the colocalization of SCD1 and DGAT2 [117].

MUFA consumption reduced lipogenesis through increasing fatty acid oxidation by PPAR-α activation or reducing SREBP-1c activation [118]. A sucrose-rich diet induces the expression of genes involved in hepatic gluconeogenesis and lipogenesis in Zucker rats (an obesity model), and this effect was reduced by MUFAs [119]. Olive oil was also able to blunt the increase in hepatic triacylglycerols by 30% in animals submitted to a methionine/choline-deficient diet (a steatosis model) [120]. Besides, oleic acid weakly induced the expression of PGC-1β in rat hepatocytes [81]. However, the consumption of oleic acid in a high-fat diet (42% of total calories) promotes SREBP-1c activation and an increase in hepatic triacylglycerols, and this effect was similar to that observed with coconut or lard intake [121]. This results support the data showing that, independent of the type of dietary fatty acids, a high-fat diet induces steatosis.

Oleic acid has been shown to be a strong stimulator of triacylglycerol synthesis and secretion by hepatocytes [36], and this was confirmed in hamsters fed diets enriched with canola oil (52.6% of oleic acid) [110]. That study reported an increase in MTP expression compared to the animals fed a SAFA (butter) or *trans* fatty acids (margarine) diet.

In conclusion, the recommended intake of MUFA in the diet does not induce hepatic lipogenesis; however, a high-fat diet or a diet enriched with SAFAs induces a higher SCD-1 activity, contributing with a higher TG synthesis. Actually, SCD-1 has been associated with undesirable alterations in lipid metabolism, including insulin resistance and metabolic syndrome.

3.4. Trans fatty acids

Although the action of the *trans* fatty acids on inflammatory biomarkers and plasma lipids is already well established, few studies have assessed their involvement in the genesis of hepatic disease. Recent work conducted by our group demonstrated that LDL receptor KO mice submitted to a high-fat diet (40% of total calories) enriched with *trans* fatty acids did not modify the expression of genes involved in fatty acids oxidation, such as PPAR-α and CPT-1, compared to PUFAs [71]. However, an increase in lipogenic gene expression (SREBP-1c and PPAR-γ) and a reduction in the MTP mRNA were observed, suggesting a lower liver capacity to export triacylglycerol, which led to the development of NASH-like lesions, a condition intimately related to metabolic syndrome [122] and with an increase in the risk of cardiovascular disease in humans [123]. It is important to emphasize that all mice studied by Machado et al. (2010) developed NAFLD due to the high-fat diet (40% of total calories), and this result was observed regardless of the type of fatty acid studied [71]. Using the same animal model, though on a normolipidemic diet with a lower *trans* concentration, an increase in lipogenic gene expression, such as SREBP and FAS, has also been observed [124]. In the latter study, however, the authors did not perform liver histological analysis. Another study involving the action of *trans* fatty acids on hepatic disease, using C57BL/6Njcl mice, demonstrated that a high-fat diet (60% of total calories) rich in *trans* fatty acids yielded severe hepatic steatosis and simultaneously raised the expression of lipogenic genes (FAS, ACC, SREBP, PPAR-γ2) compared to a diet enriched with canola oil [125]. However, the large amount of fat in the diets used in this study and the heterogeneity of the fatty acid distributions in the diets limited the conclusions.

Despite the methodological differences in the three studies, the injurious actions of the *trans* fatty acids on the hepatic lipid metabolism, leading to the development of hepatic lesions in different degrees, were unanimously observed.

4. Dietary fatty acids in adipocyte metabolism

The balance between food consumption and energy expenditure is necessary for the maintenance of an adequate body weight. However, the metabolic pathways involved in the processes of degradation and storage are completely different between the nutrients. On one hand, there is a harmonic equilibrium between these processes regarding carbohydrates and proteins; however, the same precision does not occur with fats and especially with different fatty acids [126]. Thus, in a high-caloric-intake condition, the probability of fat accumulation is higher than the oxidation ability. As a consequence, dietary fat remarkably takes part both in the phospholipid composition of the adipocyte membranes and in the modulation of transcription of different genes involved in the processes of lipolysis and lipogenesis. Moreover, fatty acids greatly influence adipocyte regulation, as they affect the secretion of different adipokines and inflammatory biomarkers [126].

High-fat diet consumption is related to elevated triacylglycerol concentrations in adipose tissue, induction of metabolic stress, increases in lipolysis and exacerbation of adipokine signaling. All of these situations culminate in an important inflammatory process. Additionally, western-type diets are related to insulin resistance, greater adipose tissue fatty acids release and less glucose uptake elicited by an imbalance between cytokines and macrophage infiltration [127]. An increase in plasma triacylglycerol concentration leads to ectopic fat deposition, especially in muscle, liver and pancreas, thereby enhancing lipotoxicity and cellular apoptosis [128,129].

All of these situations discussed above are present in obesity and may influence the genesis of metabolic syndrome, whose physiopathology can be better understood due to the recent progress in the molecular biology involving the effects of alimentary fat. The main mechanisms concerning the effects of dietary fatty acids on adipocyte metabolism are summarized in Fig. 2.

4.1. Plasma membrane, glucose carriers and insulin sensitivity

The fatty acid composition from the adipose cell membrane influences the physiological mechanisms involved in glucose uptake,

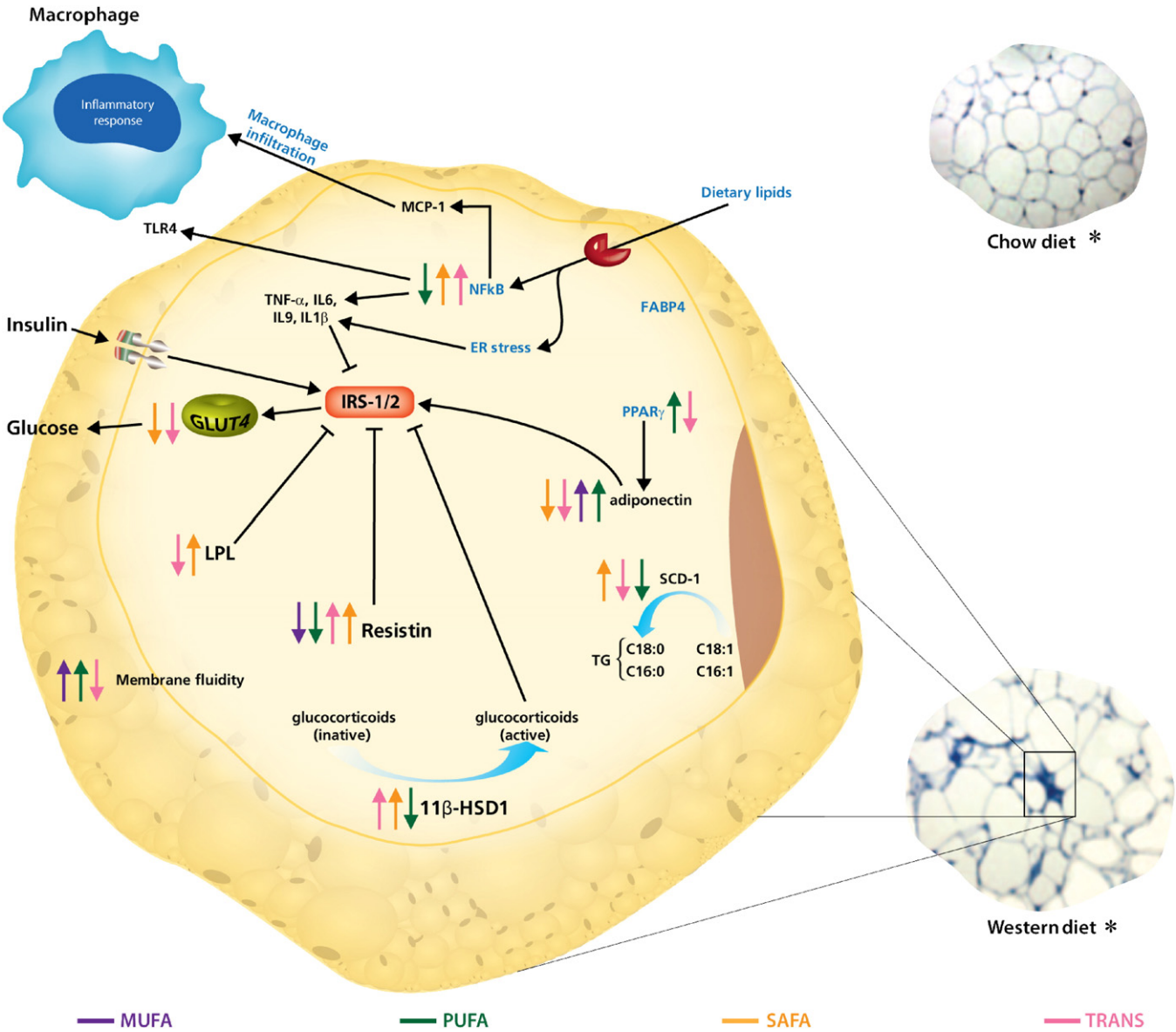

Fig. 2. Mechanisms of action of the alimentary fatty acids on the adipocyte metabolism. High-fat diets increase the expression and activity of FABP, which when overexpressed leads to endoplasmic reticulum stress. The specific activity of fatty acids is shown by arrows indicating increased and decreased actions. TRANS reduces and MUFA and PUFA increase membrane fluidity. The SAFA and TRANS stimulate inflammatory pathways and infiltration of macrophages in the adipose tissue and increase production of proinflammatory adipocytokines and MCP-1 and NFKB pathway, whereas PUFA inhibits the NF-κB pathway. A similar action on the enzyme-activating glucocorticoids, which relate to intracellular insulin signaling, is observed for TRANS, SAFA and PUFA. PUFA increases the expression of PPARγ and adiponectin and reduces the expression of resistin, whereas SAFA and TRANS have opposite actions, except for SAFA that does not modify the PPARγ expression. MUFA activates adiponectin and inhibits resistin, thereby improving the insulin sensitivity in adipocytes. Regarding the lipogenic enzyme SCD1, PUFA and TRANS suppress its expression, while SAFA overexpresses and MUFA does not interfere. The LPL expression is up-regulated by SAFA and down-regulated by TRANS, increasing free fatty acids release in blood leading to insulin resistance. SAT saturated fatty acids; TLR4: toll-like receptor 4; ER: endoplasmic reticulum; IRS1/2: insulin receptor substrates 1/2. *Ref. 131.

both by regulating the translocation of their intracellular transporters and by controlling membrane fluidity [130], factors which may be interdependent. It is well documented that the responsiveness of muscle or fat cells to insulin may depend on the fluidity of their surface membrane, which will influence the GLUT4 concentration, thus increasing glucose uptake [131].

The membrane phospholipids contain high amounts of SAFAs, although their phospholipids are predominantly formed by oleic (18:1) and palmitoleic (16:1) acids [132]. In rats, it was demonstrated that palmitic acid does not alter membrane fluidity in adipocytes [130]; however, it was associated with a lower glucose uptake [132], probably because it reduces the glucose transporter expression in rats stimulated with insulin when compared to the unsaturated fatty acids [133]. On the other hand, stearic acid does not alter GLUT4 expression in adipocyte cultures [134].

Trans-fatty-acid-rich diet was able to reduce GLUT4 expression when the linoleic acid concentration in the diet was increased [133]; however, independently of the amount of linoleic acid provided in the diet, these fatty acids are associated with lower membrane fluidity in rats [130]. Up to this point, it is possible to conclude that *trans* fatty acids reduce membrane fluidity and GLUT4 expression, which may decrease the binding of insulin to adipocytes.

In general, PUFAs are related to more fluidity, as demonstrated in the membranes of pig adipocytes [135], and their action is greater with fatty acids of the ω-3 series (e.g., EPA and DHA) compared to the ω-6 series [136]. On the other hand, ω-3 fatty acids reduced the

binding of insulin to its receptor [136]. This may in part explain the worsening glycemic control observed in type 2 diabetic subjects submitted to supplementation with ω-3 fatty acids [137]. However, regarding the actions of ω-3 fatty acids on membrane fluidity and insulin sensitivity, it is important to emphasize that there are some discrepant results between the studies conducted in animals and humans, and the effects of these fatty acids also depend on the clinical conditions of the individuals studied. A study carried out in ob/ob diabetic mice showed an improvement both in the insulin sensitivity and in the glycemic response with ω-3 fatty acids [138]. An improvement in insulin sensitivity was also demonstrated in nondiabetic women with an inflammatory profile consuming 1.3 g EPA and DHA daily for 12 weeks [139]. However, the same beneficial effects were not observed regarding glycemic control. A systematic review reported that ω-3 PUFA supplementation did not increase fasting glucose, HbA1c, fasting insulin or insulin sensitivity in type 2 diabetic people [140]. A long-term study conducted with type 2 diabetic subjects submitted to 33% ω-3 fatty acids (10% of EPA and 16.8% of DHA) showed a worsening in glycemic control, concomitant with lower glucose disposal, compared to corn oil but without alterations in insulin production [137]. Regarding the risk of developing type 2 diabetes, ALA and EPA/DHA seem to have different impact. A recent important prospective study conducted in 36,320 women showed that high consumption (based on a food frequency questionnaire) of ALA did not alter the risk of type 2 diabetes. However, an intake above 0.02 g/day of EPA and/or DHA ω-3, a value that matches two daily portions of fish, was associated with a significant increase in the risk of type 2 diabetes [141]. Therefore, it is important to emphasize that the effects of ω-3 fatty acids on insulin sensitivity and glycemic control are still debatable.

Although PUFAs are related to greater membrane fluidity, the results of studies with arachidonic acid are controversial. One study shows that incubation of this fatty acid with 3T3-L1 cells induced an increase in basal and insulin-stimulated glucose uptake concomitant with the elevation of GLUT1 and GLUT4 levels in the membrane; nevertheless, this action took place regardless of membrane fluidity, as measured by fluorescence [132]. However, other authors have observed a reduction in GLUT4 expression in the same cell line with arachidonic acid [142], but still others found a greater GLUT1 expression [143].

The influence of dietary fatty acids on insulin sensitivity also involves the modulation of PPAR-γ [144], a transcription factor that regulates the genes involved in adipocyte differentiation and insulin sensitivity, such as aP2 (also known as FABP4), LPL and CD36 [145].

Saturated fatty acids, particularly palmitic and stearic acids, do not influence PPARγ expression *in vitro* or *in vivo* [133,134,146], but they have induced an increase of its activity in human adipocytes [144]. *Trans* fatty acids (18:1t) decreased PPARγ expression in rodent adipocytes [133], which highlights the importance of avoiding *trans* fatty acids because of their strong relationship with insulin resistance [147,148].

Regarding the PUFAs, the action of EPA on PPARγ expression is still controversial. Several studies, in which these fatty acids were incubated with adipocytes of the 3T3-L1 line, showed different results, such as an increase in [149], a decrease in [134] or even no effect on [146] PPARγ gene expression. The different results may be explained by the different concentrations of EPA used in the studies, and the same was observed with DHA [131,142,146,149]. In 3T3-L1 cells, arachidonic acid metabolites, such as 15-doexy-Δ12,14-prostaglandin, promote preadipocyte differentiation into adipocytes through its binding to PPARγ [150]. However, this same action has not been directly observed with arachidonic acid [149,150].

Besides all the above effects, the action of the dietary fatty acids on the expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) was recently assessed in rat adipose tissue. This enzyme converts an inactive glucocorticoid to the active form [151], and the local increase of glucocorticoids in the adipose tissue leads to an insulin-resistant state [152]. It is well established in the literature that PPARγ down-regulates 11β-HSD1 [153], and since SAFAs and *trans* fatty acids have a lower capacity of binding to PPARγ, they are able to increase the 11β-HSD1 mRNA levels in adipocytes when compared to those observed with a PUFAs diet [152].

4.2. Enzymes involved in lipolysis and lipogenesis

The degree of unsaturation of fatty acids (stearic, EPA and oleic) does not alter the mRNA of LPL (an important marker of differentiation of preadipocytes into adipocytes) in adipocytes from the 3T3-L1 line [134]. However, similar results were not observed in *in vivo* studies, where the palmitic acid induced an increase in the expression of LPL mRNA in rat adipocytes [133]. The controversial results observed between these two reports regarding the effects of SAFAs may be explained by the different source of fatty acids utilized. Furthermore, in this study, the authors verified a lower LPL expression with *trans* fatty acids [133], and this may, in part, explain its effects on the increase in triglyceridemia.

The hormone-sensitive lipase (HSL) enzyme relates to triacylglycerol hydrolysis in the adipose tissue and is markedly insulin dependent. In cultured adipocytes from the 3T3-L1 line 3, an increase in HSL mRNA with EPA and stearic acid was reported [134]. However, oleic acid failed to influence the enzyme expression [134].

The arachidonic acid (ω-6 series) is the precursor of prostanoids, generating series-2 prostaglandins (PGE2 and PGF2α) by the action of the cyclooxygenase enzyme. These prostaglandins inhibit FAS and S14 lipogenic protein activity and expression in adipocytes [154].

SCD1, a lipogenic enzyme that also has an important effect in adipose tissue, is activated by SAFAs [155]; however, PUFAs modulate the expression of the adipocyte SCD1 gene by decreasing the stability of mRNA transcripts. As expected, MUFA had no influence in the transcription of the SCD1 gene [134,156].

4.3. Inflammatory responses

Obesity and metabolic syndrome are proatherogenic conditions since it is known that both macrophages and adipocytes take part in the genesis of these diseases. These two cell types share the same embryonic origin and, therefore, are capable of producing the same components under special circumstances [157]. In normal conditions, adipocytes store lipids and regulate metabolic homeostasis, while macrophages are related to the inflammatory response. In obesity, the metabolic and inflammatory pathways overlap [157]. Thus, gene expression becomes similar in both cells. The macrophages express proteins normally produced by adipocytes, such as the FABPs, with a simultaneous production of inflammatory cytokines in the macrophages, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and MCP-1. The FABPs modulate lipid accumulation in the adipocyte and cholesterol in the macrophage [158].

A study on LDL receptor KO mice that also lacks agouti gene submitted to either a high-fat or a normal diet revealed that both diets elicited a high infiltration of macrophages in the adipose tissue. However, this effect was more evident in the group on a high-fat diet [127], which was therefore shown to aggravate the inflammatory process. Nappo et al. [159] verified that a high-fat diet increased vascular cell adhesion molecules (VCAM-1), intercellular adhesion molecules (ICAM), IL-6 and TNF-α and that this was aggravated in diabetic subjects. The action of TNF-α on insulin resistance; induction of VCAM, ICAM and E-selectin synthesis; and the reduction of the availability of eNOS in addition to the induction of endothelial cell apoptosis is already well established [160].

The lipids take part, at the same time, in the regulation of metabolic and inflammatory pathways. By means of the FABPs, they activate intracellular kinases, such as the inhibitor-kappa B kinase (IKK), JNK and protein kinase C (PKC), which may also be activated through endoplasmic reticulum stress [158]. As a result of the consumption of a hyperlipidemic diet, these activated kinases (JNK, IKK and PKC) reduce the signaling of the insulin receptor and simultaneously induce the production of inflammatory biomarkers, such as TNF-α and interleukins, by NF-κB. Apart from their action in the inflammatory pathway, the lipids activate PPAR and LXR, both of which are involved in lipid metabolism, as well as in the efflux of cholesterol from macrophage [158].

Regarding the effects of specific fatty acids, some studies have found a strong association between the intake of *trans* and saturated fat with the modulation of a number of inflammatory cytokines [133,161], especially in comparison with the PUFAs [162,163]. An epidemiologic study conducted on overweight subjects has demonstrated an increase in IL-6 with saturated fat in those with endothelial dysfunction [161]. In comparison to oleic acid, the consumption of both SAFAs and *trans* fatty acids increased plasma IL-6, C-reactive protein and E-selectin concentrations.

The SAFAs caused an increase in expression and secretion of inflammatory cytokines, such as IL-6 and TNF-α, and also in the NF-κB activity in adipocytes [161]. Because SAFAs are ligands of toll-like receptor 4 (TLR4) that belong to the inflammatory pathway in macrophages [164], the production of proinflammatory chemokines and cytokines via NF-κB is induced [165]. The intracellular increase and release of inflammatory cytokines lead to overexpression of MCP-1, which supports increased macrophage infiltration in the adipocyte [127].

Furthermore, SAFAs also modulate cytokines involved in anti-inflammatory pathway, such as IL-10 and adiponectin, the latter also being involved in the fatty acid oxidation and insulin sensitivity [133,166]. A study using cells from the 3T3-L1 line did not find a difference in adiponectin and PPARγ genes expressions when the cells were exposed to SAFAs [146]. However, another investigation using rat adipocytes demonstrated that SAFAs reduced adiponectin expression and increased resistin expression [133], an adipokine related with insulin resistance, by inhibiting the phosphorylation of insulin receptor substrate-1 in the adipocyte [167]. Similar result was observed by Saravanan and coworkers in 2005 [133] in a study wherein an adiponectin reduction took place only in the group that received a diet simultaneously rich in *trans* fat and in linoleic acid.

Regarding MUFAs, a decrease in resistin and an increase in adiponectin expressions were observed in adipocytes [168], while no effect in NF-κB transcription factor activity was found with this fatty acid [161].

From another perspective, the DHA in adipocytes reduced NF-κB transcription factor activity [161] and elevated both adiponectin and IL-10 expressions. EPA also increased adiponectin secretion in both *in vitro* and *in vivo* studies [146,169]. Nevertheless, this increase was not observed when they were incubated together with a PPARγ antagonist [146], confirming their important role in adiponectin expression [169].

4.4. ω-3 and ω-6 fatty acids and systemic inflammation

ω-3 and ω-6 fatty acids series are precursors of the synthesis of prostaglandin and leukotriene, which are involved in coagulation and inflammation processes, respectively. ω-6 fatty acids participate in the inflammatory process, whereas ω-3 fatty acids activate the anti-inflammatory pathway [170]. Eicosanoid production by platelets and cells in the vascular wall modulates physiological processes, including arterial compliance, fluidity and platelet aggregation contributes to minimize atherosclerosis risk. The balance between the production of anti-inflammatory and inflammatory prostaglandin is essential to prevent thrombotic complications [170].

Desaturases convert linoleic and α-linolenic acids into arachidonic and eicosapentaenoic acids, respectively [170]. Arachidonic acid is the precursor of prostaglandin E_2 and leukotriene B_4, which are critical proinflammatory eicosanoids, and of thromboxane A_2, a platelet-aggregating agent and strong vasoconstrictor. However, it is important to note that arachidonic acid is also the precursor of different epoxides, which can differentially modulate vessel tone. For example, it can produce epoxyeicosatrienoic acids when mediated by 2C and 2J epoxygenases which are linked with vasodilatation, angiogenesis and anti-inflammatory effects. On the other hand, when mediated by CYP4A enzymes, arachidonic acid can also generate a potent vasoconstrictor, 20-hydroxyeicosatetraenoic acid [171,172].

In the anti-inflammatory pathway, EPA is converted into prostaglandin E_3, leukotriene B_5 and thromboxane A_3, which potentially have anti-inflammatory and antithrombotic actions [170].

Therefore, ω-3 and ω-6 fatty acids compete for enzymes along common metabolic pathways. Overall, the appropriate consumption of the two fatty acids series (ω-3 and ω-6) ensures the balance necessary to control the coagulation and inflammation processes [172,173].

4.5. Conclusion

This review provides evidence on the role of dietary fatty acids involved in metabolic and cellular signaling pathways leading to the metabolic syndrome. Some of them, such as the influence of fatty acids on plasma lipids and lipoproteins, were already elucidated years ago, whereas others, such as the effects of dietary fat on genes expression and activity in both adipose tissue and in the liver, have recently been investigated. In this regard, the importance of the influence of dietary fatty acids in the "crosstalk" among plasma lipids, adipocyte and hepatocyte was also discussed here.

A growing body of evidence suggests that not only the quantity but also the quality of dietary fatty acids influence the development of steatosis and also that the type of fatty acid accumulation in the liver may be a determinant in the progression of the hepatic disease. Very high intake of fat either as PUFAs or as SAFAs promotes the development of NAFLD, and *trans* adversely induces NASH. Moreover, the storage of SAFAs can elicit liver injury, endoplasmic reticulum stress and a proapoptotic environment.

Regarding adipose tissue, it is possible to conclude that *trans* fatty acids reduce membrane fluidity and GLUT4 expression. On the other hand, although ω-3 fatty acids induce greater fluidity, they may decrease the binding of insulin to adipocytes and worsen the glycemic control in diabetic people. However, EPA and DHA induce adiponectin secretion, therefore favorably influencing the fatty acid oxidation and insulin sensitivity. SAFAs increase adipocyte SCD1, and PUFAs decrease the stability of SCD1 mRNA transcripts expression by decreasing the stability of mRNA transcripts. Although SCD1 activity has recently been associated with undesirable effects, including insulin resistance and metabolic syndrome, it is important to state that the resultant accumulation of the SCD-1 substrate (SAFAs) of the endogenous lipogenesis may be undesirable. Finally, this review emphasizes that the recommended dietary approach supported by nutritional guidelines associated with a healthy lifestyle may provide protection against the development of the metabolic syndrome [174,175].

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