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ScienceDirect
Progress in Lipid Research 47 (2008) 127–146
Progress in Lipid Research
www.elsevier.com/locate/plipres

Review

Bioactive lipids in metabolic syndrome

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Received 8 November 2007; received in revised form 30 November 2007; accepted 5 December 2007

Abstract

The metabolic syndrome is a cluster of metabolic disorders, such as abdominal obesity, dyslipidemia, hypertension and impaired fasting glucose that contribute to increased cardiovascular morbidity and mortality. Although the pathogenesis of metabolic syndrome is complicated and the precise mechanisms have not been elucidated, dietary lipids have been recognized as contributory factors in the development and the prevention of cardiovascular risk clustering. This review explores the physiological functions and molecular actions of bioactive lipids, such as $n-3$ polyunsaturated fatty acids, conjugated fatty acids, sterols, medium-chain fatty acids, diacylglycerols and phospholipids, in the development of metabolic syndrome. Dietary bioactive lipids suppress the accumulation of abdominal adipose tissue and lipids in the liver and serum, and alleviate hypertension and type 2 diabetes through the transcriptional regulation of lipid and glucose metabolism. Peroxisome proliferator-activated receptors (PPARs), sterol regulatory element binding proteins, liver X receptor α, retinoid X receptor α, farnesoid X receptor α, hepatic nuclear factor 4α and nuclear factor κB contribute to these nuclear actions of bioactive lipids with complex interactions. Recent studies have demonstrated the striking ability of bioactive lipids to regulate the production of physiologically active adipocytokines through PPARγ activation. In particular, the function of bioactive lipids as dietary adiponectin inducers (dietary insulin sensitizers) deserves attention with respect to alleviation of metabolic syndrome by dietary manipulation.

Keywords: Bioactive lipids; Metabolic syndrome; $n-3$ PUFA; Conjugated fatty acid; CLA; Medium-chain fatty acid; Diacylglycerol; Phospholipid; Sterol; PPAR; SREBP; LXR; RXR; FXR; HNF4; NFκB

Contents

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ACC, acetyl-CoA carboxylase; ACO, acyl-CoA oxidase; CDHA, conjugated DHA; CEPA, conjugated EPA; CFAs, conjugated fatty acids; CLA, conjugated LA; CLN, conjugated LNA; CPT, carnitine palmitoyltransferase; CYP7A1, cholesterol 7α-hydroxylase; DAG, diacylglycerol; DHA, docosahexaenoic acid (22:6 $n-3$); EPA, eicosapentaenoic acid (20:5 $n-3$); FAS, fatty acid synthase; FctO, functional oil; FXRs, farnesoid X receptors; HDL, high-density lipoprotein; HNF4, hepatic nuclear factor 4; IκB, inhibitor of κB; IKK, IκB kinase; LA, linoleic acid; LCT, long-chain triacylglycerol (triglyceride); LDL, low-density lipoprotein; LDLr, LDL receptor; LNA, α-linolenic acid; LXR, liver X receptor; LXRE, LXR response element; MCFA, medium-chain fatty acid; MCT, medium-chain triacylglycerol; MCP1, monocyte chemoattractant protein 1; MLCT, medium-chain and long-chain triacylglycerol; NAFLD, non-alcholic fatty liver diseases; NFκB, nuclear factor κB; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PL, phospholipid; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR response element; PUFAs, polyunsaturated fatty acids; RXR, retinoid X receptor; SREBP, sterol regulatory element binding protein; SCD, stearoyl-CoA desaturase; SHP, small heterodimer partner; TAG, triacylglycerol; TNFα, tumor necrosis factor alpha; TZD, thiazolidinedione; UCP, uncoupling protein.

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doi:10.1016/j.plipres.2007.12.002

1. Introduction

Lifestyle-related diseases, such as obesity, hyperlipidemia, atherosclerosis, type 2 diabetes and hypertension, are widespread and increasingly prevalent in industrialized countries. Accompanied by the rapid increase in the number of elderly people, this becomes a medical and a socioeconomic issue. A clustering of metabolic disorders (in particular abdominal obesity, hypertriglyceridemia, a low level of high-density-lipoprotein (HDL)-cholesterol, hypertension and high fasting-glucose level) in an individual, defined as metabolic syndrome, is known to increase cardiovascular morbidity and mortality [1]. Although the pathogenesis of metabolic syndrome is complicated and precise details of the underlying mechanisms are not known, it has been suggested that the quality of dietary lipids may be an important modulator in terms of the risks associated with this syndrome [2]. Animal studies and clinical trials have revealed different effects of individual bioactive lipids, such as *n*−3 polyunsaturated fatty acids, conjugated fatty acids, sterols, medium-chain fatty acids, diacylglycerols, and phospholipids (Fig. 1).

Here, the effects of bioactive lipids on metabolic syndrome are reviewed, with particular emphasis on the molecular mechanisms of both lipid and glucose metabolism. Recent findings concerning attenuation of metabolic syndrome through the regulation of adipocytokine production by bioactive lipids are discussed.

2. Metabolic syndrome

According to the International Diabetes Federation, a person is defined as having metabolic syndrome if they have central obesity (waist circumference $\geqslant$94 cm for Europid men and $\geqslant$80 cm for Europid women), plus any two of the following four factors: raised triacylglycerol level ($\geqslant$150 mg/dL, or specific treatment for this lipid abnormality); reduced HDL-cholesterol (<80 mg/dL in males and <50 mg/dL in females, or specific treatment for this lipid abnormality); raised blood pressure (systolic $\geqslant$130 mmHg or diastolic $\geqslant$85 mmHg, or treatment of previously diagnosed hypertension); raised fasting plasma glucose ($\geqslant$100 mg/dL, or previously diagonosed type 2 diabetes) [3]. It is estimated that around a quarter of the world's adult population have metabolic syndrome [3–5]. Subjects with metabolic syndrome have a threefold higher risk of developing coronary heart attack or stroke, and twofold higher cardiovascular mortality than those without the syndrome [6].

Although the pathogenesis of metabolic syndrome is unclear, abdominal obesity and insulin resistance have been proposed to be the predominant causative factors. Studies using computed tomography have suggested the importance of fat distribution, and especially the contribution of abdominal obesity, to the progression of metabolic syndrome [7]. In particular, accumulation of abdominal fat induces insulin resistance, and compensatory glucose intolerance and dyslipidemia, more than subcutaneous fat [7–9]. Additionally, abdominal obesity and insulin resistance are related to the development of hypertension, type 2 diabetes and non-alcoholic fatty liver diseases (NAFLD) [7–11].

Recent advances in molecular and cell biology have shown that adipose tissue stores excess energy in the form of fat and has important roles in regulating lipid and glucose homeostasis by secreting physiologically active substances called adipocytokines [7]. For instance, the obesity

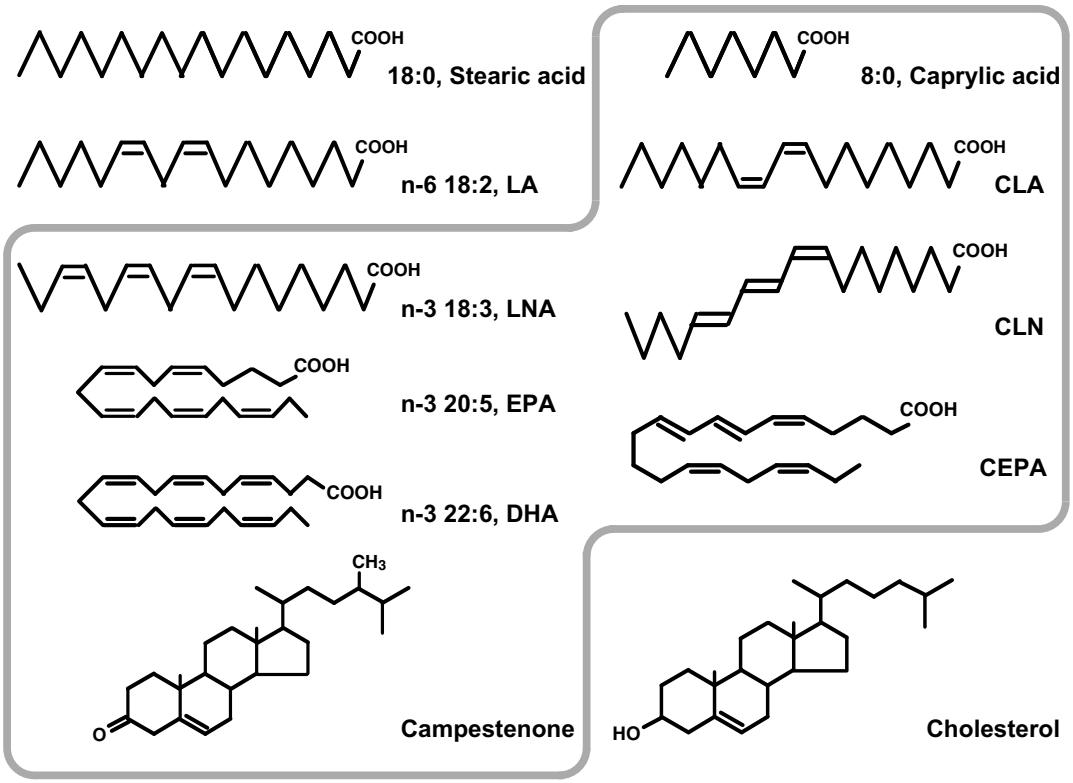

Fig. 1. Major dietary lipids and bioactive lipids.

gene product leptin, secreted in excess from the enlarged adipose tissues in obesity, acts as a signal to the central nervous system indicating the size of energy stores [12].

Adiponectin is one of the most abundant adipose-specific secretory proteins in rodents and humans [13,14]. The expression of adiponectin is reduced in obesity and blood levels are negatively correlated with abdominal fat accumulation [15–18]. Human subjects in hypoadionectinemia, caused by gene mutation of adiponectin, exhibit dyslipidemia and impaired glucose tolerance [19,20]. Adiponectin-null mice showed delayed clearance of non-esterified fatty acids in plasma and severe diet-induced insulin resistance [21]. Several reports have indicated that adiponectin can lead to enhanced insulin action *in vitro* and *in vivo* by activating insulin-receptor substrate 1-associated phosphatidylinositol-3-kinase, AMP-activated protein kinase and peroxisome proliferator-activated receptor alpha (PPARα) in liver and muscle [13,21–23], which suggests strongly that adiponectin has a protective role against insulin resistance. Over-expression of recombinant adiponectin had an antiatherogenic effect in apoE-null mice, in which plaque formation was inhibited significantly compared with control apoE-null mice [24,25]. Additionally, clinical and studies *in vitro* have indicated that levels of plasma adiponectin are positively correlated with levels of plasma HDL-cholesterol in humans [18,26] and adiponectin increased HDL assembly in human hepatocytes [27]. These results suggest that adiponectin reveals antiatherogenic action by accelerating the whole-body reverse cholesterol transport system. It has been reported that the concentration of plasma adiponectin in patients with hypertension was significantly lower than in normotensive healthy subjects [28–30], and adiponectin-null mice showed hypertension compared with wild-type mice [31]. These results suggest that plasma adiponectin is an independent regulatory factor for blood pressure.

Obesity is associated with chronic inflammation that is characterized by increased plasma levels of inflammatory mediators, such as tumor necrosis factor alpha (TNFα) and monocyte chemoattractant protein 1 (MCP1). The expression of these inflammation-related proteins in adipose tissue and plasma levels are increased in human obesity as well as in genetically and high-fat diet-induced obese diabetic rodents [32–34]. TNFα is a proinflammatory cytokine that has been recognized as a key molecule linking obesity with insulin resistance [32,33]. Neutralization of TNFα by its antibody alleviated insulin resistance in genetically obese rats [32], and TNFα-null mice were protected from high-fat diet-induced insulin resistance [35]. TNF receptor disruption from genetically obese mice demonstrated a significant, but not complete, protection from the insulin resistance associated with the *ob*/*ob* phenotype [35]. In addition, it has been reported that serum TNFα was increased significantly in adiponectin-null mice compared with wild-type controls [21]. Maeda et al. suggested that TNFα and adiponectin induce local, reciprocal suppression in adipose tissue and exhibit opposite effects in skeletal muscle [21]. MCP1, a member of the CC chemokine family, induces inflammatory responses through recruiting inflammatory cells and is up-regulated

by inflammatory stimuli such as TNFα [34,36]. Recent findings indicate that transgenic mice expressing MCP1 exhibit insulin resistance and hepatic steatosis, whereas a disappearance of MCP1 in knockout mice and an acute inhibition of MCP1 by expression of a dominant-negative mutant in mice resulted in improvement of insulin resistance and hepatic steatosis [37]. Interestingly, the study showed that serum adiponectin was increased significantly in MCP1-null mice compared with wild-type controls [37].

3. Dietary lipids

3.1. n−3 Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs), such as linoleic acid (LA, 18:2, *n*−6), α-linolenic acid (LNA, 18:3, *n*−3) and arachidonic acid (20:4, *n*−6), are important for the maintenance of biofunctions in mammals [38,39]. In particular, it is well known that the consumption of *n*−3 highly unsaturated fatty acids, such as LNA, eicosapentaenoic acid (EPA, 20:5, *n*−3) and docosahexaenoic acid (DHA, 22:6, *n*−3) (Fig. 1), is correlated with a reduced risk of cancer and cardiovascular disease in clinical and animal studies [40,41]. LNA represents a relatively high proportion of the total fatty acids in some vegetable oils, such as perilla, flaxseed, canola, rapeseed, soybean, linseed and walnut. EPA and DHA are found in fish and some other marine organisms. There are some epidemiologic data indicating that populations with a high intake of *n*−3 PUFAs, such as Eskimos and Japanese in fishing villages, have a low risk of cardiovascular diseases [42,43]. The intake of EPA and DHA varies considerably among populations, such as Greenland Eskimos (10–14 g/day), Japan and Norway (1–3 g/day) and Western populations (<0.5 g/day) [44]. Recently, Harris et al. reported that >8% in an ω−3 index (EPA + DHA expressed as a percentage of total fatty acids in red blood cells) is associated with 90% less risk for sudden cardiac death, as compared to an ω−3 index of <4% [45,46].

The main effect of *n*−3 PUFAs on plasma lipids is a reduction of the concentration of plasma triacylglycerols. The result of a meta-analysis of 72 placebo-controlled trials, at least 2 weeks in length and providing ⩽7 g of *n*−3 PUFA/day, suggests that the hypotriglyceridemic effect of *n*−3 PUFAs is well established when taken in doses of 3–4 g/day [47]. There was also a clear dose–response relationship, and the effects persisted even after 2 years [47]. These effects are attributable to the increased lipolysis and decreased lipogenesis, mainly in the liver, that have a central role in the control of whole-body lipid homeostasis [48]. In addition, there are several reports indicating that consumption of *n*−3 PUFAs increases the levels of plasma HDL-cholesterol in human [49–51].

Hypotensive effects of *n*−3 PUFAs have been shown in animal and clinical studies, and seem to be correlated to the plasma phospholipids composition in EPA and DHA that contribute to modulation of membrane fluidity, activities of membrane enzymes and receptors, and production of eicosanoids [52]. From a meta-analysis of 31 placebo-controlled clinical trials with 1356 subjects, Morris et al. reported that there is a dose-dependent effect of fish oil on blood pressure of −0.66 (systolic)/−0.35 (diastolic) mmHg/g *n*−3 PUFAs, and the hypotensive effect may be strongest in hypertensive subjects and those with clinical atherosclerotic disease or hypercholesterolemia [53].

There is limited evidence concerning the antiobesity effect of *n*−3 PUFAs. Wang et al. demonstrated in mice that feeding *n*−3 PUFAs in a high-fat diet for 7 weeks reduced body fat compared with a low-fat diet, and saturated fatty acids or *n*−6 PUFAs in a high-fat diet, all at the same energy intake [54]. Baillie et al. demonstrated a decrease in fat deposition associated with ingestion of fish oil in Fisher 344 rats [55]. Garaulet et al. measured the fatty acid composition of adipose tissue from 84 obese patients (body mass index 27–35 kg/m^2) aged 30–70 years old and found that central obesity was inversely associated with *n*−3 PUFAs in adipose tissue [56].

Although an antidiabetic effect of *n*−3 PUFAs is still controversial, epidemiological studies suggest that there is a low prevalence of diabetes in populations with a high intake of *n*−3 PUFAs [57,58]. Ebbesson et al. measured the concentration of plasma FA in 447 Norton Sound Inuits (Eskimos) (35–74 years old) and showed that concentrations of plasma *n*−3 PUFAs were highly correlated with dietary intake of *n*−3 PUFAs and inversely correlated with plasma markers for insulin resistance and glucose intolerance [59]. Delarue et al. demonstrated that consumption of fish oil induced a 40% decrease in insulinemia, with reduced carbohydrate oxidation, increased lipid oxidation and increased non-oxidative glucose disposal in healthy humans [60].

Recently, regulation of adipocytokine production by *n*−3 PUFAs has attracted considerable attention. It has been reported that feeding a diet containing fish oil for 2 months increased the level of plasma adiponectin, retarded insulin resistance and dyslipidemia, and improved adiposity in diet-induced insulin-resistant model rats [61]. Flachs et al. studied the effects of partial replacement of vegetable oils by an EPA/DHA concentrate (6% EPA, 51% DHA) over 5 weeks in mice fed a high-fat diet with either free access to food or with food intake restricted by 30% [62]. The results indicated that EPA/DHA increased plasma adiponectin through the stimulation of adiponectin mRNA expression in adipocytes independent of food intake. Furthermore, Itoh et al. reported that dietary EPA increased adiponectin secretion in genetically and high-fat diet-induced obese mice, and treatment with EPA (1.8 g/day) for 3 months increased plasma adiponectin significantly in human obese subjects [63]. Given that a low plasma level of adiponectin has been shown to increase the risk of cardiovascular diseases [19–21], the beneficial effect of fish oil and EPA/DHA could be attributable, at least in part, to the enhanced production of adiponectin.

3.2. Conjugated fatty acids

3.2.1. Natural sources and chemical production of conjugated fatty acids

Conjugated fatty acids (CFAs) are a mixture of positional and geometric isomers of PUFAs with conjugated double bonds. Theoretically, a number of CFA isomers are possible, with multiple combinations of numerical, positional and geometrical configurations of conjugation in double bonds. Conjugated linoleic acid (CLA) (Fig. 1), the CFA form of LA, has been detected in milk fat, cheese and ruminant meat [64]. The 9-*cis*,11-*trans* (9*c*,11*t*-) CLA isomer is produced through the biohydrogenation of unsaturated fatty acids by the bacterium *Butyrivibrio fibrisolvens* in ruminants such as cows, sheep, goats and camels [65,66]. The intake of CLA from a typical diet has been estimated at several 100 mg/day for various countries [67]. There are other types of CFA in some plant seed oils; for example, punicic acid (9*c*,11*t*,13*c*-conjugated linolenic acid (CLN)) in pomegranate seed oil, α-eleostearic acid (9*c*,11*t*,13*t*-CLN) in bitter gourd oil and tung seed oil (Fig. 1), catalpic acid (9*t*,11*t*,13*c*-CLN) in catalpa seed oil, and calendic acid (8*t*,10*t*,12*c*-CLN) in pot marigold seed oil are present at about 72%, 60–70%, 31%, and 33% (of total fatty acid), respectively [68,69]. It has been reported that several species of seaweed contain conjugated trienoic and tetraenoic fatty acids; for example, the red seaweed *Ptilota filicna* contains 5*t*,7*t*,9*t*,14*c*,17*c*-conjugated EPA (CEPA) and 5*c*,7*t*,9*t*,14*c*,17*c*-CEPA (Fig. 1), and *Bossiella orbigniana* contains 5*c*,8*c*,10*t*,12*t*,14*c*-CEPA [70,71], and stellaheptaenoic acid, 4*c*,7*c*,9*t*,11*t*,13*c*,16*c*,19*c*-conjugated docosaheptaenoic acid, is present in the green seaweed *Anadyomene stellata* [72].

CLA is produced commercially by alkaline isomerization of LA-rich oils and tends to contain an equimolar mixture of the 9*c*,11*t*- and 10*t*,12*c*-isomers [73]. Production of CFAs from LNA, EPA and DHA and experimental evaluation of their physiological activities *in vitro* and *in vivo* have been reported [74,75]. Alkali-hydrolyzed oils contain several CFA isomers and separation of specific isomers is of some concern in the chemical synthesis of CFAs. It has been reported that lipases from *Geotrichum candidum* and *Candida rugosa* selectively esterify the 9*c*,11*t*-isomer of CLA, and methods utilizing these lipases are effective for separating the 9*c*,11*t*-CLA and 10*t*,12*c*-CLA isomers [76–78]. Other potential methods for CLA production include the isomerization of LA using bacteria, such as *Lactobacillus plantarum* [79,80]. These methods may contribute to the preparation of a CFA fraction with maximal physiological activity.

3.2.2. Conjugated fatty acids in metabolic syndrome

Since the discovery of CLA as a grilled beef-derived antimutagen in the 1980s, about half of the studies concerning physiological functions of CFAs have been focused on their anticarcinogenic properties. However, there is an increasing number of reports of the antiobesity, antiatherogenic, antidiabetic, and hypotensive properties of CFAs in animal and human studies [73,81,82].

The fat-lowering action of CLA has received attention following a report in 1997 that a supplementation of 0.5% CLA in the diet of mice reduced body fat by 60% coupled with a 14% increase in lean body mass [83]. There are a number of studies demonstrating the antiobesity and hypolipidemic effects of CLA in animals including mice, rats and pigs [73]. These effects have been attributed to the enhanced β-oxidation of fatty acids and suppression of fatty acid synthesis in the liver. In addition, CLA enhances β-oxidation of fatty acids even in brown adipose tissue and in muscle, and enhances oxygen consumption and energy expenditure in obese rats [84,85]. There is growing evidence that individual isomers of CLA have specific physiological functions in lipid metabolism. The 10*t*,12*c*-CLA isomer reduces the secretion of apolipoprotein B100 in cultured human hepatoma HepG2 cells, and exerts antiobesity and hypolipidemic effects in obese OLETF rats [85–87]. Although the body fat-lowering effect of CLA has been reported in humans, it seems to be less marked than that observed in rodents. A small-scale randomized clinical trial conducted in Norway was the first to investigate the effect of CLA on body fat in humans. Healthy and physically active men and women took either a CLA mixture (1.8 g/day) or olive oil for 3 months [88]. By the end of the trial, subjects taking the CLA supplement had a 4% decrease in body fat. Another study from the same group examined the dose–response relationship between CLA and body fat mass in obese and overweight subjects [89]. In that study, the authors concluded that a dietary supplementation of CLA at 3.4 g/day was sufficient for body fat reduction in obese and overweight subjects over 3 months. The antiobesity effects of other non-linoleic fatty acids with conjugated double bonds have been reported in animal studies. A dietary supplementation of CLN, produced by alkaline isomerization of LNA, reduced body fat content by enhancing of β-oxidation of fatty acids in rats [90]. The antiobesity and hypolipidemic effects of CLN have been reported in studies with chickens, obese rats and human liver-derived cells [91–93]. Recently, Tsuzuki et al. prepared conjugated DHA (CDHA), which is a mixture of conjugated diene, triene, tertraene and hexaene structures, by alkaline isomerization of DHA. Feeding CDHA to rats appeared to suppress fat accumulation in the liver and epididymal adipose tissue and improved abnormalities of lipid and glucose metabolism [94]. They demonstrated also that conjugated EPA has antiobesity and hypolipidemic effects [95]. The combined effects of CFA and other dietary components are now being evaluated as new approaches for treatment of obesity. It has been suggested that the antiobesity and hypolipidemic potential of CLA could be enhanced by combination with soybean protein, sesamin and chromium picolinate [96–100]. Future studies should examine the effects of combinations of various food factors and CFA isomers.

Many claims for health benefits other than anticancer and antiobesity effects have been made for CLA in animal studies. Antiatherogenic effects of CLA have been reported in studies with rabbits and hamsters. Feeding CLA at 0.5 g/day for 22 weeks and a 1% CLA-supplemented diet for 12 weeks were sufficient to reduce aortic fatty streak area in rabbits and in hamsters, respectively [101,102]. The antidiabetic effects of CLA have been reported in studies with obese, diabetic rats. In the first study, feeding of a 1.5% CLA diet normalized impaired glucose tolerance, and the effect of CLA was similar to that of the pharmaceutical agent troglitazone [103]. In a subsequent study, it was suggested that the antidiabetic effects of CLA are attributable to the specific action of the 10*t*,12*c*-isomer [104,105]. Very recently, the hypotensive properties of CLA have been observed. In diabetic Zucker rats, obese OLETF rats and non-obese spontaneously hypertensive rats, the feeding of a CLA mixture and the 10*t*,12*c*-CLA isomer prevented the development of obesity-induced hypertension and essential hypertension [106–108]. These effects were attributable to the ability of CLA to regulate the production of physiologically active adipocytokines, such as adiponectin, leptin and angiotensinogen [106–108]. Considering the previous studies indicating that conjugated trienoic fatty acids have stronger anticarcinogenic activities than conjugated dienoic fatty acids [68,74], the evaluation of the physiological bioactivities of CFA isomers other than CLA on atherosclerosis, diabetes, and hypertension will be of great interest in future studies.

Further evaluations will be required, however, to reach a consensus regarding the health benefits of CFAs on metabolic syndrome, because beneficial properties shown in animal studies have not been apparent in some clinical trials, and detrimental effects have been observed in some studies [109,110].

3.3. Other lipids

3.3.1. Plant sterols and their derivatives

Plant sterols and stanols are chemical homologs of cholesterol that are abundant in vegetable oils and whole grains, and their cholesterol-lowering activity, in particular the effects of sitosterol and sitostanol, have been well established in a number of human studies [111–113]. Approximately 10% reduction of low-density-lipoprotein (LDL)-cholesterol is expected at a phytosterol dose of 2 g/day as recommended by The United States National Cholesterol Education program [114]. A preventive effect of atheroma formation has been reported in animal studies, and 14 weeks feeding of 2% soybean-derived phytosterols (a mixture containing 58% β-sitosterol, 19% campesterol, 13% dihydrobrassicasterol and 10% stigmasterol) resulted in a marked decrease of atherosclerotic lesion size in the aortic roots of apoE-null mice [115]. These effects have been attributed to the inhibition of cholesterol absorption through the reduction of cholesterol solubilization in intestinal micelles and the inhibition of proinflammatory cytokine production [115,116].

Suzuki et al. showed that dietary cholest-4-en-3-one, an intestinal catabolite of cholesterol, reduced visceral fat deposition in mice [117]. On the basis of these findings, they prepared various 3-oxo derivatives of cholesterol and plant sterols, and showed that some had fat-lowering and hypolipidemic effects in mice [118,119]. Campest-5-en-3-one (campestenone) (Fig. 1), a 3-oxo derivative of campesterol, was one of the most effective derivatives in reducing body fat and serum lipids and the effects were attributed to suppressed lipogenesis, enhanced lipolysis and increased energy expenditure [119,120].

3.3.2. Medium-chain fatty acids

Medium-chain fatty acids (MCFAs), which generally consist of C6–10, are found in coconut oil and palm kernel oil (Fig. 1). Since the 1950s, medium-chain triglyceride (MCT) has been used for the dietary treatment of malabsorption syndrome because of its metabolic properties. MCT is hydrolyzed rapidly and the resulting MCFAs are absorbed directly via the portal vein to the liver and used as an energy source without using the carnitine transport system for mitochondrial entry [121,122].

A physiological function of dietary MCT in influencing body composition, compared with the effect of long-chain triacylglycerol (LCT), has been reported. Consumption of MCT diminished fat deposition and enhanced thermogenesis in rats [123–125]. In clinical studies, postprandial energy expenditure was greater after consumption of MCT compared with consumption of LCT in both normal and obese subjects [126–128]. These effects have been shown even in studies with a low-dose supplementation of MCT. For example, Tsuji et al. reported that consumption of MCT at 10 g/day for 12 weeks reduced body weight and fat in subjects with BMI $\geqslant$ 23 kg/m^2 [129]. Kasai et al. observed that 5–10 g of MCT causes more diet-induced thermogenesis than that induced by LCT in healthy humans [130]. Recently, Han et al. reported that consumption of MCT at 18 g/day as part of daily food intake for 90 days resulted in reduced body weight, waist circumference and a homeostasis model assessment of insulin resistance in moderately overweight, free-living type 2 diabetic subjects [131]. These results suggest the possibility that the substitution of MCT for cooking oil would be useful to control body weight and fat in healthy subjects.

The concept of a ''structured-lipid'' implies modification of the fatty acid composition and/or their location in the glycerol backbone, and improvement of the physical and/or physiological properties of dietary lipids. Recently, structured medium-chain and long-chain triacylglycerol (MLCT) containing MCFA and a long-chain fatty acid in the same molecule as the result of transesterification of MCT with LCT, has been developed [132–137]. MLCT has a higher smoking temperature and is therefore better for cooking than a physical mixture of MCT and LCT. Feeding MLCT for 6 weeks reduced body fat accumulation

and increased postprandial hepatic β-oxidation of fatty acids compared with LCT in rats [132,133]. Healthy subjects consumed 14 g of MLCT containing 1.7 g of MCFA daily at breakfast for 12 weeks, and significant decreases of body weight, amount of body fat, subcutaneous and visceral fat were noted in the MLCT group at 8 weeks compared with the LCT group [134]. Other studies have shown that consumption of MLCT reduces the rate of variation of body fat mass, which may be due to higher postingestive total energy expenditure compared with LCT [135–137]. Additionally, St-Onge et al. prepared a functional oil (FctO) that contains MCT, plant sterol and *n*−3 PUFA-rich flaxseed oil [138]. Twenty-four overweight but otherwise healthy men consumed diets that contained either FctO or olive oil for 29 days, and the results indicated that consumption of FctO improves plasma lipid profiles, including lowered LDL-cholesterol and increased peak LDL particle size [138]. The results of these studies suggest that a blend of MCT-containing structured-lipids and oil would be useful in reducing cardiovascular disease risk through the combination of their various beneficial actions.

Antidiabetic properties of MCT in humans have been reported [139]. Non-insulin-dependent diabetes patients and non-diabetic subjects were examined with a 5 days cross-over design, in which the short-term metabolic effects of a 40% fat diet containing 77.5% of fat calories as MCT were compared with an isocaloric LCT-containing diet. The results indicated that consumption of MCT increased insulin-mediated glucose metabolism in both diabetic and non-diabetic subjects, compared with the LCT diet. Recently, Takeuchi et al. demonstrated that rats fed the MCT diet had less body fat accumulation, improved glucose tolerance, and higher levels of adiponectin in serum and adipose tissue compared with rats fed the LCT diet [140].

3.3.3. Diacylglycerol

Various fats and oils contain diacylglycerol (DAG) as a minor constituent [141]. There are two DAG isoforms, 1,2-(or 2,3)-diacyl-*sn*-glycerol (1,2-DAG or 2,3-DAG) and 1,3-diacyl-*sn*-glycerol (1,3-DAG). The 1,2-DAG and 2,3-DAG isoforms are produced as metabolic intermediates from triacylglycerol (TAG), but the major DAG isoform in refined edible DAG oils is 1,3-DAG, which is produced during the high-temperature manufacturing process.

Several human studies showed that DAG oil, rich in the 1,3-DAG isoform, suppressed postprandial hypertriglyceroleмia and reduced body fat mass compared with the corresponding TAG oil [142–147]. Antiobesity effects of DAG oil were shown in animal studies, and were attributed to an increase in β-oxidation of fatty acids, enhancement of energy expenditure and suppression of triacylglycerol synthesis [148–150]. The other mechanism proposed for the physiological functions of DAG was that the slower lymphatic transport of 1,3-DAG compared with TAG could be a factor in the suppression of postprandial hypertriglyceroleмia and fat accumulation [151].

Recently, Kim et al. produced a structured-lipid containing DAG incorporated with MCFA and CLA, and feeding this as a dietary supplement lowered the concentration of plasma triacylglycerol and decreased fat pad weight with simultaneous enhancement of lipoprotein lipase activity in Sprague–Dawley rats [152]. Dietary supplementation with LNA-rich DAG demonstrated that body weight gain and fatty liver formation are suppressed by an up-regulation of the β-oxidation of fatty acids in mice and rats [153,154]. These studies suggested that both acylglycerol structure (structural difference between TAG and DAG) and fatty acid species affect the nutritional behavior of dietary lipids.

Antiatherogenic properties of DAG have been reported in mice and rabbits [155–157]. Additionally, there are studies indicating that the cholesterol-lowering effect of plant sterols can be enhanced in rabbits and humans by combination with DAG [158]. Antidiabetic properties of DAG have been reported [159–161]; in particular, Mori et al. reported that DAG reduced postprandial hyperlipidemia and ameliorated glucose intolerance in obese rats through, in part, increased levels of serum adiponectin [161].

3.3.4. Phospholipids

Although the majority of dietary fat is TAG, it contains approximately 10% of phospholipids (PLs), of which phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the two major components. The intake of dietary PLs is estimated to be 3–4 g/day, which amounts to 5–8% of total dietary lipids [162,163]. Growing evidence indicates that dietary PLs have beneficial effects compared with dietary TAG. PLs are composed of hydrophobic (e.g. fatty acid) and hydrophilic (e.g. choline, ethanolamine, serine or inositol) constituents, and either or both of them could be responsible for the physiological function of dietary PLs. A cholesterol-lowering effect of PE and its constituent base ethanolamine has been reported in rats and the effects are attributed to an increase of the excretion of fecal neutral steroids [164,165]. Liver protective effects and cholesterol-lowering effects of PC have been reported showing that PC enhanced bile cholesterol secretion, decreased lymphatic cholesterol absorption and reduced hepatic fatty acid synthesis in rats and rabbits [166–168]. The other minor PL, phosphatidylinositol (PI), increased the levels of HDL-cholesterol in rabbits and humans [169–171]. It has been suggested that PI enhances the mobilization of cellular sterol via a cell-surface transporter and increases cholesterol excretion into the feces.

A broad definition of a "structured-lipid" may include PLs from marine sources, such as fish roe, squid meal and starfish, which contain abundant EPA and DHA in their fatty acids [172–174]. Recently, we reported that feeding of *n*−3 PUFA rich-PC from salmon roe, compared with PC from hen egg-yolk, alleviates obesity-related disorders through the suppression of fatty acid synthesis, the enhancement of fatty acid β-oxidation and an increase of the serum levels of adiponectin in obese rats [175].

Enzymatic preparation of structured-phospholipids that contain $n-3$ PUFA and CLA have been reported [176–178]. Thus, possible findings on the effects of the form, such as PL, TAG or DAG, used for the administration of bioactive fatty acids, such as $n-3$ PUFA, CFA and MCFA, would be of great interest for future study.

4. Transcriptional factors in metabolic syndrome

4.1. Peroxisome proliferator-activated receptors

PPARs are ligand-activated nuclear receptors related to the modulation of environmental and dietary stimuli. They bind to the PPAR response element (PPRE) of target genes as a PPAR/retinoid X receptor (RXR) heterodimer. There are three PPAR isoforms, termed PPARα, PPARβ/δ and PPARγ [179].

PPARα is expressed primarily in the liver and in brown adipose tissue, in which it has been shown to promote the β-oxidation of fatty acids. PPARα null-mice exhibit hepatic steatosis, myocardial lipid accumulation and hypoglycemia during short-term starvation because of an inadequate ketogenic response [180]. Fibrates, such as gemfibrozil, clofibrate and fenofibrate, bind PPARα with high affinity and are used frequently as potent hypolipidemc drugs in humans [181]. Antidiabetic effects of PPARα agonists have been reported in mice [182,183], and a 40% decrease of plasma insulin levels by treatment with 30 mg/kg fenofibrate in the hyperinsulinemic rhesus monkey [184] suggested the possibility that fibrates improve insulin sensitivity in primates.

PPARβ/δ is expressed ubiquitously but the highest level of expression is in the gut, kidney and heart. More than 90% of PPARβ/δ-null mice are embryonic lethal due to placental defects; the small number that do survive show decreased adiposity [185]. Targeted activation of PPARβ/δ in adipose tissue specifically induces expression of genes required for β-oxidation of fatty acids and energy dissipation, which in turn leads to improved lipid profiles and reduced adiposity [186]. These studies suggest that PPARβ/δ has a critical role in a coordinated metabolic program by up-regulating β-oxidation of fatty acids and energy expenditure. Very recently, Sprecher et al. were the first to report PPARβ/δ agonist administration to humans, in which GW501516 influenced HDL-cholesterol and triacylglycerol significantly in healthy volunteers [187]. These HDL: triaclyglycerol effects were related to peripheral fat utilization and lipidation, which was suggested by enhanced *in vivo* serum fat clearance and *in vitro* up-regulation in human skeletal muscle fat utilization and sterol transporter expression.

PPARγ is expressed primarily in adipose tissue and macrophages. Because PPARγ-null mouse is embryonic lethal due to placental dysfunction [188,189], and the Cre-loxP-conditioned, tissue-specific PPARγ disruptions have been examined in liver, adipose tissue and muscle. In the case of liver-specific PPARγ-null mice, they exhibit obesity, hyperlipidemia and insulin resistance [190]. Adipose-specific PPARγ-null mice develop progressive lipodystrophy, steatosis and insulin resistance in fat and liver but not in muscle [191]. Additionally, muscle-specific PPARγ-null mice showed glucose intolerance and progressive insulin resistance [192]. Consistently, humans with heterozygous mutation in PPARγ have partial lipodystrophy, insulin resistance, dyslipidemia and hypertension [193–196]. Synthetic PPARγ ligands, thiazolidinediones (TZDs), rosiglitazone and pioglitazone, are used for their potent antidiabetic effects in human [181]. It has been demonstrated that PPARγ is required for transcriptional activation of adiponectin, which promotes β-oxidation of fatty acids and insulin sensitivity, and that TZDs induce this transcription [197]. Additionally, activation of PPARγ has been suggested to reduce inflammatory adipocytokines, such as TNFα and MCP-1, through the inhibition of nuclear factor κB (NFκB) activity [198,199].

4.2. Sterol regulatory element binding proteins

Sterol regulatory element binding proteins (SREBPs) are membrane-bound transcriptional factors that belong to the basic helix–loop–helix leucine zipper family [200]. The mature nuclear form of SREBP is produced from a membrane-bound precursor by proteolytic cleavage and binds to a sterol regulatory element as well as some E-boxes. There are three SREBP isomers, termed SREBP1a, SREBP1c and SREBP2. SREBP1a and SREBP1c are identical except for the NH2-terminal transactivation domains, and SREBP2 is encoded by a separate gene. Most organs, including liver and adipose tissue, express predominantly SREBP1c and SREBP2 *in vivo* [200].

The SREBP2-null mouse is completely embryonic lethal [201]. SREBP2 transgenic mice showed increases in mRNAs encoding multiple enzymes of cholesterol biosynthesis, LDL receptor (LDLr) and fatty acid biosynthesis in the liver [202]. The mRNAs for cholesterol biosynthetic enzymes were elevated in the adipose tissue of SREBP2 transgenic mice, but the mRNAs for fatty acid biosynthetic enzymes were not. Depletion of sterols by treatment with a bile acid-binding resin and a cholesterol synthesis inhibitor led to a marked increase in the nuclear form of SREBP2 [203]. These results suggest that SREBP2 is a relatively selective activator of cholesterol synthesis, as opposed to fatty acid synthesis, in liver and adipose tissue of mice.

Studies both *in vivo* and *in vitro* demonstrated that SREBP1c has a crucial role in the regulation of most hepatic lipogenic genes, such as fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase (SCD) [200,204]. SREBP1c was cloned independently as a transcriptional factor that promotes adipocyte differentiation, and was designated as adipocyte determination and differentiation factor 1 [205]. From 50% to 85% of SREBP1-null mice are embryonic lethal, but those that survive appear normal except for elevated levels of SREBP-2 and cholesterol synthesis in the liver [201]. The livers of

SREBP1c transgenic mice were enlarged with an accumulation of triaclyglycerols, but not cholesterol [206]. Importantly, expression of SREBP1c, but not SREBP1a or SREBP2, is regulated by liver X receptor (LXR) activation [204].

4.3. Liver X receptor

LXR is one of the nuclear hormone receptors that are sensors of cholesterol metabolism and lipid biosynthesis [207]. There are LXR isomers, termed LXRα and LXRβ; LXRα is expressed in liver, spleen, kidney, adipose tissue, and small intestine, whereas LXRβ is expressed ubiquitously. LXRs are known to be activated by oxysterols and to bind to the LXR response element (LXRE) of target genes as an LXR/RXR heterodimer. LXRα-null mice exhibit impaired expression of hepatic genes involved in cholesterol and fatty acid metabolism, such as cholesterol 7α-hydroxylase (CYP7A1), HMG-CoA synthase/reductase, SREBP, and FAS [208]. In contrast, LXRβ-null mice failed to show the phenotype observed in LXRα-null mice [209]. This suggests a more prominent role of LXRα than LXRβ as a regulator of these enzymes. A recent report indicated that D-glucose and D-glucose 6-phosphate are direct agonists of both LXRα and LXRβ [210], and showed that glucose activates LXR at the physiological concentrations expected in the liver and induces expression of LXR target genes with an efficacy similar to that of oxysterol, suggesting that LXR is a transcriptional switch that integrates hepatic glucose metabolism and fatty acid synthesis.

ATP-binding cassette transporter A1 (ABCA1) is a key transporter that modulates cholesterol efflux and mediates reverse cholesterol transport from peripheral tissues [211,212]. Expression of ABCA1 and other ABC transporters is under the regulation of LXR. Bone marrow transplantation-derived selective elimination of macrophage LXRα,β mimics many aspects of Tangier disease, a human HDL deficiency caused by ABCA1 mutation, including aberrant regulation of cholesterol transporter expression, lipid accumulation in macrophages, splenomegaly and increased atherosclerosis [213]. Treatment with an LXR agonist (GW3965) reduced the atherosclerotic lesion area in LDLr-null and apoE-null mice [214]. The compound induced expression of ABCA1 and ABCG1, suggesting that the direct action of LXR ligands on vascular gene expression is likely to contribute to their antiatherogenic effects.

The antidiabetic effects of LXR ligands have been reported. Cao et al. treated diabetic rodents with the LXR agonist (T0901317) and observed marked reduction of plasma glucose, increased insulin sensitivity, suppressed gluconeogenic genes, and decreased hepatic glucose output [215]. Laffitte et al. showed that the LXR agonist (GW3965) improved glucose tolerance in a murine model of diet-induced obesity and insulin resistance. The effect was attributed to the suppression of gluconeogenic genes in the liver, and transcriptional induction of the insulin-sensitive glucose transporter GLUT4 in adipose tissue [216].

4.4. Retinoid X receptor

RXR belongs to the superfamily of nuclear receptors and was discovered as a receptor involved in transduction of the retinoid signaling pathway. RXR has been known to provide structural and signaling support to its heterodimerizing partner, such as PPARs, LXRs, and Farnesoid X receptors (FXRs), during transcriptional activation. There are three RXR isoforms, termed RXRα, RXRβ and RXRγ. RXRα is expressed in liver, kidney, spleen, placenta and epidermis; RXRβ is expressed ubiquitously; and RXRγ is expressed in muscle and brain [217]. RXRα-null mice are embryonic lethal [218]; approximately 50% of RXRβ-null mice die before or at birth, but those that survive appear normal except that the males are sterile [219]; RXRγ null-mice develop normally and are indistinguishable from heterozygous and wild-type animals [220]. In the liver of hepatocyte-specific RXRα-null mice, metabolic pathways that are mediated by RXR heterodimerization with PPARα, LXR or FXR are compromised in the absence of RXRα [221]. Selective ablation of RXRα in adipocytes results in impaired adipogenesis and lipolysis, and resistance to obesity [222].

Several reports have indicated that RXR-specific ligands (LGD1069, LGD100268, LGD101506 and AGN194204) have glucose-lowering and insulin-sensitizing effects [223–225]. The antiobesity effect of rexinoid (LG100268) due to the up-regulation of uncoupling protein 1 (UCP1) mRNA in brown adipose tissue has been reported [226]. Treatment with the RXRα agonist (LG1000364) reduced atherosclerotic lesions drastically in apoE-null mice, and the effect was attributed to a stimulated cholesterol efflux from macrophages concomitant with increased expression of ABCA1 mRNA through activation of RXR/LXR heterodimerization [227].

4.5. Farnesoid X receptor

FXR is a member of the nuclear hormone receptor superfamily and two FXR isomers, FXRα and FXRβ, are known [228,229]. FXRα is conserved from human to fish, and the single FXRα encodes four isoforms, FXRα1, FXRα2, FXRα3 and FXRα4. FXRα is highly expressed in liver, intestine, kidney and the adrenal gland, with much lower levels in adipose tissue. FXRα can bind to and activate or repress through FXR response elements, either as a monomer or as an FXR/RXR heterodimer. FXR-γ null-mice develop normally and are outwardly identical with wild-type animals, except they have higher serum bile acid, cholesterol and triacylglycerols, and increased hepatic cholesterol and triacylglycerols [231]. FXRβ encodes a functional nuclear hormone receptor in mammalian species, except humans and other primates in which it encodes a pseudogene. FXRβ has been

suggested to be a lanosterol sensor, although its physiological function is unclear [230].

FXRα is known to be activated by bile acid and to maintain cholesterol and bile acid homeostasis through the transcriptional regulation of CYP7A1, a rate-limiting enzyme of bile acid synthesis in the liver [232–234]. Recently, it has been reported that activation of FXRα results in decreased triacylglycerol levels by increasing their clearance through modulating lipoprotein lipase activity, inducing PPARα and probably inhibiting SREBP1c [228]. FXRα also controls glucose homeostasis. FXRα expression was decreased in the livers of streptozotocin-induced diabetic rats and diabetic Zucker rats [235]. Additionally, transfusion of adenovirus-mediated constitutively active FXRα into wild-type, FXRα-null or genetically diabetic rodents lowered the levels of blood glucose and lipid [236]. Activation of FXR with a highly specific synthetic FXRα agonist (GW4064) in wild-type or *db*/*db* mice, but not FXRα-null mice, also decreased the levels of plasma glucose and lipid [235,236].

4.6. Hepatic nuclear factor 4

Hepatic nuclear factor 4 (HNF4), an orphan nuclear receptor, contains two subtypes, HNF4α and HNF4γ [237,238]. Despite the high levels of homology with RXRα, HNF4α binds to direct repeat-1 motifs of target genes not as a heterodimer with RXRα but as a homodimer. Although the physiological role of HNF4γ is less well understood, HNF4α is known to positively regulate genes involved in the transport of lipids and vitamins as well as genes involved in lipid, amino acid and glucose metabolism. While the HNF4α-null mouse is embryonic lethal, studies with Cre-loxP-conditioned liver-specific HNF4α-null mice exhibited hepatic lipid accumulation, decreased levels of lipids and urea in serum, and increased concentration of bile acid and ammonia in serum [238,239]. These abnormalities in lipid and urea homeostasis were due to a marked decrease in expression of apolipoproteins A-II, A-IV, C-II and C-III, microsomal triacylglycerol transfer protein, and ornithine transcarbamylase. HNF4α has been reported to induce genes involved in carbohydrate metabolism, such as L-pyruvate kinase and glucose-6-phosphatase [240]. Heterozygous mutations in HNF4α are linked to mature onset of diabetes of the young type 1, in which patients show defects in glucose-stimulated insulin secretion [241].

Fibrates are a class of hypolipidemic drugs that reduce the availability of HNF4 [242], and fibrate-CoAs bind HNF4α and inhibit HNF4α-mediated activation of gene transcription [243]. PPARα ligands (activators for lipolytic gene transcription) interfere with HNF4α action (control of lipoprotein synthesis and secretion, and carbohydrate metabolism), which may account for the complexity of the regulation of hepatic lipid homeostasis, including fatty acid synthesis, β-oxidation of fatty acids, lipoprotein metabolism and carbohydrate metabolism in the liver.

4.7. Nuclear factor κB

NFκB is a transcriptional factor that regulates a wide range of proinflammatory and antiapoptotic genes [244]. In its inactive state, NFκB, a heterodimer of p50 and p65, is retained in the cytoplasm by interaction with an inhibitor of κB (IκB). NFκB activation is regulated by the IκB kinase (IKK) complex (IKKα, IKKβ and IKKγ). Phosphorylation of IκB by the IKK complex leads to release of NFκB from its inhibitor, and then NFκB can translocate to the nucleus. NFκB is expressed in almost all cells. The p65 subunit-null mouse is embryonic lethal [245], and p50 subunit-null mice develop normally, except they display functional defects in immune responses [246].

Activation of NFκB has been detected in atherosclerotic lesions [247], and NFκB inhibitor retarded atherosclerosis progression by reducing the extension and size of the lesions and the inflammatory cell content [248]. Inhibition of NFκB and IKKβ has been shown to reverse hyperglycemia, hyperinsulinemia and dyslipidemia by sensitizing insulin signaling in obese rodents [249]. Heterozygous deletion of IKKβ also protected against the development of insulin resistance during high-fat feeding and in obese *ob*/*ob* mice [249]. Liver-specific activation of IKKβ induces type 2 diabetes, and hepatocyte-specific disruption of IKKβ retains liver insulin responsiveness, except it develops insulin resistance in muscle and fat in response to a high-fat diet, obesity or aging [250,251]. In contrast, mice with myeloid cell-specific disruption of IKKβ exhibit global insulin sensitivity and are protected form insulin resistance [250]. These studies suggest that inhibiting NFκB signaling is a potent therapeutic target during the prevention and alleviation of metabolic syndrome.

4.8. Cross-talk among transcriptional factors

LXR/RXR has been identified as a dominant activator of SREBP1c promoter involved in lipogenic gene transcription. The same study proposed that the activation of lipolytic transcriptional factor PPAR interferes with LXR/RXR signaling by the formation of PPAR/RXR and PPAR/LXR [252]. On the other hand, the activation of lipogenic transcriptional factor LXR suppresses PPARα-targeted gene expression by inhibiting PPAR/RXR binding to its responsive element PPRE [253]. Because the PPARα/LXR complex cannot bind to either PPRE or LXRE, this heterodimer interferes with the action of both PPAR and LXR. Consistently, combined treatment with PPARα and LXR agonists resulted in simultaneous reduction of both PPARα/RXRα and LXR/RXRα [252,253].

Interestingly, LXRα expression has been shown to be regulated by PPARs [254], and PPAR activation enhanced cholesterol efflux in macrophages via the PPAR–LXR–ABCA1 pathway [255,256]. The PPAR–LXR–SREBP1c pathway, however, may not be very potent in liver because there is no hepatic induction of SREBP1c after adenoviral over-expression of PPARγ [257].

There is cross-talk among FXR, LXR and SREBP1c. FXR activation induces the expression of the atypical nuclear receptor small heterodimer partner (SHP) and SHP interferes with SREBP1c expression by inhibiting the activity of LXR [258].

5. Molecular actions of bioactive lipids

We recognize that dietary lipids act as sources of energy, cell structure, and signaling molecules, as well as regulators of nutrient metabolism and cell functions by the control of gene expression. Such regulatory lipids can be defined as "bioactive lipids" and their molecular actions in the prevention and alleviation of metabolic syndrome through regulation of the activity or abundance of several transcriptional factors, including PPARs, SREBPs, LXRα, RXRα, FXRα, HNF4α and NFκB, will now be discussed (Fig. 2).

5.1. n−3 PUFAs

The nuclear actions of $n-3$ PUFAs in the liver have been characterized extensively [259–262]. The hypolipidemic effect of $n-3$ PUFAs is believed to be due mostly to their potent enhancement of lipolysis through PPARα activation. It has been reported that $n-3$ PUFAs, including LNA and EPA, can bind to PPARα with reasonable affinity [263–265], and their metabolites have greater affinity for PPARα than their parent fatty acids [264,265]. $n-3$ PUFAs induce the expression of lipolytic genes, such as carnitine palmitoyltrasferase (CPT), UCP and acyl-CoA oxidase (ACO), which are under PPAR regulation, and enhance β-oxidation of fatty acids [266–268]. On the other hand, $n-3$ PUFAs inhibit hepatic lipogenesis by suppressing genes involved in fatty acid biosynthesis, such as ACC, FAS and SCD [268,269]. As described above (see Section 4.8), three major transcriptional factors, such as SREBP1c, PPARα and LXRα, could contribute this $n-3$ PUFA effect. The results of studies evaluating the interactions between $n-3$ PUFAs and transcriptional factors, however, suggest that SREBP1c may play the pivotal role in the suppression of hepatic fatty acid synthesis by $n-3$ PUFAs. A study with PPARα-null mice indicated that $n-3$ PUFAs suppress the hepatic lipogenic gene expression without PPARα activity [270]. Although $n-3$ PUFAs reduced the level of mRNA and the nuclear content of SREBP1c [271], disruption of LXRE from SREBP1c promoter did not affect PUFA suppression of SREBP1c gene transcription [272]. $n-3$ PUFAs have been reported to suppress LXR activation directly [273,274], but feeding $n-3$ PUFAs had no effect on the expression of LXR-regulated genes (CYP7A1, ABCG5 and ABCG8) *in vivo* [275]. These observations suggest that PPARα and LXRα are not the main targets for nuclear actions of $n-3$ PUFAs *in vivo*.

Various long-chain fatty acyl-CoA thioesters have been reported to bind specifically to HNF4α with high affinity. Thus, binding of saturated fatty acids stimulates the transcriptional activity of HNF4α, whereas binding of a PUFA, such as LNA, inhibits HNF4α-mediated gene transcription, consistent with the action of fibrates on HNF4α [276,277]. In addition, $n-3$ PUFAs inhibit L-pyruvate kinase (a glycolytic enzyme) may through the inhibition of HNF4α activity [278]. These results suggest that $n-3$ PUFAs affect hepatic lipogenesis through inhibiting glucose flux into lipid synthesis.

As well as in liver, an effect of $n-3$ PUFAs in skeletal muscle has been reported. Several studies demonstrated that the decrease in fat deposition associated with ingestion of fish oil was accompanied by a significant increase in the abundance of skeletal muscle UCP3 mRNA in rats and mice [55,266].

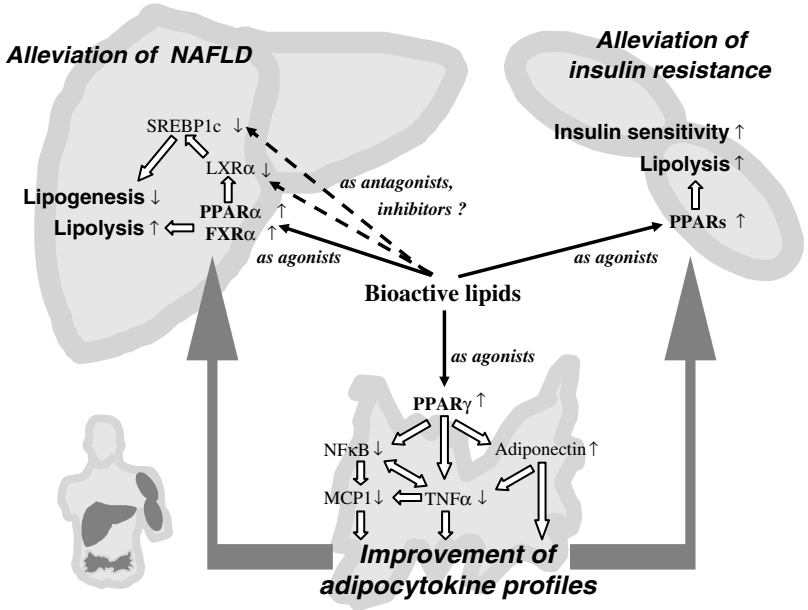

Fig. 2. Scheme showing possible mechanisms by which bioactive lipids prevent or alleviate metabolic syndrome.

The mechanism underlying the regulatory function of *n*−3 PUFAs on the production of adipocytokine and pro-inflammatory cytokines has been examined. Neschen et al. showed that consumption of fish oil raised plasma levels of adiponectin in a dose-dependent manner, and the increase was blocked completely by administration of the PPARγ inhibitor bisphenol-A-diglycidyl ether in mice [279]. In contrast, treatment with fish oil resulted in an increase in the concentration of adiponectin in PPARα-null mice. These results suggest that fish oil (or the EPA or DHA in the oil) regulates secretion of adiponectin through a PPARγ-dependent and PPARα-independent manner in adipose tissue [279]. Novak et al. demonstrated that TNFα mRNA and protein expression were inhibited by *n*−3 PUFAs, mediated though inactivation of the NFκB signal transduction pathway secondary to inhibition of IkB phosphorylation in LPS-stimulated macrophages [280]. Furthermore, Li et al. demonstrated that PPARγ activation by EPA and DHA inhibited NFκB activity, and decreased expression and secretion of MCP1 in human-derived cells [281].

As described above, the hypolipidemic and insulin-sensitizing effects of *n*−3 PUFAs have been attributed to their action as agonists of PPARs, inhibitors of SREBP1c and possibly antagonists of LXRα and HNF4α (Fig. 2). Recently, *n*−3 PUFAs have been reported to be FXR ligands [282] in a study demonstrating that *n*−3 PUFAs, such as LNA and DHA, bound to FXR and behaved as FXR antagonists in the coactivator association assay. These activities on FXR may contribute to the metabolic effects of *n*−3 PUFAs, since FXR has a critical role in lipid and glucose metabolism (Fig. 2). Additionally, FXR activation by *n*−3 PUFA may affect the down-regulation of LXR activity [258,262].

The role of *n*−3 PUFAs in the control of RXR during the alleviation of metabolic syndrome is not clear. Reporter assays and mass spectrometry studies have indicated that DHA has the capacity to specifically bind and activate the RXRα [283,284]. The authors suggest that RXRα has an active role as a fatty acid sensor *in vivo*.

5.2. CFAs

PPARα is likely involved in the regulation of lipolytic gene expression by dietary CFAs. It has been demonstrated that CLA is a potent ligand and activator of PPARα [285]. Consistently, a number of studies have demonstrated that CLA and other CFAs induce mRNA, protein and activity of PPARα-regulated lipolytic genes, including CPT, ACO and UCP in the liver, skeletal muscle and brown adipose tissue, where β-oxidation of fatty acids occurs [84,87,94,95,286]. Dietary CLA, however, induced these lipolytic genes even in PPARα-null mice [287]. The result suggests the presence of some mechanism mediating the lipolytic activities of CFAs other than the PPARα pathway, and we speculate that the activation of PPARβ/δ by CFAs could be one of these mechanism [288,289].

The precise mechanism of transcriptional regulation of lipogenic genes by CLA isomers is not known. Earlier, we showed that the 10*t*,12*c*-CLA, but not 9*c*,11*t*-CLA, decreased hepatic levels of FAS and SREBP1 mRNAs concomitant with marked attenuation of hepatic lipid accumulation in obese OLETF rats [87]. On the other hand, divergent tissue-specific effects on SREBP1c expression by 9*c*,11*t*-CLA have been reported, in which significant reduction of hepatic SREBP1c and increased adipose tissue SREBP1c expression contributes to improved abnormalities of lipid and glucose metabolism in obese *ob*/*ob* mice [290]. Additionally, hepatic lipogenic genes, including FAS, ACC and SCD, were markedly induced through the up-regulation of hepatic SREBP1c during the onset of fatty liver, second to the development of lipodystrophy in CLA-fed C57BL/6 mice [291].

CLA has been reported as an agonist of PPARγ [103,292,293], and the antidiabetic effect of CLA may be attributable to the PPARγ activation (Fig. 2) comparable to the effect of TZD such as troglitazone [103]. Additionally, the enhanced level of plasma adiponectin, whose gene expression is under the regulation of PPARγ, alleviated hyperinsulinemia and obesity-related hypertension in Zucker rats [107]. Activation of PPARγ has shown anti-inflammatory effects, including the suppression of inflammatory molecule expression, such as TNFα and MCP1, through the inactivation of NFκB [293–295]. On the other hand, Tsuboyama-Kasaoka et al. demonstrated that feeding CLA induced apoptosis in murine adipose tissues, concomitant with down-regulation of PPARγ [296].

As described above, conflicting results have been demonstrated in many trials designed to determine the effect of CFAs on transcriptional regulation of lipid and glucose metabolism. Although the efficacy and direction of CFA action in pathophysiological states varies, depending on the evaluation model, the therapeutic potential of CFAs against metabolic syndrome is still promising.

5.3. Other lipids

Ikeda et al. reported that campestenone (campest-5-3*n*−3-one) drastically increased the activities and the mRNA levels of mitochondrial and peroxisomal lipolytic enzymes, such as CPT and ACO, in the liver [119]. Additionally, marked reduction of the activities and mRNA expressions of lipogenic enzymes such as ACC, FAS, glucose-6-phosphate dehydrogenase, pyruvate kinase and ATP-citrate lyase concomitant with the decrease in expression of SREBP1 mRNA was shown in campesterone-fed rats [119]. These alterations of gene expressions were attributed to PPARα activation by campesetenone, as determined using a GAL4 ligand-binding domain chimera assay system with coactivator coexpression. The authors supposed that the PPAR activation by campestenone suppressed expression of SREBP1c mRNA through the decrease of LXR/RXR formation [119] (Fig. 2).

Takeuchi et al. [140] indicated that the antidiabetic effect of MCT with increased levels of plasma and adipocyte adiponectin was due to the enhanced expression of adiponectin mRNA in perirenal adipose tissue. The authors showed that expression of PPARγ and RXR mRNA was increased simultaneously in adipose tissue, and speculated that an increased amount of PPARγ/RXR heterodimer enhanced the promoter activity of adiponectin in adipocytes (Fig. 2).

Feeding DAG and LNA-DAG increased the expression of genes related to energy homeostasis, including ACO, acyl-CoA synthase, medium-chain acyl-CoA dehydrogenase, liver fatty acid binding protein and UCP2 in the liver of genetically and dietary-induced obese rodents [150,153,154]. The molecular mechanism underlying these alterations, however, has not been elucidated.

Our studies indicated that PC reduced the expression of FAS mRNA in the liver of olotic acid-induced fatty liver model rats [168], and PC from salmon roe reduced expression of the mRNA of lipogenic genes, such as ACC, SCD1 and SREBP1c, and enhanced expression of the mRNA of lipolytic genes, such CPT1a, CPT2 and PPARβ/δ in the liver of obese rats [175]. At present, however, there is no evidence that PC or its constituent base choline can be a ligand for any transcriptional factor.

6. Concluding remarks

This review has explored the physiological functions and molecular actions of bioactive lipids in the development of metabolic syndrome. Experimental studies demonstrate that dietary bioactive lipids suppress the accumulation of abdominal adipose tissue and lipids in the liver and serum, and alleviate hypertension and type 2 diabetes through the transcriptional regulation of lipid and glucose metabolism. PPARs, SREBPs, LXRα, RXRα, FXRα, HNF4α and NFκB contribute to these nuclear actions by bioactive lipids through complex interactions. Additionally, recent studies demonstrate the striking ability of bioactive lipids, such as *n*−3 PUFA, CLA, MCT, and DAG, to regulate the production of physiologically active adipocytokines through PPARγ activation (Fig. 2). In particular, the function of bioactive lipids as dietary adiponectin inducers (dietary insulin sensitizers) is worth considerable attention with respect to the alleviation of metabolic syndrome by food components.

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