Mechanisms by which Dietary Fatty Acids Modulate Plasma Lipids

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ABSTRACT Dietary fatty acids have a considerable effect on plasma LDL cholesterol (LDL-C) concentrations and therefore on the risk for coronary heart disease. Numerous studies have been conducted in animal models to elucidate the mechanisms by which different types of fatty acids modulate plasma cholesterol concentrations. In addition, multiple clinical trials and epidemiological data have demonstrated the effects of fatty acids in determining the concentrations of circulating LDL. SFAs and trans fatty acids have a detrimental effect on plasma lipids, whereas PUFAs of the (n-6) family and monounsaturated fatty acids decrease plasma LDL-C concentrations. Among the SFAs, stearic acid (18:0) appears to have a neutral effect on LDL-C, while lauric (12:0), myristic (14:0), and palmitic (16:0) acids are considered to be hypercholesterolemic. SFAs increase plasma LDL-C by increasing the formation of LDL in the plasma compartment and by decreasing LDL turnover. Although unsaturated fatty acids increase cholesterol synthesis, they also increase hepatic LDL receptor number and LDL turnover in vivo. Fatty acids are also ligands of important regulatory elements, which can play a role in determining plasma cholesterol. This article presents a summary of the major effects of various types of fatty acids on plasma lipid concentrations and the mechanisms involved.

KEY WORDS: dietary fat saturation • plasma cholesterol • plasma triglycerides • LDL receptor • molecular regulation

Dietary fat saturation plays a considerable role in modulating plasma cholesterol concentrations and determining the risk for coronary heart disease (CHD). In fact, SFAs are recognized as the single dietary factor that has the greatest negative effect on LDL cholesterol (LDL-C) concentrations (1). In contrast, monounsaturated fatty acids (MUFAs) and PUFAs of the (n-6) family have been shown to decrease plasma cholesterol concentrations in clinical studies (2,3) and in various animal models (4–6). According to Hu et al. (7), replacing 5% of the energy of SFAs by unsaturated fatty acids results in a 43% decrease in CHD. Recently trans fatty acids (TFAs) have emerged as the most detrimental type of fat relative to increased risk for CHD, since some studies demonstrated that in addition to increasing plasma LDL-C, TFAs also decrease plasma HDL cholesterol (HDL-C) and may increase lipoprotein (a) (8). PUFAs of the (n-3) family have multiple beneficial effects on CHD risk (9). The present review discusses only the effects of (n-3) PUFAs in modulating VLDL metabolism and reducing plasma triglycerides (TGs).

The concentration of LDL in blood is determined by the production of this lipoprotein via VLDL through the delipidation cascade and the efficiency of its removal from circulation by LDL receptor or non-receptor mechanisms (6). In addition, the secretion of VLDL is influenced by the availability of apolipoprotein (apo) B in the liver and the activities of regulatory enzymes involved in the assembly and transport of VLDL, including microsomal transfer protein and acyl-coenzyme A:cholesterol acyltransferase (ACAT). Moreover, the effects of fatty acids in regulating gene expression (10) may also contribute to the mechanisms that determine plasma LDL-C. Fatty acids regulate at least 4 families of transcription factors: the peroxisome proliferator activated receptors (PPARs), liver X receptors (LXRs), hepatic nuclear factor-4 (HNF-4), and sterol regulatory element binding proteins (SREBPs) (10). A brief review of the postulated effects of fatty acids in regulating plasma cholesterol follows.

Fat saturation and cholesterol synthesis. Modulation of cholesterol synthesis is not a major mechanism by which PUFAs lower plasma LDL cholesterol (11). This has been confirmed using deuterium incorporation into newly synthesized cholesterol as a sensitive method, with results that closely resemble those obtained from traditional methods such as sterol balance (12). Both methods revealed that although cholesterol synthesis increases with high PUFA intake (11,12), the lowering of plasma LDL-C observed with PUFAs is likely due to other mechanisms, including redistribution of cholesterol between plasma and tissue pools (11) and upregulation of the LDL receptor (13). In contrast, the observed increases in plasma cholesterol concentrations due to SFAs do not appear to be related to a rise in cholesterol synthesis (12). However, when intake of TFAs was compared to palmitic acid, an increase in both cholesterol synthesis and plasma LDL-C concentrations was observed (14), suggesting that cholesterol synthesis contributed to the higher concentration of circulating LDL observed with TFA intake.

Fat saturation and LDL receptors. Many studies have shown that dietary fatty acids regulate plasma LDL-C levels by affecting LDL receptor activity, protein, and mRNA abundance (13,15–17).

Mustrad et al. (18) demonstrated that dietary SFA (palmitic acid) markedly decreased LDL receptor protein levels in pigs.
fed a diet containing 0.25% cholesterol, compared to pigs fed a diet with cholesterol only or to controls fed a low-fat, cholesterol-free diet. In contrast, pigs fed a diet high in PUFA (linoleic acid) had increased LDL receptor levels compared to pigs fed a diet with cholesterol only or a low-fat, cholesterol-free diet (18). These distinct effects of dietary fatty acids were accompanied by parallel changes in LDL receptor mRNA levels. These data provide strong evidence for an independent and positive effect of PUFAs on the regulation of LDL receptor expression. It is important to note that these differential effects of dietary fatty acids were observed only in pigs fed the lowest level of dietary cholesterol, suggesting that high cholesterol intake has a dominant and repressive effect on LDL receptor mRNA levels that cannot be alleviated by fatty acids.

Cholesterol-raising SFA (12:0, 14:0, 16:0) decrease LDL receptor activity, protein, and mRNA abundance, while unsaturated fatty acids increase these variables. Dietary modification of hepatocyte membrane fluidity may be one way in which diets high in PUFAs affect LDL receptor activity differently than diets enriched in SFAs. Support for this suggestion comes from in vitro studies (19) and studies in rats (20), which showed significant alterations in LDL binding to the LDL receptor as a result of changes in membrane fluidity. It has also been suggested that dietary fatty acids can directly influence the number of receptors available for uptake of circulating LDL by specifically affecting LDL receptor synthesis. In vitro binding studies demonstrated that alterations in LDL uptake associated with dietary fatty acid composition can be attributed to changes in LDL maximal binding (B_max), an indicator of receptor number (13).

In support of the in vitro studies, PUFAs decreased LDL apo B pool size by 50% and increased LDL fractional catabolic rate (FCR) 2-fold when compared to SFA intake in guinea pigs (16). The differences in plasma LDL-C concentrations, as influenced by the chain length of the saturated fatty acid, were also correlated to both receptor expression (B_max) and LDL FCR (17). Guinea pigs fed the long-chain SFA had lower plasma LDL-C concentrations, which correlated with the fastest LDL FCR when compared to guinea pigs fed diets high in lauric or myristic acids (16). Similarly, in hamsters lauric, myristic, and palmitic acids increased plasma LDL-C concentrations compared to a diet high in stearic acid by decreasing LDL apo B/E receptor activity and increasing LDL production rate (21).

In vitro studies with different cell types (22) and studies with hamsters (23,24) showed that fatty acids can affect the storage of cholesterol esters and influence sterol distribution. It has been suggested that dietary fatty acids and cholesterol regulate hepatic LDL receptor activity via cholesteryl ester and free cholesterol regulatory pools. These cholesterol regulatory pools are affected by ACAT, the rate-limiting enzyme of cholesterol esterification. SFAs suppress this enzyme, which may result in a greater proportion of cholesterol remaining in the regulatory pool. An increase in hepatic cholesteryl ester is negatively correlated with LDL receptor activity in hamsters (23). However, data from many animal studies are not consistent with this hypothesis. For example, in African green monkeys, an increase in ACAT activity is correlated with increases in plasma LDL cholesterol and increased deposition of cholesterol in the aorta (25).

**Fatty acids and molecular regulation.** The PPAR-mediated regulation of several genes involved in lipoprotein metabolism leads to the following effects: 1) increased hydrolysis of TG-rich lipoproteins, 2) stimulation of cellular fatty acid uptake and conversion to acyl-CoA derivatives, 3) stimulation of β-oxidation, and 4) reductions in fatty acid and TG synthesis and VLDL production. Together, these effects help explain the hypolipidemic effect of certain types of fatty acids. PPARα interacts with both saturated and unsaturated fatty acids, although SFAs have a lower affinity (26). Transcriptional regulation is mediated through peroxisome proliferator response elements (PPREs) in the promoter regions of target genes. Target genes in the liver include apoA-I, apoA-II, apoC-III, and lipoprotein lipase (LPL) (27). The coordinated changes in the expression of these genes contribute to hepatic lipid homeostasis by regulating, either directly or indirectly, lipid flux into and out of the liver.

The TG- and cholesterol-lowering action of certain fatty acids is attributable to an enhanced catabolism of TG-rich lipoproteins (TGRLs) and inhibition of hepatic VLDL secretion (27). Effects of fatty acids on TG and cholesterol metabolism are partly mediated by changes in the expression of LPL and apoC-III. LPL hydrolyzes the TG component of chylomicron and VLDL particles, which enables the removal of the remaining lipoprotein remnants from circulation by the liver. In hepatocytes and preadipocytes, fatty acids stimulate the transcription of the LPL gene by binding to a PPRE in the LPL promoter (28). In addition, many human studies report that dietary (n-3) PUFAs decrease the residence time of VLDL in serum (9). However, dietary PUFAs have little or no effect on LPL or hepatic lipase activity in postheparin serum in humans (29). LPL may be more reactive toward VLDL with PUFA TGs as substrate, leading to more rapid lipolysis of TGRLs with dietary PUFAs (30). In addition, dietary (n-3) PUFAs accelerate chylomicron clearance in rats (31) and enhance the conversion of VLDL apoB to LDL apoB in pigs (32). Overall, the marked decrease in plasma LDL concentrations in animals fed (n-3) PUFAs could be due to reductions in the rate of LDL entry into the plasma, resulting from increased VLDL catabolism (30).

Due to its action in blocking LPL activity, apoC-III levels are positively correlated with plasma TG concentrations (33). Metabolic studies suggest that high levels of apoC-III impair the clearance of TGRLs due to interference with apoE-mediated uptake of these particles by cellular receptors (34). The reduction in apoC-III levels in response to fatty acid intake is thought to enhance the LPL-mediated effects on lipoprotein metabolism, leading to increased catabolism of VLDL particles. Consequently, the dual action of fatty acids on the expression of the LPL and apoC-III genes provides a potential model by which fatty acids reduce plasma TG concentrations.

HNF-4 is a key regulator of genes involved in glucose, cholesterol, and fatty acid metabolism (35). The promotors of apoA-I, apoA-II, apoA-IV, apoB, apoC-II, and apoC-III all contain binding sites for HNF-4 (35). Increased levels of HDL are correlated with a decreased risk for coronary artery disease. The protective effects of HDL on atherosclerosis are correlated with levels of specific HDL particles. Fatty acids exert a negative effect on apoA-I transcription (36) via a sequence located in the proximal promoter region of the human apoA-I gene. However, this negative effect is counteracted by a positive regulatory site that responds to PPAR. This regulatory site is localized in the apoA-I promoter A site and binds to other nuclear receptors, such as the retinoid X receptor (37). The subtle interaction between these two opposing mechanisms determines the overall effect of fatty acids on apoA-I gene expression.

The liver X receptor (LXR) may act as a sterol sensor that functions to help an organism cope with high free cholesterol levels in the blood (38). Tobin et al. (39) demonstrated that
in the liver, LXRα expression is induced by PUFAs. This effect occurs as a result of a direct (40) induction of LXRα gene transcription. Due to the established ability of fatty acids to serve as ligands for the PPARs, it is possible that PPARs are involved in mediating the effect of fatty acids on LXRα expression (39).

LXR regulates intracellular cholesterol levels by inducing the expression of cholesterol 7α-hydroxylase (CYP7), the initial and rate-limiting enzyme in the conversion of cholesterol to bile acids. Fatty acids not only enhance PPAR activity; they also induce LXRα protein, mRNA, and gene transcription. Through induction of LXRα via PUFAs, the LXRα-regulatory pathway facilitates the elimination of excess cholesterol by stimulating CYP7, thereby resulting in the conversion of cholesterol to bile acids. Conversion of cholesterol into bile acids is an irreversible and terminal process of cholesterol catabolism. In addition to the increase in CYP7 activity, unsaturated fatty acid synthesis is prevented through the suppression of SREBP-1c expression via the antagonistic effect of PUFAs (41). This could be an indirect mechanism by which PUFAs increase LDL receptor expression by the elimination of cholesterol from the liver via increased bile acid synthesis. A summary of the possible mechanisms by which (n-6) PUFAs may lower plasma cholesterol is depicted in Figure 1.

The major role of SREBP's in both lipogenesis and cholesterol metabolism is well established (41). The SREBP-1a isoform is a regulator of genes encoding proteins involved in both lipogenesis and cholesterol biosynthesis (42). The SREBP-1c isoform in the liver is a key regulator of the liver’s response to insulin and is a major determinant of lipogenic gene transcription (42). PUFArich diets repress the transcription of lipogenic genes by suppressing SREBP-1 gene transcription or by reducing the maturation of SREBP-1 protein, thereby reducing the levels of MUFAs, TGs, and cholesterol esters in plasma and liver. In the liver, PUFAs inhibit the expression of SREBP-1c to a greater extent compared with dietary SFAs or MUFAs (43). Moreover, (n-3) PUFAs appear to be more potent than (n-6) PUFAs in suppressing SREBP-1 expression (43).

A study by Vasandani et al. (30) showed that dietary (n-3) PUFAs markedly decreased triglyceride and cholesterol ester levels in the liver and the concentration of apoB-containing lipoproteins in the plasma of LDL-receptor–deficient mice. These results suggest an important mechanism by which dietary (n-3) PUFAs lower plasma TGs. The potential mechanisms of action by (n-3) PUFAs include the following: 1) suppression of SREBP-1 expression and processing, leading to decreased lipogenesis and decreased VLDL secretion; 2) enhanced hepatic clearance of lipoproteins through increased LPL expression and decreases in apoC-III levels; and 3) increased reverse cholesterol transport (Fig. 2).

In conclusion, fatty acids substantially affect plasma LDL-C concentrations and therefore the risk for CHD. Although SFAs have a negative effect on LDL-C levels, unsaturated fat decreases plasma cholesterol. Possible mechanisms by which (n-6) PUFAs decrease plasma cholesterol include upregulation of the LDL receptor and increased CYP7 activity, whereas (n-3) PUFAs decrease plasma TGs by decreasing lipogenesis and VLDL secretion, increasing LPL activity, and increasing reverse cholesterol transport. By reducing plasma cholesterol and TG levels, both (n-6) and (n-3) PUFAs reduce cardiovascular risk.

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