Regulation of Cholesterol Metabolism by Dietary Protein and n-6 Polyunsaturated Fatty Acids

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Summary The modulating processes of dietary vegetable protein and polyunsaturated fatty acids (PUFAs) on cholesterol (CH) metabolism are very complicated. Since dietary protein can affect PUFA absorption and synthesis through the effects of its amino acid components, the CH-lowering of PUFAs may be modulated by dietary proteins. The effect of dietary PUFAs on the CH-lowering mechanism of vegetable proteins is mainly additive and complementary, but not competitive. Dietary vegetable protein reduces intestinal CH absorption, enhances catabolism of the CH-carrying lipoproteins, increases the LDL receptor activity, and modulates CH metabolic enzymes through the amino acid-modulated action of hormones. PUFAs may modulate CH metabolism through the action of eicosanoids which modulates the activity of the enzymes responsible for CH metabolism.

Key Words Fatty acid desaturation, eicosanoids, cholesterol absorption and excretion, cholesterol metabolic enzymes, lipoproteins, amino acids, glucagon

Replacing animal protein with vegetable protein reduces CH level and atherosclerotic development in the experimental animals (1). Dietary PUFAs, mainly linoleic acid (LA, 18:2n-6), also lower blood CH in humans and animals (2). Diet deficient in either nutrients induces fatty liver, and low protein diet intensifies the symptoms of essential fatty acid (EFA) deficiency (3). Both dietary nutrients enhance CH mobilization, degradation and excretion, and are subjected to common modulators, such as species, sex and age differences. Thus, all evidence indicates that there exist an interaction between these two nutrients.

Effects of Dietary Protein and Cholesterol on n-6 EFA and Eicosanoid Metabolism

Linoleic acid (LA, 18:2n-6) in animals, is desaturated by Δ-6-desaturase (D6D) to γ-linolenic acid (GLA, 18:3n-6). GLA is rapidly elongated to form dihomo-γ-linolenic acid (DGLA, 20:3n-6) which is then desaturated by Δ-5-desaturase (D5D) to arachidonic acid (AA, 20:4n-6). N-6 metabolites are structural components of cell membranes. Among them, DGLA and AA also serve as precursors for the synthesis of prostaglandins (PG) and thromboxanes (Tx) of the 1 and 2 series. Dietary fats therefore, have significant effects on both n-6 PUFA and eicosanoid metabolism.

The levels of dietary protein also affects the synthesis of n-6 EFAs and eicosanoids. It has been shown that low protein diets or an inadequate supply of essential amino acids (e.g., vegetable protein feeding), significantly reduced D6D activity (4) and aortic PGI₂ production (5) in experimental animals. Similarly, CH-feeding suppresses hepatic D6D and D5D activity (6). This inhibitory effect reduces not only the synthesis but also the high CH-lowering potency of GLA, DGLA, and AA (7). However, concomit feeding of CH and vegetable protein to animals does not induce a cumulative suppression on desaturase activity. We have instead, observed an alleviation in the CH-induced inhibition of D5D activity in the soy protein-fed as compared with those in the casein-fed rats (8). This might be attributed to a reduced tissue CH contents which minimizes the CH-induced inhibition on PUFA metabolism.

Effect of Dietary Proteins and PUFAs on CH Metabolism

The present report gathers evidence and examines whether dietary PUFAs provide an additive, competitive or complementary action to
the CH-lowering effects of dietary vegetable proteins, and the possible action sites over which these 2 nutrients might interact with each other.

I. Absorption and excretion of cholesterol and bile acids

Protein quality has significant effect on CH absorption. Vahouny et al. (9) have shown that dietary casein, as compared to soy protein increase CH absorption, and addition of arginine to casein diet reduced, while addition of lysine to the soy diet increased the rate of CH and fatty acid absorption. The effect of dietary fats on CH absorption on the other hand, is regulated by the quantity and not by the quality (degree of unsaturation) of the fats.

Dietary proteins also affect fecal steroid excretion in animals. Vegetable protein-feeding as compared with casein-feeding increases the fecal steroid excretion. This reduces the intestinal absorption and subsequently the serum CH levels. It has been suggested that the undigested vegetable protein residues may interrupt the enterohepatic reabsorption of steroids (10).

II. CH metabolic enzymes

1) HMG-CoA reductase In animals, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme for CH biosynthesis. In case of low CH intake, tissues synthesize CH to meet the needs. Cholesterol accumulation on the other hand, inhibits CH synthesis by feedback regulation. In soybean protein-fed rats, a significant fraction of CH and bile acids in the intestinal lumen, is excreted into feces. This enhances the activity of HMG-CoA reductase to synthesize CH in order to compensate for the loss of steroids. On the other hand, dietary casein which increases CH absorption, markedly decreased the hepatic CH biosynthesis in rats (11). The effects of dietary fats on CH metabolism is less conclusive. While some reports shown that saturated fats increase the hepatic CH synthesis, the others demonstrated that dietary fats have no effect on hepatic HMG-CoA reductase activity.

2) 7α-hydroxylase Hepatic CH is disposed through fecal excretion as neutral sterols or as bile acid. The enzyme, 7α-hydroxylase, which converts CH (mainly free CH) into bile acids is twice as active in casein-fed as compared to soy protein-fed rats (12). The increase is probably due to an increase in CH absorption which leads to an increase in the supply of the substrate for the enzyme. In the soy protein-fed animals, the increasing fecal excretion of bile acids also induces an increase in bile acid synthesis and secretion. Feeding saturated fat-rich diet has been shown to reduce 7α-hydroxylase activity. PUFA-feeding on the other hand, increases fecal steroid excretion (13).

3) ACAT When exogenous and endogenous cholesteryl esters (CE) carried by lipoprotein are introduced into liver cells they are hydrolyzed to free CH. Some of the free CH are re-esterified by acyl coenzyme A: cholesterol acyltransferase (ACAT) to form CE and some are converted into bile acids by 7α-hydroxylase and secreted into the intestine. Soy protein-feeding as compared with casein-feeding reduces ACAT activity in rat livers (12). PUFA enriched diet, on the other hand, increases the ACAT activity (14), and facilitates the removal of excess plasma CH. Eicosanoids can also modify the activity of ACAT. PGE2 has been shown to inhibit ACAT activity in aortic muscle culture (15) and in rabbit aorta (16).

4) LCAT In peripheral tissues, free CH migrate to membranes, where they are removed by plasma apoprotein A-I and esterified by lecithin cholesterol acyltransferase (LCAT) into CE. Both LACT and apoprotein A-I, a LCAT activator, locate on the surface of HDL. CE migrates to the core of the HDL particle. HDL then transports CH from the extrahepatic tissues to the liver. In pigs, casein-feeding as compared to vegetable protein-feeding reduced LCAT activity (17), and thus reduced CH removal and cause CH accumulation in the peripheral tissues. LCAT activity is also affected by dietary fats. Human subjects consumed high saturated fat diet as compared with those ingesting PUFA diets tended to exhibit higher LCAT activity (18).

Effect of Dietary Proteins and PUFAs on Lipoprotein Metabolism

In rats, soybean protein as compared with casein reduces hepatic secretion of CH and triglyceride (TG), and subsequently hepatic contribution to lipid-carrying lipoproteins, LDL and VLDL (19). In rabbits, dietary soy protein significantly lowers the levels of apoprotein B associated with LDL, but increases the fractional catabolic rate of VLDL and LDL apo-B (20). Consumption of an all-plant protein diet also significantly increased the fractional catabolic rate of VLDL apolipoprotein B.
in hypercholesterolemic men. Dietary PUFAs also lower plasma CH and TG levels. The reduction of plasma CH is attributed to a decreased synthesis of CH for the formation of VLDL particle (21).

Plasma LDL is removed primarily through tissue LDL receptor that recognizes specific apoproteins (apo B and apo E) in lipoproteins. It has been shown that soybean protein increases LDL receptor activity (22), while casein-feeding changes CH and protein contents in the LDL fraction and reduced the numbers of hepatic lipoprotein receptors (23). The effect of dietary PUFAs on LDL receptors is exerted through incorporating into cell membrane phospholipids and modulating the fluidity and function of cell membranes. It has been shown that increasing unsaturation in membrane phospholipids does not affect the number of LDL receptors (24).

Effect of Dietary Proteins and PUFAs on the Release of Endocrines

Release of hormones, especially insulin and glucagon is regulated by blood amino acid composition. Increasing intake of soy protein, which as compared with casein contains twice amounts of arginine, elevates plasma arginine levels (25). In rats, casein-feeding increased the fasting insulin levels (26). Sugano and his colleagues have recently reported that the insulin-to-glucagon levels is modulated by the ratios of lysine-to-arginine in dietary protein (27).

Eicosanoids also regulate the release of hormones. It has been shown that PGE\textsubscript{1} infusion increases the release of glucagon (28). Since glucagon inhibits while insulin activates D6D activity, increasing plasma glucagon levels would reduce PUFA metabolism. In addition, glucagon also suppresses the activity of HMG-CoA reductase, and subsequently the CH biosynthesis.

REFERENCES


