The ABCs of vitamin E and β-carotene absorption\textsuperscript{1,2}

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Remember “easy as ABC”? Lipid absorption used to be like that. Lipid-soluble dietary components were thought to be absorbed according to the extent of their lipophilicity. Because triacylglycerols were hydrolyzed to fatty acids in the intestinal lumen and because enterocytes express fatty acid–binding proteins, fatty acid uptake was complete, and 100% of dietary triacylglycerols was secreted in chylomicrons. If chylomicron synthesis was impaired, fat malabsorption ensued. Thus, subjects with abetalipoproteinemia, which is a genetic defect in the microsomal triacylglycerol transfer protein (MTP) that is required for lipidating apolipoprotein B (1), had impaired chylomicron secretion. Not surprisingly, triacylglycerol absorption was impaired, as was the absorption of fat-soluble nutrients such as vitamin E and β-carotene.

Cholesterol absorption, however, has always been more complex than was thought. Whereas \( \approx 50\% \) of a dose of cholesterol is absorbed, plant sterols—even though their structures are similar to those of cholesterol—are poorly absorbed. Moreover, when they are present in gram amounts, plant sterols inhibit cholesterol absorption. In vitro studies suggest that plant sterols displace cholesterol from micelles and that, therefore, less cholesterol is delivered to the enterocyte for absorption. When plasma β-carotene and α-tocopherol decrease after plant sterol treatment, a decrease in plasma cholesterol–containing lipoproteins is assumed to be the cause. However, the report by Richelle et al (2) in this issue of the Journal suggests that things are not so simple. Those authors anticipated that plant sterols or sterol esters would reduce fractional cholesterol absorption but would have no effect on triacylglycerol absorption or on the absorption and incorporation of β-carotene and α-tocopherol into triacylglycerol-rich lipoproteins (eg, chylomicrons). Indeed, both plant free sterols and sterol esters similarly reduced cholesterol absorption by \( \approx 67\% \), whereas triacylglycerol absorption was unaffected. Remarkably, both plant sterols and sterol esters reduced β-carotene absorption by \( \approx 50\% \), whereas plant sterol esters, but not plant sterols, reduced α-tocopherol absorption by \( \approx 20\% \). The mechanisms for the reductions in the absorption of β-carotene and α-tocopherol by plant sterols and sterol esters were not investigated, but the findings suggest that lipid-soluble nutrient absorption may be modulated by ATP-binding cassette (ABC) transporters, nuclear receptors, and intracellular trafficking proteins.

The specific mechanisms for cholesterol absorption and its regulation by the enterocyte are beginning to be elucidated. Cholesterol trafficking is under the regulation of \( \geq 4 \) ABC transporters: ABCA1, ABCG1, ABCG5, and ABCG8 (3). Both ABCG5 and ABCG8 are half-transporters, which have only one nucleotide-binding domain followed by one transmembrane domain; the 2 come together to act as a transporter, and they shuttle plant sterols out of the cell into the intestinal lumen. Genetic defects in these transporters (4) cause sitosterolemia, a disorder characterized by cholesterol and plant sterol hyperabsorption and premature atherosclerosis. Plosch et al (5) showed in mice that abcg5 gene disruption causes selective dietary plant sterol hyperabsorption. Thus, ABCG5 and ABCG8 severely limit plant sterol absorption and reduce cholesterol absorption by increasing their efflux into the intestinal lumen. ABCA1 and ABCG1 also mediate cholesterol removal from enterocytes (6), but they direct their payloads toward the lymph, perhaps for uptake by HDL (7) or even newly synthesized chylomicrons.

It is important that the 4 different ABC transporters that regulate sterol trafficking are under the control of oxysterol receptors, called liver X receptors (LXRs) (8). Repa et al (9) showed that ABCA1, ABCG5, and ABCG8 mRNA increased in LXR agonist–treated mice. Sitostanol, a plant sterol, has been proposed to be an LXR agonist (10). Kaneko et al (11) examined the effects of several plant sterols and their derivatives on LXR activity and found a potent LXR agonist related to the plant sterols ergosterol and brassicasterol. Thus, a minor component of consumed plant sterols or a plant sterol conversion (oxidation) product may be the active element that binds to LXRs and up-regulates ABC transporters, thereby further limiting the absorption of both plant sterols and cholesterol.

So, what is an LXR? As a heterodimer with the 9-cis retinoic acid receptor (RXR), LXR binds to specific DNA sequences called response elements in target genes. The LXR-RXR heterodimer must bind both an LXR agonist and retinoic acid; the ligand-bound heterodimer then binds to DNA in the nucleus and activates transcription of target genes. Edwards et al (8) proposed that LXR functions as a sensor of cellular oxysterols and noted that all LXR target genes encode proteins that have major roles in controlling cholesterol or fatty acid homeostasis or both. Retinoic acid has a critical role in RXR activation; therefore, it is not surprising that β-carotene can be converted in the intestinal mucosa to 9-cis retinoic acid (12). It is possible that plant sterols activate LXR and that β-carotene provides additional retinoic acid for RXR, thereby increasing the downstream effects of plant sterols. Unfortunately, Richelle et al did not simultaneously as-

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tion of retinyl palmitate derived from \( \beta \)-carotene found by Richelle et al.

As shown by Richelle et al., \( \alpha \)-tocopherol absorption was unaffected by plant free sterols but decreased with plant sterol esters, which suggests that the increased lipophilicity of sterol ester–containing micelles limited \( \alpha \)-tocopherol uptake by enterocytes. However, enterocytes may increase the efficiency of \( \alpha \)-tocopherol transport because ABCA1 causes \( \alpha \)-tocopherol to undergo efflux into the lymph (14). ABCA1 is up-regulated by LXR-RXR, and ABCA1 increases sitosterol efflux to the basolateral (lymph) side in Caco-2 cells, a polarized intestinal cell line (6). Furthermore, LXR up-regulation increased sitosterol absorption in ABCG5-deficient mice (5). Thus, opposing effects of increased micellar solubility and increased efflux to the lymph may limit detectable alterations in \( \alpha \)-tocopherol absorption by plant sterols.

Although ABC transporters are clearly involved in sterol efflux, the influx of micellar sterols appears to depend on yet another protein. As reported by Altmann et al. (15), Niemann-Pick C1–Like 1 (NPC1L1) protein is expressed on enterocyte brush borders and facilitates cholesterol absorption, according to the observation that NPC1L1 protein–deficient mice absorbed only 15% of a cholesterol dose. NPC1L1 and NPC1 proteins share strong sequence homology, and NPC1 protein contains 13 transmembrane domains and 3 large hydrophilic luminal loops (16). This suggests that the uptake of both lipophilic nutrients and cholesterol from intestinal micelles may be facilitated by NPC1L1 protein. In addition, caveolin (17) and lipid rafts (18) have potential roles in lipophilic nutrient absorption.

Vitamins A, D, E, and K; carotenoids; and other lipophilic dietary components are absorbed and incorporated in chylomicrons for secretion into lymph. The major steps from micellar uptake to enterocyte trafficking and incorporation into chylomicrons are largely unknown for these compounds. Details from studies of the mechanisms regulating enterocyte cholesterol suggest that mechanisms for the regulation of lipophilic nutrient absorption will be highly complex but a fascinating area for future studies.

REFERENCES