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Review

Mechanisms involved in the intestinal absorption of dietary vitamin A and provitamin A carotenoids☆

Earl H. Harrison *

Department of Human Nutrition, The Ohio State University, 350 Campbell Hall, 1787 Neil Avenue, Columbus OH 43210, USA

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ABSTRACT

Vitamin A is an essential nutrient for humans and is converted to the visual chromophore, 11-cis-retinal, and to the hormone, retinoic acid. Vitamin A in animal-derived foods is found as long chain acyl esters of retinol and these are digested to free fatty acids and retinol before uptake by the intestinal mucosal cell. The retinol is then reesterified to retinyl esters for incorporation into chylomicrons and absorbed via the lymphatics or effluxed into the portal circulation facilitated by the lipid transporter, ABCA1. Provitamin A carotenoids such as β-carotene are found in plant-derived foods. These and other carotenoids are transported into the mucosal cell by scavenger receptor class B type I (SR-BI). Provitamin A carotenoids are partly converted to retinol by oxygenase and reductase enzymes and the retinol so produced is available for absorption via the two pathways described above. The efficiency of vitamin A and carotenoid intestinal absorption is determined by the regulation of a number of proteins involved in the process. Polymorphisms in genes for these proteins lead to individual variability in the metabolism and transport of vitamin A and carotenoids. This article is part of a Special Issue entitled Retinoid and Lipid Metabolism.

1. Introduction

Vitamin A deficiency affects more than 100 million children throughout the world [1,2]. Thus, knowledge about the mechanisms of absorption of vitamin A can lead to better approaches for enhancing its absorption and could be helpful in ameliorating some of the deficiencies.

Capability for the de novo synthesis of compounds with vitamin A activity is limited to plants and microorganisms [3,4]. Thus, higher animals must obtain vitamin A from the diet, either as the preformed vitamin or as a provitamin carotenoid such as β-carotene. In the intestinal mucosa β-carotene is converted to retinal by β-C 15,15′ oxygenase 1 (BCO1) and the retinal is then reduced to retinol by a retinal reductase [5]. In the human intestine about half the dietary provitamin A carotenoids are converted to retinol and about half are absorbed intact [6] although the extent of conversion varies widely among individuals. The major dietary forms of preformed vitamin A are long-chain fatty acid esters of retinol [7]. These esters must be hydrolyzed prior to intestinal absorption. Hydrolysis of the esters is catalyzed both by enzymes secreted by the pancreas into the intestinal lumen and by those associated directly with intestinal cells.

Following the hydrolysis of dietary retinyl esters, the free retinol is then taken up by the mucosal cell [8]. The free retinol, resulting either from hydrolysis of dietary retinyl esters or conversion of dietary provitamin A carotenoids, is reesterified with long-chain, mainly saturated, fatty acids by the enzyme lecithin:retinol acyltransferase (LRAT) when physiological doses of vitamin A are ingested [9,10]. The resulting retinyl esters are incorporated with other neutral lipid esters (i.e., triacylglycerols and cholesteryl esters) and intact carotenoids into chylomicrons and absorbed via the lymphatics [11,12]. In the vascular compartment much of the chylomicron triacylglycerol is hydrolyzed by lipoprotein lipase in extrahepatic tissues resulting in the production of a "chylomicron remnant" that contains most of the newly-absorbed retinyl esters [13,14]. In the rat, the chylomicron remnants are rapidly and almost quantitatively taken up by the liver, and there is evidence that the retinyl esters are rapidly hydrolyzed and reesterified during this process [15–17].

2. Dietary sources and luminal factors

As mentioned above, vitamin A activity in the diet derives from two sources: preformed vitamin A as retinyl esters in foods of animal origin and provitamin A carotenoids, such as β-carotene, α-carotene, and β-cryptoxanthin, found in plant derived foods. Stoichiometric conversion of 1 mol of β-carotene (with 2 β-ionone rings) would give rise to 2 mol of retinol (via retinal), whereas conversion of a mole of

Abbreviations: ARAT, acyl; CoA, retinol acyltransferase; BCO1, β-carotene 15,15′-oxygenase; BCO2, β-carotene 9′10′-oxygenase 2; β-C, β-carotene; α-C, α-carotene; CEL, carboxyl ester lipase; CEL KO, CEL, knockout mice; CRBP, cellular retinol-binding protein; CM, chylomicrons; DGAT, diacylglycerol acyltransferase; KO, knock out; LRAT, lecithin:retinol acyltransferase; LUT, lutein; LYC, lycopene; OA, oleic acid; PTL, pancreatic triglyceride lipase; PLRP, pancreatic lipase-related protein; RA, retinoic acid; REH, retinyl ester hydrolase; RE, retinyl esters; TG, triglycerides; TC, taurocholate; VLDL, very low density lipoproteins; WT, wild type; ZEA, zeaxanthin

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* Tel.: +1 614 292 8189; fax: +1 614 292 8880.
E-mail address: Harrison.304@osu.edu.

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either β-cryptoxanthin or α-carotene (each with only a single β-ionone ring) would give rise to a single mole of retinol. β-Carotene is the most potent vitamin A precursor of all provitamin A carotenoids. In order to exhibit a provitamin A activity, the carotenoid molecule must have at least one unsubstituted β-ionone ring and the correct number and position of methyl groups in the polyene chain [18]. In practice, α-C, β-cryptoxanthin, and γ-carotene show 30 to 50% of provitamin A activity [19,20] and 9-*cis* and 13-*cis* isomers of β-C less than 10% [21], compared to all-*trans* β-C.

Foods in the US diet with the highest concentrations of preformed vitamin A are avian and mammalian livers (4–20 mg retinol/100 g), instant powdered breakfast drinks (3–6 mg/100 g), ready-to-eat cereals (0.7–1.5 mg/100 g), and margarines (about 0.8 mg/100 g) [22]. Other than liver, the other sources derive their high retinyl ester contents from fortification. The highest concentrations of vitamin A as provitamin A carotenoids are found in carrots, sweet potatoes, pumpkin, kale, spinach, collards and squash (roughly 5–10 mg retinol activity equivalents per 100 g) [22]. A retinol activity equivalent (RAE) is equal to 1 μg retinol or 12 μg β-carotene, or 24 μg of α-carotene or β-cryptoxanthin [23]. In the United States the major contributors to the intake of preformed vitamin A are milk, margarine, eggs, beef liver, and ready-to-eat cereals, while the major sources of provitamin A carotenoids are carrots, cantaloupes, sweet potatoes and spinach. Analysis of NHANES data [24], for both genders and all age groups, showed that the mean intake of vitamin A in the US was about 600 μg RAE/day from food and that 70–75% of this was as preformed vitamin A (retinol). The provitamin A carotenoids β-C, α-C, and β-cryptoxanthin were ingested in amounts of approximately 1750, 350, and 150 μg/day, respectively.

It is clear from studies both in experimental animals and humans that the coingestion of dietary fat markedly enhances the intestinal absorption of dietary vitamin A and carotenoids [25,26]. The presence of dietary fat in the intestine can stimulate retinyl ester digestion and provitamin A conversion by [1] stimulating pancreatic enzyme secretion, [2] stimulating the secretion of bile salts, which serve to form mixed micelles of lipids, and [3] providing products of lipid digestion (i.e., lysophospholipids, monoglycerides, and free fatty acids), which themselves can serves as components of micelles. Finally, fat ingestion promotes vitamin A and carotenoid absorption by providing the lipid components for intestinal chylomicron assembly, a process discussed in more detail below.

3. Conversion of provitamin A carotenoids to retinoids

Two pathways have been described for the cleavage of β-C to retinoids (vitamin A): central and eccentric (Fig. 1). The major pathway is the central cleavage catalyzed by a cytosolic enzyme, β-C 15,15′-oxygenase 1 (BCO1), which cleaves β-C at its central double bond (15,15′) to yield retinal, a direct precursor of retinol and retinoic acid. Two mechanisms for the enzymatic central cleavage of β-C have been proposed. The first is a dioxygenase reaction that requires molecular oxygen and yields an unstable dioxetane intermediate that is rapidly converted into retinal [27]. More recently, a monooxygenase reaction mechanism that requires two oxygen atoms from two

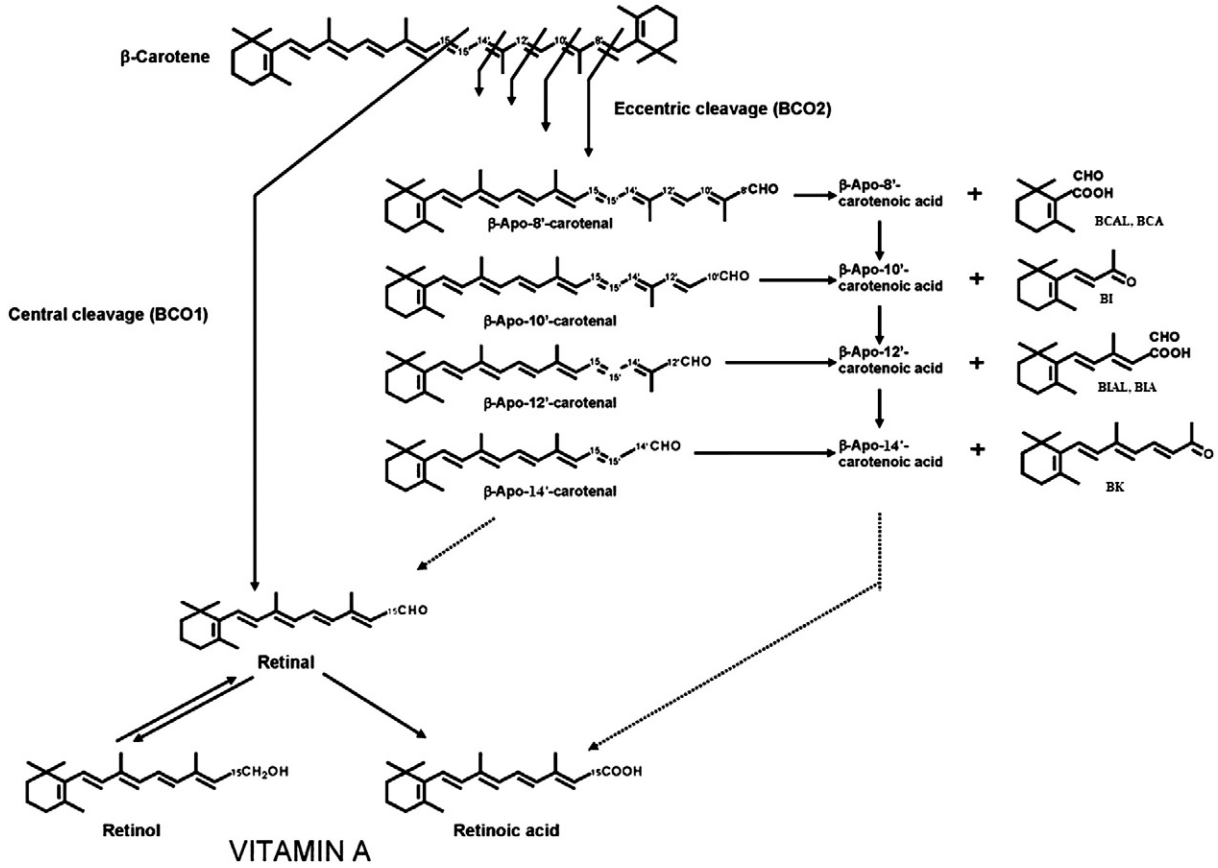

Fig. 1. Products of the central and eccentric cleavages of β-carotene. Oxidative cleavage of β-carotene at the 15,15′ double bond is catalyzed by the enzyme β-carotene 15,15′-oxygenase 1 (BCO1) and leads to the generation of two molecules of retinal. Cleavage at other double bonds leads to the formation of β-apocarotenals and β-apocarotenones. For example the cleavage at the 9′,10′ double bond is catalyzed by β-carotene 9′10′-oxygenase 2 (BCO2) and leads to the formation of β-apo-10′-carotenal and β-ionone (BI). Eccentric cleavage at other double bonds may occur nonenzymatically or may be enzyme catalyzed. Presumably the β-apocarotenals can be oxidized to the corresponding β-apocarotenoic acids by non-specific aldehyde dehydrogenases but this has not been clearly demonstrated. The mechanism of possible chain shortening of β-apocarotenals and β-apocarotenoic acids (dotted lines) is also not known.