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BIOAVAILABILITY AND BIOCONVERSION OF CAROTENOIDS

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ABSTRACT

Factors that influence the bioavailability of carotenoids and their bioconversion to retinol are species of carotenoids, molecular linkage, amount of carotenoids consumed in a meal, matrix in which the carotenoid is incorporated, effectors of absorption and bioconversion, nutrient status of the host, genetic factors, host-related factors, and mathematical interactions. In this paper, current knowledge of these factors is examined. Although data are not sufficiently comparable to allow an extensive systematic comparison of results, a number of conclusions can be drawn from the information available.

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INTRODUCTION

Carotenoids are important to humans and other animals as precursors of vitamin A and retinoids. In addition, they act as antioxidants, immunoenhancers, inhibitors of mutagenesis and transformation, inhibitors of premalignant lesions, screening pigments in primate fovea, and nonphotochemical fluorescence quenchers. Increased dietary intake of carotenoids is associated with decreased risk of (*a*) macular degeneration and cataracts, (*b*) some cancers, and (*c*) some cardiovascular events (58). Carotenoids also have a widespread function or use in coloration.

Naming

Most carotenoids can be described by the general formula $C_{40}H_{56}O_n$, where n is 0–6. Hydrocarbons ($n = 0$) are termed carotenes and oxygenated carotenoids are called xanthophylls. According to the International Union of Pure and Applied Chemistry (IUPAC) recommendation for semi-systematic names, the trivial names for carotenes, such as α- and β-carotene, should be replaced by β,ε- and β,β-carotene, respectively. However, the trivial names are well established and more convenient to use, so the trivial names rather than the IUPAC semi-systematic names are used in this paper.

Bioavailability

Bioavailability is the fraction of an ingested nutrient that is available for utilization in normal physiological functions or for storage (48). Published information on carotenoid bioavailability is based mainly on measurement of carotenoids in serum or plasma after ingestion. It should be noted that at steady state, plasma carotenoids amount to approximately 1% of the total body content of carotenoids, whereas the highest concentration can be found in the liver (92).

There are various methods for determining bioavailability of carotenoids: the balance method (59, 89, 94), measurement of recovery of radioactive β-carotene in lymph (10, 40), use of uniformly labeled β-carotene (27, 78), or comparison of the response in serum or lipoprotein fractions of carotenoids with standard doses of carotenoids. Most research has concentrated until now on determining serum or plasma concentrations of provitamin A carotenoids, especially β-carotene. Comparatively little is known about the occurrence, function, and bioavailability of non-provitamin A carotenoids. The concentration in serum may not be the best indicator of carotenoid status (34, 54) because these concentrations are a result of absorption and removal from serum for storage, bioconversion, or excretion. Furthermore, fasting serum carotenoid concentrations can be affected, sometimes quite rapidly, by a number of factors, such as smoking.

Bioconversion

Carotene bioconversion, strictly speaking, is the proportion of bioavailable carotene converted to retinol. Often, however, the term covers both the bioavailability and the bioconversion process. Provitamin A carotenoids are converted to retinol by the action of 15-15′-carotenoid dioxygenase. This process occurs primarily in the enterocytes, though enzyme activity is found in other tissues, such as the liver. There is still controversy about whether the cleavage is central or eccentric. Per molecule of β-carotene, central cleavage would result in the formation of two molecules of retinal that could be reduced to retinol and then esterified, whereas eccentric cleavage would produce one molecule of a β-apo-carotenal that could be converted not only to retinal but also to β-apo-carotenoic acids and subsequently to retinoic acid. Van Vliet and coworkers (109) suggested that the ratio of the response of retinyl esters to β-carotene may be a good indicator of intestinal β-carotene conversion. Of absorbed β-carotene, 60–70% was converted, mainly into retinyl esters, but several details with respect to the cleavage reaction remain to be elucidated (108).

There is no information about the conversion of carotenoids that escape bioconversion in intestinal enterocytes. In vivo carotenoid conversion always refers to bioavailability plus bioconversion of carotenoids. In the future, it would be worthwhile to obtain information about bioavailability, bioconversion, and the composite of both.

FACTORS AFFECTING CAROTENOID BIOAVAILABILITY AND BIOCONVERSION

De Pee & West (23) reviewed the evidence that carotene-rich fruits and vegetables can overcome vitamin A deficiency and concluded that the positive effects that get reported often come from studies with poor experimental designs. They

noted that a number of factors influence the bioavailability of carotenoids, which they grouped in the mnemonic SLAMENGHI (19, 23): Species of carotenoids, molecular Linkage, Amount of carotenoids consumed in a meal, Matrix in which the carotenoid is incorporated, Effectors of absorption and bioconversion, Nutrient status of the host, Genetic factors, Host-related factors, and mathematical Interactions. The purpose of this paper is to discuss current knowledge of the factors affecting bioavailability and bioconversion of carotenoids. Prediction of carotenoid bioavailability from different foods and under specified circumstances would be possible if each of these factors could be quantified and if observed additive effects can be split into their SLAMENGHI components. This review is restricted mainly to studies of humans but will refer to animal studies where relevant.

SPECIES OF CAROTENOIDS

Bioavailability

The naturally occurring configuration of carotenoids in plant foods is usually the all-*trans* isomer. In general, *cis* isomers are more polar, less prone to crystallization, and more soluble in oils and hydrocarbon solvents. The *cis* isomeric composition increases with food processing, particularly heating, and the quantity formed appears related to the severity and extent of the heat treatment. Rushin and coworkers (91) demonstrated that *cis* isomers (mainly 13-*cis*) had not formed after blood was drawn and that *cis* isomers of β-carotene were present at significant concentrations in the human circulation. The all-*trans* form is absorbed more readily in humans than the 9-*cis* form. When multiple doses of mixtures of the two were ingested, the proportion of the 9-*cis* form found in serum was less than one sixth of the amount found in the carotenoid mixture (8, 39, 50, 104). Also, after a single dose, the increase of all-*trans*-β-carotene in serum or in the chylomicron fraction of serum was much higher than for the 9-*cis* isomer (98, 99), which indicates a strong preferential absorption or transport of the all-*trans* isomer in comparison with the 9-*cis* isomer. After a single oral dose, more than 95% of plasma ^{13}C-labeled *trans*-β-carotene and labeled retinol was derived from labeled 9-*cis*-β-carotene. This indicates that a significant portion of the labeled 9-*cis*-β-carotene dose was isomerized to labeled *trans*-β-carotene before entering the blood stream (126). When lycopene uptake from processed and unprocessed tomato juice was studied in humans, the *cis* isomer was somewhat better absorbed than the all-*trans* form (100). This would be related to the better solubility of the *cis* form.

Larger amounts of β-carotene were incorporated into the micelles when the carotene mixtures contained 86% rather than 5% 9-*cis*-β-carotene, and an increase in the level of total carotene in the solution was accompanied by a constant or even enhanced carotene incorporation (62).

Table 1 SLAMENGHI factor S (Species): *cis-trans* isomers

Study	Details[a]	SLAMENGHI factor	
		Bioavailability[b]	Bioconversion[c]
Ben-Amotz & Levy (8)	2 × 15 M, 20–30 y; 40 mg β-carotene daily for 14 days from alga *Dunaliella bardawil* (42% all-*trans*, 43% 9-*cis*) or synthetic β-carotene (97% all-*trans*), or placebo	All-*trans*-β-carotene: 0.037, 0.522[d]; *cis*-β-carotene: 0.006, 0.016[d]	0.037, 1.60[d]
Gaziano et al (39)	7 M and 17 F; 100 mg β-carotene daily for 6 days from *Dunaliella salina* (50% all-*trans*) or synthetic all-*trans*-β-carotene	All-*trans*-β-carotene: 0.808, 1.523[d]; *cis*-β-carotene: 0.059, 0.095[d]	
Jensen et al (50)	6 M and 10 F, 18–60 y; 24 mg β-carotene daily for 7 days from *Dunaliella salina* (all-*trans*:9-*cis* = 40:60) or carrots (98% all-*trans*) or placebo	All-*trans*-β-carotene: 0.687, 0.492[e]; *cis*-β-carotene: 0.047, 0.017[e]	
Stahl et al (98)	3 M and 2 F, 23–37 y; single dose of 5.6 μmol β-carotene/kg body weight and 0.17 μmol α-carotene/kg body weight from *Dunaliella salina* (54% all-*trans*, 37% 9-*cis*, 9% other *cis* isomers, 1% α-carotene)	Serum increase of α-carotene was 5.6% of increase of all-*trans*-β-carotene, reflecting ration in Betatene; no 9-*cis* was found in serum	
Stahl & Sies (100)	5 M and 1 F, 22–36 y; single dose of 2.5 μmol lycopene per kg body weight as heated tomato juice (20–30% *cis* isomers)	*cis*-Lycopene better absorbed than all-*trans* form	
Tamai et al (104)	30 M, 20–25 y; 60 mg β-carotene daily for 44 weeks from *Dunaliella bardawil* (all-*trans*:9-*cis* = 50:50) or synthetic all-*trans*-β-carotene or placebo	All-*trans*-β-carotene: 0.559, 1.21[f]; *cis*-β-carotene: 0.084, 0.149[f]	No change
Tang et al (105)	7 M and 5 F, 23–68 y; single dose of 120 mg β-carotene	*trans*-β-carotene: 0.780; *cis*-β-carotene: 0.020	
You et al (126)	2 M and 1 F, 23–38 y; single dose of 1 mg 99.4% 9-*cis*-β-carotene	Labeling all-*trans*: >95% of plasma *trans*-β-carotene and retinol was derived from 9-*cis*-β-carotene	No 9-*cis*-retinol detected

[a]M, Male; F, female; y, years.
[b]Unless otherwise stated, increase in serum or plasma carotenoid concentration shown as micromoles per liter.
[c]Unless otherwise stated, increase in serum or plasma retinol concentration shown as micromoles per liter.
[d]Results from alga and synthetic β-carotene respectively.
[e]Results from alga and carrot, respectively.
[f]Results estimated from alga and synthetic β-carotene respectively.

In all studies on isomeric forms (see Table 1), the effect of algae supplements (containing similar amounts of 9-*cis*- and all-*trans*-β-carotene) was smaller than the response to similar concentrations of synthetic β-carotene (mainly all-*trans*). Based on studies with multiple doses, a daily intake of *cis*-β-carotene from algae or synthetic β-carotene would result in a 0.018- and 0.003-μmol β-carotene increase per mg, respectively, in serum. For all-*trans*-β-carotene, these values are 0.027 μmol for algae and 0.032 μmol for synthetic β-carotene.

Bioconversion

All carotenoids containing at least one unsubstituted β-ionone ring and a polyene side chain attached containing at least 11 carbon atoms are potential precursors of vitamin A, with β-carotene showing the highest vitamin A activity on a molar basis. Data on the relative bioconversion of various carotenoids to retinol is presented in Table 2. These data are based on the storage of retinol in the liver when its carotenoids are fed and therefore comprise not only bioconversion but also bioavailability. The FAO/WHO Joint Expert Consultation on vitamin A requirements has assumed that the vitamin A activity of other provitamin A carotenoids, including *cis* isomers of β-carotene, is 50% that of β-carotene (31). Studies using intestinal preparations have generally supported these data: α-carotene, 29% (110); β-cryptoxanthin, 55% (110); and *cis*-β-carotene, 7% (73). Intestinal perfusion studies with ferrets have shown that absorption, clearance, and metabolism of all-*trans*- and 9-*cis*-β-carotene

Table 2 SLAMENGHI factor S (Species): relative bioconversion of carotenoids[a]

Carotenoid	Relative bioconversion (% on a weight basis)
β-Carotene	100[b]
9-*cis*-β-Carotene	38[c]
13-*cis*-β-Carotene	53[c]
α-Carotene	50–54[b]; 29[d]
γ-Carotene	42–50[b]
β-Zeacarotene	20–40[b]
β-Cryptoxanthin	50–60[b]; 55[d]
3,4-Dehydro-β-carotene	75[b]
2,2′-Dimethyl-β-carotene	50[b]
β-Carotene-5′,6′-monoepoxide	21[b]
α-Carotene-5,6-monoepoxide	25[b]
4-Keto-β-carotene	44–50[b]
3-Keto-β-carotene	52[b]
4-Hydroxy-β-carotene	48[b]
β-apo-8′-Carotenal	72[b]
β-apo-12′-Carotenal	120[b]
Non-provitamin A carotenoids[e]	0[b]

[a]Unless otherwise stated, the carotenoids are in *trans* form.
[b]Bauernfeind (7).
[c]Zechmeister (127).
[d]Van Vliet et al (110).
[e]Non-provitamin A carotenoids such as lutein, lycopene, zeaxanthin, and canthaxanthin do not have at least one unsubstituted β-ionone ring and a polyene side-chain attached containing at least 11 carbon atoms.

produced similar amounts of retinoic acid, with 9-*cis*-β-carotene giving rise to equal amounts of all-*trans*- and 9-*cis*-retinoic acid (42).

MOLECULAR LINKAGE

There are few data on the effect of carotenoid esters, which are common in fruits and vegetables, on bioavailability. Herbst et al (44) found that lutein diesters showed a trend toward greater bioavailability than free lutein did, which suggests that the human gut is efficient in cleaving esters of lutein, and therefore, esterified lutein in food may be equally or better bioavailable than free lutein. No β-cryptoxanthin or esters from other carotenoids were detected in chylomicrons or serum after consumption of tangerine juice (120). Because esters are not absorbed by the enterocyte, we would not expect molecular linkage to have an effect on bioconversion.

AMOUNT OF CAROTENOIDS CONSUMED IN A MEAL

Bioavailability of β-Carotene

Serum β-carotene concentrations vary depending on the amount of β-carotene in a meal. Shiau et al (94) reported that with a meal, only 35–71% of β-carotene was recovered in rectal effluent as compared with 83% without a meal. The kinetics of serum response to orally ingested β-carotene seems independent of dose (17, 43), but other factors play a role because the responses observed in different studies vary considerably.

Many studies have measured serum or plasma response to supplementation with carotenoids, mainly β-carotene. Other studies have examined the effect supplementing a meal with a mixture of carotenoids has on such responses. Sometimes these studies have used large, pharmacologic doses of β-carotene, and often they have not been well controlled. The between-individuals response to repeated doses of β-carotene, which lead to plateau concentrations (21), appears to be generally less variable than the response to single doses. An overview of studies is given in a Table posted on the Annual Reviews' Web site (see Supplementary Materials section at http://www.AnnualReviews.org). Prince & Frisoli (82) found that administering β-carotene daily in three divided doses with meals increased the serum β-carotene concentration three times more than when the same total dose was administered once daily. The studies listed in the Table (Supplementary Material section at http://www.AnnualReviews.org) are not strictly comparable, often because the matrix in which the carotene was supplied is different (see below), and, for example, the β-carotene preparations used were different. Some supplements contained carotenoids in water-soluble beadlets whereas others contained crystalline carotenoids dissolved or

resuspended in oil. Calves receiving the beadlet sources had higher serum carotenoid levels than calves receiving carotenoids in oil. When fed water-soluble β-carotene beadlets, calves had peak β-carotene levels 28 times higher than when fed crystalline β-carotene (9).

Data from single-dose studies indicate that in normal subjects the efficiency of carotenoid absorption varies widely. Serum β-carotene concentrations rise quickly after a single oral dose and usually peak at 5 h and remain elevated for more than 24 h. Omission of a meal delays the time to peak concentrations. A delayed and less-efficient absorption was reported with higher doses (76). Some subjects do not show a plasma response after supplementation (38, 52). After a meal, there may be large intra-individual variability in triglyceride response. Thus, it may be advisable to adjust carotenoid values in serum for triglyceride response after a single dose of β-carotene (109). Most studies on carotenoid bioavailability do not report triglyceride responses.

To study the linear and dose-response relationship between β-carotene supplementation and increases in serum β-carotene concentrations, a meta-analysis was carried out that included all studies with daily β-carotene supplements of $<$50 mg that lasted $<$1 year. The analysis included 31 studies, and the heterogeneity between the study results was apparent. The 95% between-study interval in serum response per mg of supplemented β-carotene ranged from 0.0317 to 0.0388 μmol/liter. The duration of β-carotene supplementation was a significant predictor of β-carotene response.

Bioavailability of Other Carotenoids

Carotenoids may interact with each other during intestinal absorption, metabolism, and serum clearance. Data suggest that the concentration of α-carotene in plasma (18) and chylomicrons (37) and the concentration of lycopene in plasma (18) reflect the content of these carotenoids in the meal or supplement.

Some studies showed no effect of β-carotene on serum levels of α-carotene, cryptoxanthin, lycopene, and lutein (34, 43), whereas others found significantly different carotenoid concentrations after supplementation with β-carotene. The plasma lutein concentration was significantly reduced after multiple (70) and single doses (56) of β-carotene. In the presence of high amounts of β-carotene, the uptake from the intestinal lumen into chylomicrons of lutein and zeaxanthin as compared with all-*trans*-β-carotene was preferred (37). β-Carotene supplementation reduced the lycopene concentrations in low-density lipoproteins (39) and serum significantly (82). In contrast, Wahlqvist et al (114) found an increase in lycopene concentration after β-carotene supplementation, but only in men. α-Carotene concentrations were increased after β-carotene supplementation (24, 70, 114). The ingestion of concurrent doses of β-carotene and canthaxanthin reduced the peak serum canthaxanthin concentration, but canthaxanthin did not inhibit the appearance of β-carotene in serum (118).

In summary, β-carotene supplementation increases concentrations of α-carotene in a dose-dependent but nonlinear way and would appear to decrease serum concentrations of lutein, lycopene, and canthaxanthin. Related to dietary intake in milligrams per day, the increases in serum carotenoid concentration for other carotenoids are 0.06–0.15 μmol of lutein/liter, 0-0.09 μmol of lycopene/liter, and 0.11–0.27 μmol of α-carotene/liter.

Bioconversion

In 1967, the FAO/WHO (30) concluded that when consumed in a mixed meal, 6 μg of β-carotene—or 12 μg of other provitamin A carotenoids—is absorbed and converted to 1 μg of retinol. However, the FAO/WHO Joint Expert Consultation recognized in 1988 that retinol equivalence is related to dose level. When the β-carotene intake per meal is $<$1000 or $>$4000 μg, the amount of β-carotene equivalent to 1 μg of retinol was considered to be 4 and 10 μg, respectively (31).

In rats, low intake of vitamin A increases cleavage activity as measured in vitro (111, 112), and a high intake of β-carotene increases cleavage activity in the liver of rats (111). Based on the difference in liver vitamin A contents between β-carotene–supplemented and unsupplemented rats, β-carotene conversion factors were estimated at 9:1 for rats fed high amounts of vitamin A and 4:1 for rats fed normal and low amounts of vitamin A (111). Intestinal β-carotene cleavage activity was higher in vitamin A–deficient rats than in rats with a high intake of vitamin A or β-carotene. The addition of lutein to an incubation of β-carotene reduced retinal formation, whereas lycopene had no effect (110).

MATRIX IN WHICH THE CAROTENOID IS INCORPORATED

Bioavailability

β-Carotene dissolved in oil is absorbed far more readily than β-carotene from foods. It is possible to calculate relative bioavailability by comparing the effect a food has on serum β-carotene values with the effect pure β-carotene has. It should be noted that "pure" β-carotene can be water-soluble β-carotene beadlets or β-carotene in a suspension with oil. Bioavailability of β-carotene from these preparations may be different. Compared with the serum response from β-carotene supplements, the bioavailability of β-carotene from various foods is as follows: stir-fried vegetables, 7% (24); carrots, 18–26% (14, 70, 107); and spinach, 7% (JJM Castenmiller, CE West, et al, unpublished information). A subsequent study in Indonesia (25) found the serum response of β-carotene from fruits to be four times that from vegetables. The low bioavailability of carotenoids from dark-green leafy vegetables may be attributed to

their entrapment and complexing to proteins in chloroplasts and within cell structures. Such entrapment may not only be physical (matrix effect) but also molecular (effector effect, see below). The α- and β-carotene in carrots exist as crystals up to 1000 μm in length. Although soluble in the intestinal contents, the transit time is probably insufficient for extensive solubilization to take place during this passage through the intestinal tract. Similarly, lycopene also exists in tomatoes in the crystalline form. In orange and yellow fruits (mango, papaya, etc) and in pumpkin and sweet potato, carotenoids are dissolved in oil droplets in chromoplasts and can be readily extracted during digestion. Cooking increases the bioavailability of carotenoids, possibly because of the softening or disruption of plant cell walls and the disruption of carotenoid-protein complexes (29). Stahl & Sies (100) reported that lycopene concentrations in human serum increased from processed but not unprocessed tomato juice. Bioavailability of lycopene was greater from tomato paste than from fresh tomatoes (38).

Bioconversion

The FAO/WHO Joint Expert Consultation (31) concluded that 6 μg of β-carotene from a mixed meal provided 1 μg of retinol. For β-carotene dissolved in oil, the International Union of Pure and Applied Chemistry concluded from two studies (45, 113) that 3.33 μg provided 1 μg of retinol (47). The effect of the matrix, however, is almost certainly limited to phenomena that take place in the lumen of the small intestine. Thus, reported effects of the matrix on the overall yield of retinol from carotenoids can be attributed to matrix effects on bioavailability. The earlier studies on the yield of retinol from carotenoids have been reviewed by De Pee & West (23). From a carefully carried out study of schoolchildren in Indonesia, it has been calculated that 1 μg of retinol was provided by 26 μg (95% confidence interval, 13–76) of β-carotene from dark-green leafy vegetables and carrots and by 12 μg (95% confidence interval, 6–29) from yellow and orange fruits. Almost identical data have been found in a study of lactating women in Vietnam (NG Khan, CE West, S De Pee, D Bosch, HH Khôi, JGAJ Hautvast, unpublished data).

EFFECTORS OF ABSORPTION AND BIOCONVERSION

Absorption of carotenoids is similar to that of other lipids. A variety of nutrients consumed together with carotenoids may affect carotenoid absorption, metabolism, and/or bioconversion. The presence of protein in the small intestine helps stabilize fat emulsions and enhances micelle formation and carotenoid uptake. Lecithin may enhance triglyceride absorption through facilitating micelle formation, and long-chain fatty acids increase cholesterol absorption and, thus, the

absorption of fat-soluble vitamins. A decrease in carotenoid bioavailability may be caused by interaction in the gastrointestinal tract with drugs or constituents of foods, such as sulfides and acids (80, 116). Gastric pH also plays a role: a single 120-mg dose of β-carotene increased plasma concentrations of β-carotene at normal gastric pH to a level twice as high as that at a gastric pH of 6.4 (105).

Intake of Dietary Fat

The absorption and bioconversion of β-carotene is markedly reduced when the intake of fat is low (51, 82). Addition of a small quantity of fat to the diet greatly improves the absorption of vegetable carotenoids (89), with optimal absorption requiring an intake of at least 5 g of fat per day (49). We conclude that a minimum amount of fat is necessary for uptake of carotenoids. There is no dose-response relationship above the threshold value, but there is some increase in serum β-carotene response to a high-fat diet (26, 76, 94). Some data suggest that polyunsaturated fatty acid–rich dietary fat increases the serum response to β-carotene more than does mono-unsaturated fatty acid–rich dietary fat (55). The serum response to dietary β-carotene is related to the serum response to dietary triglyceride (43). The solubility of β-carotene (apolar) and zeaxanthin (polar) decreases with increased chain length in triglyceride fatty acids (11), which may explain why, after a single 120-mg dose of β-carotene, the β-carotene response in chylomicrons was lower after ingestion of a meal comprised of triglycerides from C_8 and C_{10} rather than C_{16} and C_{18} fatty acids. Also, the concentration of retinyl palmitate in chylomicrons was lower, although the conversion to retinol was not significantly different between the two meals (12). Sucrose polyester, a nonabsorbable fat analogue, reduces plasma carotenoid concentrations markedly (117).

Intake of Dietary Fiber

In a study to examine the effect of dietary fiber on serum carotene values in humans, the plasma β-carotene was reduced by 42% when pectin was given (88). Results from studies with chickens suggest that the extent of methyl esterification of the pectin is important in determining the extent of inhibition of absorption (28). One of the effects of dietary fiber on lipid metabolism centers on its interaction with bile acids, resulting in increased fecal excretion of bile acids and, thus, decreased absorption of fats and fat-soluble substances, such as carotenoids and cholesterol.

Intake of Alcohol

Several investigators (4, 60, 101) have reported that drinkers, compared with subjects with low or no alcohol intake, had lower β-carotene levels, whereas plasma retinol levels were similar (60) or higher (4, 95). The response was not

related to the level of alcohol consumption (4). Conversely, after withdrawal, plasma carotenoid levels increased, whereas retinol concentration diminished (60). In a 6-month controlled dietary study involving women who were nonsmokers, plasma α- and β-carotene concentrations were significantly higher, 19% and 13%, respectively, and the lutein/zeaxanthin concentration was significantly lower during the alcohol-intake phase of the study (32). The combination of an increase in plasma and liver β-carotene after ingesting ethanol and a relative lack of a corresponding rise in retinol suggests that alcohol interferes with the conversion of β-carotene to vitamin A (61). When ethanol was used in intestinal rat and hamster preparations as a solvent for β-carotene, retinal formation was reduced to 55% (110).

Intake of Other Food Constituents

Supplementation with vitamin E plus ascorbic acid did not alter serum β-carotene levels (77).

NUTRIENT STATUS OF THE HOST

Bioavailability

The absorption of carotenoids is likely to be dependent on vitamin A status. Mattson & Deuel (66) showed that high vitamin A intake reduces carotenoid pigmentation in chickens, an effect confirmed by others (106). Supplementation with vitamin A decreases the absorption not only of β-carotene but of canthaxanthin as well (96). It has been common practice to feed chickens high levels of vitamin A to produce pale poultry meat. It could be argued, though it is unlikely, that part of this effect is due not to an increased vitamin A status but to the concurrent ingestion of retinol with other carotenoids.

Bioconversion

Feeding β-carotene–rich foods to humans leads to an increase in serum retinol levels only when these are initially low (20, 59). Treatment with β-carotene does not significantly modify the vitamin A levels in vitamin A–replete subjects. It is assumed that a plasma level of β-carotene equal to or higher than 1.1 μmol/liter reflects a nutritional intake of provitamins sufficient to support homeostasis of retinol. Novotny et al (78) estimated from a study of one vitamin A–replete person that 22% of a single 40-mg dose of β-carotene was absorbed and that 18.5 μg of dietary β-carotene is equivalent to 1 μg of retinol.

Since ingestion of β-carotene does not lead to vitamin A toxicity, it is tempting to suggest that not only current β-carotene intake but also circulating β-carotene levels (carotene status) inhibits carotenoid bioconversion. At lower

levels of β-carotene intake, retinol levels in serum and liver are increased by ingestion of β-carotene, whereas ingestion of canthaxanthin reduces retinol levels in serum and liver (96). This could be interpreted as inhibition of bioconversion but could be readily explained by the lack of provitamin A precursor. No studies on the effect of vitamin A status on dioxygenase activity have been carried out with humans, though studies of rats (111, 112) have shown that diets low in vitamin A do increase dioxygenase activity (15). Retinol deficiency can arise despite a plentiful supply of retinol or carotene. Low-protein diets reduce dioxygenase activity in rats (41) or limit the production of retinol-binding protein. Zinc also affects the synthesis of retinol-binding protein and may also influence the conversion of β-carotene to vitamin A through retinal reductase, which is zinc dependent. Zinc-deficient rats had serum retinol levels not significantly different from controls. However, their retinol liver reserves were much lower. The results suggest that zinc deficiency impairs the efficiency of β-carotene utilization in the rat (103).

GENETIC FACTORS

Data from the Cardia study (97) showed that, in the United States, Caucasian men and women take supplements containing vitamins A and β-carotene twice as frequently as do African American men and women. They also have lower mean plasma lutein concentrations and higher mean plasma retinol concentrations than their African American counterparts have. When adjusted for influencing factors, the plasma β-carotene concentration was also higher in African Americans than in white hemodialysis patients in the United States (87). In Nigerian women (2), β-carotene levels were 1.2–13 times higher than was found in the US population. However, many of these effects could be attributed to diet. Failure to split β-carotene in humans is rare but can lead (*a*) to metabolic carotenemia with normal or even low intakes of carotenoids (71) or (*b*) to vitamin A deficiency if retinol intake is low (68).

HOST-RELATED FACTORS

Host-related factors may explain many of the differences observed in the serum response to ingestions of dietary carotenoids. One of the best predictors of the response to an oral dose of β-carotene is the initial serum β-carotene concentration (3, 76). Such initial serum carotenoid levels could be attributed to factors already discussed, such as long-term intake (status) and genetic factors. In addition, postabsorption metabolism and not bioavailability may be responsible for the differences observed. This could explain many of the effects of body

weight (76), use of alcohol, and smoking. Thus, in the discussion below, studies that indicate differences in bioavailability and not just serum concentrations of carotenoids are highlighted.

Effect of Sex and Age

The serum response to β-carotene is higher in women than in men (76); however, part of this effect could be attributed to differences in body weight and body composition. There is no evidence for a reduced serum response with ageing, which could be explained by the passive nature of the absorption process. In one study, the serum response was higher in older people (63), whereas in other studies the opposite was found (102, 124).

Effect of Illness and Protein-Energy Malnutrition

Absorption of fat-soluble substances including carotenoids is impaired in any disease in which there is fat maldigestion and malabsorption. Fat maldigestion arises when there is impaired production of lipase and bile acids and impaired neutralization of chyme in the duodenum (22, 59).

MATHEMATICAL INTERACTIONS

Mathematical interactions refers to the difference in effect observed when two factors play a role together compared with the product of the effects observed separately. However, data are not yet available to allow any estimate of mathematical interactions.

CONCLUSIONS

Carotenoid bioavailability and bioconversion are influenced by a number of factors, the SLAMENGHI factors. Each carotenoid seems to show an individual pattern of absorption, plasma transport, and metabolism. We investigated the state of knowledge with regard to SLAMANGHI factors.

We conclude that, at this stage, data are not sufficiently comparable to allow systematic comparison of results and often the effects studied with regard to bioavailability cannot be attributed to individual factors. However, a number of conclusions can be drawn.

The bioavailability and provitamin A activity of the various carotenoids and geometrical isomers of carotenoids differ. The absorption of all-*trans*-β-carotene is higher than that of 9-*cis*-β-carotene. Also, the bioconversion of β-carotene is higher for the all-*trans* isomer than for the *cis* isomers. The vitamin A activity of other provitamin A carotenoids is lower than that of β-carotene. Carotenoid esters in foods are readily split in the gut, and thus, molecular linkage does not play a role in carotenoid bioavailability and bioconversion. A positive

relationship between intake and response of β-carotene suggests that absorption is a nonsaturable passive process. β-Carotene supplementation was shown in a number of studies to increase serum concentrations of α-carotene and decrease serum concentrations of lutein, lycopene, and canthaxanthin. Recent studies of rats (111) confirm the dose-related factors for the conversion of β-carotene from a mixed meal, as suggested by FAO/WHO (31). In vitro studies would suggest that lutein interferes with the conversion of β-carotene to retinol (110), and this may explain, in part, the low conversion to retinol of β-carotene from dark-green leafy vegetables (24). Relatively few properly designed studies have been carried out to examine the effect of food matrix on carotenoid bioavailability (23). From these studies it can be concluded that bioavailability of β-carotene from foods is low, particularly from dark-green leafy vegetables (7%). Due to the low bioavailability, it has been calculated that 1 μg of retinol is provided by 26 μg of β-carotene from dark-green leafy vegetables and carrots and by 12 μg from yellow and orange fruits (25). Intake of dietary fat has a positive effect on β-carotene bioavailability and dietary fiber has a negative effect, and alcohol intake seems to interfere with the bioconversion of β-carotene to retinol. Nutrient status and genetic factors related to the host may explain some of the differences observed. Effects of season, sex, age, and smoking are largely explained by differences in long- and short-term intakes of carotenoids. Few controlled supplementation studies have been carried out to study the effect of these variables on carotenoid response in serum.

There is a need for more carefully designed studies to define the role of individual SLAMENGHI factors. The improvement in high-performance liquid chromatography methods for the quantification of carotenoids and the current development of isotopic methods should lead to the generation of much data in the coming years.

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