Bioavailability of Carotenoids from Vegetables

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The term "bioavailability" originated from pharmacology and has been historically used to describe the movement of compounds across the intestine into the circulatory system. Carotenoids have been purported to be associated with an array of biological functions, all requiring intestinal uptake. These functional roles include antioxidant activity, modulation of detoxifying enzymes, enhancing the immune system, upregulating cell-to-cell communication, inducing cellular apoptosis, and regulating gene expression. Given the potential health benefits provided by carotenoids, identification of factors that modulate the bioavailability of these compounds has been of keen scientific interest. Determinants of carotenoid concentrations in circulation encompass controllable factors (e.g., diet and smoking status), at least one factor (fat-free body mass) that is under limited control (Zhu et al., 1997), and uncontrollable factors (e.g., age, gender, hormonal status, and the innate ability to absorb carotenoids). This paper discusses the major dietary factors that have been identified as having influence on the bioavailability of carotenoids in healthy humans.

COOKING AND FOOD PROCESSING

There is a perception that carotenoids are destroyed by the heat process involved in cooking of vegetables. In fact, carotenoid loss is minimal with moderate cooking, and in many cases, carotenoids become more bioavailable after cooking, probably because heat processing liberates them from cell matrices.

Only modest changes in the concentrations of the major carotenoids were found in broccoli (*Brassica oleracea* L. Botrytis Group), green (snap) beans (*Phaseolus vulgaris* L.), and spinach (*Spinacia oleracea* L.) that had been steamed (3–5 min), microwaved (1.5–5 min), or boiled (9 min) (Khachik et al., 1992). These cooking techniques had no effect on β-carotene and lutein (*cis* and *trans*) concentrations. Some differences were found for minor carotenoids, particularly the epoxycarotenoids, which do not appear to be absorbed by humans. Loss of violaxanthin, for example, ranged from 34% to 65%, and loss of lutein 5,6-epoxide ranged from 34% to 100% with the various cooking procedures. Cooking (stewing for 8 min) did not alter the concentration of lycopene, phytofluene, or phytoene in tomatoes (*Lycopersicon esculentum* Mill.).

The widely held belief that fresh produce is nutritionally superior to commercially processed produce is not valid with regard to carotenoids—the bioavailability of carotenoids is enhanced as a result of commercial food processing. For example, plasma β-carotene concentrations of subjects were 3× higher after they consumed thermally processed (canned) carrots (*Daucus carota* L.) and spinach rather than the fresh (raw) counterparts (Rock et al., 1998). The processed vegetables were pureed and heat-treated using conventional canning techniques. Each treatment provided 9.3 mg of β-carotene per day for 4 weeks. Similarly, lycopene concentrations in plasma chylomicrons, the lipoproteins that transport newly absorbed carotenoids, were 2.0- to 2.5-fold higher at peak concentrations when subjects consumed tomato paste, a heat-treated product, rather than fresh tomatoes (Gärtner et al., 1997). The two treatments were given as a single dose along with 15 g of corn (*Zea mays* L.) oil and 100 g of bread; each provided 23 mg of lycopene. Thus, under conditions of similar intakes of tomato-derived lycopene and fat, lycopene from the heat-processed product was more bioavailable.

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CIS AND *TRANS* ISOMERS OF β-CAROTENE AND LYCOPENE

Both β-carotene and lycopene occur dominantly (typically >90%) in the *trans* form in raw vegetables. Heat treatment of vegetables promotes conversion of the *trans* isomer of β-carotene to *cis* forms. For example, higher percentages of *cis* β-carotene are reported for commercially canned fruits and vegetables (20% to 54%) than for their fresh counterparts (0% to 28%) (Chandler and Schwartz, 1987).

The relative bioavailability of the two geometric isomers has been a focus of long-standing and recent investigations. β-Carotene in human plasma and tissues is dominantly in the *trans* form; *cis*-isomers represent ≈5% or less of total β- carotene in plasma (Stahl et al., 1992). However, tissues contain substantially higher proportions of *cis* β-carotene (9-*cis*, 13-*cis*, and 15-*cis* isomers) than does plasma; ≈20% to 40% of total β-carotene in tissues is in the *cis* form.

An effort to elevate 9-*cis* β-carotene in plasma by ingesting a rich source of the isomer (an extract of the alga *Dunaliella salina* (Dunal) Teodoresco was largely unsuccessful; the 9-*cis* isomer accounted for only a small fraction of the total β-carotene (Gaziano et al., 1995). Thus, there is biological discrimination against 9-*cis* β-carotene that may be due to reduced absorption of *cis* β-carotene or to rapid clearance from plasma. Recent evidence, however, strongly suggests that, 9-*cis* β-carotene is isomerized to the *trans* isomer before entering the circulating blood (You et al., 1996). As a point of practical application, the thermal processing of spinach and carrot did not negate the enhanced bioavailability of β-carotene, relative to raw vegetables, even though 24% of the β-carotene from the processed vegetables was in the *cis* form (Rock et al., 1998).

In contrast with foods, which contain predominantly *trans* lycopene, substantial proportions (>50%) of the lycopene in plasma and tissues are present as *cis*-isomers (Stahl and Sies, 1993). Stahl and Sies (1992) suggested that *cis* isomers of lycopene (9-*cis*, 13-*cis*) may be more efficiently absorbed than the all-*trans* isomer. However, in vivo conversion is probably largely responsible for the increase in *cis* isomers that is seen in plasma and in tissues. Gärtner et al. (1997) found that chylomicrons contained mainly the all-*trans* form of lycopene, whereas plasma contained mainly *cis* lycopene. Additionally, some tissues contain proportionately more *cis* lycopene that does plasma (Clinton et al., 1996). These observations are consistent with the concept that dietary *trans* lycopene moves across the intestine, then is isomerized in vivo to yield *cis* lycopene. Additionally, lycopene differs from β-carotene, which tends to undergo heat-induced isomerization; treatments that are typical of industrial food processing produce only minimal isomerization of lycopene (Nguyen and Schwartz, 1998).

DIETARY FAT

Dietary fat is clearly required for optimal absorption of carotenoids. Populations with relatively high intakes of carotenoids can have low plasma levels if diets are habitually low in fat. In a controlled study, subjects who consumed 45 mg of β-carotene as a supplement were assessed for plasma β-carotene after consuming food differing in amount of dietary fat (Dimitrov et al., 1988). The high-fat treatment provided ≈18–24 g of fat at breakfast (immediately following the supplement) and at least 45 g of fat at lunch. The low-fat treatment provided a fat-free breakfast and 6 g of fat at lunch. Subjects ate self-selected diets at dinner. The group consuming the high-fat diet had plasma concentrations of β-carotene that were several-fold higher than those ingesting the low-fat diet. Similarly, fasting subjects had only small increases in β-carotene when given an aqueous dispersion of β-carotene, whereas subjects receiving meals had much higher levels,

especially when the foods contained lipid (40–80 g fat) (Cornwell et al., 1962). Note that in both studies, the impact of fat was tested at extreme levels.

The optimal level of dietary fat for carotenoid absorption is not known. Rock et al. (1997) did not find "percentage of energy from fat" to be an independent predictor of plasma carotenoids in women reducing their fat intake to a goal of 15% to 20% of energy. They proposed that a threshold effect exists for dietary fat, and suggested that the fat-rich, typical American diet would surpass the threshold.

Factors that interfere with lipid micelle formation or availability can reduce the bioavailability of carotenoids. These include: 1) dietary factors, such as fiber or sucrose polyesters such as Olestra™ (Weststrate and van het Hof, 1995); 2) digestive disorders, such as reduced bile formation due to gall bladder disorders; and 3) certain medications, such as the bile acid sequestering agent cholestyramine (Elinder et al., 1995). Similarly, factors that substantially reduce circulatory concentrations of lipoproteins, the plasma transport vehicles for the carotenoids (Clevidence and Bieri, 1993; Paetau et al., 1998), can also reduce circulating levels of these compounds (Elinder et al., 1995).

DIETARY FIBER

Dietary fiber can reduce the bioavailability of carotenoids, as demonstrated with subjects who ate small meals that were either low in fiber or contained 12 g of citrus pectin (Rock and Swendseid, 1992). Immediately following the meal, the subjects ingested 25 mg of β-carotene as a supplement. Thirty hours after the treatment, the subjects' plasma β-carotene concentrations increased 141% and 60%, respectively, for the low- and high-fiber treatments.

ALCOHOL CONSUMPTION

Subjects with alcoholic liver disease have low concentrations of plasma β-carotene. Yet, among heavy drinkers who have normal liver enzyme levels, β-carotene concentrations are positively correlated with amount of alcohol consumed (Ahmed et al., 1994). Similarly, baboons who received 50% of energy as alcohol had higher levels of β-carotene in response to eating a carrot daily than did controls who received no alcohol (Leo et al., 1992). These observations seem counterintuitive because alcohol is a prooxidant. However, the explanation appears to be that alcohol inhibits the conversion of β-carotene to vitamin A, as evidenced by delayed clearance of β-carotene and relatively low concentrations of plasma vitamin A even though β-carotene concentrations in plasma and liver were elevated. Information is scarce concerning the impact of alcohol at moderate intake levels on circulating carotenoid concentrations. However, data from a recent intervention study (Rock et al., 1997) suggest that the positive association of plasma carotenoid concentrations with alcohol consumption is not limited to those who are heavy consumers of alcohol. And, in a controlled diet study of women who consumed alcohol (equivalent of two drinks per day for 3 months), concentrations of circulating α- and β-carotene increased by 19% and 13%, respectively; in contrast, concentrations of lutein/zeaxanthin were lowered by 17% (Forman et al., 1995).

INTERACTIONS AMONG CAROTENOIDS

It is generally assumed that large supplemental doses of a single carotenoid will affect the bioavailability of other carotenoids. One carotenoid may enhance the absorption of another, compete with another for absorption, spare another, or otherwise alter the rate of metabolism of other carotenoids. For example, absorption (plasma response) of canthaxanthin (Paetau et al., 1997) and lutein (Kostic et al., 1995; Micozzi et al., 1992) seems to be inhibited by concurrent ingestion of β-carotene. The impact of lutein on β-carotene is less clear; lutein reduced the plasma response of β-carotene for some subjects, but increased it for others (Kostic et al., 1995). In another study, lutein, but not lycopene, inhibited β-carotene absorption when administered with an equivalent amount (15 mg) of β-carotene (van den Berg and van Vliet, 1998). Higher plasma α-carotene concentrations were observed in subjects receiving β-carotene supplements (30 mg daily for 6 weeks) (Micozzi et al., 1992). Combined ingestion of β-carotene and lycopene resulted in greater lycopene absorption, as indicated by plasma response, than did a single dose of lycopene (Johnson et al., 1997). These data indicate that β-carotene, a hydrocarbon carotene, may inhibit the absorption of oxycarotenoids, such as lutein and canthaxanthin, but enhances absorption of hydrocarbon carotenes, such as α-carotene and lycopene.

BIOAVAILABILITY OF CAROTENOIDS FROM REALISTIC AMOUNTS OF WHOLE FOODS

Americans consume, on average, ≈6 mg of carotenoids daily (Chug-Ahuja et al., 1993), with the amounts of the major carotenoids lutein, β-carotene, and lycopene ≈1.3, 1.8, and 2.6 mg·d^{-1}, respectively. Significant elevations in plasma carotenoid concentrations were observed in subjects who consumed foods providing 20 mg each of lutein, lycopene, and β-carotene from five servings of carotenoid-rich vegetables {kale (*Brassica oleracea* L. Acephala Group), tomato juice, and sweet potato [*Ipomea batatas* (L.) Lam.]} (Clevidence et al., 1997). After 3 weeks of consuming these vegetables, plasma concentrations of lutein, lycopene, and β-carotene increased 67%, 26%, and 116%, respectively. Additionally, levels of the major carotenoids increased markedly in a tissue (colon cells). Thus, realistic amounts of carotenoid-rich vegetables can increase plasma and tissue carotenoid concentrations in healthy humans.

The bioavailability of carotenoids from various plant sources is thought to differ (although the degree is uncertain) because of differences in plant matrices and content of inhibitors of carotenoid absorption. For example, de Pee et al. (1998), who studied anemic school children, observed that among β-carotene-rich foods, orange-pigmented fruit was superior to dark-green, leafy vegetables in increasing circulating concentrations of β-carotene. Ripe fruits, in general, have chromoplasts that store carotenoids, and carotenoids would be expected to be more easily liberated from chromoplasts than from chloroplasts of dark-green, leafy vegetables. Of course, many of the foods that consumers think of as vegetables [e.g., tomatoes, peppers (*Capsicum annuum* L.)] are, botanically, fruits.

BIOAVAILABILITY OF CAROTENOIDS FROM FOODS AS COMPARED WITH SUPPLEMENTS

β-Carotene is more bioavailable from supplements (typically supplied as absorption-enhancing beadlets or in oil) than from whole foods. For example, after 42 d of treatment, plasma β-carotene concentrations of subjects consuming 29 mg of β-carotene in the form of cooked carrot (272 g) were only 18% that of subjects consuming 30 mg of β-carotene as a supplement (Micozzi et al., 1992). Note, however, that while no harmful effects of carotenoids from whole foods have been found, β-carotene from supplements has been associated with lung cancer in smokers (Albanes et al., 1996) and asbestos workers (Omenn et al., 1996). There is no clear explanation for this link between β-carotene supplementation and cancer incidence in smokers and asbestos workers. Note, however, that baseline concentrations of plasma β-carotene were inversely correlated with subse-

Table 1. Lycopene, β-carotene, phytofluene, and phytoene provided by three lycopene treatments administered to humans in a study designed to compare the bioavailability of carotenoids from tomato juice and supplements.[z]

Treatment	Lycopene	β-Carotene	Phytofluene	Phytoene
	mg			
Tomato juice	74.9	2.09	5.11	5.76
Supplements				
Oleoresin	75.4	2.01	4.91	4.40
Beadlets	70.2	1.61	3.67	2.46

[z]The oleoresin, an oil extract of tomato, was administered in a soft gel capsule. The beadlets, a water-dispersible formulation of the oleoresin, were administered in capsules. The supplements and the tomato juice were supplied by LycoRed Natural Products Industries Ltd. (Beer-Sheva, Israel) and H. Reisman Corporation (Orange, N.J.). See text, above, under "Bioavailability of Carotenoids from Foods as Compared with Supplements" for brief description of the study. Adapted from Pateau et al. (1998).

Table 2. Baseline-adjusted areas under the plasma concentration vs. time curves (Area Under The Curve) from 0 to 672 h for 15 subjects (±SEM).[z]

Carotenoid	Tomato juice	Oleoresin supplement	Beadlets supplement	Placebo
	---------- μmol·h·L^{-1} ± SEM ----------			
Lycopene	95.3 ± 30.3 a[y]	145.3 ± 32.3 a	174.1 ± 31.9 a	–95.1 ± 25.2 b
β-Carotene	70.1 ± 8.8 a	16.1 ± 12.8 b	72.1 ± 17.4 a	8.1 ± 6.5 b
Phytofluene	255.0 ± 36.9 a	54.1 ± 11.7 b	101.9 ± 17.6 c	–45.7 ± 9.0 d
Phytoene	109.4 ± 16.2 a	38.5 ± 6.8 b	55.8 ± 9.5 c	–14.3 ± 4.1 d

[z]Lycopene-containing treatments are described in footnote 1 to Table 1. The water-dispersible beadlets without the oleoresin component served as the placebo. See text under "Bioavailability of Carotenoids from Foods as Compared with Supplements" for brief description of the study. Adapted from Pateau et al. (1998).
[y]Mean separation within rows by paired *t* test, $P \leq 0.05$.

quent incidence of lung cancer. This suggests either that β-carotene that was derived, presumably, from foods is protective or that β-carotene is a marker for some unidentified protective dietary or lifestyle factor.

Plasma responses to lycopene and other tomato carotenoids were assessed in subjects consuming high levels (70–75 mg·d^{-1} for 4 weeks) of lycopene from a food (tomato juice) or supplements (a beadlet formulation and an oleoresin) (Paetau et al., 1998). After 4 weeks of daily supplementation (at meals containing fat), plasma concentrations of lycopene were increased relative to baseline and to a placebo treatment, but lycopene levels did not differ among the lycopene treatments. Plasma levels of lycopene were, however, more quickly elevated with the supplements than with the food; mean areas under the curve were almost twice as high for the beadlet supplement as for the tomato juice treatment, although the difference was not statistically significant (Tables 1 and 2). The carotenoids phytoene and phytofluene were markedly more bioavailable than expected based on the low concentrations of these compounds in tomato.

SUMMARY AND COMMENT

Normal cooking and food processing procedures can enhance the bioavailability of carotenoids relative to raw vegetables. These treatments disrupt cell walls and may cleave carotenoids from proteins, facilitating the liberation and thus the absorption of carotenoids. Heat processing converts some of the naturally occurring *trans* isomers of β-carotene to the *cis* configuration. This does not appear to negate the increased bioavailability of β-carotene from moderately heat-processed foods relative to their raw counterparts. In contrast to β-carotene, heat treatment has minimal effects on isomerization of lycopene. Adequate levels of dietary fat are critical for maximal bioavailability of carotenoids, but this may be less important in Western countries where fat intake is relatively high. In the practical situation of changing diet to improve health, fat intake is lowered, and fruit and vegetable intake is increased. For women making these dietary changes, the resulting decrease in calories from fat and increase in fiber intake did not negate an elevation in plasma carotenoid concentrations (Rock et al., 1997). Alcohol consumption may increase levels of circulating carotenoids, probably by impairing normal carotenoid clearance. In some cases, carotenoids from supplements are more bioavailable, based on plasma response, than they are from whole foods. However, high levels of single oral doses of carotenoids can apparently alter bioavailability of other carotenoids because of biological interactions. Accumulating evidence strongly indicates that realistic increases in fruit and vegetable consumption can appreciably increase plasma carotenoid concentrations of Americans; in turn, epidemiological studies suggest that small but habitual increases in consumption of carotenoid-rich vegetables reduce the risk of chronic diseases, including cancer and cardiovascular disease.

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