J. Food Sci. Nutr.
Vol. 1, No. 2, p. 256~261(1996)

Carotenoids: Functions and Recent Research Progress

-Review-

Kyung-Jin Yeum

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
711 Washington St, Boston, MA 02111, USA

Abstract

Carotenoids are abundant in the Korean food supply. The intake of foods rich in carotenoids appears to be associated with optimal health, and a reduction in the risk of cancer, cardiovascular disease, macular degeneration and cataract formation. Specific dietary carotenoids may be responsible for these specific protective effects. Hydrocarbon carotenoids such as α-, β-carotenes and lycopene may reduce the risk of cancer and heart disease, whereas oxygenated carotenoids, such as lutein and zeaxanthin, may be important in protection of the eye. Dietary carotenoids, such as lutein, cryptoxanthin, α-carotene, β-carotene and lycopene can be readily obtained from the diet. Green leafy vegetables, such as spinach and broccoli, contain both oxygenated and hydrocarbon carotenoids ; yellow or orange vegetables, such as carrots, have high levels of α-carotene and β-carotene ; and tomatoes contain high amounts of lycopene. Besides being important vitamin A sources, provitamin A carotenoids, such as α-carotene, β-carotene and cryptoxanthin, participate in the cell defense systems that are associated with radical quenching. Non-provitamin A carotenoids, such as lutein and lycopene, major carotenoids in human plasma, have also been reported to possess strong antioxidant capability. The alteration of dietary sources of carotenoids can modify their levels in the circulation and target tissues, and thus prevent or delay the onset of these chronic diseases.

Key words: dietary carotenoids, β-carotene, lutein, lycopene, cancer, macular degeneration, oxidation

INTRODUCTION

More than 600 carotenoids have been characterized in nature, although, only about 10% of these carotenoids have potential vitamin A activity(1). For example, β-carotene, α-carotene and β-cryptoxanthin can be cleaved to vitamin A. However, other carotenoids such as lutein, zeaxanthin and lycopene cannot be broken down to vitamin A(Fig. 1).

There is continued interest in the study of dietary carotenoids because of the epidemiological studies that have suggested that diets rich in carotenoid-containing foods may reduce the risk of certain types of chronic diseases such as cancer(2), cardiovascular disease(3-5), macular degeneration(6) and cataracts(7,8). On the other hand, recent intervention trials indicated that supplementation of β-carotene provides either no benefit(9)
or may have an adverse effect on the incidence of lung cancer in smokers(10,11), even though baseline serum β-carotene levels were inversely correlated with the subsequent incidence of lung cancer in these studies (10,11). However, there has been no question raised as to the efficacy of the foods that contain carotenoids.

Specific dietary carotenoids may be responsible for different effects. Hydrocarbon carotenoids, such as β-carotene, may be a marker for reduced risk of cancer and heart disease(2-5), whereas oxygenated carotenoids,

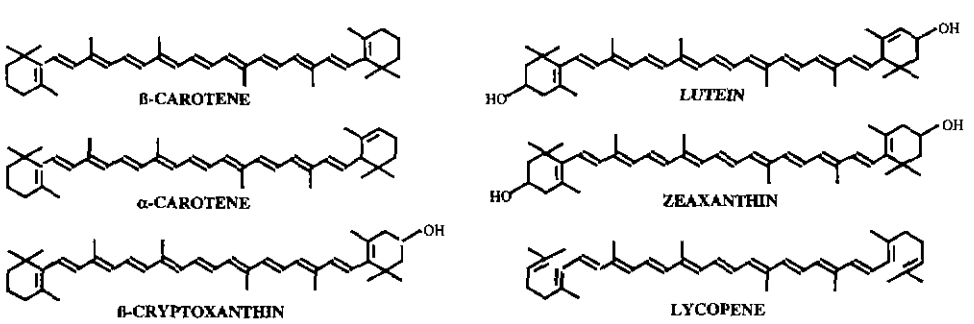

Fig. 1. Major carotenoids in human serum and tissues.

such as lutein and zeaxanthin, may be important for protecting the eye(6-8). The acyclic carotenoid, lycopene, is one of the most abundant carotenoids in human blood and tissues. Lycopene has been found to be associated with an inverse risk of both cervical cancer and prostate cancer(12,13). Green leafy vegetables contain both oxygenated and hydrocarbon carotenoids ; yellow or orange vegetables have high levels of α -carotene and β-carotene(14) ; and tomatoes contains high amounts of lycopene(15).

In this review, we will review the oxidation of provitamin A carotenoids into retinoids. Variability of human plasma carotenoids and their response to the ingestion of fruits and vegetables will be discussed. Some important new aspect of oxygenated carotenoids in human eye tissues will also be reviewed.

OXIDATION OF PROVITAMIN A CAROTENOIDS

The mechanism by which carotenoids or their metabolites may exert a protective function against cancer is not yet known. The antioxidant role of carotene may partially explain the anticarcinogenic effect of carotenoids(6,17). Carotenoid effectively quenches singlet oxygen, which may be present in biological systems as a result of photosensitivity reactions(16). Also, carotenoid is able to trap peroxyl and alkoxyl radicals effectively(17). Since β-carotene has the highest vitamin A activity among the carotenoids, and it is abundant in foods, all-*trans* β-carotene has been extensively studied. In addition to being an antioxidant, β-carotene is an important source of retinoids, such as retinol and retinoic acid, in human tissues(Fig. 2). Humans are capable of accumulating high concentrations of carotenoids in tissues without any apparent toxicity.

The metabolism of provitamin A carotenoids to retinoids has been demonstrated in cell-free systems for almost 50 years, but there is still a lack of information about the specific enzyme(s) that carry out this important biological process. It is generally accepted that oxidative cleavage of β-carotene has two pathways, central cleavage and excentric cleavage(1). Central cleavage catalyzes the formation of retinyl aldehyde, which can be reversibly reduced to retinol or irreversibly oxidized to retinoic acid. On the other hand, excentric cleavage leads to β-apo-carotenaldehydes such as β-apo-14′,-12′,-10′, -8′-carotenaldehydes and corresponding β-apo-carotenoic acids, ultimately forming retinoic acid(1).

We have studied the *in vitro* metabolism of several major provitamin A carotenoids ; β-carotene, α-carotene and β-cryptoxanthin, which have antioxidant properties. β-apo-carotenoids and retinoids were produced after 30 min incubation of normal human gastric mucosal homogenate with β-carotene. Both enzymatic and non-enzymatic oxidation occurred at the same time in this *in vitro* incubation system, although control experiments (i.e. incubation of β-carotene without tissue) indicated that only insignificant non-enzymatic oxidation took place(17). Similar to β-carotene, after incubation of normal human gastric mucosal tissue with α-carotene, both β-apo-carotenals and α-apo-carotenals were produced.

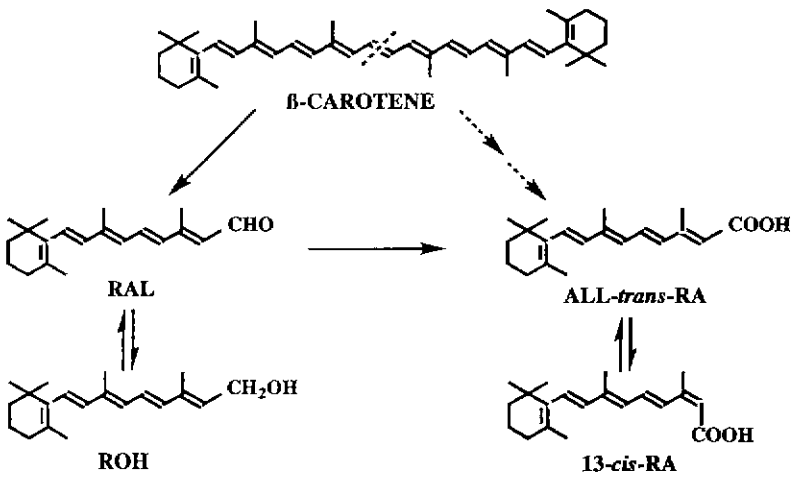

Fig. 2. Conversion of β-carotene into retinoids.
RAL, retinyl aldehyde; ROH, retinol(active vitamin A); all-*trans* RA, all-*trans* retinoic acid; 13-*cis* RA, 13-*cis* retinoic acid.

Incubation with β-cryptoxanthin also produced the β-apo-carotenoids, retinoids, as well as more polar oxidized compounds, which we believe they are hydroxylated derivatives. It is probable that the enzyme in gastric tissue can attack several carotenoids in the same manner.

A POSSIBLE MECHANISM OF CAROTENOID OXIDATION

Plant lipoxygenases, a group of isoenzymes, are known to bleach carotenoids. The reaction occurs by way of a co-oxidation reaction in which a polyunsaturated fatty acid is first oxidized to form a hydroperoxy fatty acid radical which in turn brings about the oxidation of carotenoids to produce a colorless product. It has been reported that there is *in vitro* destruction of rumen fluid carotenoids by plant lipoxygenases (18). Several publications have also reported the presence of lipoxygenase in healthy human tissues as indicated by the characteristic lipid oxidation products(19,20).

The basis for the formation of excentric cleavage products of β-carotene after incubation with human gastric mucosal homogenates was studied. The same excentric cleavage products were formed when β-carotene was incubated with either gastric tissue or lipoxygenase plus the substrate, linoleic acid. The β-carotene metabolites, β-apo-carotenoids and retinoids, were significantly increased by the addition of lipoxygenase to the gastric tissue homogenate. β-Apo-carotenoids and retinoids were also formed when β-carotene was incubated with 13-LOOH(13S-hydroperoxy-*cis*, *trans*-9, 11-octadecadienoic acid), one of the primary products of lipoxygenase action. Furthermore, the β-carotene metabolites were significantly reduced in the presence of the lipoxygenase inhibitor, NDGA(nordihydroguaiaretic acid). These results strongly suggest that lipoxygenase activity is involved in the oxidation of β-carotene in gastric tissue *in vivo*. Fig. 3 summarizes the possible mechanisms of lipoxygenase-linked oxidation of β-carotene in this *in vitro* system.

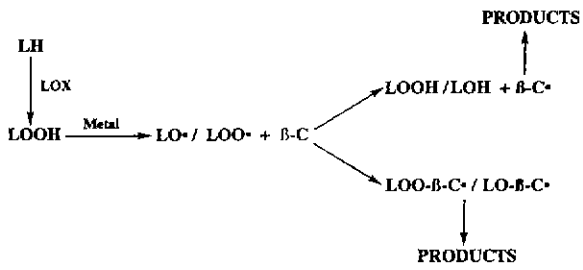

Fig. 3. Possible mechanisms of enzyme-linked oxidation of β-carotene in *in vitro* system(17)
β-C, β-carotene; β-C· , β-carotene radical; LOX, lipoxygenase; LH, linoleic acid; L· , linoleic acid radical; LO· , alkoxyl radical; LOO· , linoleic acid hydroperoxyl radical; LOOH, linoleic acid hydroperoxide.

It is conceivable that the reaction of lipoxygenase with its substrate, linoleic acid, alters the enzyme such that it now can oxidize β-carotene directly, and in the process form excentric cleavage products. An alternative process depends on the formation of a hydroperoxyl radical, LOO · , from the reaction of L · and O_2. Under these circumstances, the LOO · can either abstract a hydrogen from β-carotene, forming a carbon-centered resonance-stabilized radical, as hypothesized by Burton and Ingold(21). Included in Figure 3 is the possible reaction of alkoxyl radicals, which can be produced by a metal-catalyzed reaction with a lipid hydroperoxide, with β-carotene.

The formation of similar oxidative products following incubation of β-carotene with gastric mucosal tissue, lipoxygenase plus linoleic acid, or 13-LOOH and inhibition of β-carotene oxidation in the presence of lipoxygenase inhibitor, NDGA, illustrates that β-carotene can react with either fatty acid peroxides or their derivatives. Other major provitamin A carotenoids ; α-carotene and β-cryptoxanthin, which have antioxidant properties, also are oxidized in the same manner as β-carotene. Therefore, carotenoids should be able to participate in the cell defense systems of the healthy human body that are associated with radical quenching.

PLASMA CAROTENOIDS CAN BE MARKERS OF VEGETABLE AND FRUIT INTAKES

Green leafy vegetables such as spinach, broccoli, and kale mainly contain oxygenated carotenoids. Yellow or orange vegetables such as carrots and squash provide a high amount of hydrocarbon carotenoids. Oranges are the major contributor of cryptoxanthin, and tomatoes contain high amounts of lycopene. Therefore, the plasma concentration of each carotenoid may reflect the intakes of specific fruits and vegetables consumption.

To examine this further, serum carotenoids and

retinol were measured to determine the variability of antioxidant nutrients using reverse-phase HPLC in healthy American and Chinese adults. There was considerable differences in plasma nutrient concentrations between groups(Fig. 4).

Compared to American adults, plasma lutein/zeaxanthin concentrations were about 2 times higher, lycopene about 6 times lower, and α-carotene 5 times lower in chinese adults. Plasma β-carotene values were similar.

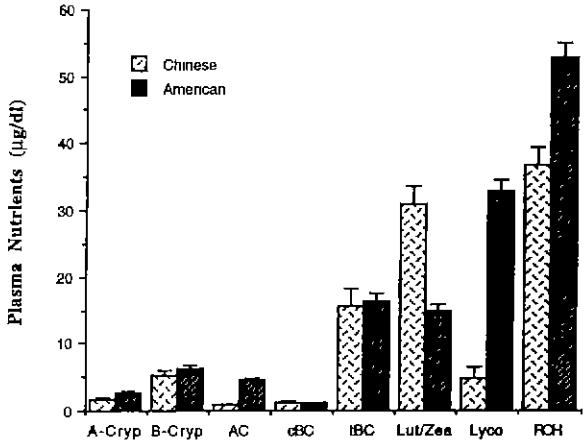

Fig. 4. Plasma concentration of carotenoids and retinol in American and Chinese healthy adults.
A-Cryp, α-cryptoxanthin; B-Cryp, β-cryptoxanthin; AC, α-carotene; cBC, *cis* β-carotene; tBC, all-*trans* β-carotene; Lut/Zea, lutein+zeaxanthin; Lyco, Lycopene; ROH, Retinol.
Chinese, n=25; American, n=54.

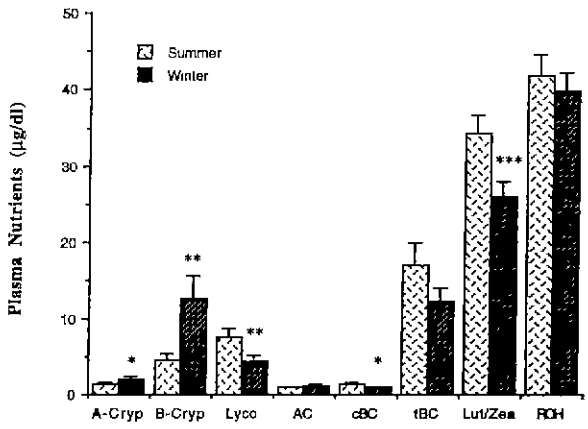

Fig. 5. Plasma concentration of carotenoids and retinol in Chinese healthy adults by season(n=17).
*p<0.05, **p<0.01, ***p<0.005; significant difference between two seasons.
A-Cryp, α-cryptoxanthin; B-Cryp, β-cryptoxanthin; AC, α-carotene; cBC, *cis* β-carotene; tBC, all-*trans* β-carotene; Lut/Zea, lutein+zeaxanthin; Lyco, Lycopene; ROH, Retinol.

These differences may reflect a higher consumption of green leafy vegetables and lower intake of tomatoes and their products in Oriental people than that in Western people.

Serum concentrations of carotenoids also showed a seasonal variability. Lutein/zeaxanthin and lycopene were statistically higher in summer than in winter, whereas cryptoxanthin was statistically higher in winter(Fig. 5).

High intakes of carotenoid-rich fruits and vegetables may alter the levels of carotenoids in serum and target tissues and thus prevent or delay the onset of certain diseases. To understand the biological function of specific carotenoids, it is essential to understand their uptake in the circulation.

Human plasma response to the ingestion of controlled diets high in fruits and vegetables were determined in 36 healthy men and women before and after being fed controlled diets of moderate fat(26% of total calories) and high carotenoid content(≈16mg/day) for a 15 day peroid(22). The concentrations of plasma lutein, cryptoxanthin, α-carotene, 13-*cis* β-carotene, all-*trans* β-carotene and *cis* and *trans* lycopenes were all significantly increased($p<0.05$) within 16 days of starting the high fruit and vegetable diets(10 servings/day). It was found that most of the carotenoids of human plasma can be increased by moderate alterations in human diets within a short period of time, although the plasma response may be related to the baseline carotenoid concentrations(22). Thus, plasma carotenoids can be used as markers of recent vegetable and fruit intake.

OXYGENATED CAROTENOIDS IN HUMAN EYE TISSUES

Very littly is known about the absorption and tissue distribution of lutein and zeaxanthin, the major oxygenated carotenoids (xanthophylls) in our diet. Although these compounds are not precursors of vitamin A, they are the only pigments found in the human lens and macular region of the human retina(23,24). High intakes of dark-green leafy vegetables, such as spinach and broccoli, which is rich in lutein and zeaxanthin, have been demonstrated to be associated with a lower risk for cataract and macular degeneration, which are major causes of blindness throughout the world(6-8).

Age-related macular degeneration is degeneration of the retina and the retinal pigment epithelium in the

macular region. Since no treatment is available for most patients, efforts focus on preventing the damage leading to this condition. It is possible that the retinal carotenoids, lutein and zeaxanthin, which form the macular pigment may help to prevent age-related macular degeneration.

A recent study showed that macular pigment density in the retina could be raised by increasing dietary intake of lutein and zeaxanthin from foods(25). A self-selected diet was supplemented with 60g of spinach (10.8mg lutein, 0.3mg zeaxanthin), and/ or 150g of corn (0.3mg lutein, 0.4mg zeaxanthin) per day throughout a 3 month period to 11 healthy adults. Macular pigment density was increased within four weeks of dietary modification for most, but not all subjects. Augmentation of macular pigment for both experimental and clinical investigation appears to be feasible for many individuals(25).

CONCLUSIONS

Carotenoids are abundant in the Korean food supply. About 80% of vitamin A provided from carotenoids in Korean diet. Carotenoids have also been suggested to have specific biological functions. The intake of foods rich in carotenoids appears to be associated with better health, and they may reduce the risk of cancer, cardiovascular disease, macular degeneration and cataract formation. Specific dietary carotenoids may play a role in reducing the risk of certain diseases.

β-Carotene can be cleaved into retinoids through central cleavage and excentric cleavage. Other provitamin A carotenoids can be oxidized enzymatically and non-enzymatically in the same manner as β-carotene. In addition to being important sources of retinoids such as retinol and retinoic acid, provitamin A carotenoids, which have antioxidant properties, may be able to participate in the cell defense systems.

The concentrations of most carotenoids (lutein, cryptoxanthin, α-carotene, 13-*cis* β-carotene, all-*trans* β-carotene, *trans*-and *cis*-lycopenes) that exist in human plasma can be increased in a relatively short period of time by increasing the intake of fruits and vegetables. Furthermore, dietary intake of dark green leafy vegetables is effective in increasing the concentration of lutein and zeaxanthin in tissues including the macula. The data have implications for making recommendations for food selections that could decrease the risk of certain diseases.

ACKNOWLEDGMENTS

I thank Dr. Robert M. Russell and Dr. Elizabeth J. Johnson at Jean Mayer USDA-Human Nutrition Research Center on Aging at Tufts University for their critical review of this paper.

REFERENCES

1. Olson, J. A. · Provitamin A function of carotenoids : the conversion of β-carotene into vitamin A. *J. Nutr.*, **119**, 105(1989)
2. Ziegler, R. · Vegetables, fruits, and carotenoids and the risk of cancer. *Am. J. Clin. Nutr.*, **53**(suppl), 251S(1991)
3. Gaziano, J. M. and Hennekens, C. H. : The role of beta-carotene in the prevention of cardiovascular disease. *New York Acad. Sciences*, **691**, 148(1993)
4. Riemersma, R. A., Wood, D. A., McIntyre, C. C. A., Elton, R. A., Gey, K. F., Oliver, M. F. : Risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene. *Lancet*, **337**, 1(1991)
5. Greenberg, E. R., Baron, J. A., Karagas, M. R., Stukel, T. A., Nierenberg, D. W., Stevens, M. M., Mandel, J. S. and Haile, R. W. : Mortality associated with low plasma concentration of beta carotene and the effect of oral supplementation. *JAMA*, **275**, 699(1996).
6. Seddon, J. M., Ajani, U. A., Sperduto, R. D., Hiller, R., Blair, N., Burton, T. C., Farber, M. D., Gragoudas, E. S., Haller, J., Miller, D. T., Yannuzzi, L. A. and Willett, W. C. : Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA*, **272**, 1413(1994).
7. Jacques, P. F. and Chylack, L. T. : Epidemiolgic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. *Am. J. Clin. Nutr.*, **53**(suppl), 352S (1991)
8. Hankinson, S. E., Stampfer, M. J., Seddon, J. M., Colditz, G. A., Rosner, B., Speizer, F. E, and Willett, W. C. : Nutrient intake and cataract extraction in women : a prospective study. *Br. Med. J.*, **305**, 335(1992)
9. Hennekens, C. H., Buring, J. E., Manson, J. E., Stampfer, M., Rosner, B., Cook, N. R., Belanger, C., LaMotte, F., Gaziano, J. M., Ridker, P. M., Willett, W. and Peto, R. : Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *New Engl. J. Med.*, **334**, 1145(1996)
10. The alpha-tocopherol, beta carotene cancer prevention study group : The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New. Engl. J. Med.*, **330**, 1029(1994)
11. Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., Keogh, J. P., Meyskens, F. L., Valanis, B., Williams, J. H., Barnhart, S. and Hammar, S. : Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New Engl. J. Med.*, **334**, 1150(1996)
12. Batieha, A. M., Armenian, H. K., Norkus, E. P., Morris,

J. S., Spate, V. E. and Comstock, G. W. : Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study. *Cancer Epidemiol. Biomarkers. Prev.*, **2**, 335(1993)
13. Clinton, S. K. Emenhiser, C., Schwartz, S. J., Bostwick. D. G., Williams. A. W., Moore, B. J. and Erdman, J. W. : cis-trans Lycopene isomers, carotenoids, and retinol in the human prostate. *Cancer Epidemiol. Biomarkers. Prev.*, **5**, 823(1996)
14. Stahl, W. and Sies, H. : Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *J. Nutr.*, **122**, 2161(1992)
15. Rock, C. L., Swendseid, M. E., Jacob, R. A. and McKee, R. W. Plasma carotenoid levels in human subjects fed a low carotenoid diet. *J. Nutr.*, **122**, 96(1992)
16. Sies, H. and Stahl, W. : Vitamins E and C, β-carotene, and other carotenoids as antioxidants. *Am. J. Clin. Nutr.*, **62**(suppl), 1315S(1995)
17. Yeum, K.-J., Lee-Kim, Y. C., Yoon, S., Lee, K. Y , Park, I. S., Lee, K. S , Kim, B. S., Tang G., Russell, R. M. and Krinsky, N. I. : Similar metabolites formed from β-carotene by human gastric mucosal homogenates, lipoxygenase, or linoleic acid hydroperoxide. *Arch. Biochem. Biophys.*, **321**, 167(1995)
18. Larsen, T. W., Yang, A. and Tume, K. : The in vitro destruction of rumen fluid carotenoid by plant lipoxygenase. *Biochem. Molecu. Biol. International*, **30**, 197(1993)
19. Baer, A. N., Costello, P. B. and Green, F. A. : In vivo activation an ω-6 oxygenase in human skin. *Biochem. Biophy. Res. Comm.*, **180**, 98(1991)
20. Joseph, P., Srinivasan, S. N. and Kulkarn, A. P. : Purification and partial characterization of lipoxygenase with dual catalytic activities from human term placenta. *Biochem. J.*, **293**, 83(1993)
21. Burton, G. w and Ingold, K. U. β-Carotene : An unusual type of lipid antioxidant. *Science*, **224**, 569(1984)
22. Yeum, K.-J., Booth, S. L., Sadowski, J. A., Liu, C., Tang, G., Krinsky, N. I. and Russell, R. M. : Human plasma carotenoid response to the ingestion of controlled diets high in fruits and vegetables. *Am. J. Clin. Nutr.*, **64**, 594(1996)
23. Handelman, G. J., Dratz, E. A., Reay, C. C. and van Kuijk, F. J. G. M. : Carotenoids in the human macula and whole retina. *Invest. Ophthalmol. Visual. Sci.*, **29**, 850(1988)
24. Yeum, K.-J., Taylor, A., Tang, G. and Russell, R. M. : Measurement of carotenoids, retinoids and tocopherols in human lenses. *Invest. Ophthalmol. Visual Sci.*, **36**. 2756 (1995)
25. Hammond, B. R., Johnson, E. J., Russell, R. M., Krinsky, N. I., Yeum, K.-J., Edwards, R. B. and Snodderly, D. M. : Dietary modification of human macular pigment density. *Invest. Ophthalmol. Visual Sci.*, (Submitted).

(Received November 23, 1996)