Overview of Lycopene, Carotenoids, and Disease Prevention (44273)

NORMAN I. KRINSKY[1]

Department of Biochemistry, School of Medicine and the Jean Mayer USDA Human Nutrition Center on Aging, Tufts University, Boston, Massachusetts 02111

Carotenoid pigments comprise a large and interesting group of compounds that first caught the attention of chemists because of their deep yellow, orange, and red colors. They represented some of the first compounds that were separated by chromatography, and to this day, that is an important analytical technique for both quantitating and characterizing carotenoids. Then in 1930, it became apparent that some of the carotenoids could replace vitamin A in animal diets, and this was followed by the realization that some carotenoids were metabolic precursors of vitamin A (1). The ability to function as a provitamin A was limited to those carotenoids with an unsubstituted β-ionone group, and included β-carotene, α-carotene, β-cryptoxanthin, and several others that are very poorly represented in the human diet. Examples of the provitamin A and nonprovitamin A carotenoids found in human plasma are depicted in Figure 1. Carotenoids such as lycopene, the major pigment of tomatoes, or astaxanthin, the major pigment of crustaceans, do not have the requisite structure and therefore, are not provitamin A carotenoids.

For about 50 years, the nutritional and health interest in carotenoids was limited to the provitamin A pigments. However, this changed when epidemiologists, investigating the relationship between diets and disease, found a relationship between diets rich in green leafy vegetables and red, orange, and yellow fruits and vegetables and a decreased risk of developing various types of cancer and other chronic diseases. At first, this effect was attributed to the vitamin A value of these diets, but a closer analysis of the early data indicated that food tables had converted the content of provitamin A carotenoids into vitamin A values. Soon investigators began focusing on the carotenoid content of diets and their relationship to disease. This efforst was greatly stimulated by the 1981 article entitled "Can Dietary β-Carotene Materially Reduce Human Cancer Rates?" by Peto *et al.* (2). Since then, there have been many articles published supporting the idea that diets rich in fruits and green vegetables reduce chronic disease risk, and other investigations have found the same relationship between plasma levels of carotenoids and decreased risk of disease (3, 4).

The epidemiological evidence for carotenoid protection was so compelling that a series of human intervention studies were initiated to see if β-carotene, the only carotenoid approved for human investigation in the United States, would confer protection against cancer. The studies selected men who were heavy smokers, men and women who were primarily smokers and/or asbestos workers, as well as a relatively low-risk population, U.S. physicians between the ages of 45–65. Those investigators who advocated the position that supplementary β-carotene would be beneficial were disappointed because the intervention studies have not yielded any evidence that benefits could accrue, even after a 12-year period of supplementation (5). In fact, heavy smokers and asbestos workers have developed an increased risk for lung cancer when receiving high-dose β-carotene supplements (6, 7).

Although the results of the β-carotene intervention studies have not indicated that single nutrient supplementation can be beneficial, there are epidemiological studies indicating that carotenoids other than β-carotene may have been neglected during the 15-year period between the Peto article (2) and the announcement of the results of the three large intervention trials.

Properties of Carotenoids

Numerous physical and chemical properties are common to many carotenoids, including β-carotene and lycopene. Among the physical properties are the ability of these molecules to absorb visible light and their facile *cis-trans* isomerization, resulting in large shape changes and color changes. In addition, carotenoids can also accept energy from various electronically excited species; that property serves an important protective function in plants exposed to excess light irradiation (8). Part of the latter effect is attributed to the ability of carotenoids to quench singlet excited oxygen, and this property has served as the basis for treatment with supplementary β-carotene for the light-sensitive disease, erythropoietic protoporphyria (9).

Among their chemical properties are their extreme lipid

[1] To whom requests for reprints should be addressed at Department of Biochemistry, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111-1837. E-mail: NKrinsky_mna@OPAL.TUFTS.EDU

0037-9727/98/2182-0095$10.50/0

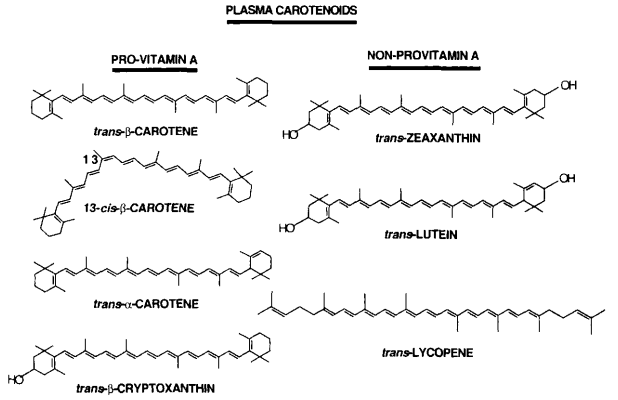

Figure 1. The provitamin A and nonprovitamin A carotenoids present in human plasma.

solubility, ready oxidation, and their ability to react with radicals to either quench radical-initiated chain reactions, or in some cases, form new radical species. It is this latter property that has led some investigators to suggest that carotenoids may act as pro-oxidants, rather than antioxidants. Although the antioxidant actions of carotenoids are not as clear cut *in vivo* as *in vitro,* the evidence that these compounds can behave as pro-oxidants under physiological conditions is not well supported (10).

The best documented antioxidant action of carotenoids is their ability to quench singlet excited oxygen, usually formed by energy transfer from a meta-stable excited photosensitizer (^{3}Sensitizer), in the following reactions:

$$\text{Sensitizer} + \text{light} \rightarrow {}^1\text{Sensitizer}$$
$${}^1\text{Sensitizer} \rightarrow {}^3\text{Sensitizer, } \textit{via} \text{ Intersystem Crossing}$$
$${}^3\text{Sensitizer} + {}^3O_2 \text{ (ground state oxygen)} \rightarrow$$
$$\text{Sensitizer} + {}^1O_2 \text{ (singlet excited oxygen)}$$

In this way, the light energy has been stored in an excited, highly reactive form of oxygen. Nature has evolved a mechanism to protect us and other living systems from singlet oxygen by the physical interaction of this dangerous form of oxygen with a carotenoid, as seen in the following reaction:

$${}^1O_2 + \text{Carotenoid} \rightarrow {}^3O_2 + {}^3\text{Carotenoid}$$

Of all the natural carotenoids that have been tested, lycopene proves to be the most efficient in quenching singlet oxygen by the above reaction. However, what then happens to the ^{3}Carotenoid? It has the ability to lose all of the newly acquired energy through a series of rotational and vibrational interactions with the solvent, and thus, regenerates the intact carotenoid. Because of this, thousands of singlet oxygen molecules can be quenched by a single carotenoid molecule before this pigment is destroyed through chemical reactions.

cis-trans Isomerization of Carotenoids

Another property of carotenoids is their ability to undergo *cis-trans* isomerization. Although the *trans*-configuration appears to be most stable, many of the double bonds can be isomerized by light and heat. Food processing induces formation of *cis* isomers, which means that we consume them in our diet. Even during carotenoid biosynthesis, some *cis* precursors are isomerized to the all-*trans*-configuration, apparently by specific isomerases. For the most part, we do not know if there are specific functions for *cis*-carotenoids, apart from a role they play in energy conservation in photosynthetic reaction centers. However, the physical properties of these isomers differ. In the halotolerant algae, *Dunaliella bardawil,* the 9-*cis* isomer accounts for about half of all the β-carotene, and is more soluble than the all-*trans* form (11). In human serum we find *cis* isomers, especially of lycopene (12). Either our tissues seem to take up *cis* isomers preferentially from our plasma, or the isomers are formed during tissue storage. It is not known if this accumulation of *cis*-isomers of carotenoids in various tissues is adventitious or plays some as yet undescribed role (13, 14).

Effects of Lycopene in Cells and Animals

The first effects of lycopene acting as a stimulator of nonspecific resistance in animals appeared in 1959 (15), but very little else had been done until a few years ago, when some very interesting results indicated that lycopene had a profound effect on tumor cells grown in culture. Levy *et al.* demonstrated that lycopene was much more effective than either α-carotene or β-carotene in inhibiting the growth of human endometrial, mammary, or lung cancer cells grown in culture, whereas this effect was not seen in normal fibroblasts (16).

Similar results have been reported in animals developing either spontaneous or carcinogen-induced tumors. In such model systems, lycopene, when tested with other carotenoids, appears to exert a more potent anticarcinogenic effect although the results are not uniform from study to study. For example, Astorg *et al* (17) reported that lycopene, and not β-carotene or astaxanthin, was able to decrease the size of preneoplastic foci initiated in rat livers by treatment with diethylnitrosamine (DEN), followed by treatment with 2-acetylaminofluorene and partial hepatectomy. However, no effect was observed using any of these carotenoids when the initiator was 2-nitropropane. Kim *et al.* (18) also reported some success of lycopene in preventing lung neoplasia initiated in mice with a combination of DEN, methylnitrosourea (MNU), and dimethylhydrazine. However, the experimental techniques used are not adequately described to permit an evaluation of this paper. Another study reported that lycopene, lutein, and α-carotene all have the ability to inhibit the formation of aberrant crypt foci in rats treated with MNU, whereas β-carotene was without effect (19).

Finally, Sharoni *et al.* (20) reported that a tomato oleoresin containing 5% lycopene was effective in significantly decreasing the number of mammary tumors in rats treated with 7,12-dimethylbenz[a]anthracene, as well as decreasing tumor size, whereas β-carotene was without effect in this model.

Effects of Lycopene in Humans

All of the information regarding the effects of lycopene in humans comes from epidemiological investigations, inasmuch as human intervention trials with lycopene have not been initiated, as yet. There have been reports of a protective effect of raw tomato intake with respect to cancer of the oral cavity and pharynx, esophagus, colon, stomach, and rectum, with the most potent effects seen with stomach neoplasia (21).

The most impressive results come from the study of Giovannucci *et al.* (22), who reported a decreased risk for the development of prostate cancer in men who consumed foods rich in lycopene, such as tomato paste, tomatoes, and pizza, but not tomato juice. The lack of an effect of tomato juice is probably related to the failure to absorb lycopene in this medium, which may be attributable to a lack of fat in the diet.

Conclusion

Ultimately, the effectiveness of a food component to prevent cancer or other chronic diseases will rest on the results of double-blind, placebo-controlled intervention trials. However, these studies should have a firm experimental basis, with results from both cellular and animal studies, to justify their expense. It would appear that we are approaching that stage with respect to lycopene, or at least to tomato products such as the oleoresin concentrate of tomatoes, which is showing very promising effects in cell and animal studies. At this time, though, there seems to be very little urgency to initiate new, large-scale intervention trials, based on the result of the three β-carotene trials already completed or aborted.

What have we learned from these intervention trials? Was the wrong carotenoid selected? Should a combination of carotenoids have been studied? Is there some, as yet unknown, interaction between β-carotene and smoking that confounded the results of the ATBC Study (6) and the CARET Study (7)? These questions are unanswerable at this time, but a close inspection of experiments done with cells grown in culture, newer animal studies, and the localization of various carotenoids in tissues suggests that other carotenoids may have more promise than β-carotene. Among these are lycopene, which may have a relationship with prostate cancer (22), zeaxanthin and lutein, which may be involved in age-related macular degeneration (23), and α-carotene, which is related to a decreased risk in the development of lung cancer (24). Only future experiments will be able to answer questions about carotenoids and disease prevention.

1. Karrer P, Morf R, Schöpp K. Zur Kenntnis des Vitamins-A aus Fischtranen II. Helvetica Chimica Acta **14:**1431–1436, 1931.
2. Peto R, Doll RJ, Buckley JD, Sporn MB. Can dietary β-carotene materially reduce human cancer rates? Nature (London) **290:**201–208, 1981.
3. Ziegler RG. Vegetables, fruits, and carotenoids and the risk of cancer. Am J Clin Nutr **53:**251S–259S, 1991.
4. Mayne ST. Beta-carotene, carotenoids, and disease prevention in humans. FASEB J **10:**690–701, 1996.
5. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, 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:**1145–1149, 1996.
6. The Alpha-Tocopherol, Beta-Carotene 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:**1029–1035, 1994.
7. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL Jr, Valanis B, Williams JH Jr, Barnhart S, Hammar S. Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. New Engl J Med **334:**1150–1155, 1996.
8. Britton G. Structure and properties of carotenoids in relation to function. FASEB J **9:**1551–1558, 1995.
9. Mathews-Roth MM. Beta-carotene therapy for erythropoietic protoporphyria and other photosensitivity diseases. Biochimie **68:**875–884, 1986.
10. Palozza P, Krinsky NI. Antioxidant effects of carotenoids *in vitro* and *in vivo*: An overview. Methods Enzymol **213:**403–420, 1992.
11. Ben-Amotz A, Mokady S, Edelstein S, Avron M. Bioavailability of a natural isomer mixture as compared with synthetic all-*trans*-β-carotene in rats and chicks. J Nutr **119:**1013–1019, 1989.
12. Yeum K-J, Booth S, Sadowski J, Lin C, Tang G, Krinsky NI, Russell RM. Human plasma carotenoid response to the ingestion of controlled diets high in fruits and vegetables. Am J Clin Nutr **64:**594–602, 1996.
13. Stahl W, Sundquist AR, Hanusch M, Schwarz W, Sies H. Separation of β-carotene and lycopene geometrical isomers in biological samples. Clin Chem **39:**810–814, 1993.
14. Clinton SK, Emenhiser C, Schwartz SJ, Bostwick DG, Williams AW, Moore BJ, Erdman JW. *cis-trans* Lycopene isomers, carotenoids, and retinol in the human prostate. Cancer Epidemiol Biomarkers Prev **5:**823–833, 1996.
15. Lingen C, Ernster L, Lindberg O. The promoting effect of lycopene on the nonspecific resistance of animals. Exp Cell Res **16:**384–393, 1959.
16. Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene. Nutr Cancer **24:**257–266, 1995.
17. Astorg P, Gradelet S, Bergés R, Suschetet M. Dietary lycopene decreases the initiation of liver preneoplastic foci by diethylnitrosamine in the rat. Nutr Cancer **29:**60–68, 1997.
18. Kim DJ, Takasuka N, Kim JM, Kazunori S, Ota T, Asamoto M, Murakoshi M, Nishino H, Nir Z, Tsuda H. Chemprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU, and DMH. Cancer Lett **120:**15–22, 1997.
19. Narisawa T, Fukaura Y, Hasebe M, Ito M, Aizawa R, Murakoshi M, Uemura S, Khachik F, Nishino H. Inhibitory effect of natural carotenoids, α-carotene, β-carotene, lycopene, and lutein, on colonic aberrant crypt foci formation in rats. Cancer Lett **107:**137–142, 1996.
20. Sharoni Y, Giron E, Rise M, Levy J. Effects of lycopene-enriched tomato oleoresin on 7,12-dimethylbenz[a]anthracene-induced rat mammary tumors. Cancer Detect Prev **21:**118–123, 1997.
21. Franceschi S, Bidoli E, La Vecchia C, Talamini R, D'Avanzo B, Negri E. Tomatoes and risk of digestive disease cancers. Int J Cancer **59:**181–184, 1994.
22. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz G, Willett WS. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst **87:**1767–1776, 1995.
23. Snodderly DM. Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins. Am J Clin Nutr **62**(Suppl):1448S–1461S, 1995.
24. Ziegler RG, Colavito EA, Hartge P, McAdams MJ, Schoenberg JB, Mason TJ, Fraumeni JF, Jr. Importance of α-carotene, β-carotene, and other phytochemicals in the etiology of lung cancer. J Natl Cancer Inst **88:**612–615, 1996.