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Carotenoids and human health

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SUMMARY. After the discovery of vitamin A in 1913, the yellow pigments of fruits and vegetables were soon implicated as compounds with similar nutritional effects. ß-Carotene was shown to be converted into vitamin A by Moore in 1929, and the chemical structures of both vitamin A and ß-carotene were determined two years later. Thus, the sole function of ß-carotene in human health was considered to be its conversion into vitamin A. On the basis of observational epidemiologic studies, conducted in the mid-1970s, however, carotenoids were implicated as protective agents, first against lung cancer and then against a variety of other chronic diseases. Intervention trials employing ß-carotene, however, either have shown no preventive effect or indeed, in two cases, have enhanced the incidence of lung cancer in middle-aged male smokers and asbestos workers. The possible protective action of carotenoids can be attributed to their properties as singlet oxygen quenchers and as antioxidants, whereas their cancer-enhancing actions in lung can be ascribed to the prooxidant action of carotenoid free radicals in damaged cells. Apart from chronic diseases, ß-carotene has shown significant therapeutic value in individuals suffering from photosensitivity disorders and provides temporary relief to persons afflicted with leukoplakia. Apart from a medical context, the colored carotenoids found in many living organisms and in many foods delight both the eye and the palate. Thus, human health and the enjoyment of life are greatly benefited by the presence of these interesting pigments in nature, whether or not they ultimately prove to have more specific protective effects against chronic diseases.

Key words: Carotenoids, human health, chronic diseases, antioxidant.

RESUMEN. Carotenoides y salud humana. Después del descubrimiento de la vitamina A en 1913, los pigmentos amarillos de frutas y vegetales fueron inmediatamente implicados como compuestos de efectos nutricionales similares. La conversión de ß-caroteno en vitamina A fue mostrada por Moore en 1929, y las estructuras químicas de la vitamina A y el ß-caroteno fueron determinadas dos años después. Así, pensábase que la única función del ß-caroteno para la salud humana sería su conversión en vitamina A. Basados en estudios de observaciones epidemiológicos, conducidos en mediados de 1970 sin embargo, los carotenoides fueron implicados como agentes protectores, primero contra el cáncer de pulmón y después contra una variedad de otras enfermedades. Ensayos de intervención utilizando ß-caroteno, no obstante, no han mostrado efecto preventivo o, en dos casos, han aumentado la incidencia del cáncer de pulmón en fumadores masculinos de mediana edad y trabajadores del asbesto. La posible acción protectora de los carotenoides puede ser atribuida a las propiedades como secuestrante de oxígeno singulete y como antioxidantes, mientras que sus acciones como promotores de cáncer en el pulmón pueden ser asignadas a la acción prooxidante de radicales libres de carotenoides en células malogradas. Además de las enfermedades crónicas, el ß-caroteno ha mostrado valor terapéutico significativo para los males de la fotosensibilidad y en individuos con leucoplaquia. Aparte del contexto médico, los carotenoides encontrados en muchos organismos vivos y en muchos alimentos agradan a los ojos y al paladar. Por lo tanto, la salud humana y el disfrutar de la vida son grandemente beneficiados por la presencia de estos interesantes pigmentos en la naturaleza, sea que finalmente se pruebe o no que tengan efectos protectores más específicos contra las enfermedades crónicas.

Palabras clave: Carotenoides, salud humana, enfermedades crónicas, antioxidante.

INTRODUCTION

Carotenoids have been known as distinct entities in nature for more than a century and a half (1). ß-Carotene, a hydrocarbon, was first crystallized from carrots in 1831 and more polar carotenoids, the xanthophylls, were isolated from autumn leaves a few years later. A large number of carotenoids in nature were identified in the early 1900s by chromatographic techniques. Some common naturally occurring carotenoids are depicted in Figure 1 (1).

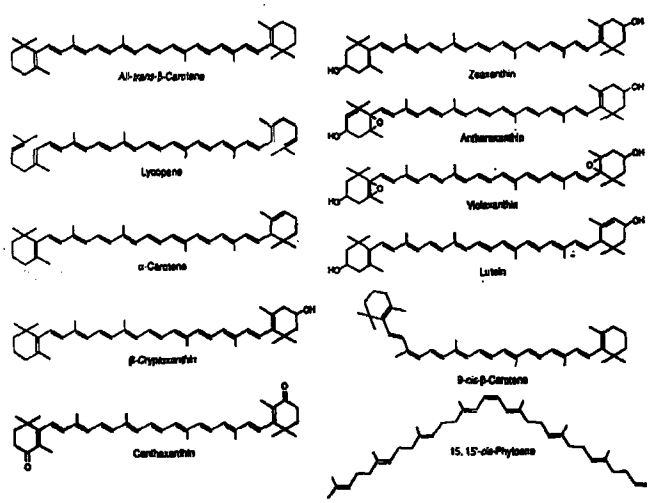
Vitamin A was discovered as a stimulant for rat growth in 1913, and some carotenoid pigments, but not all, were shown to act similarly a few years later. Various speculations concerning the possible role of carotenoids were resolved in 1929 by the demonstration that carotenoids are converted into vitamin A (2). Two years later, the chemical structures of both ß-carotene and retinol were determined by Karrer, who postulated that the addition of two molecules of water across the central bond of ß-carotene could yield vitamin A. The actual mechanism of this cleavage reaction, however, was not clarified for more than 30 years.

Carotenoids have several functions in nature. They serve as provitamin A compounds in animals and humans; they provide protective and mating coloration in birds; they serve

as ancillary light-gathering pigments in photosynthesis; and they protect chlorophyll from oxidative damage in photosynthetic organisms. They also are involved in the xanthophyll cycle in plants, by which light energy is dissipated without destroying the plant cells. In addition to these functions, carotenoids have been shown to have other actions in physiologic systems and to be associated with protection from chronic diseases.

In the 1970s, as the field of observational epidemiology grew, a dietary vitamin A index was shown to be associated with protection from lung cancer (3). It was unclear at that time whether the vitamin A index related primarily to vitamin A, primarily to provitamin A carotenoids, or to a mixture of the two. This query was resolved in large part in 1981, when dietary carotenoids, but not vitamin A, was shown to be associated with cancer chemoprevention (4). Since that time, a large number of studies have been conducted germane to the possible roles of carotenoids in the prevention of chronic diseases.

FIGURE 1
Some common naturally occurring carotenoids (1)



Therapeutic benefits

Photosynthetic disorders: Certain individuals with genetic defects in porphyrin metabolism are extraordinarily sensitive to sunlight (5). Some common conditions of this kind include erythropoietic protoporphyria, congenital porphyria and polymorphic light eruption. In erythropoietic protoporphyria the enzyme ferrochetolase is defective. As a consequence, iron is poorly incorporated into the protoporphyrin ring to yield heme, a key component of hemoglobin, the cytochromes and other heme-containing enzymes. As a consequence, free protoporphyrin circulates in the blood and is taken up by the skin, where it absorbs light and ultimately forms singlet oxygen. This highly reactive form of oxygen interacts with many components of cells, killing them and causing skin lesions.

When large amounts of ß-carotene are administered daily to patients with these disorders, the ß-carotene also accumulates in the skin, quenches the singlet oxygen, and minimizes tissue damage. Doses of 180 mg of ß-carotene, of which only a fraction is absorbed, have been ingested daily by individuals with these disorders to good effect. Interestingly, these huge doses do not cause vitamin A toxicity, primarily because of the relatively slow conversion of ß-carotene into vitamin A in the body. Nonetheless, they do cause a yellowing of the skin, termed hypercarotenosis, which is, of course, at the basis of its therapeutic utility.

At the termination of dosing, the carotenoids are slowly cleared from tissues, and the sensitivity to light returns. Thus, ß-carotene does not cure but only ameliorates the condition as long as it is present.

Human leukoplakia: Cancer of the oral cavity is a common malignancy in many parts of the world (6). Leukoplakia, namely a white patch or plaque on the buccal mucosa that cannot be rubbed off, is considered to be a pre-malignant lesion. When relatively large doses (30-180 mg) of ß-carotene are administered daily to humans for 3-9 months, 40-60% of the subjects respond positively as compared to 10-20% of patients treated with a placebo (6). Large doses (400 IU) of vitamin E show a similar effect. Upon termination of treatment, however, the lesions return. Thus, this response also tends to be phenotypic rather than curative. Supplements of ß-carotene have not been shown to decrease the incidence of cancer of the oral cavity.

Cancer

Carotenoid intakes, including supplements, have been implicated as protective factors against a wide variety of human cancers (7-11) (Table 1).

TABLE 1
Organs that may be protected against cancer by carotenoids

Lung
Oral cavity, pharynx and larynx
Esophagus and stomach
Colon and rectum
Breast
Prostate
Cervix
Skin

Lung: Lung cancer is the leading cause of cancer death in men and women in the United States. Heavy smoking is by far the dominant controllable risk factor. Diet also seems to be important. A large number of observational epidemiologic studies, namely 8 of 8 prospective studies and 18 of 20 retrospective studies, for example, showed a significant association between the intake of carotenoid-containing

vegetables and fruits and a reduced lung cancer risk (7-10). These findings stimulated the conduct of a large clinical trial in Finland in which α-tocopherol and ß-carotene were used as supplements (12). In this study, 29,133 Finnish male smokers, aged 50-69 years, were divided into four groups; namely, a ß-carotene supplement group, an α-tocopherol supplement group, a ß-carotene plus α-tocopherol group, and a placebo group. Treated groups received 20 mg of ß-carotene and/or 50 mg of α-tocopherol daily for 5-8 years. The results of the study were highly unexpected. Rather than preventing lung cancer, ß-carotene enhanced lung cancer incidence by 18% (95% confidence interval, 1.03-1.36) and death by 8% (95% confidence interval, 1.01-1.16). α-Tocopherol had no effect on lung cancer incidence, either in a positive or negative fashion.

The findings in the Finnish study were confirmed in a large similar study conducted in the northwestern United States (13). In this case, 14,254 American men and women smokers, 50-69 years, plus 4,060 male asbestos workers either were supplemented with 30 mg ß-carotene plus 25,000 IU vitamin A daily or received a placebo. The study, which originally was scheduled to continue for 5.5 years, was stopped at 3.7 years because of the outcome. Supplements of ß-carotene and vitamin A enhanced lung cancer by 28% (95% confidence interval, 1.04-1.57) and mortality by 17% (95% confidence interval, 1.03-1.33).

In another major intervention trial, the Physicians Health Study (14), 22,071 U.S. male physicians, 40-84 years of age, were given 50 mg ß-carotene or a placebo on alternate days for 12 years. In the initial five years of the study, 325 mg of aspirin was also provided on alternate days. In this study, ß-carotene had no effect on the incidence of lung cancer or of total neoplasms (relative risk = 0.98, 95% confidence interval, 0.91-1.06). Only 11% of the subjects in this study, however, were current smokers. In a smaller study, 755 asbestos workers in Tyler, TX, were given a supplement of 50 mg ß-carotene plus 25,000 IU retinyl acetate every other day for five years. No differences were noted between control and treated groups in the prevalence of sputum atypia (8, 10).

Thus, a dichotomy exists. While evidence obtained from observational epidemiology supports a protective role of dietary carotenoids against cancer risk, intervention studies do not (Table 2). Some possible reasons for these differences between the outcomes of intervention trials and observational epidemiologic studies are that: (a) observational epidemiology focuses on foods that contain many components, whereas intervention trials employ single compounds, (b) the amount of a carotenoid ingested is small in dietary studies but large in intervention trials, (c) the physiologic effects of supplements may differ from those of the same nutrient in foods, and (d) utilization of other protective components of foods may be inhibited by large doses of ß-carotene. Whatever the explanation, the universal lack of a protective effect of ß-carotene supplements in cancer trials, as well as the enhancement of lung cancer found in two major trials, has discouraged the initiation of further studies of this kind.

TABLE 2
Effects of ß-carotene supplements on some cancers

Site	N	Dose	Duration	RR*	95% CI
Esophagus	3,318	15 mg	6 Y	0.96	0.78-1.18
Stomach	3,318	15 mg	6 Y	1.18	0.76-1.85
Colon/rectum	864	25 mg	5 Y	1.01	0.85-1.20
Skin	1,805	50 mg	5 Y	1.05	0.91-1.22
Prostate	29,133	20 mg	5-8 Y	1.23	0.96-1.59

*Relative risk is the ratio of cancer incidence in the cited organ of the ß-carotene group relative to that in the placebo group.

Mechanisms

Carotenoids might well be protective against cancer and other chronic diseases by a number of known mechanisms (8-10) (Table 3). For example, carotenoids quench singlet oxygen, which is a highly reactive form of the oxygen atom. Carotenoids can also scavenge peroxyl radicals and can modulate the metabolism of carcinogens. Cell proliferation is inhibited and cell differentiation enhanced by carotenoids, either directly or via their conversion to retinoids. Both vitamin A and several carotenoids stimulate cell-to-cell communication and, similarly, enhance the immune response.

TABLE 3
Possible protective mechanisms of carotenoids against chronic diseases

- Quenching of singlet oxygen
- Scavenging of peroxyl radicals
- Modulation of carcinogen metabolism
- Inhibition of cell proliferation
- Enhancement of cell differentiation via retinoids
- Stimulation of cell-to-cell communication
- Enhancement of the immune response
- Filtering of blue light

The unexpected finding that ß-carotene enhances lung cancer in heavy smokers and asbestos workers also requires explanation. Some possibilities are given in Table 4. First of all, a tissue must be damaged in order for the enhancement of cancer to occur. Thus, primarily lung cancer, of many known cancers, has been enhanced by supplementation with ß-carotene. In the presence of the free radicals of cigarette smoke and relatively high oxygen tensions, ß-carotene can form peroxides and free radicals that can enhance tissue damage. When a different organ, liver, is damaged by alcohol or carbon tetrachloride, both vitamin A and ß-carotene also can enhance hepatotoxicity and the risk of liver cancer (15).

TABLE 4
Possible mechanisms by which ß-carotene enhances lung cancer

- Concurrent exposure to ß-carotene and either cigarette smoke or asbestos fibers is essential
- Risk primarily relates to the lung
- Smoke contains many free radicals
- Lung oxygen pressures are high
- ß-Carotene can form peroxides and free-radicals that can enhance tissue damage
- Cells already damaged by components in smoke may be highly susceptible to mutations

Other possible mechanisms exist, however, to explain the enhancement of lung cancer by ß-carotene (9). ß-Carotene might inhibit the absorption of other potentially protective dietary components, such as lutein, canthaxanthin or α-carotene. Smoke might also activate macrophages to secrete oxidizing agents, which then might form ß-carotene-free radicals. Finally, ß-carotene might increase the survival of neoplastic cells by inhibiting their apoptosis. None of these mechanisms, of course, is mutually exclusive.

Other chronic diseases

A number of other chronic diseases may well be affected by carotenoid ingestion, namely, cardiovascular disease, age-related macular degeneration, cataracts and HIV infections.

Cardiovascular disease: The results of studies relating carotenoid intake or supplementation to cardiovascular disease are mixed (8-10). In a variety of studies, some have shown a protective effect, some no effect at all, and yet others an enhancing effect, albeit nonsignificant. Mechanistically, carotenoids may play a role in reducing the oxidation of low-density lipoproteins, which seem to play a key role in atherogenesis. On the other hand, carotenoids can also serve as prooxidants under appropriate conditions.

Age-related macular degeneration: Age-related macular degeneration is a major cause of blindness among the elderly (16). Major risk factors tend to be smoking, age and gender, with females having a higher incidence. Many nutritionally related risk factors exist, including lower intakes of vitamin A and zinc and lower concentrations of glutathione and ascorbic acid in eye tissue. Interestingly, the macula of the eye primarily contains only two carotenoids, lutein and zeaxanthin, which are distributed in a very specific pattern within that organ. Markedly increased intakes of lutein and zeaxanthin increase blood concentrations many-fold but have a much smaller effect on the deposition of macular pigments. Mechanistically, lutein and zeaxanthin can serve as filters of blue light, thereby protecting the retina, or might serve as antioxidants. Thus far, however, intakes of lutein and zeaxanthin have not been convincingly shown to protect against this disease.

Cataracts: Cataracts consist of a gradual opacification of the lens with aging, which may in part result from oxidative stress (7-10). Carotenoid intake, as well as that of vitamins C and E, has been associated with a reduced risk of cataract. However, supplements of ß-carotene, selenium and α-tocopherol were not associated with protection against cataracts. Thus, data supporting a role for carotenoids as protective agents against cataract is currently inconclusive.

HIV infections: In HIV infections, T-helper cells are destroyed, thereby impairing the immune response (10,17). In humans, both ß-carotene and canthaxanthin enhance the immune response. Indeed, large doses of ß-carotene have been shown to increase the CD4:CD8 ratio, which is usually depressed in HIV infections. Thus, in treating this disorder, ß-carotene seems to improve the immune response and thereby decrease the incidence of infections characteristic of the disease (10,17).

Other carotenoids

Other carotenoids have also been associated with beneficial effects on human health; namely, α-carotene in lung cancer (9), lycopene in prostate cancer (11), and lutein and zeaxanthin, as already mentioned, in age-related macular degeneration (16). In no case, however, has conclusive evidence been presented that carotenoid supplements will substantially protect against any of these chronic diseases.

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