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Is ß-carotene an antioxidant?

by

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Abbreviations:

C: carotene
$LOO^{\bullet}$: lipid peroxyl radical
$^{3}C^{*}$: excited state of carotene
$L^{\bullet}$: lipid alkyl radical
$ROO^{\bullet}$: alkyl peroxyl radical

Contents

Abstract

ß -carotene is a human nutrient found in plants or animals. It is also can be synthesized chemically. It is lipid-soluble, and is yellow, orange or red in color. ß-Carotene can be cleaved into vitamin A *in vivo.* The most abundant form of ß-carotene in human serum is *trans* isomer; *cis* isomers such as 9-*cis* ß-carotene, 13-*cis* ß-carotene, and 15-*cis* ß-carotene are only present in trace amounts. ß-carotene is a versatile antioxidant: it prevents both singlet oxygen- and free radical-mediated damage. It is believed to exert its antioxidant function at low oxygen tension. The chemical and physical mechanisms to scavenge reactive species have been proposed in a number of papers. The structure, metabolism, and possible mechanisms to scavenge reactive oxygen species are briefly reviewed in this paper.

Introduction

ß-Carotene is a fat soluble, small molecule. It is reported that supplement with ß-carotene can lower the risk of lung cancer and other cancers [1,2]. ß-carotene has two ring structures and many double bonds. In addition, it is necessary nutrient because it is transformed into vitamin A. It is also suggested to function as an antioxidant. Foote and colleagues first demonstrated the singlet oxygen quenching action of ß-carotene in 1968 [3]. Later the peroxyl radical scavenging properties of ß-carotene were reported [4]. Other groups have documented that ß-carotene can prevent lipid peroxidation [5,6].

Structure

ß-Carotene is characterized chemically by repeating isoprenoid units containing five carbon atoms. ß -Carotene has the chemical formula $C_{40}H_{56}$ and consists of eight isoprenoid units, which have been cyclized on each end to form rings. These two rings are mirror images. The normal isomer found in nature is the all-*trans* form, though it can convert the all-*trans* isomer into a range of *cis-trans* isomers particularly *in vivo.* Of these, the most commonly found is the 13-*cis* isomer, although several hundred different combinations are theoretically possible because of the number of double bonds in the long chain [7].

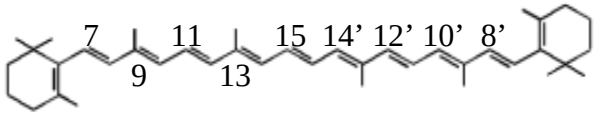

Figure 1: Structure of all-*trans* β-carotene. Adapted from [15].

Metabolism

ß-Carotene, like many (but not all) other carotenoids, is a major source of vitamin A in the natural diet of most animals. When β-carotene is absorbed in cells, carotenoid dioxygenases degrade the carotene molecule by successive oxidative cleavages. Though the structures of ß-

carotene and vitamin A molecules would suggest that cleavage of the carotene molecule in the mid-line could result in two molecules of vitamin A [8], research has shown that conversion in the intestinal lumen consists of successive removals of carbon groups from one end. The structure of vitamin A is shown in Figure 2. Figure 3 shows the current hypothesis for the various stages in converting ß-carotene to vitamin A [9].

Figure 2: The structure of vitamin A. Adapted from [9]

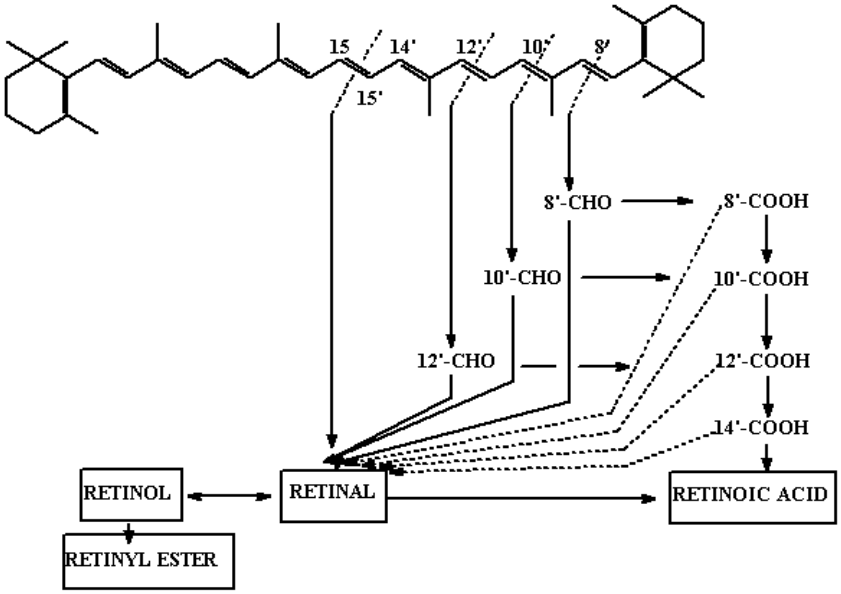

Figure 3: Cleavage of beta-carotene to form vitamin A. Cleavage at the 15,15' double bond produces of two vitamin A molecules. Adapted from [15]

The retinol formed by this conversion process is transferred to the liver for esterification and further circulation or storage. The efficiency of the conversion depends on a number of factors. In theory, 1 mole of beta-carotene should produce 1 mole of vitamin A, but this degree of efficiency is never achieved. The conversion efficiency depends on numerous factors. One important controlling factor is the body's reserves of vitamin A and other carotenoids. The greater the reserves, the lower the absorption and conversion rates of additional carotenoids [9].

Antioxidant Properties

ß-carotene is demonstrated to be a very effective scavenger of singlet oxygen. It also can scavenge peroxyl radical and nitrogen dioxide radical. The mechanisms of the reactions between ß-carotene and singlet oxygen/peroxyl radical are illustrated below.

Reaction with singlet oxygen

ß-carotene is a very effective singlet oxygen quencher [3]. The predominant quenching mechanism is the physical quenching reaction. In this process, the excitation energy from singlet oxygen ($^1O_2$) is transferred to ß-carotene; the products of this process are triplet or (ground state) oxygen and triplet excited ß-carotene(C^*). The excess energy in ß-carotene is dissipated though rotational and vibrational interactions between ß-carotene and the solvent. The rate constant for equation (1) is very fast, $k = 4 \times 10^9\ M^{-1}\ s^{-1}$ [7].

$$^1O_2 + C \rightarrow {}^3O_2 + {}^3C^* \quad (1)$$

$$^3C^* \rightarrow C + \text{Thermal energy} \quad (2)$$

For ß-carotene physical quenching is dominant. Chemical quenching is a very minor process comparing to physical quenching. In chemical quenching, carbonyl products and endoperoxides are formed, Figure 3 shows the reaction pathways [10].

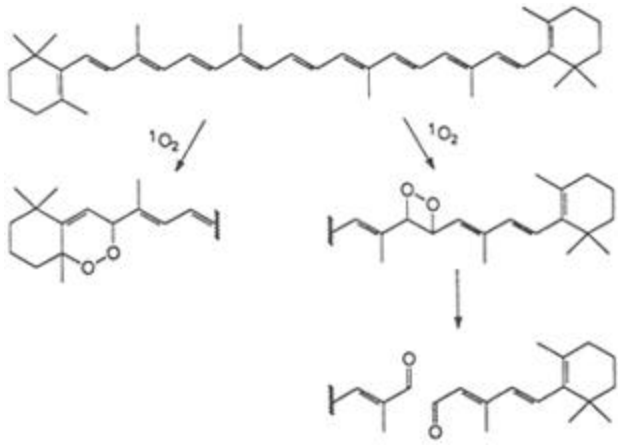

Figure 4: Reaction pathways for singlet-oxygen dependent ß-carotene oxidation [10].

Antioxidant and autoxidation reactions

Burton and Ingold demonstrated that ß-carotene inhibits lipid peroxidation primarily by reaction with peroxyl radicals, and thus it is a chain-breaking antioxidant [4]. Peroxyl radical can propagate radical chain reactions (3) [10]. ß-Carotene traps peroxyl radical to stop the chain reactions. The reaction is depicted in equation (4)

$$LOO^{?} + LH \; ? \quad LOOH + L^{?} \tag{3}$$

$$LOO^{?} + C \; ? \quad \text{radical intermediate} \tag{4}$$

To be a biological effective antioxidant, reaction 4 must be much faster than reaction 3.

In fact, ß-carotene is not a very potent antioxidant [12]. Actually, Reaction 3 and 4 are not the only reactions involved in this process. Radical intermediates formed from reaction 4 may trap a second peroxyl radical to form nonradical products 5. In addition, radical intermediates also react reversibly with oxygen to form a peroxyl radical 6.

$$\text{Radical intermediate} + LOO^{?} \; ? \quad \text{nonradical product} \tag{5}$$

$$\text{Radical intermediate} + O_2 \leftrightarrow \text{antioxidant-}OO^{?} \tag{6}$$

For vitamin E-derived radical intermediate, the equilibrium in reaction (4) goes to the left. However, for ß-carotene-derived radical intermediate, the equilibrium goes far to the right. Moreover, when oxygen tension is increased, the equilibrium is pushed further to the right.

Reaction pathways from reaction 4 to reaction 5 consume radicals and are referred to antioxidant reactions. In contrast, the reaction pathways from reaction 4 to reaction 6 consume antioxidant without removal of radicals are autoxidation reactions. ß-Carotene is considered to be a pro-oxidant because of these autoxidation reactions. Antioxidant effectiveness of ß-carotene depends on the balance between antioxidant reactions and autoxidation reactions. In the

case of ß-carotene, this balance is highly dependent on the oxygen tension in the system. That is why ß-carotene is most effective at low oxygen pressure.

Reaction with peroxyl radical

ß-carotene reacts with peroxyl radicals by two mechanisms. The most important mechanism is polyene-related addition reactions [4]. Addition to the 5,6-double bond following elimination of an alkoxyl radical yields epoxides, which is referred to pathway A in Figure 4 [11]. Addition to the polyene chain may initiate the formation of apocartenal and apocarotenone chain cleavage products. Addition another peroxyl radical will result in the formation of a *bis*-peroxyl adduct, which will then decompose into a carbonyl-containing products. Pathway B in Figure 4 shows this process [11].

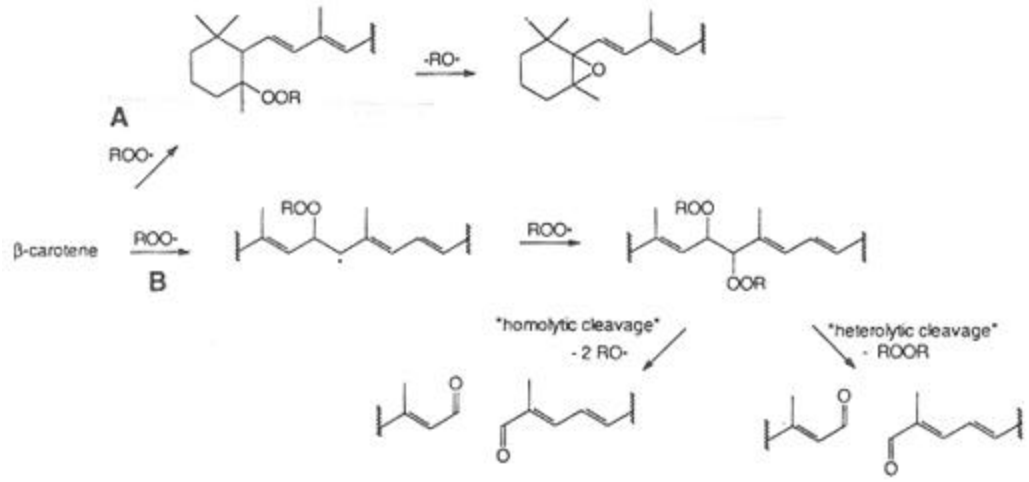

Figure 5: Reaction pathways for β-carotene with peroxyl radical

ß-carotene can react with peroxyl radicals in another mechanism. Peroxyl radicals are sufficiently strong oxidants to remove an electron from ß-carotene polyenes. The resulting ß-carotene cation radical has a characteristic absorption at 955 nm [11].

$$\text{ß-carotene} + ROO^{?} \; ? \quad \text{ß-carotene}^{? +} + ROO^{-} \qquad (7)$$

Detection

A number of methods have been developed to detect ß-carotene absorption, fluorescence, resonance Raman (rR), nuclear magnetic resonance (NMR), electronic paramagnetic resonance (EPR) and high performance liquid chromatograph (HPLC) are some of them.

The radical form of ß-carotene is mostly detected by EPR technique because of its-short life-time [14]. Fast kinetic spectrometer is used to detect the ß-carotene radical as well.

Summary

ß-Carotene's primary function *in vivo* is to serve as a reservoir for retinal, retinaldehyde and retinoic acid. Its function as a singlet oxygen quencher is already demonstrated. However, its role in free radical scavenging is still controversial partially because of the autoxidation reactions involved. Unlikely to vitamin E, which can effectively trap peroxyl radicals and inhibit lipid autoxidation in biomembranes, the potency of ß-carotene varies from system to system for reasons that are very poorly understood. ß-carotene seems to be health promoting when taken at physiological levels, but may be harmful to health when taken at high doses and in the presence of highly oxidative conditions. The mechanisms to explain it need further research.

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