β-Carotene: Radical Reactions and Cancer Associations-Leading Down a Rabbit Hole?

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Editorial

Approximately 600 carotenoids have been identified with about 100 finding their way into foodstuffs consumed by humans [1]. These pigments are widely distributed as naturally occurring constituents of fruits and vegetables. They are often added to human foodstuffs in order to achieve acceptable food coloration as they strongly absorb light in the region of 400-500 nm and are colored red, orange, and yellow. Chemically these pigments are tetraterpenoids consisting of eight isoprenoid residues. Carotenoids serve in a protective role to photosensitization by endogenous photosensitizers such as the porphyrin-containing photosynthetic pigments and in the human genetic disorder Erythropoietic protoporphyria. β-carotene is an important micronutrient for human health as it is a non-toxic precursor for the synthesis of vitamin A. Its role in affecting a reduction in cancer incidence is in question.

β-Carotene was shown to be an efficient quencher of singlet oxygen (Eq. 1) in 1968 [2]. The reverse reaction was not observed. The \( ^1\text{Car} \) does react with oxygen but by enhanced intersystem crossing and not \( ^1\text{RO}_2 \) energy transfer and thus, no singlet oxygen is produced [3]. It was generally thought that the rate of singlet oxygen quenching paralleled its protective action [4].

\[
\text{O}_2 (\Delta \lambda) + \text{Car} \rightarrow \text{Car} + \Delta \lambda
\]  

However, Mathews-Roth, et al. [5] found that the protective action of a series of carotenoids didn’t necessarily parallel the \( \text{O}_2 (\Delta \lambda) \) quenching capacity and suggested that carotenoids might interfere with radical reactions initiated \textit{in vivo} [6]. Subsequently, it was shown that carotenoids could effectively inhibit lipid peroxidation in microsomal membranes by mechanisms not initiated by \( \text{O}_2 (\Delta \lambda) \) [7]. Carotenoid antioxidant efficiency was influenced by several factors including the type of radical initiator and the site and rate of radical formation [6].

Critical to an understanding of the biological responses to carotenoids, it was shown that β-carotene exhibited good radical trapping antioxidant behavior at partial oxygen pressures significantly less than 150 Torr (pressure of \( \text{O}_2 \) in normal air). At higher \( \text{O}_2 \) pressure β-carotene lost its antioxidant capacity and exhibited autocatalytic, pro-oxidant effects [8]. However, these results were obtained in a non-biological environment (chlorobenzene solvent) so that the actual oxygen levels at which a switch from anti- to pro-oxidative behavior that was observed in this study may not be relevant to a biological environment. Related to these results, it was found that at very low oxygen concentrations only the carotenoid radical cation (\( \text{Car}^+ \)) was observed (via electron transfer) when reacting with an oxygen-centered radical such as a peroxyl radical (Eq. 2) [9]. The radical cation is observed when reacting with \( \text{CCl}_3 \), but another radical is also observed (as well as the radical cation) in the presence of oxygen, i.e., on reaction with \( \text{CCl}_3 \)O\._2·. Presumably, this second radical is a peroxyl radical adduct.

\[
\text{RO}_2^- + \text{CAR} \rightarrow \text{RO}_2^- + \text{Car}^+
\]

More recently a potential mechanism to explain a large oxygen concentration response to cell protection against \( \text{OH}^- \)-by lycopene (Lyc) was proposed [10]. β-carotene behaves in a similar manner [Boehm, Edge, Truscott, in preparation]. The \( \text{OH}^- \) was generated via high energy γ-radiation of aqueous solutions. The mechanism of cell protection did not involve carotenoid radical cations but, instead, the removal of the damaging \( \text{OH}^- \)-radical by the formation of the neutral \( \text{LycOH} \) radical. At higher oxygen concentrations the anti-oxidant effect was totally lost due to the production of reactive peroxyl radicals (\( \text{’OOLycOH} \) (Eq. 3 and 4) that are formed in increasing concentrations as the oxygen level increases.

\[
\text{Lyc} + \text{OH}^- \rightarrow \text{LycOH}
\]

\[
\text{’OOLycOH} + \text{O}_2 \rightarrow \text{OOLycOH}
\]

An epidemiological study in 1981 reported that individuals that consumed greater levels of green, leafy vegetables exhibited a lower risk for cancer [11]. Because these foods are rich in β-carotene and based upon the carotenoids specific capacity to quench singlet oxygen, scavenge oxy-radicals, and terminate free radical reactions, it was suggested that β-carotene might be responsible for this anti-cancer potential. This opened a groundswell of interest in β-carotene as an anti-cancer agent. Indeed, many observational studies, based on dietary carotenoid intake, have shown inverse relationships with cancer incidence. These include lung, colon, breast, and prostate [12].

However, in the face of rather overwhelming epidemiological evidence, clinical trials failed to support such a connection. Greenberg et al [13] reported that “in persons with a previous non-melanoma skin cancer, treatment with beta-carotene does not reduce the occurrence of new skin cancers over a five-year period of treatment and observation”. Clinical trials abruptly ended when investigators “found no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with α-tocopherol or beta-carotene” [14].

Disturbingly, they found that “among the men who received beta-carotene, an excess cumulative incidence of lung cancer was observed after 18 months and increased progressively thereafter, resulting in an 18% difference (p=0.01) in incidence by the end of the study”.

Nor were results from studies of experimental UV-carcinogenesis straightforward. Early studies had shown that β-carotene supplemented diets were significantly protective to UV-induced carcinogenesis

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Perhaps the presence of β-carotene in those yellow/green vegetables may act as a pro-oxidant and fill a pro-carcinogenic role. We may add oxygen tension to this list. Under specific conditions, radical reactions in the target tissue, localization and mobility with respect to hydrophobic and hydrophilic domains and turnover rates could result in accumulation of the carotenoid radical cation, a highly oxidative species that might participate in the pro-carcinogenic activity.

\[
\text{RO}_2^- + \text{TOH} \rightarrow \text{TOH}^- + \text{ROOH} \quad (5)
\]

\[
\text{TOH}^- + \text{Car} \rightarrow \text{TOH} + \text{Car}^- \quad (6)
\]

\[
\text{Car}^- + \text{Asch} \rightarrow \text{Car} + \text{Asc}^- \quad (7)
\]

However, when vitamin C supplementation was increased 6-fold in the semi-defined diet or eliminated from the diet, there were no significant changes in the level of exacerbation induced with β-carotene [21]. Nor was there any effect of increasing vitamin E levels 10-fold. Nonetheless, when vitamin E levels were lowered to that found in the closed-formula diet, exacerbation of tumor multiplicity increased nearly 6-fold [22]—confirming an interaction of vitamin E and β-carotene. Assuming that vitamin E and β-carotene interact to terminate oxy-radical propagation with the formation of the β-carotene radical cation, then what repairs this highly oxidative radical? Could it be other carotenoids, isomers of carotenoids, or, as yet, undesignated phytochemicals?

As the free radical theory of disease (cancer) developed, the major participants were painted with a broad brush stroke radical reactions were deleterious and anti-oxidants were beneficial. The difficulties in understanding the physiological responses by an anti-/pro-oxidant such as β-carotene are becoming more and more apparent from studies reflected here and influenced by factors such as target tissue concentrations, absorption by the target tissue, rate constants for radical reactions in the target tissue, localization and mobility with respect to hydrophobic and hydrophilic domains and turnover rates and cyclization [23] – all are factors that will affect β-carotene’s action. We may add oxygen tension to this list. Under specific conditions, β-carotene may act as a pro-oxidant and fill a pro-carcinogenic role [24]. Perhaps β-carotene is a red-orange herring that has led hundreds of researchers down the proverbial rabbit hole, consuming millions in resources for the past 37 years in search of its anti-cancer properties. Perhaps the presence of β-carotene in those yellow/green vegetables merely cloaks the real anti-cancer agent. Nevertheless, the game remains afoot to explain how β-carotene, a molecule with superior antioxidant capacity under specific conditions and a singlet oxygen quencher, can act as a pro-carcinogen in UV-carcinogenesis and in lung cancer patients.

References