Beta-Carotene, Aging & Degenerative Disease

Beta Karoten, Yaşlanma ve Dejeneratif Hastalık

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ABSTRACT Aging, as already postulated in the 1950s in the "free-radical theory of aging", is associated with oxidative stress. Furthermore, there is unequivocal evidence for the contribution of oxidative stress in the development of many age-related degenerative diseases, in particular cancer, cardiovascular and neurodegenerative diseases. Therefore, to delay aging and to prevent degenerative processes antioxidants appear to be the measure of choice, amongst which β-carotene received particular attention, since it has been demonstrated to scavenge radicals, quenches singlet oxygen and inhibits lipid peroxidation. In fact it turned out, that an increased consumption of β-carotene reduces the risk for certain degenerative diseases, however, two large-scale cancer chemoprevention trials unexpectedly showed an increased risk of lung cancer in smokers. In vitro investigations point at the formation of toxic cleavage products as the primary cause and indicate, that supplementation with antioxidants such as N-acetyl-cysteine may inhibit this effect.

Key Words: β-carotene, β-carotene cleavage products, aging, degenerative disease

ÖZET Yaşlanma, 1950'lerde "yaşlanma serbest radikal teorisinde" öne sürüldüğü gibi, oksidatif stresle ilişkilidir. Ayrıca, oksidatif stresin başta kanser, kalp damar ve nörodejeneretif hastalıklar olmak üzere yaşla ilişkili dejeneratif hastalıkların birçoğunun gelişimindeki katkısı hakkında kesin kanıtlar bulunmamaktadır. Bu nedenle, yaşlanmayı geciktirmek ve dejeneratif süreçleri engellemek için, antioksidanlar önemli arasında bulunmaktadır. Bu seçeneklerden birisi de, radikalleri uzaklaştırdığı, tekli oksijenleri bastırdığı ve lipid peroksidasyonu önlediği için β-karotendir. Aslında, β-karotenin aşırı tüketilmesinin belirli dejeneratif hastalıklarla ilgili riski azalttığı ortaya çıkmıştır ancak iki büyük ölçekli kanser kemo-önleme çalışması şaşırtıcı şekilde sigara içicilerde akciğer kanseri riskinin arttığını ortaya koymuştur. In vitro araştırmalar ana neden olarak toksik klevaj ürünlerinin oluşumuna işaret etmektedir ve N-asetil-sistein gibi antioksidan takviyesinin bu etkinin önüne geçtiğini göstermektedir.

Anahtar Kelimeler: β-karoten, β-karoten klevaj ürünleri, yaşlanma, dejeneratif hastalık

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CAROTENOIDS

Carotenoids are fat-soluble natural pigments, mostly of plant origin. Chemically they belong to the tetraterpenoids. Depending on the number of double bonds several cis/trans configurations are possible and enable a large number of different carotenoids – approximately 600 are known. Carotenoids can be subdivided into carotenes, consisting only of carbon and hydrogen, and xanthophylls, which are oxygen-containing derivatives of carotenes.

B-CAROTENE: BIOLOGICAL AND HEALTH EFFECTS

β-Carotene is found principally in plants, where it serves as an accessory light-gathering pigment and to protect these organisms from toxic effects of oxygen. Human sources of β-carotene are fruits, i.e. apricots and peaches, and vegetables, i.e. carrots, squash and broccoli.

β-Carotene is also known as pro-vitamin A. Being a symmetrical molecule, enzymatic cleavage in the intestinal mucosa leads to the formation of two molecules vitamin A (retinol), which is further converted enzymatically into the vision pigment retinal.

Apart from its action as a pro-vitamin β-carotene has been demonstrated to have antioxidant activity in vitro i.e. by scavenging peroxyl radicals, in particular lipid peroxyl radicals, nitrogen dioxide ($NO_2^{\bullet}$)-, thiyl ($RS^{\bullet}$)- and sulfonyl ($RSO_2^{\bullet}$)-radicals, quenching singlet oxygen and inhibiting lipid peroxidation.[1-4]

At the cellular level β-carotene has been demonstrated to address signalling pathways, i.e. β-carotene induces cell cycle arrest and apoptosis via down-regulation of cyclin A and Bcl-2 family proteins.[5] Further, it has been shown to stimulate cell communication via gap junctions, an effect which is correlated with the ability to inhibit chemically induced neoplastic transformation.[6,7] Additionally, carotenoids can modulate phase I and phase II metabolic enzymes involved in the metabolism of mutagens/carcinogens and can thus inhibit the formation of reactive metabolites.[8,9]

β-Carotene has also been found to modulate immune function, i.e. it stimulates blood neutrophil killing activity via increased myeloperoxidase and phagocytic activity, an enhanced antibody response, an increased mitogen-induced lymphocyte proliferation and an increased respiratory burst.[10]

The effects described serve as explanation for the observation that the increased intake of carotenoids or fruits and vegetables as primary source of carotenoids reduce the risk to develop certain degenerative diseases. In particular this effect was associated with cardiovascular diseases, age-dependent macula degeneration, cataract formation and certain types of cancer such as colon, lung, stomach and prostate.[11-16]

B-CAROTENE AND AGING

Since its postulation by Harman in 1957 the free radical theory of aging, - explaining aging as a cumulative damage by endogenous oxygen radicals – has received continuous scientific support and currently represents the most accepted aging theory.[17] Since the aforementioned degenerative diseases and other disorders are also associated with oxidative stress, and their occurrence in general is age-dependent, they can be considered to be one facet of the common motif aging, and the use of antioxidants should therefore delay aging and prevent degenerative diseases.[18,19] In fact there are reports from animal experiments indicating that the survival can be prolonged by dietary antioxidants.[20] Human epidemiological studies on the other hand are not conclusive.[21] However, beneficial effects on age-related aspects such as cognitive impairment and immunological parameters are documented.[22,23]

THE B-CAROTENE PARADOX

Beside the data summarized above, a beneficial role of β-carotene could not be supported by several cancer chemoprevention trials. Strikingly, in two major trials (the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and the Beta-Carotene and RETinol Efficacy Trial) cancer incidence was increased with β-carotene supplementation in both smokers and asbestos workers.[24,25]

It was therefore suggested by Wang and Russell, that β-carotene metabolites are responsible for the carcinogenic response, and Siems et al. were the first to demonstrate that β-carotene cleavage products induce oxidative stress in vitro.[26,27] Based on this observation both a cleavage product (CP) mixture generated by hypochlorite bleaching of β-carotene and one of the major carotenals contained - apo8`-carotenal - were tested for their genotoxic potential in the primary hepatocyte assay, both in the presence and absence of oxidative stress. These investigations clearly demonstrated a dose-dependent genotoxic potential of the CPs, which was further enhanced in the presence of oxidative stress by hypoxia/reoxygenation or DMNQ application. This genotoxic potential was not accompanied by cytotoxicity.[28,29] Cytotoxicity, however, appears when hepatocytes are not proliferatively stimulated and is characterized by significantly increased rates of necroses and apoptoses. This toxic effect can be inhibited by the supplementation of the treated cultures with antioxidants such as N-acetyl-cysteine, ascorbic acid and trolox, and is based upon their ability to detoxify aldehydes.

Since the outcome of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and the Beta-Carotene and RETinol Efficacy Trial indicates a higher

sensitivity of lung cells towards oxidative stress and/or β-carotene breakdown products, a culture system for primary rat pneumocytes was further established and both cyto- and genotoxic effects of β-carotene under oxidative stress by dimethoxynaphthoquinone (DMNQ) were elaborated. The results obtained indicate that pneumocytes are more sensitive towards DMNQ than hepatocytes. Increasing concentrations of β-carotene led to an increase of apoptosis and a prominent decrease of the cell density clearly indicating a cytotoxic potential. In contrast, no clear evidence for genotoxicity is provided by the results of the micronucleus and the COMET assay (supported by grant P20096 of the Austrian Science Foundation and COST action B35).

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