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Review

Insights of hypercarotenaemia: A brief review

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SUMMARY

Carotenoids are generally 40-carbon tetraterpenoids responsible for most of the yellow, orange and red colours throughout the natural world. Pro-vitamin A carotenoids serve as the precursors of vitamin A. In addition to that, carotenoids exhibit range of important protective mechanisms in human health. Hypercarotenaemia is characterized by carotenodermia resulting in yellowing of the skin specially palms and soles. Hypercarotenaemia develops in subjects consuming high levels of carotenoid rich foods or β-carotene supplements (>30 mg day^{-1}) over a period of months. Less or normal intake of carotenoids very rarely gives rise to metabolic carotenaemia due to genetic defects of the enzyme 15-15′-carotenoid dioxygenase. Moreover, it is known that those with hypothyroidism and diabetes mellitus tend to develop hypercarotenaemia with the normal intake of carotenoid rich foods. Further, hypercarotenaemia has been reported in anorexia nervosa. However, recently some studies have been shown that there is no major correlation between carotenoid intake and hypercarotenaemia indicating that a genetic factor is at play in development of hypercarotenaemia. Therefore, the subjects appear to need to be genetically predisposed to hypercarotenaemia.

1. Introduction

Hypercarotenaemia is a benign condition characterized by carotenodermia caused by the deposition of carotenoids in the stratum corneum of the epidermis resulting in jaundice-like yellowing of the skin specially palms and soles and high plasma carotenoid concentrations [1,2]. However, fat bearing tissues are the main target of carotenoids, which is adipose tissue. The carotenoid in the serum is only small indications of the total carotenoids accumulated in the body. It is hypothesized that there may be an equilibrium of carotenoids in adipose tissue, serum and liver.

Hypercarotenaemia can be differentiated by jaundice because in hypercarotenaemia, sclera of the eye and buccal mucous membrane are not converted into yellow colour as they are mainly protein-based structures. Hypercarotenaemia spontaneously recovers when the dosage is reduced or after cessation of intake. 'Canthaxanthin retinopathy' a known toxic manifestation of carotenoid intake has been reported from European countries due to large doses of canthaxanthin. Under this condition, a reversible deposition of pigmented granules in the retina had been occurred with some loss in night vision [3].

2. Occurrence of carotenoids

Carotenoids are a widespread group of natural plant pigments responsible for most of the yellow, orange and red colours throughout the natural world. They are found in the plant kingdom, providing brilliant colours to fruits, vegetables and flowers. Carotenoids are invariably found in all green plant tissues. In leaves, they are located in chloroplasts as photosynthetic pigment–protein complexes and in mature fruits and flowers within chromoplasts. In green tissues although the colour of carotenoids is masked by that of the remarkably high green pigment of chlorophyll, colour appears during maturation of fruits and in leaves with the onset of autumn or leaf fall which is associated with the degradation of chlorophyll [4].

Ripening of fruits accompanies the conversion of chloroplasts into chromoplasts with the disappearance of photosynthetic organelles. In this conversion carotenoids are concentrated in distinct structures, which can be defined as crystalline, fibrillar, tubular, membranous and globular [5].

Annual *de-novo* production of carotenoids in nature is about 100 million tons by all higher plants along with some bacteria, algae, yeast and fungi. It is estimated that more than 600 of different carotenoids excluding *cis* and *trans* isomers are widely distributed and they have now been identified. This number includes the

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extensive diversity of carotenoids in algae bacteria and fungi. Animals are incapable of synthesizing carotenoids. But, fewer amounts of these pigments have been encountered in some animal foods as a result of selectively or non-selectively absorbed carotenoids from their diet. This is known to be deposited unchanged or transformed to keto or hydroxy derivatives [6,7].

3. The structure of carotenoid

Carotenoids are generally 40-carbon tetraterpenoids, which are formed by joining eight 5-carbon isoprene units ($-CH_2-C(CH_3)=CH-CH_2-$) in a head-to-tail manner except at the center where there is a tail-to-tail linkage. As a result, the sequence is reversed at the center, which provides a symmetrical and linear basic molecule. Lateral methyl groups of this molecule are separated by six carbon atoms from the center of the molecule and five carbon atoms elsewhere in the molecule. The basic linear carotenoid structure may be subject to processes such as hydrogenation, dehydrogenation, cyclization, double bond migration, chain shortening or extension, introduction of oxygen functions, rearrangement, isomerization or any combination of these modifications resulting 'in a myriad of structures' [6]. The carotenoids mainly found in plant foods are given in Fig. 1.

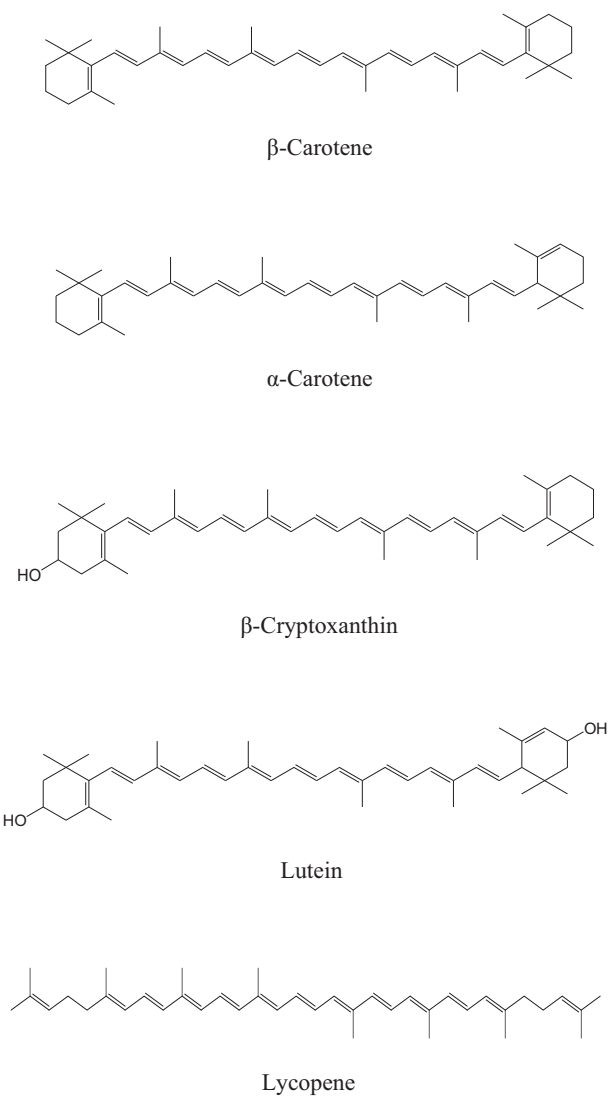

Fig. 1. Some main carotenoids found in plant foods.

4. Biological functions of carotenoids

Though more than 600 carotenoids have been found in the nature, α-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, lycopene and canthaxanthin have been detected predominantly in human blood [4]. Biological functions of carotenoids mainly include its pro-vitamin A activity. The pro-vitamin A carotenoids act as the precursor of vitamin A. Vitamin A has many health benefits and it is mainly involved with vision, cell differentiation and maintenance of cell membranes, embryogenesis and immuno-enhancement [2]. In addition to that, carotenoids exert their antioxidant activity by singlet oxygen quenching and free radical scavenging effects thereby they possess a range of important protective mechanisms for human health. This involves protection against the pathogenesis of degenerative diseases especially coronary heart diseases, cancers and an array of other free radical-mediated conditions [8–10]. Lutein and zeaxanthin are important in prevention of age-related macular degeneration [11].

5. Bioconversion of carotenoids

The proportion that is converted into retinol from the absorbed pro-vitamin A carotenoids is known as 'bioconversion'. The cleavage is catalyzed by the cytosolic enzyme 15-15′-carotenoid dioxygenase and the key enzyme is β-carotene-15-15′-dioxygenase. The central cleavage occurs at the central 15:15′ double bond and in the case of β-carotene the yield would be two molecules of retinal [12,13]. This can be either be reduced to retinol or oxidized to retinoic acid. The reaction takes place primarily in the intestinal mucosa and enzyme activity is also found in tissues such as the liver. Though central oxidative cleavage is the major pathway asymmetric cleavage is also possible [14]. Asymmetric cleavage would produce apo-carotenal intermediates that could be converted to apo-carotenoic acids, which subsequently can be converted into retinoic acid [15]. Alternative metabolic products of β-carotene by central and eccentric cleavage path ways are given in Fig. 2.

6. Biochemical basis of hypercarotenaemia

Hypercarotenaemia develops due to intake of high doses of β-carotene or carotenoid rich foods such as carrot, pumpkin, orange, tomato or β-carotene supplements (>30 mg day^{-1}) over a period of months. When carotenoids are ingested in excess for extended periods, the pro-vitamin A carotenoids are not converted into retinol if vitamin A level in the body is satisfactory. This self-limiting conversion is important in prevention of hypervitaminosis. This leads to an increase carotenoid concentration in the serum with resultant hypercarotenaemia [1,2]. On the other hand, failure to split pro-vitamin A carotenoids into retinal due to genetic defects of the enzyme 15-15′-carotenoid dioxygenase also can lead to metabolic carotenaemia under less or normal intake of carotenoids, but this is very rare [16].

Vitamin A and retinoids are metabolized in the liver. In this case liver cytochrome P_{450} plays a role to enhance the polarity of the metabolites. It is assumed that the carotenoid degradation process is likely to be similar to that of vitamin A and retinoids. Therefore, taking part of cytochrome P_{450} system in carotenoid metabolism is possible. Due to inefficient absorption, some carotenoids exit in the faeces probably via bile. The final metabolites of carotenoids excreted are still unknown [1].

It is also shown that those with hypothyroidism tend to develop hypercarotenaemia with the normal intake of carotenoid rich foods. The thyroxine and hyperthyroidism can enhance the conversion of β-carotene which is a pro-vitamin A carotenoid in to two molecules of vitamin A (retinol). Therefore, the characteristic

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