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Introductory Chapter: A Global Perspective on Vitamin A

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1. General aspects of vitamin A

Vitamin A is a globally essential nutrient belonging to the group of fat-soluble vitamins that was first described in 1913 in a study of animals fed with ethereal egg or butter extract [1]. In the same year, Osborne and Mendel [2] made the first association of this vitamin with growth. Later, observations made by Steenbock [3] concluded their association with foods of yellow pigmentation (now known as β -carotene). The importance of vitamin A in vision health has been considered since ancient Egypt (1500 BC), where people suffering from night blindness were treated with a topical extract of hepatic liver extract (recognized today as a rich source of vitamin A) [3–6].

Its deficiency has typically been associated with continued malnutrition and childhood blindness; it is estimated that 254 million people suffer from vitamin A lack or related ocular disease [7]. It is now known that its benefits go beyond its role in vision yet include numerous essential metabolic and systemic functions [8].

To supply their metabolic functions and to avoid deficiency or overdosage, daily intake requirements were established according to their activity. This activity can be expressed as international units (IU) or retinol equivalents (RE): 1 IU is equivalent to 0.3 μg of total trans retinol or 0.6 μg of total all-*trans*- β -carotene, whereas 1 RE is equivalent to 1 μg of all-*trans*-retinol, 6 μg of all-*trans*- β -carotene, or 12 μg of another provitamin A carotenoids [9].

The recommended daily requirement for adult men and women is 900 and 700 μg RE/day, respectively, while 300 and 250 μg RE/day are the minimum intake limits. During pregnancy and lactation, recommendations are 700 and 950 μg RE/day, respectively [8, 9]. In the case of children in populations considered vitamin A deficient, doses of 60,000 μg RE/day are distributed twice a year [10]. According to Stephensen et al. [11], acute toxic reactions are uncommon at the dosages below 30,000 μg RE/day.

2. Basic chemistry and potential sources

Vitamin A is a lipophilic molecule; its structure was first elucidated by Paul Karrer in 1931 from fish liver oils, for which he won the Nobel [12]. It is now known that the term “vitamin A” is a generic term for retinol and its active metabolites, such as the retinal and retinoic acid [13]. Retinyl esters and carotenoids are also considered vitamin A forms; however, they are oxidized to active forms as soon as they enter the digestive tract of mammals [14].

In general, a retinoid is C_{20} compound formally constituted of a β -ionone nucleus attached to four isoprenoid units and a functional group at the end of the acyclic chain [7]. As can be seen in **Figure 1**, retinol (all-*trans*-retinol) has an

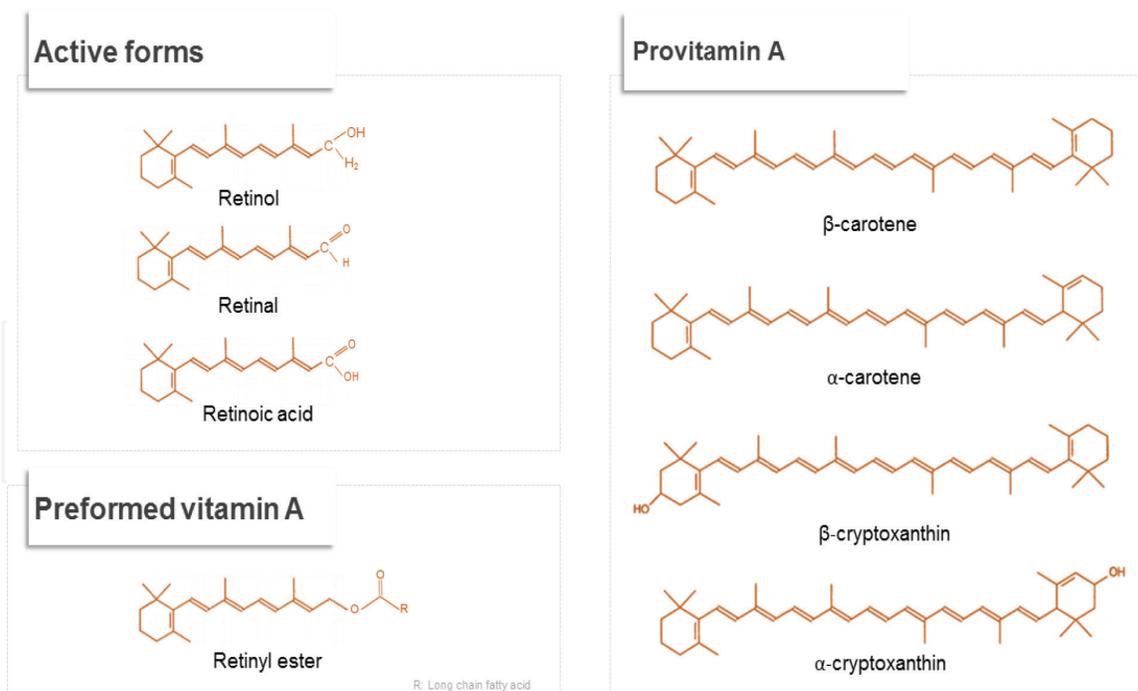


Figure 1.
Chemical structure of the different forms of vitamin A.

alcoholic end group, where oxidation of this group gives rise to an aldehyde group which characterizes the retinal (all-*trans*-retinal) structure, which may be further converted to all-*trans*-retinoic acid [15, 16].

These structures are essential for life in mammals; however, they cannot be de novo synthesized, and their supply depends on dietary intake. They are supplied to the human body in different forms, such as carotenoids provitamin A (mainly β -carotene) or preformed vitamin A (retinyl esters) [13, 17–19].

Carotenoids of provitamin A are present in both plant (via de novo synthesis) and animal products (via dietary intake) [7]. Those having provitamin A activity have at least one β -ring unsubstituted with an 11-carbon polyene chain, which undergoes enzymatic cleavage (in humans and animals) to produce at least one molecule of retinol [20–22]. It is estimated that 1178 natural carotenoids were characterized correctly and reported in the literature [23, 24]. Of these, about 60 have provitamin A activity [20]. However, only some of these carotenoids are commonly found in foods, such as β -carotene, α -carotene, β -cryptoxanthin, and α -cryptoxanthin, with β -carotene being the only one with 100% activity [25].

On the other hand, preformed vitamin A, predominantly retinyl palmitate, is obtained only from sources of animal origin, the main related foods are milk, meat, and eggs [7]. Also, for infants, breast milk is the primary source of vitamin A, aimed at meeting the daily needs and the formation of hepatic reserve of this vitamin [26].

3. Metabolism and biological functions

Regardless of the source of origin, retinol can be stored in various tissues (predominantly in the liver) to maintain adequate serum levels for extended periods [8]. Among the three states of oxidation (retinol, retinal, and retinoic acid), retinol is the most active form, whereas retinoic acid is the only one that is not stored [27].

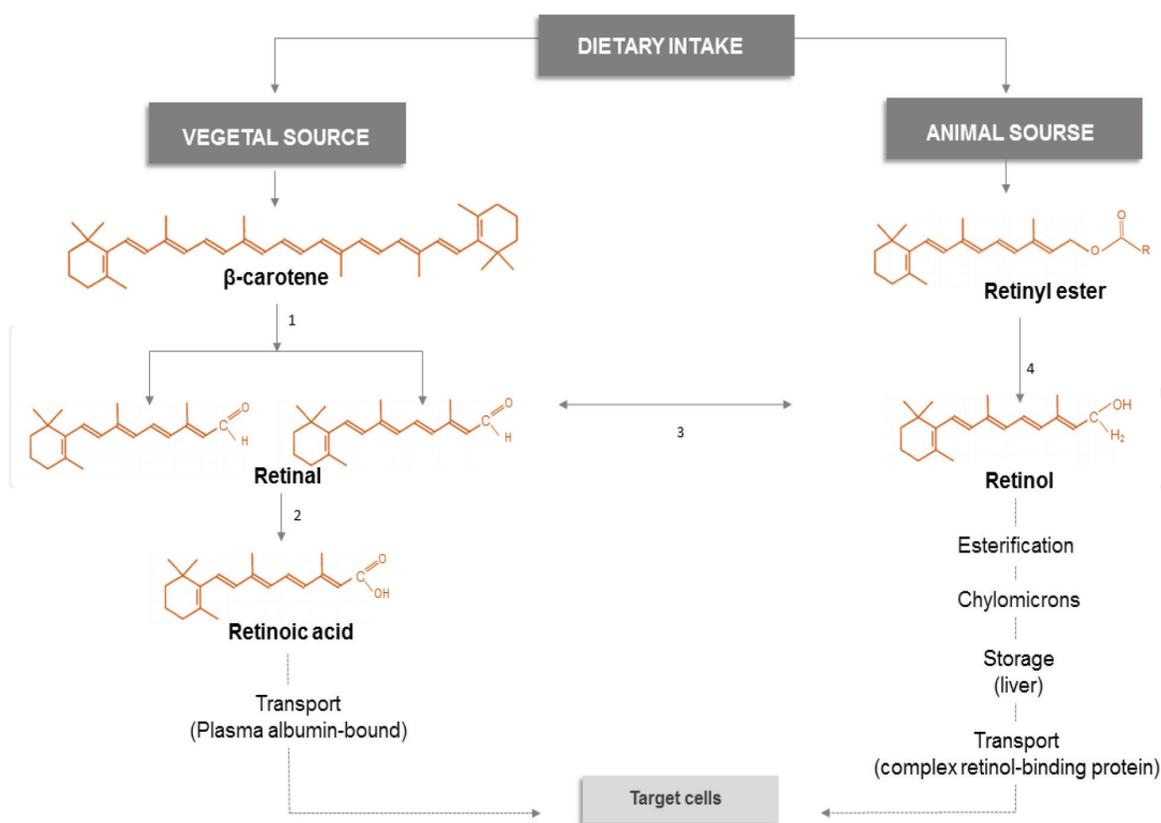


Figure 2. Metabolic fate of vitamin A. (1) β -carotene dioxygenase, (2) retinol dehydrogenase, (3) retinal reductase, and (4) ester hydrolases of retinyl.

Figure 2 summarizes the metabolic fate of vitamin A. The different forms of diet enter the digestive tract and are predominantly absorbed in the proximal part of the small intestine [8].

Pro-vitamin A carotenoids are cleaved (via β -carotene dioxygenase) to retinal [28]. This retinal can be reversibly converted to retinol (via retinal reductase) or irreversibly to retinoic acid (via retinol dehydrogenase); such interconversion occurs in the gut of all mammals [29]. On the other hand, retinyl esters of animal origin are converted to retinol via ester hydrolases of retinyl (REHs) [30].

The retinol formed is esterified to long-chain saturated fatty acids (mainly palmitic acid), packaged in chylomicrons, secreted into the lymphatic system, and stored in the liver (80% of the body supply) [31]. Minor amounts are distributed and stored in extrahepatic tissues and organs (eye, lung, adipose tissue, kidneys, small intestine, adrenal gland, testis, uterus, bone marrow, thymus, skin, and spleen) [32, 33].

When the retinoids reach the hepatic system, they are hydrolyzed and complexed with the retinol-binding protein to be transported the target cells as required. In contrast, retinoic acid is carried in plasma bound to albumin [34].

The most common benefit of this vitamin relates to vision, due to the high demand for this supply by the retina and maintenance of the cornea [8]. However, they are still associated with several functions such as the maintenance of healthy epithelium, cell differentiation, reproduction, immunity, and growth [16].

According to Engelking [29], retinol, retinal, and retinoic acid bind to nuclear proteins, where they are most likely involved in the control of gene expression. Recent research has shown that vitamin A supplementation can positively regulate the expression levels of proteins that improve the intestinal barrier [35]. Mucosal healing was significantly higher in the vitamin A-supplemented group in cases of ulcerative colitis [36].

4. Deficiency of vitamin A and strategies of fortification

Some physiological implications about the intake of high doses of vitamin A have been reported; however, it is their deficiency that causes catastrophic damage. Depletion of this nutrient has become a global problem affecting millions of people worldwide, especially those in developing countries [37]. It harms the health of approximately 190 million children and 19 million pregnant women worldwide [37].

In developing countries, it is the leading cause of childhood blindness and further contributes significantly to the morbidity and mortality of common childhood infections such as continuous malnutrition [38]. Additionally, it causes potential changes in the epithelial barrier of vital organs and tissues [39]. It further reduces the synthesis of specific glycoproteins in the intestinal mucosa and liver, as well as the gene expression of glycosyltransferases, fibronectin, and transglutaminases, disrupting macrophage function, blood clotting, and adhesion. Also, it disrupts normal bone growth as it is essential for the activity of cells in the epiphyseal cartilage [29]. Studies with animals also indicate that in the deficiency of this nutrient, the spermatogenesis is blocked causing infertility [29]. Problems in the regulation of vitamin D receptors may also be affected by the lack of vitamin A [40].

Because of all these controversial effects, highlighting the high morbidity and mortality, government agencies have recognized the problem as a public calamity situation and since then have been developing and supporting strategies to combat vitamin A deficiency [41].

Typically, these approaches are based on the fortification of basic foods, food ready for use, condiments, and mostly milk [42]. Among them are microencapsulation techniques and genetic crosses (biofortification) [18, 43, 44].

Microencapsulation has emerged as an alternative to increasing the stability and bioavailability of labile compounds such as vitamin A, and for this reason, it is believed that this process may be a strategy in food fortification to treat vitamin A deficiency [16, 45]. It is based in the encapsulation of the nutrient into microparticles of polymeric material with the variable diameter [46].

In contrast, the biofortification is an integrated approach of agriculture and nutrition, which uses traditional breeding or genetic engineering techniques [47]. In this case, species of foods containing high β -carotene content are used to obtain hybrid species adapted to places where vitamin deficiency remains a severe problem [48]. For example, genetic crosses made from yellow maize rich in β -carotene gave rise to other tropically adapted maize species [43, 44]. Besides, hybridization of sweet potatoes has also been extensively explored, especially in sub-Saharan Africa [44]. "Golden rice" is another successful example in several vitamin A-deficient countries [49]. According to Tanumihardjo [50], cassava is also included in the basic crops targeted for biofortification.

The chapters presented in this book are intended to help provide a deeper understanding and insight processes of perception and challenges for vitamin A, contributing substantially to the role of future vitamin A effects on human health.

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