COST is supported by the EU Framework Programme Horizon 2020.

SCIENTIFIC, N°5, 2017

NEWSLETTER

EUROCAROTEN

EUROPEAN NETWORK TO ADVANCE CAROTENOID RESEARCH AND APPLICATIONS IN AGRO-FOOD AND HEALTH

CAROTENOIDS IN THE HUMAN BODY: BIOAVAILABILITY AND BIOCONVERSION

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Corte-Real, J. (2017). Carotenoids in the Human Body: Bioavailability and Bioconversion. COST Action EUROCAROTEN (CA15136) Scientific Newsletter 5, 1-8.

The presence of carotenoids in the body

Although humans and other mammals are not able to synthesize carotenoids, their presence in the human body has long been known. The discovery of carotenoids in mammalian tissue dates back from the 1886 when A. Lieben and his colleague G. Piccolo found lutein in the *corpora lutea* of cows[1]. Since then, carotenoids have been identified in most organs of the human body, including the liver, adipose tissue, eyes, skin, brain, and also in human milk[2–6].

Bioavailability of carotenoids

In the context of carotenoids, bioavailability can be defined as the fraction of carotenoids that is absorbed and available for storage in the organs and tissues[7,8] (**Figure 1**). Carotenoids found in humans originate from diet, with fruits and vegetables being the main dietary source, although they can also be obtained from animal foods (like egg yolk, dairy products or the flesh of some fish, among others), algae, products containing them as additives (like some drinks, sauces and so on) and dietary supplements.

But how do carotenoids reach our organs and tissues?

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Digestion of carotenoids

Similarly to other nutrients and food constituents, carotenoids have to be, first of all, released from their food matrices during digestion[7,9] (**Figure 2**). During gastric digestion, under the action of hydrochloric acid and enzymes carotenoids are partially released from the food matrix into emulsified oil droplets. Throughout small intestinal passage, components of the food matrix and lipid droplets are further modified through the action of bile and pancreatic enzymes, and the hydrolysed triglycerides, phospholipids and other esters are partitioned into nanoscale (3 to 6 nm in diameter) sized bile-lipid mixed-micelles[10,11]. During this process, carotenoids are transferred from the oil droplets to the mixed-micelles, which serve as their carriers. The carotenoid-containing mixed-micelles will diffuse through the unstirred water layer and the intestinal mucus, until they are delivered to the surface of the intestinal mucosa of the upper gastro-intestinal lumen (i.e. duodenum and jejunum), where carotenoids can be taken up at apical surface of the enterocytes[7] (**Figure 2**). The fraction of carotenoids that is effectively released from the food, incorporated into mixed-micelles, and finally available for

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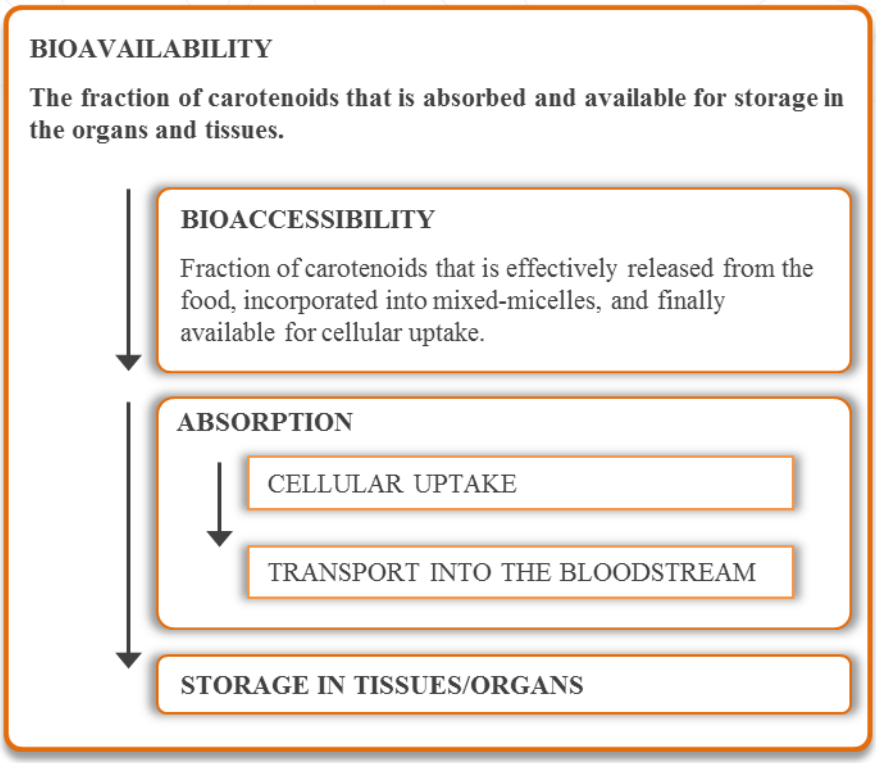

Figure 1. Representation of the concept of carotenoid bioavailability.

cellular uptake, is defined as bioaccessibility and it is integrated in the concept of bioavailability (**Figure 1**).

Uptake and transport across the intestinal epithelium

Transport across the intestinal epithelium has been partly attributed to passive diffusion, and partly to a more selective protein-facilitated diffusion[12] involving cholesterol, and other lipid transporters. Proteins identified so far as carotenoid transporters include the scavenger receptor Class B type I (SR-BI), Cluster determinant 36 (CD36), and the Nieman-Pick C1-like 1 (NPCL1)[13]. Besides of the gastro-intestinal tract, these proteins are also expressed in other organs and tissues in the human body including the liver (SR-BI and NPC1L1), the male and female gonads (SR-BI and CD36), the skin and the adipose tissue (SR-BI and CD36)[14]. The role of transport proteins in carotenoid uptake by enterocytes has been comprehensively reviewed previously[13,15] and we advise the reader to refer to the respective articles for more in depth information on the topic.

Once taken into the enterocytes, carotenoids can either be cleaved by enzymatic activity (discussed further ahead), or directed to the Golgi apparatus where they will be incorporated into triacylglyerol-rich chylomicrons, and secreted at the basolateral side of the cells. A third option is their release back into the intestinal lumen as result of normal cellular efflux[16] (**Figure 2**).

Transport of carotenoids through the bloodstream

Carotenoids that are incorporated into chylomicrons are secreted into the intercellular space, following to the lymph to finally reach the bloodstream[17]. Chylomicrons

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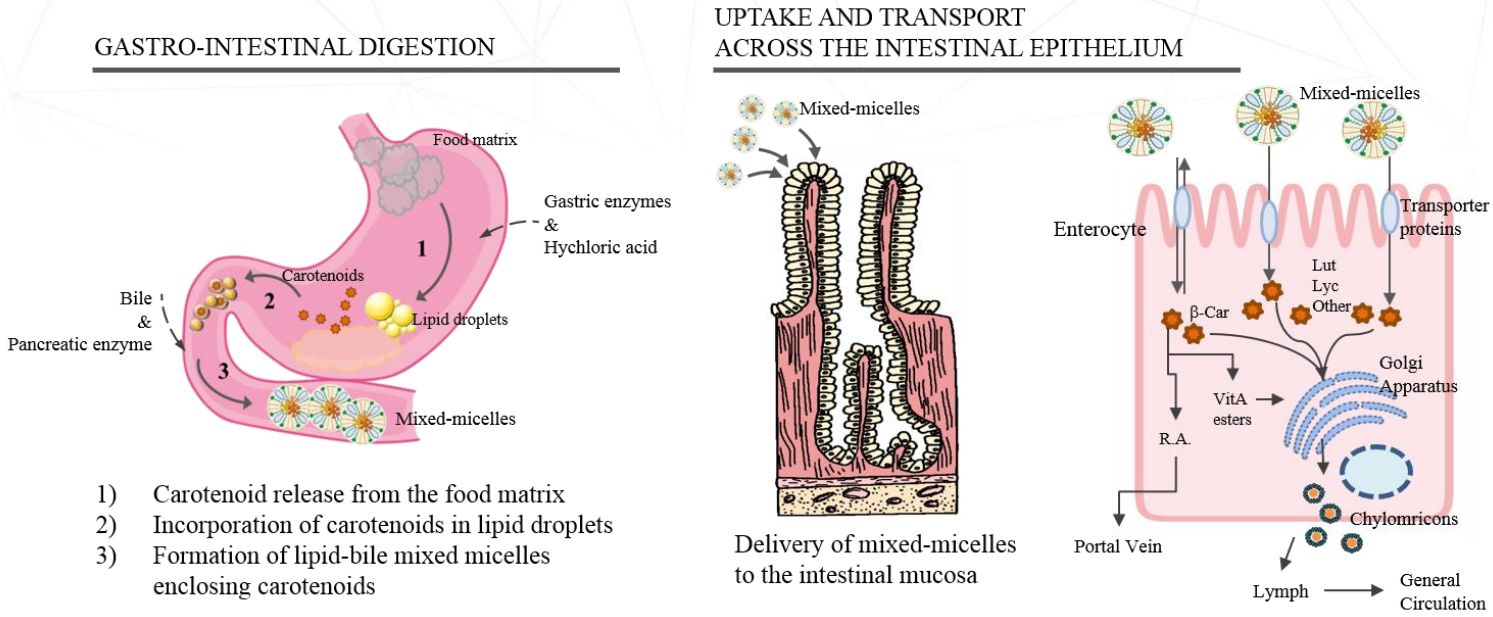

Figure 2. Schematic representation of gastro-intestinal digestion and intestinal absorption of carotenoids. Legend: β-car - β-carotene; Lut – lutein; Lyc – lycopene; R.A. – retinoic acid; VitA esters – Vitamin A esters.

represent the primary form of lipoproteins that arise from intestinal absorption, and so the chylomicron fraction is commonly used to assess the plasma concentration of newly absorbed carotenoid, i.e. its bioavailability[18]. Soon after chylomicrons have reached the bloodstream, they are hydrolysed by lipoprotein lipases, and carotenoids are released and distributed via lipoproteins across the peripheral extrahepatic tissues, including the adipose tissue. Carotenoids that are not taken up by peripheral tissues are transported to the liver as part of chymomicron remnant and stored by hepatocytes. In these cells most carotenoids are incorporated into lipoproteins, which are then released back into the systemic circulation[7]. Carotenoids secreted by the liver will be transported by very low density liproteins (VLDLs). However, in the fasting state most carotenoids that are present in plasma will be associated with low density lipoproteins (LDLs) and high density lipoproteins (HDLs). The distribution of carotenoids between different classes of lipoproteins is variable. In the fasting state, xanthophylls, like lutein and zeaxanthin, appear to be evenly carried via HDL (around 53%) and LDL, while the carotenes such as α- and β-carotene, and lycopene are mainly transported via the LDL fraction (around 58% to 73%). A smaller percentage (10% to 16%) of both xanthophylls and carotenes is carried by the VLDLs[19].

Carotenoids in human tissues and organs

Distribution and accumulation of carotenoids in the body tissues is probably dependent on the amount and type of receptors expressed, the expression of cleavage enzymes, and additional regulatory mechanisms such as the presence of specific binding proteins. This would explain the variable concentrations of carotenoids across different tissues, and why there is sometimes a carotenoid specificity in certain organs, as it is for example the case of lutein and zeaxanthin, which are the primary carotenoids found in the eye, specifically in the macula.

After meal intake, carotenoids will appear first in the chylomicron fraction of the blood, with concentrations peaks appearing sometime between 4 to 8h. However, a second peak of the plasma carotenoid concentration, is

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also regularly observed in in the first 24h to 48h after after a meal intake, reflecting the time between the transport of chylomicrons into the liver and the release of carotenoids back into the systemic circulation[20,21]. The use of plasma samples for carotenoid analysis is a less invasive method than tissue biopsies. Also plasma carotenoid concentration generally correlates with dietary intake. For these reasons blood samples are commonly used to assess carotenoid status and bioavailability in clinical and epidemiological studies[20]. The liver and the adipose tissue are two major sites for carotenoid accumulation[22]. Curiously the accumulation of carotenoids in the adipose tissue appears to be related to the location of the adipocytes, and a higher concentration of carotenoids was found in the abdomen, followed by the buttocks and thighs. Carotenoid levels in adipose tissue are also thought to be reflective of long term dietary habits, at least in healthy people[23], since adipose tissue assimilates different carotenoid concentration levels over time, and is remarkably resistant to fluctuations[24]. Lutein and zeaxanthin are by far the most abundant carotenoids in the human eye, however we can also find other carotenoids such as, lycopene, β-carotene, β-cryptoxanthin and neurosporene[25]. Lutein, zeaxanthin, and lutein's isomer meso-zeaxanthin, are commonly denominated by macular pigments (MPs). Although lutein and zeaxanthin can be found circulating in the blood and stored in different organs and tissues[2–6] they play an especially important role in eye health, were they are generally abundant in the retina, particularly in the macula[25]. This is thought to be important in reducing the risk of developing eye related chronic conditions including Age-related Macular Degeneration (AMD) and cataracts. Recently lutein has also been found in the brain of human infants[6], and of *rhesus macaque* in which lutein plays an important role in brain development[26]. Carotenoids also accumulate in the human skin protecting it against damage oxidative caused by free radicals, which is induced by, for example, solar radiation and air pollution[3]. Concentration of carotenoids in the skin can also be used to assess current lifestyle and dietary habits of the population, with lower concentrations being attributed to either unhealthy lifestyle, nutrition, illness or smoking[3].

Factors affecting carotenoid bioavailability

Absorption of carotenoids by the human body can be influenced by different factors (**BOX 1**). They are often described by the mnemonic SLAMENGHI (**BOX 2**)[27]. Perhaps the main limiting steps modulating carotenoid bioavailability are those related to the release of carotenoids from their food matrices, and the inclusion in lipid-bile mixed-micelles. Different dietary factors can affect these steps. Bioaccessibility of carotenoids varies across different types of food. Green leafy vegetables, such as spinach and kale, are rich in carotenoids. However bioavailability is low, with only around 5-10% of the total carotenoid content being bioavailable[28]. Carotenoids from fruits and vegetables, by comparison, show higher bioavailability despite their relatively lower carotenoid content. This has been shown to be related to

BOX 1

FACTORS AFFECTING CAROTENOID BIOAVAILABILITY

Carotenoid properties	*Dietary Factors*	*Host factors*
• Polarity ⇳	• Amount and type of dietary fat ⇳	• GI disorders ↓
• Isomeric form ⇳	• Proteins ⇳	• Gut microbiota ⇳
• Crystalline ↓ vs liquid/oil ↑	• Fiber ↓	• Nutritional status ⇳
	• Interactions with other carotenoids, phytochemicals, vitamins and minerals ⇳	• Genotype ⇳
	• Food Matrix and food processing	• Gastro-intestinal pH, composition of bile ⇳
	○ Subcellular localization ⇳	
	○ Raw ↓ vs processed food ↑	

Legend: ↓ factors having a negative impact; ↑ factors that have a favorable impact; ⇳ mpact on bioavailability is case-dependent

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BOX 2

MNEMONIC SLAMENGHI - MAIN EFFECTORS OF CAROTENOID BIOAVAILABILITY

- **S** pecies of carotenoids
- molecular or chemical **L** inkage
- **A** mount of carotenoids
- effects of food- **M** atrix
- **E** ffectors of absorption and bioconversion
- **N** utrient status
- **G** enetic factors
- **H** ost related factors
- **I** nteractions of the above factors

the properties of the food matrix and form of storage of carotenoids[28–30]. One important dietary aspect to the bioavailability of carotenoids is the presence of fat in a meal. As these are lipophilic molecules, the type and amount of fat is paramount to ensure the solubilisation and absorption of carotenoids[31,32]. In fact it has been shown that including a full-fat dressing, as opposed to a fat-reduced dressing, improved significantly the bioavailability of carotenoids from a salad-based meal[33]. The fibre type and its amount, on the other hand, has been shown to be potentially detrimental to the bioavailability of carotenoids[28,34,35]. In the presence of dietary fibre, carotenoids: i) are not well released from the fruit and vegetable matrices; ii) are potentially entrapped during upper intestinal digestion and not accessible to cellular uptake; iii) may be bound to polysaccharides requiring additional enzymatic hydrolysis to be absorbed[36]. Finally, the processing of the food matrix and treatments such as heating, pureeing or juicing help break the food matrix, which will consequently help the liberation of carotenoids from its matrix improving the amount of carotenoids that are transferred into mixed-micelles[37,38].

Also certain host-related factors may be of importance concerning upper intestinal digestion and the formation of mixed-micelles. Bile production, and the pancreatic enzymatic activity, are important aspects to lipid digestion and consequently to carotenoid bioavailability as well. Deficient bile production/excretion or pancreatic insufficiency can compromise lipid digestion having a negative impact on carotenoid absorption[39].

Bioconversion of carotenoids

The concept of bioconversion can be defined as a conversion of an organic compound into another compound or form of energy by living organisms. As such, carotenoids can be bioconverted by humans into shorter metabolites with potential biological functions. Several carotenoid bioconversion products, i.e. metabolites, from carotenoids such as lycopene, lutein/zeaxanthin and β-carotene, have been identified and quantified so far in humans for example in serum[40,41], breast milk[5], in eye[25], and adipose tissue[42]. However, the main challenge when discussing bioconversion in humans is to discern whether the identified metabolites were converted in the body after intake of parent carotenoid molecules, or whether they originate directly from external dietary sources.

General description of carotenoid cleavage

Oxidative cleavage of carotenoids into their metabolites occurs by a centric/symmetric (conversion to retinoids) or eccentric/asymmetric cleavage (conversion to apo-carotenals) of the parent molecule modulated by enzymatic activity. Currently two enzymes have been identified and confirmed to be responsible for the cleavage of parent carotenoids in humans: β, β-carotene 15,15'-monooxygenase 1 (BCMO1) and β, β-carotene 9',10'-dioxygenase (BCDO2)[43]. These iron dependent enzymes catalyse the oxidative cleavage of double bonds at specific locations of the carotenoid polyene backbone[44]. BCMO1 has a specificity for the pro-vitamin A carotenoids, β -carotene, β -cryptoxanthin and α-carotene, and is responsible for its symmetric cleavage resulting in 1 molecule of all-trans-retinal in the case or β-cryptoxanthin and α-carotene cleavage, or 2 all-trans-retinal molecules in the case of β-carotene. BCDO2, on the other hand, has a much broader specificity being able to cleave asymmetrically the cyclic carotenoids, such as β-carotene and lutein as well as acyclic ones, such as lycopene, at positions C9, C10 and C9′, C10′ and giving rise to a larger spectrum of apo-carotenals. The reaction mechanism of these enzymes has been comprehensively reviewed elsewhere[43,44]. Other differences between BCMO1 and BCDO2 include their

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cellular localisation, abundance and tissue specific expression. While BCMO1 is a cytosolic enzyme, BCDO2 is expressed in the mitochondria and at lower levels when compared to BCMO1. Although BCDO2 can be found in most cell types also expressing BCMO1, some tissues seem to express either one or the other. BCMO1 but not BCDO2 is found in skin, ovary cells and colon epithelial cells, whereas BCDO2 but not BCMO1 is found in cardiac and skeletal muscle cells, prostate and endometrial connective tissue and the endocrine pancreas[43].

The specific case of pro-vitamin A carotenoids and Vitamin A production

Bioconversion of carotenoids starts after intake at the gastro-intestinal level. Probably the most well-known example relative to the metabolism of carotenoids, is Vitamin A. Upon uptake by the intestinal mucosa, pro-vitamin A carotenoids are partly converted by BCMO1 in the cytosol into retinal, which will either be reversibly reduced to retinol or irreversibly oxidised to retinoic acid[45]. The transport into the bloodstream is different for retinol and retinoic acid. Intact retinoic acid molecules leave the cell and are transported in the plasma while bound to albumin. Retinal molecules have first to be converted to retinyl esters, before being transferred into chylomicrons and transported into bloodstream[46]. The main site for vitamin A accumulation is the liver, where retinyl esters are converted back to retinol prior to their release, and distribution to the peripheral tissues[45]. Most target tissues will be able to further metabolize retinol into the biologically active hormone all-trans-retinoic acid in order to take part in different cellular functions including differentiation, growth, and inflammatory response[46].

Concluding Remarks

While aspects of bioavailability related to the digestion and intestinal uptake of carotenoids is fairly well studied, what occurs upon absorption and during bioconversion is more challenging to study and comprehend. Some of the aspects in need of further investigation include:

- the uptake of carotenoids by the different tissues in the human body
- the organ specificity for some carotenoid species;
- bioconversion of carotenoid parent molecules into metabolites/degradation products
- biological role of carotenoids and their metabolites in the organs and tissues in both health and disease conditions

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When referring to this article, please use:

Corte-Real, J. (2017). Carotenoids in the Human Body: Bioavailability and Bioconversion. COST Action EUROCAROTEN (CA15136) Scientific Newsletter 5, 1-8.

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