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Overview of carotenoid bioavailability determinants: from dietary factors to host genetic variations[1,2]

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Abbreviations: ABCA1, ATP binding cassette AI; BCO1, beta-carotene oxygenase 1; BCO2, beta-carotene oxygenase 2; CD36, cluster of differentiation 36; NPC1L1, Niemann–Pick C1-Like 1; SNP, single nucleotide polymorphism; SR-BI, scavenger receptor class B member 1.

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Abstract

Background: Carotenoids are C-30 or C-40 based pigments with antioxidant/anti-inflammatory properties, some possessing vitamin A activity. Their dietary intake, especially within fruits and vegetables, has been associated with a decreased risk of chronic diseases, including type-2 diabetes, cardiovascular diseases, age-related macular degeneration, and several types of cancer. However, their bioavailability is wide ranging and is affected by numerous factors. Recent findings showing that the intestinal absorption of carotenoids involves proteins have raised new relevant questions about factors that can affect their bioavailability. It is therefore opportune to present a current overview of this topic.

Scope and Approach: This review begins by exploring what is known, as well as what is unknown, about the metabolism of carotenoids in the human upper gastrointestinal tract and then presents a methodical evaluation of factors assumed to affect carotenoid bioavailability.

Key Findings and Conclusions: Numerous unanswered questions remain about the metabolism of carotenoids in the intestinal lumen and about the factors affecting their absorption efficiency. These gaps need to be filled to be able to better understand individual, variable responses to these compounds so as to promote guidelines towards personalized dietary recommendation in order to increase carotenoid absorption efficiency and hence their health effects. Two main conclusions can be drawn. First, the efficiency of carotenoid absorption is affected by several dietary factors (*e.g.* food matrix, fat, and fat-soluble micronutrients). Second, carotenoid bioavailability also depends on host-related factors, *e.g.* diseases, life-style habits, gender and age, as well as genetic variations including single nucleotide polymorphisms.

Key words: Lutein, beta-carotene, lycopene, food matrix, single nucleotide polymorphism, absorption.

Introduction

Carotenoids are natural pigments produced in many fruits and vegetables, mushrooms and algae and are responsible for colours ranging from red to yellow, although colorless carotenoids are also found (*e.g.* phytoene, phytofluene). Carotenoids are lipids and most of them can be described by the chemical formula $C_{40}H_{56}O_n$, with n ranging from 0 to 6. They are split into 2 classes:

- carotenes are non-oxygenated carotenoids (*i.e.* n=0).
- xanthophylls are oxygenated carotenoids (*i.e.* n>0).

To date, more than 750 different carotenoids have been identified but only about 40 are consumed in significant amounts in the human diet, of which the most abundant are ß-carotene, lycopene, lutein, ß-cryptoxanthin, α-carotene, and zeaxanthin. Around 20 different carotenoids have been identified in human blood (Khachik, Beecher, Goli, Lusby, & Smith, 1992). The 6 most concentrated carotenoids are those found at the highest quantities in the human diet. Astaxanthin and canthaxanthin are only found in the blood of subjects with an elevated intake of foods rich in these carotenoids (*i.e.* some fish and seashells for the former, some mushrooms for the latter). Carotenoids are ~~potent antioxidant~~ molecules with antioxidant properties and their dietary intake and plasma levels have been associated with a decreased risk of chronic diseases, including type-2 diabetes (Akbaraly, Fontbonne, Favier, & Berr, 2008), cardiovascular diseases (Y. Wang, Chun, & Song, 2013) and several types of cancer (Tanaka, Shnimizu, & Moriwaki, 2012). Some exhibit provitamin A properties, although only a few of these are present in significant amounts in the human diet, namely ß- and α-carotene, and ß-cryptoxanthin. The importance of carotenoids as a source of vitamin A largely depends on the diet: a recent meta-analysis has shown that provitamin A carotenoids represented 35% of total vitamin A intake (β-carotene: 86%, α-carotene: 10%, β-cryptoxanthin: 4% thereof respectively) in developed countries (Weber & Grune, 2012). In vegans, 100% of vitamin A originates from provitamin A carotenoids. ~~In countries where animal product consumption is low (*e.g.* in developing countries), 70 to 90% of vitamin A originates from carotenoids.~~ The xanthophylls lutein and zeaxanthin, which are present at high concentrations in the macula, can absorb incident blue light and hence protect the retina from light-induced damages (Mares, 2016) and their consumption has been associated with protection from age-related macular degeneration (Aronow & Chew, 2014).

Carotenoids are lipid molecules: they are insoluble in water and partially soluble in plant oils, animal fat and biological membranes. They share common transport mechanisms

with other lipids: in the lumen of the human digestive tract, they are found in structures allowing the solubilisation of lipids, *i.e.* micelles and probably vesicles. They are transported in the blood via lipoproteins and are found in membranes and lipid droplets in cells. Their bioavailability, *i.e.* the proportion of carotenoids, or one of their metabolites, that is available for use or storage by the organism, is wide-ranging, *i.e.* values between 3.5 % and 90 % have been reported for ß-carotene (Haskell, 2012), and very little data is available for other carotenoids. It depends on the extraction efficiency from their food matrix to mixed micelles (*i.e.* bioaccessibility), their uptake efficiency by enterocytes, their blood transport, their uptake efficiency by target tissues and their tissue elimination (through *e.g.* catabolism). The fundamental mechanisms that govern their absorption and the factors that influence their absorption efficiency and their postprandial blood concentrations are not accurately known. This review will present an overview of what is known/unknown about the fate of carotenoids in the human upper gastrointestinal tract and then list the factors hypothesized to affect carotenoid bioavailability following a methodical evaluation.

2. Carotenoid fate in the human upper gastrointestinal tract

It is very difficult to give an absorption efficiency value for carotenoids in humans. Indeed, values between 3.5 % and 90 % have been reported for ß-carotene (Haskell, 2012), and very little data is available for other carotenoids. The high variability reported for ß-carotene probably comes from the different methodological approaches used to evaluate it. Indeed, different formulations (food *vs* supplements, *see* section 6.3), doses (nutritional or pharmacological), and models (postprandial chylomicron response, stable isotopes, ileostomised subjects…) have been used.

Carotenoid metabolism starts in the stomach, where foods rich in these molecules (essentially fruits and vegetables) are submitted to an acidic pH (between 2 and 5 during digestion) and to the action of gastric secretions, which contain several enzymes (pepsin, amylase, gastric lipase…). In a clinical study where 10 healthy men were given liquid test meals intragastrically, some carotenoids (lutein and ß-carotene) were shown to be partially released from their food matrix in the stomach and to be transferred to the oil phase of the meal (Tyssandier, et al., 2003). This suggests that the stomach plays a significant role in carotenoid bioavailability by participating in their release from the food matrix. The extent of this phenomenon depends most likely on the physico-chemical properties of the different carotenoids (lycopene only exhibited a very low transfer to the oil phase of the meal in the

same study), on the quantity and the nature of lipids present at the same time as carotenoids in the food bolus, and on the characteristics of the matrix in which carotenoids are incorporated.

Some carotenoids are consumed as esters, *e.g.* ß-cryptoxanthin in some citruses, lutein in some supplements from Marigold and also in tropical fruits (Breithaupt & Bamedi, 2001). It is hence possible that a fraction of these esters are hydrolysed by gastric lipase (Carriere, Barrowman, Verger, & Laugier, 1993). There is no data on the role of this enzyme on the hydrolysis of carotenoid esters but it might affect their bioavailability in subjects exhibiting a sub-optimal intestinal lipolytic activity (*e.g.* new-born babies and patients with pancreatic insufficiency).

In the duodenum, digestive enzyme (proteases, amylases, lipases…) participate in the release of carotenoids from the food matrix by degrading it further. It is widely accepted that carotenoids are then transferred to the lipid phase and to mixed micelles. However, it is not known if carotenoids are also present in other structures that solubilise lipids in the duodenum, *i.e.* vesicles (Staggers, Hernell, Stafford, & Carey, 1990), and if this has an effect on their absorption. Pancreatic lipase has been shown to facilitate the transfer of carotenoids from emulsified lipid droplets towards mixed micelles (Borel, et al., 1996). This transfer depends among others on pH, bile acid concentration and carotenoid hydrophobicity (Tyssandier, Lyan, & Borel, 2001). As it is accepted that only free carotenoids are taken up by enterocytes, hydrolysis of carotenoid esters in the duodenum has been questioned. The enzyme responsible for this hydrolysis is apparently bile-salt dependent lipase, also known as cholesteryl ester hydrolase, cholesterol esterase or carboxyl ester lipase (Breithaupt, Bamedi, & Wirt, 2002), secreted by the exocrine pancreas, but it is not known if pancreatic lipase-related protein 2, which can hydrolyse retinyl esters (Reboul, Berton, et al., 2006), is also involved.

3. Uptake, metabolism and secretion of carotenoids by enterocytes

After their extraction from the food matrix and incorporation into mixed micelles, bioaccessible carotenoids can be taken up by enterocytes. The main absorption site of carotenoids is in the duodenum (upper part of the intestinal tract), as suggested by beta-carotene oxygenase 1 and 2 (BCO1 and BCO2) cellular localization (Raghuvanshi, Reed, Blaner, & Harrison, 2015). Carotenoids can then be metabolised in the enterocytes before their incorporation into chylomicron, and possibly also intestinal HDL, and secretion in the blood circulation via the lymph. These processes are summarized in **Figure 1**.

3.1 Carotenoid uptake at the apical membrane of the enterocyte

Carotenoids have long been thought to enter enterocytes by simple passive diffusion. This dogma was mostly based on one study carried out in rats with ß-carotene (Hollander & Ruble, 1978). However, several apical membrane proteins have been shown to facilitate carotenoid uptake (Reboul & Borel, 2011). Niemann–Pick C1-Like 1 (NPC1L1) is involved in the uptake of lutein (Sato, et al., 2012). Cluster of differentiation 36 (CD36) facilitates β-carotene uptake (Borel, et al., 2013) and could also facilitate lycopene uptake (Moussa, et al., 2011). Scavenger receptor class B member 1 (SR-BI), which is encoded by *SCARB1*, participates in the uptake of β-carotene (Borel, et al., 2013; van Bennekum, et al., 2005), lutein (During, Dawson, & Harrison, 2005) and lycopene (Moussa, et al., 2008). Several SNPs in the genes encoding these proteins have been reported to be associated with the variability in carotenoid plasma concentrations and bioavailability (*see* section 6.6).

3.2 Intracellular transport of carotenoids in the enterocyte

There is no data on the transfer mechanism of carotenoids from the apical membrane of the enterocyte to the Golgi apparatus (assembling site of chylomicrons, in which a fraction of carotenoids are incorporated). However, it is unlikely that these hydrophobic molecules could cross the aqueous intracellular compartment without being bound to (a) transport protein(s). Liver fatty acid binding protein (L-FABP), which can transport large molecules in its hydrophobic pocket, or cellular retinol-binding protein (CRBP), which transport vitamin A (M. S. Levin, 1993) could be good candidates. It is also possible that SR-BI-associated carotenoids are transported together towards the cytoplasm (G. H. Hansen, Niels-Christiansen, Immerdal, & Danielsen, 2003).

3.3 Carotenoid metabolism in the enterocyte

Following their transport into the enterocyte, carotenoids can be metabolised by two enzymes: BCO1 (dela Sena, et al., 2014) and BCO2 (Amengual, et al., 2013). BCO1 cleaves carotenoids centrally and yields at least one retinal molecules (2 for ß-carotene) while BCO2 cleaves carotenoids eccentrically and yields apo-carotenals. BCO1 catalyses the oxidative cleavage of provitamin A carotenoids, beta-apocarotenals, and possibly also lycopene, but not that of lutein (dela Sena, et al., 2013). While BCO1 is thought to be the main cleaving-

enzyme for β-carotene (von Lintig, 2012), lycopene has been suggested to be mostly cleaved by BCO2 (Lindshield, Canene-Adams, & Erdman, 2007). BCO2 has also been shown to be involved in lutein metabolism (Amengual, et al., 2011). While BCO1 is a cytosolic enzyme, BCO2 localizes to the inner mitochondrial membrane which suggest the existence of a compartmentalization between provitamin A carotenoid and xanthophyll metabolism (Palczewski, Amengual, Hoppel, & von Lintig, 2014; Raghuvanshi, et al., 2015). Most β-carotene conversion (>70%) has been shown to take place in the intestine (Tang, Qin, Dolnikowski, & Russell, 2003; Z. Wang, Yin, Zhao, Russell, & Tang, 2004). Additionally, carotenoid isomerisation can occur in the enterocyte and it has actually been reported that this was the key site for lycopene isomerisation during absorption in human subjects, since no isomerisation was observed in the gastro-intestinal lumen (Richelle, et al., 2010).

3.4 Carotenoid secretion from the basolateral side of the enterocyte to the blood circulation

It is widely accepted that carotenoids follow the fate of other newly absorbed lipid molecules (fatty acids, monoglycerides, cholesterol…) and that they are incorporated with them in chylomicrons in the Golgi apparatus before secretion in the lymph (apolipoprotein B-dependent route). Nevertheless, another secretion pathway could exist. Indeed, since some carotenoids are found in HDL and since the small intestine synthesizes HDL, which can transport other newly absorbed lipid molecules, namely cholesterol and vitamin E, it can be hypothesized that a fraction of carotenoids is secreted into the lymph in HDL (apolipoprotein A1-dependent route) involving the transporter ATP binding cassette AI (ABCA1). This has been confirmed *in* vitro and in a hamster model for lutein and zeaxanthin where up- and down-regulation of ABCA1 expression, via activation of the liver X receptor and statin treatment respectively, led to respectively increased and decreased HDL-lutein and -zeaxanthin concentrations (Niesor, et al., 2014). The metabolic pathways of carotenoid transport through the enterocyte are summarized in **Figure 1**.

4. Blood transport of carotenoids

Since some carotenoids (notably xanthophylls) are principally localized at the surface of chylomicrons (Borel, et al., 1996), a fraction of carotenoids is probably transferred to other classes of lipoproteins and/or to some tissues during intravascular metabolism of

chylomicrons (Tyssandier, Choubert, Grolier, & Borel, 2002). Carotenoids that reach the liver via chylomicrons are stored in this organ, or eliminated in the bile, or re-secreted into VLDL to be distributed to peripheral tissues. It can be hypothesized that a fraction of VLDL-carotenoids (notably xanthophylls for the above-mentioned reasons) is exchanged with some other classes of lipoproteins during the metabolism of these lipoproteins. A part of VLDL-carotenoids, notably carotenes which are preferentially located in the hydrophobic core of these triglyceride-rich lipoproteins (Borel, et al., 1996), is found in LDL, which originate from VLDL metabolism. LDL-carotenoids are probably taken up by tissues together with LDL. It can be hypothesized that a fraction of LDL-carotenoids, preferentially xanthophylls, is exchanged with other classes of lipoproteins. The origin of HDL-carotenoids is not known but they can come from peripheral tissues, which would be somehow a reverse metabolism of carotenoids, or from other lipoprotein classes (through the exchanges between lipoproteins described above), or from the intestine (*see* section 3.4), or from a combination of some of these factors. Following these exchanges, xanthophylls are transported mostly in HDL while carotenes are transported mostly in LDL (Thomas & Harrison, 2016). **Figure 2** summarizes the current knowledge on the blood transport of carotenoids in humans.

5. Tissue distribution of carotenoids

Carotenoids are found in numerous tissues but at ~~very~~ different concentrations (Schmitz, Poor, Wellman, & Erdman, 1991). The adipose tissue and the liver respectively contain 80 and 10% of total carotenoids in the body, although the highest concentrations are not found in these organs. Very little is known on the mechanisms governing carotenoid tissue distribution. It is accepted that these lipophilic pigments follow the fate of lipids. It is thus hypothesized that carotenoids incorporated into LDL are taken up by tissues together with these lipoproteins (*see* chapter 4). Moreover, since some putative membrane transporters of carotenoids (*i.e.* SR-BI, CD36~~ABCA1~~…) are found at the cell surface of some tissues (Moussa, et al., 2011; Rigotti, Miettinen, & Krieger, 2003), it is possible that the cell internalisation of some carotenoids present at the surface of lipoproteins (xanthophylls notably) is facilitated by these transporters. It is also possible that some membrane proteins are involved in the efflux of carotenoids from peripheral tissues to the blood circulation.

Carotenoid analysis in the eyes of dead bodies have shown that, although around 40 carotenoids are consumed by humans, only very few are found in this organ, namely lutein, zeaxanthin, *meso*-zeaxanthin, and to a lesser extent lycopene and ß-carotene (Bernstein, et al.,

2001). Since among dietary carotenoids, only lutein and zeaxanthin are found in the human lens and retina, these carotenoids are sometimes considered as the "carotenoids of vision". The macular pigment density, *i.e.* the concentration of carotenoids present in the macula, is partly correlated to lutein+zeaxanthin and β-carotene consumption and serum lutein and zeaxanthin concentration (Curran-Celentano, et al., 2001), and dietary intakes of lutein increase macular pigment density (Landrum, et al., 1997). Regarding *meso*-zeaxanthin (3R,3'S-zeaxanthin), it comes from lutein metabolism, as it has been shown when monkeys were fed either lutein or zeaxanthin (Johnson, Neuringer, Russell, Schalch, & Snodderly, 2005). These studies in monkeys have also shown that lutein and zeaxanthin in the macula cannot interconvert, which suggests it is necessary to have a dietary intake of both carotenoids to maintain a normal macular pigment composition. Recently, a mechanism has been proposed to explain the selective uptake of zeaxanthin and lutein in the retina, where zeaxanthin transport from HDL is facilitated by SR-BI while lutein transport from LDL is probably facilitated by the LDL receptor (Thomas & Harrison, 2016).

Xanthophylls, and more precisely esterified lutein, have been found in the skin (Wingerath, Sies, & Stahl, 1998), but it is not known if these esters are formed in this tissue, through esterification of free lutein, or if they are absorbed as such and then transported to the skin (*see* section 3.5). Lycopene and ß-carotene are the main carotenoids found in the prostate (Clinton, et al., 1996) with concentrations ranging from 0 to 2.6 nmol/g for lycopene and from 0.09 to 1.7 nmol/g for ß-carotene. The presence of significant amounts of lycopene in this organ support the results of epidemiological studies which suggest this carotenoid plays a preventive role against the development of prostate cancer (Jian, Du, Lee, & Binns, 2005; Wertz, Siler, & Goralczyk, 2004).

Lutein and zeaxanthin have been found at relatively high concentrations in the human brains where they have been suggested to have a beneficial role on cognitive function (Johnson, 2012).

6. Factors modulating the bioavailability of carotenoids

To be absorbed, carotenoids have to be extracted from the food matrix in which they are ingested (usually a vegetable matrix, oil or a dietary supplement) and presented to enterocytes in a structure enabling their absorption, *i.e.* in mixed micelles. Carotenoid absorption depends on many variables: (i) food processing (raw, dehydrated, frozen, cooked…), (ii) meal composition, (iii) the activity of digestive enzymes, (iv) transport

efficiency across the enterocyte, etc. The mnemotechnic term "SLAMENGHI" has been proposed to list all factors susceptible to affect carotenoid bioavailability (West & Castenmiller, 1998). Each letter represents one factor:

– S for "**S**pecies of carotenoids" (referring to the relative bioavailability of the different carotenoids depending on their physico-chemical properties)

– L for "molecular **L**inkage" (referring to additional functional groups sometimes linked to carotenoids: esters, aldehyde...)

– A for "**A**mount of carotenoid consumed in the meal" (referring to the relative absorption efficiency as a function of the quantity of carotenoids consumed in a meal)

– M for "**M**atrix in which the carotenoid is incorporated" (referring to the effect of the matrix in which carotenoids are incorporated)

– E for "**E**ffectors of absorption" (referring to the effect of nutrients and drugs on carotenoid absorption)

– N for "**N**utrient status of the host" (referring to the effect of the vitamin A status of the host)

– G for "**G**enetic factors" (representing the effect of genetic polymorphisms or epigenetic modifications)

– H for "**H**ost-related factors" (referring to individual characteristics such as age, gender, pathologies…)

– I for "mathematical **I**nteractions" (referring to the differences in effects observed when two of the above-mentioned factors play a joint role compared with the sum of their effects observed separately).

6.1 Species of carotenoids and molecular Linkage

The study of the effect of carotenoid species on their bioavailability is not straightforward due the variability of the matrices in which they are incorporated (*see* section 6.3). To differentiate between these effects, it is necessary to measure the bioavailability of pure carotenoids. This was done in a study carried out in rats which showed that carotenoid bioavailability was inversely correlated with their hydrophobicity (*i.e.* the bioavailability of carotenoids was as follows: astaxanthin>lutein>β-carotene>lycopene), which was mainly due to differences in their bioaccessibility according to the authors (Sy, et al., 2012).

Due to their many conjugated double bonds, each carotenoid can theoretically form many geometrical isomers. For example, ß-carotene, with 9 double bonds in its polyene chain, can form 272 isomers while lycopene can theoretically form 1056 geometrical isomers.

However, the steric hindrance of some configurations limits the number of *cis* isomers to a few dozens. As a consequence, carotenoids are found in the human diet under 4 main chemical forms: all-*trans* carotenoids, all-*trans* esterified carotenoids (Weller & Breithaupt, 2003), *cis* carotenoids and *cis* esterified carotenoids. However, most carotenoids are usually present as all-*trans* non-esterified carotenoids. The fraction of *cis* isomers present in our diet is usually produced by technological treatments, in particular elevated temperatures (Milanowska & Gruszecki, 2005; Rodriguez-Amaya, 1999; Updike & Schwartz, 2003). A "*trans* to *cis*" conversion in the acidic environment of the stomach has also been proposed (Mortensen & Skibsted, 2000), although it has not been observed *in vivo* (Richelle, et al., 2010; Tyssandier, et al., 2003). However, Richelle *et al.* reported lycopene conversion to occur within the enterocyte (Richelle, et al., 2010). *Cis* isomers have different physico-chemical properties compared to corresponding all-*trans* isomers: they are no longer linear, rigid molecules, which affect their capacity to solubilize into mixed micelles (Milanowska, Polit, Wasylewski, & Gruszecki, 2003). Their tendency to crystallise or aggregate is also diminished (Britton, 1995). As a consequence, it has been hypothesized that they have different absorption efficiency. This has been investigated in several studies. *Cis* lycopene isomers have been shown to display a higher bioavailability than the all-*trans* isomer (Boileau, Boileau, & Erdman, 2002; Cooperstone, et al., 2015), which would be due to a higher solubility in mixed micelles. *Cis* ß-carotene isomers also display a higher solubility in mixed micelles compared to all-*trans* ß-carotene (G. Levin & Mokady, 1995; Tyssandier, et al., 2003) but surprisingly, they have a lower absorption efficiency (Ben-Amotz & Levy, 1996). This apparent discrepancy could originate from the fact that *cis* ß-carotene isomers are isomerised to all-*trans* ß-carotene in enterocytes (You, Parker, Goodman, Swanson, & Corso, 1996), which leads to an underestimation of their absorption efficiency. Of note, whether all-*trans* ß-carotene enterocyte uptake is favoured remains controversial since a study with synthetic mixed micelles has shown a greater uptake of all-*trans* ß-carotene *vs cis* ß-carotene (During, Hussain, Morel, & Harrison, 2002) while another study did not observe any difference using micelles produced following *in vitro* digestions (Ferruzzi, Lumpkin, Schwartz, & Failla, 2006).

As mentioned earlier, carotenoids are found in the diet either as free carotenoids (for carotenes and xanthophylls) or esterified (for xanthophylls only). However, it is estimated that in the usual French diet, more than 90% carotenoids are consumed as free. Since, by analogy with what is observed with cholesterol and retinyl esters, carotenoids are supposed to be absorbed only as free, the absorption efficiency of esterified carotenoids was thought to be

inexistent. However, it was shown in a clinical study that lutein esters had a bioavailability equivalent to that of free lutein (Bowen, Herbst-Espinosa, Hussain, & Stacewicz-Sapuntzakis, 2002), and the bioavailability of zeaxanthin dipalmitate was even greater than that of free zeaxanthin in another clinical study (Breithaupt, Weller, Wolters, & Hahn, 2004). This has also been observed with another xanthophyll ester, namely esterified ß-cryptoxanthin (Breithaupt, Weller, Wolters, & Hahn, 2003). These results suggest that the hydrolysis of xanthophyll esters in the intestinal lumen is a highly efficient process. It can also be hypothesized that the facilitated transport of xanthophyll esters ~~are more soluble in mixed micelles than free xanthophylls or that their facilitated transport~~ by membrane proteins is more efficient than that of free xanthophylls.

6.2 Amount of carotenoids consumed in a meal

The absorption efficiency of carotenoids is thought to remain constant to amounts up to 20-30 mg and then decrease for greater amounts due to several factors: limited capacity of mixed micelles to solubilise carotenoids, saturation of membrane proteins involved in their intestinal transport (*see* section 3.1), saturation of the solubilisation capacity of the intracellular compartment and/or chylomicrons (Stahl, et al., 2002). This saturation of the absorptive capacity has been reported for lycopene (Diwadkar-Navsariwala, et al., 2003).

6.3 Matrix in which carotenoids are incorporated

This factor is considered to be the key factor governing carotenoid bioavailability because, to be absorbed, carotenoids first need to be extracted from their food matrix and to be incorporated into mixed micelles in the upper part of the digestive tract. In plants, carotenoids are found in different structures: they can be present in chloroplasts in the photosynthetic system (in particular in the leaves of green plants) or in chromoplasts, dissolved in lipid droplets (in some fruits), or in a semi-crystal state associated to membranes (in carrots and tomatoes for example) (Vishnevetsky, Ovadis, & Vainstein, 1999). These differences in their localization and physical form are supposed to significantly affect their extraction efficiency and hence their bioaccessibility (*i.e.* % found in micelles) (Reboul, Richelle, et al., 2006; Xia, McClements, & Xiao, 2015) and bioavailability (Schweiggert & Carle, 2015). To illustrate this point, lutein and β-carotene were more bioavailable from broccolis (a flower) or green peas (a seed) than from spinach (where carotenoids are found in

chloroplasts) (van het Hof, Tijburg, Pietrzik, & Weststrate, 1999). Likewise, the bioavailability of carotenoids present in food not from plant origin is usually higher than that of carotenoids present in food from plant origin, probably because they are then not trapped by plant membranes and dietary fibres. For example, lutein from eggs was more bioavailable than lutein from spinach and supplements (Chung, Rasmussen, & Johnson, 2004).

Technological treatments and cooking usually improve carotenoid bioavailability and can thus compensate, at least partly, for their degradation. This is explained by the fact that these treatments alter plant cell walls and lead to a higher carotenoid extraction. Several studies have thus shown a higher carotenoid bioaccessibility following thermal or non-thermal processing (Buniowska, Carbonell-Capella, Frigola, & Esteve, 2017; Gupta, Kopec, Schwartz, & Balasubramaniam, 2011; Reboul, Richelle, et al., 2006). These differences in bioaccessibility usually translate to differences in bioavailability. For example, lutein bioavailability from spinach is higher when the spinach matrix is altered (through chopping in this case) (van het Hof, et al., 1999) and it is higher in vegetable juices compared to raw or cooked vegetables (McEligot, et al., 1999). Likewise, the bioavailability of β-cryptoxanthin has been shown to be higher in pasteurized orange juice compared to fresh oranges (Aschoff, et al., 2015).

6.4 Effectors of absorption

6.4.1 Lipids

Dietary triglycerides have been shown to be necessary to promote carotenoid absorption. Lipids increase the bioavailability of both free (Unlu, Bohn, Clinton, & Schwartz, 2005) and esterified lutein (Roodenburg, Leenen, Hof, Weststrate, & Tijburg, 2000). When raw vegetables were consumed together with cooked whole eggs (each egg provided 5 g lipids), lutein, zeaxanthin, α-carotene, β-carotene, and lycopene bioavailability increased 3-8 fold (Kim, Gordon, Ferruzzi, & Campbell, 2015). Similarly, consumption of avocado together with tomatoes or raw carrots has been shown to increase the bioavailability of β-carotene and its conversion efficiency to vitamin A (Kopec, et al., 2014). Lipids can modulate carotenoid absorption by several mechanisms:

- They can facilitate the extraction of carotenoids from their food matrix by providing a hydrophobic phase in which carotenoids can solubilise.

- They can stimulate biliary secretion and consequently, micelle production, which would increase the quantity of carotenoids solubilised in micelles and hence available for absorption.
- By promoting chylomicron secretion, triglycerides could increase carotenoid secretion outside the enterocyte and thus prevent their intracellular accumulation, which would in turn increase their absorption.

Several characteristics of dietary lipids are thought to affect carotenoid bioavailability:

- the species of fatty acids from triglycerides (Borel, et al., 1998; Gleize, et al., 2013; Schaeffer & Hamilton, 1990). For example, olive and coconut oils have been shown to increase similarly the intestinal absorption of lutein in mice when compared to groundnut, soybean, sunflower, rice bran, corn, palm and fish oil (Nidhi, Ramaprasad, & Baskaran, 2014). In humans, canola oil, which is rich in monounsaturated fatty acids, was shown to trend to promote higher lutein and α-carotene bioavailability compared to butter, which is rich in saturated fatty acids (Goltz, Campbell, Chitchumroonchokchai, Failla, & Ferruzzi, 2012).
- the amount of amphiphilic lipids (mostly phospholipids).
- the species of amphiphilic lipids. It is supposed that, before its hydrolysis to lysophosphatidylcholine, phosphatidylcholine could affect carotenoid absorption by decreasing lipolysis speed and hence micelle formation speed. Phosphatidylcholine inhibits lutein absorption while lysophosphatidylcholine has the opposite effect (Sugawara, et al., 2001).
- the extent of lipid emulsification. For example, the use an excipient emulsion with decreasing droplet size has been shown to increase the bioaccessibility of α- and β-carotene from carrot juice *in vitro* (Zhang, et al., 2016) and an emulsion with small droplet size increased enterocyte uptake of β-carotene in Caco-2 cells (Lu, et al., 2016).

6.4.2 Dietary fibers

Dietary fibres could affect carotenoid absorption by several mechanisms:

- by sequestering micelle components (Eastwood & Mowbray, 1976).
- by inhibiting pancreatic lipase (W. E. Hansen, 1987)**,** which would decrease carotenoid extraction from lipid droplets (Tyssandier, et al., 2001).

- by increasing the viscosity of the intestinal content (Gallaher, Hassel, Lee, & Gallaher, 1993) which would impair the diffusion of carotenoid-rich micelles towards the brush border.

This was confirmed in a study showing that a diet rich in pectin, guar gum, alginate cellulose or wheat bran (0.15 g/kg body weight) decreased lutein bioavailability (Riedl, Linseisen, Hoffmann, & Wolfram, 1999).

6.4.3 Fat absorption inhibitors

Since obesity is a major health problem, several drugs have been designed to decrease fat absorption. However, these drugs could decrease lipid micronutrient absorption as well. Orlistat, an inhibitor of gastric and pancreatic lipase, has been shown to decrease the absorption of α- and β-carotene (McDuffie, Calis, Booth, Uwaifo, & Yanovski, 2002) while Olestra, a saccharose polyester used as a lipid substitute, has been shown to decrease the absorption of β-carotene and lycopene (Weststrate & Hof, 1995). Similarly, phytosterols, which are used to decrease cholesterol absorption efficiency, also decrease the absorption of some carotenoids (α- and ß-carotene and lycopene) (Clifton, et al., 2004; Richelle, et al., 2004) although no effect was observed on β-cryptoxanthin bioavailability following the consumption of a milk-based fruit drink with or without plant free sterols for 28 days (Granado-Lorencio, Donoso-Navarro, Sanchez-Siles, Blanco-Navarro, & Perez-Sacristan, 2011).

6.4.4 Micronutrients

Since carotenoids are consumed together with other micronutrients, and since common absorption mechanisms are involved, it is hypothesized that some micronutrients compete with carotenoids regarding their absorption. Some results support this hypothesis: indeed, carotenoids have been shown to compete together for their incorporation into mixed micelles and subsequent uptake by enterocytes (During, et al., 2002; Tyssandier, Cardinault, et al., 2002; Tyssandier, et al., 2001; van den Berg, 1999). However, the effect of such competition on long term carotenoid status is not yet certain (Tyssandier, Cardinault, et al., 2002). On the other hand, microconstituants such as vitamin C, polyphenols and vitamin E are thought to protect carotenoids against oxidative degradation in the gastro-intestinal tract, and thus increase their absorption efficiency. The results are here conflicting since vitamin C has been suggested to increase lutein absorption (Tanumihardjo, Li, & Dosti, 2005), but results from

our lab are in disagreement: the postprandial lutein response to a lutein-rich meal containing a mixture of antioxidants, including vitamin C, was not different compared to a lutein-rich meal only (Reboul, et al., 2007). Additionally, vitamin C had no effect on lutein uptake by Caco-2 cells.

6.4.5 Minerals

Divalent minerals have been suggested to impair the *in vitro* bioaccessibility of lutein, neoxanthin, lycopene and β-carotene, with calcium having the most pronounced effect (100% reduction when added at 1000 mg/l) (Corte-Real, et al., 2016). In agreement with these results, the bioavailability of lycopene in humans has recently been shown to be significantly diminished when calcium was added at a nutritional dose to a test meal (83% reduction) (Borel, et al., 2017). These results call for a thorough assessment of the effects of calcium, or other divalent minerals, on the bioavailability of carotenoids.

6.5 Vitamin A (Nutrient) status of the host

The variability in β-carotene absorption has been associated with host vitamin A status: following its activation by retinoic acid, the intestinal transcription factor Intestine Specific Homeobox (ISX) has been shown to function as a repressor of *SCARBI* and *BCO1* expression (Lobo, et al., 2010). This mechanism is thought to serve as a negative feedback loop regulating retinol status through modulation of provitamin A carotenoid absorption and cleavage efficiencies. Moreover, the presence of a SNP in the ISX binding site in the *BCO1* promoter was associated with decreased conversion rates by 50% and increased fasting blood levels of β-carotene (Lobo, et al., 2013). Since lutein and lycopene are also absorbed via SR-BI, it can be hypothesized that the host vitamin A status also has an effect on the absorption of these carotenoids (Widjaja-Adhi, Lobo, Golczak, & Von Lintig, 2015).

6.6 Genetic factors

The involvement of several proteins in the intestinal absorption of carotenoids (apical uptake) suggests that variations in the genes encoding these proteins could modulate carotenoid absorption efficiency. This has been confirmed in an association study by Borel *et al.* (2007) where the influence of candidate SNPs of genes involved in lipid metabolism on

the fasting blood concentration of several carotenoids was investigated. More specifically, SNPs in *SCARB1* were associated with β-carotene but not with lycopene concentrations. These SNPs explained differences in β-carotene plasma concentrations by up to 50%. Several additional SNPs have meanwhile been identified (Borel, 2012), including several in *BCO1* in genome-wide association studies (Ferrucci, et al., 2009; Wood, et al., 2013). Three recent studies have reported associations of combinations of SNPs involved in interindividual variability of the bioavailability of lutein (Borel, et al., 2014), lycopene (Borel, Desmarchelier, Nowicki, & Bott, 2015b) and β-carotene (Borel, Desmarchelier, Nowicki, & Bott, 2015a), employing a candidate gene approach in postprandial studies. In these studies, plasma chylomicron carotenoids, representing newly absorbed carotenoids, were measured in healthy male adults. These combinations were associated with 73, 72 and 69% of the interindividual variability of the bioavailability of lutein, lycopene and β-carotene, respectively. While some SNPs were located in genes expressed in other tissues or were closely involved in plasma chylomicron metabolism, others were involved with carotenoid transport or metabolism at the enterocyte level. These included *ABCA1*, *ABCG5*, *BCO1*, *CD36*, *ELOVL2* (*ELOVL fatty acid elongase 2*), and *ISX*. Interestingly, one SNP in *ELOVL2* (rs9468304) was very strongly associated with all three phenotypes, possibly due to the inhibitory effect of eicosapentaenoic acid, which is further elongated to docosapentaenoic acid and docosahexaenoic acid by ELOVL2, on carotenoid absorption, as has been shown with β-carotene (Mashurabad, et al., 2016).

6.7 Host-related factors

Several studies have shown that some host-related factors could modulate carotenoid absorption (*see* (Bohn, et al., 2017) for a recent review).

6.7.1 Gender

Females usually exhibit higher blood carotenoid concentrations than men (Brady, Maresperlman, Bowen, & Stacewiczsapuntzakis, 1996). This can be due to several reasons: differences in fruit and vegetable consumption (which are the main sources of carotenoids), differences in carotenoid absorption efficiency, differences in total blood volume (which is lower in women and hence will lead to a higher blood carotenoid concentration following the consumption of a similar amount of carotenoids) and differences in metabolism. The second

hypothesis was ruled out by a study in which no differences in ß-carotene bioavailability (including the corresponding appearance of retinyl palmitate in the chylomicron fraction) was observed between men and women following the consumption of 40 mg encapsulated ß-carotene with a standard meal (O'Neill & Thurnham, 1998).

6.7.2 Age

The observed deterioration of gastro-intestinal tract functions concomitant with aging (Ikuma, Hanai, Kaneko, Hayashi, & Hoshi, 1996; Vellas, Balas, & Albarede, 1991) could affect carotenoid absorption efficiency. Although this has been shown in the case of lycopene, no differences in α-, ß-carotene and lutein absorption efficiency were observed between young and older subjects (Cardinault, et al., 2003).

6.7.3 Diseases

Any disease that alter the intestinal mucosal surface area can potentially alter carotenoid absorption efficiency. As most studies do not directly measure carotenoid bioavailability but rather look at carotenoid status (usually their fasting blood concentration), it is of paramount importance to control for carotenoid dietary intake since indirect effects of the disease on carotenoid absorption can also occur (through dietary adaptations, *e.g.* high fibre or low fat diet). Patients with cystic fibrosis have been shown to have lower plasma lutein and zeaxanthin concentrations compared to healthy subjects (Homnick, Cox, DeLoof, & Ringer, 1993; Schupp, et al., 2004). Several studies have shown that patients with Crohn's disease also exhibited lower fasting blood carotenoid concentrations (Drai, et al., 2009; Geerling, Badart-Smook, Stockbrugger, & Brummer, 1998; Genser, Kang, Vogelsang, & Elmadfa, 1999). In another study, subjects with Celiac disease and Crohn's disease showed 37% decreased levels of macular carotenoids compared to controls despite normal serum carotenoids levels (Ward, Zhao, & Bernstein, 2008).

Surgical removal of parts of the gastro-intestinal tract can also reduce carotenoid absorption efficiency. Patients undergoing bariatric surgery (Roux-en-Y gastric bypass and biliopancreatic diversion) have been reported to display lower blood carotenoid concentrations despite apparently normal fruit and vegetable consumption (Granado-Lorencio, Simal-Anton, Blanco-Navarro, Gonzalez-Dominguez, & Perez-Sacristan, 2011). Short bowel syndrome, usually due to large resections of the small intestine to treat

pathologies such as Crohn's disease or gastrointestinal tumours, have also been associated with carotenoid malabsorption: Edes *et al.* (1991) reported undetectable β-carotene blood levels following supplementation, despite adequate fat absorption, in a patient with extensive small intestinal resection (serum vitamin A levels appeared normal) while in another study, no increase in blood carotenoid concentration were reported in patients given a 12-week-long supplementation with β-carotene, lutein and lycopene, most likely due to low fat absorption in these patients (about 30% *vs* >95% in healthy subjects) (Luo, et al., 2009).

Intestinal parasites and gastro-intestinal tract dysbiosis (*e.g.* bacterial overgrowth) can also damage mucosal cells and result in increased permeability and decreased absorption of nutrients. Indonesian children infected with intestinal helminths exhibited greater increase in serum retinol concentrations when they were dewormed following consumption of red sweet potato (Jalal, Nesheim, Agus, Sanjur, & Habicht, 1998), possibly due to improved fat absorption.

6.8 Mathematical Interactions

Several of the above-mentioned factors can interact together, with an additive, synergistic or antagonist effect. Albeit there are no dedicated studies, it can be hypothesized that, although there is no effect of lutein esterification on its bioavailability in healthy subjects (*see* section 6.1), it is likely that this effect will be significantly higher in patients with lipid malabsorption, *i.e.* with low pancreatic secretion and thus esterases which hydrolyse lutein esters.

Conclusions

The absorption mechanisms of carotenoids are complex. This review underlines the vast amount of work still needed to improve our knowledge of carotenoid absorption and its modulating factors ("SLAMENGHI") (*see* (Bohn, et al., 2015) for a recent review). Indeed, several key points still need to be investigated:

- Is a fraction of carotenoids solubilised in the vesicles present in the lumen of the duodenum during digestion and if so, how does this affect their absorption?
- What are the best dietary sources of carotenoids as far as absorption efficiency is concerned?
- What are the other membrane proteins involved in carotenoid absorption?

- What is the intracellular enterocyte metabolism of carotenoids?
- Is a fraction of carotenoids secreted in intestinal HDL? If so, does it affect their metabolism or their tissue distribution?
- How to explain carotenoid distribution between the different tissues?
- Is there a reverse transport of carotenoids from peripheral tissues towards liver?

Several strategies can be applied in order to improve carotenoid bioavailability, *e.g.* to modify technological treatments or to provide food preparation advice, to provide nutritional recommendations (*e.g.* to consume carotenoids with lipids), to create formulations protecting carotenoids or improving their absorption (*e.g.* nanoencapsulation). There is a high interindividual variability of carotenoid bioavailability, which is partly due to genetic polymorphisms. The identification of additional SNPs and epigenetic factors involved in this variability is a promising area of research which, together with the identification of other factors might lead to propose more personalised recommendations in order to increase the health effects of carotenoids.

Figure 1. Proteins involved in uptake, transport and secretion pathways of carotenoids and their metabolites across the enterocyte.

(A) Unidentified apical uptake transporter; (B) unidentified apical efflux transporter; (C) passive diffusion; (D) unidentified basolateral efflux transporter. The transport into the enterocyte of carotenoids incorporated into mixed micelles following digestion is facilitated by apical membrane proteins: SR-BI (scavenger receptor class B type I), CD36 (cluster of differentiation 36) and NPC1L1 (Niemann–Pick C1-Like 1) and possibly other transporters. A fraction thereof might be effluxed back to the intestinal lumen via apical membrane transporters (SR-BI and possibly other transporters) while the remaining fraction is transported to the site where they are incorporated into chylomicrons. Although some proteins are hypothesized to be involved in intracellular transport of carotenoids, none has been identified yet. However, CRBPII (cellular retinol binding protein II) has been shown to be involved in the intracellular transport of retinol. Carotenoids can be metabolized by BCO1 (beta-carotene oxygenase 1), which is located in the cytosol, and BCO2 (beta-carotene oxygenase 2), which is associated with the inner mitochondrial membrane, while non-metabolized carotenoids are secreted into the lymph in chylomicrons. A fraction of carotenoids could also be secreted into the lymph in HDL (apolipoprotein AI dependent route) involving the transporter ATP binding cassette AI (ABCA1), as has been shown for lutein and zeaxanthin. Carotenoid metabolites, *e.g.* apo-carotenoids, are assumed to be secreted into the portal vein by unknown mechanisms.

Figure 2. Blood transport of carotenoids in humans.

Following their uptake (see **Figure 1** for details), carotenoids are secreted into the blood circulation in chylomicrons (apolipoprotein B-dependent route) or also possibly in HDL (apolipoprotein A1-dependent route), as has been shown for lutein and zeaxanthin. Carotenoids that reach the liver can then be stored, or metabolised following BCO1 and BCO2 enzymatic cleavage, secreted in VLDL or excreted in the bile. A part of carotenoids secreted in VLDL are then found in LDL, following VLDL metabolism, and can then be exchanged with other lipoproteins and/or be taken up by target tissues. The blood transport of carotenoid metabolites is scarcely known and hence not depicted in this figure.

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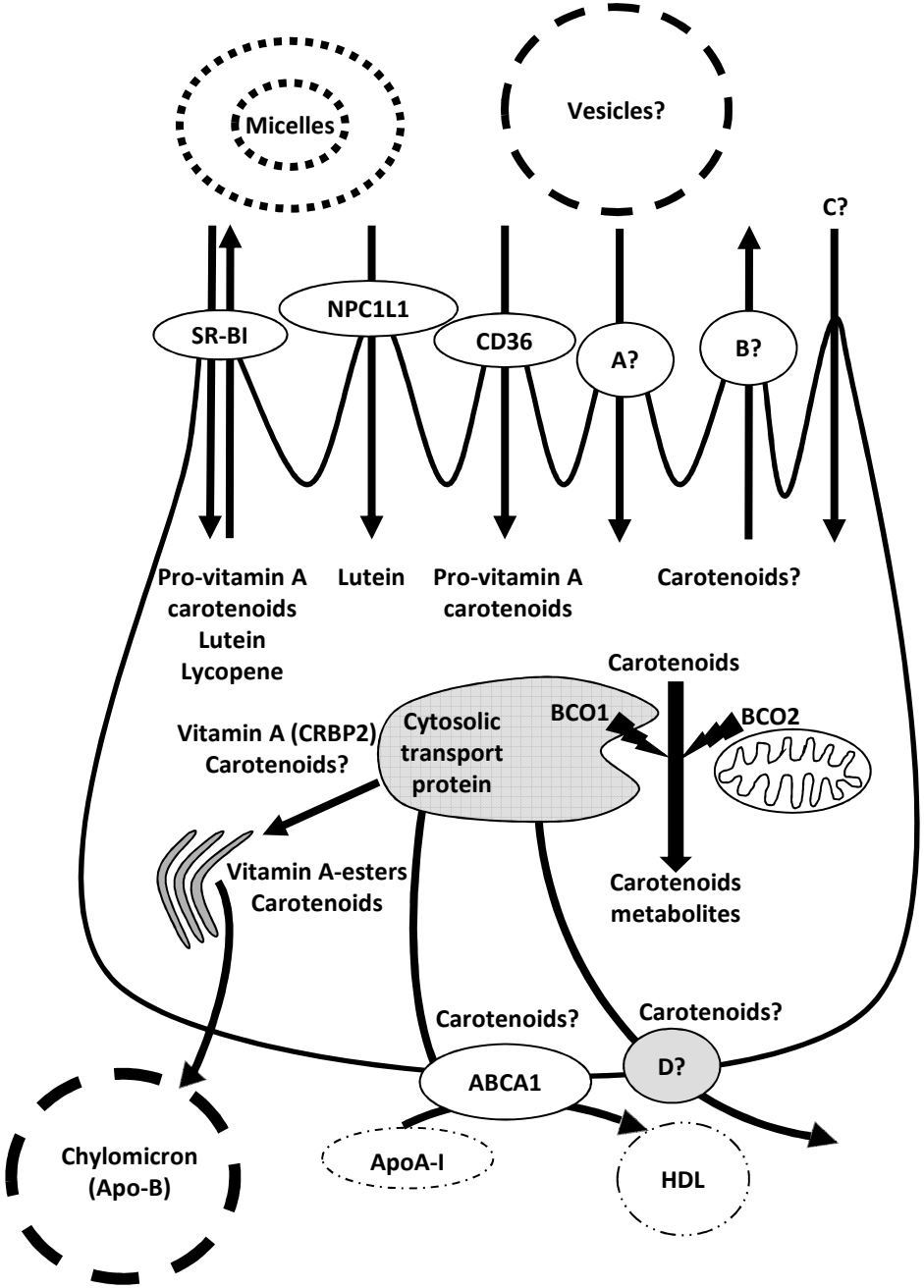
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Pro-vitamin A carotenoids
Carotenoids?
Carotenoids
Vitamin A (CRBP2)
Carotenoids?
Cytosolic transport protein
BCO1
BCO2
Vitamin A-esters
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ABCA1
D?
Chylomicron (Apo-B)
ApoA-I
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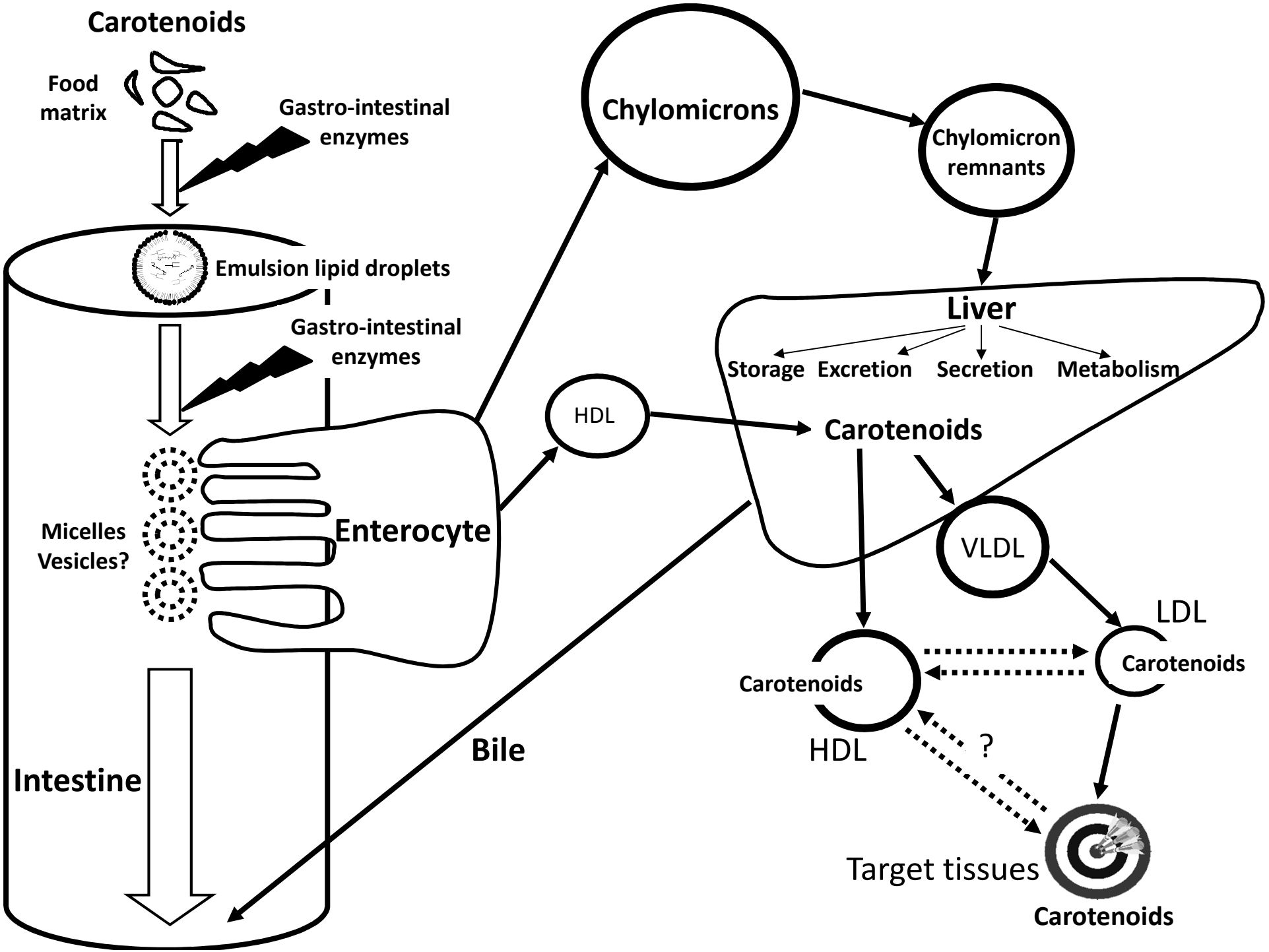

- Carotenoid bioavailability displays a relatively high variability.
- The absorption mechanisms of carotenoids are complex and involve numerous steps.
- Carotenoid bioavailability is affected by dietary factors (*e.g.* food matrix, fat).
- It is also affected by host-related factors (*e.g.* diseases, genetic variations).
- A better knowledge thereof could lead to more personalised dietary recommendations.