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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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1 **Abstract**

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

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

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

23
24 **Key words:** Lutein, beta-carotene, lycopene, food matrix, single nucleotide polymorphism,
25 absorption.

26

27 Introduction

28

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

34 - carotenes are non-oxygenated carotenoids (*i.e.* $n=0$).

35 - xanthophylls are oxygenated carotenoids (*i.e.* $n>0$).

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

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

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

75

76 **2. Carotenoid fate in the human upper gastrointestinal tract**

77

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

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

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

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

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

119

120 **3. Uptake, metabolism and secretion of carotenoids by enterocytes**

121

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

129

130 **3.1 Carotenoid uptake at the apical membrane of the enterocyte**

131 Carotenoids have long been thought to enter enterocytes by simple passive diffusion.
132 This dogma was mostly based on one study carried out in rats with β -carotene (Hollander &
133 Ruble, 1978). However, several apical membrane proteins have been shown to facilitate
134 carotenoid uptake (Reboul & Borel, 2011). Niemann–Pick C1-Like 1 (NPC1L1) is involved
135 in the uptake of lutein (Sato, et al., 2012). Cluster of differentiation 36 (CD36) facilitates β -
136 carotene uptake (Borel, et al., 2013) and could also facilitate lycopene uptake (Moussa, et al.,
137 2011). Scavenger receptor class B member 1 (SR-BI), which is encoded by *SCARB1*,
138 participates in the uptake of β -carotene (Borel, et al., 2013; van Bennekum, et al., 2005),
139 lutein (During, Dawson, & Harrison, 2005) and lycopene (Moussa, et al., 2008). Several
140 SNPs in the genes encoding these proteins have been reported to be associated with the
141 variability in carotenoid plasma concentrations and bioavailability (*see* section 6.6).

142

143 **3.2 Intracellular transport of carotenoids in the enterocyte**

144

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

154

155 **3.3 Carotenoid metabolism in the enterocyte**

156

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

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

174

175 **3.4 Carotenoid secretion from the basolateral side of the enterocyte to the blood** 176 **circulation**

177

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

191

192 **4. Blood transport of carotenoids**

193

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

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

213

214 **5. Tissue distribution of carotenoids**

215

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

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

231 2001). Since among dietary carotenoids, only lutein and zeaxanthin are found in the human
232 lens and retina, these carotenoids are sometimes considered as the “carotenoids of vision”.
233 The macular pigment density, *i.e.* the concentration of carotenoids present in the macula, is
234 partly correlated to lutein+zeaxanthin and β -carotene consumption and serum lutein and
235 zeaxanthin concentration (Curran-Celentano, et al., 2001), and dietary intakes of lutein
236 increase macular pigment density (Landrum, et al., 1997). Regarding *meso*-zeaxanthin
237 (3R,3'S-zeaxanthin), it comes from lutein metabolism, as it has been shown when monkeys
238 were fed either lutein or zeaxanthin (Johnson, Neuringer, Russell, Schalch, & Snodderly,
239 2005). These studies in monkeys have also shown that lutein and zeaxanthin in the macula
240 cannot interconvert, which suggests it is necessary to have a dietary intake of both carotenoids
241 to maintain a normal macular pigment composition. Recently, a mechanism has been
242 proposed to explain the selective uptake of zeaxanthin and lutein in the retina, where
243 zeaxanthin transport from HDL is facilitated by SR-BI while lutein transport from LDL is
244 probably facilitated by the LDL receptor (Thomas & Harrison, 2016).

245 Xanthophylls, and more precisely esterified lutein, have been found in the skin
246 (Wingerath, Sies, & Stahl, 1998), but it is not known if these esters are formed in this tissue,
247 through esterification of free lutein, or if they are absorbed as such and then transported to the
248 skin (*see* section 3.5). Lycopene and β -carotene are the main carotenoids found in the prostate
249 (Clinton, et al., 1996) with concentrations ranging from 0 to 2.6 nmol/g for lycopene and from
250 0.09 to 1.7 nmol/g for β -carotene. The presence of significant amounts of lycopene in this
251 organ support the results of epidemiological studies which suggest this carotenoid plays a
252 preventive role against the development of prostate cancer (Jian, Du, Lee, & Binns, 2005;
253 Wertz, Siler, & Goralczyk, 2004).

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

257

258 **6. Factors modulating the bioavailability of carotenoids**

259

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

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

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

270 – L for “**L**inkage” (referring to additional functional groups sometimes linked to
271 carotenoids: esters, aldehyde...)

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

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

276 – E for “**E**ffectors of absorption” (referring to the effect of nutrients and drugs on carotenoid
277 absorption)

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

279 – G for “**G**enetic factors” (representing the effect of genetic polymorphisms or epigenetic
280 modifications)

281 – H for “**H**ost-related factors” (referring to individual characteristics such as age, gender,
282 pathologies...)

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

286

287 **6.1 Species of carotenoids and molecular Linkage**

288

289 The study of the effect of carotenoid species on their bioavailability is not
290 straightforward due the variability of the matrices in which they are incorporated (*see* section
291 6.3). To differentiate between these effects, it is necessary to measure the bioavailability of
292 pure carotenoids. This was done in a study carried out in rats which showed that carotenoid
293 bioavailability was inversely correlated with their hydrophobicity (*i.e.* the bioavailability of
294 carotenoids was as follows: astaxanthin>lutein> β -carotene>lycopene), which was mainly due
295 to differences in their bioaccessibility according to the authors (Sy, et al., 2012).

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

299 However, the steric hindrance of some configurations limits the number of *cis* isomers to a
300 few dozens. As a consequence, carotenoids are found in the human diet under 4 main
301 chemical forms: all-*trans* carotenoids, all-*trans* esterified carotenoids (Weller & Breithaupt,
302 2003), *cis* carotenoids and *cis* esterified carotenoids. However, most carotenoids are usually
303 present as all-*trans* non-esterified carotenoids. The fraction of *cis* isomers present in our diet
304 is usually produced by technological treatments, in particular elevated temperatures
305 (Milanowska & Gruszecki, 2005; Rodriguez-Amaya, 1999; Updike & Schwartz, 2003). A
306 “*trans* to *cis*” conversion in the acidic environment of the stomach has also been proposed
307 (Mortensen & Skibsted, 2000), although it has not been observed *in vivo* (Richelle, et al.,
308 2010; Tyssandier, et al., 2003). However, Richelle *et al.* reported lycopene conversion to
309 occur within the enterocyte (Richelle, et al., 2010). *Cis* isomers have different physico-
310 chemical properties compared to corresponding all-*trans* isomers: they are no longer linear,
311 rigid molecules, which affect their capacity to solubilize into mixed micelles (Milanowska,
312 Polit, Wasylewski, & Gruszecki, 2003). Their tendency to crystallise or aggregate is also
313 diminished (Britton, 1995). As a consequence, it has been hypothesized that they have
314 different absorption efficiency. This has been investigated in several studies. *Cis* lycopene
315 isomers have been shown to display a higher bioavailability than the all-*trans* isomer
316 (Boileau, Boileau, & Erdman, 2002; Cooperstone, et al., 2015), which would be due to a
317 higher solubility in mixed micelles. *Cis* β -carotene isomers also display a higher solubility in
318 mixed micelles compared to all-*trans* β -carotene (G. Levin & Mokady, 1995; Tyssandier, et
319 al., 2003) but surprisingly, they have a lower absorption efficiency (Ben-Amotz & Levy,
320 1996). This apparent discrepancy could originate from the fact that *cis* β -carotene isomers are
321 isomerised to all-*trans* β -carotene in enterocytes (You, Parker, Goodman, Swanson, & Corso,
322 1996), which leads to an underestimation of their absorption efficiency. Of note, whether all-
323 *trans* β -carotene enterocyte uptake is favoured remains controversial since a study with
324 synthetic mixed micelles has shown a greater uptake of all-*trans* β -carotene *vs cis* β -carotene
325 (During, Hussain, Morel, & Harrison, 2002) while another study did not observe any
326 difference using micelles produced following *in vitro* digestions (Ferruzzi, Lumpkin,
327 Schwartz, & Failla, 2006).

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

333 inexistent. However, it was shown in a clinical study that lutein esters had a bioavailability
334 equivalent to that of free lutein (Bowen, Herbst-Espinosa, Hussain, & Stacewicz-Sapuntzakis,
335 2002), and the bioavailability of zeaxanthin dipalmitate was even greater than that of free
336 zeaxanthin in another clinical study (Breithaupt, Weller, Wolters, & Hahn, 2004). This has
337 also been observed with another xanthophyll ester, namely esterified β -cryptoxanthin
338 (Breithaupt, Weller, Wolters, & Hahn, 2003). These results suggest that the hydrolysis of
339 xanthophyll esters in the intestinal lumen is a highly efficient process. It can also be
340 hypothesized that the facilitated transport of xanthophyll esters ~~are more soluble in mixed~~
341 ~~micelles than free xanthophylls or that their facilitated transport~~ by membrane proteins is
342 more efficient than that of free xanthophylls.

343

344 **6.2 Amount of carotenoids consumed in a meal**

345

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

352

353 **6.3 Matrix in which carotenoids are incorporated**

354

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

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

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

384

385 **6.4 Effectors of absorption**

386

387 6.4.1 Lipids

388

389 Dietary triglycerides have been shown to be necessary to promote carotenoid
390 absorption. Lipids increase the bioavailability of both free (Unlu, Bohn, Clinton, & Schwartz,
391 2005) and esterified lutein (Roodenburg, Leenen, Hof, Weststrate, & Tijburg, 2000). When
392 raw vegetables were consumed together with cooked whole eggs (each egg provided 5 g
393 lipids), lutein, zeaxanthin, α -carotene, β -carotene, and lycopene bioavailability increased 3-8
394 fold (Kim, Gordon, Ferruzzi, & Campbell, 2015). Similarly, consumption of avocado together
395 with tomatoes or raw carrots has been shown to increase the bioavailability of β -carotene and
396 its conversion efficiency to vitamin A (Kopec, et al., 2014). Lipids can modulate carotenoid
397 absorption by several mechanisms:

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

400 - They can stimulate biliary secretion and consequently, micelle production, which would
401 increase the quantity of carotenoids solubilised in micelles and hence available for
402 absorption.

403 - By promoting chylomicron secretion, triglycerides could increase carotenoid secretion
404 outside the enterocyte and thus prevent their intracellular accumulation, which would in turn
405 increase their absorption.

406

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

408 - the species of fatty acids from triglycerides (Borel, et al., 1998; Gleize, et al., 2013;
409 Schaeffer & Hamilton, 1990). For example, olive and coconut oils have been shown to
410 increase similarly the intestinal absorption of lutein in mice when compared to groundnut,
411 soybean, sunflower, rice bran, corn, palm and fish oil (Nidhi, Ramaprasad, & Baskaran,
412 2014). In humans, canola oil, which is rich in monounsaturated fatty acids, was shown to
413 trend to promote higher lutein and α -carotene bioavailability compared to butter, which is
414 rich in saturated fatty acids (Goltz, Campbell, Chitchumroonchokchai, Failla, & Ferruzzi,
415 2012).

416 - the amount of amphiphilic lipids (mostly phospholipids).

417 - the species of amphiphilic lipids. It is supposed that, before its hydrolysis to
418 lysophosphatidylcholine, phosphatidylcholine could affect carotenoid absorption by
419 decreasing lipolysis speed and hence micelle formation speed. Phosphatidylcholine inhibits
420 lutein absorption while lysophosphatidylcholine has the opposite effect (Sugawara, et al.,
421 2001).

422 - the extent of lipid emulsification. For example, the use an excipient emulsion with
423 decreasing droplet size has been shown to increase the bioaccessibility of α - and β -carotene
424 from carrot juice *in vitro* (Zhang, et al., 2016) and an emulsion with small droplet size
425 increased enterocyte uptake of β -carotene in Caco-2 cells (Lu, et al., 2016).

426

427 6.4.2 Dietary fibers

428

429 Dietary fibres could affect carotenoid absorption by several mechanisms:

430 - by sequestering micelle components (Eastwood & Mowbray, 1976).

431 - by inhibiting pancreatic lipase (W. E. Hansen, 1987), which would decrease carotenoid
432 extraction from lipid droplets (Tyssandier, et al., 2001).

433 - by increasing the viscosity of the intestinal content (Gallagher, Hassel, Lee, & Gallagher,
434 1993) which would impair the diffusion of carotenoid-rich micelles towards the brush
435 border.

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

439

440 6.4.3 Fat absorption inhibitors

441

442 Since obesity is a major health problem, several drugs have been designed to decrease
443 fat absorption. However, these drugs could decrease lipid micronutrient absorption as well.
444 Orlistat, an inhibitor of gastric and pancreatic lipase, has been shown to decrease the
445 absorption of α - and β -carotene (McDuffie, Calis, Booth, Uwaifo, & Yanovski, 2002) while
446 Olestra, a saccharose polyester used as a lipid substitute, has been shown to decrease the
447 absorption of β -carotene and lycopene (Weststrate & Hof, 1995). Similarly, phytosterols,
448 which are used to decrease cholesterol absorption efficiency, also decrease the absorption of
449 some carotenoids (α - and β -carotene and lycopene) (Clifton, et al., 2004; Richelle, et al.,
450 2004) although no effect was observed on β -cryptoxanthin bioavailability following the
451 consumption of a milk-based fruit drink with or without plant free sterols for 28 days
452 (Granado-Lorencio, Donoso-Navarro, Sanchez-Siles, Blanco-Navarro, & Perez-Sacristan,
453 2011).

454

455 6.4.4 Micronutrients

456 Since carotenoids are consumed together with other micronutrients, and since common
457 absorption mechanisms are involved, it is hypothesized that some micronutrients compete
458 with carotenoids regarding their absorption. Some results support this hypothesis: indeed,
459 carotenoids have been shown to compete together for their incorporation into mixed micelles
460 and subsequent uptake by enterocytes (During, et al., 2002; Tyssandier, Cardinault, et al.,
461 2002; Tyssandier, et al., 2001; van den Berg, 1999). However, the effect of such competition
462 on long term carotenoid status is not yet certain (Tyssandier, Cardinault, et al., 2002). On the
463 other hand, microconstituants such as vitamin C, polyphenols and vitamin E are thought to
464 protect carotenoids against oxidative degradation in the gastro-intestinal tract, and thus
465 increase their absorption efficiency. The results are here conflicting since vitamin C has been
466 suggested to increase lutein absorption (Tanumihardjo, Li, & Dosti, 2005), but results from

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

471

472 6.4.5 Minerals

473

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

481

482 6.5 Vitamin A (Nutrient) status of the host

483

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

494

495 6.6 Genetic factors

496

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

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

521

522 **6.7 Host-related factors**

523

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

526

527 **6.7.1 Gender**

528

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

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

539

540 6.7.2 Age

541

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

547

548 6.7.3 Diseases

549

550 Any disease that alter the intestinal mucosal surface area can potentially alter
551 carotenoid absorption efficiency. As most studies do not directly measure carotenoid
552 bioavailability but rather look at carotenoid status (usually their fasting blood concentration),
553 it is of paramount importance to control for carotenoid dietary intake since indirect effects of
554 the disease on carotenoid absorption can also occur (through dietary adaptations, *e.g.* high
555 fibre or low fat diet). Patients with cystic fibrosis have been shown to have lower plasma
556 lutein and zeaxanthin concentrations compared to healthy subjects (Homnick, Cox, DeLoof,
557 & Ringer, 1993; Schupp, et al., 2004). Several studies have shown that patients with Crohn's
558 disease also exhibited lower fasting blood carotenoid concentrations (Drai, et al., 2009;
559 Geerling, Badart-Smook, Stockbrugger, & Brummer, 1998; Genser, Kang, Vogelsang, &
560 Elmadfa, 1999). In another study, subjects with Celiac disease and Crohn's disease showed
561 37% decreased levels of macular carotenoids compared to controls despite normal serum
562 carotenoids levels (Ward, Zhao, & Bernstein, 2008).

563

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

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

576

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

583

584 **6.8 Mathematical Interactions**

585

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

592

593 **Conclusions**

594

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

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

603 - What is the intracellular enterocyte metabolism of carotenoids?
604 - Is a fraction of carotenoids secreted in intestinal HDL? If so, does it affect their metabolism
605 or their tissue distribution?
606 - How to explain carotenoid distribution between the different tissues?
607 - Is there a reverse transport of carotenoids from peripheral tissues towards liver?
608 Several strategies can be applied in order to improve carotenoid bioavailability, *e.g.* to modify
609 technological treatments or to provide food preparation advice, to provide nutritional
610 recommendations (*e.g.* to consume carotenoids with lipids), to create formulations protecting
611 carotenoids or improving their absorption (*e.g.* nanoencapsulation). There is a high
612 interindividual variability of carotenoid bioavailability, which is partly due to genetic
613 polymorphisms. The identification of additional SNPs and epigenetic factors involved in this
614 variability is a promising area of research which, together with the identification of other
615 factors might lead to propose more personalised recommendations in order to increase the
616 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, CRBP II (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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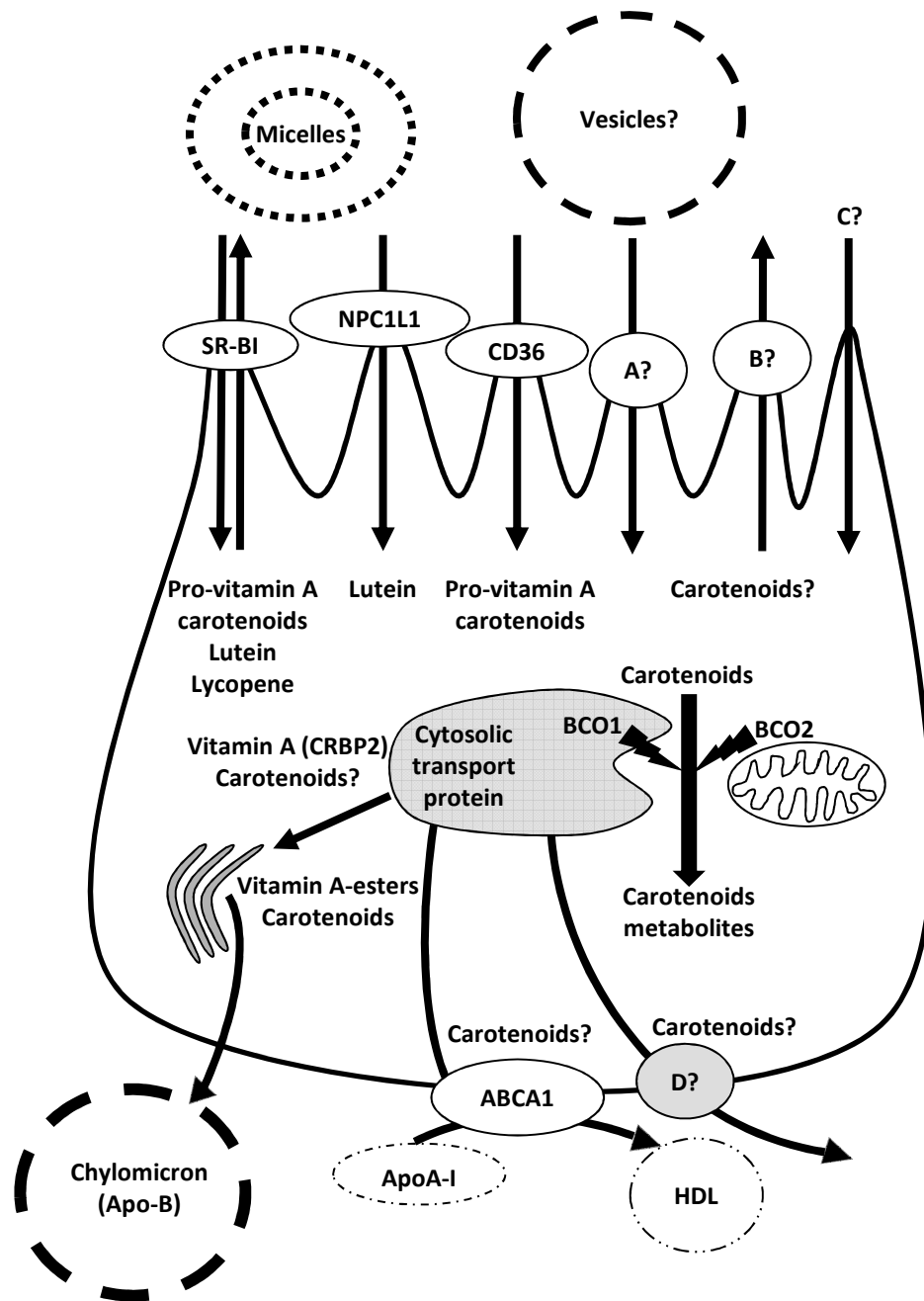
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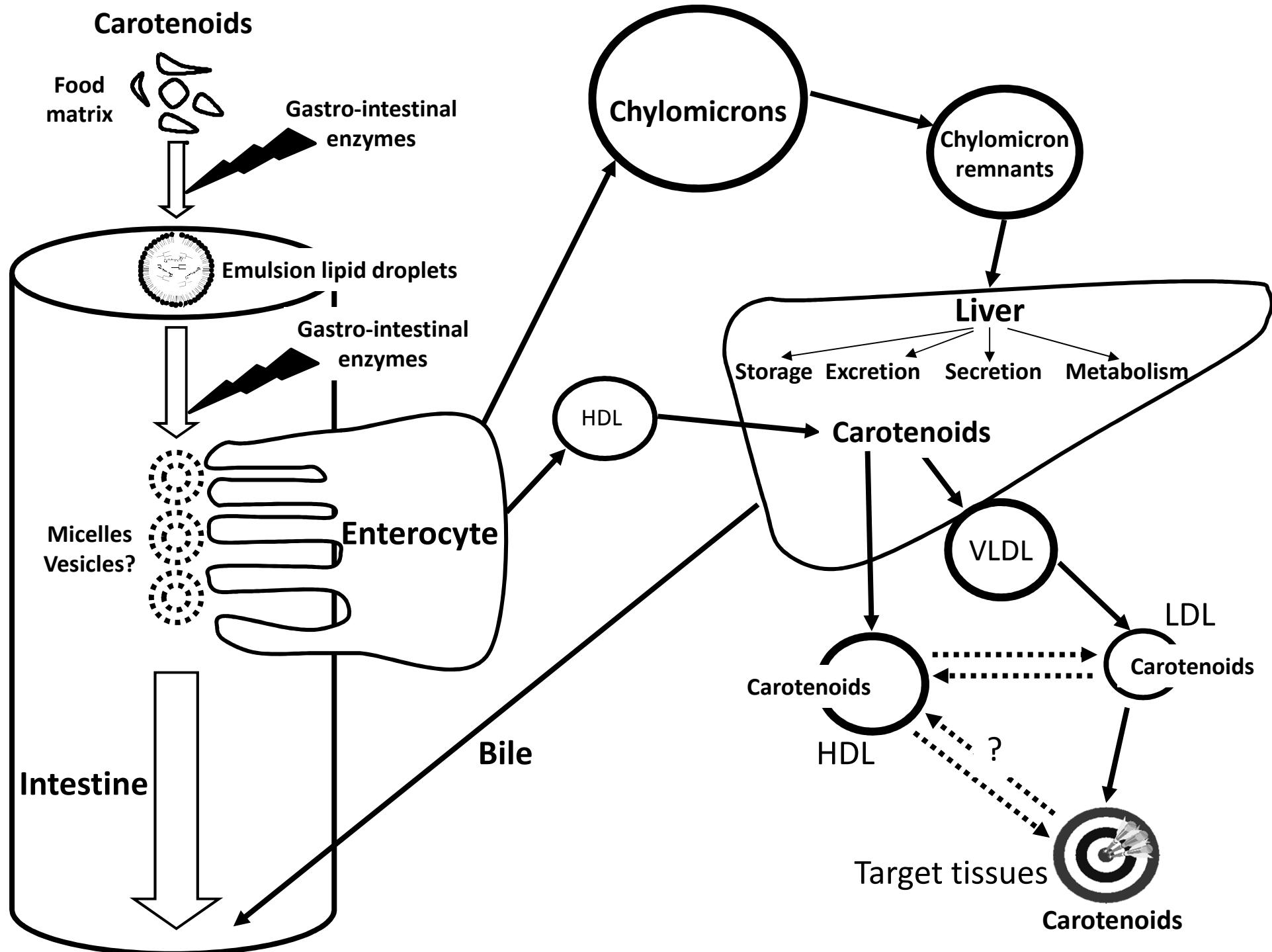
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- Carotenoid bioavailability displays a relatively high variability.
- The absorption mechanisms of carotenoids are complex and involve numerous steps.
- Carotenoid bioavailability is affected by dietary factors (*e.g.* food matrix, fat).
- It is also affected by host-related factors (*e.g.* diseases, genetic variations).
- A better knowledge thereof could lead to more personalised dietary recommendations.

ACCEPTED MANUSCRIPT