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Abstract

Vitamin E is an essential molecule for our development and health. It has long been thought that it was absorbed and transported through cellular membranes by a passive diffusion process. However, data obtained during the past 15 years showed that its absorption is actually mediated, at least in part, by cholesterol membrane transporters including the Scavenger Receptor Class B type 1 (SR-BI), CD36 molecule (CD36/SRB2), NPC1 like transporter 1 (NPC1L1) and ATP-binding cassettes A1 and G1 (ABCA1 and ABCG1). This review focuses on the absorption process of vitamin E across the enterocyte. A special attention is given to the regulation of this process, including the possible competition with other fat-soluble micronutrients, and the modulation of transporter expressions. Overall, recent results noticeably increased the comprehension of vitamin E intestinal transport, but additional investigations are still required to fully appreciate the mechanisms governing vitamin E bioavailability.

Keywords: tocopherol; intestine; mixed micelles; membrane transporters; uptake; chylomicrons; HDL; fat-soluble vitamins, bioavailability, competition.

Introduction

The vitamin E family includes four tocopherols and four tocotrienols (Figure 1) originating from plants and other photosynthetic organisms (1). The main vitamin E sources are vegetable oils such as sunflower oil, and nuts such as almond (2). The human diet mainly provides RRR-α-tocopherol in Europe (3), while RRR-γ-tocopherol is highly consumed in the US (4). RRR-α-tocopherol is also the main vitamer present in human blood and tissues (3). In this review, we will thus mainly focus on both α-tocopherol and γ-tocopherol.

Vitamin E has primarily been identified as an essential factor to restore fertility in deficient female rats (3). Further investigations showed that vitamin E was also a potent antioxidant (3), as well a key molecule in the modulation of signal transduction and gene expression in the context of inflammation and immune system disorders (5). However, dietary surveys highlighted that a significant part of the population in Europe and in the US did not cover the Recommended Dietary Allowance for vitamin E (6). These alarming conclusions strengthen the major interest of promoting vitamin E bioavailability from foods and to fully understand the molecular mechanisms governing its intestinal absorption.

During the digestion process, vitamin E is extracted from its food matrix, dissolved in the fat phase of the bolus at the gastric level and finally incorporated into mixed micelles with other lipid hydrolysis products during duodenal digestion (see for review (7)). Mixed micelles then diffuse through the unstirred water layer of the glycocalix area to approach the apical membrane of the enterocytes, i.e. the brush border membrane. Vitamin E absorption has long been considered to occur by passive diffusion because it was i) independent of ATP, and ii) linear up to fairly high concentrations (1.2 mM) in rat intestine (8). However, these data were conflicting with other results showing that vitamin E

postprandial responses after a tocopherol load were highly variable in humans (9). Vitamin E transport mechanisms in the intestine have thus been reinvestigated recently.

Vitamin E transport across the enterocyte (Figure 2)

Vitamin E uptake across the brush border membrane: role of SR-BI, CD36 and NPC1L1

In 2006, we showed for the first time that both α- and γ-tocopherol intestinal uptake was facilitated by SR-BI (scavenger receptor class B type I) (10). This observation is not surprising because SR-BI contributes to vitamin E uptake in liver cells (11), porcine brain (12), rat retina (13) and pneumocytes (14). Furthermore, vitamin E metabolism is altered in SR-BI-deficient mice (15) and a protein analog to SR-BI can mediate vitamin E uptake in *Drosophila* (16). SR-BI was later confirmed to be a major protein in vitamin E intestinal uptake, at least in Caco-2 cell and mouse models (17), as well as in the uptake of fat-soluble micronutrients and phytochemicals in general (7). Interestingly, SR-BI was also shown to mediate vitamin E efflux from the cytosolic compartment of Caco-2 cells to the apical medium, suggesting a potential regulatory role of this protein in vitamin E cellular concentrations (10). The molecular mechanisms underlying vitamin E transport through SR-BI are still unknown. SR-BI was primarily shown to selectively mediate the uptake of α-tocopherol from HDL (12), which suggests a direct interaction with this ligand. However, SR-BI has also been shown to traffic in clathrin-coated lipid vesicles after a lipid load (18), and we demonstrated that SR-BI extracellular loop could bind mixed micelles (19). Finally, SR-BI has recently been described as an intestinal lipid sensor (20), and it appeared to be a modulator of chylomicron secretion (21). These last results suggest that SR-BI may actually promote lipid flux through the enterocyte and thus indirectly enhance

vitamin E absorption. Further research is therefore required to understand the nature of interactions between SR-BI and vitamin E.

We later showed that besides its ability to transport carotenoids (22) and possibly vitamin D (23) and K (24), intestinal CD36 (CD36 molecule) could contribute to tocopherol absorption process (25). However, despite the fact that the extracellular loop of this protein could bind mixed micelles (19) and that CD36 was clearly involved in vitamin E uptake *in vitro*, its effect on vitamin E absorption *in vivo* in mice was rather due to its impact on lipid general absorption process. Conversely to what was expected, CD36-deficient mice showed an accumulation of plasma vitamin E during the postprandial state, due to a defect of clearance of the produced chylomicrons (25).

Finally, by using both Caco-2 and rodent models, it was shown that the major intestinal cholesterol transporter, i.e. NPC1L1 (NPC1 like intracellular cholesterol transporter 1) was another contributor to α-tocopherol absorption (26, 17). Accordingly, the overexpression in Caco-2 cells of clustered variants of NPC1L1, presenting either a decreased expression level, an altered subcellular localization or a lower intrinsic activity compared with wild-type NPC1L1, led to a decreased vitamin E absorption (27). Additionally, it was recently revealed in transfected cells that α-tocopherol could compete with cholesterol to bind to the NPC1L1-N terminal domain. This interaction promoted NPC1L1 endocytosis, which may in turn enhance lipid and vitamin E transport in clathrin-coated lipid vesicles (28). As expected ezetimibe, which is a potent inhibitor of NPC1L1, can reduce vitamin E absorption *in vivo* in rats (26). As recent data also suggested that Orlistat could also inhibit NPC1L1 functioning (29), further research is needed to evaluate the long-term effects of these drugs on vitamin E status in humans.

Vitamin E basolateral secretion from the enterocyte: chylomicron and intestinal HDL pathways

Vitamin E trafficking across the enterocyte is poorly understood. Due to its lipophilic nature, vitamin E should likely be targeted to cytosolic lipid droplets or organelle membranes after absorption. Indeed, a recent work showed that in cultured liver cells, both α- and γ-tocopherol were associated with lysosomes and endoplasmic reticulum membrane (30). It may also traffic bound to binding proteins, the best candidate being Sec14p-like proteins TAP1, 2 and 3 (31). Vitamin E is then packed into chylomicrons without esterification in the Golgi apparatus to be released to the lymph (7). Besides, a non-apoB pathway involving ABCA1 (ATB-binding cassette A1) (32, 33) and maybe ABCG1 (34) has been demonstrated in mice and in Caco-2 cells. These data are supported by the fact that ABCA1 has been described as an important vitamin E exporter in several cell types including human fibroblasts, mouse macrophages (35) and liver cells (36). Similarly, ABCG1 has also been involved in vitamin E membrane transport in transfected CHO cells, Hep3B hepatocytes and THP-1 macrophages, and vitamin E metabolism was abnormal in ABCG1-deficient mice (37). The mechanisms responsible for vitamin E transport *via* ABC transporters have not been resolved yet, but we propose a process similar to the one suggested for cholesterol. It is believed that ABCA1 acts like a flippase that induces the rearrangement of plasma membrane phospholipids, thus favoring the anchoring of apo A-I (apolipoprotein A-I) to the cellular membrane. Once bound to the membrane, apoA-I can then be loaded with phospholipids and cholesterol, allowing their removal from the cell (38).

Vitamin E intestinal absorption sites and competition for absorption with other (micro)nutrients

The assumption that vitamin E was absorbed in the proximal or mid-intestine (39) has recently been challenged by the observation that after a gavage, vitamin E accumulation in intestinal mucosa was mainly located in the distal part of mouse small intestine, i.e., in the distal jejunum and the ileum (17, 40). This seems contradictory with duodenal or jejunal expression of SR-BI (41), CD36 (42) and NPC1L1 (43). We could hypothesize a better clearance of vitamin E from enterocyte cytosol in the upper part of the intestine compared to the distal part. However, this is unlikely because we would have observed a similar phenomenon for other fat-soluble vitamins, and this is not the case for vitamin A, which accumulates in the proximal intestine as expected (40). In fact, the expression of these 3 proteins is highly variable along the intestine and they can be highly expressed in the ileum (44). Moreover, although more expressed in the duodenum, SR-BI is present in significant amount on the basolateral membrane of the ileum enterocytes (45), where it may play a role in vitamin E release to the lymph or the blood compartments.

The existence of membrane proteins facilitating vitamin E transport in the enterocyte raises the possibility of a discrimination between the different vitamers, a saturation of absorption, as well as possible competitions for absorption between the different ligands. Interestingly, the intestine does not discriminate between vitamers (46, 10) or stereoisomers (47) of vitamin E. However, a higher absorption of α-tocopherol compared to γ- and δ- forms has been observed in in lymph-cannulated rats (48), likely due to a preferential metabolization and excretion of γ- and δ-tocopherols (49). Vitamin E absorption efficiency assessed with deuterium- or ^{14}C-labeled vitamin E ranged from 10 to 81 % in humans (50, 51). This high variability may be partly linked to factors related to the food matrix used to provide vitamin E (apples *vs* milk). Among the dietary factors negatively affecting vitamin E absorption (see for review (7)), we showed in Caco-2 cells

that α-tocopherol could compete for absorption with cholesterol, as well as with γ-tocopherol, vitamin A, D, K and carotenoids (10, 22, 24). Except for vitamin A, these competitions are likely due to shared uptake routes involving common transporters. Regarding vitamin A, it has been hypothesized that vitamin E was protecting retinol (preformed vitamin A) from luminal oxidation, leading to a degradation and thus a reduced absorption of vitamin E (52). Phytosterols may also inhibit vitamin E absorption in normocholesterolemic patients (53) through similar mechanisms than the ones leading to reduce cholesterol absorption, i.e. a competition for incorporation into mixed micelles and a reduction of uptake by the enterocyte. Finally, the flavanone naringenin altered vitamin E uptake by Caco-2 cell monolayers (54), probably by interfering with membrane transporter functioning, as previously shown with digestive enzymes (55).

Finally, the identification of membrane proteins facilitating vitamin E uptake does not rule out the possibility of a partial transport by passive diffusion. Indeed, we previously showed that vitamin D uptake was facilitated by membrane transporters at dietary doses while it was driven by passive diffusion at higher doses (23). Passive diffusion contribution may be more or less important along the duodenal-ileal axis, which would partly explain why transporter expressions do not correlate with vitamin E accumulation in mouse intestinal mucosa.

Regulation of vitamin E membrane transport in the intestine

The fact that vitamin E transport is, directly or indirectly mediated by lipid transporters, raise two additional questions: "Can vitamin E regulate the expressions of these transporters and thus impact on both its own transport and other lipid transport?" and

"Can other factors, by regulating the expression of these transporters, modulate vitamin E fluxes in the intestine?"

Vitamin E and SR-BI regulation

Vitamin E effect on intestinal SR-BI expression has not been investigated yet. However, it is worth to mention that vitamin E-depleted diet induced a drastic increase in SR-BI expression in rat liver, while HepG2 incubation with vitamin E could conversely reduce SR-BI expression, putatively through a PKC (protein kinase C)-dependent signaling pathway (56). Such regulation may also occur in the enterocyte.

Besides, oleic acid and ecosapentaenoic acid (EPA) were shown to moderately increase SR-BI expression in Caco-2 cells (57), while ezetimibe (58) and chokeberry polyphenols (59) could decrease it. Using both human cell and mouse models, it was also shown that SR-BI expression was subject to control by retinoid signaling via the intestinal transcription factor ISX, which can repress its expression (60). Conversely, insulin resistance state increased SR-BI intestinal expression in hamsters (61). Finally, SR-BI post-transcriptional regulation was shown to be dependent on bile component delivery to the intestine (i.e. in cholestasis conditions), bile salts leading to an increased in SR-BI expression in rodent intestines (62). All these factors may thus modulate vitamin E absorption via their effects on intestinal SR-BI regulation (Table 1).

Vitamin E and CD36 regulation

Vitamin E effect on transcriptional regulation of CD36 has first been described about 20 years ago (63). If no data are available on such regulation at the intestinal level, it was consistently shown that vitamin E could inhibit CD36 expression in aortic smooth muscle

cells (64), human macrophages (65) and liver of rats (66) and guinea pigs (67), while vitamin E deficiency led to an upregulation of CD36 in HepG2 cells (68). This downregulation may be due to a reduction of lipid peroxidation and cellular oxidative stress (69) or to an inhibition of tyrosine kinase (65). Although not demonstrated, such regulation by vitamin E may also involve transcription factors such as PXR (70, 71), possibly via its long chain metabolite α-tocopherol-13'-COOH (72).

Interestingly, CD36 intestinal expression is downregulated by dietary fat, and especially by fatty acids such as oleic acid (73, 74), which can subsequently impact on vitamin E absorption (Table 1).

Vitamin E and NPC1L1 regulation

If no data are available on vitamin E effect on NPC1L1 expression, it is noteworthy that this protein is regulated by SREBP2 (75) and LXR (76), making it a putative target of tocopherol signaling. Indeed, tocopherol can target these transcription factors in an indirect manner (37).

NPC1L1 is downregulated by several dietary compounds including fat (77), cholesterol (78), fatty acids (79, 57), calcium (80), curcumin (81), sitosterol (82) and lactobacillus from fermented foods (83), while dietary glucose was shown to increase its expression (84). NPC1L1 expression is also regulated by hormones: estrogen (85) and cholecystokinin (86) could increase it while PYY reduced it (87). The effects of these factors are summarized in Table 1.

Vitamin E and ABC transporter regulation

We previously reported in Caco-2 cells that vitamin E, probably via *SREBP2*, led to an inhibition of cholesterol synthesis, which resulted in a decrease in cellular cholesterol and thus in cellular oxysterol concentration. This induced an important decrease in the expression level of genes regulated by LXR, such as *ABCA1* and *ABCG1* (88). This effect was confirmed *in vivo* in rat liver and macrophages (37).

Additionally, as presented in Table 1, intestinal ABCA1 can be downregulated by fat, fatty acids (79, 57), phytosterols (89), glucose (90), chokeberry polyphenols (59) or ezetimibe (58). However, the subsequent effect of such regulation on vitamin E absorption still need to be demonstrated.

Conclusions

The mechanisms of vitamin E intestinal absorption are only partly comprehended. The discovery of vitamin E intestinal transporters with broad substrate specificity has raised many questions regarding the potential interactions with other nutrients and/or drugs during the vitamin E absorption process, due to possible competitions or because of indirect effects on transporter expressions. Besides, it is very likely that other proteins involved in vitamin E membrane transport still need to be identified (7), which is of major importance because genetic polymorphisms in these proteins can partly explain the high interindividual variability regarding vitamin E absorption in humans (91). Further research is thus needed to answer these questions and propose personalized intake recommendations for vitamin E taking into accounts both genetic factors and lifestyle.

Conflicts of Interest: The author declares no conflict of interest.

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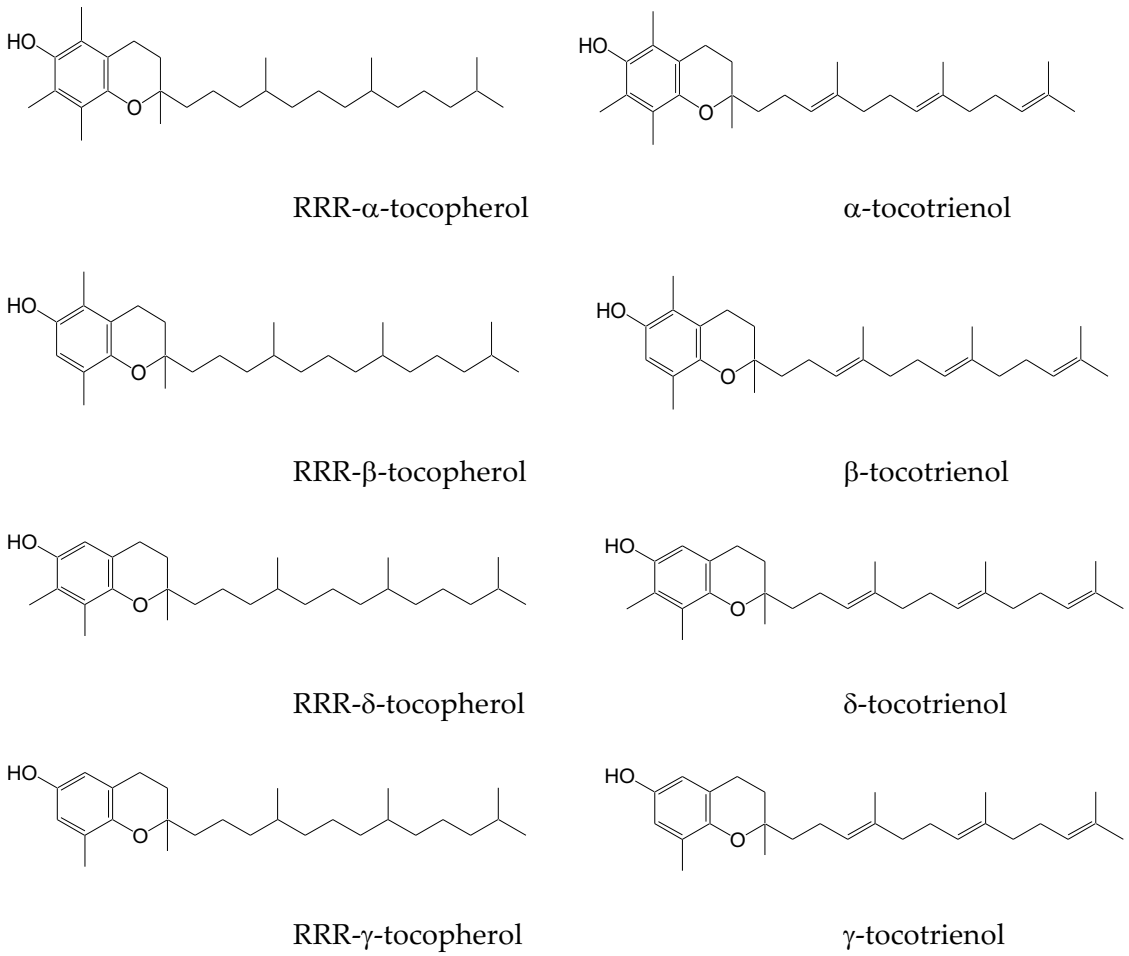

Figure 1. The vitamin E family

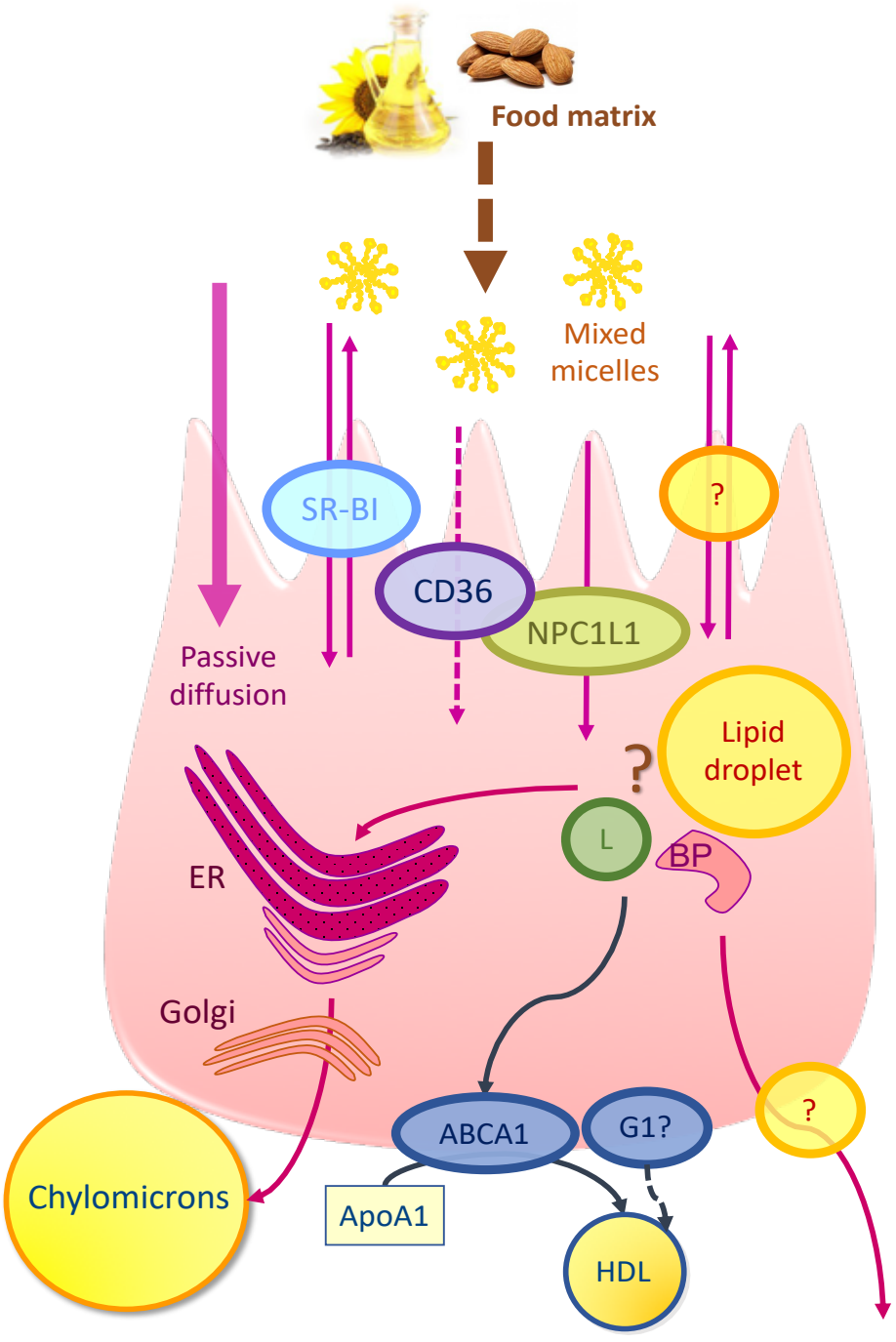

Figure 2 : Vitamin E fate across the enterocyte

? = putative pathways, --> Indirect transport, L = lysosomes, BP = binding protein, ER = endoplasmic reticulum

Vitamin E is released from its food matrix during digestion and incorporated into mixed micelles. Micellar vitamin E apical transport is facilitated by membrane proteins including SR-BI, CD36 and NPC1L1. A fraction of vitamin E may be effluxed back to the intestinal lumen via apical membrane transporters (SR-BI and possibly other transporters). Intracellular vitamin E might be associated to lipid droplets, lysosomes, ER membrane and/ or specific binding proteins. The major fraction of vitamin E is secreted in the lymph into chylomicrons, while a minor part may also be secreted at the basolateral side via ABCA1 (apoAI pathway) and possibly ABCG1.

Table 1. Factors modulating intestinal transporter expression

Factors		Membrane transporter	Model	Effect	Signaling/ regulation pathway	References
Dietary and/or host factors	Vitamin E	SR-BI	Rat liver/ HepG2 cells	↓	PKC ?	(54)
		CD36	Rat liver/ guinea pig liver		Independent of LXRα, PXR and PPARγ. Posttranslational regulation ?	(64, 65)
			Macrophages		Tyrosine kinase (Tyk2).	(63)
			Muscle cells		nd	(62)
		ABCA1/G1	Caco-2 cells	↓	SREBP2, cholesterol synthesis genes, LXR	(85)
	Fat	CD36	Mouse intestine	↓	nd	(70)
		NPC1L1	Mouse intestine	↓	Linked to a posttranslational increase in HMGCR activity	(74)
		ABCA1				
	Oleic acid and EPA	SR-BI	Caco-2	↑	nd	(55)
	Oleic acid	CD36	Rat enterocytes	↓	nd	(71)
	EPA, DHA	NPC1L1	Caco-2 cells	↓	LXR/RXR ?	(76, 55)
	ARA, DHA	ABCA1	Caco-2 cells	↓	LXR/RXR ?	
	cholesterol	NPC1L1	Mouse intestine	↓	nd	(75)
	25-hydroxycholesterol	NPC1L1	Caco-2 cells	↓	SREBP-2	(72)
	Sitosterol	NPC1L1	FHs 74 intestinal cells	↓	nd	(79)
	Phytosterols	ABCA1	Caco-2 cells	↓	27 hydroxycholesterol/ LXRα	(86)
	Glucose	NPC1L1	Caco-2 cells, mice	↑	Phosphatase-dependent transcriptional pathways	(81)
		ABCA1	Caco-2 cells	↓	nd	(87)
	Calcium	NPC1L1	Ovariectomized hamsters	↓	Independent of SREBP2, LXR and HMGCR	(77)
	Polyphenols (chockeberry)	SR-BI	Caco-2 cells	↓	HMGCR, SREBP2, SREBP1C ?	(57)
		NPC1L1				
		ABCA1				
	Curcumin	NPC1L1	Hamster intestine	↓	SREBP2 ?	(78)
	Retinoid	SR-BI	Mouse/cell lines	↓	ISX	(58)
	Lactobacillus plantarum Lp27	NPC1L1	Caco-2 cells, rat intestine	↓	nd	(80)
	Bile salts	SR-BI	Mouse and rat intestines	↑	Postranscriptionnal regulation	(60)

Hormones	Insulin resistance	SR-BI	Hamster intestine	↑	nd	(59)
	Estrogen	NPC1L1	Mouse intestine	↑	ERα	(82)
	Cholecystokinin	NPC1L1	Mouse intestine, Caco-2 cells	↑	CCK1R/CCK2R, Gβγ, PI3K, Akt, Rab11a	(83)
	PYY	NPC1L1	Caco-2 cells	↓	nd	(84)
Drugs	Ezetimibe	SR-BI	Caco-2 cells	↓	RARγ, SREBP-1 and -2, LXRβ ?	(56)
		NPC1L1				
		ABCA1				

nd = not described, ecosapentaenoic acid (EPA), arachidonic acid (ARA), docohexaenoic acid (DHA), 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), CCK receptor 1 and 2 (CCK1R and CCK2R), G protein βγ dimer (Gβγ), phosphatidylinositide 3-kinase (PI3K)