Chapter 1

The Hepatic Fate of Vitamin E

Lisa Schmölz, Martin Schubert, Stefan Kluge,
Marc Birringer, Maria Wallert and Stefan Lorkowski

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http://dx.doi.org/10.5772/intechopen.79445

Abstract

Vitamin E is a lipophilic vitamin and thus is naturally occurring mainly in high-fat plant products such as oils, nuts, germs, seeds, and in lower amounts in vegetables and some fruits. The term "vitamin E" comprises different structures that are classified as tocopherols, tocotrienols, and "vitamin E-related structures." Vitamin E follows the same route in the body like other lipophilic substances. In brief, vitamin E is absorbed in the intestine, packaged into chylomicrons together with other lipophilic molecules, and distributed via lymph and blood in the body. As the liver is the central organ in lipoprotein metabolism, it is also essential for the uptake, distribution, metabolism, and storage of vitamin E. Based on the current knowledge on that field, the physiological, nonphysiological, and pathophysiological factors influencing the hepatic handling of vitamin E, verifying the crucial role of the liver in vitamin E homeostasis, are described.

Keywords: vitamin E, liver, hepatic handling, vitamin E homeostasis, AVED

1. Introduction

Vitamin E is a lipophilic vitamin and thus naturally mainly occurring in high-fat plant products such as oils, nuts, germs, seeds, and in lower amounts in vegetables and some fruits. The term "vitamin E" comprises different structures that are classified as tocopherols (TOH), tocotrienols (T3), and "vitamin E-related structures". However, α-TOH is considered as the most important representative of vitamin E in humans as the central vitamin E metabolizing organ, the liver, discriminates for this form [1]. Notwithstanding the classification as vitamin, the way vitamin E exactly contributes to human health is controversially discussed. Vitamin

E deficiency has been linked to several disease states like ataxia with vitamin E deficiency (AVED) [2, 3] and Alzheimer's disease [4, 5], indicating a role in the preservation of human health. AVED has severe neurological consequences and is caused by a defect in the α-TOH transfer protein (α-TTP); the protein responsible for the discrimination of α-TOH from the other vitamin E forms in the liver [2, 3]. This emphasizes the role of the liver as a central organ in human vitamin E handling. The liver further distributes vitamin E in the body [6] and metabolizes excess vitamin E in order to form products for excretion [6] or presumably to produce activated metabolites of vitamin E as known for other lipophilic vitamins [7]. Given the crucial role of the liver for vitamin E handling, this review aims to summarize the knowledge on the physiological hepatic handling of vitamin E as well as on factors influencing hepatic handling of vitamin E.

2. Physiological hepatic handling of vitamin E

The liver is the central organ of vitamin E handling. While intestinal absorption efficiency is similar for all forms of vitamin E [8], the plasma concentrations of vitamin E forms differ a lot (e.g., 22.1 μM for α-TOH vs. 2.2 μM for γ-TOH [9]). The preference of α-TOH in the human body is mediated by several complex and interacting hepatic mechanisms.

2.1. Hepatocellular uptake of vitamin E

Vitamin E is absorbed in the intestine along with lipids (for details, see [8]) and is packed into lipoproteins. These are transported via lymph or blood toward the liver (via chylomicron remnants, low density lipoproteins (LDL), and high density lipoproteins (HDL) [10, 11]). Different mechanisms facilitate the cellular uptake of vitamin E: (i) via lipid transfer proteins or lipases, (ii) receptor-mediated lipoprotein endocytosis, and (iii) selective lipid uptake [12]. The degradation of chylomicrons to chylomicron remnants by lipoprotein lipase (LPL) seems to be highly important for vitamin E uptake in the liver; when lipolysis of triglyceride-rich chylomicrons by LPL is inhibited, the α-TOH uptake in the liver is diminished [13]. The phospholipid transfer protein (PLTP) mediates the exchange of phospholipids between lipoproteins [14] and is also able to bind α-TOH *in vitro* [15]. PLTP-null mice have lower hepatic levels of vitamin E than the wild-type mice [16]; hence, the transfer of vitamin E between the lipoproteins seems to be important for its effective hepatic uptake. The chylomicron remnants and LDL are taken up by the liver via endocytosis, mainly mediated through the LDL receptor (LDLR) or LDLR-related proteins [6, 17]. In addition, the cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1) is involved in hepatic vitamin E uptake; α-TOH binds to the N-terminal domain of NPC1L1, which mediates α-TOH uptake via endocytosis (mechanism similar to intestinal cholesterol uptake) [18]. The scavenger receptor B type I (SR-BI) is known to mediate the uptake of vitamin E in several tissues (e.g., intestine [19], epithelium [20], and hepatocytes [21]) by channeling the molecules into the cells (shown for cholesterol or triglycerides [22]). Furthermore, the scavenger receptor cluster of differentiation 36 (CD36) is likely involved in hepatic uptake of vitamin E [23].

2.2. Intracellular trafficking of vitamin E

Following its lipophilic nature, vitamin E is transported by intracellular carrier proteins [24]. The intestinally absorbed vitamin E is taken up via endocytosis [25] and follows endosomal fate. Here, the hepatic sorting of vitamin E forms starts as a specific protein, called α-TTP selectively recognizes and preferentially binds α-TOH, which is then extracted from endosomes and transported to the inner leaflet of the plasma membrane [26]. α-TTP is therefore considered to be a "gatekeeper", which discriminates non-α-TOH forms [27] and regulates the plasma concentrations of α-TOH [1]. The affinity of α-TTP to the different forms of vitamin E differs greatly: it is defined as 100% for α-TOH, whereas β-TOH has 38%, γ-TOH 9%, δ-TOH 2%, and α-tocotrienol (T3) 12% affinity to α-TTP [28]. The regular function of α-TTP is crucial, since missense mutations lead to the disruption of α-TOH distribution and the development of a severe degenerative disease, termed AVED [29]. The transfer of α-TOH from endosomes to the plasma membrane is a multi-step process. First, it is speculated whether the ATP-binding cassette transporter A1 (ABCA1) enriches the outer layer of endosomes with α-TOH [30]. The cholesterol transporter NPC1 may also be involved, as a genetic missense mutation of the *NPC1* gene leads to an accumulation of α-TOH in late endosomes [31]. Second, α-TTP extracts the α-TOH from endosomes, and third, α-TTP mediates its transport to the plasma membrane [24]. This process seems to depend on phosphatidylinositol phosphates (PIPs; preferentially $PI(4,5)P_2$ and $PI(3,4)P_2$) in the plasma membrane, as α-TTP binds to them, in turn targeting α-TOH to the plasma membrane and stimulating its release [32]. Chung et al. analyzed the localization of α-TTP depending on the cellular α-TOH concentration [33]. They found (i) perinuclear localization for α-TOH-depleted cells, (ii) a directional transport of α-TOH/α-TTP toward the plasma membrane, when depleted cells were pulsed with a low dose of α-TOH, and (iii) a homogenous cytosolic pattern under long-term and high-dose treatment of cells with α-TOH, which was suggested to be the picture of several α-TOH transport cycles [33]. Furthermore, the authors also postulated a bi-phasic concentration-dependent circulation of α-TTP: the $PI(4,5)P_2$ gradient (low in endosomes and high in plasma membrane) forces the α-TTP-mediated transport of α-TOH toward the plasma membrane, whereas the α-TOH gradient (low in plasma membrane and high in endosomes) triggers the recycling of α-TTP toward the endosomes [33]. It has been proposed that once α-TOH is incorporated into the plasma membrane, it is mediated toward the outer leaflet of the membrane by a flippase, maybe ABCA1, and is then available for the uptake via very low density lipoproteins (VLDL) [34]. For more details on the process, please see Section 2.5 "Release of vitamin E".

2.3. Intracellular storage of vitamin E

Intracellular storage of vitamin E is limited to the lipophilic sites of the cell, which are membranes and lipid droplets [33]. Not much is known about a specific localization of vitamin E accumulation in liver cells, apart from the observation that lysosomal membranes of rat livers seemed to have the highest concentration of all membranes [35–37]. However, it is known that one-third of the total body vitamin E is stored in the liver [38]. Within membranes, vitamin E is thought to stabilize the membrane bilayers due to colocalization with phosphatidylcholine [39] and cholesterol (leading to an association to lipid rafts) [40]. It was further hypothesized

that vitamin E also colocalizes with poly-unsaturated fatty acids (PUFAs) in nonraft domains in order to provide protection from lipid peroxidation [41]. Newly added α-TOH in cell culture enriches in the same organelles as the endogenous α-TOH pool [42]. Hereby, the subcellular content of α-TOH was directly proportional to the lipid content [43].

Our knowledge about the storage of vitamin E in lipid droplets is also limited. It was recently reported that newly endocytosed vitamin E was also found in lipid droplets, thus indicating endosome-lipid-droplet interactions [33].

2.4. Hepatic metabolism of vitamin E

The hepatic metabolism of vitamin E has not been fully characterized. However, the principle steps of vitamin E degradation, that is, the shortening of the side chain without the alteration of the chroman ring, are generally accepted. Hence, the metabolites are classified as α-, β-, γ-, and δ-metabolites according to their respective precursors.

In principle, TOHs and T3s are degraded like long branched chain fatty acids (TOH) or long unsaturated branched chain fatty acids (T3) via β-oxidation in peroxisomes. However, as TOHs and T3s do not bear a terminal carboxy function in their side chain, they are not susceptible to β-oxidation. Hence, the initial and rate-limiting step in vitamin E degradation is the introduction of a carboxy function to the ω-terminus of the side chain. This first step is carried out in the endoplasmic reticulum (ER) of liver cells [44]. Here, two representatives of the cytochrome P450 (CYP) protein family, namely, CYP4F2 [45] and CYP3A4 [46, 47], have been identified to catalyze the initial ω-hydroxylation step. The resulting 13′-hydroxychromanol (13′-OH) is then further metabolized via ω-oxidation, a step that most likely involves alcohol dehydrogenase and aldehyde dehydrogenase [44], leading to 13′-carboxychromanol (13′-COOH). The carboxylated side chain resembles a long branched chain fatty acid that is further degradable via β-oxidation. However, a transport mechanism for the carboxychromanol from the ER to the peroxisomes has not been identified so far. Nevertheless, two cycles of peroxisomal β-oxidation after the activation of α-13′-COOH to the respective CoA ester have been suggested [44], as the peroxisomal β-oxidation system has a higher affinity toward long branched chain fatty acids than the mitochondrial counterpart [48]. The proposed 11′- and 9′-COOH metabolites have indeed been identified in human and mouse samples [49] as well as in a hepatic cell line [45, 50]. Subsequently, three more cycles of β-oxidation are needed to form the final product of vitamin E degradation, namely, carboxyethyl hydroxychromanol (CEHC) or 3′-COOH. These steps, however, are assigned to mitochondrial β-oxidation, as CEHC has solely been found in the mitochondria of hepatic cells [44]. Again, the transport mechanisms of the long-chain metabolites (LCM) (13′- to 9′-COOHs) from peroxisomes to the mitochondria are not known. The respective products for each cycle of β-oxidation (7′-COOH, 5′-COOH, and 3′-COOH) have been identified in different human and murine tissues [49, 51–54] as well as the hepatic cell line HepG2 [45, 47, 51]. Taken together, the hepatic metabolism of vitamin E is characterized by a series of β-oxidation steps after an initial introduction of a carboxy moiety at the ω-terminus of the phytyl-like side chain. The metabolism likely takes place in different cell compartments depending on the enzymatic systems needed for the different degradation steps. However, a concept of vitamin E degradation exclusively in mitochondria cannot be excluded [44]. T3 degradation is believed to follow the same route as TOH degradation but requiring further steps due to the unsaturated side

chain. In line with this assumption is the identification of the respective unsaturated metabolites from 13′-carboxytrienol down to carboxymethylbutadienylhydroxychromanol (CMBenHC) in human and mouse samples [49]. According to these findings, the side chain of the T3 metabolites needs a saturation step before the shortening of the chain. Enzymes involved in the degradation of unsaturated fatty acids like 2,4-dienoyl-CoA reductase and 3,2-enoyl-CoA isomerase were suggested to contribute to the degradation of T3s [55].

2.5. Release of vitamin E

Following the nature of the lipoprotein metabolism, hepatic release of vitamin E is mostly realized via VLDL. Thus, this section will focus on the packaging of vitamin E into VLDL particles, notwithstanding that the mechanism is not well understood. However, hepatic transfer of vitamin E to HDL has also been suggested [56]. Since it was shown that the expression of α-TTP is crucial for the maintenance of plasma α-TOH levels [57, 58] and that the liver is controlling plasma α-TOH levels [59], hepatic α-TTP is likely involved in the incorporation of vitamin E into lipoproteins. This concept is supported by the observation that nascent VLDL particles are preferentially enriched with *RRR*-α-TOH after oral administration of vitamin E ([60, 61]. In contrast, in the liver, no preferential retention of *RRR*-α-TOH was found, indicating that α-TTP is not involved in the delivery of vitamin E to the liver, but in the release from the liver [62]. Hence, efforts have been made to identify the intracellular location of VLDL enrichment with α-TOH mediated by α-TTP [30]. According to the assembly of VLDL, either the rough ER or the Golgi apparatus were assumed. However, the action of α-TTP in these compartments was not confirmed as the nascent VLDL particles contained equal amounts of SRR and RRR α-TOH forms [30]. Further, the inhibition of ER/Golgi action in cells overexpressing α-TTP did not prevent α-TOH secretion [63]. In conclusion, α-TTP is necessary for the hepatic release of vitamin E, but the enrichment of VLDL with *RRR*-α-TOH occurs after exocytosis.

Based on this, the hypothesis of α-TOH uptake by VLDL directly from the plasma membrane was developed. This idea was inspired by the proposed mechanism of the incorporation of free cholesterol into nascent VLDL [64], that is, the spontaneous transfer from membranes to lipoproteins [65]. The hypothesis involves also the α-TTP-mediated trafficking of vitamin E from late endosomes (where vitamin E occurs after cellular uptake and large parts of α-TTP are located [66]) to the plasma membrane. This process might involve ABCA1, which has been shown to transport α-TOH [67] and could thus present vitamin E to α-TTP at the outer leaflet of the endosomal membrane. After the transport to the plasma membrane, a yet unidentified flippase is required to transfer α-TOH to the appropriate site of the membrane for uptake by nascent VLDL [30]. This hypothesis is supported by findings of Chung et al. [33], which provided a model of α-TTP-facilitated trafficking of vitamin E from endosomes to the plasma membrane (the reader is referred to Section 2.2 “Intracellular trafficking of vitamin E”). Taken together, the release of α-TOH from hepatocytes depends on vesicular transport [21, 31, 63, 68, 69], but is independent from ER or Golgi [63]. Hence, lipoproteins are not loaded with TOH during their intracellular assembly, but rather after exocytosis, a mechanism is required for the presentation of α-TOH at the plasma membrane. Evidence has been provided that the trafficking of α-TOH to the plasma membrane is realized via α-TTP which is located at recycling endosomes in hepatocytes [33]. However, the mechanism of

the loading of lipoproteins with α-TOH from the plasma membrane has not been elucidated yet, although the involvement of ABC transporters has been suggested [56, 67, 70]. However, ABC transporters are fueling HDL particles, which is in contrast to the assumption that the hepatic release of α-TOH is mediated via VLDL. In turn, two explanations have evolved: first, α-TOH translocates spontaneously from the membrane to VLDL like free cholesterol [65], and second, α-TOH is transported to HDL via ABCA1 and is then spontaneously transferred to VLDL [71]. However, both hypotheses need evaluation. A recent report on the self-assembly of α-TTP to form nanoparticles and transport vitamin E to tissues protected by endothelial barriers like the brain [34] opens another possible way for the distribution of vitamin E throughout the body starting from the liver.

3. Factors influencing hepatic handling of vitamin E

3.1. Effects of vitamin E

3.1.1. Intracellular handling of vitamin E

Key factors in the hepatic handling of vitamin E have been outlined in the previous sections. This section will focus on the action of vitamin E on its own intracellular handling. As indicated above, the key enzyme for the intracellular trafficking of vitamin E is α-TTP, and the rate-limiting enzymes in vitamin E metabolism are CYP4F2 and CYP3A4. Hence, we will here focus on the known actions of vitamin E on these key players.

The key protein of the hepatic handling of vitamin E is α-TTP, with its implications in cellular trafficking, metabolism, and release of vitamin E. Hence, several studies have been conducted to elucidate a possible feedback regulation of α-TTP in response to vitamin E intake, resulting in alterations of the metabolism or the distribution of the vitamin. In principle, research is focused on three levels of regulation: mRNA expression, protein expression, and stabilization of α-TTP protein. However, contradictory results from rodent models have been reported. Fechner et al. found that hepatic α-TTP mRNA expression was strongly induced in rats depleted from vitamin E for 5 weeks after the intake of a TOH-supplemented diet for 24 h [72]. However, rats fed a vitamin E-depleted diet, control diet, or vitamin E-enriched diet for 20 weeks showed upregulation of α-TTP mRNA when vitamin E is deprived, but a downregulation when vitamin E was repleted. Hepatic α-TTP protein levels were comparable for depletion and control, but lowest in rats fed the repleted diet [73]. A similar study reported no differences in hepatic α-TTP mRNA levels of rats fed either a control diet or a diet rich in or low in vitamin E. However, in contrast to the aforementioned study, downregulation of α-TTP protein was reported in the vitamin E-depleted group, while high vitamin E intake did not alter the levels compared to control [74]. The lack of an effect of a vitamin E deficient diet for 290 days on hepatic α-TTP mRNA levels was also reported in another rat model [75]. In line with this, subcutaneous injection of vitamin E for up to 18 days did not alter α-TTP protein levels in rats [76]. However, mice fed a diet rich in vitamin E showed 20% higher hepatic α-TTP protein levels than mice fed a low vitamin E diet [77]. Taken together, some studies

report elevated α-TTP levels due to a higher intake of vitamin E [72, 77], but some revealed no effect [74–76] or even lower levels [73]. Hence, further studies are needed to clarify the role of vitamin E in the regulation of α-TTP. In addition, an *in vitro* study suggested that vitamin E does not regulate α-TTP at the level of gene expression, but stabilizes α-TTP at the protein level upon binding and thus protects the protein from degradation, leading to higher α-TTP protein levels [78]. Reports on the hepatic mRNA levels might thus be of minor importance for the interpretation of the contribution of vitamin E to α-TTP action; however, the findings on α-TTP protein expression are also inconsistent.

The rate-limiting enzymes of vitamin E metabolism are CYP4F2 and CYP3A4. The latter was reported to be under transcriptional control of pregnane-X-receptor (PXR) [79, 80]. Hence, vitamin E might regulate its metabolism by binding to PXR and subsequent alteration of the expression of the enzymes involved in the first catabolic step. Indeed, studies using cells transfected with reporter genes provided evidence for an activation of PXR by different vitamin E structures (i.e., TOHs, T3s, and metabolites) [81, 82]. Interestingly, α-, δ-, and γ-TOH as well as α- and γ-T3 activated PXR in HepG2 liver cells transfected with human PXR and chloramphenicol acetyl transferase linked to two PXR responsive elements [81], while α- and γ-TOH as well as their metabolites α- and γ-CEHC did not in transfected colon carcinoma cells [82]. However, the LCM α-13′-COOH activated PXR in the latter cellular system and so did γ-T3 [82]. This finding implicates that the LCM of TOH are the responsible mediators of reported TOH actions via PXR. Hence, the findings in hepatic HepG2 cells [81] might be due to a higher catabolic rate of TOH and in turn the more efficient formation of the LCM than in colon cells. However, these findings were made in artificial cellular reporter systems and might not resemble the actual (hepatic) situation *in vivo*. Further, the specificity of PXR might depend on the species, as γ-T3 (the vitamin E form that activated PXR in both of the aforementioned studies) fails to bind murine PXR [83]. However, results obtained *in vivo* support the regulation of Cyp3a11 (the murine orthologue of CYP3A4) by vitamin E via PXR. Mice supplemented with α-TOH show elevated hepatic expression of Cyp3a11, while their PXR-deficient counterparts as well as mice with humanized PXR showed no upregulation of Cyp3a11 in response to α-TOH [84]. The same finding was made for Cyp4f13, the murine orthologue of CYP4F2, in this model [84]. These findings suggest that both enzymes are under the control of PXR and murine, but not human PXR is susceptible to α-TOH (or its metabolites as outlined above). Further studies reporting upregulation of hepatic Cyp3a in rodent models with α-TOH supplementation support this finding [76, 83, 85]. Interestingly, in these studies, γ-TOH and γ-T3 had no effect on Cyp3a expression [83, 85], supporting the suggested specificity of murine PXR for α-TOH. In line with this, γ-TOH did not alter the expression of Cyp4f13 in mice [85]. However, subcutaneous application of α-TOH in rats did not induce Cyp4F2 levels [76], which is in contrast to the above mentioned induction of Cyp4f13 in mice via PXR [84]. The reported induction of CYP4F2 activity in HepG2 cells by α-TOH further complicates the interpretation of the data on the effect of vitamin E on CYP4F2 [45]. Taken together, there is evidence for the regulation of CYP4F2 and CYP3A4 via PXR by vitamin E in the human liver. However, several aspects need further clarification, for instance, species and vitamin E isoform specificity of PXR, the regulation of CYP4F2 by vitamin E or the relevance of the α-LCM as true mediators of α-TOH effects via PXR.

3.1.2. Vitamin E intake

Several key enzymes determine the rate of vitamin E catabolism (the reader referred to Section 2.4 "Hepatic metabolism of vitamin E") and, as outlined in the previous section, there is evidence that vitamin E in general might regulate its own metabolism. However, there are differences in the ability to regulate the metabolism depending on structural properties of the vitamin E isomers (i.e., methylation of the chroman ring, saturation of the side-chain, and stereochemistry). In principle, high intake of vitamin E, independent from the isomer, leads to enhanced formation of the respective metabolites [49]. However, the catabolic rates of the different forms of vitamin E clearly differ: the γ-isoforms are more susceptible to metabolization than the α-isoforms. Subjects supplemented with γ-T3 and α-T3 (125 mg or 500 mg) showed four to six times higher urinary excretion of the catabolic end product γ-CEHC and an induction of α-CEHC only after high dose (500 mg), but not after low dose supplementation (125 mg) [86]. In line with this, equimolar supplementation with 50 mg of α- and γ-TOH leads to a twofold increase of plasma γ-CEHC, but no alterations in α-CEHC [87]. These data indicate that there might be a threshold for the intake of α-TOH and α-T3 (or plasma levels, respectively) that needs to be exceeded to accelerate catabolism of α-TOH and α-T3 to form α-CEHC, as suggested by Schuelke et al. [88]. Interestingly, already in 1985, Handelman et al. reported that high α-TOH levels in human plasma are related to low γ-TOH levels [89]. After supplementation of α-TOH, the plasma α-TOH levels were, as expected, twofold to fourfold higher, but the γ-TOH level decreased to between one-third and one-half of the initial level [89]. Hence, α-TOH intake seems to boost γ-TOH catabolism. Supporting data were generated in a rat model, where the combined supplementation of α- and γ-TOH leads to higher excretion of γ-CEHC than the supplementation of γ-TOH alone [90], as well as the reported stimulation of γ-TOH catabolism by α-TOH in HepG2 liver cells [91]. Although the underlying mechanisms are not fully unraveled, there is evidence that α-TOH induces the activity of enzymes involved in the metabolism of vitamin E, leading to the degradation of non-α-forms, while α-TOH remains protected (please refer to Section 3.1.1 "Intracellular handling of vitamin E").

3.2. Effects of other compounds

3.2.1. Intake of sesamin

Sesamin is a lignan, a group of natural compounds derived from vegetable sources, like sesame seeds [92]. Sesamin is known as a natural inhibitor of the metabolism of TOH [93–97]. The cell regulatory actions of sesamin have been initially investigated in *in vitro* models, where Parker et al. showed that sesamin acts as a selective inhibitor of CYP3A4, an initial enzyme of TOH metabolism [46]. In this study, the authors compared the inhibitory potential of sesamin on TOH metabolism in human HepG2 cells to the well-characterized CYP3A4 inhibitor ketoconazole. HepG2 cells were treated with one of the mentioned compounds in combination with either 25 μM α-TOH or 25 μM γ-TOH. Afterwards, the concentration of the corresponding CEHC was determined as a marker for TOH metabolism in cell culture media. It became apparent that ketoconazole (1 μM) and sesamin (1 μM) inhibited the formation of α- and γ-CEHC. This result provides evidence that sesamin is able to modulate TOH metabolism via the inhibition of

CYP3A4 [46]. In addition to the *in vitro* data, Uchida and coworkers investigated the inhibitory effects of sesamin on vitamin E metabolism in rats. Vitamin E-deficient rats (vitamin E free diet for 4 weeks) were treated with 50 mg/kg *RRR*-α-TOH alone or in combination with 200 g/kg sesame seeds [95]. Next, the concentration of α-TOH in different tissues as well as the urinary excretion of α-CEHC was measured. The urinary excretion of α-CEHC in the sesamin group was significantly lower compared to the α-TOH control group. Further, the combination of α-TOH and sesamin provoked a significant increase of hepatic α-TOH concentrations compared to α-TOH treated animals [95]. These observations have been confirmed in other animal studies [93, 94]. Beside the investigations in animal models, there are also a few results originating from studies in humans. In 2004, Frank and colleagues used muffins enriched with sesame oil (94 mg sesamin/muffin) or corn oil (control) to investigate the effect of a single dose sesamin application on urinary excretion of γ-CEHC as well as blood levels of γ-TOH in 10 healthy volunteers [97]. Both, control and intervention group, received the muffins together with a capsule containing deuterium-labeled γ-TOH (50 mg) in a crossover design. Blood and urine samples were collected over 72 hours after the application of the muffins and capsules. While the urinary excretion of γ-CEHC was significantly lowered, the sesamin treatment did not affect γ-TOH concentrations in blood compared to the corn oil control group [97]. Unfortunately, the study does not provide data on the elevation of the hepatic γ-TOH concentration in response to the reduced urinary excretion of γ-CEHC. Taken together, *in vitro* and *in vivo* studies provide evidence that the dietary intake of sesamin leads to an increase of the hepatic concentration of TOH via the inhibition of vitamin E metabolism, but further experiments are needed to characterize the interaction of sesamin and vitamin E metabolism in more detail.

3.2.2. Pharmacological activation or inhibition of CYP3A4

The pharmacological modification of the enzymatic activity of CYP3A4 represents an effective way to influence vitamin E homeostasis in the human body. Mechanistically, the direct or indirect interference of vitamin E metabolism is usually just a side effect of the pharmacological inhibition or induction of CYP3A4 by various chemical compounds. Thus, it is not surprising that the first evidence for the involvement of CYP3A4 in vitamin E metabolism was provided in an experimental subset using ketoconazole as a specific inhibitor for CYP3A4 [46, 98]. In HepG2 liver cells, different concentrations of ketoconazole (1 mmol/l or 0.25 mmol/l) inhibited the metabolic conversion of γ- and δ-TOH (25 μmol/l cell culture media) to γ- or δ-CEHC by almost 90% [46]. This finding has been confirmed by the reproduction of the same experiment with sesamin, the natural inhibitor of CYP3A4, revealing comparable results [46]. The inhibitory effect of ketoconazole on vitamin E metabolism has further been observed in an *in vivo* model. Here, rats were supplemented with ketoconazole (50 mg/kg body weight) together with α-TOH (10 mg/kg body weight), γ-TOH (10 mg/kg body weight) or mixture of different T3s (29.5 mg/kg body weight). Ketoconazole significantly reduced the catabolism of all applied vitamin E forms resulting in impaired urinary excretion of the respective CEHCs [99]. Beside its inhibition, the pharmacological induction of CYP3A4 represents another way to modulate vitamin E metabolism. Birringer and coworkers demonstrated that 50 μmol/L rifampicin, an inducer of CYP3A4 activity [100], induced the degradation of all-*rac*-α-TOH

in HepG2 cells fivefold [47]. In this study, the cell culture medium has been preconditioned with 100 μmol/L α-TOH for 10 days, as the standard medium was deficient for α-TOH [47]. Further, an indirect approach for the modulation of vitamin E metabolism via the modification of CYP3A4 expression could be realized by triggering PXR, a nuclear receptor that regulates the expression of metabolic enzymes and transporters involved in the metabolism of xenobiotics and endobiotics [101, 102]. Landes and coworkers showed that γ-T3 as well as rifampicin acts as PXR agonists, thus upregulating CYP3A4 mRNA expression in HepG2 liver cells [81]. Given the fact that enhanced mRNA expression of CYP3A4 results in enhanced enzymatic activity, the stimulation of PXR by various pharmacological agonists or antagonists could also modulate the hepatic metabolism of vitamin E. In summary, the direct or indirect regulation of CYP3A4 by various pharmacological means represents an effective way to modify the hepatic vitamin E metabolism.

3.3. Nonmodifiable factors influencing handling of vitamin E

The handling of vitamin E is also influenced by nonmodifiable factors. These are aging, gender, and individual genetics. Published data in this area are sparse but interesting.

3.3.1. Aging

The aging process is characterized by nine hallmarks: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [103]. In particular, the mitochondrial dysfunction leads to higher formation of reactive oxygen species (ROS) and enhanced oxidative damage [104]. Both processes can be diminished by the antioxidant function of vitamin E [105]. Consequently, two questions arise: (i) can vitamin E modulate the aging processes or prevent age-related diseases? This has been subject of several reviews [106–109]. (ii) And how is the concentration, distribution, and function of vitamin E modulated by the aging process? In humans, age-dependent changes of α-TOH plasma concentrations are known. In healthy aged humans, the α-TOH plasma concentrations are higher than in younger individuals [110–113]. However, this might be due to the age-related increase of plasma cholesterol concentrations, as the age-related increase in α-TOH plasma concentrations disappear after adjustment for cholesterol plasma concentrations [112] or serum lipids [113]. Traber et al. suggested that α-TOH plasma concentrations are more dependent on control mechanisms for plasma lipids rather than on α-TOH absorption [113]. Hospitalized elderly patients [114] as well as older persons with cognitive impairments (dementia or Alzheimer's disease [115, 116]) have low α-TOH plasma concentrations [117]. However, an unfavorable nutrient status of the hospitalized patients was discussed as the cause of the lower α-TOH plasma concentrations.

Several studies analyzed the age-dependent changes of α-TOH tissue concentrations and handling in mice [37, 117–119] and rats [120]. In brain [37, 117, 118] and kidney [37, 117], epididymal adipose tissue [117] and aortic vessel wall [120], a consistent increase in α-TOH was found with age. In old rats, however, an age-dependent increase in intestinal absorption was found [121]. This was considered as a "*self-protective age-dependent adaption*" [120], which

is thought to counteract increased oxidative stress during aging. In the liver and heart, however, data are conflicting: while some found increased concentrations [37, 119, 120], Takahashi et al. found decreased values [117]. Two studies also analyzed the age-dependent regulation of genes, known to be involved in vitamin E handling, which are α-TTP, ABCA1, and Cyp4f14 (murine orthologue of CYP4F2) [117] as well as NPC1, NPC2, and LPL [37]. Takahashi et al. found increasing (mice with the age of 3–12 month) and then decreasing (12—24 months) α-TTP protein levels in the liver, while mRNA expression was stable over age [117]. Overall, Cyp4f14 mRNA expression decreased during aging (60% decrease in mRNA expression at the age of 24 months compared to the age of 3 weeks), while ABCA1 mRNA expression slightly increased (20% in the same age range as measured for Cyp4f14) [117]. The authors concluded that the age-related changes of hepatic α-TOH levels cannot be explained by the metabolism of α-TOH via Cyp4f14. König et al. analyzed protein expression in kidney tissue or its lysosomal membranes and found a significant decrease of NPC1 and NPC2, but a prominent increase in LPL (361% compared with the tissue from younger mice) [37]. The increased expression of LPL may explain the accumulation of α-TOH in aged mice. Furthermore, NPC1 and NPC2 may be responsible for the transport of α-TOH from the endosomes to the cytosol [69] and their reduced expression may explain the accumulation of α-TOH in lysosomal membranes [37]. In summary, there are age-dependent changes in α-TOH tissue and plasma concentrations and also in the expression of genes responsible for vitamin E handling; however, the underlying regulatory processes are not unraveled completely yet.

3.3.2. Gender

The sex-dependent differences in vitamin E handling were described recently by Schmölz et al. [6] and will be summarized here briefly for humans only. While intake of vitamin E in total is higher in men than in women [122], the intake per kcal is higher for women than for men [123]. The absorption of α-TOH seems not to be influenced by sex, but is mainly regulated by downstream regulatory processes (likely by hepatic sorting or metabolism) [113]. The data on serum concentrations of vitamin E are inconsistent: while some researchers reported elevated α-TOH serum concentrations for women compared to men [124, 125], others found contradictory results [123]. Sex-dependent regulation of vitamin E metabolism is specific for the different forms of vitamin E. Women degrade γ-TOH to a higher degree than men, while the metabolism of α-TOH seems to be independent [87]. Two mechanisms may be relevant for sex-dependent regulation of vitamin E metabolism: the hormonal status of individuals and the activation of the CYP enzymes involved in vitamin E metabolism [6]. Further studies could illuminate gender-specific differences in more detail. In the light of the discovery of vitamin E as a factor that limits female fertility, this is of special interest.

3.3.3. Genetics

The influence of genetics on vitamin E handling was summarized in detail in a recent review (for more details, please see [6]). Therefore, only a short overview will be provided here. Interindividual differences in the handling of vitamin E can be caused by individual genetic constitutions. Polymorphisms in genes, which are responsible for vitamin E handling such as

CYP4F2 [126], NPC1L1 [127], and CD36 [128] are likely to contribute to variations in vitamin E status. The best-studied gene in this context is α-TTP, as its genetic variability may cause AVED. Two genetic variants are known, which are located in or nearby the proposed tocopherol-binding domain and cause reduced α-TOH serum concentrations [129]. Furthermore, mutations in the promoter region of α-TTP (with increased or decreased activity) were also reported [130]. In summary, vitamin E handling is influenced by several mechanisms, one of which is the variability of genes involved in these processes. This might held responsible for interindividual differences in vitamin E serum concentrations.

3.4. Pathophysiological factors influencing handling of vitamin E

3.4.1. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease encompasses a histological spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). NASH is a clinical symptom characterized by a pattern of steatosis, inflammation, and hepatocyte ballooning, which can result in the development of cirrhosis and liver cancer [131]. Although the molecular mechanisms of NASH development remain poorly understood, studies provide evidence for a critical role of oxidative stress together with an impaired antioxidative response [132, 133]. In line with this, Erhardt and coworkers observed significantly lower plasma levels of α-TOH and other antioxidants in NASH patients compared to healthy controls [134]. Given the fact that an induction of CYP3A4 or CYP4F2 results in decreased vitamin E concentrations in the human body, it has been expected that NASH leads to an enhanced activity or expression of these enzymes. Thus, Woolsey and coworkers investigated the enzymatic activity as well as the mRNA expression of CYP3A4 in NASH patients [135]. The authors used liver biopsies for mRNA analyses and determined the concentration of 4β-hydroxycholesterol in plasma as an endogenous biomarker for CYP3A4 activity. Interestingly, NASH patients showed a 37% reduced enzymatic activity of CYP3A4 as well as a 69% lower CYP3A4 mRNA expression compared to healthy controls [135]. Unfortunately, there is no further data on the activity or the expression of CYP4F2 in NASH patients. However, Athinarayanan and coworkers investigated the influence of two different CYP4F2 genotypes (V433 M and W12G) on vitamin E plasma concentrations in NASH patients [136–138]. The V433 M genotype was associated to higher baseline levels of vitamin E, indicating lower enzymatic activity compared to the W12G genotype [136–138]. Thus, the authors hypothesized that the W12G genotype in NASH patients could explain the lower vitamin E plasma concentrations. However, this hypothesis has been disproved by the finding that the vitamin E plasma concentrations of NASH patients did not differ between the two CYP4F2 genotypes [136–138]. Based on the available data, CYP4F2 and CYP3A4 seem to have no influence on vitamin E plasma concentrations during the NASH development. Next to the CYPs, α-TTP could also be involved in a potential mechanism explaining the observation of Erhardt and coworkers mentioned above. In line with this, Ban and coworkers used a rat model to investigate whether an exposure to hyperoxia (>95% O_2 for 48 h), an established stimulus for ROS production [139], could alter the expression of hepatic α-TTP [140]. Indeed, hyperoxia decreased the expression of α-TTP mRNA in rat liver, while α-TTP protein expression remained unchanged [140]. As oxidative stress and ROS

formation are crucial factors for NASH development, lowering α-TTP expression by ROS could explain the lower vitamin E levels in NASH patients. In summary, the concentration of vitamin E and other antioxidants is reduced in NASH patients by yet not fully understood molecular mechanisms, potentially involving α-TTP. Nevertheless, recent human intervention trials provide evidence that vitamin E treatment could improve primary NASH outcomes (i.e., steatosis, inflammation, hepatocellular ballooning, and fibrosis) [137, 138].

3.4.2. Cancer

The current data on vitamin E as a potential agent for cancer therapy are inconsistent. While *in vitro* and early epidemiological studies provided evidence for cell growth-inhibiting, antiproliferative and pro-apoptotic effects of vitamin E in cancer treatment [141–145], more recent investigations reported contradictory results [146–148]. These findings were further sustained by the "Selenium and Vitamin E Cancer Prevention Trial (SELECT)," a randomized intervention study to determine the long-term effect of a supplementation of vitamin E (400 IU/d all-*rac*-α-tocopheryl-acetate) and selenium (200 μg/d L-selenomethionine) on the risk of prostate cancer in healthy men. Interestingly, the authors observed an increased incidence for prostate cancer in subjects supplemented with vitamin E [149]. Beside the investigations on beneficial effects of vitamin E in cancer therapy, almost nothing is known about the influence of cancer on human vitamin E homeostasis. An early study by Knekt, who investigated the association of vitamin E serum concentrations and the risk for different types of female cancer, showed an inverse relation between α-TOH serum concentrations and cancer risk [150]. Thus, women with the lowest α-TOH levels were at enhanced risk for cancer compared to those with higher α-TOH levels. Indeed, this association was restricted to cancer outcomes in tissues and organs, which were not exposed to estrogens [150]. Thus, Knekt hypothesized that low vitamin E levels could represent a potential risk factor for several, but not all types of cancer [150]. Nevertheless, the molecular mechanisms underlying this impairment of vitamin E serum concentrations in cancer patients remain unclear. The enhanced metabolic conversion of vitamin E might represent a mechanistic explanation. In line with this, investigations of tissues from cancer patients showed elevated expression of CYP3A4 [151] and CYP4F2 [152], the two major enzymes of vitamin E catabolism. Unfortunately, vitamin E serum concentrations have not been determined in these studies. Further, *in vitro* studies provided evidence that cancer also affects transporters for vitamin E, such as the tocopherol-associated protein (TAP) [153]. Tissue samples from prostate cancer patients showed significantly lower TAP mRNA expression compared to healthy controls, indicating that cancer may affect the intracellular transport of vitamin E. In addition, the overexpression of TAP in prostate cancer cells leads to a significant reduction of cell growth, while a TAP knockdown by small interfering RNA increased their growth [153]. Interestingly, these effects appeared without additional vitamin E treatment, indicating that TAP not only mediates vitamin E transport but also functions as a vitamin E-independent tumor suppressor gene [153]. In summary, the promising cancer preventive effects of vitamin E shown *in vitro* have not been confirmed in recent *in vivo* trials. Nevertheless, cancer could probably be associated with reduced vitamin E concentrations in the human body, because of an enhanced vitamin E catabolism and/or the alteration of its intracellular transport. However, further investigations are required to validate these results.

3.4.3. Disorders of lipoprotein metabolism

After its intestinal absorption, the transport of vitamin E, including its transfer to and its export from the liver as well as the subsequent distribution of vitamin E in the human body, strictly depends on different lipoproteins [7]. Thus, disorders of the lipoprotein metabolism can lead to disturbances of vitamin E homeostasis. Abetalipoproteinemia or Bassen-Kornzweig syndrome is a rare form of neurodegenerative ataxia with a strong impact on the hepatic handling of vitamin E. Abetalipoproteinemia is caused by mutations in the gene encoding for the microsomal triglyceride transfer protein (MTP), which is required for the assembly and secretion of the apolipoprotein B (apoB) forms in the liver and the intestine [154]. The apoB forms are the primary apolipoproteins associated to chylomicrons or VLDL, IDL, and LDL, respectively, and are thus essential for the distribution of vitamin E in the human body [7, 155]. As a result of the disturbed intestinal absorption and hepatic excretion of all lipid soluble molecules, patients with abetalipoproteinemia show vitamin E deficiency as well as low serum concentrations of cholesterol and triglycerides [156]. Next, the hepatic handling of vitamin E can be affected by familial hypobetalipoproteinemia. This lipoprotein disorder is caused by mutations in the *APOB* gene, leading to disturbances of translation of the apoB proteins and/or impaired secretion of VLDL [157]. Thus, familial hypobetalipoproteinemia displays the same clinical features as abetalipoproteinemia. In summary, lipoprotein disorders exert clear impact on the hepatic and systemic handling of vitamin E.

3.4.4. Other relevant pathophysiological factors

AVED is a neurological disorder, which has for the first time been described in a 12-year-old boy with cerebellar ataxia and low serum vitamin E concentrations. Interestingly, the boy showed no lipid malabsorption or a lack of lipoproteins, like it has been observed in abetalipoproteinemia [158]. Subsequent studies identified a mutation in the *TTPA* gene, the gene encoding for α-TTP, as the disease causing factor [159]. Thus, AVED patients have impaired expression of α-TTP, leading to impaired incorporation of vitamin E (α-TOH) into VLDL as well as a higher metabolic conversion and excretion of vitamin E [154]. In addition, AVED patients show very low plasma vitamin E concentrations together with normal absorption rates for vitamin E in the absence of intestinal malabsorption and abetalipoproteinemia [2, 154]. In summary, AVED represents a clinical condition that includes altered hepatic handling of vitamin E without affecting lipoprotein homeostasis.

4. Conclusion

In the last decades of vitamin E research, the liver appeared as the central organ for the uptake, distribution, metabolism, and storage of vitamin E. Thus, it is also a starting point for various strategies for the modulation of the vitamin E homeostasis. Based on current knowledge, we identified physiological, nonphysiological as well as pathophysiological factors influencing the hepatic handling of vitamin E, verifying the crucial role of the liver in vitamin E homeostasis (a brief schematic overview is provided in **Figure 1**). Nevertheless, further studies

http://dx.doi.org/10.5772/intechopen.79445

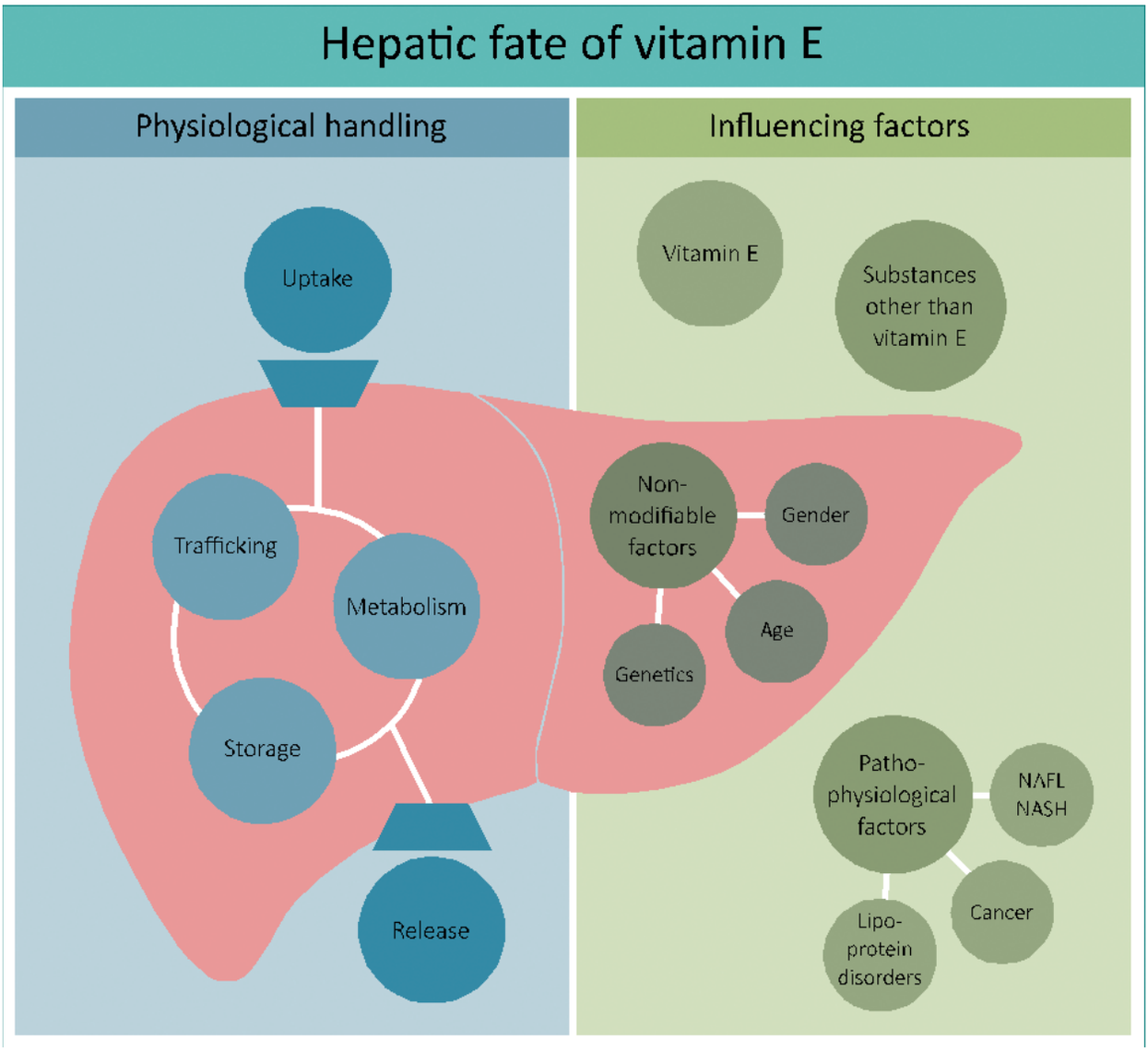

Figure 1. The crucial role of the liver in vitamin E homeostasis.

are needed to unravel the molecular mechanisms underlying the described disturbances of hepatic vitamin E handling by various factors.

Acknowledgements

The work of S.L. is supported by grants from the Federal Ministry of Education and Research (01EA1411A), the Deutsche Forschungsgemeinschaft (DFG; RTG 1715), and the German Ministry of Economics and Technology (AiF 16642 BR) via AiF (German Federation of Industrial Research Associations) and FEI (Research Association of the German Food Industry) and by the Free State of Thuringia and the European Social Fund (2016 FGR 0045). The work of L.S. is supported by the Free State of Thuringia and the European Social Fund (2016 FGR 0045). The work of M.W. is also funded by the DFG (Wa 3836/1-1).

Author details

Lisa Schmölz[1,2†], Martin Schubert[1,2†], Stefan Kluge[1,2†], Marc Birringer[3], Maria Wallert[2,4] and Stefan Lorkowski[1,2*]

*Address all correspondence to: stefan.lorkowski@uni-jena.de

1 Department of Nutritional Biochemistry and Physiology, Institute of Nutritional Sciences, Friedrich Schiller University Jena, Germany

2 Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Halle-Jena-Leipzig, Germany

3 Department of Nutritional, Food and Consumer Sciences, University of Applied Sciences Fulda, Germany

4 Baker Heart and Diabetes Institute, Melbourne, Australia

†These authors contributed equally

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