Chapter 4
Bioavailability and Metabolism of Vitamin E

Sandra Flory, Marc Birringer, and Jan Frank

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Key Points

- Vitamin E has a high oral bioavailability of ca. 50–80% and follows the general absorptive route of dietary fats.
- All eight forms of the lipid-soluble vitamin E (α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol) are absorbed to a similar extent and reach the liver.
- The liver selectively metabolizes the non-α-tocopherol congeners to their water-soluble short-chain metabolites.
- The first and rate-limiting step in vitamin E degradation is controlled by the activity of tocopherol-ω-hydroxylase (cytochrome P_{450} 4F2) and is the most important factor regulating the retention of the different vitamin E congeners in the organism.
- The hepatic α-tocopherol transfer protein facilitates the secretion of α-tocopherol with lipoproteins into the systemic circulation and is required to maintain sufficient concentrations of α-tocopherol in blood and tissues.

Introduction

Dietary vitamin E is ingested from plant foods and fortified foods as a more or less complex mixture of tocopherols and tocotrienols and to a lesser extent tocomonoenols and other related chemical structures (see Chap. 5) in individual amounts of only a few milligrams. Intakes of higher doses of single vitamin E congeners can only be achieved by ingestion of dietary supplements. Natural sources of

S. Flory · J. Frank (✉)
Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany
e-mail: jan.frank@nutres.de

M. Birringer
University of Applied Sciences Fulda, Nutritional, Food and Consumer Sciences, Fulda, Germany

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vitamin E contain both free and esterified (e.g. with fatty acids) forms [1]. Because tocopheryl esters, such as αT acetate, are oxidatively more stable than free tocopherols, α-tocopherol (αT) supplements more often contain esters than free αT. The simultaneous intake and amount of dietary fat as well as the vitamin E dose ingested may affect the extent of uptake of the vitamin into the organism. Furthermore, the route of administration (oral vs. injection) may not only determine its uptake but also its fate inside the body (see below).

Vitamin E Bioavailability

Early studies in humans found that 55–79% of an oral dose of radioactively labelled α-tocopherol (αT) was absorbed, appeared in plasma 1–3 h after administration, and reached peak concentrations between 5 and 9 h after intake [2]. The high bioavailability of vitamin E was later confirmed in healthy humans given a single oral dose of 0.78 mg radioactively labelled *RRR*-αT, in whom 81% of the oral dose was absorbed [3].

In a human trial comparing the uptake of αT in the small intestine, when administered as deuterium-labelled *RRR*-αT or its ester *RRR*-αT acetate, the authors found free αT derived from the administered αT acetate in the distal jejunum, indicating that enzymes in the brush border cleave the acetyl group and release the free αT, which then is available for absorption. The uptake of the free and (upon intake) esterified form in the jejunum was similar, with ca. 6% of both being absorbed within 1 h [4].

The amount of dietary fat consumed together with vitamin E determines to some extent how much of the vitamin is absorbed. In healthy humans, ca. 10% of a 22 mg dose of deuterated *RRR*-αT acetate eaten with a fat-free breakfast were recovered in blood, whereas 33% were absorbed when the vitamin was ingested together with a breakfast containing 11 g fat [5]. In agreement, Jeanes and colleagues found a dose-dependent increase in αT bioavailability with increasing dietary fat in subjects consuming 150 mg deuterated *RRR*-αT acetate together with breakfasts providing 0, 2.7, or 17.5 g fat. Interestingly, they also found the food matrix to be an important factor in the bioavailability of vitamin E. αT was absorbed better when the 17.5 g fat were ingested from toast with butter compared to a cereal breakfast with whole milk [6].

The bioavailability of orally ingested compounds is influenced by a multitude of factors, including absorption, distribution, metabolism, and excretion, which in turn are governed by a large number of parameters themselves. The most important determinants of the bioavailability of vitamin E, absorption, metabolism, and excretion, are discussed below.

Vitamin E Absorption

The intestinal absorption of vitamin E generally parallels the absorption of dietary fat. In the acidic conditions of the stomach and subsequently by enzymatic activity of steryl-ester acylhydrolase (also known as cholesterol ester hydrolase or bile salt-dependent lipase) in the small intestine, vitamin E esters are hydrolyzed, and only the nonesterified vitamin E is absorbed in the small intestine [4, 7]. The liver secretes bile acids into the small intestine to aid the digestion of lipids and the formation of mixed micelles. Although dietary fat is required to aid the absorption of vitamin E, the amount of dietary fat is of limited importance, and even low-fat diets grant a sufficient uptake of the vitamin [8]. The micelles and micellar lipids enter the enterocytes either by receptor-mediated transport or passive diffusion [9]. The scavenger receptor class B type I (SR-BI), scavenger receptor cluster-determinant 36 (CD36), and the Niemann-Pick C1-like protein 1 (NPC1L1) have been identified as receptors involved in the intestinal uptake of free vitamin E [7, 10, 11]. Unlike other lipid-soluble vitamins,

vitamin E has no specific plasma transport protein. In order to be transported in the aqueous environment of the circulation, vitamin E is incorporated into chylomicrons, which are secreted into the lymphatic system by enterocytes with the involvement of the ATP-binding cassette transporter A1 (ABCA1) [9]. The chylomicrons pass through the thoracic duct into the systemic circulation where a fraction of the transported vitamin E is transferred to high-density lipoproteins (HDL), from where it is distributed to all circulating lipoproteins or tissues. Chylomicron degradation, catalyzed by lipoprotein lipase, ultimately results in the formation of chylomicron remnants, which are taken up into the liver facilitated by the hepatic low-density lipoprotein receptor-related protein 1 (LRP1) [12]. Up to this point, there appears to be no discrimination between vitamin E congeners [13].

Our present understanding of the intracellular trafficking of vitamin E, or more specifically αT, in liver cells (see Chap. 9) is as follows: αT is internalized by endocytosis and accumulates in the late endosome, from where it is transported to the plasma membrane and secreted with lipoproteins into the systemic circulation. A cytosolic protein in liver cells, α-tocopherol transfer protein (αTTP), binds αT (and probably, albeit to a smaller degree, the non-αT congeners) in the outer leaflet of the endosomal membrane and expedites its transport to the plasma membrane, where the binding to phosphatidylinositol 4,5-bisphosphate induces a conformational change that results in the release of αT and its integration into the membrane [14–16]. The secretion of αT from liver cells involves ABCA1, which is required for the incorporation of vitamin E into lipoproteins that deliver the vitamin to extrahepatic tissues. The fraction of the lipid-soluble vitamin E congeners that is not secreted into the bloodstream is degraded to water-soluble carboxyethylhydroxychromanol (CEHC) metabolites by side-chain degradation without modification of the chromanol head and excreted via bile and urine [9] (see next paragraph). The hepatic secretion of vitamin E favors the (natural) *RRR*-α-tocopherol, probably as a result of the selectivity of αTTP toward the two *R*-congeners (*R* configuration at carbon 2) [15, 17] in combination with the preferential metabolism of the non-αT congeners (see below) [18, 19].

Vitamin E Metabolism

In the 1950s, tocopheronic acid and tocopheronolactone, the so-called Simon products (Fig. 4.1), were discovered in human urine as the first vitamin E metabolites [20]. These Simon metabolites were thought to be degradation products of vitamin E that had exerted its antioxidant function, as ring opening occurs when the tocopheroxyl radical is formed [21]. Approximately 30 years later, this theory was rejected when a new metabolite derived from δ-tocopherol was found in human urine. This side-chain shortened metabolite, which was later called δ-carboxyethylhydroxychromanol (δCEHC), had an intact chromanol ring structure that was conjugated with sulfuric acid [22]. The detection of this metabolite unmasked the Simon metabolites as oxidative artifacts generated during sample extraction and cleanup and was the start of further research into vitamin E metabolism [20].

The metabolism of vitamin E, which occurs mainly in the small intestine and the liver [23], comprises a number of enzymatic steps that are identical for all four tocopherol respectively four tocotrienol congeners (Fig. 4.2). The first and rate-limiting step is the terminal ω-hydroxylation of the side chain by cytochrome P_{450} enzymes (CYP) in the endoplasmic reticulum [18], resulting in the formation of the long-chain metabolite 13′-hydroxychromanol (13′-OH) [9]. CYP4F2 appears to be the main enzyme responsible for catalyzing this reaction in humans [24]. However, other CYP, including CYP3A4, appear to have minor ω-hydroxylation activity [25].

The side chain of 13′-OH then undergoes α-oxidation to 13′-carboxychromanol (13′-COOH) in peroxisomes. Subsequently, β-oxidation in the mitochondria results in the stepwise removal of 2-carbon units and thereby the formation of the intermediate-chain metabolites (ICM) and eventually the water-soluble short-chain metabolite (SCM) CEHC (Fig. 4.2) [9].

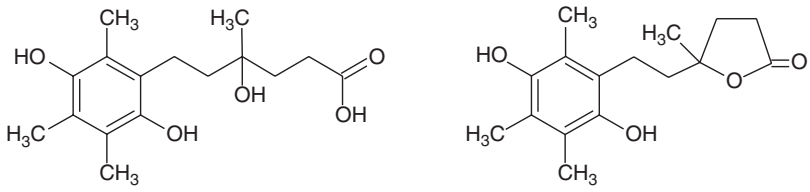

Fig. 4.1 Chemical structures of the originally isolated Simon products, which were later shown to be artifacts produced by oxidation reactions during sample isolation and cleanup

Bardowell et al. investigated the role of a murine orthologue of the human *CYP4F2* gene in vitamin E metabolism in Cyp4f14-knockout mice and found two new metabolites, namely, 12′-hydroxy-tocopherol (12′-OH: γ- and δ-12′-OH) and 11′-hydroxy-tocopherol (11′-OH: γ- and δ-11′-OH), in fecal pellets of mice fed a diet rich in γ-tocopherol [23, 26]. The metabolites derive from ω-1 and ω-2-hydroxylation and were excreted via bile into feces.

Tocotrienols are metabolized similar to tocopherols except that their unsaturated side chain undergoes saturation reactions, similar to the metabolism of unsaturated fatty acids (Fig. 4.2). Consequently, some additional metabolites are generated, which have been found in mouse and human feces and urine [27, 28]. In addition, tocotrienols are metabolized to a larger extent than their corresponding tocopherols [29, 30]. Carboxymethylbutylhydroxychromanol (CMBHC), not CEHC, seems to be the quantitatively major metabolite derived from tocotrienols in cultured liver cells (see also section "Regulation of Vitamin E Metabolism") [30].

All generated vitamin E metabolites are excreted via feces and urine. In feces, all of the metabolites, including the lipid-soluble long-chain metabolites, can be detected, whereas in urine, only the more water-soluble short-chain metabolites are present [28]. Similar to xenobiotics, around 90% of the urinary metabolites are conjugated by the phase II enzymes UDP-glucuronosyltransferase and sulfotransferase [9, 31]. Hence, vitamin E metabolites in rat urine are mainly sulfate conjugates and in human urine mainly glucuronidated conjugates [32].

Regulation of Vitamin E Metabolism

The first and rate-limiting step of vitamin E metabolism, which therefore regulates the formation of the vitamin's degradation products, is controlled by CYP, mainly CYP4F2, but perhaps to a limited extent also CYP3A4, in humans [18, 24, 25, 33]. The nuclear pregnane X receptor (PXR) is a central point of regulation for the expression of CYP as well as other phase I and II enzymes. Tocotrienols, and to a much smaller degree tocopherols, activated PXR and consequently the expression of CYP in cultured liver cancer cells (HepG2) [34]. In another study, only the four tocotrienols (α, β, γ, δ) but none of the four tocopherols activated PXR in HepG2 and human colon cancer cells (LS 180) [35]. The induction of PXR by tocotrienols and the lack thereof by tocopherols were confirmed by other independent experiments in LS 180 and HEK cells [36, 37]. The latter trial also found no PXR-activating activity of CEHC but for the first time observed a potent induction of PXR by the long-chain metabolite α-13′-COOH (see also Chap. 6) [36].

In vivo studies also show conflicting results with regard to the activation of PXR and the induction of CYP in different animal models. Mice given high doses of *all rac*-αT acetate (1000 mg/kg diet) for 4 months had a small but statistically significant increase in the mRNA expression of Cyp3a11, the murine homologue to human CYP3A4, in the liver compared to control animals fed 35 mg *all rac*-αT acetate per kilogram diet [38]. In mice fed *RRR*-α-tocopheryl acetate for 3 months

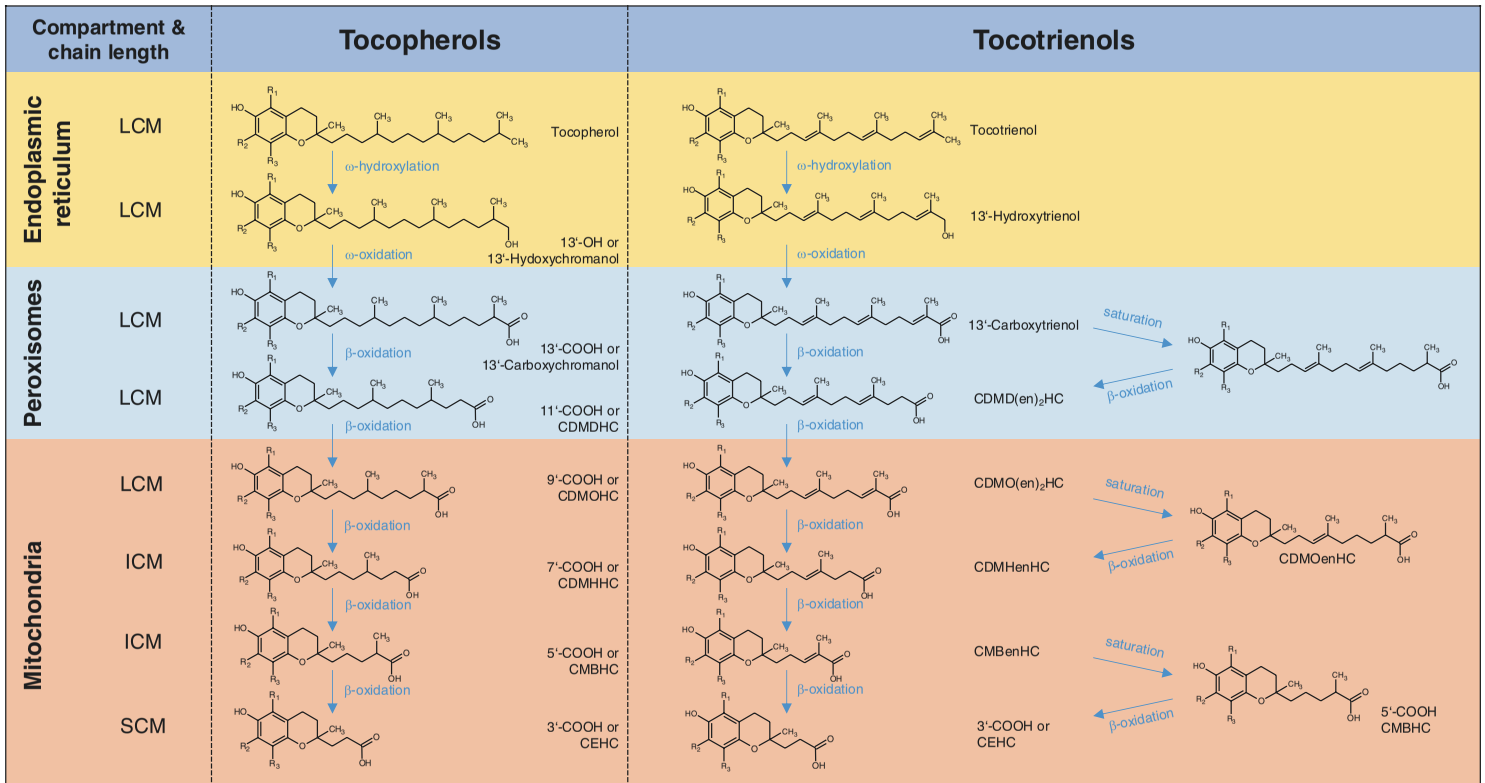

Fig. 4.2 Steps in the side-chain degradation of tocopherols and tocotrienols to their side-chain shortened water-soluble carboxyethyl hydroxychromanol metabolites
In the first and rate-limiting reaction, the side chain of the tocopherols and tocotrienols (α, R1 = CH_3, R2 = CH_3; β, R1 = CH_3, R2 = H; γ, R1 = H, R2 = CH_3; δ, R1 = H, R2 = H) is terminally hydroxylated in the endoplasmic reticulum and then terminally carboxylated in the peroxisomes. After five cycles of β-oxidation, the short-chain metabolites CEHC are formed. The steps in the metabolism of tocopherols and tocotrienols are largely similar, but some additional enzymes are required for the saturation of the side chain of tocotrienols (see right side of the figure)
Abbreviations: LCM long-chain metabolite, ICM intermediate-chain metabolite, SCM short-chain metabolite, α-CDMDHC α-carboxydimethyldecylhydroxychromanol, α-CDMOHC α-carboxymethyloctylhydroxychromanol, α-CDMHHC carboxymethylhydroxychromanol, α-CMBHC α-carboxymethylbutylhydroxychromanol, α-CEHC α-carboxyethylhydroxychromanol, α-CDMD(en)2HC α-carboxydimethyldecadienylhydroxychromanol, α-CDMO(en)2HC α-carboxydimethyloctadienylhydroxychromanol, α-CDMOenHC α-carboxydiemethyloctenylhydroxychromanol, α-CDMHenHC α-carboxymethylhexenylhydroxychromanol, α-CMBenHC α-carboxymethylbutadienylhydroxy chromanol

at 2 (deficient), 20 (sufficient), or 200 mg/kg diet (supplemented), a reduced mRNA expression of Cyp3a11 was observed in the deficient group, but no significant differences were seen between sufficient and supplemented animals [39]. The addition of γ-tocotrienol to these diets did not result in an increased mRNA expression of Cyp3a11 [39]. In rats, the feeding of diets deficient or adequate in vitamin E (<2 or 60 mg *RRR*-αT) for up to 9 months did not change the mRNA of any of the 33 hepatic CYP expressed [40]. In guinea pigs fed 20 or 250 mg *RRR*-αT per kg diet for 6 weeks, the hepatic protein expression of CYP3A4 and CYP20A1 and the serum concentrations of products of the enzymatic activity of CYP3A4 were similar in both groups [41]. The differences between the study by Mustacich et al. [38] and the other animal studies reviewed above [39–41] might be explained by the significantly higher oral dose of vitamin E administered; 1000 mg/kg diet of synthetic αT acetate in mice is 33 times more than the recommended dietary dose and corresponds to ca. 7–10 g per day for an average human, which would be >450–660-fold higher than the recommended dietary allowance of 12 mg/d. This is further supported by studies using subcutaneous injection of high doses of αT in rats, which results not only in very high hepatic concentrations of the vitamin but also an induction of CYP mRNA [42].

The notion that vitamin E does not induce PXR and CYP at dietary doses that can be reasonably achieved in humans is in agreement with studies in humans addressing the effects of αT supplementation on CYP3A4-mediated drug metabolism. In patients treated with drugs that are CYP3A4 substrates and simultaneously supplemented with 400 mg/d *RRR*-α-tocopheryl acetate for 8 weeks, CYP3A4 activity was unchanged [43]. In another human trial, healthy volunteers were given the CYP3A4 substrate midazolam intravenously prior to and following a 3-week oral supplementation with 503 mg *RRR*-αT per day. No differences in CYP3A4 activity were observed between placebo- and vitamin E-treated subjects [44].

In summary, there is no convincing evidence to suggest that orally ingested tocopherols or tocotrienols may induce CYP activity in animals or humans, even when consumed at high but reasonably achievable doses.

Quantitative Differences in the Retention and Excretion of Vitamin E Congeners in Humans

Although γ-tocopherol (γT) is the main vitamin E form in the human diet in some populations, such as the United States, αT is the predominant congener in human and animal tissues [45]. Plasma concentrations of αT (11–37 μmol/L) are higher than those of γT (2–5 μmol/L) [9]. The extent of the retention in and excretion from the organism differs between the different vitamin E forms.

Findings in human subjects show that the urinary excretion and plasma concentrations of γCEHC exceed those of αCEHC by a factor of ~4–5 and ~14–16, respectively, [46]. In agreement, up to ~50% of ingested γT was excreted in urine as the corresponding γCEHC metabolite in humans [47], while only 1–3% of the consumed αT dose was converted to urinary αCEHC [48]. Furthermore, the urinary excretion of deuterated αCEHC derived from natural *RRR*-α-tocopherol and synthetic *all rac*-α-tocopherol was 2–4 times higher for the synthetic vitamin E [49].

Because the extent of vitamin E absorption and transport to the liver is similar for all vitamers [13], there must be a regulation of the different rates of retention inside the liver. The two potential key factors regulating the retention and excretion of vitamin E congeners are the rate-limiting steps in their metabolism, namely, the binding to the hepatic αTTP and the ω-hydroxylation of the side chain.

The first key factor that was proposed to be responsible for the preferential retention of αT over the non-αT congeners was the αTTP (Chap. 9). The hepatic protein facilitates the secretion of αT from the liver into the bloodstream [15]. Hosomi and co-workers determined the binding affinities of αTTP for some vitamers relative to that for *RRR*-α-tocopherol and observed the following lower values:

RRR-β-tocopherol, 38%; *RRR*-γ-tocopherol, 9%; *RRR*-δ-tocopherol, 2%; *SRR*-α-tocopherol, 11%; and α-tocotrienol, 12% [50]. Interestingly, the binding affinity values for the tocopherols reflect, at least in part, their plasma concentrations, which led to the original proposal that αTTP may be the primary determinant of the discrimination between the congeners [50], a notion that has been challenged by more recent findings (see below).

If αTTP were the key factor regulating the discrimination against non-αT congeners, a knockout of the αTTP gene would be expected to result in increased retention (concentrations) of γT. In conflict with this expectation, the concentrations of γT in αTTP knockout mice were lower than in wild-type mice after feeding a γT-enriched diet or a diet containing equimolar concentrations of both αT and γT [19, 51]. The assumption now is that vitamin E metabolism and not αTTP is the major factor responsible for the regulation of the organismal concentrations of the congeners [19]. This is emphasized by observations in the model organism *Drosophila melanogaster*, an organism that does not express a protein equivalent to αTTP but shows the overall discrimination against non-αT forms. In addition, tocopherol-ω-hydroxylase activities for the individual vitamers in *Drosophila melanogaster* are comparable to the ones in rat and human microsomes [29, 52]. In line with these observations, lower plasma concentrations of γT than αT were observed in αTTP knockout mice [19, 53]. Generally, decreased plasma concentrations of all vitamers in αTTP knockout mice indicate that αTTP is important for their general retaining in the body, but not the discrimination between them, which is more likely facilitated by vitamin E metabolism [19].

The first and rate-limiting step in the metabolism of vitamin E is catalyzed by CYP4F2, an enzyme which has also been called tocopherol-ω-hydroxylase [18]. In vitro, CYP4F2 exhibited similar binding affinities for αT and γT but much higher catalytic activity toward γT [18, 24]. Sontag and Parker identified the following structural features as important factors favoring a rapid conversion by CYP4F2: absence of methyl groups at the chromanol ring, particularly at carbon 5 (γ and δ congeners), and unsaturation of the side chain (tocotrienols). This is in agreement with earlier observations that HepG2 cells produce less CEHC and CMBHC from αT and α-tocotrienol than from γT and γ-tocotrienol [30].

Not only the position but also the number of methyl groups is another factor influencing the enzyme activity, which is higher for the dimethyl γT than for the trimethyl αT [29]. Tocopherols with fewer methyl groups are able to penetrate deeper into the membranes of the endoplasmic reticulum, where the CYP4F2 is positioned. Consequently, the dimethyl congener γT may be more easily available for interactions with the enzyme than the trimethyl αT, as previously reported for interactions with the membrane-localized enzyme phospholipase A2 [54]. Furthermore, an inhibitory effect on the metabolism of γT was observed in HepG2 cells co-incubated with αT and γT [19, 29] and may be explained by competition for enzymatic degradation by CYP4F2 [29].

The central role of the ω-hydroxylase activity of CYP for the retention and excretion of vitamin E congeners is furthermore supported by experiments with phytochemicals with CYP inhibitory activity [55]. The cereal lipids alkylresorcinols greatly increased the concentrations of γT, but not αT, in rats by competitive inhibition of tocopherol-ω-hydroxylase [56]. The sesame lignan and potent tocopherol-ω-hydroxylase inhibitor sesamin played an important role in the elucidation of the role of vitamin E metabolism for the retention and excretion of different vitamin E forms. In HepG2 cells [19, 33, 56], mice [19], rats [57–62], and humans [46, 63], administration of sesamin increases the concentrations of γT and reduces the production of its metabolite γCEHC. Consumption of sesamin with sesame oil muffins by human volunteers significantly inhibited γT metabolism and resulted in a reduced urinary excretion of γCEHC, proving the importance of the in vitro findings for human nutrition [46, 63, 64].

The central role of the ω-hydroxylase activity in the regulation of vitamin E metabolism was confirmed using knockout mice without ω-hydroxylase activity. The knockout leads to significantly reduced concentrations of urinary metabolites of α-, γ-, and δ-tocopherol and higher excretion of unmetabolized tocopherols; the disruption of the enzyme activity furthermore had a larger impact on the metabolism of γT than that of αT [23, 26].

However, the processes underlying the selective retention of αT and the preferential excretion of the non-αT congeners as metabolites may not be as black and white, as an interaction between the αTTP and ω-hydroxylase activities has been proposed [19]. Grebenstein and colleagues observed an inverse relationship between the expression of αTTP in hepatocytes and their ability to convert γT to γCEHC. The authors hypothesized that αTTP may bind γT, albeit to a lesser extent than αT, and thereby prevent the contact of γT with CYP4F2, which would protect the congener from side-chain degradation [19].

In summary, the above findings indicate that the tocopherol-ω-hydroxylase activity is the most important factor regulating the degradation of vitamin E to its short-chain metabolites destined for excretion. This activity also appears to be the main determinant controlling the retention of the different vitamin E congeners in humans. αTTP is required for the secretion of vitamin E from the liver and appears to limit the excretion of mainly αT, but to a smaller extent also the non-αT congeners from the body, thus making sure that sufficient vitamin E is retained for its essential biological functions.

Research Gaps/Conclusion

Around 70 years ago, the short-chain metabolites of vitamin E were detected for the first time. By now, the main steps of vitamin E metabolism have been discovered and characterized and the regulating factors described. Nevertheless, some gaps in our understanding of these processes exist, such as how the different metabolites are transported from one cellular compartment to the other (e.g., endoplasmic reticulum to peroxisomes to mitochondria). Furthermore, the rate-limiting step, which is mainly catalyzed by CYP4F2, may also be facilitated by additional as yet undiscovered enzymes. Last but not least, an important question that still awaits a conclusive answer is: Is the main aim of vitamin E metabolism the prevention of excessive accumulation of all or certain vitamin E congeners by facilitating their elimination from the body? Or does the formation of the long-chain metabolites represent the conversion of vitamin E into the actual biologically active molecules (see also Chap. 6)?

References

1. Krauß S, Darwisch V, Vetter W. Occurrence of tocopheryl fatty acid esters in vegetables and their non-digestibility by artificial digestion juices. Sci Rep. 2018;8:7657. https://doi.org/10.1038/s41598-018-25997-2.
2. MACMAHON MT, NEALE G. The absorption of à-tocopherol in control subjects and in patients with intestinal malabsorption. Clin Sci. 1970;38:197–210.
3. Novotny JA, Fadel JG, Holstege DM, Furr HC, Clifford AJ. This kinetic, bioavailability, and metabolism study of RRR-α-tocopherol in healthy adults suggests lower intake requirements than previous estimates. J Nutr. 2012;142:2105–11. https://doi.org/10.3945/jn.112.166462.
4. Nagy K, Ramos L, Courtet-Compondu M-C, Braga-Lagache S, Redeuil K, Lobo B, et al. Double-balloon jejunal perfusion to compare absorption of vitamin E and vitamin E acetate in healthy volunteers under maldigestion conditions. Eur J Clin Nutr. 2013;67:202–6. https://doi.org/10.1038/ejcn.2012.183.
5. Bruno RS, Leonard SW, Park S-I, Zhao Y, Traber MG. Human vitamin E requirements assessed with the use of apples fortified with deuterium-labeled alpha-tocopheryl acetate. Am J Clin Nutr. 2006;83:299–304. https://doi.org/10.1093/ajcn/83.2.299.
6. Jeanes YM, Hall WL, Ellard S, Lee E, Lodge JK. The absorption of vitamin E is influenced by the amount of fat in a meal and the food matrix. BJN. 2004;92:575. https://doi.org/10.1079/BJN20041249.
7. Reboul E. Vitamin E bioavailability: mechanisms of intestinal absorption in the spotlight. Antioxidants (Basel). 2017. https://doi.org/10.3390/antiox6040095.
8. Parks E, Traber MG. Mechanisms of vitamin E regulation: research over the past decade and focus on the future. Antioxid Redox Signal. 2000;2:405–12. https://doi.org/10.1089/15230860050192189.

9. Schmölz L, Birringer M, Lorkowski S, Wallert M. Complexity of vitamin E metabolism. World J Biol Chem. 2016;7:14–43. https://doi.org/10.4331/wjbc.v7.i1.14.
10. Yamanashi Y, Takada T, Kurauchi R, Tanaka Y, Komine T, Suzuki H. Transporters for the intestinal absorption of cholesterol, vitamin E, and vitamin K. J Atheroscler Thromb. 2017;24:347–59. https://doi.org/10.5551/jat.RV16007.
11. Goncalves A, Roi S, Nowicki M, Niot I, Reboul E. Cluster-determinant 36 (CD36) impacts on vitamin E postprandial response. Mol Nutr Food Res. 2014;58:2297–306. https://doi.org/10.1002/mnfr.201400339.
12. Azzi A, Stocker A. Vitamin E: non-antioxidant roles. Prog Lipid Res. 2000;39:231–55. https://doi.org/10.1016/S0163-7827(00)00006-0.
13. Kayden HJ, Traber MG. Absorption, lipoprotein transport, and regulation of plasma concentrations of vitamin E in humans. J Lipid Res. 1993;34:343–58.
14. Chung S, Ghelfi M, Atkinson J, Parker R, Qian J, Carlin C, Manor D. Vitamin E and phosphoinositides regulate the intracellular localization of the hepatic α-tocopherol transfer protein. J Biol Chem. 2016;291:17028–39. https://doi.org/10.1074/jbc.M116.734210.
15. Qian J, Morley S, Wilson K, Nava P, Atkinson J, Manor D. Intracellular trafficking of vitamin E in hepatocytes: the role of tocopherol transfer protein. J Lipid Res. 2005;46:2072–82. https://doi.org/10.1194/jlr.M500143-JLR200.
16. Horiguchi M, Arita M, Kaempf-Rotzoll DE, Tsujimoto M, Inoue K, Arai H. pH-dependent translocation of alpha-tocopherol transfer protein (alpha-TTP) between hepatic cytosol and late endosomes. Genes Cells. 2003;8:789–800. https://doi.org/10.1046/j.1365-2443.2003.00676.x.
17. Kono N, Ohto U, Hiramatsu T, Urabe M, Uchida Y, Satow Y, Arai H. Impaired α-TTP-PIPs interaction underlies familial vitamin E deficiency. Science. 2013;340:1106–10. https://doi.org/10.1126/science.1233508.
18. Sontag TJ, Parker RS. Cytochrome P450 omega-hydroxylase pathway of tocopherol catabolism. Novel mechanism of regulation of vitamin E status. J Biol Chem. 2002;277:25290–6. https://doi.org/10.1074/jbc.M201466200.
19. Grebenstein N, Schumacher M, Graeve L, Frank J. α-Tocopherol transfer protein is not required for the discrimination against γ-tocopherol in vivo but protects it from side-chain degradation in vitro. Mol Nutr Food Res. 2014;58:1052–60. https://doi.org/10.1002/mnfr.201300756.
20. Zingg J-M. Vitamin E: an overview of major research directions. Mol Asp Med. 2007;28:400–22. https://doi.org/10.1016/j.mam.2007.05.004.
21. Simon EJ, Eisengaet A, Sundheim L, Milhorat AT. Purification and characterization of urinary metabolites of α-tocopherol. J Biol Chem. 1956;221:807–17.
22. Chiku S, Hamamura K, Nakamura T. Novel urinary metabolite of d-delta-tocopherol in rats. J Lipid Res. 1984;25:40–8.
23. Bardowell SA, Ding X, Parker RS. Disruption of P450-mediated vitamin E hydroxylase activities alters vitamin E status in tocopherol supplemented mice and reveals extra-hepatic vitamin E metabolism. J Lipid Res. 2012;53:2667–76. https://doi.org/10.1194/jlr.M030734.
24. Parker RS, Sontag TJ, Swanson JE, McCormick CC. Discovery, characterization, and significance of the cytochrome P450 omega-hydroxylase pathway of vitamin E catabolism. Ann N Y Acad Sci. 2004;1031:13–21. https://doi.org/10.1196/annals.1331.002.
25. Birringer M, Drogan D, Brigelius-Flohe R. Tocopherols are metabolized in HepG2 cells by side chain ω-oxidation and consecutive β-oxidation. Free Radic Biol Med. 2001;31:226–32. https://doi.org/10.1016/S0891-5849(01)00574-3.
26. Bardowell SA, Duan F, Manor D, Swanson JE, Parker RS. Disruption of mouse cytochrome p450 4f14 (Cyp4f14 gene) causes severe perturbations in vitamin E metabolism. J Biol Chem. 2012;287:26077–86. https://doi.org/10.1074/jbc.M112.373597.
27. Yang Z, Lee M-J, Zhao Y, Yang CS. Metabolism of tocotrienols in animals and synergistic inhibitory actions of tocotrienols with atorvastatin in cancer cells. Genes Nutr. 2012;7:11–8. https://doi.org/10.1007/s12263-011-0233-y.
28. Zhao Y, Lee M-J, Cheung C, Ju J-H, Chen Y-K, Liu B, et al. Analysis of multiple metabolites of tocopherols and tocotrienols in mice and humans. J Agric Food Chem. 2010;58:4844–52. https://doi.org/10.1021/jf904464u.
29. Sontag TJ, Parker RS. Influence of major structural features of tocopherols and tocotrienols on their omega-oxidation by tocopherol-omega-hydroxylase. J Lipid Res. 2007;48:1090–8. https://doi.org/10.1194/jlr.M600514-JLR200.
30. Birringer M, Pfluger P, Kluth D, Landes N, Brigelius-Flohé R. Identities and differences in the metabolism of tocotrienols and tocopherols in HepG2 cells. J Nutr. 2002;132:3113–8. https://doi.org/10.1093/jn/131.10.3113.
31. Lodge JK, Traber MG, Elsner A, Brigelius-Flohé R. A rapid method for the extraction and determination of vitamin E metabolites in human urine. J Lipid Res. 2000;41:148–54.
32. Kiyose C, Ueda T. Distribution and metabolism of tocopherols and tocotrienols in vivo. J Clin Biochem Nutr. 2004;35:47–52. https://doi.org/10.3164/jcbn.35.47.
33. Parker RS, Sontag TJ, Swanson JE. Cytochrome P4503A-dependent metabolism of tocopherols and inhibition by sesamin. Biochem Biophys Res Commun. 2000;277:531–4. https://doi.org/10.1006/bbrc.2000.3706.
34. Landes N, Pfluger P, Kluth D, Birringer M, Rühl R, Böl G-F, et al. Vitamin E activates gene expression via the pregnane X receptor. Biochem Pharmacol. 2003;65:269–73. https://doi.org/10.1016/S0006-2952(02)01520-4.

35. Zhou C, Tabb MM, Sadatrafiei A, Grün F, Blumberg B. Tocotrienols activate the steroid and xenobiotic receptor, SXR, and selectively regulate expression of its target genes. Drug Metab Dispos. 2004;32:1075–82. https://doi.org/10.1124/dmd.104.000299.
36. Podszun MC, Jakobi M, Birringer M, Weiss J, Frank J. The long chain α–tocopherol metabolite α-13′-COOH and γ-tocotrienol induce P-glycoprotein expression and activity by activation of the pregnane X receptor in the intestinal cell line LS 180. Mol Nutr Food Res. https://doi.org/10.1002/mnfr.201600605.
37. Podszun MC, Grebenstein N, Spruss A, Schlueter T, Kremoser C, Bergheim I, Frank J. Dietary alpha-tocopherol and atorvastatin reduce high-fat-induced lipid accumulation and down-regulate CD36 protein in the liver of guinea pigs. J Nutr Biochem. 2014;25:573–9. https://doi.org/10.1016/j.jnutbio.2014.01.008.
38. Mustacich DJ, Gohil K, Bruno RS, Yan M, Leonard SW, Ho E, et al. Alpha-tocopherol modulates genes involved in hepatic xenobiotic pathways in mice. J Nutr Biochem. 2009;20:469–76. https://doi.org/10.1016/j.jnutbio.2008.05.007.
39. Kluth D, Landes N, Pfluger P, Müller-Schmehl K, Weiss K, Bumke-Vogt C, et al. Modulation of Cyp3a11 mRNA expression by alpha-tocopherol but not gamma-tocotrienol in mice. Free Radic Biol Med. 2005;38:507–14. https://doi.org/10.1016/j.freeradbiomed.2004.11.010.
40. Hundhausen C, Frank JAN, Rimbach G, Stoecklin E, Muller PY, Barella L. Effect of vitamin E on cytochrome P450 mRNA levels in cultured hepatocytes (HepG2) and in rat liver. Cancer Genomics Proteomics. 2006;3:183–90.
41. Podszun MC, Grebenstein N, Hofmann U, Frank J. High-dose supplementation with natural α-tocopherol does neither alter the pharmacodynamics of atorvastatin nor its phase I metabolism in guinea pigs. Toxicol Appl Pharmacol. 2013;266:452–8. https://doi.org/10.1016/j.taap.2012.11.018.
42. Mustacich DJ, Leonard SW, Devereaux MW, Sokol RJ, Traber MG. Alpha-tocopherol regulation of hepatic cytochrome P450s and ABC transporters in rats. Free Radic Biol Med. 2006;41:1069–78. https://doi.org/10.1016/j.freeradbiomed.2006.06.022.
43. Leonard SW, Joss JD, Mustacich DJ, Blatt DH, Lee YS, Traber MG. Effects of vitamin E on cholesterol levels of hypercholesterolemic patients receiving statins. Am J Health Syst Pharm. 2007;64:2257–66. https://doi.org/10.2146/ajhp070041.
44. Clarke MW, Burnett JR, Wu JHY, Hodgson JM, Ledowski T, Puddey IB, Croft KD. Vitamin E supplementation and hepatic drug metabolism in humans. J Cardiovasc Pharmacol. 2009;54:491–6. https://doi.org/10.1097/FJC.0b013e3181bfae18.
45. Jiang Q, Christen S, Shigenaga MK, Ames BN. Gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. Am J Clin Nutr. 2001;74:714–22. https://doi.org/10.1093/ajcn/74.6.714.
46. Frank J, Lee S, Leonard SW, Atkinson JK, Kamal-Eldin A, Traber MG. Sex differences in the inhibition of gamma-tocopherol metabolism by a single dose of dietary sesame oil in healthy subjects. Am J Clin Nutr. 2008;87:1723–9. https://doi.org/10.1093/ajcn/87.6.1723.
47. Swanson JE, Ben RN, Burton GW, Parker RS. Urinary excretion of 2,7,8-trimethyl-2-(β-carboxyethyl)-6-hydroxychroman is a major route of elimination of γ-tocopherol in humans. J Lipid Res. 1999;40:665–71.
48. Schuelke M, Elsner A, Finckh B, Kohlschütter A, Hübner C, Brigelius-Flohé R. Urinary α-tocopherol metabolites in α-tocopherol transfer protein-deficient patients. J Lipid Res. 2000;41:1543–51.
49. Traber MG, Elsner A, Brigelius-Flohé R. Synthetic as compared with natural vitamin E is preferentially excreted as α-CEHC in human urine: studies using deuterated α-tocopheryl acetates. FEBS Lett. 1998;437:145–8. https://doi.org/10.1016/S0014-5793(98)01210-1.
50. Hosomi A, Arita M, Sato Y, Kiyose C, Ueda T, Igarashi O, et al. Affinity for α-tocopherol transfer protein as a determinant of the biological activities of vitamin E analogs. FEBS Lett. 1997;409:105–8. https://doi.org/10.1016/S0014-5793(97)00499-7.
51. Traber MG, Siddens LK, Leonard SW, Schock B, Gohil K, Krueger SK, et al. Alpha-tocopherol modulates Cyp3a expression, increases gamma-CEHC production, and limits tissue gamma-tocopherol accumulation in mice fed high gamma-tocopherol diets. Free Radic Biol Med. 2005;38:773–85. https://doi.org/10.1016/j.freeradbiomed.2004.11.027.
52. Parker RS, McCormick CC. Selective accumulation of alpha-tocopherol in Drosophila is associated with cytochrome P450 tocopherol-omega-hydroxylase activity but not alpha-tocopherol transfer protein. Biochem Biophys Res Commun. 2005;338:1537–41. https://doi.org/10.1016/j.bbrc.2005.10.124.
53. Terasawa Y, Ladha Z, Leonard SW, Morrow JD, Newland D, Sanan D, et al. Increased atherosclerosis in hyperlipidemic mice deficient in alpha -tocopherol transfer protein and vitamin E. Proc Natl Acad Sci U S A. 2000;97:13830–4. https://doi.org/10.1073/pnas.240462697.
54. Grau A, Ortiz A. Dissimilar protection of tocopherol isomers against membrane hydrolysis by phospholipase A2. Chem Phys Lipids. 1998;91:109–18. https://doi.org/10.1016/S0009-3084(97)00101-1.
55. Frank J. Beyond vitamin E supplementation: an alternative strategy to improve vitamin E status. J Plant Physiol. 2005;162:834–43. https://doi.org/10.1016/j.jplph.2005.04.017.

56. Ross AB, Chen Y, Frank J, Swanson JE, Parker RS, Kozubek A, et al. Cereal alkylresorcinols elevate gamma-tocopherol levels in rats and inhibit gamma-tocopherol metabolism in vitro. J Nutr. 2004;134:506–10. https://doi.org/10.1093/jn/134.3.506.
57. Ikeda S, Tohyama T, Yamashita K. Dietary sesame seed and its lignans inhibit 2,7,8-trimethyl- 2(2′-carboxyethyl)-6-hydroxychroman excretion into urine of rats fed gamma-tocopherol. J Nutr. 2002;132:961–6. https://doi.org/10.1093/jn/132.5.961.
58. Kamal-Eldin A, Pettersson D, Appelqvist LA. Sesamin (a compound from sesame oil) increases tocopherol levels in rats fed ad libitum. Lipids. 1995;30:499–505.
59. Kamal-Eldin A, Frank J, Razdan A, Tengblad S, Basu S, Vessby B. Effects of dietary phenolic compounds on tocopherol, cholesterol, and fatty acids in rats. Lipids. 2000;35:427–35. https://doi.org/10.1007/s11745-000-541-y.
60. Yamashita K, Iizuka Y, Imai T, Namiki M. Sesame seed and its lignans produce marked enhancement of vitamin E activity in rats fed a low α-tocopherol diet. Lipids. 1995;30:1019–28. https://doi.org/10.1007/BF02536287.
61. Yamashita K, Ikeda S, Iizuka Y, Ikeda I. Effect of sesaminol on plasma and tissue α-tocopherol and α-tocotrienol concentrations in rats fed a vitamin E concentrate rich in tocotrienols. Lipids. 2002;37:351–8. https://doi.org/10.1007/s11745-002-0902-6.
62. Hanzawa F, Nomura S, Sakuma E, Uchida T, Ikeda S. Dietary sesame seed and its lignan, sesamin, increase tocopherol and phylloquinone concentrations in male rats. J Nutr. 2013;143:1067–73. https://doi.org/10.3945/jn.113.176636.
63. Cooney RV, Custer LJ, Okinaka L, Franke AA. Effects of dietary sesame seeds on plasma tocopherol levels. Nutr Cancer. 2001;39:66–71. https://doi.org/10.1207/S15327914nc391_9.
64. Frank J, Kamal-Eldin A, Traber MG. Consumption of sesame oil muffins decreases the urinary excretion of gamma-tocopherol metabolites in humans. Ann N Y Acad Sci. 2004;1031:365–7. https://doi.org/10.1196/annals.1331.046.