Vitamin E Regulatory Mechanisms

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Key Words

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Abstract

Dietary and supplemental vitamin E is absorbed and delivered to the liver, but of the various antioxidants with vitamin E activity, only α-tocopherol is preferentially recognized by the α-tocopherol transfer protein (α-TTP) and is transferred to plasma, while the other vitamin E forms (e.g., γ-tocopherol or tocotrienols) are removed from the circulation. Hepatic α-TTP is required to maintain plasma and tissue α-tocopherol concentrations. The liver is the master regulator of the body's vitamin E levels in that it not only controls α-tocopherol concentrations, but also appears to be the major site of vitamin E metabolism and excretion. Vitamin Es are metabolized similarly to xenobiotics; they are initially ω-oxidized by cytochrome P450s, undergo several rounds of β-oxidation, and then are conjugated and excreted. As a result of these various mechanisms, liver α-tocopherol and other vitamin E concentrations are closely regulated; thus, any potential adverse vitamin E effects are limited.

Contents

INTRODUCTION

Vitamin E was discovered in 1922, when Evans & Bishop (28) reported that rats fed rancid fat resorbed their fetuses during early pregnancy. The description of vitamin E deficiency in humans almost 60 years later then led the way to our understanding that the liver controls vitamin E with respect to the form and amounts of the vitamin. This review seeks to outline these major regulatory steps, show areas where consensus has been reached with respect to vitamin E trafficking, and emphasize areas that remain undeciphered with respect to regulatory mechanisms.

ROO·: peroxyl radicals

ROOH: lipid hydroperoxides

VITAMIN E BIOAVAILABILITY PARADOX

In general, the term "vitamin E" includes four tocopherols and four tocotrienols (designated as α-, β-, γ-, and δ-) found in food. Unlike other nutrients, the body cannot interconvert these forms. Moreover, although these vitamin Es have similar antioxidant activities, only α-tocopherol meets human vitamin E requirements (30). Interestingly, the U.S. diet contains as much as ten times the concentration of γ-tocopherol, yet the body has ten times the concentration of α-tocopherol. Thus, the importance of bioavailability and the factors that determine vitamin E bioavailability are critical for understanding the mechanisms for regulation.

Vitamin E Antioxidant Activity

Vitamin E's antioxidant function is that of a peroxyl radical scavenger that terminates chain reactions of oxidation of polyunsaturated fatty acids (PUFAs) (18). When lipid hydroperoxides (ROOH) are oxidized to peroxyl radicals (ROO·), as could occur in the presence of free metals such as iron or copper, the ROO· react faster with α-tocopherol (Vit E-OH) than with PUFAs (17):

In the presence of vitamin E:

$$ROO\cdot + \text{Vit E-OH} \rightarrow ROOH + \text{Vit E-O}\cdot$$

In the absence of vitamin E:

$$ROO\cdot + RH \rightarrow ROOH + R\cdot$$
$$R\cdot + O_2 \rightarrow ROO\cdot$$

In this way, α-tocopherol acts as a chain-breaking antioxidant, preventing the further auto-oxidation of PUFAs in membranes or lipoproteins.

The tocopheroxyl radical (Vit E-O·) reacts with vitamin C or other hydrogen donors, such as thiols (104), especially glutathione (58, 69, 80, 81), returning vitamin E to its reduced state (16).

$$\text{Vit E-O}\cdot + \text{AH} \rightarrow \text{Vit E-OH} + \text{A}\cdot$$

Importantly, this interaction between vitamins E and C has been demonstrated in humans; cigarette smokers have faster vitamin E turnover that can be normalized by vitamin C supplementation (13, 15).

Vitamin E in the Human Diet

All naturally occurring vitamin E forms, as well as those of synthetic *all rac*-α-tocopherol, have relatively similar antioxidant activities, so why does the body prefer the natural stereoisomeric *RRR*-α-tocopherol as its form of vitamin E? Lack of various dietary vitamin E forms does not appear to be the answer. The richest dietary sources of vitamin E are edible vegetable oils (79). These oils contain all four homologs: α-, β-, γ-, and δ-tocopherols in varying proportions. Nonetheless, because α-tocopherol is present in appreciable amounts only in foods such as nuts (almonds), some seeds (sunflower), and vegetable oils (olive), obtaining sufficient vitamin E to meet requirements appears to be challenging for most Americans. Estimates of dietary vitamin E intakes suggest that 90% of men and 96% of women in the United States do not consume the recommended amounts of vitamin E (63) [estimated average requirement 12 mg α-tocopherol (30)].

Most Americans eat a diet that is relatively high in soybean oil. This vegetable oil contains approximately 70 mg γ-tocopherol per 100 g oil, but only about 7 mg α-tocopherol (26). Nonetheless, the plasma contains primarily α-tocopherol; how does this occur?

Basis for the Preference for α-Tocopherol

Regulatory steps in absorption. All of the various vitamin E forms are absorbed apparently to the same extent, and perhaps tocotrienols even better than tocopherols (106). There is limitation in vitamin E absorption if there is inadequate fat intake (14). Vitamin E is a fat-soluble vitamin and requires biliary and pancreatic secretions in order to form micelles for uptake by the intestine. Moreover, chylomicron secretion is also required for transport from the intestine to the circulation. However, none of these steps apparently exerts a preference for one form of vitamin E over another (102).

Despite the relative paucity of α-tocopherol in the diet, it is surprising that the fractional absorption of vitamin E is relatively limited. Estimates in humans of the percentage of a dose of vitamin E absorbed range from 68%, using the collection of fecal radioactivity after administration of radioactive vitamin E (55), to 33% from plasma concentrations following administration of deuterium-labeled vitamin E (14). These data demonstrate our lack of knowledge about vitamin E absorption. We do not know how vitamin E enters the intestinal cell, how it moves through the cell, or how it is incorporated into chylomicrons. Given that absorption of cholesterol, a molecule with similar hydrophobicity to α-tocopherol, is regulated by ATP-binding cassette family transporters (ABC transporters) (7), it seems likely that there may be very specific mechanisms for the regulation of vitamin E absorption that have not yet been described.

Liver—the master regulator. Once vitamin E is absorbed and taken up by the liver, the regulation of the forms and the concentrations appears to take place (**Figure 1**). It is not clear which lipoprotein receptors are involved in vitamin E uptake by the liver, but since all lipoproteins transport vitamin E, all lipoprotein receptors could hypothetically take up vitamin E–containing lipoproteins (95). Specifically, involvement of the low-density lipoprotein (LDL), high-density lipoprotein (HDL), and scavenger receptors modulates

αTTP: α-Tocopherol transfer protein. A liver cytosolic protein critical for the maintenance of plasma α-tocopherol concentrations

vitamin E uptake by various cells (4, 33, 65, 93, 98).

Plasma α-tocopherol concentrations in humans range from 11 to 37 μmol/L, whereas γ-tocopherol concentrations are roughly 2 to 5 μmol/L, and tocotrienol concentrations are less than 1 μmol/L, even in subjects supplemented with tocotrienols (70). When plasma lipids are taken into account, the lower limits of normal are 1.6 μmol α-tocopherol/mmol lipid (sum of cholesterol and triglycerides) or 2.5 μmol α-tocopherol/mmol cholesterol (97). The liver is responsible for the disposition, metabolism, and excretion of vitamin E. It does this through (*a*) the α-tocopherol transfer protein that returns α-tocopherol to the plasma, (*b*) the excretion of excess vitamin E into the bile, and (*c*) the metabolism of vitamin E. These topics are explored further in the following sections.

α-TOCOPHEROL TRANSFER PROTEIN

The major regulatory mechanism for controlling plasma α-tocopherol concentrations is the α-tocopherol transfer protein (α-TTP). α-TTP has been isolated and its cDNA sequences reported from a variety of species including human, mouse, rat, dog, and cow (see Entrez retrieval system, National Center for Biotechnology Information). α-TTP has been crystallized and the α-tocopherol-binding pocket identified (59, 62). Interestingly, the structure has a hinge and a cover that entraps α-tocopherol in the binding pocket. α-TTP has differing affinities for various forms of vitamin E with *RRR*-α-tocopherol = 100%, β-tocopherol = 38%, γ-tocopherol = 9%, δ-tocopherol = 2%, α-tocopherol acetate = 2%, α-tocopherol quinone = 2%, *SRR*-α-tocopherol = 11%, α-tocotrienol = 12%, or trolox = 9% (37). Thus, the affinity of α-TTP for vitamin E forms is one of the critical determinants for their plasma concentrations (37).

The human protein has 94% homology to the rat protein and some homology to the retinaldehyde-binding protein in the retina and to sec14, a phospholipid transfer protein (1). The human α-TTP gene is located at the 8q13.1–13.3 region of chromosome 8 (1, 25).

α-TTP expression was first reported in hepatocytes (108). α-TTP mRNA has also been detected in rat brain, spleen, lung, and kidney (38) and in mouse liver and adrenals, but is low or undetectable in mouse cerebral cortex, lungs, heart, and spleen (32). α-TTP protein has been detected in human brain (22). Furthermore, α-TTP is present in pregnant mouse uterus and human placenta (41, 42). Muller-Schmehl et al. (64) reported that concentrations of placental α-TTP mRNA were second only to those in the liver. The reports of uterine and placental α-TTP emphasize the importance of vitamin E during pregnancy and emphasize that the fetal resorption test (54) is not likely to be dependable for assessing bioavailability for various forms of vitamin E because any trace amounts of α-tocopherol present in the test vitamin E would be preferentially taken up by α-TTP to protect the uterus and placenta.

CRAL-TRIO Family

The CRAL-TRIO family is a small group of lipid-binding proteins, including the cellular retinaldehyde binding protein (CRALBP), α-TTP, yeast phosphatidylinositol transfer protein (Sec14p), and supernatant protein factor (SPF), a protein involved in cholesterol biosynthesis (73). CRAL-TRIO members can bind α-tocopherol, but only α-TTP had sufficient affinity for α-tocopherol to serve as a physiological α-tocopherol transfer protein (73). Human SPF also reportedly complexes with *RRR*-α-tocopheryl quinone, the two-electron α-tocopherol oxidation product (91). However, at present, it appears that only α-TTP serves as a regulator of plasma and tissue α-tocopherol concentrations (73).

α-TTP Function

The mechanism by which α-TTP facilitates secretion of α-tocopherol from the liver into

the plasma has not been fully described. In general, triglyceride-rich (chylomicrons and VLDL) and low-density lipoproteins carrying vitamin E are taken up by the liver via receptor-mediated endocytosis, delivering vitamin E to multivesicular bodies. Horiguchi et al. (36) suggest that α-TTP acquires α-tocopherol from the endosomes, and then this α-TTP-α-tocopherol complex moves to the plasma membrane, where α-TTP releases α-tocopherol to the membrane to be acquired by lipoproteins, e.g., nascent VLDL. The ATP-binding cassette protein A1 (ABCA1) in endosomes could play a role in this process since ABCA1 can also transfer α-tocopherol (71). Thus, ABCA1 could enrich the outer membrane of the endocytic vesicles with α-tocopherol; then α-TTP could preferentially remove *RRR*-α-tocopherol from the outer leaflet of the endosomal membrane for transfer to the plasma membrane. It remains to be clarified as to whether ABCA1 participates in α-tocopherol transfer directly to and from α-TTP, as was suggested by Horiguchi et al. (36), or if some other proteins are also involved in hepatic α-tocopherol trafficking.

CAUSES OF HUMAN VITAMIN E DEFICIENCY

The importance of α-TTP function in determining human vitamin E status was elucidated when patients with vitamin E deficiency caused by defects in the α-TTP were described, as discussed further below. Overt vitamin E deficiency occurs only rarely in humans. Most often, vitamin E deficiency had been described as a symptom secondary to fat malabsorption. α-Tocopherol deficiency causes both peripheral neuropathy (103) and increased erythrocyte hemolysis (45).

Ataxia with Vitamin E Deficiency

Genetic defects in α-TTP are associated with a characteristic syndrome, ataxia with vitamin E deficiency [AVED, previously called familial isolated vitamin E (FIVE) deficiency]. AVED patients have neurologic abnormalities, which are similar to those of patients with Friedreich's ataxia (5, 6). The symptoms are characterized by a progressive peripheral neuropathy with a specific dying back of the large caliber axons of the sensory neurons, which results in ataxia (86).

AVED: ataxia with vitamin E deficiency

Retinitis pigmentosa is also a symptom associated with vitamin E deficiency, and the defect in the α-TTP gene in patients with AVED has been described (57, 107). Importantly, vitamin E supplementation stops or slows the progression of retinitis pigmentosa in these patients (107).

Fat Malabsorption Syndromes

Vitamin E deficiency secondary to fat malabsorption occurs because vitamin E absorption requires biliary and pancreatic secretions. Children with cholestatic liver disease, who have impaired secretion of bile into the small intestine, have severe fat malabsorption (82). Neurologic abnormalities, which appear as early as the second year of life, become irreversible if the vitamin E deficiency is uncorrected (82–84).

Children with cystic fibrosis can also become vitamin E deficient because the impaired secretion of pancreatic digestive enzymes causes steatorrhea and vitamin E malabsorption, even when pancreatic enzyme supplements are administered orally (41). More severe vitamin E deficiency occurs if bile secretion is impaired (23, 27, 87, 90).

It should be emphasized that any disorder that causes chronic fat malabsorption, including chronic diarrhea in children, can lead to vitamin E deficiency. Thus, poor intake of nutrients generally could lead to vitamin E deficiency if the fat malabsorption is sufficiently severe and the child has low body stores.

Genetic Defects in Lipoprotein Synthesis

Studies of patients with hypobetalipoproteinemia or abetalipoproteinemia (low to

RDA: recommended dietary allowance

nondetectable circulating chylomicrons, VLDL, or LDL) have demonstrated that lipoproteins containing apolipoprotein B are necessary for effective absorption and plasma vitamin E transport (77). These patients have steatorrhea from birth because of the impaired ability to absorb dietary fat, which also contributes to their poor vitamin E status. Clinical features also include retarded growth, acanthocytosis, retinitis pigmentosa, and a chronic progressive neurological disorder with ataxia. Clinically, both hypobetalipoproteinemic or abetalipoproteinemic subjects become vitamin E deficient and develop a characteristic neurologic syndrome—a progressive peripheral neuropathy—if they are not given large vitamin E supplements (approximately 10 g per day) (77, 99). Despite low plasma concentrations, adipose tissue α–tocopherol concentrations reach normal levels in patients given large (10 g/day) vitamin E doses (99). These findings emphasize the difficulty of assessing vitamin E status in patients with abnormal plasma lipid concentrations. Tissue concentrations can be altered, but the plasma vitamin E concentrations reflect the abnormal circulating lipid levels (85).

Severe Malnutrition

Hepatic α-TTP is required to maintain normal plasma α-tocopherol concentrations (72). It is, therefore, not surprising that vitamin E–deficiency symptoms have been reported in children with severely limited food intake, which not only might be limiting in vitamin E, but also limiting in the dietary protein necessary to synthesize α-TTP. Kalra et al. (43) reported that 100 patients with protein energy malnutrition (PEM) had low plasma α-tocopherol concentrations (8 μmol/L or less) and low α-tocopherol/lipid ratios, as well as neurologic abnormalities characteristic of vitamin E deficiency. With 6 weeks vitamin E supplementation, not only were the subjects' circulating α-tocopherol levels normalized, but there was also improvement in their neurologic abnormalities (44). This pair of reports clearly identifies vitamin E deficiency as a cause of the PEM neurologic syndrome (43, 44). In general, the degree to which vitamin E deficiency is associated with kwashiorkor and/or marasmus is not clear because fat malabsorption has been reported as a confounding factor during recovery from extreme malnutrition (66).

HUMAN VITAMIN E EXCESS

It has been estimated that 35 million Americans take vitamin E supplements (31). Although the vitamin E recommended dietary allowance (RDA) is 15 mg of *RRR*-α-tocopherol, vitamin E supplements are available in doses of 100 to 1000 international units (IU) (mg *dl* α-tocopheryl acetate). The Institute of Medicine's Food and Nutrition Board set the upper tolerance level (UL) for α-tocopherol at 1000 mg [1100 IU synthetic (*all rac*); 1500 IU natural (*RRR*)] per day using data from studies in rats (30). No clinical trial has shown that any dose of vitamin E supplements causes adverse side effects in healthy people (34).

Vitamin E Supplements and Mortality

Within the past five years, a vitamin E intervention trial suggested adverse vitamin E effects in patients taking antihyperlipidemic drug therapy. The intervention study was a three-year, double-blind trial of antioxidants (vitamins E and C, β-carotene, and selenium) or placebos in 160 subjects taking both simvastatin and niacin (12, 20). Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that is widely utilized in the treatment of hypercholesterolemia. In subjects taking antioxidants, the drugs provided less of a benefit in raising HDL cholesterol than was expected (20).

A widely cited meta-analysis comparing 19 clinical trials has suggested that supplemental

vitamin E may increase the risk of death due to any cause (61). This analysis has been criticized for a variety of reasons, especially since simpler meta-analysis models did not report finding statistical significance of an effect of vitamin E supplements on all-cause mortality (3, 10, 19, 24, 35, 40, 48, 51, 56, 60, 76). However, the Heart Outcomes Prevention Evaluation Study Extension (HOPE-TOO) trial has reported a higher risk of heart failure and hospitalization for heart failure in cardiovascular disease patients taking vitamin E supplements (400 IU/day) for seven years compared with a placebo group (53). There were no differences with respect to primary outcomes of cancer incidence, cancer deaths, or major cardiovascular events and deaths in this study. To date, no vitamin E–related mechanism for the increased rate of heart failure has been described. This is an important area of study because identification of the mechanism for adverse vitamin E effects (if any exist) is clearly needed to be able to set upper limits for vitamin E intakes.

Vitamin E and Decreasing Chronic Disease Risk

Several studies have reported that vitamin E supplements are associated with decreased risk of various chronic diseases. The Women's Health Study, a ten-year prevention trial in normal, healthy women 45 years and older, found that 600 IU vitamin E taken every other day significantly decreased cardiovascular mortality by 24% and in women over 65 by 49% (49). Additionally, in hypercholesterolemic (78) and in heart transplant patients (29), supplementation with both vitamins E and C slowed atherosclerotic progression in intimal thickness of coronary and carotid arteries. The Cache County Study reported that antioxidant use (vitamin E >400 IU and vitamin C >500 mg) was associated with reduced Alzheimer disease prevalence and incidence in the elderly (109). Regular vitamin E supplement use for ten years or more was associated with a lower risk of dying of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) (2). Again, these reports of beneficial vitamin E effects encourage the use of vitamin E supplements and highlight the need for furthering our understanding of vitamin E metabolism.

CEHC: carboxyethyl hydroxychroman

HEPATIC VITAMIN E REGULATION

Dietary vitamin E is absorbed and delivered to the liver, but only α-tocopherol is preferentially recognized by α-TTP and transferred to plasma, as discussed above. The fate of hepatic vitamin E is just beginning to be studied, and it is apparent that there are large gaps in our knowledge about hepatic vitamin E trafficking and its mechanisms to regulate vitamin E concentrations (**Figure 1**).

Vitamin E Metabolism

Unlike other fat-soluble vitamins, vitamin E is not accumulated; thus, excretion and metabolism likely are important steps in regulation. Vitamin E metabolites are tail-shortened, carboxylated forms of vitamin E with intact head groups that are derived from tocopherols and tocotrienols, respectively (9, 52). Both α-CEHC [2,5,7,8-tetramethyl-2-(2′-carboxyethyl)-6-hydroxychroman] and γ-CEHC [2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman] are readily detected in plasma (50); δ-CEHC was the first of the metabolites reported (21).

Vitamin Es are metabolized similarly to xenobiotics (8) in that they are initially ω-oxidized by cytochrome P450s (CYPs), they undergo several steps of β-oxidation, and then they are conjugated and excreted in urine (11) or bile (46). The ω-oxidation of α- and γ-tocopherols has been shown to be carried out by CYP 4F2 (88), but CYP 3A may also be involved (8, 9, 39, 74). Following β-oxidation, CEHCs are sulfated or glucuronidated (75, 89, 92). Xenobiotic transporters are likely candidates for mediating hepatic CEHC excretion because

CEHCs are found in plasma, urine, and bile. Additionally, α-tocopherol alone has been demonstrated to be excreted into bile via the multidrug-resistance gene product, MDR2 (p-glycoprotein) (68), an ATP-binding cassette phospholipid transporter that facilitates biliary phospholipid excretion.

Vitamin E Kinetics

The rates of α-tocopherol entering or leaving the plasma are dependent on absorption, delivery to tissues, and excretion (**Figure 1**). The apparent half-life of *RRR*-α-tocopherol in plasma of normal subjects is approximately 48 h (100), up to 60 h (15), whereas that of *SRR*-α-tocopherol is only 15 h (100). This relatively fast turnover of 2*S*-α-tocopherol is also accompanied by increased metabolism (96). The relatively fast disappearance of the 2*S*-α-tocopherols means that by 48 h nearly 90% of the 2*S* forms have been removed from the plasma, while 50% of the 2*R* forms remain. Remarkably, the rate of γ-tocopherol disappearance from the plasma is similar to that of *SRR*-α-tocopherol, about 15 h (50). Moreover, this fast γ-tocopherol turnover is also accompanied by a fast disappearance of γ-CEHC (50). These kinetic studies emphasize that vitamin E forms other than α-tocopherol are rapidly removed from the body while α-tocopherol concentrations are maintained.

Vitamin E Disposition and Excretion

α-Tocopherol compared with γ-tocopherol (50), as well as synthetic, *all rac*-α-tocopherol compared with natural, *RRR*-α-tocopherol (96), is preferentially metabolized, a finding that suggests that forms of vitamin E that are not actively transported to the plasma by α-TTP are metabolized. However, if the vitamin E is not salvaged from the endosomal-lysosomal pathway that leads to biliary excretion mediated by p-glycoprotein (68), it is not obvious how the vitamin E is diverted to be metabolized. Regulation of hepatic vitamin E trafficking is an important area for further study.

Hepatic Vitamin E Regulation in Rodents

Although all forms of vitamin E are absorbed, the liver preferentially secretes α- but not γ-tocopherol into plasma. Therefore, to assess the fate of dietary γ-tocopherol, mice that do or do not express α-TTP (*Ttpa*$^{-/-}$, $^{+/-}$, and $^{+/+}$ mice) were fed for five weeks diets that contained either γ-tocopherol (550 mg γ-tocopherol/kg diet or 60 mg γ-tocopherol/kg diet), a vitamin E–deficient diet, or a control diet [30 mg α-tocopherol/kg diet (101)]. The two γ-tocopherol diets also contained about 3% α-tocopherol. Irrespective of genotype after a 12 h fast, the liver γ-tocopherol concentrations in mice fed the highest γ-tocopherol diets were no higher than the α-tocopherol concentrations of wild-type mice fed chow diets. Remarkably, the other tissues did not contain high γ-tocopherol concentrations. To determine the fate of γ-tocopherol, mechanisms of hepatic metabolism were assessed in the mice. Cyp4F protein, suggested to be the tocopherol ω-hydroxylase (88), did not vary between any of the dietary groups. (Note: In rats and humans, CYP protein nomenclature is capitalized; in mice, only the first letter is capitalized.) Hepatic Cyp3a protein concentrations correlated with hepatic α-tocopherol, but not γ-tocopherol concentrations. Similarly, hepatic Cyp3a mRNA increased in mice fed α-tocopherol compared with mice fed a tocotrienol-containing diet (47). Apparently, α-tocopherol modulates a subset of CYP enzymes, thereby increasing its own metabolism and preventing accumulation of "excess" α-tocopherol or other forms of vitamin E.

To evaluate the role of metabolism in protection against excess accumulation of α-tocopherol, studies were undertaken in rats that were injected subcutaneously with 0.5 g α-tocopherol (100 mg/kg body weight) over the course of 18 days (67). In addition

to α-tocopherol and α-CEHC, hepatic α-tocopherol intermediate metabolites, 13′-OH-α-tocopherol and 5′-α-CMBHC (5′-α-carboxy-methyl-butyl-hydroxy-chromanol), were measured. By the third day of injections, liver concentrations of α-tocopherol had increased 40- to 75-fold, α-CEHC had increased ∼100-fold, 13′-OH-α-tocopherol had increased 20-fold, and 5′-α-CMBHC, which was undetectable prior to α-tocopherol supplementation, had increased to 1.0 nmol/g tissue. These data demonstrate that excess liver α-tocopherol leads to increases of its own metabolites. At the same time, hepatic protein levels of CYP3A, CYP2B, and CYP2C, but not CYP4F, doubled and remained increased over the 18 days of daily α-tocopherol injections despite continuously decreasing α-tocopherol concentrations after day nine (67). Importantly, after nine days hepatic MDR1 protein concentrations increased and this increase in MDR1 corresponded with the decrease in hepatic α-tocopherol levels (67). These data suggest that MDR1 mediates the biliary excretion of α-tocopherol; however, biliary tocopherol concentrations were not measured, so this hypothesis requires further experimentation for confirmation.

The preceding studies used rats given daily injections of vitamin E such that over the course of the study more than 0.5 g had been injected into each rat. Such extraordinary increases in hepatic α-tocopherol concentrations are not likely to be observed in humans taking vitamin E supplements. Therefore, it is noteworthy that in the mice fed dietary vitamin E increases in Cyp 3A were also observed. These data suggest that the interactions of vitamin E metabolism and xenobiotic metabolism may occur in human liver (94).

SUMMARY AND PERSPECTIVES

It is apparent from the discussion above that there are several gaps in our knowledge about the regulation of vitamin E concentrations. Although it is clear that there is an overwhelming preference for α-tocopherol by the various regulatory mechanisms, the reason for this preference is controversial and remains undetermined. Largely, differences observed in cell culture are not dependent upon most of the various regulatory mechanisms described in this review and, thus, various spurious effects can occur and need confirmation in vivo.

The preference for α-tocopherol in vivo is largely accomplished by the action of α-TTP, whose absence in humans causes vitamin E deficiency. Presumably, α-TTP salvages α-tocopherol from the lysosomal degradation pathway and, ultimately, biliary excretion. However, the precise steps by which α-TTP accomplishes this feat are unknown.

γ-Tocopherol serves as an example of the fate of non-α-tocopherols. Promptly upon absorption in humans, γ-tocopherol is metabolized to γ-CEHC (50). Cell culture studies recapitulate this process in that in cells given equal amounts of α- and γ-tocopherols, a 100-fold excess of γ-CEHC is produced (8, 9). Thus, it is clear that the body actively metabolizes forms of vitamin E other than α-tocopherol.

There are several unknowns concerning metabolism. Although the liver has been demonstrated to contain elevated vitamin E metabolites, other tissues may also be capable of vitamin E metabolism; however, other sites have not been documented. Moreover, the various intracellular locations of vitamin E metabolism and the specific xenobiotic systems involved in catabolism, conjugation, and excretion have not been identified. Additionally, the means by which these steps are regulated have not been elucidated. Given the importance of vitamin E for protection against chronic disease mortality (105) and the propensity of the public for the use of vitamin E supplements, as well as the likelihood that some of the observed abnormal findings in trials that combine pharmacologic agents and vitamin E supplements result in vitamin E–drug interactions (12), it is clear that further studies in vitamin E–regulatory mechanisms are needed.

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Observes not only ataxia due to vitamin E deficiency, but also retinitis pigmentosa, in humans with a defective α-TTP gene.

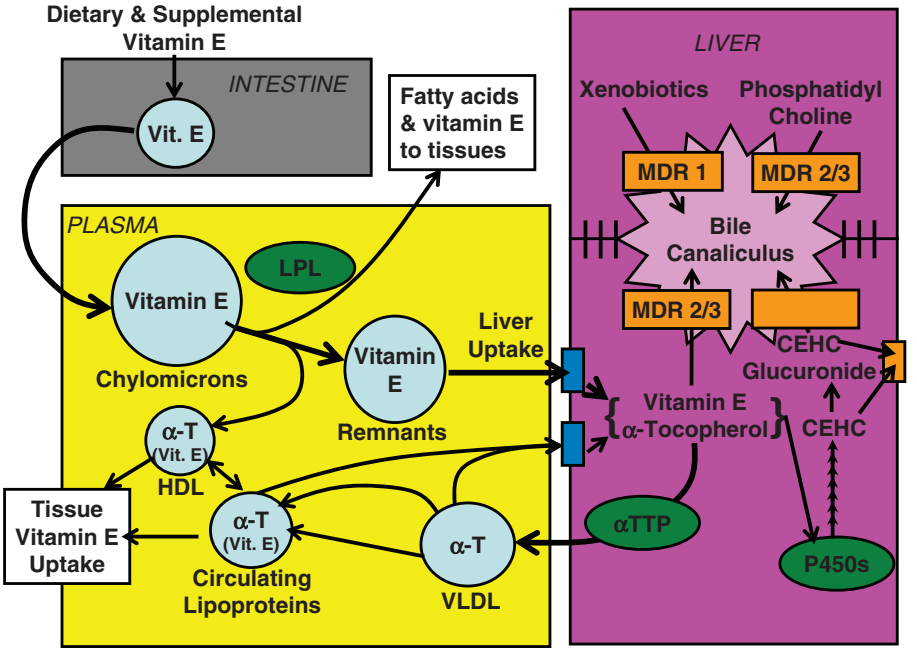

Figure 1

All forms of vitamin E are absorbed in the intestine (*gray*) and secreted into the circulation in chylomicrons. Lipoprotein lipase (lpl) hydrolyzes the chylomicron triglyceride and transfers fatty acids, as well as vitamin E, to tissues. During the formation of chylomicron remnants in the plasma compartment (*yellow*), some of the vitamin E is transferred to high-density lipoproteins (HDLs) and subsequently to other lipoproteins. The chylomicron remnants are taken up by the liver, where the α-tocopherol transfer protein (α-TTP) salvages α-tocopherol (α-T) from the lysosomal degradation pathway and returns it to the circulating lipoproteins, principally very-low-density lipoproteins (VLDLs). During lipoprotein catabolism in the circulation, α-T is redistributed among the various lipoproteins. Lipoproteins are taken up by the liver (and peripheral tissues) by various receptors (*blue rectangles*), and thus tocopherols are delivered to tissues by this process. In the liver, excess α-T and other vitamin E forms can be excreted into bile via the multidrug-resistance gene products (MDR 2/3), e.g., p-glycoprotein [ATP-binding cassette (ABC) and other transporters; *orange rectangles*]. Excess vitamin E is also metabolized by a cytochrome P450 (CYP)-mediated process to carboxy ethyl hydroxy chromans (CEHCs) that can be glucuronidated (or sulfated) and excreted in bile or urine. High α-T concentrations in the liver upregulate various xenobiotic pathways, including CYP3A and MDR1.

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Errata

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