Molecular and Cellular Activities of Vitamin E Analogues

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Abstract: Natural vitamin E comprises 8 different analogues, the α-, β-, γ-, and δ-tocopherols and the α-, β-, γ-, and δ-tocotrienols. However, only α-tocopherol is selectively enriched by the liver; the other vitamin E analogues and also excess α-tocopherol are converted to several metabolites and eliminated. Recently, a novel phosphorylated form of tocopherol, α-tocopheryl phosphate, was shown to occur naturally in animal and human tissues as well as in foods. Several synthetic vitamin E derivatives have been synthesized that are either converted by esterases to the natural form, or exert novel or vitamin E related biological activities. During the last years, specific cellular effects for each individual vitamin E analogue have been described that are the consequence of modulating signal transduction and gene expression. These effects possibly reflect specific interactions of each of the vitamin E analogues with enzymes, structural proteins, lipids and transcription factors. In this review, the different natural vitamin E analogues and synthetic derivatives are compiled in relation to their major molecular and cellular activities.

Key Words: Vitamin E, α-tocopheryl acetate, α-tocopheryl phosphate, tocopheryl succinate, tocopherol derivatives, tocopherol binding proteins, gene regulation, signal transduction, transport, metabolism.

1. INTRODUCTION TO VITAMIN E

Vitamin E, which is an essential nutrient for higher organisms, occurs naturally in plants in different relative amounts in eight analogues, having more or less equal antioxidant potency (the α-, β-, γ-, δ-tocopherols and the α-, β-, γ-, δ-tocotrienols). In higher organisms, only α-tocopherol is enriched in plasma 20 - 30 fold by means of the "α-tocopherol salvage pathway", whereas the other tocopherols and tocotrienols are metabolized and excreted (reviewed in [1]). The selective plasma enrichment of α-tocopherol occurs *via* the liver α-tocopherol transfer protein (α-TTP) which incorporates preferentially α-tocopherol into very low density lipoproteins (VLDL).

Vitamin E was first described as an essential nutrient for reproduction in rats [2]. Based on this finding, the units definition (United States Pharmacopoeia (USP)) of the different vitamin E analogues has been based on the rat fetal resorption assay (1 USP of vitamin E = 1 mg of *all-rac*-α-tocopheryl acetate, or 0.67 mg *RRR*-α-tocopherol, or 0.74 mg *RRR*-α-tocopheryl acetate) [3]. Vitamin E deficiency in humans, resulting from mutations in the human liver α-TTP gene and impaired selective α-tocopherol retention, leads to development of a rare familial disease, ataxia with vitamin E deficiency (AVED), associated with low levels of α-tocopherol in plasma and neurodegenerative symptoms closely resembling those of Friedreich's ataxia [4]. The symptoms of AVED can be prevented by supplementation with high doses of vitamin E [5]. In addition to that, vitamin E supplementation has been tested in many studies as preventive treatment against atherosclerosis, certain types of cancer, fibrotic disease, or neurodegenerative diseases such as Alzheimer's or Parkinson's disease, however clear beneficial effects have not always been observed (reviewed in [1,6-8]). All these studies are based on the finding that vitamin E levels can be increased by extra dietary supplementation, implying that the pathways involved in vitamin E uptake and body distribution are often not saturated. This is in particular the case in several lipid malabsorption diseases that are associated with vitamin E deficiency, in which vitamin E supplementation is clearly beneficial (chapter 2.1).

Vitamin E acts chemically as free radical chain breaking molecule in the lipid phase (lipoprotein and membranes) and thus protects the organism against the attack of those radicals [9-11]. Alternative roles of vitamin E such as the modulation of cellular signaling, enzymatic activity and gene expression have been proposed (reviewed in [1,12-16]). These effects are unrelated to the antioxidant activity of vitamin E, and possibly reflect specific interactions of each of the tocopherol analogues with enzymes, structural proteins, lipids and transcription factors (chapter 2). Several tocopherol binding proteins have been described, that may mediate the non-antioxidant signaling and cellular functions of vitamin E and its correct intracellular distribution (chapter 4).

Since the natural vitamin E analogues are relatively unstable, several stabilized vitamin E derivatives have been synthesized for usage in supplements and cosmetics (chapter 3). Whereas these derivatives may have advantages for processing, storage and absorption, they usually are rapidly converted to the natural forms by intestinal or epidermal esterases, and thus can be considered to be pro-vitamins, ultimately performing the same functions in the body as the natural vitamin E. These stabilized derivatives are usually derived from α-tocopherol, based on the finding that the enrichment by liver α-TTP is specific for α-tocopherol. In fact, it can be assumed that the high selectivity of α-TTP for α-tocopherol may be a limiting factor in developing orally used tocopherol derivatives with increased vitamin E activity and pharmacokinetics. However, even before ester hydrolysis, the stabilized tocopherol derivatives may perform important cellular functions, for example during their transport through the gastrointestinal tract or possibly also within the skin [17].

Several further synthetic tocopherol derivatives show activities that are independent of their conversion to the natural tocopherols, and these derivatives may not necessarily need to be enriched by liver α-TTP. These molecules often act as completely novel compounds, are transported differently and have their own effects on gene expression, cellular signalling and apoptosis. Some of these derivatives, such as α-tocopheryl succinate, have been proposed to exert a dual function, first as pro-vitamin E in the non-hydrolyzed form, and second as vitamin E, in the hydrolyzed form [18].

This review summarizes the different natural vitamin E analogues and synthetic derivatives and discusses their major molecular and cellular activities.

2. NATURAL VITAMIN E ANALOGUES

Natural vitamin E comprises 8 different forms, the α-, β-, γ-, and δ-tocopherols and the α-, β-, γ-, and δ-tocotrienols. The tocotrienols have an unsaturated side chain, whereas the tocopherols contain a phytyl tail with three chiral centres which naturally occur in the *RRR* configuration (Fig. (**1**)).

2.1. Tocopherols

The tocopherols are exclusively synthesized in photosynthetic organisms including higher plants; significant amounts are found in all green tissues and also in seeds. In the human diet, the major sources of vitamin E are dietary oils, which contain the four tocopherols in different relative amounts (reviewed in [1]). In palm oil

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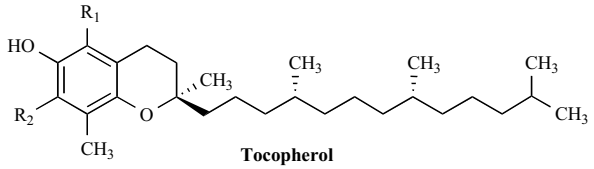
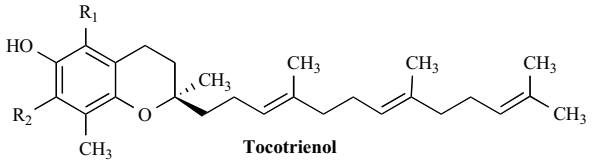


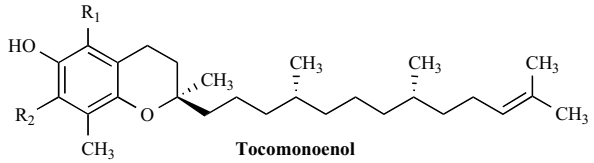
Tocopherol

R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



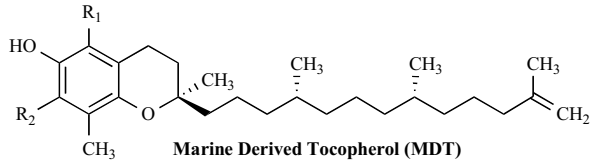
Tocotrienol

R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



Tocomonoenol

R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



Marine Derived Tocopherol (MDT)

R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

Fig. (1). Structure of the four natural tocopherols, the tocotrienols, the tocomonoenols and the marine derived tocopherol.

there is also α-tocomonoenol, and some marine organisms contain also marine derived tocopherol (MDT), with a single unsaturated bond at the end of the phytyl side chain, which is assumed to be the result of cold-water adaptation (Fig. (**1**)) [19].

The overall antioxidant activity of the tocopherols is more or less similar; however, clear individual chemical, physical and biological effects can be distinguished at the molecular level (reviewed in [20]). The free radical scavenging reactivity of the four tocopherols has been measured as being in the order of α >γ > β > δ [21]. The chemical reactivity with singlet molecular oxygen ($^1O_2$) has been found to be very low, with α > γ > δ> β. The physical quenching ability of $^1O_2$ has been measured as being in the order of α≥ β> γ> δ [22]. The biological potency can be summarized with the order of α >> γ >δ > β, what is most likely a result of selective retention of α-tocopherol by the liver α-tocopherol salvage pathway.

The normal average plasma concentration of α-tocopherol is 23.2 μM, a plasma level below 11.6 μM is regarded as deficient [5]. Vitamin E deficiency in humans with full neurological symptoms is rare, and usually is the consequence of mutations of the α-tocopherol transfer protein (α-TTP) leading to ataxia with vitamin E deficiency (AVED). These patients with plasma α-tocopherol concentrations below 2.2 μM are affected by ataxia, loss of neurons, retinal atrophy, massive accumulation of lipofuscin in neurons and retinitis pigmentosa [23-25]. More frequent than vitamin E deficiency is vitamin E insufficiency, with suboptimal vitamin E supply in the diet or inefficient uptake and distribution of vitamin E. Certain diseases, like abetalipoproteinemia, chronic cholestatic liver disease, cystic fibrosis, chronic pancreatitis, progressive systemic sclerosis, short-bowel syndrome or several other lipid malabsorption syndromes are associated with a low efficiency of vitamin E uptake, that can at the extreme lead to similar symptoms as in AVED. These symptoms clearly can be prevented and in some situation reversed by supplemental vitamin E (reviewed in [5]).

In most tissues, the tocopherol analogue with the highest concentration is *RRR*-α-tocopherol, as a consequence of selective α-tocopherol plasma enrichment by the liver α-tocopherol transfer protein (α-TTP), with the exception of skin and muscle where γ-tocopherol is also high (reviewed in [1]). In human plasma of unsupplemented individuals, average α-tocopherol concentrations (22 - 28 μM) are about 10 and 100 times higher than that of γ-tocopherol (2.5 μM) and of δ-tocopherol (0.3 μM) concentrations, respectively [23,26]. In tissues, the highest contents of α-tocopherol are found in adipose tissue (150 μg/g tissue) and the adrenal glands (132 μg/g tissue), other organs like kidney, heart or liver contain between 7 and 40 μg/g tissues, and erythrocytes have a relatively low content (2 μg/g tissue) [27,28]. These differences in the relative amounts of the different tocopherols suggest tissue specific mechanisms for enrichment and/or storage of tissue tocopherols.

2.1.1. Molecular and Cellular Differences Between α-, β-, γ- and δ-Tocopherol

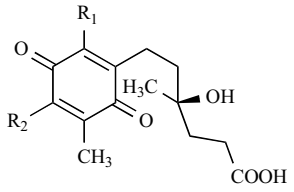
It is to date still unknown why nature selected specifically the α form of tocopherol to selectively increase its plasma and tissue concentration. Several possibilities can be envisioned to explain the selective enrichment of α-tocopherol. It can be speculated that α-tocopherol has some specific characteristics; e. g. the fully methy-

lated chromanol-head group may be required for optimal interactions with enzymes and/or "α-tocopherol receptors". On the other hand, the β-, γ-, and δ- tocopherols and tocotrienols and their metabolites may be specifically recognized, metabolized by the liver and later eliminated, because they possibly interact with enzymes and other proteins and have biological effects at higher concentrations that interfere with normal cellular processes. It is unknown whether the not-retained tocopherol analogues and their metabolites have an essential cellular function at low concentration.

In the liver, α-tocopherol is specifically sorted by α-TTP into vesicles destined for incorporation into VLDL [29]. Only when the level of α-tocopherol exceeds the capacity of α-TTP, transport to the metabolic enzymes occurs. The other tocopherols and tocotrienols are not retained by α-TTP, activate the pregnane X receptor (PXR) and then become metabolized and eliminated by CYP3A or CYP4F2 (chapter 2.4) [30]. Thus, the selective retention of α-tocopherol and the elimination of all the others tocopherol analogues may be the result of weaker PXR activation by α-tocopherol and the consequent absence of induction of enzymes involved in its metabolism. This is in fact the case in *Drosophila melanogaster*, where α-tocopherol is preferentially retained independent of α-TTP, as a result of much weaker activation of tocopherol-ω-hydroxylase by α-tocopherol when compared to γ- or δ-tocopherol [31]. In higher organisms, the tocopherol binding proteins, such as α-TTP and the tocopherol associated proteins (TAP), could mediate the recognition of the different tocopherol analogues and thus increase the specificity to the metabolism and action of the tocopherols and tocotrienols (chapter 4).

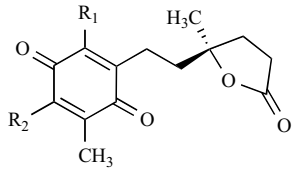
A unique feature of α-tocopherol is the location of the reactive -OH group between two methyl groups; after reacting with a lipid peroxide the unpaired electron can delocalize over the fully substituted chromanol ring thus increasing its stability and chemical reactivity [20,32]. As a consequence, α-tocopherol and α-tocotrienol, but not the other forms of tocopherol, can reduce *in vitro* Cu(II) to give Cu(I) together with α-tocopheryl quinones and α-tocotrienyl quinone, respectively, and they can exert pro-oxidant effects in the oxidation of methyl linoleate in sodium dodecyl sulfate (SDS) micelles [33]. Nevertheless, α-tocopherol and α-tocotrienol have the same chromanol head group, and albeit α-tocotrienol has higher antioxidant activity than α-tocopherol in membranes [34], only α-tocopherol is retained; this again may suggest that α-tocotrienol is not retained and eliminated because at high concentrations it would interfere with normal cellular reactions. In line with this model, it was shown that α-tocotrienol is often more potent in many cellular reactions (chapter 2.2).

A unique feature of γ-tocopherol is that it inhibits lipid hydroperoxide formation in liposomes more effectively than α-tocopherol by different mechanisms [35,36]. γ-Tocopherol inhibits cyclooxygenase-2 (COX2) activity, leading to decreased prostaglandin E2 (PGE2) production [37,38]. γ-Tocopherol and also its metabolite γ-CEHC (Fig. (**2**)) can react with peroxynitrite, forming 5-NO_2-γ-tocopherol and 5-NO_2-γ-CEHC, respectively (Fig. (**2**) [39,40]. Peroxynitrite is formed by a reaction of active oxygen and nitric oxide, molecules that are released by macrophages during inflammation. The higher reactivity of γ-tocopherol with reactive nitrogen species renders it a better anti-inflammatory agent; however, with the exception of skin, γ-tocopherol is not specifically enriched, suggesting that the anti-inflammatory activity may not be the only function of vitamin E. Moreover, the scavenging by γ-tocopherol becomes significant only after α-tocopherol depletion, implying that γ-tocopherol alone is insufficient to remove any peroxynitrite-derived reactive nitrogen species [41]. Nevertheless, in a model for Parkin-



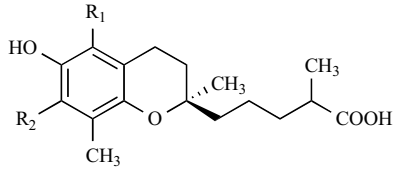
R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

Tocopheronic acid



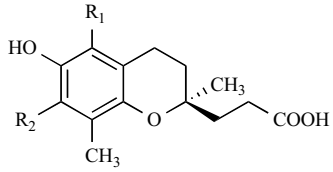
R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

Tocopherono lactone



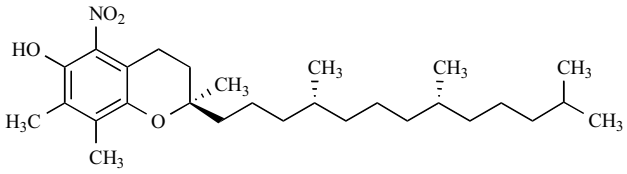
R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

CMBHC

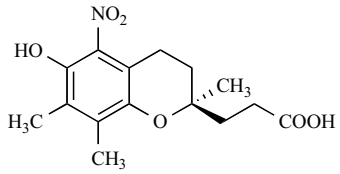


R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

CEHC



5-Nitro-γ-tocopherol



5-Nitro-γ-CEHC

Fig. (2). Structure of the natural tocopherol and tocotrienol metabolites as drawn in the non-glucuronized form. The Simon metabolites tocopheronic acid and tocopheronolactone; the metabolites CMBHC and CEHC; and the nitrated forms of γ-tocopherol and γ-CEHC, 5-NO_2-γ-tocopherol and 5-NO_2-γ-CEHC, respectively.

son's disease, the damage of dopaminergic neurons after treatment of mice with 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) is better prevented by γ-tocopherol, when compared to α-tocopherol [42]. Moreover, in a recent study with insulin resistant rats, neointima formation induced by vascular injury is reduced by γ-tocopherol by reducing nitrosative stress, whereas the effects seen with α-tocopherol are much weaker [43].

Taken together, the data about the uptake, metabolism and distribution of the different natural vitamin E analogues suggest that enriching the body with the maximum of vitamin E-based antioxidant activity is not the only reason for selective α-tocopherol retention. Further molecular and cellular effects of the different tocopherols and tocotrienols have been described that can be classified as either antioxidant, prooxidant, antialkylating or non-antioxidant (reviewed in [1,13,44-50]). At the cellular level, these molecular properties of each vitamin E analogue translate into specific effects on cellular signalling and gene expression affecting the cellular behaviour and survival (reviewed in [1,12-14]). To date, the molecular and cellular differences between the natural vitamin E analogues are not yet completely resolved. In many situations only α-tocopherol has been checked, and it is unclear whether other tocopherols or tocotrienols work equally well. In other experiments, the effects of vitamin E have been only tested in the test tube, and need to be confirmed *in vivo*. When all the experimental data are considered, it can be assumed that each of the tocopherols modulates cellular behaviour differently by specific interactions with enzymes, structural proteins, lipids and transcription factors.

2.1.2. Modulation of Signal Transduction by Tocopherols

The four natural α-, β-, γ-, and δ-tocopherols often show different potency in cellular assays, suggesting that the number of methyl groups at the chromanol moiety and the extent of exposure of the hydroxy group play an important role for the interaction with specific proteins (Table (**1**)). As examples, β-tocopherol, which occurs in low amounts in the diet, shows much weaker effects in inhibiting smooth muscle proliferation [51], in reducing protein kinase C activity [52], in reducing NADPH-oxidase activation in monocytes [53], and in inhibiting CD36 expression [54]. γ-Tocopherol, on the other hand, shows the strongest inhibition of cell cycle progression and of cyclin expression in prostate cancer cells [55,56], stimulates best peroxisome proliferators activated receptor gamma (PPARγ) and transglutaminase-1 expression [57,58], and increases most apoptosis *via* disruption of sphingolipid synthesis [59] (reviewed in [60,61]). δ-Tocopherol is most potent in inducing apoptosis and reducing proliferation of several cell types, and inhibits best the phosphorylation of protein kinase B (PKB) at Ser 473 [62-65].

The main effects of the tocopherols on signalling at the enzymatic level (reviewed in [1,14,66]) are inhibition of protein kinase C alpha and delta (PKCα and PKCδ) activity [67,68] and consequent inhibition of NADPH-oxidase [69], activation of protein

Table 1. List of Natural Tocopherol Analogues and Some of Their Tested Properties

Tocopherol Analogues	Most Important Cellular Activities (See text for references)
1) Natural analogues (Fig. (1))	
α-Tocopherol	enriched by liver α-TTP, highest biological activity, inhibition of cell proliferation, modulation of signal transduction and gene expression (chapter 2.1)
β-Tocopherol	weakest tocopherol analogue (chapter 2.1)
γ-Tocopherol	can form 5-NO_2-γ-tocopherol, acts anti-inflammatory, can induce apoptosis, inhibition of cell proliferation, modulation of signal transduction and gene expression (chapter 2.1)
δ-Tocopherol	reduces best PKB Ser 473 phosphorylation and induces apoptosis, inhibition of cell proliferation, modulation of signal transduction and gene expression (chapter 2.1)
α-Tocomonoenol	cold water adaptation in some marine organism (chapter 2.1)
α-Tocotrienol	inhibition of HMG-CoA reductase, inhibition of cell proliferation, induction of apoptosis, modulation of signal transduction and gene expression (chapter 2.2)
β-Tocotrienol	weakest tocotrienol analogue (chapter 2.2)
γ-Tocotrienol	inhibition of HMG-CoA reductase, inhibition of cell proliferation, induction of apoptosis, modulation of signal transduction and gene expression (chapter 2.2)
δ-Tocotrienol	inhibition of HMG-CoA reductase, inhibition of cell proliferation, induction of apoptosis, modulation of signal transduction and gene expression (chapter 2.2)
α-Tocopheryl phosphate (Fig. (**3**))	naturally occurring phosphorylated form of vitamin E, inhibition of cell proliferation, modulation of signal transduction and gene expression, induction of apoptosis (chapter 3.3)
2) Natural metabolites (Fig. (2))	
α-, β-, γ-, δ-CMBHC	intermediates of tocopherol metabolism (chapter 2.4)
α-, β-, γ-, δ-CEHC	inhibition of cell proliferation, modulation of signal transduction and gene expression, γ-CEHC is natriuretic (chapter 2.4)
α-, β-, γ-, δ-Tocopheryl quinones	oxidized from of the tocopherols, γ- and δ-tocopheryl quinones are cytotoxic (chapter 2.3)
α-, β-, γ-, δ-Tocopheryl hydroquinones	reduced forms of tocopheryl quinones (chapter 2.3)
Tocopheronic acid	Simon metabolite (chapter 2.4)
Tocopheronolactone	Simon metabolite (chapter 2.4)
5-NO_2-γ-tocopherol	nitrated γ-tocopherol (chapter 2.4)
5-NO_2-γ-CEHC	nitrated γ-CEHC (chapter 2.4)

phosphatase 2A (PP2A) [70], inhibition of protein kinase B (PKB) [64,71,72], inhibition of protein tyrosine kinases [73,74], modulation of phospholipase A2 activity (PLA2) [75,76], activation of diacylglycerol kinase (DAGK) [77,78], inhibition of cyclooxygenase-2 activity (COX-2) [79] and of 5-lipoxygenase (5-LOX) [80]. The crystal structure of phospholipase A2 with the inhibitory vitamin E is a clear example of non-antioxidant vitamin E/enzyme interaction with regulatory function [81]. The translocation of several of these enzymes to the plasma membrane is affected by vitamin E, suggesting that the modulation of protein-membrane interactions may be a common theme for vitamin E action (reviewed in [82]). Thus, the elucidation of the mechanisms involved in modulating enzyme translocation to the plasma membrane by natural vitamin E analogues and synthetic derivatives could reveal novel strategies and molecular targets for developing drugs affecting signal transduction.

2.1.3. Modulation of Gene Expression by Tocopherols

The main effects of vitamin E on gene expression have been recently summarized [1,14,66]. Several different molecular mechanisms and regulatory pathways may be involved in the modulation of tocopherol analogue-specific gene expression:

(I) Modulation of the Activity of Transcription Factors by Tocopherols

The modulation of the signal transduction pathways described above (chapter 2.1.2) can change the activity of transcription factors and thus influence gene expression (reviewed in [1]). Phosphorylation of the retinoid X receptor alpha (RXRα) is inhibited by α-tocopherol as a result of PKC inhibition, leading to increased expression of the cellular retinaldehyde binding protein II (CRABP-II) gene [83]. Similar to that, α-tocopherol leads to activation of AP1 in the absence of phorbol myristate acetate (PMA); in the presence of PMA and thus with activated PKC, AP1 is inhibited whereas β-tocopherol has no effect [84]. Several transcription factors, such as the pregnane X receptor (PXR) [30,85], nuclear receptors such as the peroxisome proliferators activated receptors (PPARs) [57,58], or possibly other orphan nuclear receptors, are modulated by vitamin E. PPARγ and PXR have been shown to respond differently depending on the tocopherol analogue (chapter 2.4) [57,58].

(II) Modulation of the Transport and Concentration of the Tocopherols

The tocopherols may also influence gene expression by binding to proteins like α-TTP and TAP (chapter 4), which may regulate the access of the tocopherols to specific enzymes and transcription factors, or control the level of not-membrane-bound, "free", cellular tocopherols concentrations [15,16,86,87]. These proteins bind the four tocopherol analogues with different affinity [88]. The TAP proteins modulate *in vitro* the activity of recombinant phosphatidylinositol-3-kinase and α-tocopherol modulates kinase activity in a TAP-dependent manner, possibly by competition with phosphatidylinositol. Thus, by modulating the intracellular concentration and targeting of these ligands to enzymes and organelles, the TAP proteins may influence the activity of lipid dependent enzymes involved in signal transduction and gene expression [87,89].

(III) Metabolism to Bioactive Compounds

The tocopherols may be metabolized to bioactive compounds, which can bind to enzymes or transcription factors and modulate their activity (chapter 2.4). Several metabolites are generated from tocopherols, and some of them influence cellular reactions in an analogue-specific manner (chapter 2.4).

2.2. Tocotrienols

The tocotrienols (Fig. (**1**)) are the major vitamin E components of palm oil, significant amounts are also found in barely, oat and rice bran. The uptake and distribution of the tocotrienols in the body is not very efficient (plasma concentration < 1 μM) [90]; nevertheless, studies have shown that sufficient amounts of tocotrienols, given as dietary supplements, can reach the brain and perform neuroprotective functions [91-93]. The tocotrienols possess powerful neuroprotective, anti-cancer and cholesterol lowering properties that are often not exhibited by the tocopherols (Table (**1**) (reviewed in [47,94]). These additional effects of the tocotrienols in mammalian cells can be explained partially by their influence on the mevalonate-cholesterol biosynthesis pathway.

α-Tocotrienol is more potent than α-tocopherol in reducing cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) activity and its mRNA translation, in decreasing the secretion of apoB, and in enhancing its proteasomal degradation [95-99]. The tocotrienols inhibit the HMG-CoA reductase at the posttranscriptional level by specifically modulating the intracellular mechanism for its controlled degradation. γ-Tocotrienol inhibits the rate of [^{14}C]-acetate but not [^{3}H]-mevalonate incorporation into cholesterol in a concentration- and time-dependent manner, with 50% inhibition observed at approximately 2 μM. Maximum inhibition (80%) is observed in HepG2 cells within 6 h. HMG-CoA-reductase total activity and protein levels are reduced concomitantly with the decrease in cholesterol synthesis [96]. Similar to the tocotrienols, several further isoprenoids inhibit HMG-CoA reductase synthesis and accelerate reductase degradation, leading to suppression of cell proliferation and induction of apoptosis in cancer cells, suggesting that these effects are mainly mediated by the unsaturated isoprenoid side chain of the tocotrienols [100,101].

During ischemia/reperfusion, the tocotrienols restore both 20S- and 26S- proteasome activities and significantly inhibit the phosphorylation of c-Src (cellular homolog of the v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene) [102]. Among the vitamin E analogues examined, α-tocotrienol exhibits the most potent neuroprotective actions in rat striatal cultures [103], and is able to block glutamate-induced cell death [104]. Oral supplementation of α-tocotrienol to spontaneously hypertensive rats leads to increased α-tocotrienol levels in the brain and higher protection against stroke-induced injury compared with matched controls. Such protection is associated with lower c-Src activation and 12-lipoxygenase (12-LOX) phosphorylation at the stroke site, what can be explained by blocking glutamate-induced death by suppressing early activation of c-Src kinase and 12-LOX in neuronal cells, at nmol/L concentrations of α-tocotrienol, but not of α-tocopherol [93]. In cultured cortical neurons, α- and γ-tocopherol as well as α- and γ-tocotrienol stimulates the activities of PI3K, PKB, and ERK1/2, leading to increased survival in response to H_2O_2 *via* induction of the anti-apoptotic Bcl-2 protein [105].

Potential anti-proliferative and apoptotic effects of the tocotrienols have been described in several cell lines such as in both estrogen-responsive and estrogen-unresponsive human breast cancer cells. Complete suppression of growth is achieved at 8 μg/mL (in the estrogen-responsive) and at 20 μg/mL tocotrienol (in the estrogen unresponsive cells), in both the presence and absence of estradiol. The γ- and δ-tocotrienols are the most potent inhibitory forms [106]. Similar to that, the tocotrienols are more potent than the tocopherols in inhibiting proliferation and inducing apoptosis in the estrogen-responsive MCF7 and estrogen-non-responsive MDA-MB-435 human breast cancer cell lines in culture [107], as well as in preneoplastic and neoplastic mouse mammary epithelial cells [62,63,108]. Recent studies show that tocotrienol-induced apoptosis results from the activation of specific intracellular cysteine proteases (caspases) associated with death receptor activation and signal transduction (reviewed in [109]). The α- and γ-tocotrienols are effective against transplantable murine tumors (sarcoma 180, Ehrlich carcinoma, and IMC carcinoma), whereas α-tocopherol has

only a slight effect [110]. Using human Tenon's capsule fibroblast cultures as a model for a fibrotic response that can occur after glaucoma filtration surgery, the anti-proliferative and cytotoxic effects of the different vitamin E forms (α-tocopherol, α-tocopheryl acetate, α-tocopheryl succinate and α-tocotrienol) were compared with those of mitomycin C; besides mitomycin C, only α-tocotrienol significantly inhibits growth at non-toxic concentrations [111].

Similar to the tocopherols, the tocotrienols affect also the expression of a number of genes, including the cytochrome P_{450} metabolic enzyme, CYP3A4, *via* activation of the pregnane X receptor (PXR) [30]. α-Tocotrienol is the most effective vitamin E analogue for reducing endothelial expression of adhesion molecules and consecutive adhesion of monocytes [112]. Furthermore, the efficacy of α-tocotrienol for reduction of vascular cell adhesion molecule 1 (VCAM-1) expression and adhesion of THP-1 cells and monocytes to human umbilical vein endothelial cells (HUVECs) is 10-fold higher than that of α-tocopherol, and this is explained by a higher cellular uptake of α-tocotrienol in these cells [112-114]. The tocotrienols increase the transcription of the IkappaB kinase complex-associated protein (IKAP) mRNA in patients with familial dysautonomia, a neurodegenerative genetic disorder that is caused by mutations in the IKBKAP gene encoding IKAP. These findings suggest that *in vivo* supplementation with tocotrienols may elevate IKBKAP gene expression [115]. Supplementation with α-tocotrienol, but not with α-tocopherol, improves bone calcium content in vitamin E deficient rats, suggesting that the tocotrienols play also an important role in bone calcification [116].

2.3. Tocopheryl Quinones

The tocopherols are converted by oxidation to tocopheryl quinones, which upon reduction become tocopheryl hydroquinones (Table (**1**)). The reduction of α-tocopheryl quinone to α-tocopheryl hydroquinone occurs either *via* NADPH-cytochrome P_{450} reductase [117], NAD(P)H:quinone oxidoreductase 1 [118,119] or L-ascorbic acid [118], for the other tocopherols these pathways have not been tested. The tocopheryl hydroquinones can regenerate the tocopheroxyl radical and thus preserve α-tocopherol with different efficiencies (α > β > γ-tocopheryl hydroquinone) [120]. The ratio between α-tocopheryl quinone and α-tocopherol tends to be higher in mitochondrial inner membranes than in outer membranes suggesting α-tocopheryl quinone formation by respiratory oxidative stress *in vivo*. The comparison of the catalytic activities using short-chain homologues of α-tocopheryl quinone suggests some binding to enzymes of the electron transport chain, indicating that α-tocopheryl quinone potentially can interfere with mitochondrial electron transfer [121].

δ-Tocopheryl quinone and γ-tocopheryl quinone, but not α-tocopheryl quinone, are cytotoxic to cultured aortic smooth muscle cells, acute lymphoblastic leukaemia (ALL) cells and AS52 Chinese hamster ovary cells [122,123]. In HL-60 cells and colon adenocarcinoma WiDr cells, γ-tocopheryl quinone induces apoptosis *via* caspase-9 activation and cytochrome c release [124]. Furthermore, γ-tocopheryl quinone is mutagenic in AS52 cells whereas α-tocopheryl quinone is not, possibly giving an evolutionary advantage to organisms limiting γ-tocopherol, the precursor of γ-tocopheryl quinone [123]. *In vivo*, dietary α-tocopherol decreases genetic instability in the mouse mutatect tumor model, whereas γ-tocopherol has no effects [125].

Recently, the tocopherol associated protein (TAP/SPF) has been described to bind, in addition to several other ligands, α-tocopheryl quinone, and the structure of the complex has been resolved. However, the *in vivo* concentration of tocopheryl quinones (nanomolar) may not be sufficiently high to compete with other ligands of the TAP proteins (chapter 4), and it remains to be shown whether any of the effects seen with tocopheryl quinones are mediated *via* these proteins [88,126,127].

2.4. Tocopherol Metabolites

The selectivity of higher organisms for α-tocopherol has been impressively demonstrated in recent years by analysing the metabolism of vitamin E. Excess α-tocopherol and the other tocopherol and tocotrienol analogues are extensively metabolized before excretion. This finding suggests that the organism maintains the correct vitamin E level by selective retention of α-tocopherol, and by specific metabolism of all the other tocopherols, tocotrienols, and of the excess α-tocopherol. Interestingly, some of the tocopherol metabolites can also act as bioactive compounds, which can bind to transcription factors, membrane channels and enzymes and modulate their activity (see below). Several different metabolites of vitamin E have been described (Table (**1**)):

(I) Simon Metabolites

Initially, two major metabolites of α-tocopherol, the so-called Simon metabolites (tocopheronic acid and tocopheronolactone) were described (Fig. (**2**)) [128,129]. These metabolites have a shortened side chain, and their opened, oxidized, chroman structure is often quoted to demonstrate their antioxidant function *in vivo*. These metabolites are excreted in the urine as glucuronides or sulfates. The level of these metabolites increases markedly in the urine of healthy volunteers after a daily intake of 2-3 g *all rac*-α-tocopherol.

(II) Carboxyethyl Hydroxychromans (CEHCs)

Further analysis of the vitamin E metabolism in humans led to the discovery of a novel pathway of tocopherol metabolism (reviewed in [130,131]). Instead of Simon-metabolites, a compound with a shortened side chain but an intact chroman structure, α-carboxyethyl hydroxychroman (α-CEHC) (Fig. (**2**)), was identified after supplementation with *RRR*-α-tocopherol [132]. This metabolite is analogous to that of δ-tocopherol found previously in rats (δ-CEHC) [133], and that of γ-tocopherol identified in human urine and proposed as a natriuretic factor (γ-CEHC) [134]. The CEHCs can also act as antioxidants [135], however, the intact chroman structure of these CEHCs suggests that they are derived from tocopherols which have not reacted as antioxidants.

The proposed pathway of side-chain degradation of the tocopherols and tocotrienols includes first ω- and then β-oxidation, and proceeds *via* intermediate metabolites, e. g. the carboxymethylbutyl hydroxychromans (CMBHCs) (Fig. (**2**)) [133]. The initial step, the ω-hydroxylation of the side chain is catalyzed by the action of cytochrome P_{450} (CYP)-dependent hydroxylases, such as CYP3A and CYP4F2 [136-138]. Vitamin E activates the expression of the human pregnane X receptor (PXR) in a tocopherol specific manner, possibly depending on the extent the chromanol hydroxyl group is exposed: α-tocopherol activates weakly, whereas β-, γ-, and δ-tocopherol and the tocotrienols lead to stronger induction [30], whereas the tocopherol metabolic products do not activate (reviewed in [139]). PXR is involved in the drug hydroxylation and elimination pathways and activates genes such as cytochromes P_{450} (CYP), e.g. CYP3A and some ABC transporters [85]. Inhibitors of the CYP3A family, like sesamin and ketoconazole, inhibit the formation of γ-CEHC, and dietary intervention with sesame oils in humans leads to increased serum γ-tocopherol levels, suggesting that the tissue concentration of natural tocopherols could be increased by inhibiting their metabolism [136,140]. On the other hand, the induction of CYP3A by rifampicin results in an higher generation of the α-tocopherol metabolites in HepG2 cells [137]. α-CEHC excretion is augmented with increasing vitamin E intake after a threshold of plasma α-tocopherol has been exceeded [132].

The metabolites are known to have cellular effects *in vitro*, but since they occur at rather low concentrations in plasma (nM), it remains to be proven whether they perform an essential function *in vivo*. CEHCs accumulation may mediate anti-inflammatory and antioxidative effects or have other regulatory properties [26,141,142].

The metabolite of γ-tocopherol (γ-CEHC) has natriuretic activity by inhibition of the 70 pS potassium channel of the thick ascending limb of the loop of Henle, whereas the Na^+/K^+-ATPase is not inhibited. The analogous α-tocopherol metabolite (α-CEHC) shows no inhibition implying non-antioxidant mechanisms [143]. γ-CEHC inhibits also cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) synthesis in activated macrophages and epithelial cells, events that could change the cellular behaviour and affect gene expression [37,60]. In carrageenan-induced inflammation in male Wistar rats, administration of γ-tocopherol or γ-CEHC, but not α-tocopherol, reduces PGE2 synthesis at the site of inflammation, and inhibits leukotriene B4 formation, a potent chemotactic agent synthesized by the 5-lipoxygenase of neutrophils [38]. In prostate cancer cells, γ-tocopherol and γ-CEHC exert inhibitory effects on cyclin D1 expression with parallel retardation of cell proliferation [56]. Interestingly, the inhibition of cyclin D1 expression by γ-CEHC is competed for by α-CEHC suggesting a non-antioxidant mechanism. Both α-CEHC and γ-CEHC inhibit microglial PGE(2) production, nitrite production, and reduce iNOS mRNA and protein expression, but neither α- nor γ-tocopherol is effective in reducing these cytokine-stimulated inflammatory processes [142].

(III) Nitrated γ-Tocopherol and γ-CEHC

γ-Tocopherol can become nitrated to 5-NO_2-γ-tocopherol (Fig. (**2**)); however, the nitrated metabolite of γ-CEHC, 5-NO_2-γ-CEHC (Fig. (**2**)), does not occur in urine from healthy volunteers, as well as patients with coronary heart disease or type 2 diabetes, while γ-CEHC is abundant. The absence of 5-NO_2-γ-CEHC in the urine can therefore be explained by inefficient incorporation of 5-NO_2-γ-tocopherol into liver cells suggesting a possible alternative route for its metabolism [40]. In line with this, 5-NO_2-γ-tocopherol is poorly incorporated into HepG2 cells and therefore not metabolized. It is unknown whether 5-NO_2-γ-tocopherol or 5-NO_2-γ-CEHC exerts any cellular activity at higher concentrations.

3. SYNTHETIC VITAMIN E DERIVATIVES

Cells incubated with different natural vitamin E analogues or synthetic derivatives show striking differences in cellular response. Since the natural tocopherols and tocotrienols have essentially equal antioxidant activity, the differences seen among them can not be the result of scavenging free radicals. Similar to that, the synthetic derivatives with a modified -OH group have no chemical antioxidant activity in their non-hydrolyzed form. Thus, cellular differences seen with each vitamin E derivative can only be explained by specific non-antioxidant interactions with cellular signaling and gene expression pathways.

Commercially available vitamin E consists of either a mixture of naturally occurring tocopherols and tocotrienols, *RRR*-α-tocopherol (formerly called d-α-tocopherol), or synthetic racemic α-tocopherol, consisting of all possible combinations of R and S side-chain stereoisomers at equal amounts (*all rac*-α-tocopherol, formerly called dl-α-tocopherol). Some of these natural and the non-natural tocopherol isomers are excluded from the plasma and secreted with the bile [144,145]. The biological potency of natural-source vitamin E is 1.36 greater compared to its racemic counterpart produced by chemical synthesis. The biopotency differences between *RRR*-α-tocopherol and *all-rac*-tocopherol in the rat fetal resorption assay are mainly the result of the better recognition of *RRR*-α-tocopherol by the liver α-TTP and its selective enrichment in plasma; in line with this, *RRR*-α-tocopherol and *all-rac*-α-tocopherol essentially share an identical transcriptional activity, i.e. induce/repress the expression of the same set of genes [146,147].

Since the natural vitamin E analogues are relatively unstable and not soluble in water, several stabilized vitamin E derivatives (e. g. α-tocopheryl acetate, α-tocopheryl succinate, α-tocopheryl phosphate) (Fig. (**3**)) have been synthesized for usage in supplements and cosmetics. In addition to stabilization, their solubility, transport and metabolism may also be different. These stabilized tocopherol derivatives are modified at the -OH group of the chromanol ring and thus are not susceptible to oxidation. They are usually based on *RRR*-α-tocopherol, since this is the analogue which is selectively enriched by the liver α-TTP. Some of these stabilized esters of α-tocopherol can be considered to be pro-vitamins, since they are usually converted to the natural forms by intestinal or epidermal esterases and thus ultimately perform the same function in the body as the natural vitamin E. Once in the gut, the esters of vitamin E are split to their unesterified forms under the action of pancreatic and intestinal esterases and only the non-esterized tocopherols are efficiently taken up [148-151].

Many further vitamin E derivatives with modified -OH group have been synthesized and their cellular effects investigated. A list of synthetic tocopherol and tocotrienol derivatives and some of their tested properties is shown in (Table (**2**)). These molecules often act as completely novel compounds, are transported differently and have their own effects on cellular signalling, gene expression, proliferation and apoptosis [23,152-157]. The different cellular activity of these vitamin E derivatives may reflect their ability to interact with specific enzymes or proteins involved in their transport. Most of these derivatives are modified at the tocopherol-6-O position, it is often unknown to what degree these derivatives become hydrolyzed and to what degree they enhance or disrupt pathways usually targeted by the natural tocopherols.

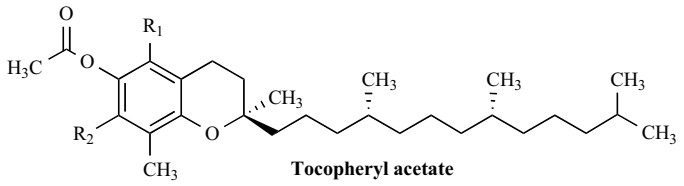
Another group of synthetic α-tocopherol derivatives is modified at the phytyl moiety. Trolox C (Fig. (**4**)), a water soluble derivative originally designed for food preservation, lacks the phytyl chain completely and is the most water soluble α-tocopherol derivative known. Another derivative of vitamin E, 2,2,5,7,8-pentamethyl-6-chromanol (PMCol) (Fig. (**4**)), inhibits growth of androgen-sensitive prostate carcinoma cells, which is due to the potent anti-androgenic activity of this compound [158]. PMCol and 2,2,5,7,8-Pentamethylchromane (PMC) (Fig. (**4**)) exerts anti-platelet aggregation activity by inhibiting cyclooxygenase activity, which leads to reduced prostaglandin thromboxane A2 (TxA2) formation, and finally inhibition of $[Ca_2^+]_i$ mobilization and ATP-release [159]. In PMCol, the phytyl chain is replaced by a single methyl group and thus it is less water soluble that Trolox C, but still more soluble than α-tocopherol. Troglitazone (Fig. (**4**)), a 2,4-thiazolidinedione and agonists of the peroxisome proliferators activated receptor gamma (PPARγ), contains a chromanol moiety similar to α-tocopherol able to scavenge free radicals, but besides that acts on several additional cellular targets [160]. The antioxidant activity of these derivatives in reducing hepatocytes lipid peroxidation and cytotoxicity has been measured to be in the order of PMCol > troglitazone > Trolox C > α-tocopherol > γ-tocopherol > δ-tocopherol [161]. When oxidized by non-toxic concentrations by H_2O_2/peroxidase, these derivatives also act as prooxidant and induce hepatocytes cytotoxicity in the order of troglitazone > Trolox C > δ-tocopherol > γ-tocopherol > α-tocopherol > PMCol [161]. Photo-excitation of α-tocopherol or PMCol generates tocopheroxyl radicals leading to singlet oxygen production and lipid peroxidation [162].

In the following the molecular and cellular activities of the three most commonly used and studied tocopherol derivatives, α-tocopheryl acetate, α-tocopheryl succinate and α-tocopheryl phosphate are summarized.

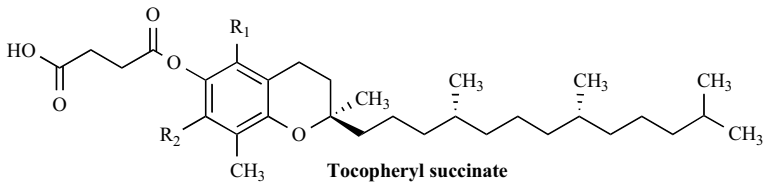
3.1. α-Tocopheryl Acetate (TA)

α-Tocopheryl acetate (Fig. (**3**)) is a stabilized vitamin E derivative commonly used in food supplements and cosmetics. It is rapidly converted to α-tocopherol by esterases and not many further cellular activities have been described for its unconverted form.

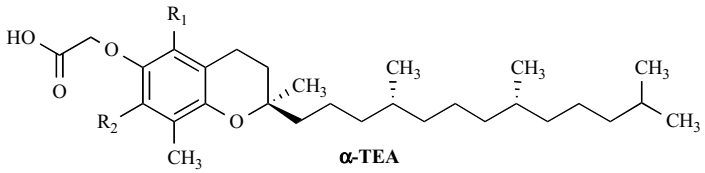
α-Tocopheryl acetate prevents the efflux of creatine kinase from normal rat skeletal muscles induced by treatment with the Ca^{2+} ionophore A23187. Since no reduction of non-enzymatic lipid



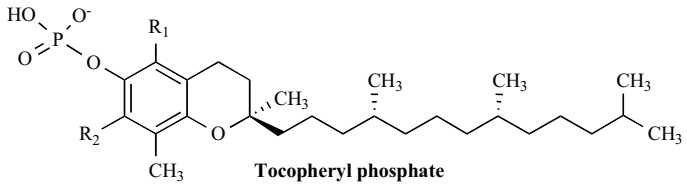
R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ



R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

Fig. (3). Structure of tocopheryl acetate, tocopheryl succinate, α-TEA, and tocopheryl phosphate.

peroxidation occurs by treatment with α-tocopheryl acetate, this effect is independent of free radical scavenging [163]. α-Tocopherol, and at high concentrations also α-tocopheryl acetate, is able to translocate diacylgylcerol kinase alpha (DAGKα) to the plasma membrane, again suggesting that an antioxidant effect is not necessary for this event [78]. Both, α-tocopherol as well as α-tocopheryl acetate protect against UVB-induced damage of keratinocytes by inhibiting of NF-κB activation, by increasing the stability of cell membranes, and by reducing DNA photodamage [164,165]. Although most studies show no adverse effects of dl-α-tocopheryl acetate [166], repeated direct injection into mouse and rats increases the incidence of transplantable tumours [167], and potentates the ability of 1,2-dimethylhydrazine dihydrochloride (1,2-DMH) to induce tumours in the intestine [168]. In p53 knockout mice, high doses of dl-α-tocopheryl acetate were recently associated with increase tumorigenesis, possibly by a pro-oxidative mechanism [169].

3.2. α-Tocopheryl Succinate (TS)

α-Tocopheryl succinate (Fig. (**3**)) has growth-inhibitory and apoptotic activity in a wide spectrum of *in vitro* and *in vivo* cancer models (including prostate, breast, neuroblastoma, mesothelioma, etc) and also acts as anti-inflammatory and anti-atherosclerotic agent (reviewed in [18,170-173]).

α-Tocopheryl succinate is a redox-silent derivative of α-tocopherol with potent pro-apoptotic activity. Interestingly, apoptosis induction by α-tocopheryl succinate is specific to malignant cells whereas normal cells are not affected. The higher apoptotic activity in malignant cells is due to the frequent absence of esterases in these cells, as well as to the higher cellular uptake efficiency. The pH in tumour cells is lower than in normal cells, thus favouring the accumulation of the protonated and un-charged α-tocopheryl succinate, whereas in normal cells at neutral pH, the charged, de-protonated form cannot easily pass the plasma membrane. Moreover, the uptake of α-tocopheryl succinate is enhanced by tocopherol binding proteins (such as TAP1), suggesting that the expression level of these proteins may play an additional role [15,16,174].

During the last years several studies addressed the molecular mechanisms involved in the induction of apoptosis by α-tocopheryl succinate. Generally, α-tocopheryl succinate affects membrane properties, leading to destabilization of lysosomes and mitochondria through sphingomyelinase activation [175]. These events ultimately lead to a number of apoptotic events, such as the release of cytochrome c, the production of reactive oxygen species (ROS), and the activation of pro-apoptotic proteins such as caspase 9 and the Bcl-2 protein family. α-Tocopheryl succinate exerts a cooperative pro-apoptotic activity with the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [176,177].

α-Tocopheryl succinate inhibits the proliferation and induces apoptosis of NIH3T3 cells stably transfected with oncogenic K-Ras and H-Ras, but not NIH3T3 cells expressing empty vector. α-Tocopheryl succinate treatment decreases Ras protein levels leading to down-regulation of the transcriptional targets of oncogenic Ras

Table 2. List of Synthetic Tocopherol Derivatives and Some of Their Tested Properties

Tocopherol Derivatives	Most Important Cellular Activities Tested
1) Side-chain modified derivatives	
Trolox C [157,240,241] (Fig. (4))	water soluble, does not induce apoptosis, antioxidant, modulates gene expression
Lactosylphenyl-Trolox, polylysine-Trolox, dextran-Trolox [242]	antioxidant
2,2,5,7,8-Pentamethylchromane (PMC) [158] (Fig. (4))	inhibition of proliferation, androgen receptor antagonist
2,2,5,7,8-Pentamethyl-6-chromanol (PMCol) [75,158,159,164] (Fig. (4))	inhibits NF-κB, reduces platelets aggregation by inhibiting cyclooxygenase, inhibits phospholipase, inhibits proliferation, androgen receptor antagonist
Vitamin E derivative with 4-substituted resorcinol moiety (TM4R) [291]	antioxidant, inhibition of tyrosinase
Phosphatidylchromanol (PCh) [292]	antioxidant
Troglitazone (CS-045) [160,243] (Fig. (4))	PPARγ agonist, antioxidant, several cellular effects
α-2-Geranylchromanol (α-T2H) [157]	apoptosis
2-(α-D-Glucopyranosyl)methyl-2,5,7,8-tetra-methylchroman-6-ol (TMG) [244]	water soluble, anti-inflammatory
(+/-)-(E)-2,5,7,8-Tetramethyl-2(4,8,12-trimethyl-trideca-1,3,5,7,11-pentaenyl)chroman-6-ol (FeAox-6) [245,246]	antioxidant
2RS-n-Alkyl-2,5,7,8-Tetramethyl-6-hydroxychromans [247]	side chain derivatives of different length and without methyl-branching. In the rat curative myopathy assay, the side chain length is important, methyl-branching not
Fluorescent tocopherols [213,214]	for tocopherol transport studies (chapter 3.5)
Mitochondrial-targeted tocopherols (MitoVitE) [206]	antioxidant, apoptosis, targeted to mitochondria (chapter 3.4)
2) Chromanol-ring modified	
4-Hydroxy-2,2,3,5,6-penta-methyl-benzoselenete and derivatives of it containing Selenium, Tellurium, Sulphur in 4-membered and 6-membered rings [248]	antioxidant
Oxachromanol and Twin-chromanol [249]	antioxidant
1-Thio-α-tocopherol [250]	less active than α-tocopherol in the rat curative myopathy assay
all-rac-2,4,6,7-Tetramethyl-2-(4',8',12'-trimethyltridecyl)-5-hydroxy-3,4-dihydrobenzofuran [251]	more active than α-tocopherol in the rat curative myopathy assay
3) OH-modified	
δ-Tocopheryloxycarbonyl-3-morpholinosydnonimine [252]	release of nitric oxide upon enzymatic activation
α-, and δ-Tocopheryl maleate (α-TOM and δ-TOM) [253]	apoptosis
α-Tocopheryl 2-methylsuccinate (α-TO2MS) [157], α-tocopheryl oxalate, α-tocopheryl pimelate, and α-tocopheryl succinate ethylester [293]	apoptosis
α-Tocopheryl glutarate (α-TOG) [157]	apoptosis
α-Tocopheryl 3-methylglutarate (α-TOG) [157]	apoptosis
α-Tocopheryl 3,3-dimethyl-glutarate (α-TO33DMG) [157]	apoptosis
α-Tocopheryl 2,2-dimethyl-glutarate (α-TO22DMG) [157]	apoptosis
α-, β-, γ-, δ-Tocopheryl succinate (α-, β-, γ-, δ-TOS) [157] (Fig. (3))	apoptosis, gene expression, signal transduction (chapter 3.2)
γ-Tocotrienyl succinate [157]	apoptosis
α-, and δ-Tocopheryl succinyl methyl ester (α-TOSM and δ-TOSM) [157]	apoptosis
α-Tocopheryl succinyl amide methyl ester (α-TASM) [253]	apoptosis
α-Tocopheryl succinyl amide (α-TAS) [253,254]	apoptosis
α-Tocopheryl maleyl amide (α-TAM) [253,254]	apoptosis
α-, and γ-Tocopheryl-2-phenylselenyl succinate [255]	apoptosis
γ-Tocotrienyl-2-phenylselenyl succinate [255]	apoptosis
α-Tocopheryloxybutyric acid [256,257]	apoptosis, PKB inhibition, p38 activation
6-O-Carboxypropyl-α-tocotrienol [258]	apoptosis
Tocopheryl acetate (Fig. (**3**))	pro-vitamin E (chapter 3.1)
Tocopheryl linoleate/oleate [166]	pro-vitamin E
5-Nicotinoxymethyl-α-tocopherylnicotinate [259]	anti-hypertensive
Tocopheryl nicotinate [151,166,260]	pro-vitamin E, anti-hypertensive
Potassium ascorbyl tocopheryl phosphate (EPC-K1) [166] and further derivatives between vitamin E and C, like vitamin CE [294] or other [295]	pro-vitamin E and pro-vitamin C, many studies with EPC-K1 acting as an antioxidant
Tocophersolan [166]	pro-vitamin E

(Table 2. Contd.)

Tocopherol Derivatives	Most Important Cellular Activities Tested
Dioleyl tocopheryl methylsilanol [166]	pro-vitamin E
3-Aminopropyl-DL-α-tocopheryl phosphate [246]	antioxidant
2,5,7,8-Tetramethyl-2R-4R,8R,12-trimethyltridecyl chroma-6-yloxyacetic acid (α-TEA) [171] (Fig. (3))	apoptosis, signal transduction and gene expression (Chapter 3.2)
α-Tocopherol polyethylene-glycol 1000 succinate [261-263]	water soluble pro-vitamin E, changes fibronectin distribution
Tocopheryl ferulate [154,264]	inhibition of melanogenesis, depigmentation, inhibition of tyrosinase
Tretinoin tocopheryl [265]	improves wound healing, increases expression of extracellular matrix proteins
Tocopherol-monoglucoside (TMG) [266]	radioprotection
d-α-Tocopheryl N,N-dimethyl-aminoacetate hydrochloride (TDMA) [267]	pro-vitamin E
Aminoalkanecarboxylic acid esters of d-α-tocopherol [268]	pro-vitamin E
Tocopherol with cationic substituents (phosphonium, sulfonium, acylhyrazinium) [269]	antioxidant
2,3-Dihydro-2,2,4,6,7-pentamethyl-3-(4-methylpiperazino) methyl-1-benzofuran-5-ol dihydrochloride (MDL74180) [270,271] and its R-(+)-enatiomer (MDL74722) [272]	water soluble, antioxidant, rapid brain penetration
3,4-Dihydro-6-hydroxy-N,N,N,2,5,7,8-heptamethyl-2H-1-benopyran-2-ethanaminium 4-methlybenzenesulfonate (MDL73404) [273,274]	water soluble, cardioselective, antioxidant
Hybrids of vitamin E with procainamide or lidocaine [275,276]	antioxidant
3,4-Dihydroxy-5R-2(R,S)-(6-hydroxy-2,5,7,8-tetramethyl chroman-2(R,S)yl-methyl)-1,3-dioxolan-4S-yl-5H-furan-2-one [277]	antioxidant combination of L-ascorbic acid with tocopherol
γ-Tocopheryl-N,N-dimethyl-glycinate hydrochloride (γ-TDMG) [278-280]	pro-vitamin E (converted to γ-tocopherol and to γ-CEHC), increased bioavailability in skin, inhibits tyrosinase activity, prevents photo-induced skin pigmentation
α-, β-, γ-, δ-Tocopheramine [281]	antioxidant
N-Methyl-α-tocopheramine [282]	antioxidant
dl-α-Tocopheryl glucoside [283]	inhibits histamine release
dl-α-Tocopheryl mannoside [283]	inhibits histamine release
dl-α-Tocopheryl galactoside [283]	pro-vitamin E
dl-δ-Tocopheryl glucoside [283]	pro-vitamin E
dl-δ-Tocopheryl mannoside [283]	pro-vitamin E
dl-δ-Tocopheryl galactoside [283]	pro-vitamin E
4) Side-chain and OH- modified	
Troloxoxycarbonyl-3-morpholinosydnonimine [252]	release of nitric oxide upon enzymatic activation
α-Trolox succinate (α-TroS) [157]	does not induce apoptosis
6-Acetyloxy-3,4-dihydro-N,N,N,2,5,7,8-heptamethyl-2H-1-benzopyran-2-ethanaminium, 4-methylbenzenesulfonate (MDL74270) and its derivative (MDL74366) [284]	cardioselective and antioxidant
5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetic acid (IRFI016, Raxofelast) [285]	antioxidant, anti-inflammatory, modulates gene expression, inhibits NF-κB, active metabolite is IRFI005 [286]
2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl acetic acid (IRFI948) [287]	antioxidant
Butanedioic acid, mono[2-[2-(acetylthio)ethyl]-2,3-dihydro-4,6,7-trimethyl-5-benzofuranyl] ester, (±) (IRFI042) [288,289]	antioxidant, anti-inflammatory, modulates gene expression
S-(-)-3,4-Dihydro-6-hydroxy-N,N,N-2,5,7,8-heptamethyl-2H-1-benzo pyran-2-ethanaminium 4-methylbenzene sulfonate (MDL74405) [290]	cardioselective and antioxidant
α-Tocopheryl succinate with various side chain length (TS-1, TS-2, TS-1, TS-5) [179]	apoptosis, inhibits Bcl-xl and Bcl-2 function
5) Side chain only	
Oleyl succinate (OS) and phytyl succinate (PYS) [157]	apoptosis

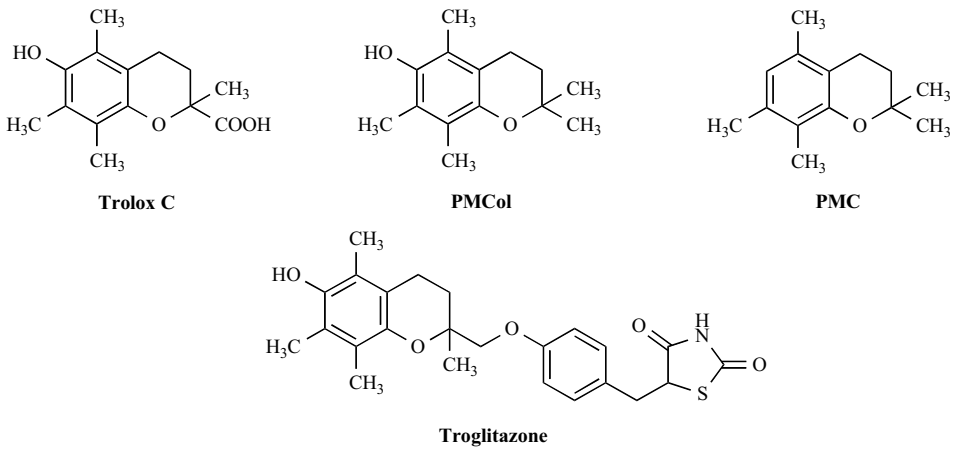


Fig. (4). Structure of the synthetic tocopherol derivatives, Trolox C, PMCol, PMC, and Troglitazone.

such as c-Myc, cyclin D1, and E2F1. Taken together, α-tocopheryl succinate down-regulates the Ras signalling pathways, and modulates Mek/Erk and phosphoinositide-3-kinase/PKB leading to inhibition of proliferation and survival of transformed cells [178]. A recent study suggests that the inhibition of Bcl-xL/Bcl-2 function represents a major pathway whereby α-tocopheryl succinate induces apoptosis in prostate cancer cells. α-Tocopheryl succinate disrupts the binding of the Bak BH3-peptide to Bcl-xL and Bcl-2 and reduces the association of Bcl-xL and Bcl-2 with Bak, leading to caspase-dependent apoptosis. Interestingly, docking studies of α-tocopheryl succinate into the Bak peptide-binding site suggest direct binding to Bcl-xL/Bcl-2 proteins, and two derivatives (TS-1 and TS-5) (Table **2**) with improved binding affinity show significantly higher potency in inhibiting Bak-peptide binding and in suppressing prostate cancer cell proliferation [179].

In addition to leading to cell death, α-tocopheryl succinate modulates several signal transduction and gene expression pathways. In lung epithelial cells, α-tocopheryl succinate inhibits cyclooxygenase 2 activity (COX-2) leading to less prostaglandin E2 (PGE2) production despite the lack of antioxidant activity [180]. α-Tocopheryl succinate increases AP1 activity, as measured by binding to the consensus DNA oligomer, by activating an AP1-promoter/luciferase reporter construct, or by assessing the mRNA expression of the AP1-dependent endogenous collagenase gene (MMP-1). Increased AP1 activity is due to elevated expression of c-jun mRNA and protein and a higher c-jun amino-terminal kinase activity [181]. α-Tocopheryl succinate increases the levels of biologically active TGF-β1, -β2, -β3 and of TGF-β type II receptor in human breast cancer cells (MDA-MB-435), what is possibly involved in the induction of apoptosis in these cells [182,183]. α-Tocopheryl succinate also suppresses NF-κB activation [164,184], activates PP2A leading to inhibition of PKCα [156], enhances Fas-mediated apoptosis [185], and deregulates the cell cycle transition by inhibition of cyclin A binding to E2F [186].

α-Tocopheryl succinate induces differentiation of human breast cancer cells as characterized by morphological changes, by induction of lipid droplets, by up-regulation of β-casein mRNA expression, and by down-regulation of Her2/neu protein. The treatment of cells with PD98059, a chemical inhibitor of mitogen-activated protein kinase kinase (MEK1/2), blocks the ability of α-tocopheryl succinate to induce differentiation [187]. Further studies show that MEK1, ERK1, the transcription factor c-jun, and the cyclin-dependent kinase inhibitor p21 (Waf1/Cip1) play a part in α-tocopheryl succinate-induced differentiation of human breast cancer cells [188].

Whereas the ester-linked succinate in α-tocopheryl succinate can be cleaved by cellular esterases, the non-hydrolysable ether linkage in the related α-tocopherol derivative α-TEA (*RRR*-α-tocopherol ether-linked acetic acid analogue, or 2,5,7,8-tetramethyl-2R- (4R,8R,12-trimethyltridecyl)chroman-6-yloxy acetic acid) (Fig. (**3**)) remains intact [189]. As a consequence, α-TEA has increased apoptotic activity compared to α-tocopheryl succinate in several cancer cell lines, including ovarian, breast, prostate, colon, lung, cervical, and endometrial tumor cells, and decreases tumor burden and metastasis in mouse cancer models [171]. α-TEA induces prolonged activation of c-Jun N-terminal kinase (JNK) and its substrate c-Jun, mediates a conformational change in Bax and triggers cleavage of Bid and caspases-8, -9 and -3 [190]. Morevoer, α-TEA decreases phosphorylation of protein kinase B (PKB) and extracellular signal-regulated kinase (ERK1/2), as well as cellular FLICE-like inhibitory protein (c-FLIP) and survivin protein levels [190].

3.3. α-Tocopheryl Phosphate (TP)

The phosphorylated form of α-tocopherol, α-tocopheryl phosphate (Fig. (**3**)), was synthesized already in the 50[ties]; however, only recently after developing a novel isolation method, it was shown to occur naturally in foods and in animal as well as in human tissues [191]. In some cases, the amounts of α-tocopheryl phosphate have been reported to be higher than free α-tocopherol, e. g. in chocolate and certain cheeses [191]. In animal tissues (including humans) the amounts of α-tocopheryl phosphate is of the same order of magnitude as that of α-tocopherol [191]. Furthermore, supplementation of the diet of rats with α-tocopheryl phosphate results in an increased deposition of α-tocopheryl phosphate and α-tocopherol in liver and adipose tissue [191] and no significant toxicity is observed in several animal models [192].

The natural occurrence of α-tocopheryl phosphate prompts a number of questions, ranging from the possibility that α-tocopheryl phosphate is a storage form of α-tocopherol to the hypothesis that it may represent an active compound or "second messenger" capable of exerting regulatory effects at a cellular level [193]. α-Tocopheryl phosphate has *per se* no antioxidant activity since it is phosphorylated at the chromanol -OH group, which in α-tocopherol is essential for the scavenging of free radicals. Despite that, it was suggested to reduce oxidative stress by preventing the propagation of free radicals in membranes from one polyunsaturated fatty acid to another, or possibly by interference with their enzymatic generation [194].

Several functions and activities have been suggested for α-tocopheryl phosphate; induction of hippocampal long term potentiation [195], protection of mouse skin against ultraviolet-induced damage [196], activation of cAMP phosphodiesterase [197], and activation of rat liver phenylalanine hydroxylase [198]. In human THP-1 monocytic leukaemia cells and rat aortic smooth muscle

cells (RASMC), α-tocopheryl phosphate is more potent than α-tocopherol in inhibiting CD36 mRNA and protein expression and cell proliferation [199]. Contrary to α-tocopherol, α-tocopheryl phosphate is cytotoxic to THP-1 monocytes at high concentrations [199]. Atherosclerosis progression and CD36 over-expression in hypercholesterolemic rabbits is better prevented by α-tocopheryl phosphate when compared to α-tocopheryl acetate [200]. The higher potency of α-tocopheryl phosphate may be due to a better uptake of the molecule and to its intracellular hydrolysis, providing more α-tocopherol to sensitive sites. Alternatively, a direct effect of the α-tocopheryl phosphate ester on specific cellular targets may be considered.

It seems possible that α-tocopheryl phosphate acts as a signaling molecule mediating some of the effects seen with α-tocopherol on gene expression and cellular signaling. In particular, it seems possible that α-tocopheryl phosphate plays a similar "second messenger" role as known for the phosphorylated forms of phosphatidylinositol, by attracting or preventing the access of enzymes such as kinases, phosphatases or NADPH-oxidase to the plasma membrane, leading to their activation/inactivation. In fact, low amounts of tocopherol may become phosphorylated and de-phosphorylated, suggesting that the inter-conversion may serve some cellular signaling functions. Preliminary results suggest that α-tocopherol can be phosphorylated in cell culture and animals [193,201], whereas other studies suggest that α-tocopheryl phosphate can be de-phosphorylated [193,196,201].

3.4. Mitochondria-Targeted Vitamin E Derivatives

The symptoms of ataxia with vitamin E deficiency (AVED) are similar to that of Friedreich's ataxia, a disease caused by defective expression of frataxin and the consequent increased mitochondrial oxidative damage and cell death [4]. The combined coenzyme Q(10) (400 mg/d) and vitamin E (2100 IU/d) therapy of patients with Friedreich's ataxia results in sustained improvement in mitochondrial energy synthesis that is associated with a slowing of the progression of certain clinical features and a significant improvement in cardiac function [202]. This implies that vitamin E is transported to the mitochondria, exerting there beneficial effects on disease progression. In fact, higher concentrations of vitamin E have been described in particular organelles, such as mitochondria as well as Golgi and lysosomes. Most α-tocopherol is located in the mitochondrial fractions and in the endoplasmic reticulum, whereas little is found in cytosol and peroxisomes [152]. In mitochondria, more α-tocopherol is found in the inner membrane (83.7 %) than in the outer membrane (14.3 %) [203]. Vitamin E is enriched at the soma-neurite junction where it may play a direct role in the regulation of adult hippocampal neurogenesis by acting as an exogenous factor [204]. This organelle and cell-compartment specific tocopherol distribution can be explained by specific cellular tocopherol transporters (chapter 4 and 5). In support for this, α- and γ-tocopherols are differently taken up in cultured human endothelial cells, suggesting specific tocopherol transporters and receptors for selective transport across the endothelial cell layer [205].

To increase the level of vitamin E in mitochondria, α-tocopherol was modified by coupling it with a lipophilic triphenylphosphonium cation through an alkyl linker (Table (**2**)), so that it is targeted to mitochondria and cancer cells [206]. The so modified tocopherol derivative easily permeates lipid bilayers, and is taken up into the cytoplasm and concentrated in mitochondria, driven by the plasma membrane potential (negative inside). In Friedreich's ataxia fibroblasts, cell damage can be more efficiently prevented by using such a mitochondria-targeted vitamin E derivative (MitoVitE) than by using α-tocopherol [207]. Superoxide-induced uncoupling is abolished by low concentrations of the mitochondrially-targeted antioxidants (MitoQ or MitoVitE), but is not affected by similar concentrations of the non-targeted antioxidants [208]. Similar to that, MitoQ or MitoVitE supplementation of endothelial cells mitigates peroxide-mediated oxidant stress and maintains proteasomal function with consequent inhibition of transferrin receptor-dependent iron uptake and apoptosis [209]. In ethanol-exposed cerebellar granule cells, MitoVitE mitigates ethanol-induced accumulation of intracellular oxidants and counteracts suppression of glutathione peroxidase/glutathione reductase (GSH-Px/GSSG-R) functions, of protein expression of gamma-glutamylcysteine synthetase (γ-GCS), and of total cellular glutathione (GSH) levels [210].

Contrary to the above results, TNFα-induced apoptosis is increased by MitoVitE by activating caspase 3 and by decreasing or delaying the expression of the protective anti-apoptotic proteins in U937 cells [211]. After acute perinatal hypoxic-ischemic brain injury, continuous MitoVitE was not significantly neuroprotective for striatal medium-spiny neurons, suggesting that mitochondrial oxidative damage does not contribute significantly to the death of these cells [212].

3.5. Fluorescent Vitamin E Derivatives

Sixteen fluorescent derivatives of α-tocopherol were prepared by incorporating different fluorophores at the terminus of omega-functionalized 2-n-alkyl-substituted chromanols (Table (**2**)). Two of these derivatives bind specifically and reversibly to recombinant human tocopherol transfer protein (α-TTP), and one of them (NBD-TOH) was further studied as probe for the ligand binding and intermembrane transfer activities of α-TTP [213,214]. In addition to these intracellular transport studies, these fluorescent tocopherol derivatives may be useful for *in vivo* transport studies of the tocopherols within peripheral tissues and their incorporation into lipoproteins.

4. INTRACELLULAR DISTRIBUTION OF VITAMIN E BY TOCOPHEROL BINDING PROTEINS

In the last decade, several proteins have been described that can bind the natural tocopherols, however, their role in intracellular distribution of the tocopherols remains to be shown in detail [215-219]. Among the human tocopherol binding proteins, only α-TTP, three human tocopherol associated proteins (hTAP1, hTAP2, hTAP3, also named sec14p-like 2, sec14p-like 3 and sec14p-like 4, respectively), and the albumin-related protein afamin present in plasma and the cerebrospinal fluid, have been cloned and shown *in vitro* to bind natural tocopherols with reasonable affinity [87,88, 126,220-224]. A yet uncloned 14.2 kDa tocopherol binding protein (TBP) was shown to enhance up to 10 fold the transport of α-tocopherol to the mitochondria [216].

The hTAP proteins may participate in the intracellular distribution of vitamin E and mediate tocopherol transport to the Golgi apparatus or to the mitochondria by means of their GOLD domain [87,225]. In fact, the hTAP1 protein increases the uptake of α-tocopherol and α-tocopheryl succinate into prostate and mesothelioma cells [15,16]. Moreover, the role of the hTAP proteins may be that of conferring specificity to the action of the different tocopherols, through recognition and selective transport to enzymes, transcription factors, nuclear receptors, or organelles. Indeed, the hTAP1 protein recognizes the different natural tocopherols with different specificity, and it is often not known whether these proteins bind and transport also the synthetic tocopherol derivatives [88]. Furthermore, the hTAP proteins bind squalene and several phospholipids (phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, and phosphatidic acid), and α-tocopherol can compete with these ligands, suggesting that lipid-dependent signaling may be modulated by the tocopherols *via* the hTAP proteins [87,126,226]. Taken together, the hTAP proteins may influence the intracellular and tissue tocopherol concentrations and modulate lipid-dependent signal transduction and gene expression [87,89]. In addition to that, in analogy with α-TTP in the liver, the related TAP

proteins may be involved in the incorporation of tocopherols into lipoproteins such as chylomicrons, LDL or HDL in peripheral cells.

5. CELLULAR IMPORT AND EXPORT OF VITAMIN E

Several proteins play a role in the uptake or distribution of natural vitamin E, whether the synthetic vitamin E derivatives are transported by the same route is often not known. The plasma phospholipid transfer protein (PLTP) enhances the vitamin E exchange between lipoproteins and between lipoproteins and cells [227]. PLTP-deficient mice show reduced vitamin E content associated in brain with elevated lipofuscin, cholesterol oxides and cellular peroxides [228], whereas in testes, reduced sperm motility and impaired fertility are observed [229]. These mice have increased levels of vitamin E in circulating apoB-lipoprotein containing lipoproteins at the expense of the vascular wall [230].

The cellular uptake of vitamin E transported by chylomicrons and LDL is mediated *via* the LDL-receptor, e.g. in liver, adipose tissues, adrenal glands, ovary, and kidney [231]. Vitamin E uptake transported by HDL is mediated by the scavenger receptor SR-BI, e. g. in enterocytes, in type II pneumocytes, as well has in the brain capillary endothelial cells forming the blood-brain barrier [232-236]. SR-BI-deficient mice have defective tissue uptake of α-tocopherol what may contribute to the reproductive, cardiovascular and neurodegenerative pathologies exhibited by these animals [237].

The cellular export and secretion of vitamin E occurs, apart from the α-TTP-mediated VLDL incorporation, also *via* ABCB4 (the P-glycoprotein transporter encoded by the multidrug resistance gene MDR2) [238], *via* ABCA1 [239], and *via* other not yet characterized processes. ABCA1 is an ATP-binding cassette protein that transports cellular cholesterol and phospholipids to lipid-poor high density lipoprotein (HDL) and apolipoproteins such as apoA-I [239]. Cells lacking an active ABCA1 pathway markedly increase secretion of α-tocopherol to apoA-I after overexpression of ABCA1.

CONCLUSIONS

Vitamin E is synthesized in plants as α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols, but only the tocopherols are efficiently absorbed in the proximal part of the intestine together with dietary lipids and bile, and later incorporated into chylomicrons. All four tocopherols are taken up with equal efficiency (30%) suggesting that at this level there is no selectivity. However, the plasma level of vitamin E reached by chylomicron transport by a normal diet is apparently not sufficient, so that the liver "α-tocopherol salvage pathway" evolved in higher organism, which selectively enriches *RRR*-α-tocopherol in VLDL, whereas the other tocopherol analogues are metabolized and excreted.

It is still unclear, whether the selection of *RRR*-α-tocopherol over the other analogues occurred with a specific reason, or whether one analogue, once selected, was sufficient to serve its cellular function. The selection of α-tocopherol may also reflect the dependency of the specific organism, in which the evolution of the "α-tocopherol salvage pathway" happened, on foods containing mainly α-tocopherol. Synthetic tocopherol derivatives, if not converted to the natural α-tocopherols, may not be recognized by the liver α-TTP protein, and thus may not reach the same concentrations as natural α-tocopherol. Nevertheless, these derivatives can influence cellular events, such as gene expression, signal transduction and apoptosis, possibly even at low concentrations. The many cellular effects of the tocopherol metabolites seen *in vitro,* still need to be confirmed *in vivo*.

The results summarized in this review strongly indicate that each natural vitamin E analogue and synthetic derivative can have its specific biological effects. Thus, the term vitamin E should only be used when also specifying the exact composition, and in the case of modified vitamin E derivatives, to what degree they are converted to the natural forms. Synthetic derivatives that are not or inefficiently converted to natural tocopherol analogues obviously should not be named vitamin E. At the molecular level, the different vitamin E analogues are modulating signal transduction and gene expression most likely by specific interactions of each analogue with specific enzymes, lipids, structural proteins and transcription factors, and these effects are often not linked to their antioxidant activity.

The many cellular activities of the natural tocopherols and tocotrienols reviewed in this article suggest that the selective retention of *RRR*-α-tocopherol is most likely the result of the desired antioxidant and non-antioxidant activities specific to this analogue. It is likely that the other natural tocopherol analogues have as well important activities at lower concentrations. At higher concentrations these analogues may interfere with the normal cellular performance, so that they are metabolized and excreted. All of these molecular and cellular activities may explain the health promoting effects described for vitamin E.

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