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Forum Review Article

Tocopherol-Binding Proteins: Their Function and Physiological Significance

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ABSTRACT

The present review is a continuation of earlier essays on the uptake mechanisms and the biological function of vitamin E. There are eight naturally occurring homologues of vitamin E, which differ in their structure and in biological activity *in vivo* and *in vitro*. Various studies have suggested that after normal gastrointestinal absorption of dietary vitamin E specific mechanisms favor the preferential accumulation of one of its homologues, α-tocopherol, in the human body. This process is thought to be mediated in part by the α-tocopherol transfer protein (α-TTP) in the liver cytoplasm. The mechanism and pathway by which α-TTP specifically incorporates α-tocopherol into plasma lipoproteins is not yet fully understood. Because α-tocopherol is widely distributed in tissues in various concentrations but α-TTP resides only in liver, its role as intracellular carrier of α-tocopherol seems unlikely. However, recent data indicate that a system of α-tocopherol-binding proteins is involved in these processes that favor the localization of α-tocopherol at the sites where it is required. The current status of the evidence for the regulation of α-tocopherol levels and their impact on cellular signaling is discussed. Antiox Redox Signal. 2, 397–404.

INTRODUCTION

VITAMIN E is one of the most researched compounds in medicine. It is an essential nutrient known to function as a chain-breaking antioxidant that prevents the propagation of free radical reactions in the human body (Burton *et al.*, 1983). It is essential, by definition, because the body cannot manufacture its own vitamin E and thus it must be provided by foods and supplements. The term vitamin E is actually a general name for the various chemical forms of this compound. In nature, molecules having vitamin E activity include two groups of closely related fat-soluble compounds, tocopherols and tocotrienols. The members of each group are designated as α, β, γ, or δ, depending on the numbers and position of the methyl groups attached to the chromanol ring structure (Kwiatkowska, 1988) (Fig. 1).

RRR-α-tocopherol and *RRR*-γ-tocopherol are the most common vitamin E homologs deriving mainly from diets rich in edible plant oils, vegetables, and fruits. Major sources for tocopherols are sunflower seeds, containing predominantly *RRR*-α-tocopherol, and oil from soybeans, which contain a mixture of γ-, δ-, and α-tocopherol (Crawley, 1993). Within the human body, all homologs of vitamin E encounter a rapid clearance from tissues and plasma with the exception of RRR-α-tocopherol (Traber and Kayden, 1989). Thus, the regulation of α-tocopherol levels in the plasma as well as the specific transport of α-tocopherol toward intracel-

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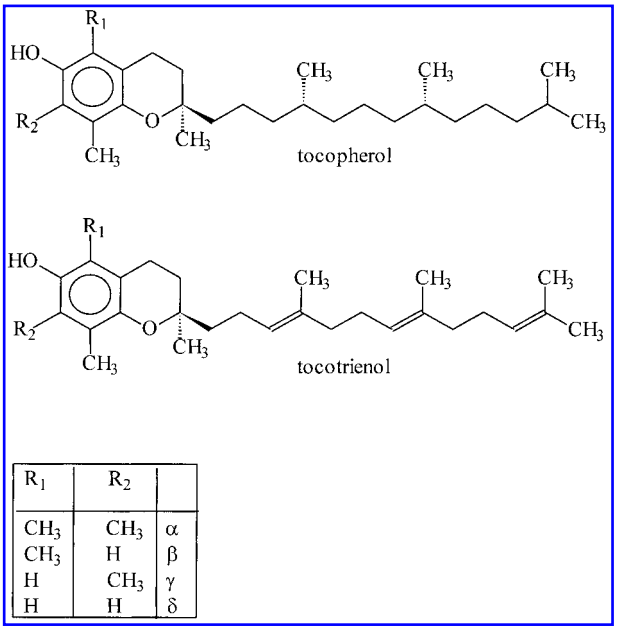

R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

FIG. 1. Naturally occurring components of vitamin E.

lular compartments may represent essential events in modulating the biological activity of this compound.

ABSORPTION, TRANSPORT, AND DISTRIBUTION OF VITAMIN E

Vitamin E requires, because of its hydrophobicity, special transport mechanisms in the aqueous environment of the plasma, body fluids, and cells (Buttriss and Diplock, 1988). In human vitamins, E is taken up in the proximal part of the intestine depending on the amount of food lipids, bile, and pancreatic esterases. Vitamin E is solubilized together with the fat-soluble components of the food. Lipolysis and emulsification of the formed lipid droplets leads then to the spontaneous formation of mixed micelles that are absorbed at the brush border membrane of the mucosa by passive diffusion (Gallo-Torres, 1970) (Fig. 2).

Together with triglycerides, phospholipids, cholesterol, and apolipoproteins, vitamin E is then reassembled to chylomycrons in the Golgi apparatus of the mucosa cells (Bjorneboe *et al.*, 1990). The chylomycrons are stored as secretory granula and eventually excreted by exocytosis to the lymphatic compartment, from where they reach the blood stream via the ductus thoracicus (Bjornson *et al.*, 1976). The rather high clearance rate (24–48 hr) of a bolus of vitamin E from the plasma and the concomitant rapid uptake by the liver parenchyma indicate that the intravascular degradation of the chylomycrons to remnants by the endothelial lipoprotein lipase (LPL) is a prerequisite for the hepatic uptake of vitamin E (Mathias *et al.*, 1981; Handelman *et al.*, 1985). Most probably, the exchange between apolipoproteins of the cylomycrons (type AI, AII, and B_{48}) and high-density lipoprotein (HDL) (types C and E) triggers the formation of the remnants and in this way favors their rapid uptake via hepatic receptors for apolipoprotein E (apo-E) and (apo-B) (Fig. 3).

LIVER α-TOCOPHEROL TRANSFER PROTEIN

In contrast to the unspecific uptake pathway of vitamin E from ingested food to the liver parenchyma, the transfer of α-tocopherol from the hepatic cells into plasma is mediated by a specific protein, the α-tocopherol transfer protein (α-TTP) (Arita *et al.*, 1995). This protein specifically selects α-tocopherol from all incoming tocopherols and promotes its transfer into lipoproteins (Hosomi *et al.*, 1997). It has

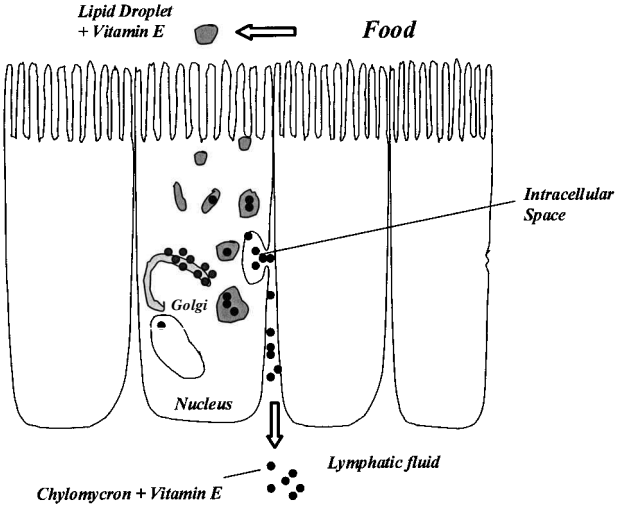

FIG. 2. Duodenal absorption of vitamin E from the food and its transport into the intestinal lymphatic fluid by exocytosis of the chylomycrons. (Adapted from Löffler and Petrides, 1997).

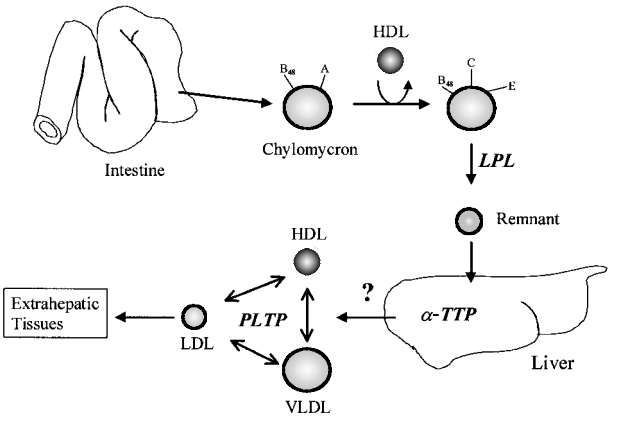

FIG. 3. Unselective hepatic uptake of vitamin E via remnants and subsequent selective transfer of α-tocopherol to extrahepatic tissues.

been suggested by several groups that α-tocopherol taken up by the liver is resecreted into the plasma in very low density lipoprotein (VLDL) (Peake *et al.*, 1972; Bjornson *et al.*, 1976). Nevertheless, it could be shown recently that α-TTP present in the liver cytosol functions to stimulate secretion of cellular α-tocopherol into the extracellular medium and that the reaction uses a novel non-Golgi-mediated pathway. It was concluded that this novel pathway may be linked to cellular cholesterol metabolism and/or transport (Arita *et al.*, 1997; Fragoso and Brown, 1998). α-TTP has been shown to possess both stereospecificity as well as regiospecificity toward the most abundant isomer of vitamin E, *RRR*-α-tocopherol. As consequence of the selectivity of α-TTP, major parts of the natural homologs and nonnatural isomers of α-tocopherol are excluded from the plasma and secreted with the bile (Traber and Kayden, 1989). Genetic defects in the hepatic α-TTP have been reported that have led to the discovery of a rare genetic disease, resulting in vitamin E deficiency (ataxia with isolated vitamin E deficiency, AVED) (Ouahchi *et al.*, 1995). AVED patients have very low plasma vitamin E concentrations and suffer from progressive peripheral neuropathy and ataxia (Amiel *et al.*, 1995). The highly tissue-specific pathology associated with AVED would suggest a tissue target of action rather than a general antioxidant function for vitamin E. Several studies have shown that α-TTP is expressed only in liver in significant amounts. Thus the incorporation of extracellular α-tocopherol into extrahepatic tissues would relate to a series of unknown transport processes (Fig. 3).

PHOSPHOLIPID TRANSFER PROTEIN AND LIPOPROTEINS

Because of its hydrophobicity, α-tocopherol is mainly transported in association with lipoproteins in the plasma compartment (Kayden and Traber, 1993). All plasma lipoproteins can constitute α-tocopherol vehicles, and the contribution of distinct lipoprotein fractions to α-tocopherol transport actually depends on their relative proportions in one given plasma sample (Desrumaux *et al.*, 1999). The plasma phospholipid transfer protein (PLTP), which is known to catalyze the exchange of phospholipids and other amphipatic compounds between lipid structures, has been reported to facilitate several fold the exchange of α-tocopherol between lipoproteins (Kostner *et al.*, 1995). The binding of tocopherol-containing lipoproteins to cells and the subsequent preferential uptake of LDL into these cells has been well documented. Using LDL and HDL labeled with [^{3}H]-α-tocopherol characteristics for receptor binding and cell uptake could be established (Gurusinghe *et al.*, 1988). It was shown that binding and uptake appear to be specific to LDL receptors whereas HDL, which also binds to cells, shows no evidence of internalization (Fig. 3).

Although a basal α-tocopherol uptake by muscle cells from both HDL and LDL has been observed, the receptor-mediated uptake appears to be about one order more effective (Cohn and Kuhn, 1989). These findings are supported by the fact that the highest α-tocopherol content of all subcellular compartments is found in lysosomes (14.6 mmol/mol lipid) (Buttriss and Diplock, 1988).

TOCOPHEROL-ASSOCIATED PROTEIN

Recently, a cytosolic tocopherol binding protein with broad tissue distribution has been discovered in our group (Stocker *et al.*, 1999). This

46-kD protein has been purified from bovine liver by conventional chromatographic methods using [^{3}H]-α-tocopherol. The corresponding human 46-kD protein has been identified, but its function is still unknown and therefore it has been given the name tocopherol-associated protein (TAP). So far, human TAP has been shown to be ubiquitous, but more highly expressed in adult liver, prostate, and brain tissue. Sequence homology of TAP ascribes it to a family of hydrophobic ligand binding proteins including α-TTP (Gu *et al.,* 1992). Another member of this family is phosphatidylinositol-transfer protein (SEC14). This protein catalyzes the transfer of phospholipids between membrane bilayers and plays an essential role in yeast Golgi function (Bankaitis *et al.,* 1990). A structural analysis of SEC14 obtained by X-ray diffraction provides insights in its function and new information concerning the architecture of the entire family of evolutionary conserved proteins (Sha *et al.,* 1998) (Fig. 4).

The structural homology of TAP with phosphatidylinositol-transfer protein (SEC14) and its broad tissue distribution make TAP a probable candidate responsible for the regulation of tissue α-tocopherol levels. Moreover, regulatory functions of this protein cannot be excluded at the present time and are the object of present studies.

PHYSIOLOGICAL SIGNIFICANCE OF VITAMIN E REGULATION

The mechanisms by which tissue specific levels and turnover rates of *RRR*-α-tocopherol are regulated still remain obscure. Nevertheless, the role of *RRR*-α-tocopherol in intracellular signaling has been intensively studied on different cellular levels in the last decade (Azzi *et al.,* 1998). RRR-α-tocopherol was identified as a cell-cycle specific negative regulator of cell proliferation in our group (Azzi *et al.,* 1997). Numerous experiments consistently show that *RRR*-α-tocopherol, but not *RRR*-β-tocopherol, inhibits proliferation of vascular smooth muscle cells from rats and humans at physiological concentrations, although both homologs are taken up at the same rate. The lack of inhibition by β-tocopherol cannot be explained by physicochemical arguments, since the relative

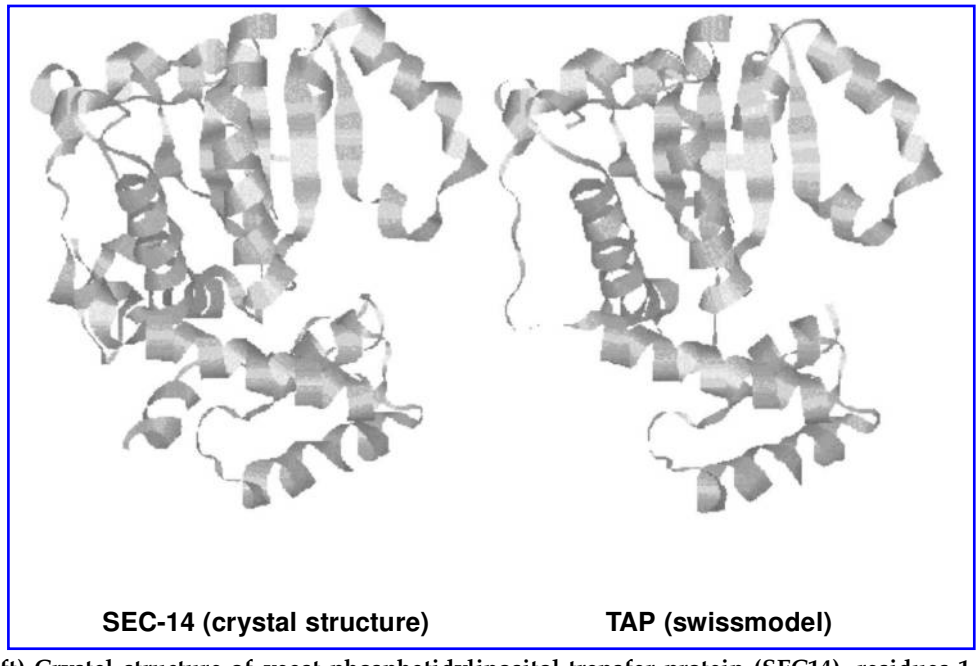

FIG. 4. (Left) Crystal structure of yeast phosphatidylinositol-transfer protein (SEC14), residues 1–246. (Right) Computational model (Swissmodel) of the three-dimensional structure of human TAP, residues 1–246.

free radical quenching efficiencies of both homologs are very similar (Kaiser *et al.*, 1990). The preferential uptake of α-tocopherol in the human body is accompanied by specific inhibition of protein kinase C (PKC), a key enzyme in the proliferative pathway of a number of cells (Boscoboinik *et al.*, 1991). PKC inhibition may be linked to the activity of protein-phosphatase 2A (PP2A). This phosphatase is stimulated by *RRR*-α-tocopherol in a dose-dependent way and may lead to the dephosphorylation and inactivation of PKC-α (Boscoboinik *et al.*, 1991). The data reported can be rationalized by a model in which α-tocopherol affects molecules, at the level of signal transduction, ending with the inhibition of cell proliferation. Platelet aggregation, monocyte adhesion, oxygen radical release from macrophages and neutrophils, and mesangial cell growth inhibition are examples of some of the consequences of PKC inhibition in different cells. Genes that directly or indirectly are under the control of this cascade are the gene of collagenase (MMP1), the gene of α-tropomyosin (Aratri *et al.*, 1999), and the gene for one of the scavenger receptors (CD36) (Ricciarelli *et al.*, 1999). Thus, it is reasonable to postulate a regulation system that controls vitamin E at cellular levels as well as a direct molecular interaction of α-tocopherol in analogy with the mechanisms involved in retinoid function (Morriss-Kay and Ward, 1999).

VITAMIN E REQUIREMENTS

Recent studies on the uptake, metabolism, and degradation of vitamin E have shown that synthetic all-rac-α-tocopherol, as well as the natural homologs of α-tocopherol, are preferentially degraded in humans (Traber *et al.*, 1998; Swanson *et al.*, 1999). Despite this known human preference for RRR-α-tocopherol, synthetic α-tocopherol (all-rac-α-tocopherol) is widely used in many types of medical preparations and food additives. A number of articles support the notion that an assessment of vitamin E requirements must be based on protective levels, preventing undesirable chronic lipid peroxidation, and not on suppressing signs of deficiency, which are infrequently seen in humans. Overt vitamin E deficiency occurs only rarely in humans and is caused by a genetic defect of the α-TTP (AVED) (Cavalier *et al.*, 1998) or as the result of various malabsorption syndromes (Traber and Sies, 1996). Severe vitamin E deficiency has also been reported in cases of Retinitis pigmentosa (Yokota *et al.*, 1996).

Apparently very little vitamin E is required by healthy adults (10–40 mg/day) to prevent nutritional deficiency (Weber *et al.*, 1997). However, possible effects of inadequate vitamin E intake may develop over a long time, typically decades, and have been linked to degenerative diseases such as atherosclerosis (Davey *et al.*, 1998) and with prostate cancer (Heinonen *et al.*, 1998). The Cambridge Heart Antioxidant Study (CHAOS) (Stephens *et al.*, 1996) reported in over 2,000 patients with angiographycally proven coronary atherosclerosis that vitamin E supplementation (400–800 IU/day) significantly reduced the incidence of cardiovascular death.

A decrease in lipid peroxidation of low-density lipoproteins (LDL), due to the antioxidant action of α-tocopherol, has been assumed to be the major mechanism leading to such a result. The discovery that LDL oxidation is a prerequisite for foam cell formation has led to the "oxidative modification hypothesis" of atherosclerosis (Witztum and Steinberg, 1991). According to this hypothesis, LDL traverses the subendothelial arterial space where it is subjected to oxidation. *In vitro* evidence indicates that once oxidized, LDL becomes a ligand for scavenger receptors, leading to foam cell formation. Oxidized LDL is also chemotactic for cultured monocytes (Quinn *et al.*, 1987) and stimulates cellular production of chemokines (Cushing *et al.*, 1990), potentially leading to inflammatory cell recruitment into the arterial wall. Thus, LDL oxidation triggers a number of events that can promote establishment and progression of atherosclerosis. Studies on cholesterol-induced atherosclerosis in rabbit have shown no protection by probucol but a strong protection by α-tocopherol, indicating a specific role for vitamin E (Ozer *et al.*, 1998). Recent studies in Watanabe heritable hyperlipidemic rabbits have shown that inhibition of aortic lipid peroxidation might not correlate with an antiatherogenic effect in this animal model (Wit-

ting *et al.,* 1999). These findings are in line with our observation that the major role of α-tocopherol is not in its action as antioxidant by preventing the oxidation of LDL, but by down-regulating the scavenger receptor, leading to a diminution of the uptake of oxidized LDL (Ricciarelli *et al.,* 2000). Nevertheless, the mechanisms by which vitamin E is transported and regulated within cells and how it is involved in cellular signaling still remain obscure. Furthermore, the possibility that α-tocopherol acts similarly to retinol derivatives is being considered. Recently, the major urinary metabolite (α-CEHC) of α-tocopherol has been discovered (Schonfeld *et al.,* 1993). It appears in human urine after vitamin E supplementation and is formed directly from α-tocopherol without previous oxidative splitting of the chromane ring. The correlation of tocopherol intake and urinary excretion of α-CEHC was examined in human volunteers supplemented with *RRR*-α-tocopherol in the range from 0 to 800 mg/day. The analysis revealed that α-CEHC is only excreted above a daily intake of 150 mg of α-tocopherol. This amount was interpreted as an indicator of plasma saturation by vitamin E (∼80 μM) and may be considered as marker of optimum vitamin E intake (Schultz *et al.,* 1995). If prevention of oxidative damage and promotion of an optimal health status are taken as end point, current estimates suggest that roughly an amount 10 times higher than that recommended to prevent symptoms of vitamin E deficiency is needed (Lemoyne *et al.,* 1987). In the light of our current knowledge, it might be reasonable to conclude that supplementation with *RRR*-α-tocopherol is preferable for human supplementation and prevention of disease.

ABBREVIATIONS

α-CEHC, α-Carboxyethylhydroxychroman; α-TTP, α-tocopherol transfer protein; phosphatidylinositol-transfer protein (SEC14); apo-E, Apolipoprotein E; AVED, ataxia with isolated vitamin E deficiency; CD36, platelet glycoprotein IV/thrombospondin receptor/class B scavenger receptor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, endothelial lipoprotein lipase; MMP1, matrix metalloproteinase I; PKC protein kinase C; PLTP, plasma phospholipid transfer protein; PP2A, protein phosphatase 2A; SEC, secretory protein gene products; TAP, α-tocopherol associated protein; VLDL, very-low-density lipoprotein.

REFERENCES

AMIEL, J., MAZIERE, J.C., BEUCLER, I., KOENIG, M., REUTENAUER, L., LOUX, N., BONNEFONT, D., FEO, C., and LANDRIEU, P. (1995). Familial isolated vitamin E deficiency. Extensive study of a large family with a 5-year therapeutic follow-up. J. Inherit. Metab. Dis. **18,** 333–340.

ARATRI, E., SPYCHER, S.E., BREYER, I., and AZZI, A. (1999). Modulation of alpha-tropomyosin expression by alpha-tocopherol in rat vascular smooth muscle cells. FEBS Lett. **447,** 91–94.

ARITA, M., NOMURA, K., ARAI, H., and INOUE, K. (1997). Alpha-tocopherol transfer protein stimulates the secretion of alpha-tocopherol from a cultured liver cell lines through a brefeldin A-insensitive pathway. Proc. Natl. Acad. Sci. USA **94,** 12437–12441.

ARITA, M., SATO, Y., MIYATA, A., TANABE, T., TAKAHASHI, E., KAYDEN, H.J., ARAI, H., and INOUE, K. (1995). Human alpha-tocopherol transfer protein: cDNA cloning, expression and chromosomal localization. Biochem. J. **306,** 437–443.

AZZI, A., ARATRI, E., BOSCOBOINIK, D., CLEMENT, S., OZER, N.K., RICCIARELLI, R., and SPYCHER, S. (1998). Molecular basis of alpha-tocopherol control of smooth muscle cell proliferation. Biofactors **7,** 3–14.

AZZI, A., BOSCOBOINIK, D., CLEMENT, S., OZER, N.K., RICCIARELLI, R., STOCKER, A., TASINATO, A., and SIRIKCI, O. (1997). Signaling functions of alpha-tocopherol in smooth muscle cells. Int. J. Vitamin Nutr. Res. **67,** 343–349.

BANKAITIS, V.A., AITKEN, J.R., CLEVES, A.E., and DOWHAN, W. (1990). An essential role for a phospholipid transfer protein in yeast Golgi function. Nature **347,** 561–562.

BJORNEBOE, A., BJORNEBOE, G.E., and DREVON, C.A. (1990). Absorption, transport and distribution of vitamin E. J. Nutr. **120,** 233–242.

BJORNSON, L.K., KAYDEN, H.J., MILLER, E., and MOSHELL, A.N. (1996). The transport of alpha-tocopherol and beta-carotene in human blood. J. Lipid Res. **17,** 343–352.

BOSCOBOINIK, D., SZEWCZYK, A., HENSEY, C., and AZZI, A. (1991). Inhibition of cell proliferation by alpha-tocopherol. Role of protein kinase C. J. Biol. Chem. **166,** 6188–6194.

BURTON, G.W., CHEESEMAN, K.H., DOBA, T., INGOLD, K.U., and SLATER, T.F. (1983). Vitamin E as an antioxidant in vitro and in vivo. CIBA Found. Symp. **101,** 4–18.

BUTTRISS, J.L., and DIPLOCK, A.T. (1988). The alpha-tocopherol and phospholipid fatty acid content of rat liver subcellular membranes in vitamin E and selenium deficiency. Biochim. Biophys. Acta **963,** 61–69.

CAVALIER, L., OUAHCHI, K., KAYDEN, H.J., DI DONATO, S., REUTENAUER, L., MANDEL, J.L., and KOENIG, M. (1988). Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. Am. J. Hum. Genet. **62,** 301–310.

COHN, W., and KUHN, H. (1989). The role of the low density lipoprotein receptor for alpha-tocopherol delivery to tissues. Ann. N.Y. Acad. Sci. **570,** 61–71.

CRAWLEY, H. (1993). *The Technology of Vitamins in Food,* vol 2. (Chapman & Hall Inc., Glasgow).

CUSHING, S.D., BERLINER, J.A., VALENTE, A.J., TERRITO, M.C., NAVAB, M., PARHAMI, F., GERRITY, R., SCHWARTZ, C.J., and FOGELMAN, AM., (1990). Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proc. Natl. Acad. Sci. USA **87,** 5134–5138.

DAVEY, P.J., SCHULZ, M., GLIKSMAN, M., DOBSON, M., ARISTIDES, M., and STEPHENS, N.G. (1998). Cost-effectiveness of vitamin E therapy in the treatment of patients with angiographically proven coronary narrowing (CHAOS trial). Cambridge Heart Antioxidant Study. Am. J. Cardiol. **82,** 414–417.

DESRUMAUX, C., DECKERT, V., ATHIAS, A., MASSON, D., LIZARD, G., PALLEAU, V., GAMBERT, P., and LAGROST, L. (1999). Plasma phospholipid transfer protein prevents vascular endothelium dysfunction by delivering alpha-tocopherol to endothelial cells. FASEB J. **13,** 883–892.

FRAGOSO, Y.D., and BROWN A.J. (1998). In vivo metabolism of alpha-tocopherol in lipoproteins and liver: studies on rabbits in response to acute cholesterol loading. Rev. Paul Med. **116,** 1753–1759.

GALLO-TORRES, H.E. (1970). Obligatory role of bile for the intestinal absorption of vitamin E. Lipids **5,** 379–384.

GU, M., WARSHAWSKY, I., and MAJERUS, P.W. (1992). Cloning and expression of a cytosolic megakaryocyte protein-tyrosine-phosphatase with sequence homology to retinaldehyde-binding protein and yeast SEC14p. Proc. Natl. Acad. Sci. USA **89,** 2980–2984.

GURUSINGHE, A., DE NIESE, M., RENAUD, J.F., and AUSTIN, L. (1988). The binding of lipoproteins to human muscle cells: binding and uptake of LDL, HDL, and alpha-tocopherol. Muscle Nerve **11,** 1231–1239.

HANDELMAN, G.J., MACHLIN, L.J., FITCH, K., WEITER, J.J., and DRATZ, E.A. (1985). Oral alpha-tocopherol supplements decrease plasma gamma-tocopherol levels in humans. J. Nutr. **115,** 807–813.

HEINONEN, O.P., ALBANES, D., VIRTAMO, J., TAYLOR, P.R., HUTTUNEN, J.K., HARTMAN, A.M., HAAPAKOSKI, J., MALILA, N., RAUTALAHTI, M., RIPATTI, S., MAENPAA, H., TEERENHOVI, L., KOSS, L., VIROLAINEN, M., and EDWARDS, B.K. (1998). Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial [see comments]. J. Natl. Cancer Inst. **90,** 440–446.

HOSOMI, A., ARITA, M., SATO, Y., KIYOSE, C., UEDA, T., IGARASHI, O., ARAI, H., and INOUE, K. (1997). Affinity for alpha-tocopherol transfer protein as a determinant of the biological activities of vitamin E analogs. FEBS Lett. **409,** 105–108.

KAISER, S., DI MASCIO, P., MURPHY, M.E., and SIES, H. (1990). Physical and chemical scavenging of singlet molecular oxygen by tocopherols. Arch. Biochem. Biophys. **277,** 101–108.

KAYDEN, H.J., and TRABER, M.G. (1993). Absorption, lipoprotein transport, and regulation of plasma concentrations of vitamin E in humans. J. Lipid Res. **34,** 343–358.

KOSTNER, G.M., OETTL, K., JAUHIAINEN, M., EHNHOLM, C., ESTERBAUER, H., and DIEPLINGER, H. (1995). Human plasma phospholipid transfer protein accelerates exchange/transfer of alpha-tocopherol between lipoproteins and cells. Biochem. J. **305,** 659–667.

KWIATKOWSKA, J. (1988). [Nomenclature of tocopherols and related compounds]. Postepy Biochem. **34,** 461–465.

LEMOYNE, M., VAN GOSSUM, A., KURIAN, R., OSTRO, M., AXLER, J., and JEEJEEBHOY, K.N. (1987). Breath pentane analysis as an index of lipid peroxidation: a functional test of vitamin E status. Am. J. Clin. Nutr,. **46** 267–272.

LÖFFLER, G., and PETRIDES, P.E. (1997). *Biochemie und Pathobiochemie,* 5. Auflage edn. (Springer-Verlag, Berlin, Heidelberg, New York).

MATHIAS, P.M., HARRIES, J.T., PETERS, T.J., and MULLER, D.P. (1981). Studies on the in vivo absorption of micellar solutions of tocopherol and tocopheryl acetate in the rat: demonstration and partial characterization of a mucosal esterase localized to the endoplasmic reticulum of the enterocyte. J. Lipid Res. **22,** 829–837.

MORRISS-KAY, G.M., and WARD, S.J. (1999). Retinoids and mammalian development. Int. Rev. Cytol. **188,** 73–131.

OUAHCHI, K., ARITA, M., KAYDEN, H., HENTATI, F., BEN HAMIDA, M., SOKOL, R., ARAI, H., INOUE, K., MANDEL, J.L., and KOENIG, M. (1995). Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein. Nature Genet. **9,** 141–145.

OZER, N.K., SIRIKCI, O., TAHA, S., SAN, T., MOSER, U., and AZZI, A. (1998). Effect of vitamin E and probucol on dietary cholesterol-induced atherosclerosis in rabbits. Free Radic. Biol Med. **24,** 226–233.

PEAKE, I.R., WINDMUELLER, H.G., and BIERI, J.G. (1972). A comparison of the intestinal absorption, lymph and plasma transport, and tissue uptake of tocopherols in the rat. Biochim. Biophys. Acta **260,** 679–688.

QUINN, M.T., PARTHASARATHY, S., FONG, L.G., and STEINBERG, D. (1987). Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. Proc. Natl. Acad. Sci. USA **84,** 2995–2998.

RICCIARELLI, R., ZINGG, J.M., and AZZI, A. (2000). Vitamin E reduces the uptake of oxidized LDL by inhibiting CD36 scavenger receptor expression. Circulation **102,** 82–87.

SCHONFELD, A., SCHULTZ, M., PETRIZKA, M., and GASSMANN, B. (1993). A novel metabolite of RRR-alpha-tocopherol in human urine. Nahrung **37,** 498–500.

SCHULTZ, M., LEIST, M., PETRZIKA, M., GASSMANN, B., and BRIGELIUS-FLOHE, R. (1995). Novel urinary metabolite of alpha-tocopherol, 2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply? Am. J. Clin. Nutr. **62,** 1527S–1534S.

SHA, B., PHILLIPS, S.E., BANKAITIS, V.A., and LUO, M. (1998). Crystal structure of the Saccharomyces cerevisiae phosphatidylinositol-transfer protein. Nature **391,** 506–510.

STEPHENS, N.G., PARSONS, A., SCHOFIELD, P.M., KELLY, F., CHEESEMAN, K., and MITCHINSON, M.J. (1996). Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet **347,** 781–786.

STOCKER, A., ZIMMER, S., SPYCHER, S.E., and AZZI, A. (1999). Identification of a novel cytosolic tocopherol-binding protein: structure, specificity, and tissue distribution. IUBMB Life **48,** 49–55.

SWANSON, J.E., BEN, R.N., BURTON, G.W., and PARKER, R.S. (1999). Urinary excretion of 2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman is a major route of elimination of gamma-tocopherol in humans. J. Lipid Res. **40,** 665–671.

TRABER, M.G., ELSNER, A., and BRIGELIUS-FLOHE, R. (1998). Synthetic as compared with natural vitamin E is preferentially excreted as alpha-CEHC in human urine: studies using deuterated alpha-tocopheryl acetates. FEBS Lett. **437,** 145–148.

TRABER, M.G., and KAYDEN, H.J. (1989). Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins. Am. J. Clin. Nutr. **49:** 517–526.

TRABER, M.G., and SIES, H. (1996). Vitamin E in humans: demand and delivery. Annu. Rev. Nutr. **16,** 321–347.

WEBER, P., BENDICH, A., and MACHLIN, L.J. (1997). Vitamin E and human health: rationale for determining recommended intake levels. Nutrition **13,** 450–460.

WITTING, P., PETTERSSON, K., OSTLUND-LINDQVIST, A.M., WESTERLUND, C., WAGBERG, M., and STOCKER, R. (1999). Dissociation of atherogenesis from aortic accumulation of lipid hydro-(pero)xides in Watanabe heritable hyperlipidemic rabbits. J. Clin. Invest. **104,** 213–220.

WITZTUM, J.L., and STEINBERG, D. (1991). Role of oxidized low density lipoprotein in atherogenesis. J. Clin. Invest. **88,** 1785–1792.

YOKOTA, T., SHIOJIRI, T., GOTODA, T., and ARAI, H. (1996). Retinitis pigmentosa and ataxia caused by a mutation in the gene for the alpha-tocopherol-transfer protein [letter]. N. Engl. J. Med. **335,** 1770–1771.

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1. Emmanuelle Reboul, Patrick Borel. 2011. Proteins involved in uptake, intracellular transport and basolateral secretion of fat-soluble vitamins and carotenoids by mammalian enterocytes. *Progress in Lipid Research* . [CrossRef]
2. Kishorchandra Gohil, Vihas T. Vasu, Carroll E. Cross. 2010. Dietary #-tocopherol and neuromuscular health: Search for optimal dose and molecular mechanisms continues!. *Molecular Nutrition & Food Research* **54**:5, 693-709. [CrossRef]
3. Kishorchandra Gohil, Saji Oommen, Hung T. Quach, Vihas T. Vasu, Hnin Hnin Aung, Bettina Schock, Carroll E. Cross, Govind T. Vatassery. 2008. Mice lacking #-tocopherol transfer protein gene have severe #-tocopherol deficiency in multiple regions of the central nervous system. *Brain Research* **1201**, 167-176. [CrossRef]
4. Antoni Sureda, Pedro Tauler, Antoni Aguiló, Nuria Cases, Isabel Llompart, Josep A. Tur, Antoni Pons. 2007. Antioxidant supplementation influences the neutrophil tocopherol associated protein expression, but not the inflammatory response to exercise. *Central European Journal of Biology* **2**:1, 56-70. [CrossRef]
5. S. Ekanayake-Mudiyanselage, J. J. Thiele. 2006. DieTalgdrüse als Transporter für Vitamin E. *Der Hautarzt* **57**:4, 291-296. [CrossRef]
6. Stefano Ginanni Corradini, Fausta Micheletta, Silvia Natoli, Massimo Iappelli, Emanuele Di Angelantonio, Rosanna De Marco, Walter Elisei, Maria Siciliano, Massimo Rossi, Pasquale Berloco, Adolfo Francesco Attili, Ulf Diczfalusy, Luigi Iuliano. 2005. High preoperative recipient plasma 7#-hydroxycholesterol is associated with initial poor graft function after liver transplantation. *Liver Transplantation* **11**:12, 1494-1504. [CrossRef]
7. Etsuo NikiNew Horizons in Vitamin E Research **20055781**, 217-223. [CrossRef]
8. Robert Gianello, Roksan Libinaki, Angelo Azzi, Paul D. Gavin, Yesim Negis, Jean-Marc Zingg, Phillip Holt, Hooi-Hong Keah, Annike Griffey, Andrew Smallridge, Simon M. West, Esra Ogru. 2005. #-Tocopheryl phosphate: A novel, natural form of vitamin E. *Free Radical Biology and Medicine* **39**:7, 970-976. [CrossRef]
9. UMA SINGH, ISHWARLAL JIALAL. 2004. Anti-inflammatory Effects of #-Tocopherol. *Annals of the New York Academy of Sciences* **1031**:1, 195-203. [CrossRef]
10. SWARNA EKANAYAKE-MUDIYANSELAGE, KLAUS KRAEMER, JENS J. THIELE. 2004. Oral Supplementation with All-Rac - and RRR -#-Tocopherol Increases Vitamin E Levels in Human Sebum after a Latency Period of 14-21 Days. *Annals of the New York Academy of Sciences* **1031**:1, 184-194. [CrossRef]
11. Jonathan Himmelfarb, Jane Kane, Ellen Mcmonagle, Eric Zaltas, Steve Bobzin, Sekhar Boddupalli, Stephen Phinney, Guy Miller. 2003. Alpha and gamma tocopherol metabolism in healthy subjects and patients with end-stage renal disease. *Kidney International* **64**:3, 978-991. [CrossRef]
12. A. J. O'Sullivan, Y. C. O'Callaghan, J. A. Woods, N. M. O'Brien. 2003. Toxicity of cholesterol oxidation products to Caco-2 and HepG2 cells: modulatory effects of?- and?-tocopherol. *Journal of Applied Toxicology* **23**:3, 191-197. [CrossRef]
13. Ute Obermuller-Jevic a, Lester Packer bVitamin E . [CrossRef]
14. J.A. Joseph, D.R. Fisher, J. Strain. 2002. Muscarinic receptor subtype determines vulnerability to oxidative stress in COS-7 cells. *Free Radical Biology and Medicine* **32**:2, 153-161. [CrossRef]
15. Sampath Parthasarathy, Nadya Khan-Merchant, Meera Penumetcha, Bobby V. Khan, Nalini Santanam. 2001. Did the antioxidant trials fail to validate the oxidation hypothesis?. *Current Atherosclerosis Reports* **3**:5, 392-398. [CrossRef]