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α-Tocopheryl Phosphate as a Bioactive Derivative of Vitamin E: A Review of the Literature

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ABSTRACT. α-Tocopheryl phosphate (α-TP) is a naturally occurring derivative of α-tocopherol (α-T), one of the eight isoforms of vitamin E. α-TP is present at very low intracellular concentrations, traffics across plasma membranes, and affects many important cellular functions. In addition to being a signaling molecule, α-TP has also been shown to possess antioxidant and potentially antiatherosclerotic properties that are more potent than its parent compound (α-T). However, there is little published data on the clinical effects of α-TP supplements, the mechanisms involved in its metabolism and cellular function, and reliable methods for its determination in plasma.

KEYWORDS. Antioxidant, atherosclerosis, α-tocopheryl phosphate, vitamin E

INTRODUCTION

α-Tocopheryl phosphate (α-TP) is the naturally occurring phosphorylated ester of vitamin E [α-tocopherol (α-T)]. Since its discovery (Ogru et al., 2003), α-TP has been the subject of increasing research in relation to its functional, biological, and pharmacological properties.

α-T is converted into α-TP by esterification by phosphoric acid of its 6-OH on its chroman ring (Figure 1). The kinase responsible for this phosphorylation is yet to be identified, but involvement of a tyrosine kinase in this reaction is likely given

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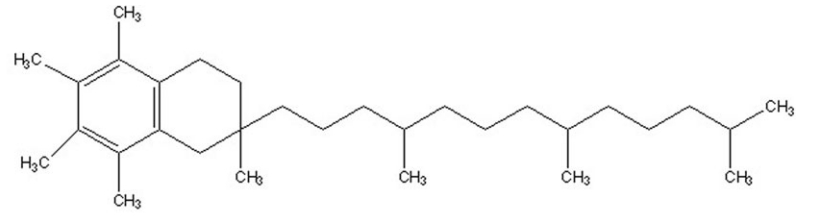
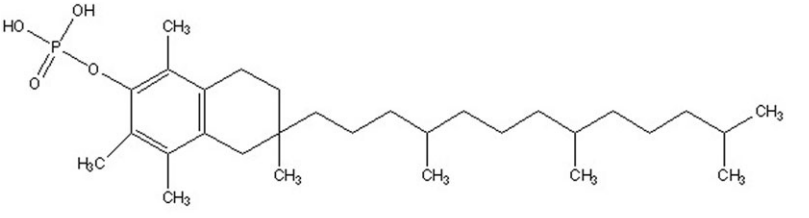


RRR-α-tocopherol



RRR-α-tocopheryl phosphate

FIGURE 1. Chemical structures of α-tocopherol and α-tocopheryl phosphate.

the role of the same kinase in the phosphorylation of γ-and δ-tocopherols (Negis et al., 2005).

α-TP was originally made synthetically in the 1940s. However, it was also found to exist as a naturally occurring compound, that was produced endogenously and readily hydrolyzed in adipose and hepatic tissues in man and other organisms (Ogru et al., 2003; Gianello et al., 2005; Libinaki et al., 2010; Negis et al., 2005; Rezk, van der Vijgh, Bast, & Haenen, 2007; Negis, Meydani, Zingg, & Azzi, 2007; Zingg & Vitamin, 2007; Zingg, Meydani, & Azzi, 2010a; Mukherjee, Lekli, Das, Azzi, & Das, 2008; Nishio et al., 2011). α-TP has also been shown to be synthesized in isolated cells in culture (Negis et al., 2005).

Hepatic and adipose tissues are the principal sites for the storage of tocopherols (TCs), and are also the main tissues containing endogenous α-TP (Gianello et al., 2005). However, it is unlikely that α-TP simply represents a storage form of α-T; only small amounts can be recovered from these tissues (Negis et al., 2005).

α-TP has been shown to traffic across plasma membranes and affect several important intracellular processes. In addition to being a signaling molecule, α-TP has also been shown to possess potentially toxic properties (Munteanu et al. 2004; Lirangi, Meydani, Zingg, & Azzi, 2012), and to be a more potent antioxidant than its parent compound (α-T) (Williams & Clapp, 1953; Amer, Zelig, & Fibach, 2008; Nishio et al., 2011). The present review aims to bring about the existing data on different aspects of α-TP studied to date including its structure, assay methods, and biological concentrations, as well as in vitro and in vivo findings on the biological actions of this vitamin E derivative.

SELECTION OF ARTICLES

PubMed-Medline and Google Scholar databases were searched to retrieve studies on the structure, assay and biological activities of α-TP in cell culture, animals and humans.

CHEMICAL STRUCTURE OF α-TP

Like other TC esters, α-TP possesses three structural domains: (1) a functional domain (domain I) that is the hydrophilic part of the molecule, (2) a signaling domain (domain II) that accounts for cell signaling activity, and (3) a hydrophobic domain (domain III) that allows α-TP to integrate into the cell membrane (Rezk et al., 2007). Esterification of α-TP at the 6-OH position of the chroman ring may be responsible for modifying several cellular functions including cell signaling, modulation of enzymatic activity, and oxidant-protected intracellular transport (Munteanu et al., 2004; Gianello et al., 2005). However, structure-function studies are yet to be conducted in order to elucidate the mechanism(s) by which 6-OH phosphorylation affects the functions described above.

The phosphate group of α-TP is not as flexible as that of other α-T esters. Since the length and flexibility of terminal carboxyl moiety is inversely associated with its apoptotic activity, the stability of α-TP could explain its antiproliferative and apoptotic effects (Rezk et al., 2007).

MEASUREMENT OF α-TP IN BIOLOGICAL SAMPLES

The stability of α-TP under alkaline conditions means that it is not converted into free α-T in the routine methods employed for the α-T assay. Alkaline treatment converts α-TP to a salt which is insoluble in organic solvents. Hence, standard assays for α-T cannot detect α-TP (Gianello et al., 2005). In order to detect α-TP in biological specimens, Ogru and colleagues introduced an acidification step in the extraction procedure. Acidification of the α-TP salt in the aqueous phase leads to the retrieval of free acid and subsequent trapping in the organic layer (Ogru et al., 2003). A proof-of-concept study validated the above method for the extraction of α-TP from liver and adipose tissue and subsequent quantification using electrospray mass spectrometry (ESMS), high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LCMS), and liquid chromatography tandem mass spectrometry (LCMS/MS) (Gianello et al., 2005). These data established that α-TP is a naturally occurring derivative of α-T. It is important to note that electrochemical detectors cannot be used for the quantification of α-TP as it lacks redox activity. α-TP may be identified using fluorescence detectors and, ideally, an MS-based method. The phosphate protected phenolic group of α-TP is chemically inert and thus resistant to chemical derivatization. This property eliminates the possibility of using gas chromatography-based methods for α-TP analysis (Birringer, 2010). Currently, HPLC is the technique most often used for the analysis of α-TP and other derivatives of vitamin E, and when coupled with fluorescence detection α-TP can be determined with a sensitivity as low as 20 nmol/l (Gianello et al., 2005).

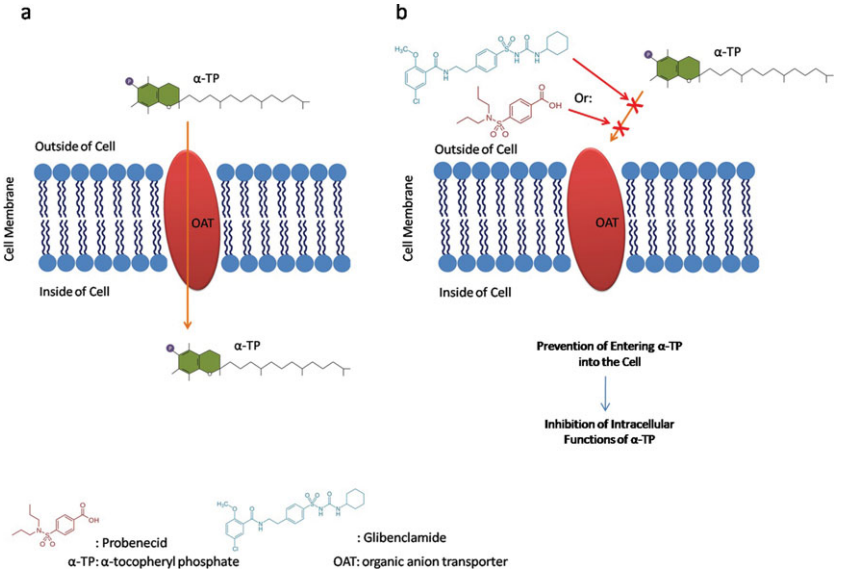


FIGURE 2. α-TP is transported across the cell membrane by a carrier-mediated system. The carrier is thought to be a member of the organic anion transporters (OAT) family (a). Intracellular transport of α-TP is inhibited by glibenclamide and probenecid leading to prevent α-TP-associated inhibition of cellular proliferation (b).

α-TP TRANSPORT ACROSS THE PLASMA MEMBRANE

When α-T derivatives enter the gut, pancreatic and intestinal esterases convert them to unesterified tocopherols which can then be absorbed and enter the plasma (Zingg, Meydani, & Azzi, 2010a). α-TP is an exception because it cannot be absorbed in large amounts (Zingg et al. , 2010a). It is transported across cell membranes by a carrier-mediated process. The carrier is thought to be a member of the organic anion transporters (OAT) family (Figure 2).

It is less likely that the cellular uptake of α-TP is mediated by an ATP binding cassette (ABC) transporter, as ABC transporters are involved in the cellular efflux of solutes while α-TP traffics in the opposite direction (Kim, 2003; Schiffer et al., 2003; Negis et al., 2007; Sekine, Miyazaki, & Endou, 2006). Intracellular transport of α-TP is inhibited by glibenclamide and probenecid. Furthermore, these compounds prevent α-TP-associated inhibition of cellular proliferation (Negis et al., 2007). This observation further corroborates the notion that intracellular uptake of α-TP is a prerequisite for its biological effects. Although α-TP appears to affect the expression and transcription of several genes following its entry into the cell (Munteanu et al., 2004; Lirangi et al., 2012), its intracellular disposition between the nucleus, cytoplasm, and other organelles requires further elucidation.

ENZYME ACTIVITIES AFFECTED BY α-TP

In vitro and in vivo studies have suggested that α-T and α-TP are interconvertible through the action of phosphorylation and dephosphorylation enzymes. While a kinase is essential to catalyze the synthesis of α-TP and a phosphatase in cells would be necessary to prevent overproduction (Negis et al., 2005; Negis et al.,

2007; Rezk et al., 2007; Zingg & Vitamin, 2007), the enzymes responsible for this inter-conversion are still unknown (Nishio et al., 2011). Negis et al. (2005) have reported that porcine intestinal alkaline phosphatase has an ability to hydrolyze α-TP. However, the activity of the enzyme would need to be low to avoid rapid and complete hydrolysis of α-TP as only a small proportion of α-TP has been shown to undergo dephosphorylation (Zingg et al., 2010b).

Because α-T and α-TP are hydrophobic and amphipathic molecules, respectively, they are mainly located in cell membranes. Therefore, it is believed that the presence of transporters and specific lipid transfer proteins are required to make them more accessible to modifications by kinases, phosphatases, and degrading enzymes. In addition, it is believed that these proteins are necessary to present α-T and α-TP to membrane domains and organelles, specific receptors, membrane transporters, and transcription factors (Zingg et al., 2010a).

α-TP inhibits glutathione S-transferase omega 1 in vitro, suggesting that it may possess a role in modulating the anti-inflammatory effects of α-T (Sampayo-Reyes & Zakharyan, 2006). Moreover, α-TP inhibits the activity of succinoxidase and restores oxygen consumption and metabolism in vitamin E-deficient muscles, while α-T does not possess such properties (Houchin, 1942; Houchin & Mattill, 1942; Jacobi et al., 1950a, 1950b). α-TP also inhibits diphosphopyridine nucleotidase (DPN), suppressing succinoxidase activity by the promotion of oxalocetate by malic dehydrogenase (Govier & Jetter, 1948). α-T and α-TP are also able to activate diphosphopyridine nucleotide- and succinate cytochrome c reductase (Detwiler, Garrett, & Nason, 1966). Furthermore, α-TP inhibits several other enzymes, including: glutathione S-transferase omega (Sampayo-Reyes & Zakharyan, 2006), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) phosphodiesterase (Sakai, Okano, Makino, & Tsudzuki, 1976), and mitochondrial succinate oxidase of complex II (Rabinovitz & Boyer, 1950). α-TP also stimulates rat liver phenylalanine hydroxylase leading to the conversion of L-phenylalanine to L-tyrosine (Abita, Parniak, & Kaufman, 1984).

THE FUNCTIONS OF α-TP (Figure 3)

α-T and α-TP may be present in some tissues at similar concentrations, but α-TP has been reported to possess some more potent biological activities compared to α-T (Rezk et al., 2004, 2007). One possible explanation for the more potent biological activities of α-TP over α-T is its greater stability and water solubility (Mukherjee et al., 2008).

Early studies on the functions of synthetic α-TP were performed nearly 60 years ago. One of these studies indicated the effect of α-TP in suppression of erythrocyte hemolysis and oxidative stress in paroxysmal nocturnal hemoglobinuria (Williams & Clapp, 1953; Amer et al., 2008). More recently, it has been proposed that α-TP plays a role in cellular signaling, or as a lipid messenger, involved in modulating signal transduction and gene expression (Negis et al., 2007; Zingg & Vitamin, 2007; Birringer, 2010). Furthermore, Negis et al. (2005) have reported that α-TP is produced in mast cells and primary cells derived from human coronary artery, and they have suggested that α-TP might have a regulatory function. Negis et al. (2007) speculated that α-TP modulates some cellular and enzymatic events such as signal transduction, gene expression, and inhibition of proliferation possibly via

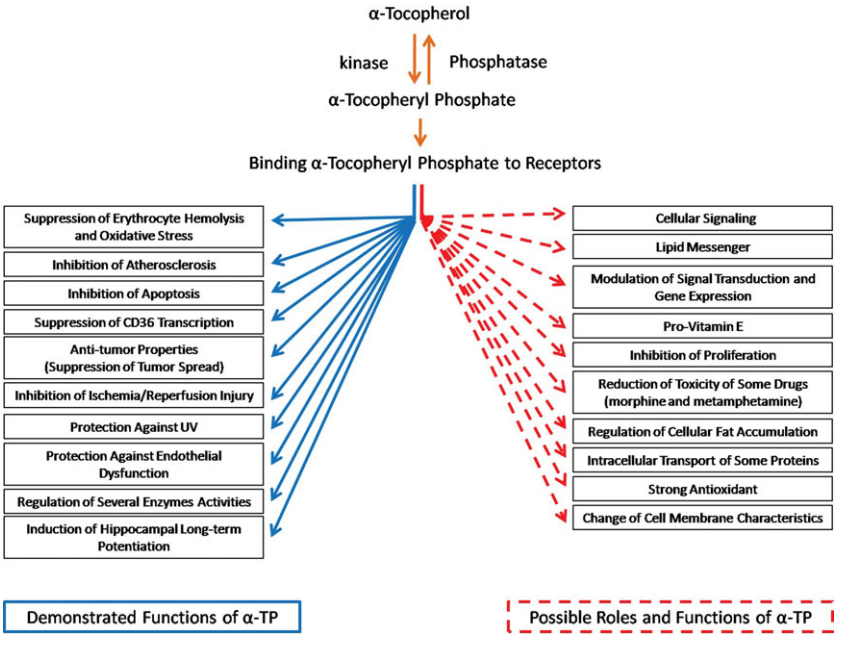


FIGURE 3. Established functions (blue arrows) and potential roles and functions (red arrows) of α-tocopheryl phosphate.

binding to a specific protein which recognizes α-TP as a unique signal. This has been supported by using two inhibitory drugs, glibenclamide, and probenecid. The modulation of signal transduction pathways by α-TP is still relatively poorly understood and has not been comprehensively investigated by mechanistic and molecular studies. However, α-TP does appear to be involved in the conversion of a death signal into survival signal in cardiomyocytes by inhibiting apoptosis (Mukherjee et al., 2008).

BIOLOGICAL ACTIVITIES OF α-TP

The concentration of α-TP in human plasma has been reported to be 28 ± 19 nmol/l (Zingg et al., 2010b; Nishio et al., 2011). In rat liver tissue, the concentration of α-TP was reported to be in the order of 0.1 μg/g and that of α-T around 10 μg/g liver (Gianello et al., 2005). However, it is clear that further data are required in order to obtain reliable values for the plasma and tissue concentrations of α-TP under physiological conditions.

Several medicinal and pharmacological properties have been reported for α-TP including: the inhibition of ischemia/reperfusion injury and atherosclerosis; the induction of hippocampal long-term potentiation possibly involved in memory and learning (Xie & Sastry, 1993; Zingg et al., 2010a; Zingg et al., 2010b); the regulation of the activity of several enzymes and modulation of proliferation, apoptosis, signal transduction, and gene expression (Zingg et al., 2010b); antitumor properties, protection of keratinocytes against ultraviolet-induced damage (Nakayama et al., 2003); and a reduction of morphine- and methamphetamine-induced toxicity (Ito et al., 2007; Mori et al., 2007) (Table 1).

TABLE 1. Summary of the Reported Biological Effects of α-TP in vitro and in vivo

Biological Effects	Test Model	Reference
In vitro		
Increase in phenylalanine hydroxylase activity	Isolated rat liver	Rezk et al. (2007)
Protection against UV-B triggered skin damage	Cultured mouse skin	Ricciarelli et al. (2007); Nakayama et al., 2003
Inhibition of the transcription of the scavenger receptor CD36 (ox-LDL receptor)	HCASMC	Catalgol & Ozer (2012)
Prevention of damage induced by UV-B	Rat intestinal sections	Felemovicius et al. (1995)
Repression of invasion fibrosarcoma cells; attenuation; intracellular reactive oxygen; suppression of cell motility or adhesion to extracellular matrix; induction of diagnostic morphological changes; exertion of anti-invasive activities	Human fibrosarcoma HT-1080 cells	Saitoh, Yumoto, & Miwa (2009)
Inhibition of ischemia/reperfusion injury and atherosclerosis, regulation of the activity of several enzymes, modulation of proliferation, apoptosis, signal transduction, and gene expression	THP-1 monocytes	Ito, Mori, Kanazawa, & Sawaguchi (2007)
Mitigation of glutamate-induced cytotoxicity; mitigation of oxidative stress	Mouse primary cortical neuronal cells	Detwiler et al. (1966)
Protection against various type of skin damage; Enhancement of skin moisture-retention	Mouse skin and normal human epidermal keratinocytes in vitro	Sakai et al. (1976); Kato et al., 2011
Activation of genes: *TRB3*, *SESN2* and *INSIG1* preventing fat accumulation of them; inhibition of the same genes in differentiated adipocytes facilitating the uptake and storage of fat	NIH3T3-L1 preadipocytes	Guarnieri, Giordano, Muscari, Grossi, & Caldarera (1996)
In vivo		
Biological Effects	Test Model	Reference
Inhibition of the succinoxidase activity	Homogenates of the muscle and liver of normal albino rats	Sampayo-Reyes & Zakharyan (2006)
Inhibition of malic oxidase system including cytochrome *c*, and cholinesterase; increasing the activity of catalase	Adult albino rats	Schiffer et al. (2003)
Effective protection against gamma-irradiation	In rat heart, muscle, liver and brain	Pérez-Pé, Cebrián-Pérez, Muiño-Blanco (2001)
Protection against acute irradiation (x-irradiation) enteritis	In rat mid-small bowel	Paranich et al. (1993)

(Continued on next page)

TABLE 1. Summary of the Reported Biological Effects of α-TP in vitro and in vivo *(Continued)*

Biological Effects	Test Model	Reference
Improvement of acetylcholine-dependent relaxation in the aged	Rat aortic strips exposed to oxidative stress	Sekine et al. (2006)
Improvement of sperm survival	Rat spermatozoa	Williams & Clapp (1953)
Mitigation of lipid peroxidation	Rat liver microsomes	Xie & Sastry (1993)
Reduction of atherosclerotic lesion progression; reduction of CD36 expression	In rabbits	Rabinovitz & Boyer (1950)
Free radical scavenging: attenuation of morphine-induced withdrawal syndrome	Mouse	Mori et al., 2007
Cardioprotection and reduction of myocardial reperfusion injury	Rat heart	Brase & Westfall (1972)
Induction of Akt and Bcl-2 activation;Reduction of pro-apoptotic factor c-Src (Src kinase)	Rat heart	Brase & Westfall (1972)
Protection against vascular dysfunction occurred by cholesterol diet; decrease in plasma levels of key pro-inflammatory cytokines and markers (IL-1β, IL-6, IL-8, TNF-α, CRP and PAI-1)	In rabbits	Birringer (2010)
Suppression of glutamatergic and GABAergic transmission	In rodent hippocampus	Ogru et al. (2004)
Skin protection; reduction of UVB-induced damage and PGE2 production	Hairless mice	Kato & Takahashi, 2012; Kato et al., 2011
Induction of VEGF expression, angiogenesis, and vasculogenesis	in the placenta	Zingg, Meydani, & Azzi (2012)

UV-B: ultraviolet B; LDL: low-density lipoprotein; HCASMC: human coronary artery smooth muscle cells; TRB3: Tribbles Homolog 3; SESN2: sestrin-2; INSIG1: Insulin-Induced Gene 1; IL-1β: interleukin-1β, IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-α, CRP: C-reactive protein; PAI-1: plasminogen activator inhibitor-1; GABA: gamma-amino butyric acid; PGE2: prostaglandin E2; VEGF: vascular endothelial growth factor.

IN VITRO FINDINGS

During atherogenesis, phagocytic monocytes actively uptake atherogenic lipoproteins such as low-density lipoprotein (LDL) and turn into foam cells. This process is mediated by the action of different receptors. Among these, scavenger receptor CD36 is of special importance due to its affinity for oxidized LDL (oxLDL) and internalization of this atherogenic molecule into a variety of cells such as macrophages, monocytes, endothelial cells and cultured human aortic smooth muscle cells (Catalgol & Ozer, 2011). α-T has been found to modulate signaling cascades and gene expression in vitro in macrophages and smooth muscle cells, potentially protecting against atherosclerosis and other inflammatory states (Munteanu et al., 2004). These effects of α-T may be attributed, at least partly, to the down-regulation of CD36 mRNA and protein expression (Munteanu et al., 2004), which can limit the uptake of oxLDL and subsequent foam cell formation and reactive oxygen species (ROS) generation. α-TP can also suppress the transcription of the oxLDL receptor, CD36, in human coronary artery smooth muscle cells but with a

markedly higher (40 folds) potency (Negis et al., 2005). α-TP affects the expression of CD36 on the cell surface (Zingg et al., 2010b). As mentioned before, these effects of α-TP are greater than those of α-T (Munteanu et al., 2004).

Lirangi et al. (2012) have reported that α-TP activates a set of genes including TRB3 (Tribbles Homolog 3), sestrin-2 (SESN2), and Insulin-Induced Gene 1 (INSIG1)] in NIH3T3-L1 preadipocytes, thereby potentially preventing fat accumulation in these cells. However, α-TP also inhibits the transcription of the same genes in differentiated adipocytes which may facilitate the uptake and storage of fat. Such a dual effect of α-TP on proliferating preadipocytes and differentiated adipocytes may have implications in the prevention of lipotoxicity, the regulation of fat accumulation, and obesity (Lirangi et al., 2012). The transportation of α-TP has been shown to involve intracellular transport proteins, e.g., tocopherol associated proteins (TAPs), which have also been shown to increase the transport of the synthetic vitamin E derivative, α-tocopheryl succinate, into the cell (Negis et al., 2007).

There has been evidence indicating the antiproliferative effects of α-TP. Munteanu et al. (2004) reported inhibitory effects of TPm on the proliferation of rat aortic smooth muscle cells and human THP-1 monocytic leukaemia cells. These antiproliferative activity of TPm was more potent compared with α-T. These findings were further confirmed in cultured mouse NIH3T3-L1 preadipocytes, where α-TP was found to possess greater cytotoxic properties compared with α-T, suggesting antiproliferative mechanisms other than conversion to the parent compound (Lirangi et al., 2012). Likewise, it has been shown that the growth inhibitory effects of TPm, at least at low concentrations, is not the result of apoptosis induction (Munteanu et al., 2004). One potential mechanism for the antiproliferative effects of α-TP is via the down-regulation of 20 S proteasome activity, an effect that has not been observed with α-T succinate. Using THP-1 monocytes, Munteanu et al. (2004) found that α-TP inhibits proteasome activity and upregulates p53 and p27Kip1, proteins that block the cell cycle (Ricciarelli, Massone, & Zingg, 2007).

α-TP has been reported to be a strong antioxidant, protecting biomembranes against lipid peroxidation. α-TP may also act indirectly by changing characteristics of the cell membrane including its curvature, the formation of lipid rafts, and fluidity (Royer et al., 2009). Reduction of cell membrane fluidity by α-TP causes erythrocyte hemolysis in a pH-dependent manner (Rezk et al., 2007).

In an investigation on the interactions of α-T and α-TP with the cannabinoid system in the rodent hippocampus, it was reported that these compounds affect glutamatergic and gamma-amino butyric acid (GABA)ergic transmission in opposing directions. α-T stimulates these neurotransmissions while α-TP suppresses them, and the effect of both compounds is mediated by cannabinoid receptors (CB1Rs) (Crouzin et al., 2011). α-TP and α-T do not directly bind CB1R but reduce depolarization-induced inhibition of excitation and CB1R agonist-mediated hypothermia (Crouzin et al., 2011).

IN VIVO FINDINGS

Mukherjee and colleagues showed that α-TP confers significant cardioprotection in the rat heart by decreasing cardiomyocyte apoptosis and infarct size as well as

improving ventricular performance in a model of myocardial ischemia (Mukherjee et al., 2008). The antiapoptotic effects of α-TP were accompanied by an upregulation of p42/44 extracellular signal-regulated kinase (ERK) kinase and p38 mitogen-activated protein kinaseβ (MAPKβ) and a reduction of the proapoptotic proteins p38 MAPKα and c-Jun N-terminal kinase (JNK). α-TP treatment was also associated with a decrease in the phosphorylation of proapoptotic c-Src (Mukherjee et al., 2008). Furthermore, α-TP increased the DNA binding of the redox-sensitive transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and potentiated the activation of antideath protein B-cell lymphoma 2 (Bcl-2) and survival signaling protein Akt (Mukherjee et al., 2008). Mukherjee et al. (2008) also reported that α-TP has the ability to ameliorate myocardial ischemia/reperfusion (I/R) injury by converting I/R-mediated death signal into a survival signal by modulating MAPK pathway.

Felemovicius, Bonsack, Baptista, & Delaney (1995) have shown that chronic treatment with α-TP protected rats from the damaging effects of x-ray. Paranich and colleagues have also shown that α-TP confers protection against a potentially lethal dose of gamma-irradiation in the heart, liver, muscles, and brain of rats (Paranich et al., 1993). These protective effects of α-TP against ionizing radiation is possibly mediated by interruption of free radical chain reaction and subsequent membrane lipid peroxidation, biological properties that elicit following hydrolysis to α-T (Nishio et al., 2011).

α-TP appears to be more effective than α-T in regulating several cell properties (Libinaki et al., 2010). Negis et al. (2006) showed that feeding rabbits with α-TP led to a significant reduction in atherosclerotic lesion development and a significant reduction in the expression of CD36. Libinaki et al. (2010) have also reported that α-TP can protect cholesterol-fed rabbits against endothelial dysfunction. α-TP treatment was associated with decreased plasma levels of several key proinflammatory cytokines and markers including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1). The effects observed for α-TP were significantly greater than those exerted by α-T succinate. Aside from direct effects, it has been suggested that α-TP also has provitamin E effects (Zingg et al., 2010a).

It has been proposed that the transport of α-TP to its sites of action may be more efficient than α-T (Munteanu et al., 2004). Thus, the greater effects of TPm (a mixture of α-tocopheryl phosphate and di-α-tocopheryl phosphate) at lower concentrations relative to α-T may be due to its higher local concentrations. It has also been proposed that the enhanced activity of α-TP over α-T could be attributed to a possible interference of α-TP with the signaling and gene expression pathways (Munteanu et al., 2004).

The uptake and hydrolysis of α-TP has been investigated in vitro and in vivo in mice using deuterated α-TP (CD3). α-TP is taken up and readily hydrolyzed to α-T in both cultured cells (THP-1 monocytes) and in vivo, in mice. In both situations, more genes have been reported to be affected by α-TP (mostly upregulated) compared to α-T (Zingg et al., 2010a). In addition, α-TP treatment reduces glutamate-induced cytotoxicity in primary cortical neuronal cells, and following oral supplementation in mice, also reduces oxidative stress (Nishio et al., 2011).

CONCLUSIONS

α-TP appears to be a potent signaling molecule and regulator of cellular activities. Several in-vitro and in-vivo studies have provided evidence on the antiatherosclerotic, cardioprotective, antiproliferative, proapoptotic, radioprotective, and antioxidant effects of α-TP (Negis et al., 2006; Mukherjee et al., 2008; Libinaki et al., 2010; Zingg et al., 2010b). However, previous studies reporting antiatherosclerotic effects have used TPm which is a mixture of α-TP and di-α-tocopheryl phosphate or bis-tocopheryl phosphate ester (T_2P) (60–360 mg/kg equivalent to low amounts of α-TP) (Munteanu et al., 2004; Ogru et al., 2004; Negis et al., 2006; Libinaki et al., 2010). Hence, the potential specific efficacy of α-TP in atherogenesis remains open to question.

Vitamin E (α-T) analogues are well-known antioxidants, but at the same time are highly oxidizable and unstable molecules. On the other hand, vitamin E derivatives such as α-TP, α-tocopheryl acetate and several other esters, have greater stability which enable their use as anticancer agents or antioxidant in cosmeceutical and dietary supplements. However, the antioxidant capacity of these 6-OH-modified derivatives is exerted following hydrolysis and conversion to the parent α-T. These derivatives also possess properties that are different from vitamin E analogues in terms of transport, metabolism, solubility, and cellular activities (Zingg et al., 2010a).

Further investigations are required to evaluate the dose-dependence of α-TP actions at low versus high concentrations. It remains unclear to what extent the biological effects of α-TP are due to the direct effect of phosphate ester or conversion of α-TP into parent α-T. Although there is evidence supporting the higher potency of α-TP versus α-T in certain biological effects, further studies particularly with respect to antioxidant actions are warranted in order to make a more conclusive comparison between these two compounds. Finally, the potential clinical benefit associated with α-TP supplementation is relatively unexplored.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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