



Review

Do tocotrienols have potential as neuroprotective dietary factors?

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ABSTRACT

Tocotrienols (T_3) belong to the family of vitamin E compounds (α -, β -, γ -, δ -tocopherols and -tocotrienols) and have unique biological properties that make them potential neuroprotective dietary factors. In addition to their antioxidant activity, T_3 at micromolar concentrations exert cholesterol-lowering activities in cells, animal models and some, but not all, human studies by means of inhibition of the activity of the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase. At lower concentrations (~ 10 nmol/L), T_3 modulate signalling pathways involved in neuronal cell death in cell culture experiments. Targets of T_3 include prenyl transferases, non-receptor tyrosine kinase, phospholipase A_2 , 12-lipoxygenase, cyclooxygenase-2, and nuclear factor κB . The low bioavailability and rapid excretion of T_3 represents a major hurdle in their preventive use. Fasting plasma concentrations, even after supplementation with high doses, are below $1 \mu\text{mol/L}$. T_3 bioavailability may be enhanced by ingestion with a high-fat meal, self-emulsifying drug delivery systems, or phytochemicals that inhibit T_3 metabolism and excretion. T_3 have no known adverse effects when consumed as part of a normal diet and the studies reviewed here support the notion that they may have potential as neuroprotective agents. However, experiments in relevant animal models and randomised human intervention trials addressing the neuroprotection mediated by T_3 are scarce and, thus, highly warranted.

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1. Introduction

It was estimated that by the year 2050 approximately one-third of the world's population will be older than 60 years (Lutz et al., 2008). Advanced age is the most important risk factor for the development of neurodegenerative disorders of the brain, which lead to cognitive impairment and dementia. As the number of people who live beyond the age of 60 years is constantly growing, both cognitive impairment and dementia become increasingly preva-

lent (Fratiglioni et al., 2000). Alzheimer's disease (AD) is the most common neurodegenerative disorder of the brain and accounts for about 50–70% of all dementia cases (Mattson, 2004). AD is usually diagnosed beyond the age of 65 years, although cases of familial AD, which are associated with mutations in certain predisposing genes (e.g. presenilin-1, presenilin-2, amyloid β precursor protein), do occur at an earlier age (Lin and Beal, 2006). Progression of AD is slow, but end-stage patients are usually left bedridden, incontinent, and depend on custodial care (Citron, 2002). Currently, AD affects about 24 million patients worldwide and this number is expected to double every 20 years (Ferri et al., 2005). Given the projected demographics and the fact that age-dependent dementias and AD cause much suffering in affected individuals and their families and give rise to enormous costs to healthcare systems, these age-dependent neurodegenerative diseases pose to develop into a serious healthcare crisis if treatments, either preventive or curative, cannot be introduced within the next decade or so (Citron, 2002).

Clinical symptoms of AD and other dementias include progressive loss of memory, reduced cognitive ability, and emotional and behavioural changes (Strittmatter and Roses, 1996). The underlying pathophysiological mechanisms in the brain include the extracellular accumulation of mis-folded proteins, synaptic dysfunction, mitochondrial dysfunction, massive progressive loss of neurones by apoptosis, especially in the hippocampus and cortex, and a

Abbreviations: 12-HPETE, 12-hydroperoxy-eicosatetraenoic acid; α -TTP, α -tocopherol transfer protein; A β , amyloid- β ; AD, Alzheimer's disease; AHA, American Heart Association; APP, amyloid precursor protein; DMBA, 7,12-dimethylbenz[α]anthracene; ERK, extracellular signal-regulated kinase; FPP, farnesylpyrophosphate; GGPP, geranylpyrophosphate; H_2O_2 , hydrogen peroxide; HCA, homocysteic acid; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LOX, lipoxygenase; NF- κB , nuclear factor- κB ; PLA $_2$, phospholipase A_2 ; cPLA $_2$, cytosolic phospholipase A_2 ; SEDDS, self-emulsifying drug delivery systems; SH, Src homology; T, tocopherol(s); T_3 , tocotrienol(s); TRF, tocotrienol-rich fraction.

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selective depletion of neurotransmitter systems (e.g. acetylcholine) (Bredesen et al., 2006; Leuner et al., 2007; Lin and Beal, 2006; Mattson, 2004; Mattson and Magnus, 2006). On the cellular level, the processes leading to neuronal death and, thus, neurodegenerative events are caused by or result in an increased formation of reactive oxygen and nitrogen species. Such an imbalance between free radical generation and elimination is termed *oxidative stress* and was causally connected with the incidence of inter alia AD (Lin and Beal, 2006). Consequently, antioxidant nutrients, such as tocotrienols (T₃) and other members of the vitamin E family, are thought to be beneficial in the prevention of neurodegeneration and dementia. In fact, epidemiological studies indicate that a high intake of vitamin E from food sources, but not from dietary supplements, may contribute to the prevention of age-related neurodegenerative disorders (Engelhart et al., 2002; Morris et al., 1998, 2005). Morris and colleagues evaluated the contribution of the different vitamin E congeners toward the prevention of AD. While a higher dietary intake of both α -tocopherol (α T) and γ -tocopherol (γ T) was associated with a decreased risk of developing AD, their data suggested that the combination of the different vitamin E congeners may be more effective in preventing AD than the intake of α T alone (Morris et al., 2005).

2. Vitamin E

Vitamin E (Fig. 1) is a generic name for all substances exerting the biological functions of α -tocopherol. Of the eight recognised natural vitamin E compounds α -, β -, γ -, and δ -tocopherol (T) and -tocotrienol, α T and γ T are quantitatively the two major vitamers in the human body, whereas the T₃ are present at much lower concentrations (Kamal-Eldin and Appelqvist, 1996). Upon ingestion, the lipid-soluble T and T₃, together with other dietary lipids, are absorbed and transported to the liver, where they are packaged into lipoproteins and secreted into the circulation or metabolised to water-soluble carboxyethyl hydroxychroman (CEHC) metabolites (Fig. 2), which are excreted in the urine (Birringer et al., 2002). As the organism favours the retention of α T and preferentially degrades and excretes all non- α T-forms of vitamin E, T₃ concentrations in humans are generally very low (Table 1) (O'Byrne et al., 2000). Under normal dietary conditions, T₃ are not detectable in plasma from fasted humans (O'Byrne et al., 2000). Even after daily supplementation with high doses of 250 mg α T₃, γ T₃, or δ T₃ for 8 weeks, their respective fasting plasma concentrations remained below 1 μ mol/L (O'Byrne et al., 2000). For comparison, α T and γ T plasma concentrations in fasted subjects typically range from 11 to 37 and 1 to 5 μ mol/L, respectively (Frank and Rimbach, 2009). The limited bioavailability of T₃ has led to attempts to augment their plasma and tissue concentrations by enhancing their absorption and retention in the body (see below Section 4).

2.1. Food sources

Vitamin E is exclusively synthesised by photosynthetic organisms and while T are the predominant vitamin E congeners in plants per se, T₃ are present in the seed endosperm of most monocotyledons, such as palm, wheat, rice, and barley, and are also found in the seed endosperm of a limited number of dicotyledons, e.g. tobacco (Sen et al., 2007). Cereal grains, such as oat, rye, and barley, and plant oils, such as palm, rice bran, and wheat germ oils (Table 2), are the major food sources for T₃ in the Western diet (Sundram et al., 2003; Theriault et al., 1999). Palm oil, in particular, is one of the best natural sources of T₃ with up to 800 mg T₃/kg crude oil (Sen et al., 2006). A recent Japanese study identified cereals and grains (3 mg T₃/kg each), nuts, seeds, and confectionary (1.5 mg T₃/kg each) as the food sources with the highest T₃ content and estimated a daily intake of T₃ of 2 mg (mainly from rice) in the Japanese population

(Sookwong et al., 2010). T₃-containing foods and their respective vitamin E contents are compiled in Table 2.

3. Biological activities of tocotrienols that may be beneficial in the prevention of age-dependent neurodegenerative diseases

3.1. Antioxidant activity of tocotrienols

Oxidative stress, that is an imbalance of the generation of reactive species and antioxidant defences, can lead to damage of DNA, proteins, and lipids and is thought to be involved in the pathogenesis of a large number of diseases, including age-dependent neurodegenerative disorders and dementia (Ames et al., 1993; Sies, 1997). Vitamin E congeners in general are components of biological membranes, where they may act as chain-breaking antioxidants to protect membrane lipids from oxidative damage (Burton et al., 1982; Suzuki et al., 1993). T₃ in particular have been reported to exert antioxidant activity in many different in vitro and in vivo systems (Adachi and Ishii, 2000; Begum and Terao, 2002; Ghafoorunissa et al., 2004; Kamat et al., 1997; Nafeeza et al., 2002; Nesaretnam et al., 1993; Noguchi et al., 2003; Qureshi et al., 2000; Reznick et al., 1992; Serbinova et al., 1991; Suarna et al., 1993; Suzuki et al., 1993; Thiele et al., 1997; Weber et al., 1997, 2003; Yoshida et al., 2003, 2007). As part of a so-called antioxidant network, T₃ may quench lipid radicals and in the process become radicals themselves, albeit less reactive ones. These radicals can then be reduced back to their native form by vitamin C or, indirectly, by thiol antioxidants (e.g. glutathione and lipoic acid) (Rimbach et al., 2002) or, in the absence of reducing substances, tocotrienoxyl radicals may exhibit pro-oxidant effects and further propagate radical chain reactions (Suarna et al., 1993; Yoshida et al., 2003). Kagan et al. (1992) reported the recycling of endogenous vitamin E (α T and α T₃) by ascorbic acid in human LDL in vitro.

The efficacy of any antioxidant is governed by the physico-chemical properties of the system in which it is active. This is of particular importance for the antioxidant capacity of T₃ relative to that of T (Serbinova et al., 1991; Suzuki et al., 1993). In liposomes, α T₃ is a 1.5-fold more efficient peroxy radical scavenger than α T, while both are equally active in homogeneous solutions of hexane (Serbinova et al., 1991). α T₃ was a more potent radical scavenger than α T in dipalmitoyl phosphatidylcholine liposomal membranes, but not in hexane (Suzuki et al., 1993). Likewise, α T₃ has greater antioxidant activity against lipid peroxidation in rat liver microsomal membranes and is 6.5 times more effective in the protection of cytochrome P₄₅₀ against oxidative damage than α T (Serbinova et al., 1991). A tocotrienol rich fraction (TRF) isolated from palm oil significantly inhibited oxidative damage to both lipids and proteins induced by ascorbate Fe²⁺, azobis (2-amidopropane)dihydrochloride (a free radical initiator), and photosensitization in isolated rat brain mitochondria at concentrations as low as 5 μ mol/L. This protection was conferred by γ T₃, and to a lesser extent by α T₃ and δ T₃, and was much more potent than that of α T (Kamat and Devasagayam, 1995; Kamat et al., 1997).

A TRF from palm oil (α T, 12.5%; α T₃, 10.8%; γ T₃, 22.0%; δ T₃, 5.2%) significantly inhibited H₂O₂-induced death of primary cultures of rat striatal neurones (Osakada et al., 2004). The minimum concentrations of isolated α T₃, γ T₃, and δ T₃ that significantly inhibited H₂O₂-induced neurotoxicity were 0.1, 1, and 10 μ mol/L, respectively, while α T did not protect striatal neurones from cell death at all (Osakada et al., 2004). In primary astrocyte cultures, γ T₃, up to 100 μ mol/L, dose-dependently protected against H₂O₂-induced cell death and apoptosis; concentrations higher than 200 μ mol/L, however, were cytotoxic. α T, up to 750 μ mol/L in the culture medium, was not cytotoxic, but was less effective in maintaining

Table 1

Tissue concentrations of tocotrienols in humans and animals receiving single or repeated doses of individual or mixed tocotrienols with food, dietary supplements, or via intragastric administration.

Species	T ₃ preparation	Administration	Fasting [h]	Sampling [h after T ₃ administration]	αT ₃	γT ₃	δT ₃	Citation
Adrenal glands [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		6.1	6.6	0	Hayes et al. (1993)
Brain [nmol/g]								
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈2	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		≈0.6	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ 50 mg each per kg diet	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Brown adipose tissue [nmol/g]								
Rat	None	None	10		23.3	1.0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	29.7	8.0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	49.2	20.0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	94.6	65.6	n.a.	Okabe et al. (2002)
Cerebellum [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		<0.02	0	0	Hayes et al. (1993)
Cerebrum [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		<0.02	0	0	Hayes et al. (1993)
Epididymal adipose tissue [nmol/g]								
Rat	αT ₃ 50 mg/kg diet	Diet, ad libitum, 8 wk	24		≈25.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ 50 mg each per kg diet	Diet, ad libitum, 8 wk	24		≈11.8	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈20.9	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ 50 mg each per kg diet	Diet, ad libitum, 8 wk	24		n.a.	≈20.0	n.a.	Ikeda et al. (2003)
Rat	None	None	10		9.6	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	4		11.8	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	8		11.8	2.7	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	24		15.5	10.5	n.a.	Okabe et al. (2002)
Heart [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		4.7	1.2	<0.02	Hayes et al. (1993)
Hairless mouse	Chow (αT, 30; γT, 10; αT ₃ , 3; γT ₃ , 7 mg/kg diet)	Diet, ad libitum	No info		0.1	0.2	n.a.	Podda et al. (1996)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈20.0	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		<9.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈1.0	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈1.0	n.a.	Ikeda et al. (2003)
Rat	None	None	10		0	1.9	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	7.8	4.4	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	10.5	9.4	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	16.2	11.2	n.a.	Okabe et al. (2002)
Intestinal mucosa [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T (53 ppm all rac-α-T-acetate)	Diet, 4 wk		3, Postprandial	25.9	46.3	17.7	Hayes et al. (1993)
Kidney [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		1.2	<0.02	<0.02	Hayes et al. (1993)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈4.7	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		≈1.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈1.0	n.a.	Ikeda et al. (2003)
Hairless mouse	Chow (αT, 30; γT, 10; αT ₃ , 3; γT ₃ , 7 mg/kg diet)	None	No info		0.06	0.15	n.a.	Podda et al. (1996)
Liver [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		1.4	<0.02	<0.02	Hayes et al. (1993)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈4.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		<1.4	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Rat	None	None	10		0	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	22.4	14.9	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	75.6	29.5	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	23.3	0	n.a.	Okabe et al. (2002)
Hairless mouse	Chow (αT, 30; γT, 10; αT ₃ , 3; γT ₃ , 7 mg/kg diet)	None	No info		0.1	0.2	n.a.	Podda et al. (1996)

Table 1 (Continued)

Species	T ₃ preparation	Administration	Fasting [h]	Sampling [h after T ₃ administration]	αT ₃	γT ₃	δT ₃	Citation
Lung [nmol/g]								
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈9.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		≈1.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈1.9	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈1.9	n.a.	Ikeda et al. (2003)
Rat	None	None	10		0	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	16.0	15.3	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	22.8	21.9	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	4.9	5.8	n.a.	Okabe et al. (2002)
Mesenteric lymph node [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T (53 ppm all rac-α-T-acetate)	Diet, 4 wk	3 h post-prandial		588.6	975.2	909.1	Hayes et al. (1993)
Rat	None	None	10		0	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	104.8	72.3	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	78.6	93.3	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	31.3	32.4	n.a.	Okabe et al. (2002)
Muscle [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		2.1	0.7	0.8	Hayes et al. (1993)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈8.0	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		≈2.6	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈2.4	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈2.4	n.a.	Ikeda et al. (2003)
Pancreas [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		3.8	2.9	0.5	Hayes et al. (1993)
Plasma [nmol/L]								
Human	None	None	No info		19	10	40	Chow (1975)
Human	None	None	6		0	0	277	Hayes et al. (1993)
Human	Palm Vitee capsules (80 mg T + 64 mg T ₃)	2 Capsules/d for 10 d	6		<24	<24	327	Hayes et al. (1993)
Human	Palm Vitee capsules (80 mg T + 64 mg T ₃)	2 Capsules/d for 10 d	Not fasted	2, Postprandial	377	316	302	Hayes et al. (1993)
Hamster	223 ppm T ₃ + 70 ppm T (53 ppm all rac-α-T-acetate)	11 wk	Overnight		<24	<24	0	Hayes et al. (1993)
Hamster	223 ppm T ₃ + 70 ppm T (53 ppm all rac-α-T-acetate)	4 wk	3, postprandial		706	243	<25	Hayes et al. (1993)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		<2	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		<2	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	0	n.a.	Ikeda et al. (2003)
Platelets [nmol/10 ¹¹ cells]								
Human	None	2 Capsules/d for 10 d	6		0	0	6.1	Hayes et al. (1993)
Human	Palm Vitee capsules (80 mg T + 64 mg T ₃)	2 Capsules/d for 10 d	6, Semi-fasted (light breakfast)		0	0	12.4	Hayes et al. (1993)
Renal adipose tissue [nmol/g]								
Rat	None	None	10		15.5	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	12.2	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	17.9	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	14.1	7.8	n.a.	Okabe et al. (2002)
Seminal vesicle [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		0.5	0.5	<0.1	
Serum [nmol/L]								
Rat	None	None	10		0	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	2826	1217	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	2826	1461	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	942	243	n.a.	Okabe et al. (2002)
Skin [nmol/g]								
Human	None	Biopsy			0.1–1.3	0.1–1.6	n.a.	Fuchs et al. (2003)
Rat	αT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		≈11.1	n.a.	n.a.	Ikeda et al. (2003)
Rat	αT + αT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		≈4.9	n.a.	n.a.	Ikeda et al. (2003)
Rat	γT ₃ (50 mg/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈3.9	n.a.	Ikeda et al. (2003)
Rat	αT + γT ₃ (50 mg each/kg diet)	Diet, ad libitum, 8 wk	24		n.a.	≈3.9	n.a.	Ikeda et al. (2003)

Table 1 (Continued)

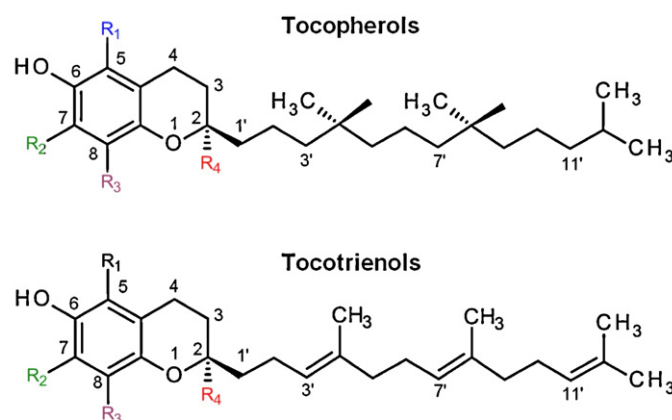
Species	T ₃ preparation	Administration	Fasting [h]	Sampling [h after T ₃ administration]	αT ₃	γT ₃	δT ₃	Citation
Hairless mouse	Chow (αT, 30; γT, 10; αT ₃ , 3; γT ₃ , 7 mg/kg diet)	None	No info		0.2	0.8	n.a.	Podda et al. (1996)
Skin and subcutis [nmol/g]								
Hairless mouse	Chow (αT, 30; γT, 10; αT ₃ , 3; γT ₃ , 7 mg/kg diet)	None	No info		0.1	0.4	n.a.	Podda et al. (1996)
Spleen [nmol/g]								
Hamster	223 ppm T ₃ + 70 ppm T	Diet, ad libitum, 11–15 wk	>15		0.5	0.2	0	Hayes et al. (1993)
Rat	None	None	10		0	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	5.4	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	9.6	1.0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	1.4	0	n.a.	Okabe et al. (2002)
Subcutaneous adipose tissue [nmol/g]								
Rat	None	None	10		7.8	0	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	4	11.1	1.2	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	8	5.6	1.7	n.a.	Okabe et al. (2002)
Rat	T ₃ mix (67 mg T + T ₃) ^a	Intragastric	10	24	11.1	3.9	n.a.	Okabe et al. (2002)

n.a., not analyzed; n.d., not detected; no info, no information provided in the paper.

^a The T₃ mix contained (all in %): αT, 20.5; βT, 0.7; γT, 1.0; δT, 0.5; αT₃, 21.4; βT₃, 3.5; γT₃, 36.5; δT₃, 8.6.

the number of viable astrocytes (Mazlan et al., 2006). Treatment of SY5Y neuronal cells with αT₃ significantly counteracted butyl hydroxyl peroxide and hydrogen peroxide induced cytotoxicity. Importantly αT₃ was more potent than αT in protecting SY5Y cells against these oxidative insults (Huebbe et al., 2007). Furthermore it has been recently shown that both T and T₃ protect neuronal cells from glutamate-induced toxicity primarily by a direct antioxidant action. The higher protective capacity of αT₃ compared to αT may be mainly related to its faster cellular uptake (Saito et al., 2010). This is also supported by uptake studies in cerebellar granule neuron cultures, where intracellular concentrations of γT₃ and

αT reached 7 and 1 μmol/million cells, respectively, after incubation with 10 μmol/L of the respective vitamers for 24 h (Then et al., 2009). On the other hand, no differences in cellular uptake of these two vitamin E forms was observed in the authors' previous study with primary astrocyte cultures (Mazlan et al., 2006). In agreement with the previous study (Mazlan et al., 2006), γT₃ concentrations below 10 μmol/L protected the neurons from H₂O₂-induced cell death, whereas unphysiologically high concentrations of 200 μmol/L or more induced apoptosis (Then et al., 2009). Fukui et al. (2011) confirmed the superior neuroprotective activities of αT₃ and γT₃ compared to αT against H₂O₂-induced cell



Common Name	Methyl positions				Activity based on rat assay	
	R1	R2	R3	R4	IU/mg ¹	Relative to αT
α-Tocopherol	CH ₃	CH ₃	CH ₃	CH ₃	1.49	100
β-Tocopherol	CH ₃	H	CH ₃	CH ₃	0.75	50
γ-Tocopherol	H	CH ₃	CH ₃	CH ₃	0.15	10
δ-Tocopherol	H	H	CH ₃	CH ₃	0.05	3
α-Tocotrienol	CH ₃	CH ₃	CH ₃	CH ₃	0.75	50
β-Tocotrienol	CH ₃	H	CH ₃	CH ₃	0.08	5
γ-Tocotrienol	H	CH ₃	CH ₃	CH ₃	?	?
δ-Tocotrienol	H	H	CH ₃	CH ₃	?	?
Desmethyl-tocotrienol ²	H	H	H	CH ₃	?	?
Didesmethyl-tocotrienol ²	H	H	H	H	?	?

Fig. 1. Chemical structures and methyl positions of tocopherols and tocotrienols, their plasma concentrations in humans, and biological activities. ¹One IU (international unit) is defined as the biological activity of 1 mg all rac-α-tocopheryl acetate and is equivalent to 0.67 mg RRR-α-tocopherol (Hoppe and Krennrich, 2000). ²Desmethyl and didesmethyl tocotrienol, although structurally related, are not officially recognised as vitamin E congeners.

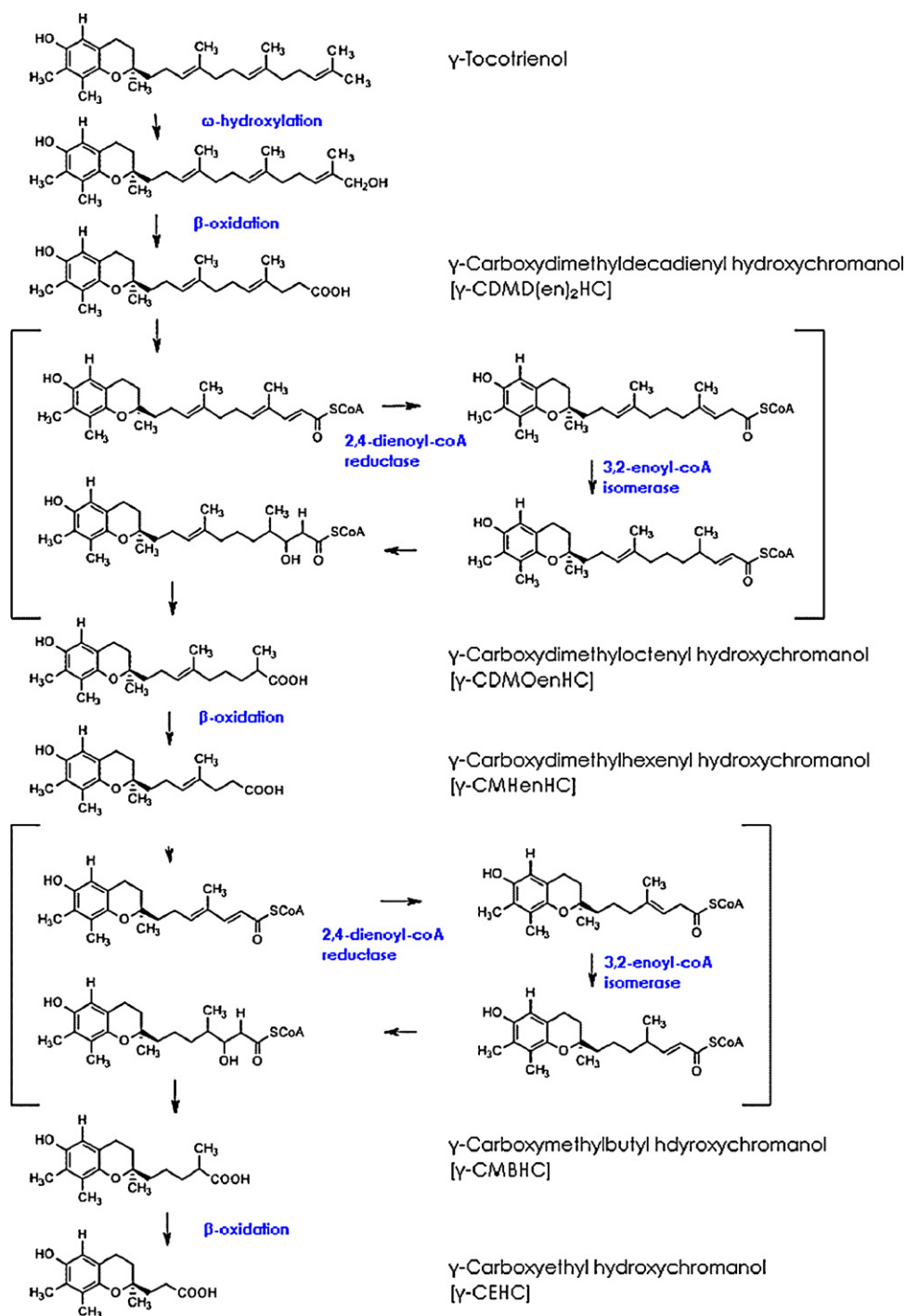


Fig. 2. Steps in the side-chain degradation of tocotrienols shown with γ -tocotrienol as example. The reactions displayed in brackets apply to tocotrienols only, the enzymatic degradation of tocopherols proceeds without these auxiliary enzymes. Modified from Birringer et al. (2002).

death and neurite degeneration using Neuro2a cell cultures. Neurite degradation in response to H_2O_2 stimulation was accompanied by induction of collapsin response mediator protein-2 (CRMP-2), a protein involved in microtubule polarity and axon guidance, whose expression is increased in neurons in the vicinity of amyloid- β plaques in the cerebral cortex of APP(Swe) Tg2576 mice, a mouse model of Alzheimer's disease (Petras et al., 2008). Incubation of the Neuro2a cells with T_3 did not alter the expression of CRMP-2, but reduced that of an unidentified variant of CRMP-2 compared to H_2O_2 -treated cells. This unknown form of CRMP-2 may, at least

in part, play a role in mediating the neuroprotective activities of T_3 (Fukui et al., 2011).

In the model organism *Caenorhabditis elegans*, the protein carbonyl content, an indicator for protein oxidation, in 15-day old nematodes was reduced by treatment with TRF isolated from palm oil (αT_3 , 22; αT_3 , 24; γT_3 , 37, δT_3 , 12%) but not with αT (Adachi and Ishii, 2000). *C. elegans* maintained on agar plates with TRF displayed a 20% increase in mean lifespan, possibly as a result of reduced oxidative stress (Adachi and Ishii, 2000). TRF treatment also blunted the effects of ultraviolet irradiation-induced oxidative stress and

Table 2
Tocopherol and tocotrienol concentrations (mg/kg) in foods.

Foods	Tocopherols [mg/kg]				Tocotrienols [mg/kg]				Citation
	α	β	γ	δ	α	β	γ	δ	
Oils									
Avocado oil	34–55	6–68		12–24	n.d.–5	n.d.–9		n.d.–8	Cerretani et al. (2010)
Corn oil	257	9	752	32	15	n.d.	20	n.d.	Syväoja et al. (1986)
	157–269	10–27	341–532	52–87	<0.5–20	36–44	28–34	<0.5	Franke et al. (2007)
	52–83	125–237		11–22	2–12	5–7		5–7	Cerretani et al. (2010)
	67–276	0–20	583–1048	12–71	46–89	53–164	?	?	Goffman and Bohme (2001)
Coconut oil (hardened)	18	2	traces	4	11	n.d.	3	n.d.	Syväoja et al. (1986)
Linseed oil	6	n.d.	757	n.d.	1	n.d.	8	17	Bozan and Temelli (2008)
Grapeseed oil	36–309	21–153	21–26	n.d.	102–228	217–383	n.d.	n.d.	Beveridge et al. (2005)
	<10–229	<10–133	<10–168	<10–69	<10–352	<10–125	<10–785	<10–82	Crews et al. (2006)
	6–55	6–17		6–10	2–12	10–31		0–8	Cerretani et al. (2010)
Hazelnut oil	245	8	10	1	2	0.3	1	n.d.	Amaral et al. (2006)
	71–120	19–32		7–12	n.d.	n.d.	n.d.	n.d.	Cerretani et al. (2010)
Oil from roasted hazelnuts	214–236	7–9	5–12	0.6–1	2–6	0.2–0.3	1–2	n.d.	Amaral et al. (2006)
Olive oil	93–260	1–3	3–10	0.1–0.4	0.3–1	n.d.	0.3–1	n.d.	Cunha et al. (2006)
	52–112	7–10		n.d.–6	n.d.	n.d.	n.d.	n.d.	Cerretani et al. (2010)
Palm oil	60	n.d.	traces	n.d.	57	8	113	33	Syväoja et al. (1986)
	47	8		n.d.	75	96		24	Milagros Delgado-Zamarreno et al. (2009)
Palm oil (crude)	420	n.d.	n.d.	n.d.	260	n.d.	360	80	Ng et al. (2004)
Palm oil (red)	7–21	4–8		n.d.	15–35	27–40		9–11	Cerretani et al. (2010)
Peanut oil	43–44	37–74		7–31	n.d.	n.d.	n.d.	n.d.	Cerretani et al. (2010)
Poppy-seed oil	55	17	217	n.d.	n.d.	n.d.	15	6	Bozan and Temelli (2008)
Safflower oil	123–575	7–31	3–19	<0.5–25	<0.5–5	<0.5–26	4–18	<0.5–125	Franke et al. (2007)
	441	72	n.d.	n.d.	7	n.d.	12	n.d.	Bozan and Temelli (2008)
Sesame oil	48–82	50–157	382–383	<0.5	<0.5	<0.5	<0.5	<0.5	Franke et al. (2007)
Soybean oil	17–53	95–177		67–88	n.d.	n.d.	n.d.	n.d.	Cerretani et al. (2010)
Sunflower oil	542	21	42	15	<0.5	20	<0.5	<0.5	Franke et al. (2007)
Wheat germ oil	1507	312	527	n.d.	36	n.d.	18	n.d.	Syväoja et al. (1986)
Walnut oil	<10–19	<10	247–525	<10–299	<10	<10	<10	<10	Crews et al. (2005)
Fats									
Margarine, 60% fat	29–38	5	190–240	72–105	<0.5	15–17	<0.5	1	Franke et al. (2007)
Margarine, 70% fat	63	6	285	82	<0.5	19	<0.5	1	Franke et al. (2007)
Margarine, hardened	40–90	n.d.	62–280	14–111	0–17	n.a.	0–23	0–8	Syväoja et al. (1986)
Margarine, semisoft	102–163	n.d.	207–428	60–104	n.d.	n.a.	0–2	0–3	Syväoja et al. (1986)
Margarine, soft	176–446	0–14	27–437	7–166	0–2	n.a.	0–10	0–6	Syväoja et al. (1986)
Nuts									
Almonds, honey-roasted	185	2	5	1	2	4	1	<0.5	Franke et al. (2007)
Chestnuts	≤0.1	n.d.	4–5	≤0.3	n.d.	n.d.	≤0.4	0.1	Barreira et al. (2009)
Hazelnuts	110–177	3–9	1–5	≤1	≤1	≤0.3	≤0.6	n.d.	Amaral et al. (2005b)
Macadamia nuts, dry-roasted	≤1.5	≤0.5	≤1.4	<0.5	13–23	≤0.8	1–2	<0.5	Franke et al. (2007)
Peanuts, boiled	37	1	25	7	<0.5	3	1	<0.5	Franke et al. (2007)
Peanuts, dry roasted	69–70	24–27	35–48	11–15	<0.5	9–11	<3	<0.5	Franke et al. (2007)
Walnuts	9–17	0.6–2	173–262	8–17	n.a.	n.a.	2–5	n.a.	Amaral et al. (2005a)
Cereals, cereal products and seeds									
Barley	9±3	1±0.1	6±3	1±0.2	40±7	9±2	10±3	1±0.3	Panfili et al. (2003)
	6–8	3–6		1	23–42	8–14		<1	Ehrenbergerova et al. (2006)
	n.d.	n.d.	n.d.	n.d.	7±0.3	4±0.9		n.d.	Milagros Delgado-Zamarreno et al. (2009)
Buckwheat groat fagopyrum	1	30	n.d.	n.d.	0.1	n.d.	n.d.	n.d.	Zielinski et al. (2006)
Buckwheat groat extrudate	0.3	10–11	n.d.	n.d.	0.1	n.d.	n.d.	n.d.	Zielinski et al. (2006)
Einkorn	7–12	2–5	n.d.	n.d.	8–12	25–45	n.d.	n.d.	Lampi et al. (2008)
Emmer	6–9	2–4	n.d.	n.d.	4–6	15–40	n.d.	n.d.	Lampi et al. (2008)
Linseed	1	n.d.	139	n.d.	1	n.d.	2	3	Bozan and Temelli (2008)
Maize	4	0.2	45	1	5	n.d.	11	0.4	Panfili et al. (2003)
	n.d.	14		n.d.	n.d.	6	n.d.	n.d.	Milagros Delgado-Zamarreno et al. (2009)
Oat	15	3	0.4	n.d.	56	5	n.d.	n.d.	Panfili et al. (2003)
	3	1		n.d.	6	2		n.d.	Milagros Delgado-Zamarreno et al. (2009)

Table 2 (Continued)

Foods	Tocopherols [mg/kg]				Tocotrienols [mg/kg]				Citation
	α	β	γ	δ	α	β	γ	δ	
Oat, rolled	4–5	0.4–2	n.a.	n.a.	10–11	1–2	n.a.	n.a.	Bryngelsson et al. (2002)
Oat, wholemeal	0.1–6	12–14	n.a.	n.a.	0.5–16	1–2	n.a.	n.a.	Bryngelsson et al. (2002)
Oat, raw hulls	1	0.1	n.a.	n.a.	0.2	0.1	n.a.	n.a.	Bryngelsson et al. (2002)
Oat, autoclaved hulls	3	13	n.a.	n.a.	2	0.4	n.a.	n.a.	Bryngelsson et al. (2002)
Poppy seed	14	5	87	n.d.	n.d.	n.d.	2	2	Bozan and Temelli (2008)
Rye	7	2		n.d.	n.d.	4		n.d.	Milagros Delgado-Zamarreno et al. (2009)
Rye bread	1–21	0–7	?	?	27–80	23–48	?	?	Kamal-Eldin et al. (2009)
Safflower seed	0.6–3	0.1–0.6	0.2–0.4	n.d.	0.1–1.8	0.2–1.5	n.d.	n.a.	Michalska et al. (2007)
Spelt	102	12	n.d.	n.d.	1	n.d.	1	4	Bozan and Temelli (2008)
Triticale	13	7	n.d.	n.d.	5	33	n.d.	n.d.	Panfili et al. (2003)
Wheat	10–12	5–7	n.d.	n.d.	3–6	20–27	n.d.	n.d.	Lampi et al. (2008)
White bread	14	6	n.d.	n.d.	6	32	10	n.d.	Panfili et al. (2003)
Durum wheat	16	9	n.d.	n.d.	6	42	n.d.	n.d.	Panfili et al. (2003)
Whole wheat flour	9–20	3–13	n.d.	n.d.	2–8	10–44	n.d.	n.d.	Lampi et al. (2008)
Whole wheat flour	7	4	n.d.	n.d.	n.d.	9	n.d.	n.d.	Milagros Delgado-Zamarreno et al. (2009)
Whole wheat flour	10–20	4–11	?	?	3–10	10–50	?	?	Lampi et al. (2010)
White bread	1–3	2–3	2–15	0.4–7	≤ 0.6	7–9	< 0.2	< 0.1	Franke et al. (2007)
White bread	2–4	1	4–11	0.5–5	< 1	4–10	< 0.1	< 0.1	Franke et al. (2007)
Durum wheat	8	5	n.d.	n.d.	7	40	n.d.	n.d.	Panfili et al. (2003)
Durum wheat	8–13	4–9	n.d.	n.d.	5–8	19–35	n.d.	n.d.	Lampi et al. (2008)
Animal products									
Atlantic salmon (raw, filet)	23–50	< 0.01	0.5–0.7	< 0.01	< 0.2	< 0.5	< 1	< 0.01	Franke et al. (2007)
Atlantic salmon (raw, steak)	33	< 0.01	0.2	< 0.01	0.1	< 0.01	< 0.01	< 0.01	Franke et al. (2007)
Chicken breast meat of broilers	2.6–3.1	0.05–0.07	0.4–0.6	n.d.	0.6–0.8	n.d.	1.1–1.5	0.1–0.2	Ponte et al. (2008)
Hen eggs [mg/egg]	n.a.	n.a.	n.a.	n.a.	< 0.2	n.d.	< 0.2	≤ 0.02	Sookwong et al. (2008)

effectively protected the nematodes from a shortening of lifespan (Adachi and Ishii, 2000).

The antioxidant activities of T_3 are not restricted to the test tube, but also apparent in vivo. Oral supplementation (60 mg/kg bw) of male Sprague-Dawley rats with αT_3 reduced levels of gastric malondialdehyde (MDA; a biomarker of lipid peroxidation) to a similar extent as αT (Azlina et al., 2005). Orally supplemented T_3 were also effective suppressors of protein oxidation in skeletal muscles of rats, where they effectively attenuated exercise induced-oxidative damage (Reznick et al., 1992). In rats, intracerebroventricular injection of streptozotocin causes oxidative stress and leads to cognitive dysfunction inter alia by inhibiting the synthesis of ATP and acetyl-coenzyme A (Tiwari et al., 2009a). Daily oral gavage of T_3 (a mixture of αT_3 , βT_3 , and γT_3 ; 50 or 100 mg/kg bw, respectively) or αT (100 mg/kg bw) for 3 weeks attenuated the reduction in glutathione and catalase and decreased MDA and nitrite concentrations in the brains of streptozotocin-injected adult male Wistar rats (Tiwari et al., 2009a). While T_3 and αT treatments were generally comparable in their potency to prevent oxidative damage and cognitive impairment (determined by Morris water maze and elevated plus maze tasks) in this model, a trend toward a better protection by T_3 was observed (Tiwari et al., 2009a).

In summary, T_3 appear to be more potent antioxidants than T in many in vitro studies, especially in membrane systems (Kamat and Devasagayam, 1995; Osakada et al., 2004; Serbinova et al., 1991; Suzuki et al., 1993), which might be explained by the faster recycling of αT_3 than of αT from the respective chromanoxyl radical forms in liposomal membranes and lipoproteins (Serbinova et al., 1991). Studies using nuclear magnetic resonance spectroscopy show that αT_3 is located closer to the membrane surface compared to αT and this may facilitate its faster recycling (Suzuki et al., 1993). Inter-membrane mobility of T_3 in multilamellar liposomes is also higher than that of T (Yoshida et al., 2003). Furthermore, the dis-

tribution of αT_3 within the membrane bilayer is more uniform and αT_3 has a stronger disordering effect on membrane lipids (Suzuki et al., 1993). All these factors may enhance the interaction of T_3 with lipid radicals, thus making T_3 more potent antioxidants in liposomal membranes (Serbinova et al., 1991). Yoshida et al. (2007) also demonstrated that T_3 are more readily incorporated into liposomal membranes compared to T and may therefore be more readily available antioxidants in membranes.

It has been suggested that antioxidants that are capable of reducing metal ions (e.g. copper) may act, at least under certain circumstances, as pro-oxidants. Thus, in addition to the antioxidant activities of T and T_3 their potential pro-oxidant properties need to be considered. In this context, Yoshida et al. (2003) systematically studied the effects of vitamin E homologues on copper-induced oxidation of methyl linoleate in vitro. Interestingly αT and αT_3 were oxidized by $Cu^{(II)}$ to give corresponding quinones, whose formation was followed by an increase in absorption at 268 nm. Thus, under the conditions investigated, αT and αT_3 acted as pro-oxidants in vitro. In contrast to the α -forms, neither α -, β -, γ -tocopherols nor -tocotrienols did exert any pro-oxidant activity. The pro-oxidant activity of αT and αT_3 may be prevented in the presence of vitamin C (ascorbic acid) as a reducing agent (Packer et al., 2001).

Most of the above-described antioxidative properties of T_3 were determined in vitro and such data should be interpreted with caution. In vivo, physiological processes such as absorption, distribution, metabolism, and excretion, in addition to their physicochemical characteristics, will affect – and limit – the antioxidative properties of T_3 . Overall, from the few in vivo studies published, it may be concluded that T_3 are at least equally potent as T in terms of their antioxidant activity (Adachi and Ishii, 2000; Azlina et al., 2005; Reznick et al., 1992; Thiele et al., 1997; Weber et al., 1997).

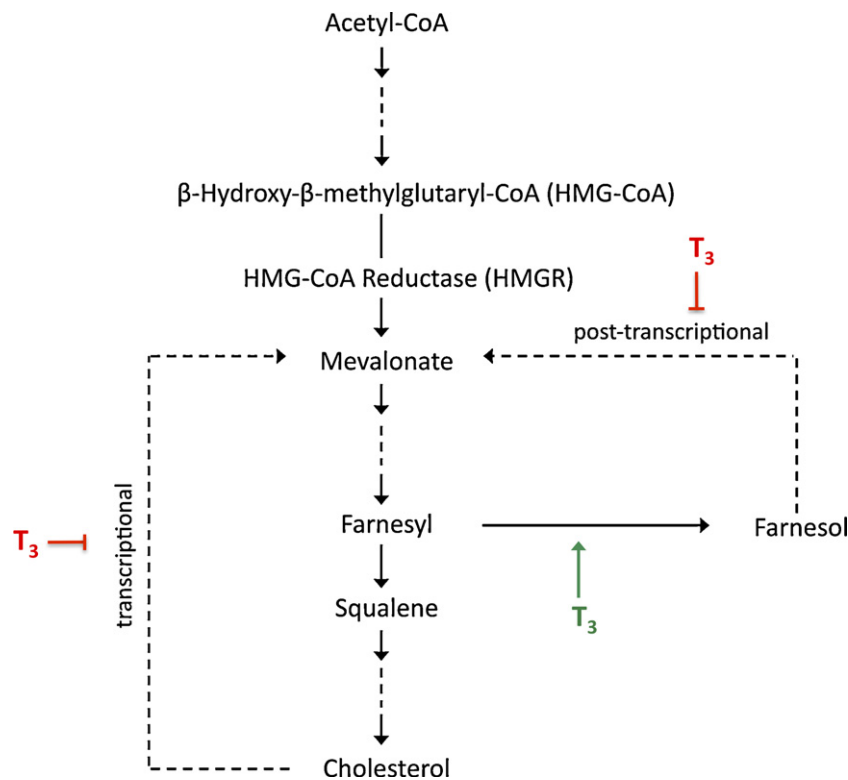


Fig. 3. Potential pathways leading to the hypocholesterolemic effect of tocotrienols. The prenylated side-chain of T_3 induces prenyl pyrophosphatase which catalyses the dephosphorylation of farnesyl, resulting in an increase in cellular farnesol. Farnesol down-regulates 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity post-transcriptionally by increasing enzyme degradation, without reducing HMG-CoA gene expression. In comparison, cholesterol down-regulates HMG-CoA activity by reducing the transcription of the enzyme. Modified from Theriault et al. (1999).

3.2. Cholesterol-lowering activity of tocotrienols

Hypercholesterolemia in midlife is a known risk factor for age-dependent dementia and might increase the production of A β , a neurotoxic peptide involved in the pathogenesis of AD (Whitmer et al., 2005). In vitro, cholesterol-depletion reduces neuronal A β secretion and hypercholesterolemia was shown to speed up amyloid pathology in a transgenic AD mouse model (Hooff et al., 2010a; Peters et al., 2009; Refolo et al., 2000). Hence, cholesterol-lowering may be helpful in the control of vascular and dementia risk factors.

The hypocholesterolemic effects of T_3 were first described by Qureshi et al. (1986), who had isolated T_3 -rich fractions from barley that inhibited cholesterol biosynthesis both in vitro in rat and chicken hepatocytes as well as in vivo in broiler chicks fed the T_3 -fractions for 3 weeks. The cholesterol-lowering activity was exerted by T_3 and not T, and was the first unique biological property of T_3 described. The authors identified the reduction of the activity of the rate-limiting enzyme in cholesterol-biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, as the underlying mechanism (Qureshi et al., 1986). The activity of HMG-CoA reductase is not reduced by direct interactions with the enzyme, but by post-transcriptional suppression of HMG-CoA reductase protein. Incubation of HepG2 cells with T_3 stimulated the degradation of the enzyme, while HMG-CoA reductase gene expression was only marginally reduced (Parker et al., 1993). It was reported that γT_3 and δT_3 selectively enhance the ubiquitination of HMG-CoA reductase and its degradation by the 26S proteasome (Song and DeBose-Boyd, 2006).

The effects of T_3 on cholesterol biosynthesis and HMG-CoA reductase activity were corroborated in primary rat hepatocytes and human hepatoma HepG2 cells. A TRF from palm oil as well as the isolated compounds γT_3 and δT_3 inhibited cholesterol biosyn-

thesis in rat hepatocytes several-fold more potently than αT_3 , while αT and γT did not affect cholesterol biosynthesis at all (Pearce et al., 1992). Natural RRR- T_3 and synthetic all rac- T_3 inhibited HMG-CoA reductase activity in HepG2 cells to comparable extents (Pearce et al., 1992). The authors concluded that side-chain unsaturation and the absence of a 5-methyl substitution on the chromanol ring, both features of γT_3 and δT_3 , are the most important requirements for a potent cholesterol-lowering activity of vitamin E (Pearce et al., 1992, 1994) (Fig. 3).

These initial in vitro findings were subsequently confirmed in various animal models; TRF from rice bran oil lowered blood cholesterol in rats, chickens, and pigs (e.g. Chen and Cheng, 2006; Iqbal et al., 2003; Minhajuddin et al., 2005; Qureshi et al., 2000, 2001). Normolipemic rats treated with the chemical carcinogen 7,12-dimethylbenz[α]anthracene (DMBA), which, in addition to mammary cancer, induces hypercholesterolemia, were supplemented with TRF (10 mg/kg bw/d) for 6 months. While DMBA caused a significant 30% increase in plasma cholesterol and 111% increase in LDL cholesterol, TRF supplementation reduced total cholesterol by 30% and LDL cholesterol by 67% relative to DMBA-treated animals. This effect was accompanied by a 23% and 28% reduction in HMG-CoA reductase enzyme activity and protein expression, respectively, in the TRF-fed animals (Iqbal et al., 2003). In rats fed an atherogenic diet (5% hydrogenated fat, 0.5% cholic acid, 1% cholesterol by wt) for 3 weeks and subsequently treated for 1 week with different doses of rice bran TRF, the TRF dose-dependently decreased concentrations of plasma triacylglycerol and LDL-cholesterol with an optimum effect observed at 8 mg TRF/kg bodyweight/d (Minhajuddin et al., 2005). A dose-dependent reduction in plasma cholesterol concentrations by T_3 was also observed in hamsters fed a high-fat diet fortified with different doses of either γT_3 (23, 58, 263 mg/kg bw/d) or a mixture of T_3 (39

or 263 mg/kg bw/d) for 4 weeks. Compared to control, total cholesterol decreased by 7–15% and LDL-cholesterol by 12–32% in the T₃-fed animals (Raederstorff et al., 2002). Reductions by 44% in total serum cholesterol and by 60% in LDL-cholesterol were observed in genetically hypercholesterolemic pigs fed a TRF from palm oil (α T, 10–20%; α T₃, 15–20%; γ T₃, 30–35%; δ T₃, 20–25%) at concentrations of 50 mg/kg diet for 6 weeks (Qureshi et al., 1991a). Interestingly, this cholesterol-lowering effect persisted for 8 weeks after the TRF supplementation was discontinued (Qureshi et al., 1991a).

In addition to the four known T₃, rice bran oil contains two novel T₃: desmethyl tocotrienol and didesmethyl tocotrienol (Fig. 1). Each of these novel T₃ reduced serum total and LDL cholesterol concentrations and hepatic HMG-CoA reductase activity more potently than a TRF or the individual α T₃, β T₃, γ T₃ and δ T₃ in chickens fed these compounds at concentrations of 50 mg/kg diet for 24 days (Qureshi et al., 2000). To confirm these findings in a different animal model, pigs with hereditary hypercholesterolemia were fed diets supplemented with either 50 mg TRF (from rice bran), γ T₃, desmethyl-T₃, or didesmethyl-T₃ per kg diet for 6 weeks (Qureshi et al., 2001). Serum total cholesterol was reduced by 32–38%, LDL cholesterol by 35–43%, and triacylglycerols by 15–19% in T₃ fed pigs compared to control. No differences in their cholesterol-lowering potencies were observed between the desmethyl-T₃, didesmethyl-T₃, γ T₃, and the TRF (Qureshi et al., 2001).

First evidence for a hypocholesterolemic activity of T₃ in humans, determined as reduced serum total cholesterol (by 5–36%) and LDL cholesterol concentrations (by 1–37%) after intervention compared to baseline, was observed in healthy subjects taking capsules containing TRF (from palm oil; T, 18 mg; T₃, 42 mg; and palmolein, 240 mg) for 30 days. However, the significance of this study was limited by the absence of a control group (Tan et al., 1991). In a placebo-controlled, double-blind, crossover study with 25 hypercholesterolemic subjects, 4-week intake of eight capsules of a similar palm oil TRF (named palmvitee; daily dose (in mg): α T, 60–80; α T₃, 48–60; γ T₃, 120–160; δ T₃, 100–120) per day, a significant 15% reduction in serum total cholesterol and 8% reduction in LDL-cholesterol was observed. Palmvitee supplemented subjects continued to have lower serum cholesterol concentrations even 6 weeks after supplementation was discontinued (Qureshi et al., 1991b). In a larger human trial with a TRF isolated from rice bran oil, 90 hypercholesterolemic subjects were divided into groups of 18 and instructed to follow the American Heart Association's (AHA) Step 1 diet (max. intake of 300 mg cholesterol/d) for the reduction of blood cholesterol for 35 days and then supplemented with either 0, 25, 50, 100, or 200 mg/d of TRF (all in %: α T, 8.7; δ T, 4.4; α T₃, 15.5; β T₃, 1.6; γ T₃, 39.4; δ T₃, 5.2; desmethyl-T₃ and didesmethyl-T₃, 20.9; unidentified T₃, 4.3) while still on the AHA diet for 35 days. TRF intake of 50 mg/d or more resulted in significantly reduced total and LDL cholesterol concentrations in serum compared to control, with maximum effects observed in the 100 mg/d group (total cholesterol, –20%; LDL cholesterol, –25%) (Qureshi et al., 2002).

Although there have been numerous in vitro and animal studies indicating that T₃ inhibit cholesterol biosynthesis, data from human supplementation studies are inconclusive. Tomeo et al. (1995) supplemented 25 carotid atherosclerosis patients with four capsules per day containing TRF (from palm oil; 240 mg palm superolein [a triacylglycerol mixture composed of mainly oleic, palmitic, and linoleic acids], 16 mg α T, and 40 mg γ T₃ + δ T₃) or placebo (240 mg palm superolein; n = 25) for 3 months, the number of capsules was then increased to five for another 3 months, after which the dose was increased to six capsules/day for an additional 12 months. T₃ and T supplementation for 18 months, however, did not alter serum total, LDL or HDL cholesterol or triacylglycerols (Tomeo et al., 1995). In agreement, 20 weeks supplementation of hypercholesterolemic subjects with a similar palm oil TRF did not change any of these serum lipids despite a significant increase in serum T₃ in

the verum but not in the placebo group (Wahlqvist et al., 1992). In a randomised, double-blind, placebo-controlled parallel trial, male subjects with mild hypercholesterolemia (total serum cholesterol, 6.5–8.0 mmol/L) were supplemented for 6 weeks with either 140 mg T₃ plus 80 mg α T per day (n = 20) or placebo (80 mg α T/d only, n = 20). T₃ supplementation resulted in no significant changes in total serum or LDL cholesterol (Mensink et al., 1999). Hypercholesterolemic subjects adhering to low-fat diets for 4 weeks and then additionally supplemented with 250 mg/d of purified α -, γ -, or δ -tocotrienyl acetate for 8 weeks did not demonstrate reduced cholesterol levels compared to subjects given placebo. This lack of effect of the T₃ was not due to poor absorption of the tocotrienyl acetates, as levels of plasma T₃ were undetectable in the placebo group, but reached ~1, ~0.5, and ~0.1 μ mol/L after supplementation with α T₃, γ T₃ or δ T₃, respectively (O'Byrne et al., 2000). Rasool et al. (2006, 2008) performed two randomised, blinded endpoint, placebo-controlled parallel-design clinical trials in healthy male subjects who took TRF (80, 160, or 320 mg daily for 2 months) or self-emulsifying preparations (see Section 4) of tocotrienol-rich vitamin E (50, 100, and 200 mg daily for 2 months). In neither study, serum total cholesterol and LDL cholesterol were significantly changed (Rasool et al., 2006, 2008).

The contradicting results from human supplementation studies might be in part explained by the use of mixed forms of vitamin E containing significant amounts of α T, which was reported to attenuate the HMG-CoA reductase inhibition by T₃ in chickens (Qureshi et al., 1996). More recently, it has been reported that supernatant protein factor, a transcription factor involved in cholesterol biosynthesis, has identical protein sequence with α -tocopherol-associated protein. α T-induced activation of supernatant protein factor was thought to provide the link between α T and its observed stimulating effects on cholesterol biosynthesis (Porter, 2003; Stocker and Baumann, 2003). Qureshi et al. (1996) concluded from a literature review of the cholesterol-lowering effects of α T-containing TRF, that T₃ preparations reported to be effective contained between 15% and 20% α T and approximately 60% γ T₃ and δ T₃, and that preparations with 30% α T or more were ineffective.

Zaiden et al. (2010) recently addressed the hypocholesterolemic activities of T₃ and the potential antagonistic interaction of α T in HepG2 cells, LDL-receptor knockout mice, and a human trial. Incubation of HepG2 cells with 20 μ mol/L γ T₃, δ T₃, or γ T₃ + δ T₃, in agreement with the experiments reviewed above, did not alter HMG-CoA reductase mRNA, but reduced its expression on the protein level. The same was true for the sterol regulatory binding proteins 1 and 2 (Zaiden et al., 2010), which are transcription factors regulating the gene expression of HMG-CoA reductase and other proteins of the cholesterol biosynthesis pathway as well as that of the LDL receptor (Goldstein and Brown, 2009). The combination of γ T₃ + δ T₃ in HepG2 cells induced the expression of LDL receptor protein (Zaiden et al., 2010), which is important for hepatic uptake of LDL cholesterol from the bloodstream (Goldstein and Brown, 2009). Neither gene nor protein expression levels of HMG-CoA reductase, LDL receptor or the transcription factors sterol regulatory binding proteins 1 and 2 were altered by the addition of 20 μ mol/L α T to the culture media (Zaiden et al., 2010). In agreement with the in vitro data, LDL receptor knockout mice, which suffer from hypercholesterolemia, who were orally gavaged with 1 mg/d of the mixture of γ T₃ and δ T₃ for 4 weeks had significantly lower total cholesterol (15% lower), triacylglycerol (19% lower), and LDL concentrations (51% lower), respectively, than vehicle-only (dimethyl sulfoxide) treated control mice. Co-administration of the T₃-mixture with 1 mg/d α T over the duration of the trial did not diminish the lipid-lowering effects of the T₃ (Zaiden et al., 2010). Despite these hypocholesterolemic effects of the γ T₃ and δ T₃ mixture in vitro and in vivo, the authors did not find any alterations

in serum lipids of hypercholesterolemic subjects ($n = 10$) supplemented for 8 weeks with 120 mg of the $\gamma T_3/\delta T_3$ mixture dissolved in olive oil versus placebo (olive oil only; $n = 9$) (Zaiden et al., 2010). However, as αT is the predominant form of vitamin E in olive oil (Table 2) (Gliszczynska-Swiglo and Sikorska, 2004), the lack of effect could again be caused by the presence of αT and its potential antagonistic effect on the hypocholesterolemic activity of the T_3 , in addition to the possibilities that the T_3 mixture might not alter cholesterol regulation in humans at all and that the small trial may have simply been underpowered. Thus, the conundrum whether or not the lack of cholesterol-lowering activity of the T_3 in humans may be due to the presence of αT in the intervention still awaits clarification.

3.3. Cellular targets of the potential neuroprotective activities of tocotrienols

As discussed earlier, T_3 provide antioxidant activity in neuronal cell models at micromolar concentrations (Mazlan et al., 2006; Osakada et al., 2004; Sen et al., 2000; Shichiri et al., 2007), which might be difficult to achieve by dietary means (see Section 4). At nanomolar concentrations, however, T_3 modulate cellular signalling processes involved in neurodegenerative diseases and thus exert neuroprotective effects (Khanna et al., 2003; Sen et al., 2000, 2004) independent of their antioxidant activity. Cellular targets of T_3 , particularly of αT_3 , include prenyl transferases, non-receptor tyrosine kinases, phospholipases, lipoxygenases, and nuclear transcription factors (see below).

3.3.1. Prenyl transferases

The isoprenoid side-chain of the T_3 is structurally related to farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) (Elson and Yu, 1994). FPP and GGPP are intermediates in the mevalonate pathway and are essential for the isoprenylation of small Rho-GTPases by prenyl transferases, which are involved in synaptic functions (Hooff et al., 2010b). Recently, elevated FPP and GGPP levels were observed in post-mortem brain tissue from AD patients, indicating that enhanced isoprenoid levels and subsequent disturbance of isoprenylation of small GTPases may play a role in the pathophysiology of dementia (Eckert et al., 2009). T_3 may compensate excessive prenylation of small GTPases in neuronal cells by inhibition of prenyl transferases. Experiments supporting this mechanism have been reported for RhoA (Ras homolog gene family, member A) prenylation in human colon cell lines treated with T_3 . Incubation of HCT116 and HT29 cells with γT_3 (10–20 $\mu\text{mol/L}$) reduced the levels of membrane bound RhoA, suggesting the inhibition of geranylgeranylpyrophosphate transferase activity by the T_3 (Yang et al., 2010). To date, this potential neuroprotective activity of T_3 has not been investigated in detail and well-designed in vivo and in vitro studies are warranted.

3.3.2. Non-receptor tyrosine kinases

pp60^{c-Src} Kinase is a member of a family of intracellular non-receptor tyrosine kinases (c-Src) that participate in the signal transduction pathways of several surface transmembrane receptors (Bolen et al., 1992). High expression levels of pp60^{c-Src} kinase were found in the brain, especially in synaptic vesicles and growth cones of hippocampal cells (Sorge et al., 1985; Zhao et al., 2000). c-Src expression in neurones and astrocytes is 15–20 times higher than in fibroblasts and its activity is 6–12-fold higher in neuronal than in astrocyte cultures (Brugge et al., 1985), which suggests an important function of the protein in neuronal cells (Khanna et al., 2003). In rats, spatial maze training resulted in up-regulation of c-Src mRNA and pp60^{c-Src} protein in the hippocampus, which led to the conclusion that c-Src may participate in the regulation of

hippocampal synaptic activity during learning and memory (Zhao et al., 2000).

The potential involvement of c-Src in the pathogenesis of neurodegenerative conditions has been suggested by several observations. In mice, c-Src knockout and chemical inhibition of Src activity, respectively, reduced cerebral ischaemia-induced brain injury (Paul et al., 2001). Also in rats, treatment with a Src family kinase inhibitor significantly reduced focal ischemic brain injury (ca. 50% reduction in infarct size) (Lenmyr et al., 2004). Rapid activation of c-Src appears to be an important step in bringing about glutamate toxicity in neurones and in murine HT4 cells (Khanna et al., 2007). Pre-treatment of HT4 cells with 250 nmol/L αT_3 effectively protected from glutamate toxicity and neuronal cell death by activation of pp60^{c-Src} kinase and inhibition of ERK1 and ERK2 phosphorylation (Sen et al., 2000). Extracellular signal-regulated kinases (ERK) are a subfamily of mitogen-activated protein kinases that have been implicated in mediating the signalling events that precede apoptosis. Interestingly, this protective effect at nanomolar concentrations was only observed for αT_3 but not αT (Sen et al., 2000). In another study 10 $\mu\text{mol/L}$ αT_3 significantly protected rat striatal neurones from staurosporine-induced apoptosis, γT_3 and δT_3 as well as lower concentrations of αT_3 were ineffective (Osakada et al., 2004).

3.3.3. Phospholipase A₂

Phospholipase A₂ (PLA₂) enzymes catalyse the hydrolysis of the sn-2 ester bond of cell membrane phospholipids to liberate free fatty acids, mainly arachidonic acid, and lysophospholipids (Dennis et al., 1991; Sun et al., 2004). The PLA₂ family can be subdivided into classes and the group IV calcium-dependent cytosolic PLA₂, the group II secretory PLA₂, and the group VI Ca²⁺-independent PLA₂ have recently received considerable research attention because of their potential involvement in the pathogenesis of neurodegenerative disorders (Sun et al., 2004). Particularly the cytosolic PLA₂ (cPLA₂) appears to be involved in neurotoxicity and neurodegenerative diseases associated with ischaemia-reperfusion and oxidant injury (Sun et al., 2004).

Arachidonic acid can be toxic to neurones and is a substrate for lipoxygenases (LOX, see next paragraph) (Fig. 4) (Sen et al., 2007). While glutamate insult activates cPLA₂ in HT4 neuronal cells, incubation with 250 nmol/L of αT_3 inhibited the glutamate-induced activation of cPLA₂, blocked the release of free arachidonic acid, and prevented the loss of cell viability (Khanna et al., 2010). Modulation of PLA₂ by αT_3 is mediated by inhibition of PLA₂ serine phosphorylation (Khanna et al., 2010), which is critical for the catalytic function of the enzyme (Murakami and Kudo, 2002). The phosphorylation of serine is regulated by ERK1 and ERK2, which themselves are inactivated in HT4 cells by pre-incubation with nanomolar concentrations of αT_3 but not αT (see below) (Sen et al., 2000).

3.3.4. 12-Lipoxygenase

12-Lipoxygenase (12-LOX) is an oxidoreductase that inserts molecular oxygen at carbon 12 of its main substrate arachidonic acid (Needleman et al., 1986). 12-LOX plays a role in oxidative glutamate toxicity and is the predominant LOX in the brain (Hagmann et al., 1993; Li et al., 1997; Nishiyama et al., 1993; Rao et al., 1993). The 12-LOX-catalysed reaction of arachidonic acid with molecular oxygen results in the formation of 12-hydroperoxy-eicosatetraenoic acid (12-HPETE) (Fig. 4), a precursor in the synthesis of pro-inflammatory eicosanoids (Needleman et al., 1986). 12-HPETE and its derivatives may play a role as second messengers in synaptic transmission and as retrograde messengers in learning and memory (Shimizu and Wolfe, 1990). The significance of 12-LOX in glutamate-induced cell death was discovered when neurones isolated from 12-LOX deficient mice were found

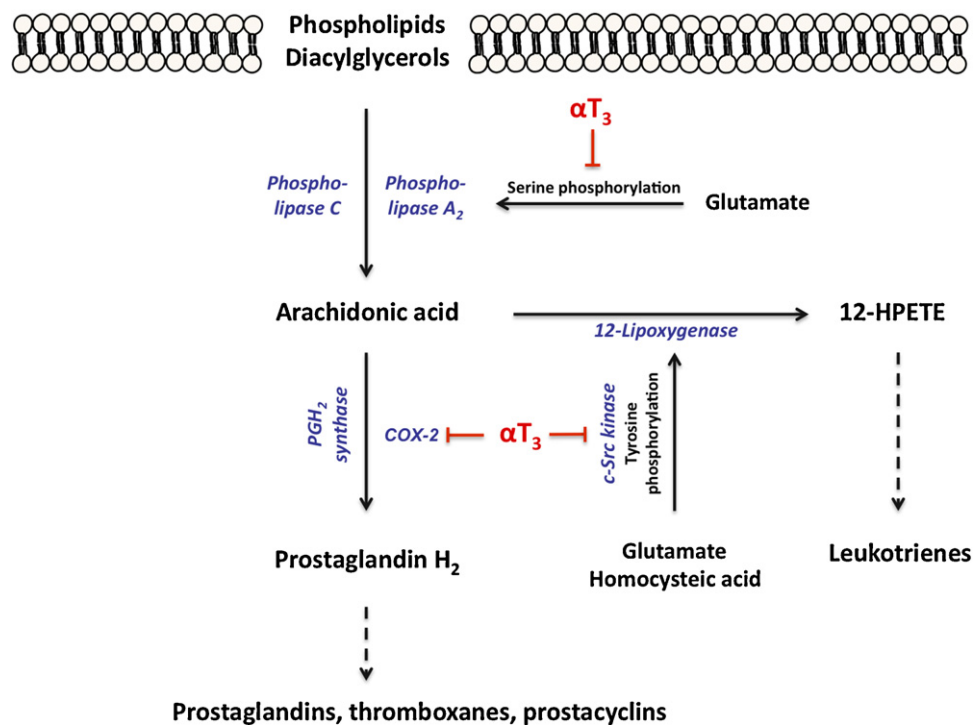


Fig. 4. The role of phospholipase A₂ and 12-lipoxygenase in the synthesis of pro-inflammatory eicosanoids from arachidonic acid and the influence of tocotrienols.

to be resistant to glutamate-induced cell death (Khanna et al., 2003). Metabolites of 12-LOX activity, that were not detectable at basal conditions, were significantly increased following glutamate treatment. The observation that 12-LOX might be sensitive to T₃ was made when HT4 cells were treated with 250 nmol/L of αT₃ before exposure to glutamate and a reduced production of 12-LOX metabolites was observed. Microinjection of 10⁻¹⁹ mol of αT₃ into the cytosol of HT4 or immature cortical neurones protected the cells from glutamate-induced cell death (Khanna et al., 2005) confirming that αT₃ targets cytosolic components (Khanna et al., 2003; Sen et al., 2000). Further examinations confirmed that αT₃ effectively inhibited the activity of the isolated enzyme in a dose-dependent manner. In silico investigation of possible docking sites suggested that αT₃ may bind at the opening of a solvent cavity close to the active site of 12-LOX and thus interferes with access of the natural substrate arachidonic acid to the active site of the enzyme (Khanna et al., 2003).

Interestingly, 12-LOX is subject to tyrosine phosphorylation by c-Src kinase in response to glutamate (Fig. 4). Glutamate-induced 12-LOX tyrosine phosphorylation was inhibited by αT₃ and pharmacological inhibitors of c-Src kinase in vitro and these findings were confirmed in an in vivo stroke model. T₃ supplementation reduced stroke-induced brain damage and analysis of tissues from the stroke site revealed reduced phosphorylation of 12-LOX and suppressed activation of stroke-induced c-Src kinase activity in T₃-supplemented rats (Khanna et al., 2005).

Inducible activation of c-Src kinase and 12-LOX are also early events preceding neuronal death induced by homocysteic acid (HCA) (Khanna et al., 2006). HCA is an oxidised metabolite of homocysteine, which is a known trigger of neurotoxicity that seems to affect neurodegenerative pathways similar to those induced by glutamate (Sagara et al., 2002). In a study using HT4 cells and primary cortical neurones, HCA-induced neuronal death was completely prevented when cells were pretreated with 250 nmol/L αT₃ but not by αT (Khanna et al., 2006), consistent with observations from previous studies (Sen et al., 2000). The protective effects of αT₃ were also observed when 250 nmol/L of αT₃ was added to cells up

to 8 h after the exposure to HCA (Khanna et al., 2006). Nanomolar concentrations of αT₃ prevented cells from HCA-induced increases in intracellular Ca²⁺ and reduction in mitochondrial membrane potential (Khanna et al., 2006), indicating anti-apoptotic effects. Further support for the anti-apoptotic activity of αT₃ comes from increases in the expression of the anti-apoptotic protein Bcl-2 in cultured cortical neurones incubated for 24 h with 10 nmol/L of either αT₃, γT₃, αT, or γT (Numakawa et al., 2006).

3.3.5. Nuclear factor-κB signalling pathway

The nuclear factor-κB (NF-κB) family of transcription factors regulates genes that are critical for inflammation, immunity, cell survival, and apoptosis and thus represents a therapeutic target against neurodegenerative diseases (Ahn et al., 2007; Kaileh and Sen, 2010; Kaltschmidt et al., 2005; Karin and Lin, 2002). NF-κB has been implicated in processes of synaptic plasticity and memory (Albensi and Mattson, 2000). During the development of the nervous system, NF-κB is activated in growing neurons by neurotrophic factors and can induce the expression of genes involved in cell differentiation and survival. In the mature nervous system, NF-κB is activated in synapses in response to excitatory synaptic transmission and may play a pivotal role in processes such as learning and memory (Boersma et al., 2011; Gutierrez and Davies, 2011; Mattson, 2005). Constitutive activation of NF-κB (Meffert and Baltimore, 2005) as well as evidence for a compartmentalized clustering of NF-κB pathway components in the axon initial segment of neurons have been documented (Schultz et al., 2006). The hippocampal region-specific regulation of NF-κB may contribute to learning-associated synaptic reorganization (O'Sullivan et al., 2010). NF-κB activity is tightly regulated by its primary inhibitor IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) through a unique autoinhibitory loop promoting proper brain development and function (Shim et al., 2011). On the other hand, by inducing the production and release of inflammatory cytokines, reactive oxygen molecules, and excitotoxins, activation of NF-κB in microglia and astrocytes may contribute to neuronal degeneration (Mattson, 2005). However, astroglial NF-

κ B is also an important regulator of learning, memory, and synaptic plasticity (Bracchi-Ricard et al., 2008). T_3 are currently discussed as anti-apoptotic and anti-inflammatory agents (Ahn et al., 2007; Kaileh and Sen, 2010; Wilankar et al., 2011) and emerging findings suggest roles for NF- κ B as a mediator of effects of dietary factors on neuronal plasticity (Mattson, 2005). NF- κ B activation in neurones can increase survival by induction of antioxidant enzymes and anti-apoptotic proteins such as Bcl-2, while in microglia and astrocytes, its activation may result in the release of pro-inflammatory cytokines and may thus contribute to neurodegeneration (Mattson, 2005).

On the other hand, T_3 are thought to exert anti-inflammatory activity by inhibition of NF- κ B signalling (Ahn et al., 2007; Kaileh and Sen, 2010). Orally gavaged T_3 (a mixture of αT_3 , γT_3 , and δT_3 ; 50, 100, or 200 mg/kg bodyweight daily for 10 weeks) prevented chronic alcohol-induced neuroinflammation and cognitive impairment (Tiwari et al., 2009b). Similarly treated streptozotocin-injected rats receiving 25, 50 or 100 mg/kg bodyweight daily of the T_3 mixture for 10 weeks were protected from cognitive impairment, oxidative, and nitrosative stress compared to streptozotocin-injected control animals (Kuhad et al., 2009; Tiwari et al., 2009a). T_3 treatment significantly reduced the levels of tumor necrosis factor- α and inhibited NF- κ B signalling in both ethanol-challenged (Tiwari et al., 2009b) and streptozotocin-injected animals (Kuhad et al., 2009). T_3 also attenuated a streptozotocin-induced increase in acetylcholinesterase activity, which resulted in improved synapse signalling (Kuhad et al., 2009).

Although the reduction of chemical-induced activation of NF- κ B by T_3 is generally considered beneficial, it may also have a downside. Activation of NF- κ B in neurones has been implicated in synaptic plasticity and memory, although the responsible target genes have not been identified yet (Albensi and Mattson, 2000). Inhibition of NF- κ B signalling in neurones may therefore bear the risk of unwanted effects on synaptic plasticity. Although the hypothetical risk of harm may, in light of the above discussed studies suggesting protection from cognitive impairment by T_3 (Kuhad et al., 2009; Tiwari et al., 2009a,b), appear small, it still needs to be considered and should be addressed in future experiments aimed at studying the prevention of neurodegenerative diseases by modulating NF- κ B signalling.

In summary, a number of molecular targets for T_3 were identified including prenyl transferases, pp60^{c-Src} kinase, ERK1, ERK2, 12-LOX, PLA₂, and NF- κ B signalling. In these pre-clinical studies, T_3 exerted neuroprotective effects at nanomolar concentrations, which can be reached in human plasma following T_3 supplementation (Khosla et al., 2006; O'Byrne et al., 2000) and may explain the positive outcome of some human studies. For example it has been reported from the Chicago Health and Aging Project, which monitored the incidence of AD over 6 years in community residents older than 65 years, that the intake of mixed forms of vitamin E, rather than αT alone, was associated with a slower rate of cognitive decline (Morris et al., 2005). These findings were confirmed recently in a dementia-free sample of 232 subjects aged ≥ 80 years from the Kungsholmen Project (Mangialasche et al., 2010). After 6 years, subjects with vitamin E plasma levels in the highest tertile had a reduced risk of developing AD in comparison to persons in the lowest tertile. However, the neuroprotective effect seemed to be related to the combination of different vitamin E forms, rather than to αT alone (Mangialasche et al., 2010), whose efficacy in interventions against AD is currently debated (Uoro and Mousa, 2010). In a randomised double-blind placebo-controlled study with 64 older healthy adults (37–78 years), half of which were supplemented with 160 mg/d vitamin E (74% T_3 , 26% T) and the other half with placebo capsules for 6 months, markers for oxidative DNA damage were significantly reduced in the vitamin E group (Chin et al., 2008). In light of the role that oxidative stress and potentially DNA dam-

Table 3

Main enzymes and signalling pathways that are induced by glutamate and inhibited by nanomolar concentrations of α -tocotrienol and their physiological roles.

Enzyme	Events
pp60 ^{c-Src} kinase	- Early event in the signal transduction pathways of glutamate induced-cell death - Possibly induces phosphorylation of ERK1 and ERK2
ERK1 and ERK2	- Activates 12-LOX by phosphorylating tyrosine residues - Implicated in mediating signalling pathways preceding apoptosis
PLA ₂	- Regulates serine phosphorylation on PLA2 - Hydrolyzes membrane phospholipids to release arachidonic acid
12-LOX	- Initial step in arachidonic metabolism - Predominant LOX in brain cells - Produces 12-HPETE through lipoxygenation of arachidonic acid, which is thought to be neurotoxic

age might play in the development of neurodegenerative diseases (see above), these findings are encouraging and warrant further randomised clinical trials aimed at studying the neuroprotective properties of T_3 in humans (Table 3).

4. Enhancing the bioavailability of tocotrienols

Although all forms of vitamin E appear to be absorbed (Tsuzuki et al., 2007) and transported to the liver to a similar extent (Kayden and Traber, 1993; Traber et al., 1992), the rapid hepatic degradation of T_3 (Fig. 2) (Birringer et al., 2002; Sontag and Parker, 2007) and their subsequent urinary excretion (Lodge et al., 2001; Zhao et al., 2010) substantially limit their plasma and tissue concentrations (Table 1) (Fairus et al., 2006; Podda et al., 1996; Yamashita et al., 2002). Both, T and T_3 pass the blood-brain-barrier and are detectable in the brain at concentrations in the low albeit significantly different nanomolar ranges (e.g. αT , 2–30; αT_3 , <0.2 nmol/g) (Gaedicke et al., 2009; Table 1), where they thus may exert neuroprotective activities. Based on the health beneficial properties of T_3 described above and the assumption that higher plasma and tissue concentrations of T_3 will lead to enhanced biological activities, researchers have attempted different strategies to increase the oral bioavailability of T_3 .

Yap et al. (2001) studied the pharmacokinetics of T_3 in eight healthy males given a single oral dose of mixed vitamin E (αT_3 , 87; γT_3 , 166; δT_3 , 43; αT , 93 mg) and observed 2.5–3.7-fold higher maximum plasma concentrations (C_{max} ; γT_3 : fasting, 1.4; fed, 5.2 μ mol/L) and 2.5–2.9-fold higher areas under the plasma concentration-time curves (AUC) when T_3 were ingested following a high-fat breakfast instead of after a ≥ 12 h fast. These authors later investigated the suitability of self-emulsifying T_3 formulations, so-called self-emulsifying drug delivery systems (SEDDS), as a means of enhancing their bioavailability (Yap and Yuen, 2004). In a three-armed crossover study with 1-week washout periods, six fasted (≥ 12 h) healthy males were given in random order two different SEDDS or a non-self-emulsifying formulation containing 200 mg mixed T_3 each (αT_3 , 55; γT_3 , 112; δT_3 , 33 mg). T_3 delivered as SEDDS resulted in 2.5–4.5-times higher C_{max} and 2.3–2.7-fold higher AUC than T_3 formulated as a non-self-emulsifying emulsion. Furthermore, the lag time for the onset of absorption was 1 h from SEDDS and 2 h from the non-self-emulsifying formulation, indicating a faster absorption of T_3 from SEDDS (Yap and Yuen, 2004). However, in none of these trials was the half-life of the T_3 different between fed or fasting state or between the different emulsion systems, respectively (Yap and Yuen, 2004; Yap et al., 2001), suggesting that faster and increased absorption does not affect metabolism and excretion kinetics of T_3 . Furthermore, as reviewed in a previous chapter, T_3 delivered as SEDDS in a human trial still remained without significant effect on the primary out-

come parameters, such as blood lipid concentrations (Rasool et al., 2008).

Another feasible approach to enhance the bioavailability of T and T₃ is the inhibition of their metabolic degradation and excretion (reviewed in Frank, 2005). We and others have previously observed a marked increase (>10-fold) in vitamin E plasma and tissue concentrations in rats when the vitamin was administered together with certain bioactive compounds (Frank et al., 2002, 2003a,b, 2004a, 2006; Kamal-Eldin et al., 1995, 2000; Ross et al., 2004; Yamashita et al., 1992, 1995), such as sesamin, a lignan found in sesame seeds and oils, or rye alkylresorcinols (Kamal-Eldin et al., 2000; Ross et al., 2004). Parker and colleagues later confirmed the potent inhibition of the metabolic degradation of vitamin E (Fig. 2) by sesamin (Parker et al., 2000; Sontag and Parker, 2002) and alkylresorcinols in HepG2 cells (Ross et al., 2004). In humans, intake of sesame seeds or oils increased plasma concentrations of γ T (Cooney et al., 2001; Lemcke-Norojärvi et al., 2001), reduced its conversion to γ CEHC and the excretion of the metabolite in urine (Frank et al., 2004b, 2008). Rats fed a TRF together with sesame seeds accumulated α T₃ and γ T₃ in their adipose tissue and skin, but not in other organs or plasma, to a much larger extent than rats fed a TRF alone (Ikeda et al., 2001). In line with the concept that elevating T₃ concentrations might enhance their biological activities, Gu et al. (1997) reported significantly improved immune-modulatory properties of α T and mixed T₃ when fed in combination with the sesame lignans sesamin and episesamin (1:1 by wt; 2 g/kg diet). The activity-enhancing effect of the lignans was more pronounced for T₃ than for α T (Gu et al., 1997), which is in accord with the observations that T₃ are preferentially metabolised (Sontag and Parker, 2007) and that inhibition of tocopherol- ω -hydroxylase activity will primarily affect non- α T congeners.

A potential disadvantage of this approach, however, lies in the possibility that the health-promoting effects of T₃ might in part be facilitated by one of their metabolites rather than the respective parent compounds. In that case, inhibition of tocopherol- ω -hydroxylase would reduce the concentration of the bioactive metabolite. Indeed, T₃ decrease the cyclooxygenase 2-catabolised production of prostaglandin E₂ (a pro-inflammatory eicosanoid, Fig. 4) in human lung epithelial A549 cells more potently than T (in decreasing order of activity: γ T₃ \approx δ T > γ T \gg α T = β T), an effect that is partly blocked by addition of sesamin to the culture medium (Jiang et al., 2008). The IC₅₀ for cyclooxygenase 2-inhibition by the long-chain metabolite δ 13'-carboxychromanol (4 μ mol/L) was comparable to that of ibuprofen (5 μ mol/L), an anti-inflammatory drug, and much lower than the IC₅₀ of the shorter-chain metabolites δ 9'-, α 5'-(α CMBHC), and γ 3'-carboxychromanol (γ CEHC), which were >20, 140, and 450 μ mol/L, respectively (Jiang et al., 2008) (see Fig. 2 for chemical structures of the metabolites).

Furthermore, genetic heterogeneity needs to be considered as a factor modulating the tissue concentrations of T and T₃. The apolipoprotein E4 genotype, for example, which is an important genetic risk factor for Alzheimer's disease (Strittmatter and Roses, 1996), is associated with increased plasma α T (Borel et al., 2007; Huebbe et al., 2010) in the presence of reduced tissue concentrations of the vitamin (Huebbe et al., 2010).

In summary, the absorption of T₃ and maximum plasma concentrations can be increased by simultaneous ingestion of dietary fat (Yap et al., 2001) and the onset of absorption might be shortened by use of self-emulsifying systems (Yap and Yuen, 2004). However, none of these approaches will result in better retention of the vitamin in the body. Inhibition of the metabolic degradation of T₃ by co-ingestion of tocopherol- ω -hydroxylase inhibitors, such as sesamin or alkylresorcinols (Frank, 2005; Frank et al., 2008; Parker et al., 2000; Ross et al., 2004), might increase retention in the organism, but also bears the risk of unwanted side-effects such as

decreased formation of potentially active metabolites (Jiang et al., 2008).

5. Conclusions

The presented data suggest that T₃ may have some potential in the prevention of neurodegenerative disorders, which can be explained on the basis of three distinct mechanisms: Firstly, as antioxidants, T₃ may protect cells from oxidative stress, which itself plays an important role in neurodegeneration. Secondly, T₃ may inhibit cholesterol biosynthesis and may thus protect against hypercholesterolemia and the metabolic syndrome, which are important risk-factors for neurodegenerative diseases. Thirdly, T₃ may alter signal transduction pathways that are involved in neuronal cell death. The T₃ concentrations that are required to affect cellular signalling pathways are very low, in the nanomolar range, and physiologically achievable through dietary means.

As the pathophysiological processes underlying neurodegenerative diseases may persist for decades before symptoms become evident, T₃ have little chance of success as treatment or cure for such afflictions. As a dietary measure for the prevention of neurodegenerative diseases, on the other hand, T₃ offer some promise. Importantly, T₃ are naturally occurring congeners of the vitamin E family that have no known adverse effects when consumed as part of a normal diet. However, the in vivo evidence for the neuroprotective activities of T₃ is still scarce and therefore properly designed experiments in relevant animal models of neurodegenerative disorders and age-dependent dementias, and ultimately human intervention trials, are highly warranted.

Competing interests

The authors declare that they have no competing interests.

Contributors

All authors wrote the first draft, read and approved the final manuscript.

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