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Review Article

Interactions between α-tocopherol, polyunsaturated fatty acids, and lipoxygenases during embryogenesis

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ABSTRACT

α-Tocopherol is a lipid-soluble antioxidant that is specifically required for reproduction and embryogenesis. However, since its discovery, α-tocopherol's specific biologic functions, other than as an antioxidant, and the mechanism(s) mediating its requirement for embryogenesis remain unknown. As an antioxidant, α-tocopherol protects polyunsaturated fatty acids (PUFAs) from lipid peroxidation. α-Tocopherol is probably required during embryonic development to protect PUFAs that are crucial to development, specifically arachidonic (ARA) and docosahexaenoic (DHA) acids. Additionally, ARA and DHA are metabolized to bioactive lipid mediators via lipoxygenase enzymes, and α-tocopherol may directly protect, or it may mediate the production and/or actions of, these lipid mediators. In this review, we discuss how α-tocopherol (1) prevents the nonspecific, radical-mediated peroxidation of PUFAs, (2) functions within a greater antioxidant network to modulate the production and/or function of lipid mediators derived from 12- and 12/15-lipoxygenases, and (3) modulates 5-lipoxygenase activity. The application and implication of such interactions are discussed in the context of α-tocopherol requirements during embryogenesis.

Contents

α-Tocopherol and lipid peroxidation

α-Tocopherol, a lipid-soluble antioxidant, is one of the eight vitamin E forms synthesized by plants [1] and is the only form that meets human vitamin E requirements [2]. α-Tocopherol scavenges peroxyl radicals during the propagation of lipid peroxidation (Fig. 1) and is termed a chain-breaking antioxidant because it prevents the chain reaction of lipid peroxidation, but it does not prevent the formation of the initial lipid peroxyl radical [3]. α-Tocopherol is particularly enriched in neuronal tissue, especially the brain, where it is tenaciously retained during inadequate vitamin E intake even after the peripheral tissues become α-tocopherol-depleted [4]. Overt vitamin E deficiency occurs rarely in humans, but does occur in patients with fat malabsorption syndromes or genetic defects in the hepatic α-tocopherol transfer protein (α-TTP) [5] and in severe malnutrition [6,7]. Humans with vitamin E deficiency present initially with a mild sensory neuropathy, which leads to a progressive, peripheral neuropathy caused by a dying back of large-caliber, sensory neurons that advances to a spinocerebellar ataxia and ultimately death [5].

α-Tocopherol protects cellular membranes from lipid peroxidation in association with a larger antioxidant network (Fig. 1). Once α-tocopherol reduces lipid peroxyl radicals to lipid hydroperoxides,

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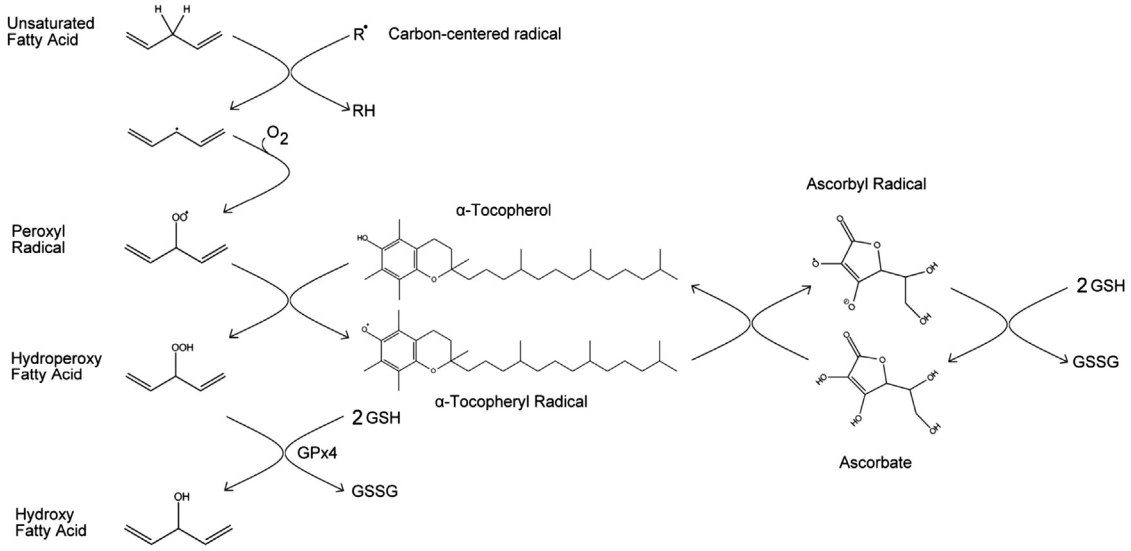

Fig. 1. Lipid peroxidation and the antioxidant network. During the propagation stage of lipid peroxidation, a carbon-centered radical (R•) abstracts an allylic hydrogen from a neighboring, unsaturated fatty acid. Molecular oxygen reacts with the fatty acid radical, generating a peroxyl radical, which can be reduced by α-tocopherol, creating a hydroperoxy fatty acid and the α-tocopheryl radical. The hydroperoxy fatty acids are converted to hydroxy fatty acids via phospholipid hydroperoxide glutathione peroxidase (GPx4), using two glutathiones (GSH) as the reducing agents and creating oxidized glutathione disulfide (GSSG). To replenish the α-tocopherol, the α-tocopheryl radical is reduced by ascorbate. The oxidized ascorbyl radical is subsequently reduced back to ascorbate via GSH.

the selenium-dependent enzyme phospholipid hydroperoxide glutathione peroxidase (GPx4) converts the hydroperoxides to the less toxic lipid hydroxides at the expense of glutathione. Ascorbate (vitamin C) reduces the α-tocopherol radical, regenerating active α-tocopherol [8]. Subsequently, ascorbate is regenerated at the expense of glutathione. Maintenance of this antioxidant network is crucial to protect cellular membranes against radical-mediated degradation [9]. For example, vitamin E disappears faster from plasma in individuals who smoke, but vitamin C supplementation corrects the rapid α-tocopherol disappearance [10,11]. In adult zebrafish, chronic vitamin E deficiency causes a secondary depletion of vitamin C and, concomitantly, a severe degeneration of skeletal muscle [12].

α-Tocopherol protects polyunsaturated fatty acids (PUFAs), notably arachidonic acid (ARA; 20:4 ω-6) and docosahexaenoic acid (DHA; 22:6 ω-3). Indeed, human α-tocopherol requirements increase in parallel with dietary PUFA consumption or with an increasing index of fatty acid unsaturation [13]. α-Tocopherol is postulated to colocalize with PUFA-enriched phospholipid domains of the cell membrane [14]. Moreover, a peroxyl radical generated from the PUFA will localize to the air–water interface, where the hydroxyl group of α-tocopherol intercepts the radical and reduces it [15]. Studies in animals fed experimental diets have demonstrated the importance of α-tocopherol in protecting PUFAs. For example, when zebrafish are fed diets that require them to synthesize ARA and DHA from their respective precursors, the vitamin E-deficient fish have decreased percentages of total ω-6 and ω-3 PUFAs compared with those fed a vitamin E-sufficient diet [16], suggesting that vitamin E protects these long-chain PUFAs. Similarly, feeding fish oil to pregnant rats decreased fetal brain α-tocopherol concentrations [17].

Is vitamin E deficiency a significant cause of spontaneous embryonic death?

In 1922, α-tocopherol was discovered because vitamin E-deficient, pregnant rats fed rancid fat failed to carry their offspring to term [18]. α-Tocopherol and α-TTP have critical roles in embryonic development [19]. α-TTP is expressed in the human yolk sac [20]; therefore, we studied zebrafish (*Danio rerio*) embryos, which abundantly express α-TTP by 48 h postfertilization (hpf) and upregulate α-TTP in response to oxidative stress [21]. Remarkably, adult α-tocopherol-deficient zebrafish could spawn and produce viable eggs, but within days the embryos suffered developmental impairment and increased mortality [22]. Similar findings have been reported for α-TTP-knockout mice [23]. Importantly, we found that the zebrafish embryonic brain accumulates α-tocopherol and expresses α-TTP. α-TTP knockdown caused head and eye malformations before 15 hpf [19]. Intriguingly, the α-tocopherol requirement for neurologic development in zebrafish coincides with increased synthesis of highly peroxidizable lipids by the zebrafish embryo, evidenced by increased Elovl4 [24] and Elovl5 [25] expression in the head/brain region.

Our knowledge of how vitamin E is delivered to the brain is very limited. α-Tocopherol is transported in the circulation by all lipoproteins and is delivered by pathways that deliver other lipids to cells [26]. α-Tocopherol is readily exchanged between high-density lipoprotein (HDL) and apolipoprotein B (apoB)-containing lipoproteins [27]. HDL, however, is probably more important in brain development, because the central nervous system (CNS) does not contain apoB, but rather large apoE particles serve this function [28]. Scavenger receptor class B, type I facilitates selective uptake of HDL-associated α-tocopherol by the blood–brain barrier in vitro [29]. In vivo the cerebrospinal fluid (CSF) contains only HDL [30] and CSF-HDL contains α-tocopherol [31].

The importance of both HDL and apoB-containing lipoproteins is illustrated in patients with the autosomal recessive disorder abetalipoproteinemia. These patients have extraordinarily low circulating lipids because they have only HDL and no lipoproteins containing apoB (e.g., chylomicrons, very low density lipoproteins (VLDL), or low-density lipoproteins) [32]. Vitamin E deficiency in humans was first described in abetalipoproteinemic patients [33]. When these patients were supplemented with large vitamin E doses (150 mg/kg body wt), they did not experience the neurologic defects seen in unsupplemented patients; moreover, they were able to bear normal children [34,35].

Abetalipoproteinemia is distinct from homozygous hypobetalipoproteinemia [36]. The latter is caused by a defect in the apoB gene [36], whereas abetalipoproteinemia is caused by a defect