Chapter 46

Vitamin E

Overview

- There are several naturally occurring forms of vitamin E in plants.
- Vitamin E is passively absorbed in conjunction with other lipid-soluble vitamins by the intestinal tract, and subsequently packaged into chylomicrons.
- Vitamin E is the first and selenium the second line of defense against peroxidation of lipids contained in cell membranes.
- Tocopherols act as antioxidants by breaking free-radical chain reactions.
- Vitamin C helps to regenerate the active form of vitamin E.
- Vitamin E deficiency can result in erythrocyte fragility, muscular degeneration, steatitis, retinopathy, and reproductive failure.
- Vitamin E excess appears to be non-toxic.

There are several naturally occurring forms of **vitamin E** (**tocopherol**) in plants, and all are isoprenoid-substituted 6-hydroxychromanes (tocols). **α-Tocopherol**, which is methylated in the 5, 7, and 8 position, has the widest natural distribution and greatest physiologic activity; however, the **β**, **γ**, and **Δ-tocopherols** are also of dietary significance (**Fig. 46-1**). The **β** and **γ** forms are used as natural preservatives in pet foods. With the exception of fat and liver tissue, animal foods are generally considered to be poor sources of this vitamin.

Vitamin E and **selenium** (**Se**) act synergistically in protecting membranes against lipid peroxidation (see below). Vitamin E is absorbed in conjunction with other lipid-soluble vitamins across the intestine, thus requiring the presence of bile acid micelles (see Chapter 62). Malabsorption due to intestinal resection or disease, or that secondary to liver disease, are common causes of vitamin E deficiency. This vitamin is initially distributed from the intestine through the lymphatic circulation as a part of chylomicrons (CMs), from where it is said to "rub off" onto cells, such as erythrocytes. From the liver onward, the distribution of vitamin E follows that of triglyceride and other lipids, via lipoproteins (particularly CMs and liver-derived VLDL; see Chapters 64 and 65) to adipose tissue and cell membranes. Vitamin E is thought to become more evenly distributed throughout the body than the other fat-soluble vitamins, with highest concentrations found in plasma, liver, and adipose tissue. As with the other fat-soluble vitamins, plasma levels of vitamin E are not, however, a good index of total body stores.

Vitamin E appears to be the first and selenium (Se) the second line of defense against peroxidation of unsaturated fatty acids (UFAs) contained in cell membrane phospholipids. Cholesterol and phospholipids in the plasma membrane, as well as those in subcellular membranes (e.g., mitochondria, endoplasmic

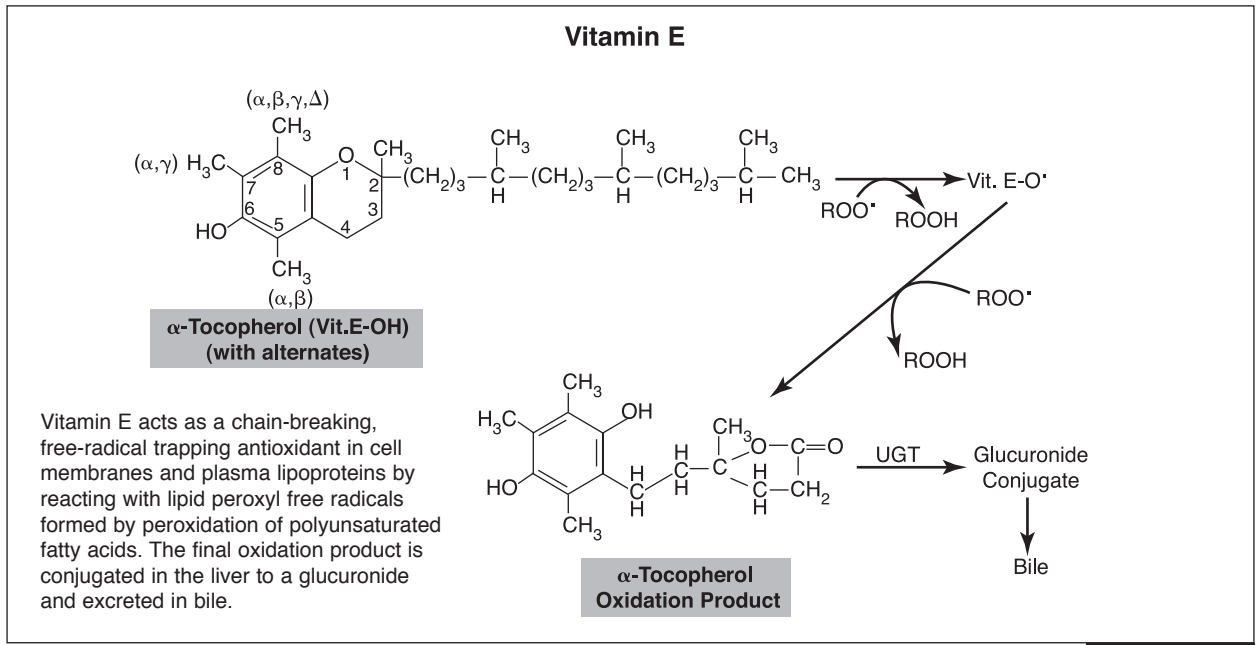

Figure 46-1

reticulum, etc.), possess high affinities for α-tocopherol. This works against injury to cell membranes, as in red blood cell fragility and the muscular degeneration of animals. It also aids in the normal functioning of the seminiferous epithelium (and therefore sperm production), and assists with implantation (thus sustaining the fetus in the uterus). The **antioxidant** action of tocopherol is effective at high oxygen levels, and thus tends to be concentrated in lipid structures exposed to high partial pressures of O_2 (e.g., membranes of the respiratory tree, the retina, and erythrocytes; see **deficiency symptoms below**).

Tocopherols act as antioxidants by **breaking free-radical chain reactions** through transfer of a phenolic hydrogen (H) to a **peroxyl free radical** of an UFA (**H + ROO· —> ROOH**; **Fig. 46-1**). The need for vitamin E, therefore, partially depends upon the dietary intake of UFAs. Animals consuming large quantities of fish-based diets (which normally contain high amounts of UFAs) without adequate antioxidants such as vitamins C or E, can experience peroxidation of body fat and fat necrosis. Phenoxy free radicals (**Vit. E-O·; Fig. 46-2**) formed may react with the reduced form of **vitamin C** to regenerate tocopherol, or with other peroxyl free radicals (**ROO·**), thus oxidizing the chromane ring and side chain. This **oxidation product** is typically removed from the circulation by the liver, and through the action of **UDP-glucuronosyltransferase** (**UGT**; see Chapter 29), conjugated to a **glucuronide** and excreted into bile. Elimination of vitamin E in this manner generally requires that new tocopherol be obtained through the diet.

Glutathione peroxidase (**GP**), of which **Se** is an integral component (see Chapters 30 and 51), constitutes the second line of defense against hydroperoxides which could otherwise damage membranes, and inhibit some membrane-bound enzymes (see **Fig. 46-2**). Following the action of **phospholipase A_2** on membrane-bound phospholipid, the UFA in position 2 is released into the cytosol where it is now available to enter into eicosanoid biosynthesis (see Chapters 68 and 69). Peroxides generated from these UFAs can now be acted upon by cytoplasmic enzymes such as **GP** and **catalase**, which are capable of converting **H_2O_2** to **O_2** and **H_2O**. Catalase is a rather ubiquitous enzyme, present in most aerobic tissues.

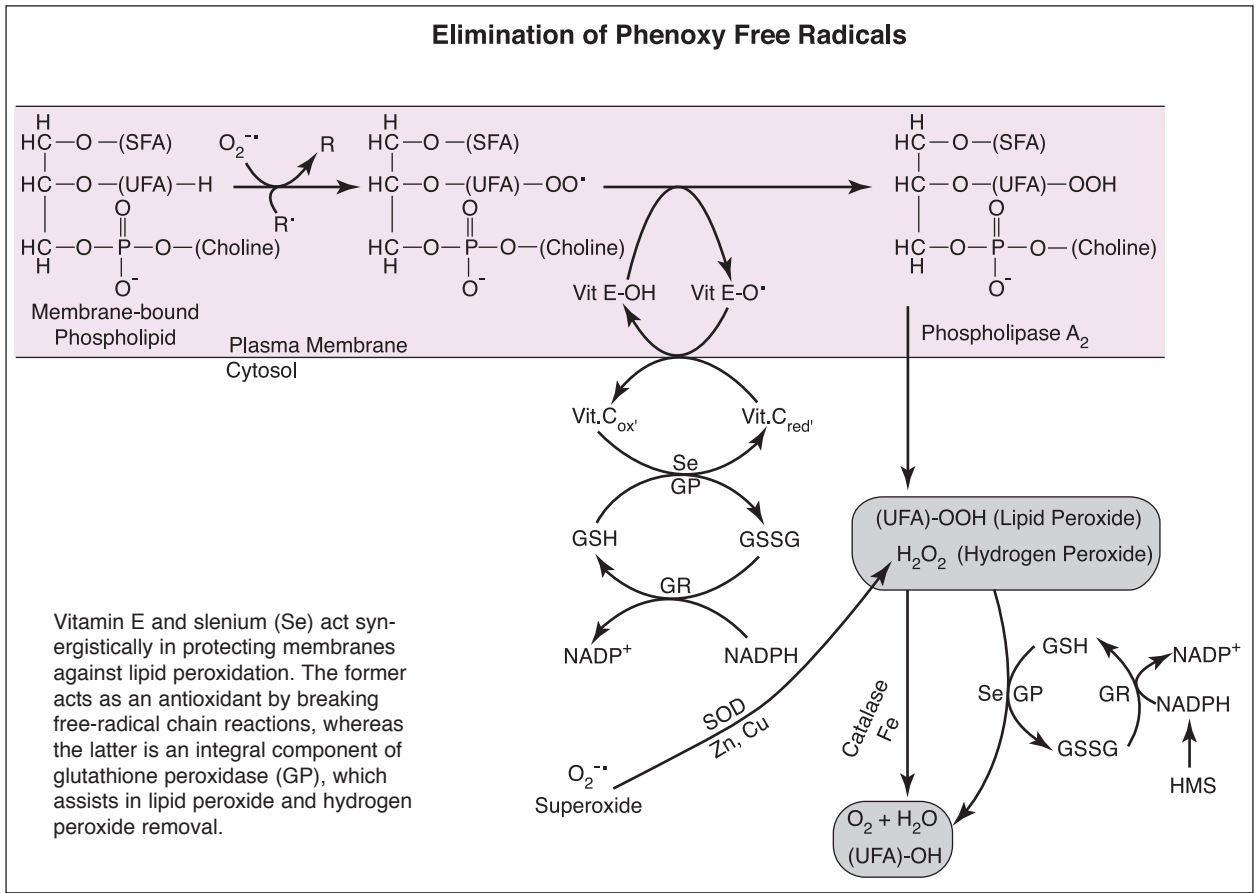

Figure 46-2

However, patients with a catalase deficiency reportedly show few toxic symptoms, presumably because of the redundant actions of GP, particularly in erythrocytes.

For its activity, GP requires the reduced form of **glutathione** (**GSH**). Through continual reduction of the oxidized form of glutathione (GSSG) to GSH (accomplished by the FAD-containing enzyme, **glutathione reductase** (**GR**), and **NADPH** (produced by the hexose monophosphate shunt (HMS))), GSH again becomes available in the cytosol to protect against a buildup of H_2O_2.

Another source of cytoplasmic H_2O_2 evolves through the action of **superoxide dismutase (SOD)** on oxygen free radicals ($\mathbf{O_2^{-\cdot}}$). This zinc- and copper-containing enzyme is present in all aerobic tissues, as well as in erythrocytes (see Chapter 30).

An atom or molecule with one or more unpaired electrons is a free radical, and free radicals are highly reactive because of their tendency to acquire electrons from other substances. Not all reactive oxygen species are, however, free radicals (e.g., singlet oxygen (O_2), and H_2O_2). Three important reactive species that are known to damage tissues are $\mathbf{O_2^{-\cdot}}$, $\mathbf{H_2O_2}$, and the **hydroxyl free radical** (**OH·**; **Table 46-1**). Although the OH· is highly reactive, it is normally short-lived. Additional sources of reactive species include **xanthine oxidase** (**XO**); see Chapter 17), which may generate superoxides during reperfusion injury in ischemic organs (see **Case Study #3**), and **cyclooxygenase** and **lipoxygenase** (see Chapters 68 and 69), important control enzymes in eicosanoid pathways that can give rise to OH· and peroxyl radicals. **Uric acid**, the product of XO activity, may itself possess antioxidant activity.

Table 46-1

Reactive Oxygen Species and Their Antioxidants

Abbreviation	Reactive Species	Antioxidants
O_2		Singlet oxygen
Vit A & E, β-carotene		
$O_2^{-\cdot}$	Superoxide free radical	SOD, Vit E, β-carotene
ROO·	Peroxyl free radical	Vit E & C
H_2O_2	Hydrogen peroxide	Catalase, GP

The metabolism of xenobiotics via the cytochrome P_{450} system can also give rise to free radicals, particularly in liver tissue. Because these molecules are so reactive, they generally act close to their point of origin. Therefore, many cell structures become vulnerable to these agents, including structural proteins, enzymes, membranes, and nucleic acids, which can result in mutation and apoptosis.

Vitamin E Deficiency

Vitamin E deficiency can result from severe **fat malabsorption** with consequent steatorrhea, some forms of **cholestatic liver disease**, **abetalipoproteinemia**, and **intestinal resection**. In experimental animals vitamin E deficiency has resulted in fetal resorption, premature infants have been born with inadequate reserves, and in males testicular atrophy has occurred.

Excessive lipid peroxidation of membranes and other sites of fat accumulation accounts for most of the symptoms associated with **vitamin E deficiency**. The most clear-cut example is **enhanced erythrocyte fragility**, where RBCs exhibit a marked change in morphology and become easily destroyed. Vitamin E is also essential for the development and maintenance of normal **nerve** and **muscle** cell activity. Either vitamin E or selenium deficiency can result in a massive influx of Ca^{++} into cells; mitochondria become loaded with this element, and reduce their ATP output. This mineral influx results in **muscular degeneration**, and gives muscle a characteristic appearance (i.e., "**white muscle disease**"), which is usually more prominent in young animals. Myocardial involvement with this disease may result in sudden death.

White muscle disease is sometimes confused with the **muscular dystrophies** of animals, which are hereditary degenerative diseases of skeletal muscle. Dystrophic muscles usually contain fewer fibers, an increase in the number and size of nuclei, and myofibrillar degeneration without effective regeneration.

Another outcome of the lack of antioxidant action of vitamin E, and which occurs in its deficiency, is the accumulation of "**lipofuscin**" or "ceroid pigment" granules in many tissues, including the CNS, lungs, kidneys, adipocytes, and muscle. These granules contain oxidized unmetabolizable lipids that have partially crosslinked with protein or peptides to form a hard globule that cannot be disposed of by the organism. These granules normally accumulate with age, and this accumulation is inhibited by a high vitamin E intake, at least in mice. Fatty tissue inflammation (i.e., "**steatitis**"), is also associated with vitamin E deficiency.

Animals with **cholestasis** (e.g., bile duct obstruction) absorb fat-soluble vitamins poorly. In chronic conditions **neuromuscular damage** occurs that can be somewhat alleviated through parenteral administration of vitamin E. Additionally, **retinopathy** can occur in vitamin E deficiency upon exposure to high oxygen tensions. Again, this condition has been reversed with vitamin E administration.

Studies in several animal species have shown that in males, vitamin E deficiency results first in **sperm immotility**, then in degeneration of the seminiferous epithelium, and then **cessation of sperm production**. In females there is a **failure of uterine function** in vitamin E deficiency, with a lack of development of the vasculature that would allow the conceptus to implant in the uterine wall. Although vitamin E supplementation can help to reverse these symptoms, **Se** does not effectively prevent fetal resorption in rats, nor encephalomalacia in chickens, and thus, is not a complete substitute for vitamin E.

Although several health problems have been associated with vitamin E deficiency, as discussed above, high intakes of this vitamin do not appear to be as debilitating as do those for vitamins A, D and K. Vitamin E, however, can act as an **anticoagulant**, therefore hypervitaminosis E may increase the risk of bleeding.

OBJECTIVES

- Identify locations in the body normally containing the highest concentrations of vitamin E.
- Explain why vitamin E is considered to be the first, and Se the second line of defense against membrane lipid peroxidation.
- Understand why animals consuming fish-based diets have an increased need for vitamin E.
- List the reactive oxygen species known to damage tissues and their antioxidants.
- Recognize how vitamin C helps to regenerate the active form of vitamin E.
- Explain how vitamin E is metabolized and excreted by the body.
- Summarize the redundant activities of catalase and glutathione peroxidase, and show how H_2O_2 is produced in aerobic tissues.
- Explain pathophysiologic findings related to vitamin E deficiency.
- Compare vitamin E toxicity symptoms to those of the other fat-soluble vitamins.

QUESTIONS

1. Which one of the following elements acts synergistically with vitamin E in protecting membranes against lipid peroxidation?
a. Cobalt
b. Zinc
c. Lead
d. Selenium
e. Oxygen

2. The need for vitamin E partially depends upon the dietary intake of:
a. Protein.
b. Starch.
c. Sucrose.
d. Iron.
e. Unsaturated fatty acids.

3. Vitamin E is a (an):
a. Ergosterol.
b. Retinoid.
c. Tocopherol.
d. Menaquinone.

4. An atom or molecule with one or more unpaired electrons is a (an):
a. Free radical.
b. Enzyme.
c. Cytochrome.
d. Free fatty acid.
e. Phospholipid.

5. Vitamin E deficiency is associated with all of the following, EXCEPT:
a. Muscular degeneration.
b. Cholestasis.
c. Lipofuscin accumulation.
d. Retinopathy.
e. Diabetes insipidus.

6. Which one of the following can regenerate vitamin E?
a. SOD
b. GSH
c. Vitamin C
d. Catalase

7. Hydrogen peroxide is normally acted upon (i.e., detoxified) by:
a. Vitamins E and C.
b. GSH and catalase.
c. SOD and glutathione reductase.
d. Superoxides and hydroxyl free radicals.

ANSWERS
1. d
2. e
3. c
4. a
5. e
6. c
7. b