Protective role of vitamin E in biological systems[1,2]

Lester Packer

ABSTRACT Vitamin E is well accepted as nature's most effective lipid-soluble, chain-breaking antioxidant, protecting cell membranes from peroxidative damage. Free-radical–mediated pathology has been implicated in the development over time of degenerative diseases and conditions. This paper reviews the current research on the protective role and requirements for vitamin E and the other antioxidants in preventing or minimizing free-radical damage associated with specific diseases and lifestyle patterns and processes, including cancer, aging, circulatory conditions, arthritis, cataract, pollution, and strenuous exercise. While awaiting results of further human studies, research evidence suggests that an adequate intake of vitamin E and the other antioxidants can provide protection from the increasingly high free-radical concentrations caused by air pollutants and current lifestyle patterns. *Am J Clin Nutr* 1991;53:1050S–5S.

KEY WORDS Vitamin E, antioxidants, free radicals, cancer, aging, pollution, exercise

Introduction

Although our aerobic lifestyle provides us with many advantages, the utilization of oxygen by cells results in production of highly reactive free-radical products. Uncontrolled free-radical reactions can result in damage to cell structures and functions (1). Free radicals are implicated in the progressive accumulation of tissue changes, which in some individuals may eventually be recognized as disease (2). The present paper will review the current research on free-radical–related pathology and the protective role of vitamin E and the other antioxidants in preventing or controlling peroxidation associated with certain diseases and processes in biological systems.

Antioxidant defenses

Antioxidant defenses that protect the body from free-radical damage include the enzymes superoxide dismutase, catalase, and glutathione peroxidase and the antioxidant vitamins (3). Vitamin E plays a critical role in membranes and it has long been known that the naturally occurring tocopherols and tocotrienols present in plant oils are essential dietary components (4). Palm oil, second highest in volume of vegetable oils produced in the world, is a potential new source of vitamin E (5, 6). Some of the tocopherol isomers present in palm oil, the tocotrienols, are not normally present in other edible oils (7). Vitamin E, despite its low molar concentration in membranes, effectively serves as the major lipid-soluble, chain-breaking antioxidant (8). Vitamin E is well accepted as the first line of defense against lipid peroxidation, protecting polyunsaturated fatty acids in cell membranes through its free-radical–quenching activity in biomembranes at an early stage of free-radical attack (9, 10). Selenium-containing glutathione peroxidase destroys lipid peroxides before they can damage cell membranes (11).

Vitamin E appears to be highly efficient as an antioxidant. After being oxidized and before being decomposed, vitamin E can be rereduced by ascorbic acid and glutathione. This reaction is dependent on the concentration of these substances and/or the enzymes that maintain them in their reduced form. Indeed, a vitamin E radical (tocopheroxyl radical) reductase activity has recently been discovered in our laboratory. In this way the tocopheroxyl radical may be regenerated to the native form of vitamin E (12). D-α-tocopherol is the major biological dietary component with prominent antioxidant activity, but its effect and that of other vitamin E forms as biological-response modifiers have not yet been evaluated. **Figure 1** shows the various modes of action attributed to vitamin E (tocopherols) in membranes (4).

Vitamin E requirements in health and disease

Although clinical evidence of vitamin E deficiency that is ameliorated by vitamin E therapy has been observed in premature infants and in patients with malabsorption syndromes, research on vitamin E requirements for healthy adults has not been conclusive (13). Vitamin E requirements may vary more than fivefold, depending on dietary intake and/or tissue composition from previous dietary habits. Animal research has demonstrated that a high polyunsaturated fatty acid intake increases the vitamin E requirement (9).

The recommended dietary allowance (RDA) for vitamin E was 30 IU in the 1968 edition, based on a long-term study, but was decreased to 15 IU for subsequent editions, partly due to the difficulty in obtaining 30 IU of vitamin E from normal diets without supplementation (9). Interpretations of vitamin E requirements should consider whether an increased vitamin E intake above levels required to avoid a deficiency has proven benefits in preventing free-radical damage. When breath pentane excretion was used as an index of lipid peroxidation, daily intake of 1000 IU vitamin E for 10 d significantly reduced breath-pentane output in healthy adults consuming a normal, mixed diet (**Fig 2**) (14). On the basis of these study results, it may be

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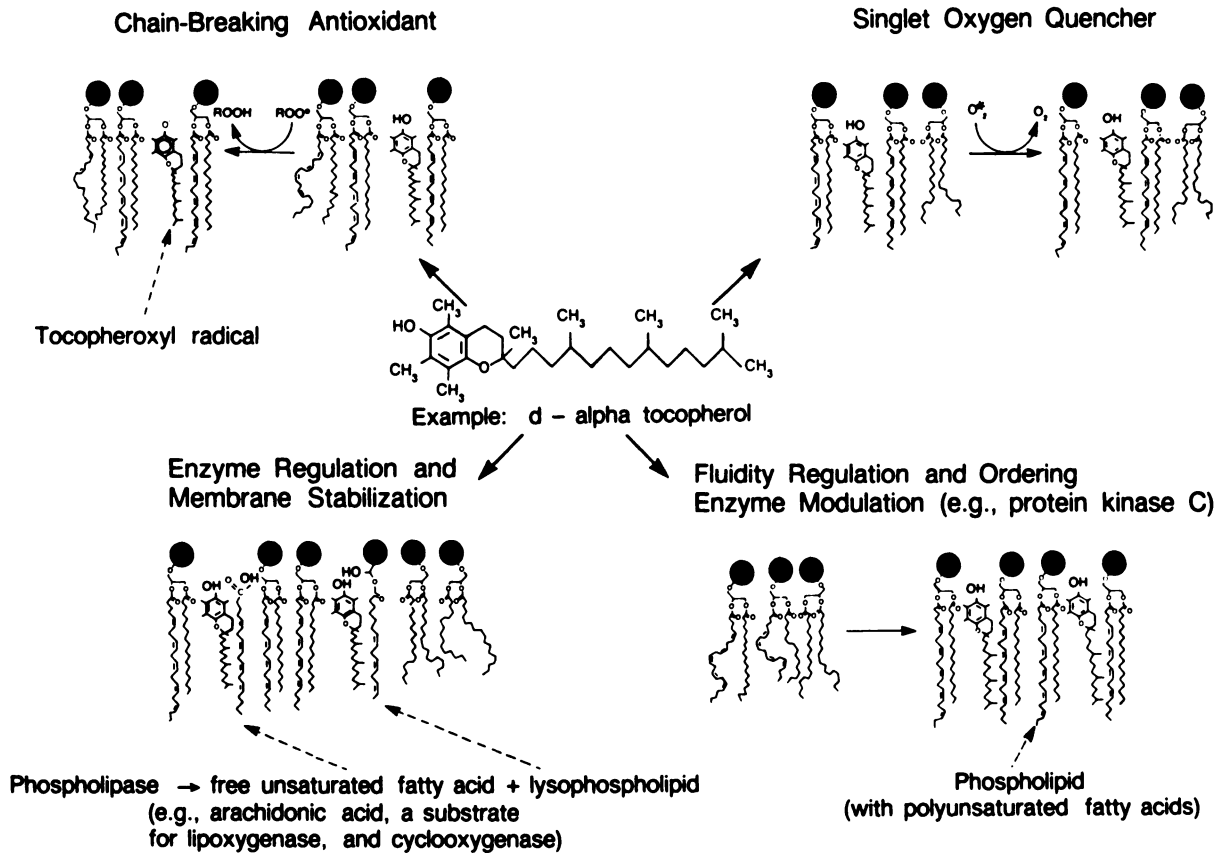

FIG 1. Vitamin E as a biological-response modifier.

inferred that an undesirable chronic level of peroxidation occurs in cell membranes and other tissue components and that lipid peroxide concentrations can be decreased by vitamin E supplementation (14). These results may be significant, considering research data demonstrating a role for free-radical damage in normal body processes and certain diseases and protective effects of vitamin E in preventing or controlling lipid peroxidation in body tissues (10, 14).

Cancer

Cancer is believed to be the result of external factors combined with a hereditary disposition for cancer. Research data indicate that reactive oxygen species are involved in the process of cancer initiation and promotion (2, 15). Increased incidence of cancer with advancing age may be due, at least in part, to the increasing level of free-radical reactions with age, along with the diminishing ability of the immune system to eliminate the altered cells (2). Several functions of vitamin E are relevant in considering its role in cancer prevention and control. In addition to its role as a free-radical scavenger, vitamin E at high intakes enhances the body's immune response. Vitamin E also inhibits the conversion of nitrites to nitrosamines in the stomach (16).

From cell culture and animal research, it appears that vitamin E and the other antioxidants alter cancer incidence and growth through their action as anticarcinogens, quenching free radicals or reacting with their products (17–21). In animal and cell culture studies, vitamins E and C, acting as scavengers of nitrite compounds, prevented the formation of cancer-promoting nitrosamines (22, 23). Although controlled human studies on the antioxidants and cancer are very limited, the majority of epidemiological data suggest that vitamin E and the other antioxidants may decrease cancer incidence. In several studies subjects with the highest serum concentrations of vitamin E and other antioxidants had a lower subsequent risk of certain cancers than did subjects with lower serum antioxidant concentrations (24–30). Other studies did not show a significant relationship between serum antioxidant concentrations and subsequent cancer risk or showed a relationship with only one of the antioxidants (31, 32). Although research evidence suggests that vitamin E reduces incidence of certain cancers, results of current and future studies will, one hopes, provide additional documentation on the functions of vitamin E and the other antioxidants in cancer prevention and risk.

Aging

Cellular damage by active oxygen species, including damage associated with lipid peroxidation, is believed to be involved in the aging process itself, causing the pathological changes associated with aging (2). Early studies at the University of Nebraska demonstrated that exposure of laboratory animals to radiation appeared to rapidly age the animals and caused an increase in free-radical levels in their cells (33). Research has also documented the progressive accumulation of lipofuscin in the aging process in every animal species studied (34).

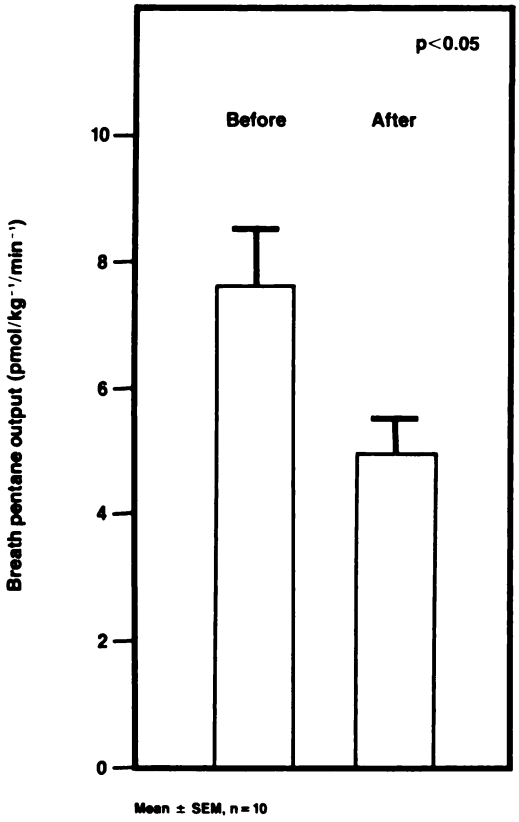

FIG 2. Breath-pentane output in adult humans before and after oral supplementation with vitamin E (1000 IU/d for 10 d). (Source: ref 14.)

Daily supplementation with vitamins C and E resulted in a decrease in average blood lipid peroxide concentrations in a study of elderly people in Poland (35). In an evaluation of the effects of vitamin E and selenium supplementation on mental well-being of nursing home patients in Finland, a noted improvement in general condition was observed after only 2 mo (36). In another study in Finland, serum lipid peroxide concentrations were initially higher in the elderly people but decreased to values of younger control subjects after 3 mo of supplementation with vitamins C, E, and B-6, β-carotene, zinc, and selenium (37).

Platelet hyperaggregability

Platelet hyperaggregability is a significant factor in the development of atherosclerosis and other vascular diseases. Vitamin E inhibits platelet aggregation and production of prostaglandins, which further stimulate platelet aggregation (38). In rats feeding of palm oil (which contains vitamin E) resulted in decreased production of thromboxane, a potent platelet-aggregation promoter (39). An atherosclerosis-promoting diet fed to rabbits almost completely suppressed production of prostacyclin, a powerful inhibitor of platelet aggregation, but supplementation with vitamin E protected the prostacyclin-generating system in arteries (40). Platelet adhesiveness to collagen was not affected by aspirin but was significantly reduced in healthy adults treated with vitamin E plus aspirin, suggesting that vitamin E supplementation could have a beneficial effect in patients with atherosclerosis (41). In a group of healthy adults, daily supplementation of 400 IU vitamin E for 4 wk resulted in a significant reduction in platelet adhesion on all four adhesive surfaces studied (42). In long-term contraceptive users vitamin E supplementation reduced the increase in clotting activity and platelet response to induced aggregation observed in unsupplemented women after 3 wk on hormonal contraceptives (43). In hyperlipidemic subjects, daily vitamin E supplementation effectively reduced plasma lipid peroxide concentrations to those of healthy control subjects (40).

Ischemia and reperfusion injury

Restoration of blood flow to previously ischemic organs results in a rapid increase in tissue oxygen tension, which promotes lipid peroxidation after initiation of free-radical reactions during ischemia (44). Animal studies have indicated that vitamin E is depleted during cerebral ischemia and that vitamin E helps prevent peroxidative damage associated with ischemia and reperfusion (44, 45). In patients with coronary artery disease undergoing cardiopulmonary bypass, hydrogen peroxide levels did not increase significantly during or after bypass surgery in patients pretreated with vitamin E 12 hours before surgery but progressively increased during bypass surgery in unsupplemented patients (**Fig 3**) (46).

Arthritis

Animal research has demonstrated the effectiveness of vitamin E supplementation in inhibiting the elevation of free-radical concentrations associated with arthritis (47). In a crossover study on the effects of vitamin E on osteoarthritis, vitamin E supplementation was significantly more effective than was placebo in relieving pain (48). A double-blind study of patients with osteoarthritis also showed that vitamin E was significantly superior to placebo in regard to pain relief and necessity of additional analgesic medications and improvement of mobility (49).

Cataract

Oxidative mechanisms are believed to play a major role in development of cataract, a leading cause of impaired vision and blindness in elderly people (50). Research has shown that vitamin E delays or minimizes development of induced cataract in isolated rat lenses. Addition of vitamin E to the medium had a protective effect against cataract formation induced by radiation, glucose, or galactose (51–53). In rats made diabetic by streptozotocin, there was extensive cataractous degeneration of the cortical cells within 6 wk; vitamin E–supplemented diabetic animals showed only slight lens changes (54). In an epidemiological study on cataract risk in adults aged > 55 y, daily vitamin E or vitamin C supplementation or a combination of the two antioxidants reduced cataract risk (55). Results of another study in adults (aged 40–70 y) suggest that subjects with high plasma concentrations of at least two of the three antioxidant vitamins had a reduced risk of senile cataract. As noted by the researchers, their results appear to support the hypothesis that the lens antioxidant defense may be a factor in cataract development (50).

Air pollution

Ozone and nitrogen dioxide, present in high concentrations in polluted air, can initiate free-radical reactions that lead to

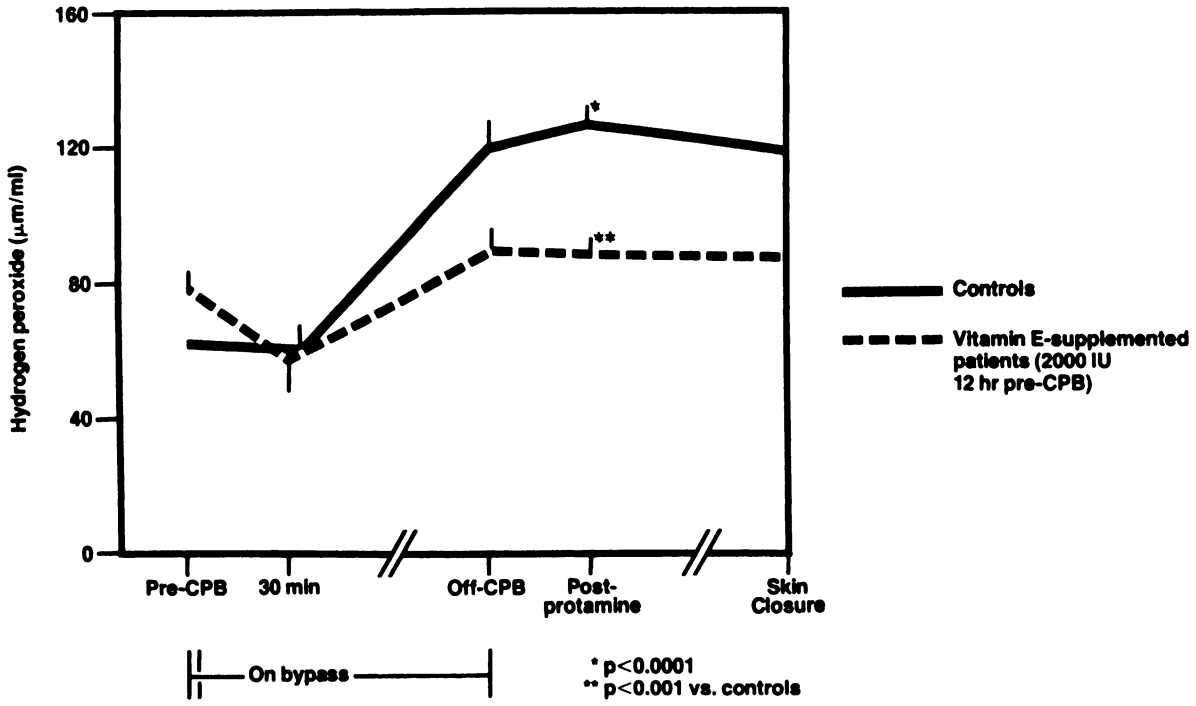

FIG 3. Free-radical generation during cardiopulmonary bypass (CPB) (μm/mL = mmol/L). (Source: ref 46.)

lung injury. Cigarette smoke contains free radicals and compounds that generate free radicals and leads to a significant increase in the number of inflammatory cells in the lung, which are potent producers of free radicals (56). Vitamin E may be an important component of the lung's defense against free-radical–related injury. Research in rats showed a protective effect of vitamin E on the lungs of rats exposed to ozone or cigarette smoke (57, 58).

In a study of smokers, baseline breath-pentane excretion was significantly higher in smokers than nonsmokers but breath-pentane output was suppressed by daily supplementation with 800 IU vitamin E (59). In another study, lower-respiratory tract-fluid of smokers was relatively deficient in vitamin E; vitamin E concentrations increased with daily intake of 2400 IU vitamin E for 3 wk but still remained much lower than baseline concentrations of nonsmokers (**Fig 4**) (56). The researchers suggest that the vitamin E deficiency in young smokers may expose their lungs to increased free-radical damage (56). Until the sources of pollution are eliminated, research shows, vitamin E may help protect the lungs from damage associated with exposure to common air pollutants.

Exercise

In exercise-exhausted animals, free-radical concentrations are increased two- to threefold in muscle and liver, and accelerated

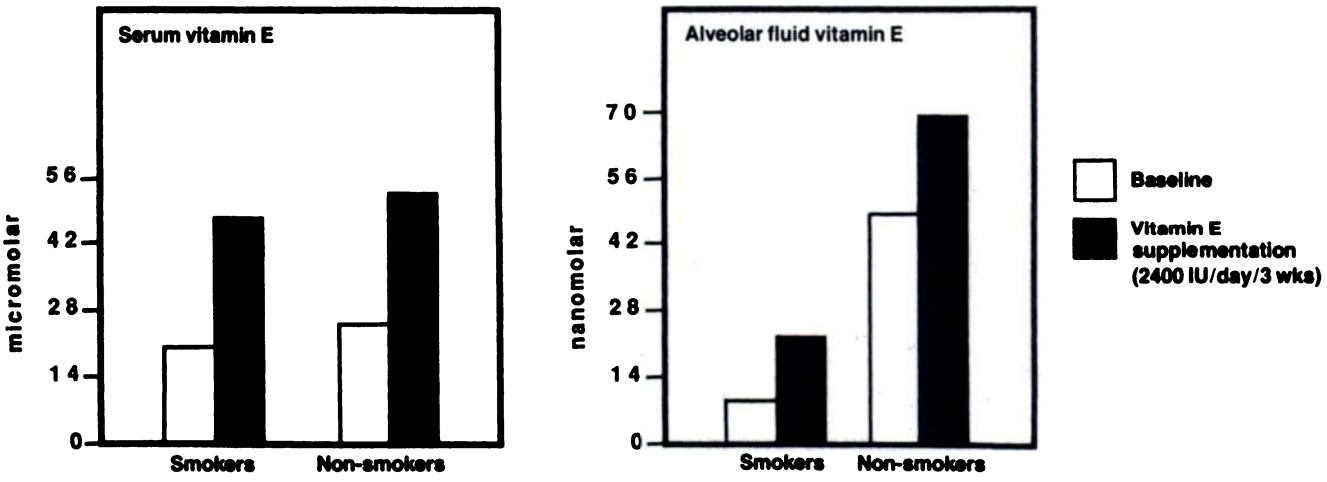

FIG 4. Increased vitamin E levels in human serum and alveolar fluid of smokers and nonsmokers. (Source: ref 56.)

lipid peroxidation and mitochondrial damage have been observed (60). More rapid depletion of vitamin E from liver and muscle have been observed in rats undergoing endurance training than in sedentary controls at similar vitamin E intakes (61). Because the primary antioxidant vitamin E is consumed by body tissues during increased physical exercise, results suggest that there is an increased vitamin E requirement during endurance training (62). In a study in human subjects, daily supplementation with 1200 IU vitamin E for 2 wk significantly reduced the increased pentane production documented in strenuous physical exercise (63).

Research has also investigated the effects of vitamin E supplementation on athletic performance. In two studies of trained swimmers, vitamin E–supplemented swimmers did not show a difference in swimming speed compared with swimmers on the placebo diet (64, 65). In mountain climbers prolonged exposure to high altitudes led to reduced physical performance in unsupplemented climbers, as demonstrated by a significant decrease in anaerobic threshold, and significantly increased breath-pentane exhalation. In comparison, physical performance capacity and breath-pentane excretion did not change significantly in vitamin E–supplemented mountain climbers and the researchers concluded that vitamin E has a beneficial effect on physical performance and cell protection, at least at high altitudes (66).

Summary

Evidence is increasing that free-radical reactions are implicated in the development of degenerative diseases. The body's susceptibility to free-radical stress and related damage is associated with the overall balance between the stress level and the antioxidant potential of body tissues. As we await results of additional human studies, it may seem prudent to increase the intake of vitamin E and the other antioxidants to protect the body from the increasingly high levels of free radicals derived from the environment and from endogenous sources. Beneficial effects of vitamin E and other antioxidants in counteracting free radical damage in biological systems should be most apparent when viewed on a long-term basis, since free radical–related pathology occurs over time.

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