VITAMIN E AND IMMUNE FUNCTIONS

Adrianne Bendich

Clinical Nutrition
Hoffmann La Roche Inc.
Nutley, NJ 07110, U.S.A.

INTRODUCTION

All circulating cells that are derived from the common hemopoietic stem cell precursor demonstrate membrane changes when vitamin E is absent from the diet. Red blood cells from vitamin E deficient animals and humans lyse in the presence of hydrogen peroxide, whereas red blood cells from vitamin E supplemented animals are not lysed. Platelets from vitamin E-deficient animals are more adhesive and produce more thromboxane than platelets from vitamin E-replete animals. Neutrophils from vitamin E-deficient animals have an increased level of peroxidized lipid in their membranes, produce more hydrogen peroxide, and have depressed chemotaxis and phagocytosis.[1]

It should not be suprising that cells involved in the generation of specific immune responses, macrophages, T lymphocytes and B lymphocytes are also affected by the level of vitamin E in the diet. The objective of this report is to examine the effects of vitamin E on immune responses. In addition, the immunomodulating effects of other nutritional components associated with vitamin E will be discussed.

VITAMIN E AND IMMUNE CELL FUNCTION

The initiation of the immune response is considered to occur at the level of the cell membrane.[2] Vitamin E, the major fat-soluble antioxidant, is an essential constituent of all cellular membranes, including the outer cellular membrane and the internal mitochondrial and nuclear membranes.[3] In addition, vitamin E is important in maintaining the lymphocyte membrane fluidity necessary for proliferative responses.[4]

The vitamin E content of lymphocytes and mononuclear cells is usually ten times greater than that found in platelets and red blood cells.[5] The importance of vitamin E was clearly demonstrated when lymphocyte membranes from vitamin E-deficient animals were compared with those from animals given the vitamin. Electron micrographs of mitochondrial membranes from lymphocytes from vitamin E-deficient animals showed swollen and disrupted areas.[6]

When laboratory animals were placed on vitamin E deficient diets, many immune responses were severely depressed.[7-10] Macrophage membrane receptors were altered, interleukin 2 production was lowered (Bendich, in

press) and production of prostaglandins was altered.[11-13] Low levels of dietary vitamin E, sufficient to protect against many of the adverse effects of vitamin E deficiency, were insufficient to enhance lymphocyte proliferative responses even though the diet contained all other nutrients at recommended levels.[14]

In certain instances, the immune system can develop aberrant responses which can result in harmful self-destructive effects. An example would be the chronic inflammatory response seen in the joints of arthritics. The damage caused in these joints has been associated with the increase in free radicals generated in the inflamed tissues. A recent study by Tappel's group has directly linked the level of dietary vitamin E with the degree of lipid peroxidation and inflammatory responses seen in an animal model of arthritis. Vitamin E deficient animals given an injection of vitamin E had significantly less inflammation and produced less of the peroxidative intermediates. Furthermore, vitamin E protected these animals against chronic inflammation and bone distortion.[15]

In the initial studies to determine the effect of vitamin E on immunity, higher than normal dietary levels were fed to laboratory and farm animals. These animals were then challenged with pathogenic bacteria. Vitamin E supplementation resulted in increased resistance to infection and decreased morbidity and mortality.[16-17] In agreement with these findings of a correlation of high vitamin E status with enhanced lymphocyte responses to infection in animals, Chavance et al.,[18] in an epidemiological study, found a significant association between high plasma vitamin E levels and a lower number of infections in healthy adults over the age of 60.

VITAMIN E AND PUFA: EFFECTS ON IMMUNITY

It is well recognized that the requirement for vitamin E increases as the level of polyunsaturated fats in the diet increases. If the fat source in animal diets was corn oil (high in polyunsaturated fatty acids [PUFA]), rather than lard or coconut oil (high in saturated fatty acids), immune responses of T and B lymphocytes to mitogens and in vitro antigen dependent antibody production were depressed.

The degree of immunodepression was directly related to the concentration of dietary PUFA. Shapiro et al.[19] found no depression of mouse T and B lymphocyte mitogen responses when 5% PUFA replaced 5% saturated fat in the diet. Corwin and Schloss [20] found depression when 8% PUFA replaced saturated fat in mouse diets. Bendich et al. [21] found significant depression in these responses when rats were fed 10% PUFA instead of lard. Vitamin E deficiency as well as low vitamin E (15 IU/kg diet) exacerbated this immunosuppression. Higher than normal dietary levels of vitamin E could partially overcome the immunosuppressive effects of these high PUFA diets (Fig 1).

VITAMIN E AND VITAMIN C

The antioxidant capacity of vitamin E has been associated with the donation of an electron from vitamin C and the subsequent regeneration of tocopherol from the tocopheryl free radical.[22] These cell-free experiments have prompted us to determine the interaction of vitamin E and vitamin C on T and B lymphocyte responses to mitogens. Guinea pigs were fed diets with either a low but anti-scorbutic level of vitamin C or a high level of vitamin C and either 0, 30, or 200 IU/kg vitamin E (six

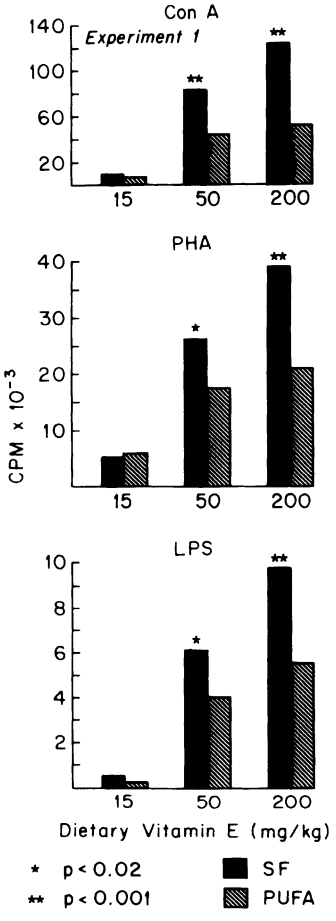

Fig 1. Groups of rats were fed diets containing 10% saturated fat (SF) or 10% polyunsaturated fatty acids (PUFA) and either 15, 50 or 200 mg/kg vitamin E for 10 wk. Splenic lymphocyte proliferative responses were determined using the T lymphocyte mitogens, Con A and PHA, and the B lymphocyte mitogen, LPS.

dietary groups). As in mice and rats, vitamin E-deficient guinea pigs had depressed responses to mitogens compared to guinea pigs fed diets containing vitamin E. The two levels of vitamin C did not affect these responses. However, guinea pigs fed the high vitamin C diet had a significantly higher concentration of vitamin E in the lung and plasma than the guinea pigs fed the low level of vitamin C, even though both groups were fed diets containing the same level of vitamin E.[23] These data could be interpreted as an in vivo verification of the cell-free experiments showing that vitamin C can help regenerate vitamin E.

VITAMIN E AND SELENIUM

Along with the antioxidant vitamins, there are several enzymes which can protect against damage which can be caused by free radicals. While vitamin E can protect against lipid peroxidation in cell membranes, the enzyme glutathione peroxidase can reduce the level of lipid peroxidation within the cell. Selenium is part of the metalloenzyme glutathione peroxidase, which can scavenge free radicals formed during lipid peroxidation and is also one of the catalysts for the destruction of hydrogen peroxide.[24]

When rats were fed a vitamin E and selenium-deficient diet for 4-8 wk, the T and B lymphocyte responses to mitogens were severely depressed. When 0.2 mg/kg sodium selenite was added to the diet, the responses were not significantly enhanced; however, when 200 IU/kg vitamin E was added to the basal diet, both T cell responses to the mitogen PHA and B cell responses to LPS were significantly enhanced. When both nutrients were included in the diet, a further enhancement of T cell responses to Con A was noted.

In experiments reported by Mulhern et al.[25, 26] the lymphocyte mitogen responses of first generation selenium-deficient, vitamin E-adequate mice were the same as animals fed the diet containing selenium; however, specific antibody responses (IgG) were reduced following challenge with sheep red blood cells. When mice were kept selenium deficient through two generations, mitogenesis, specific and nonspecific antibody titers as well as thymic size were depressed. It may be that selenium is required during the critical period of embryonic development when immune functions are iniated. This would be a possible explanation for the immunodepression seen in the mice born to selenium-deficient dams. If this is the case, the immunodepression seen in the second generation mice should be found whether or not the diet contains selenium.

SUMMARY

Vitamin E, the major lipid-soluble antioxidant present in all cellular membranes, is an important nutrient for optimal immune function. When animals are fed nutritionally complete diets lacking vitamin E, immune responses are adversely affected. Supplementation of these diets with higher than nutritionally adequate levels of vitamin E enhances immune responses.

High levels of PUFA are immunosuppressive, and vitamin E can partially overcome this immunosuppression. High levels of vitamin C can protect tissue levels of vitamin E and may indirectly contribute to the immunoenhancement by vitamin E. Severe selenium deficiency is immunosuppressive. Vitamin E can protect some aspects of immune responses from the adverse effects of selenium deficiency.

These data clearly indicate that nutrients that affect the overall antioxidant status have important effects on immune functions. In addition, antioxidant nutrient interactions can synergize to overcome the adverse effects of polyunsaturated fatty acids on immune functions (Fig 2).

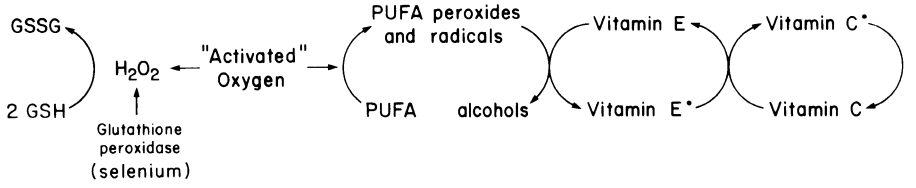

Fig 2. Antioxidant nutrient interactions.

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