Dietary vitamin E and T cell-mediated function in the elderly: effectiveness and mechanism of action

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Abstract

One of the most dramatic and consequence-bearing age-related phenomena is the decline of the immune function with old age. Age-related T cell-mediated immunity dysfunction has been implicated in the etiology of many of the chronic degenerative diseases of the elderly, including arthritis, cancer, autoimmune diseases and increased susceptibility to infectious diseases. T cells from aged individuals are impaired in their response to mitogens and in their cytokine production. In recent years, several studies have emphasized the importance of intracellular anti-oxidant levels for preserving the immune function. Recent progress in understanding the mechanisms of action of anti-oxidants on cellular metabolism, have shown that anti-oxidants may modulate signal transduction and gene expression in immune cells. Vitamin E is widely recognized as a major lipid-soluble chain-breaking anti-oxidant in the biological membrane, where it scavenges free radicals, inhibiting the initiation and chain propagation of lipid peroxidation and protecting cellular structures against oxidative stress damage. Experimental studies have provided evidences for a role of vitamin E in protecting the immune system of elderly subjects. This article reviews the studies concerning the effect of both vitamin E deficiency and supplementation on T cell-mediated immune function in aging. Following a chronological pathway, the present article will also discuss the knowledge regarding the underlying mechanism of action of vitamin E. © 2000 ISDN. Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

Immune function is dependent on a variety of different factors, such as hormonal status, age, nutritional status, etc. In humans two types of immunity are present: natural and acquired. The former involves polymorphonuclear leukocytes, natural killer (NK) cells, mononuclear phagocytes, and uses the complement cascade as its main soluble protein effector mechanism [49]. The latter can be divided in humoral and cell-mediated; the distinction between the two is somewhat artificial, as both B and T cells can participate in each type of reaction [49]. The humoral type of immune response produces antibodies, generated by differentiated bone marrow-derived lymphocytes (B cells), while the cellular immune response is primarily mediated by thymus-derived lymphocytes (T cells), that can be identified as helper or suppressor based on their cell surface receptors [49].

The ‘evolution theory’ suggests that aging is caused by a life-long accumulation of random damages in somatic cells and tissues. These damages are due to an evolved limitation in the levels of key maintenance factors and functions, and they can lead to a progressive decline in the biochemical and physiological functions of the various organs in an individual [99]. Perhaps one of the most dramatic and consequence-bearing age-related phenomena, is the decline of the immune function with old age [65]. A wealth of data shows that the immune function declines with age. This phenomenon has been recently documented thoroughly in several reviews [59,74].

Among the different types of immunity, age-related T cell-mediated immunity dysfunction has been impli-
cated in the etiology of many of the chronic degenerative diseases of the elderly, including arthritis, cancer, autoimmune diseases and increased susceptibility to infectious diseases [48]. Numerous studies [47,73,88] show how T cell populations fluctuate with aging in both humans and animals. For example, immature T lymphocytes (CD2+CD3–), NK cells and memory T lymphocytes increase during aging [57,58,62], whereas the number of ‘naïve’ T lymphocytes [57] decreases during aging. T cells from aged individuals are impaired in their response to mitogens such as phytohemagglutinin (PHA) and concanavalin A [97] (Con A). Moreover, this age-related reduction in the proliferative response to mitogen is associated with a diminished production of interleukin (IL)-2 [80], responsible for progression of T lymphocytes from G1 to S phase in the cell cycle and major mediator of T-cell proliferation [20], and a decreased density of IL-2 receptor expression [31,82]. It is very likely that defects in the production of IL-2 and in the response to IL-2 contribute to the age-related decline in immune function. Prostaglandin (PG) E2, an arachidonic acid (AA) metabolite, has been implicated in age-related changes of cellular immunity. PGE2 is a feedback inhibiting factor of T-cell proliferation in humans [28]. T cells from the elderly are more sensitive to inhibition by PGE2 than the young [23,26]. Excessive production of PGE2 by macrophages (MΦ) extracted from old mice, has been shown to suppress T-cell proliferation, and IL-2 production [5].

Among the factors that can cause damage during an organism's life-span are the free radical species (FRS). According to the free radical theory of aging proposed by Harman about 40 years ago [36,37], FRS produced during aerobic metabolism in the life time, cause oxidative stress [35], with a subsequent cumulative cell damage leading to aging and cell death. Oxidative stress has been shown to damage cell membrane [35], altering in vitro binding activity of AP-1 [94] and suppressing in vitro Con A-induced T-cell proliferation and IL-2 production [85].

Aside from the negative actions of oxidative stress, in recent years, several studies have emphasized the importance of intracellular anti-oxidant levels for preserving the immune function [107]. Recent progress in understanding the mechanisms of action of anti-oxidants on cellular metabolism, have shown that anti-oxidants may modulate signal transduction factors [86], transcription of genes involved in cell mediated immunity, and cytokines production [85]. Dietary glutathione (γ-glutamylcysteinylglycine, GSH) supplementation has been shown to improve the immune response in old rats [19], and in peripheral blood mononuclear cells (PBMC), in both young and old subjects [107], and to magnify the effect of IL-2-dependent cytotoxic T cells [60]. β-carotene supplementation has been shown to enhance mitogenic response of spleen-derived T and B cell in rats [7], and in human lymphocyte [78].

Vitamin E, is a term that comprises a family of lipophilic anti-oxidants: the tocopherols. Tocopherols contain a chromanol ring and an isoprenoid chain. Each individual tocopherol differs for position and number of methyl substitutes on the aromatic ring. Among the naturally occurring tocopherols, α-tocopherol (R,R,R-α-tocopherol) is the most abundant, with the highest biological activity [64], as compared to the other isomers (β,γ,δ). The R,R,R-α-tocopherol is also the preponderant form in tissues, due to the liver that favors the secretion of this isomer into lipoproteins [101]. Abundant sources in vitamin E are the seed oils (soybean, safflower and corn), nuts, whole grains and wheat germ, while animal products are generally poor sources of this vitamin [64]. For practical purposes, one International Unit (IU) of vitamin E is referred to as 1 mg of the synthetic form, all-rac-α-tocopheryl acetate (formerly dl-α-tocopheryl acetate).

Vitamin E is widely recognized as a major lipid-soluble chain-breaking anti-oxidant in the biological membrane, where it scavenges FRS inhibiting the initiation and chain propagation of lipid peroxidation [35]. Vitamin E contributes to membrane stability [61], regulates fluidity, and protects cellular structures against oxidative stress damage [35]. Epidemiological studies have provided evidences of a protective effect of vitamin E in reducing the incidence of degenerative diseases such as Parkinson’s Disease [15], and Heart Disease [54,98]. Experimental studies have also provided evidences for a role of vitamin E in protecting the immune system of elderly subjects [68].

This article reviews the studies concerning the effect of both vitamin E deficiency and supplementation on T cell-mediated immune function in aging. In the present article it will be also discussed, following a chronological pathway, the evolution of the knowledge regarding the underlying mechanism of action of vitamin E.

1.1. Vitamin E deficiency and cell-mediated immune function

Because of the relative rarity of vitamin E deficiency in aged humans of western countries, there are few studies on human vitamin E deficiency. Most of the studies here described have been conducted using animal models.

Mice fed a diet deficient in vitamin E showed a lower hemagglutination titer in response to sheep red blood cell injection, than mice fed a control diet with adequate levels of vitamin E [100]. Furthermore, vitamin E repletion of the deficient animals improves these responses [100]. Moreover, vitamin E deficiency has
been reported to depress lymphocyte proliferation in lambs [102], pigs [50], chickens [10] and dogs [56].

A case-report study [53] showed that vitamin E deficiency in a 59-year-old woman, as a consequence of intestinal fat malabsorption, caused an impairment of T cell-mediated function, measured as T cell response to Con A, IL-2 levels, and delayed-type hypersensitivity (DTH) response, an in vivo measure of cell-mediated immunity. The subject was treated with \( \alpha \)-tocopherol acetate (100 IU/day) orally for 3 months, followed by an injection of \( \alpha \)-tocopherol (50 mg i.m.) daily for 5 days, and by maintenance injections three times a week. After the vitamin E administration, the increase in plasma \( \alpha \)-tocopherol levels correlated with an improved proliferative response to T cell mitogen, IL-2 production, and DHT as well.

From the limited number of studies, it is still possible to speculate that vitamin E deficiency in humans may be associated with impaired cell-mediated immunity that can be a cofactor in the development of some diseases, such as AIDS, and that repletion of such a deficiency may restore the optimal function.

1.2. Vitamin E supplementation and immune function in elderly

In the past few years there has been increasing evidence supporting the proposition that age-related immune dysfunction might be partially prevented, or even reversed by dietary intervention [68,69].

Improvement of cell-mediated immunity by vitamin E has been extensively documented in animals: dietary vitamin E supplementation has been shown to increase lymphocyte proliferation in mice [72,104] and rats [6,77] and increase IL-2 production as well [104]. Although, data derived from animal studies provide important insights to the understanding of human physiology, there is a limited amount of direct information on the effect of vitamin E on the immune response in humans.

Several epidemiological studies have investigated the interaction between vitamin E supplementation and immune function in the elderly. In a cross-sectional study of a population of 270 healthy elderly subjects, Goodwin and Garry [24] studied the immunological effects of large doses of vitamin supplementation by comparing the immunological functions of healthy elderly subjects taking a supplement containing vitamin E, vitamin C, folate, niacin, with the immunological function of subjects not taking any supplements. The authors did not observe any correlation between vitamin E supplementation and mitogen (PHA) stimulated lymphocyte proliferation and DTH. Moreover, the authors did not observe any significant correlation between dietary intake of vitamin E and any of the indices of cellular immunity, such as DTH and lymphocyte count [25].

Chavance and colleagues [11] conducted an epidemiological survey in non-institutionalized healthy elderly subjects to measure indicators of cellular immunity, and susceptibility to infections according to their vitamin status. The authors found an inverse correlation between blood vitamin E levels, and the number of infectious diseases in the previous 3 years (i.e. the higher the levels of blood vitamin E the lower the incidence of infections). However, no other association between vitamin E intake, T cell subsets, and lymphoproliferative response to mitogens, and DTH was found [11].

Payette and colleagues [87], examining the relationship between nutrition and immunological status in non-institutionalized elderly subjects, found an inverse association between intake of vitamin E and IL-2 production, indispensable growth factor for T lymphocytes. However, in this study, 69% of the elderly subjects had no detectable IL-2 activity (threshold of <0.005 kU/l), and researchers correlated IL-2 production with the dietary vitamin E intake instead of measuring vitamin E plasma levels. For admission of the authors, in the Canadian Nutrient File the values for vitamin E was incomplete, probably leading to a misclassification of the dietary intake. Following that, the use of this observational measure, biased by incomplete information, has introduced a strong confounding factor. Moreover, in contrast with other laboratories showing consistent age-related declines in IL-2 production from older humans and mice [21,43,44], no relationship between age and IL-2 activity was observed in these elderly subjects.

Meydani and colleagues [68] conducted the first double-blind placebo-controlled clinical trial analyzing the effect of vitamin E supplementation on immune response in the elderly (>60 years old). Supplementation with 800 mg dl-\( \alpha \)-tocopheryl acetate/day for 30 days, significantly raised PBMC \( \alpha \)-tocopherol levels from 0.12±0.02 nmol/ml to 0.39±0.05 nmol/ml \( \times 10^7 \) cells; \( \beta < 0.001 \). The changes in \( \alpha \)-tocopherol concentration in the cells were associated with changes in plasma levels that increase from 25.6±1.4 \( \mu \)mol/l to 70.9±6.3 \( \mu \)mol/l \( \beta < 0.0001 \) after supplementation. It is interesting to note that the rise in cellular and plasma levels was of the same order of magnitude, three-fold compared to base-line levels.

The changes in vitamin E status were associated with significant enhancement of cell-mediated immunity in healthy elderly subjects. In fact, vitamin E supplementation, significantly improved DTH skin response, and enhanced the in vitro mitogenic response of lymphocytes to optimal doses of Con A, but not to phytohemoagglutinin (PHA), implying a specificity of vitamin E effect: ConA stimulate preferentially T-sup-
pressor cells and PHA is more specific for the T-helper population. Vitamin E supplementation was also associated with decreased PGE$_2$ production by PBMC, and decreased plasma lipid peroxide concentrations, measured as TBARs, from 2.76 ± 0.67 μmol/l to 1.20 ± 0.60 μmol/l. Moreover, in contrast with Payette’s findings, a significant increase in IL-2 formation in response to Con A was observed after vitamin E supplementation. As previously described, IL-2 is an essential T-cell growth factor that declines in parallel with lymphocyte proliferation with age. The increase in IL-2 production after vitamin E supplementation observed in Meydani’s study, was paralleled by an enhancement of the lymphocyte proliferation, partially restoring the age-related alteration of the immune function, thus confirming the tight link between IL-2 levels and lymphocyte proliferation in aging.

To investigate the effect of long-term supplementation, and the optimal levels of vitamin E supplementation on immune function, the same group conducted another trial in which 80 non-institutionalized elderly subjects received one of the following treatments: placebo, 60, 200, or 800 mg/d of vitamin E per day/4.5 months [71]. Plasma vitamin E levels significantly increased in a dose-dependent manner in the vitamin E-treated groups: 38.4 ± 5.3 μmol/l, 51.0 ± 13.6 μmol/l and 71.5 ± 26.5 μmol/l, respectively, for the 60, 200, and 800 mg/d groups. At the end of the supplementation, all groups receiving vitamin E showed increased DTH responses, with the largest increase being observed in the group receiving 200 mg vitamin E/day. The subjects in this latter group also showed an increase in antibody titer to hepatitis B and tetanus. In contrast, the subjects treated with 800 mg/day, showed an increase only in the titer to hepatitis B. From previous results, the authors concluded that a dietary supplement of 200 mg vitamin E/day represents the previous results, the authors concluded that a dietary supplement of 200 mg vitamin E/day represents the optimal level for an efficient immune response, suggesting that there may be a threshold level for the immunostimulatory effect of vitamin E, but this hypothesis needs further study to be proved.

In contrast with the studies carried out by Meydani’s group, a 3-month long double-blind placebo-controlled intervention trial on elderly subjects (> 65 years old) treated with 100 mg DL-α-tocopheryl acetate/day, did not show any change in the in vitro proliferative response of lymphocyte to PHA and Con A, nor did it find changes in the antibody concentrations against common antigens [13]. The possible reason for the lack of effect could be the smaller increase (+16.7%) in plasma vitamin E obtained in this study, as compared to the Meydani’s trial (three-fold respect to base-line values) [71], unfortunately the authors did not measure vitamin E cellular levels. It may be necessary to supplement elderly patients with higher levels of vitamin E to improve lymphocyte proliferation, therefore, supporting the threshold hypothesis formulated by the Meydanis’ group.

1.3. Safety of vitamin E supplementation

The question of the safety of vitamin E oral administration needs to be addressed, especially when vitamin E is used in pharmacological amounts for ‘therapeutic’ purposes in the elderly. Dr Herbert recently [41] raised concerns on the safety of vitamin E supplementation in the elderly, asking whether an immunostimulatory vitamin E supplementation may really result in an overall decrease in morbidity, and mortality. Dr Herbert was concerned about the possible effect of vitamin E supplementation on immune homeostasis, and its effects on patients with undiagnosed and latent autoimmune disorders. In these patients, a vitamin E-stimulated immune system could lead to a manifestation of the symptoms. These concerns were addressed by Dr Meydani and colleagues [41] in their reply to Dr Herbert. Meydani and colleagues state that there is no evidence for vitamin E-enhanced risk of autoimmune disease. In contrast, different studies suggest that vitamin E supplementation could reduce the pathogenesis of autoimmune diseases such as arthritis, diabetes, and systemic lupus erythematosus. Moreover, Meydani’s group showed that vitamin E supplementation is safe in the elderly, and that there are no significant adverse effects after 4 months of consumption of vitamin E doses ranging from 60 to 800 IU per day on a series of measures such as general health, nutrient status, elimination of Candida Albicans by neutrophils, and bleeding time [70]. Furthermore, it has been extensively demonstrated in animal studies that vitamin E has neither mutagenic, nor carcinogenic, or teratogenic properties. Several reports show that vitamin E has a very low toxicity in humans, and that even a dosage greater than 1000 mg/day (1000 IU) is considered to be safe. Therefore, a daily dosage of 100–300 mg of vitamin E can be considered harmless from a toxicological point of view [51]. High concentrations are contra-indicated only in subjects with vitamin K-associated blood coagulation disorders. In this condition, coagulation disorders mediated by vitamin K deficiency may be exacerbated by high vitamin E administration, however, vitamin E does not cause coagulation problems in persons who have no coagulation abnormalities [17].

1.4. Mechanism of action for the immunostimulatory effect of vitamin E in aging

Many theories have been formulated in the attempt to elucidate the immuno-modulatory mechanism of
vitamin E during aging. One of the theories dealing with the immuno-enhancing effects of vitamin E in aging considers its anti-oxidant properties. According to this theory, vitamin E protects the cells of the immune system from the attack of FRS, preserving membrane integrity and fluidity. It has been proposed that this protective effect might delay the immuno-suppressive action of oxidative stress on lymphocyte proliferation during aging. However, it has become progressively clear that the effect of vitamin E cannot only be related to its anti-oxidant capacities, and that some other mechanisms must be involved.

In the T cell-mediated immune function, cell cooperation between T cells and MΦ is essential [103], the lymphocyte response to antigens requires the presence of the ‘professional antigen-presenting cells’: dendritic cells, MΦ and B cells, specialized to process and deliver activating signals to T cells. MΦ are specialized to internalize and to present particulate antigens from different sources to T cells, and make a crucial contribution to the effector phase of the immune response [49].

In vitro studies utilizing co-culture techniques have demonstrated an age-related defect in cell–cell communication between MΦ and T cells [9,91], cytokines, and other soluble compounds secreted by MΦ that can affect T cells activity [30,32,105]. Upon stimulation, MΦ release up to 50% of their AA content in the form of oxygenated metabolites such as prostaglandins and leukotriens [8,45]. Moreover, MΦ release a number of FRS and other potentially injuring compounds such as hydrogen peroxide (H₂O₂). FRS are necessary for certain aspects of cellular response, such as activation of the nuclear transcription factors NFkB or AP-1 [84,95]. However, over-production of FRS has been shown to depress lymphocyte proliferation [27,29,63,67]. Moreover, it has been suggested that age-associated changes in MΦ functionality contribute to a decline in T cell-mediated functions with age [18,79]. Hayek and colleagues [38] compared the levels of fatty acids, H₂O₂ and eicosanoids production in splenocytes from young and old mice. The authors did not find a difference in H₂O₂ production PMA-stimulated between young and old animals. PGE₂ production was higher in splenocytes from old mice than in young mice, and differences were also observed in 5-lipoxygenase products such as leukotriene (LT) B₄ and LTC₄, without any changes in 12 or 15 lipoxygenase products. When the splenocytes were stimulated with specific 5-lipoxygenase and cyclooxygenase (COX) inhibitors, only the inhibition of COX with indomethacin resulted in an increase in T-cell proliferation in old mice. Furthermore, PGE₂ addition to splenic T cells decreased their proliferation. MΦ are the main source of PGE₂ production in splenocytes and, as with the splenocytes, lipopolysaccharide-stimulated MΦ from old mice produced higher levels of PGE₂ compared to MΦ from young mice.

The age-dependent increase of PGE₂ production reported in rats [1], mice [72] and humans [68] has been shown to inhibit T-cell proliferation, and therefore to be immuno-suppressive [22]. In fact, when PGE₂ synthesis is inhibited in vitro, T-cell proliferation increases [90,105]. Moreover, it was also shown that MΦ from old mice were able to suppress T-cell proliferation and IL-2 production [5].

The evidence discussed in this review suggests that PGE₂ could have a role in the age-associated decline of T cell-mediated immunity by affecting IL-2 production as well as T-cell proliferation. Moreover, vitamin E could act through an effect on these mediators (IL-2 and PGE₂) of immune function by decreasing the MΦ production.

Beharka et al. [5], using an in vitro model of co-culture of MΦ and T cells, showed that MΦ from old mice were suppressive for the T cells from young mice and the effect was explained by the increased production of PGE₂ by MΦ. The addition of vitamin E to co-cultures of MΦ from old mice and T cells, increased T-cell proliferative response to mitogen (Con A), and IL-2 production regardless of T cell source. Furthermore, the authors showed that when vitamin E-loaded MΦ (cells were pre-incubated with vitamin E before addition to the co-cultures) from old mice were substituted into cultures containing young T cells, Con A induced proliferation increased by 50%, indicating that the effect of vitamin E is mostly mediated through an effect on MΦ from old mice. Moreover, cells loaded with vitamin E (20 µg/ml), reduced MΦ PGE₂ production from old mice by 30%. These results suggest that PGE₂ decrease by vitamin E may play a central role in restoring compromised immune function in aging [68,72]. In a later study, Meydani and colleagues [39] showed that the age-associated increase in PGE₂ production by murine MΦ, was linked to an increased activity of the enzyme cyclooxygenase COX. In fact, the authors showed that MΦ isolated from old mice presented an increased mRNA for COX-2 (the inducible form of COX), and consequently an increased protein expression of COX-2, in lieu of the constitutively expressed form COX-1, that did not show age-related changes.

To determine whether the vitamin E immuno-enhancing effect is due to its effect on COX-2 expression, the same group conducted an in vivo study feeding mice with 30 ppm (adequate level) or 500 ppm of vitamin E for 30 days. Vitamin E supplementation did not have a significant effect on COX activity in young mice. However, vitamin E supplementation (500 ppm) completely reversed the age-related increase in COX activity in both LPS-stimulated and un-stimulated MΦ from old mice, bringing the levels back to those of
young animals [108]. Moreover, vitamin E supplementation did not affect COX-2 mRNA and protein levels following LPS stimulation [108].

On the basis of these evidences, the reversal of the age-associated increases in PGE2 synthesis and COX activity in murine macrophages by vitamin E does not seem to be mediated through a direct effect on COX-2 gene expression. Rather, a post-translational mechanism of COX inhibition, is more likely to be implicated in the decrease of the enzyme activity by vitamin E.

The mechanism of activation of COX has been the object of extensive reviews [42,109], briefly, COX is a membrane-bound bi-functional enzyme that exhibits a cyclooxygenase and a peroxidase activity. The protein contains two separate binding sites for both activities that require heme as a cofactor. The enzyme is produced as an inactive homodimer, each subunit of about 70 kDa. The enzyme requires that hydroperoxide activators [40,96] bind to the heme prosthetic group to generate a protein radical, needed to catalyze the oxidation of AA [16,96]. The resulting arachidonyl radical can then undergo transformations leading to a peroxyl radical, immediate precursor of PGG2. In the process, the heme protein radical is regenerated and ready to again start the cycle. The peroxidase activity, catalyzes the reduction of the hydroperoxy group of PGG2 to PGH2, a precursor for prostaglandins, prostacyclin and thromboxane A2 [14]. Peroxide is needed continuously throughout catalysis, since at any time, anti-oxidants can inhibit the activity of the enzymes by removing the intermediate radicals necessary for COX to function. Vitamin E may directly reduce the level of hydroperoxide, the best post-translational regulator of COX activity, therefore preventing COX activation.

Alternatively, the effect of vitamin E on COX activity could involve the modulation of another molecule described as a post-translational regulator of the enzyme: nitric oxide (NO). NO is a potent effector molecule, synthesized from L-arginine in the enzyme: nitric oxide (NOS) and NADPH-dependent enzyme existing in an inducible isoform [76]. Macrophage-derived NO plays an important role in host defense in response to an infection, contributing to the elimination of the offending microbes [66]. Intracellular parasites such as malaria [83] and Leishmania [34] are especially sensitive to NO, as are also some viruses [52], fungi [33], and bacteria [66].

The pathway leading to NO-mediated COX activation is unknown, but NO appears to influence PGE2 production through a modulation of COX activity. NO influences PGE2 production by macrophages and there are several reports describing that NOS inhibitors reduce PGE2 production both in vitro and in vivo [75,93], while the addition of exogenous NO increased PGE2 production [92,93], suggesting that in the condition in which both enzymes (NOS and COX) are active, there is a NO-mediated increase of the production of pro-inflammatory substances [92].

Moreover, NO production appears to be affected by aging [4,12]. Resident peritoneal and thioglucolate-induced Mφ from old mice have been shown to produce higher levels of NO than those from young mice in response to LPS in C57BL/NIA [4] and CBA/CA mice [12]. Over-production of NO is potentially cytotoxic, damaging indiscriminately the surrounding cells and tissues. Wink and colleagues reported that NO is capable of deaminating deoxy-nucleotides and intact DNA [106].

The hypothesized post-translational effect of Vitamin E could take place through a modulation of NO production. Beharka and colleagues [4] reported that peritoneal Mφ from old C57Bl/6NIA mice produced more NO than those from young mice, when the mice diet was supplemented with 500 ppm vitamin E for 6 months. Mφ from old mice produced significantly lower levels of NO, in response to stimulation by LPS or LPS + interferon (IFN) gamma than Mφ from old mice fed a control diet (30 ppm pf vitamin E). A shorter-term supplementation (1 month) of the same dose of vitamin E, also reduced NO production in Mφ extracted from old mice compared to animals that did not receive vitamin E supplementation, while in young mice vitamin E supplementation did not influence NO production [3].

However, the mechanism by which vitamin E reduces NO production is still unclear. Vitamin E could act as a pure anti-oxidant, reducing NO levels as it is produced, or, alternatively, vitamin E could inhibit the induction of iNOS by preventing the expression of its gene via inhibition of NFkB activation.

Landino and colleagues [55] formulated an interesting hypothesis about the link between NO and PGE2. Landino showed how the immuno-suppressive in vitro effect of NO was mediated by peroxynitrite (ONOO), a powerful oxidant produced by the reaction of NO with superoxide anion (SO) [46,55] and able to damage nucleic acids, lipids, and proteins [2,89]. Peroxynitrite was able to stimulate COX activity, but not its expression, suggesting that ONOO is a potential substrate for the peroxidase activity of COX. To verify whether the immunostimulatory effect of vitamin E was mediated by a decrease in ONOO production, Meydani’s group conducted in vivo experiments feeding old mice (24 months old) with 30 and 500 ppm E/d for one month [3]. Peroxynitrite produced by the specific generator 3-morpholinosydonimine N-ethylcarbamide (SIN-1), and enzymatically by addition of S-nitroso-N-acetyl-penicillamine (SNAP) and xantine/xanthine oxidase (X/XO), increased COX activity in
МΦ from old mice fed 500 ppm E/d as compared to MΦ without ONOO donors. No changes were observed in MΦ from old mice fed 30 ppm vitamin E/day. When inhibitors of NO (N-monomethyl-L-arginine; L-NMMA) or SO (Mn(III) tetrakis (1-methyl-4-pyridyl)porphyrin; MnTMPyP) production were used, no effect on COX activity was described, suggesting that both molecules and the product of their reaction (ONOO), has to be present to increase COX activity. When the two inhibitors were combined to reduce ONOO production, COX activity was significantly reduced in MΦ from old mice fed 30 ppm vitamin E as compared to the control. Moreover, the expression of COX protein was not affected by modification in peroxynitrite production, suggesting that vitamin E may reduce COX activity in old MΦ mainly through a decrease in ONOO production, but not through a modulation of protein synthesis.

2. Conclusions

In summary, it appears that vitamin E supplementation plays a beneficial role in restoring the compromised immune response of human elderly subjects. Vitamin E supplementation significantly enhances lymphocyte proliferation, IL-2 production and delayed-type hypersensitivity skin response and decreases PGE2. Vitamin E supplementation significantly enhances lymphocyte proliferation, IL-2 production and delayed-type hypersensitivity skin response and decreases PGE2, but not through a peroxynitrite production, suggesting that vitamin E may reduce COX activity in the elderly population.

References


