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Inhibition of Inflammation and Carcinogenesis in the Lung and Colon by Tocopherols

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Abstract

Tocopherols, which exist in α , β , γ , and δ forms, are antioxidative nutrients also known as vitamin E. Although α -tocopherol (α -T) is the major form of vitamin E found in the blood and tissues, γ - and δ -T have been suggested to have stronger anti-inflammatory activities. In the present study, using a tocopherol mixture that is rich in γ -T (γ -TmT, which contains 57% γ -T), we demonstrated the inhibition of inflammation as well as of cancer formation and growth in the lung and colon in animal models. When given in the diet at 0.3%, γ -TmT inhibited chemically-induced lung tumorigenesis in the A/J mice as well as the growth of human lung cancer cell H1299 xenograft tumors. γ -TmT also decreased the levels of 8-hydroxydeoxyguanosine, γ -H2AX, and nitrotyrosine in tumors. More evident anti-inflammatory and cancer preventive activities of dietary γ -TmT were demonstrated in mice treated with azoxymethane and dextran sulfate sodium. These results demonstrate the anti-oxidative, anti-inflammatory, and anti-carcinogenic activities of tocopherols.

Keywords

Tocopherols; Antioxidant; Anti-inflammation; Anti-Carcinogenesis; Lung; Colon

Introduction

Tocopherols are important dietary antioxidants, collectively known as vitamin E (1). They are a family of fat-soluble phenolic compounds; each contains a chromanol ring system and a 16-carbon tail. Depending upon the number and position of methyl groups on the chromanol ring, they exist as α -, β -, γ -, or δ -tocopherols (α -, β -, γ -, and δ -T). The structures of these tocopherols are shown in Figure 1. Whereas α -tocopherol (α -T) is trimethylated at the 5, 7, and 8 positions of the chromanol ring, the 5 position is not methylation in γ -T, and both the 5 and 7 positions are not methylated in δ -T. These unmethylated carbons are electrophilic centers and are effective in trapping reactive nitrogen species (RNS). The formation of 5-nitro- γ -T, 5-nitro- δ -T, 7-nitro- δ -T, and 5,7-dinitro- δ -T have been reported (2). The ring structure and the hydrocarbon tail provide the lipophilicity for tocopherols to be incorporated into the lipid bilayers of biological membrane. The phenolic groups in the chromanol moiety effectively traps lipid free radicals. By donating one electron to reduce the free radical, the tocopherol molecule is oxidized to a phenoxy radical which can be reduced by ascorbic acid or glutathione

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to regenerate the tocopherol molecule. This is probably the most important physiological antioxidant mechanism to protect the integrity of biological membranes. In this chapter, we will first briefly discuss the existing results from human studies to serve as a background for our animal studies, and then we will describe our recent results on the anti-inflammatory and anti-carcinogenic activities of different tocopherols in the lung and colon.

Human Studies

Based on their chemical properties, tocopherols are expected to be effective agents in protecting against environmental toxicity and carcinogenesis. There is evidence to support this concept. For example, of the three reported cohort studies on lung cancer, two studies found a significant inverse association between dietary intake of vitamin E and risk of lung cancer (3,4). In both of these studies, the protective effects were found in current smokers, suggesting a protective effect of vitamin E against insult from cigarette smoking. In four previous case-control studies on lung cancer, three studies found lower serum α -T levels in lung cancer patients than in matched control (5–7). In a recent case-control study involving 1,088 incident lung cancer patients and 1,414 healthy matched controls, Mahabir *et al.* observed that the odds ratios of lung cancer for increasing quartiles of dietary α -T intake were 1.0, 0.63, 0.58, and 0.39, respectively (P -trend < 0.0001) (8). Similar results on dietary γ -T were also observed in this study. They concluded that α -T accounts for 34–53% reduction in lung cancer risk (8), but the beneficial effect could be due to the combined effects of all the forms of tocopherols. γ -T is 3 to 4 times more abundant than α -T and δ -T could also be more abundant than α -T in our diet. γ -T and δ -T have also been shown to be more effective in trapping reactive oxygen/nitrogen species (2).

Because blood and tissue levels of α -T are much higher than other tocopherols and α -T has the highest activity in the classical fertility-restoration assay, α -T is generally considered to be “the vitamin E” (1). Therefore, many studies have been conducted with α -T, either the naturally occurring d- α -T or the synthetic all-rac α -T, which consist of eight isomers. The results from several large-scale intervention studies with α -T, however, have been disappointing. For example, in the Women’s Health Study, with 39,876 healthy US women, taking 600 IU d- α -T on alternate days did not significantly affect the incidence of lung, colon or total cancers (9). In the Physicians Health Study II Randomized Control Trail, supplementation with 400 IU synthetic α -T every other day or 500 mg synthetic ascorbic acid daily to physicians for 8 years did not reduce the risk of prostate or all other cancers (10). In the recent Selenium and Vitamin E Cancer Prevention Trial (SELECT), taking 400 IU all-rac α -tocopherol acetate, or 300 μ g selenium from L-selenomethionine, or both per day, for an average of 5 years, did not prevent prostate or other cancer (11). It was noted that the α -T supplement caused a 50% decrease in median plasma γ -T levels (11). There are at least two interpretations of the result: 1) supplementation of a nutrient to a population that is already adequate in this nutrient may not produce any beneficial effects; and 2) supplementation of a large quantity of α -T decreases the blood and tissue levels of γ -T, which has been suggested to have stronger anti-inflammatory and cancer preventive activities (12–17). The exact reasons for this negative result, however, are not known. Nevertheless, the outcome of this large-scale trial reflects our lack of understanding of the biological activities of tocopherols and points to the need for systematic studies on the cancer preventive activities of the different forms of tocopherols and their mixtures.

Inhibition of Lung Tumorigenesis by Tocopherols in Animal Models

Many cancer prevention studies have been conducted in different animal models previously with pure α -T, but the results have not been consistent (reviewed in (18)). Recent studies from our research team at Rutgers University have demonstrated the inhibition of cancer formation

and growth in the lung, colon, mammary gland, and prostate by a tocopherol mixture that is rich in γ -T (γ -TmT) (19–25). γ -TmT is a by-product in the distillation of vegetable oil and usually contains (per g) 130 mg α -T, 15 mg β -T, 568 mg γ -T, and 243 mg δ -T.

In studying the cancer preventive activity of γ -TmT, we used two classical models to induce lung tumorigenesis in A/J mice with the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or NNK plus benzo[a]pyrene (B[a]P), a ubiquitous environmental pollutant. The experimental design is shown in Fig.2. In the first model, female A/J mice (6 weeks old) were administered weekly NNK plus B[a]P, 2 μ mol each, by oral gavages for 8 weeks from Weeks 1 to 8. At Week 19, the mice in the control group (on AIN93M diet) developed 21 tumors per mouse (25). The tumors were adenomas in a solid, papillary, or mixed growth pattern and were generally composed of well-differentiated cells. Treatment of the mice with 0.3% γ -TmT in the diet during the entire experimental period significantly lowered the tumor multiplicity to 14.8 (30% inhibition, $P < 0.05$). Tocopherol treatment also significantly reduced the average tumor volume from 0.08 to 0.04 mm³ and tumor burden (the total tumor volume per animal) from 1.71 to 0.77 mm³ (50% and 55% inhibition, respectively; $P < 0.05$) in this experiment (25).

In the second model, tumorigenesis was induced by NNK (i.p. injection of 100 mg/kg on Week 1 and then a second i.p. injection of 75 mg/kg on Week 2). The 0.3% γ -TmT diet was given during the carcinogen-treatment stage, the post-initiation stage, or the entire experimental period. γ -TmT treatment during these three time protocols all significantly reduced the tumor multiplicity (17.1, 16.7 and 14.7, respectively, as compared to 20.8 in the control group; $P < 0.05$). Moreover, the tumor burden was reduced by the tocopherol treatment given during the tumor initiation stage or during the entire experimental period (36% and 43% inhibition, respectively; $P < 0.05$). No lung tumors were found in the saline- or glycerol trioctanoate-treated negative control animals, which did not receive carcinogen treatment (25).

Immunohistochemistry with an antibody against cleaved-caspase 3 indicated that in the NNK plus B[a]P-treated model, dietary 0.3% γ -TmT significantly increased the apoptotic index from 0.09% to 0.25% ($P < 0.05$) in the lung tumors; whereas the treatment did not affect apoptosis in non-tumorous lung tissues. The dietary treatment also significantly decreased the percentage of cells with positive immunostaining for 8-hydroxydeoxyguanine (8-OHdG) (from 26% to 17%), a marker for oxidative DNA damage, as well as for γ -H2X (from 0.51% to 0.23%), a reflection of double-strand break-induced DNA repair. The plasma levels of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) were markedly elevated in the tumor-bearing A/J mice at Week 19 as compared to mice that received no carcinogen treatment. Dietary γ -TmT treatment resulted in lower plasma levels of PGE2 (by 61%, $P < 0.05$) and LTB4 (by 12.7%, $P < 0.1$). These results suggest the antioxidant and anti-inflammatory activities of γ -TmT. The antiangiogenic activity of dietary γ -TmT was demonstrated with anti-endothelial cell CD31 antibodies. CD31-labeled capillary clusters and blood vessels were observed mainly in the peripheral area of the adenomas, and dietary γ -TmT significantly reduced the microvessel density (blood vessels/mm²) from 375 to 208 ($P < 0.05$) (25).

Inhibition of Lung Cancer Cell Growth in Xenograft Tumors

When 0.3% γ -TmT was given to mice in the diet one day after implantation of human lung H1299 cells (1×10^6 cells injected s.c. per site to both flanks of Ncr-nu/nu mice), an inhibitory effect on xenograft tumor growth was observed (25). After six weeks, the tumor size and weight were significantly reduced by 56% and 47%, respectively, as compared to the control group. The γ -TmT treatment also caused a 3.3-fold increase in apoptotic index as well as a 52% decrease in 8-OHdG positive cells and a 57% decrease in γ -H2AX positive cells in the xenograft tumors. Strong cytoplasm staining of nitrotyrosine was observed in xenograft tumors, and the

staining intensity was decreased by 44% in mice that received γ -TmT. γ -TmT treatment also reduced the plasma LTB₄ level by 36.5% ($P < 0.05$) (25).

In a similar experiment, the effectiveness of different forms of tocopherols in the inhibition of H1299 xenograft tumor growth was compared (Li, GX and Yang, CS, unpublished results). Pure δ -T was most effective, showing dose-response inhibition when given at 0.17% and 0.3% in the basal AIN-93M diet. γ -TmT and pure γ -T were also effective when given at 0.3% in the diet, but α -T was not effective at diet levels of 0.17% and 0.3%. Studies of H1299 cells in culture also showed that δ -T was more effective than γ -TmT and γ -T in inhibiting cell growth, whereas α -T was not active (25).

In another transplanted tumor study, dietary 0.1% and 0.3% γ -TmT were found to inhibit the growth of subcutaneous tumors (formed by injection of murine lung cancer CL13 cells) in A/J mice by 54% and 80%, respectively, on Day 50 (24). Histopathological analysis showed that dietary γ -TmT treatment resulted in increased tumor necrosis.

Inhibition of Colon Inflammation and Tumorigenesis by γ -TmT

Previous studies concerning the effect of α -T on colon carcinogenesis have yielded mostly negative results (reviewed in (18)). Newmark *et al.* (20), however, demonstrated that 0.1% γ -TmT in an AIN76A diet significantly inhibited azoxymethane (AOM)-induced aberrant crypt foci (by 55%) in the colon of male F344 rats. Recently, we studied the effect of γ -TmT in the colon of mice that had been treated with AOM and dextran sulfate sodium (DSS) (19). In one experiment, 6-week-old male CF-1 mice were given a dose of AOM (10 mg/kg body weight, i.p.), and 1 week later 1.5% DSS in drinking water for 1 week. The mice were maintained on either a γ -TmT (0.3%)-enriched or a standard AIN93M diet, starting 1 week before the AOM injection, until the termination of experiment. In the AOM/DSS-treated mice, dietary γ -TmT treatment resulted in a significantly lower colon inflammation index (52% of the control) on day 7 and reduced the number of colon adenomas (to 9% of the control) on week 7. γ -TmT treatment also resulted in higher apoptotic index in adenomas, lower PGE₂, LTB₄, and nitrotyrosine levels in the colon, and lower PGE₂, LTB₄, and 8-isoprostane levels in the plasma on week 7. Some of the decreases were observed even on day 7. In a second experiment, with AOM/DSS-treated mice sacrificed on week 21, dietary 0.17% or 0.3% γ -TmT treatment, starting 1 week before the AOM injection, significantly inhibited adenocarcinoma and adenoma formation in the colon (to 17–33% of the control). Dietary 0.3% γ -TmT that was initiated after DSS treatment also exhibited a similar inhibitory activity. In a third experiment, mice received dietary treatment with 0%, 0.1%, and 0.3% γ -TmT in the AIN 93M basal diet. One week later, 1% DSS was given to mice in drinking water for one week to induce inflammation, and the mice were maintained on the same diet for one week before sacrifice. A dose dependent anti-inflammation was also observed (G.X. Li and C.S. Yang unpublished results). These studies demonstrate the anti-inflammatory and anti-carcinogenic activities of γ -TmT in the colon.

Tissue Levels of Tocopherols and their Metabolites

After supplementation with 0.1% or 0.3% of γ -TmT, the plasma levels of α -T did not show a significant change, maintaining in the range of 10–16 μ M in the CF-1 mice (19). However, the γ -T and δ -T levels are dose-dependently increased to a level of approximately 5 μ M and 1 μ M, respectively, with 0.3% γ -TmT supplementation. The colonic levels of γ -T and δ -T were much higher than in plasma, but the colonic levels of α -T were much lower than colonic levels of γ -T and δ -T as well as plasma levels of α -T. The xenograft tumor levels of α -T increase from 5 to 10 μ mol/kg upon supplementation with 0.3% γ -TmT, whereas the γ -T and δ -T showed even larger fold increase from 0.36 to 4.59 μ mol/kg for γ -T and from 0.08 to 1.7 μ mol/kg for δ -T.

Tocopherols, especially γ - and δ -T, are extensively metabolized by the side-chain degradation pathway, which is initiated by the ω -oxidation of the hydrocarbon tail, followed by β -oxidation. Almost all the side-chain degradation product can be detected in the feces and colon with a sensitive HPLC-electrochemical detection system (Zhao, Y. and Yang, C.S. unpublished results). The concentration of carboxymethylbutyl hydroxychroman (CMBHC) and carboxyethyl hydroxychroman (CEHC) are the most prominent ones that can be found in the blood, colon and other tissues. With the supplementation of 0.3% γ -TmT, the serum levels of γ - and δ -CMBHC were 1–3 μ M and 1–2 μ M respectively. For γ - and δ -CEHC, the level can reach 0.2–0.3 μ M and 0.3–0.5 μ M, respectively. The colonic levels of γ - and δ -CMBHC are in the ranges of 5–10 μ M and 2–5 μ M and of γ - and δ -CEHC are in the ranges of 1–2 μ M and 0.5–1 μ M, respectively. Since some of the metabolites have been shown to have biological activities, such as the inhibition of cyclooxygenase-2 activities (26), these metabolites can contribute to the anti-inflammatory and anti-carcinogenic activities, especially in the colon.

The present study demonstrates the anti-inflammatory and anti-carcinogenic activities of γ -TmT in the lung and colon. These activities are associated with the reduction of oxidative damage, trapping of reactive nitrogen species, and inhibition of aberrant arachidonic acid metabolism. All tocopherols are effective antioxidants. γ - and δ -T are known to trap reactive nitrogen species and they are better anti-inflammatory agents than α -T (2,27). In cell line and xenograft studies we have demonstrated the higher activity of δ -T over other tocopherols. In cancer prevention models, however, it remains to be demonstrated whether a single form of tocopherol is more effective than mixtures of tocopherols. From a nutritional point of view, mixtures of tocopherols should be better than single forms of tocopherols. γ -TmT is readily available and its composition is similar to the ratios of tocopherols in our diet. Additional studies are needed to determine whether γ -TmT can be used as an effective supplement to help prevent environmental toxicity and carcinogenesis in humans.

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Figure 1.
Structures of tocopherols

Figure 2.
Study design on the cancer preventive activity of tocopherols