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Extended Abstract

Nutrition Congress 2015: Vitamin E isoforms regulate allergic disease - Joan Cook-Mills- North-western University School of Medicine

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Abstract

Asthma occurs as complex interactions of the environmental and genetics. Clinical studies and animal models of asthma indicate dietary factors like vitamin E and vitamin D as protective for asthma risk. In this review, we discuss opposing regulatory functions of tocopherol isoforms of vitamin E and regulatory functions of vitamin D in asthma and the way the variation in global prevalence of asthma may be explained, at least in part, by these dietary components.

Asthma is a heterogeneous disease resulting from complex interactions of environmental and genetic factors. The World Health Organization reported that the prevalence of asthma from 1950 to the present has increased many countries including, countries with high rates of asthma, intermediate rates of asthma or low rates of asthma, over only a few decades suggesting an important role of the local environment. The marked rise in rates of asthma over a few decades and the differences in rates among countries and in migrating populations suggest an important role of the local environment, such as diet, in development of asthma. One environmental change over the past 40 years has been a rise within the d-γ-tocopherol isoform of vitamin E within the diet and in infant formulas. We recently demonstrated that γ-tocopherol increases allergic lung inflammation in a mouse model of asthma and, we reported that, in humans, high plasma γ-tocopherol levels are associated with lower lung function. It is also suggested that a reduction over time in another vitamin, vitamin D, associates with the increase incidence in asthma. In this review, we discuss the regulation of asthma by vitamin D and the complex and potentially protective effects of specific isoforms of vitamin E on asthma in humans and in animal models of lung inflammation. We will also review how the variation in global prevalence of asthma may be explained, at least in part, by country-specific plasma γ-tocopherol concentrations. Our studies specialise in regulation of allergic inflammation by the 2 most abundant sorts of vitamin E (d-α-tocopherol and d-γ-tocopherol) within the diet and tissues. We demonstrated that α-tocopherol inhibits and γ-tocopherol elevates leukocyte recruitment across endothelium in vitro and endothelial cell protein kinase Cα activation for eosinophil and dendritic cell recruitment during allergic inflammation. Specifically, γ-tocopherol is an agonist and α-tocopherol is an antagonist of PKC. In vivo, α-tocopherol supplementation blocks eosinophilic allergic lung responses in adult mice and that α-tocopherol associate with better lung spirometry in adult humans. Notably, γ-tocopherol has the opposite function. In humans, a 5-folds higher plasma γ-tocopherol level associate with lower lung spirometry in adults by age 21, suggesting tocopherol isoforms have a regulatory role early in life. In clinical readings and animal models, offspring of allergic mothers have improved responsiveness to allergen challenge.

The average human plasma γ-tocopherol levels are 2 to 5 times higher in the United States than those of many European and Asian countries whereas the average human plasma α-tocopherol levels are relatively similar among these countries. This 5-fold higher level of human plasma γ-tocopherol is similar to the 5-fold increase in plasma γ-tocopherol in mice that increased allergic lung inflammation with γ-tocopherol administration. The high human plasma γ-tocopherol levels in the United States are consistent with soybean oil, which is high in γ-tocopherol, as the predominant food oil in the United States. It is reported that dietary oils influence plasma tocopherol levels in humans. In studies with soybean oil administration, plasma γ-tocopherol is elevated 2–5 fold in humans and hamsters. Also, in a study in which olive oil or soybean oil was administered to preterm human infants starting 24 hrs after birth, there was a significant 1.5 fold increase in plasma α-tocopherol after feeding with olive oil as compared to feeding with soybean oil, but unfortunately, γ-tocopherol was not reported. It is reported that as countries assume western lifestyles, diets change including increased consumption of soybean oil. In contrast to high levels of γ-tocopherol in soybean oil, γ-tocopherol is low in other oils such as sunflower oil, safflower oil and olive oil that are used in several European and Mediterranean countries. There are also differences in asthma prevalence among racial and ethnic groups. However, studies examining vitamin E association with clinical outcomes generally adjust for several known confounding factors such as gender, age, body mass index, race, and smoking. Although there may be other differences regarding the environment and genetics of people in different countries, the outcomes for tocopherol isoforms and asthma in clinical studies are consistent with the studies

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demonstrating opposing functions of the tocopherol isoforms on leukocyte recruitment and allergic inflammation in mice.

We reported that the findings of opposing regulatory functions of tocopherol isoforms in animal models can be translated to human lung function. We analyzed 4526 adults in the United States in the Coronary Artery Risk Development in Young Adults (CARDIA) multi-center cohort with available spirometry and tocopherol isoform data. In this cohort, there were equal numbers of blacks and whites and equal numbers of females and males by study design. Interestingly, increasing serum concentrations of γ-tocopherol were associated with lower FEV1 or FVC, whereas increasing serum concentrations of α-tocopherol were associated with higher FEV1 or FVC. Since these two tocopherols have opposing functions, we suggest that the analysis of opposing functions of tocopherol isoforms in clinical studies should include quartiles of plasma tocopherols with determination of whether there is an association of a tocopherol isoform with the clinical outcome when the concentration of the opposing tocopherol is low and causing the least competing opposing effects. Using this approach, in the analysis of the CARDIA cohort, we recently demonstrated that plasma γ-tocopherol is inversely associated with lung function (FEV1) and plasma α-tocopherol is positively associated with lung function (FEV1) in non-asthmatics and asthmatics with adjustments for several known confounding factors such as gender, age, body mass index, race, and smoking. Thus, there were opposing outcomes for association of plasma α-tocopherol and γ-tocopherol with lung function. This is consistent with our mechanistic studies for these tocopherols in animal models.

We demonstrated that development of allergic responses in offspring is inhibited or elevated by maternal supplementation with α-tocopherol or γ-tocopherol, respectively. These results have inferences for supplementation of allergic mothers with tocopherol isoforms and for growth of allergies in future groups.

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