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Reply: Understanding the Roles of the Vitamin E Isoforms α - and γ -Tocopherol in Allergic Airway Disease

From the Authors:

We appreciate the opportunity to briefly discuss the very interesting and still not fully understood roles of the vitamin E tocopherols (α -tocopherol and γ -tocopherol) in allergic airway disease, as well as to comment on the letter from Wagner and colleagues. We have much to learn from each other, and working together we can best discern the important role of these tocopherols in human disease. In this letter, we build on the discussion begun by Wagner and colleagues, providing insights into the cited studies and available data and further explaining how they contribute to our understanding of airway inflammation.

Wagner and coworkers commented that we have misinterpreted their studies on the role of γ -tocopherol on neutrophilic airway inflammation. In the study cited in our review article, we stated (1), “ γ -tocopherol supplementation reduced antigen induction of rat lung inflammation that was primarily neutrophils.” We did not state a reduction in neutrophils; we stated that in the presence of a very large neutrophil infiltration, there was a reduction in inflammation. In the cited study (2), the mean decrease in proportion of neutrophils in the lung lavage was 40%, with γ -tocopherol supplementation with a large standard deviation and with more than 2.5 times more neutrophils than eosinophils. In contrast, in rats challenged with chicken egg ovalbumin (OVA), the lung lavage has been shown to be predominantly eosinophilic, with the numbers of lung lavage neutrophils after OVA challenge

several-fold lower than the number of eosinophils (3–6). However, in the presence of LPS in OVA inhalations, the lung lavage becomes predominantly neutrophilic (two to three times more neutrophils than eosinophils) (6). In acute models of inflammation with large numbers of neutrophils, such as with LPS or ozone, there is generation of nitric oxide (7, 8); it is known that γ -tocopherol scavenges nitric oxide, whereas α -tocopherol does not (9–11). Therefore, during acute predominantly neutrophilic inflammation with generation of nitric oxide, we hypothesize that there may be a benefit of short-term administration of γ -tocopherol. Acute neutrophilic inflammation, however, is not the hallmark of chronic or acute allergic airway inflammation.

Contrary to the comment by Wagner and colleagues, tocopherols administered subcutaneously do not bypass liver metabolism. With oral delivery of tocopherol, it exits the intestine via the lymph, where it travels to the thoracic duct, next to the blood, and then to the liver. Similarly, during subcutaneous administration, tocopherol enters the draining lymph, traveling to the thoracic duct before entering the blood, and then the liver. As previously described, the subcutaneous administration of tocopherols, compared with oral administration, results in rapid elevation of tocopherol levels (a few days compared with weeks) (12). To study the effect of γ -tocopherol on the rapid recruitment of leukocytes to the lung after OVA challenge, we have previously studied the subcutaneous administration of tocopherol to mice (12, 13) to rapidly increase γ -tocopherol tissue levels in the short time interval between OVA/alum sensitization and OVA challenge. We have also demonstrated that oral administration of γ -tocopherol in supplemented rodent chow increases eosinophilic inflammation in the OVA model in mice (unpublished data). In addition, we recently reported that rodent chow supplemented with α -tocopherol inhibits development of allergic responses in mice (13).

Wagner and colleagues importantly comment on the epidemiologic data on γ -tocopherol levels and lung diseases and on the relationship between tocopherols and saturated and polyunsaturated fatty acids in oils, the primary source of tocopherols and fatty acids. We agree with Wagner and colleagues, and as pointed out in our perspective, “further intervention studies are necessary to examine tocopherol isoform regulation of allergic lung inflammation and asthma.” In addition, we recently reported that in a US study population of 4,500 individuals (with and without asthma) studied over the course of 20 years, higher plasma γ -tocopherol levels were associated with lower spirometric measures, whereas higher plasma α -tocopherol levels were associated with higher spirometric measures (14).

Further, Wagner and colleagues comment on their two published γ -tocopherol oral intervention studies in humans. These studies are important, as they demonstrate the potential role of γ -tocopherol on acute nonallergic airway inflammation. However, we feel it is important to point out that in these human studies, the tocopherol administered contained both α - and γ -tocopherol (the composition of tocopherols contained 50 mg α -tocopherol, 240 mg β -tocopherol and δ -tocopherol, and 540 mg γ -tocopherol). They report that plasma γ -tocopherol was increased after supplementation; however, there were no measurements of the other tocopherol isoforms. Moreover, the liver preferentially transfers α -tocopherol over γ -tocopherol, resulting in 10-fold more α -tocopherol *in vivo*. Therefore, because they studied a mixture of tocopherols administered *in vivo*, the data and tocopherol isoform function are difficult to interpret. As discussed earlier, during acute neutrophilic response with

generation of nitric oxide, acute administration of γ -tocopherol may indeed have benefit. In contrast, in both the US and Chinese population-based studies (unpublished data) we have conducted, chronic exposure to γ -tocopherol was associated with both lower spirometric values and higher incidence of asthma, respectively, and those individuals with asthma and high levels of γ -tocopherol had the lowest lung spirometric measures (14). In contrast, in these population-based studies, higher α -tocopherol levels were associated with higher spirometric parameters and a lower risk for incident asthma, respectively (14).

How do we put these studies into context, learn from them, and advance our understanding of the role of these dietary factors in allergic airway disease? We believe these studies should not necessarily be seen as contradictory, that these antioxidants may be beneficial in different types of airway inflammation, with γ -tocopherol playing a role as an acute antioxidant in primarily neutrophilic lung inflammation and α -tocopherol playing a protective role in allergic airway inflammation. In contrast, γ -tocopherol increases allergic inflammation in mice and is associated with reduced spirometry in individuals with and without asthma (14). We have made great progress in the last decade in understanding the role of these tocopherols; however, we still have much to learn. It is acknowledged that future long-term chronic intervention studies are challenging, but needed. In addition, these studies will require use of purified tocopherol isoforms, as well as studies of the dual effect of combined isoforms to fully understand the functions of these tocopherols in allergic airway and other diseases. We believe that the modification of the human diet offers tremendous promise in primary disease prevention of allergic airway disease. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Erratum: Club Cell Protein 16 and Disease Progression in Chronic Obstructive Pulmonary Disease

The authors have corrected the reported source of the mice used in the study, published in the December 15, 2013, issue of the *Journal* (1).

In the METHODS: ANIMAL STUDY section on p. 1414, the corrected line now reads: “. . . we obtained CC-16^{-/-} mice on a C57BL/6J genetic background from Drs. Luis Ortiz and Barry Stripp (University of Pittsburgh, Pittsburgh, PA)” [the source of the mice was originally incorrectly reported as Jackson Laboratories (Bar Harbor, ME)]. ■

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