To the Editor:

A recent Brief Critical Review addressed the observation that elevated intakes of α-tocopherol consistently result in lower plasma concentrations of γ-tocopherol. The article concludes that recent publications reveal that the underlying mechanism involves α-tocopherol-induced expression of the cytochrome P450 enzyme CYP3A, which causes enhanced efficiency of catabolism of γ-tocopherol to its side-chain shortened metabolite, γ-CEHC. We find this conclusion premature and the proposed mechanism unlikely. In 2002, it was reported that human and rat liver microsomes possess a novel activity that results in the hydroxylation of one of the terminal methyl groups of the side chain of γ-tocopherol and the 13-hydroxytocopherol product was identified by mass spectrometry; the activity was termed tocopherol-ω-hydroxylase. The authors additionally identified a specific human liver cytochrome P450 isozyme, CYP4F2, which exhibited tocopherol-ω-hydroxylase activity and demonstrated its substrate preference for γ-tocopherol over α-tocopherol. Importantly, several other major human liver CYP enzymes tested, including CYP3A, exhibited no such activity. Therefore, CYP3A expression is unlikely to be relevant to the effect of α-tocopherol on ω-oxidation of γ-tocopherol. The confusion that currently exists regarding the role of CYP3A in vitamin E metabolism could be due in part to an earlier publication from our laboratory, in which we proposed such a role based on inhibition of γ-tocopherol metabolism by ketoconazole, which at the time was considered a specific inhibitor of CYP3A. Ketoconazole was subsequently shown to lack such specificity, in part stimulating our screening of specific cytochrome P450 isozymes for tocopherol-ω-oxidation activity.

Secondly, while it is possible that supplementation with α-tocopherol induces a tocopherol-metabolizing activity (ω-oxidation or other as-yet unidentified activities), we are not aware that this has actually been tested. None of the articles discussed in the review assessed enzyme activity.

Lastly, it is possible to explain the observed suppression of plasma γ-tocopherol by α-tocopherol without invoking altered protein abundance and/or gene expression. While the hepatic tocopherol transfer protein αTTP exhibits preferential affinity for α-tocopherol over γ-tocopherol, αTTP clearly interacts with both vitamers in vivo, because αTTP-null mice exhibit equivalent proportional decrements in both vitamers relative to wild-type mice. Thus, elevated α-tocopherol intake may competitively reduce αTTP-mediated export of γ-tocopherol from the liver, increasing its catabolism to γ-CEHC by constitutive hepatic CYP4F. This hypothesis remains to be tested.

Robert S. Parker, PhD
Division of Nutritional Sciences
Cornell University
Ithaca, New York

REFERENCES