Antioxidant activity of gamma-tocopherol may protect tetrahydrobiopterin

The endothelial dysfunction common to a number of systemic vascular disorders — diabetes, hypertension, hypercholesterolemia, etc. — is characterized by increased endothelial oxidant stress attributable to increased superoxide production; NADPH oxidase appears to be the chief source of this superoxide [1–6]. This oxidant stress opposes the vasoprotective activity of NO synthase (eNOS) in several distinct ways: direct quenching of NO by spontaneous reaction with superoxide; disabling of the enzyme (DDAH) responsible for the catabolism of asymmetric dimethylarginine (ADMA), a competitive inhibitor of eNOS [7–10]; and oxidation of tetrahydrobiopterin (BH4), an essential cofactor for eNOS [11–16]. The latter mechanism is particularly pernicious, inasmuch as, in the absence of adequate concentrations of BH4, eNOS is ''uncoupled'' and becomes a generator of superoxide [12].

Peroxynitrite, the product of the spontaneous reaction of NO and superoxide, is a potent oxidant.
In particular, it is highly active in the oxidation of BH4, and may be the chief mediator of BH4 oxidation in oxidant-stressed endothelium [13,17–19]. Gamma-tocopherol functions physiologically to quench peroxynitrite and other nitrogenous oxidants; in this respect, it is far more active that alpha-tocopherol, reflecting the presence of an unmethylated nucleophilic 5-carbon in its chromanol ring [20–22]. A recent study has demonstrated that, in rats supplemented with gamma-tocopherol, renal content of nitrotyrosine (stemming from the spontaneous reaction of peroxynitrite and tyrosine) is decreased by 30–50%; this presumably indicates that gamma-tocopherol decreases renal peroxynitrite levels [23]. In light of these findings, it is reasonable to suspect that, analogously, gamma-tocopherol may have the potential to scavenge peroxynitrite in inflamed vascular endothelium — thereby limiting the oxidation of BH4 and helping to preserve effective eNOS activity.

Gamma-tocopherol-rich walnuts boost endothelium-dependent vasodilation

This thesis may help to rationalize a recent clinical study demonstrating that walnuts have a favorable effect on endothelium-dependent vasodilation in hypercholesterolemic subjects [24]. Using a cross-over design, the study evaluated two “Mediterranean” diets; in one of the diets, approximately a third of the lipid content was provided by walnuts, substituted for olive oil and other monounsaturated-rich foods. Endothelium-dependent hyperemia-induced vasodilation of the brachial artery was significantly greater after the walnut-rich diet: 5.9% vs. 3.6% (p = 0.043). Endothelium-independent vasodilation did not differ between the diets — consistent with the possibility that walnuts were improving the capacity of endothelium to generate bioactive NO (albeit the study did not clarify whether increased NO was indeed responsible for this effect). Although LDL cholesterol was about 6% lower on the walnut-rich diet, this seems unlikely to fully explain the improvement in endothelial function. In attempting to rationalize their findings, the authors noted that walnut ingestion increased intakes of arginine by 0.9–1.4 g daily, and of alpha-linolenic acid by 3.7–6.0 g daily. It is not known whether modest intakes of alpha-linolenate influence endothelial function; there is no direct evidence that they do. In one recent study, serum alpha-linolenate correlated positively with endothelium-dependent vasodilation in men but not women [25]. It seems unlikely that a relatively modest increase in arginine intake would exert the rather substantial effect on endothelial function observed in the walnut study.

The authors also measured the gamma-tocopherol content of the walnuts used in their study, finding 155 mg per 100 g; this implied that the walnut-rich diets provided 90–135 mg daily of gamma-tocopherol. The measured gamma-tocopherol content of LDL particles roughly doubled during the walnut-rich diet. It should be noted that a much earlier study determined that the gamma-tocopherol content of walnuts was far lower — about 17 mg per 100 g — though walnuts still emerged as one of the richest food sources of this vitamin [26].

Gamma-tocopherol promotes no synthase activity in previous studies

A previous controlled clinical study evaluated the impact of mixed tocopherol supplementation — providing 100 mg daily of gamma-tocopherol and lower doses of several other tocopherols — on platelet function ex vivo [27]. ADP-induced platelet aggregation was decreased after mixed tocopherol supplementation — an effect associated with increased NO production by the stimulated platelets. A portion of the increase in platelet eNOS activity was apparently attributable to increased phosphorylation of Ser1177, a modification which boosts the activity of the enzyme and lessens its calcium dependence [28]. However, the authors did not measure the BH4 content of the platelets to determine whether mixed tocopherol supplementation had influenced this.

A previous study by this group found that administration of gamma-tocopherol (100 mg/kg diet) to rats led to an increase in the ex vivo production of NO by arterial tissue; the arterial eNOS was found to be more phosphorylated, and arterial expression of eNOS protein was also increased [29]. BH4 content was not measured. These findings suggest that gamma-tocopherol might work in a variety of complementary ways to increase the eNOS activity of vascular tissue.

Epidemiological evidence is equivocal

Epidemiological studies examining possible links between gamma-tocopherol intake or plasma levels have yielded inconsistent findings. A Swedish case-control study reported that lipid-corrected
serum gamma-tocopherol levels were significantly lower in patients with coronary disease than in age-matched healthy controls [30]. Two subsequent case-control studies also observed lower plasma gamma-tocopherol in subjects with coronary disease or recent myocardial infarction [31,32]. However, when the recent MI patients were followed up for a year, their gamma-tocopherol rose toward normal levels — possibly indicating that their former low gamma-tocopherol status had been an effect rather than a cause of infarction [32]. In a study comparing plasma parameters in residents of Vilnius (considered at high risk for coronary disease) vs. those of residents of Linköping (at lower risk), gamma-tocopherol was much lower in Vilnius group [33]. Another ecologic study, comparing serum gamma-tocopherol in a high-risk city (Karuna) with those in a low-risk city (Upssala), likewise found lower gamma-tocopherol levels in the high-risk group. However, two recent prospective case-control studies have failed to correlate increased baseline gamma-tocopherol status (plasma or adipose tissue levels) with reduced risk for MI [34,35] — indeed, one of these studies found that higher plasma gamma-tocopherol predicted increased risk [35]. Confounding factors might be at work here: plasma gamma-tocopherol has been reported to be relatively high in subjects whose diets are high in saturated fats and low in fruits and vegetables [36] — even though such diets are not characteristically high in gamma-tocopherol.

Thus, the available epidemiological data do not provide clear support for the thesis that ambient variations in plasma or tissue gamma-tocopherol levels have a major impact on coronary health. This however does not rule out the possibility that high-nutritional dietary or supplemental intakes of gamma-tocopherol could indeed provide benefit in this regard. Clinical studies examining the impact of supplemental gamma-tocopherol on the endothelial function of at-risk patients would be desirable.

References


