

Abstract

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In Vivo Angiogenesis Is Suppressed by Unsaturated Vitamin E, Tocotrienol.

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BACKGROUND: Antiangiogenic therapy using drugs and food components is a recognized strategy for the prevention of various angiogenesis-mediated disorders such as tumor growth, diabetic retinopathy, and rheumatoid arthritis. Our preliminary cell culture studies, using both bovine aortic endothelial cells and human umbilical vein endothelial cells (HUVEC) on screening for food-derived antiangiogenic compounds, showed **tocotrienol (T3), an unsaturated version of vitamin E**, to be a potential angiogenic inhibitor.

METHODS: We therefore investigated the in vivo antiangiogenic properties of T3 using 2 well-characterized angiogenic models [mouse dorsal air sac (DAS) assay and the chick embryo chorioallantoic membrane (CAM) assay].

RESULTS: In the DAS assay, the increased neovascularization (angiogenesis index, 4.8 +/- 0.6) in tumor cell-implanted mice was suppressed (angiogenesis index, 2.7 +/- 0.6) by dietary supplementation of 10 mg T3-rich oil/d (equivalent to 4.4 mg T3/d). In the CAM assay, T3 (500-1000 mug/egg) inhibited new blood vessel formation on the growing CAM and increased the frequency of avascular zone (36-50%). To evaluate the antiangiogenic mechanism, we conducted cell-culture studies and found that T3 significantly reduced fibroblast growth factor -induced proliferation, migration, and tube formation in HUVEC ($P < 0.05$), with delta-T3 having the highest activity. Western blot analysis revealed that delta-T3 suppressed the phosphorylation of phosphoinositide-dependent protein kinase (PDK) and Akt, and increased the phosphorylation of apoptosis signal-regulating kinase and p38 in fibroblast growth factor-treated HUVEC, indicating that the antiangiogenic effects of T3 are associated with changes in growth factor-dependent phosphatidylinositol-3 kinase /PDK/Akt signaling as well as induction of apoptosis in endothelial cells.

CONCLUSION: **Our findings suggest that T3 has potential as a therapeutic dietary supplement for preventing angiogenic disorders**, and therefore future clinical study will be required to evaluate the efficacy and safety of T3.

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