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Gamma-Tocopherol

DESCRIPTION

Gamma-tocopherol is one of the four natural tocopherol homologues or isoforms, the others being alpha-, beta- and delta-tocopherol. Tocopherols and tocotrienols comprise the vitamin E family (See Vitamin E). Gamma-tocopherol is the principal tocopherol found in the lipid fraction of many seeds

and nuts, including soybeans, corn and walnuts, and is the major tocopherol in the American diet. Because of the wide use of oils derived from these sources, gamma-tocopherol makes up approximately 65 to 70% of the total dietary intake of tocopherols, the other major dietary tocopherol being alpha-tocopherol.

Although gamma-tocopherol is the principal dietary tocopherol, plasma levels of this tocopherol average five times lower than alpha-tocopherol. Apparently, alpha-tocopherol is the only tocopherol maintained in human plasma. This situation is believed to be accounted for by the presence in the liver of alpha-tocopherol transfer protein (alpha-TTP). Alpha-TTP preferentially secretes alpha-tocopherol from the liver into the blood. This protein binds most strongly to alpha-tocopherol. Because alpha-tocopherol is the only tocopherol maintained in human plasma, the Food and Nutrition Board in their most recent report, and for the purpose of establishing RDAs for vitamin E, included only certain alpha-tocopherol forms in their definition of vitamin E activity.

Gamma-tocopherol is also known as d-gamma-tocopherol, RRR-gamma-tocopherol, 2R, 4'R, 8'R-gamma-tocopherol and 2, 7, 8-trimethyl-2 (4', 8', 12'-trimethyldecyl)-6-chroman-ol. It is abbreviated as gamma-TOH, gamma-T and gamma-TH. Gamma-tocopherol is a slightly viscous, pale yellow oil which is practically insoluble in water. Alpha-tocopherol differs from gamma-tocopherol by the presence of a methyl group in the 5 position of the chromanol ring. Gamma-tocopherol lacks this methyl group. Practically all supplemental RRR-alpha-tocopherol, commonly known as d-alpha-tocopherol, is produced from soybean oil-derived gamma-tocopherol by a chemical methylation. The structure is identical to natural d-alpha-tocopherol, but, since it is a semi-synthetic product, it is called natural-source alpha-tocopherol. In contrast to alpha-tocopherol, synthetic forms of gamma-tocopherol, such as *all rac*-gamma-tocopherol or d1-gamma-tocopherol, are not sold as nutritional supplements. Supplemental gamma-tocopherol is marketed as the free or unesterified form.

ACTIONS AND PHARMACOLOGY

ACTIONS

Gamma-tocopherol has antioxidant activity. It may also have anti-atherogenic, anti-apoptotic, antithrombotic, anticoagulant, anticarcinogenic and immunomodulatory actions.

MECHANISM OF ACTION

Gamma-tocopherol is a lipid soluble, chain-breaking, peroxy radical scavenger. It can protect polyunsaturated fatty acids (PUFAs) within membrane phospholipids, as well as PUFAs within such plasma lipoproteins as low density lipoproteins (LDL), from oxidation. In this regard, gamma-

tocopherol is considered to be a less-efficient scavenger of reactive oxygen species (ROS), such as peroxy radicals, than alpha-tocopherol. This belief is based mainly on *in vitro* studies comparing the various tocopherol homologues.

A recent rat study demonstrated that both alpha- and gamma-tocopherol decreased arterial peroxidation and LDL oxidation and also increased endogenous superoxide dismutase activity. Interestingly, the effects of gamma-tocopherol were found to be more potent than those of alpha-tocopherol. The relative antioxidant activity of the various tocopherol homologues against ROS needs clarification.

It is clear, however, that gamma-tocopherol is a more effective scavenger of reactive nitrogen species (RNS) than is alpha-tocopherol. Gamma-tocopherol is more effective than alpha-tocopherol in inhibiting the oxidation of phospholipids by the RNS peroxynitrite. Peroxynitrite is formed by the reaction of nitric oxide with superoxide and may cause significant cellular damage by reacting with DNA and proteins, as well as with phospholipids. It is postulated by one group of investigators "that gamma-tocopherol acts *in vivo* as a trap for membrane-soluble electrophilic nitrogen oxides and other electrophilic mutagens, forming stable carbon-centered adducts through the nucleophilic 5-position, which is blocked in alpha-tocopherol." The chemical difference between alpha-tocopherol and gamma-tocopherol is the presence in alpha-tocopherol of a methyl group in the 5-position of the chromanol ring.

Gamma-tocopherol may have antiatherogenic activity. One study reported that those with coronary artery disease (CAD) have lower serum levels of gamma-tocopherol but not alpha-tocopherol, when compared with those without CAD. A few mechanisms have been postulated to account for the possible antiatherogenic activity of gamma-tocopherol. These include inhibition of LDL oxidation, inhibition of platelet aggregation and inhibition of apoptosis of coronary artery endothelial cells. Oxidized (ox)-LDL induces apoptosis of human coronary artery endothelial cells in culture, in part by activation of the NF-Kappa B signal transduction pathway. Gamma-tocopherol has been found in cell culture to inhibit ox-LDL-induced apoptosis of human coronary artery endothelial cells by inhibiting the activation of NF-Kappa B. In another study in human coronary smooth muscle cells, ox-LDL was found to mediate apoptosis of these cells, and both gamma- and alpha-tocopherol were found to inhibit this process. Both of these tocopherol homologues — alpha more so than gamma — were found to inhibit two of the pathways leading to apoptosis in these cells, the mitogen-activated protein kinase (MAPK) and Jun kinase pathways. Peroxynitrite is a potent mutagenic oxidant. It is formed during activation of phagocytes (polymorphonuclear leukocytes, monocytes and macrophages). Chronic inflammation in-

duced by these cells is thought to play a major role in the etiology of cancer and other degenerative disease. The possible anticarcinogenic activity of gamma-tocopherol may be accounted for, in part, by its peroxynitrite-scavenging activity.

Gamma-tocopherol, as well as the other tocopherol homologues, enhance both spontaneous and mitogen-stimulated lymphocyte proliferation. The mechanism of the possible immunomodulatory activity of gamma-tocopherol, as well as that of the other homologues, is unclear.

PHARMACOKINETICS

The efficiency of absorption of gamma-tocopherol, as is true for all the members of the vitamin E family, is low and variable. Absorption is lower on an empty stomach than with meals. Gamma-tocopherol is absorbed from the lumen of the small intestine into the enterocytes by passive diffusion. Prior to its absorption, gamma-tocopherol participates in micelle formation with dietary fats and products of lipid hydrolysis. This is aided by bile salts secreted by the liver. Gamma-tocopherol is secreted by the enterocytes into the lymphatics in the form of chylomicrons. Chylomicrons undergo metabolism in the circulation via lipoprotein lipase to form chylomicron remnants. During this process, some gamma-tocopherol is transferred to various tissues such as adipose tissue, muscle and possibly the brain. Chylomicron remnants can transfer it to LDL and very low density lipoproteins (VLDL). Chylomicron remnants can also acquire apolipoprotein E (apoE), which directs them to the liver for metabolism.

The chylomicron remnants are taken up by the liver. Gamma-tocopherol does not bind very well to hepatic alpha-tocopherol transfer protein (alpha-TTP). This is the protein that is involved in the secretion of alpha-tocopherol in VLDLs. It is for this reason, that even though gamma-tocopherol is the major dietary tocopherol in the American diet, (excluding alpha-tocopherol from nutritional supplements), alpha-tocopherol levels in plasma and most other tissues are about five-fold higher than gamma-tocopherol. Gamma-tocopherol is also more rapidly taken up and turned over in tissues, compared with alpha-tocopherol.

Reaction of gamma-tocopherol and peroxynitrite *in vitro* results in the formation of four major products: 2, 7, 8-trimethyl-2-(4, 8, 12-trimethyldecyl)-5-nitro-6-chromanol (NGT or tocoyellow), 2, 7, 8-trimethyl-2-(4, 8, 12-trimethyldecyl)-5,6-chromaquinone (tocored) and two diastereomers of 8a-(hydroxy)-gamma-tocopherol.

About half of ingested and absorbed gamma-tocopherol is excreted in the urine, mainly as a glucuronide conjugate of 2, 7, 8-trimethyl-2-(2'-carboxyethyl)-6-hydroxychroman or gamma-CEHC. Fecal excretion is the main route of

excretion of oral gamma-tocopherol. Fecal excretion substances includes non-absorbed gamma-tocopherol and gamma-tocopherol that may be excreted via the biliary route.

The gamma-tocopherol metabolite gamma-CEHC, also known as LLU (Loma Linda University)-alpha, is reported to have natriuretic activity. This is thought to be mediated by inhibition of a potassium channel in the apical membrane of the thick ascending limb of the kidney.

INDICATIONS AND USAGE

There is some evidence that both alpha- and gamma-tocopherol may have complementary antioxidant activities. There might thus be indications and uses of gamma-tocopherol that are distinct from those of alpha-tocopherol, or circumstances in which one works better than the other. In general, however, gamma-tocopherol is likely to have some or most of the same indications and uses as alpha-tocopherol (See Vitamin E), although it has not been as extensively studied as alpha-tocopherol. There is preliminary evidence that gamma-tocopherol may be more protective against cardiovascular disease than alpha-tocopherol. There is also some preliminary evidence that it could be more effective in preventing some cancers. On the other hand, there is one recent report that elevated blood levels of gamma-tocopherol may be associated with an increased incidence of knee osteoarthritis, especially in those who are black.

RESEARCH SUMMARY

Some studies have indicated that gamma-tocopherol is more potent than alpha-tocopherol in protecting against nitric-oxide initiated lipid peroxidation. This has been demonstrated in vitro and in animal experiments. Human data are more equivocal. Some studies have suggested that both tocopherols are required for optimal protection against reactive nitrogen species. Several researchers have thus suggested that gamma-tocopherol should be part of "standard" vitamin E supplements.

Recently, an *in vitro* study showed that gamma-tocopherol significantly reduced oxidized-LDL-induced apoptosis of human coronary artery endothelial cells. In a recent animal study, gamma-tocopherol, significantly more than alpha-tocopherol, was found to decrease platelet aggregation and to delay intra-arterial thrombus formation. Research continues.

There are some experimental data suggesting that gamma-tocopherol may, more effectively than alpha-tocopherol, prevent neoplastic transformation. Recently, gamma-tocopherol was shown to inhibit (more effectively than alpha-tocopherol) the growth of a human prostate cancer cell line.

There is one study in which an association has been made between high blood levels of gamma-tocopherol and increased incidence of knee osteoarthritis, especially in those

who are black. More research will have to be done before causality can be determined. Research is continuing.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Gamma-tocopherol is contraindicated in those with known hypersensitivity to the substance.

PRECAUTIONS

Those on warfarin should be cautious in using high doses of gamma-tocopherol (doses greater than 100 milligrams daily) and, if they do so, they should have their INRs carefully monitored and their warfarin doses appropriately adjusted if indicated. Likewise, those with vitamin K deficiencies, such as those with liver failure, should be cautious in using high doses of gamma-tocopherol. Gamma-tocopherol should be used with caution in those with lesions with a propensity to bleed (e.g., bleeding peptic ulcers), those with a history of hemorrhagic stroke and those with inherited bleeding disorders (e.g., hemophilia).

High dose gamma-tocopherol supplementation should be stopped about one month before surgical procedures and may be resumed following recovery from the procedure. Those taking iron supplements should not take gamma-tocopherol concomitantly with the iron.

ADVERSE REACTIONS

Gamma-tocopherol has only recently been introduced into the nutritional supplement marketplace. No adverse reactions have been reported.

INTERACTIONS

DRUGS

Antiplatelet drugs, such as aspirin, dipyridamole, eptifibatide, clopidogrel, ticlopidine, tirofiban and abciximab: High doses of gamma-tocopherol may potentiate the effects of these antiplatelet drugs.

Cholestyramine: may decrease gamma-tocopherol absorption.

Colestipol: may decrease gamma-tocopherol absorption.

Isoniazid: may decrease gamma-tocopherol absorption.

Mineral oil: may decrease gamma-tocopherol absorption.

Neomycin: may impair utilization of gamma-tocopherol.

Orlistat: is likely to inhibit gamma-tocopherol absorption.

Sucralfate: may interfere with gamma-tocopherol absorption.

Warfarin: High dose (greater than 100 milligrams daily) gamma-tocopherol may enhance the anticoagulant response of warfarin. Monitor INRs and appropriately adjust dose of warfarin if necessary.

NUTRITIONAL SUPPLEMENTS

Alpha-tocopherol: Supplemental alpha-tocopherol may decrease plasma concentration of gamma-tocopherol.

Desiccated ox bile: may increase the absorption of gamma-tocopherol.

Iron: Most iron supplements contain the ferrous form of iron. This form can oxidize gamma-tocopherol, which is marketed in a free, unesterified form, to its pro-oxidant form, if taken concomitantly.

Medium-chain triglycerides: may enhance absorption of gamma-tocopherol if taken concomitantly.

Phytosterols and phytosterols, including beta-sitosterol and beta-sitostanol: may lower plasma gamma-tocopherol levels.

Plant phenolic compounds and flavonoids: may participate in redox cycling reactions and help maintain levels of reduced gamma-tocopherol.

Selenium: may function synergistically with gamma-tocopherol.

Vitamin C: may help maintain gamma-tocopherol in its reduced (antioxidant) form.

FOODS

Olestra: is likely to inhibit the absorption of gamma-tocopherol. Although alpha-tocopherol is added to olestra, gamma-tocopherol is not.

HERBS

Some herbs, including garlic and ginkgo, possess antithrombotic activity. High doses of gamma-tocopherol used concomitantly with these herbs may enhance their antithrombotic activity.

OVERDOSAGE

There are no reports of gamma-tocopherol overdoses in the literature.

DOSAGE AND ADMINISTRATION

Presently marketed forms of gamma-tocopherol contain about 60% gamma-tocopherol along with smaller amounts of the other tocopherol homologues. The gamma-tocopherols, as well as the other tocopherols, are present in the free (unesterified) form. Typical doses are about 200 milligrams daily (as gamma-tocopherol).

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