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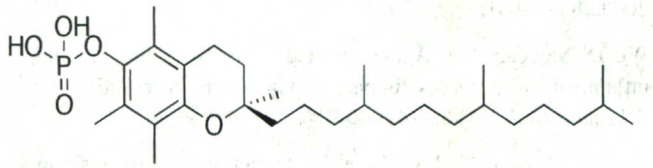
Vitamin E Phosphate

DESCRIPTION

Vitamin E phosphate is the phosphate ester of d-alpha-tocopherol. It was one of the first vitamin E derivatives studied, in the 1940s, but it garnered little attention until recently, when it entered the dietary supplement marketplace as one of the available forms of vitamin E (See Vitamin E).

Vitamin E phosphate is chemically described as [(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-yl] dihydrogen phosphate. It is also known as RRR-alpha-tocopheryl phosphate, alpha-tocopherol phosphate, alpha-tocopheryl phosphate, alpha-tocopherylphosphate, tocopherol phosphate, tocopheryl phosphate, all-rac-tocopherol phosphate and alpha-tocopherol-6-O-phosphate. Its molecular weight is 510.69, its molecular formula is $C_{29}H_{51}O_5P$ and its CAS registry number is 38976-17-9. Vitamin E Phosphate is represented by the following chemical structure.



Tocopherol phosphate

In 1942, it was reported that administration of vitamin E phosphate, but not alpha-tocopherol, to dystrophic rabbits, restored to normal the excessive *in vitro* oxygen consumption and excessive metabolic rate of muscle tissue of the rabbits. This was the first experimental evidence that vitamin E played a role in cellular respiration. It appeared that vitamin E was required to be in the phosphorylated form for this effect to occur. This would make it similar to other vitamins that enter into biological oxidation, and it was speculated that the mechanism of the vitamin E phosphate action might be one that involved its dephosphorylation. That vitamin E phosphate had an effect on vitamin E-deficient muscle slices, *in vitro*, which alpha-tocopherol did not, raised the question whether vitamin E was naturally present in tissues as its phosphate ester. However, when others tried to repeat these studies with vitamin E phosphate, they found that the addition of vitamin E *in vitro* had no significant effect on the respiration of muscle strips or slices, either from normal or dystrophic animals. By the end of the 1940s, vitamin E phosphate went out of favor as a form of vitamin E to explore.

Recently, there have been reports that vitamin E phosphate exists naturally in the tissues of plants and animals, including humans. Small amounts of vitamin E phosphate have been reported in wheat germ, chocolate and cheeses such as cheddar and brie. The reason given for not having detected vitamin E phosphate in plant and animal tissue previously is that vitamin E phosphate is a water-soluble substance that is resistant to both acid and alkaline hydrolysis and that the standard analytical methods for detection and assay of alpha-tocopherol would not have detected vitamin E phosphate. Using techniques such as electrospray mass spectrometry (ESMS), high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LCMS), liquid chromatography tandem mass spectrometry (LCMS/MS and gas chromatography mass spectrometry (GCMS) appeared to be necessary in order to identify vitamin E phosphate as a natural form of vitamin E. These techniques were not available to those researchers of the 1940s who believed that vitamin E phosphate was a natural form of vitamin E.

One of the big mysteries in nutritional biochemistry is what the unique biological role of vitamin E is. To date, that mystery has not been solved. There are some who believe that vitamin E phosphate may help to do so.

ACTIONS AND PHARMACOLOGY

ACTIONS

Vitamin E phosphate has possible antioxidant activity. It may also have possible apoptotic, antiatherogenic, cardioprotective and UVB-protective activities. Vitamin E phosphate may also have activity as a transdermal delivery form for insulin and other biological molecules.

MECHANISM OF ACTION

Antiatherogenic activity: Both vitamin E acetate and vitamin E phosphate, but more so vitamin E phosphate, were reported to have atherosclerotic-preventing effects in rabbits fed with a high-cholesterol diet. Vitamin E phosphate was also found to be more potent than vitamin E acetate in downregulating the expression of CD36. CD36 is an integral membrane protein found on the surface of many cell types. It is a member of the class B scavenger receptor family of cell surface proteins. CD36 is thought to be involved in atherosclerosis, among other disorders.

The mechanism of the possible antiatherogenic effect of vitamin E phosphate is not clear.

Antioxidant activity: Vitamin E is the principal antioxidant of the lipid domains of the body, such as cellular membranes. It is a chain-breaking antioxidant that prevents the propagation of free radical activities. It is a peroxyl radical scavenger and especially protects the polyunsaturated fatty acids (PUFAs) within membrane phospholipids and in plasma lipoproteins against oxidation. This antioxidant activity depends on the free hydroxyl group of the chromanol ring, which reacts with an organic peroxyl radical to form the corresponding organic hydroperoxide and the tocopheroxyl radical. The tocopheroxyl radical is the pro-oxidant form of vitamin E and is thought to be regenerated to the antioxidant form by a network of other antioxidants, including vitamin C and glutathione.

When the phenolic hydroxyl group is in its esterified form—for example, vitamin E acetate or vitamin E succinate—it no longer can inhibit lipid peroxidation until it is converted back to its unesterified form. One therefore would expect that

vitamin E phosphate would also be unable to inhibit lipid peroxidation unless converted to its unesterified form. It has now been reported that, unlike vitamin E acetate and vitamin E succinate, vitamin E phosphate per se inhibits lipid peroxidation. The mechanism of action of this effect is not completely understood, but it is thought that vitamin E phosphate acts as a detergent and forms a barrier that might inhibit the transfer of radicals from one polyunsaturated fatty acid to another. In other words, the detergent barrier acts as a chain terminator of the lipid peroxidation chain reaction. This would be a highly unusual antioxidant mechanism, and more study is needed to determine if this is indeed the antioxidant mechanism of action of vitamin E phosphate.

Incidentally, vitamin E succinate is also known to have detergent-like activity, but in contrast to vitamin E phosphate, vitamin E succinate does not appear to possess an antioxidant effect per se.

Apoptotic activity: Vitamin E phosphate was found to inhibit proliferation and induce apoptosis (programmed cell death) in an MG-63 osteosarcoma cell line and in a THP-1 monocytic leukemia cell line, both in tissue culture. The apoptotic effect was more potent than that obtained with vitamin E succinate and was explained by membrane destabilizing activity due to its action as a detergent. Vitamin E phosphate was found to be more potent than vitamin E succinate in inducing DNA fragmentation and nucleus condensation, two events in the apoptosis process.

The mechanism by which vitamin E phosphate induces apoptosis is not fully understood. It is thought that the apoptotic activity is due, in part, to a detergent-like effect of vitamin E phosphate causing membrane destabilization of the malignant cells.

Cardioprotective activity: In a laboratory study, one group of rats was gavaged with vitamin E phosphate for a period of 30 days while a control group of rats were given water only. After 30 days, the rats were sacrificed and their hearts were excised. Both the treated and control groups were subjected to 30 minutes of global ischemia, followed by two hours of reperfusion.

Myocardial reperfusion injury refers to the damage to myocardial tissue caused when blood returns to the tissue after a period of ischemia.

The vitamin E phosphate-fed rats exhibited significant cardioprotection as evidenced by improved ventricular performance and reduced myocardial infarct size and apoptosis of the cardiomyoctes. Supplementation of vitamin E phosphate appeared to convert the mitogen activated protein (MAP) kinase-induced death signal into a survival signal via enhancing anti-apoptotic p42/44 extracellular signal-regulated (ERK) kinase and p38 MAPKbeta and reducing pro-apoptotic proteins p38 MAPKalpha and c-JUN N-terminal kinases (JNK). In concert, the phosphorylation of pro-apoptotic cellular sarcoma-inducing gene (c-Src) was also reduced. Vitamin E phosphate increased the DNA binding of the redox-sensitive transcription factor, nuclear factor (NF)-kappaB, and potentiated the activation of anti-death protein Bcl-2 and survival signaling protein Akt (protein kinase B). In summation, vitamin E phosphate appeared to ameliorate myocardial ischemia reperfusion injury by converting the ischemia/reperfusion-mediated death signal into a survival signal via modulating MAP kinase signaling.

Thus, signaling may be the most important feature of vitamin E phosphate. Vitamin E phosphate clearly does not qualify as a storage form of vitamin E, since the amounts found in tissue are so small. Signaling molecules are present in small amounts in tissue. Perhaps this is what the investigators of the 1940s (see Description above) were looking at, but the concepts to explain what they were looking at were not yet invented.

Continued study of this area is needed and warranted. Looking for kinases and phosphatases, major components of signaling systems, should be high priority. And, the next time this type of experiment is performed with vitamin E phosphate, vitamin E succinate, vitamin E acetate and alpha-tocopherol should be used as additional controls.

Protection against ultraviolet B-induced damage to skin: Cultured mouse skin that is exposed to ultraviolet B (UVB) rays undergoes photodamage manifested as sunburn cell formation, DNA degradation and lipid peroxidation. Alpha-tocopherol-6-O-phosphate was found to significantly protect against UVB photodamage when the mouse skin was pretreated with a solution of the vitamin. The protection was found to be greater than that seen with alpha-tocopherol acetate, a common form of vitamin E used in commercial skin care products.

UVB damage to skin is mediated mainly via oxidative stress. The effect of alpha-tocopherol-6-O-phosphate is probably via its antioxidant activity. It was found, however, that the difference in UVB protection of vitamin E phosphate when compared with vitamin E acetate may be explained by the greater conversion of vitamin E phosphate to alpha-tocopherol. In that case, vitamin E phosphate serves as a better delivery form of alpha-tocopherol to the skin than vitamin E succinate, and the protective effect has to do with the antioxidant activity of alpha-tocopherol, not vitamin E phosphate per se.

Transdermal delivery form for insulin: It has been reported that vitamin E phosphate can penetrate the skin nine times more than alpha-tocopherol. Vitamin E phosphate is present-

ly being studied in a transdermal delivery form system for insulin. In this regard, vitamin E phosphate can be considered to be a penetration enhancer. Again, this may be due, at least in part, to its detergent-like activity.

PHARMACOKINETICS

There is very little known on the pharmacokinetics of vitamin E phosphate.

Esterified forms of vitamin E—vitamin E acetate and vitamin E succinate—undergo hydrolysis via esterases secreted by the pancreas. The alpha-tocopherol produced via esterase action is emulsified together with dietary lipids. Bile acids and salts secreted by the liver aid in the emulsification process. Lipolysis and emulsification of the formed lipid droplets lead to the spontaneous formation of mixed micelles. The micelles containing vitamin E are absorbed at the brush border of the intestinal mucosa in the enterocytes. Vitamin E is secreted by the enterocytes into the lymphatics in the form of chylomicrons. (See Vitamin E for a more complete discussion of the pharmacokinetics of vitamin E).

There are animal studies suggesting that vitamin E phosphate, or at least a fraction of it that enters the small intestine, is not hydrolyzed by esterases or phosphatases, but is absorbed intact and reaches the circulatory system, which carries it to various organs. A recent *in vitro* study found that vitamin E phosphate is transported across cell membranes via an organic anion transporter (OAT) mechanism.

Much more study is needed on the absorption, distribution, metabolism and excretion of vitamin E phosphate.

INDICATIONS AND USAGE

Though efforts have been made recently to market vitamin E phosphate as the most important biological form of vitamin E and/or as something "new," there is little support for these marketing claims. Research on vitamin E phosphate dates back to at least the 1940s. There is some very preliminary nonclinical evidence that vitamin E phosphate may have some anticancer and cardioprotective effects, related in part to reported antioxidant, apoptotic and signaling activities. Some very dated research has suggested a possible favorable effect on muscle metabolism. In nonsupplement form, vitamin E might be a useful sun blocker and, possibly, a vehicle for transdermal insulin delivery, according to more preliminary research.

RESEARCH SUMMARY

In a study of rat liver microsomes, vitamin E phosphate was said to be a more effective inhibitor of lipid peroxidation than some other vitamin E-related compounds. It was also said to be superior to those other compounds in its ability to conserve its oxidative potential. And reportedly acting as a detergent capable of forming a barrier that might be able to inhibit the transfer of radicals from one fatty acid to another, vitamin E phosphate was said by this group of researchers to possibly constitute a new antioxidant class. The validity and significance of these findings needs further clarification and research.

There is some *in vitro* evidence that vitamin E phosphate may have some ability to favorably modulate signaling cascades and gene expression in macrophages and smooth muscle cells, inhibiting some important atherogenic events in the process. In a study of rabbits fed a high cholesterol diet, vitamin E phosphate was more effective than vitamin E acetate in inhibiting atherosclerotic progression, as measured by aortic plaque formation. In a study of rats fed 5mg/kg body weight of vitamin E phosphate daily for 30 days, significant cardioprotection was demonstrated (compared with controls that received no supplement). After sacrifice, hearts were removed and subjected to an ischemia/reperfusion challenge. Protection was demonstrated in terms of improved ventricular performance, reduced myocardial infarct size and cardiomyocyte apoptosis. Further research is warranted.

One study demonstrated that vitamin E phosphate has apoptotic effects in an osteosarcoma cell line. This effect was attributed to the substance's detergent-like activity. Again, more research is indicated.

Two papers from the same laboratory in the 1940s reported some favorable vitamin E phosphate *in vitro* effects on muscle metabolism. Reported results are so preliminary and equivocal that no useful conclusion can be drawn concerning a role for this substance in muscle health. Similarly, far more research will be needed to confirm suggestions that vitamin E phosphate might be an effective sun blocker and that it might be a useful vehicle for transdermal delivery of insulin.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Vitamin E phosphate is contraindicated in those with known hypersensitivity to any component of a vitamin E phosphate-containing product.

PRECAUTIONS

Vitamin E phosphate possesses anticoagulant and antithrombotic activities. Those taking warfarin should avoid vitamin E phosphate. Likewise, individuals with vitamin K deficiencies, such as those with liver failure, should avoid vitamin E phosphate. Vitamin E phosphate should be avoided by those with lesions that have a propensity to bleed (eg, bleeding peptic ulcers), a history of hemorrhagic stroke or inherited bleeding disorders (eg, hemophilia). Vitamin E phosphate should be avoided by pregnant women and nursing mothers.

Vitamin E phosphate supplementation should be stopped about two to four weeks before surgical procedures, including dental procedures, and may be resumed following recovery from the procedure.

ADVERSE REACTIONS

None known.

INTERACTIONS

DRUGS

Antiplatelet drugs (eg, aspirin, dipyridamole, clopidogrel, ticlopidine, tirofiban, abciximab and eptifibatide): Vitamin E phosphate may potentiate the effects of these antiplatelet drugs.

Anticoagulants (eg, warfarin and heparin): Vitamin E phosphate may potentiate the effects of these anticoagulant drugs.

NUTRITIONAL SUPPLEMENTS

Fish oils possess antiplatelet activity. Vitamin E phosphate may potentiate the antiplatelet activity of fish oils.

HERBS

Some herbal products, including garlic, ginkgo, ginseng and curcuminoids, possess antithrombotic activity. Vitamin E phosphate used at the same time as these herbs may enhance their antithrombotic activity.

OVERDOSAGE

There are no reports of overdosage with vitamin E phosphate.

DOSAGE AND ADMINISTRATION

Vitamin E phosphate is available in 400 IU capsules. Doses higher than 400 IU daily are not recommended.

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Vitamin K

DESCRIPTION

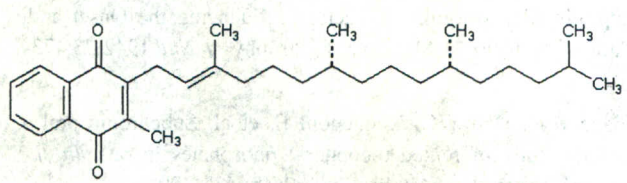
Vitamin K is a generic term for a group of substances which contain the 2-methyl-1, 4-naphthoquinone ring structure and which possess hemostatic activity. Substances with vitamin K activity were originally identified in green leafy vegetables, hemp seeds, liver and fish meal. These substances were found to have antihemorrhagic activity and their collective name was derived from koagulation, the German word for clotting. In addition to its essential role in hemostasis, vitamin K is involved in bone metabolism, among other processes.

Vitamin K_1 or phylloquinone is the principal dietary source of vitamin K and its predominant circulating form. Green leafy vegetables are rich in vitamin K_1 and contribute 40%-50% of total dietary intake of the vitamin. The next largest contributors to dietary vitamin K intake are the vegetable oils olive oil, canola oil, soybean oil and cottonseed oil. These vegetable oils also contain vitamin K_1. Vitamin K_1 is a fat-soluble substance. Vitamin K_2, which is also fat soluble, is the collective term for a number of substances known as menaquinones. Vitamin K_2 is found in chicken egg yolk, butter, cow liver, certain cheeses and fermented soybean products such as natto. This form of vitamin K is also produced by certain bacteria, including some of the bacteria that comprise the microflora of the intestine. The dietary contribution of vitamin K_2 is much less than that of vitamin K_1. The amount of vitamin K contributed to the body by the intestinal microflora remains unclear. Vitamin K_3 or menadione is a fat-soluble synthetic compound which is used in animal feed and dog and cat food. It is metabolized to vitamin K_2.

Vitamin K is involved as a cofactor in the posttranslational gamma-carboxylation of glutamic acid residues of certain proteins in the body. These proteins include the vitamin K-dependent coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor), X (Stuart factor), protein C, protein S, protein Zv and a growth-arrest-specific factor (Gas6). In contrast to the other vitamin K-dependent proteins in the blood coagulation cascade, protein C and protein X serve anticoagulant roles. The two vitamin K-dependent proteins found in bone are osteocalcin, also known as bone G1a (gamma-carboxyglutamate) protein or BGP, and the matrix G1a protein or MGP. Gamma-carboxylation is catalyzed by the vitamin K-dependent gamma-carboxylases. The reduced form of vitamin K, vitamin K hydroquinone, is the actual cofactor for the gamma-carboxylases. Proteins containing gamma-carboxyglutamate are called G1a proteins.

Vitamin K deficiency can occur under certain conditions. These include, inadequate dietary intake, malabsorption syndromes (cystic fibrosis, Crohn's disease, ulcerative colitis, Whipple's disease, celiac sprue, short bowel syndrome) and loss of storage sites due to hepatocellular disease. Vitamin K deficiency frequently occurs in those with chronic liver disease, such as primary biliary cirrhosis. Coumarin anticoagulants, such as warfarin, induce a state analogous to vitamin K deficiency by inhibiting the reduction and recycling of vitamin K, and certain cephalosporin antibiotics (see Interactions) may also induce a vitamin K deficiency state by inhibiting the reduction and recycling of the vitamin. Recently, it has been found that space flight may impair vitamin K metabolism and also induce a state of vitamin K deficiency. Symptoms of vitamin K deficiency include easy bruisability, epistaxis, gastrointestinal bleeding, menorrhagia and hematuria. Chronic vitamin K deficiency may also result in osteoporosis and increased risk of fractures. There is some evidence that chronic warfarin use may also cause osteoporosis.

Vitamin K_1, in addition to being known as phylloquinone, is also known as phytonadione and 2-methyl-3-phytyl-1, 4-naphthoquinone. The lipophilic side chain is located at position 3 of the naphthoquinone ring. Its molecular formula is $C_{31}H_{46}O_2$ and its molecular weight is 450.71 daltons. The structural formula is:



Vitamin K_1

Vitamin K_2 is the collective term for a group of vitamin K compounds called menaquinones. The menaquinone homolgues are characterized by the number of isoprene residues comprising the side chain. The side chain is located at position 3 of the naphthoquinone ring. The group chemical name of the menaquinones is 2-methyl-3-all-*trans*-polyprenyl-1, 4-naphthoquinones. Menaquinones with side chains of up to 15 isoprene units have been described. Menaquinones