

Vitamin E and the Role of Water-soluble α - Tocopheryl Phosphate

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The discovery of tocopherol or vitamin E over 90 years ago by Evans and Bishop [1] initially focused on its reproductive role in rats. Since then its real biological import has remained somewhat elusive. Subsequent work by Olcott and Emerson [2] identified it as a powerful antioxidant which has generally been associated with its ability to reduce oxidative stress (Reactive Oxygen Species, ROS) and possibly the development of cardiovascular diseases, cancers and neurological diseases. Traditional thinking was that vitamin E quenched free radicals formed in the lipid phase in membranes or lipoproteins [3,4]. Current efforts are targeted towards its possible role in gene regulation and cellular signalling [5]. Of the 8 major analogues of vitamin E, α -tocopherol (α -T) has been a particular focus because of its strong antioxidant properties. In addition, only α -T is enriched in the plasma of humans and higher animals 10-100-fold to an average of 23.2 μ M [6]. Vitamin E isomers, including α -T, are all fat-soluble vitamins. The recent discovery of α -tocopherol phosphate (α -TP), a naturally occurring water-soluble form of vitamin E by Ogru et al. [7] and Gianello et al. [8], has raised new questions regarding whether α -TP is the mode of transport for α -T or exerts regulatory function at the cellular level? Curiously, α -TP was first synthesized and studied in the 1940's [9] but is only now being re-examined after it was found to be naturally present in low amounts in the plasma and tissues of animals and humans.

The enzymes, α -T kinase and α -TP phosphatase or esterase, capable of phosphorylating α -T to α -TP as well as the reverse reaction have been detected in cells, cultures and tissues [8,10]. While α -T has strong antioxidant activity, the chromanol OH group in α -TP is phosphorylated so that it has no antioxidant activity *per se*. Possible indirect antioxidant effects, however, have been proposed for α -TP. Rezk and co-workers [10] reported that α -TP acts as a detergent forming a barrier which might inhibit the transfer of free radicals from one polyunsaturated fatty acid. Current evidence suggests α -TP may act as pro-vitamin E but may also exhibit some novel regulatory activities in the cell such as an active lipid mediator by modulating signal transduction and gene expression. The latter was confirmed by Zingg et al. [11] using a human THP-1 acute monocytic leukemia cell line. α -TP more efficiently modulated atherosclerotic and inflammatory events than α -T by reducing THP-1 cell proliferation and expression of the CD36 scavenger receptor. The anti-cancer activity recently reported for α -TP could be due to its inhibition of cell proliferation [11]. Gene expression microarrays showed α -TP regulated more genes than α -T [12]. The ability of α -TP to form insoluble salts with Ca^{2+} [13] could partially explain its ability to modulate enzyme activities.

Current research suggests that both α -TP and α -T act as lipid mediators modulating signal transduction and gene expression. Antagonistic signalling effects between α -TP and α -T on Akt (ser473) phosphorylation and induction of ROS was suggested by Zing et al. [11] to be important in maintaining cellular homeostasis as observed for other compounds [14]. The rediscovery of α -TP has opened up new research that will help to expand our understanding of the biological importance of vitamin E and the distinct physiological roles for α -T and α -TP. Zingg and co-workers [15] reported that the stimulatory effect of α -T on angiogenesis and vasculogenesis was potentiated when phosphorylated to α -TP which could have potentially important pathophysiological implications.

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