Cell Signaling by Vitamin E

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Molecular aspects of α-tocotrienol antioxidant action and cell signaling,
Other chemical antioxidants with different biological function

- Vitamin A
- Estrogens
- Melatonin

The discovery


"Factor X" was vitamin E missing from the diet, and present in lettuce

The antioxidant function

The problem

The following thesis has been very frequently embraced

1. α-tocopherol has chemical radical scavenging properties, shown by test-tube chemistry
2. All events mediated by α-tocopherol are due to this property
α-tocopherol selection, through α-TTP structural conservation, has been maintained over time: this requires the existence of an evolutionary pressure for the uptake of a unique molecule, α-tocopherol, rather than of a generic antioxidant.
Yoshimi Takai, Akira Kishimoto, Ushio Kikkawa, Terutoshi Mori and Yasutomi Nishizuka

Biochemical and Biophysical Research Communications, 95, 1979, 1218-1224

Unsaturated diacylglycerol as a possible messenger for the activation of calcium-activated, phospholipid-dependent protein kinase system.

PKC inhibition by different tocopherols in smooth muscle cells


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Cell proliferation, % Protein kinase C activity % of control
Control dEαEtocopherol dEβEtocopherol dEαEtocopherol + dEβEtocopherol

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Inhibition of NADPH-oxidase assembly by α-tocopherol

Diabetes, 1994, 43: 1072-3
Caste, O., Seno, J. E., Pedruzzi, E., Descomps, B., Gougerot-Pocidalo, M. A., Leger, C. L.
Alpha-tocopherol inhibits the respiratory burst in human monocytes. Attenuation of p47(phox)

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Vitamin E Reduces the Uptake of Oxidized LDL by OverExpressing CD36 Scavenger Receptor Expression in Cultured Aortic Smooth Muscle Cells

Circulation, 2000, 102: 92-7
Animal studies (Barella, et al.; Gohil, et al.)

No genes expressing antioxidant enzymes appear to be upregulated in the absence of alpha-tocopherol as expected by an obvious compensatory mechanism.

A new family of tocopherol-associated proteins


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Specificity of α-tocopherol binding to TAP


GTPase activity of hTAPs

CTAEKSTVKOMK is a common peptide of G proteins

GTPase activity of hTAPs

Antagonistic effects of oxidized low density lipoprotein and α-tocopherol on CD36 scavenger receptor expression in monocytes: involvement of protein kinase B and peroxisome proliferator-activated receptor-γ.

Adelina Munteanu, Michele Taddei, Ilaria Tamburini, Ettore Bergamini, Angelo Azzi and Jean-Marc Zingg, JBC, 2006, 281(10): 6489-67
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The PKC-PI3 kinase regulation systems

A) Lipid peroxidation

B) Signalling by α-tocopherol

C) α-tocopherol protection by L-ascorbate

Production and uptake of oxLDL by macrophages → Foam cells → Atherosclerotic plaques → Smooth muscle cell


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Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the alpha-tocopherol, beta-carotene cancer prevention study.


Documented effects of α-tocopherol

- AVED prevention and some regression of ataxia symptoms
- Protection against Alzheimer’s and Parkinson’s diseases with high intake of dietary antioxidants, including vitamin E (Jimenez-Jimenez et al., 1997; Sano et al., 1997)
- Supplemental intake of vitamin E has been shown to improve cell-mediated immunity and reduce the incidence of upper respiratory tract infection in elderly subjects (Bleyler et al., 2006)
In animal studies α-tocopherol is generally active

- Almost all the mice trials showed a significant effect of vitamin E
- One-third of the rabbit trials responded positively
- The high doses of vitamin E required to affect experimental atherosclerosis may, if applicable to other species, help explain the absence of effects in many human trials


No cytotoxicity of tocopheryl phosphate

Production and uptake of oxLDL by macrophages → Foam cells
→ Atherosclerotic plaques → Smooth muscle cell

Inhibition of superoxide production by tocopherol and tocopheryl phosphate in THP cells
Inhibition of CD36 expression by α-tocopheryl phosphate occurs at concentrations lower than by α-tocopherol.

TP inhibits - tocopherol does not – THP-1 cell proliferation.

TP is only minimally converted to tocopherol.
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Tocopherol is transported into cells

<table>
<thead>
<tr>
<th>THP-1 Cells treated with α-tocopherol</th>
<th>pmol α-tocopherol/µg protein (mean ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.03 ± 0.00</td>
</tr>
<tr>
<td>10 µM α-toc</td>
<td>2.31 ± 0.38</td>
</tr>
<tr>
<td>25 µM α-toc</td>
<td>5.16 ± 2.36</td>
</tr>
<tr>
<td>50 µM α-toc</td>
<td>11.03 ± 3.18</td>
</tr>
</tbody>
</table>

Incubation of THP-1 cells with glybenclamide and tocopheryl phosphate and measurement of their tocopheryl phosphate content

Glybenclamide abolishes ABCA1-mediated cholesterol efflux, phospholipid efflux, apoA-I binding
Inhibition of cell proliferation by tocopheryl phosphate and its prevention by glybenclamide

Mean absorbance (490 nm)

- 0 hour control
- 24 hour control
- 10 microM glybenclamide
- 25 microM TP + 10 microM GC
- 50 microM TP + 10 microM GC
- 100 microM TP + 10 microM GC
- 200 microM TP + 10 microM GC


Production and uptake of oxLDL by macrophages → Foam cells → Atherosclerotic plaques → Smooth muscle cell

Tocopheryl phosphate given with the diet is not converted to tocopherol

- Plasma concentrations of tocopherol and tocopheryl phosphate
- **Group** | α-tocopherol (µg/mL) | TP (µg/mL)
- TA (1 g/kg) | 32 ± 11.79** | 4.80 ± 6.38*
- TP (1.33 g/kg) | 11.95 ± 7.14 | 15.02 ± 1.29

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Tocopheryl phosphate is more effective than the acetate ester in vivo

A → Control diet (no cholesterol, no treatments)
B → 2% cholesterol diet alone
C → 2% cholesterol + TP 0.33 g/kg in the diet (62% diminution of plaque formation)
D → 2% cholesterol + TA 1 g/kg in the diet (17% diminution of plaque formation)

Disease protection