The Virtual Free Radical School

Regulation of Vitamin E, a Nutritional Antioxidant

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RRR-α-Tocopherol

d-α-Tocopherol
Synthetic vitamin $E$: all rac-$\alpha$-tocopherol
Naturally Occurring Tocopherols

\( \alpha \)-tocopherol

\( \beta \)-tocopherol

\( \gamma \)-tocopherol

\( \delta \)-tocopherol

Vitamin E

Oxygen Society Education Program

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Naturally Occurring Tocotrienols

α-tocotrienol

β-tocotrienol

γ-tocotrienol

δ-tocotrienol

Vitamin E

Oxygen Society Education Program

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Vitamin E Functions

- Specific role in a required metabolic function has not been found
- Major function appears to be as a fat-soluble, “chain-breaking” antioxidant
  - Peroxyl radical scavenger
  - Protects polyunsaturated fatty acids (PUFAs) within membranes and lipoproteins
Lipid Peroxidation

Initiating Event

Carbon-centered Free Radical

Oxygen Society Education Program

Vitamin E
Chain Breaking
Antioxidant

Initiating Event

Carbon-centered Free Radical

Initiation

Propagation

Termination via Antioxidant

Vitamin E

Oxygen Society Education Program


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Potential Cellular/Molecular Mechanisms of Vitamin E

- **Endothelial cells**
  - Adhesion, NO production, superoxide production

- **Smooth muscle cells**
  - Proliferation

- **Macrophages**
  - Adhesion, invasion, signaling recruitment, ROS production

- **Platelets**
  - Adhesion, aggregation, clotting
Vitamin E Biologic Activity in Humans

- **Absorption & Chylomicron Catabolism**
  - All forms absorbed and transported to liver

- **Lipoprotein Transport**
  - All lipoproteins transport vitamin E

- **Liver Trafficking**
  - $\alpha$-Tocopherol specifically secreted into plasma

- **Metabolism**
  - Vitamin E metabolites are NOT oxidation products

Vitamin E Delivery to Tissues & Lipoproteins During Chylomicron Catabolism

CIRCULATING LIPOPROTEINS

Intestine

Vit. E

LPL

Fatty acids & vitamin E to tissues

CHYLOMICRON REMNANTS

Liver Uptake

Vitamin E Uptake

Tissue Vitamin E

Preferential Secretion of $\alpha$-Tocopherol in VLDL and Its Delivery to Tissues

Vitamin E

CHYLOMICRON REMNANTS

LIVER

VITAMIN E

Preferred Secretion

VLDL

Tissue Uptake

Regulation of Liver Vitamin E

- Liver is involved in the regulation of vitamin E levels.
- Chylomicron remnants and lipoproteins are key factors in this process.
- Vitamin E (\(\alpha\)-tocopherol) transfer protein plays a role in the transfer of vitamin E to bile and plasma.

Vitamin E Deficiency in Humans

- Malabsorption Syndromes
  - Abetalipoproteinemia
  - Cholestatic Liver Disease
  - Cystic Fibrosis
  - Short Bowel Syndrome
  - Total Parenteral Nutrition

- Genetic Abnormalities in \( \alpha \)-Tocopherol Transfer Protein
  - Familial Isolated Vitamin E Deficiency (FIVE)
  - Friedreich's Ataxia Variants (AVED)

Clinical Features and Associated Neuromuscular Lesions in Human Vitamin E Deficiency

- Loss of Position and Vibratory Sensation
  - Peripheral Nerve
  - Posterior Columns

- Ataxia
  - Cerebellum
  - Spinocerebellar tracts

- Weakness
  - Skeletal Muscle

Plasma deuterated $\alpha$-tocopherol concentrations in controls and subject with ataxia with vitamin E deficiency (AVED)

Vitamin E Definition

- Recommended intakes limited to the 2R–stereoisomer forms of α–tocopherol
  - RRR-α-tocopherol
  - Half of the stereoisomers in all rac-α-tocopherol
  - No other forms such as γ–tocopherol or tocotrienols meet vitamin E requirement

- All forms of supplemental α–tocopherol used to establish the UL (upper limit)

## Estimated Average Requirement (EAR) and Recommended Daily Allowance (RDAs) for α-Tocopherol (mg/day)

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>EAR</th>
<th>RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>19+ yrs, M</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>19+ yrs, F</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Pregnancy</td>
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<td>15</td>
</tr>
<tr>
<td>Lactation</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
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Plasma $\alpha$-Tocopherol in Response to Vitamin E Supplements

$\alpha$-tocopherol ($\alpha$ -T) and $\alpha$-tocopheryl acetate ($\alpha$ -TAC) from supplements:
1 IU $RRR$-$\alpha$-TAC divided by 1.36 equals mg $RRR$-$\alpha$ -TAC
1 IU $all$ $rac$ $\alpha$ -TAc divided by 2 equals mg $2R$-$\alpha$-TAC

400 IU Vitamin E = 294 mg $RRR$-$\alpha$-TAc
or 268 mg $RRR$-$\alpha$ -T

200 mg $2R$-$\alpha$-TAc
Or 182 mg $2R$-$\alpha$ -T

Vitamin E Metabolites

$\alpha$-tocopherol metabolite, $\alpha$CEHC

2,5,7,8-tetramethyl-2(2’-carboxy-ethyl)-6-hydroxychroman

$\gamma$-tocopherol metabolite, LLU$\alpha$

2,7,8-trimethyl-2(2’-carboxy-ethyl)-6-hydroxychroman


Summary

- Vitamin E requirement in humans limited to \(\alpha\)-tocopherol
- Liver controls plasma vitamin E concentrations
  \(\alpha\)-TTP facilitates \(\alpha\)-tocopherol secretion into plasma
- Vitamin E deficiency results from genetic defects in \(\alpha\)-TTP
- Vitamin E metabolism may be important in regulating liver vitamin E