دانشگاه علوم پزشکی تهران

ویتامین

(K, B8, B9, B12)

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Overview of vitamin classification

Vitamins
- Water-soluble
  - Non-B-Complex
    - Ascorbic acid (vitamin C)
  - B-Complex
- Fat-soluble
  - Energy-releasing
    - Thiamine (vitamin B₁)
    - Riboflavin (vitamin B₂)
    - Niacin (vitamin B₃)
    - Biotin
    - Pantothenic acid
  - Hematopoietic
    - Folic acid
    - Vitamin B₁₂
  - Other
    - Pyridoxine (vitamin B₆)
    - Pyridoxal
    - Pyridoxamine
1. Coenzyme for reactions of carboxylation
   - Biotin
     • Addition of a CO2 group (COO) to a compound
     • Carbon fixation, Carboxylation, CO2 fixation
   - Vitamin K
     • Post-translational carboxylation, γ-carboxylation

2. Hematopoiesis
   • The formation of blood or blood cells in the living body
     • Folic acid
     • Vitamin B_{12}
8. BIOTIN

نامهای دیگر:

- ویتامین H
- ویتامین B₈
- فاکتور تحريك کننده رشد در باکتری ریزوبیوم

گرفته شده از کلمات آلمانی Harr und Haut (به معنی مو و پوست)
ساختمان شیمیایی

• ساختمان دو حلقه ای (bicyclic)
  1. Ureido یک حلقه حاوی گروه tetrahydroimidizalone ring
  2. حلقة دیگر حاوی یک اتم سولفور tetrahydrothiophene
  3. گروه یا زنجیر جانبی اسید والریک

ureido group

thiophene
هولوکروبوکسیلазها

آپوکروبوکسیلاز

بیوتین

هولوکروبوکسیلاز

بخش آمینواسیدی آنزیم
= آپوکروبوکسیلاز
= آپوآنزیم

بخش غیرپرتوتئینی آنزیم
= آپوکروبوکسیلاز
= آپوآنزیم

هولوپرتوتئین یا 
هولوآنزیم
گوناگونی برای آنزیم‌های هولوکربوسیلاز - نحوه اتصال به آنزیم

به‌طور خلاصه، به‌طوری‌که تشکیل این پیوند کووالانس کاتالیز می‌کند. هولوکربوسیلاز سنتتاز است
کوآنزیم بیوتین در متابولیسم چربی‌ها، متابولیسم لوسین، و در ساخته شدن گلوكز از مواد غیر قندی در کبد (گلدوکونئوزنز) عمل می‌کند.

در انسانها، چهار کربوکسیلیاز مهم عبارتند از:

1. استیل کوآ کربوکسیلیاز

2. تبادل استیل کوآ به مالونیل کوآ (آگاز مسیر سنتز چربی)

3. پروپیونیل کوآ کربوکسیلیاز

4. تبادل پروپیونیل کوآ به ماتیل مالونیل کوآ (تبادل متابولیتهای سه کربن‌های به متابولیتهای چهار کربن‌های کره‌کبندی)

5. ماتیل کروتونیل کوآ کربوکسیلیاز
Biotin (functions)

Acetyl CoA to malonylCoA
(acetyl CoA carboxylase)

Propionyl CoA to methylmalonyl CoA
(propionyl CoA carboxylase)
Deficiency symptoms

- Rare because of widespread distribution in plant and animal food and significant lower gut synthesis.
  - **Sources**
    - Yeast, rice, soybeans, peanuts, fish, mushrooms and bananas, liver and milk are rich sources.
  - Can be induced by eating raw egg white
    - In the egg, the yolk is very rich in biotin. One of the highest concentration in nature.
    - Eat the egg whole together with the egg white and you will be fine.
    - Egg whites contain a glycoprotein called "avidin"
    - **Avidin** binds biotin very effectively.
    - The cooking process deactivates the avidin in the egg by **denaturation**

Aajonus Vonderplanitz, in his book “We Want to live” is a strong proponent of raw eggs.
Deficiency symptoms of Vitamin H

- Hair loss (alopecia)
- Seborrheic dermatitis (cradle cap)
- Anemia
- Depression
- Hallucinations
- Fatigue
- Nausea
- Anorexia
- Dry, scaly skin
- High blood sugar
- Inflammation or pallor of the skin and mucous membranes
- Insomnia
- Loss of appetite
- Muscular pain
- Soreness of the tongue
- Biotin deficiency is chief cause of fatty liver and kidney syndrome.

This baby developed severe biotin deficiency during intravenous feeding without biotin.
Biotin Cycle

Biotinidase deficiency is a treatable, inherited metabolic disorder in which the body cannot process the vitamin biotin in a normal manner.

Biotin and apocarboxylases are the substrates. ATP and magnesium also participate in the reaction.
How Biotin Works

1- Biotin carrier protein
2- Biotin carboxylase
3- Transcarboxylase
Vitamin K

- The "K" in vitamin K comes from the German word "koagulation," which refers to blood clotting (coagulation).

- Vitamin K is essential for the functioning of several proteins involved in normal blood clotting.

- There are several forms K1-K7
Vitamin K (important types)

Vitamin K₁ (Phylloquinone)

Vitamin K₂ (Menaquinone)

MK-4
MK-7
MK-8

Vitamin K₃
Menadione
Functions

• Post-translational $\gamma$-carboxylation of some glutamate residues in some proteins.
  – Metal ion chelation
  – This carboxylation occurs in the liver

1. Vitamin K is needed for the body to make four of the blood's coagulation factors, including
   • Prothrombin (factor II)
   • Proconvertin (factor VII)
   • Christmas factor (factor IX)
   • Stuart-Power factor (factor X)

2. Calcium binding proteins
   – Carboxylation of specific glutamate residues in calcium binding proteins.
Prothrombin γ-Carboxylation

Vitamin K-dependent carboxylase
Vitamin K role in $\gamma$-Carboxylation
Causes of Deficiency

1. Prolonged use of antibiotics

2. Malabsorption and biliary tract obstruction

3. Spoilt sweet-clover hay
   - Contains dicumarol (vit K antagonist)

4. Short circuiting of the bowel

5. In immediate post-natal infants
   - (bruising/bleeding in infants)
   - Hemorrhagic disease of the newborn
   - Sterile bowels (no intestinal microflora)
   - Low Vit K in mothers milk
Vitamin K

- Bacterial synthesis (GI)
- Liver
- Leafy green vegetables, cabbage-type vegetables
- Milk
9. Folic acid = folate

- Other names: Folacin (leaf), vitamin B<sub>C</sub>, vitamin B9
- Folic acid is obtained primarily from yeasts and leafy vegetables as well as animal liver.
- Animals cannot synthesize PABA nor attach glutamate residues to pteroic acid, thus, requiring folate intake in the diet.

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2-Amino-4-hydroxy-6-methylpteridine

Folate

\( \text{NH}_3^+ \)

\( \text{p-Aminobenzoic acid} \)

\( \text{Glutamic acid} \)

\( \text{CH}_2\text{NH} - \text{CONHCHCH}_2\text{CH}_2\text{COO}^- \)

\( \text{COO}^- \)

\( \text{Pteroylglutamic acid (folic acid)} \)

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“Microorganisms Only can synthesize Folacin”
Sulfanilamides can kill bacteria

- Sulfanlamides and antibiotics block PABA incorporation by competitive inhibition

\[
\text{SO}_2\text{NH}_2
\]

\[
\text{COOH}
\]

Sulphanilamide

\[
\text{p-Aminobenzoic acid}
\]

\[
\text{NH}_2
\]

\[
\text{NH}_2
\]
Folic acid exists in a polyglutamate form. Intestinal mucosal cells remove some of the glutamate residues through the action of the lysosomal enzyme, conjugase.

In foods, folate naturally occurs as polyglutamate. (Folate occurs as monoglutamate in fortified foods and supplements.)

In the intestine, digestion breaks glutamates off... and adds a methyl group. Folate is absorbed and delivered to cells.
Humans and microorganisms:

Folic acid is reduced within cells (principally in the liver where it is stored) to tetrahydrofolate (THF or H4folate) through the action of folate reductase [or dihydrofolate reductase (DHFR)] which is an NADPH-requiring enzyme.

Tetrahydrafolic acid

- THF
- H4folate
Active center (N5 and N10)
Folate is a carrier of one-carbon units

N⁵-Methyl-tetrahydrofolate carries methyl groups
N⁵-N¹⁰-Methylene-tetrahydrofolate carries methylene groups
N⁵-N¹⁰-Methenyl-tetrahydrofolate carries methenyl groups
N⁵-Formyl-tetrahydrofolate carries formyl groups
N¹⁰-Formyl-tetrahydrofolate carries formyl groups
N⁵-Formimino-tetrahydrofolate carries methenyl groups
The different folate coenzymes are specific for particular reactions.

Origin of one-carbon unit
- Tryptophan
  - Formate
  - 10-Formyl H₄-folate
    - donates methyl to Purine-C₂
- Histidine
  - Formiminoglutamate
  - 5-Formimino H₄-folate
    - donates methyl to Purine-C₈

Destination of one-carbon unit
- H₄-folate
  - Serine
  - Glycine
- 5,10-Methenyl H₄-folate
  - donates methyl to Homocysteine
  - donates methyl to Methionine
- 5,10-Methylene H₄-folate
  - donates methyl to Thymidylate
- 5-Methyl H₄-folate
  - donates methyl to Methyl B₁₂

Folic Acid

کمبود ویتامین B₁₂ در این مرحله منجر می‌شود به folate trap
In the cells, folate is trapped in its inactive form.

To activate folate, vitamin B\textsubscript{12} removes and keeps the methyl group, which activates vitamin B\textsubscript{12}.

Both the folate coenzyme and the vitamin B\textsubscript{12} coenzyme are now active and available for DNA synthesis.
Folic Acid

Functions

• Effect of folate deficiency on cellular processes is upon DNA synthesis.
  – Impairment in dTMP synthesis and purine synthesis
  – Cell cycle arrest in S-phase of rapidly proliferating cells, especially hematopoietic cells.
• The result is megaloblastic anemia as for vitamin B12 deficiency.
  – The inability to synthesize DNA during erythrocyte maturation leads to abnormally large erythrocytes termed macrocytic anemia.
  – Red cells are large and immature, have irregular shapes
Participation of H4folate in dTMP synthesis

deoxyuridine monophosphate (dUMP) → deoxythymidine monophosphate (dTMP)

5,10-methylene-THF

Glycine → Serine transhydroxymethylase

Dihydrofolate reductase

NADPH + H⁺

NADP⁺
Deficiency is rare due to the adequate presence of folate in food. Deficiency can occur when there is:
1. Poor dietary habits as those of chronic alcoholics.
2. Impaired absorption or metabolism
   - Certain drugs such as anticonvulsants and oral contraceptives and methotrexate can impair the absorption of folate.
3. An increased demand for the vitamin.
   - Pregnancy
   - Folate will nearly double by the third trimester of pregnancy.
Neural Tube Defect: Spina bifida

• Folic Acid is believed to have a role in decreasing the risk of Neural Tube Defect (NTD) such as Spina bifida, where the spine does not develop normally due to lack of proper development of the vertebrae. In NTD, the covering of the spinal cord remains open and is extended outside the body. Spina bifida occurs when the neural tube fails to close properly during the early stages of pregnancy.

[Image showing Spina Bifida, Anencephaly, and Encephalocele]
Vitamin B12

• Other names:
  • Cobalamin
  • Antipernicious-anemia
  • Castle’s extrinsic factor
  • Animal protein factor
Vitamin B12 structure

- It is built from:
  1. A complex tetrapyrrol ring structure (corrin ring)
  2. A cobalt ion in the center.
  3. A nucleotide and
  4. A R- group

- When R is cyanide (CN), vitamin B12 takes the form of cyanocobalamin
- In hydroxycobalamin, R equals the hydroxyl group (-OH)
- In the coenzyme forms of vitamin B12
  - R equals an adenosyl group in adenosylcobalamin
  - R equals a methyl (-CH3) group in methylcobalamin
Known as the "red" vitamin because it exists as a dark red crystalline compound, Vitamin B12 is unique in that it is the only vitamin to contain cobalt (Co\(^{3+}\)) metal ion, which, gives it the red color.

The vitamin must be hydrolyzed from protein in order to be active.

**Intrinsic factor**, a protein secreted by parietal cells of the stomach, carries it to the ileum where it is absorbed.

It is transported to the liver and other tissues in the blood bound to **transcobalamin II**.

It is stored in the liver attached to **transcobalamin I**.

- It is released into the cell as **Hydroxocobalamin**
  - In the cytosol it is converted to **methylcobalamin**.
  - Or it can enter mitochondria and be converted to **5’-deoxyadenosyl cobalamin**
Vitamin B12

In the cytosol

In mitochondria
Methionine and Folate cycles are interrelated

**Folate cycle**

- Methionine $\rightarrow$ SAM $\rightarrow$ CH$_3$-THF $\rightarrow$ CH$_2$-THF $\rightarrow$ Homocysteine

**Methionine cycle**

- Homocysteine $\rightarrow$ SAM $\rightarrow$ CH$_3$-THF $\rightarrow$ Homocysteine

**Transulfuration pathway**

- Cystathionine $\rightarrow$ Cysteine

**Vitamin B12**

- Methyl acceptor
- Methyl transferases

- CBS (cystathionine synthase)
- B6 (pyridoxine)

- THF (tetrahydrofolate)
- MS (methyl sulfoxide)

- SAH (s-adenosylhomocysteine)
Function of vitamin B₁₂

Vitamin B₁₂ and N5-methyl-THF in the conversion of homocysteine to methionine is important in helping cells to regenerate needed THF.
Deficiency symptoms

• **Pernicious anemia** in humans (inability to absorb B12 because of lack of gastric intrinsic factor).

• **Neurological disorders** due to progressive demyelination of nerve cells.
  – This results from increase in methylmalonyl-CoA.
  – Methylmalonyl-CoA is a competitive inhibitor of malonyl-CoA in fatty acid biosynthesis.
  – Can substitute malonyl-CoA in any fatty acid biosynthesis and create branched-chain fatty acid altering the architecture of normal membrane structure of nerve cells.