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MICRONUTRIENTS

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M1 GI Sequence
Winter, 2009

University of Michigan
Medical School

Goals and Objectives

1. Describe the concept of essential mineral elements and how their content in the body is regulated.
2. Describe the factors influencing intestinal mineral absorption.
3. Describe the cellular mechanism of iron absorption and its regulation.
4. Describe the consequences of iron deficiency and abnormal increased absorption.
5. Have a general understanding of their function and how different classes of vitamins are absorbed by the intestine.
6. Describe the function and absorption of folates.
7. Describe the function and dietary source of vitamins E and K.
8. Describe the function, dietary source and absorption of Vitamin A and B-carotene.

Required Reading: None

ESSENTIAL MINERAL ELEMENTS

1. **Required to maintain normal physiology and health**
2. **Occur in diet, sometimes as trace elements**
3. **Variable absorption may be regulated**
4. **In steady state intestinal absorption equals body losses**

Specific Elements		**Dietary Intake**
Ca, P, Mg	**---**	**100's of mgs per day**
Fe, Cu, Zn, Mn, Se, I		**micrograms to mgs/day (essential trace elements)**

MINERAL ABSORPTION BY SMALL INTESTINE IS AFFECTED BY:

1. **Intraluminal pH**
2. **Redox state of metals**
3. **Formation of chelates to enhance solubility**
4. **Formation of insoluble complexes**

Mechanisms of Absorption

Facilitated Diffusion

Active Transport

Paracellular at High Concentrations

Role for Intracellular Binding Proteins

IRON

1. **Essential for oxidative energy metabolism and DNA synthesis**

2. **Body stores contain about 4 g with 2.5 g in red blood cells**

3. **To maintain iron balance, the gut absorbs 1-2 mg/day from dietary supply of 10-20 mg**

4. **Because there is no mechanism for active excretion of iron, regulation of body iron is at point of absorption**

CELLULAR IRON HOMEOSTASIS

1. **All cells take up iron-transferrin from plasma by transferrin receptor endocytosis.**

2. **Iron is stored intracellularly complexed to the binding protein ferritin.**

3. **Iron regulatory proteins function as cytoplasmic iron sensors and increase Tf Receptors by stabilizing mRNA when more iron is needed.**

4. **Efflux from cells such as macrophages is by ferroportin.**

IRON ABSORPTION

1. **Dietary iron present as heme (minor) and nonheme iron compounds (major).**

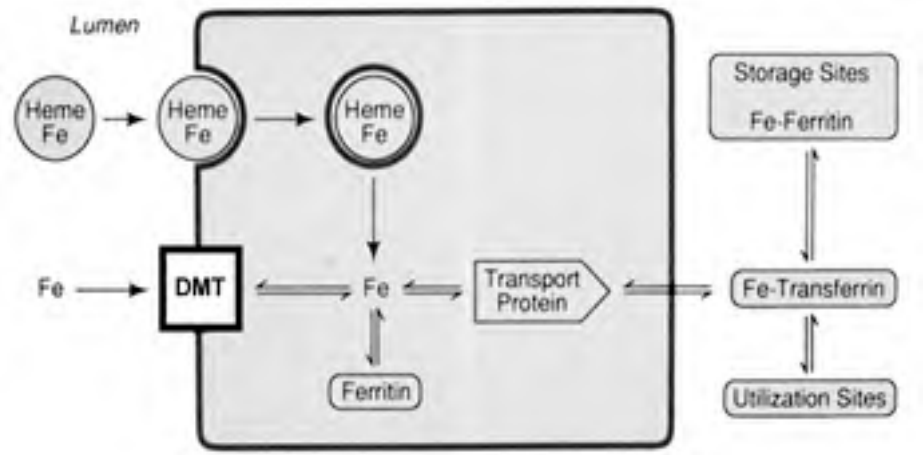
2. **Nonheme iron in the Fe^{3+} ferric state requires gastric acid for solubilization.**

3. **Fe^{3+} mainly reduced to Fe^{2+} (ferrous) prior to absorption.**

4. **Iron absorption occurs primarily in the duodenum and upper jejunum.**

5. **Amount of iron absorbed is influenced by body iron stores, rate of erythropoesis, and inflammation.**

Two Pathways for Absorption of Iron by the Small Intestine



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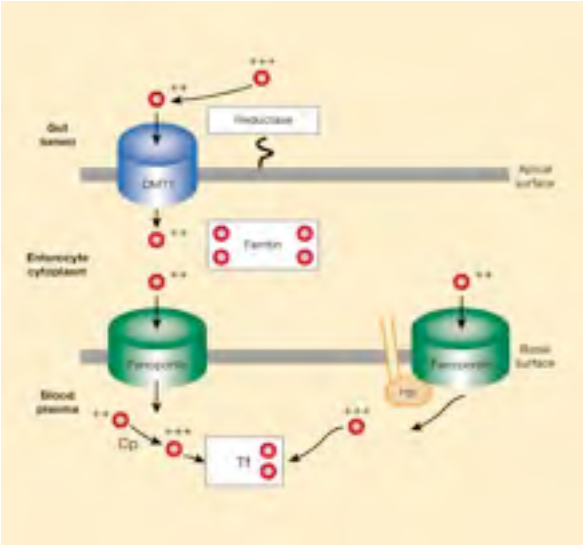
Mechanism of Iron Absorption by Enterocytes



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CELLULAR MOLECULES INVOLVED IN INTESTINAL ABSORPTION

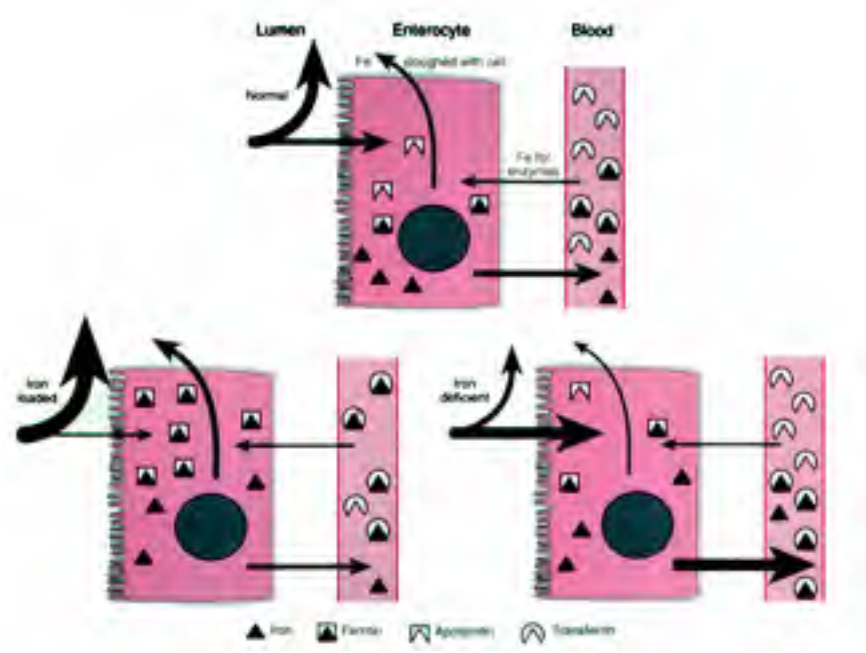
1. **An apical membrane (brush border) ferrireductase enzyme that converts Fe^{3+} to Fe^{2+}.**

2. **An apical membrane divalent metal transporter termed DMT-1 which mediates entry of Fe^{2+} as well as Ca^{2+}, Zn^{2+} and other divalent minerals. Its expression is regulated inversely by body iron stores.**

3. **A basolateral membrane transporter known as ferroportin which mediates exit of Fe^{2+}.**

4. **A basolateral membrane protein, hephaestin (Hp), which facilitates the transport of iron out of cells and oxidizes Fe to the Fe^{3+} state.**

Role of Ferritin in the Regulation of Iron Absorption



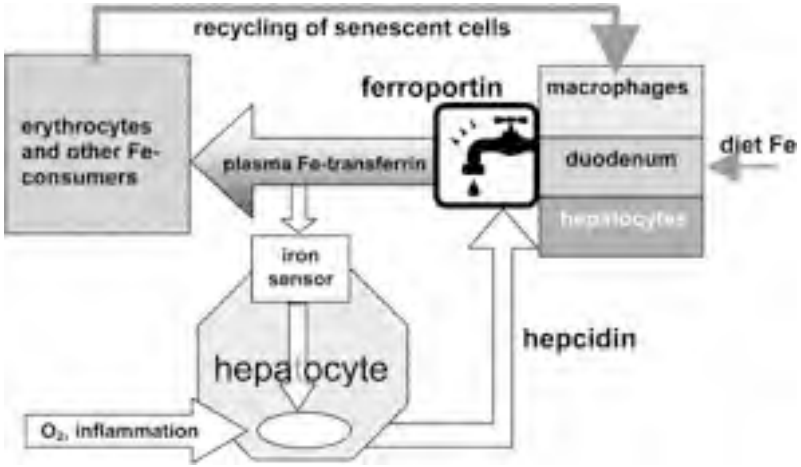
PD-INEL Fig. 29-16 Rhoades, R, Tanner, G. *Medical Physiology*. 1995: 568.

The synthesis of intestinal ferritin is increased when body iron stores are high. This is mediated by iron response proteins which bind to an iron response element (IRE) in ferritin mRNA. With iron deficiency little ferritin is synthesized and iron absorption increases. With iron excess ferritin increases, binds iron in the enterocyte and is sloughed with the cells from the villous tip. After intestinal absorption, iron in blood binds to the plasma protein transferrin.

Role of Liver in Regulating Iron Absorption

1. Liver is main storage site for excess iron
2. Hepcidin is an antimicrobial peptide secreted by hepatocytes which it acts as an inhibitor of iron absorption by the gut and release from macrophages.
3. Production of hepcidin is decreased by iron deficiency and increased with iron loading and inflammation
4. Hepacidin interacts directly with ferroportin leading to its degradation. This leads to decreased iron absorption and release

ORGANISMAL IRON HOMEOSTASIS



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Ferroportin functions as a hepcidin-regulated valve to control the efflux of recycled, dietary and stored iron. In turn hepcidin levels are controlled by body iron stores and are also increased by inflammation.

CAUSES OF IRON DEFICIENCY

1. Dietary deficiency
2. Excess phytate or oxylate in diet
3. Gastric achlorhydria
4. Hookworm infestation
5. Excessive bleeding

CONSEQUENCES OF IRON DEFICIENCY

1. Anemia (microcytic, hypochromic)
2. Poor growth in children
3. Impaired energy metabolism

HEREDITY HEMOCHROMATOSIS

1. Common form is autosomal recessive with gene frequency as high as 1 in 10 in individuals of Northern European descent
2. Excessive mucosal iron absorption relative to need
3. Clinical manifestations are a result of iron deposition in liver, heart, pancreas and joints
6. >80% of patients have a single mutation in HFE protein which leads to decreased plasma hepcidin
7. Other causes of hemachromatosis include mutations in hepcidin or ferroportin

ABSORPTION OF VITAMINS

1. Water soluble vitamins
   -facilitated diffusion (Na+-coupled)
2. Fat soluble vitamins
   -absorbed same as other lipids
3. Vitamin B_{12}
   -special receptor
   -requires intrinsic factor

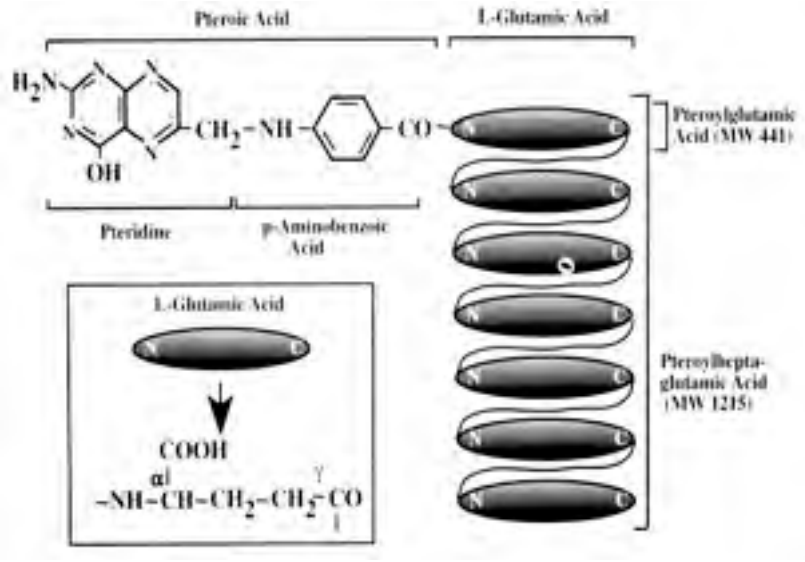
WATER SOLUBLE VITAMINS

Thiamine	Pyridoxine	Folate
Riboflavin	Pantothenate	Cobalamin (B_{12})
Niacin	Biotin	Ascorbic Acid (C)

Generally metabolized to forms acting as coenzymes

Vit C functions as a water soluble antioxident

Structure of Conjugated Folates



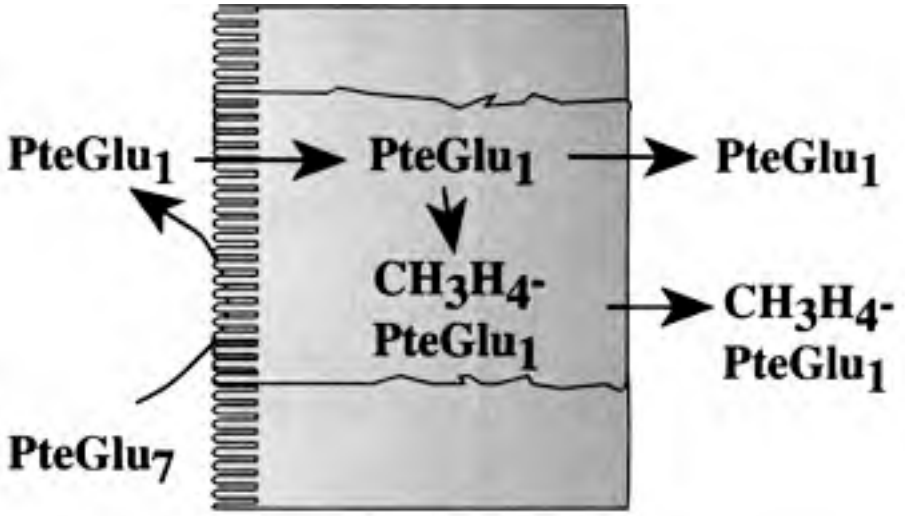
PD-INEL Fig. 1 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 190.

FOLATE DEFICIENCY

1. **Folates function as coenzymes in 1 carbon transfers; important in nucleic acid synthesis and amino acid metabolism**
2. **Deficiency results in megaloblastic anemia and growth retardation**
3. **Recent studies show a relationship to neuronal tube birth defects**

   PHS recommends women of childbearing age consume 400 μg daily

Metabolism and Absorption of Conjugated Folates



PD-INEL Fig. 2 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 191.

1. **Polyglutamyl folates must be hydrolyzed to the monoglutamyl form before absorption**
2. **A specific enzyme, folate conjugase, is involved which is inhibited by ethanol and some drugs (Dilantin, sulfasalazine)**
3. **Absorption is by a saturable mechanism involving a folic acid: OH- exchange mechanism**
4. **Within enterocyte folic acid is reduced and methylated**

FAT SOLUBLE VITAMINS

A – Retinol, carotenoids

D – Cholecalciferol (D_3); Ergosterol (D_2)

E – α-Tocopherol

K – Phylloquinone (K_1); Menaquinones (K_2)

Generally absorbed with fat by similar mechanisms
Can get vitamin deficiency with fat malabsorption

VITAMIN E

1. **The major lipid soluble antioxidant in plasma and cell membranes**
2. **Dietary Sources are vegetable oils, wheat germ, nuts, green leafy vegetables. Recommended intake 15 mg/day.**
3. **Absorption varies from 10-80% by passive diffusion and packaging into chylomicrons**
4. **Role in therapy unclear (macular degeneration, cardiovascular disease, prostate cancer)**

VITAMIN K

Biological function is to serve as a cofactor for essential post-translational modifications essential for certain proteins including blood clotting factors

Dietary form (K1) most abundant in green leafy vegetables

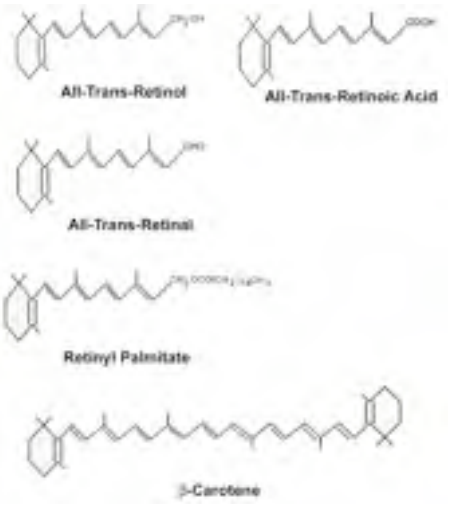
Insoluble in water; requires bile salts for absorption

Importance of bacterially derived K2 controversial but prevents severe deficiency in humans unless colonic flora absent

VITAMIN A

Term vitamin A refers to a group of compounds related to all-trans-retinol that are required for vision, growth, cellular differentiation, reproduction, and the integrity of the immune system.

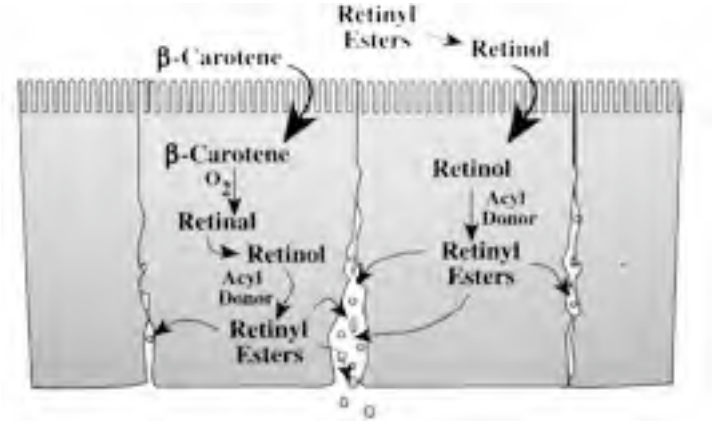
Vitamin A Family



PD-INEL Source Undetermined

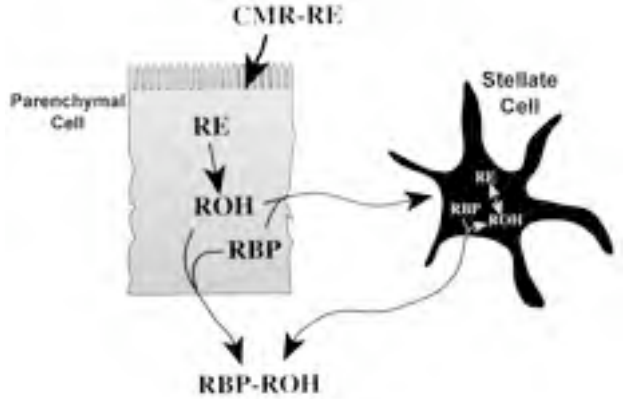
Retinoids – present in liver, milk
Carotenoids – present in carrots and green leafy vegetables
Recommend daily allowance 1000 μg retinoids or 6000 μg B carotene per day
Some functions of carotenoids are distinct from retinal and reflect antioxidant and other functions

Intestinal Absorption and Metabolism of Vit A



PD-INEL Fig. 3 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 166.

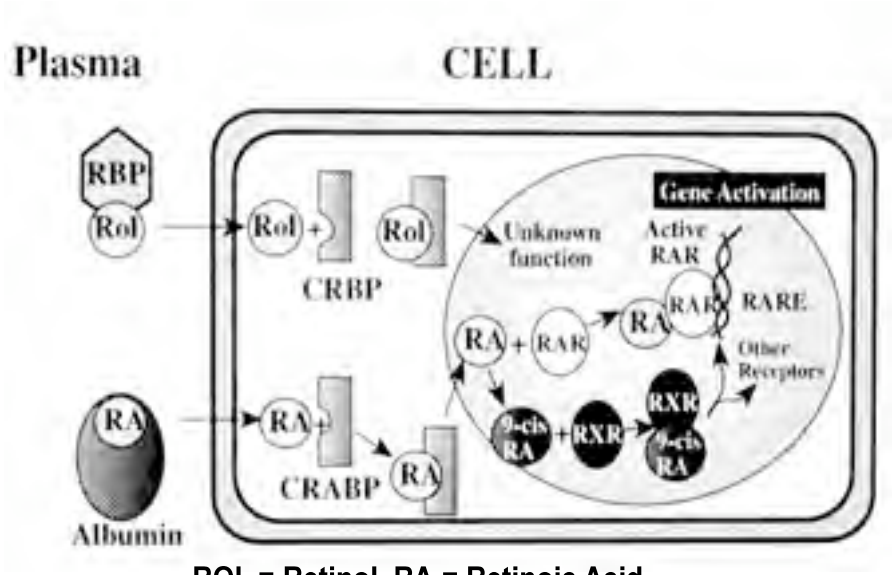
Hepatic Vit A Metabolism and Storage



PD-INEL Fig. 6 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 19961: 70.

Resynthesized retinyl esters are incorporated into chylomicrons and enter the lacteals. Chylomicron remnants (CMR-RE) taken up from blood by hepatocytes. Retinol is then secreted by hepatocytes bound to a retinol binding protein (RBP) and taken up for storage in the hepatic sinusoid by the Stellate Cells. Plasma retinol is relatively constant in spite of variations in dietary intake.

Uptake, Metabolism and Action of Retinol and Retinoic Acid



ROL = Retinol RA = Retinoic Acid
RBP = Serum Retinol Binding Protein
CRABP = Cellular Retinol Binding Protein
RXR = Retinoid X Receptor
RAR = Retinoic Acid Receptor

PD-INEL Fig. 7 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 171.

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Slide 9 – (Left) Fig. 1 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 190.

Slide 9 – (Right) Fig. 2 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 191.

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Slide 11 – (Top right) Fig. 3 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 166.

Slide 11 – (Bottom right) Fig. 6 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 170.

Slide 12 – Fig. 7 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 171.