VITAMINS AND CO-FACTORS

Kenneth Alonso, MD, FACP

Catalysts

- Organic substances have high reaction energy that the reacting molecules have to reach before they can react.
- In aqueous solution, a large proportion of the activation energy is required to remove the hydration shells
- During the course of a reaction, resonance-stabilized structures are often temporarily suspended; this also requires energy.
- The highest point on the reaction coordinates corresponds to an energetically unfavorable transition state.

Catalysts

- A catalyst creates a new pathway for the chemical reaction.
- As the starting and ending points of the reaction are unchanged, there is no change in the enthalpy of the reaction.
- The equilibrium state is not disturbed
- That is the function of a co-enzyme.

Soluble co-enzymes

- Bind as substrate
- Undergo a chemical reaction
- Are released and regenerated by a second reaction.
- NAD^+ transports reducing equivalents from catabolic pathways to the respiratory chain.
- Reduced $NADP^+$ is the most important reductant in biosynthesis.

Prosthetic groups

- Coenzymes that are tightly bound to the enzyme and remain associated with it during the reaction.
- The part of the substrate bound by the coenzyme is later transferred to another substrate or coenzyme of the same enzyme.
- FMN and FAD contain flavin as a redox-active group.
- To avoid damage to cell contents by radical intermediates, flavins remain bound as prosthetic groups to the enzyme.
- Found in dehydrogenases, acidases, and mono-oxygenases.

Group transferring co-enzymes

- The nucleoside phosphates are not only precursors for nucleic acid biosynthesis; many of them also have coenzyme functions.
- They serve for energy conservation, and as a result of energetic coupling also allow endergonic processes to proceed.
- Metabolites are often made more reactive ("activated") as a result of the transfer of phosphate residues (phosphorylation).

Group transferring co-enzymes

- Bonding with nucleoside diphosphate residues (mainly UDP and CDP) provides activated precursors for polysaccharides and lipids.
- Endergonic formation of bonds by ligases also depends on nucleoside triphosphates.

Other co-enzymes

- Ascorbic acid is a powerful reducing agent.
- Lipoic acid and Glutathione function as coenzymes in disulfide/dithiol reactions.
- Mercury binds with high affinity to thiol groups.
- Iron-Sulfur clusters occur as prosthetic groups in oxidoreductases and lysases (aconitase).
- Stable only in interior of proteins.
- Common in respiratory chain.

Other co-enzymes

- Heme coenzymes are found in the respiratory chain.
- Found as well as in mono-oxygenases and peroxidases.
- Iron changes from ferrous to ferric state in contrast to hemoglobin, myoglobin.

Group transferring co-enzymes

- Pyridoxal phosphate is the most important coenzyme involved in amino acid metabolism
- Transmaination, decarboxylation, dehydration
- Aldehyde form covalently bound to ε-amino group of lysine residue (Schiff base) in the absence of substrate.
- Reverts to aldehyde form by reacting with 2-oxoacids.

Group transferring co-enzymes

- Biotin is the coenzyme of carboxylase reactions.
- Forms a Schiff base.
- Reacts with HCO_3^- (using ATP) to prepare intermediate that permits transfer of carboxyl group.

Group transferring co-enzymes

- Tetrahydrofolate is a coenzyme that can transfer one Carbon residue in different oxidation states.
- Plays a role in methionine metabolism, purine nucelotide and dTMP synthesis.
- Adenosyl-cobalamin
- Derived from Vitamin B12.
- It is a coenzyme of isomerase reactions
- Permits degradation of fatty acids and branched chain amino acids.

Quinone/hydroquinone system

- Ubiquinone (Coenzyme Q)
- Transfers reducing equivalents in the respiratory train.
- During reduction, the quinone is converted into the hydroquinone (ubiquinol).
- The isoprenoid side chain of ubiquinone can have various lengths.
- It holds the molecule in the membrane, where it is freely mobile.
- Vitamin E and Vitamin K also belong to the quinone/hydroquinone system.

Table 9-9 Vitamins: Major Functions and Deficiency Syndromes

Vitamin	Functions	Deficiency Syndromes
Fat-soluble		
Vitamin A	A component of visual pigment Maintenance of specialized epithelia Maintenance of resistance to infection	Night blindness, xerophthalmia, blindness Squamous metaplasia Vulnerability to infection, particularly measles
Vitamin D	Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone	Rickets in children Osteomalacia in adults
Vitamin E	Major antioxidant; scavenges free radicals	Spinocerebellar degeneration
Vitamin K	Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, and X; and protein C and protein S	Bleeding diathesis (Chapter 14)
Water-soluble		
Vitamin B_1 (thiamine)	As pyrophosphate, is coenzyme in decarboxylation reactions	Dry and wet beriberi, Wernicke syndrome, Korsakoff syndrome (Chapter 28)
Vitamin B_2 (riboflavin)	Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism	Ariboflavinosis, cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization
Niacin	Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate, involved in a variety of redox reactions	Pellagra—"three Ds": dementia, dermatitis, diarrhea
Vitamin B_6 (pyridoxine)	Derivatives serve as coenzymes in many intermediary reactions	Cheilosis, glossitis, dermatitis, peripheral neuropathy (Chapter 28) Maintenance of myelinization of spinal cord tracts
Vitamin B_{12}	Required for normal folate metabolism and DNA synthesis	Megaloblastic pernicious anemia and degeneration of posterolateral spinal cord tracts (Chapter 14)
Vitamin C	Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen	Scurvy
Folate	Essential for transfer and use of one-carbon units in DNA synthesis	Megaloblastic anemia, neural tube defects (Chapter 14)
Pantothenic acid	Incorporated in coenzyme A	No nonexperimental syndrome recognized
Biotin	Cofactor in carboxylation reactions	No clearly defined clinical syndrome

Water soluble vitamins

- B_1 Thiamine
- TPP is a cofactor for:
- Oxidative decarboxylation of α-ketoacids
- Branched chain amino acid dehydrogenase
- Transketolase in the HMP shunt.
- Thiazolium ring
- Found in cereal grains, beans, nuts, milk, brewer's yeast
- Assay for thiamine measures transketolase activity in RBCs.

Thiamine deficiency

- Beriberi
- Wet
- Edema, heart failure.
- Dry
- Polyneuritis, symmetrical muscle wasting.
- Wernicke-Korsakoff syndrome
- Alcohol-induced.
- Confabulation and dementia.

Water soluble vitamins

- B_2 Riboflavin
- $FADH_2$ synthesis
- FMN and FAD cofactors reversibly accept two hydrogen atoms in oxidation-reduction reactions:
- Fatty acid oxidation
- TCA cycle
- Pyruvate dehydrogenase reactions.
- Found in milk, meat, wheat, green leafy vegetables, fish.

Riboflavin deficiency

- Corneal vascularization.
- Desquamation leads to red tongue (glossitis) as well as fissures at the angles of the mouth (angular stomatitis).

Water soluble vitamins

- B_3 Niacin
- Made in the body from tryptophan using B_6
- Required for NADH and NADPH synthesis.
- Used as electron carrier
- Participates in oxidation-reduction reactions:
- Glycolysis, gluconeogenesis, and HMP pathway
- TCA cycle
- Fatty acid oxidation and synthesis
- Steroid synthesis.
- Found in milk, meat, tomato, turnip greens, collards.

Niacin deficiency and excess

- Deficiency is called pellagra.
- Characterized by dermatitis, diarrhea, dementia.
- Common in the “homeless” population
- Fatal if untreated.

- Niacin in large doses inhibits lipolysis in adipose tissue as well as VLDL and LDL synthesis in the liver.

Water soluble vitamins

- B_5 Panthothenic acid
- Used as an acetyl and acyl carrier (thioester bond).
- Needed for formation of:
- CoA
- Fatty acid synthetase.
- Found in liver, eggs, yeast, milk
- Dermatitis, enteritis, alopecia, adrenal insufficiency characterize deficiency state.

Water soluble vitamins

- B_6 Pyridoxine
- Pyridoxal phosphate is a co-factor used in amino acid reactions:
- Transamination and demanination
- Decarboxylation
- Condensation reactions
- Also a co-factor in:
- Glycogen phosphorylase reactions
- Heme synthesis.
- Requred for synthesis of niacin from tryptophan.
- Found in eggs, liver, yeast, peas, beans, milk

Pyridoxine deficiency

- Macrocytic anemia
- Dermatitis
- Susceptibility to infections
- Irritability. Convulsions in infants
- Peripheral neuropathy.

Water soluble vitamins

- Biotin
- Co-factor for carboxylation
- Co-factor in fat synthesis
- Found in beef liver, yeast, peanuts, chocolate, eggs.
- Deficiency presents with dermatitis, diarrhea, alopecia.
- Caused by eating raw egg whites
- Avidin protein binds to biotin

Water soluble vitamins

- Folate
- Co-enzyme for 1-Carbon transfers
- Apteridine ring bound to para-amino-benzoic acid (PABA) with a glutamate terminus. This is the form absorbed.
- The N_5 (pteridine ring) and N_{10} (PABA) are the most important atoms in the molecule
- Bond directly to the carbon being transferred.
- N_5-methyl-tetrahydrofolate is the most stable form.
- The dietary sources of folate may have seven glutamates chained
- The form found in red cells may have five.

Water soluble vitamins

- Involved in methylation reactions.
- Important for purine synthesis.
- The various forms of folate (tetrahydrofolate and dihydrofolate) shuttle a single carbon off serine and onto the RNA base uracil to convert it into the DNA base thymidine.
- Homocysteinemia linked to low folate levels.
- However, folate replacement does not appear to affect cardiovascular state impaired by homocysteine.
- Serum folate correlates better with homocysteine levels than does red cell folate and is not affected by Oxygen saturation

Folate

- Deficiency linked to neural tube defects.
- May also see macrocytic anemia.
- Cerebral folate deficiency
- Presents at 5 months of age
- Poor muscle tone and coordination
- Seizures
- SLC46A1 mutation at 17q11.2 (Proton coupled folate transporter)
- Low CSF folate (serum folate may be normal)

Water soluble vitamins

- B_{12} Cobalamin
- Co-factor for methyl group transfer to homocysteine to form methionine
- Thus, S-adenosyl methionine to facilitate methylation reactions generally
- Co-factor for conversion of methylmalonyl CoA to succinyl CoA.
- Co-factor for isomerase reactions.
- Stored in liver.

Vitamin B_{12} deficiency

- Methylmalonate accumulates in deficiency state.
- Peripheral neuropathy results because odd-chain fatty acids are required for incorporation into the myelin sheaths.
- Deficiency does not permit demethylation of stable form of tetrahydrofolate (trap), blocking downstream action.
- Macrocytic anemia.
- Absorption requires intrinsic factor secreted by parietal cells of fundic mucosa.
- Absorbed by ileal cells.

Water soluble vitamins

- C Ascorbic Acid
- Necessary for hydroxylation of proline and lysine of procollagen. (Copper dependent)
- Co-factor for domapine conversion to norepinephrine (Zinc dependent)
- Antioxidant.
- Scavenge free radicals.
- Not rate limited
- Regenerate the anti-oxidant form of vitamin E.
- Enhance absorption of Fe^{2+} from intestine.

Water soluble vitamins

- Anti-viral as well as anti-finflammatory in high doses.
- Found in citrus, tomatoes, green peppers, cabbage, breadfruit.
- Scurvy is a manifestation of increased capillary fragility and is seen in vitamin C deficiency.

Lipid soluble vitamins

- A β-carotene; retinol
- β-carotene has only 1/6 the efficiency of retinol.
- β-carotene oxidatively cleaved in the intestine to two retinols.
- Retinol-esters are hydrolyzed in the intestine and diffuse into intestinal cells.
- Retinol is re-esterified and released in chylomicra.
- Delivered to liver (apolipoprotein E receptor) for storage in peri-sinusoidal stellate cells.
- From liver, retinol is bound to retinol-binding protein in blood for transport.

Vitamin A

- Retinol is oxidized to all trans-retinal
- Isomerized to 11-cis-retinal
- Covalently bound to the 7-transmembrane rod protein, opsin, to form rhodospin.
- The irreversible oxidation of retinol produces retinoic acid
- Nuclear receptors in target tissues (RAR, RXR)
- Regulate gene expression and cell growth as well as epithelial cell maintenance.

Vitamin A

- 9-cis-retinoic acid activates RXR
- Form heterodimers with the vitamin D receptor as well as peroxisome proliferator-activated receptor (PPARγ)
- Regulates lipid metabolism.
- Carrots, broccoli, squash, sweet potatoes, green leafy vegetables, liver eggs, butter, fish, cheese are sources of β-carotene.

Vitamin A excess

- Teratogenic
- Cleft palate, congenital heart disease
- Hypervitaminosis A
- Increased intracranial pressure
- Common with use of tretinoin (trans-retinoic acid) in treatment of acne as well as acute promyelocytic leukemia
- Retinoic acid also used in treatment of psoriasis
- Fatigue
- Arthralgias
- Alopecia.

Vitamin A deficiency

- Night blindness.
- Xerophthalmia as a result of squamous metaplasia of corneal epithelium.
- Loss of hair as a result of squamous metaplasia of follicles.
- Mild form treated with retinol or retinyl esters.

Vitamin D

- D Cholcalciferol
- Lipid soluble
- Sunlight leads to the photochemical conversion of provitamin D in the skin.
- The interposition of glass diminishes the effectiveness of sunlight.
- The provitamin, 7-dehydrocholesterol, is protein bound, and
- Hydroxylated (25-hyodroxylases) in the liver
- Hydroxylated later in the kidney (1α-hydroxylase)
- 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3), cholcalciferol, is active form

Vitamin D

- A light skin reddening due to sun exposure is equivalent to an intake of 10,000 IU of Vitamin D.
- Vitamin D binds to intranuclear receptors VDR and RXR
- The active form increases:
- Intestinal uptake of Ca^{2+}
- Ca^{2+} mobilization from bone.
- Generation of the active molecule is stimulated by parathyroid hormone and low phosphate levels.
- Feedback inhibition.
- Only the active molecule is regulated.

Vitamin D

- Within macrophages, vitamin D synthesis occurs in mitochondria.
- Pathogen induced activation of TLR in macrophages leads to transcription of VDR and increased production of vitamin D
- Leads to synthesis of cathelicidin (a defensin)
- Antimicrobial peptide active against Mycobacterium tuberculosis.

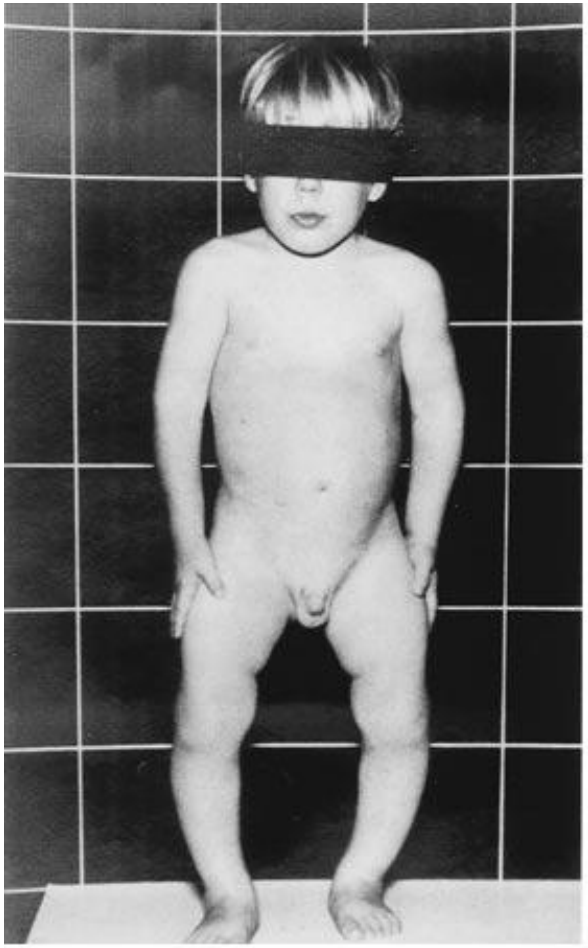
Vitamin D

- Secretion of insulin, parathormone, thyroxine
- Cytokine function
- Vitamin D is acquired in the diet from plants and animal tissues or produced endogenously from cholesterol.

Vitamin D deficiency

- In children, rickets.
- In the adult, osteomalacia
- Inadequate levels of vitamin D. Impaired Ca^{2+} absorption.
- Poor bone formation:
- Excess unmineralized matrix.
- Impaired endochondral ossification (poor mineralization of epiphsyal cartilage).
- Overgrowth of epiphyseal cartilage.
- Unable to cope with stress on bones; bowing.
- May be seen as well in chronic renal failure.

Vitamin D deficiency



(Photograph courtesy of Dr. Sara Arnaud.) Fig. 9-28 Accessed 07/01/2010

Vitamin E

- Lipid soluble
- Antioxidant.
- Part of quinone/hydroquinone system
- Scavenge free radicals
- Found in wheat germ oil, green vegetables, egg yolks, and meat.
- Optimal dose is 400 IU daily. (“U” shaped benefit curve.)
- Deficiency associated with muscular dystrophy, eye damage, brain lesions, hemolysis.

Vitamin K

- Lipid soluble
- Part of quinone/hydroquinone system
- Catalyzes γ-carboxylation of glutamic acid residues of procoagulants (factors) II, V, VII, IX, X, as well as protein C and S.
- This modification permits the binding of Ca^{2+}.
- Found in egg yolk, liver, spinach, cabbage, cauliflower.
- Synthesized by intestinal flora.
- Warfarin blocks Vitamin K synthetase.
- Prolongs prothrombin time.

Co-enzyme A

- Nucleotide.
- Activates residues of carboxylic acid (acyl residues).
- When acyl residue combines with thiol group of coenzyme, forms thioester bond in which acyl residue has high chemical potential.
- Hydrolysis of Acetyl CoA generates as much energy as ATP hydrolysis.
- In addition to thioester bond, seven other hydrolyzable bonds are present in CoA.

Co-enzyme A

- A reactive thiol group of CoA is located in that portion of the molecule derived from cysteamine.
- The amine group of cysteamine bonds with β-alanine through an acid amide bond.
- With a second amide bond, bonding occurs with pantoinate
- Creates a compound that permits the formation of an ester bond with a phosphate residue.
- Pantothenic acid
- Provides the β-alanine and pantoinate needed by the cell to permit the formation of CoA

Co-enzyme A

- The functional unit of Coenzyme A is 4-phospho-pantetheine.
- This unit is also found in fatty acid synthetase.
- The nucleotide Adenine is bound to the C_1 of ribose by a N-glycosidic bond.
- Phosphate ester bonds are present at C_4 and the methyl group at C_5 of ribose.
- That phosphate residue at C_5 bonds with the phosphate residue of the functional unit via an energy rich phosphoric acid anhydride bond.
- Acetate is bound to cysteamine at one end of the functional unit to form Acetyl CoA.

Acetyl co-enzyme A

- Fats, phospholipids, and glycolipids are synthesized from acetyl CoA.
- A second pathway leads to the formation of the isoprenoids.
- Isoprene is utilized by the cell to biosynthesize linear and cyclic oligomers and polymers.
- The isoprenes, vitamins A, D, E, and K, cannot be synthesized by human cells.
- Cholesterol, steroids, and retinoate are all isoprenoids.
- Pantothenic acid in humans is a vitamin that must be consumed

Metals

Metals	Enzymes
Cu^{2+}	Cytochrome oxidase
K^{+}	Pyruvate kinase
Mg^{+}	Creatinine kinase Hexokinase
Mn^{2+}	Arginase
Se^{+}	Glutathione peroxidase Deiodinase
Zn^{2+}	Carbonic anhydrase Carboxypeptidase