

Vitamins & Co-enzymes

Lecture 2

12/22/2004

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Vitamin

- Essential nutrient
 - Organic compound
 - Trace requirements
- Not including
 - Essential amino acids
 - More than trace
 - Trace metals
- Often cofactor or coenzyme

Definitions

Cofactor

- Low molecular weight component essential for protein function
 - Metal ions
 - Prosthetic groups
 - Organic / bioorganic
 - Apoprotein → Holoprotein
 - Eg. Heme groups
 - Coenzymes

Coenzymes

- Apoenzyme + coenzyme → Holoenzyme
- Often integrated for many catalytic cycles
- Sometimes - more like substrate

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Why Cofactors / Coenzymes?

- Most enzymes are proteins (or nucleic acids)
- Some chemistry is not easy with amino acid / nucleotide functional groups
- Examples:
 - Oxygen-binding (hemoglobin)
 - C—O bonding ~irreversible (physiological T)
 - Solution - covalent attachment to metal-bound protein
 - Chemical capture of light
 - Photon energy change covalent structure / denature
 - Solution - reversible isomerization of cofactor
 - Electron transfer reactions
 - Protein / NA radicals reactive → denaturation
 - Poly-aromatic / conjugated co-factors / enzymes like NAD, FAD, Quinones...

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History

- 1905: UK - Fletcher → unpolished rice prevents beri-beri
- 1906: UK - Hopkins → Essential nutrients that are not proteins, carbohydrates, lipids...
- 1911: Poland - Funk → unpolished rice - essential amine
 - "Vital Amine" → "Vitamin"
- Hopkins/Funk theory vitamin deficiencies → diseases
- Animal studies (1912 - 1957) → vitamins A_n, B_n, C, D, E, Q...
- 1926 - 1958 identified / synthesized
 - Not all amines
 - 2nd set of names

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Historical Baggage → Idiosyncrasies

- Some no longer considered essential
 - Vitamin D - steroid synthesized w/ UV exposure
- Some not cofactors, but hormones
 - Vitamin D - Ca^{++} deposition / release
- Vitamins of same class may be chemically unrelated
 - But obtained from similar foods, or
 - Deficiencies → similar diseases
 - Eg. B_1 , B_2 , B_3 , B_5 .

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Classification of Vitamins

Water soluble

- Thiamine (B_1)
- Riboflavin (B_2)
- Niacin [nicotinic a.] (B_3)
- Panthothenic acid (B_5)
- Pyridoxine [al] (B_6)
- Cobalamin (B_{12})
- Lipoic acid
- Biotin
- Ascorbic acid (C)

- Limited long term storage
 - Except B_{12}
 - Excreted in urine

Fat-soluble

- Retinol [al] [retinoic a.] (A)
- Ergocalciferol (D2)
- Cholecalciferol (D3)
- Tocopherols (E family)
- Quinones (K family)
- Require carrier proteins
 - Get around insolubility
- Generally several years supply stored - liver, fatty tissue...

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Water soluble vitamins → Coenzymes

Vitamin	Coenzyme	Biochem. Role
Thiamine (B ₁)	Thiamine pyrophosphate	C—(CO) cleavage rxn, eg. decarboxylation
Riboflavin (B ₂)	Flavin adenine dinucleotide (FAD) / Flavin mononucleotide (FMN)	Oxidoreductases of sugars & lipids
Niacin (B ₃)	NAD ⁺ / NADP ⁺	NAD - oxidative phosphorylation NADP - reduction in biosynthesis
Panthenic acid (B ₅)	Coenzyme A	C—C bonds with two-carbon additions - central to metabolism
Pyridoxal (B ₆)	Pyridoxal phosphate	Transamination reactions
Cobalamin (B ₁₂)	Various eg. methyl~	Single-carbon addition reactions
Biotin	Biocytin	Carboxylation reactions - activates CO ₂ (leaving group)
Lipoic acid	Lipoamide	Pyruvate dehydrogenase complex
Folic acid	Tetrahydrofolate	Single-carbon addition reactions

➤ Exception - Vitamin C does not become coenzyme
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Clinical vitamin tests

- Serum levels
 - Often reflect latest meal...
 - Concentrations too low to detect
- Measure activity of co-factor's holoenzyme

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Vitamin & coenzyme essentials

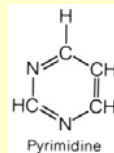
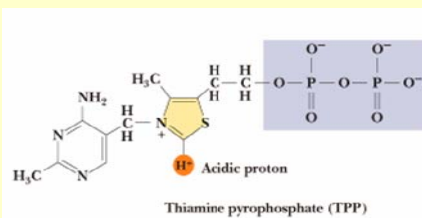
- A few structure / chemistries remembered
 - E.g. NAD⁺ / NADH.
- Most - functional groups / types of chemistry
 - No-one will expect full memorization
 - Enough to see likely similarities
 - Predict pathologies of deficiencies
- Comments about selected vitamins... → → →

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Thiamine B₁.



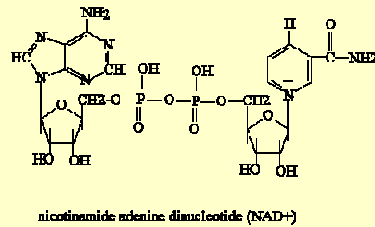
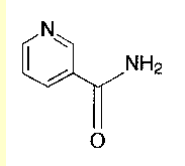
- Heterocyclic components
 - Pyrimidine (C₄N₂)
 - Thiazole (C₃SN)
- Required for
 - Decarboxylation rxn
 - Transketolase rxn
 - Carbohydrate metabolism
- Sources
 - Grains, seeds, meat
- Deficiency →
 - Beri-beri
 - Neuropathies
 - Alcoholism incr. risk

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Niacin → NAD(P)⁺



- Provides nicotinamide (substituted pyridine) to NAD(P)
- Required for
 - Oxidative phosphorylation
 - Reduction rxn in biosynthesis
- Deficiency
 - Pellagra - very rare
- NAD is example of many nucleotide cofactors
 - Nucleotide is not "functional"
 - Binding "handle" / specificity
 - A few highly conserved nucleotide-binding domains
 - Eg. dehydrogenase enzymes
 - Lactate, alcohol...

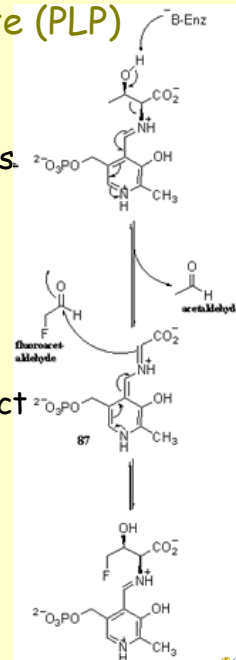
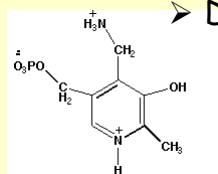
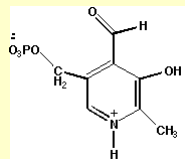
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Vitamin B6 → Pyridoxal phosphate (PLP)

- Required for:
 - Transamination reactions
 - Decarboxylation of amino acids
- Transamination
 - Transient transfer of NH₂ to CHO
 - From substrate to coenzyme
 - Pyridoxal P → Pyridoxamine P
 - Then from coenzyme to product
 - N⁺ electron sink mechanism
- Deficiency rare
 - Exacerbated by:
 - Isoniazid (TB antibacterial)
 - Oral contraceptives



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Panthothenic acid (B₅) → Coenzyme A

4-Phosphopantetheine

β-Mercaptoethylamine

Pantoic acid

3',5'-ADP

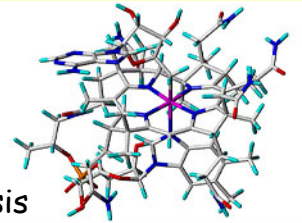

- Functional thiol → CoA-SH
 - Mercaptoethylamine
- New C-C bonds through 2-carbon addn.
 - Acyl group: -(CO)-CH₃.
 - Activated acyl ← thioester
 - CoA-S-(CO)-CH₃.
- Carbonyl C susceptible to nucleophilic attack
 - Thioalkoxide (R-S⁻) excellent leaving group
 - -S-(CO)- thioester less stable than ester -O-(CO)-
 - ~-10kJ/mol
 - Less double-bond (π) resonance
- Prominent in CHO, fatty acid metabolism

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Folate & B₁₂ (cobalamin)

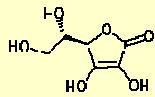
- Chemically unrelated
- Both involved in one-carbon transfers
 - (methyl, formyl...)
 - Deficiencies → similar symptoms
- Higher levels required w/ DNA synthesis
 - Pregnancy, lactation
 - Tumors, bacterial infections
 - Folate-interfering drugs:
 - trimethoprim & methotrexate.
- Folate supplements during pregnancy
 - Periconceptual supplements (400µg)
 - → risk of spina bifida
 - learning experience
- B₁₂ deficiencies rare except w/ long-time vegans

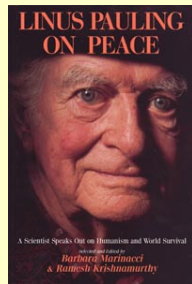
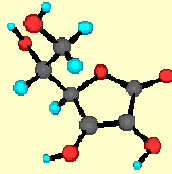
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Ascorbic acid (Vitamin C)



ascorbic acid



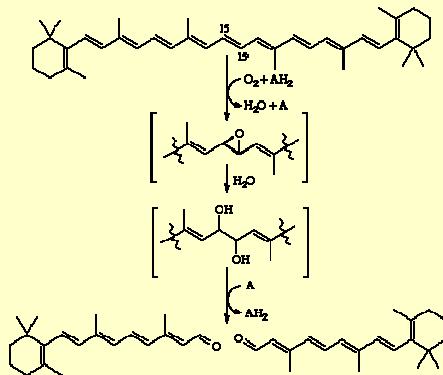
- Only soluble vitamin neither:
 - B-group nor coenzyme
- Scurvy / citrus / peppers
- Isolation / synthesis → Nobel prize → Hopkins & Szent-Gyorgi (1937)
- Antioxidant
- Keeps Fe²⁺, Cu⁺ cofactors in lower oxidation states
- Deficiency now rare
 - Many effects
 - Connective tissue / collagen
 - Mild immunodeficiency
- Megadoses to keep away colds / cancer?

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Lipid soluble A vitamins



- Class of retinol-like compounds
 - Toxic in excess
- Derived from β-carotene
 - Non-toxic
- Several functions, eg.
- Opsin + retinal → rhodopsin
 - Light sensitive protein in retina
- Deficiency night-blindness
- Source - liver, milk, carrots

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Other Lipid-soluble Vitamins

- Vitamin D family - prohormones
 - Precursors of steroids involved w/ Ca^{++} homeostasis
 - Deficiency - rickets (soft bones)
 - Source: milk, fortified foods
 - Excess is toxic
- Vitamin E family - tocopherols
 - Lipid antioxidants
 - Deficiency rare - anemia
 - Cancer, Alzheimer's, arteriosclerosis prevention???
- Vitamin Ks - cofactors in several clotting factors
 - Dicoumarin treatment of thrombosis blocks regeneration
 - Example - Warfarin - antidote is vitamin K

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Assignments

Reading

- G&G 17.4

Correction

- Panthothenic acid \neq B₃.
 - Page 561
 - Panthothenic acid = B₅.
 - Niacin = B₃.

Problems

- G&G 17.11 - 17.14

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