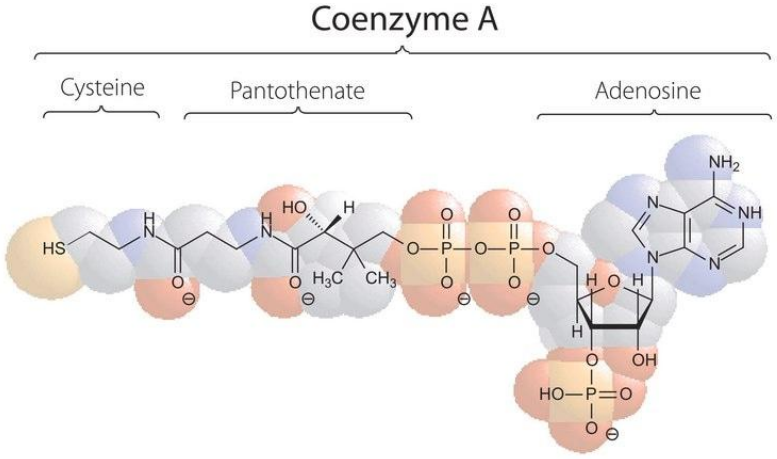
Lecture 6
Discipline: Bioorganic Chemistry
Lecturer: Associate Professor, Dr. Gulnaz Seitimova

Title: Coenzymes. Chemical structure, properties and physiological role in the body.
Objective: The aim of this lecture is to provide an in-depth understanding of coenzymes, their chemical nature, functional properties, mechanisms of participation in enzymatic catalysis, and physiological significance in key metabolic pathways of the human body.
Main Questions: Definition of coenzymes and their distinction from cofactors. Structural organization and chemical classes of coenzymes. Vitamin-derived coenzymes and their biological importance. Mechanisms of coenzyme participation in enzyme-catalyzed reactions. Redox coenzymes: NAD^+/NADH, $NADP^+$/NADPH, FAD, FMN. Coenzymes involved in group transfer reactions: CoA, TPP, PLP, biotin, folates. Activation-transfer roles of coenzymes and transient covalent intermediates. Physiological role of coenzymes in metabolism and cellular regulation. Clinical significance of coenzyme deficiencies and disorders.

Key Notes and Theses
Definition and General Characteristics
- Coenzymes are small, non-protein organic molecules required for enzyme activity.
- They participate directly in catalysis by acting as carriers of electrons, atoms, or functional groups.
- Most coenzymes are derived from vitamins (B-group, vitamin C, vitamin K).
- Coenzymes bind to enzymes either loosely (cosubstrates) or tightly (prosthetic groups).

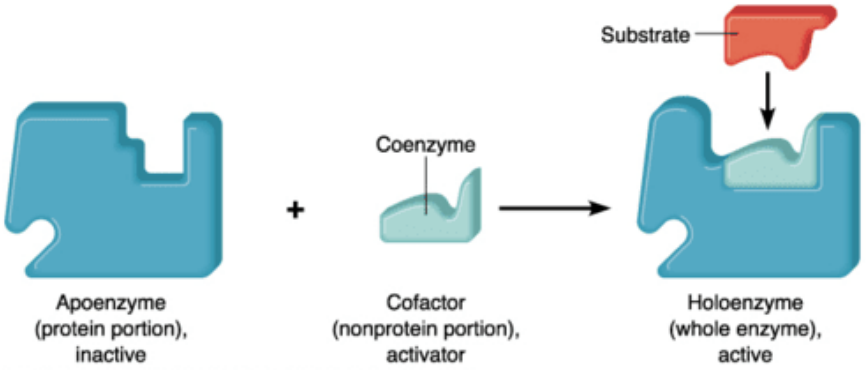
A coenzyme is a molecule required by a particular enzyme to carry out the catalysis of a chemical reaction. Many are derived from vitamins, particularly those that are phosphorylated derivatives of water-soluble vitamins. Coenzymes participate in catalysis when they bind to the active site of the enzyme (called apoenzyme) and subsequently form the active enzyme (called holoenzyme). Although coenzymes activate enzymes they are not considered as substrates of the reaction. The main function of the coenzyme is to act as an intermediate carrier of transferred electrons or functional groups in a reaction.



Coenzyme A (CoA, CoASH or HSCoA) is the key cofactor in first step of the TCA cycle, responsible for transferring the acetyl group from pyruvate oxidation to oxaloacetate yielding citrate.
Coenzyme A is also a critical cofactor in fatty acid metabolism. Coenzyme A carries fatty acids through the catabolic/oxidation process in the mitochondria and transfers acetyl groups during the elongation process of fatty acid synthesis in the cytosol.

Examples of coenzymes: nicotineamideadenine dinucleotide (NAD), nicotineamide adenine dinucelotide phosphate (NADP), and flavin adenine dinucleotide (FAD). These three coenzymes are involved in oxidation or hydrogen transfer. Another is coenzyme A (CoA) which is involved in the transfer of acyl groups.

Some vitamins act as coenzymes participating in biochemical processes such as catabolism, anabolism, and the production of energy. Vitamins A and K are two fat-soluble vitamins that act as coenzymes or cofactors, while all the water-soluble enzymes can act as cofactors or coenzymes. In addition to their action as cofactors, vitamins have a critical role in several vital processes such as the production of hormones, the integrity of collagen in bones, blood coagulation, and proper vision.



A cofactor is a non-protein chemical compound that is required for the protein's biological activity. Many enzymes require cofactors to function properly.

Distinction: Cofactors vs. Coenzymes

- Cofactor – any non-protein component (metal ions or organic molecules).
- Coenzyme – specifically an organic cofactor.
- Holoenzyme = apoenzyme (protein) + cofactor/coenzyme.
- Coenzymes often undergo reversible chemical changes during reactions.

Chemical Structure of Coenzymes

Coenzymes belong to several structural classes:

1. Nucleotide-based coenzymes
   - NAD^+, $NADP^+$ (nicotinamide nucleotides)
   - FAD, FMN (flavin nucleotides)
   - Coenzyme A (adenosine-3′-phosphate derivative)
2. Vitamin-derived coenzymes
   - Thiamine pyrophosphate (TPP) – vitamin B_1
   - Pyridoxal phosphate (PLP) – vitamin B_6
   - Biotin – vitamin B_7
   - Tetrahydrofolate (THF) – folic acid
   - Cobalamin (coenzyme B_{12})
3. Lipid-based coenzymes
   - Ubiquinone (CoQ10, coenzyme Q)
   - Lipoic acid

Properties of Coenzymes

- Flexibility and mobility allow them to bind transiently to active sites.
- Capable of reversible oxidation–reduction, group transfer, or isomerization.
- Often form covalent intermediates, stabilizing reaction transition states.
- Work as universal carriers in metabolism.

Major Coenzymes and Their Functions

1. Redox Coenzymes

- NAD^+/NADH: carries hydride ions; central in glycolysis, TCA cycle, oxidative pathways.
- $NADP^+$/NADPH: reducing agent in anabolic processes, lipid synthesis, antioxidant defense.
- FAD/$FADH_2$: carries electrons via two sequential hydrogen transfers; active in TCA cycle, *β*-oxidation.

2. Coenzymes of Group Transfer

- Coenzyme A (CoA-SH): transfers acyl groups; essential in fatty acid metabolism and TCA cycle.
- Thiamine pyrophosphate (TPP): catalyzes decarboxylation of α-ketoacids.
- Pyridoxal phosphate (PLP): transamination, deamination, decarboxylation of amino acids.
- Biotin: carboxylation reactions; carries CO_2.
- Tetrahydrofolate (THF): transfers one-carbon units (methyl, methylene, formyl).
- Cobalamin (B_{12}): methyl group transfer, rearrangement of odd-chain fatty acids.

3. Energy-Related Coenzymes

- Coenzyme Q10: electron transport chain component.
- Lipoamide: participates in oxidation of pyruvate and α-ketoglutarate.

Functions of Coenzymes

Minerals and vitamins play an important role in the anabolic and catabolic pathways that lead to the synthesis of biomolecules such as lipids, nucleic acids, proteins, and carbohydrates as coenzymes or cofactors.

Vitamins as coenzymes: Vitamin A metabolite form, retinoic acid, functions as genes regulator, therefore, it is very important for the normal development of cells. Vitamin K is a coenzyme for enzymes that move —CO_2 groups (g-carboxylases). The released carboxylic group binds to calcium, this step is important for the formation of osteocalcin, an important protein for bone remodelling. Additionally, it is important for the formation of prothrombin, which plays a crucial role in blood coagulation.

Minerals as cofactors and catalysts: Minerals can function in biological processes as cofactors and catalysts. When minerals act as catalysts they do not integrate with an enzyme or its substrate. However, they accelerate the biochemical reaction between the enzyme and its substrate. Alternatively, when minerals act as cofactors, they become a part of the enzyme or protein structure that is essential for the biochemical reaction to proceed. Minerals that act as cofactors include manganese, selenium, magnesium, and molybdenum. Some minerals, such as cobalt, iodine, calcium, and phosphorus, act as cofactors for certain non-enzymatic

proteins. Others, like copper, zinc, and iron, act as cofactors for both non-enzymatic and enzymatic proteins.

Mechanism of Action

Coenzymes contribute to catalysis via:

- Electron transfer (NAD^+, FAD)
- Acyl transfer (CoA)
- Amino group transfer (PLP)
- Carboxyl group transfer (biotin)
- One-carbon metabolism (THF)
- Radical-based rearrangements (B_{12})

They temporarily accept or donate chemical groups, making reactions more energetically favorable.

Physiological Role

Coenzymes are indispensable for:

- Carbohydrate metabolism
- Lipid oxidation and synthesis
- Protein and amino acid metabolism
- Methylation reactions (DNA, epigenetics)
- Antioxidant protection (NADPH)
- Cellular respiration (ATP generation)
- Detoxification processes

Their absence leads to impaired enzymatic function, metabolic blocks, and disease.

Clinical Significance

Coenzyme deficiencies lead to:

- Beriberi (vitamin B_1 deficiency → lack of TPP)
- Pellagra (vitamin B_3 deficiency → low NAD^+/$NADP^+$)
- Anemia and neural tube defects (folate deficiency)
- Pernicious anemia (B_{12} deficiency)
- Dermatitis and neurological disorders (vitamin B_6 deficiency)

Coenzymes are used in:

- Supplement therapy
- Metabolic support
- Neurological and cardiovascular treatment
- Antioxidant therapy (e.g., CoQ10)

Questions for Knowledge Assessment

1. What is a coenzyme? How does it differ from a cofactor?
2. Describe the structure and function of NAD^+/NADH.
3. What role does Coenzyme A play in metabolism?
4. Name at least five vitamin-derived coenzymes and their functions.
5. Explain how PLP participates in transamination reactions.
6. What is the physiological importance of NADPH?

7. Describe the mechanism of biotin-dependent carboxylation.
8. Why are coenzymes essential for enzymatic catalysis?
9. What metabolic disorders arise from coenzyme deficiencies?
10. Compare tightly bound prosthetic groups and loosely bound cosubstrates.

Recommended Literature

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