BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biochemistry

Course Title : Enzymology
Course Code : BC102CR

Unit-4

Introduction of co-enzymes

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Coenzyme	Derived From	Structure	Function	Reactive Site
Pyridine Nucleotides (NAD^+/$NADP^+$)	Vitamin B3 (Niacin)	Nicotinamide, ribose, adenine, phosphate	**Redox reactions**, electron carriers in metabolism (e.g., glycolysis, TCA cycle, and biosynthesis).	Nicotinamide ring
Flavin Nucleotides (FMN/FAD)	Vitamin B2 (Riboflavin)	Isoalloxazine ring, ribitol, phosphate (FMN); with adenine in FAD	Electron carriers in redox reactions (e.g., oxidative phosphorylation, beta-oxidation).	Isoalloxazine ring
Coenzyme A (CoA)	Vitamin B5 (Pantothenic acid)	ADP, pantothenic acid, reactive thiol group	Transfers **acyl groups** (e.g., acetyl-CoA in TCA cycle, fatty acid metabolism).	Thiol group (-SH)

Coenzyme	Derived From	Structure	Function	Reactive Site
Pyridoxal Phosphate (PLP)	Vitamin B6 (Pyridoxine)	Pyridoxal (aldehyde form), phosphate	**Amino acid metabolism**: Transamination, decarboxylation, racemization.	Aldehyde group
Thiamine Pyrophosphate (TPP)	Vitamin B1 (Thiamine)	Thiazolium ring with a diphosphate group	Catalyzes **decarboxylation of alpha-keto acids** and transketolation reactions.	Thiazolium ring
Tetrahydrofolate (THF)	Vitamin B9 (Folate)	Pteridine ring, p-aminobenzoate, glutamate side chain	Carries **one-carbon units** for biosynthesis (e.g., purines, thymidine, methionine synthesis).	N^5 and N^{10} positions of pteridine

Coenzyme	Derived From	Structure	Function	Reactive Site
B12 Coenzymes	Vitamin B12 (Cobalamin)	Corrin ring with cobalt ion and variable R groups (methyl or adenosyl)	**Methylation (homocysteine to methionine)** and isomerization reactions (e.g., methylmalonyl-CoA to succinyl-CoA).	Cobalt ion in corrin ring

Key Highlights of Functions

1.Energy Metabolism:

1. **Pyridine Nucleotides (NAD^+/$NADP^+$)**: Essential for redox reactions in catabolic (NAD^+) and anabolic (NADPH) pathways.
2. **Flavin Nucleotides (FMN/FAD)**: Participate in electron transport and beta-oxidation.

2.Acyl Group Transfer:

1. **Coenzyme A**: Transfers acyl groups in fatty acid metabolism, TCA cycle, and other pathways.

3.Amino Acid Metabolism:

1. **Pyridoxal Phosphate (PLP)**: Involved in transamination, decarboxylation, and racemization of amino acids.

4.Decarboxylation and Carbon Transfers:

1. **Thiamine Pyrophosphate (TPP)**: Catalyzes decarboxylation of alpha-keto acids and transketolase reactions in carbohydrate metabolism.

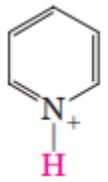
5.One-Carbon Metabolism:

1. **Tetrahydrofolate (THF)**: Transfers single-carbon groups in purine and pyrimidine biosynthesis.

6.Specialized Functions:

1. **B12 Coenzymes**: Participate in rearrangement (adenosylcobalamin) and methylation (methylcobalamin) reactions.

Structure of coenzymes



Pyridine

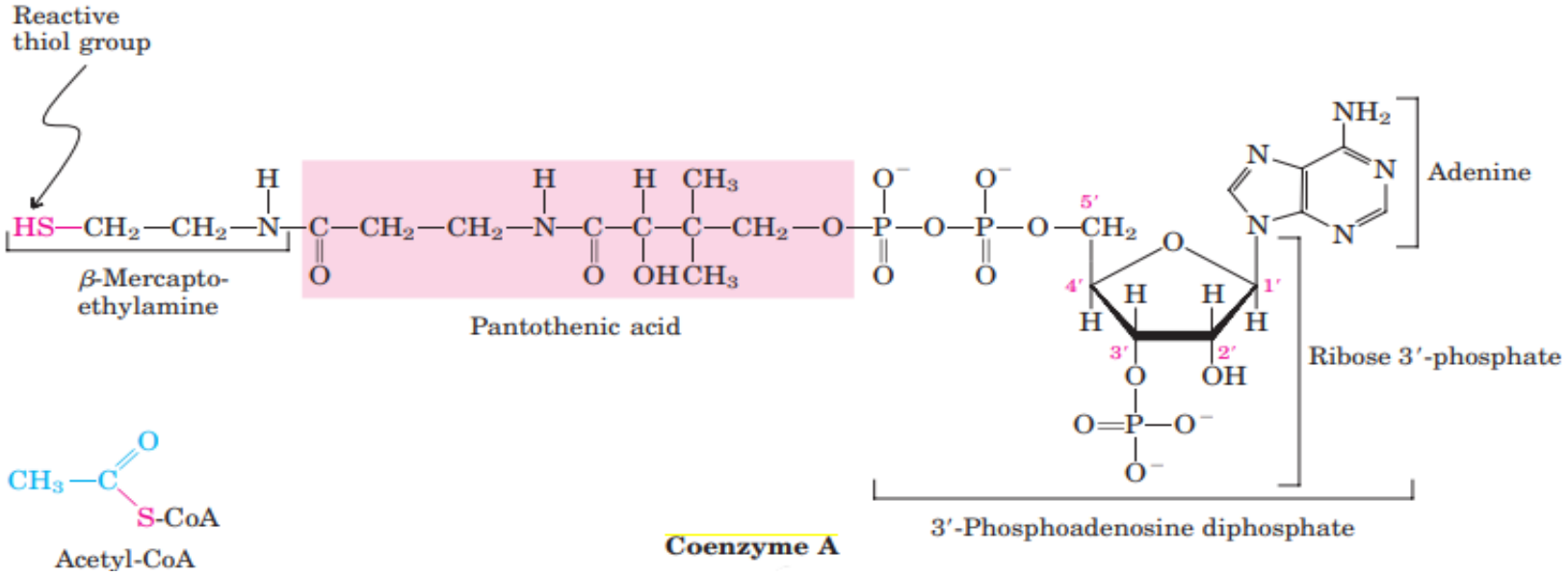


FIGURE 1: Coenzyme A (CoA). A hydroxyl group of pantothenic acid is joined to a modified ADP moiety by a phosphate ester bond, and its carboxyl group is attached to -mercaptoethylamine in amide linkage. The hydroxyl group at the 3 position of the ADP moiety has a phosphoryl group not present in free ADP. The OSH group of the mercaptoethylamine moiety forms a thioester with acetate in acetylcoenzyme A (acetyl-CoA) (lower left)

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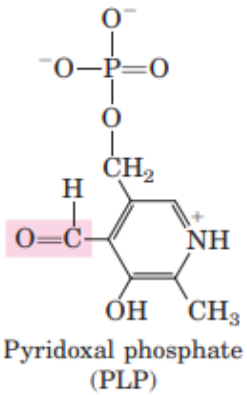

FIGURE 2:– Pyridoxal phosphate, the prosthetic group of aminotransferases. (a) Pyridoxal phosphate (PLP) and its aminated form, pyridoxamine phosphate, are the tightly bound coenzymes of aminotransferases. The functional groups are shaded.

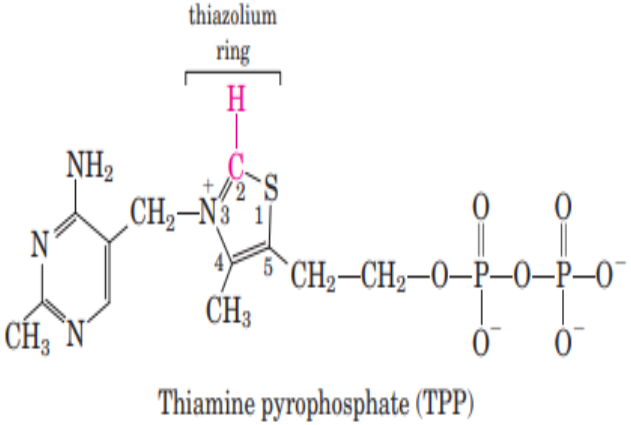

FIGURE 3:- Thiamine pyrophosphate (TPP) and its role in pyruvate decarboxylation. (a) TPP is the coenzyme form of vitamin B1 (thiamine). The reactive carbon atom in the thiazolium ring of TPP is shown in red. In the reaction catalyzed by pyruvate decarboxylase, two of the three carbons of pyruvate are carried transiently on TPP in the form of a hydroxyethyl, or "active acetaldehyde," group

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Enzyme Repression

Enzyme repression is a regulatory mechanism used by cells to inhibit the synthesis of enzymes when they are not needed. This process is commonly associated with gene regulation and occurs at the transcriptional level.

Mechanism of Enzyme Repression:

1.Presence of an Effector Molecule:

1. Often triggered by the presence of a specific metabolite, commonly the **end product** of a metabolic pathway.
2. This is part of a negative feedback loop.

2.Regulation at the DNA Level:

1. A **repressor protein** binds to the **operator region** of the gene encoding the enzyme, blocking RNA polymerase from initiating transcription.
2. The effector molecule (often a corepressor) enhances the binding of the repressor to the operator.

1.Reduced Enzyme Synthesis:

1. As transcription is inhibited, no new mRNA is produced, and enzyme synthesis is halted.

Examples:

- **Tryptophan Operon in Bacteria**:
    - When tryptophan levels are high, it acts as a corepressor, activating the repressor protein, which binds to the operator to block transcription of tryptophan-synthesizing enzymes.

Significance:

- Prevents overproduction of enzymes, conserving energy and resources.
- Ensures metabolic balance by halting the synthesis of enzymes involved in pathways where end products are already abundan

Covalent Modifications of Enzymes

Covalent modifications involve the addition or removal of specific chemical groups to or from enzymes, altering their activity, stability, or localization. These modifications are usually reversible and play a significant role in regulating enzyme function.

Types of Covalent Modifications:

1.Phosphorylation:

1. Addition of a phosphate group to specific amino acids (serine, threonine, or tyrosine) by **kinases** and removal by **phosphatases**.
2. **Effect**: Can activate or deactivate enzymes.
3. **Example**: Glycogen phosphorylase is activated by phosphorylation in glycogen metabolism.

2.Acetylation:

1. Addition of an acetyl group to lysine residues by acetyltransferases and removal by deacetylases.
2. **Effect**: Alters enzyme activity or DNA-binding properties (e.g., histone acetylation regulates gene expression).

3.Methylation:

1. Addition of a methyl group to arginine or lysine residues by methyltransferases.
2. **Effect**: Often affects enzyme activity or protein interactions.

1.ADP-Ribosylation:

1. Transfer of ADP-ribose from NAD^+ to a specific amino acid in the enzyme.
2. **Effect**: Can inhibit or activate enzymes (e.g., diphtheria toxin ADP-ribosylates elongation factor EF-2, inhibiting protein synthesis).

2.Ubiquitination:

1. Addition of ubiquitin molecules to lysine residues of enzymes.
2. **Effect**: Tags proteins for degradation by the proteasome or alters their activity.

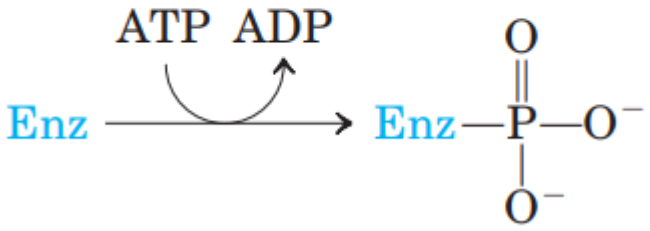
3.Glycosylation:

1. Attachment of carbohydrate groups to asparagine (N-linked) or serine/threonine (O-linked) residues.
2. **Effect**: Influences enzyme stability, activity, or localization.

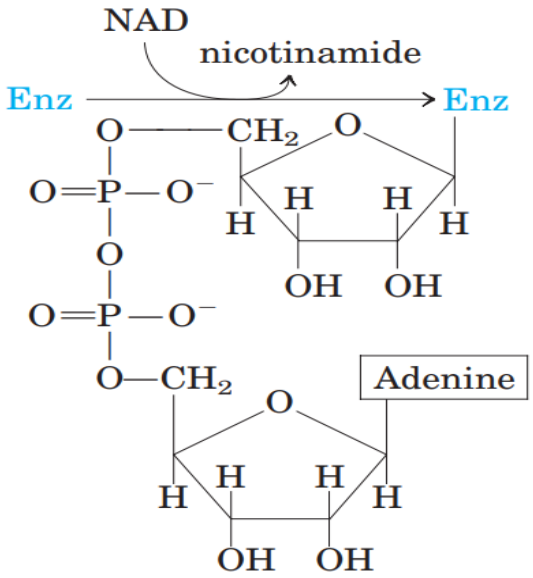
4.Proteolytic Cleavage:

1. Irreversible removal of specific peptide bonds to activate or deactivate enzymes.
2. **Example**: Activation of zymogens (inactive enzyme precursors) like trypsinogen to trypsin.

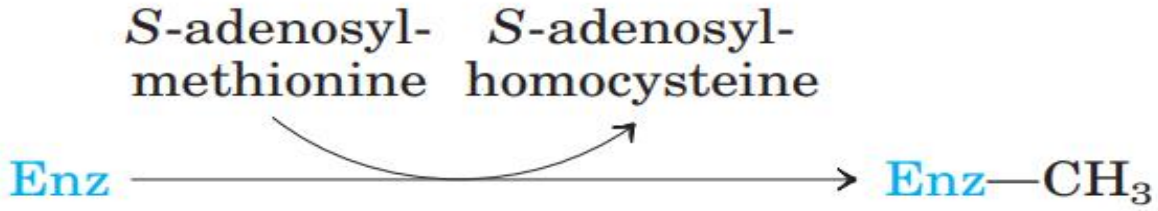
Phosphorylation
(Tyr, Ser, Thr, His)



ADP-ribosylation
(Arg, Gln, Cys, diphthamide—a modified His)



Methylation
(Glu)



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Regulatory Role of Covalent Modifications:

- **Signal Transduction**: Phosphorylation cascades in cell signaling.
- **Metabolic Regulation**: Activation/inhibition of enzymes in metabolic pathways (e.g., phosphorylation of enzymes in glycolysis and gluconeogenesis).
- **Adaptation to Environmental Changes**: Quick response to stimuli by reversible modifications.

Significance:

- Enables fine-tuning of enzyme activity in response to cellular and environmental cues.
- Provides a rapid and reversible mechanism for regulating metabolic pathways.

Zymogen Activation

Zymogens, also called **proenzymes**, are inactive precursors of enzymes. They require specific biochemical changes, typically proteolytic cleavage, to become active. This mechanism prevents the enzyme from exerting its catalytic function prematurely, which could be damaging to the cell or tissue.

Mechanism of Zymogen Activation

1. Proteolytic Cleavage:
   - A specific peptide bond in the zymogen is cleaved by a protease.
   - This cleavage exposes the enzyme's active site or induces conformational changes necessary for activity.
2. Irreversible Process:
   - Once activated, the enzyme remains active until degraded.
   - This ensures tight regulation of enzymatic activity.

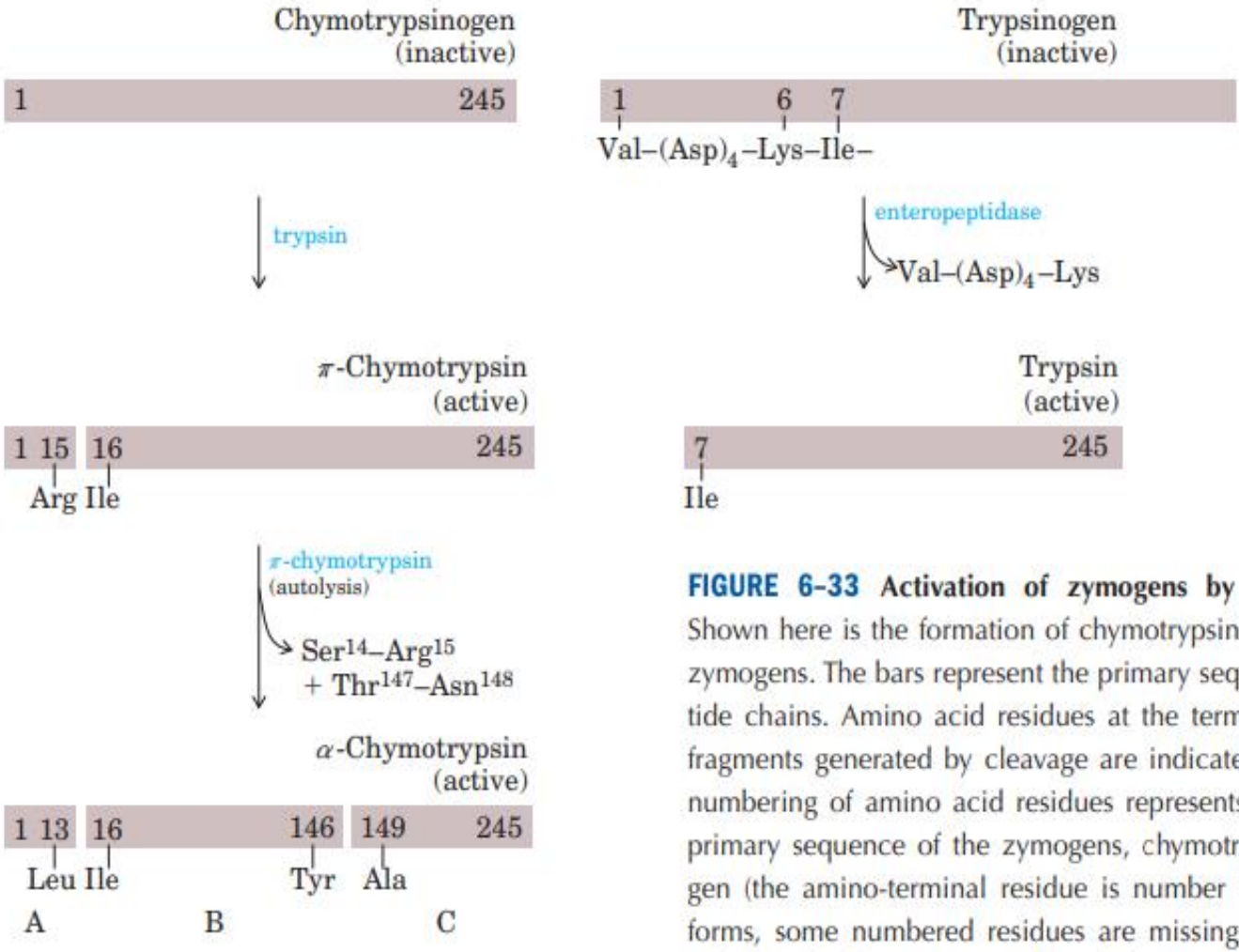

FIGURE 6–33 Activation of zymogens by proteolytic cleavage. Shown here is the formation of chymotrypsin and trypsin from their zymogens. The bars represent the primary sequences of the polypeptide chains. Amino acid residues at the termini of the polypeptide fragments generated by cleavage are indicated below the bars. The numbering of amino acid residues represents their positions in the primary sequence of the zymogens, chymotrypsinogen or trypsinogen (the amino-terminal residue is number 1). Thus, in the active forms, some numbered residues are missing. Recall that the three polypeptide chains (A, B, and C) of chymotrypsin are linked by disulfide bonds (see Fig. 6–18).

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Examples of Zymogens:

1.Digestive Enzymes:

1. **Pepsinogen** (stomach): Activated to **pepsin** in acidic conditions (pH < 2) to digest proteins.
2. **Trypsinogen** (pancreas): Activated to **trypsin** by enterokinase in the small intestine, which then activates other zymogens like chymotrypsinogen and procarboxypeptidase.

2.Blood Clotting Enzymes:

1. **Prothrombin**: Converted to **thrombin**, a key enzyme in the coagulation cascade.

3.Complement Proteins:

1. **C3** and **C5** are inactive precursors activated during immune responses.

REFERENCES

1. Enzymes: Biochemistry, Biotechnology, Clinical Chemistry, 2ndedition,2008 Trevor Palmerand Philip Bonner
2. 2. Principles of Biochemistry, 1993. A.L. Lehninger, Nelson &Cox (CBS, India) and newedition.
3. 3. Biochemistry, 2004, Donald Voet and Judith Voet, John Wiley and sons. ISBN - 047119350