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Enzymes and coenzymes (2)

Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

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MED439

Objectives:

- Understand the enzyme kinetics, types of inhibition and regulation of enzyme activity.
- Discuss the clinical role enzymes in the diagnosis of diseases.

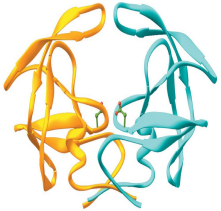
Enzymes inhibition

A helpful video

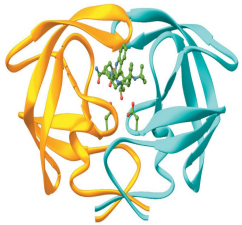
A helpful video

- **Inhibition** is a process by which the enzyme activity is regulated or controlled or stopped .
- To inhibit means to stop enzyme activity .

Types of enzyme inhibition		
Competitive	Non-competitive	Uncompetitive
- Similar structure as the substrate or modified from it. - It competes with the substrate for the same active site. - It has two reactions and always reversible . - when it becomes reversible ? when there're high concentrations of the substrate .	- The structure is not similar to the substrate. - It doesn't compete with the substrate for the same active site . - It has two reactions and it can be reversible or irreversible . - more explanation about reversible and irreversible enzyme inhibitions click here .	- This type is not important, all you have to know is that there is a third type.



An enzyme without inhibitor



An enzyme with inhibitor

K_i inhibitions

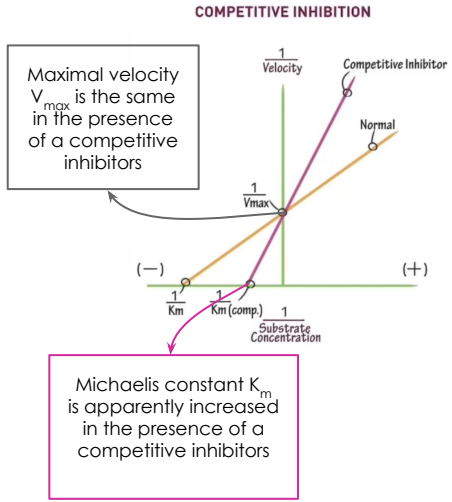
- K_i is a measure of the affinity of inhibition for enzyme .
- Also called dissociation constant .
- 435 Note: **Affinity** is the tendency of a molecule to associate with another.

Competitive inhibition

- The inhibitor is a structural analogue that competes with the substrate for binding at the active site of enzyme.
- **Two equilibria are possible**:

  1. E + S ⇌ ES complex → Product (active).
  2. E+I ⇌ EI (inactive)

- E: Enzyme , S: Substrate , ES Complex: Substrate binded to an enzyme , Vmax: Highest point of velocity in a ES Complex reaction .
- In competitive inhibition, V_{max}→unchanged in the presence and the absence of inhibitor .
- The value of K_m→ increased because S and I compete for the same active site .
- A higher substrate concentration is required to saturate the enzymes and to reach half-maximum velocity .
- The enzyme can bind to the substrate or the inhibitor, it depends on which one has more affinity to the enzyme .

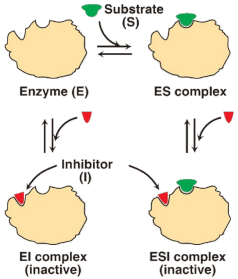


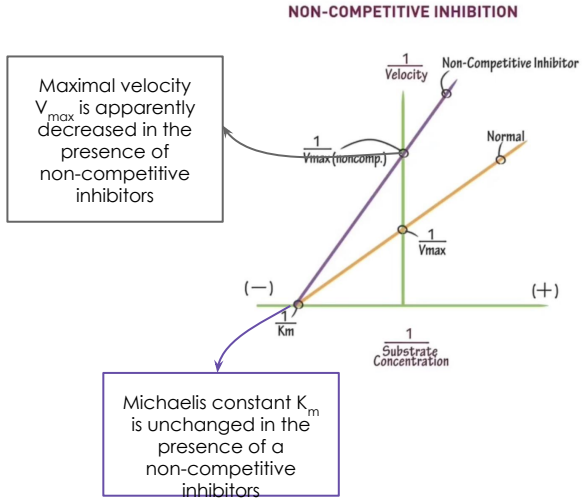
Competitive inhibition

- The inhibitor binds to the enzyme at a site away from the substrate binding site "Allosteric site" .
- To understand what does **allosteric site** mean imagine that you want to take something (inhibit) from your friend's hand but instead of taking it directly from his/her hand (active site) you twist his or her other hand and he or she will be forced to give you the object you're trying to obtain (inhibiting the enzyme) .
- The inhibitor does not have structural similarity to the substrate .
- No competition exists between the substrate and the inhibitor .
- **The inhibitor can bind to a free enzyme or to an enzyme-substrate complex** (In both cases the complex is catalytically inactive).

  1. ES+I ⇌ ESI (inactive) .
  2. E+I ⇌ EI (inactive) .

- The value of V_{max} → decreased by the inhibitor .
  But
- K_m → Unchanged because the affinity of Substrate (S) for the enzyme (E) is unchanged .
- K_m doesn't change in Non-competitive inhibition because the inhibitor is not competing with the substrate .



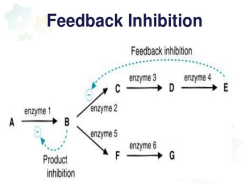


Regulation of enzyme activity

- Regulatory enzymes usually catalyze the first or an early reaction in a metabolic pathway so it regulate metabolic activities .
- They catalyze a rate limiting reaction that controls the overall pathway .
- They may also catalyze a reaction unique " specific " to that pathway known as committed step .
- Enzymes control the overall pathway by utilizing or giving energy .

Feedback inhibitions

- When the end-product of a metabolic pathway exceeds its conc. limit, it inhibits the regulatory enzyme to normalize the pathway .
- Cells use feedback inhibition to slow down the production, conserve energy and to maintain a state of homeostasis.



Feedback activation

- When the end-product of a metabolic pathway is below its conc. limit, it activates the regulatory enzyme to normalize the pathway .

Types of regulation
" 1- Allosteric regulation "

- The enzymes in metabolic pathways whose activities can be regulated by certain compounds (ligands) that bind to enzyme other than the catalytic site (we call it regulatory site) are known as **allosteric enzymes** .
- The term " allosteric" came from the Greek word " allos " meaning "other".
- Most allosteric enzymes are oligomers (two or more polypeptide chains or subunits).
- The subunits are known as protomers .

  If you forgot what oligomers mean, go back to protein structure lecture , we're kidding, here you go!:
  - A multi subunit protein is called oligomer. (An oligomer usually refers to a macromolecular complex).
  - Composed of a_2 β_2 subunits (4 subunits).
  - Two same subunits are called protomers. (a protomer is the structural unit of an oligomeric protein).
- Effect of a modulator (the effect of aligand) may be :
  1. Positive (Activation) : increased E (enzyme) , S (substrate) affinity .
  2. Negative (inhibition) : decreased E (enzyme), S (substrate) affinity .

Types of interactions in Allosteric enzymes

- **Homotropic** — Effect of one ligand on the binding of a different ligand
- **Heterotropic** — Effect of one ligand on the binding of the same ligand .
  - It's A regulatory enzyme controlled by its own substrate.

Types of regulation
" cooperative regulation "

A helpful video

- The process by which binding of a ligand to the regulatory site affects the binding of the same or of another ligand to the enzyme is known as cooperative binding .
  - The term " Cooperative" means working together (helping).
  - The regulatory site; is a site other than the active site where regulatory ligands "molecules" binds to .
- Binding of an allosteric modulator causes a change in the conformation of the enzyme .
- This causes a change in the binding affinity of enzyme for the substrate e.g. Hemoglobin .

Enzymes diagnosis & prognosis of the disease

- The most commonly used body fluids for measuring enzyme activity are serum and plasma
  There are:

1. Plasma-specific enzymes (Present in the blood) .
2. Non Plasma-specific enzymes .

- Enzymes are used clinically in three ways:

1. **Therapeutic Agents**
2. **Analytical reagents**
   - in measuring activity of other enzymes or compounds in body fluids.
3. **As indicators of enzyme activity or conc. in body fluids**
   - (serum, urine) in the diagnosis or prognosis of diseases

- Serum markers in the diagnosis of diseases:
  - Heart disease (troponin T and I), Pancreatic diseases (Lipase and amylase), Liver diseases (ALT & AST).

Take home messages

- Enzymes are essential for all biochemical reactions in the body .
- A number of diseases are treated by inhibiting specific enzymes .
- Many enzymes are used as biomarkers for diagnosis of diseases .

Quiz

Q1 : Which one of the following type of inhibitors requires more substrate to reach ½ V_{max} ?			
A) Competitive	B) Non-competitive	C) None of them	D) All of them
Q2 : What happens to V_{max} in the case of Non-competitive inhibition ?			
A) Decreases	B) Increases	C) Stays the same	D) All of them
Q3 : Most allosteric enzymes are :			
A) Monomers	B) Protomers	C) Oligomers	D) Enantiomers
Q4 : Where do ligands bind ?			
A) Active site	B) Regulatory site	C) None of them	D) All of them
Q5 : What does positive modulator do ?			
A) increase E , S affinity	B) decrease E , S affinity	C) doesn't Change E , S affinity	D) None of them
Q6 : Regulatory enzymes are :			
A) always activated	B) always inhibited	C) modulated	D) None of them

SAQs :

Q1: Enumerate the uses of enzymes in the diagnosis and prognosis of diseases .

Q2: What happens to K_m in case of competitive inhibitions ?

★ **MCQs Answer key:**

1) A 2) A 3) C 4) B 5) A 6) C

★ **SAQs Answer key:**

1) 1. Therapeutic Agents
   2. analytical reagents
   3. indicators of enzyme activity

2) Increase

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Do something today
that your future self
will thank you for

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