Lecture 8

# Enzymes and Coenzymes II

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Editing File

Biochemistry
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MED 442

# Objectives

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

## Enzyme inhibition

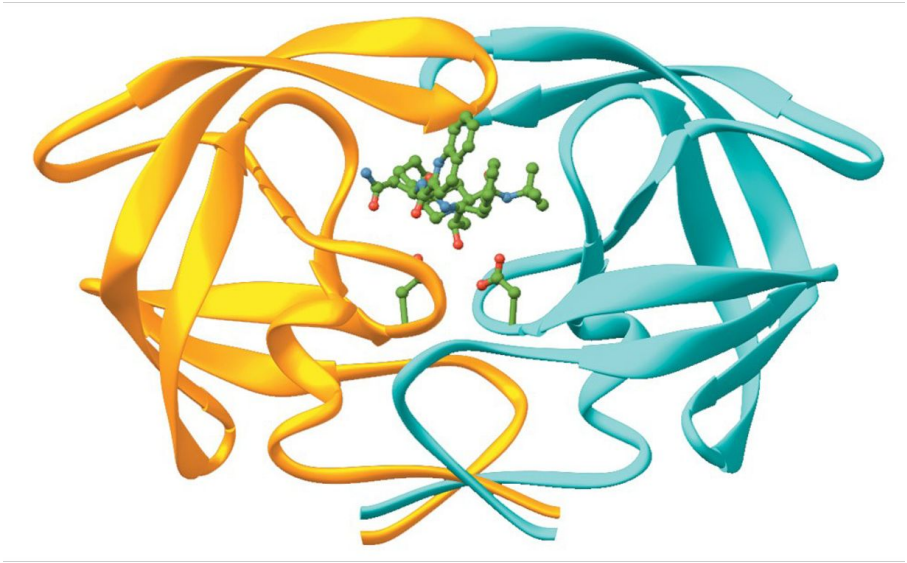
- Inhibition is a process by which the enzyme activity is regulated or controlled or stopped.
- To inhibit means to stop enzyme activity. (the inhibition might be 100% or partial).

## $K_i$ (inhibitor constant)

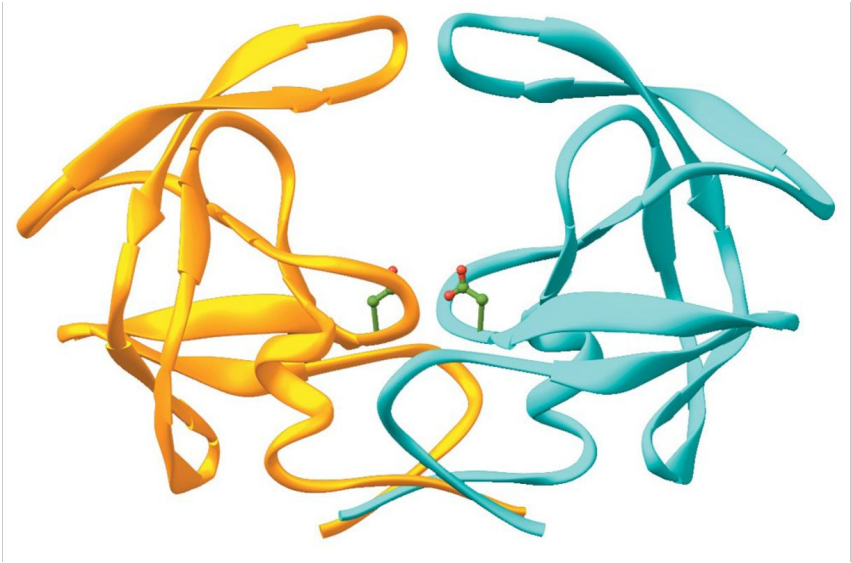
- Ki is a measure of the **affinity** of the inhibitor for the enzyme. (how potent an inhibitor is)

- Also known as dissociation constant.

Affinity means our lecture: attraction. here we mean the attraction of the substrate for the enzyme.



An enzyme with inhibitor



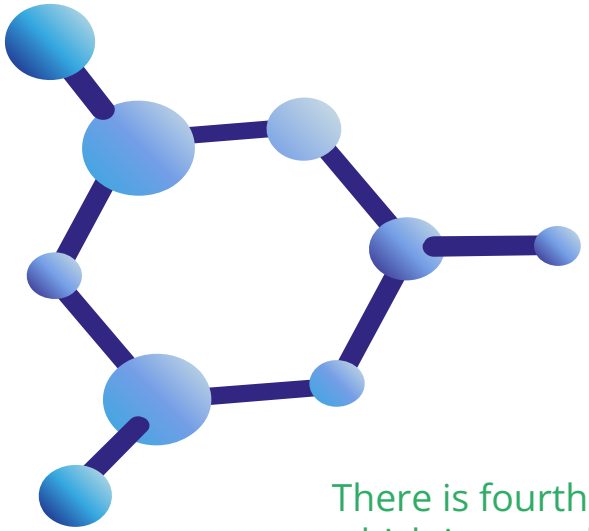
An enzyme without inhibitor

# Enzyme inhibition

Competitive

Our lecture

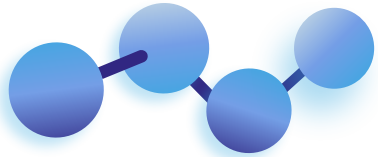
Noncompetitive



Uncompetitive

There is fourth type called mixed type which is a combination of these types (at least two types).

# 1- Competitive inhibition



1/ The inhibitor is a structural analogue (similar) that competes with the substrate for binding at the active site of enzyme .

2/ Two equilibria (reactions) are possible:

$E + S \rightleftharpoons ES \rightarrow E + P$

$E + I \rightleftharpoons EI$ (nothing happened , no product formation)

E: enzyme, S: substrate, ES: enzyme-substrate complex. P: product.

3/ In competitive inhibition, **Vmax** is **unchanged** in the presence and the absence of Inhibitor. Vmax: Highest point of velocity in a ES Complex reaction

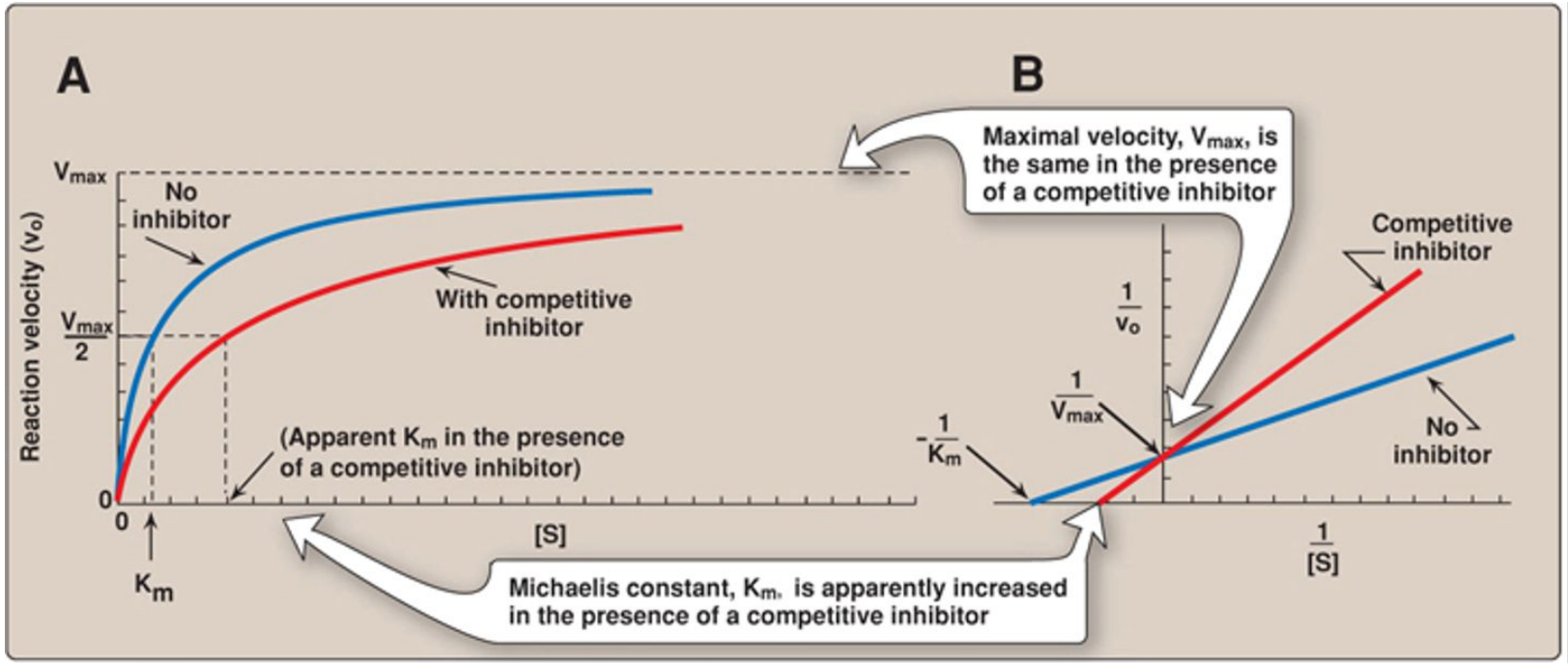
4/ The value of **Km** is **increased** because substrate and inhibitor compete for binding at the same site (active site) (increase Km =decreasing affinity ) (K = [S] required to saturate half of M all the active sites)

5/ A higher concentration of substrate [S] is required to achieve ½ Vmax.

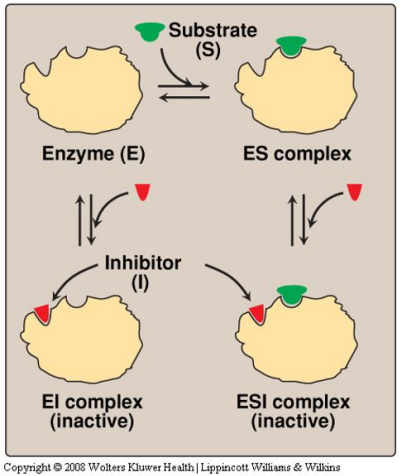
Enzyme can bind to substrate or the inhibitor, it depends on which one has more affinity to the enzyme .

helpful video

# Competitive inhibition



# 2- Noncompetitive inhibition





The inhibitor does not have structural similarity to the substrate.

The inhibitor binds to the enzyme at a site away from the substrate binding site (Allosteric site)

No competition exists between the inhibitor and the substrate.

The inhibitor can bind to a free enzyme or to an enzyme-substrate complex.
(In both cases the complex is catalytically inactive).
ES + I ⟷ ESI (inactive) & E + I ⟷ EI (inactive)

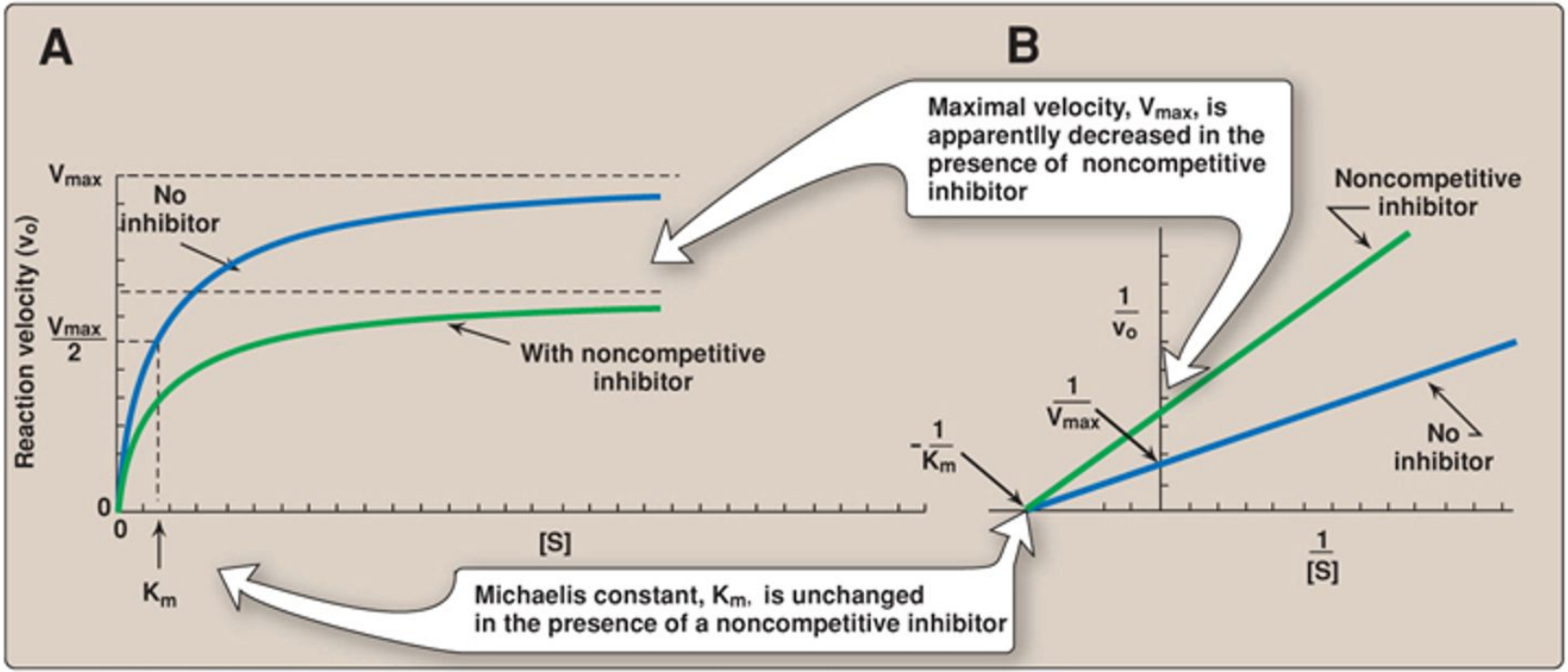
Helpful video

The value of **Vmax** is **decreased** by the inhibitor

**Km** is **unchanged** because the affinity of S for E is unchanged. (because m substrate and inhibitor aren't competing for the same sitme).

when the noncompetitive inhibitor bind to the allosteric site it will change the shape of the active site which will prevent the substrate from binding. ( it can control the active site positively or negatively). Med441

# NonCompetitive inhibition



# Regulation of enzyme activity

Regulatory (regulation can be activating or inhibiting ) enzymes usually catalyze the first or an early reaction in a metabolic pathway, (The earliest it's stopped the best)

They catalyze a rate limiting reaction (the most important reaction) that controls the overall pathway. (It requires energy )

They may also catalyze a reaction unique to that pathway known as committed step. Enzymes control the overall pathway by utilizing or giving energy . Med439

# Regulation of enzyme activity

| Feedback inhibition (Negative) | Feed positive activation |
|---|---|
| When the end product of a metabolic pathway **exceeds** its concentration limit | When the end product of a metabolic pathway is **below** its concentration limit |
| It **inhibits** the regulatory enzyme to normalize the pathway. | It **activates** 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.
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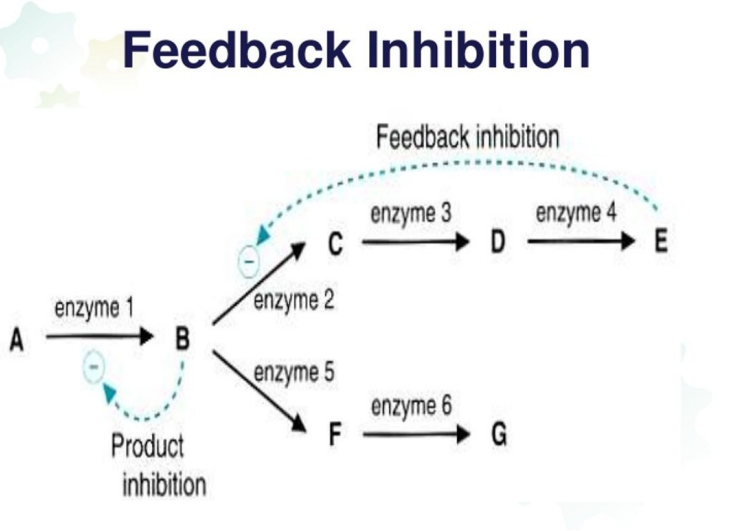



e.g. If you have enough of **product E** you can't stop enzyme 1 because you will affect **enzyme 5** so the first committed step is stopping **enzyme 2 .**

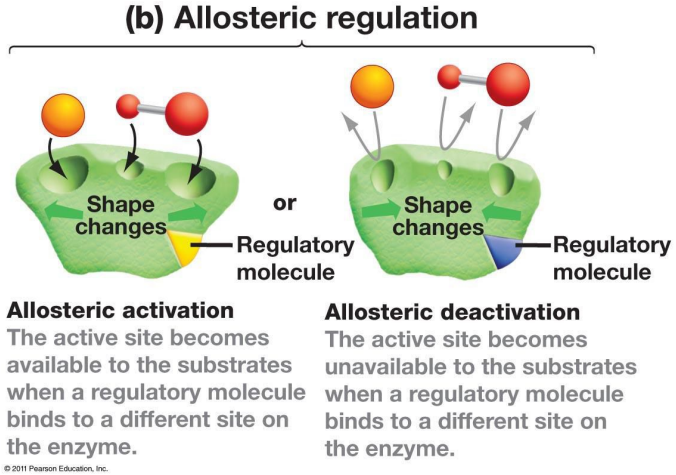
# Types of regulation

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).

## Allosteric

The regulatory sites are called "Allosteric sites"
The regulatory molecules are not the same as the catalyzed substrates.
-binding of an allosteric modulator causes conformational changes in the enzyme.
-this causes a change in binding affinity of the enzyme for the substrate.

Effect of a modulator (the effect of a ligand) may be : 1. Positive (Activation) : increased enzyme & substrate affinity .
2. Negative (inhibition) : decreased enzyme & substrate affinity.




## Cooperative

Binding of a ligand to a regulatory site affects binding of the same or of another ligand to the enzyme.

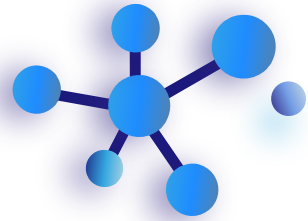
# Allosteric enzymes effects

There are two types of interactions occur in allosteric enzymes:

Homotropic: Effect of one ligand on the binding of the same ligand (A regulatory enzyme controlled by its own Substrate)

Heterotropic: Effect of one ligand on the binding of a different ligand

# Enzymes diagnosis and 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 .

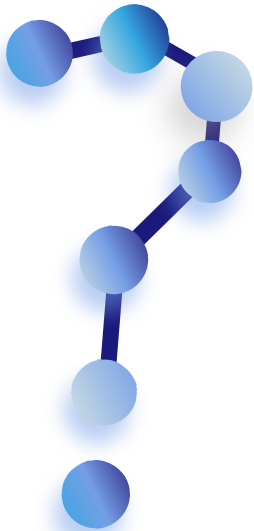
- Enzymes are used clinically in three ways:
  1. Therapeutic Agents
  2. Analytical reagents “Measuring the activity of other enzymes or compounds in body fluids”.
  3. As indicators of enzyme activity or conc. in body fluids “(serum, urine) in the diagnosis or prognosis of diseases”

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

# Quiz

| Q1- Enzymes in metabolic pathways are regulated by certain compounds called: | | | |
|---|---|---|---|
| a) ligands | b) protomere | c) allosterase | d) phosphate |
| **Q2- In non-competitive inhibition the km is:** | | | |
| a) decreased | b) increased | c) eliminated | d) unchanged |
| **Q3- Ki is a measure of the :** | | | |
| a) efficacy | b) affinity | c) speed | d) diverge |
| **Q4- Which of these mechanisms increase the km :** | | | |
| a) competitive inhibition | b) competitive activation | c) non-competitive inhibition | d) non-competitive activation |
| **Q5- Feedback inhibition ..... the regulatory enzyme to normalize the pathway :** | | | |
| a) activates | b) inhibits | c) speeds up | d) initiates |

1a - 2d - 3b - 4a - 5b



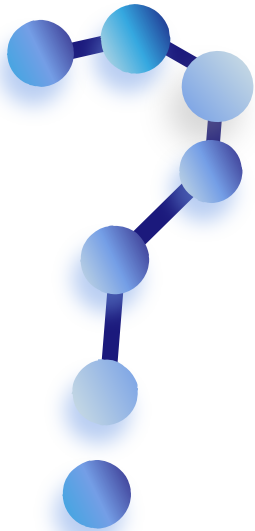
# Quiz

Q6- enzymes could be beneficial in the clinical use such as :
*1- therapeutic agent 2- analytical reagent 3- indicator of enzyme activity*

Q7- in allosteric regulation the ligand bind to :
*Allosteric site*

Q8-What are the most commonly used body fluids for measuring enzymes activity?
*serum & plasma*

Q9-in which regulatory mechanism is the inhibitor a structural analogue that competes with the substrate?
*Competitive inhibition*



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E4
D2