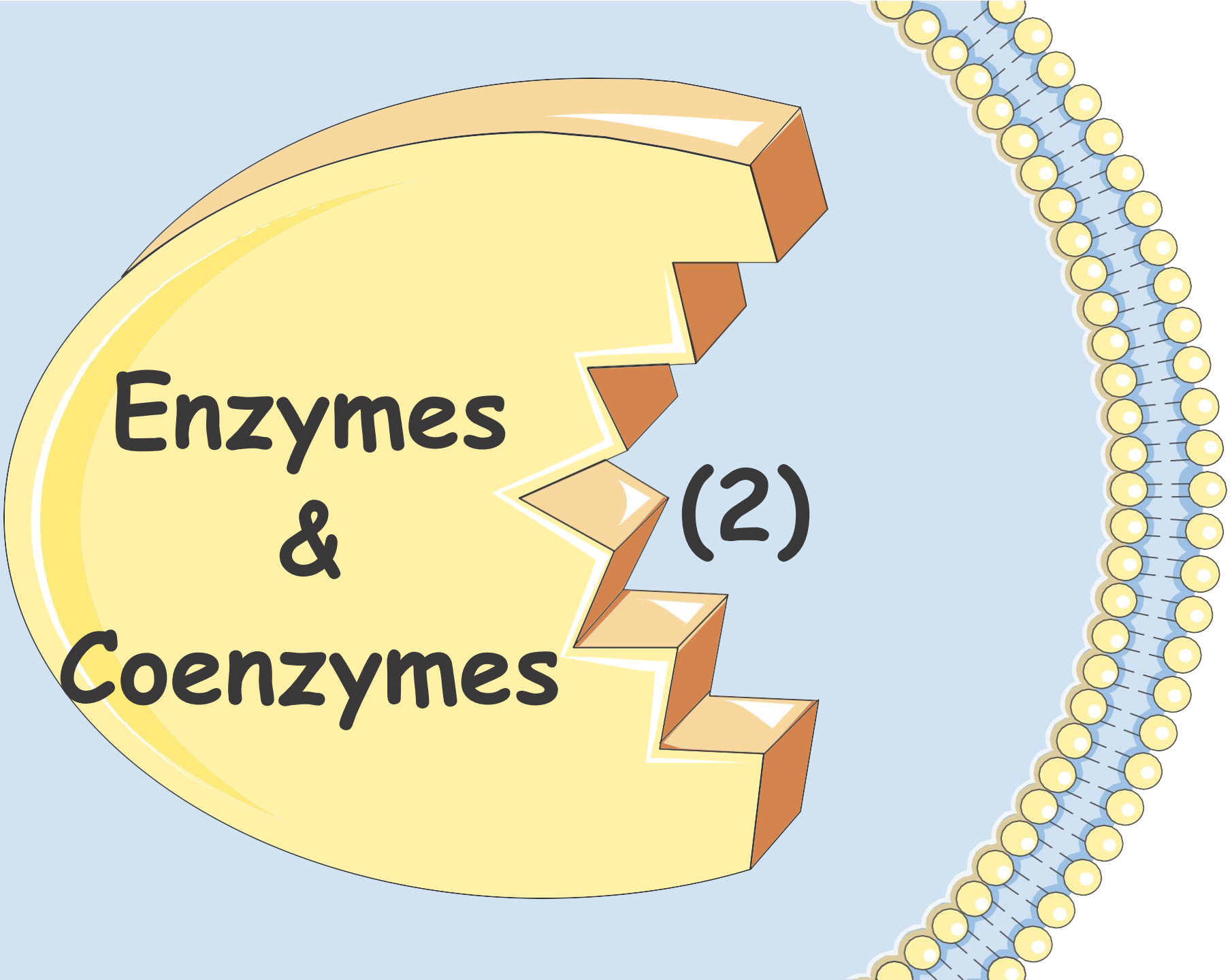
Enzymes & Coenzymes (2)



MED441
KING SAUD UNIVERSITY

8
V1

Foundation Block - KSU

Revised & Reviewed by:
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Color Index:

- Main text
- Important
- Notes
- Boys slides'
- Girls slides'
- Extra

Editing File

Objectives

- Understand the enzyme kinetics, types of inhibition and regulation of enzyme activity.

- Discuss the clinical role enzymes in the diagnosis of diseases.

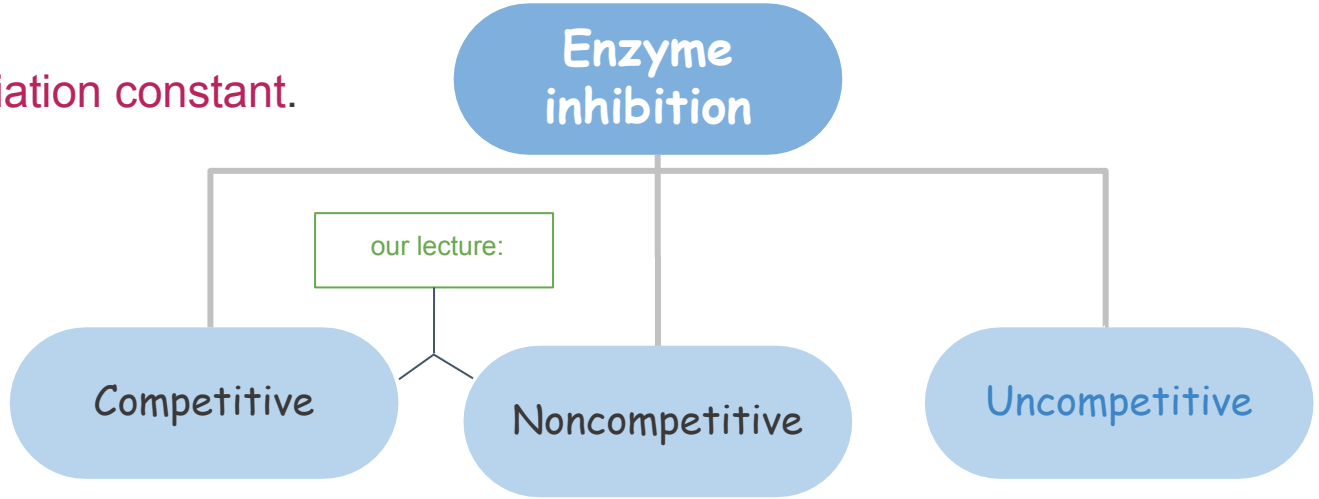
Enzyme inhibition

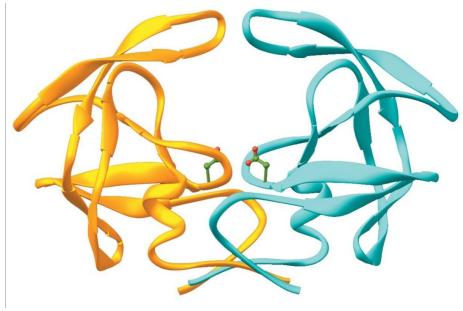
- **Inhibition** is a process by which the enzyme activity is regulated or controlled or stopped.
- To inhibit means to stop enzyme activity. (the inhibition might be 100% or partial).

K_i (inhibitor constant)

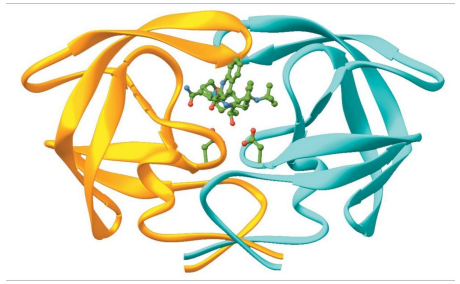
- K_i is a measure of the **affinity** of the inhibitor for the enzyme. (how potent an inhibitor is)
- Also known as dissociation constant.

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





An enzyme without inhibitor



An enzyme with inhibitor

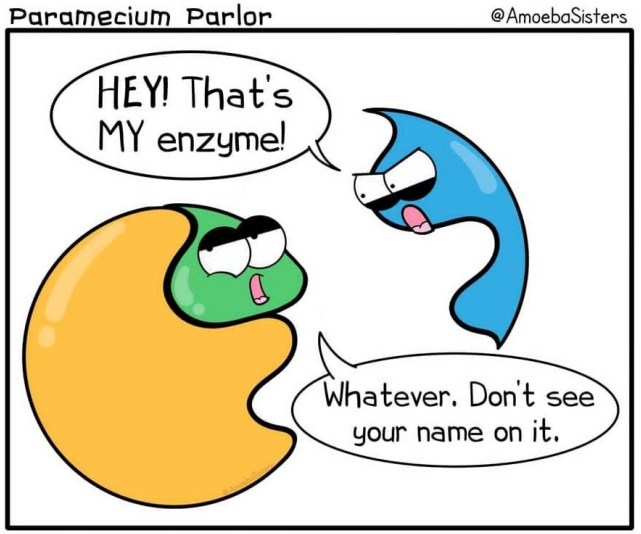
-There is fourth type called mixed type which is a combination of these types (at least two types).

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.



Helpful video

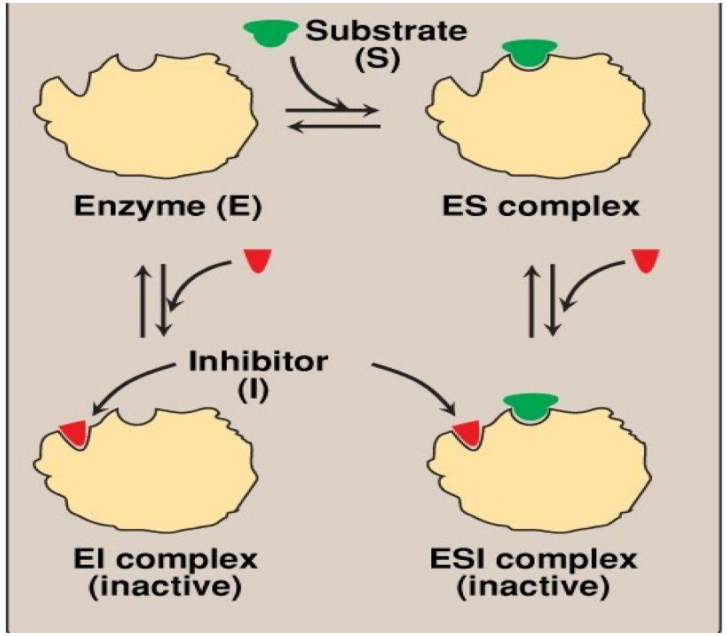
3. In competitive inhibition, V_{max} is unchanged in the presence and the absence of inhibitor. Vmax: Highest point of velocity in a ES Complex reaction

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

5. A higher [S] is required to achieve ½ V_{max}.

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

2- Noncompetitive inhibition



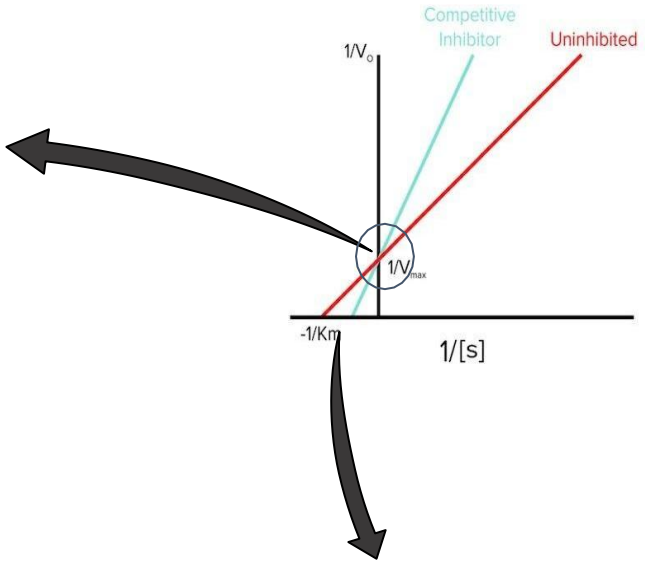
- The inhibitor does not have structural similarity to the substrate.
- The inhibitor binds to the enzyme at a site away from the substrate binding site (Allosteric site)
- No competition exists between the inhibitor and the substrate.
- The inhibitor can bind to a free enzyme or to an enzyme-substrate complex. (In both cases the complex is catalytically inactive).
  ES + I ⟷ ESI (inactive) & E + I ⟷ EI (inactive)
- The value of V_{max} is **decreased** by the inhibitor
- K_m is **unchanged** because the affinity of S for E is unchanged. (because 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)

Helpful video

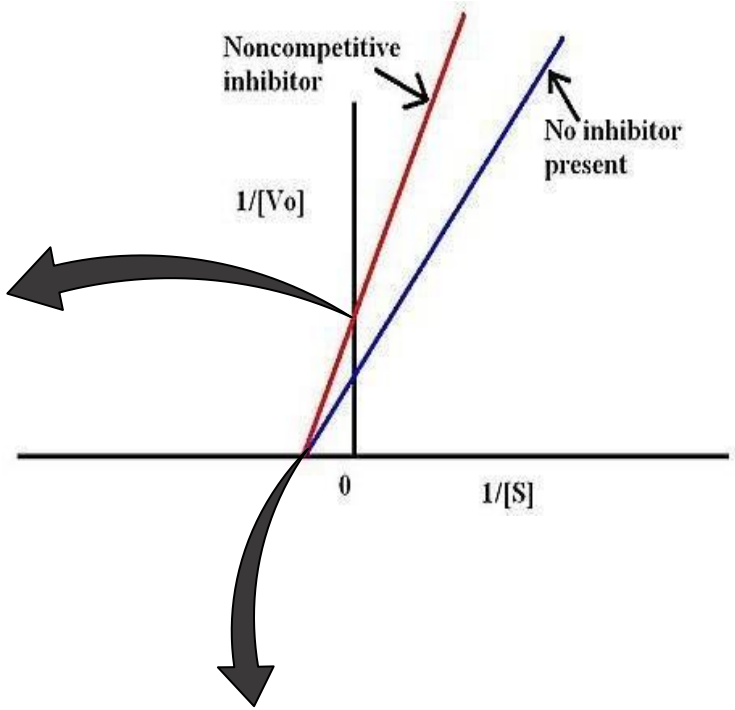
Competitive and NonCompetitive inhibition

Maximal velocity Vmax is the same in the presence of a competitive inhibitors



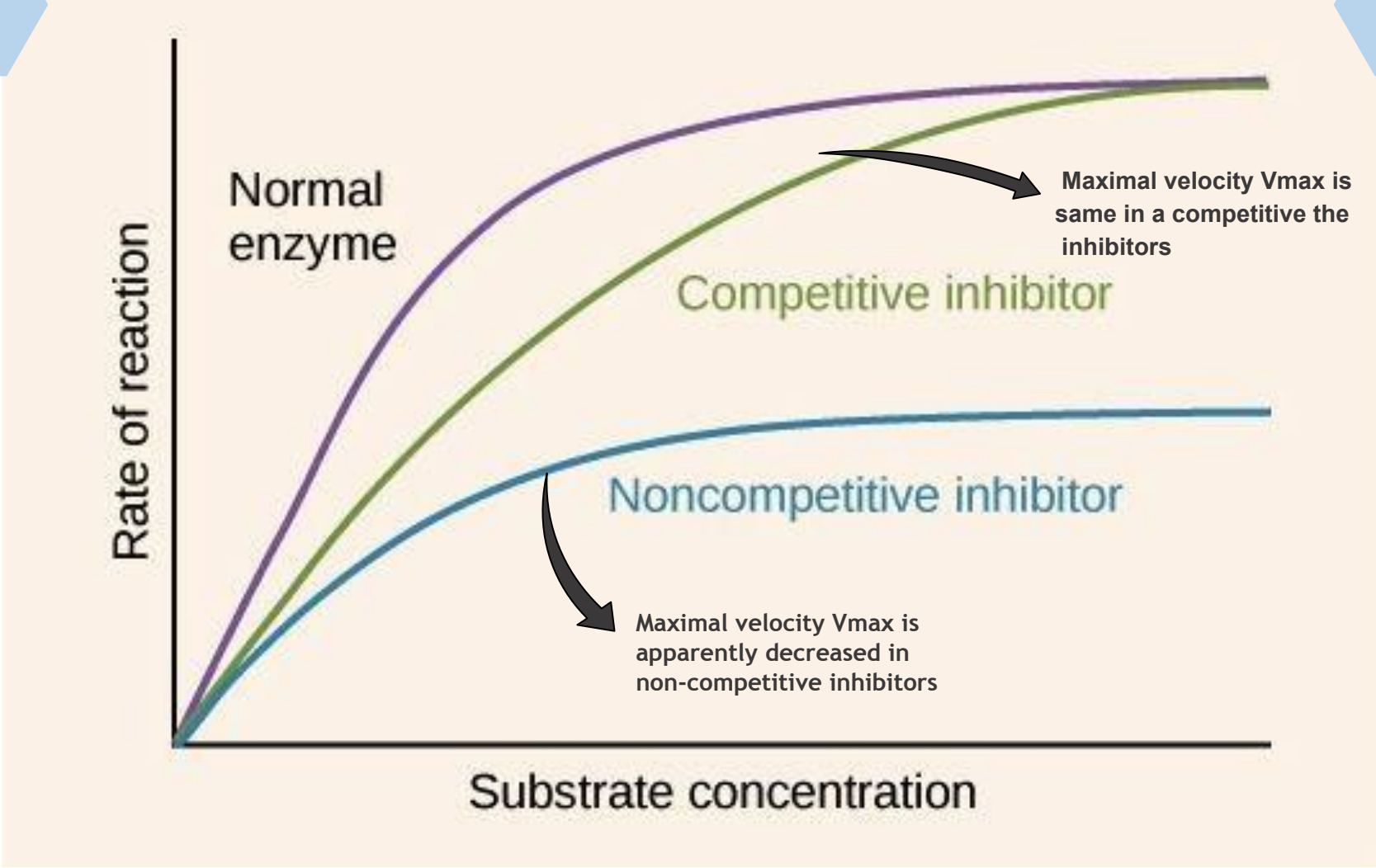
Michaelis constant Km is apparently increased in the presence of a competitive inhibitors

Maximal velocity Vmax is apparently decreased in the presence of non-competitive inhibitors



Michaelis constant Km is unchanged in the presence of a non-competitive inhibitors

Competitive and NonCompetitive inhibitors

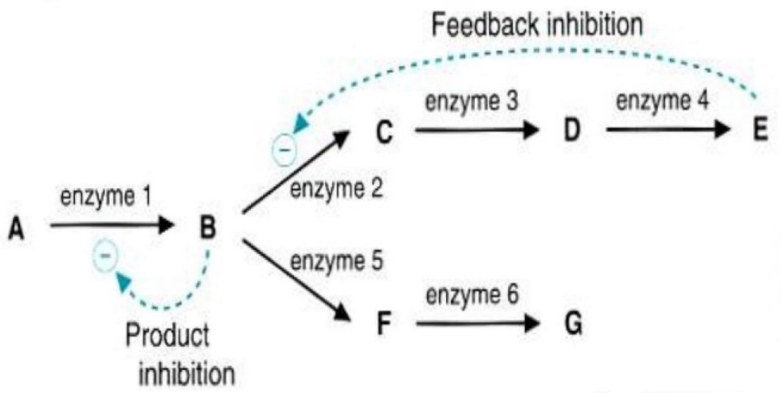


Regulation of enzyme activity

- 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

Feedback Inhibition



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**

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.

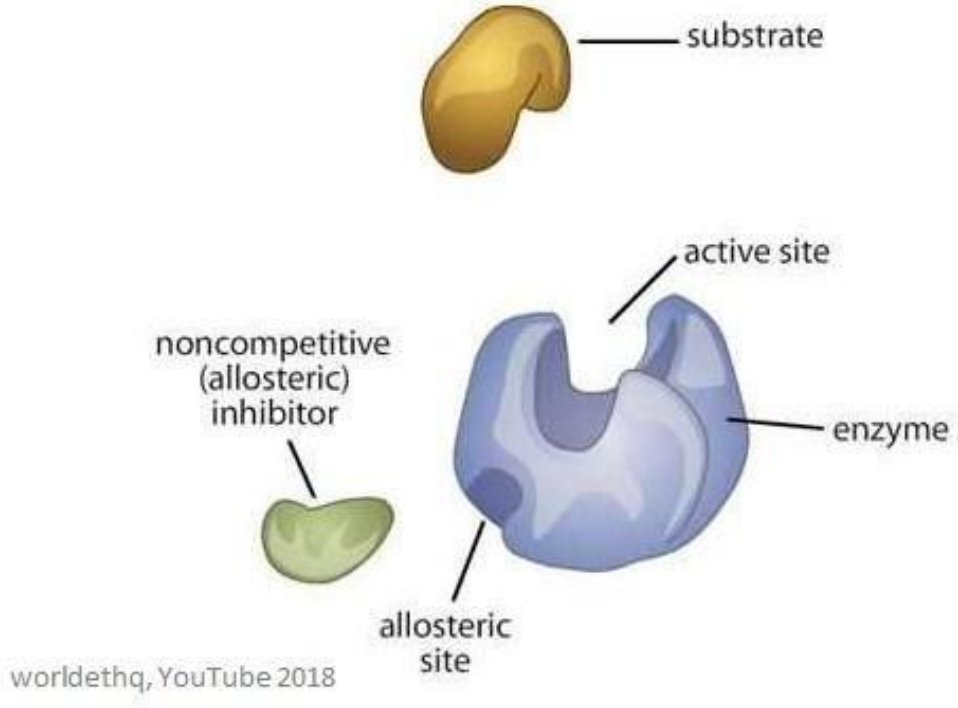
Cells use feedback inhibition to slow down the production, conserve energy and to maintain a state of homeostasis. Med439

Types Of enzyme Regulation:

Helpful Video until 1:12 min

Allosteric regulation: (Non-Competitive)

- Enzymes in metabolic pathways are regulated by certain chemical compounds called Ligands
- These ligands **don't** bind to the active site
- They bind to other site (regulatory / **allosteric** site) on the enzyme (allosteric enzyme)
- The term "**allos**teric" came from Greek word "**allos**" meaning "**other**"
- Most allosteric enzymes are oligomers (two or more polypeptide chains or subunits)
- The subunits are known as protomers

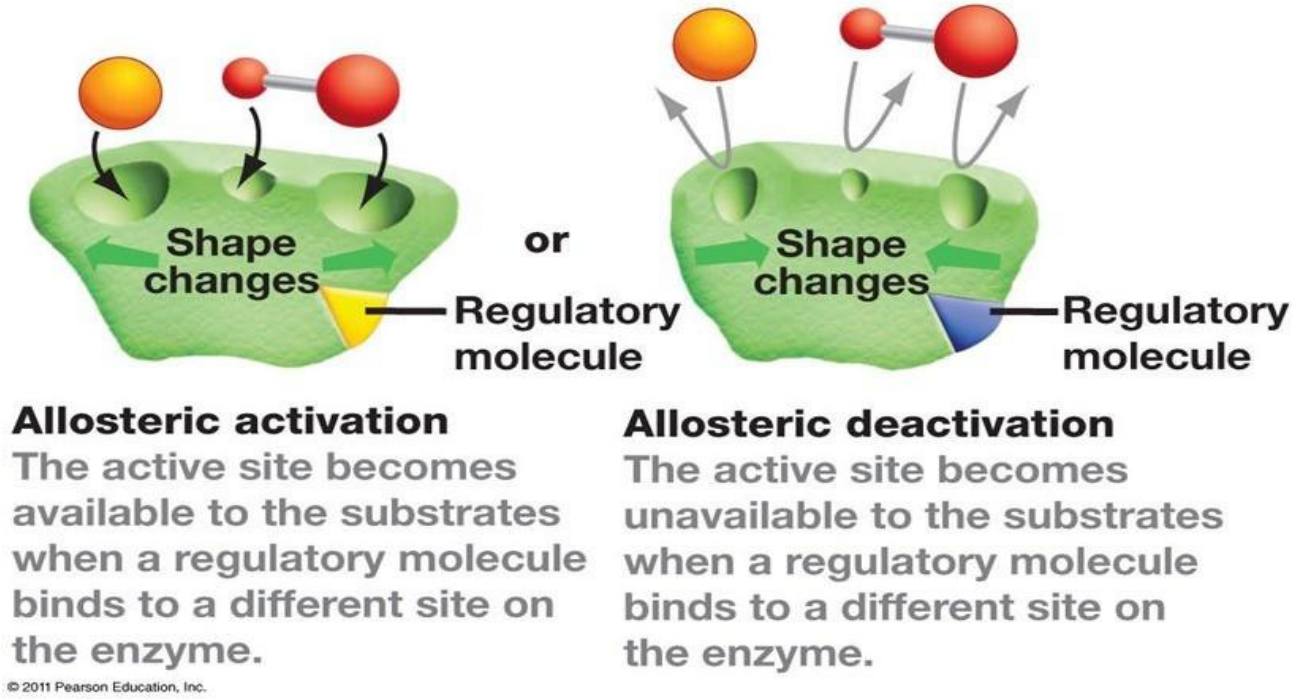


Helpful Video

Allosteric regulation cont...

Cooperative binding:

- The process by which binding of a ligand to a regulatory site affects binding of the same or of another ligand to the enzyme
- 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

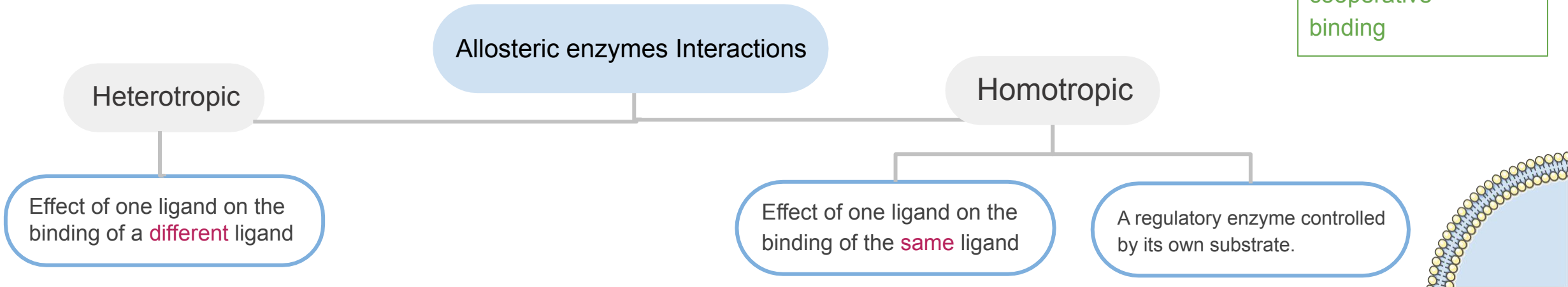


- The effect of a modulator (ligand) can be:

1- +ve (activation) increased E & S affinity

2- -ve (inhibition) decreased E & S affinity

- this type of binding called cooperative binding



Enzymatic Diagnosis and Prognosis of Diseases

- Enzymes are used clinically in three ways:
  - **As therapeutic** agents
  - **As analytical** reagent in measuring activity of other enzymes or compounds of body fluid.
  - **As indicators** of enzyme activity or concentration in body fluids: e.g. serum, urine in the diagnosis or prognosis of diseases

- Serum and Plasma are the most commonly used body fluids for measuring enzyme activity

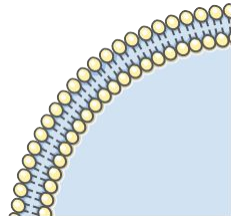
- There are:

- Plasma-specific enzymes
- Non-plasma-specific enzymes

- Serum markers in the diagnosis of Heart, **Pancreatic**, Liver diseases. (Measuring enzyme can help us in diagnosing a lot of diseases)

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: binding of a ligand to a regulatory site affects binding of the same or of another ligand to the enzyme. this binding is called ?

A	Cooperative binding	B	allosteric binding	C	Both B and C	D	None of them

Q2:known as dissociation constant :

A	K_m	B	V_{max}	C	K_i	D	Competitive inhibition

Q3: The effect of negative modulator :

A	Increase E,S affinity	B	Decrease E,S affinity	C	Both	D	Doesn't affect the affinity

Q4:In competitive inhibition, V_{max} is :

A	increased	B	unchanged	C	decreased	D	changed

Q5: Which of these mechanism that doesn't doesn't affect K_m? :

A	competitive inhibition	B	competitive activation	C	noncompetitive inhibition	D	A and C

Answer Key: 1) A 2) C 3) B 4) B 5) C

Q6: What are the most commonly used body fluids for measuring enzymes activity?

Q7: Which type of feedbacks occurs when the end product of metabolic pathway is below it's conc.?

Q8:What happens to V_{max} in case of Noncompetitive inhibition?

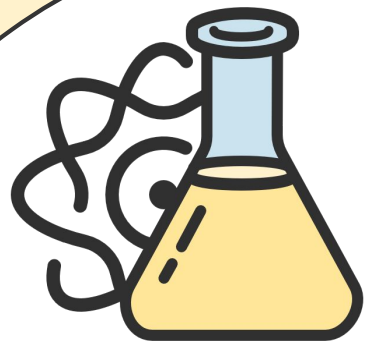
Q9: Catalyzing a reaction unique to the metabolic pathway known as?

A6:
Serum and Plasma

A7:
Feed positive activation

A8:
decreased

A9:
Committed step



Biochemistry 441

Girls

Boys

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Wareef Almousa
Joud Alangari
Fay Alluhaidan
Sarah Alhamlan
Arwa Almobeirek
Jumana AL-qahtani
Latifa Alkhdiri
Alanoud Alhaider
Futoon Almotairi
Manal Aldhirgham
Raaoum Jabor
Norah alawlah
Shahad Helmi
Rand Aldajani

Khalid Alhamdi - Leader

Ahmed Alayban
Sultan Alosaimi
Abdullah Alomran
Bassam Alghizzi
Ibrahim Aljurayyan
Mohammed Almutairi
Turki Alkhalifa
Malik Alshaya
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