Enzyme Inhibition

Biochemistry team

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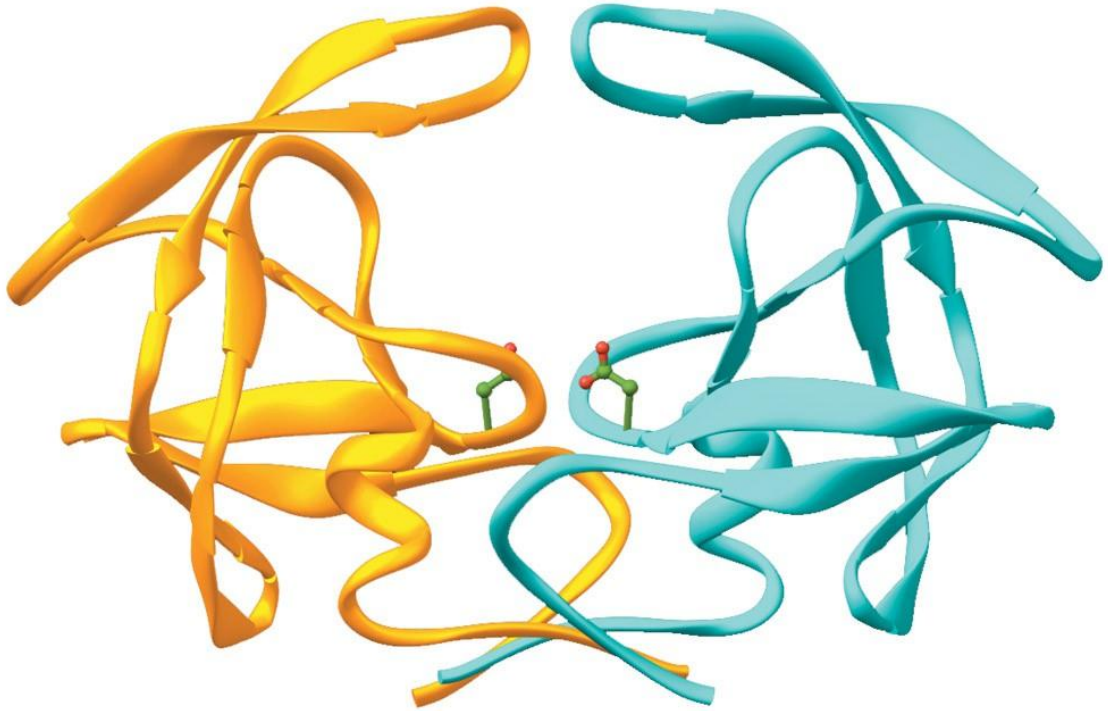
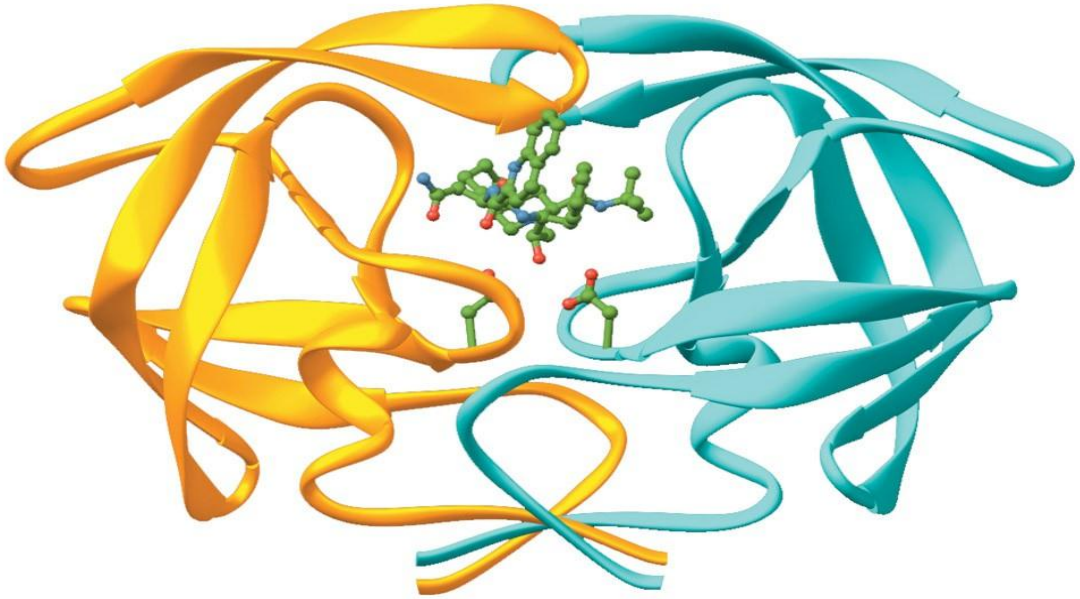
- Inhibition is a process by which the enzyme activity is regulated or controlled or stopped

- To inhibit means to stop enzyme activity

An enzyme without inhibitor



An enzyme with inhibitor



Ki (Inhibitor constant)

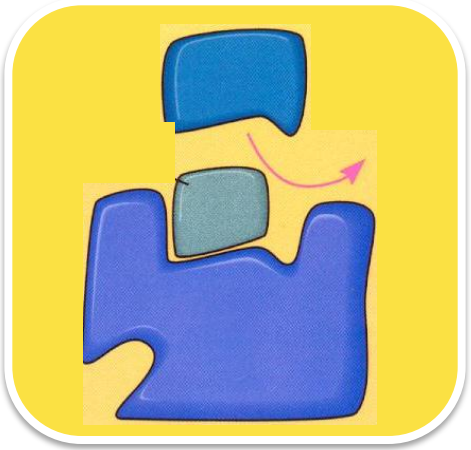
- **K_i** is a measure of the affinity of inhibitor for enzyme
- Also called **dissociation constant**

There are three types of enzyme inhibition:

1) Competitive
2) Noncompetitive
3) Uncompetitive
ماهو مطلوب

Enzyme inhibition

Competitive



Noncompetitive

Competitive inhibition

Km is increased
Vmax is unchanged

- The inhibitor is a structural analogue (similar) that competes with the substrate for binding to the active site of enzyme.
- Two reactions are possible:

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

and

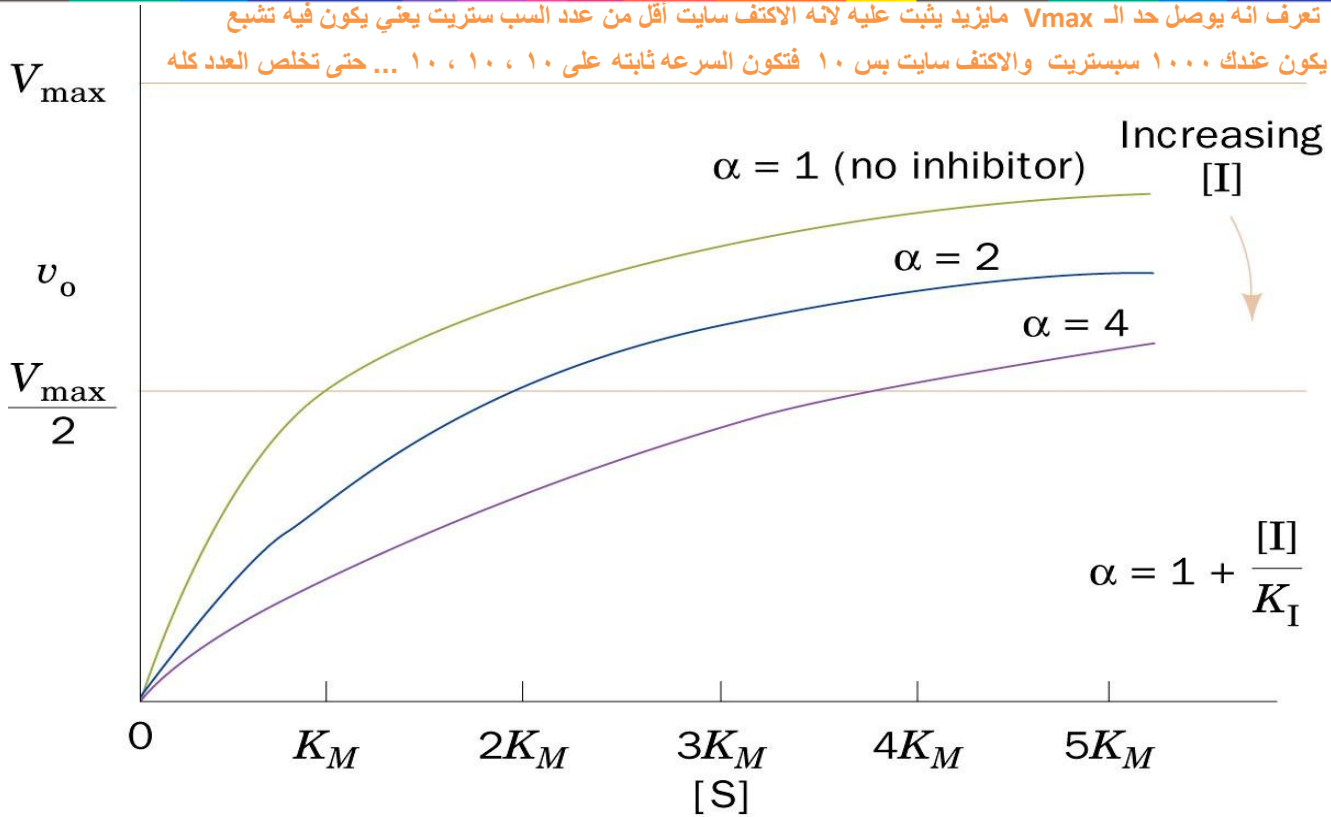
$$E + I \leftrightarrow EI$$

S = Substrate
E = Enzyme
P = Product
I = inhibitor

Competitive inhibition

فهم فقط .. Km , Vmax
تعرف الكيرف يمثل علاقة بين ايش وايش ،،

تعرف انه يوصل حد الـ Vmax مايزيد يثبت عليه لانه الاكتف سايت أقل من عدد السب ستريت يعني يكون فيه تشبع
مثال لما يكون عندك ١٠٠٠ سبستريت والاكتف سايت بس ١٠ فتكون السرعه ثابته على ١٠ ، ١٠ ، ١٠ ... حتى تخلص العدد كله



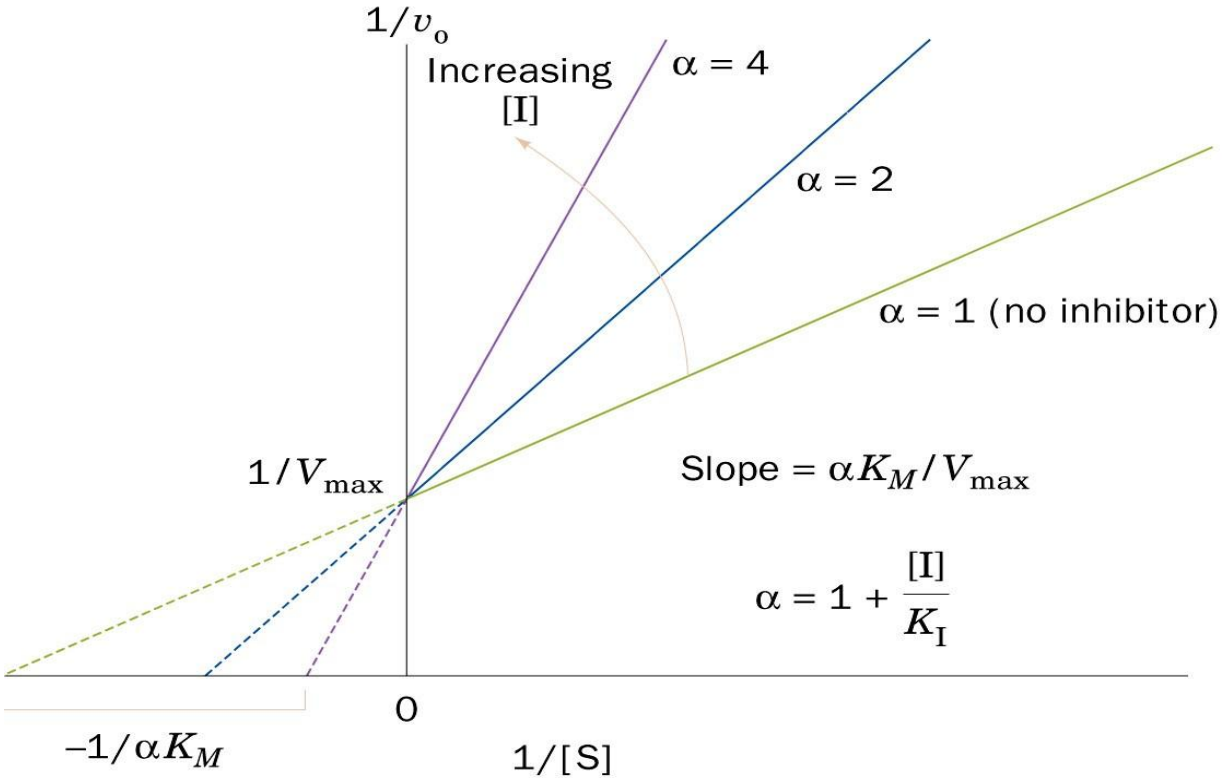
Vmax = is the maximum velocity or rate at which the enzyme catalyzes a reaction,

it happens when all enzyme active sites are saturated with substrate.

Km = The Substrate Concentration at half **V**max

[S] = Substrate Concentration

Lineweaver–Burk plot of the competitively inhibited Michaelis – Menten enzyme



Km 1 mmol
Km 2 mmol
Which one has the High affinity ?

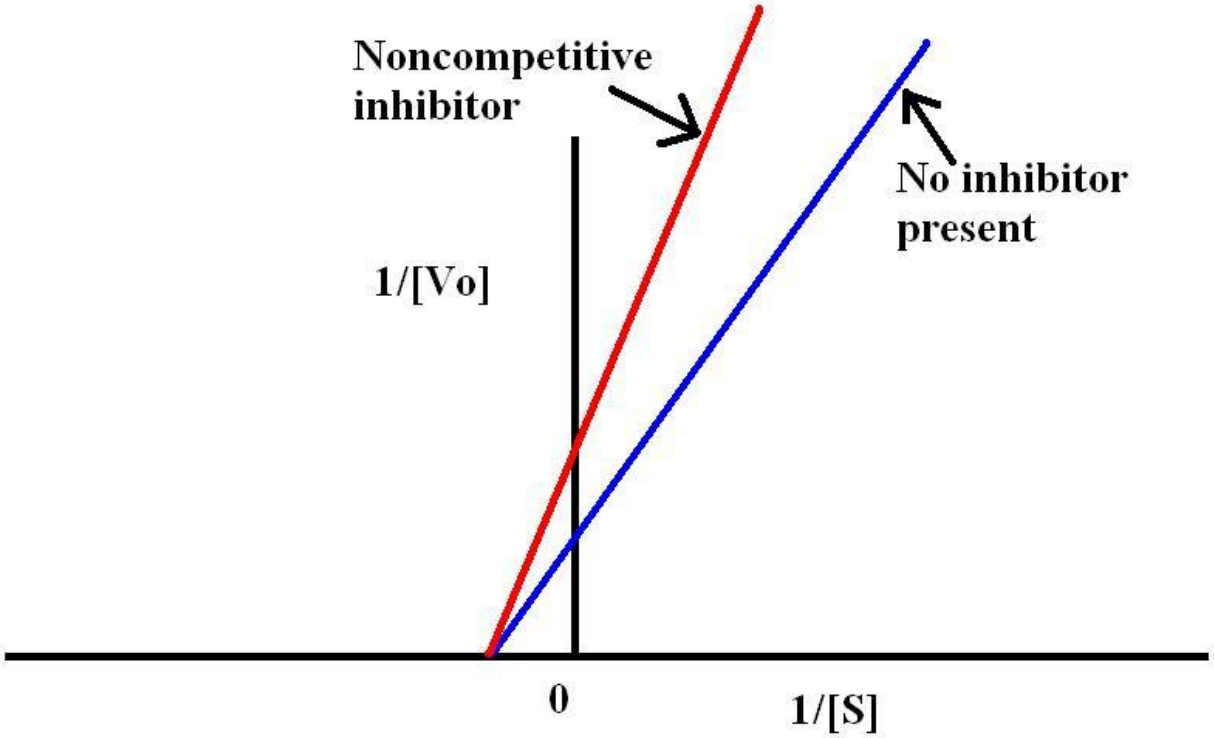
1 mmol has more affinity
The reason : less amount is required to saturate the enzyme

- In competitive inhibition, V_{max} is unchanged in the presence and the absence of inhibitor
- The value of K_m is increased because S and I compete for binding at the same site
- A higher [S] is required to achieve half-maximal velocity

Noncompetitive inhibition

Km is unchanged
Vmax is decreased

- 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
- 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


Noncompetitive inhibitor
No inhibitor present
1/[Vo]
0
1/[S]

$$ES + I \leftrightarrow ESI \text{ (inactive)}$$
$$E + I \leftrightarrow EI \text{ (inactive)}$$

- The value of V_{max} is decreased by the inhibitor
- K_m is unchanged because the affinity of S for E is unchanged

Regulation of enzyme activity

- Regulatory enzymes usually catalyze the first or an early reaction in a metabolic pathway
- They catalyze a rate limiting reaction that controls the overall pathway
- They may also catalyze a reaction unique to that pathway known as committed step

- **Feedback inhibition:** اذا زاد تركيز البرودكت فالجسم يحاول الانهبتور يرجع البرودكت لتركيزه الطبيعي

  When the end-product of a metabolic pathway exceeds its conc. limit, it inhibits the regulatory enzyme to normalize the pathway (feedback inhibition)

- **Feed positive activation:** اذا قل تركيز البرودكت فالجسم يحاول الانهبتور يرجع البرودكت لتركيزه الطبيعي

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

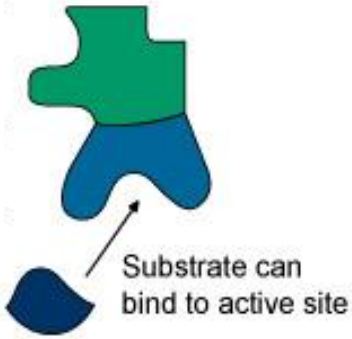
Types of regulation

- **Allosteric enzyme regulation**
  - Enzymes in metabolic pathways are regulated by certain compounds (ligand)
  - These ligands do not bind to active site
  - They bind to other site (regulatory site) on the enzyme **(allosteric enzymes)**
  - **The term "allosteric" came from Greek word "allos" meaning "other"**

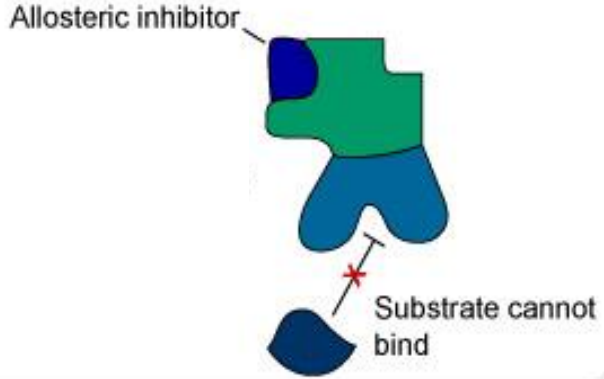
Types of regulation

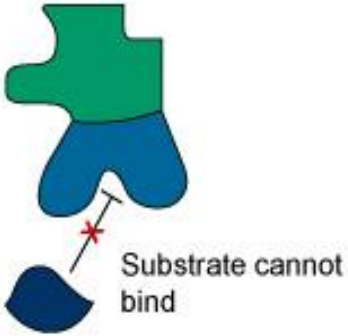
- **Cooperative binding**
  - Binding of a ligand to a regulatory site affects binding of the same or of another ligand to the enzyme
  - This is called **cooperative binding**

Allosteric Regulation

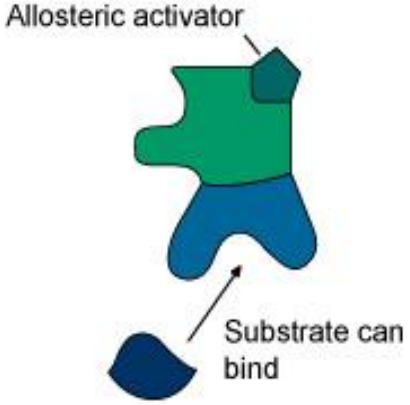


Negative





Positive



- **Binding of a ligand causes a change in the active site of enzyme**
  - This causes a change in the binding affinity of enzyme for the substrate

- **The effect of a ligand may be positive (activation) or negative (inhibition)**
  - Positive: increased E, S affinity
  - Negative decreased E, S affinity
- Most allosteric enzymes are oligomers (two or more polypeptide chains or subunits)
  - The subunits are known **as protomers**

- **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

Enzymatic diagnosis and prognosis of diseases

- **Enzymes are used clinically in three ways:**
  - As indicators of enzyme activity or conc. in body fluids (serum, urine) in the diagnosis/prognosis of diseases
  - As analytical reagents in measuring activity of other enzymes or compounds in body fluids
  - As therapeutic agents

Enzymatic diagnosis and prognosis of diseases

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

- **There are:**
  - Plasma-specific enzymes
  - Non plasma-specific enzymes

What body fluids are more commonly used to measure enzyme activity ?

-Plasma
-Serum

Serum markers in the diagnosis of diseases:

Heart disease

Pancreatic diseases

Liver diseases

الكبد لها انزيمات خاصه موجود فقط داخل الكبد فـ اذا لقيتها فالبلازما يعني الكبد فيها مشكله

Choose the correct answer ,,

1) A Competitive inhibitor of an enzyme :

The answer is A

a- increases Km without affecting Vmax
b- decrease Km without affecting Vmax
c- increases Vmax without affecting Km

2) The Km is :

The answer is C

a- numerically equal to 1/2 Vmax
b- independent of ph
c- numerically equal to the substrate concentration that gives half-maximal velocity