MED437
KING SAUD UNIVERSITY

BIO TEAM

Enzyme inhibition

Color index:

Doctors slides

Notes and explanations

Extra information

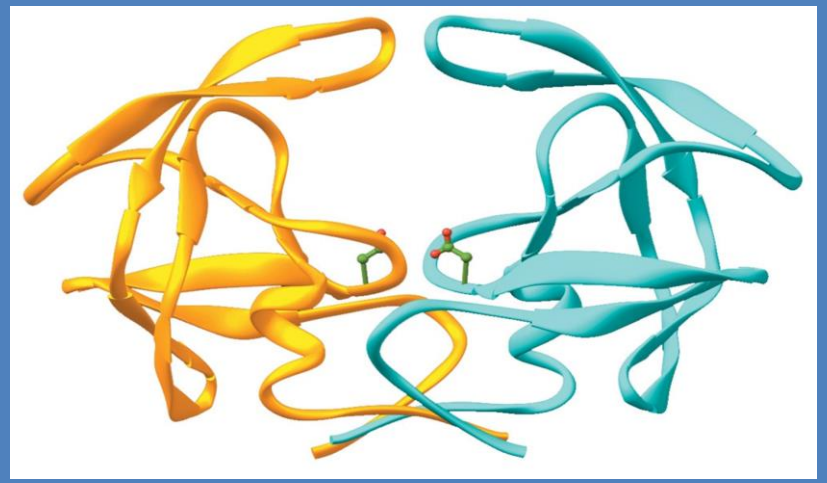
highlights

Inhibition is a process in which the enzyme activity is regulated or controlled or stopped.
- Ki (inhibitor constant) is a measure of the affinity of the inhibitor
for the enzyme. Also, known as dissociation constant.

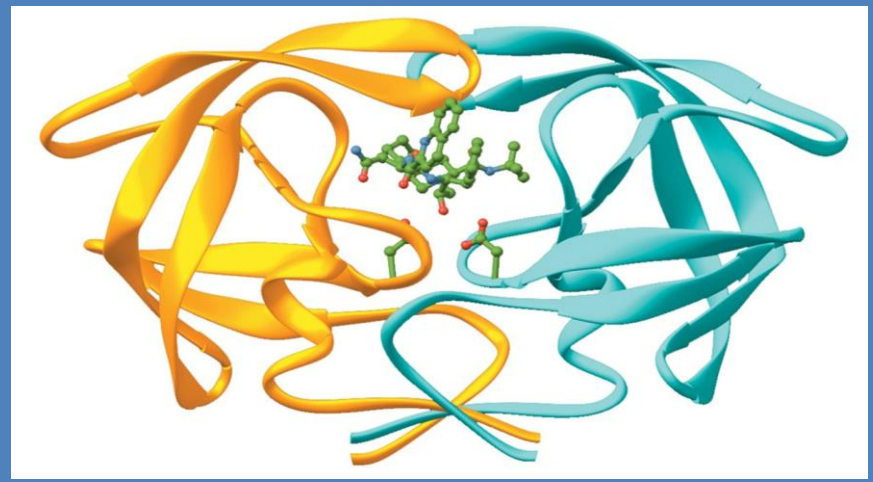
Affinity: تعني انجذاب المركب لمركب اخر

There are three types of enzyme inhibition:

Uncompetitive (this type of inhibition was only mentioned in boys slides).	Competitive - Inhibitor has a similar structure to substrate - It competes with substrate for binding to active site of enzyme.	**Noncompetitive** - Inhibitor does not have similar structure to substrate -No competition exists between inhibitor and substrate



An enzyme **without** inhibitor



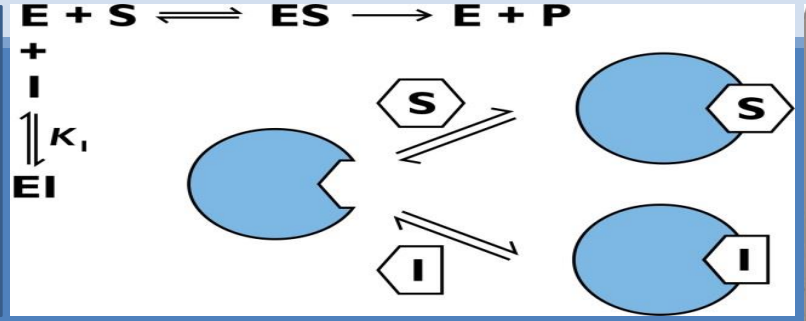
An enzyme **with** inhibitor

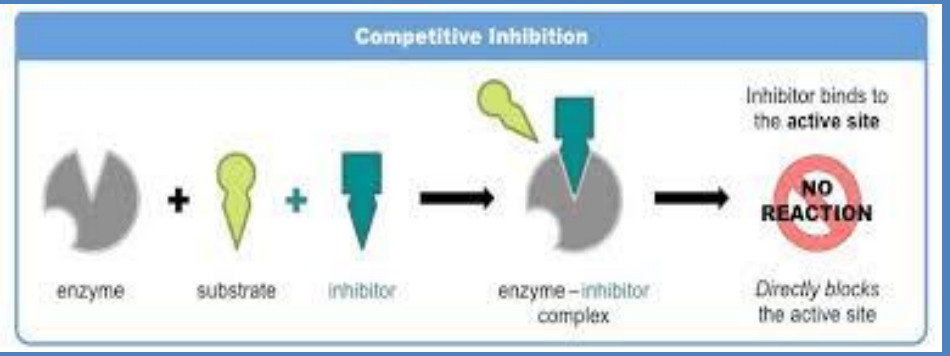
COMPETITIVE INHIBITION

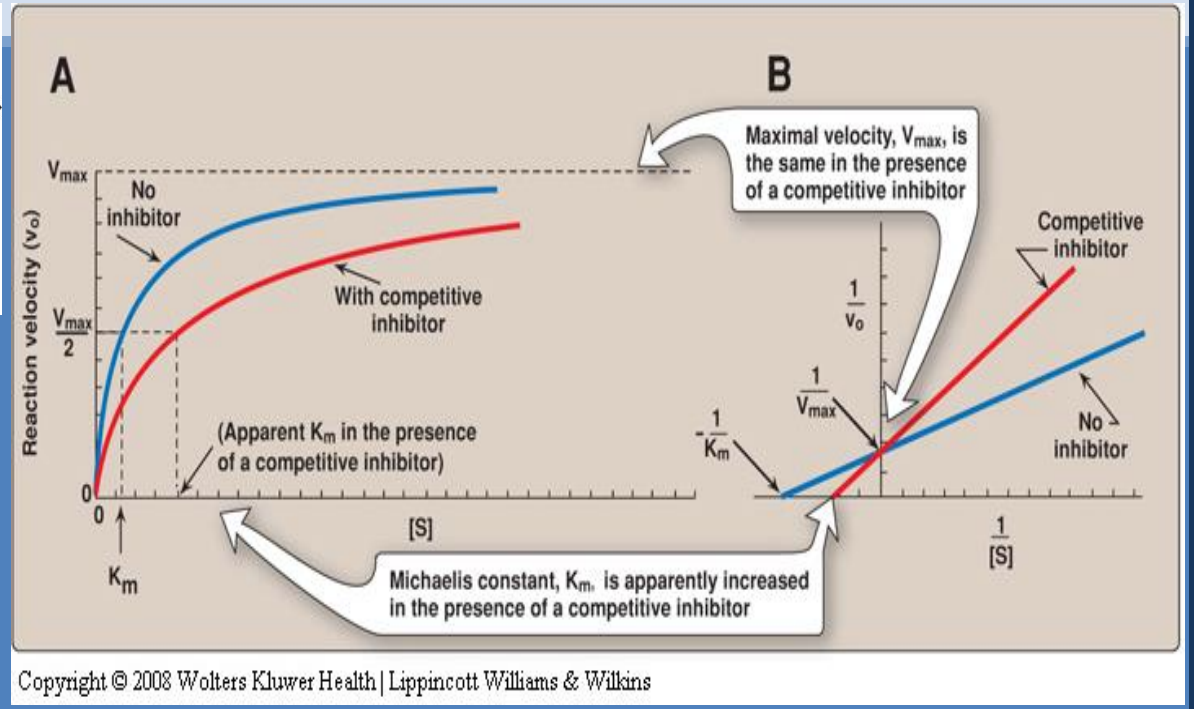
- The inhibitor is a structural analogue (similar) *to the substrate* that competes with the substrate for binding to the same active site of enzyme (competitive). Thus prevent the enzymatic reactions
- Competitive inhibition is always reversible reaction.
- **Vmax →** unchanged in the presence and the absence of inhibitor.
- **Km →** increased, because **Substrate** and **Inhibitor** compete for binding **at the same site.**

A higher concentration of substrate is required to achieve half-maximal velocity*

Two reactions are possible:
E + S ↔ ES → E + P
and
E + I ↔ EI
I: inhibitor, S: substrate







Noncompetitive inhibition

- Inhibitor doesn't have a similar structure to the substrate.
- It binds somewhere other than the active site.
- Non-competitive inhibition could be irreversible or reversible.
- The inhibitor can bind to: a free enzyme or to an enzyme-substrate complex. In both cases the complex is catalytically inactive

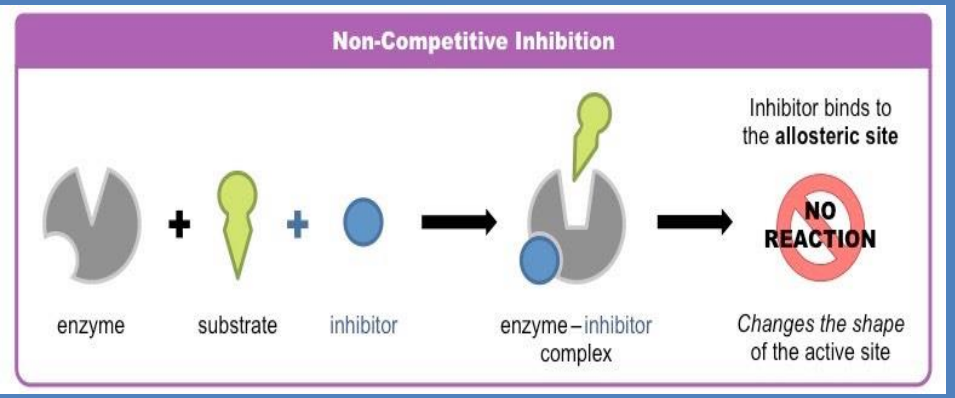
Vmax → decreased by the inhibitor.

Km → unchanged because the affinity of Substrate for Enzyme is unchanged

Two reactions are possible:

ES + I ↔ ESI (inactive)

E + I ↔ EI (inactive)



Vmax: الحد الذي يصل عنده المركب للتشبع

Km: السبب انها لم تتغير أن المثبط لا يرتبط في نفس الجهة لذا لا يؤثر على انجذاب المكب للإنزيم

Vmax: يوثر عليها لأنه زاد تشبع الانزيم يعني أصبحت الانزيمات الفارغة للمركب للتفاعل معها اقل و بالتالي كانه قلت كمية الانزيمات و زاد التشبع.

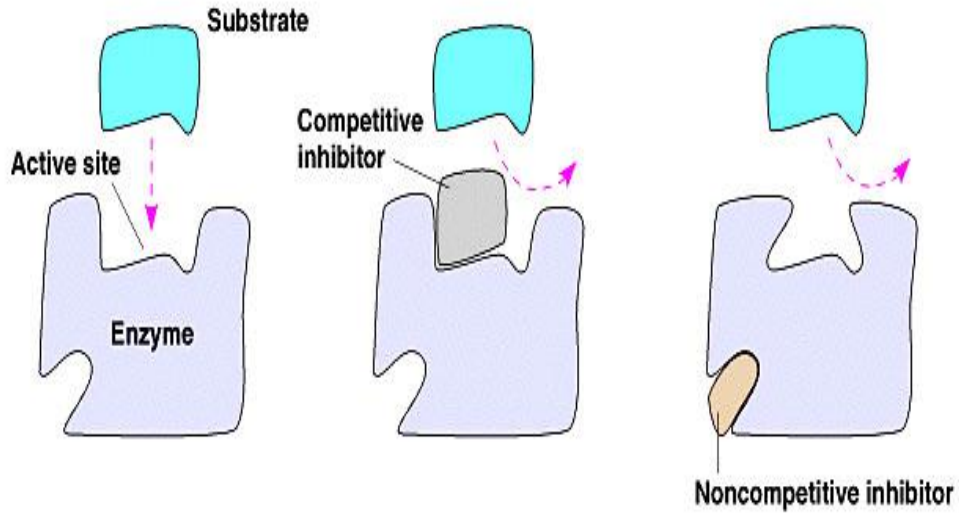
Summary

Reversible inhibitors can be divided into two main categories; **competitive inhibitors** and **noncompetitive inhibitors**, with a third category, **uncompetitive inhibitors**, rarely encountered.

Inhibitor Type	Binding Site on Enzyme	Kinetic effect
1) Competitive Inhibitor	Specifically at the catalytic site, where it competes with substrate for binding in a dynamic equilibrium- like process. Inhibition is reversible by substrate.	V_{max} is unchanged; K_m, as defined by [S] required for ½ maximal activity, is increased.
2)Noncompetitive Inhibitor	Binds E or ES complex other than at the catalytic site. Substrate binding unaltered, but ESI complex cannot form products. Inhibition cannot be reversed by substrate.	K_m appears unaltered; V_{max} is decreased proportionately to inhibitor concentration.
3) Uncompetitive Inhibitor	Binds only to ES complexes at locations other than the catalytic site. Substrate binding modifies enzyme structure, making inhibitor-binding site available. Inhibition cannot be reversed by substrate.	Apparent V_{max} decreased; K_m, as defined by [S] required for ½ maximal activity, is decreased.

The hallmark of all the reversible inhibitors is that when the inhibitor concentration drops, enzyme activity is regenerated. Usually these inhibitors bind to enzymes by non-covalent forces and the inhibitor maintains a reversible equilibrium with the enzyme.

Figure 6.14 Enzyme inhibition



(a) Substrate can normally bind to active site of enzyme.

(b) Competitive inhibitor mimics substrate and competes for active site.

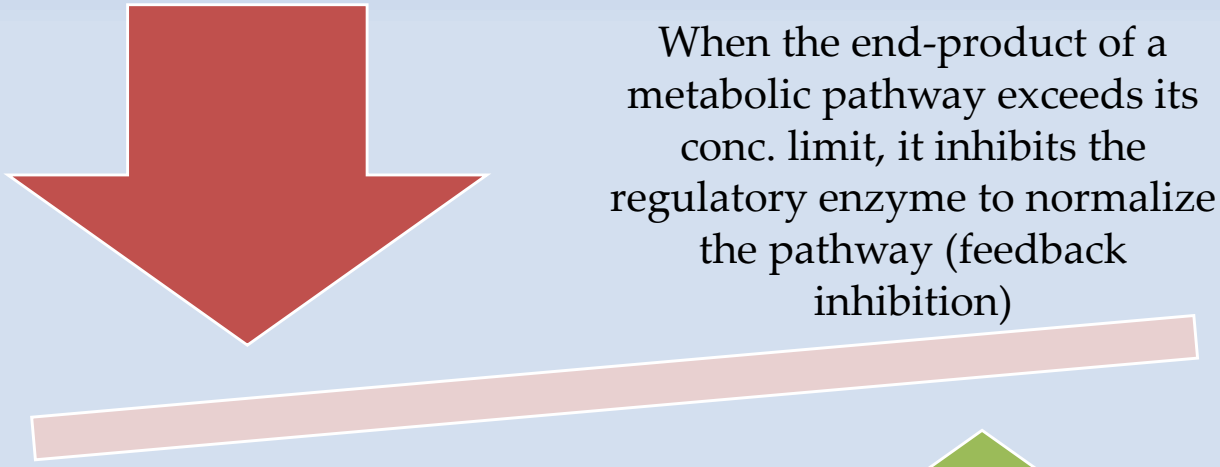
(c) Noncompetitive inhibitor alters conformation of enzyme so active site is no longer fully functional.

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:

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

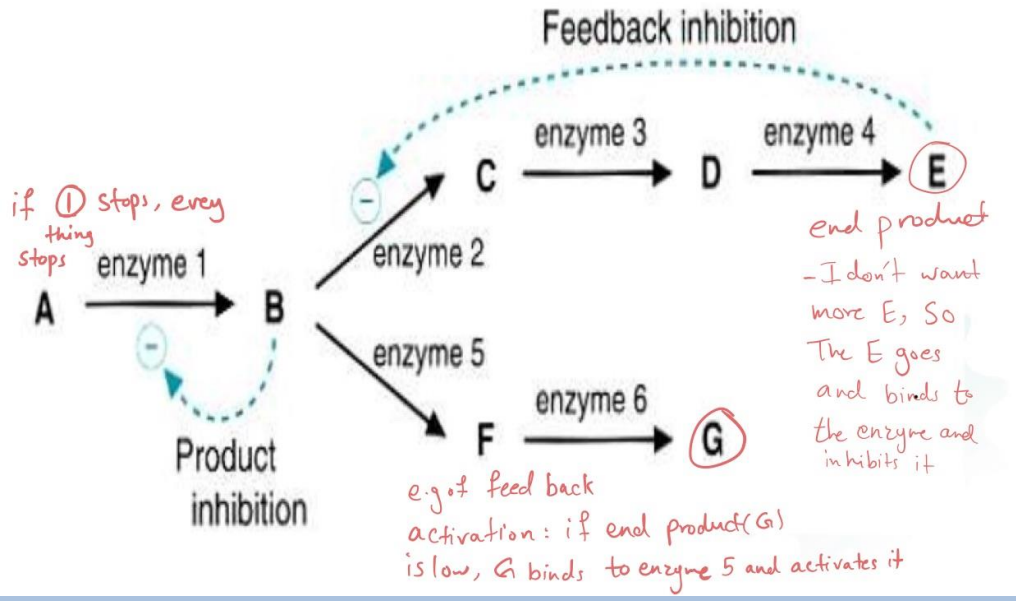


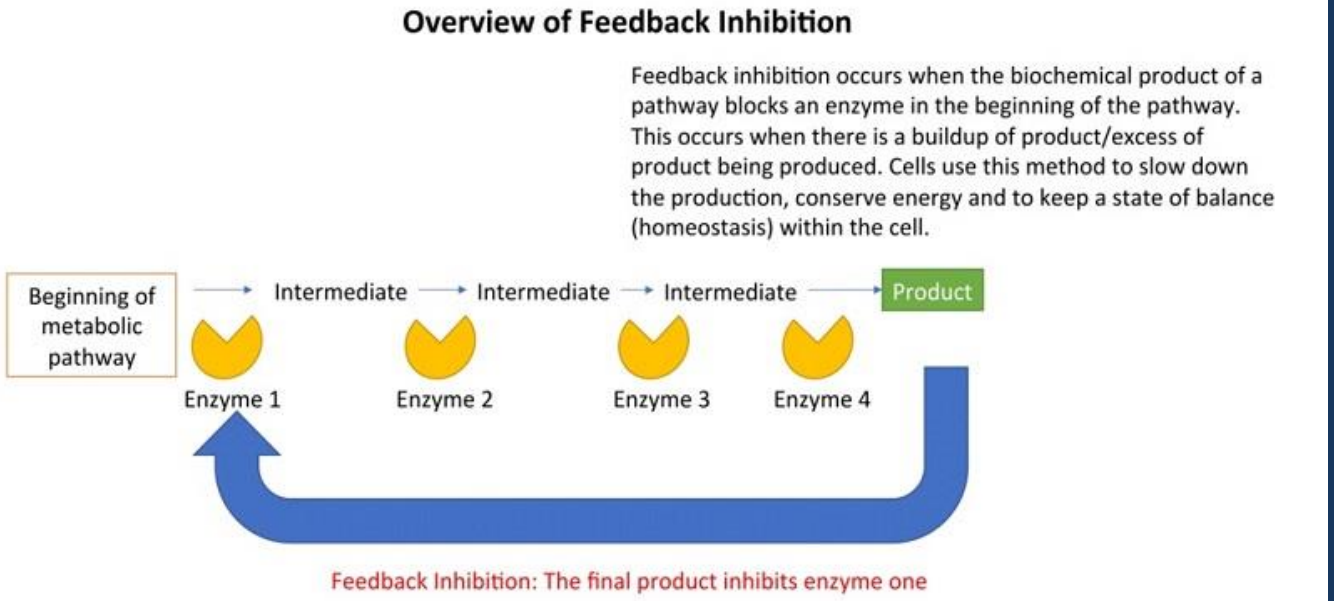
Feed positive activation:

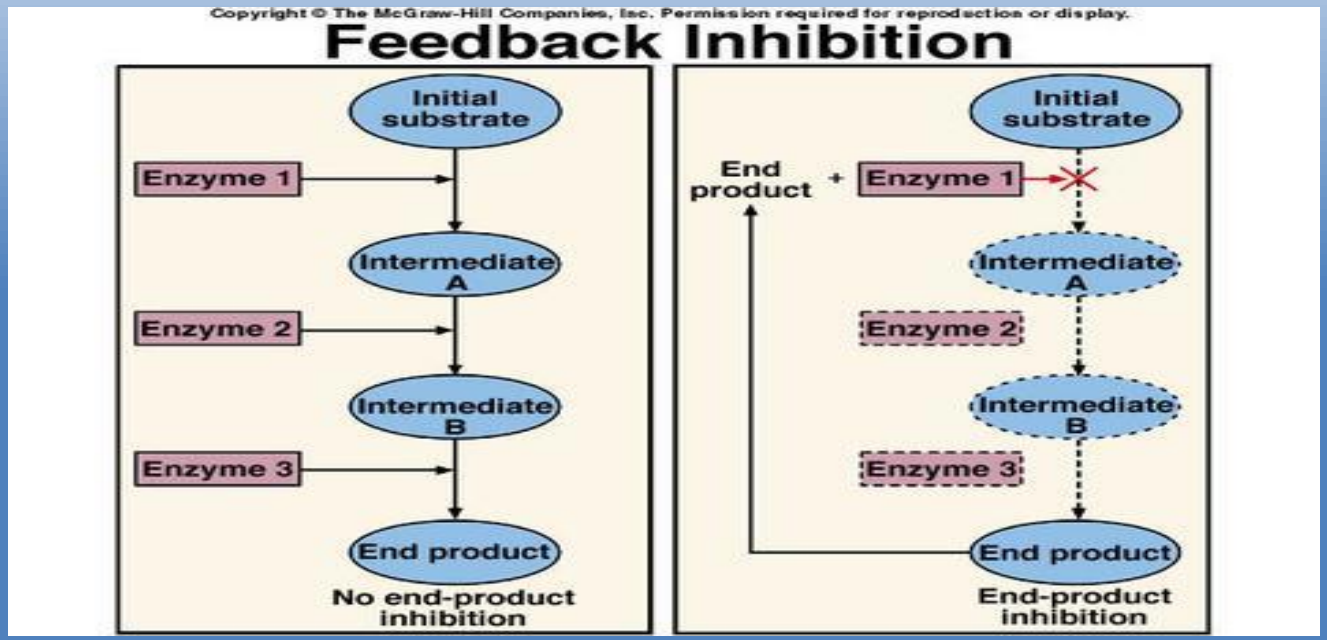
When the end-product of a metabolic pathway is below its conc. limit, it activates the regulatory enzyme to normalize the pathway

الانزيم يتم تنظيم عمله عبر عملية تسمى التغذية الراجعة (زي مهارات التواصل تذكرها) لكي يعرف الانزيم متى يشتغل و متى يوقف, هذه العملية يا تكون إيجابية (تأمره بالعمل), او مثبطة (توقفه عن عمله) و كل ذلك ليصل الجسم لحالة توازن.
و هذه العملية (التغذية الراجعة) لها عدة طرق ركز في الصور

Feedback Inhibition







-Feedback Inhibition of biochemical pathways :

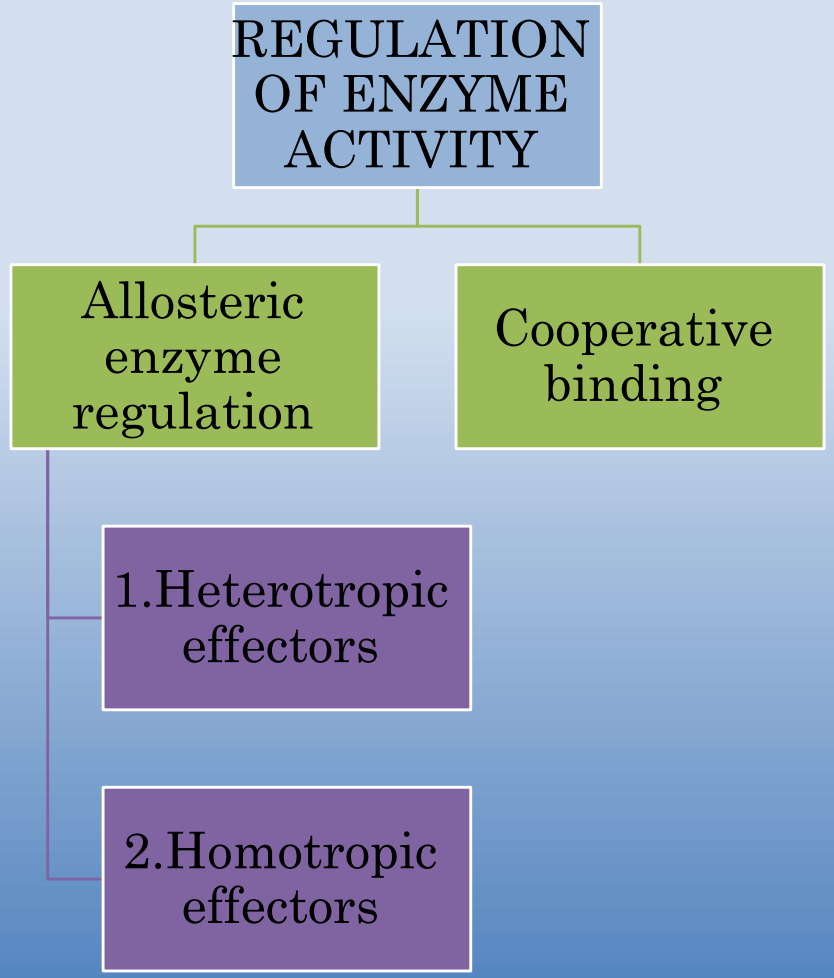
https://www.youtube.com/watch?v=n3i7XMQTZ_s

- Feedback Inhibition or End Product Inhibition of Enzymes:

https://www.youtube.com/watch?v=bRGsmNLMn4I
Better video
https://www.youtube.com/watch?v=WAZXqhtduFw

Regulation of allosteric enzymes

- Allosteric enzyme regulation
  - Enzymes in metabolic pathways are regulated by certain compounds (ligands)
  - 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



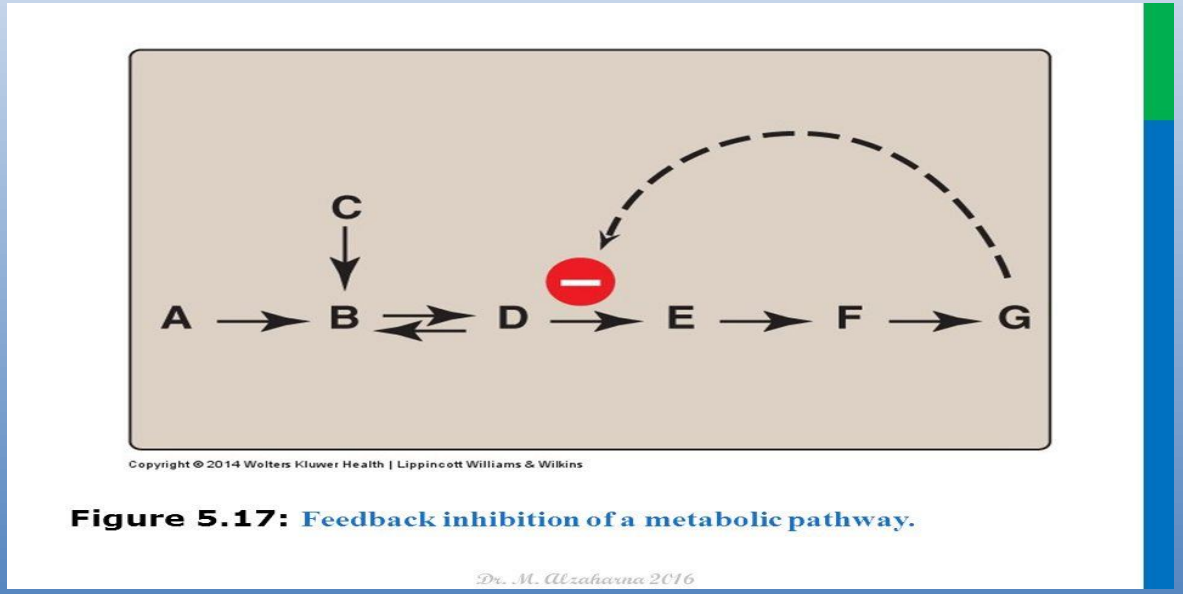
Homotropic: Effect of one ligand on the binding of the same ligand

A regulatory enzyme controlled by its own substrate

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

بالمختصر المفيد الامر متعلق بالمركب المثبط , لو كان هو نفسه المتفاعل قلنا انه (homotropic)

لو كان المركب المثبط ليس من المتفاعلات لهذا الانزيم انما ناتج او غيره مثل الصورة تحت قلنا عنه (heterotropic)

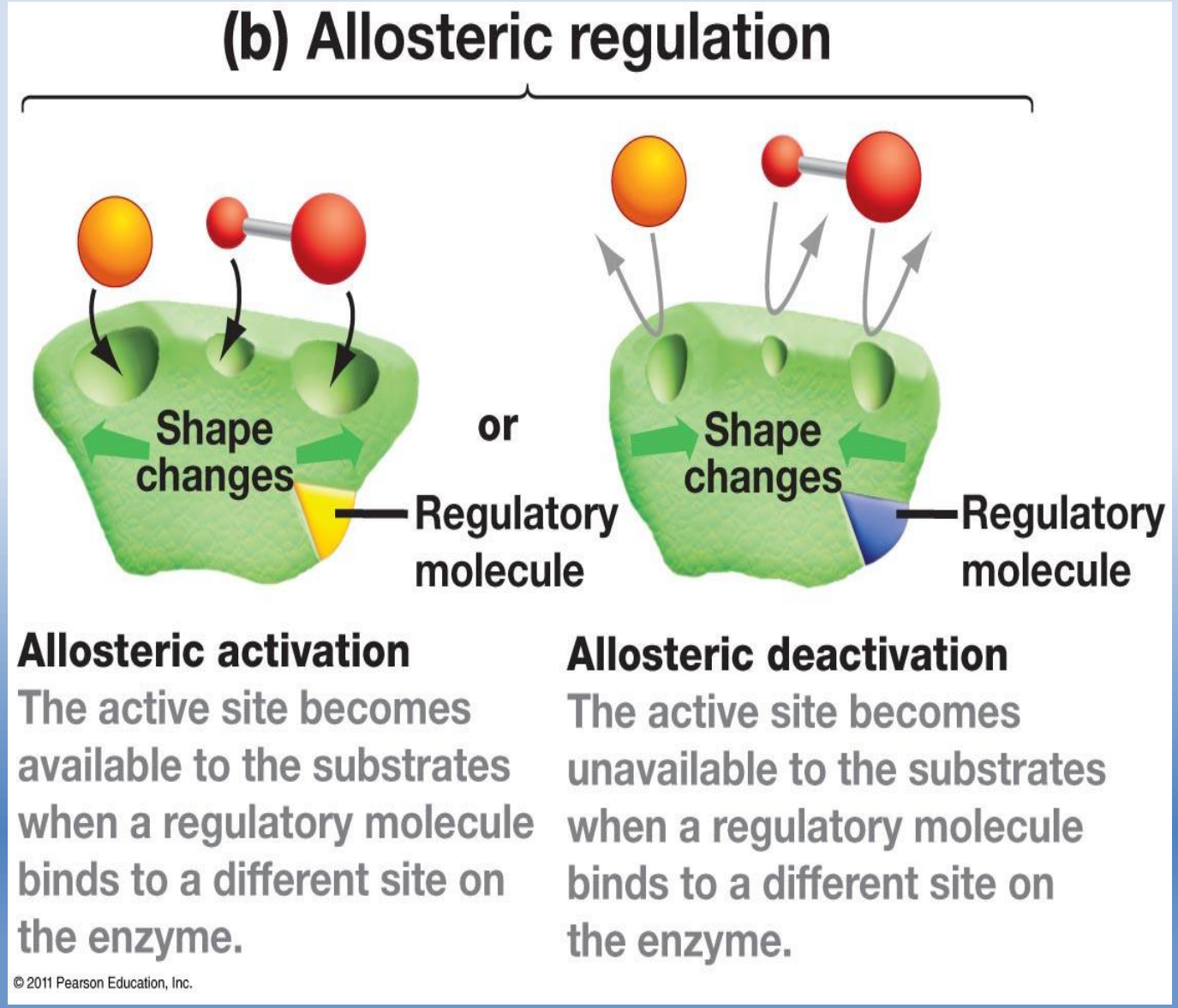


Cooperative binding

- It is the process by which binding of a **ligand** to a **regulatory site affects** binding of the same or of another **ligand** to the **enzyme**. بمعنى ارتباط المادة مع الانزيم في منطقة وحدة يحفّز المناطق الأخرى بنفس الإنزيم.
- 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 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

Cooperative binding: binding of one molecule facilitates binding of another molecule.
The first molecule to bind always takes the longer time



Enzymatic diagnosis and prognosis of diseases
They are used as:

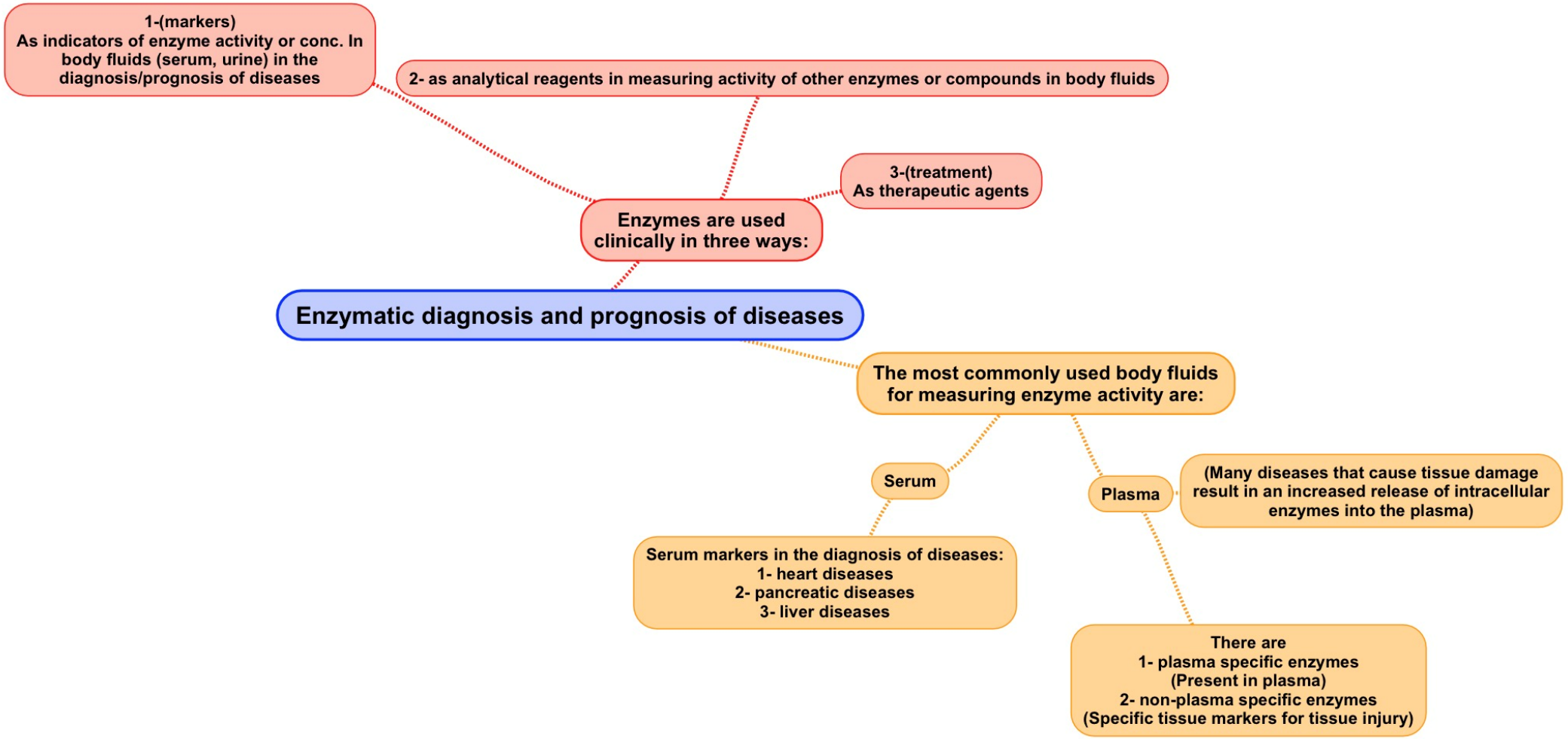
As indicators of enzyme activity or conc. in body fluids (serum, urine) in the diagnosis/prognosis of diseases	As analytical reagents in measuring activity of other enzymes or compounds in body fluids	As therapeutic agents
e.g if we find liver enzymes in the blood, that means there is something wrong with the liver		

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

- Plasma-specific enzymes
- Nonplasma-specific enzymes

Serum markers in the diagnosis of diseases

Heart disease
Pancreatic diseases
Liver diseases


Enzymatic diagnosis and prognosis of diseases
Enzymes are used clinically in three ways:
1-(markers)
As indicators of enzyme activity or conc. In body fluids (serum, urine) in the diagnosis/prognosis of diseases
2- as analytical reagents in measuring activity of other enzymes or compounds in body fluids
3-(treatment)
As therapeutic agents
The most commonly used body fluids for measuring enzyme activity are:
Serum
Plasma
(Many diseases that cause tissue damage result in an increased release of intracellular enzymes into the plasma)
Serum markers in the diagnosis of diseases:
1- heart diseases
2- pancreatic diseases
3- liver diseases
There are
1- plasma specific enzymes
(Present in plasma)
2- non-plasma specific enzymes
(Specific tissue markers for tissue injury)

summary

- ✓ -Regulatory enzymes usually catalyze the first or an early reaction in a metabolic pathway.
- ✓ -There are two types of regulation allosteric enzyme regulation and cooperative binding
- ✓ -Feedback inhibition inhibits the regulatory enzyme to normalize the pathway (feedback inhibition) while the feedback positive activation
- ✓ activates the regulatory enzyme to normalize the pathway.
- ✓ -Two types of interactions occur in allosteric enzymes:
- ✓ Homotropic: Effect of one ligand on the binding of **the same** ligand .
- ✓ Heterotropic: Effect of one ligand on the binding of **a different** ligand.
- ✓ Enzymes are used clinically in three ways.

	Competitive inhibition	Noncompetitive
meaning	similar to the structural of the substrate and competes with it for binding at the active site	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
V_{max}	V_{max} is unchanged in the presence and the absence of inhibitor	The value of V_{max} is decreased by the inhibitor
K_m	K_m is increased because substrate and inhibitor compete for binding at the same site	K_m is unchanged because the affinity of S for E is unchanged

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