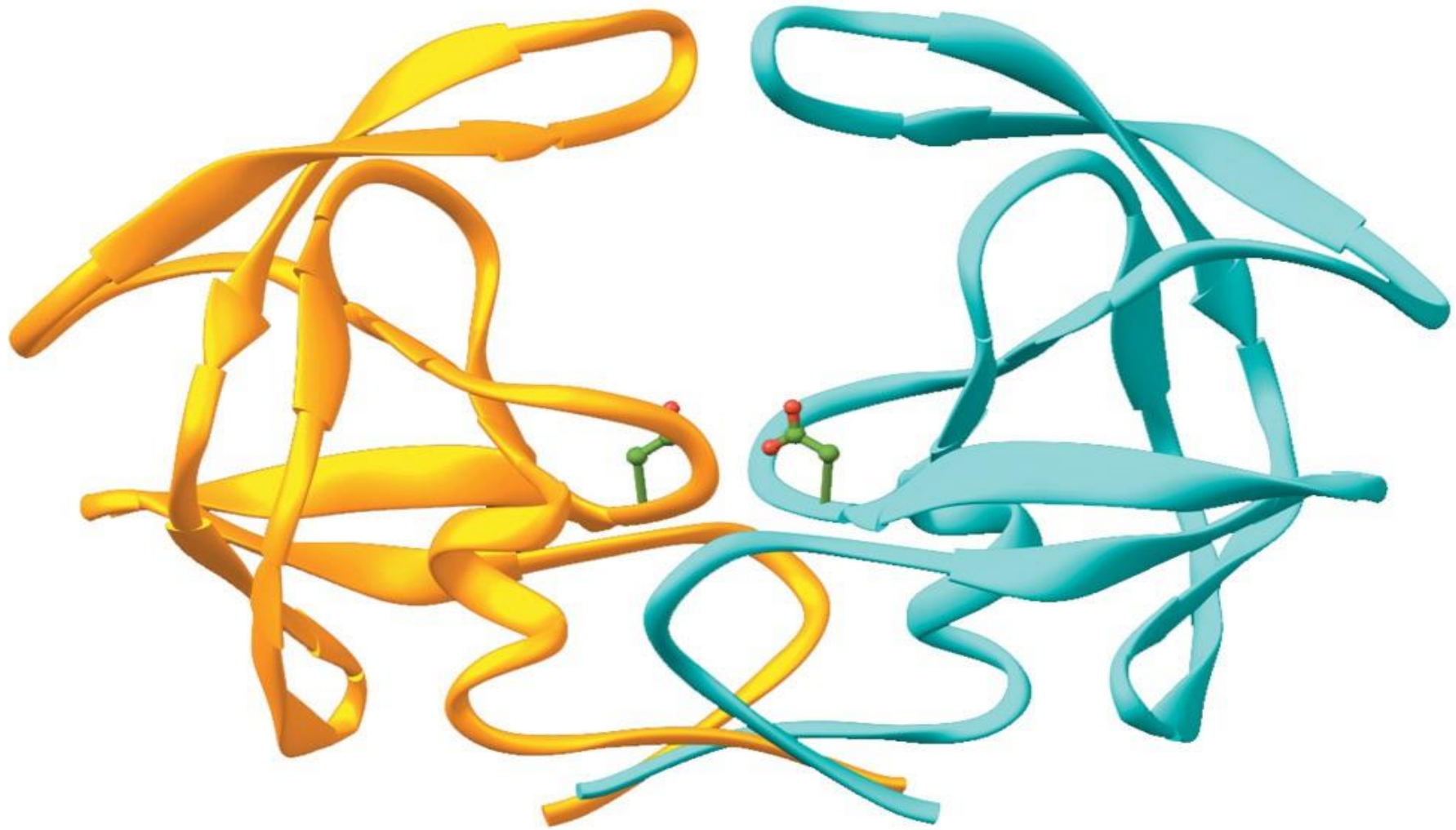
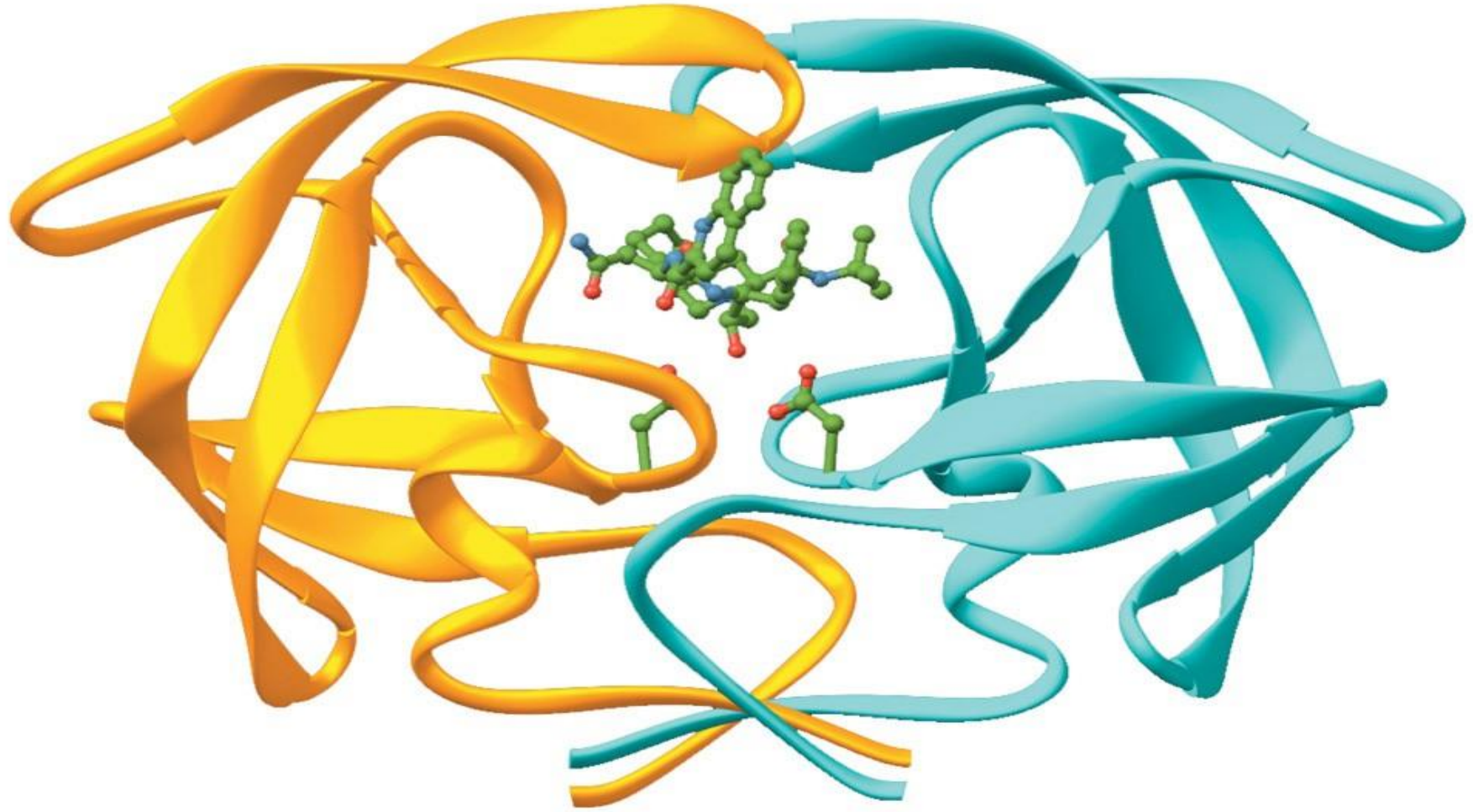


Enzyme inhibition

- 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

K_i (Inhibitor constant)

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

Enzyme inhibition

- There are three types of enzyme inhibition:
 - ◆ Competitive
 - ◆ Noncompetitive
 - ◆ Uncompetitive

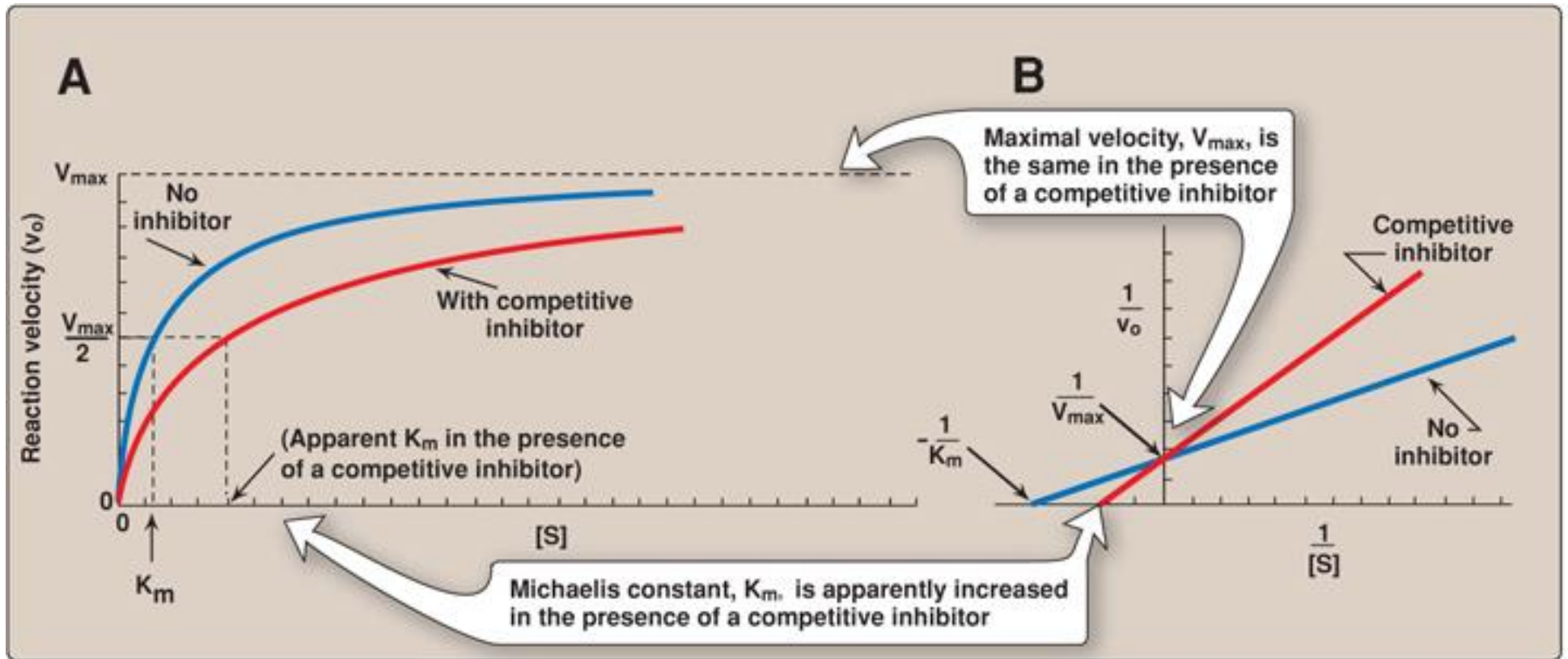
Competitive inhibition

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



and





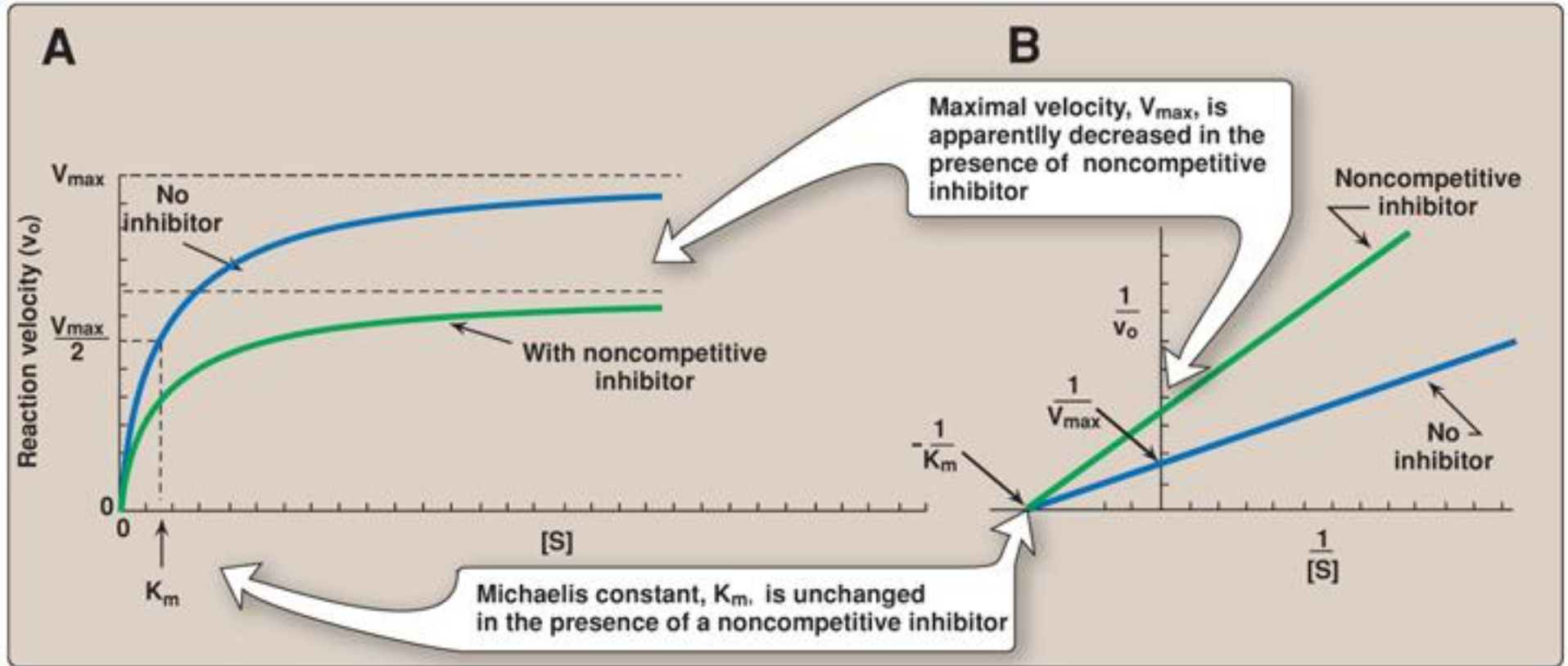
Copyright © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

Competitive inhibition

- 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

- 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

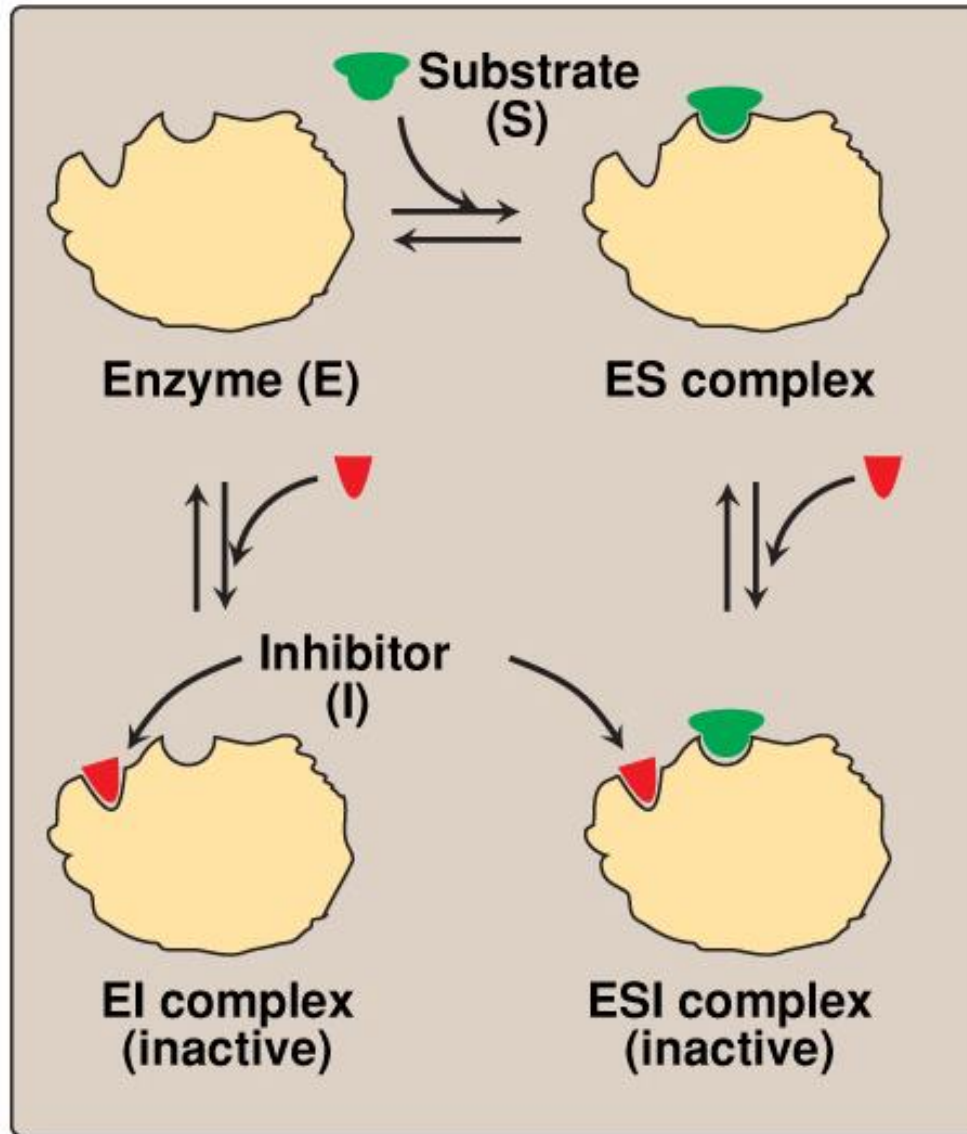


Copyright © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

Noncompetitive inhibition



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



Copyright © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

Noncompetitive inhibition

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

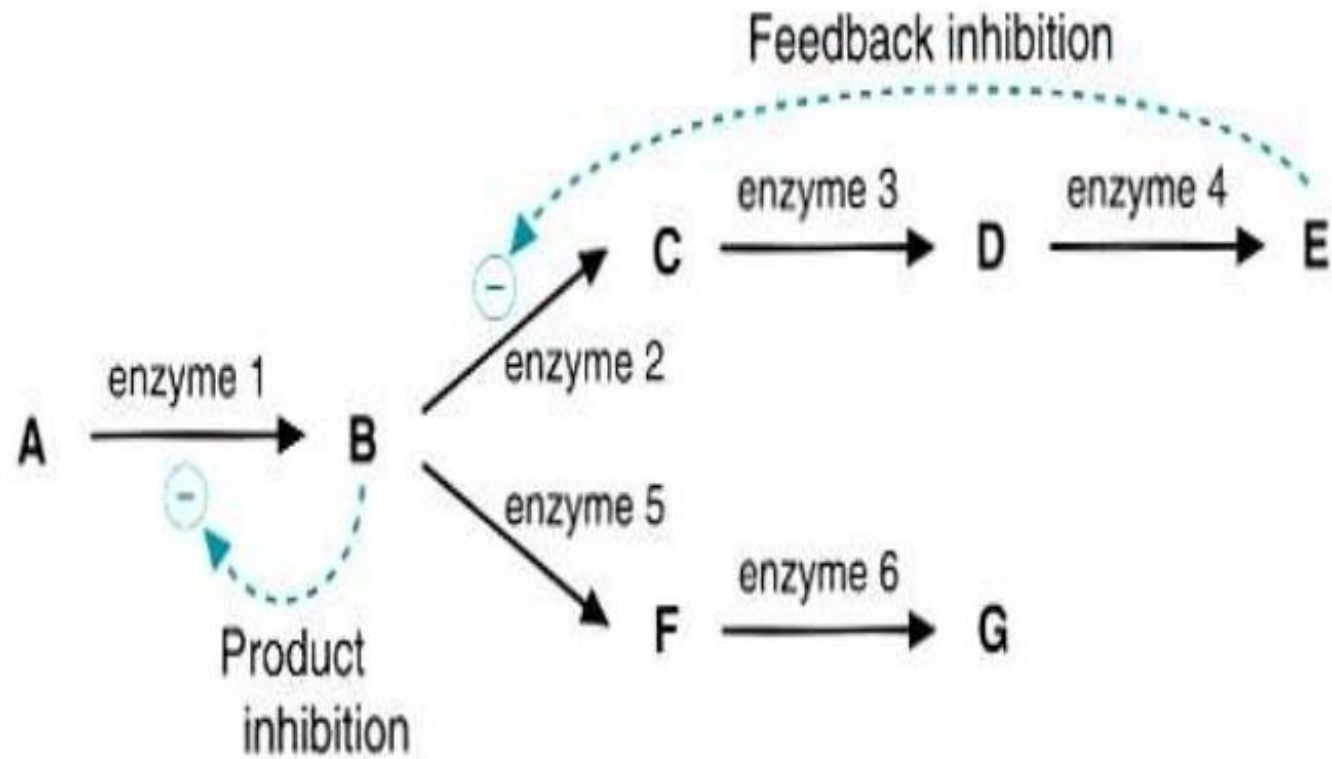
- **Feedback inhibition:**

- ◆ 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

Feedback Inhibition



Types of regulation

■ Allosteric enzyme regulation

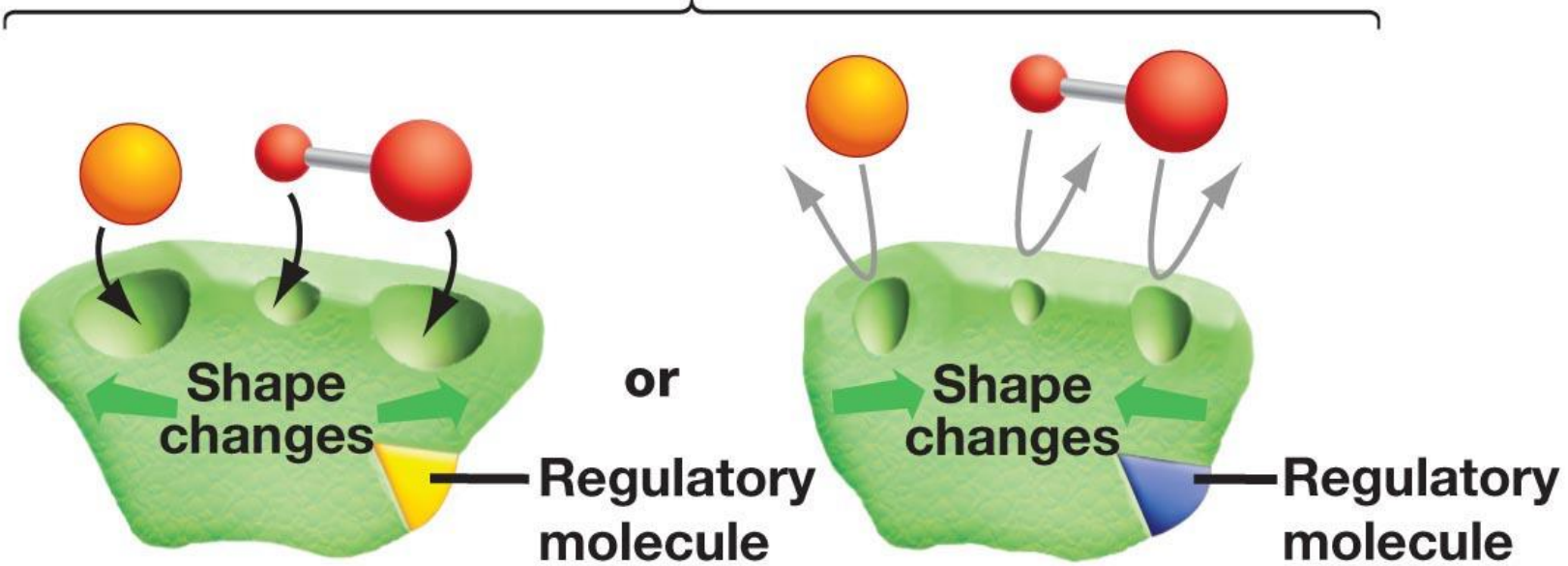
- ◆ Enzymes in metabolic pathways are regulated by certain compounds (ligands)
- ◆ These ligands do not bind to active site
- ◆ They bind to other site (regulatory site) on the enzyme (**allosteric enzymes**)
- ◆ The term “allosteric” came from Greek word “allos” meaning “other”

- **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**

- 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

(b) Allosteric regulation



Allosteric activation

The active site becomes available to the substrates when a regulatory molecule binds to a different site on the enzyme.

Allosteric deactivation

The active site becomes unavailable to the substrates when a regulatory molecule binds to a different site on the enzyme.

- 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
 - ◆ Heterotropic
- 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

- 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

Take home message

- 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

References

- Lippincott's Biochemistry
5th Edition, pp 53-68, Lippincott Williams
& Wilkins, New York, USA