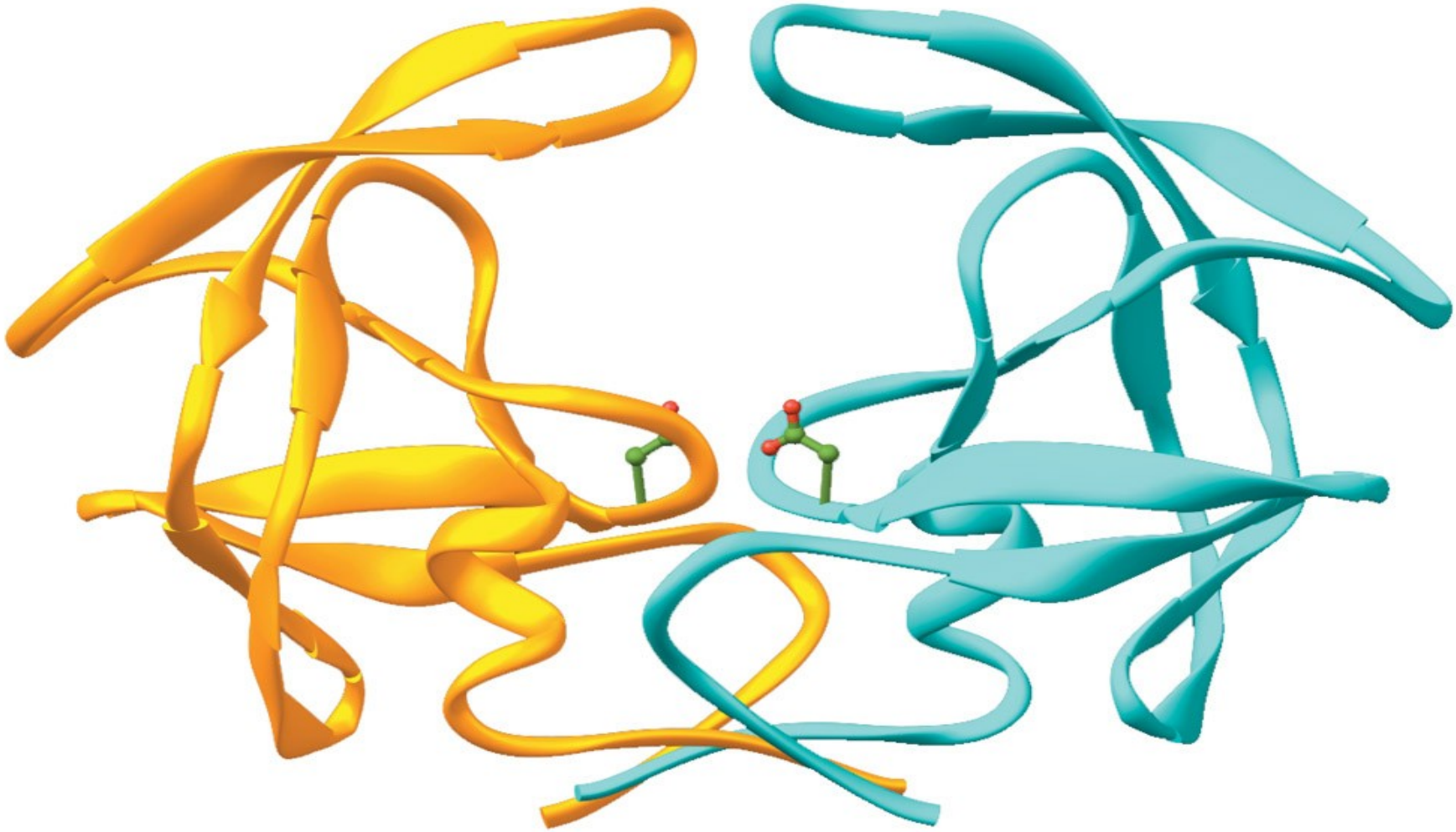
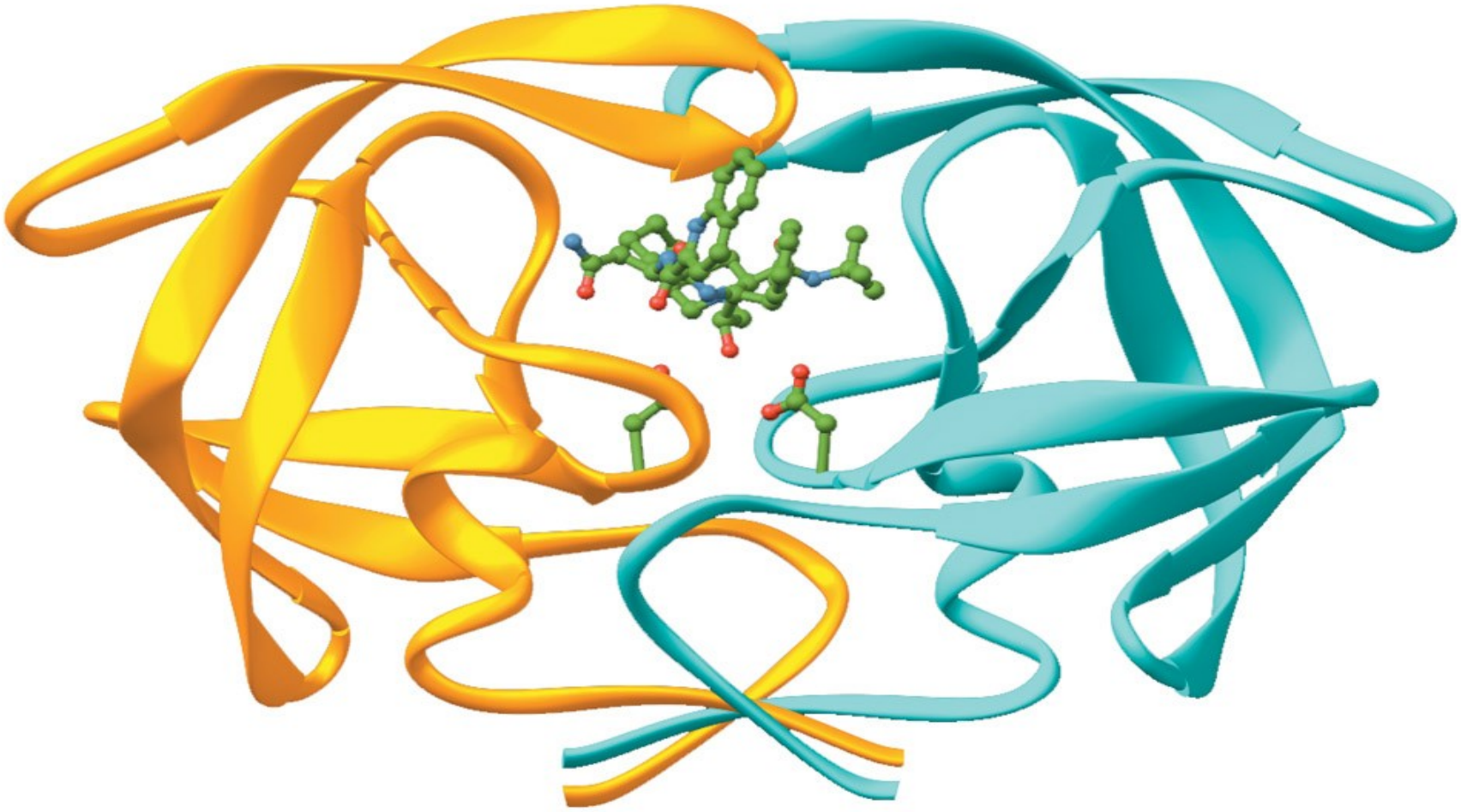
Enzyme inhibition

- 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

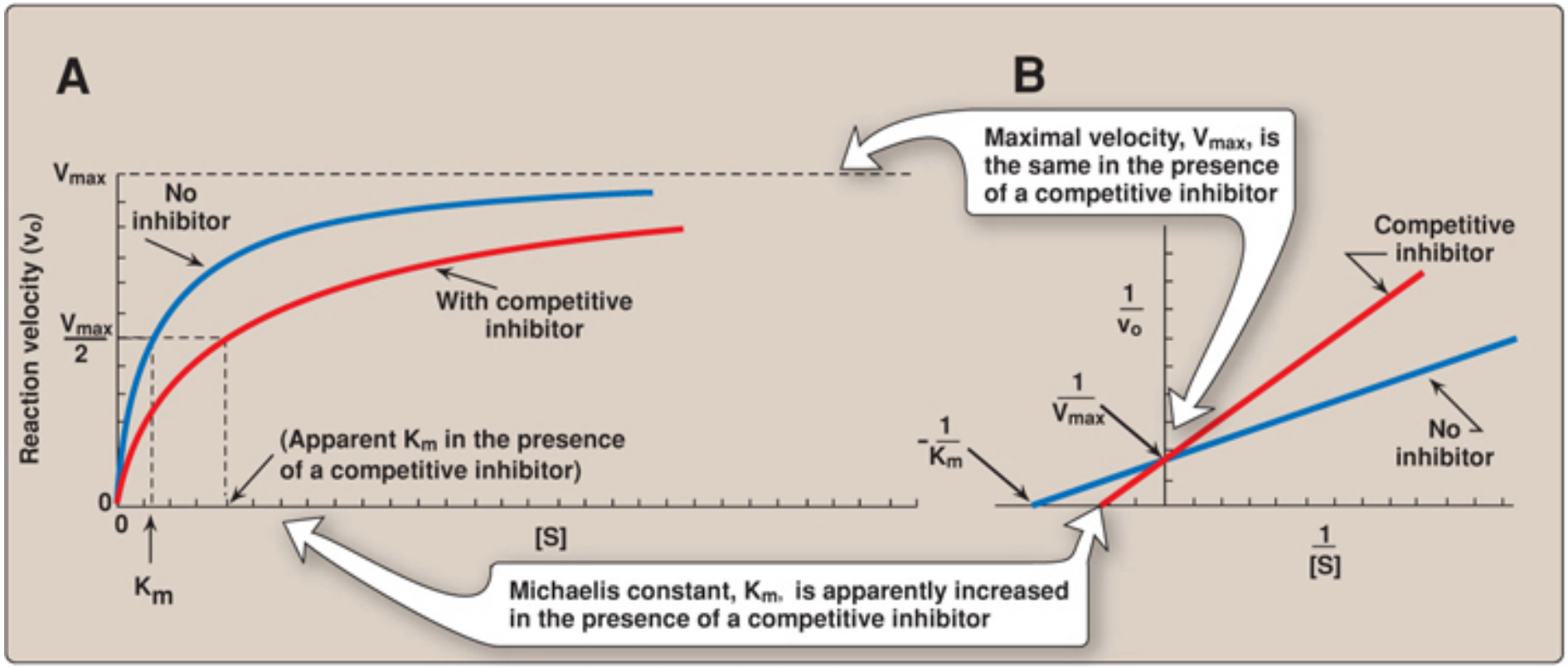
Competitive inhibition

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

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

and

$$E + I \leftrightarrow EI$$

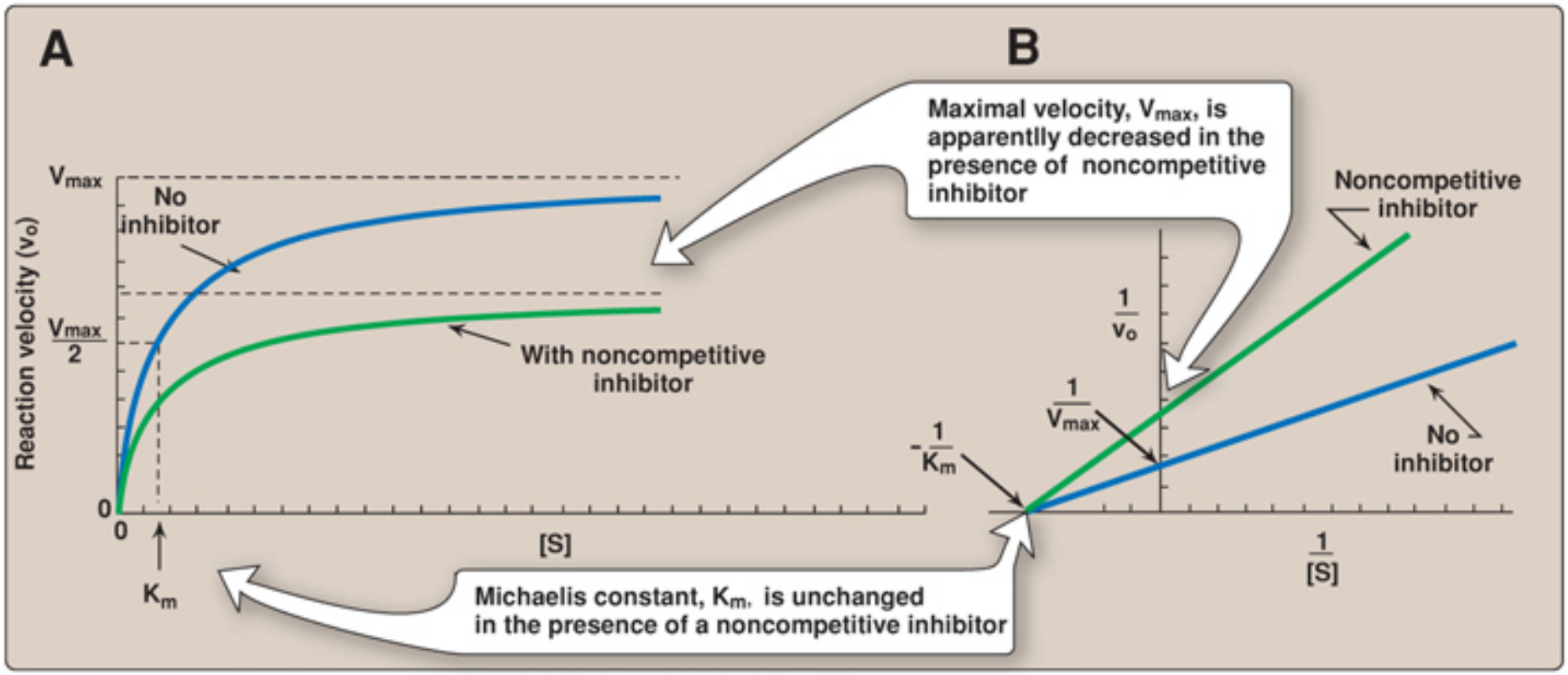


Competitive inhibition

- 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

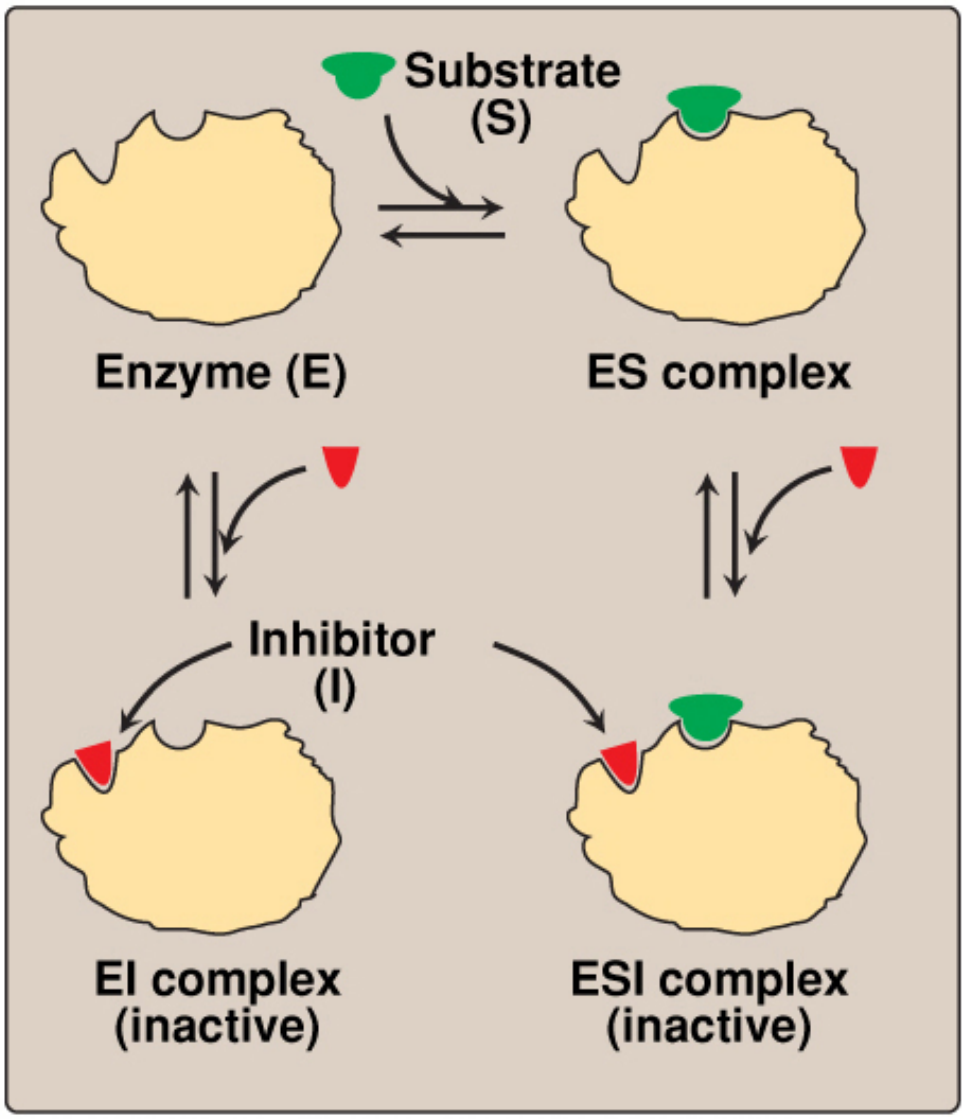


Noncompetitive inhibition

$ES + I \leftrightarrow ESI$ (inactive)

$E + I \leftrightarrow EI$ (inactive)

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



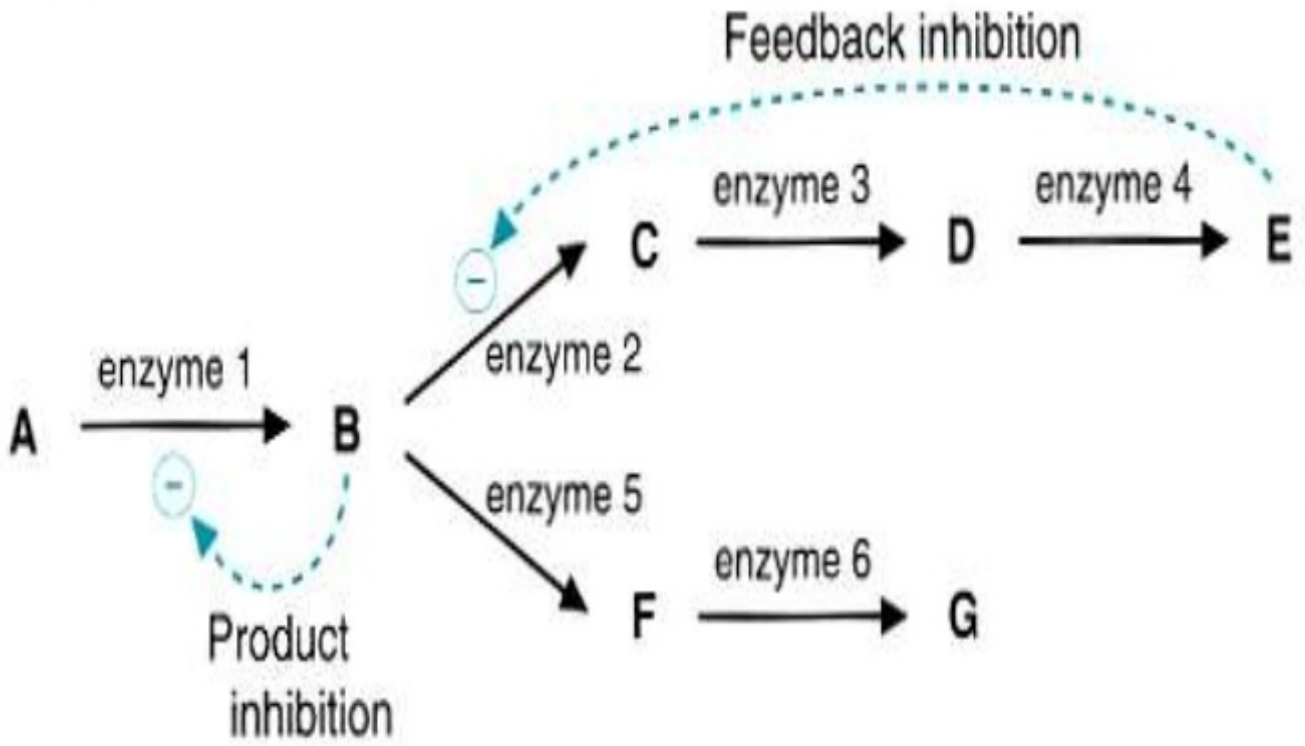
Noncompetitive inhibition

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



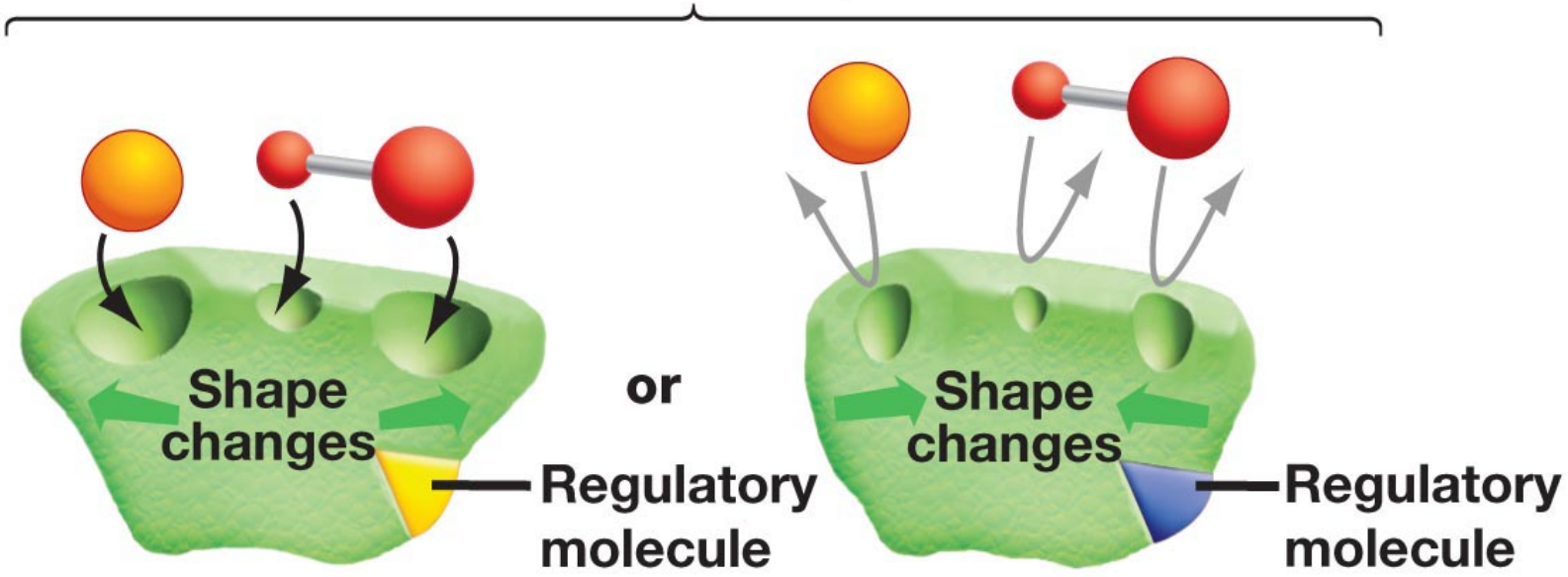
Types of regulation

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

- 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