Enzyme Regulation

Chapter 6: Pages 96 - 103

Enzyme Regulation

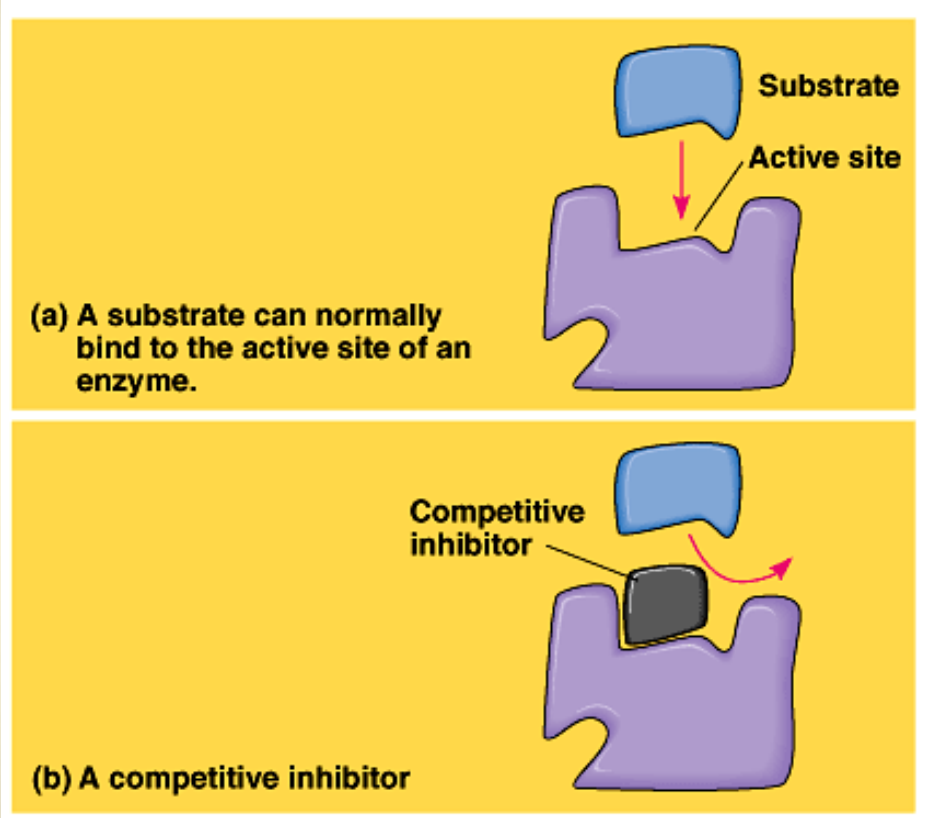
- Inhibition
  - Competitive
  - Noncompetitive
- Allosteric Regulation
  - Activation
  - Inhibition
- Cooperativity

Inhibitors

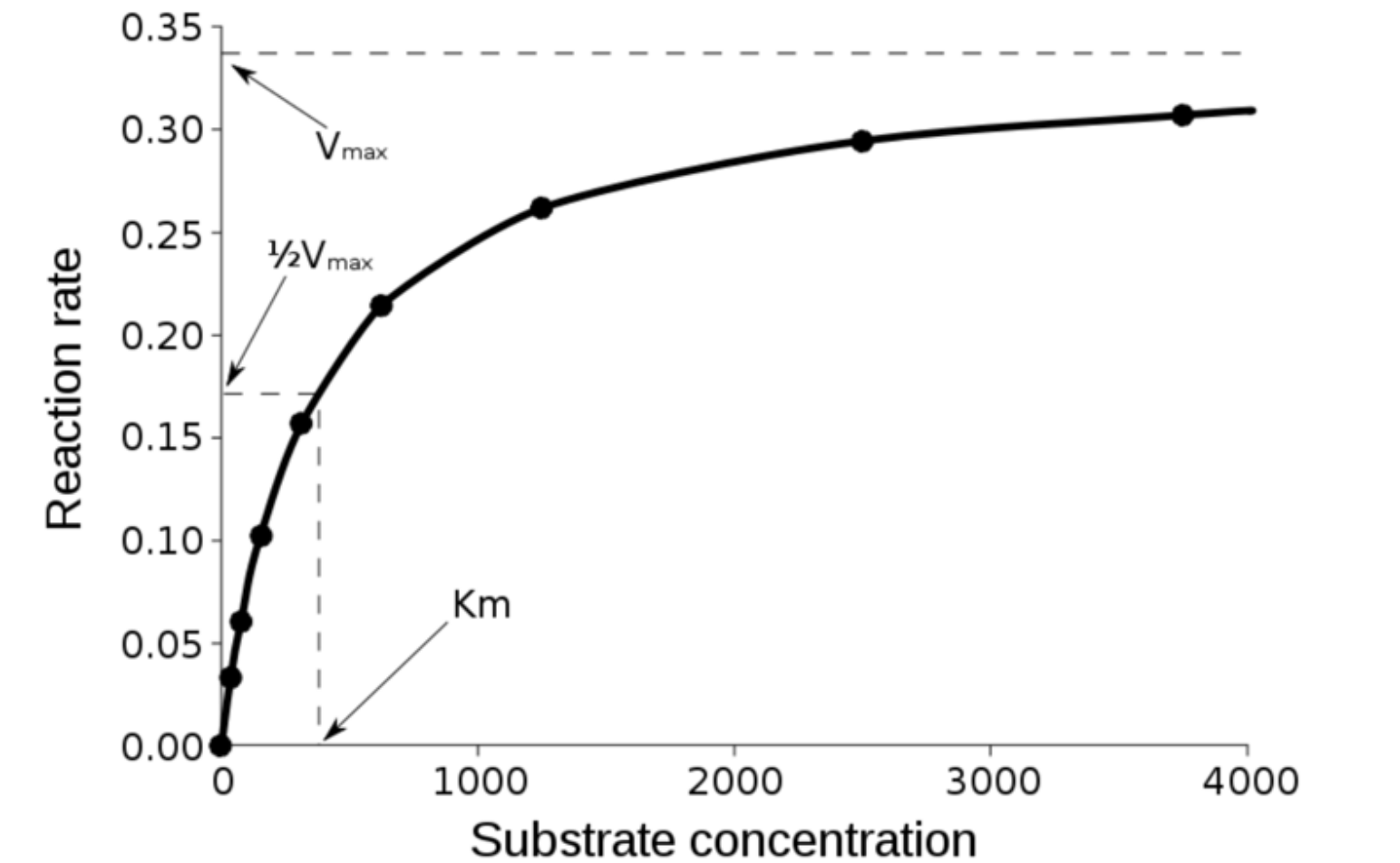
- A molecule that binds to an enzyme preventing it from catalyzing reactions.
- If binding involves covalent bonds, then inhibition is often irreversible.
- If binding is weak, inhibition may be reversible.
- Reversible inhibition of enzymes is a natural part of the regulation of metabolism.

Competitive Inhibition

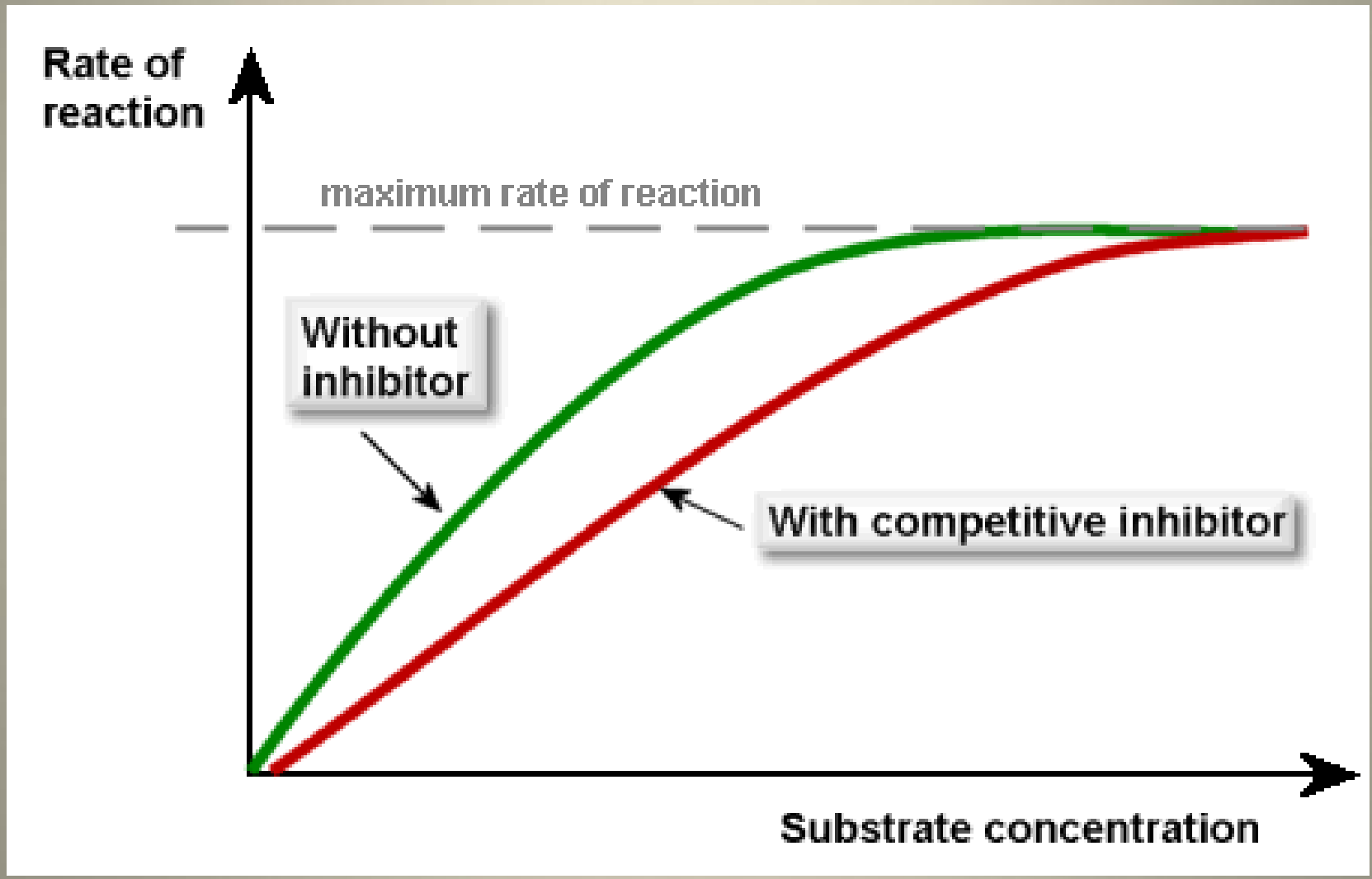
- Inhibitor binds to the same site as the substrate
- Think: How do you overcome a competitive inhibitor?



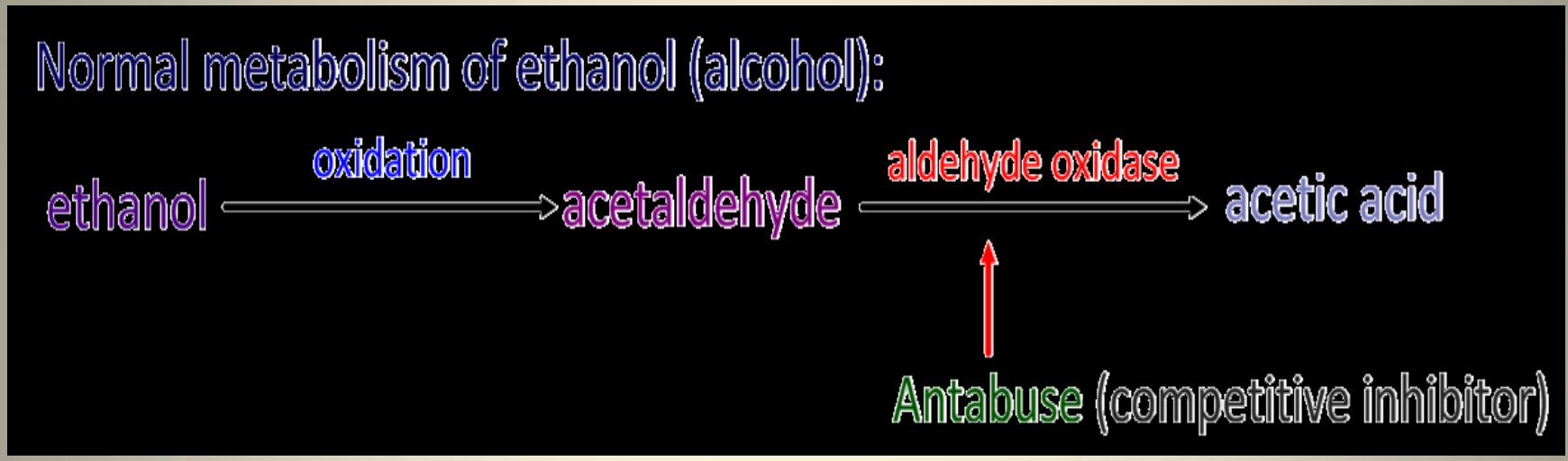
How does a competitive inhibitor change the saturation curve?



Effect of competitive inhibitor on saturation curve



Application of competitive inhibition: overcoming alcoholism



Antabuse (disulfiram) competes with the aldehyde oxidase and prevents the acetaldehyde from being converted to acetic acid.

A build up of acetaldehyde follows, resulting in a strong feeling of nausea and other strong hangover symptoms - a good deterrent from drinking.

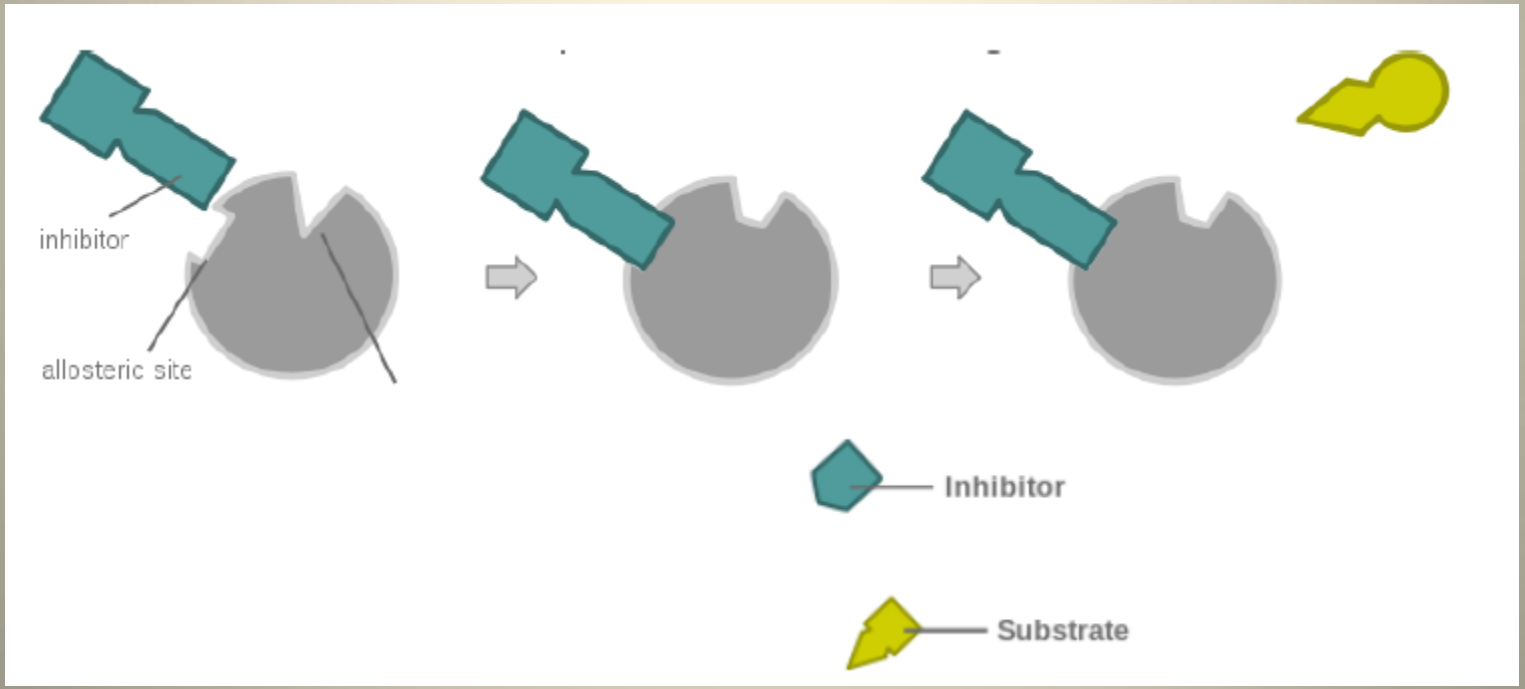
Antabuse is administered as a daily pill, so its efficacy relies on the patient's own motivation - if they stop taking it, they can drink again.

Noncompetitive Inhibition

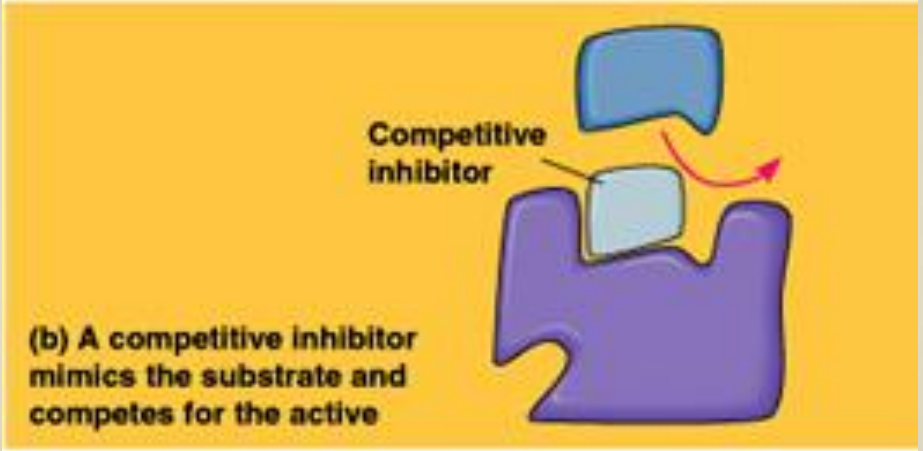
- Inhibitor binds somewhere other than the active site
- Causes enzyme to become insensitive to substrate concentrations

Mechanism of Noncompetitive Inhibition

Alters enzyme conformation rendering the active site unreceptive or less effective



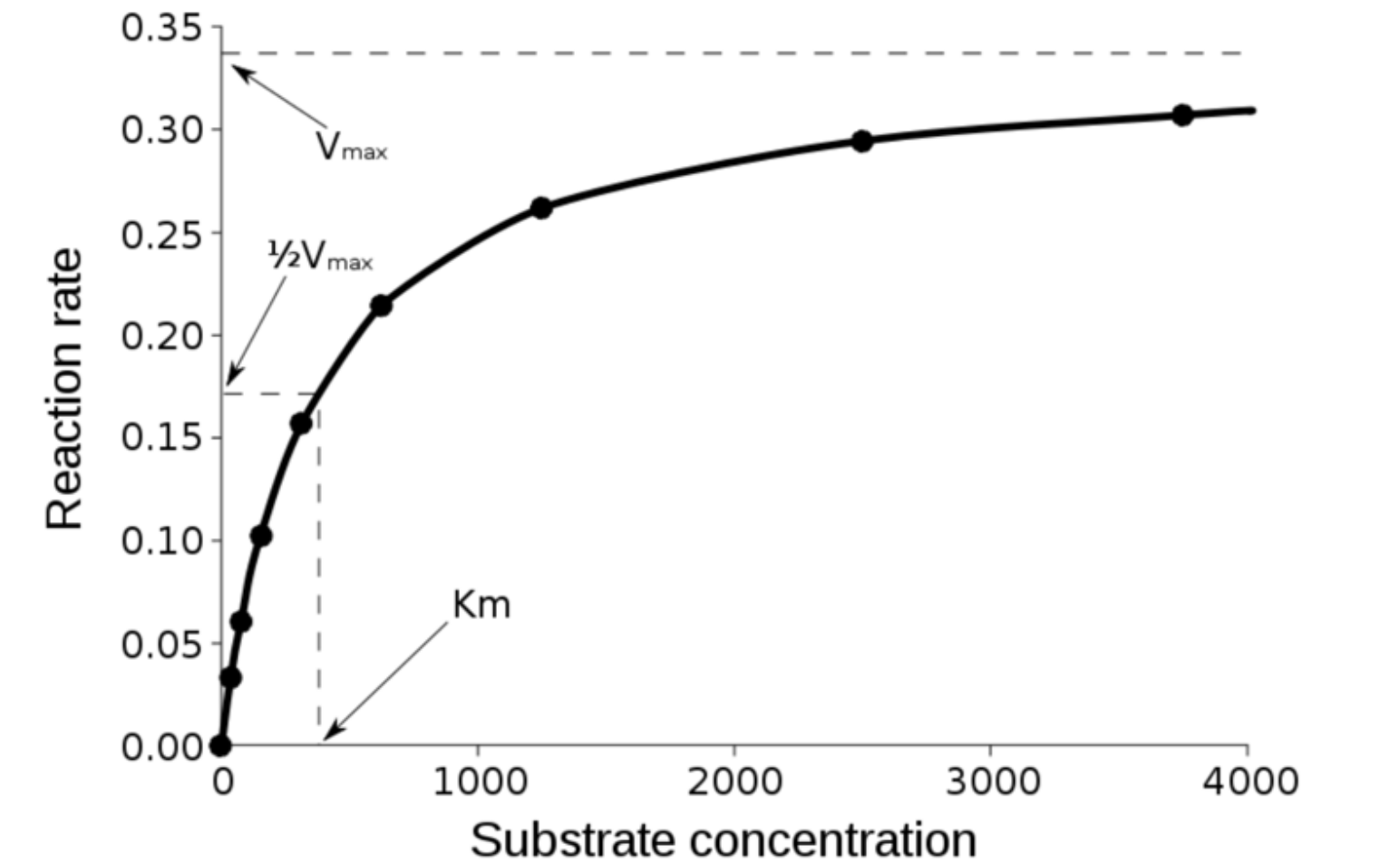
(a) A substrate can normally bind to the active site of an enzyme.



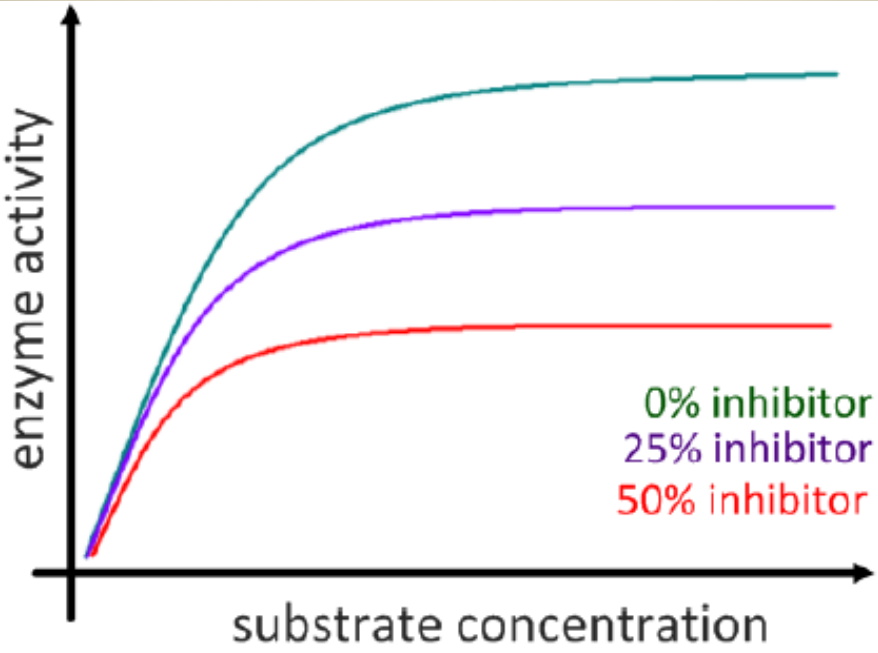
(b) A competitive inhibitor mimics the substrate and competes for the active

(c) A noncompetitive inhibitor binds to the enzyme at a location away from the active site, but alters the conformation of the enzyme so that the active site is no longer fully functional.

How does a noncompetitive inhibitor change the saturation curve?



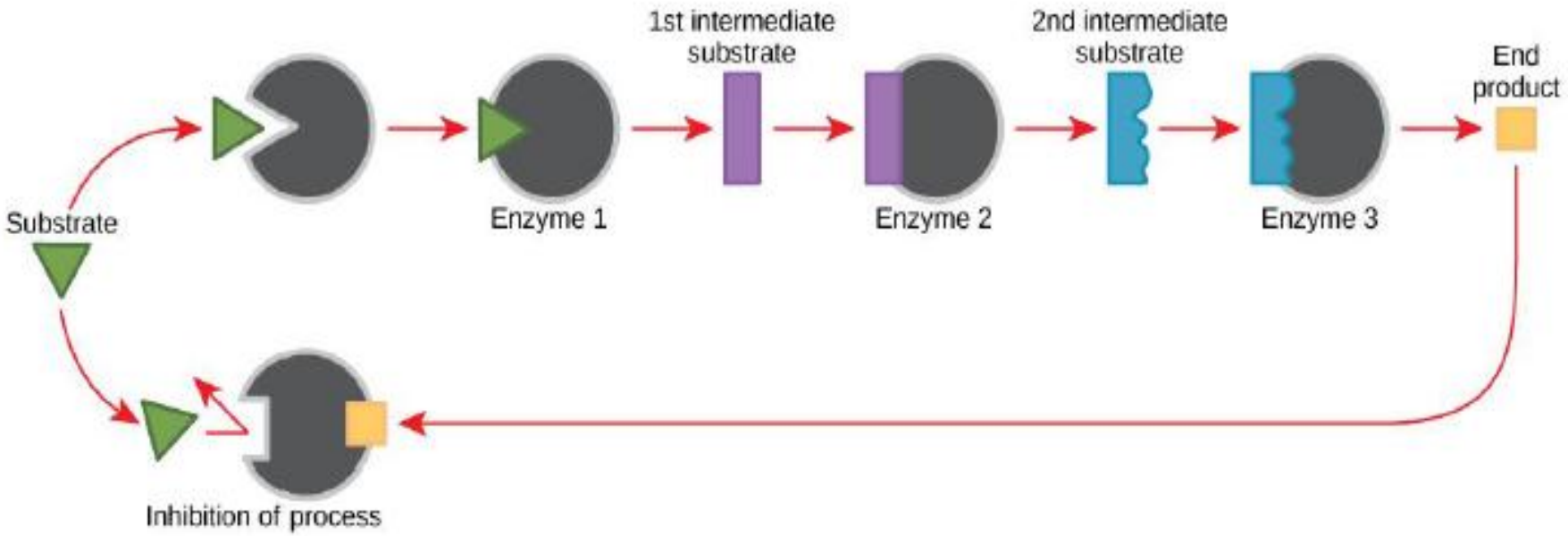
Effect of noncompetitive inhibitor on saturation curve



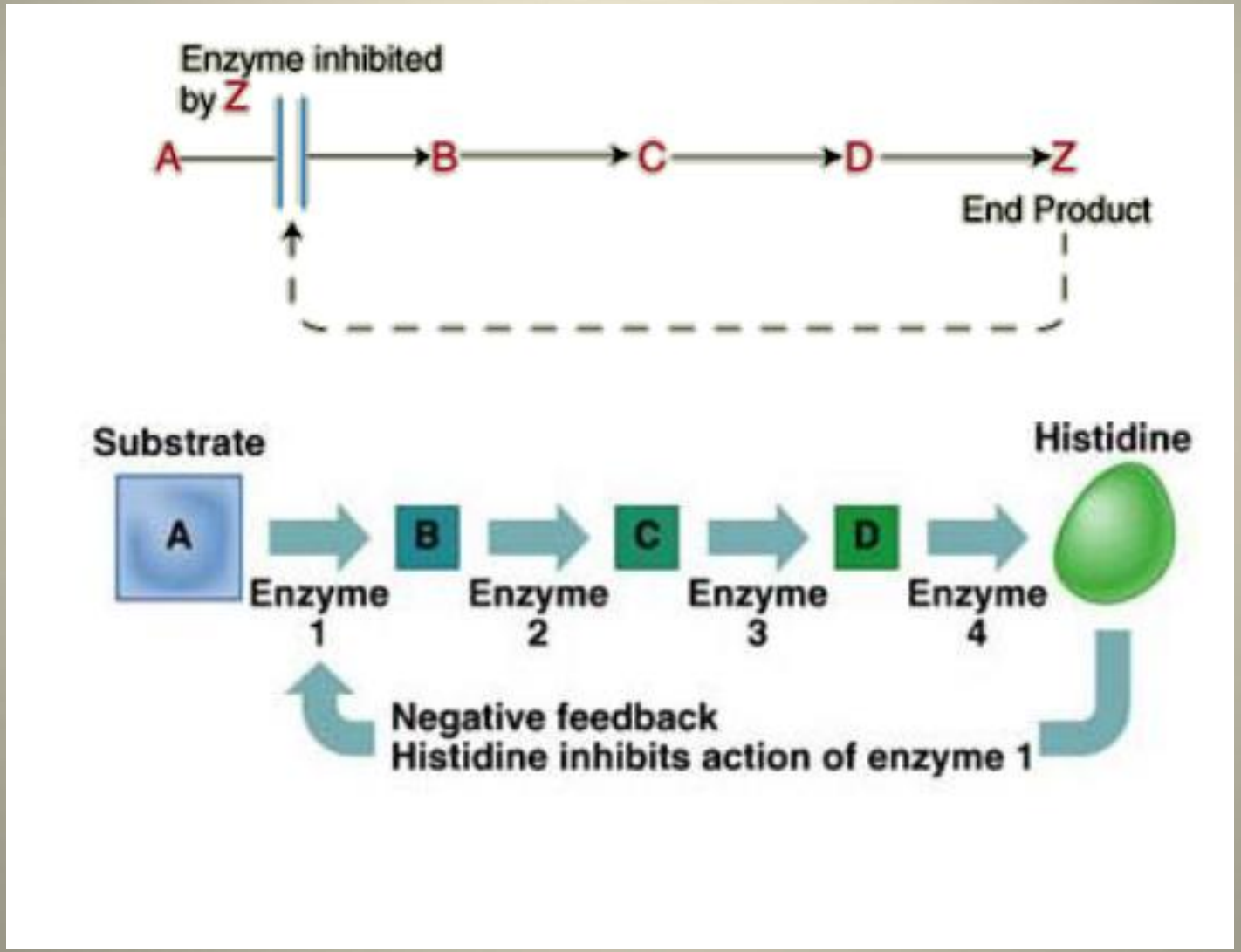
As concentration of inhibitor increases, the rate of reaction decreases.

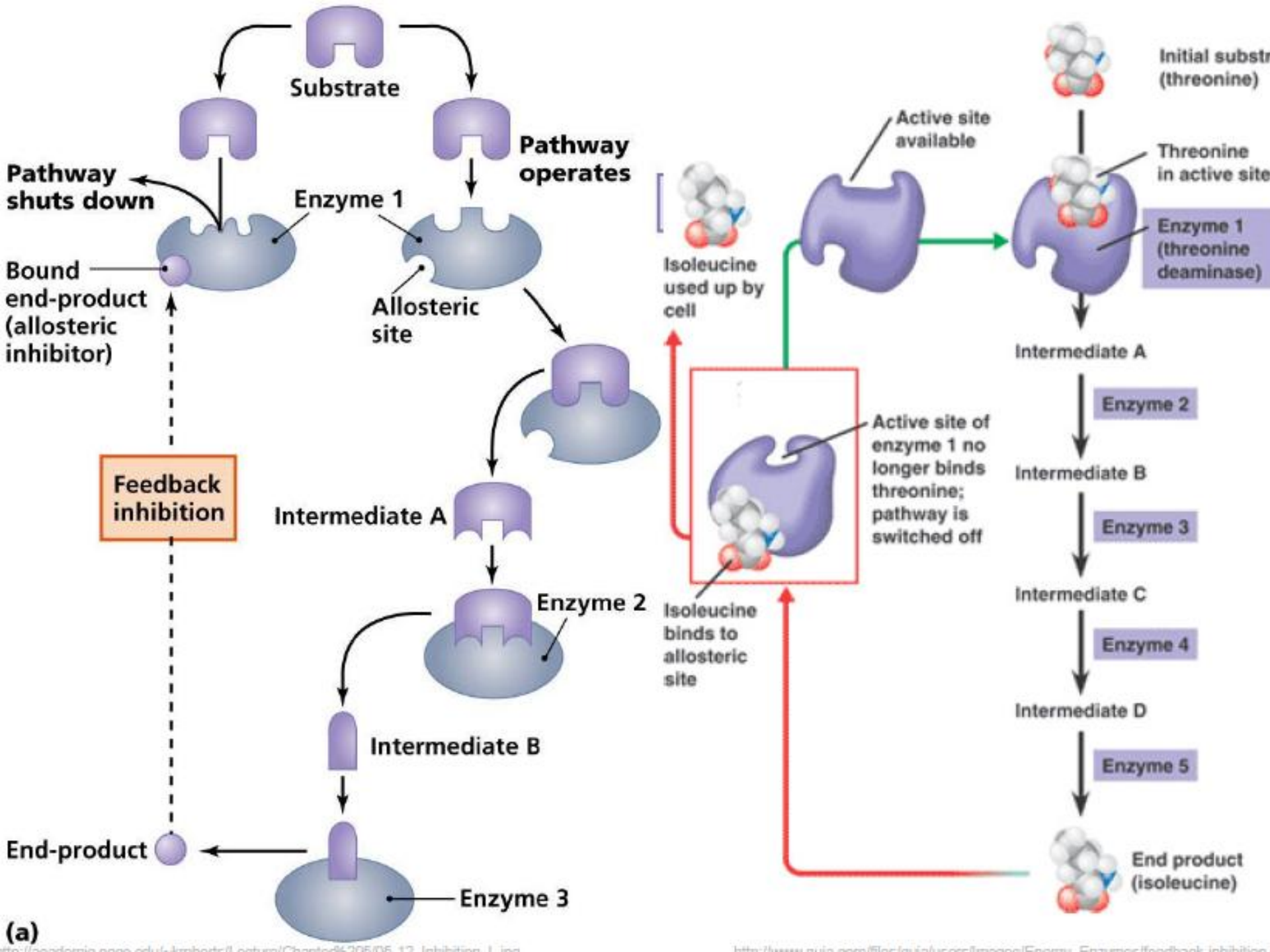
This is because there are fewer functional active sites available for reaction.

Why do inhibitors exist?



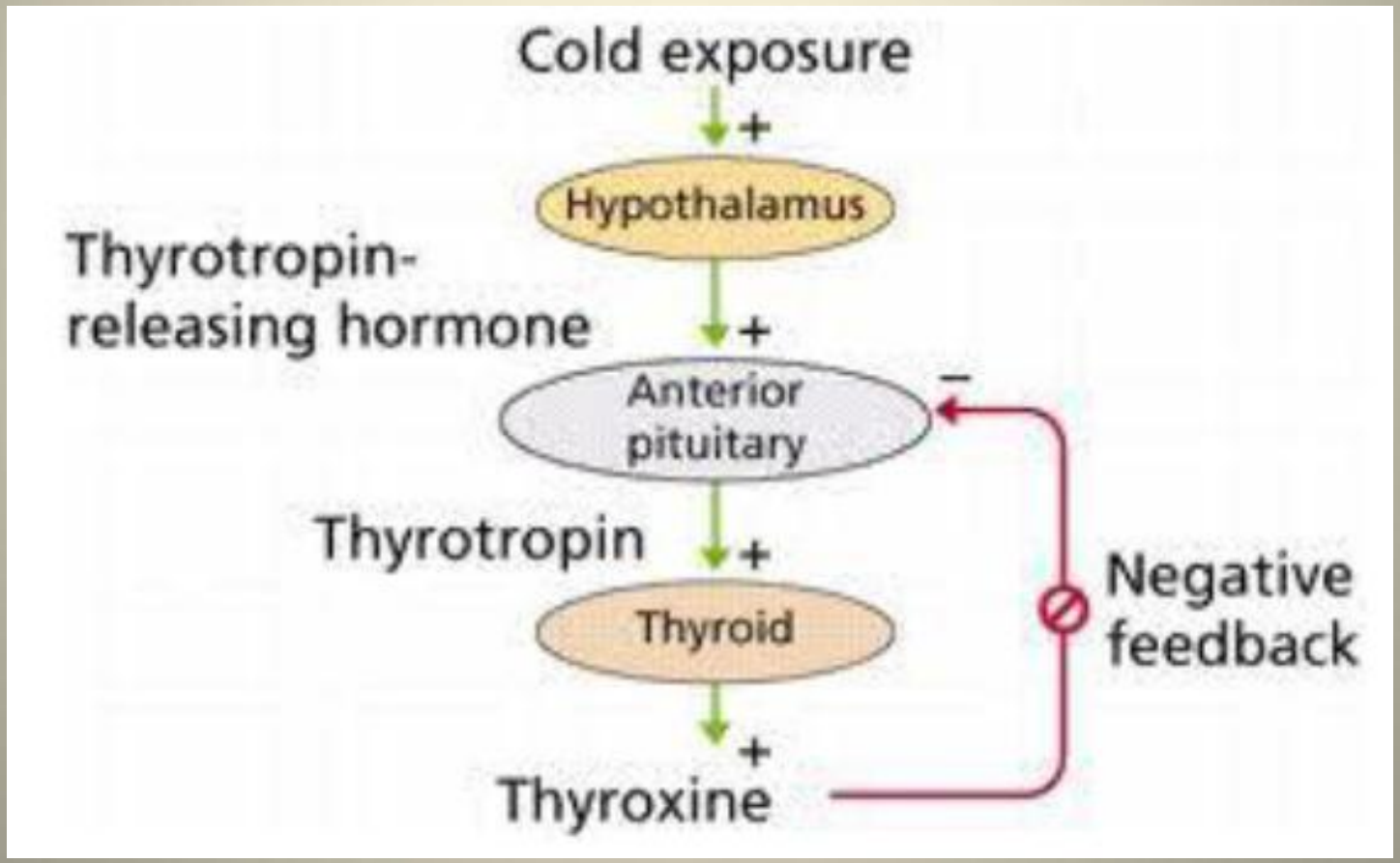
Negative feedback or feedback inhibition




Substrate
Pathway shuts down
Pathway operates
Enzyme 1
Bound end-product (allosteric inhibitor)
Allosteric site
Feedback inhibition
Intermediate A
Enzyme 2
Intermediate B
End-product
Enzyme 3
(a)
Isoleucine used up by cell
Active site available
Active site of enzyme 1 no longer binds threonine; pathway is switched off
Isoleucine binds to allosteric site
Initial substr
(threonine)
Threonine in active site
Enzyme 1 (threonine deaminase)
Intermediate A
Enzyme 2
Intermediate B
Enzyme 3
Intermediate C
Enzyme 4
Intermediate D
Enzyme 5
End product (isoleucine)

Why do inhibitors exist?

- Maintaining homeostasis



Video: Enzyme Inhibition

Tutorial Animation

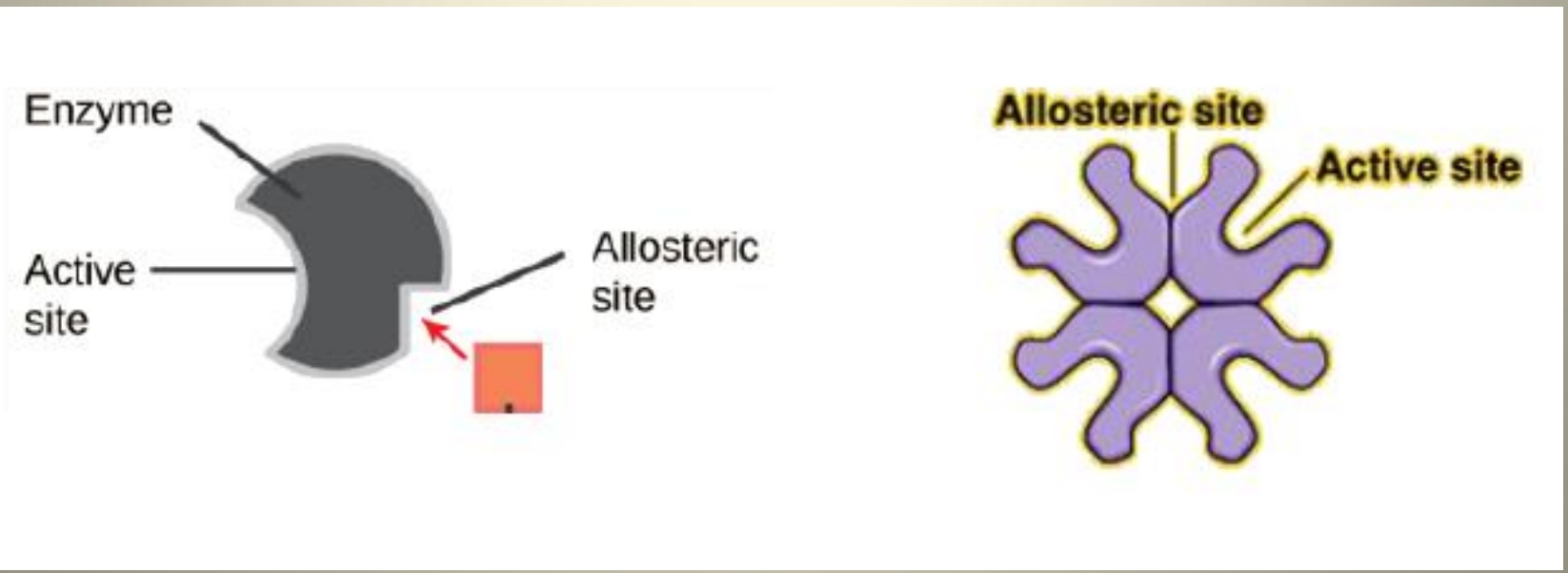
http://www.wiley.com//legacy/college/boyer/0470003790/animations/enzyme_inhibition/enzyme_inhibition.htm

Allosteric Enzyme

- has a second binding site that is not the active site (allosteric site)

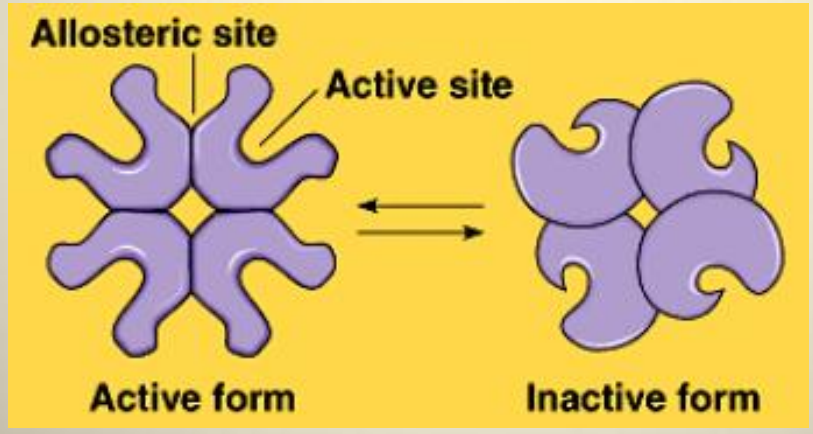
Allosteric Site

- a specific binding site on the enzyme that is not the active site
- can be located between subunits (where subunits join)



Allosteric Enzyme

- has two conformations: active and inactive
- naturally oscillates between the two conformations



Allosteric Enzyme

- binding of the molecule (effector) to the allosteric site can stabilize one of the conformations

Effectors: Allosteric Regulators

- a regulator that can activate or inhibit the enzyme by binding to an allosteric site
- changes enzymatic activity by binding weakly to an allosteric site
- Classifications:

  - Allosteric **inhibitor:** stabilizes the conformation that lacks an active site (inactive form)

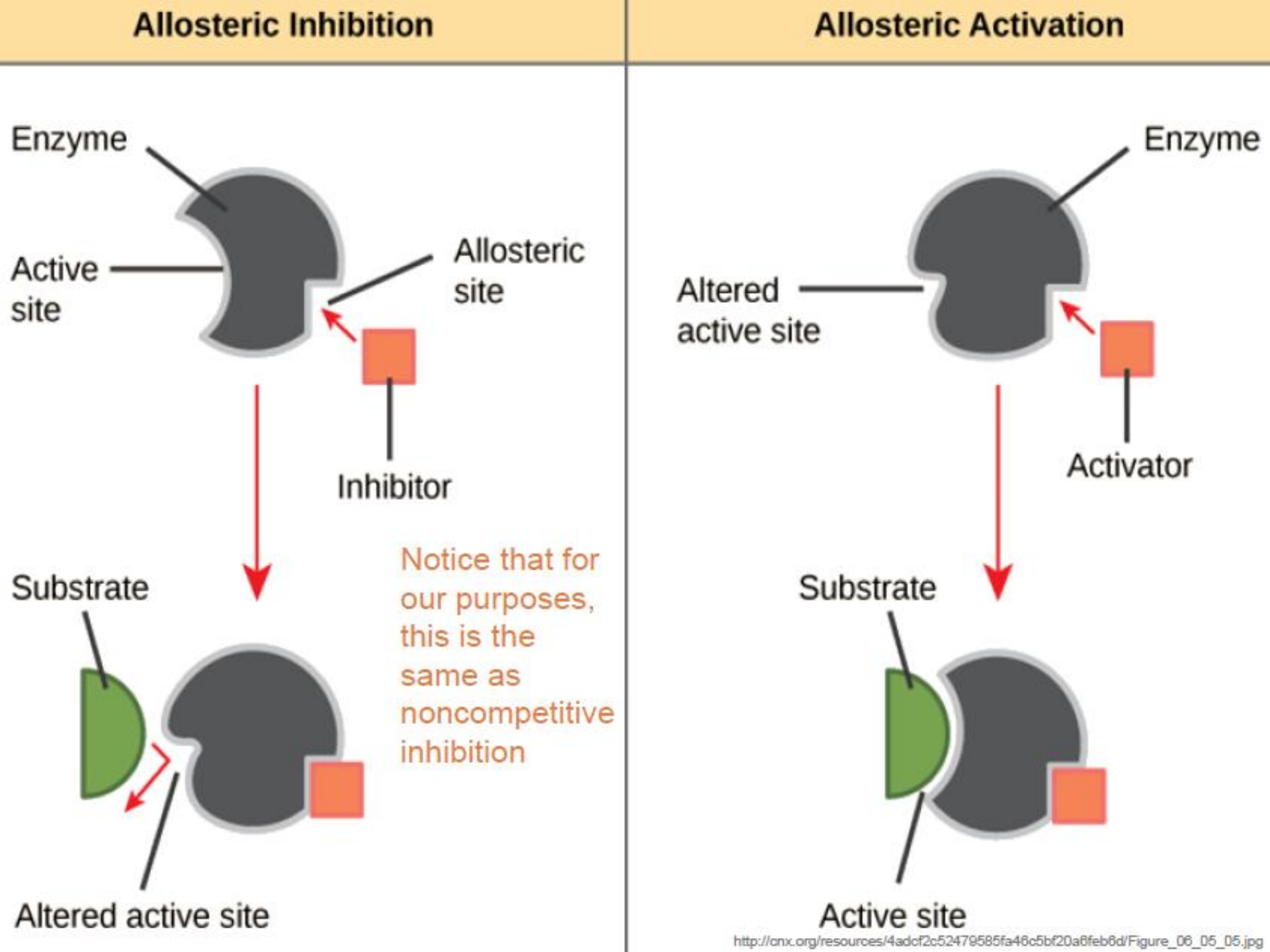
  -Allosteric **activator:** stabilizes the conformation that has a functional active site

Allosteric Regulation

- Regulating an enzyme's activity with an allosteric regulator (effector) that binds to the allosteric site
- Type of effector results in one of two allosteric regulation mechanisms:

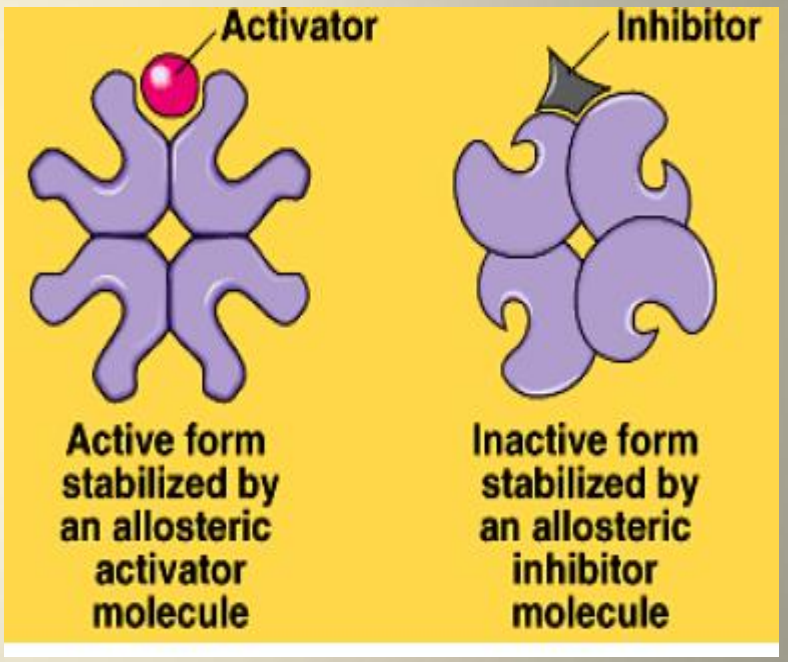
    - Allosteric Inhibition

    -Allosteric Activation


Allosteric Inhibition
Allosteric Activation
Enzyme
Active site
Allosteric site
Inhibitor
Substrate
Altered active site
Notice that for our purposes, this is the same as noncompetitive inhibition
Enzyme
Altered active site
Activator
Substrate
Active site
http://cnx.org/resources/4adcf2c52479585fa46c5bf20a8feb6d/Figure_06_05_05.jpg

Allosteric Regulation & Cooperativity

- If the allosteric site is located between subunits, then the binding of one effector could stabilize the conformation of all the other subunits
- This is known as cooperativity



Cooperativity

- Binding of a molecule (substrate or effector) stabilizes a conformational change on all the other subunits
- Can only occur in enzymes with multiple subunits (quaternary structure)
- Can result in an increase or decrease in substrate affinity

Cooperativity

Positive cooperativity:

-Substrate binding

-Effector (activator) binding

Negative cooperativity:

-Effector (inhibitor) binding

-Example: some forms of noncompetitive inhibition

Activity: Consolidate Terms

- Use a graphic organizer to show the relationship between these terms listed on the right
- Graphic organizers that may be useful in this activity are:

  -Mind map

  -Flow charts

  -Venn diagram

Terms

- Inhibition
- Competitive inhibition
- Noncompetitive inhibition
- Allosteric regulation
- Allosteric inhibition
- Allosteric activation
- Effector
- Allosteric inhibitor
- Allosteric activator
- Cooperativity
- Positive cooperativity
- Negative cooperativity
- Substrate
- Active site
- Allosteric site