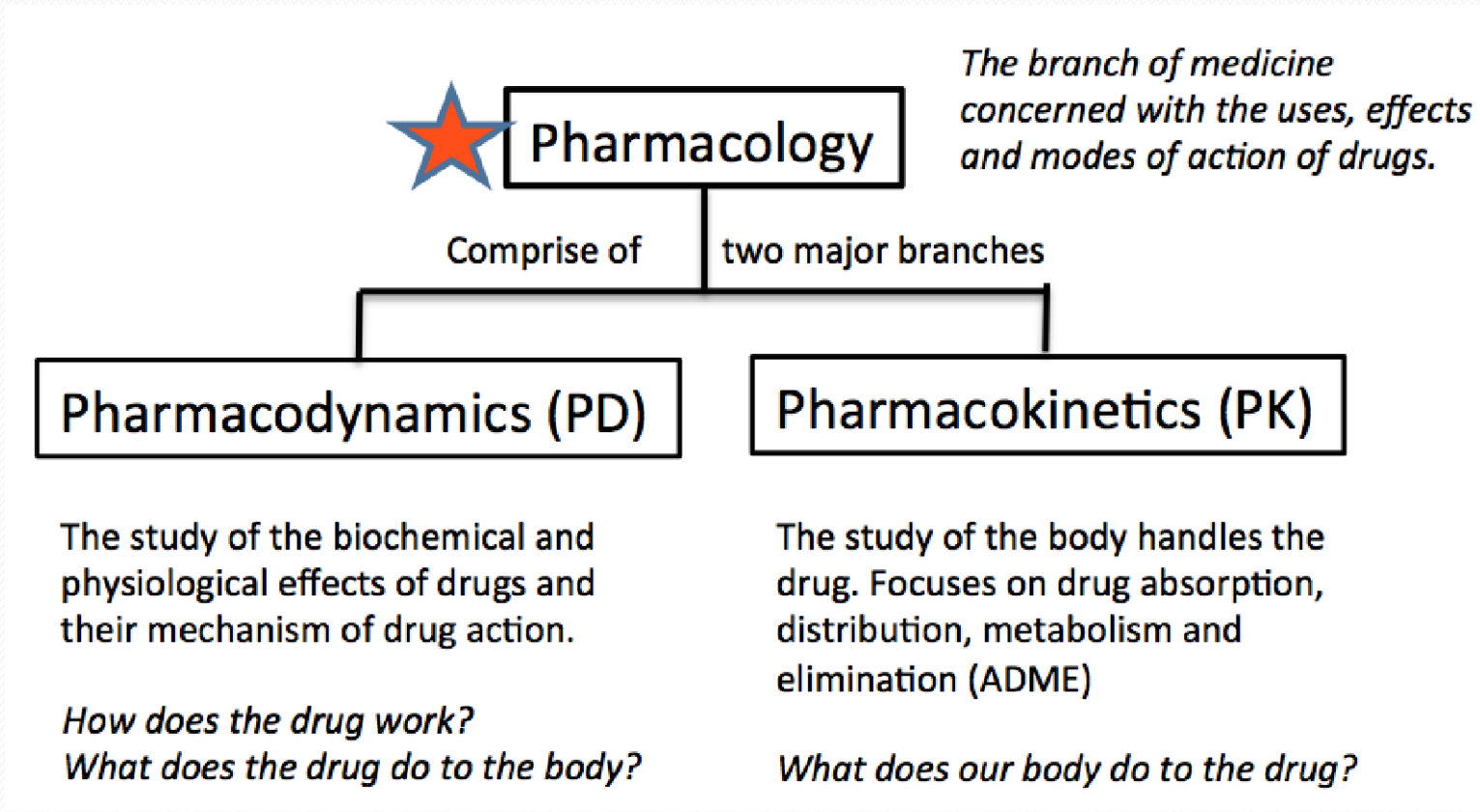
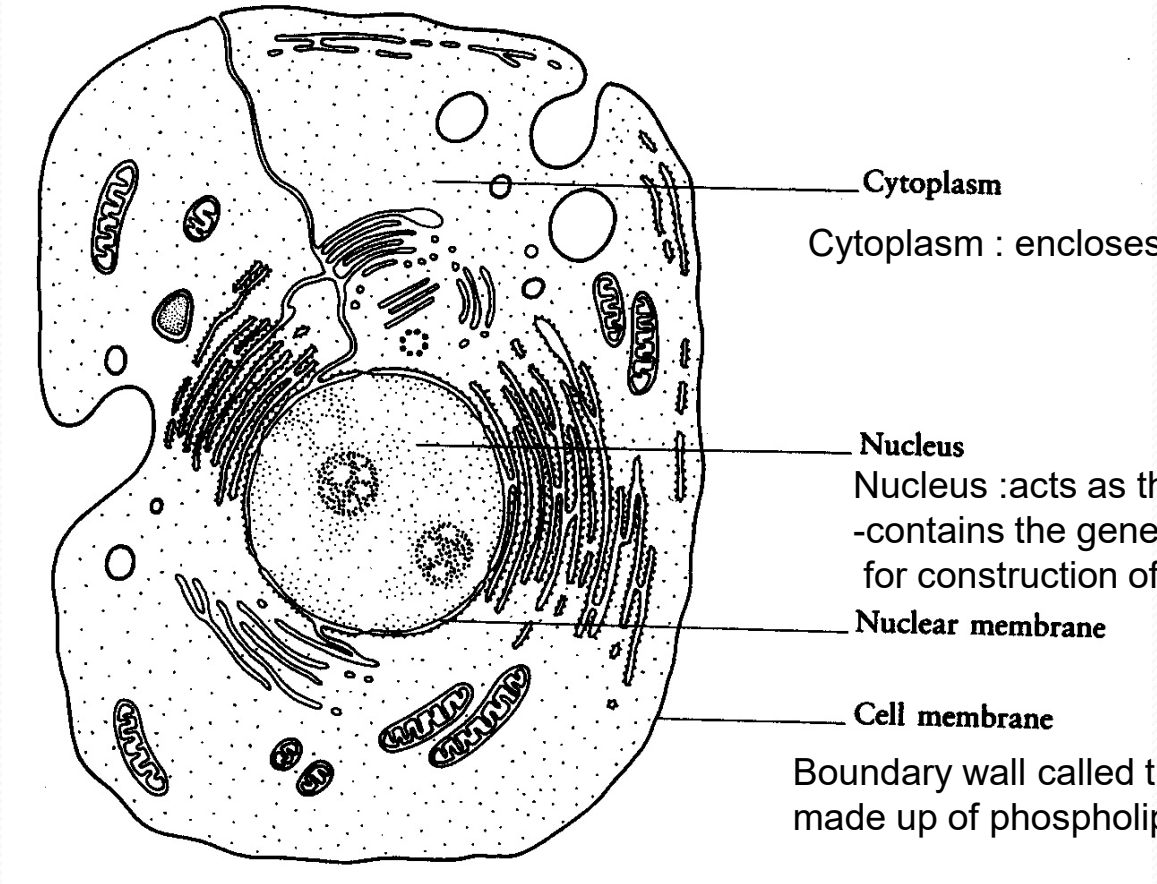
CP4163 : Pharmacology and pharmaceutical chemistry

Topic 2:
Introduction to Pharmacodynamics

Pharmacology – An overview



Drugs act on cells



Cytoplasm : encloses the contents of the cell

Nucleus :acts as the 'control centre' of the cell.
-contains the genetic code, DNA and blueprints for construction of all the cell's proteins .

Boundary wall called the cell membrane :
made up of phospholipids and proteins.

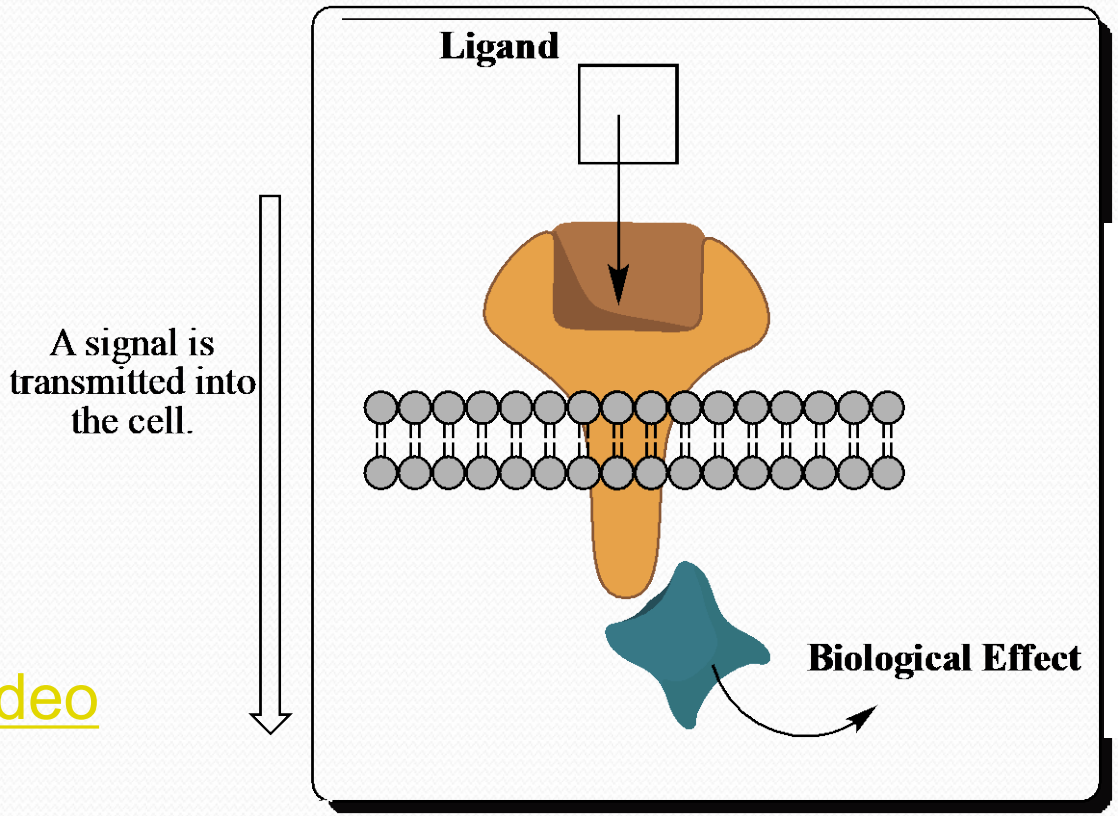
Biological targets of drugs

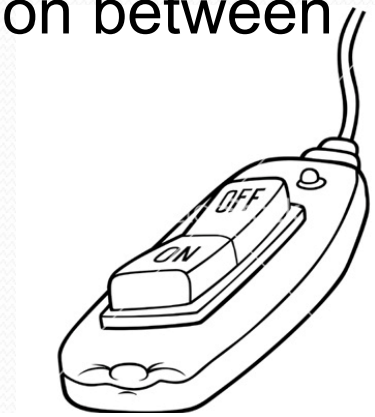
- **Receptors**
- **Enzymes**

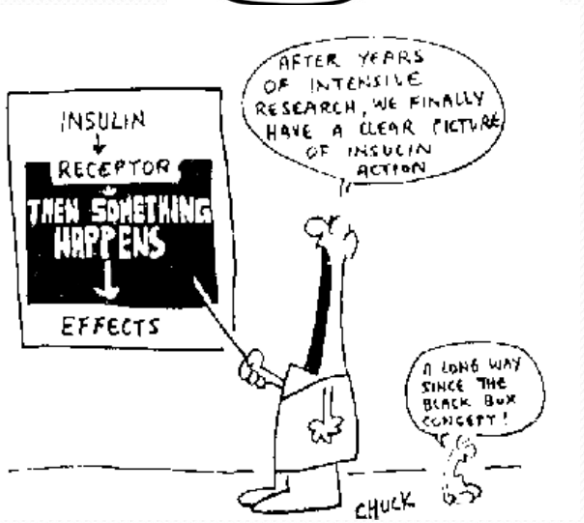
Proteins

Receptors

Receptors are proteins usually on the cell membrane that are involved in communication and coordination between and within cells.



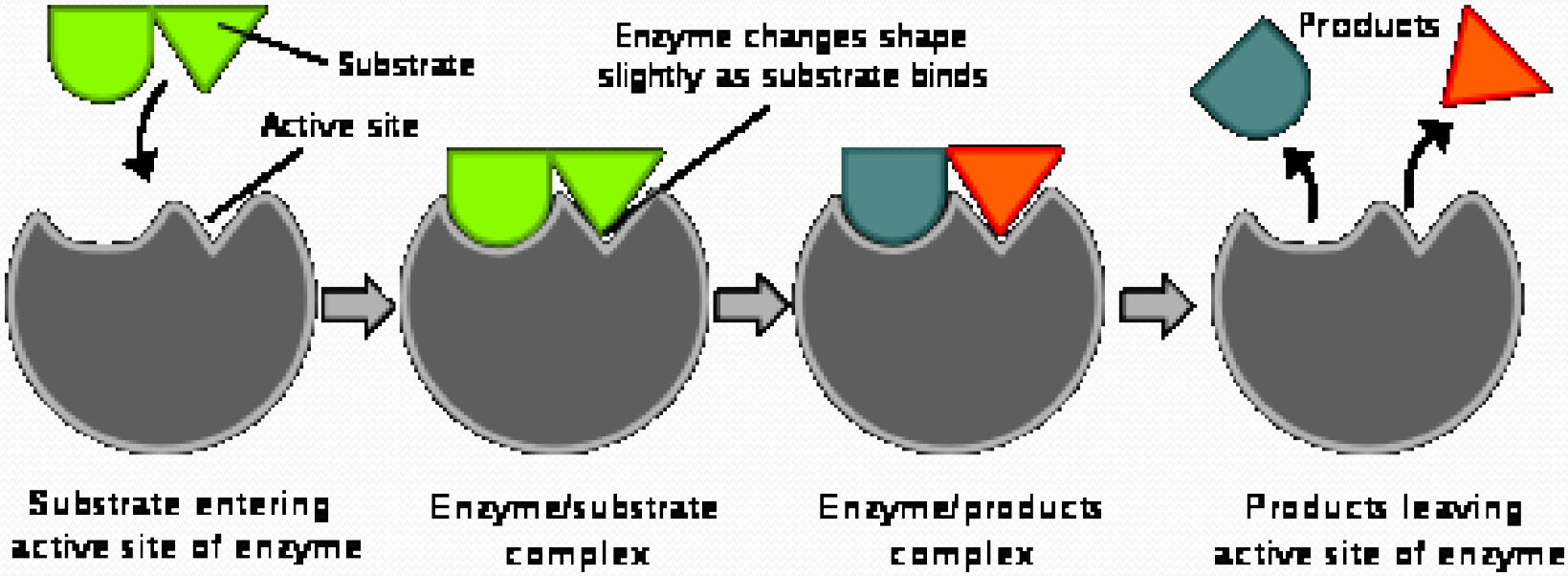




Video

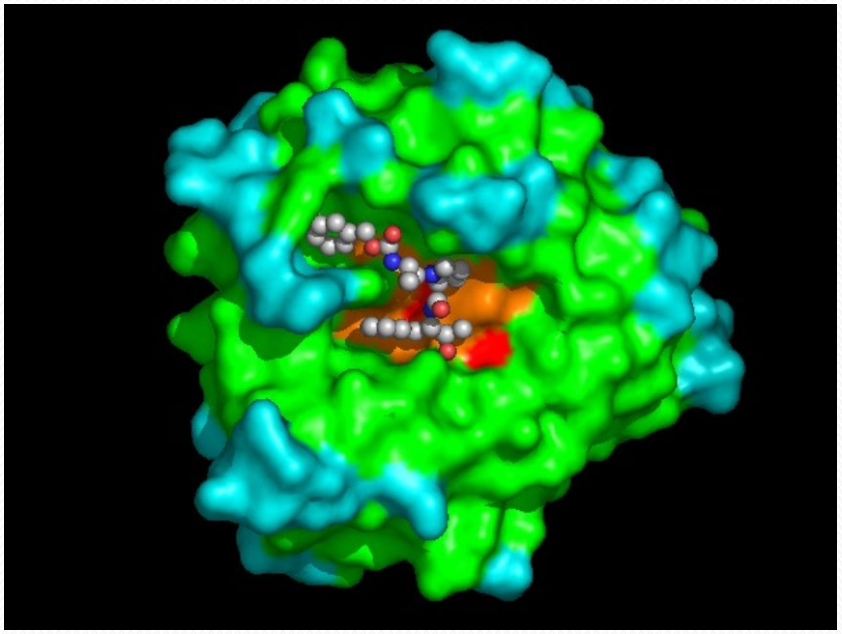
Enzymes

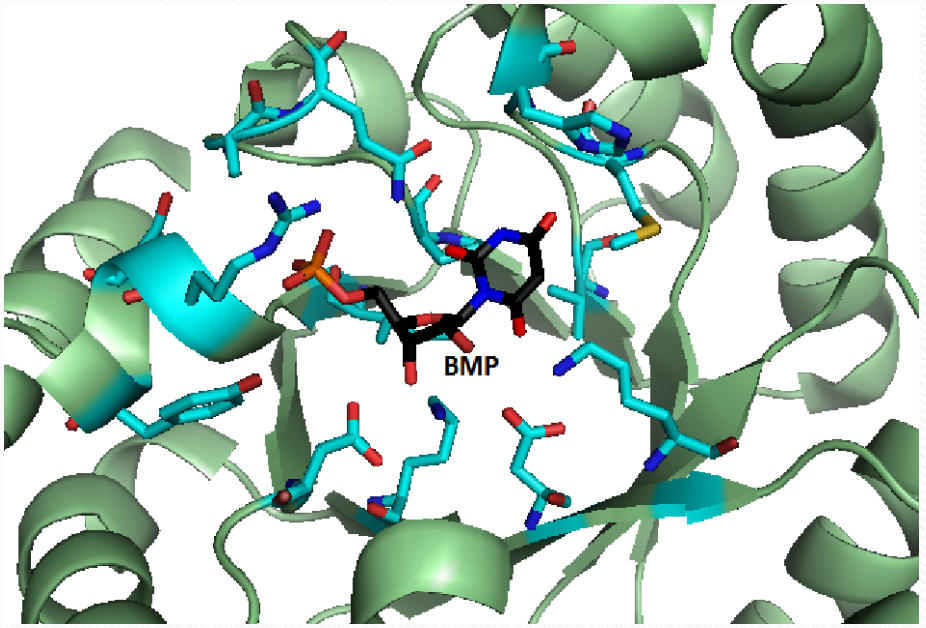
Enzymes are proteins that catalyze chemical reactions in the cell.



Active Site

Where drug binds

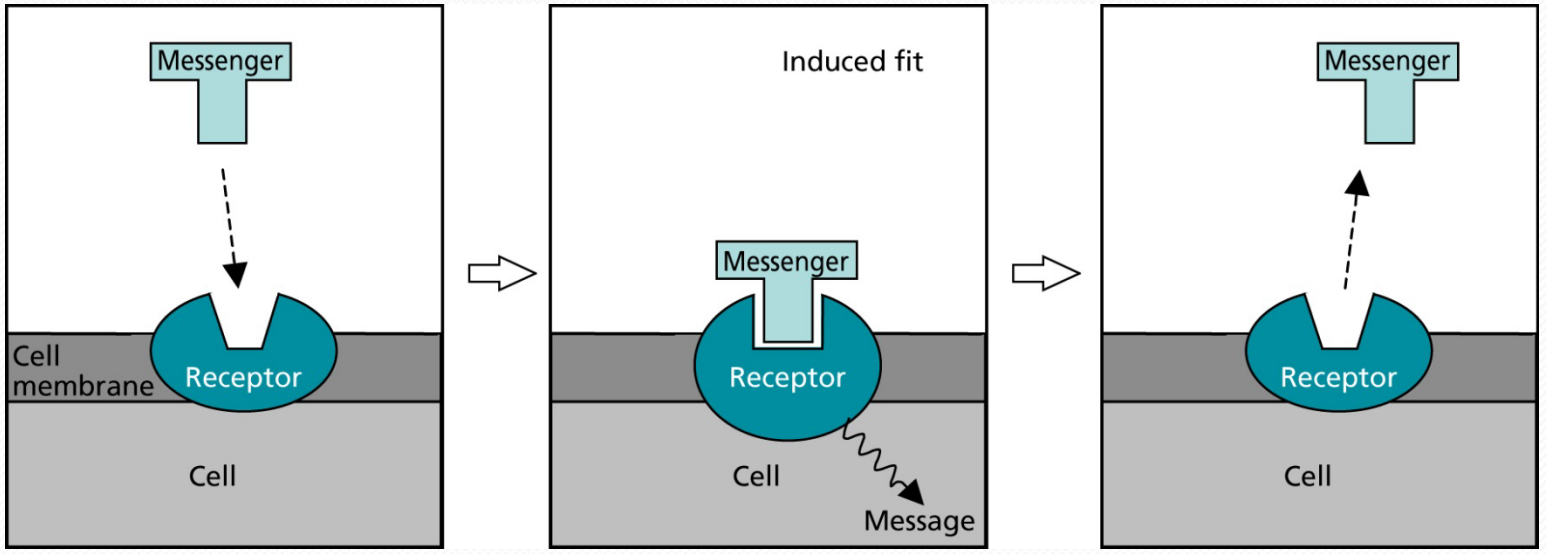




Video – changes in protein conformation

Drug Receptor Theory

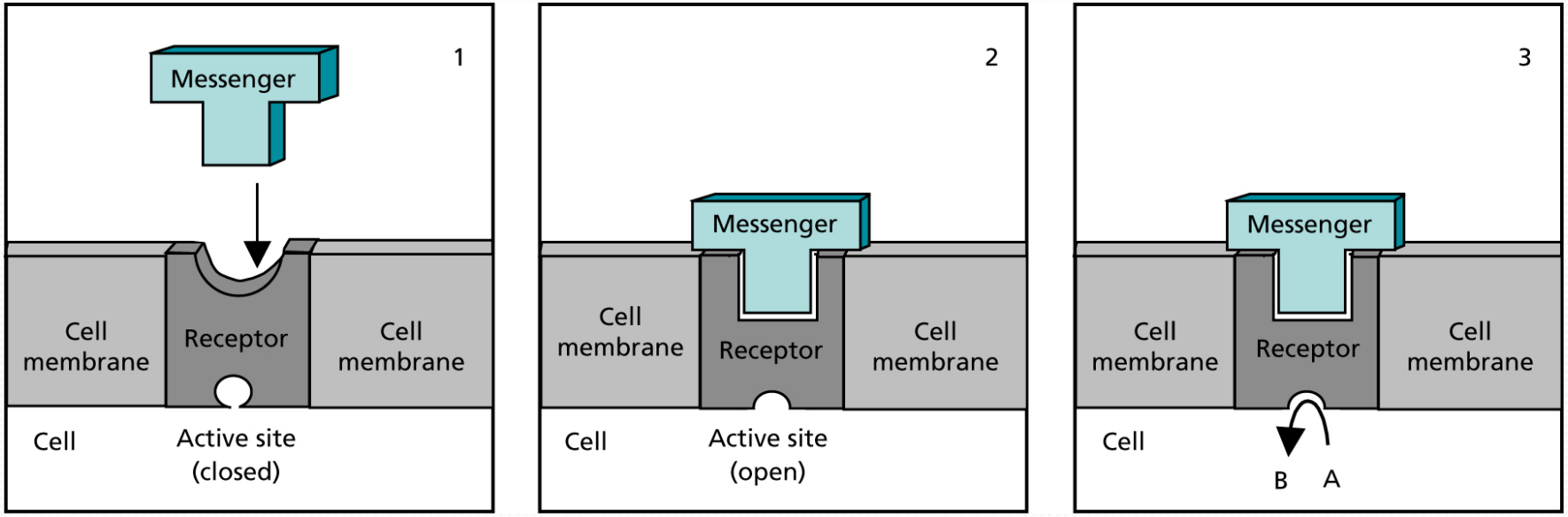
Molecules that interact with receptors are called **ligands.** Each receptor commonly has at least 1 naturally occurring ligand that interacts with its binding site. This is called the **ligand binding site**. When a ligand binds, it switches on the receptor and a message is propagated.



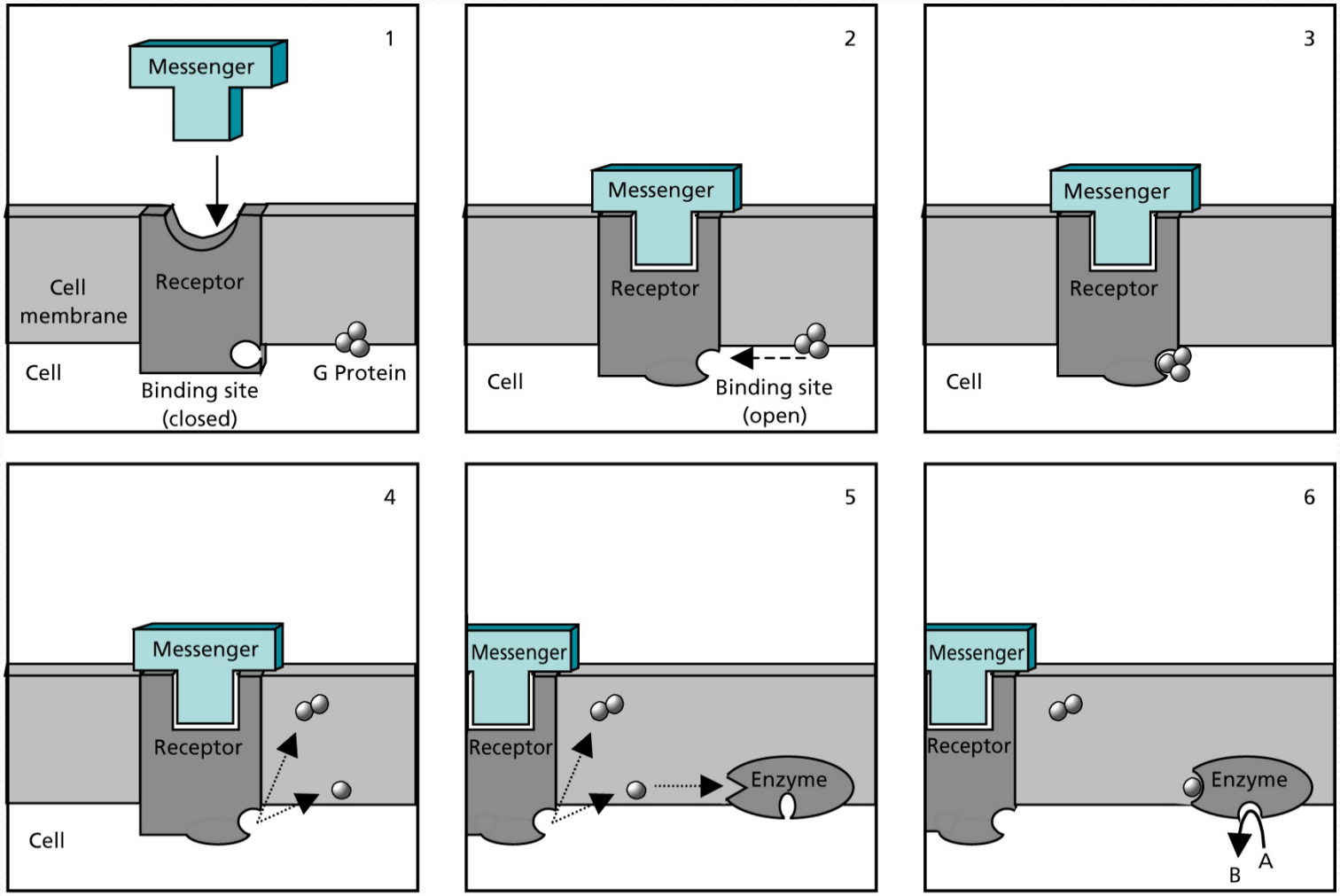
When the ligand binds, it **changes the shape of the receptor protein** once it has binds into the binding site. It does not fit the binding site exactly. Instead, as it binds at the site, various attractions between the ligand the functional groups on the binding site pull toward each other, distorting the shape of the rest of the protein.

Effect of a ligand-receptor interaction:

- **Activation of a membrane bound enzyme.**



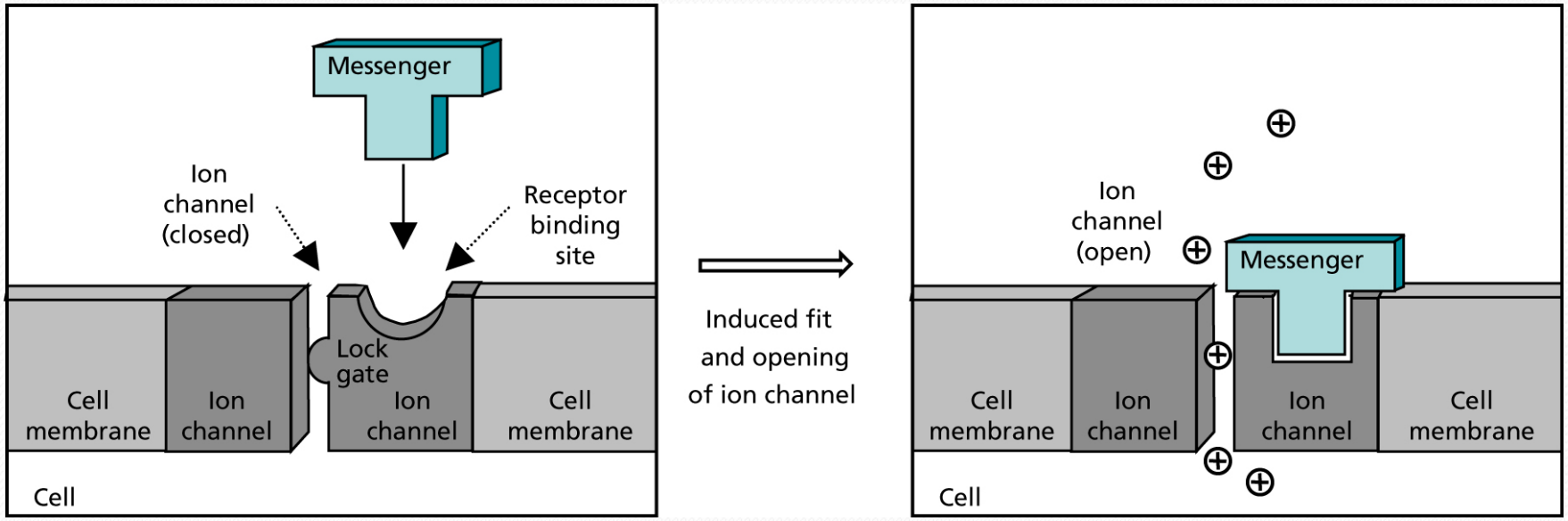
- **Release of secondary messengers within the cell's membrane which migrate to other parts of the membrane and either activate or inhibit further enzymes**



Video

G-Protein

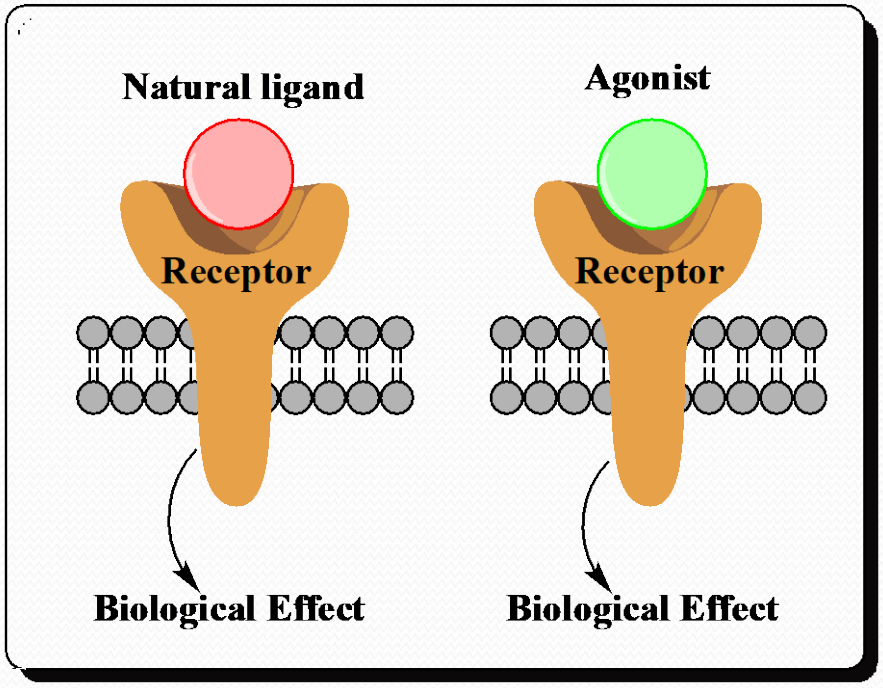
- **Open (or close) an ion channel through the membrane, allowing hydrophilic ions to pass through the hydrophobic cell membrane.**

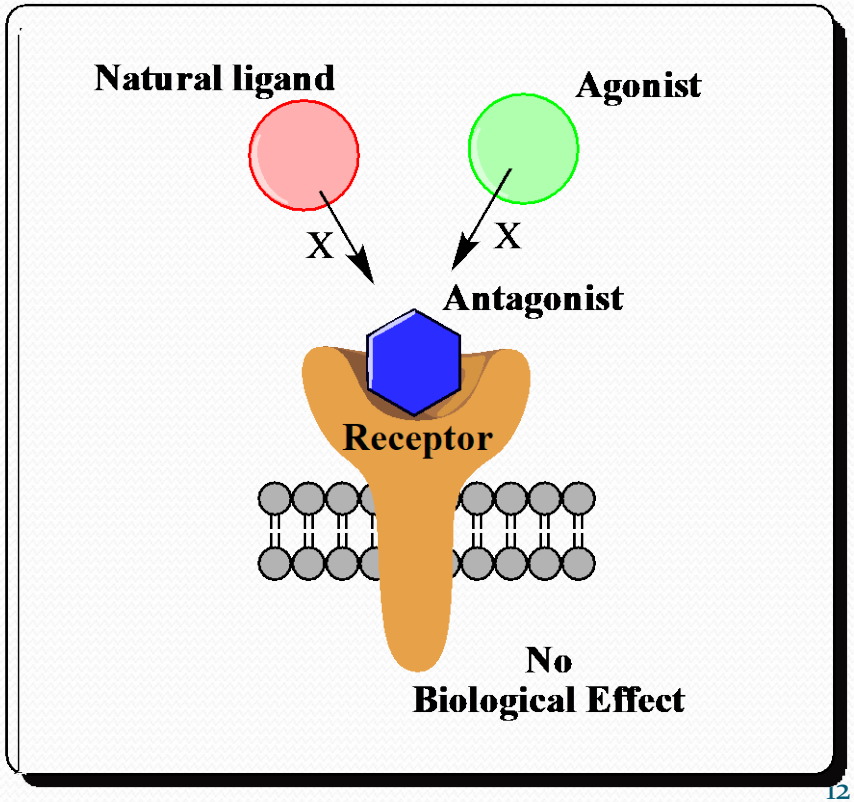


Video Video2

Agonist vs Antagonist

- **Agonists** and **antagonists** are ligands of a receptor.
- Most drugs that you see in the market are either agonists or antagonists of either receptors, or enzymes.





Natural ligand = **endogenous ligand**

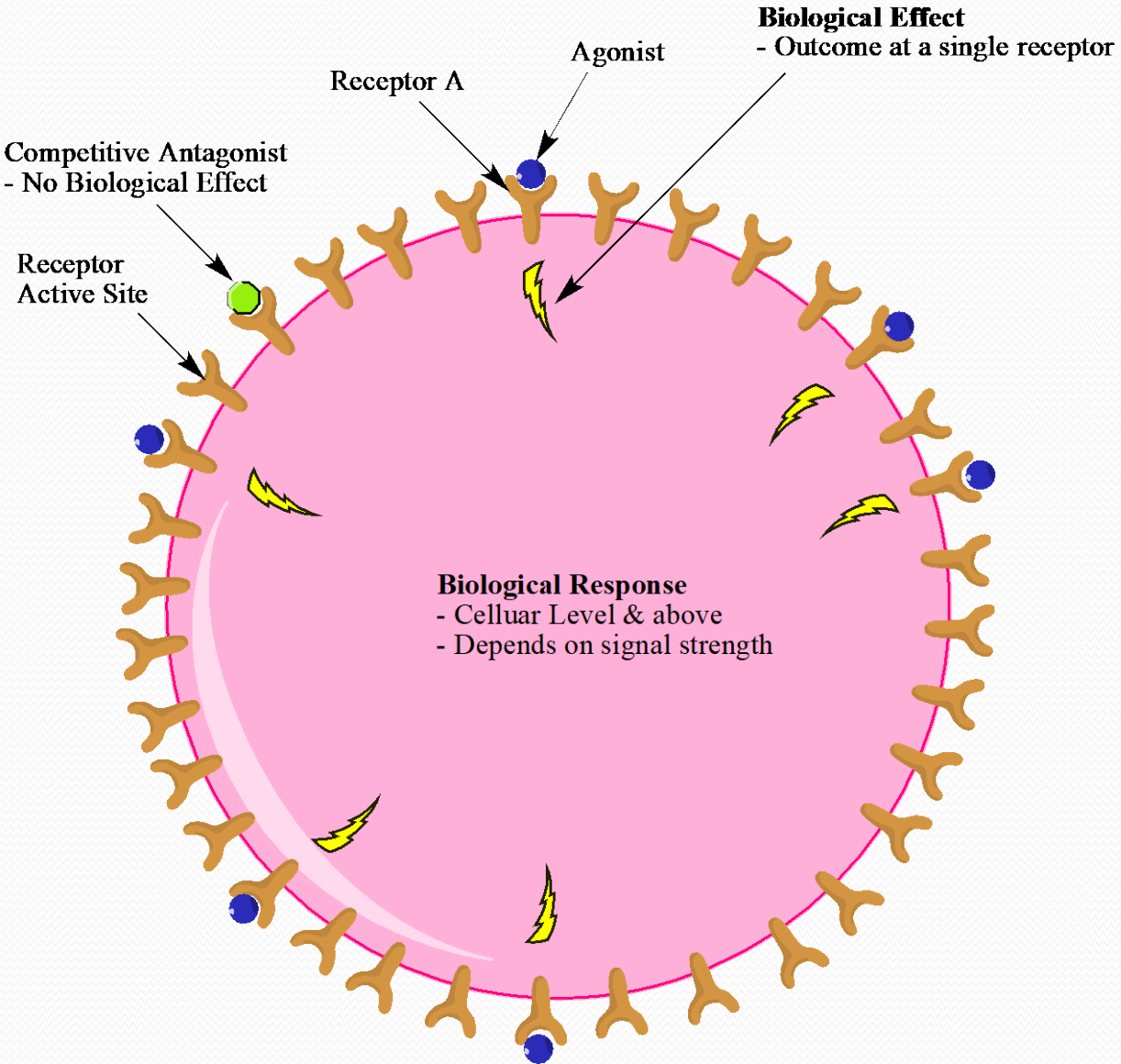
Agonist

- **Agonists** often have structures that are similar to that of the endogenous ligand.
- Endogenous ligands are naturally occurring molecules in the body that have innate biological functions.
- An agonist is a molecule that gives rise to biological effect. It mimics the endogenous ligand.
- **Both endogenous ligand and agonists produces similar biological effect**.
- ***When the biological response is lacking in a disease, an agonist drug can restore the biological function*.**

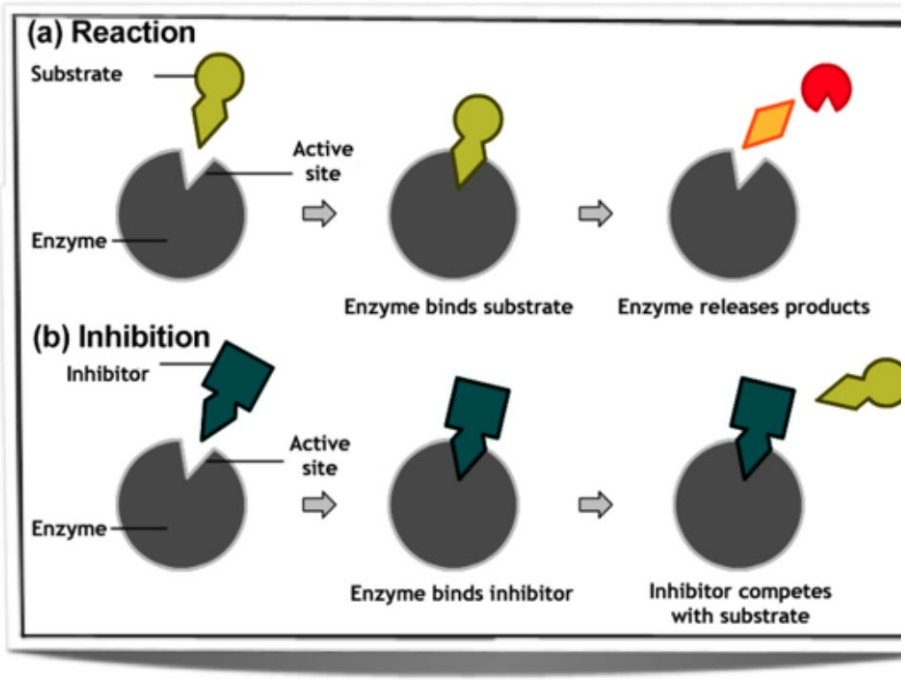
Antagonist

- Binds to the receptor but **does not produce a biological effect**.
- Prevents the binding of the endogenous ligand or agonist.
- Blocks the action of a receptor. This would reduce the effect of an endogenous ligand.
- ***When the biological response is too overwhelming, a drug that serves as an antagonist would restore the biological function.***

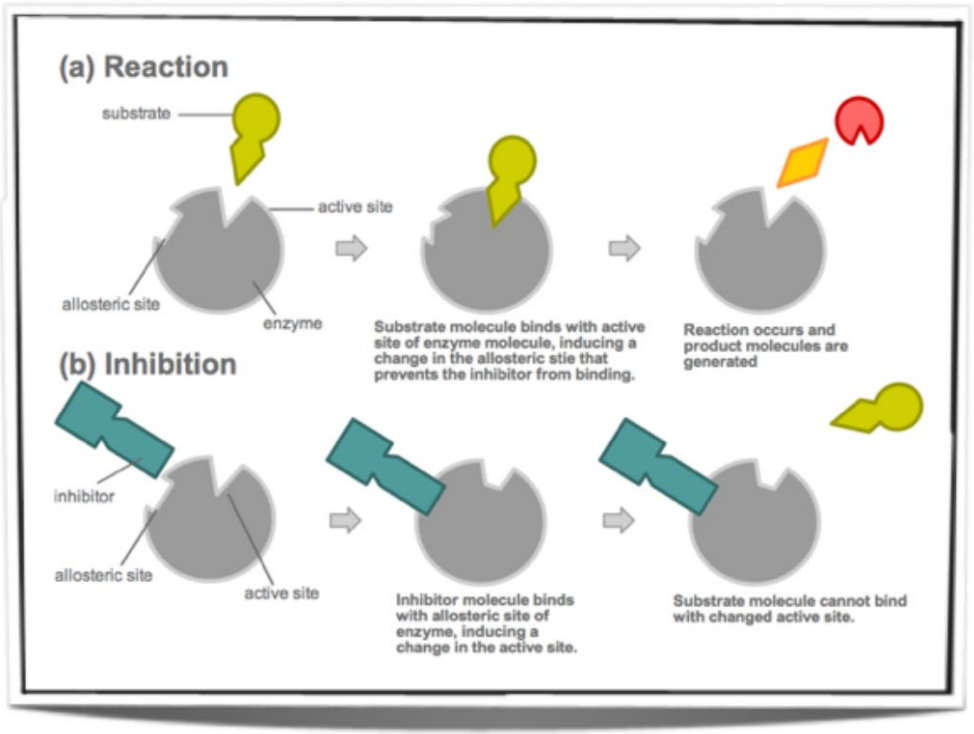
Difference between Biological Effect and Biological Response



Competitive vs Non-competitive Antagonists / Inhibitors

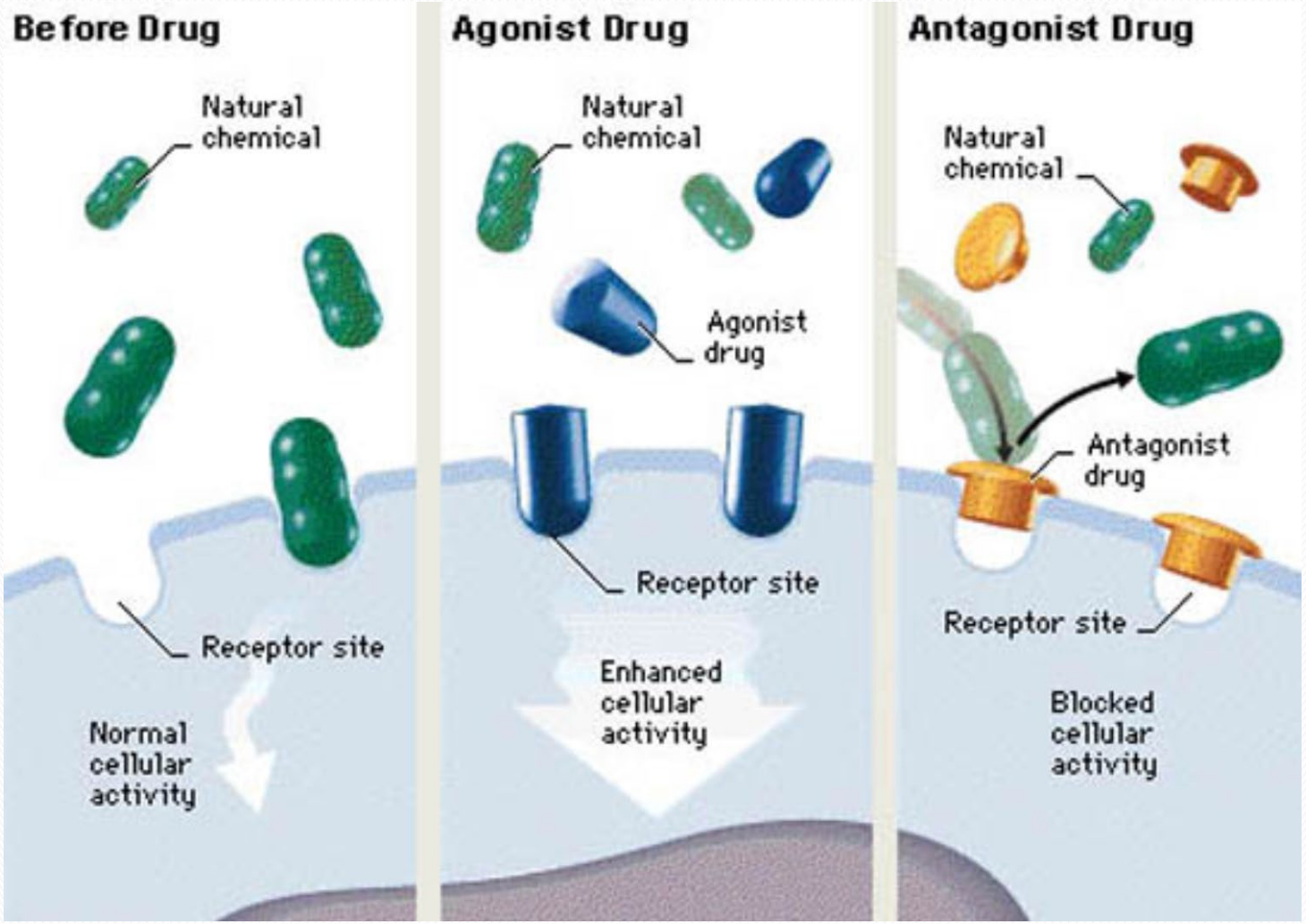


Competitive

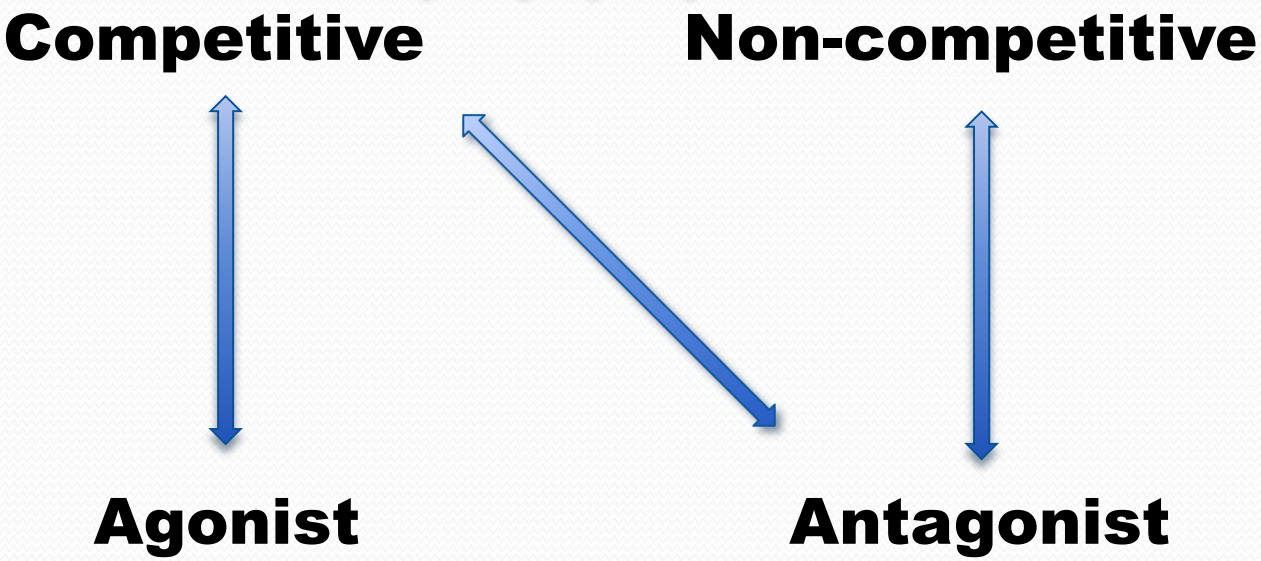


Non-competitive

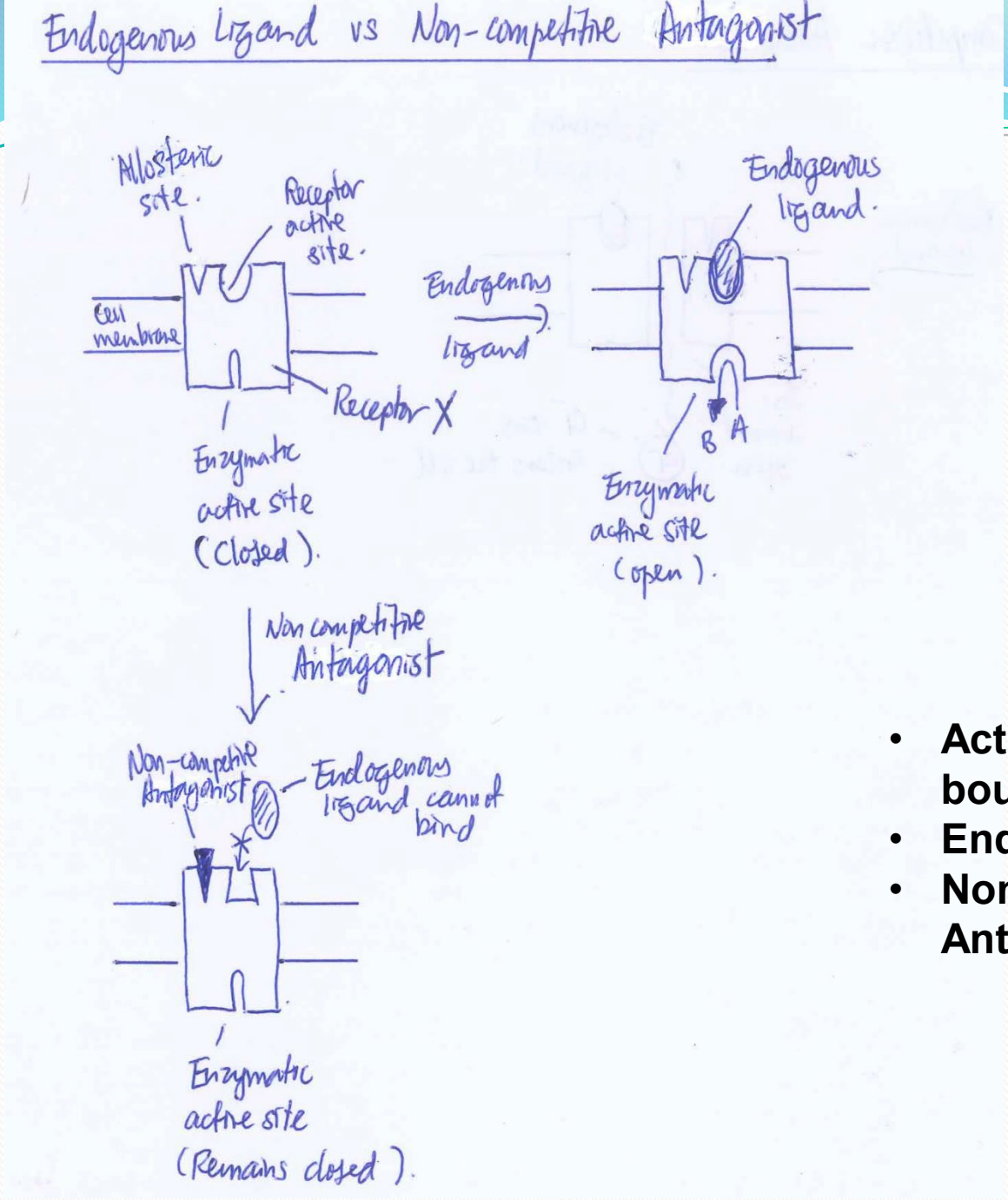
Summary of Agonist & Antagonists



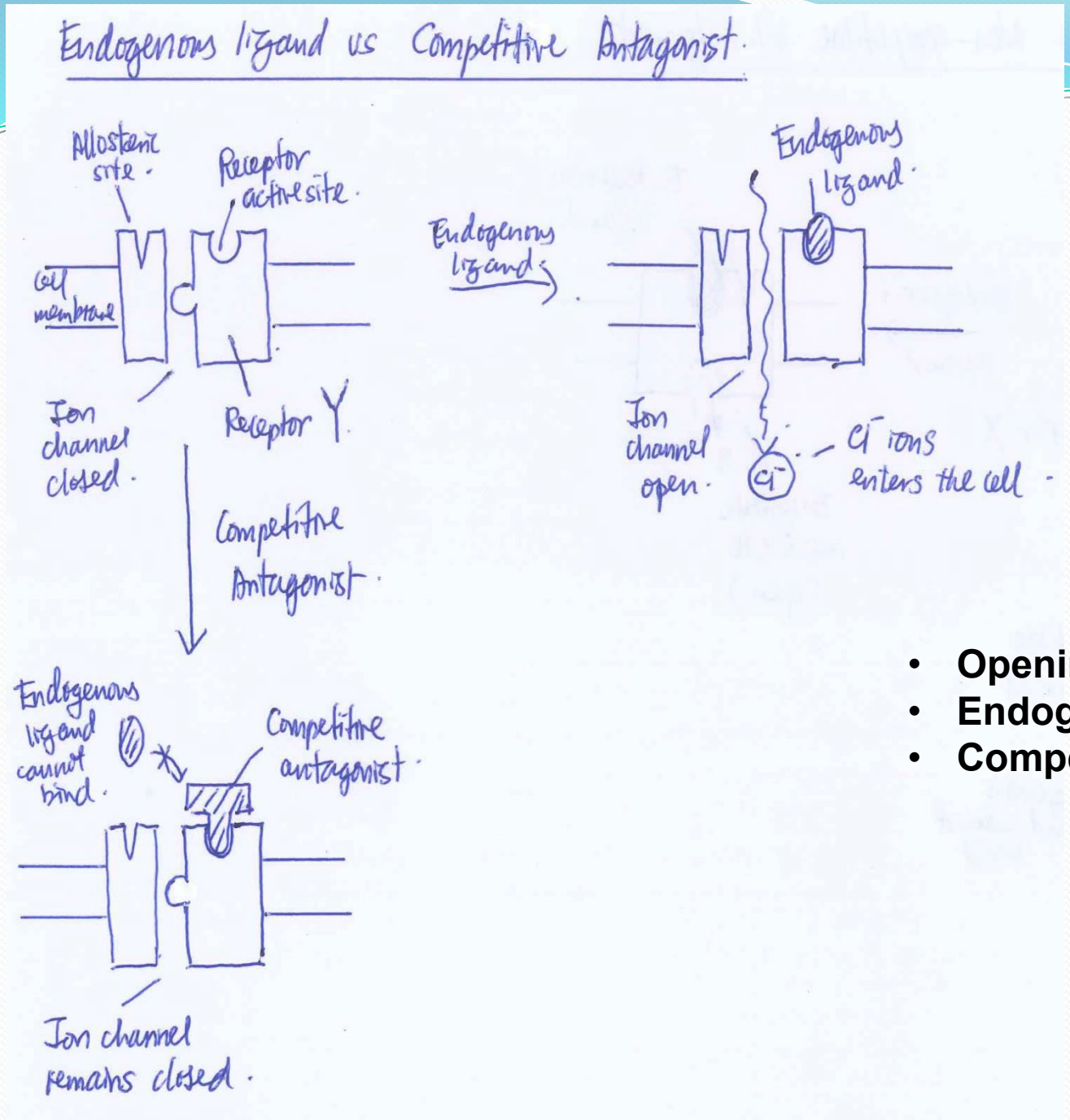
Summary



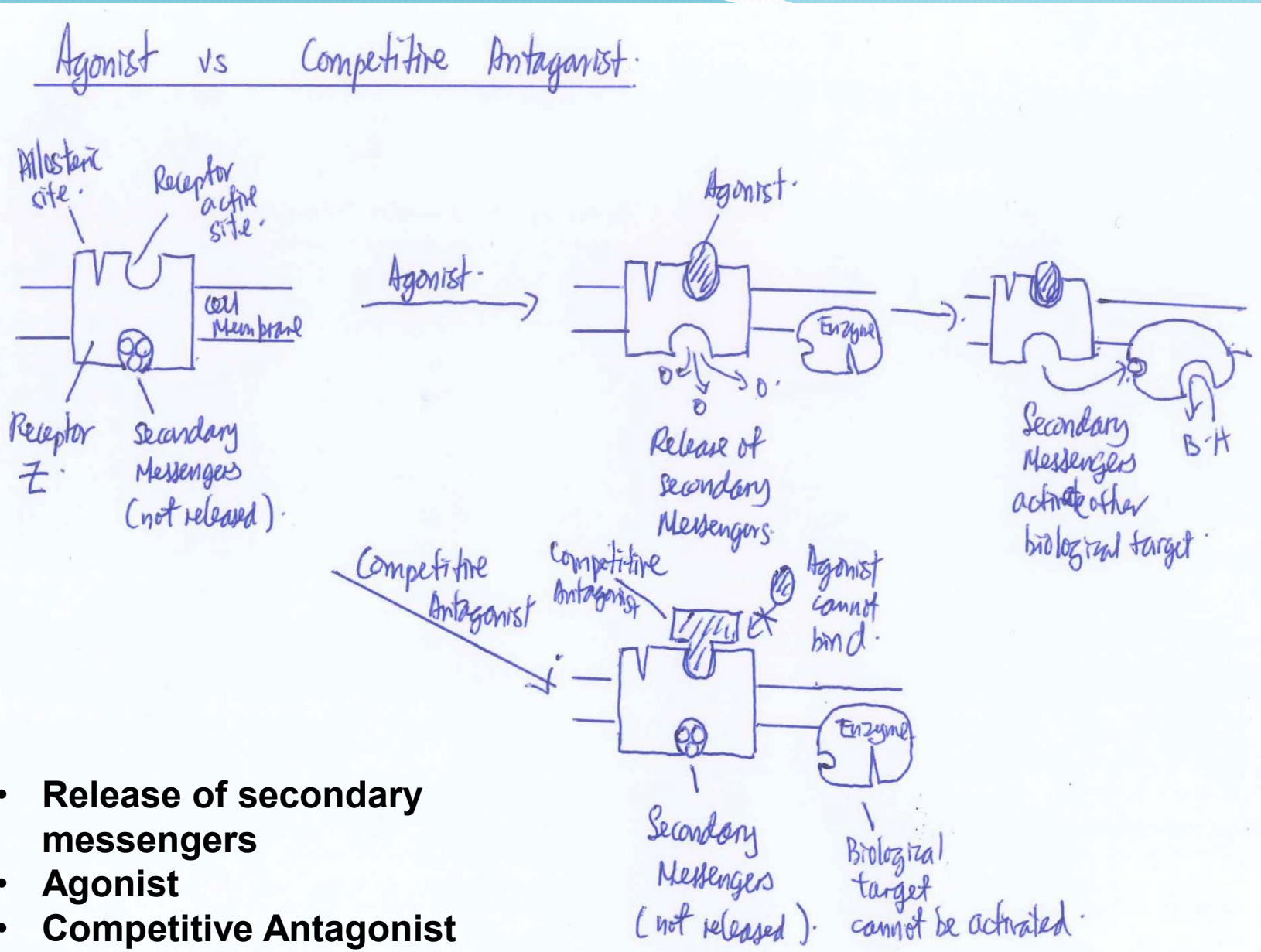
- Activation of Membrane-bound enzyme
- Release of Secondary Messengers
- Open/Close Ion-channels



- **Activation of membrane bound enzyme**
- **Endogenous ligand**
- **Non-competitive Antagonist**



- **Opening Ion Channel**
- **Endogenous ligand**
- **Competitive Antagonist**



- **Release of secondary messengers**
- **Agonist**
- **Competitive Antagonist**

Pharmacodynamics of drug binding

The binding of a drug molecule to the active site of a receptor is classified into 2 types: Irreversible binding and reversible binding.

Irreversible binding

✓Involves strong covalent bonds
✓Drug molecule cannot detach from the receptor active site

Drug + Receptor ⟶ (Drug – Receptor) Complex

Reversible binding

✓Involves ionic interaction, hydrogen bonds, ion dipole interactions, van der waals interactions and permanent dipole interacts.
✓Drug molecule can be unbound from the active site because drug binding and unbinding is in an equilibrium process.

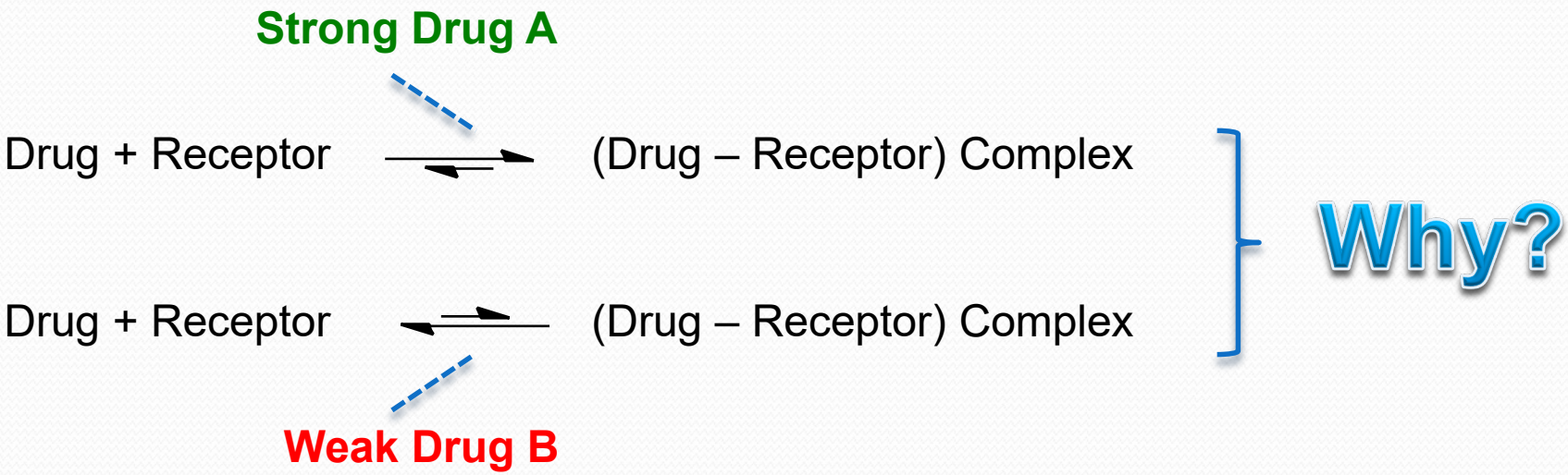
Drug + Receptor $\rightleftharpoons$ (Drug – Receptor) Complex → **Biological Effect**

Le Chatelier's principle?

Why is it much more favourable to have a drug that binds reversibly at the receptor?

Why do potent drugs usually require a lower dose and weaker drug require a higher dose?

Why do potent drugs usually require a lower dose and weaker drug require a higher dose?



- The **strength of the interaction** between a drug molecule and its receptor can be determined the equilibrium constant , K_d for the interaction:

$$K_d = \frac{[\text{drug}][\text{receptor}]}{[\text{complex}]}$$

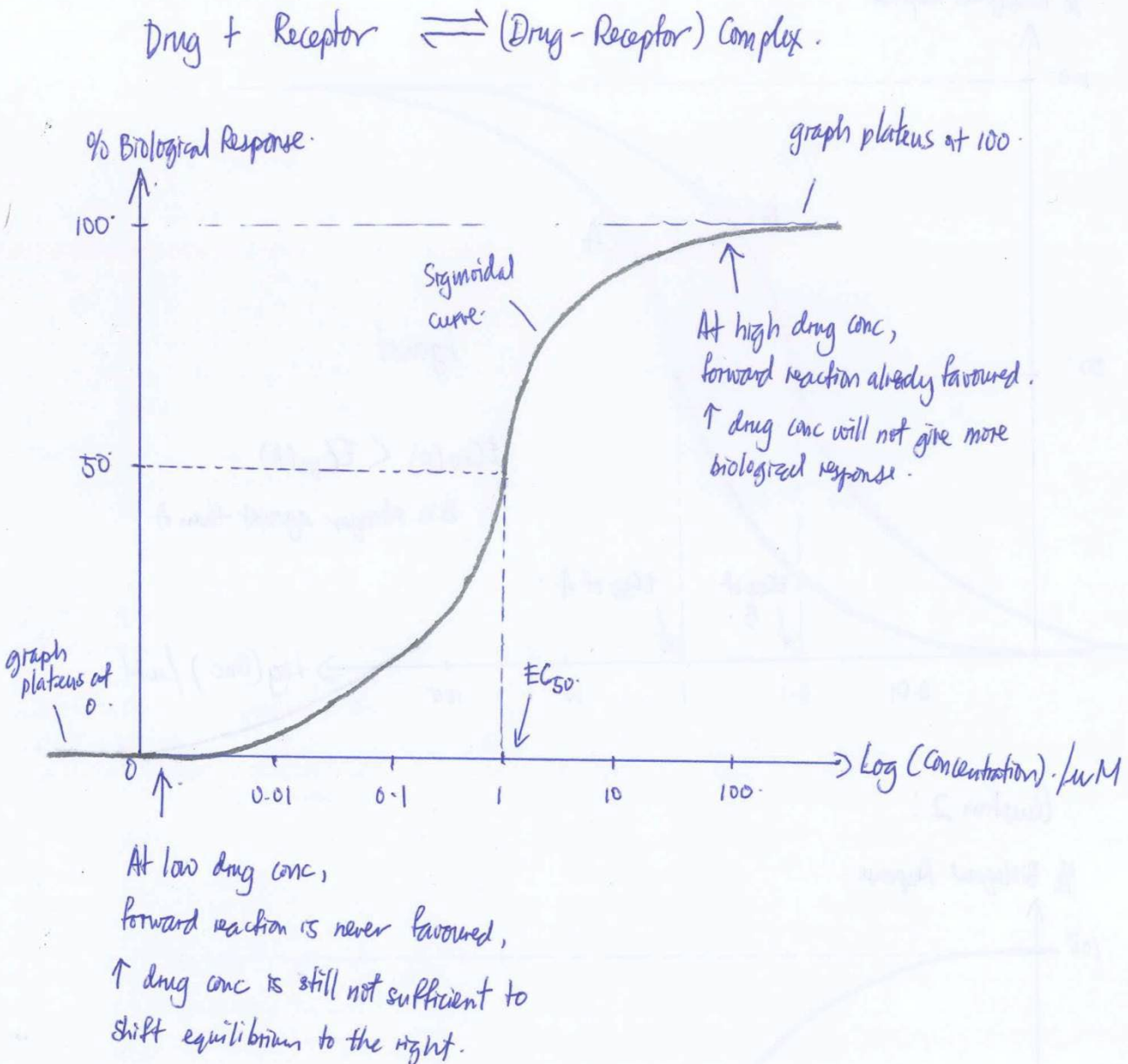
K_d reflects how strong the drug molecule have bound.

Drug + Receptor $\rightleftharpoons$ (Drug – Receptor) Complex

K_d

(Dissociation reaction – backward reaction)

Dose Response Curve

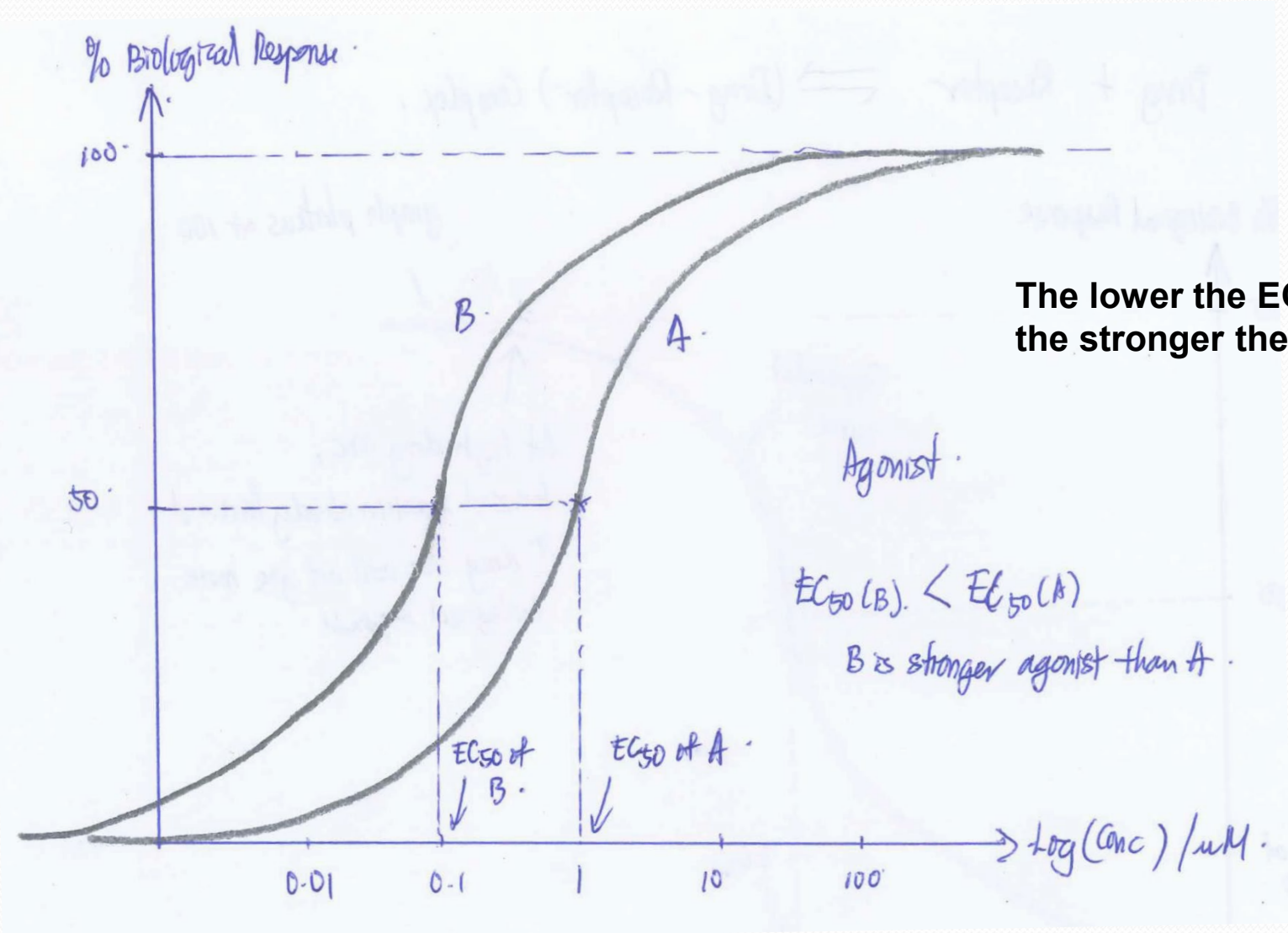


Copy the graph on to your lecture notes

Dose Response Curve

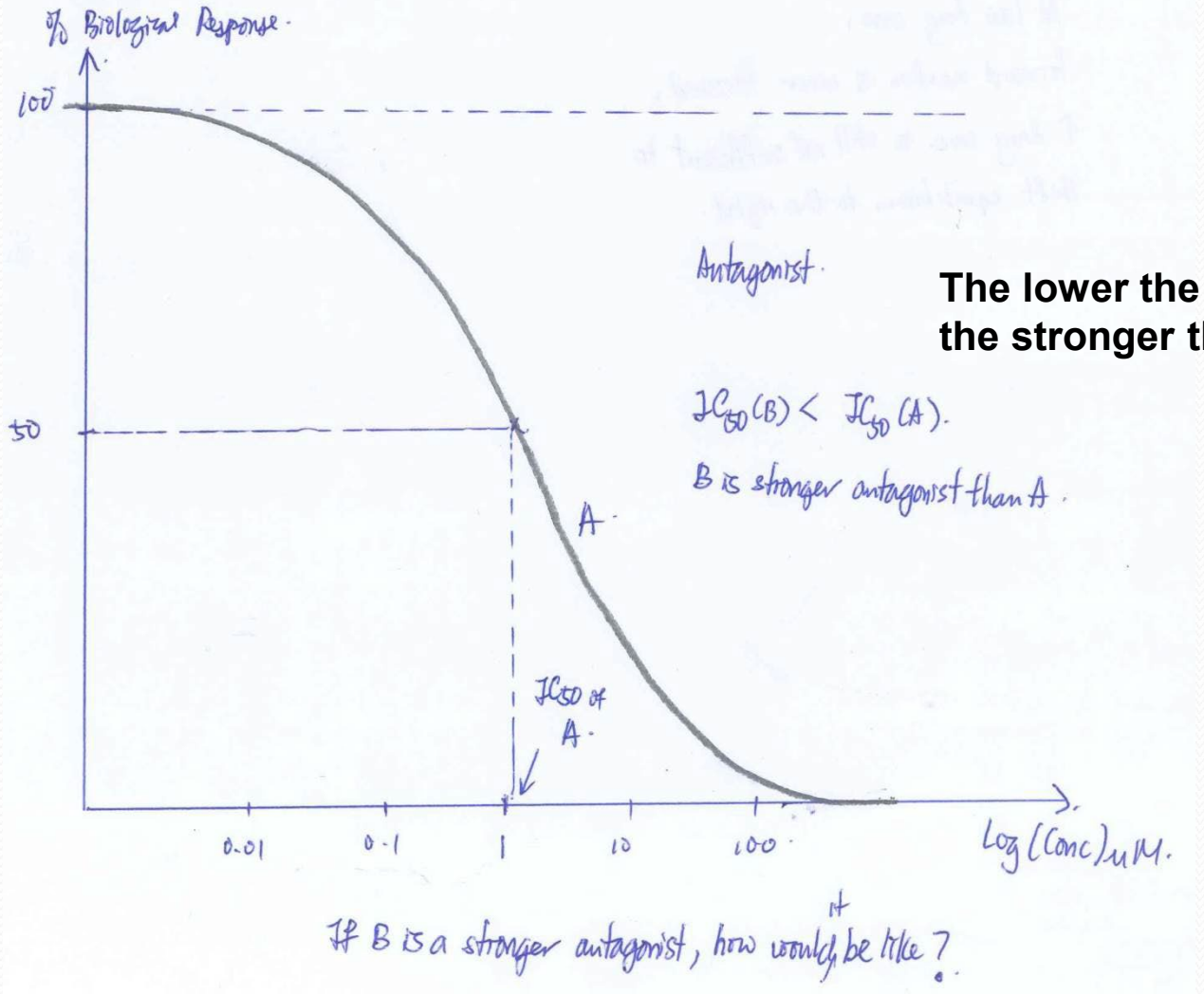
- EC_{50} = The plasma drug concentration required to achieve 50% of the maximum biological response.
- ED_{50} = The effective dose required to achieve 50% of the maximum biological response.

- *Question 1: If I have 2 similar agonists "A" and "B" and the dose response curve of drug A is provided in figure 2.12, how would the graph of B look like if B is a more potent drug? [Assuming that both give the same maximum biological response]*



The lower the EC_{50} value, the stronger the agonist

- *Question 2: How would a dose response curve of an antagonist drug look like?*

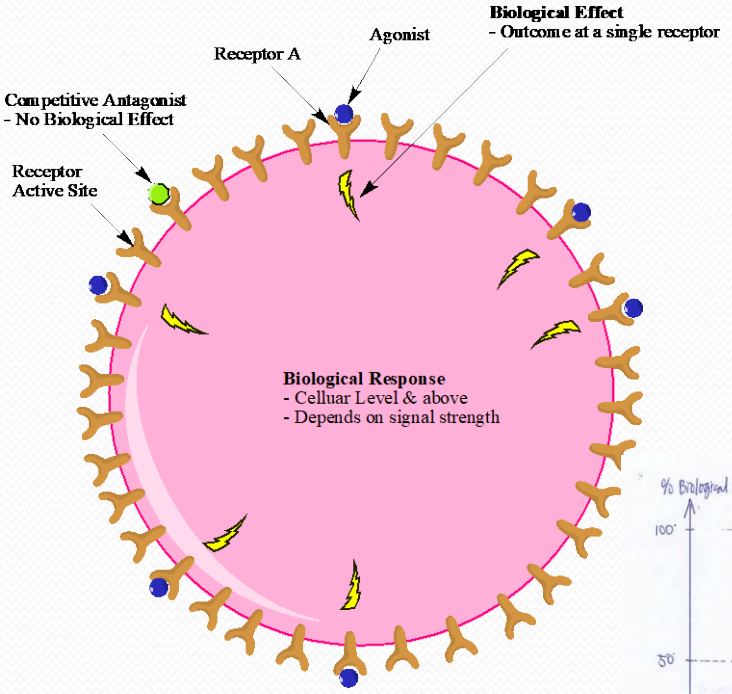


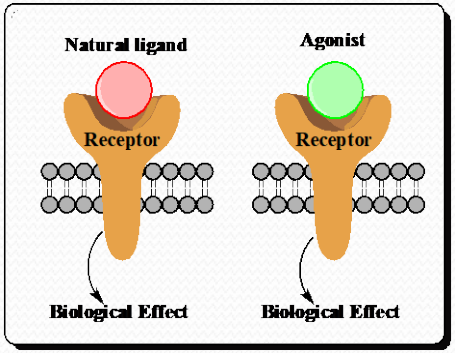
The lower the IC_{50} value, the stronger the antagonist

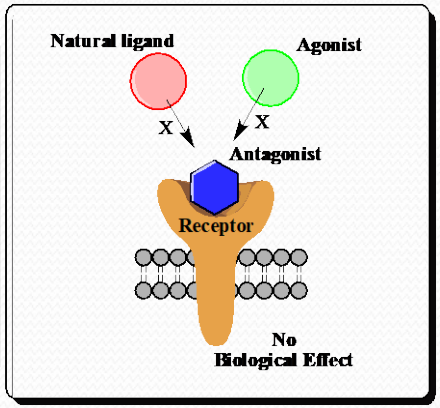
- **IC_{50}** (half maximal inhibitory concentration) is the concentration of the drug required to achieve 50% inhibition. This applies for competitive enzyme inhibitors and competitive antagonists.

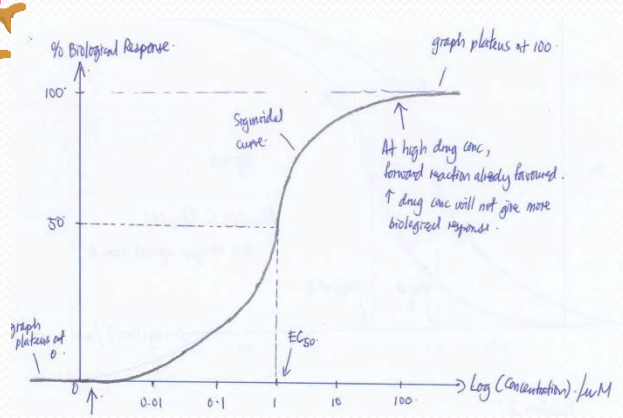
- *Question 3: If I have 2 similar antagonists "A" and "B", and B is a stronger antagonist than A, how would the dose response curve look like? Indicate in your graph above.*

Summary









Agonist *vs* Antagonist
Competitive *vs* Non-competitive

Chemistry

Activation of Membrane-bound enzyme
Release of Secondary Messengers
Open/Close Ion-channels

Drug + Receptor ⇌ (Drug – Receptor) Complex

Intermolecular Interactions
(Next Topic)

Biological Effect ⟹ ∑ (Signals) ⟹ Biological Response

(Drug Topics)

Biology