Pharmacodynamics 2

Dr. Alia Shatanawi

Modified by Dima Rafaiah

G protein-coupled receptors

Those receptors encompass many drugs used in the market

- Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.

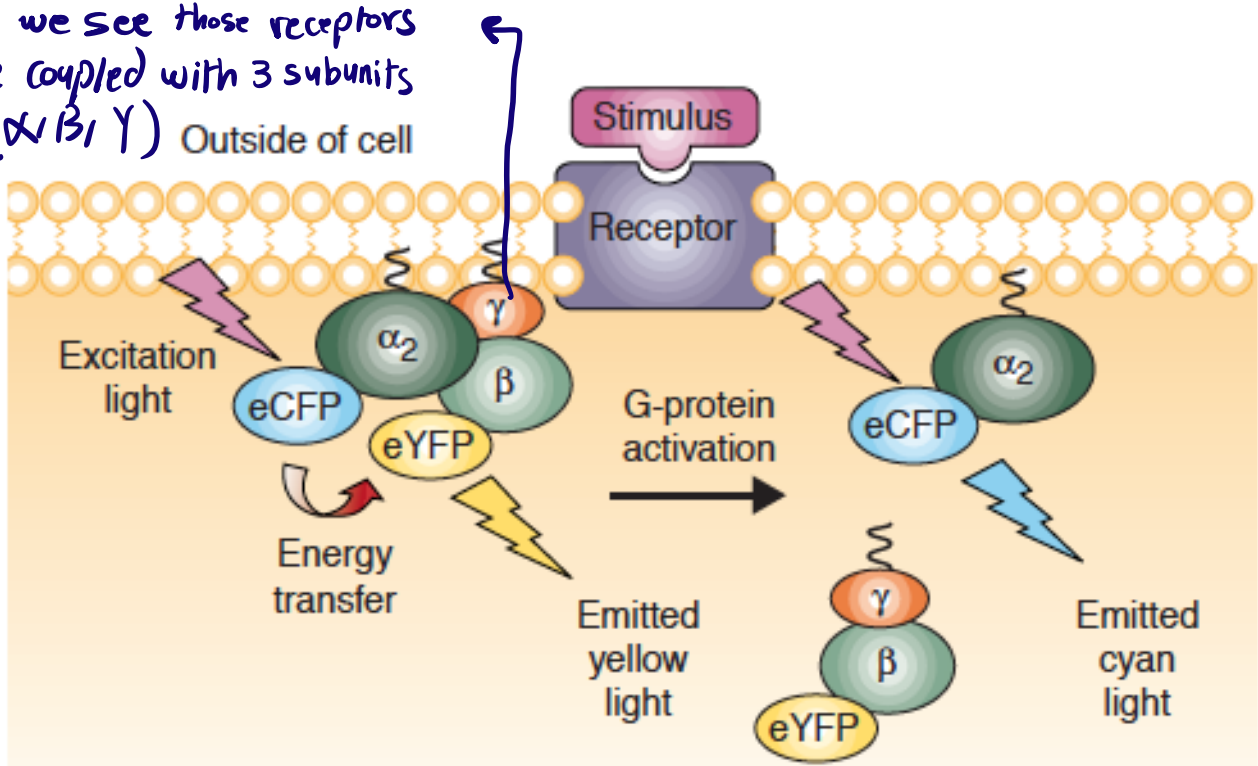
- Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend on the G proteins) mediate their action on cells.

sympathetic nervous system

parasympathetic

So those receptors exist all over our body

as we see those receptors are coupled with 3 subunits (α, β, γ)



-activation of α subunit occurs through conversion of GDP into GTP resulting in dissociation of the α subunit from the complex. Each one of the subunits (α, β, γ) can make its own activation pathway which amplifies the signal (That's why they're a big group of drug target)

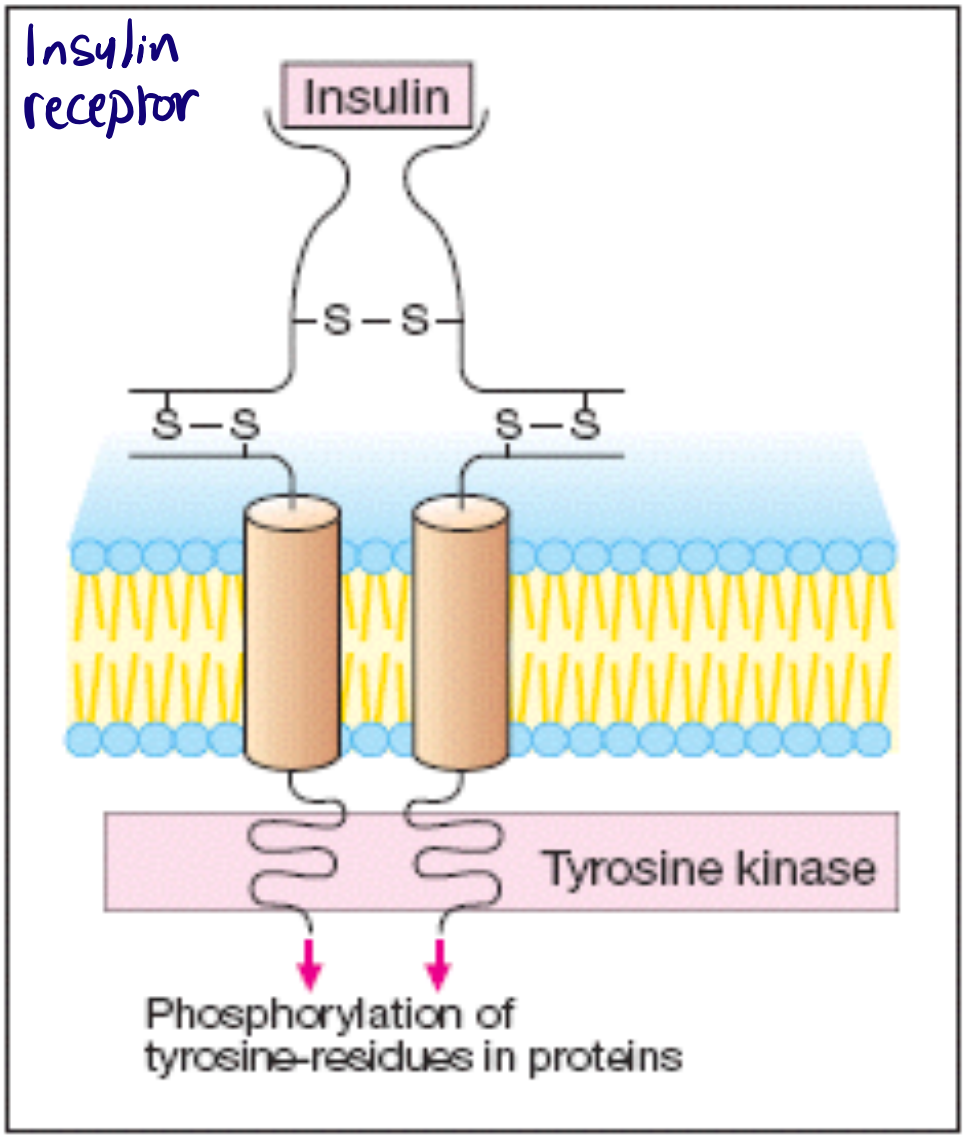
Enzyme-linked receptors

(They contain a catalytic domain, so apart of the receptor is able to produce an enzymatic activity, ex. kinases)

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme.

- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein.

- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch.



C. Ligand-regulated enzyme

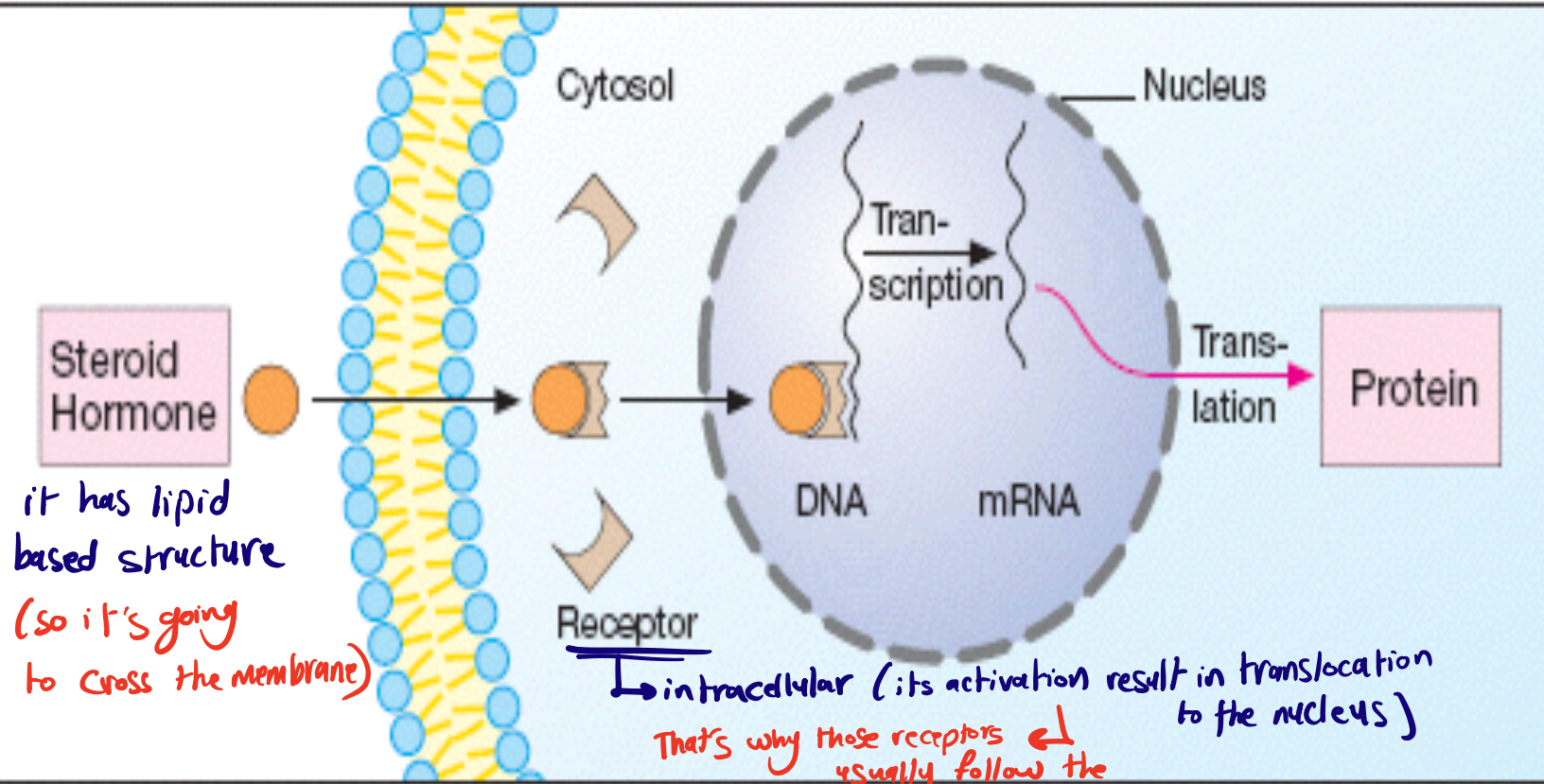
* it's coupled to a tyrosine kinase enzyme (responsible for phosphorylation)
So it's going to phosphorylate another protein or sometimes it phosphorylates itself resulting in the activation of further signaling mechanism.

intra
~~Inter~~cellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors.

- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.

- The best example being the steroids hormones. (→ ex. cortisone) In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.



it has lipid based structure (so it's going to cross the membrane)

intracellular (its activation result in translocation to the nucleus)

That's why those receptors usually follow the family of transcription factors because they bind to DNA and affect the transcription of genes, by either increasing or decreasing it

D. Protein synthesis-regulating receptor

For example steroid hormones increase the build up of the muscle mass by increasing the expression of certain proteins

HOW DO DRUGS WORK?

Most work by interacting with endogenous proteins:

- Some *antagonize, block or inhibit endogenous proteins*
- Some *activate endogenous proteins*
- A few have *unconventional mechanisms of action*

- we already know that proteins (receptors, enzymes) have ligands (hormones, neurotransmitters) that bind to them causing activation of those proteins to give a particular response (ex. adrenaline causing relaxation of bronchi when binding to B_2 adrenergic receptor)

So I want to utilize that protein to make a drug that will either

→ activate that protein (ex. asthma treatment)

→ block or inhibit the activation of that protein (ex. tachycardia treatment, that will inhibit the activation of B_1 adrenergic receptor, by preventing adrenaline from binding to B_1)

* pharmacologically, an antagonist is a drug that's gonna bind to the receptor and prevent the agonist from binding.

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

Definition of *CELL SURFACE RECEPTOR*:

A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment.

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS? KEY CONCEPTS:

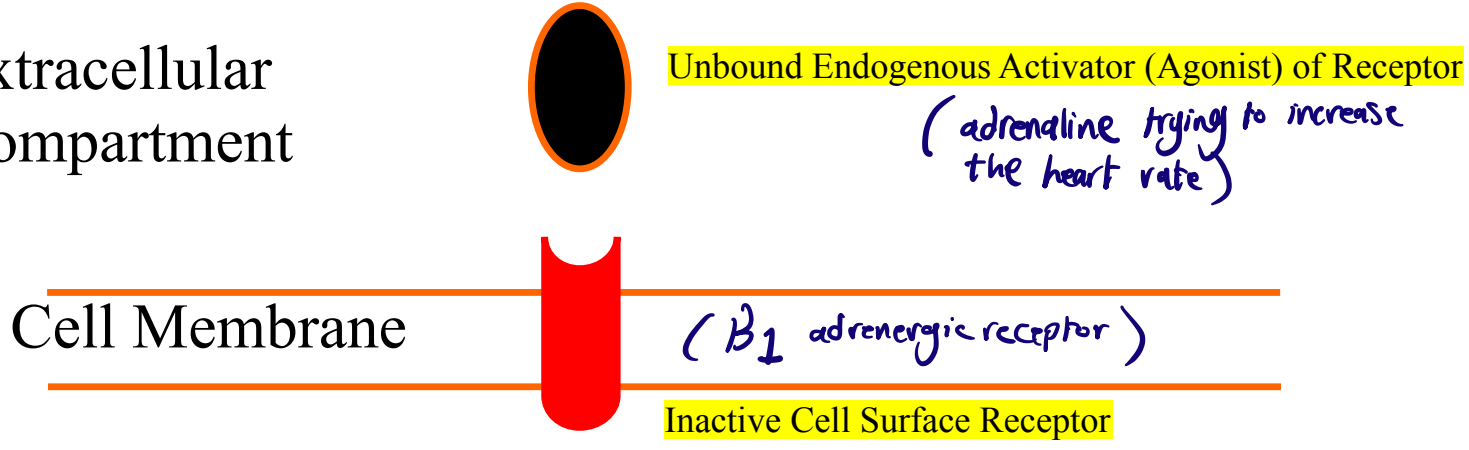
- **Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.**
- **Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.**

antagonist

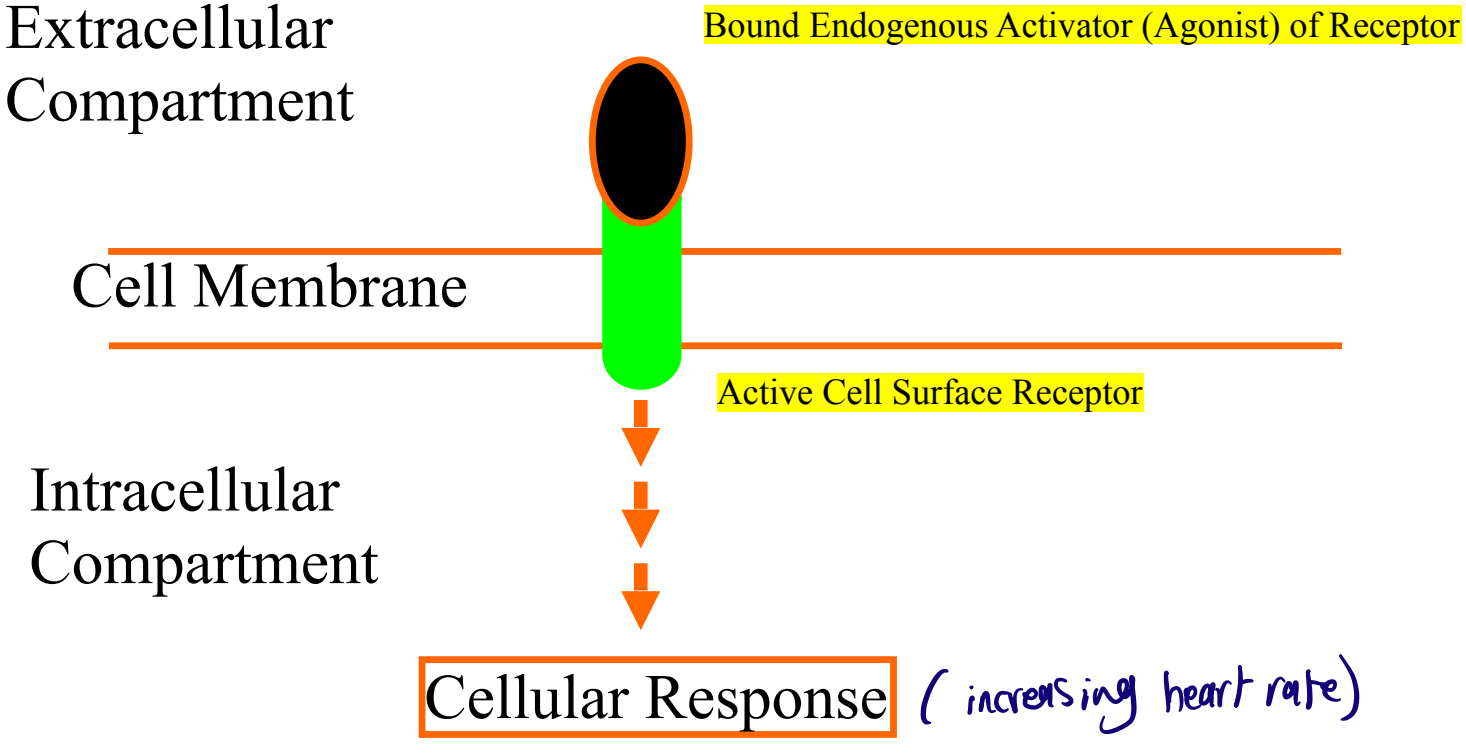
- **When cell surface receptors bind the molecule, the endogenous chemical cannot bind to the receptor and cannot trigger a response.**

- **The compound is said to "antagonize" or "block" the receptor and is referred to as a receptor antagonist.** (ex. β blocker)

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



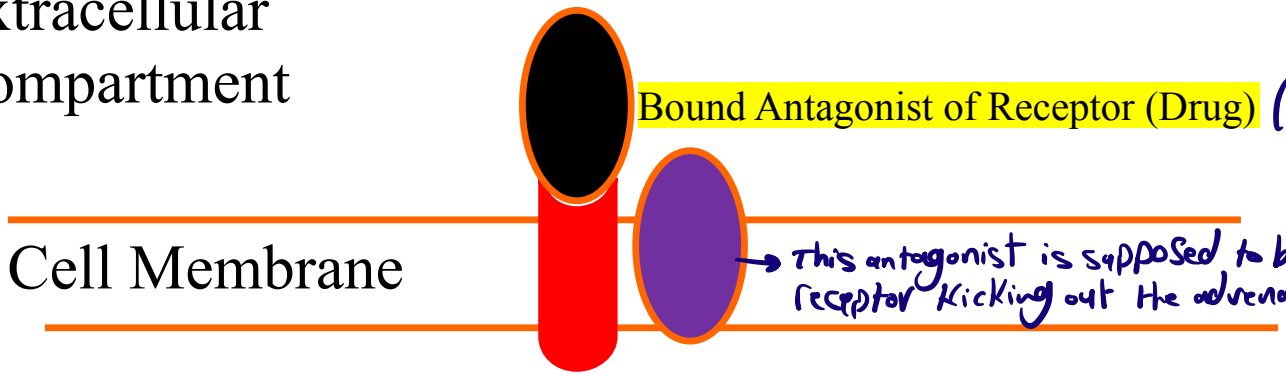
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Displaced Endogenous Activator (Agonist) of Receptor

Extracellular Compartment



Intracellular Compartment

Inactive Cell Surface Receptor Upon being Bound

→ because the receptor is now unable to give a response

(heart rate stay constant)

* They won't produce a new response like decreasing heart rate, they just prevent a certain response

⇐ they decrease the already increased rate, so the net effect of them is zero on that receptor

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Footnote:

Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding.

→ by occupying its space

If binding is reversible - Competitive antagonists

If binding is irreversible - Noncompetitive antagonists

→ through covalent bonds

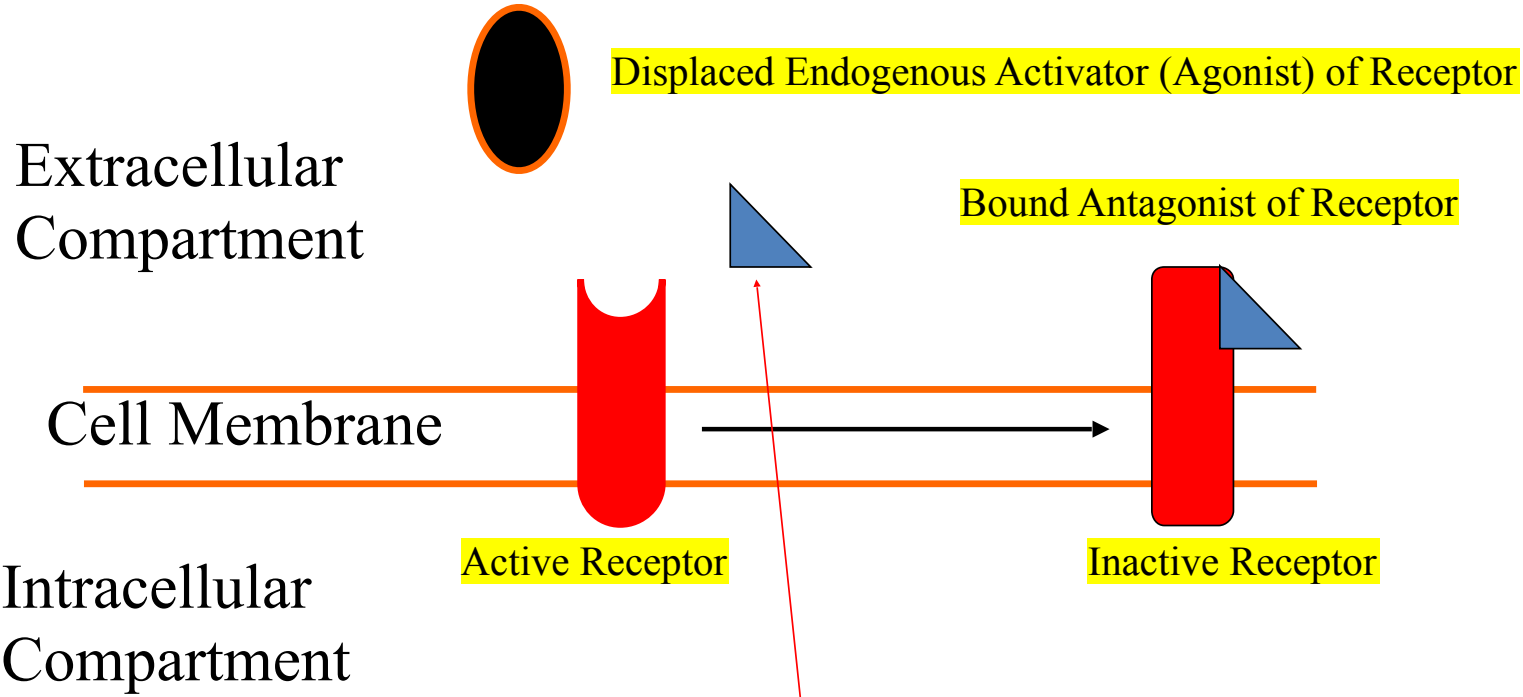
→ the effect stays for longer time

Because the drug will bind all the available receptors covalently, so no matter how high the ligand concentration gets, it won't be able to kick the drug out

However, antagonists may bind to remote site on receptor and cause allosteric effects that displace endogenous agonist or prevent endogenous agonist from activating receptor. (Noncompetitive antagonists)

→ if the duration of binding is short ⇒ it gives the original ligand the chance to re-bind its receptor depending on the concentrations of both the antagonist and the ligand, it also depends on the affinity of them (so it's competitive)

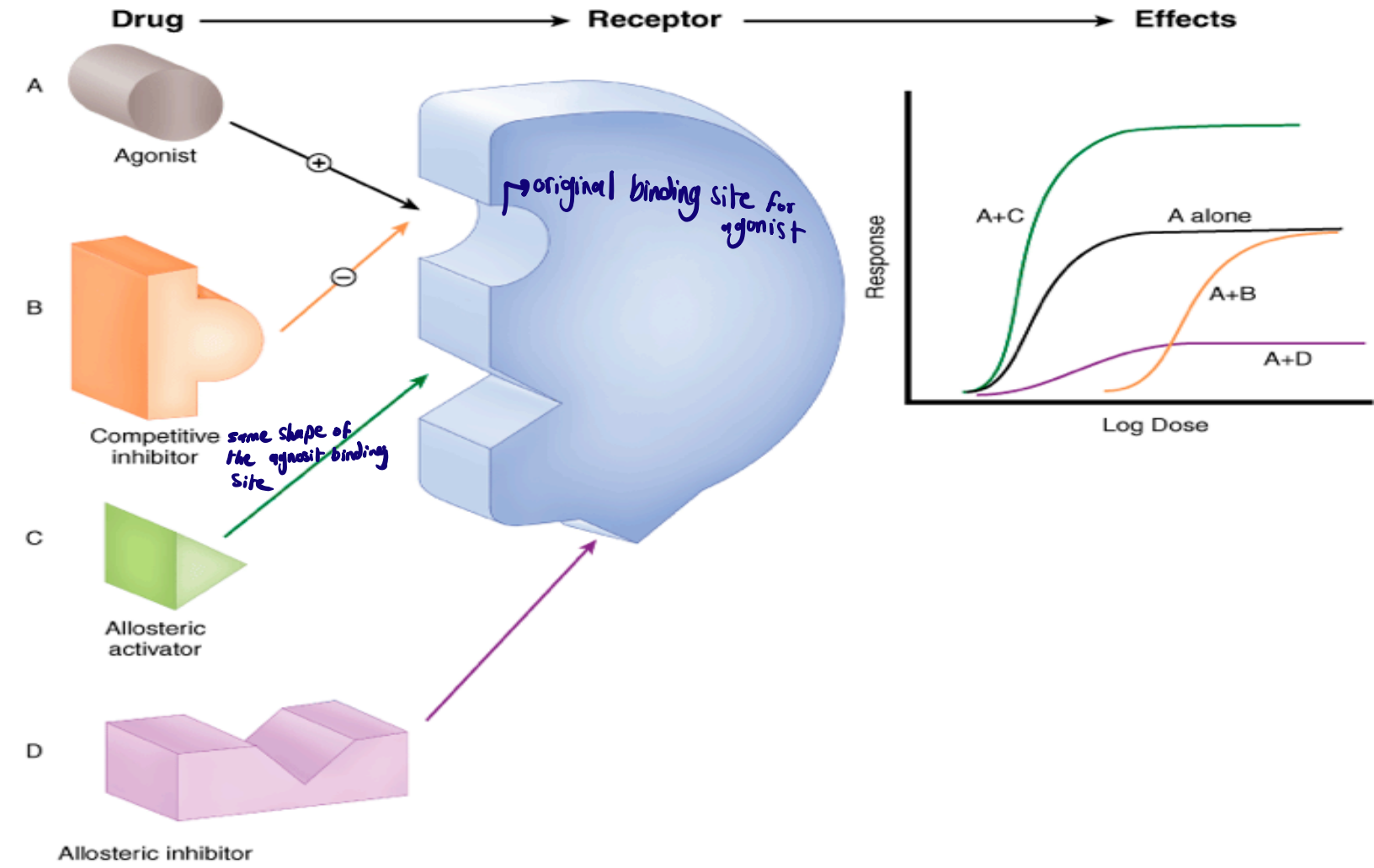
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



In this case the allosteric inhibitor binds to another site and causes a conformational change to the receptor preventing the ligand from binding (non-competitive)

(it doesn't look like the ligand so it won't fit into the binding site)

Drug Receptor Interactions



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*,

ARE DRUGS THAT ANTAGONIZE CELL SURFACE RECEPTORS CLINICALLY USEFUL?

*Don't memorize drugs names just read the examples and at least know the purpose of each receptors

Some important examples:

Angiotensin Receptor Blockers (ARBs) for high blood pressure, heart failure, chronic renal insufficiency
(losartan [Cozaar®]; valsartan [Diovan®])

Beta-Adrenoceptor Blockers for angina, myocardial infarction, heart failure, high blood pressure, performance anxiety
(propranolol [Inderal®]; atenolol [Tenormin®])

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT ANTAGONIZE NUCLEAR RECEPTORS CLINICALLY USEFUL?

read only

Some important examples:

- Mineralocorticoid Receptor Antagonists for edema due to liver cirrhosis and for heart failure (spironolactone [Aldactone®])

- Estrogen Receptor Antagonists for the prevention and treatment of breast cancer (tamoxifen [Nolvadex®])

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

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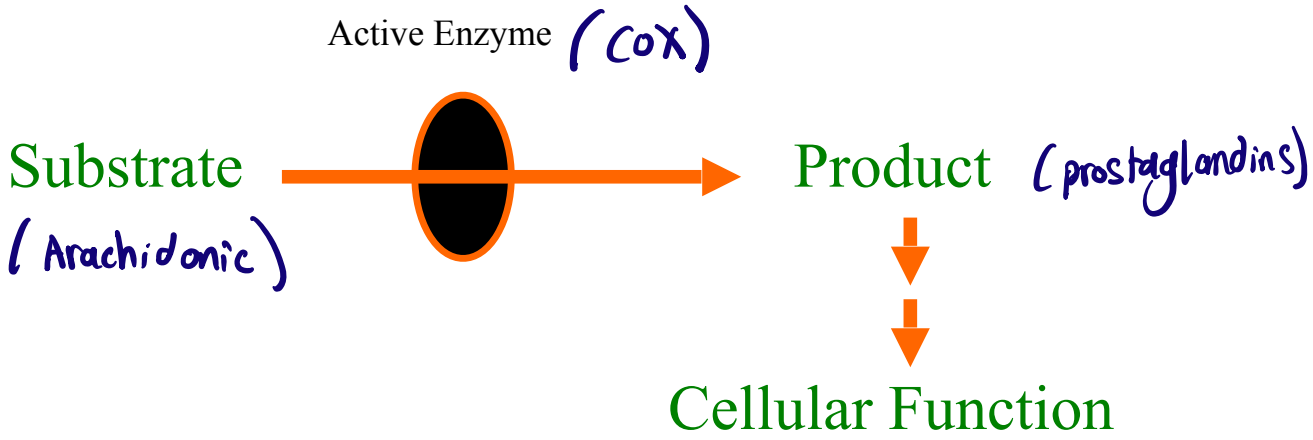
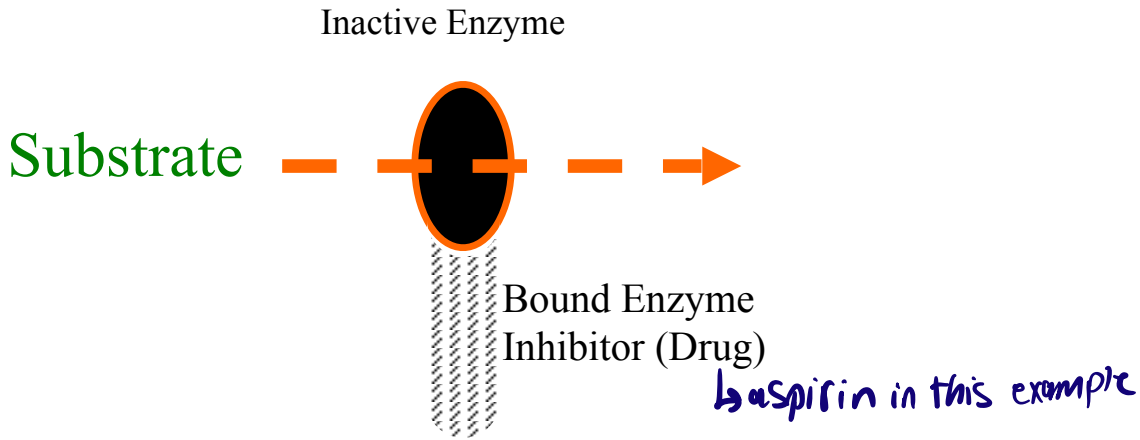
HOW DO DRUGS WORK BY INHIBITING ENZYMES?





HOW DO DRUGS WORK BY INHIBITING ENZYMES? KEY CONCEPTS:

Enzymes catalyze the biosynthesis of products from substrates.

- Some drugs bind to enzymes and inhibit enzymatic activity.

- Loss of product due to enzyme inhibition mediates the effects of enzyme inhibitors.

ARE DRUGS THAT INHIBIT ENZYMES CLINICALLY USEFUL?

read only

Some important examples:

(مش مطلوب تحفظو بس
فقط تاخدو فكرة للاحتياط)

- Cyclooxygenase Inhibitors for pain relief, particularly due to arthritis (aspirin; ibuprofen [Motrin®])

HMG-CoA Reductase Inhibitors for hypercholesterolemia (atorvastatin [Lipitor®]; pravastatin [Pravachol®])

Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency (captopril [Capoten®]; ramipril [Altace®])

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers (Ca+2 channel blocker for muscle contraction)
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT BLOCK ION CHANNELS CLINICALLY USEFUL?

Some important examples:

Calcium Channel Blockers (CCBs) for angina and high blood pressure
(amlodipine [Norvasc®]; diltiazem [Cardizem®])

- Sodium Channel Blockers to suppress cardiac arrhythmias
(lidocaine [Xylocaine®]; amiodarone [Cordarone®])

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

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ARE DRUGS THAT INHIBIT TRANSPORTERS CLINICALLY USEFUL?

Some important examples:

Selective Serotonin Reuptake Inhibitors (SSRIs) for the treatment of depression
(fluoxetine [Prozac®]; fluvoxamine [Luvox®])

Inhibitors of Na-2Cl-K Symporter (Loop Diuretics) in renal epithelial cells to increase urine and sodium output for the treatment of edema
(furosemide [Lasix®]; bumetanide [Bumex®])

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
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- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT INHIBIT SIGNAL TRANSDUCTION PROTEINS CLINICALLY USEFUL?

Some important examples:

→ can be involved in certain cancers

Tyrosine Kinase Inhibitors for chronic myelocytic leukemia (imatinib [Gleevec®])

Type 5 Phosphodiesterase Inhibitors for erectile dysfunction (sildenafil [Viagra®])

- This is a major focus of drug development

HOW DO DRUGS WORK BY ACTIVATING ENDOGENOUS PROTEINS?

Agonists of Cell Surface Receptors
(*e.g.* alpha-agonists, morphine agonists)

↳ pain killer, it binds to a receptor in the brain and cause a stronger effect than the endogenous ligand

- Agonists of Nuclear Receptors
(*e.g.* HRT for menopause, steroids for inflammation)

- Enzyme Activators
(*e.g.* nitroglycerine (guanylyl cyclase), pralidoxime)

- Ion Channel Openers
(*e.g.* minoxidil (K) and alprazolam (Cl))

HOW DO CHEMICALS WORK BY ACTIVATING CELL SURFACE RECEPTORS?
KEY CONCEPTS:

•Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

• Some chemicals bind to cell surface receptors and trigger a response.

• Chemicals in this group are called receptor agonists.

• Some agonists are actually the endogenous chemical signal, whereas other agonists mimic endogenous chemical signals.

meaning that I could give adrenaline (an endogenous ligand) as a drug or I could give a drug that mimics adrenaline

HOW DO CHEMICALS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION?

- Disrupting of Structural Proteins
  e.g. vinca alkaloids for cancer, colchicine for gout
- Being Enzymes
  e.g. streptokinase for thrombolysis
- Covalently Linking to Macromolecules
  e.g. cyclophosphamide for cancer
- Reacting Chemically with Small Molecules
  e.g. antacids for increased acidity
- Binding Free Molecules or Atoms
  e.g. drugs for heavy metal poisoning, infliximab (anti-TNF)

- Distrupting of structural proteins

examples are vinca alkaloids and colchicine

These are two different drugs for two different diseases which happen to have somewhat the same mechanism of action, since they target Tubulin, they prevent its polymerization

Tubulin is a cytoskeleton protein that is responsible for separation of chromosomes during cell division. Basically polymerization of tubulin result in microtubules, which in turn will make mitotic spindles which are responsible for separating chromosomes.

So preventing polymerization of tubulin →
preventing formation of microtubules →
prevents cell division →
"Treatment of cancer" (vinca alkaloids)

Gout is an inflammatory disease, to help decrease the inflammatory response, we prevent the formation of microtubules by preventing polymerization of tubulin. Note that microtubules mediate the movement of macrophages to the site of action, so by blocking microtubles we prevent the action of macrophages, which decreases the inflammatory symptoms (colchicine)

- Being enzymes

Streptokinase an enzyme present in bacteria, it works on lysing blood clot. By recombinant DNA technology we can generate this drug and use it in some emergency situations of clotting disorders.

- Covalently linking to macromolecules

A lot of cancer drugs work by interfering with DNA like cyclophosphamide.

- Reacting chemically with small molecules

In case of heartburn (high acid secretions), we can control it by taking a base (anti acid). So we're gonna have a chemical reaction between an acid and a base.

HOW DO DRUGS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION (Continued)?

- Being Nutrients (calcium supplements for example supply us with things we need or can't synthesize)
  e.g. vitamins, minerals

- Exerting Actions Due to Physical Properties
  e.g. mannitol (osmotic diuretic), laxatives They just work by being bulk-forming compounds, that will stimulate the intestine to contract.

- Working Via an Antisense Action
  e.g. fomivirsen for CMV retininitis in AIDS

- Being Antigens
  e.g. vaccines (stimulate immune response to provide protection from certain conditions)

- Having Unknown Mechanisms of Action
  e.g. general anesthetics (they have been used for hundred of years, but we don't know their mechanism of work yet)

- Orphan receptors

By gene sequencing we recognized a lot of receptors that we haven't identify their activating ligand yet. Those are called orphan receptors