4

Pharmacology

Doctor 2017 | Medicine | JU

Sheet ○ Slides

Done By

Tala Saleh

Contributed in the Scientific Correction

Leen AlSahele

Contributed in the Grammatical Correction

...

Doctor

Alia Shatanawi

Characteristics of Drug-Receptor Interactions:

1) **Drugs interact with receptors by means of chemical bonds like :**
   - **a-** Ionic
   - **b-** Hydrogen Bonds
   - **c-** Van der Waals
   - **d-** Covalent

2) **Drug-Receptor interactions are saturable**.
   The amount of drug-receptor binding is **limited**, depending mainly on the **number of receptors available.**

   Example: Hypothetically, on one cell's surface we have **10 receptors**. 50 molecules of a drug that's specific to those receptors were injected in a patient, the **maximum number of drug-receptor complexes** would be **10** no matter how much the dosage in increased. So even if we keep giving a higher dosage of that drug the effect **will not change.**
   (Since side effects at high dosages might be fatal, drugs shouldn't be overdosed)

3) **It is competitive**
   The **drug** would compete with the endogenous ligand (**an agonist)** over a specific **receptor** and block it from binding.

4) **Specific**
   Specificity states that each receptor binds only to a specific ligand over others.
   Example: An **adrenergic drug** binds **to adrenergic receptors *(alpha/beta)*** specifically.

5) **Selective *(depends on the isoform of the receptor)***
   Selectivity talks about **the selective pathway stimulated receptors** perform.
   Example: If **alpha 1 receptors** were stimulated by an **adrenergic drug**, it will cause **vasoconstriction**, while if that **same** drug stimulates **beta 2 receptors** it will cause **vasodilation**.

6) **Structure-Activity relationships**
   Different drugs can cause the **same general effect** on the body yet show **different potencies** or **side effects** by changing the **structure of the drug** to **suit** the **receptor** more.

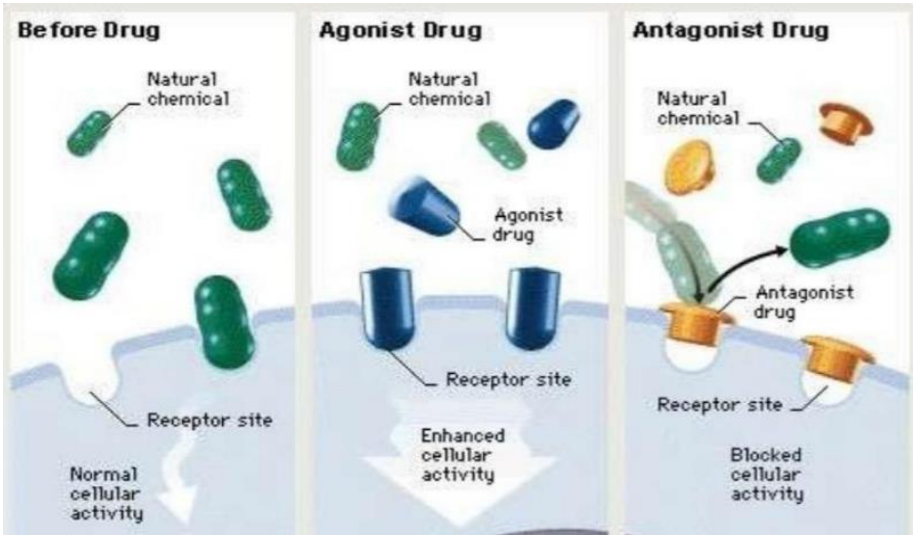
7) Transduction mechanism

Each receptor is **unselectively bound** to a certain **signal transduction mechanism** *(series of molecular events)* which ultimately results in a **cellular response** after being stimulated by a certain drug.

8) Sensitivity

One receptor can reach a **maximum effect** using **less dosage** of Drug 1 than Drug 2, indicating that the receptor is **more sensitive** towards **Drug 1**.
Stated differently, at **equal dosages**, Drug 1 would cause a bigger **amplification** of action upon binding to the receptor compared to Drug 2.

How do drugs work on cell surface receptors?



1) By activating receptors as agonists

An agonist is any ligand that **triggers a response** or **enhances it.**

Note: *An agonist is an **endogenous chemical** and if its given orally it is considered a **drug***

2) By antagonizing cell receptors

Cell surface receptors exists to **transmit chemical signals** from the outside to the inside of the cell. An **antagonist** would **bind** to the receptor and **prevent** binding of the **agonist**.

→ Receptor is antagonized/blocked → Blocked cellular activity.

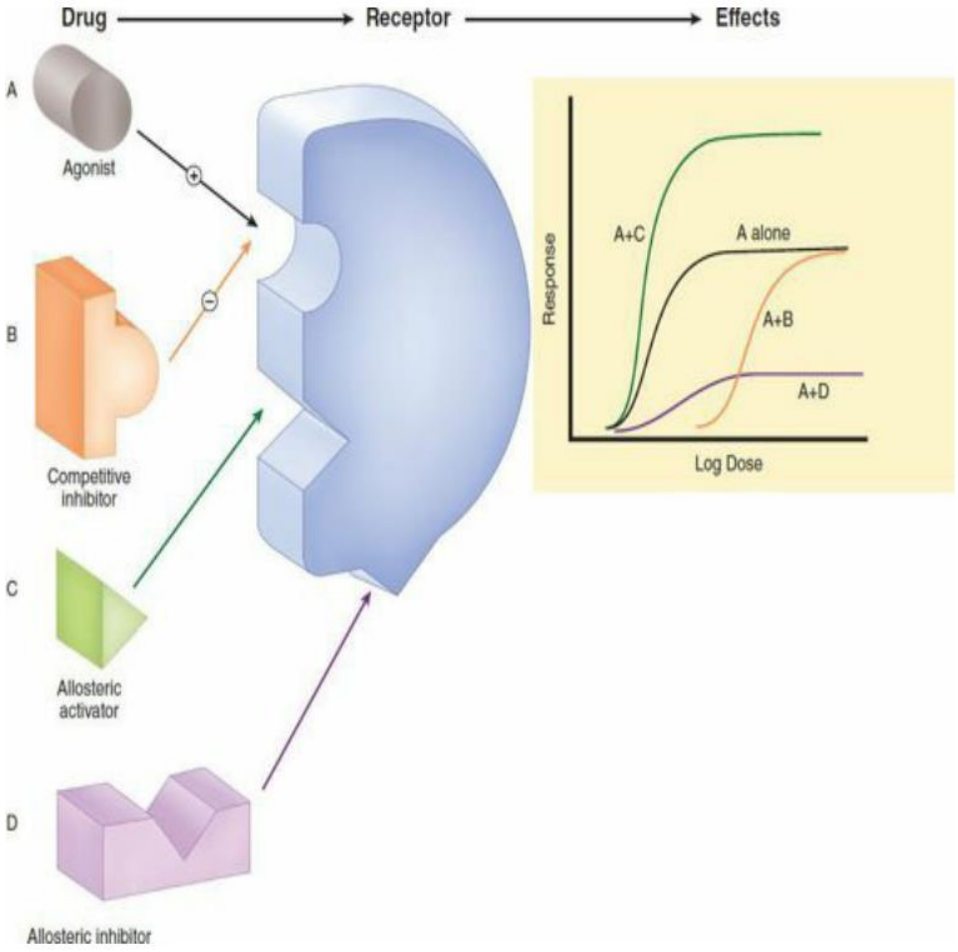
Note: *An antagonist prevents the ligand from **binding and causing action**, it does not **oppose** the **mechanism** of the receptor when stimulated.*

The binding of the antagonist to the receptor can be:

a- **Reversible:** Competitive antagonist
*Can be overcome by having **more concentrations** of the **agonist**.*

b- **Irreversible:** Noncompetitive antagonist
*Antagonist-receptor complex must be **recycled** to get rid of it.*

Drugs may interact with receptors in several ways as mentioned before. The effects resulting from these interactions are diagrammed in the following dose-response curves.



***A alone:** The agonist is giving its **normal response** upon binding to the receptor.*

A+B:** The competitive inhibitor is competing with the agonist **decreasing its effect.

***A+C:** The curve shifted to the left indicates an **increase in the response** for the agonist.*

***A+D:** The curve shifted to the right indicating a **decrease in response** for the agonist.*

Note: *Allosteric drugs bind to the* ***same receptor molecule*** *but do not* ***prevent binding*** *of the* ***agonist*** *(on a remote site not the binding site). They may* ***enhance*** *or* ***inhibit*** *the action of the agonist molecule. Also, Allosteric inhibition* ***is not*** *overcome by* ***increasing*** *the dose of agonist.*

How do drugs work on other targets? *(other than the cell surface receptors previously discussed)*

Antagonists:

1) Antagonists of Nuclear Receptors
2) Enzyme Inhibitors
3) Ion Channel Blockers
4) Transport Inhibitors
5) Inhibitors of Signal Transduction Proteins

Agonists:

1) Agonists of Cell Surface Receptors *(e.g. alpha-agonists, morphine agonists)*
2) Agonists of Nuclear Receptors *(e.g. HRT for menopause, steroids for inflammation)*
3) Enzyme Activators *(e.g. nitroglycerine (guanylyl cyclase), pralidoxime)*
4) Ion Channel Openers *(e.g. minoxidil (K) and alprazolam (Cl))*

Note: *Dr. Alia said that the examples are* ***not*** *required, if you are curious check google.*

How do drugs/chemicals work by unconventional mechanisms of action?

Unconventional: not based on what is generally done.

1) Disrupting of Structural Proteins *(e.g. vinca alkaloids for cancer, colchicine for gout)*
2) Being Enzymes *(e.g. streptokinase for thrombolysis)*
3) Covalently Linking to Macromolecules *(e.g. cyclophosphamide for cancer)*
4) Reacting Chemically with Small Molecules *(e.g. antacids for increased acidity)*
5) Binding Free Molecules or Atoms *(e.g. drugs for heavy metal poisoning, infliximab)*
6) Being Nutrients *(e.g. vitamins, minerals)*
7) Exerting Actions Due to Physical Properties *(e.g. mannitol (osmotic diuretic), laxatives)*
8) Working Via an Antisense Action *(e.g. fomivirsen for CMV retininitis in AIDS)*
9) Having Unknown Mechanisms of Action *(e.g. general anesthetics)*
10) Being Antigens *(e.g. vaccines)*

Note: *The examples are* ***not*** *for memorizing.*

Additional Information for the previous examples that is not required:

1) *Vinca alkaloids are a set of anti-mitotic and anti-microtubule alkaloids (Disrupt proteins) that prevents cells from dividing, thus minimizing cancerous cells from spreading.*
2) *Colchicine is used to treat gout mainly which is an intense acute inflammatory disease. Colchicine simply stated decrease macrophages, therefore decreasing the inflammatory response.*
3) *Streptokinase acts as a thrombolysis by causing the lysis of blood clots.*
4) *Antacids contain alkaline ions that neutralizes increased acidity.*
5) *Antigens are what induces immune response in the body to create antibodies.*

How are drugs antagonizing cell surface receptors useful? ***(Not for memorizing)***

Example 1: Angiotensin Receptor Blockers (ARBs) for high blood pressure, heart failure, chronic renal insufficiency (losartan [Cozaar®]; valsartan [Diovan®])

Example 2: Beta-Adrenoceptor Blockers for angina, myocardial infarction, heart failure, high blood pressure, performance anxiety (propranolol [Inderal®]; atenolol [Tenormin®])

----------*End of Slide-1*----------

Receptor occupancy theory

Theory: The **intensity** of the body's **response** to a drug is **directly related** to the **number of receptors** occupied by the drug, the **maximum response** occurs when all the receptors are **bound** to the **drug** molecules

Assumptions:

1) Association is limited by collision, orientation and energy
2) All receptors are equally accessible
3) All receptors are either free or bound, there is no partial binding
4) Neither drug or receptor are altered by binding
5) Binding is reversible

Note: *these are **only assumptions** it **doesn't** mean that they are **true.***

Drug-Receptor Binding

$$D + R \xrightarrow{k} DR$$

$$DR \xrightarrow{k^{-1}} D + R$$

K : Rate constant for the **formation** of the DR complex.

K^{-1} : Rate constant for the **dissociation** of DR complex.

$$\frac{k^{-1}}{k} = K_D$$

K_D: The equilibrium dissociation constant.

It is the **concentration of a drug** needed to saturate **50%** of the receptors.

K_D indicates **affinity**; If the **K_D** is **low**, binding affinity is **high**, and vice versa.

$$B/B_{max} = \frac{[D]}{[D]+K_D}$$

B: Relates to the **drug bound** receptors.

B_{max}: The **maximum number of receptors'** sites available for the drug to bind to.

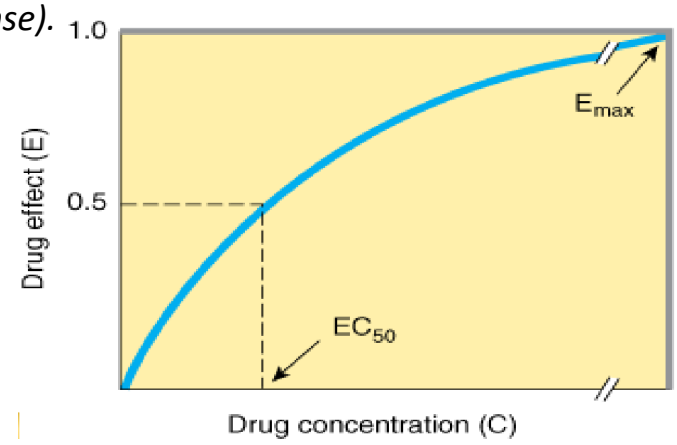
B/B_{max} ratio indicates the **occupancy** of receptors.

The higher the concentration of the drug is used, the higher the occupancy will be until all receptors are full showing the maximum effect

Drug Receptors & Pharmacodynamics

Receptors largely **determine the quantitative** relations between **dose/concentration** of a drug and its **pharmacologic effects** *(response).*

The receptor's **affinity** to a drug determines the **concentration** of drug required to form a **significant number of drug-receptor complexes**. The **total number of receptors** may limit the **maximal effect** a drug may produce.



Side Note: *Concentration → **Amount** of a drug measured in mg/L*
*Dose → **Concertation** of the drug **taken per day** (mg/day) varies in effect for each individual*

The maximal effect of a drug depends on two factors:

a- The **total number** of receptors **available.**
b- **Intrinsic activity**: The capacity to **induce functional change** on the receptor.

An example for further explanation: *Morphine and Tramadol **both** bind to **opioid receptors** in the brain but morphine show a **higher effect** because it has a better **intrinsic activity** inducing **more** cellular **activity**.*

Sometimes we don't need to occupy all receptors available to reach maximal effect.

Spare receptors: For a **given** pharmacologic **response**, if it is possible to reach a **maximal effect** at a **concentration** of agonist that **does not result** in **occupancy** of **all** of the available **receptors** → The leftover unbound receptors are said to be **"spare".**

In other words, only a **fraction of the total receptors** require occupation to reach E_{max}.

Example: *Insulin receptors **reach Emax** when they are only **1% occupied,** 99% are spare*.

Potency

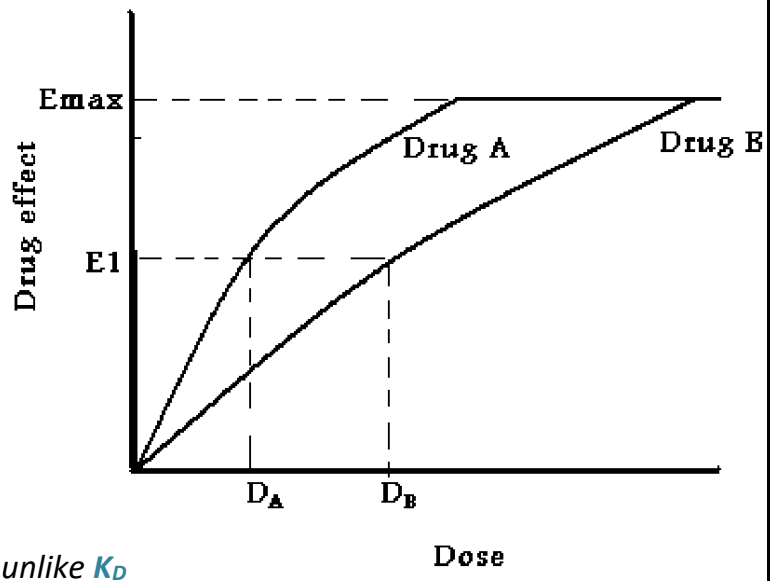
It is a measure of **drug activity** expressed in terms of the **amount required** to produce an **effect of given intensity**. A **highly potent** drug evokes a **given response** at **low concentrations**, while a drug of **lower potency** evokes the **same response** only at **higher concentrations**.

Measures of potency: ED50 *(Effective dose),* EC50 *(Effective concentration),* and K_D.

On a **dose-response** curves **potency** is measured **on the X-axis**.

From the graph, we can see that the ED50 of **drug A** is **less** than ED50 for **drug B**.

- → To reach the **same effect**, the dose needed from drug **A < Drug B.**
- → **Potency** of **drug A > drug B**
- → This can indicate that **drug A** has a **higher affinity**.



Is potency the same as K_D?

*It is very similar in definition, but **potency** depends on the intrinsic activity of the drug unlike **K_D***

Efficacy

It is the **maximum response** *(Emax)* **achievable** from a **dosed drug**. It depends on:

1) Number of **drug-receptor complexes** formed
2) Efficiency of the of coupling of receptor **activation to cellular responses** *(intrinsic activity).*

Example: *Aspirin and Morphine produce the **same pharmacologic effect** (analgesia) but have **very different levels of efficacy** since Morphine shows **higher activation** to cellular responses (intrinsic activity) than Aspirin does.*

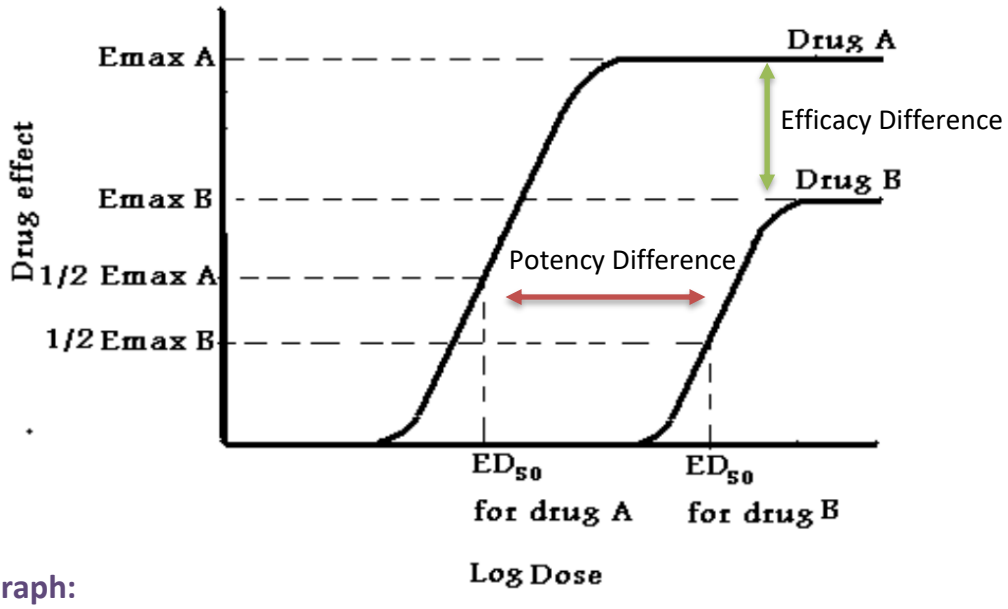
Note: *Efficacy is **not the same as** intrinsic activity.*

Even though drugs may occupy the same number of receptors, the magnitude of their effect may differ.

Example: *Morphine can **reach Emax** with **100% occupancy** of receptors, while Tramadol would reach a **submaximal** response even with **100% occupancy**.*

Here Morphine is said to be **a full agonist**, while Tramadol is a **partial agonist**.

Log dose-Response Curve



From the graph:

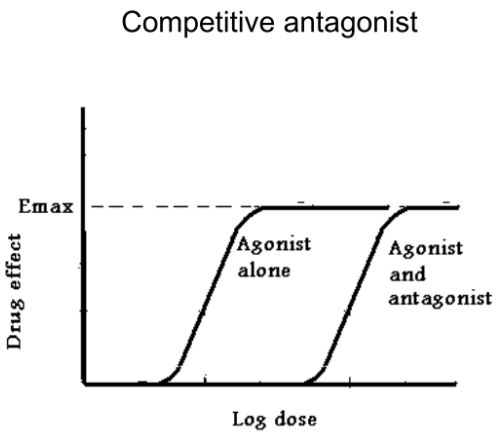
1) The **smaller** the ED50, the **greater** the **potency**.
   Since potency may depend on ED50, it can also depend on Emax (proportionally).
2) Efficacy is **indicated** by the **height of the log dose response**
3) Drug A is **more potent** than drug B since it required **less dosage** to reach a **higher effect**.

Antagonism between drugs

1) **Pharmacologic Antagonism:** It occurs when an **antagonist prevents** an **agonist** from **interacting** with its **receptors** to produce an effect, and it can be either:

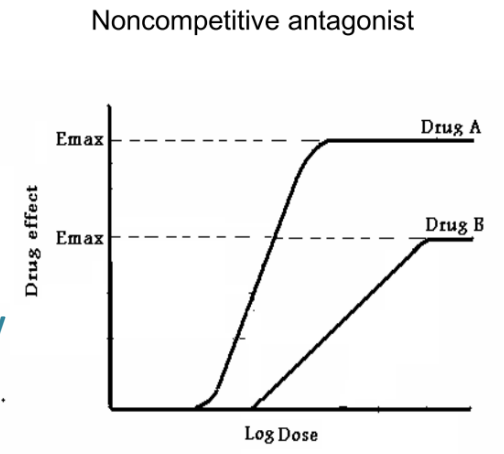
A- Competitive

- The antagonist binds **reversibly** to the **agonist site** on the receptor.
- The log dose-response curve is shifted to the **right**, indicating that a **higher concentration** of agonist is needed to **overcome** the antagonist.
- **Doesn't shift** equilibrium towards active or inactive conformation
- ED50 is **increased** and E_{max} is **not altered**



B- Noncompetitive

- The antagonist binds **irreversibly** to the **receptors site** or to **another side** *(allosteric)* which **inhibits** the response of the agonist.
- The shift in the log response curve in this case is a **nonparallel** shift to the **right**.
- The shift is **antiparallel** because noncompetitive antagonists bind **irreversibly** to the receptor which kind of **destroys the receptor**, thus the number of receptors that are available are **less** which ultimately **decreases the E_{max}**.



- No matter how much agonist is given, the action of the antagonist **can not** be overcome.
- ED50 **may or may not be changed** depending on the drug, Emax however is **altered.**

Inverse agonist and Neutral antagonists

1) **Neutral antagonists** has **no activity** in the absence of an agonist or inverse agonist but can **block the activity** of either.

   Example: *Competitive antagonists are considered neutral antagonists.*

2) **Inverse agonists** are agents that bind to the **same receptor as an agonist** but **induces** a response **opposite** to that of the agonist.

   They are **not considered antagonists** since antagonists **only block** but do not induce any response.

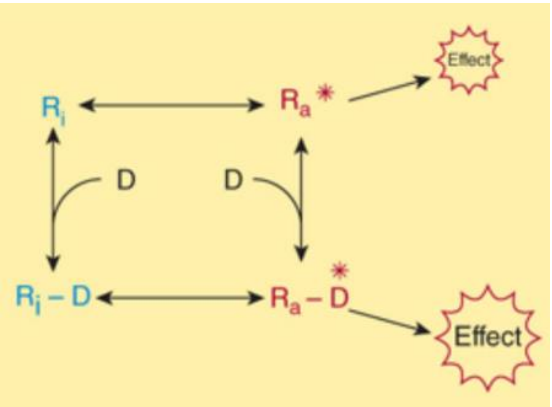
   Inverse agonists have **opposite actions** to those of agonists, but the **effects** of both of them can be **blocked** by **antagonists.**

   Example: *Cones and rods receptors in the eyes are **always active**. Using an inverse agonist on them will **induce a response that opposes its continuous** work shifting the receptors' state from **active into inactive.***

   Note: *Inverse agonists shift equilibrium towards **the inactive conformation***

Two-state model of drug-receptor interaction

- The receptor is theorized to exist in the **inactive form** (R) and in the **activated form** (R*), switching between them at equilibrium.
- **Thermodynamic indicate** that even in the **absence of any agonist**, some of the receptors **must exist in the (R*)** form for some time and may also **produce the same physiologic** effect as an **agonist induced activity**.
- Agonists **shift the equilibrium more towards the active state** and **stabilize** it, so that a large percentage of the total receptors are in the (R*) form producing a large effect.

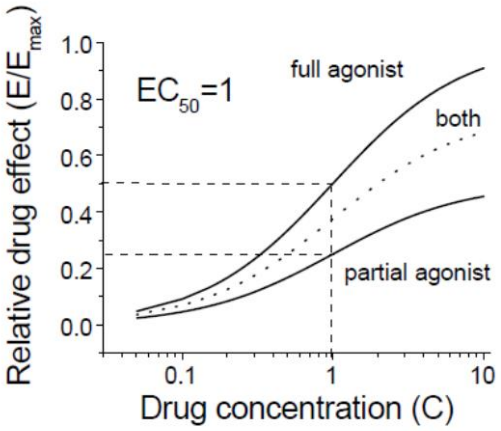


The receptor in the **absence of an agonist** drug yet showing **some effect** in the **active form.**

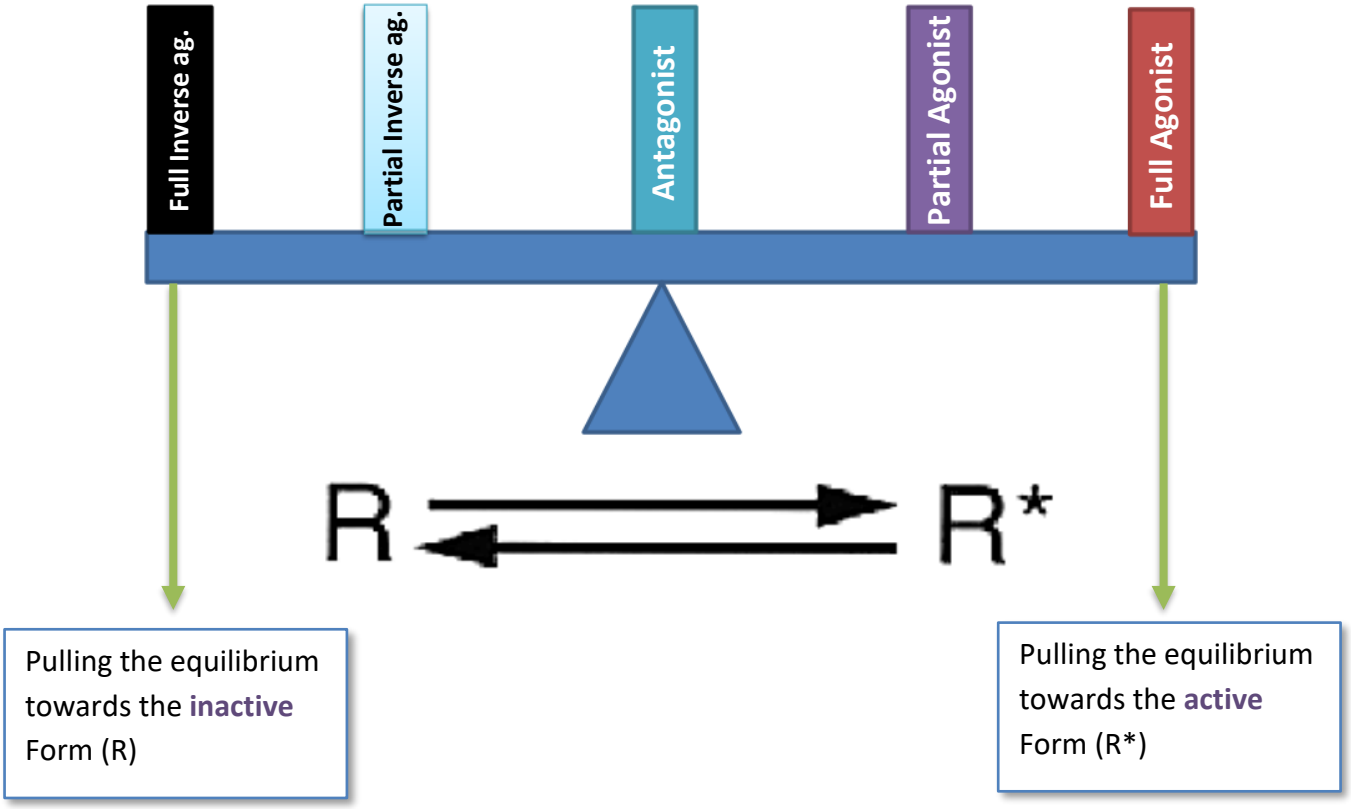
The **receptor is bound to an agonist** drug, causing a bigger shift towards **the active form** thus giving a **higher effect**.

- **Full agonists** shift equilibrium **"fully"** towards the active conformation
- **Partial agonists** shift equilibrium **"partially"** towards the active conformation

Reminder: *Partial agonists are those who show a* ***submaximal effect*** *even if receptors* ***were completely occupied****.*



Imagine this balance scale, observe how different type of drugs affect the equilibrium.



Note: The antagonist *(Reversible/Irreversible)* **does not** affect the **equilibrium** since it doesn't **induce any functional** change on the receptor.

The sheet was made upon where section 1 reached in the material

Good Luck and sorry for any mistakes 😊