Receptors and Signal Transduction

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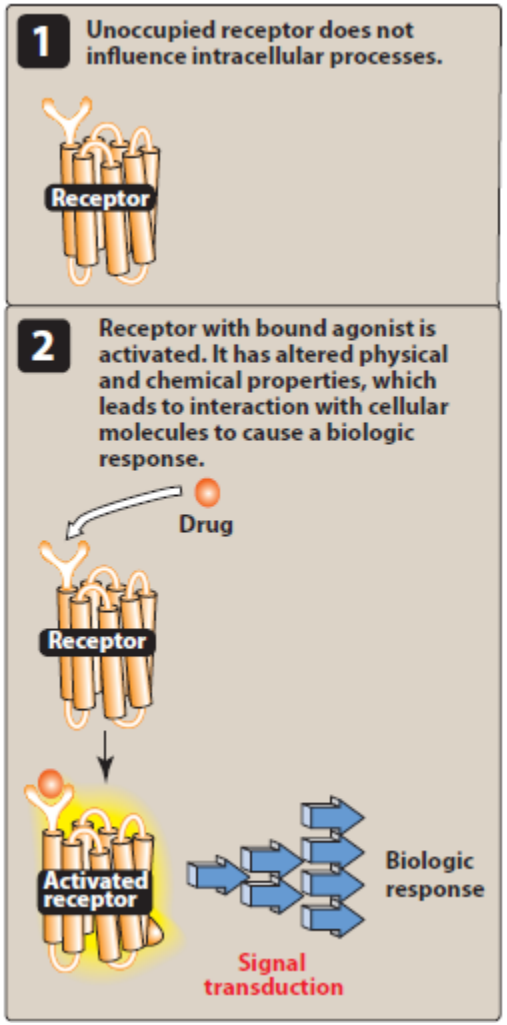
- Receptor: specialized target macromolecules present on the cell surface or within the cell.
- The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction



Receptors and Signal Transduction

- Drugs act as signals, and their receptors act as signal detectors
- initiating a series of reactions that ultimately result in a specific intracellular response
- Agonist is a naturally occurring small molecule or a drug that binds to a site on a receptor protein and activates it

Receptors and Signal Transduction

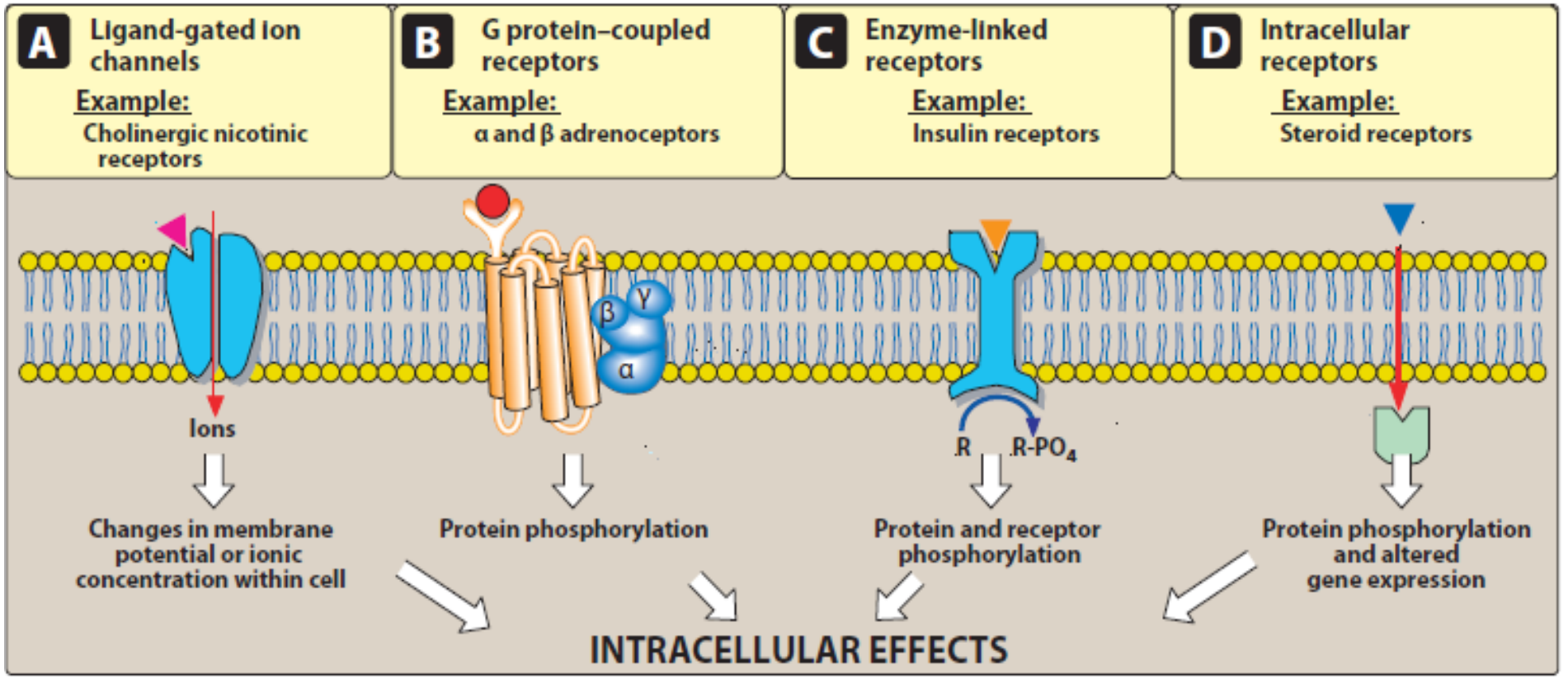
- “Second messenger” or effector molecules are part of the cascade of events
- The magnitude of the response is proportional to the number of drug– receptor complexes
- Most receptors are named for the type of agonist that interacts best with it
- Not all drugs exert their effects by interacting with a receptor, E.g: Antacids chemically neutralize excess gastric acid, thereby reducing the symptoms of “heartburn.”

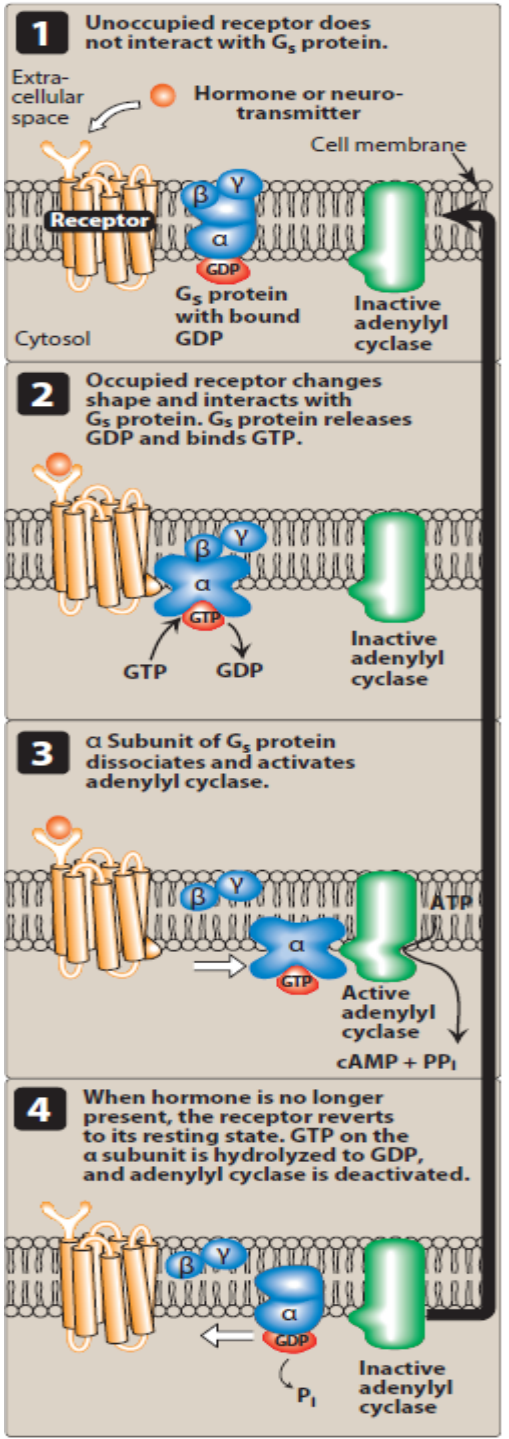
Receptors and Signal Transduction

- Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state.

- Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response.

Types of Receptors

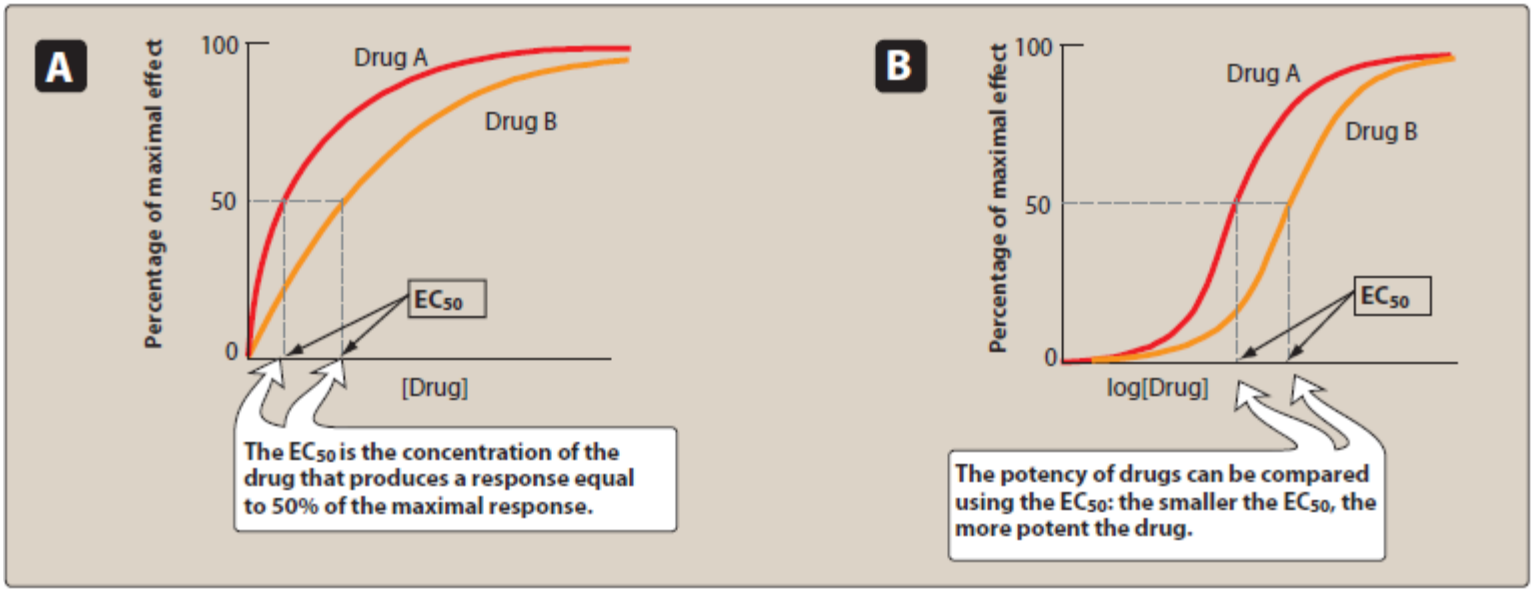



1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_I
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_I
Inactive adenylyl cyclase

- Signal transduction has two important features: **1. Signal amplification:**
- A characteristic of G protein–linked and enzyme-linked receptors is their ability to amplify signal intensity and duration.
- **2. Desensitization and down-regulation of receptors**
- Changes in the responsiveness of the receptor
- When a receptor is exposed to repeated administration of an agonist, the receptor becomes desensitized (tachyphylaxis)

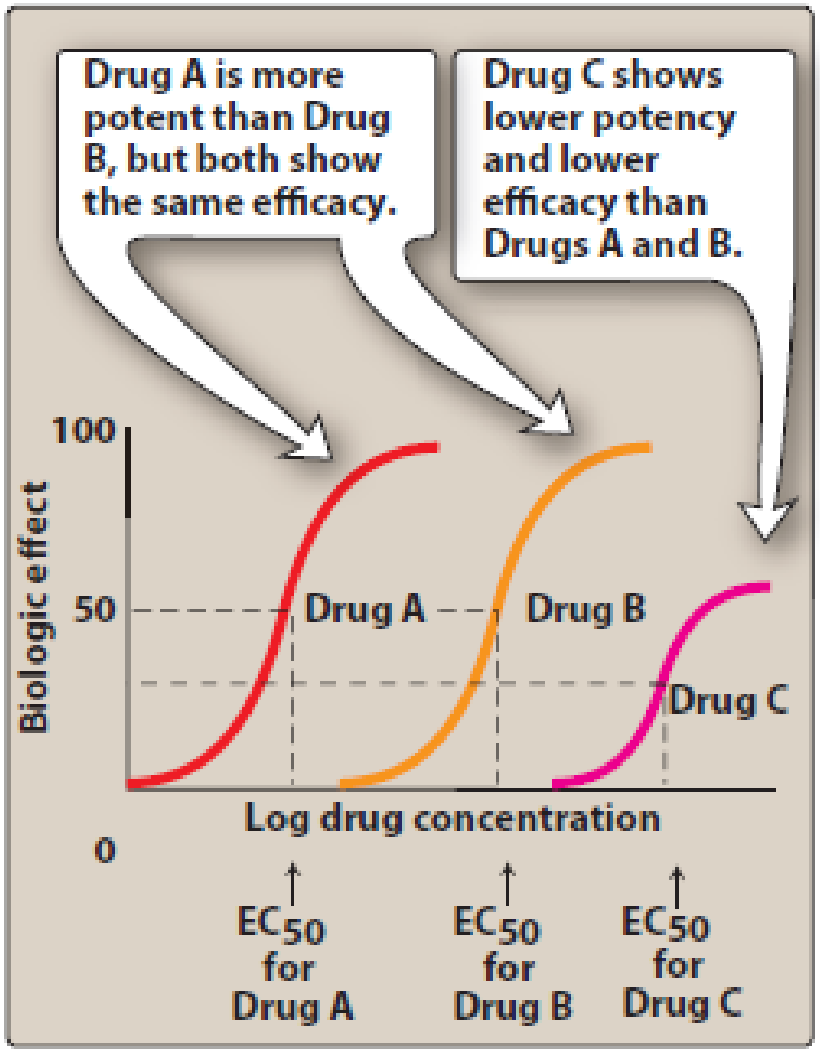
- Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again
- During this recovery phase, unresponsive receptors are said to be “refractory.”
- Up-regulation of receptors can make the cells more sensitive to agonists and/or more resistant to the effect of the antagonist.

- The magnitude of the drug effect depends on the drug concentration at the receptor site



- **Efficacy:** Efficacy is the magnitude of response a drug causes when it interacts with a receptor.

- **Intrinsic activity** of the drug is the ability of drug to activate the receptor and cause a cellular response.


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C