Pharmacodynamics: Mechanisms of drug action and Drug Receptor Interactions

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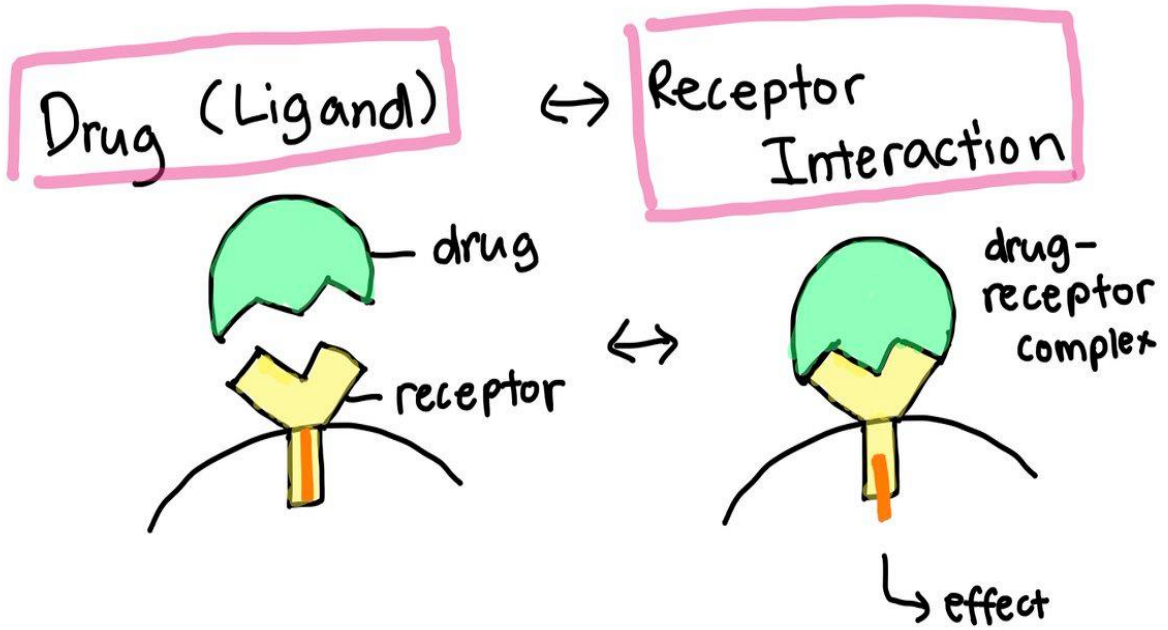
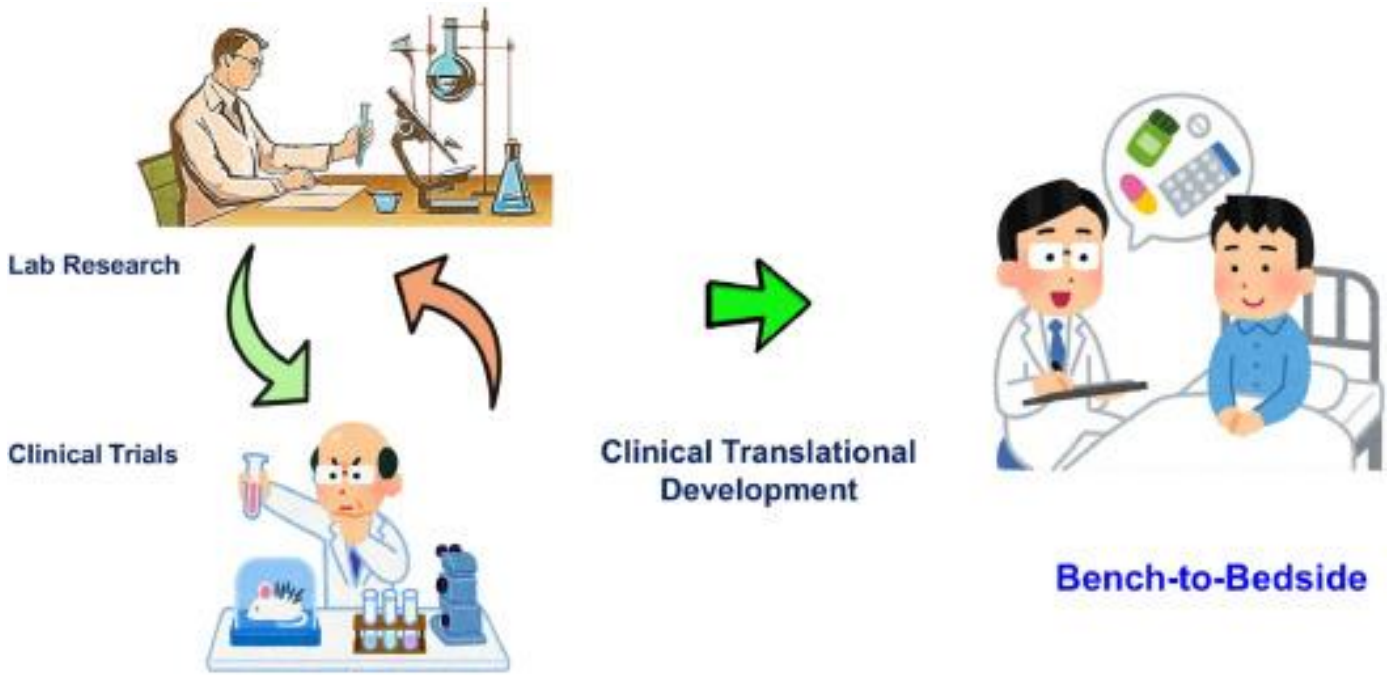


Lecture objectives

- Define and explain the terms: clinical pharmacology, pharmacokinetics, pharmacodynamics, pharmacoepidemiology, pharmacogenetics, pharmacoeconomics and pharmacologistics.
- Describe the drug binding to the receptor and explain the meanings of ligand, affinity, Kd, selectivity, spare receptors,
- Describe the main targets of drug action: receptors, carriers, ion channels, enzymes and others with examples of the drugs.
- Describe the four main types of receptors and provide examples of the drugs binding to different types of the receptors.
- Define agonist and antagonist and describe the different types of agonist and antagonists: Competitive and non-competitive antagonists, full and partial agonists.
- Describe graded and quantal dose-response curves
- Define potency and efficacy of drugs and compare them in terms of clinical significance.

Clinical Pharmacology

- Clinical pharmacology encompasses all aspects of the relationship between drugs and humans.
- It closes the gap between basic experimental pharmacology and therapeutics.
- It is the only medical specialty focusing on the safe, effective and economic use of medicines.



Pharmacodynamics

- Pharmacodynamics studies the biochemical and physiologic effects of drugs and their mechanisms of action.
- Pharmacodynamics answers the question

What a drug does to the body?

Pharmacokinetics

- Pharmacokinetics studies processes that a drug undergoes after administration (absorption, distribution, metabolism and excretion)
- Pharmacokinetics answers the question

What the body does to the drug?

Pharmacoepidemiology

- Studies the use and effects of medications in large populations.
- It combines principles of pharmacology and epidemiology to understand how drugs affect public health, focusing on the distribution, determinants, and outcomes of drug use in real-world settings.
- Key aspects of pharmacoepidemiology include:

1. **Drug utilization:** These studies examine patterns of drug use in a population, such as how often a drug is prescribed
2. **Pharmacovigilance:** Identifies, quantify, and analyze the occurrence of ADRs.

Pharmacogenetics

- Studies how an individual's genetic makeup influences their response to drugs. It is a subfield of pharmacogenomics, which examines how all of a person’s genes (the genome) interact with drugs
- The primary goal of pharmacogenetics is to understand why people respond differently to the same medication and to use that knowledge to personalize treatment.
- Key concepts in pharmacogenetics include:

1. **Drug metabolism**: Genetic differences can affect how quickly or slowly an individual metabolizes a drug.
2. **Drug efficacy**: Genetic variations can influence efficacy of the drug for an individual
3. **Adverse drug reactions**: Certain genetic variations can increase the likelihood of experiencing ADRs.

Pharmacoeconomics

- Studies the cost and value of drugs and pharmaceutical interventions in relation to their health outcomes.
- It combines principles from economics and healthcare to evaluate the economic impact of pharmaceutical products and treatments.
- The key pharmacoeconomic analyses are:

1. **Cost-Minimization Analysis (CMA)**
2. **Cost-Effectiveness Analysis (CEA)**
3. **Cost-Utility Analysis (CUA)**
4. **Cost-Benefit Analysis (CBA)**

Pharmaceutical logistics (Pharm logistics)

- It is the management and process of efficiently handling the storage, transportation, and distribution of pharmaceutical products from manufacturers to end users (such as hospitals, pharmacies, and healthcare providers).
- Key components of pharmaceutical logistics include:

1. Storage

2. Transportation

3. Inventory management

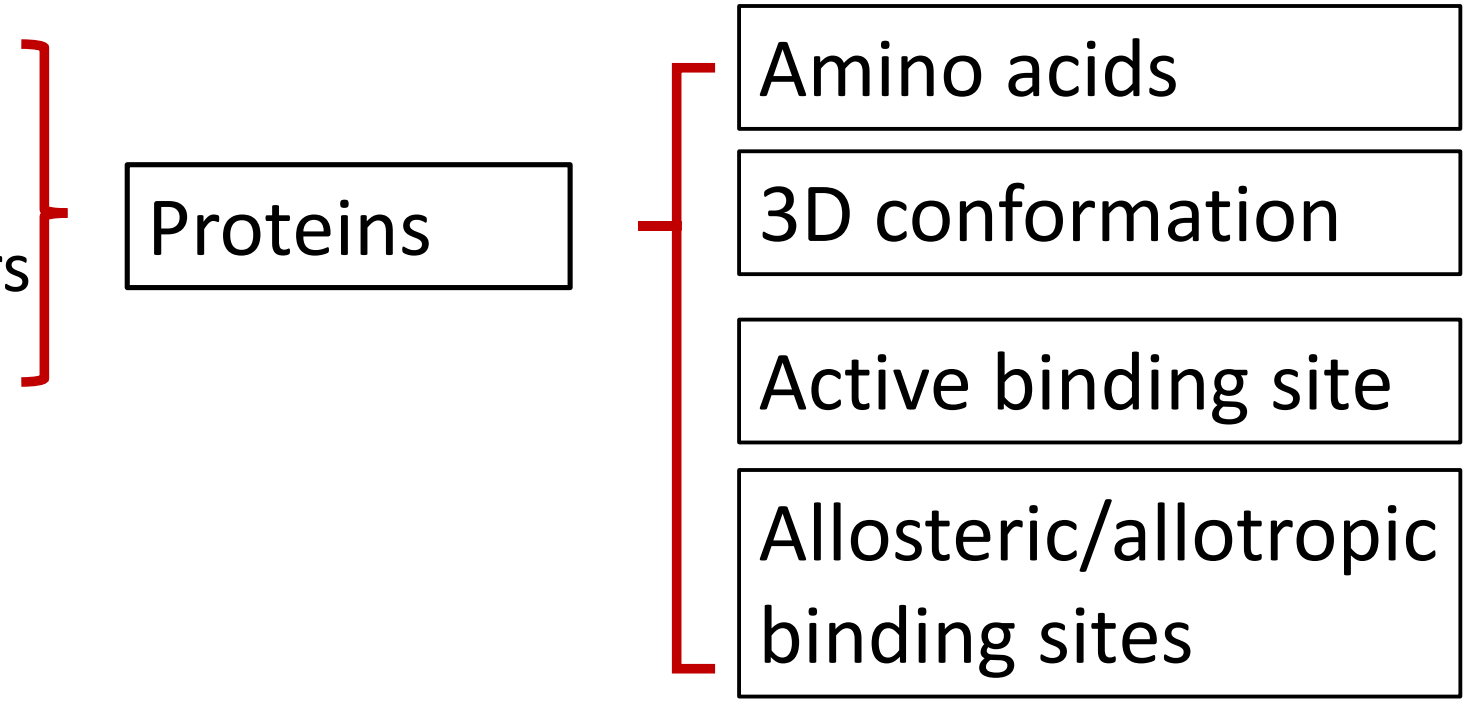
4. Regulatory compliance

5.Supply chain monitoring

Pharmacodynamics

Types / Targets for Drug Action

- Receptors
- Enzymes
- Carriers / Transporters
- Ion channels
- Other
  - Physical action
  - Chemical reaction



Binding to a Protein Target

- Ligand is a substance (hormone / mediator / drug) which binds to a target and alters its 3D conformation.

Endogenous ligands

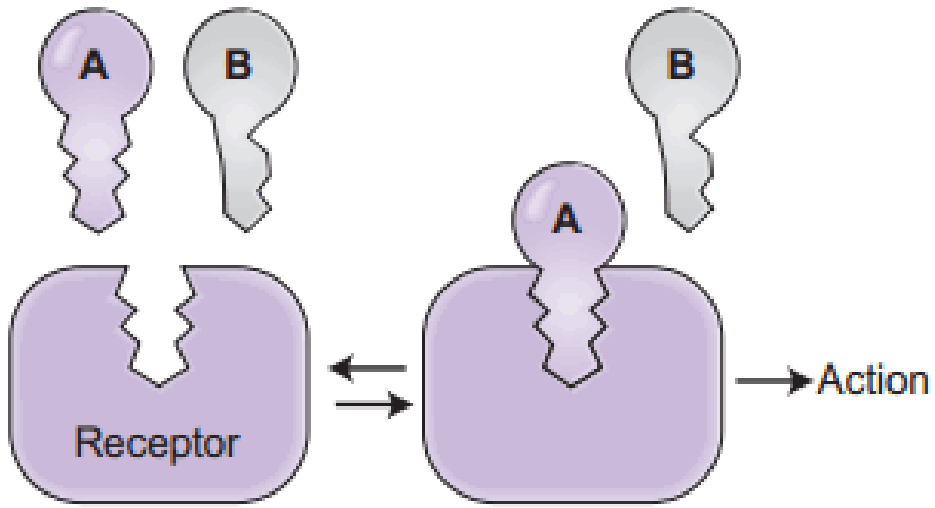
- Hormones / mediators/ cytokines

Exogenous ligands

- Drugs / toxins /poisons

Binding to Protein Target

- Affinity is ability of a ligand to bind the target

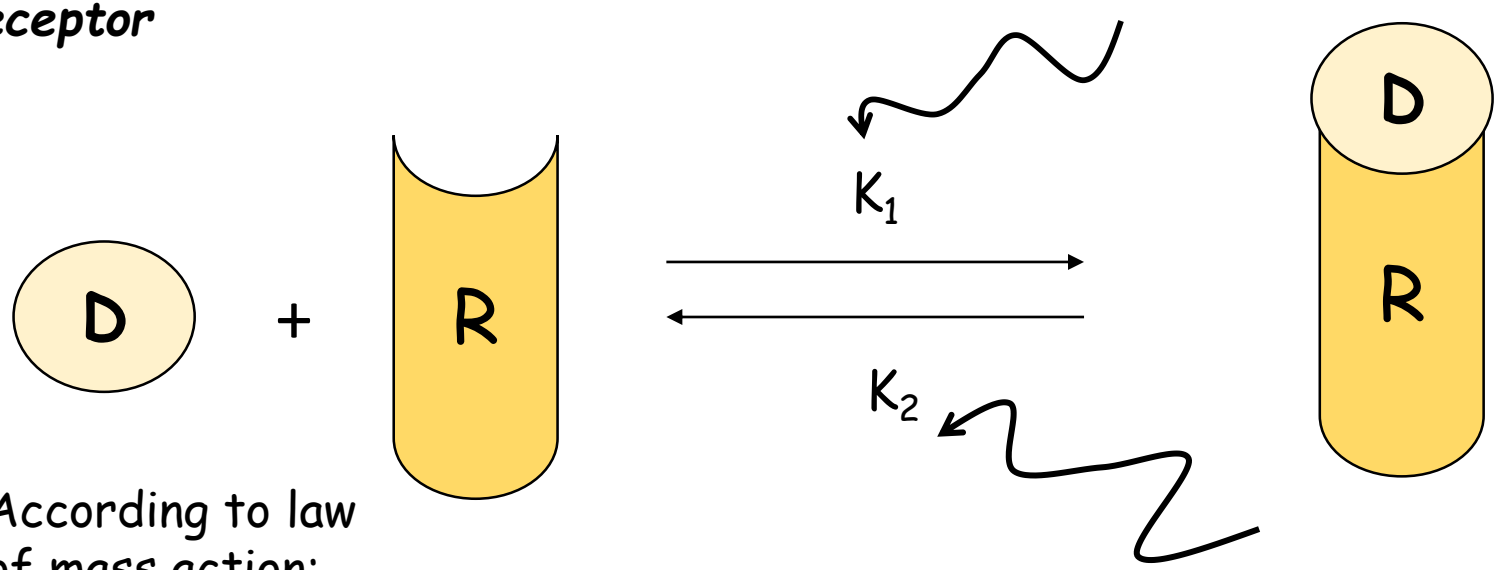


Lock and key theory

Affinity

Higher the k_D: smaller the affinity
Lower the k_D: higher the affinity
k_D indicates the degree of affinity

Affinity is the tendency of a ligand/drug to bind to the receptor



According to law of mass action:

At equilibrium

$k1[D][R]=k2[DR]$

At equilibrium

$$\frac{[D][R]}{[DR]} = \frac{k2}{k1} = k_D$$

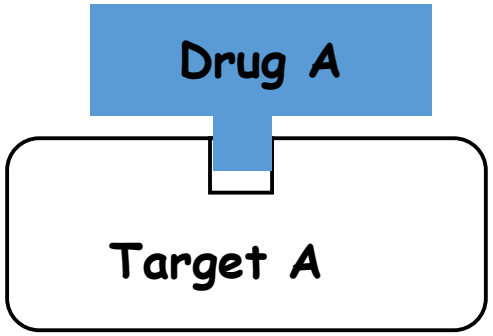
Equilibrium dissociation constant = The concentration of drug that binds 50% of the receptors in the system

Binding to Protein Target

- Specificity is ability of a ligand to bind the specific target /receptor / enzyme / channel etc.

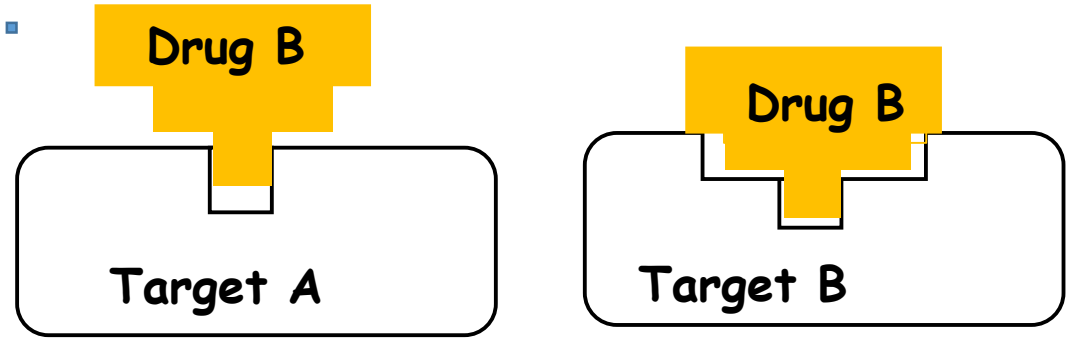
Specific / Selective Drugs

1 ligand / drug → 1 single target / receptor



Nonspecific / Nonselective Drugs

1 ligand /drug → Many targets /receptors

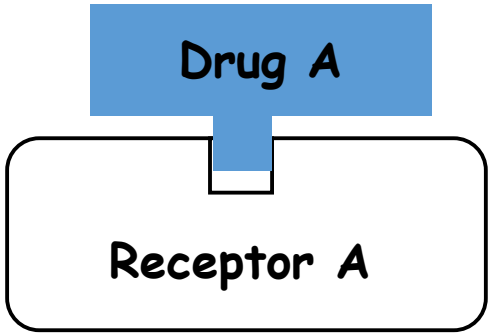


No drugs are completely selective in their actions

Selectivity /Specificity to Receptor

Specific / Selective Drugs

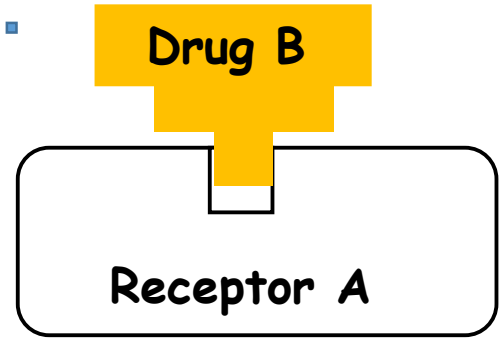
Drug A has affinity to Receptor A only

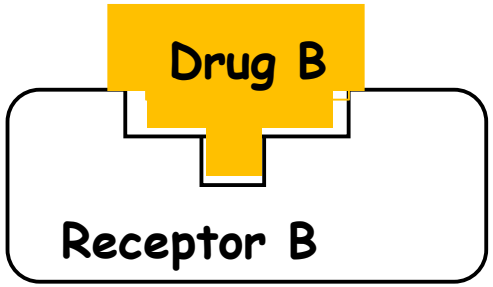


Nonspecific / Nonselective Drugs

Drug B has affinity to both Receptor A and Receptor B
Affinity to Receptor A may be:

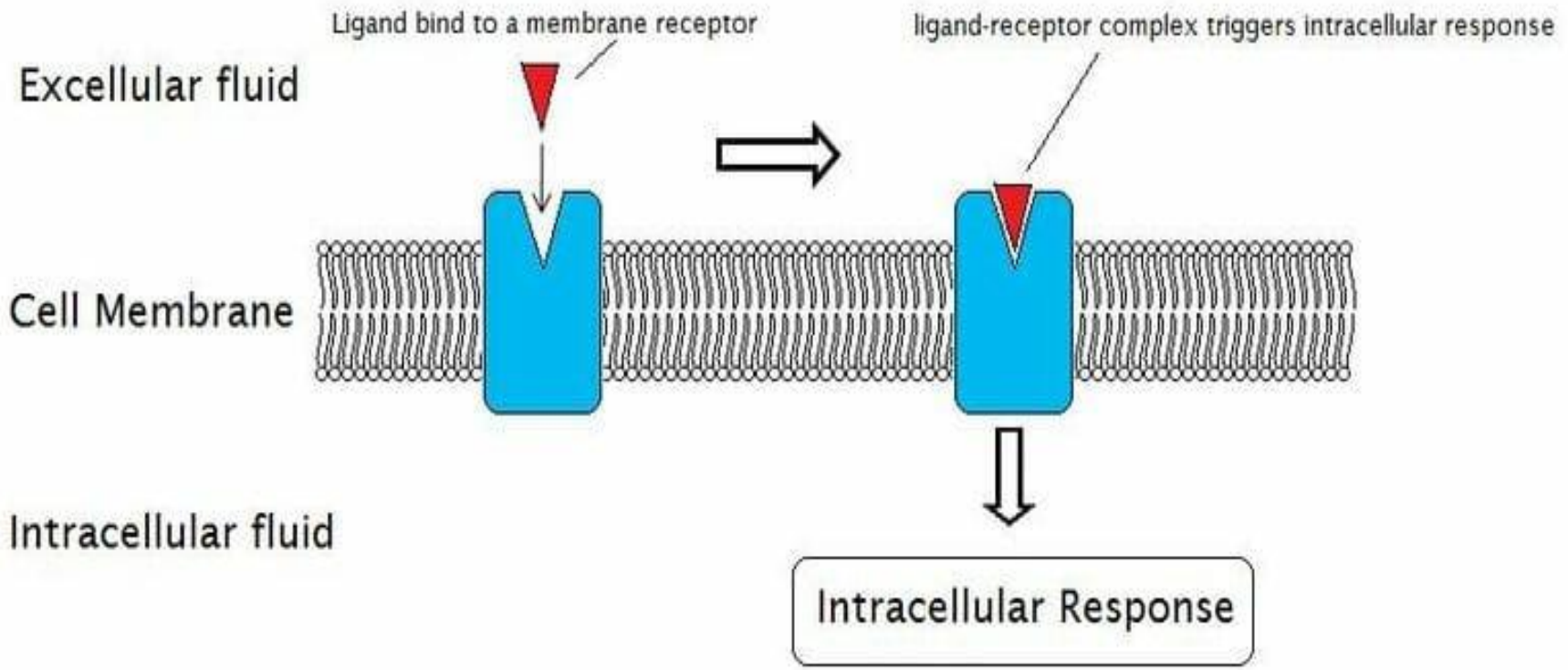
Affinity to Receptor A = Affinity to Receptor B
Affinity to Receptor A > Affinity to Receptor B
Affinity to Receptor A <Affinity to Receptor B



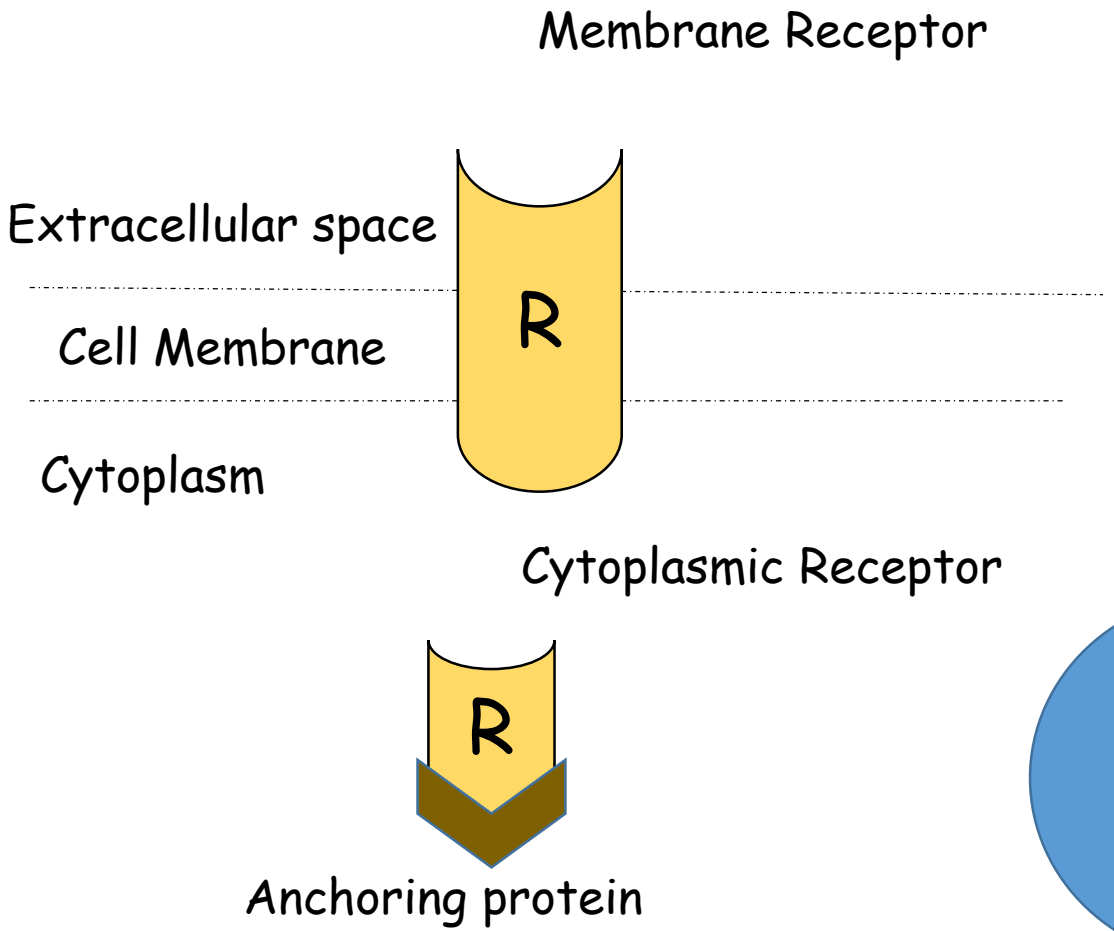


Receptors

- Receptors are proteins that receive and transduce signals (chemical messengers) and cause different cellular/tissue response.



Types of Receptors

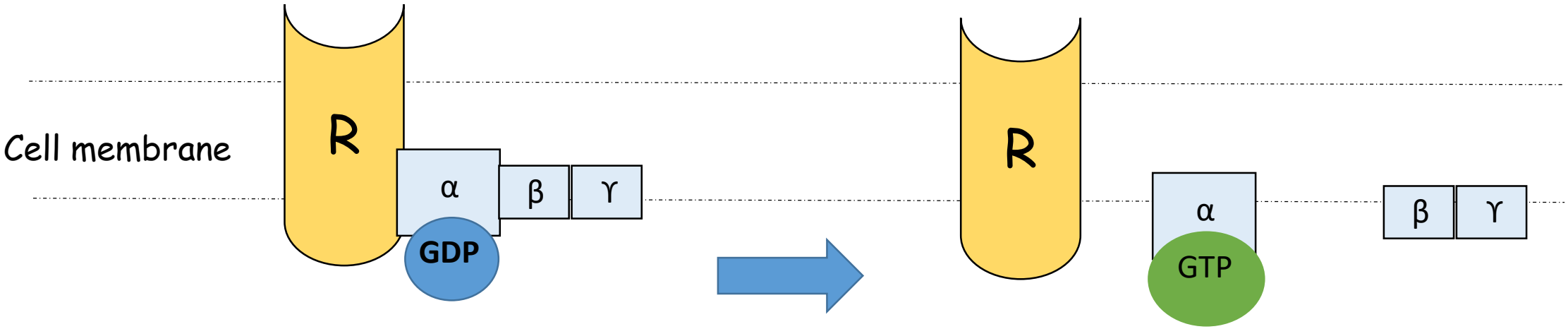


- Membrane/Surface Receptors
  - linked to G-proteins **GPCR** (metabotropic receptors)
  - linked to ion channels (ionotropic receptors)ligand gated ion channels
  - linked to enzymes
- Cytoplasmic/nuclear (affecting gene transcription)

Metabotropic receptors (GPCR)

A

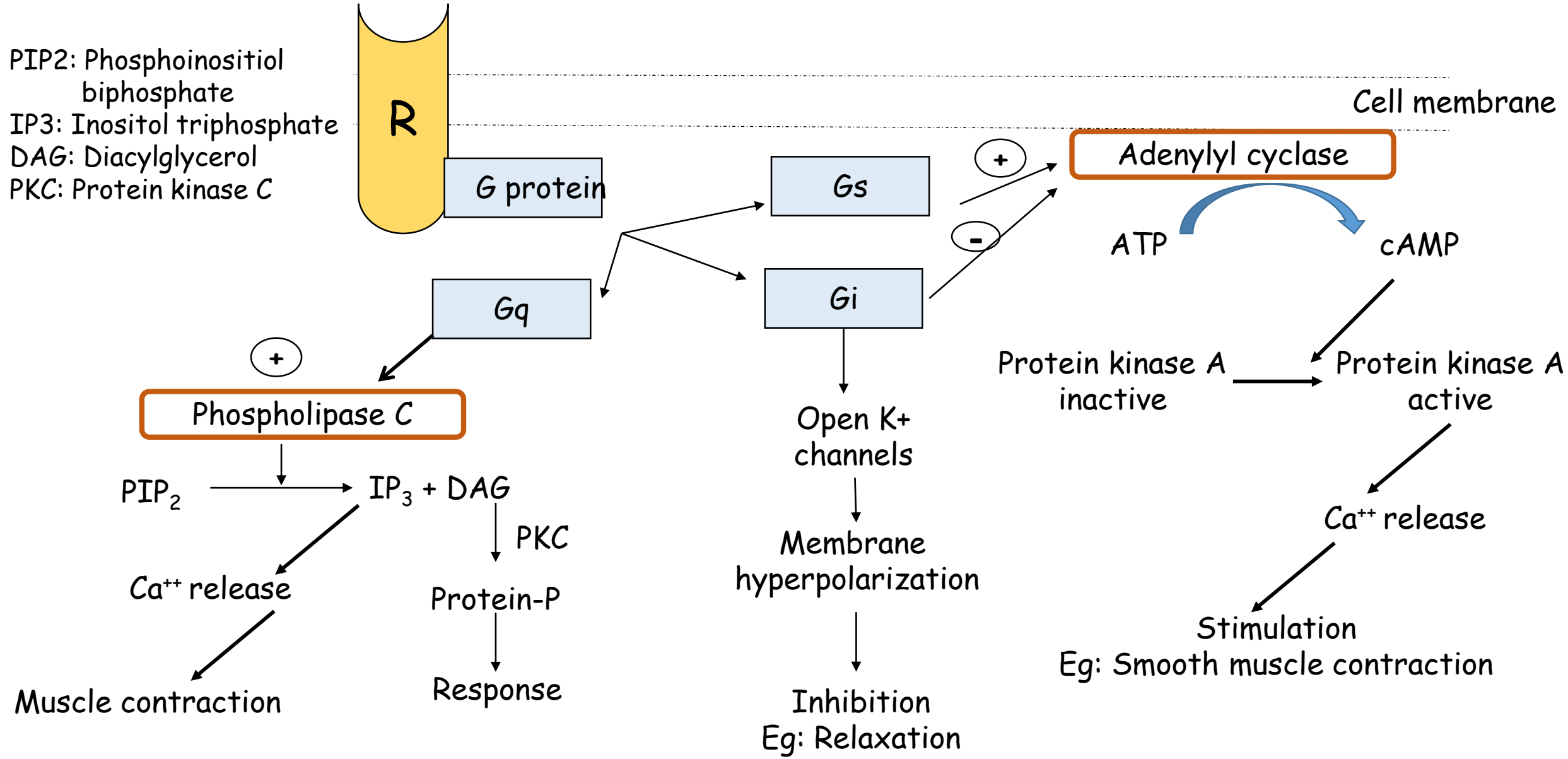
Humans alone have nearly 1,000 different GPCRs



GDP: Guanosin diphosphate
GTP: Guanosin triphosphate

Second messengers activation

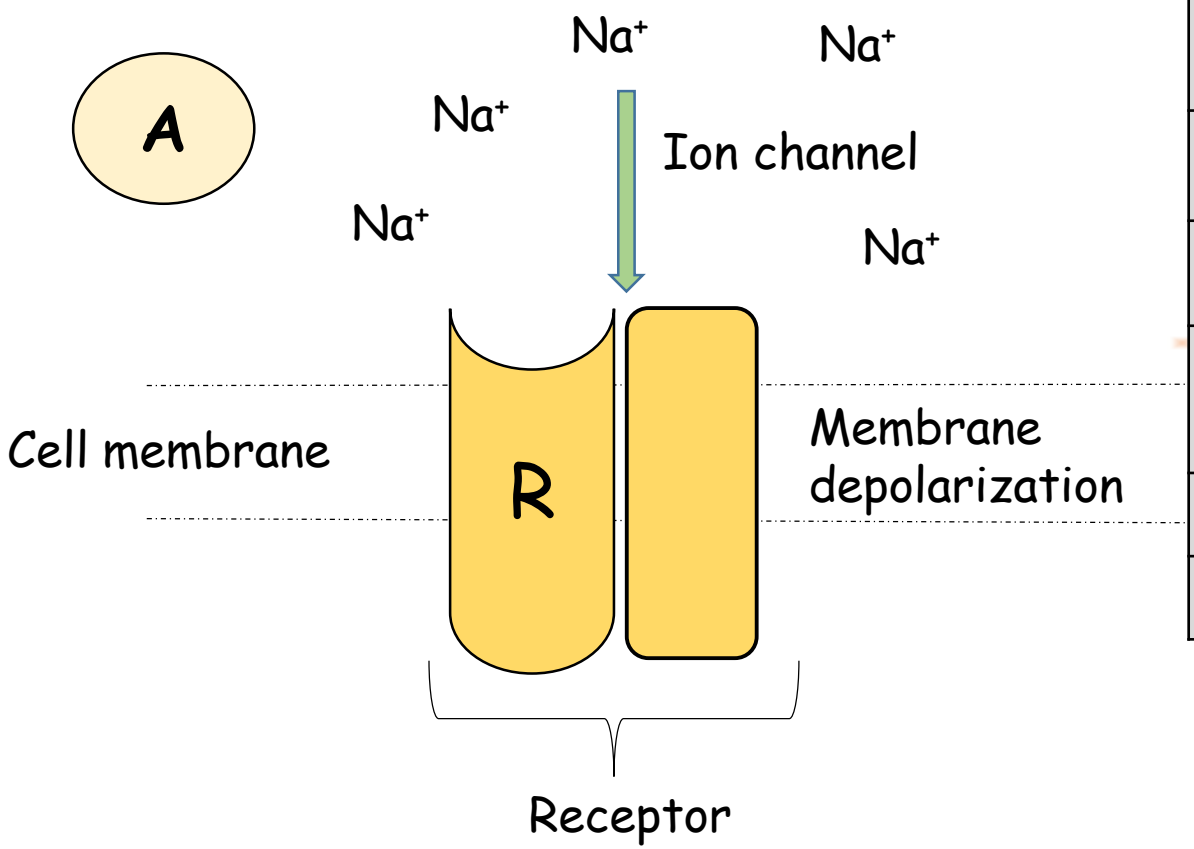
Second Messengers



G-protein Coupled Receptors

Agonist	Receptor	G-protein activation	Second messengers Effector	Effect
Histamine	H1	Gq ----- (+)	Phospholipase C → IP3+DAG → IP3+DAG → Ca/ protein P	Smooth muscle contraction
Adrenalin	β1	Gs------- (+)	Adenylyl cyclase → cAMP → PKA → Calcium	Cardiac contraction
Adrenalin	α2	Gi------- (-)		Smooth muscle relaxation
Acetylcholine	M2	Gi ------- (-)	K+ channel → Hyperpolarization	Cardiac slowing

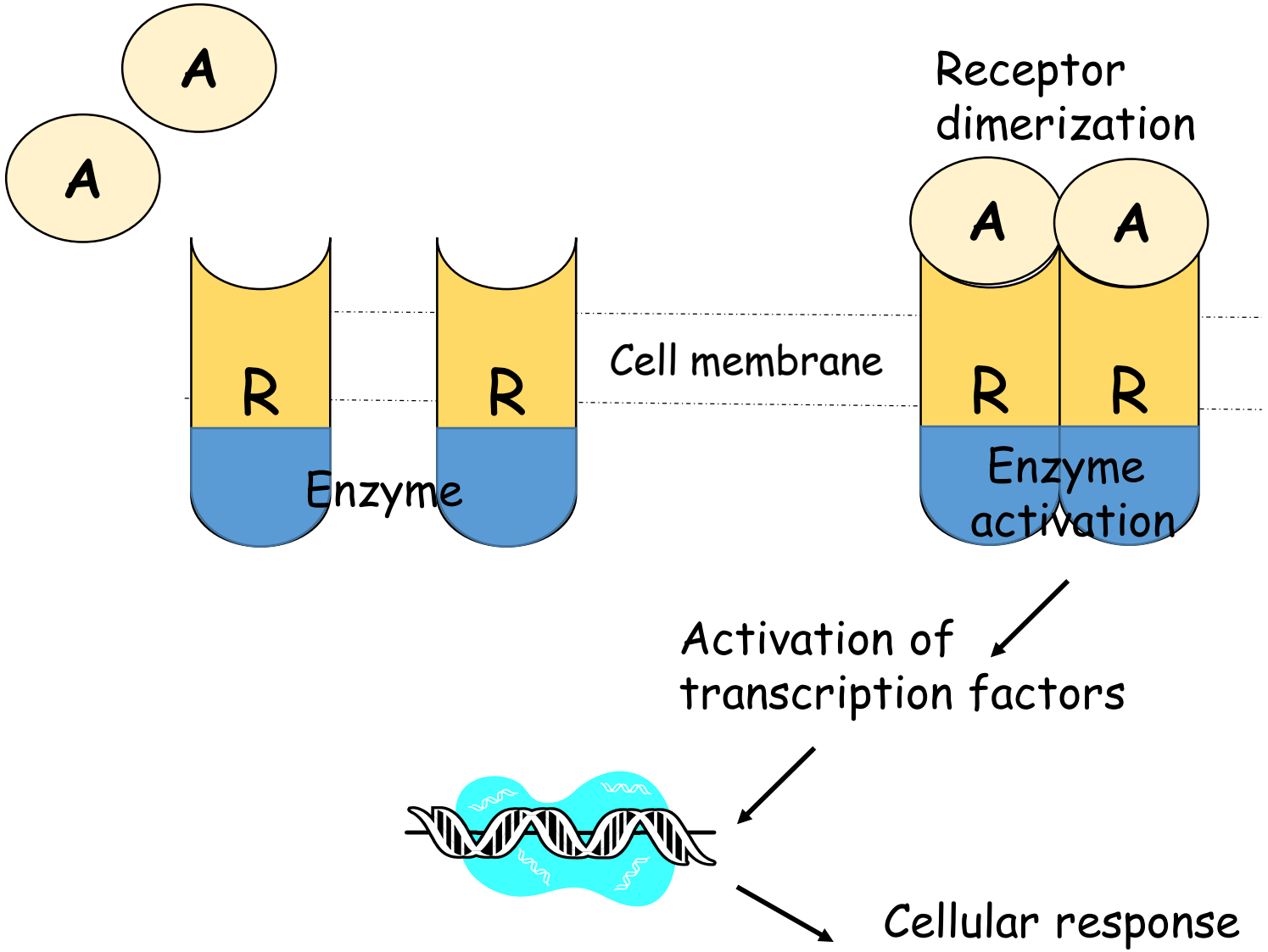
Receptors Linked to Ion Channels



Drug / Substance	Receptor	Ion channel
Nicotine	Nicotinic	Na^+
Succinylcholine		
Gamma aminobutyric acid (GABA)	$GABA_A$	Cl^-
Phenobarbital		
Diazepam		

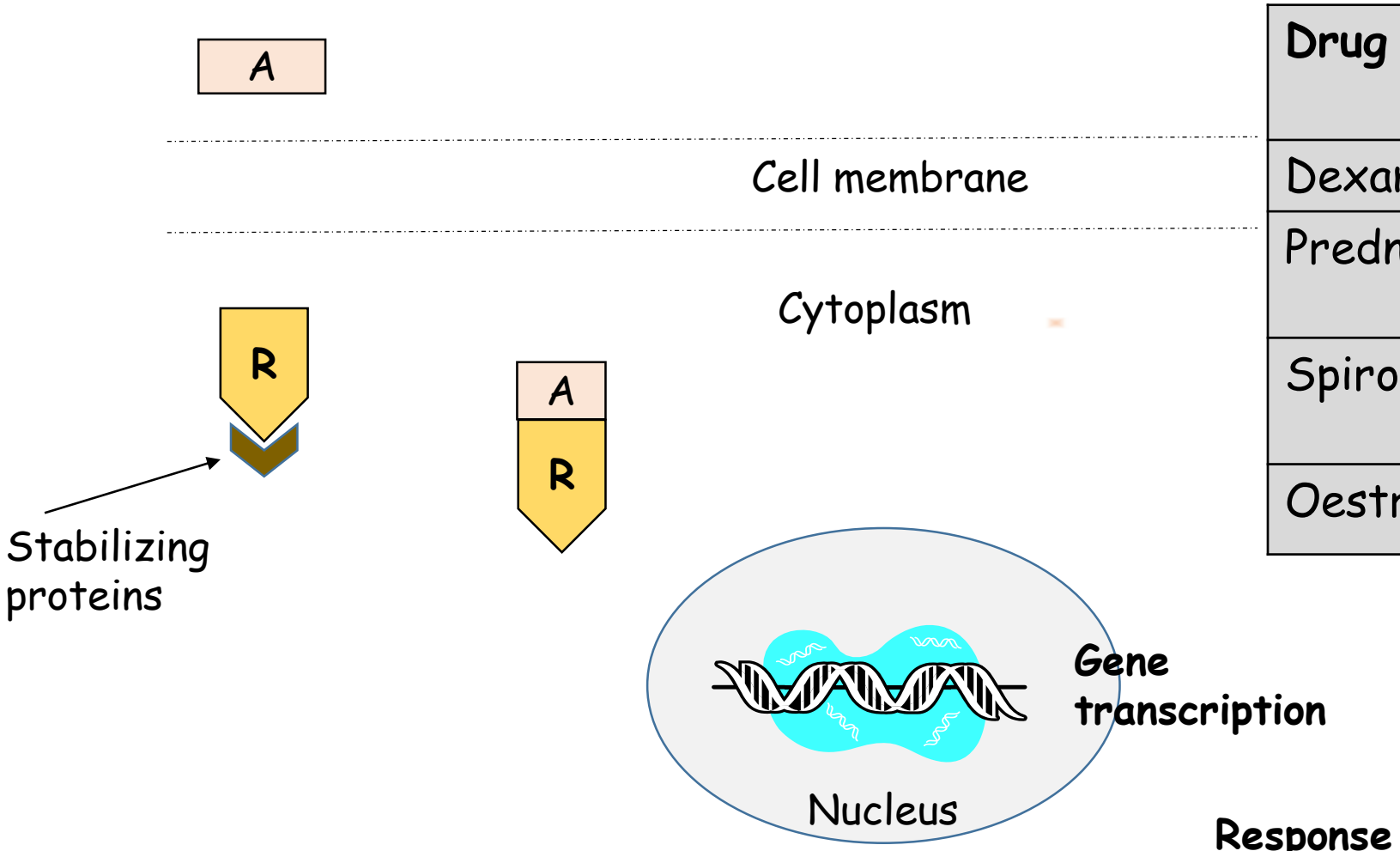
Nicotinic receptor

Receptors Linked to Enzymes (Tyrosine Kinase)



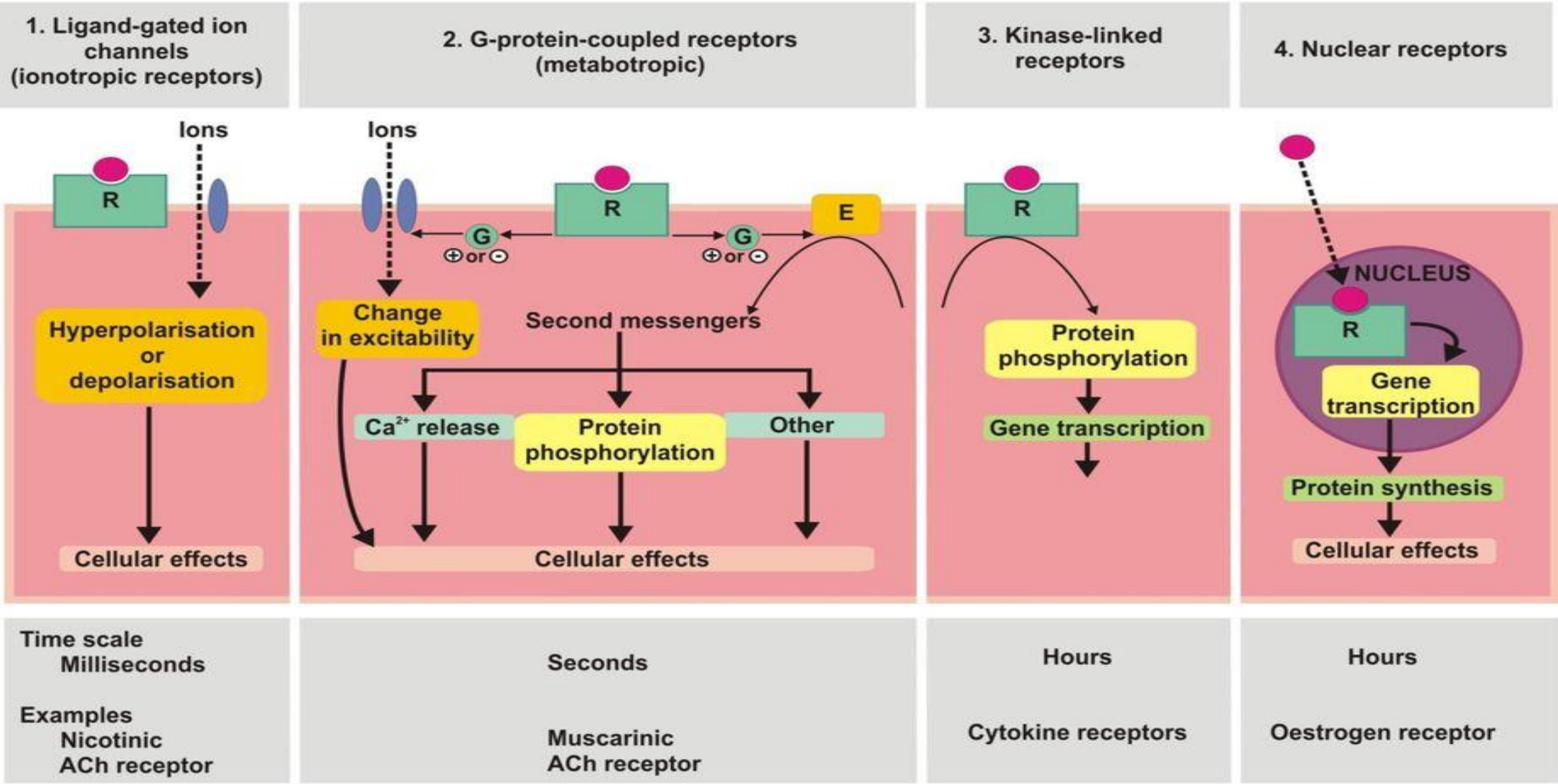
Drug	Receptor
Insulin	Insulin receptor
Cytokines	Cytokine receptor

Cytoplasmic/Nuclear Receptors



Drug	Receptor
Dexamethasone	Glucocorticoid
Prednisolone	
Spironolactone	Mineralocorticoid
Oestriol	Oestrogen

Types of receptor - effector linkage



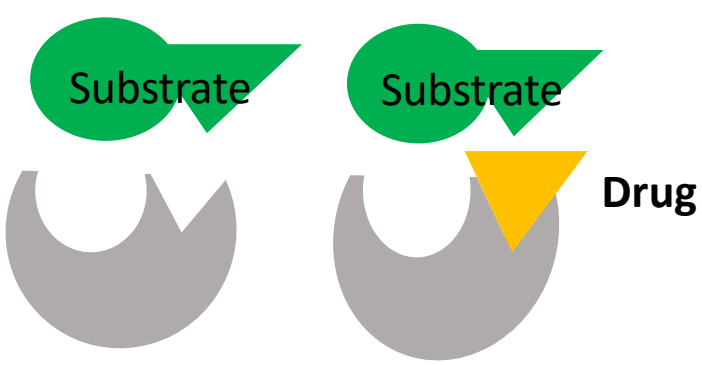
R = receptor
G = G-protein
E = enzyme
ACh = acetylcholine

According to Rang and Dale Pharmacology, 2007

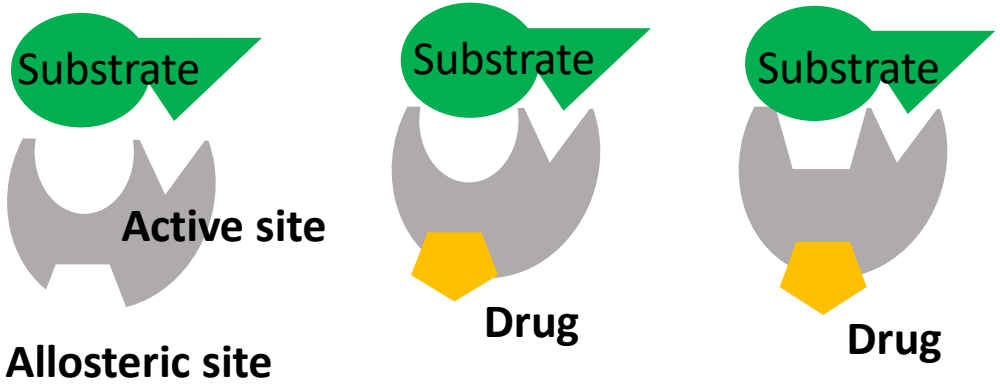
Enzymes as Targets for the Drug Action

Enzymatic reaction

Enzymatic reaction inhibited



Binding to active site



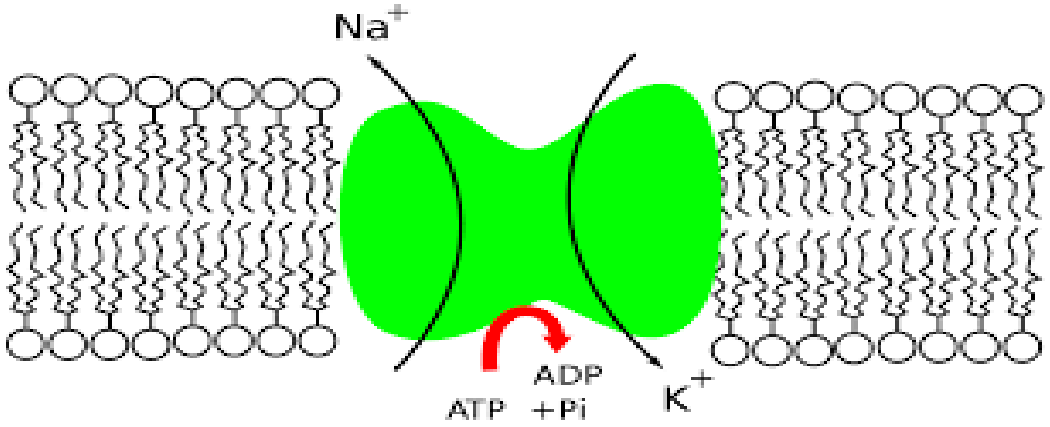
Binding to allosteric site

Enzymes as Targets for the Drug Action

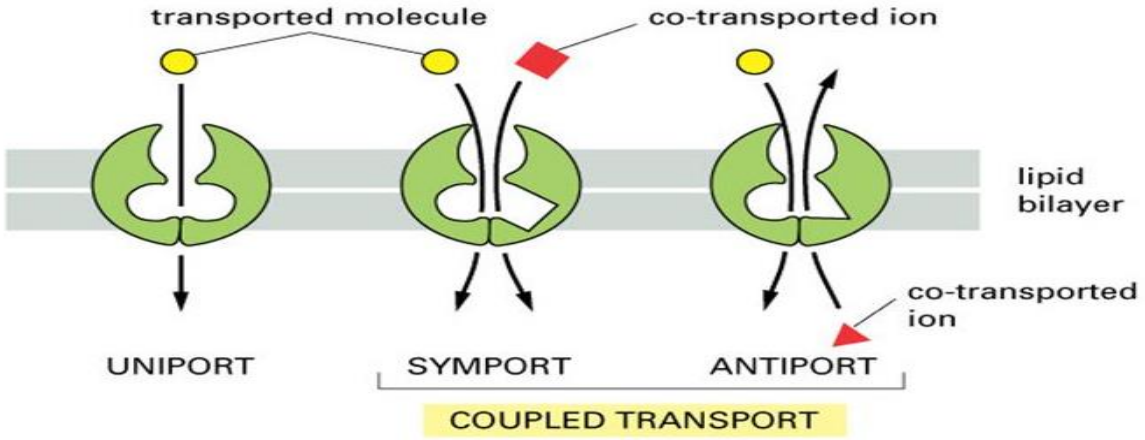
Drug	Enzyme	Effect
Neostigmine	Acetylcholinesterase	Inhibition
Enalapril	Angiotensin converting enzyme (ACE)	Inhibition
Aspirin	Cyclooxygenase (COX)	Inhibition
Phenobarbital	Cytochrome P 450	Inducer

Transporters / Carriers as Targets of Drug Action

- ATP-powered ion pump (Primary Active Transport) – the energy for the transport against concentration gradient derives from ATP

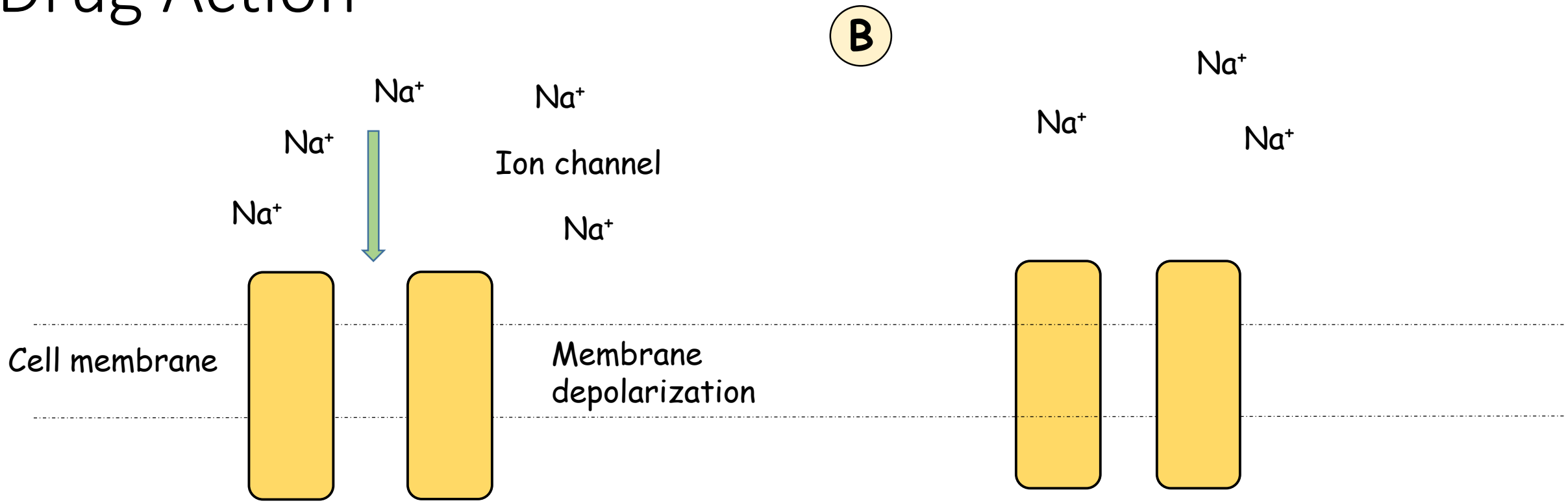


- Coupled Transport (Secondary Active Transport) – the energy derives from another co-transported molecule down its concentration gradient



Drug	Carrier	Effect
Digoxin	Na^+/K^+ ATPase	Inhibition
Omeprazole	Na^+/H^+ ATPase	Inhibition
Furosemide	$Na^+/K^+/Cl^-$ cotransporter	Inhibition

Ion Channels (Voltage Channels) as Targets of Drug Action



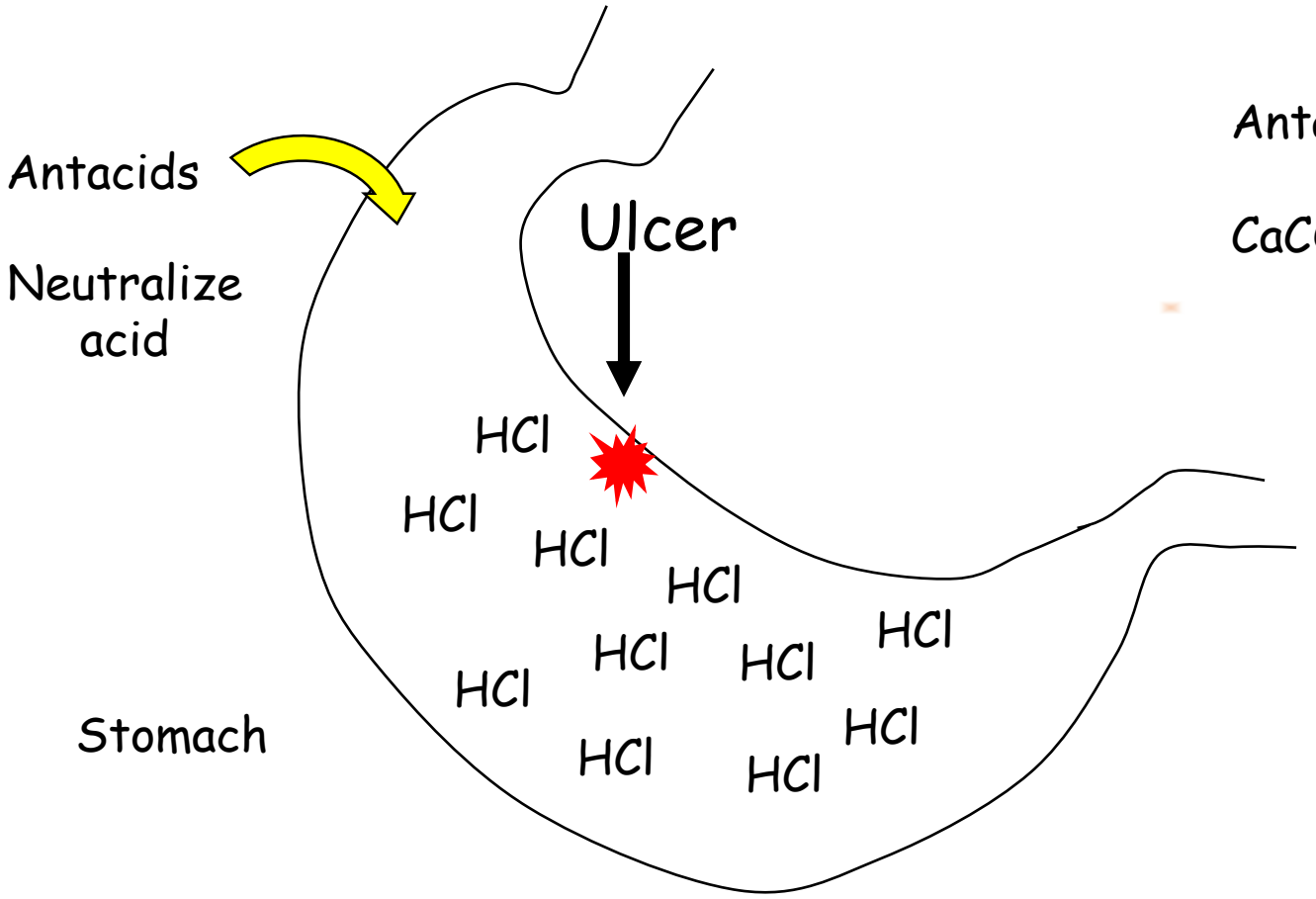
Drug	Channel	Effect
Lidocaine	Na^+	Blockade
Nifedipine	Ca^{++}	Blockade
Amiodarone	K^+	Blockade

Other Mechanisms of Drugs Action

- Direct chemical or physical interaction with molecules and cells

Chemical	Physical
Antacids	Radioactive Iodine (I^{131})
Cyclophosphamide	Osmotic Diuretics

Drugs acting by chemical recation

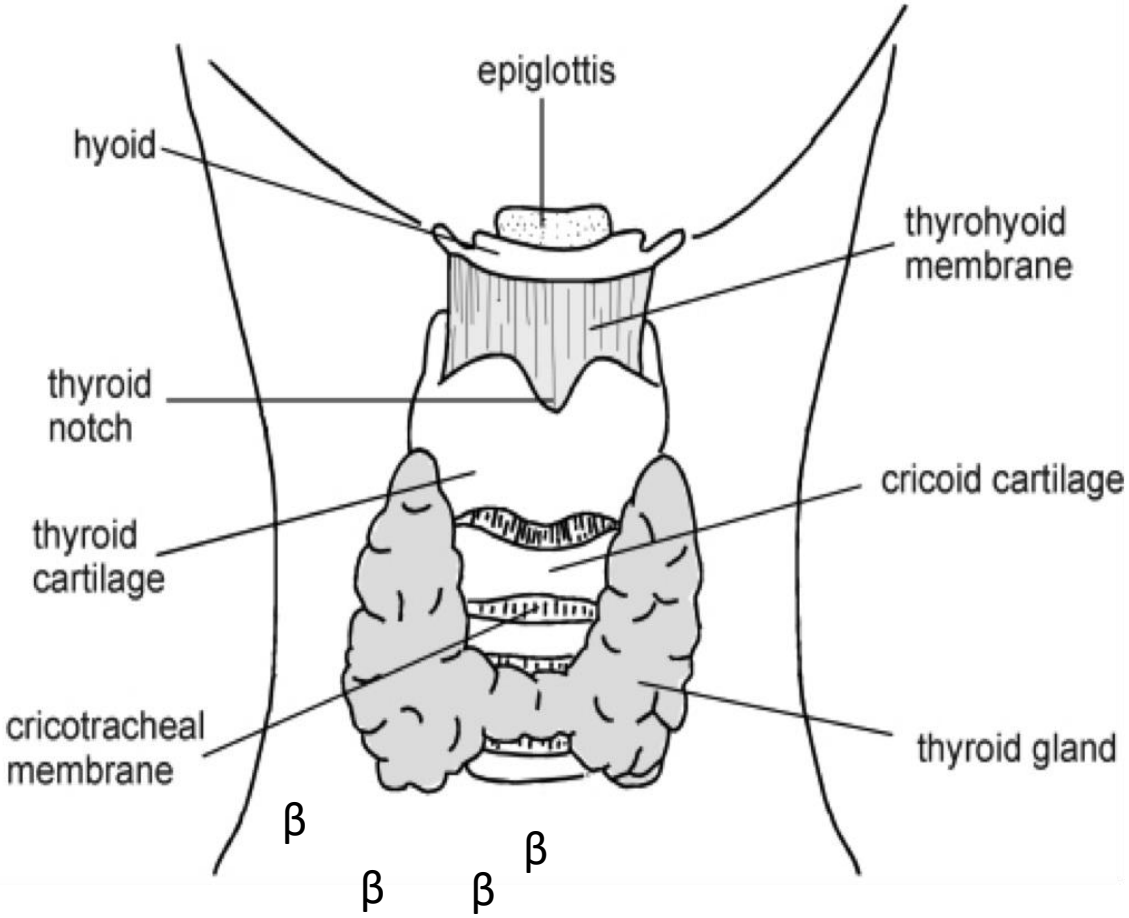


Antacids: $NaHCO_3$, $CaCo_3$, $Mg(OH)_2$, $Al(OH)_3$

$CaCO_3 + 2HCl = CaCl_2 + H_2O + CO_2$

Drugs Acting by Physical Action

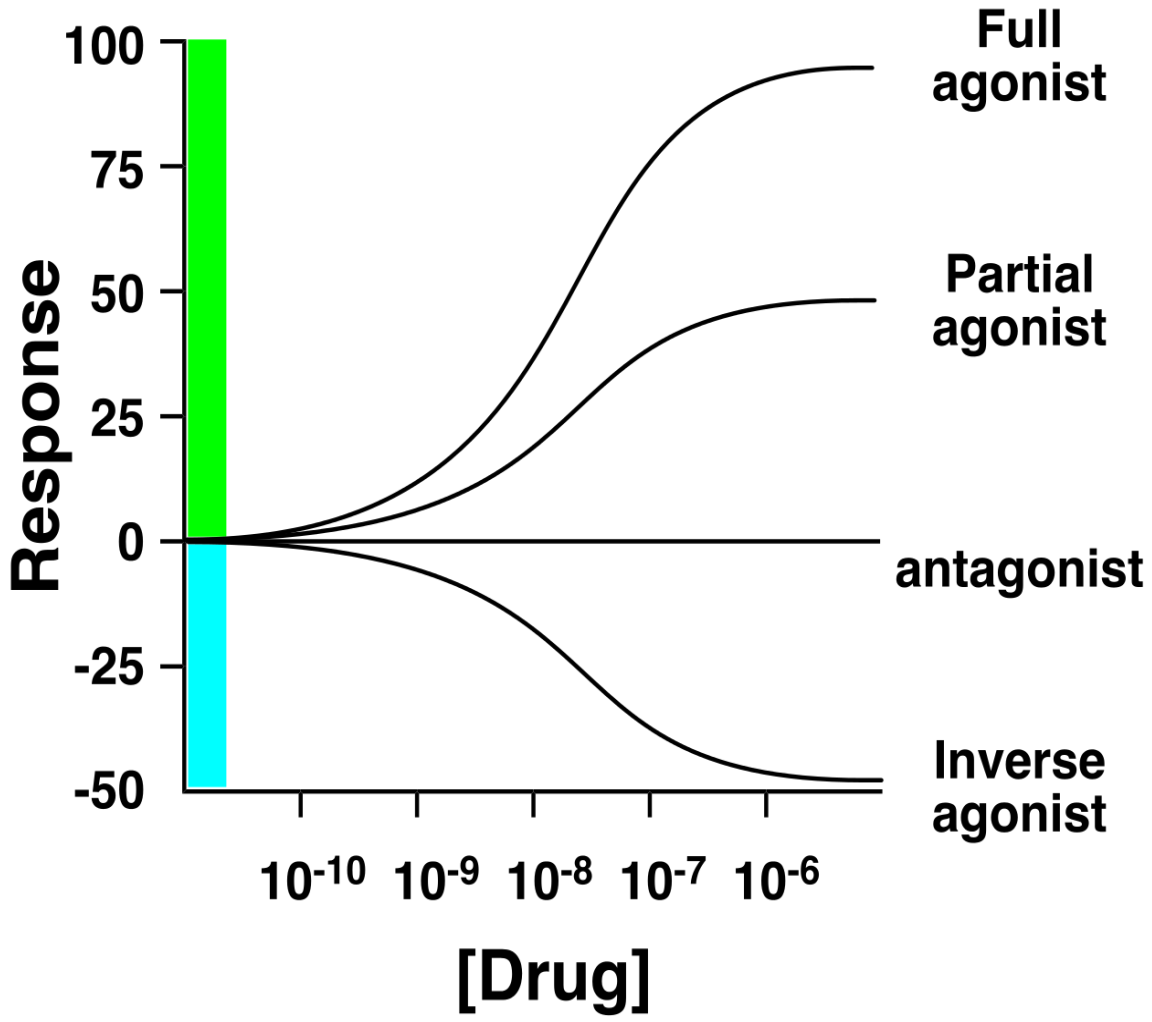
I^{131} I^{131} I^{131} I^{131}



Drug Receptor Interaction

Efficacy is ability to activate receptor

- Full agonist - binds to receptor and produces maximal effect/response
- Antagonists – binds to receptor and has no effect (prevent activation of the receptor by agonist)
- Partial agonist – binds to receptor and produces submaximal effect (less than 100%)
- Inverse agonists – binds to receptor and produces opposite to the agonist effect



Receptor Occupancy

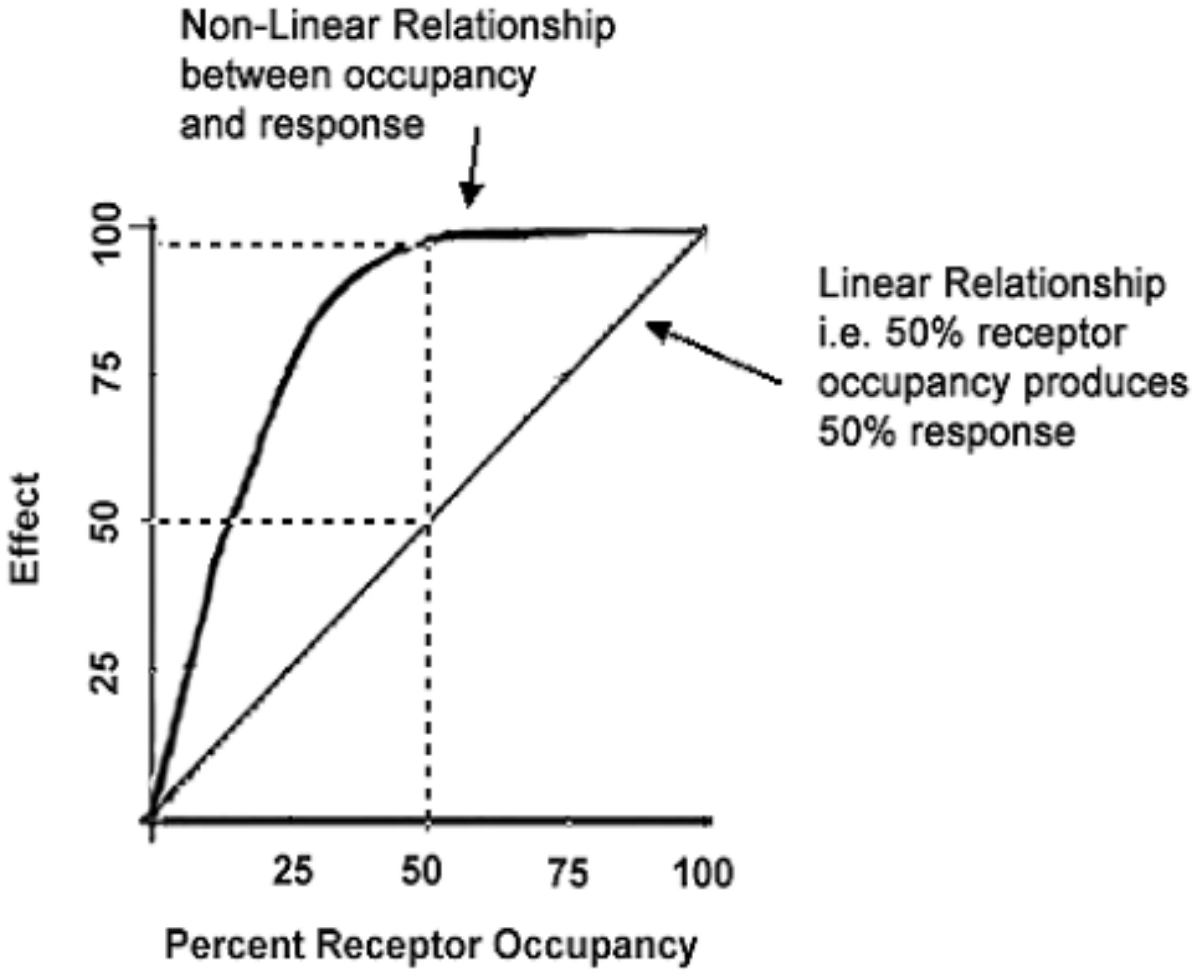
- Drug does not have to occupy all the receptors on cell/tissue to produce maximum effect.
- If a cell has 100 receptors for an agonist, maximum response may be produced when drug occupies only 10 receptors.

= just 10% receptor occupancy.

- What about the remaining 90%??

They are called spare receptors

Spare Receptors



Without spare receptors

- 50% occupancy = 50% response (effect)
- To produce 100% response the drug needs to occupy 100% receptors
- Biological effect is proportional to the dose at all drug concentrations

With spare receptors

- Less than 100% occupancy = 100% response (effect)
- Biological effect is proportional to the dose only at low drug concentrations

Spare Receptors and Sensitivity

- Consider a tissue with 90% spare receptors…….

You can block these 90% receptors with an antagonist…and still get full response/effect with small amount of agonist that can occupy just 10% receptors.

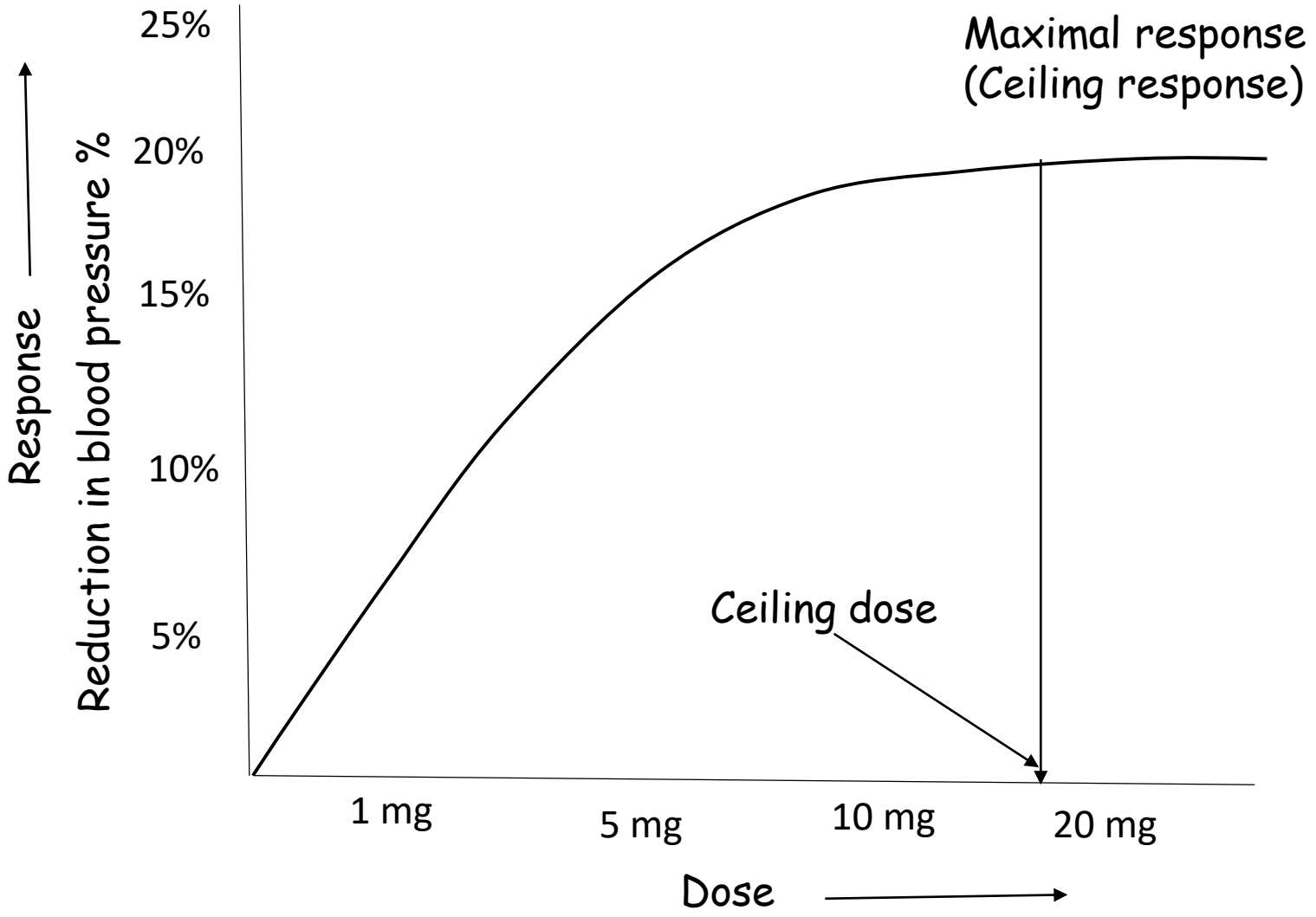
- Consider a tissue with 10% spare receptors…….

If you block 90% receptors with an antagonist…you will not get a response/effect even with large amount of agonist as only 10% receptors are available.

More the number of spare receptors, more is the sensitivity of that tissue for that particular agonist
Eg: Myocardium is extremely sensitive to adrenaline

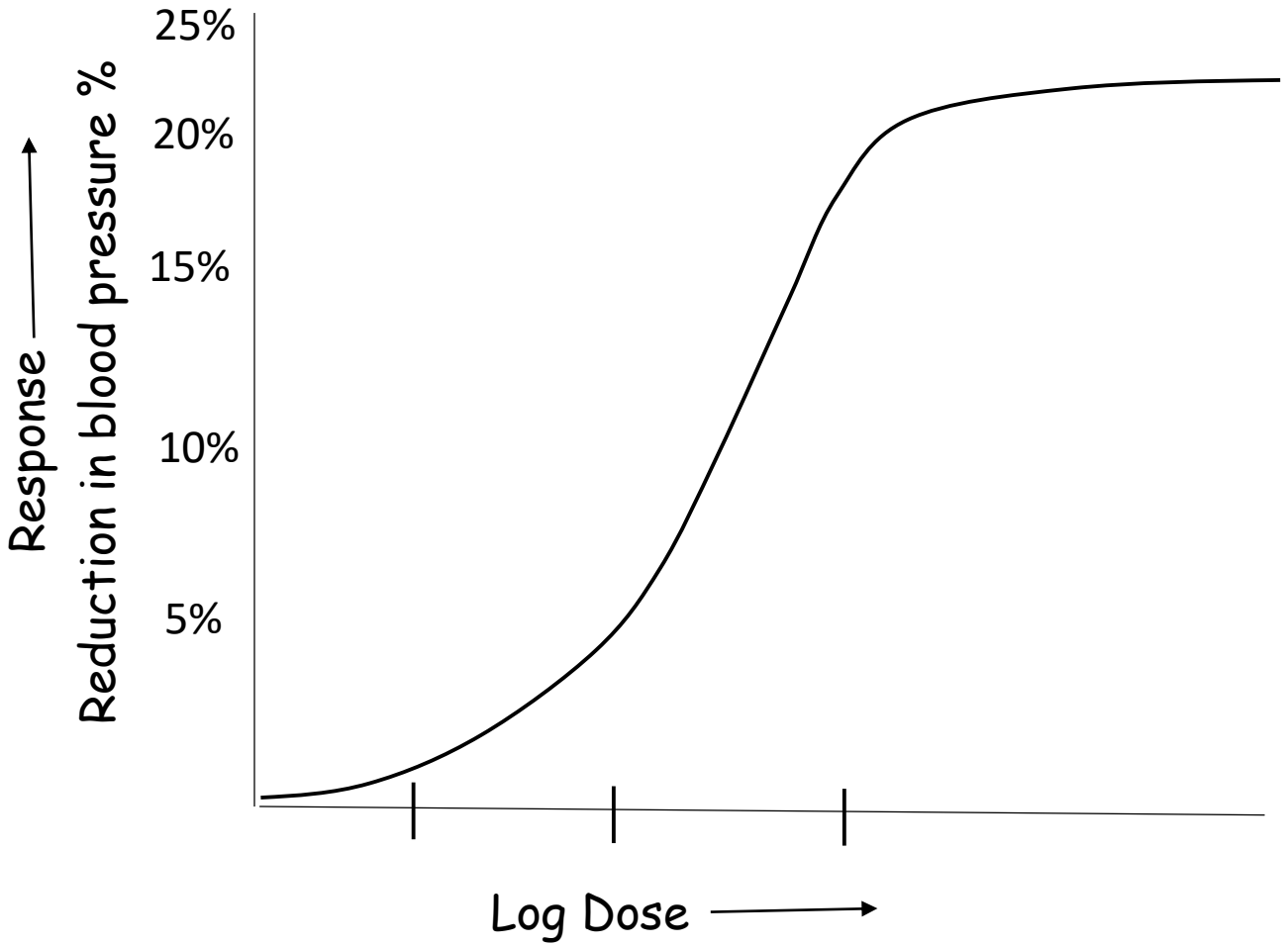
Different tissues have different sensitivity to a same drug

Graded Dose-Response Curve (DRC)



- It relates the dose with the intensity of effect
- Plotting a range of doses against corresponding responses.
- Doses are administered to one individual or isolated tissue
- Obtained by administering several doses to one individual/tissue
- Curve is hyperbolic
- Subsequently, a plateau is achieved.
- Difficult to analyze mathematically

Graded Log Dose-Response Curve

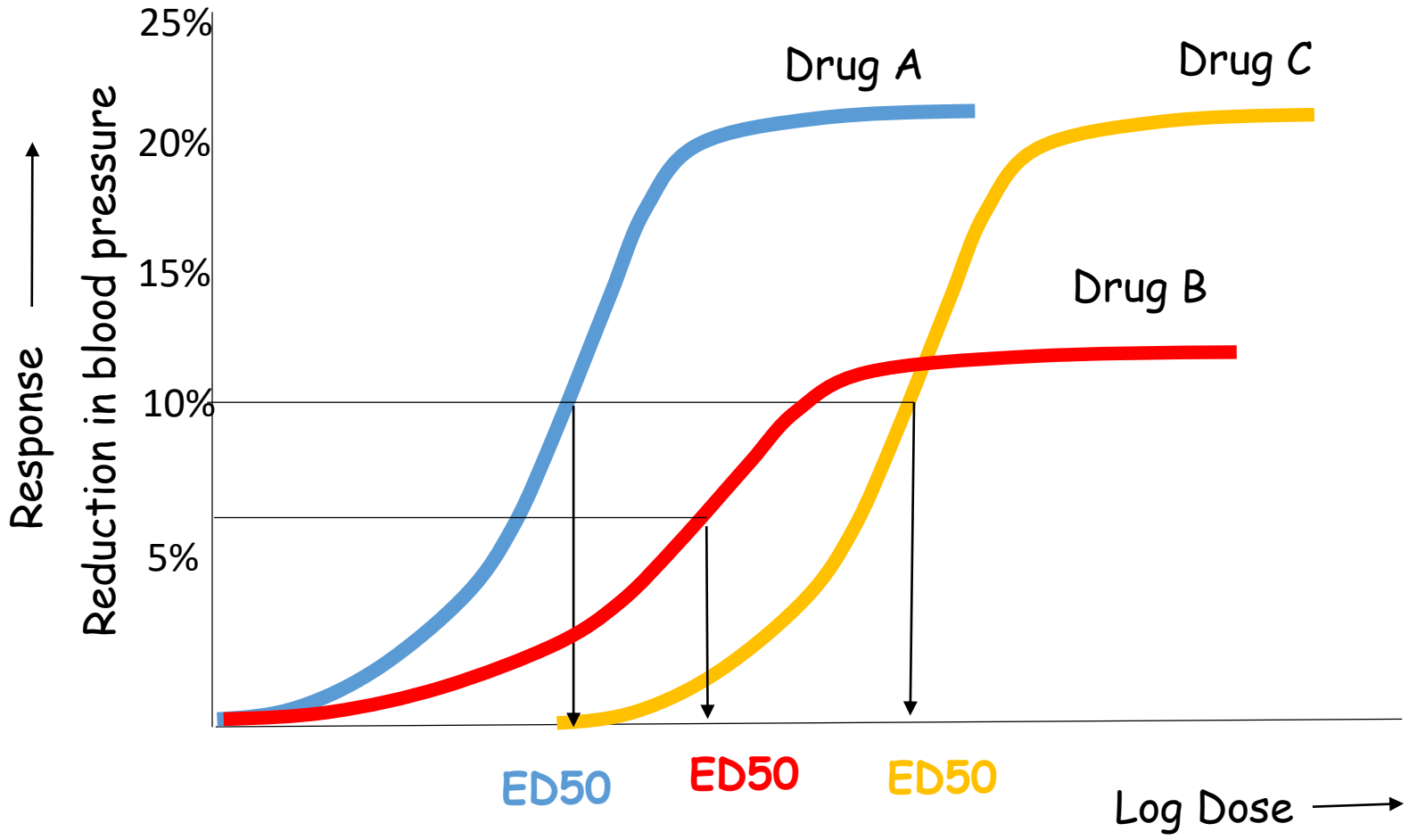


- transforms hyperbolic curve to a sigmoid (almost a straight line)
- compresses dose scale
- straightens line
- easier to analyze mathematically

What Information Can You Get from Graded DRC?

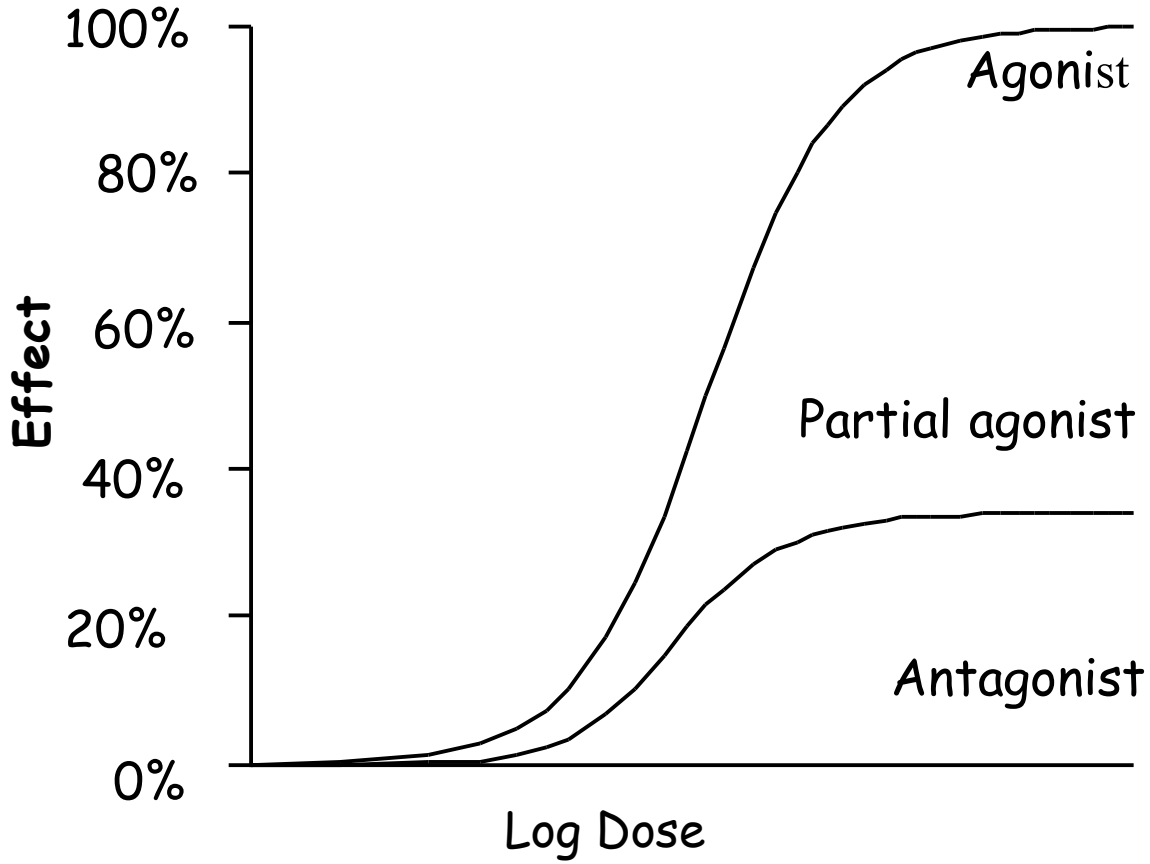
- Potency
- Efficacy
- To predict the nature of drug-receptor interaction:
  - Full Agonist
  - Antagonist
  - Partial agonist

Potency and Efficacy



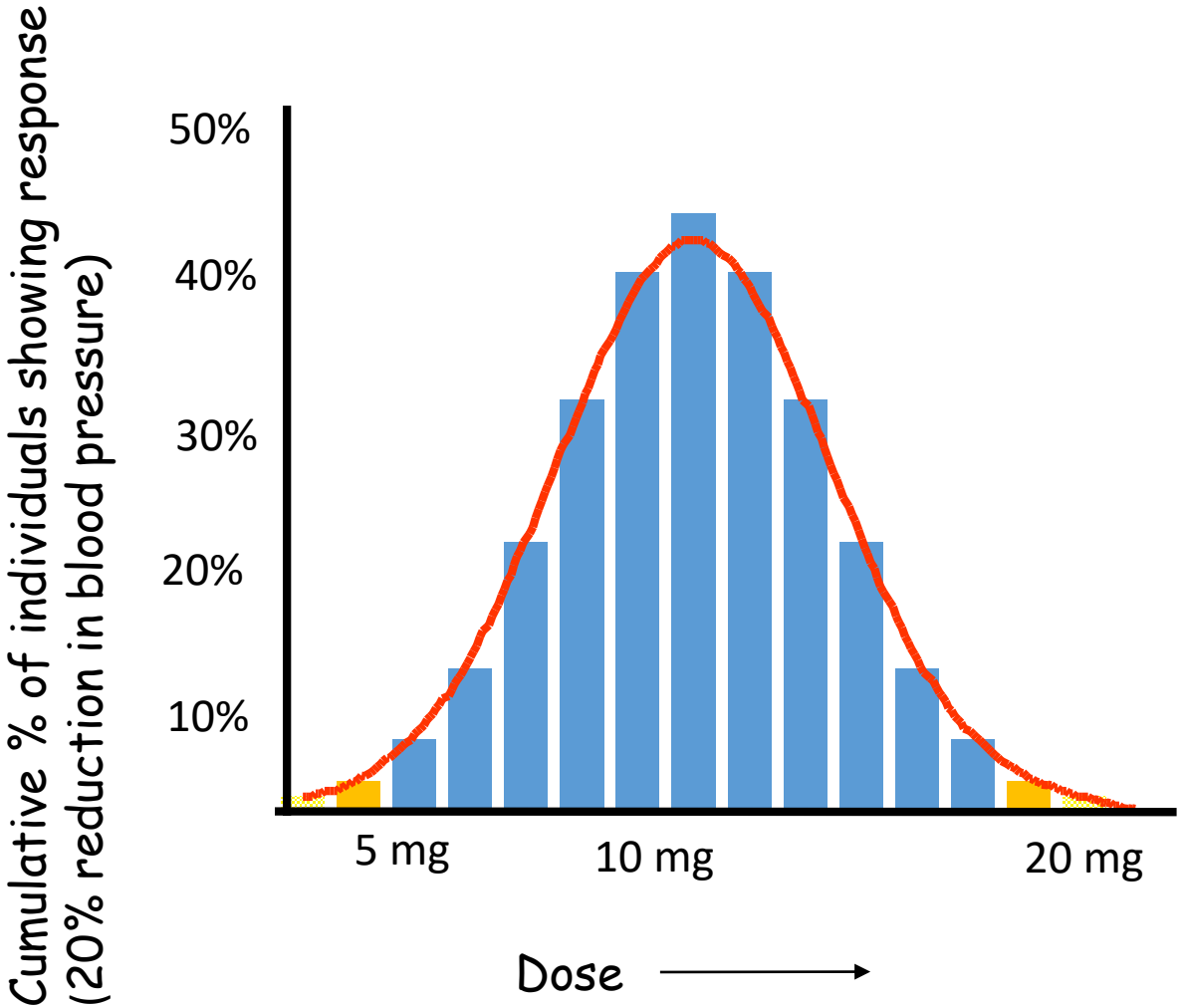
- **Efficacy** is the maximum possible effect of the drug.
- **Potency** is the amount of drug needed to produce a given effect
- Drugs must
  - have equal efficacy
  - produce same type of responses
  - same mechanism of action

Efficacy



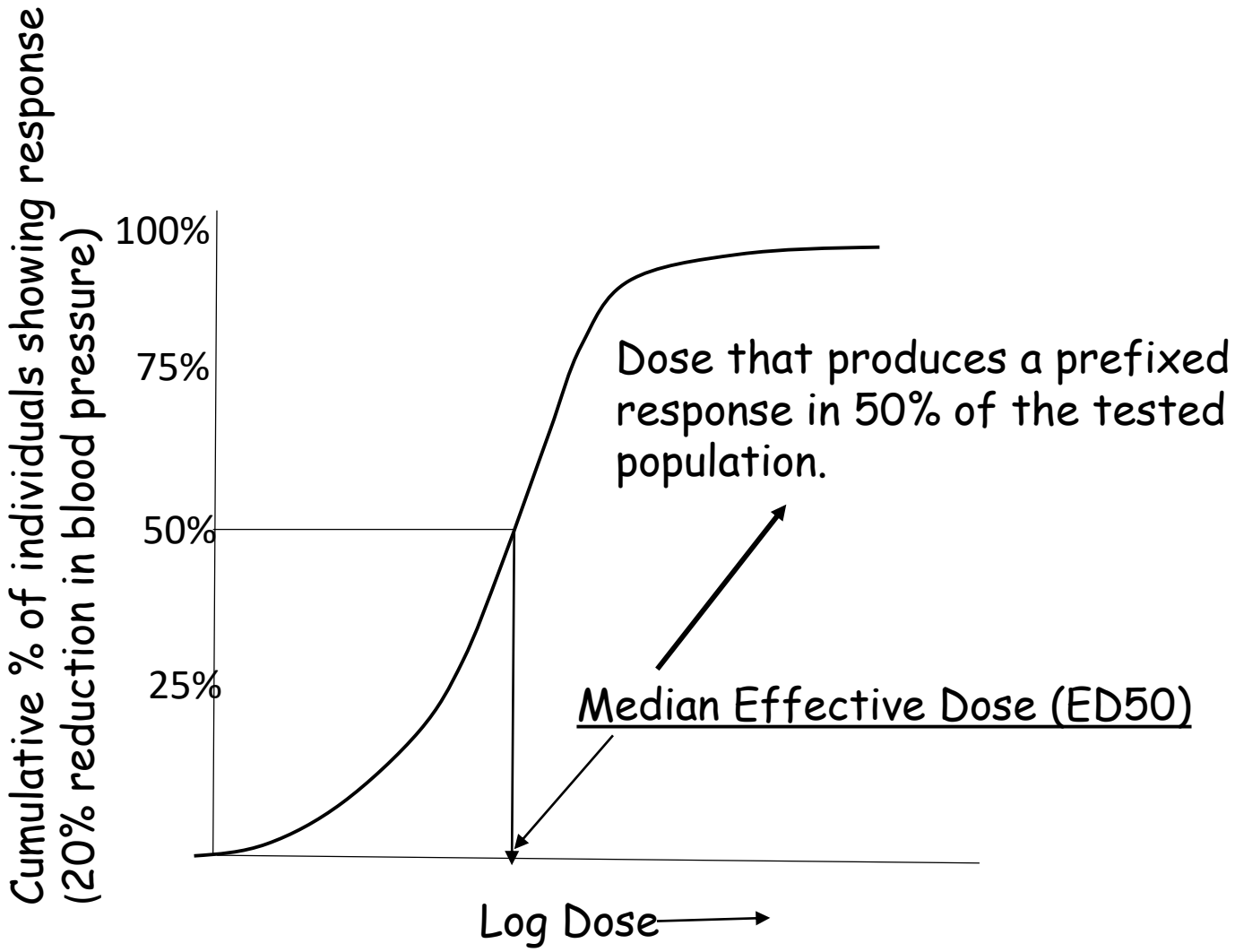
- Efficacy is ability to activate receptor:
  - Full agonist - binds to receptor and produces maximal effect
  - Antagonists – binds to receptor and has no effect (prevent activation of the receptor by agonist)
  - Partial agonist – binds to receptor and produces submaximal effect

Quantal DRC

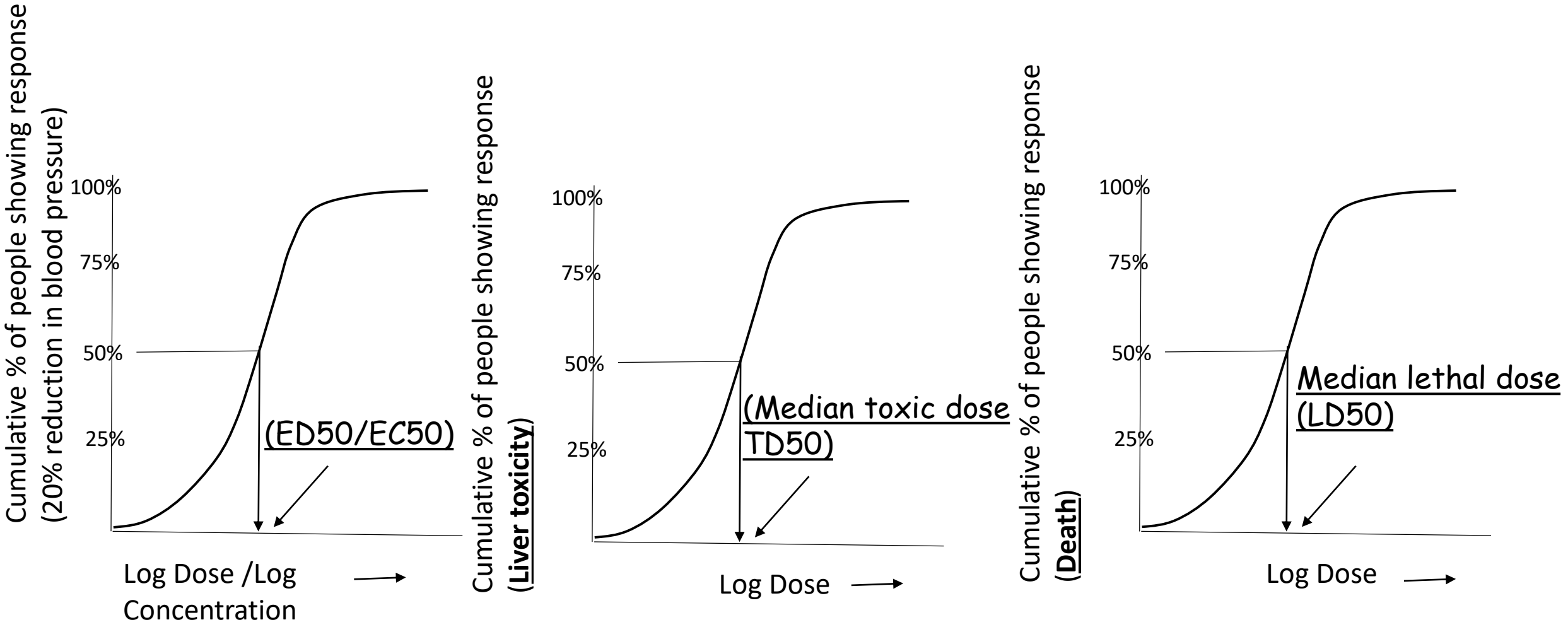


- **It relates the dose with the number of individuals showing a particular effect.**
- Plotting a range of doses against % of individuals showing a particular response.
- The response is prefixed [Yes or None]
- Doses are administered to a group of individuals / population.

Quantal Log DRC



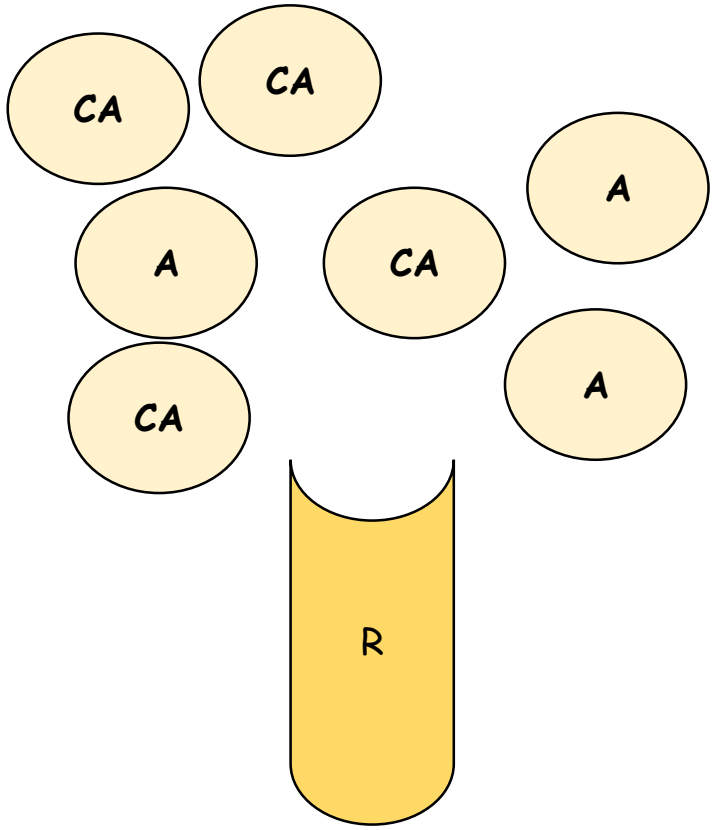
Quantal DRC


Cumulative % of people showing response
(20% reduction in blood pressure)
100%
75%
50%
25%
(ED50/EC50)
Log Dose /Log Concentration
Cumulative % of people showing response
(Liver toxicity)
100%
75%
50%
25%
(Median toxic dose TD50)
Log Dose
Cumulative % of people showing response
(Death)
100%
75%
50%
25%
Median lethal dose (LD50)
Log Dose

Antagonists

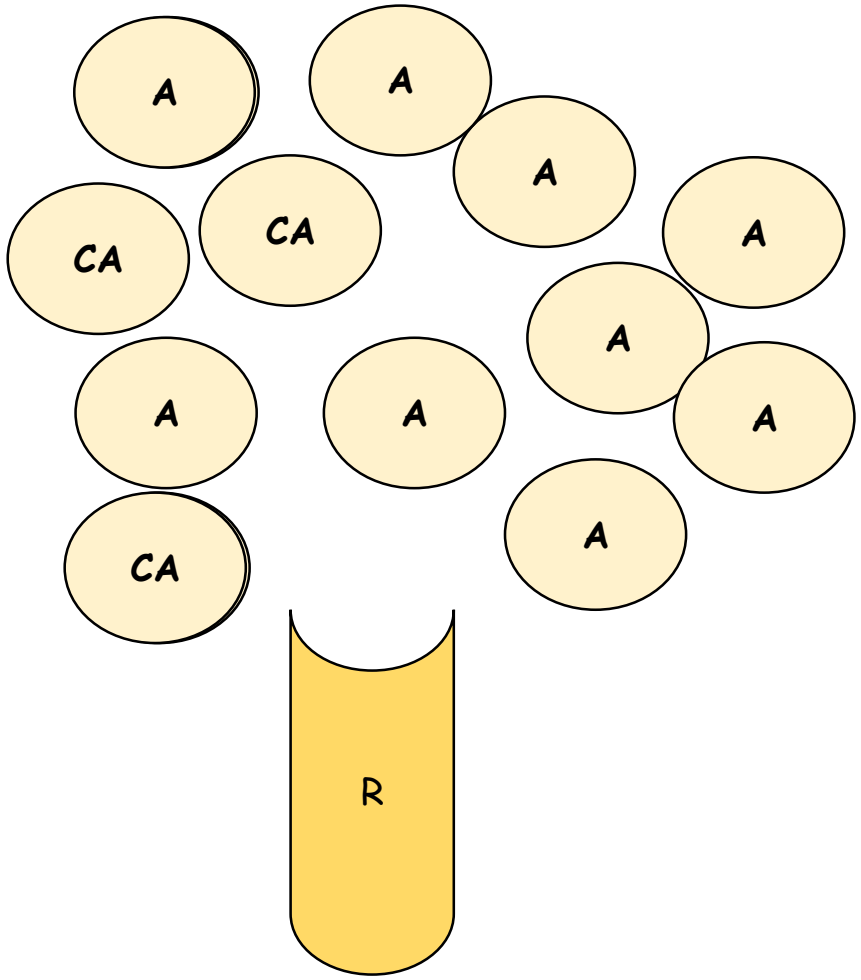
- Antagonists interact with the receptor but do NOT activate the receptor.
- They have affinity but NO efficacy.

Competitive Antagonism



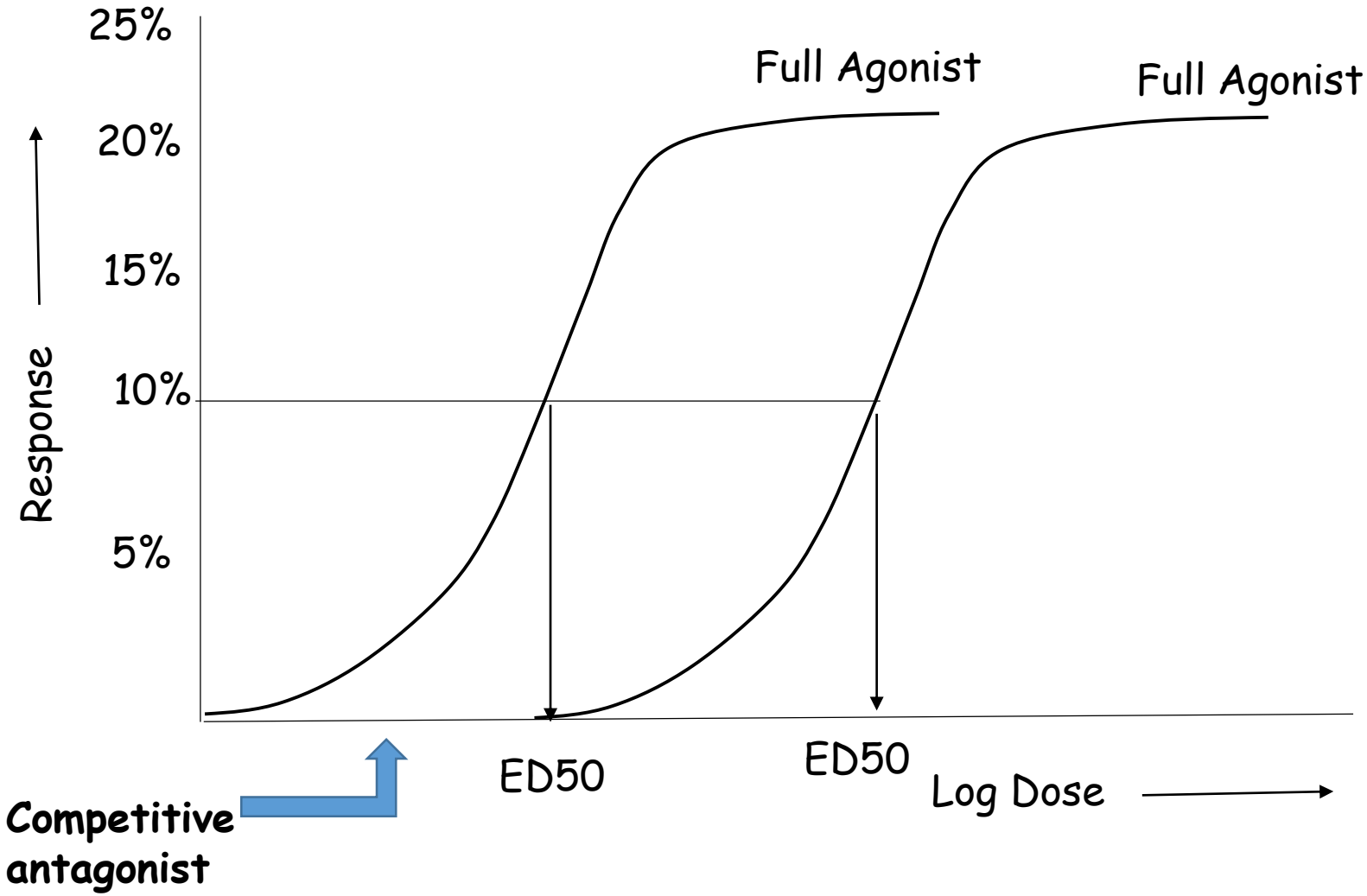
- Competitive antagonists are structurally similar to agonists.
- Hence competitive antagonists **compete** with agonist for binding with same receptor.
- The binding of competitive antagonist with receptor is **reversible** → Effect lasts for short (definite) time.
- This antagonism is also known as **reversible antagonism**.

Competitive Antagonism



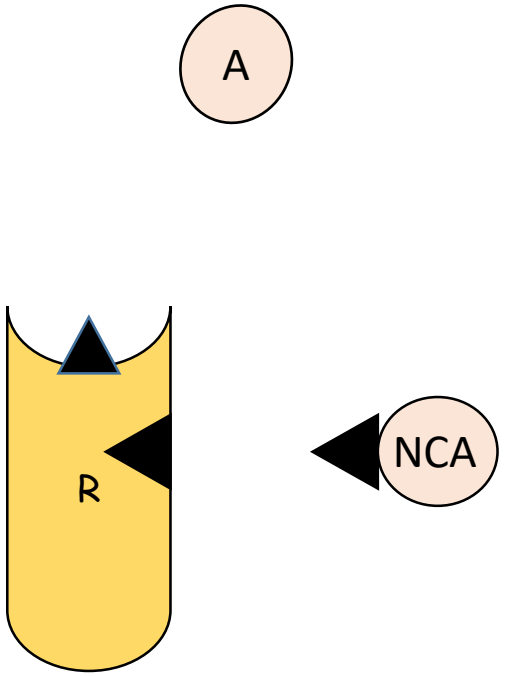
- If the quantity/dose of agonist is increased, it can overcome the antagonist and occupy the receptor again.
- In other words, the competitive/reversible antagonism is **surmountable.**

Effect of Competitive Antagonism on Graded DRC of Agonist



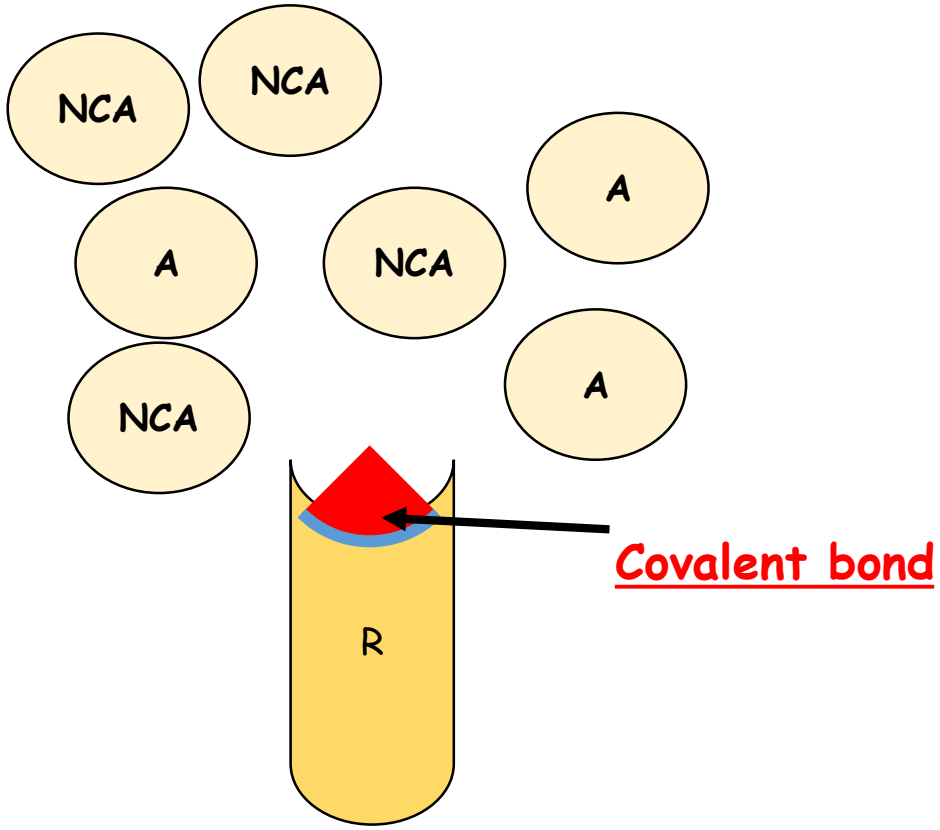
- In the presence of competitive antagonist, greater amount of full agonist is needed to produce a given effect.
- Maximum efficacy can still be achieved.
- The DRC of agonist shifts to **right in parallel**

Non Competitive Antagonism (NCA)



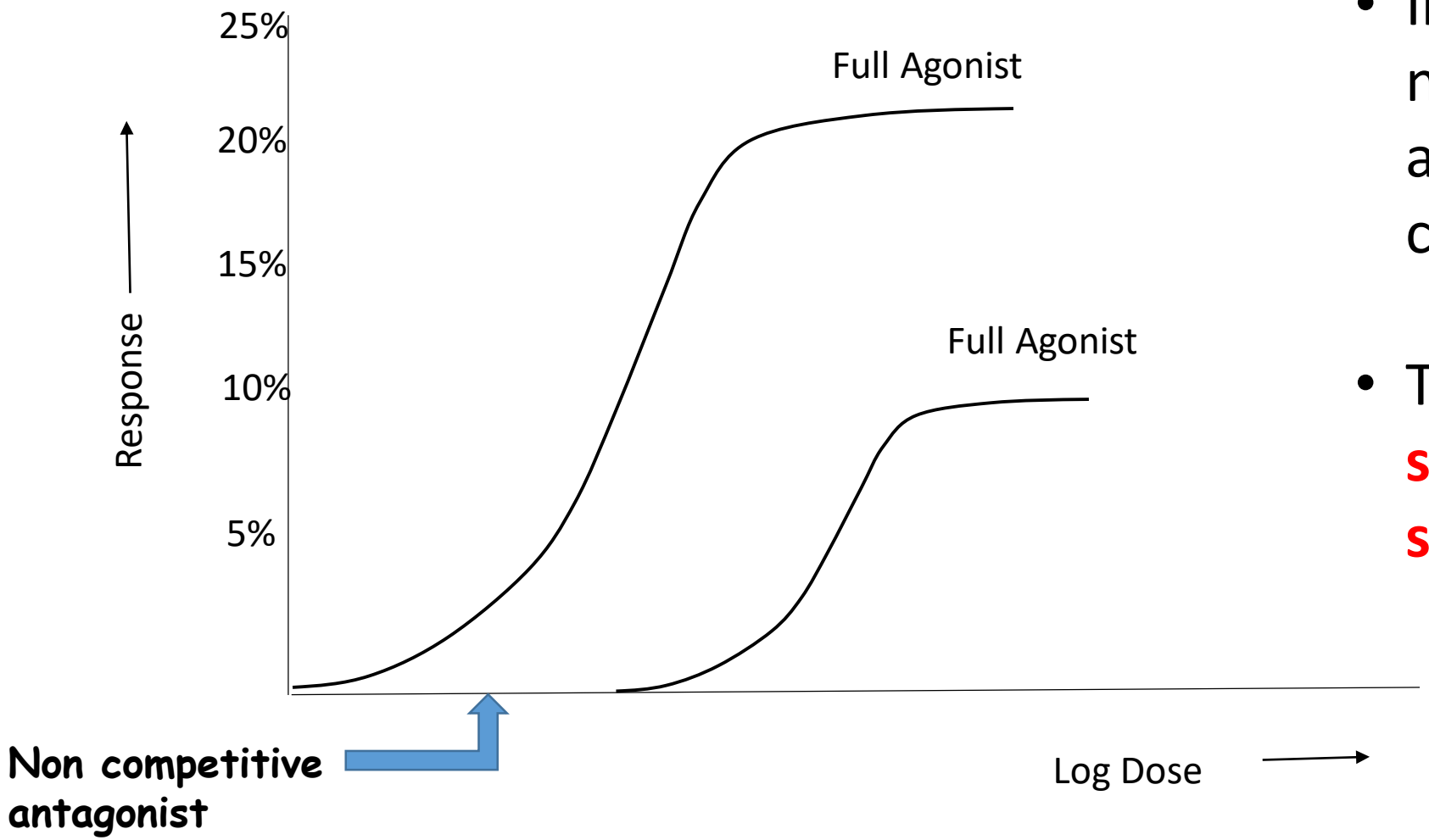
- Non competitive antagonists are often structurally different from agonists and bind at a site other than agonist binding site (Allosteric binding).
- Allosteric binding produces conformational change in the structure of main binding site of the receptor which is **irreversible.**
- Agonist fails to bind with receptor.
- Effect lasts for long time because agonist produces effects only when new receptors are synthesized.

Non Competitive Antagonism (NCA)



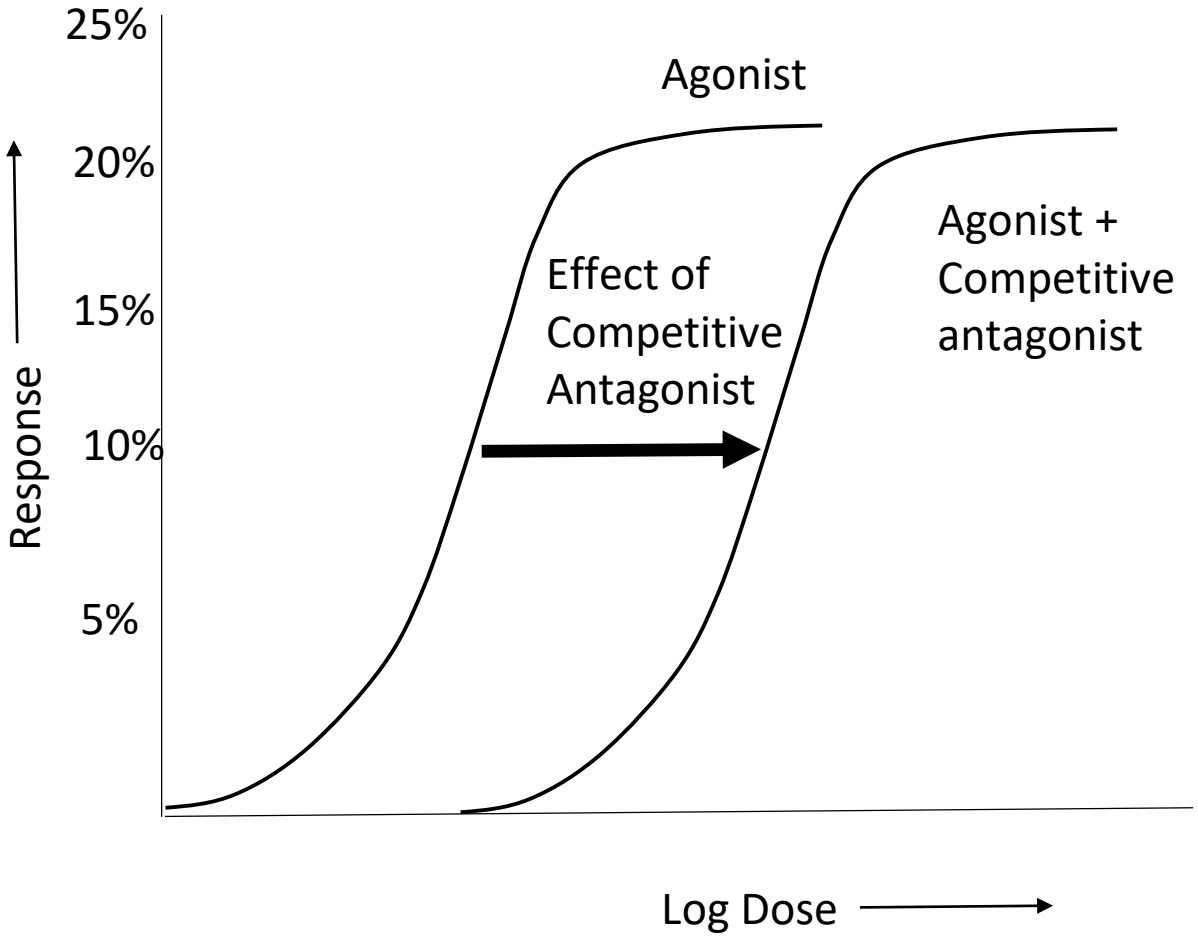
- Non competitive antagonists may be structurally similar to agonists and may bind with the same receptors.
- The binding is strong due to covalent bonds and hence **irreversible.**
- Effect lasts for long time because agonist produces effects only when new receptors are synthesized.

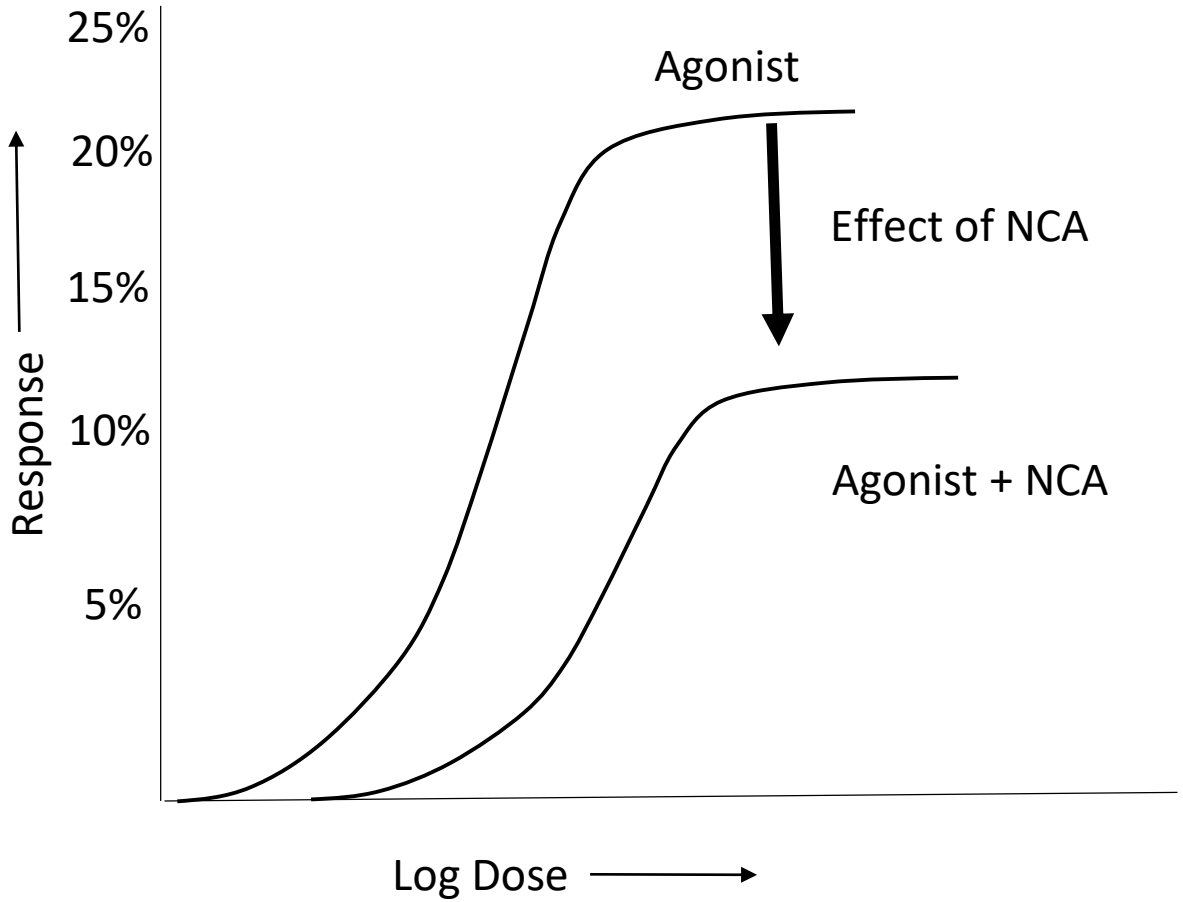
Effect of NCA on Graded DRC of Agonist



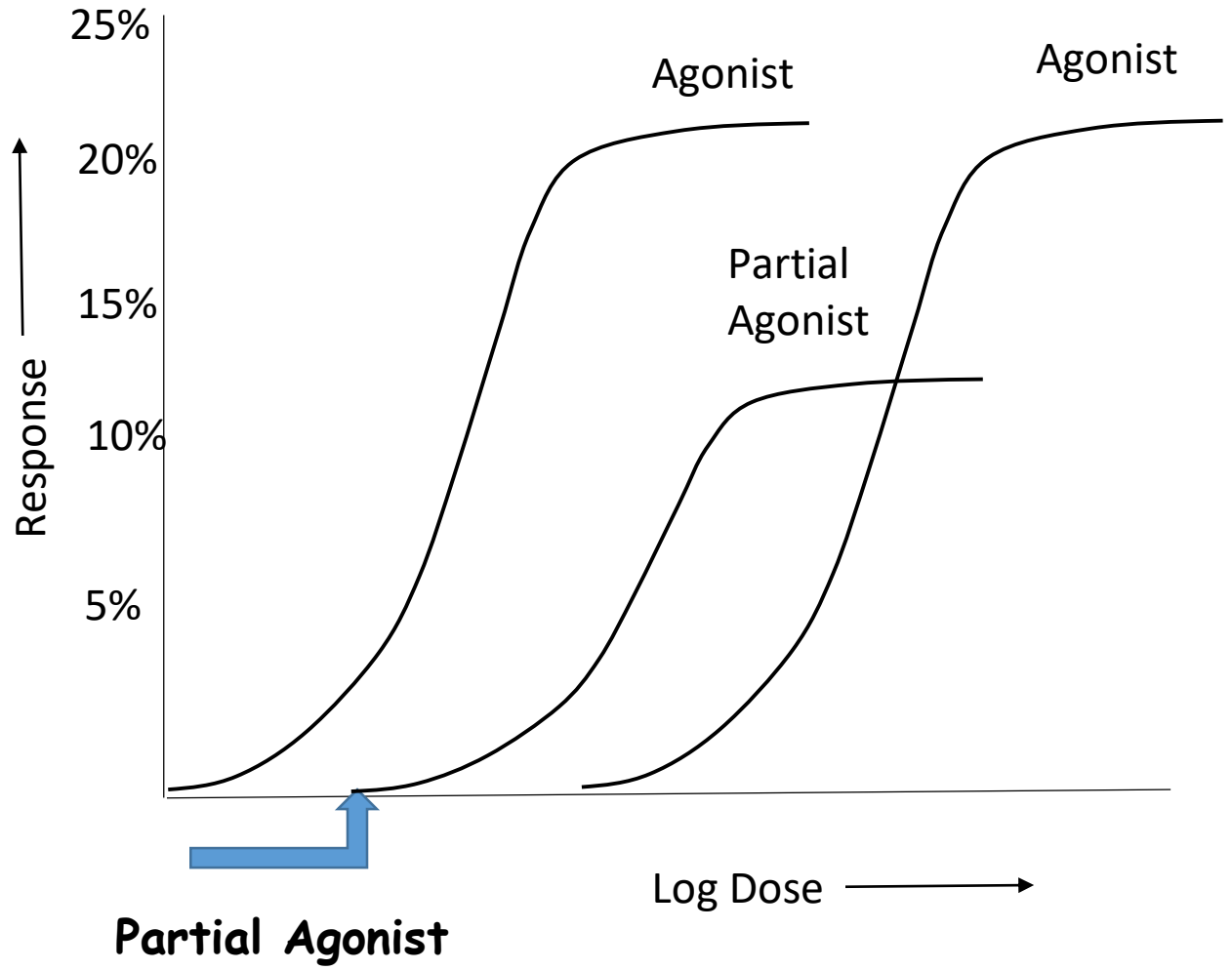
- In the presence of noncompetitive antagonist, the efficacy can never be achieved.
- The DRC of agonist has **smaller height and shifts to right.**

Agonist-Antagonist Interactions





Agonist - Partial Agonist Interactions



- In the presence of full agonist partial agonist beehive as an antagonist.

Receptor Downregulation and Upregulation

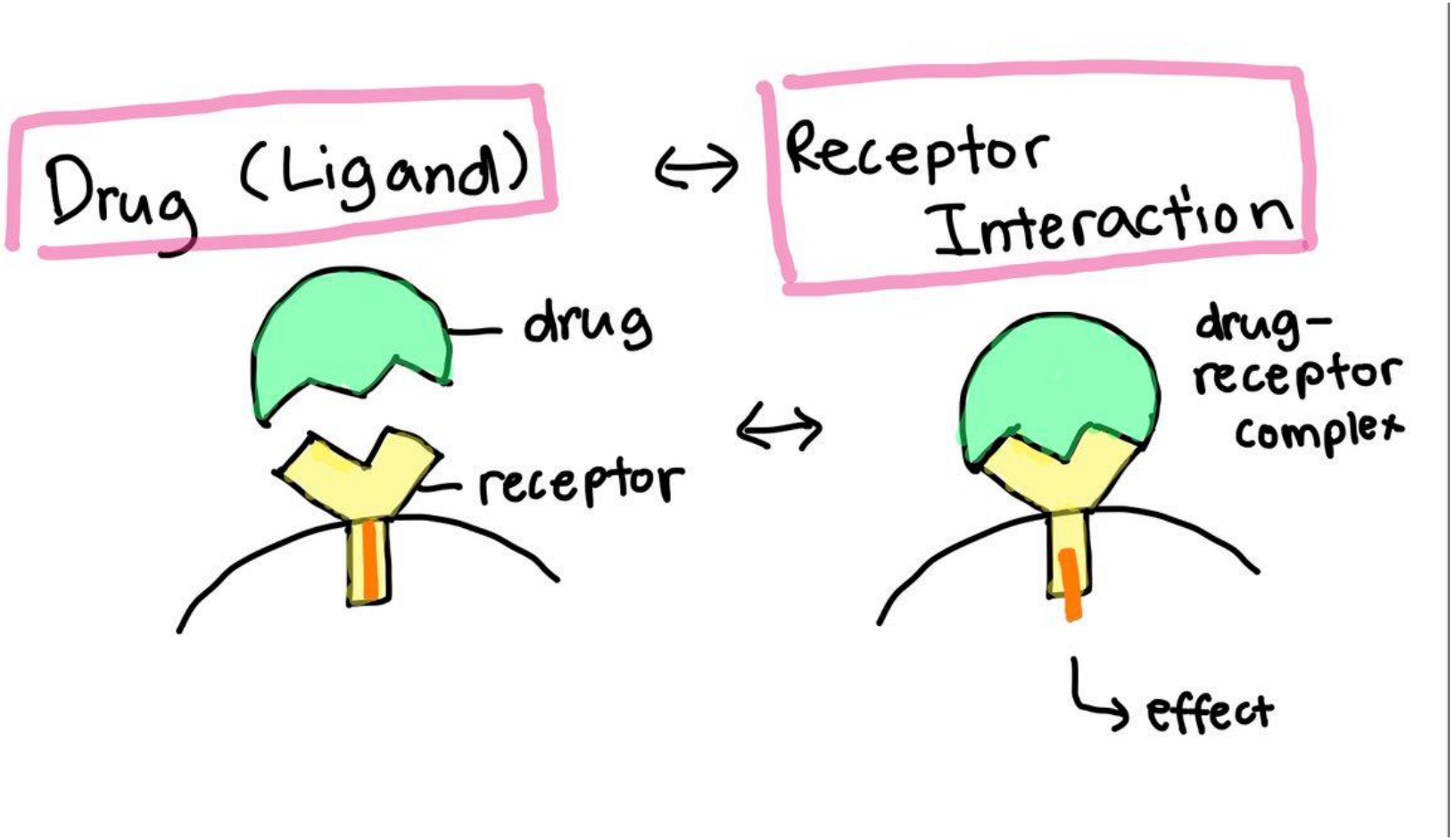
Downregulation / Desensitization

- Prolonged exposure to **agonists** causes reduced sensitivity of tissue to agonist due to:
  - Reduction in the total number of receptor in the tissue.
  - Reduced signal transduction.
- Results in reduced therapeutic effect after prolonged exposure (Pharmacodynamics Tolerance).

Upregulation / Sensitization

- Prolonged exposure to **antagonists** causes increased sensitivity of tissue to agonist due to:
  - Increased number of new receptors in the tissue.
  - Activation signal transduction
- Results in excessive response upon sudden withdrawal of antagonist after prolonged exposure (Withdrawal Syndrome).

Thank You!


Drug (Ligand)
↔
Receptor Interaction
drug
receptor
↔
drug-receptor complex
effect