THE UNIVERSITY OF WESTERN AUSTRALIA

DENT 3005:Introduction to Pharmacology

Pharmacodynamics

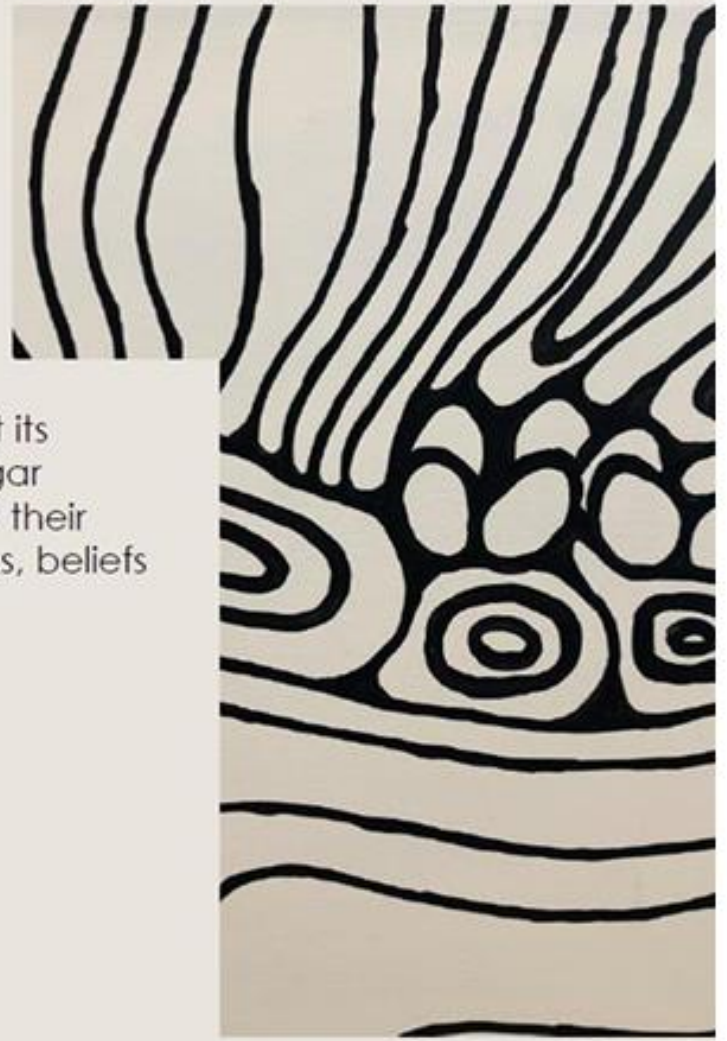
Dr Thuy Linh Truong
thuy.truong@uwa.edu.au

Acknowledgement: Sheetal Maria Rajan

THE UNIVERSITY OF WESTERN AUSTRALIA

Acknowledgement of country

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.



Artist: Dr Richard Barry Walley OAM

DENT3005: assessment breakdown

Assessment #	Assessment Task	Weight %	Assessment Period/ date	Module assessed	Waiver
1	SAQ	50%	30/09/25 9AM – 11AM	General Medicine and Pharmacology: all lectures content	No
2	MCQ	50%	Main Campus: Semester 2 examination period	General Medicine and Pharmacology: all lectures content	No

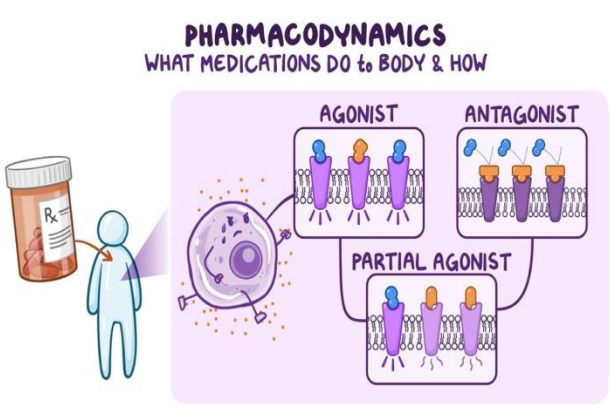
Learning outcomes

Broad

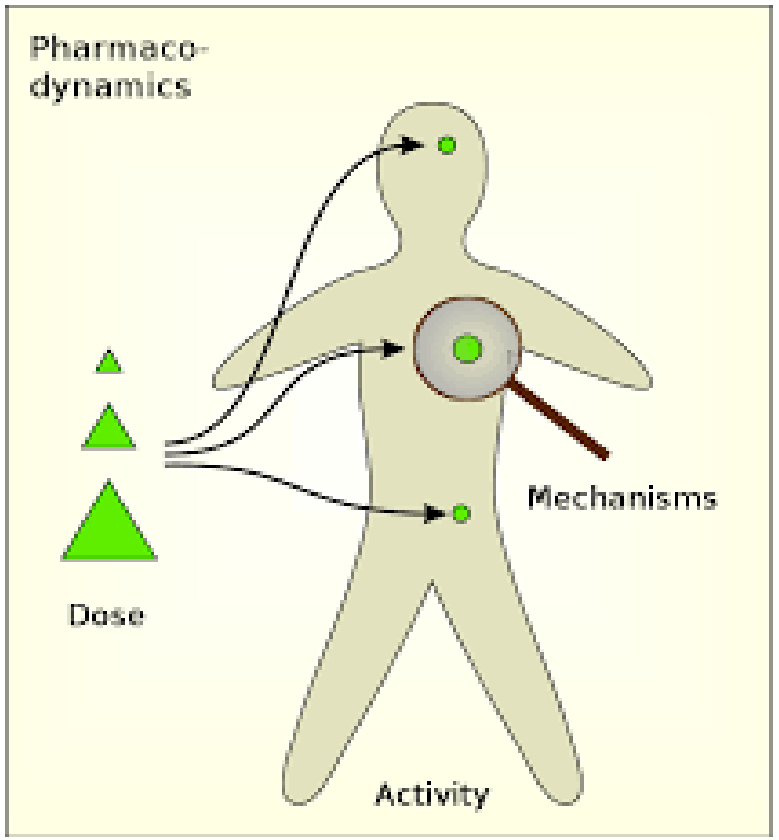
- *Explain the principles of drug delivery, drug metabolism, and associated pharmacological aspects as they relate to dental practice*
- *Define the terms receptor, drug agonist, and drug antagonist*
- *Describe the different types of receptor and pharmacodynamic factors influencing drug-receptor interactions*

Specific topics we will cover:

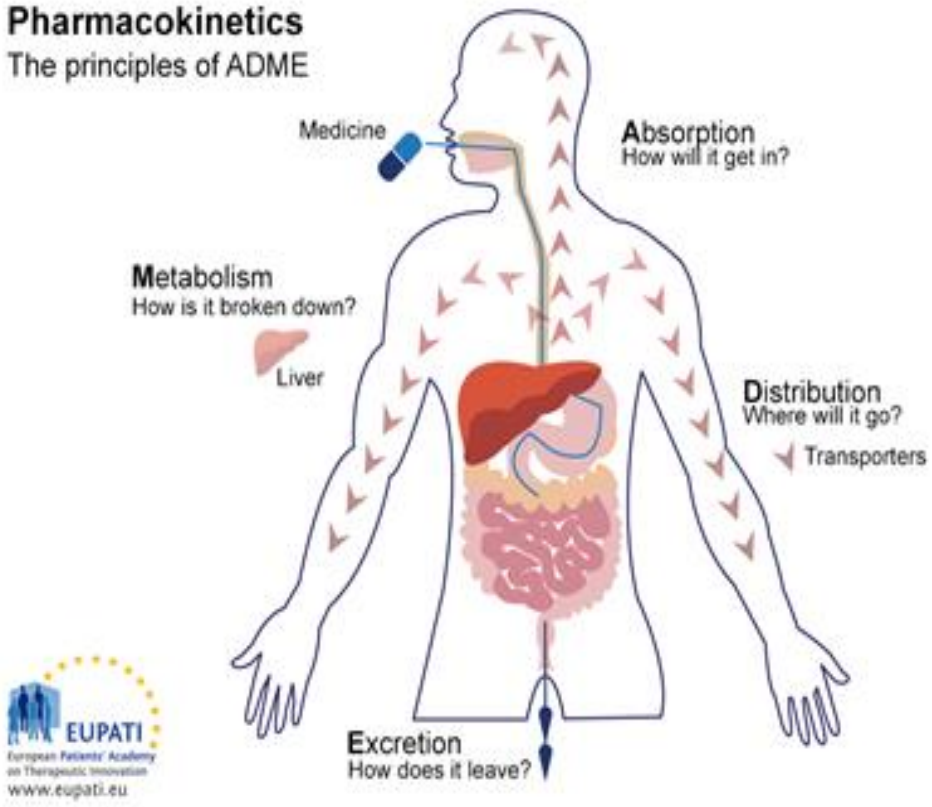
- Receptors
- Drug-induced responses
- Receptor agonist and antagonist
- Possible drug targets
- Four main drug receptors: Ion channels, G protein-coupled receptors, kinase-linked receptors, nuclear receptors



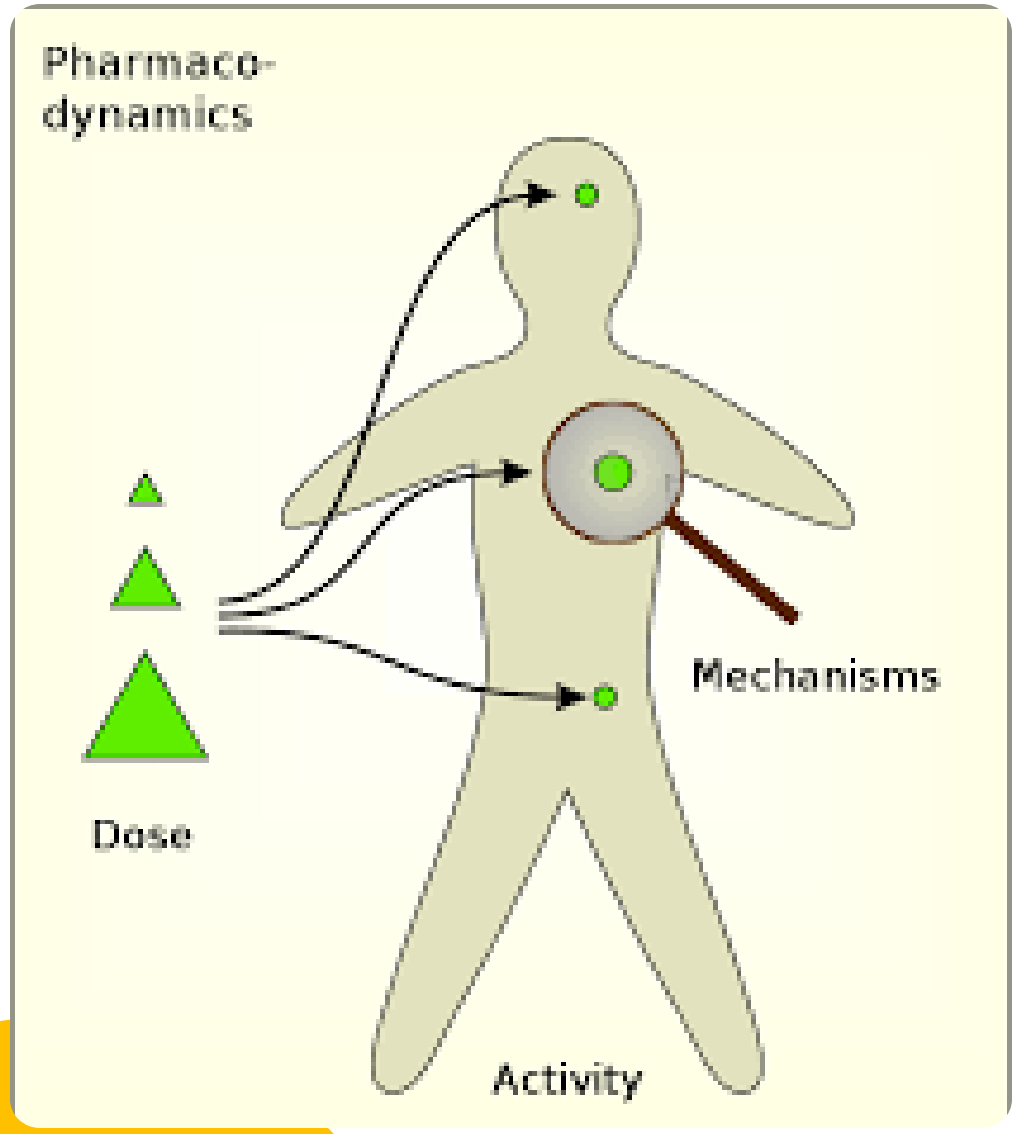
Pharmacodynamics *vs.* Pharmacokinetics



Pharmacodynamics = What the DRUG does to the BODY



Pharmacokinetics = What the BODY does to the DRUG



Pharmacodynamics

- Mechanism whereby drug exert their effect on body → therapeutic response
- Usually acting on physiological processes
- Aim of drug therapy: reverse changes → homeostasis
- Modification of processes
- Examples
  - Hypertension: antihypertensives

Key terms

- Receptor
- Affinity
- Agonism
- Antagonism
- Competitive and noncompetitive enzyme inhibition
- Efficacy
- Potency
- Receptors
- Specificity

- **What is a drug?**
  - A chemical → produce biological effect

- **How are drugs classified?**
  - Chemical structure
  - Mechanism of action- *how does it work*?
  - Therapeutic use – *what is it designed to do*?

- **Drug nomenclature**
- Chemical name
  - Eg. 7,8-didehydro-4,5a-epoxy-17-methylmorphinan-3,6a-diol sulfate!!!!!
- Generic name
  - Eg. Morphine sulfate
- Brand name
  - Eg. Kapanol, Ms Contin, Ms Mono…

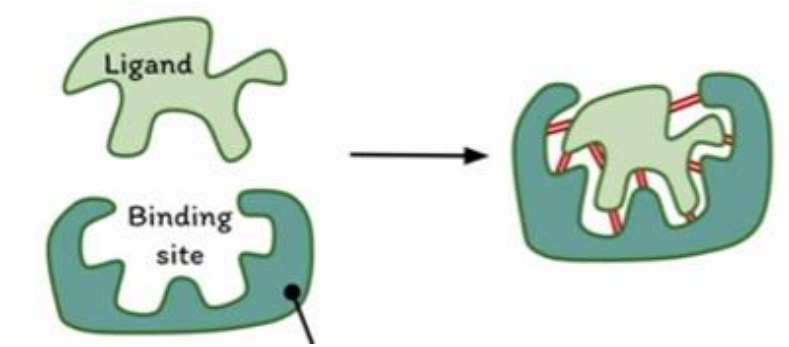
- **Basic principle**
  - Drug molecule exerting chemical influence → pharmacological response
  - Non-uniform distribution
  - Drug must be bound to a critical binding site "target"

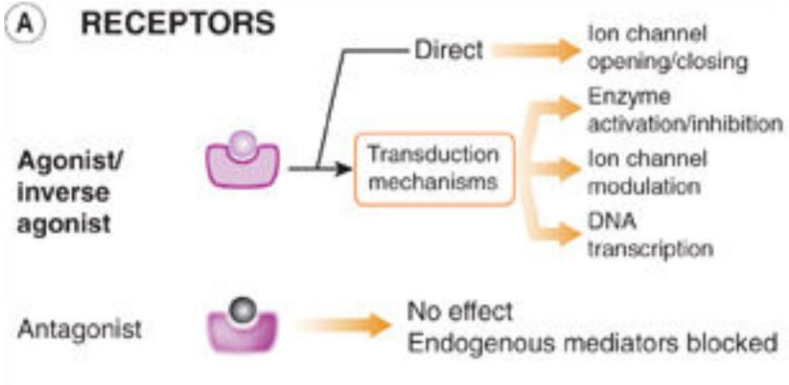
- **Protein targets**
  - Receptors
  - Enzymes
  - Carrier molecules (transporters)
  - Ion channels

- **How drugs function?**
  - Agonist
  - Antagonist
  - Inverse agonist
  - Toxicity?

- **What is a receptor?**
  - Specialized proteins
  - On cell surfaces/within cells
  - Transmit signals in the body

- **Importance**
  - Key players in mediating the effects of drugs
  - Cellular communication
- **Binding:** ligand-receptor interaction
- **Signal transduction** – ligand binding triggering cellular changes



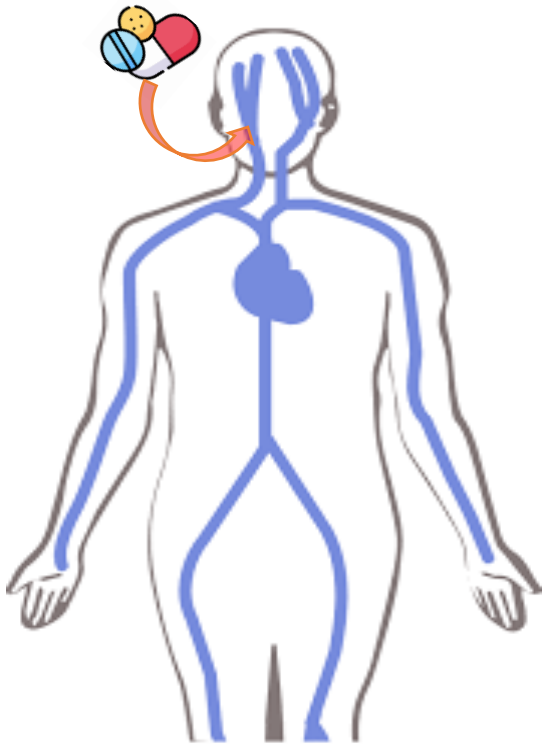


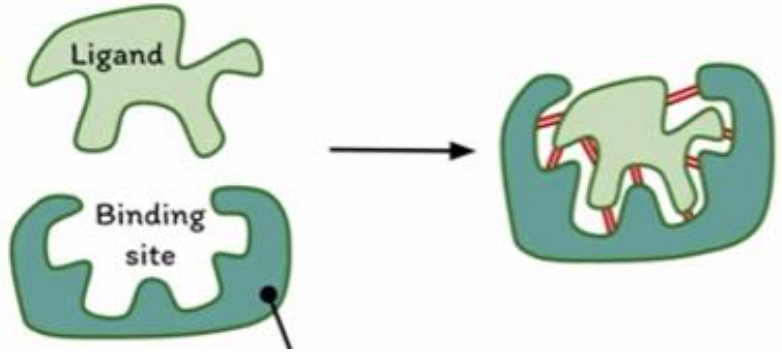
Drug-receptor interactions:

- Chemical structure
- Molecular size and shape
- Lipophilicity
- pH & Ionization

Drug binding & receptor activation

- Affinity
- Efficacy



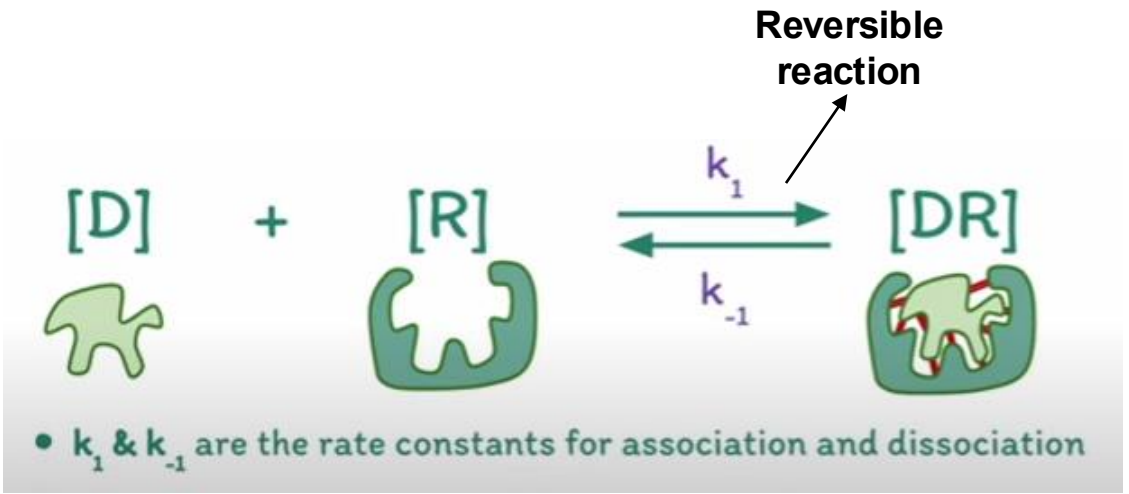


Drug-Receptor Binding

Affinity: Tendency of a drug to bind to a receptor
- ↑ Affinity = Greater binding tendency
- Measured by **Kd (Equilibrium dissociation constant, mol/L)**
- Lower Kd = Higher affinity

Efficacy: Ability of a drug to produce an effect at the receptor
- ↑ Efficacy = Greater maximum effect
- More efficacious drug = Greater effect, not necessarily stronger binding

Agonist: Has both **affinity** and **efficacy**
Antagonist: Has **affinity**, but **no efficacy**



$$K_D = \frac{k_{-1}}{k_1}$$

Drugs with ↓Low Kd = ↑Affinity

Drugs with ↑ High Kd = ↓ Affinity

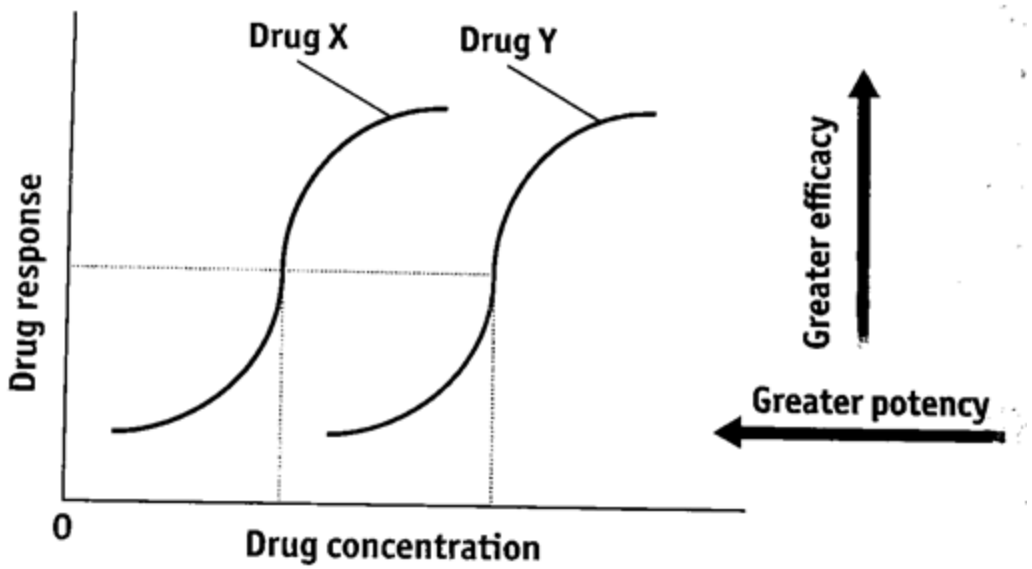
Drug-Receptor Binding

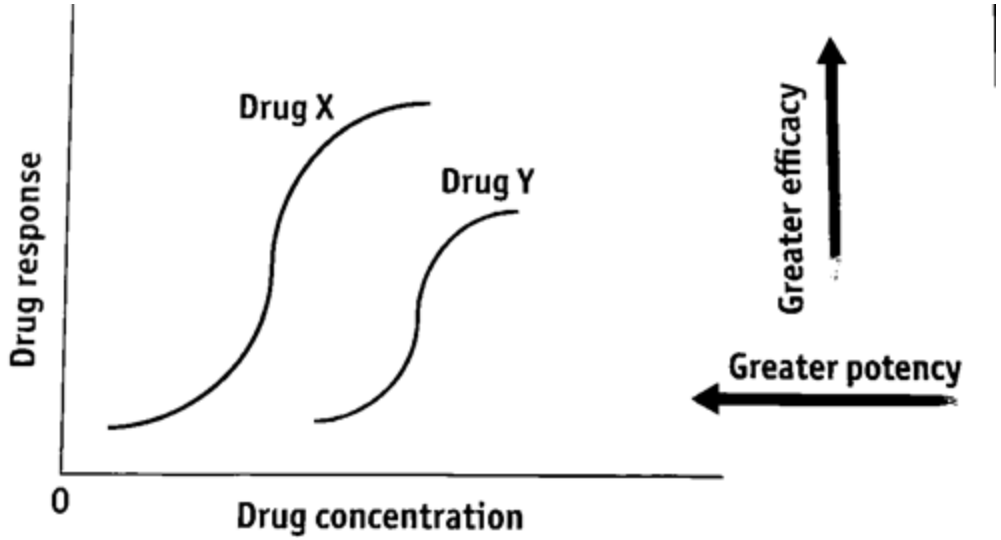
Potency: *the relative amount of drug that has to be present to produce an effect*

- **EC_{50}** –the concentration at which **50% of the max response (to the drug) is observed**
- **↑EC_{50}: more drug req = lower potency**

Specificity: *relates to degree of selectivity*

- **↑Specificity: targeted action, lowered side-effects**

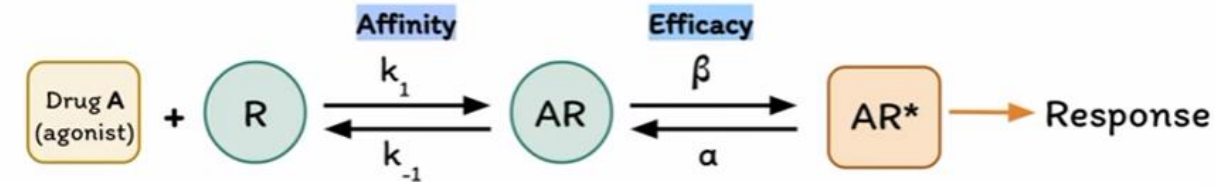


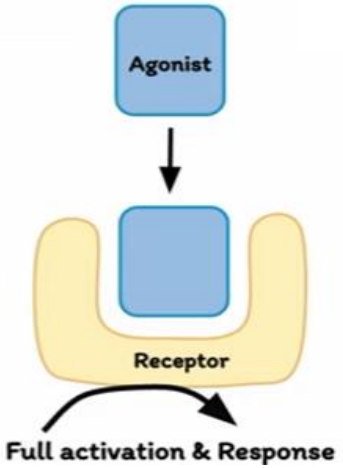


Drug-Receptor Binding

Agonist

An agonist is a drug that binds to and activates a receptor





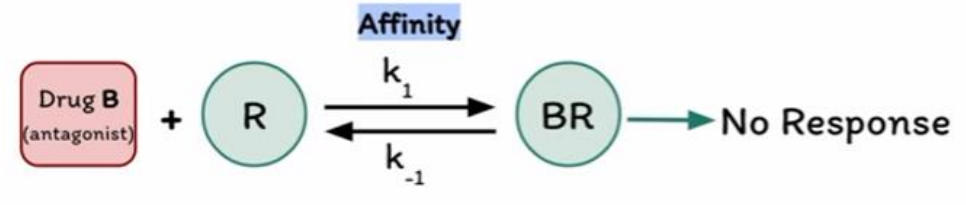
Partial agonist – can bind to and activate the receptor

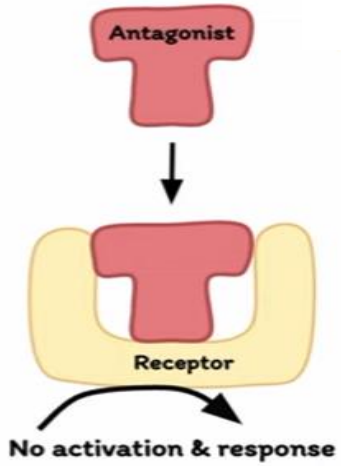
- **Lower efficacy** – cannot produce the same maximum effect as a full agonist

RECAP Efficacy: *The ability of the agonist-receptor complex to initiate changes that induce a response*

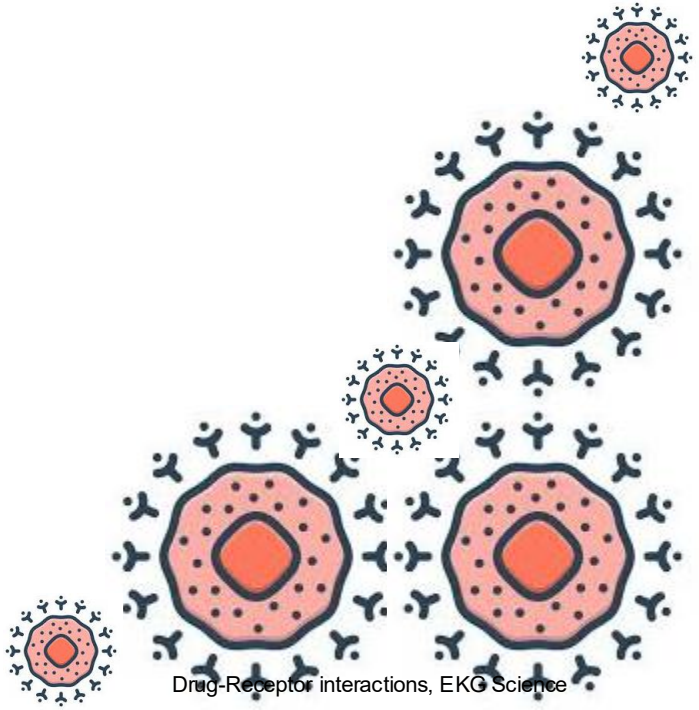
Antagonist

An antagonist is a drug that binds to the receptor & does NOT cause activation





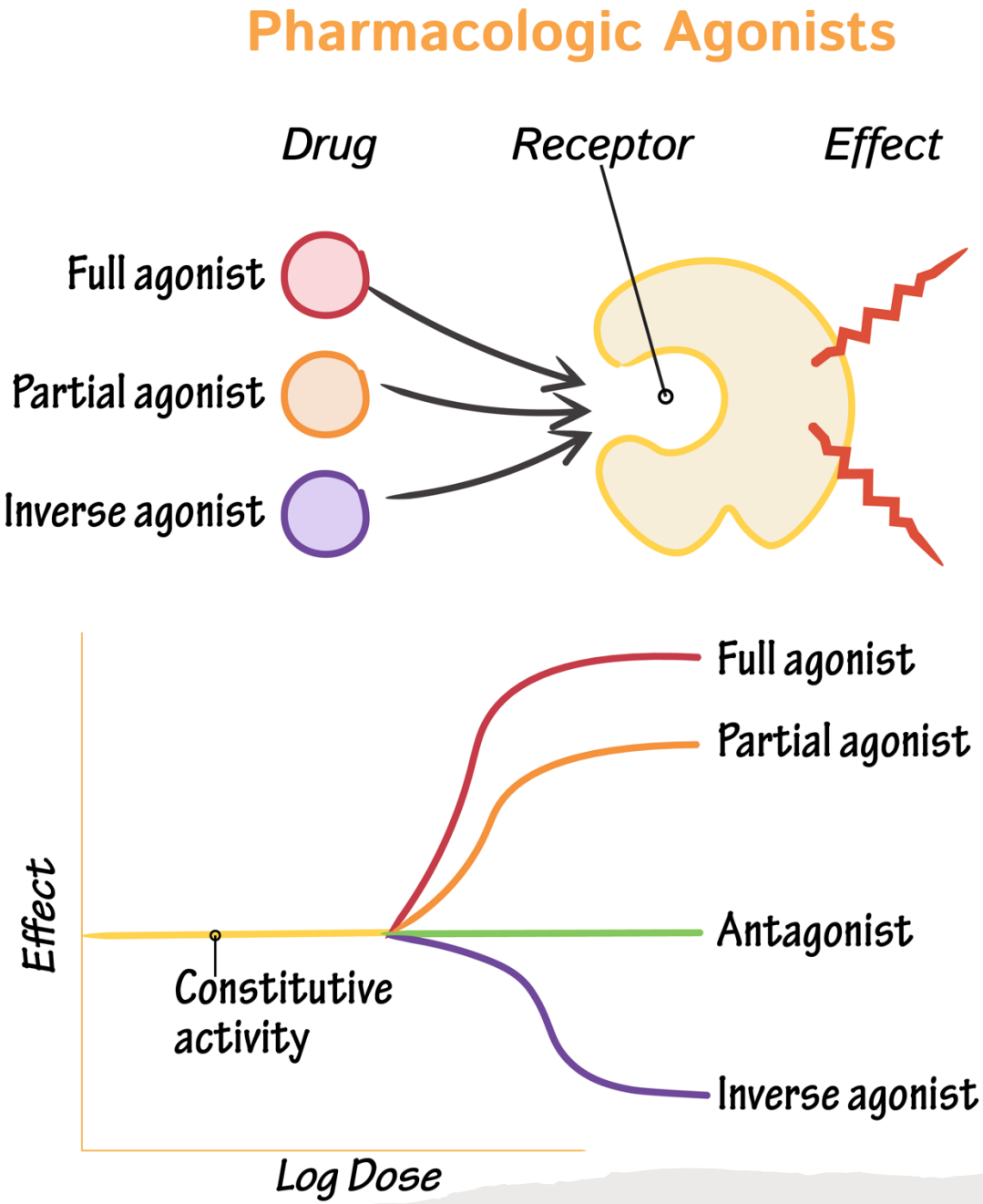
- **Competitive antagonist**: reversible/ surmountable
- **Non-competitive antagonist**: irreversible/ insurmountable
- **Physiological antagonism:** 2 drugs have effects that are functionally the opposite



Drug-Receptor interactions, EKG Science

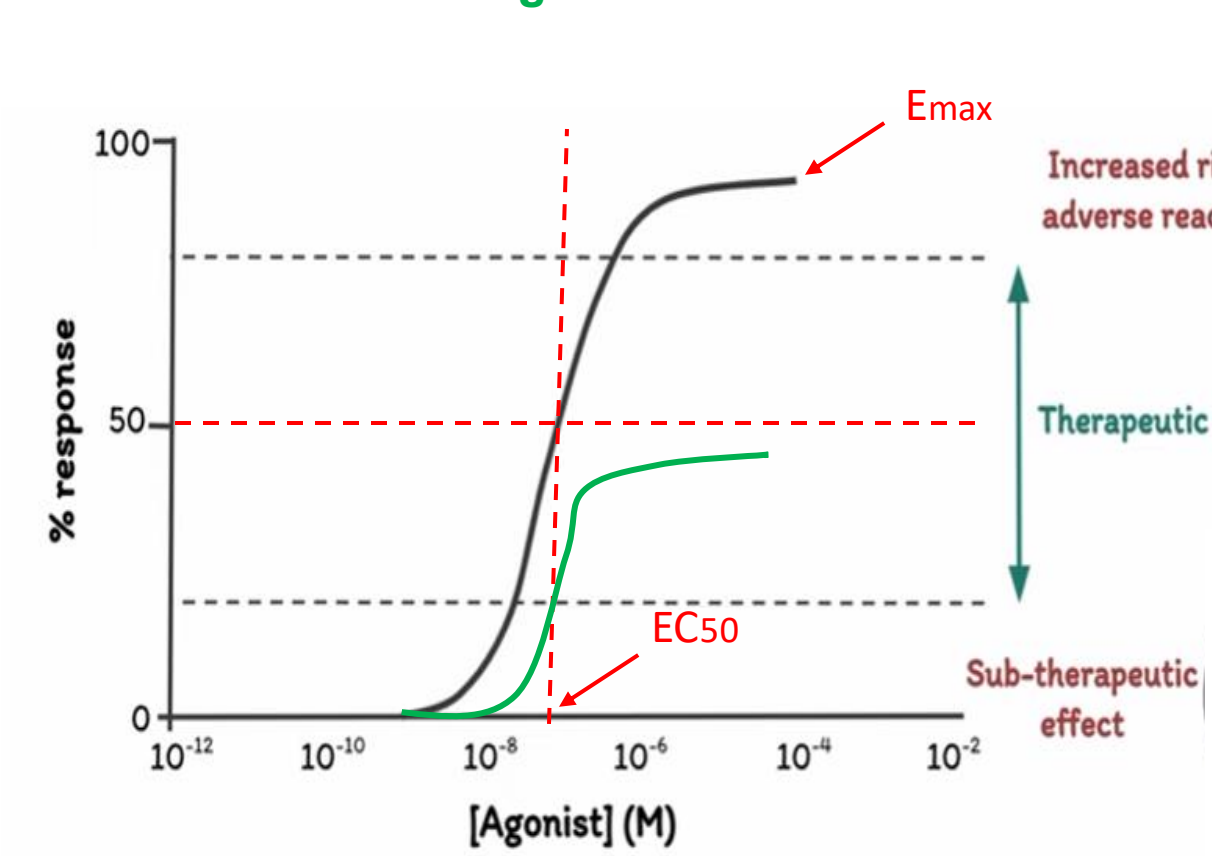
Inverse Agonist

- **Inverse agonist are special**
- Pharmacological agonist
- Decrease level of receptor activation
  - Negative efficacy
- NOT an antagonist
  - Do not cause activation (zero efficacy**)**



Drug-Receptor Binding

Concentration-response curves (CRC): Tool for understanding the connection between a **drug and its biological effects**



Emax – is the maximum response that can be achieved by the drug under the given conditions

EC_{50} – is the drug concentration at which **50% of the maximum response (to the drug) is observed**

EC_{50} provides a measure of **drug potency**

RECAP Potency: *measure of drug activity/ amount of drug that is required to produce a particular effect*

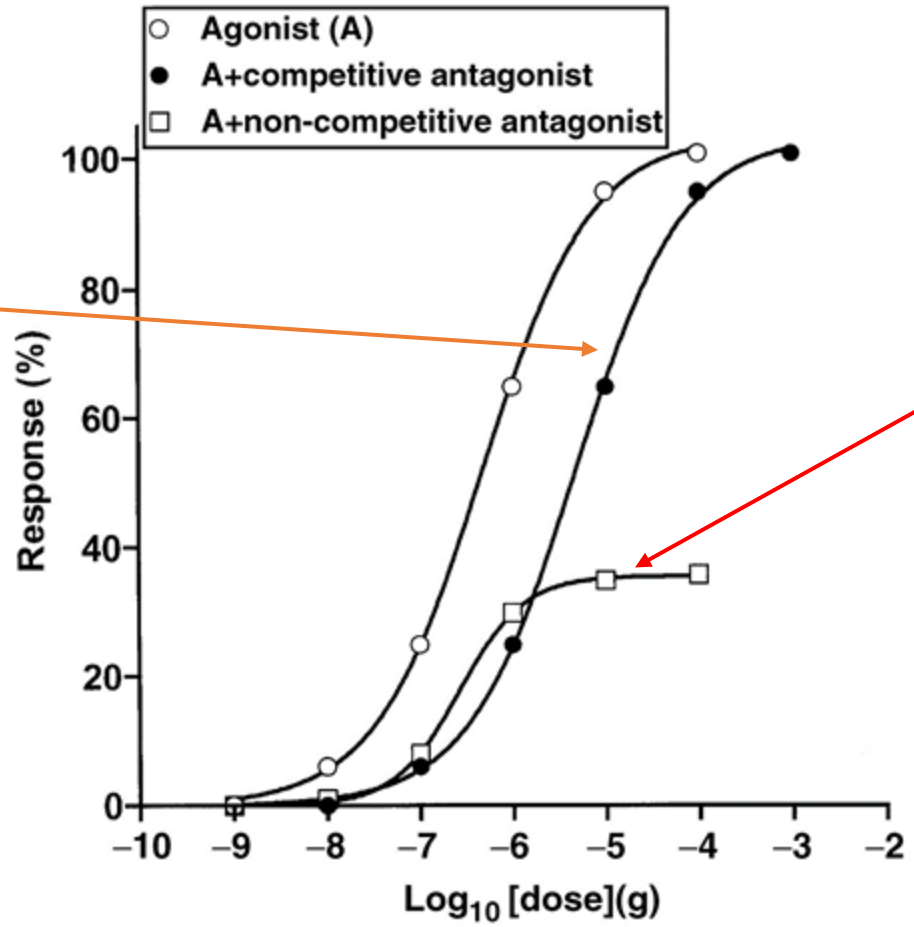
- **Lower EC_{50} = Higher potency**
- Low potency – requires a higher concentration

Drug-Receptor Binding

Concentration-response curves (CRC) for Antagonists

Competitive Antagonist

- Agonist and antagonist compete for the same Ortho steric site
- Surmountable – increasing the con. of the agonist can overcome the binding of the competitive antagonist
- Increasing con. of a competitive antagonist will cause a parallel rightward shift in the agonist CRC



Lambert DG. (2004). Drugs and receptors. Continuing Education in Anaesthesia Critical Care & Pain; 4(6):181–184.

Non-competitive antagonist

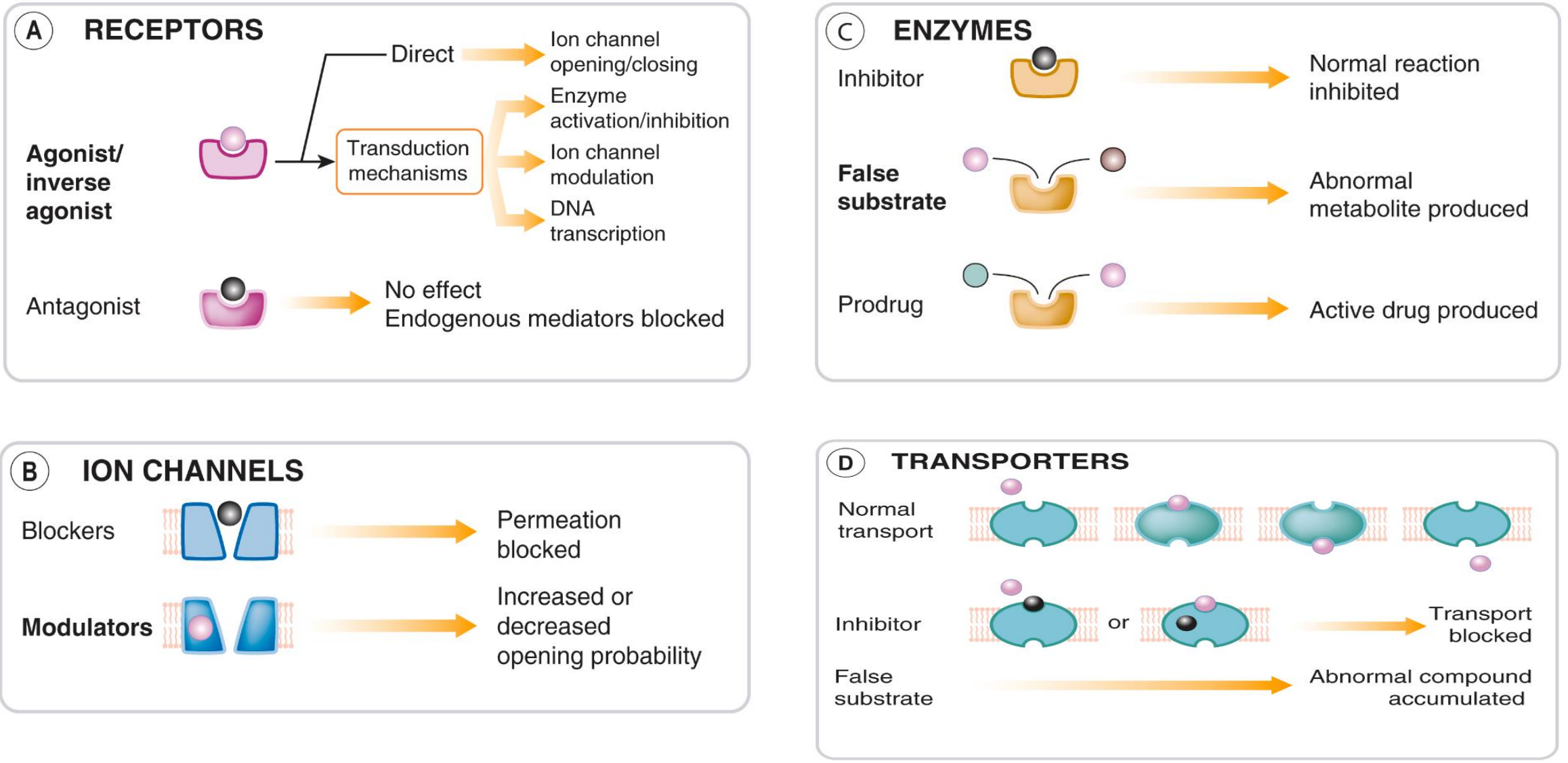
- Insurmountable – antagonist drug reduces the maximum effect of the agonist
- Irreversibly alters the target receptors (e.g. forming covalent bonds)
- High affinity for the receptor- dissociates slowly.
- Maximum response cannot be achieved

Review!

Other considerations

- **Drugs that work by simple chemical or physical action**
  - Neutralization of acidic environment
  - Chelating
  - Osmosis

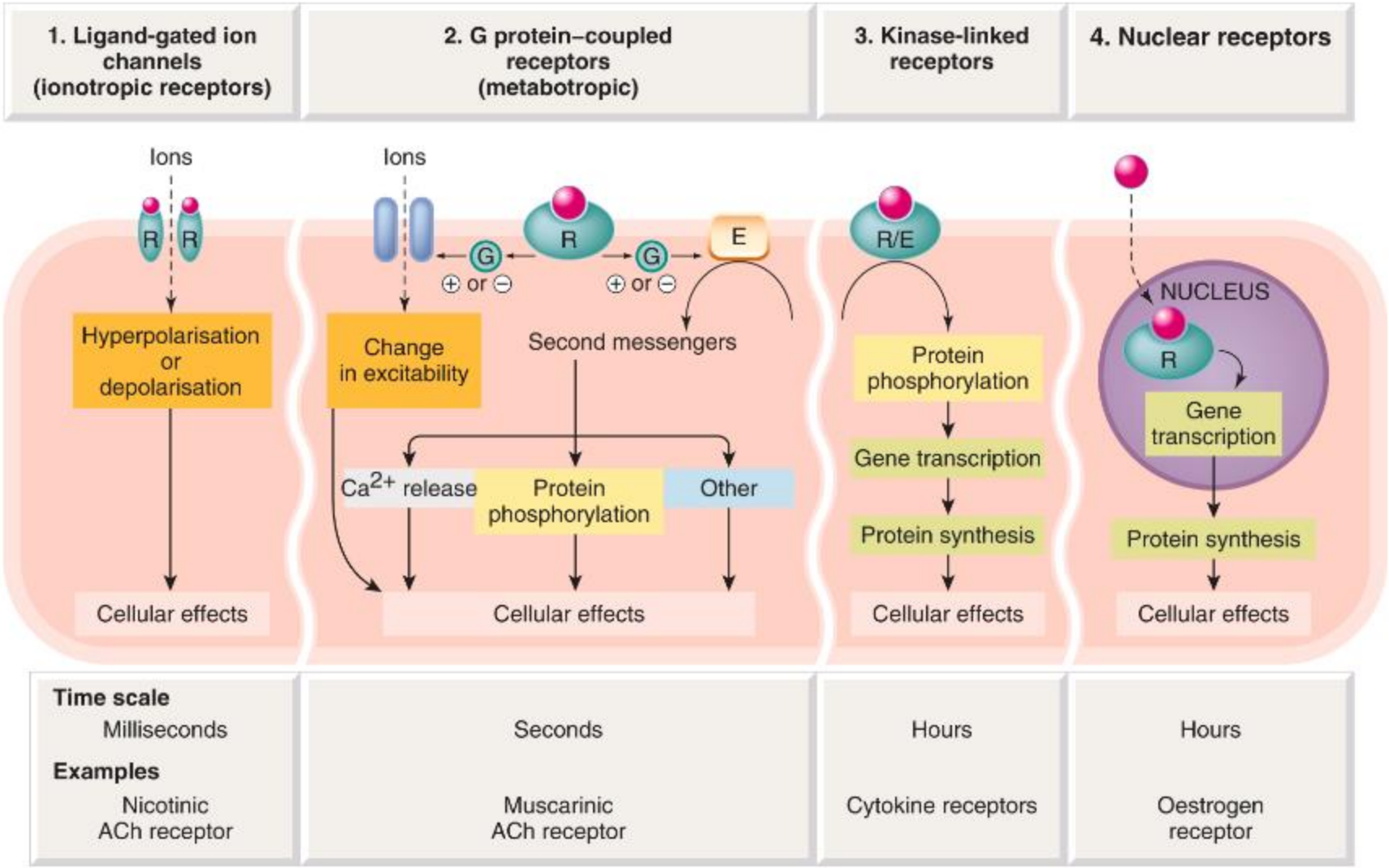
Protein Targets for Drug Action



Rang & Dale's Pharmacology, Tenth Edition

Types of Receptors

Receptor: Specialized proteins located on cell surfaces/within cells that are responsible for transmitting signals in the body



Rang & Dale's Pharmacology, Tenth Edition

Types of Receptors: in a nutshell!

	Type 1: Ligand gated ion channels	Type 2: G-Protein coupled receptors	Type 3: Receptor kinases	Type 4: Nuclear receptors
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion Channel	Channel or enzyme	Protein Kinases	Genes Transcription
Coupling	Direct	G Protein or arrestin	Direct	Via DNA
Examples	Nicotinic acetylcholine receptor, $GABA_A$ receptor	Muscarinic acetylcholine receptors, adrenoceptors	Insulin, growth factors, cytokine receptors	Steroid receptors
Structure	Oligomeric assembly of subunits surround central pore	Monomeric/oligomeric assembly of subunits: 7 trans-membrane helices with intracellular G-Protein coupling domain	Single transmembrane helix linking extracellular receptor domain to intracellular kinase domain	Monomeric structure with receptor and DNA binding domains

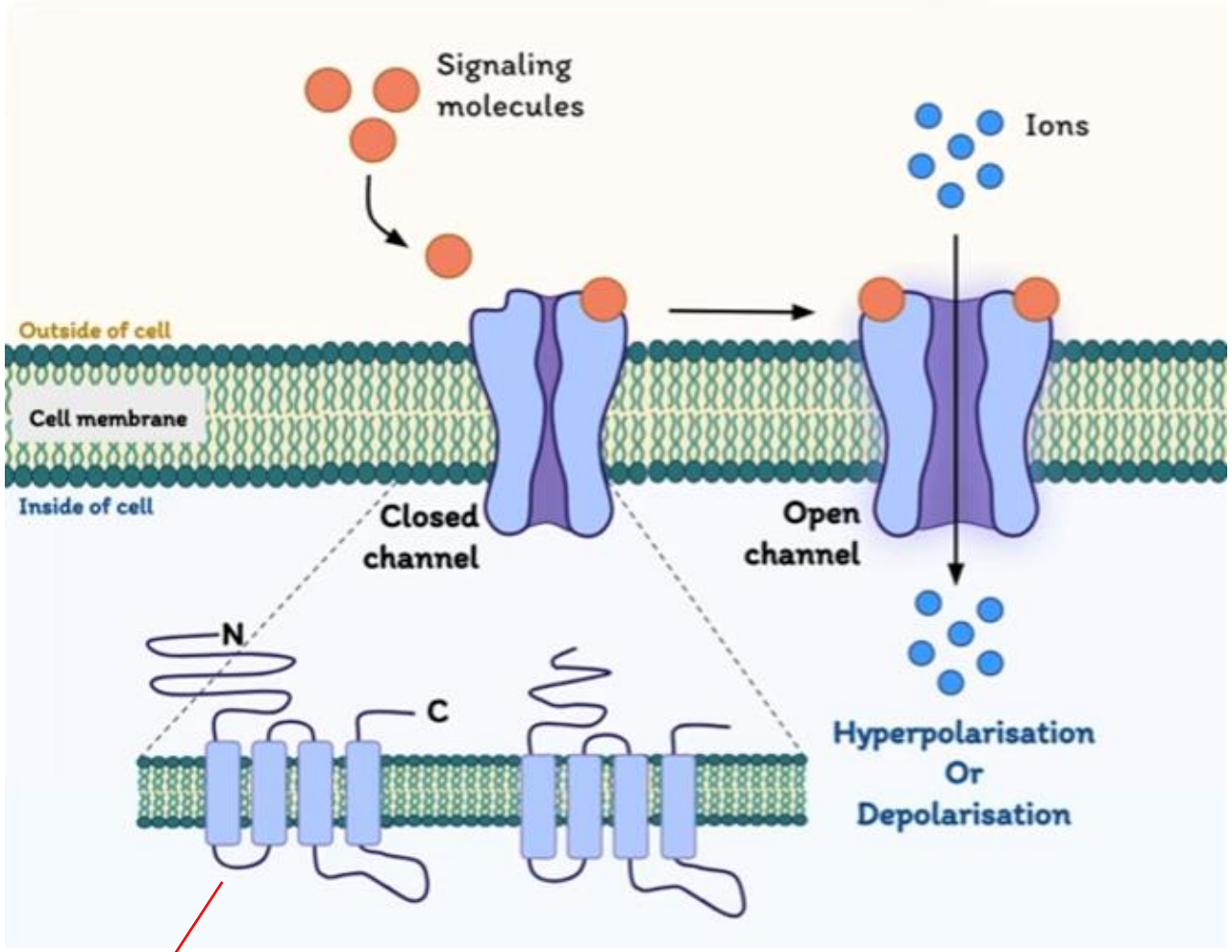
Rang & Dale's Pharmacology, Tenth Edition

Type 1: Ligand-gated Ion Channel receptors

- **Ionotropic**
- **Neurotransmitters**
- **Timescale:** milliseconds
- **Localization:** membrane
- **Effector:** ion channel
- **Coupling:** direct

Ion channels are characterized by

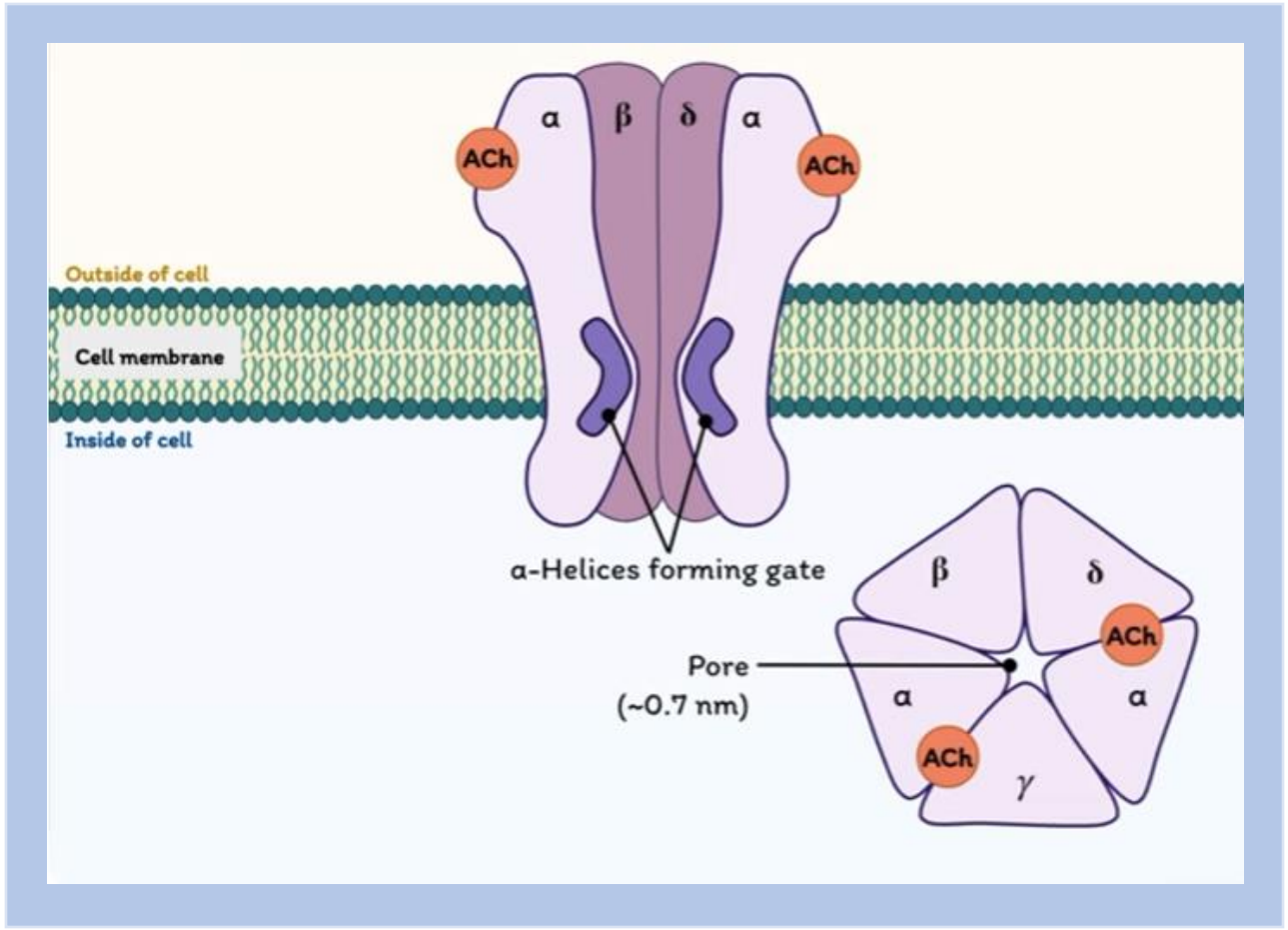
1. Selectivity for particular ion species
   - Size of the pore and nature of its lining
   - Cations: Na^+, Ca^{2+}, K^+
   - Anions: Cl^-
2. Gating properties
   - Control transition from open to closed states
3. Molecular structure



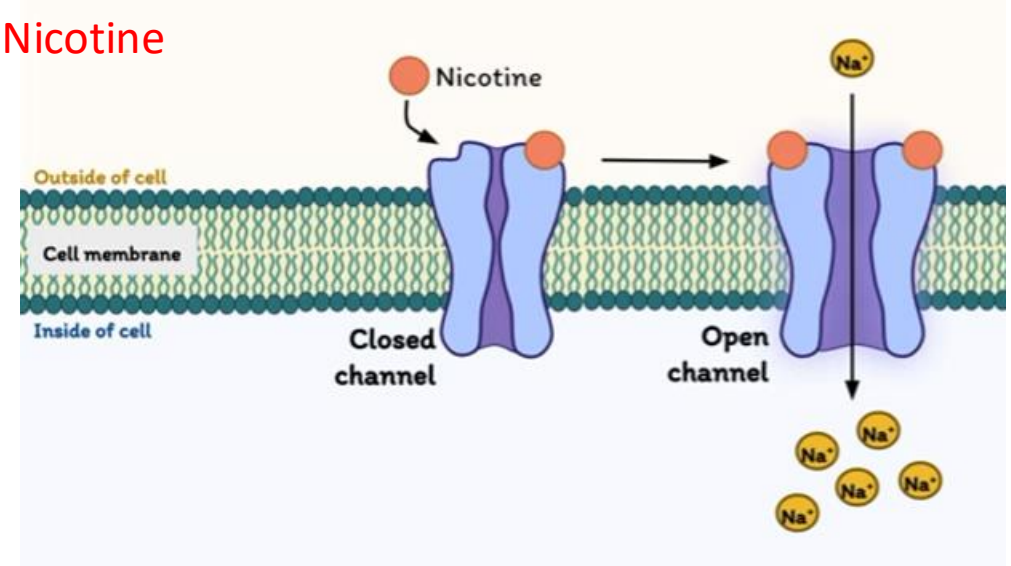
Examples

Nicotinic Ach Receptor
$GABA_A$ Receptor
Glutamate Receptor
Glycine Receptor

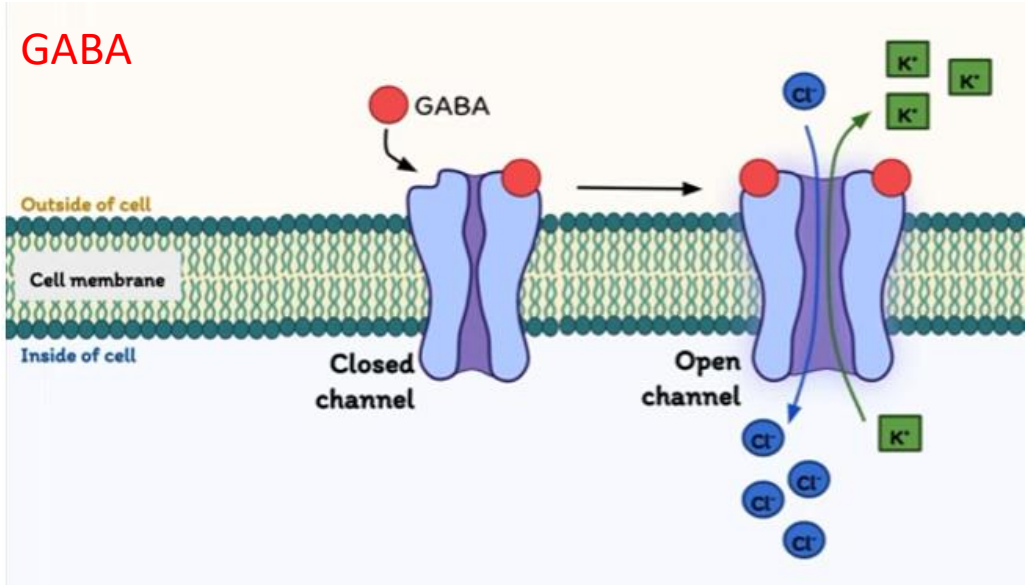
Example: Nicotinic Acetylcholine Receptor



Nicotine



GABA



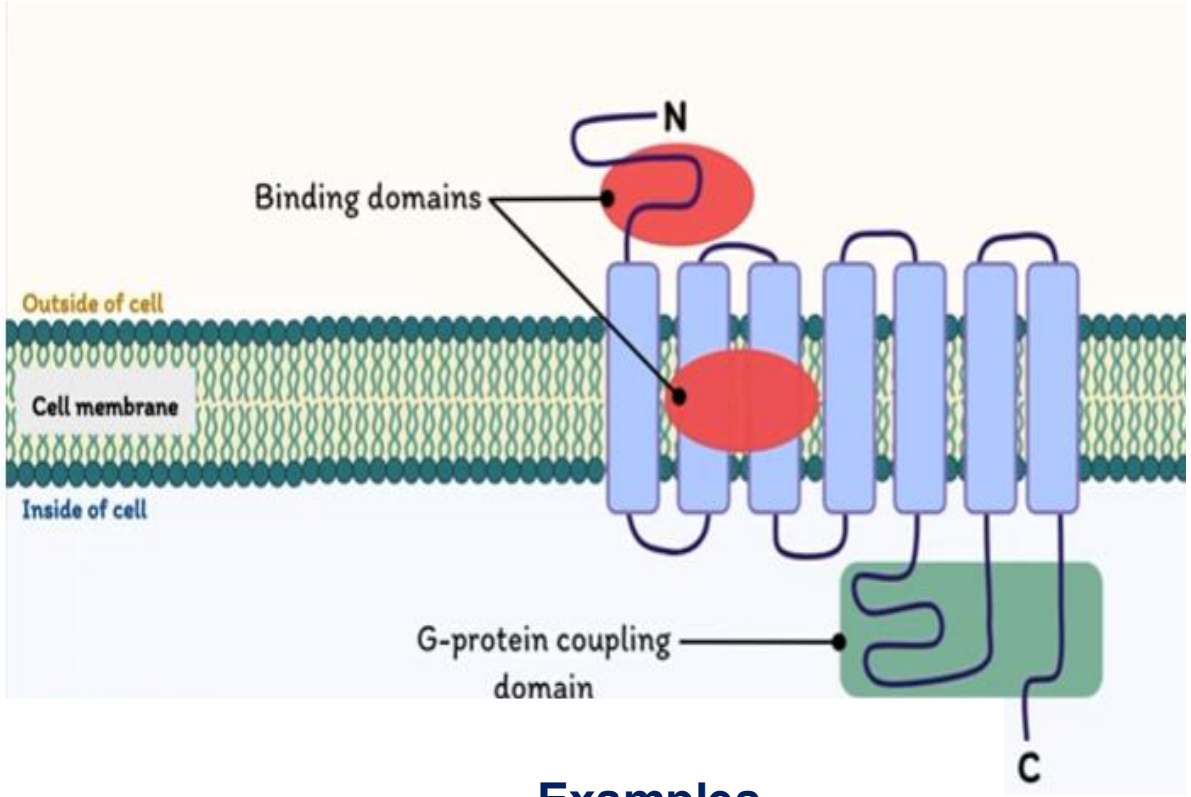
Review!

Type 2: G-protein coupled receptors

- **Metabotropic**
- **Largest family**
- **Timescale:** seconds
- **Location:** membrane
- **Effector:** channel or enzyme
- **Coupling:** G-Protein

Function

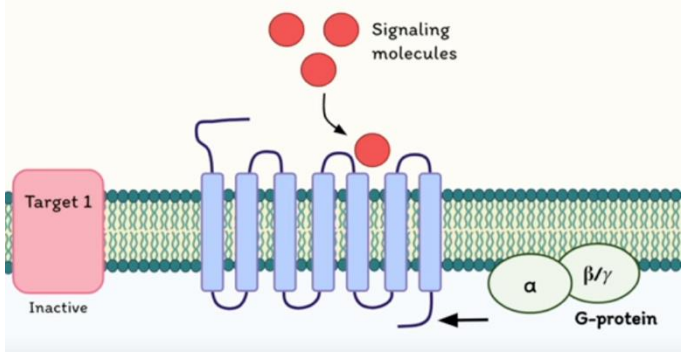
- Recognise and activate GPCRs → pass message to effector system → generate cellular response
- Signal amplification
- Four main classes



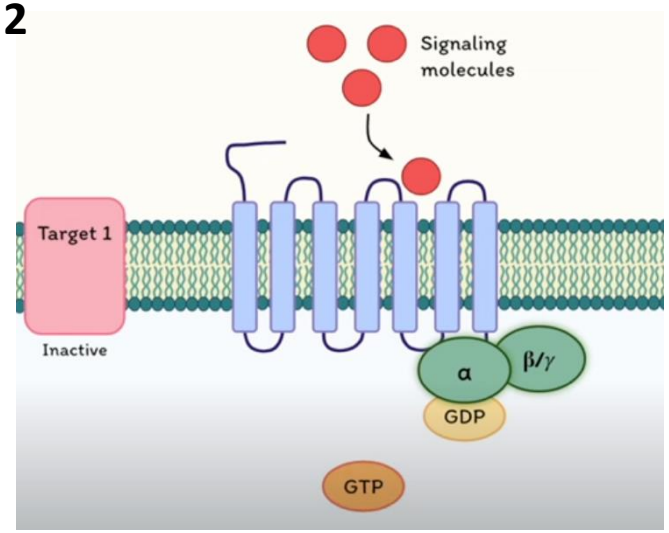
Examples

Adrenoceptors
Muscarinic Ach
Histamine
Serotonin
Opioid

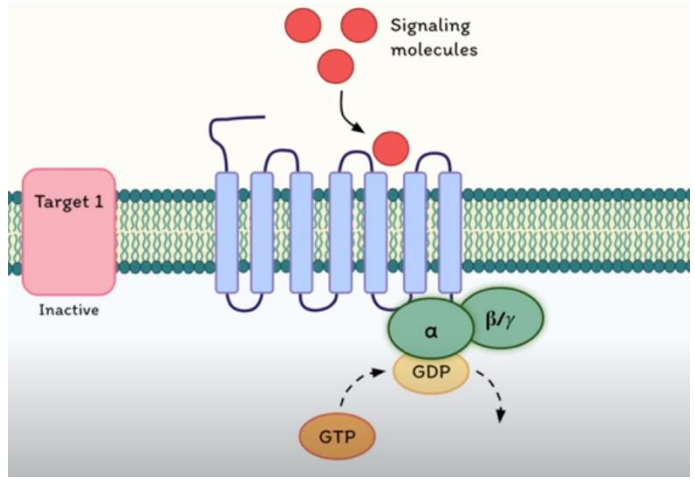
1


Signaling molecules
Target 1
Inactive
α
β/γ
G-protein

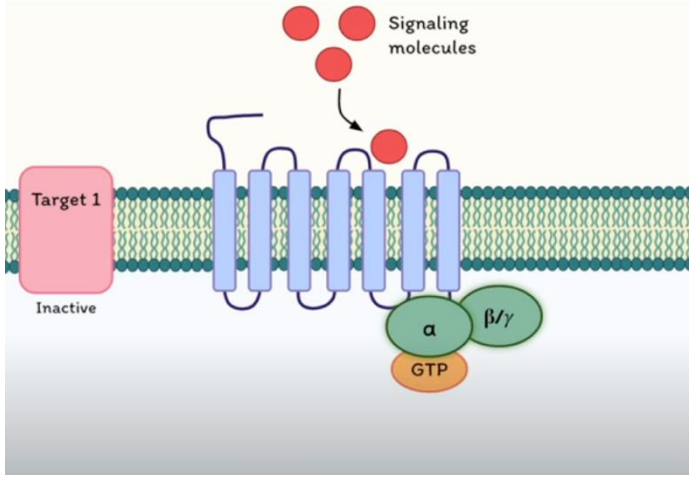
2


Signaling molecules
Target 1
Inactive
α
β/γ
GDP
GTP

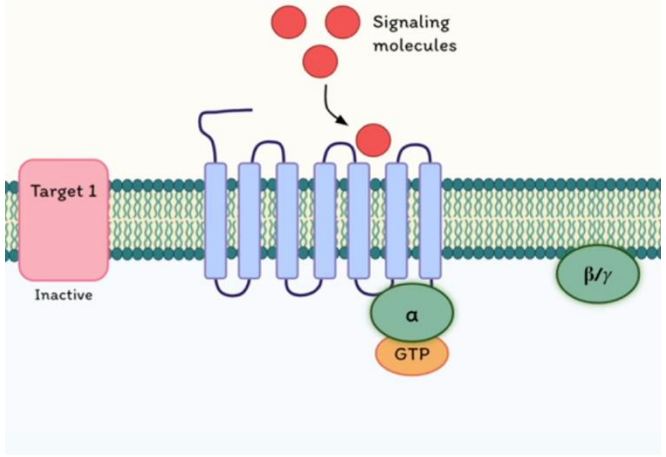
3


Signaling molecules
Target 1
Inactive
α
β/γ
GDP
GTP

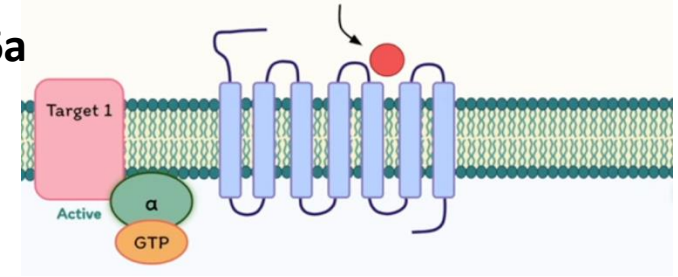
4


Signaling molecules
Target 1
Inactive
α
β/γ
GTP

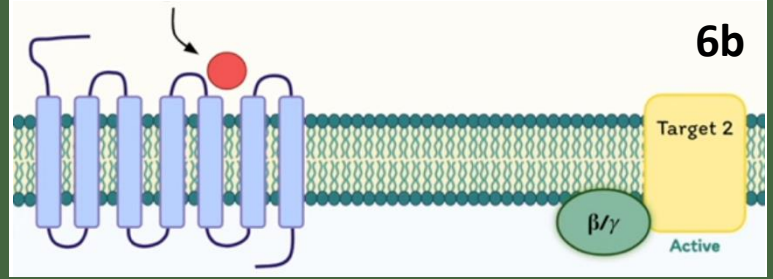
5


Signaling molecules
Target 1
Inactive
α
β/γ
GTP

6a


Target 1
Active
α
GTP

6b


Target 2
β/γ
Active

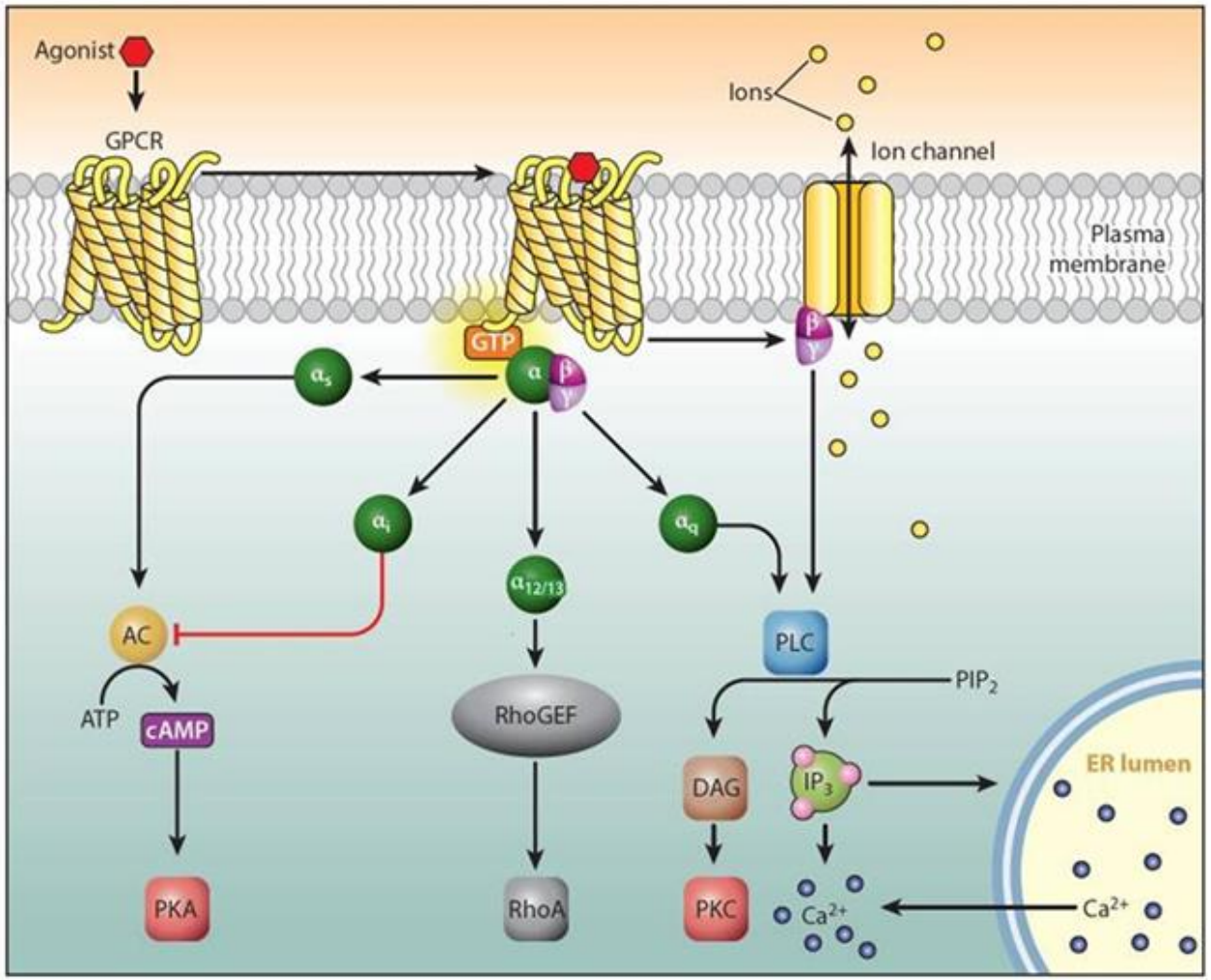
Example: cyclic AMP pathways

- G-protein coupling domain comprises of 3 subunits (α,β,γ)

- Gα proteins link GPCRs to effector proteins that generate intracellular second messengers
  - Gαs - Activates adenylate cyclase- Generates cAMP
  - Gαi- Inhibits adenylate cyclase
  - Gαq - Activates phospholipase C- Generates inositol triphosphate and diacylglycerol

Adenylate cyclase signal transduction pathway

1. GTP binds to Gα → Activation of G protein
2. Gα dissociates from Gβγ → Binds to adenylate cyclase → activation of cAMP
3. Gα dissociates from adenylate cyclase & binds to Gβγ → inactivation of cAMP
4. Returning to G state



Chen Y, Palczewski K. (2016). Systems Pharmacology Links GPCRs with Retinal Degenerative Disorders. Annu Rev Pharmacol Toxicol;56:273-98.Rang & Dale's Pharmacology, Ninth Edition

Gα subunits [b]		
$G\alpha_s$	Stimulates adenylyl cyclase, causing increased cAMP formation	Activated by cholera toxin, which blocks GTPase activity, thus preventing inactivation
$G\alpha_i$	Inhibits adenylyl cyclase, decreasing cAMP formation	Blocked by pertussis toxin, which prevents dissociation of αβγ complex
$G\alpha_o$	Limited effects of α subunit (effects mainly due to βγ subunits)	Blocked by pertussis toxin. Occurs mainly in nervous system
$G\alpha_q$	Activates phospholipase C, increasing production of second messengers inositol trisphosphate and diacylglycerol thus releasing Ca^{2++} from intracellular stores and activating protein kinase C (PKC)	
$G\alpha_{12/13}$	Activates Rho and thus Rho kinase	
Gβγ subunits		
	Activate potassium channels Inhibit voltage-gated calcium channels Activate GPCR kinases (GRKs) Activate mitogen-activated protein kinase cascade Interact with some forms of adenylyl cyclase and with phospholipase Cβ	Many βγ isoforms identified, but specific functions are not yet known

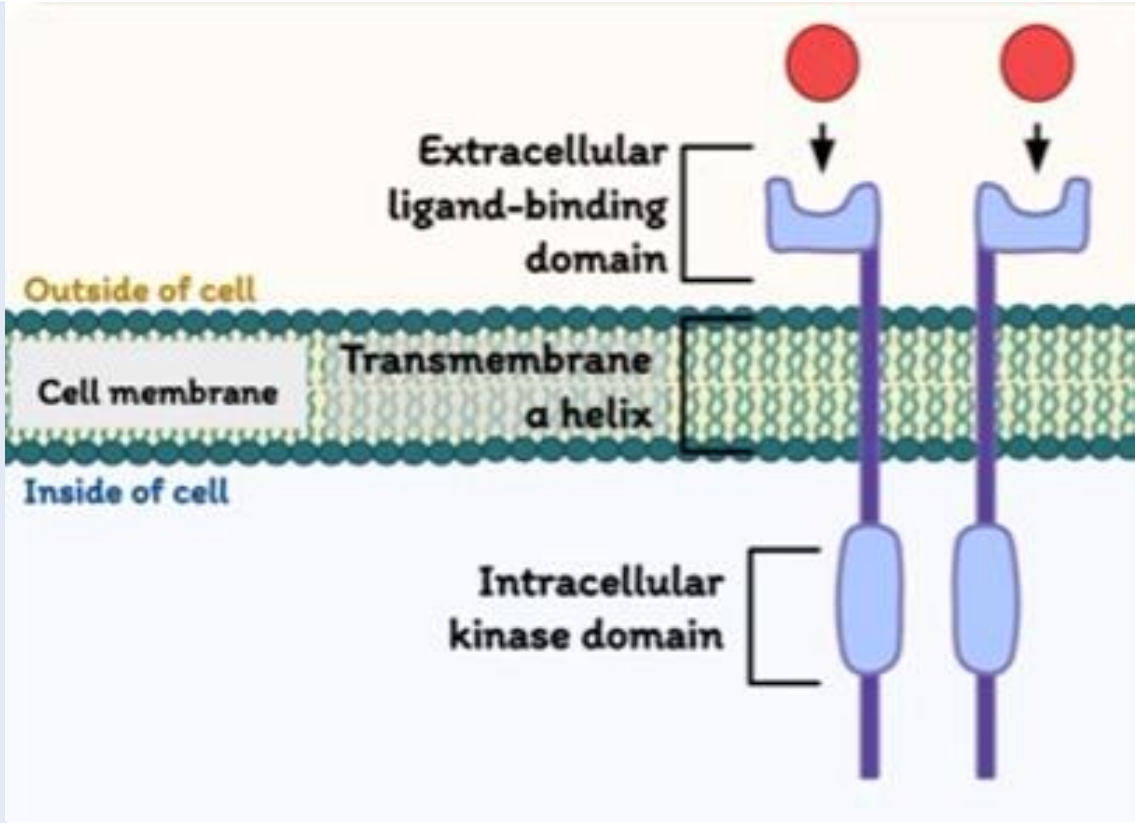
Review!

Type 3: Kinase linked receptors

Large heterogenous group responding mainly to protein mediators
Time scale: hours
Location: membrane
Effector: protein kinases
Coupling: direct
Structure: single transmembrane helix- linking extracellular receptor domain to intracellular kinase domain

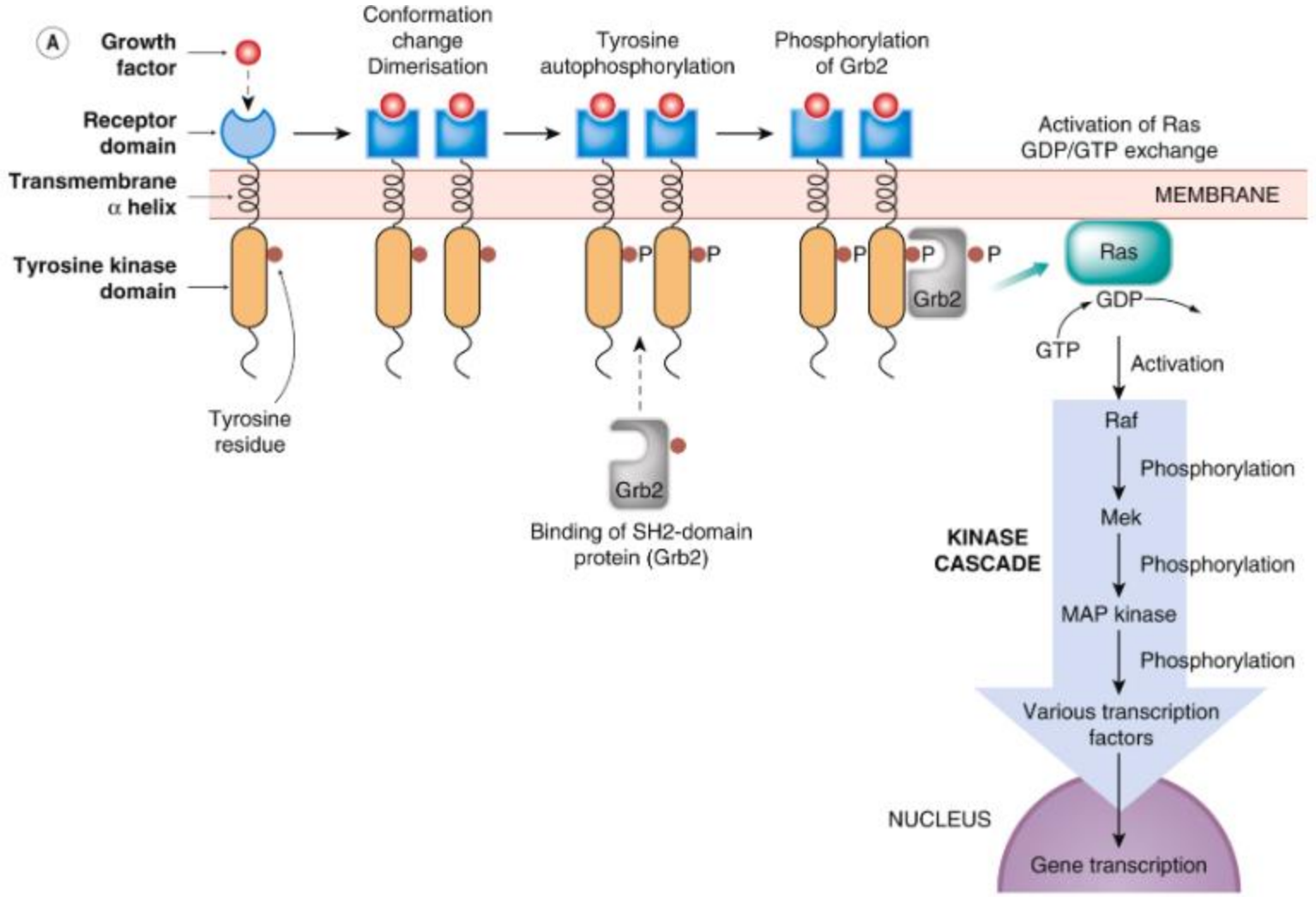
Receptor types

- Receptor tyrosine kinase – growth factors, insulin and IGF (insulin-like growth factor)
- Receptor serine/threonine kinase – transforming growth factor
- Cytokine receptor – interleukins and interferons
- Receptor guanylate cyclase – natriuretic peptides



Examples
Insulin
Growth Factors
Cytokine
ANF receptors

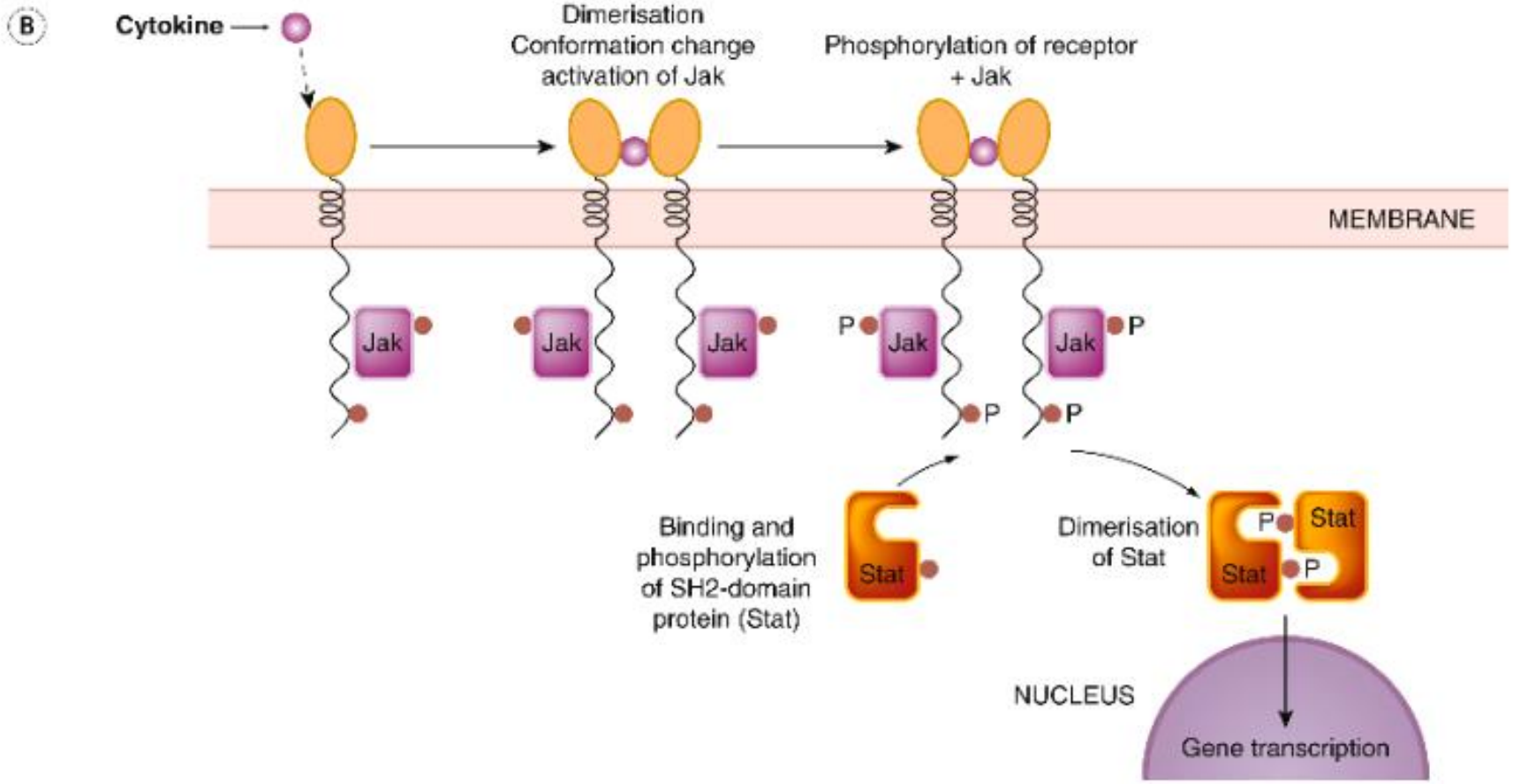
Receptor tyrosine kinase
Ras/Raf/MAP kinase pathway



1. Ligand binding
2. Receptor dimerises
3. Tyrosine autophosphorylation
4. Binding of SH2- domain protein (Grb2)
5. Kinase cascade (Raf, Mek, MAPkinase)
6. Transcription factor
7. Gene transcription

*Grb2- Growth factor receptor bound protein 2 (an adaptor protein); SH – Src homology

Receptor tyrosine kinase
Jak/stat pathway



1. Ligand binding
2. Receptor dimerises
3. Phosphorylation of receptor and Jak
4. Binding of SH2- domain protein (Stat)
5. Dimerization of Stat
6. Gene transcription

*JAK – Janus kinase; STAT – signal transducer and activator of transcription

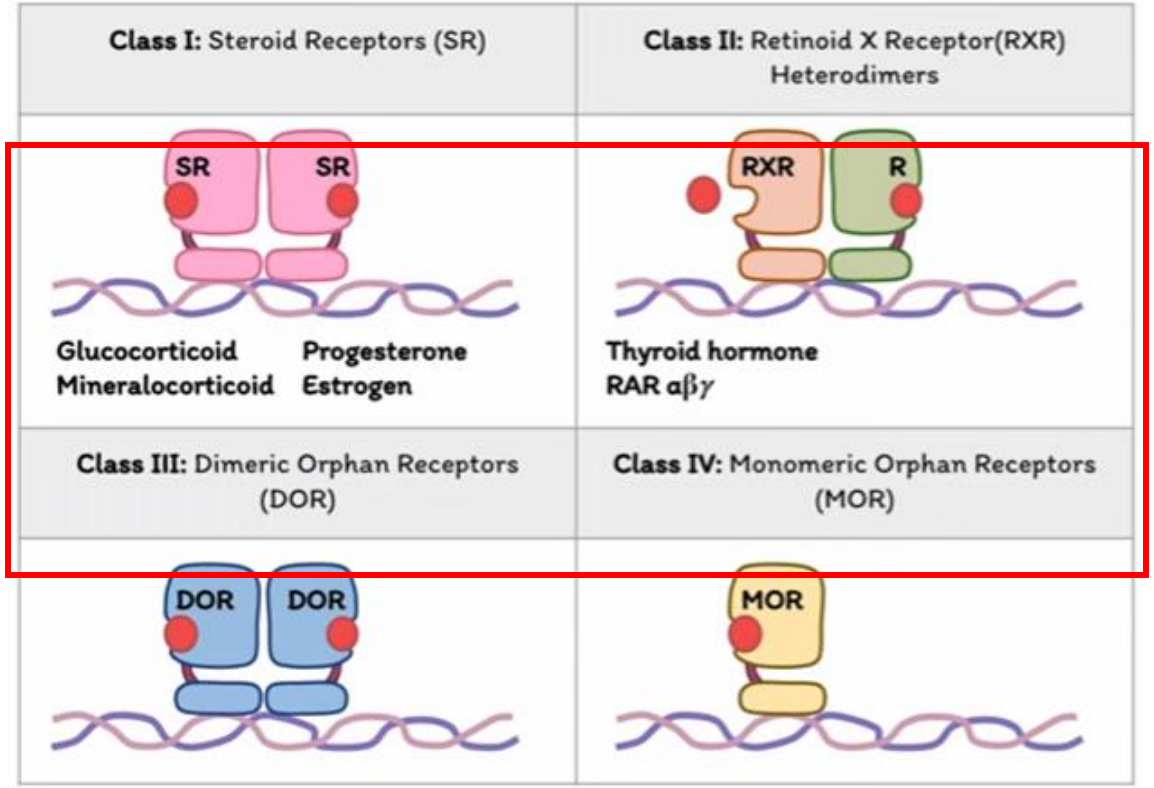
Rang & Dale's Pharmacology, Tenth Edition

Review!

Type 4: Nuclear receptors

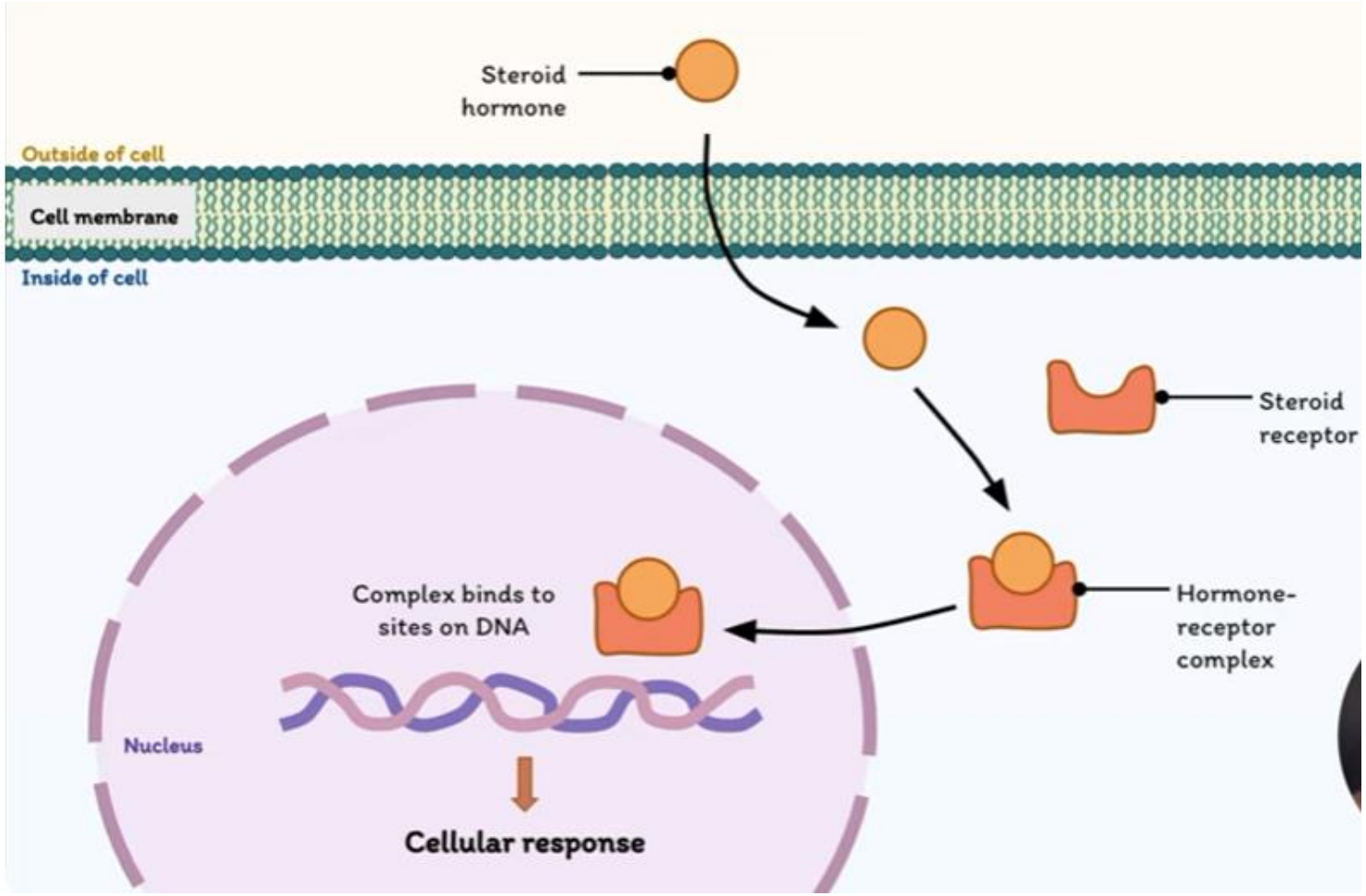
Regulate gene transcription, metabolic and developmental processes
Not always in the nucleus
Time scale: Hours
Location: intracellular
Effector: Gene transcription
Coupling: via DNA
Structure: monomeric proteins typically composed of several domains each with distinct functions

- N-terminal domain
- Core domain
- Hinge Region
- C-terminal domain



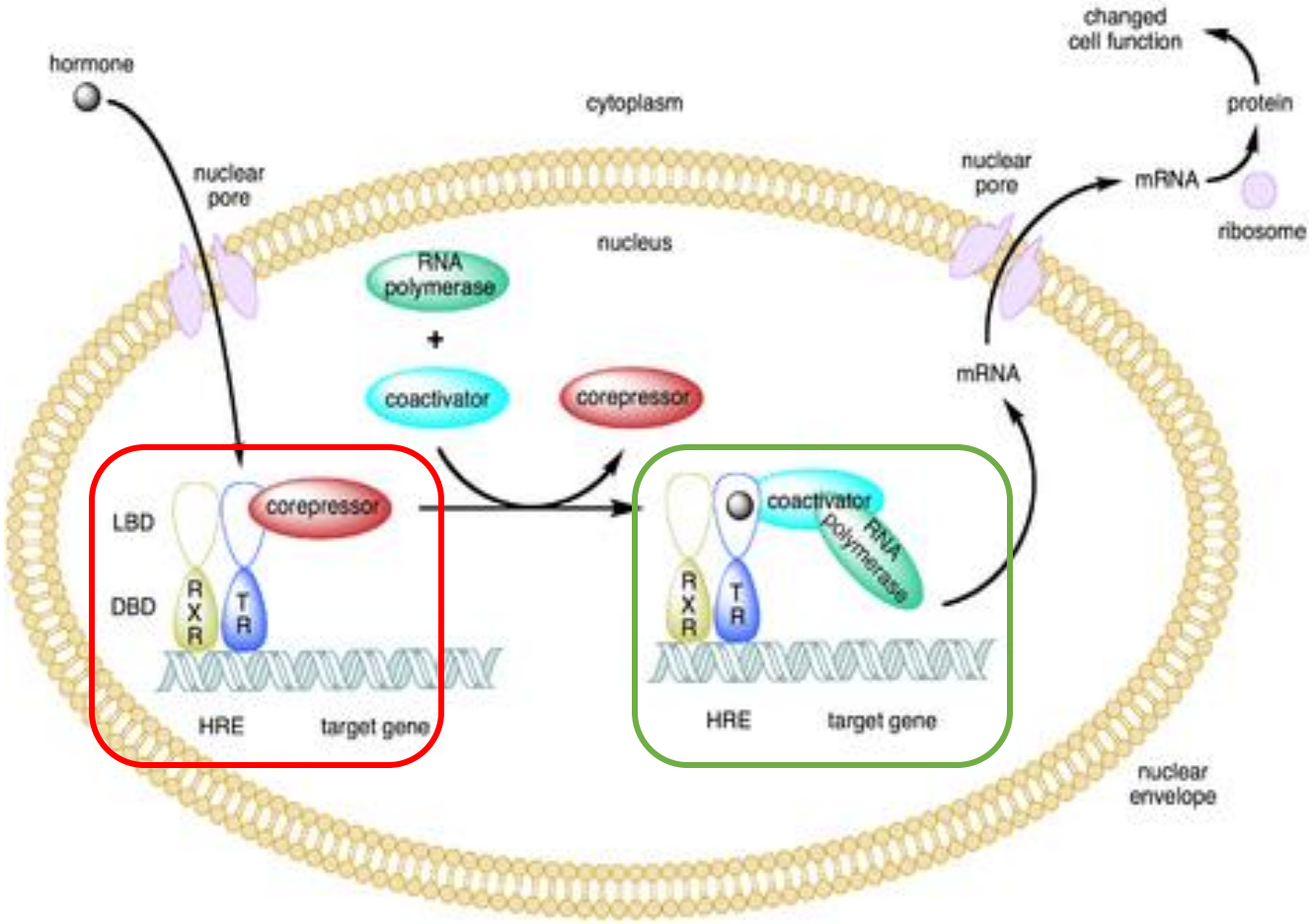
Examples
Steroid hormones
Thyroid hormones
Retinoic acid
Vitamin D receptors

Type 4: Nuclear receptors
Steroid Receptors (Class I)



- Steroid hormones are lipophilic and can easily enter cell membranes
- Lipophilic ligands interact with nuclear receptors once inside the cell
- Functional effects of nuclear receptors are slow due to their role in gene transcription and protein synthesis
- In the absence of ligand, nuclear receptors are mostly in the cytoplasm, bound to heat shock proteins (HSPs)

Type 4: Nuclear receptors
Steroid Receptors (Class II)



- Operate as heterodimers with RXR
- **Two types of heterodimers:**
- Non-permissive: activated only by RXR ligand
- Permissive: activated by retinoic acid or partner ligand
- Typically bound to co-repressor proteins to suppress gene expression
- Ligand binding causes dissociation of co-repressors and recruitment of co-activators
- Co-activator recruitment initiates gene expression

Review!

Key information

- Most drugs bind to, and act through receptors
- Majority of drugs receptors are proteins
- Four superfamilies of receptors are presented
- Effects of drug after binding to a receptor is called signal transduction
- Agonists at a given at a given receptor can be distinguished based upon affinity and efficacy
- Antagonists are drugs that bind to receptors and block the effects of agonists

References

- Ritter JM, Flower RJ, Henderson G, Loke YK, MacEwan D, Robinson E, editors. *Rang & Dale's pharmacology*. 10th ed. Edinburgh: Elsevier; 2023
- Becker DE, Reed KL. *Pharmacology and Therapeutics for Dentistry*. 7th ed. St. Louis: Elsevier; 2017.
- Bullock S, Manias E. *Fundamentals of pharmacology*. 8th ed. Frenchs Forest, NSW: Pearson Australia; 2017
- Stringer JL. *Basic concepts in pharmacology*. 6th ed. New York (US): McGraw Hill Medical; 2022 Feb 18