

Pharmacodynamics

What the drug does to the body?

Overview



Drug(Ligand) + Receptor \rightleftharpoons Drug-receptor complex \rightarrow Biologic effect

“A drug doesn’t work unless it is bound”

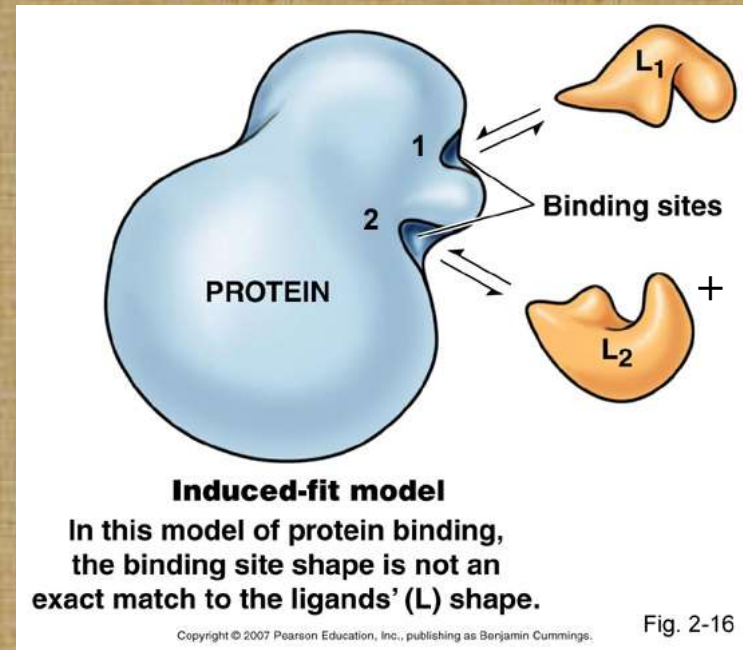
Drugs only modify underlying biochemical and physiological processes, they do not create effects de novo (anew)

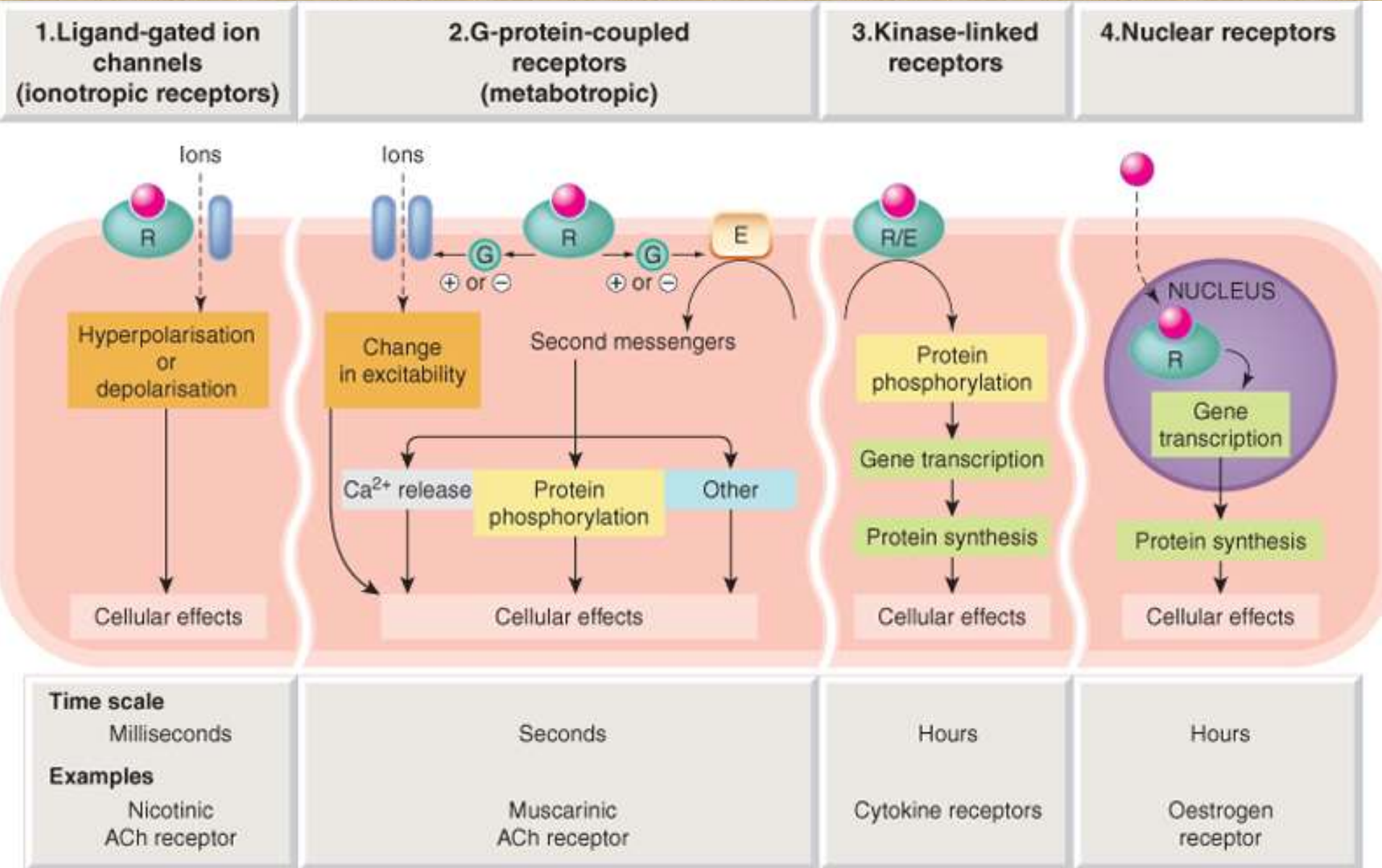
Topics of Discussion

- **DRUG RECEPTOR INTERACTION**
- **DRUG DOSE-RESPONSE RELATIONSHIP**
- **THERAPEUTIC INDEX**

Chemistry of Receptors and Ligands

- Drugs typically exert their effects by interacting with a receptor
- Chemical bonds
 - Electrostatic
 - Hydrogen bond
 - Van der Waals
- Binding
 - Receptor selective
 - Requires exact fit
 - Usually reversible





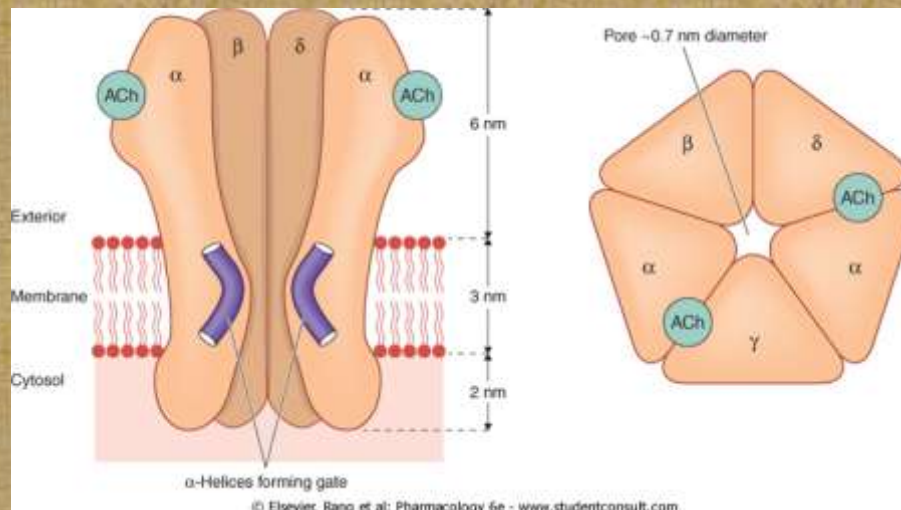
© Elsevier. Rang et al: Pharmacology 6e - www.studentconsult.com

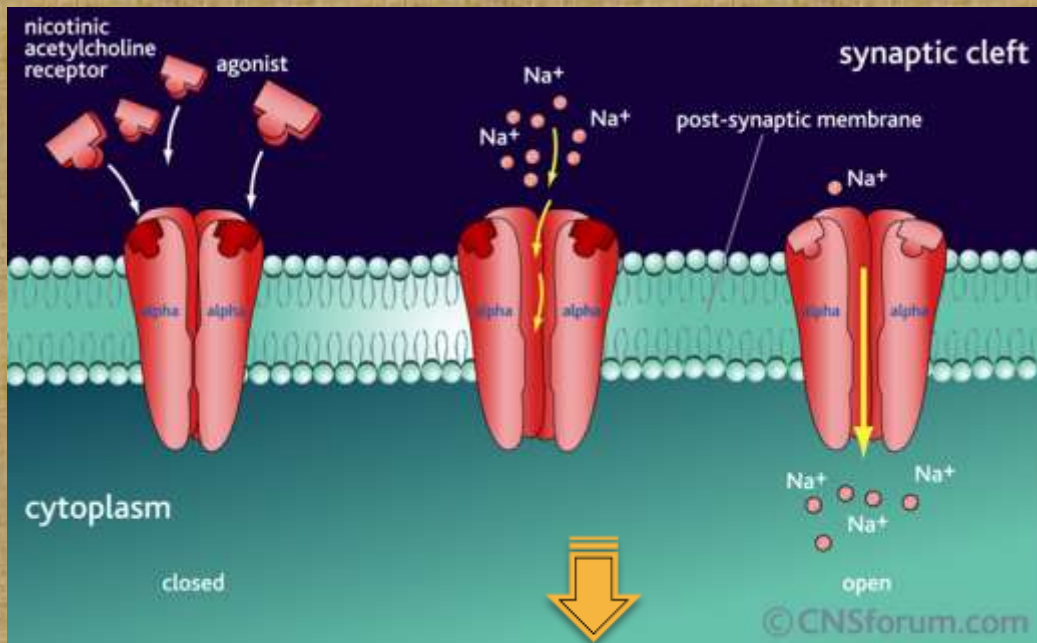
Types of receptor-effector linkage: E, enzyme; G, G-protein; R, receptor.

Major Receptor Families

1. Ligand-Gated Ion Channels

- Regulation of flow of ions across cell membranes
- Depolarization/Hyperpolarization of membrane
- Associated with receptors for fast neurotransmitters
 - ✦ Nicotinic receptor - Na^+





Major Receptor Families

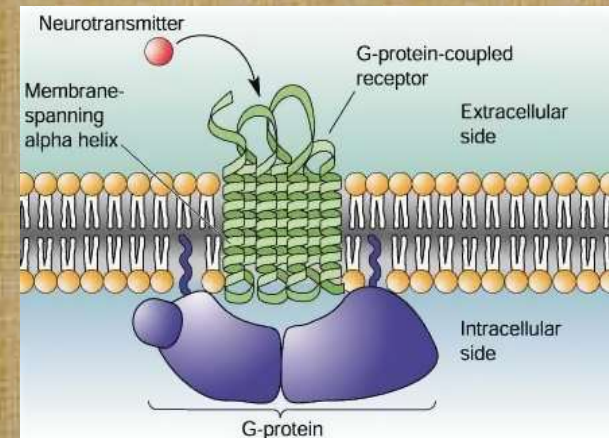
2. G-Protein coupled receptors – Largest family

○ 3 components

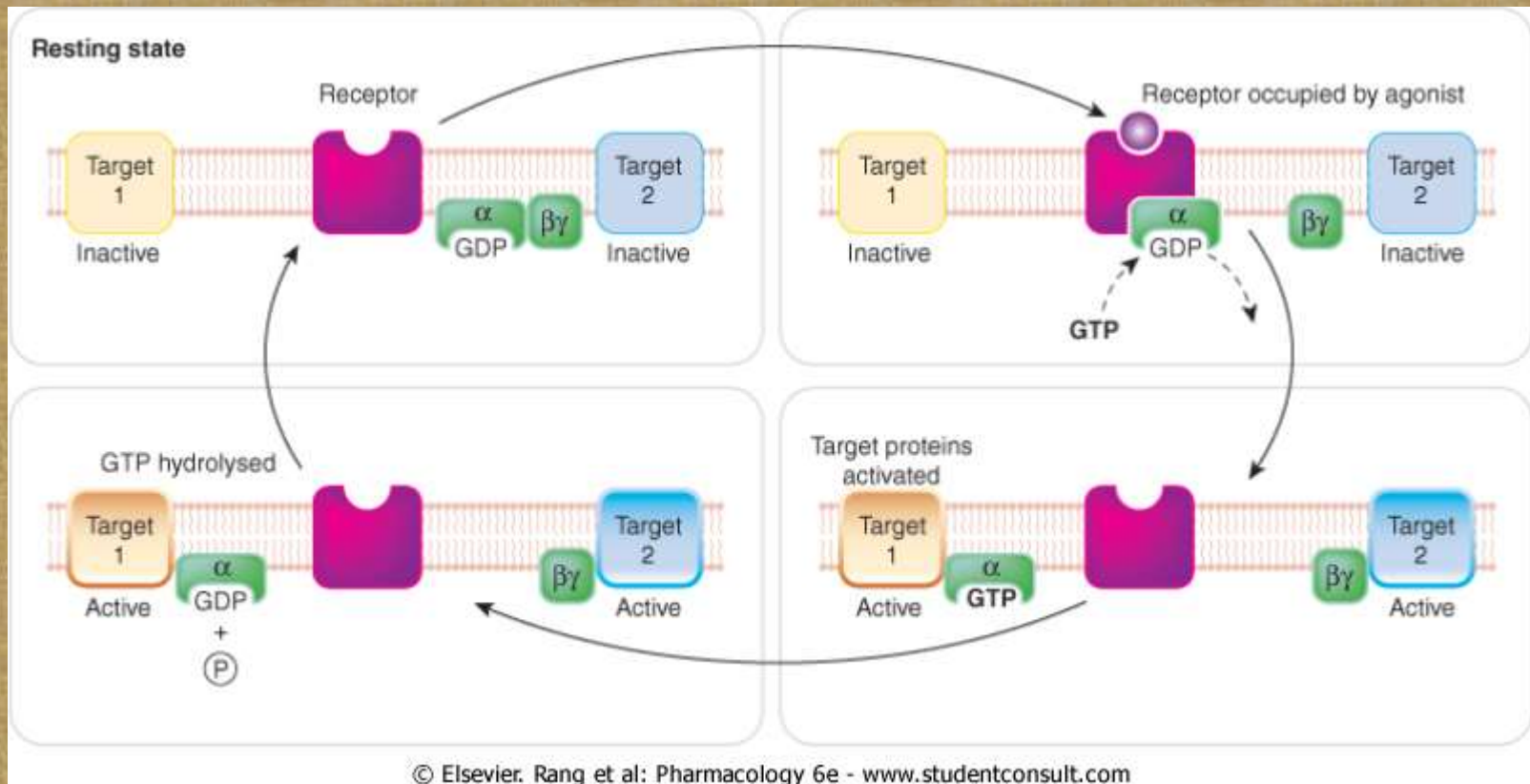
- ✦ 7 membrane-spanning α helices
- ✦ G protein – α subunit – GTPase & $\beta\gamma$
- ✦ cAMP / IP3 / Phospholipase A2 / ion Ch

○ Four Steps

- ✦ Ligand binding
- ✦ G protein activation (cytoplasmic side)
- ✦ Activity of effector (ion channel or enzyme) changed
- ✦ Intracellular second messenger concentration changes
 - cAMP: effector enzyme -- adenylyl cyclase, converting ATP to cAMP – phosphorylates proteins



G-Protein Coupled Receptor



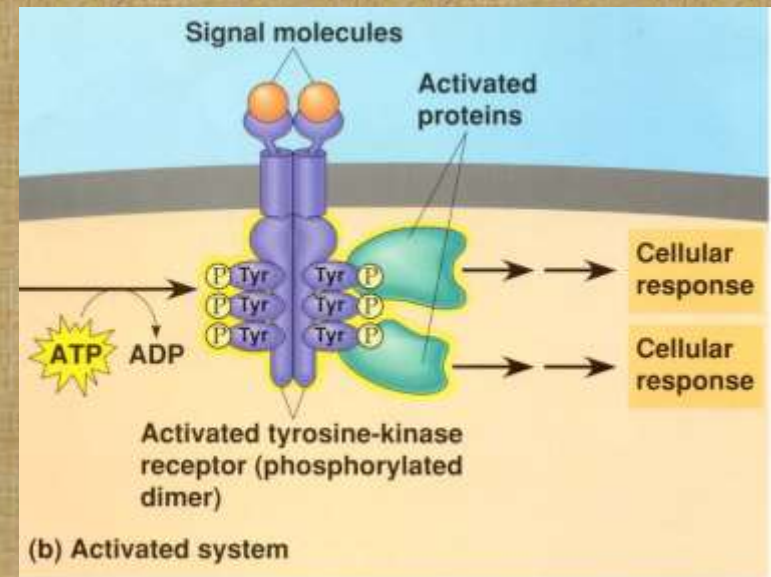
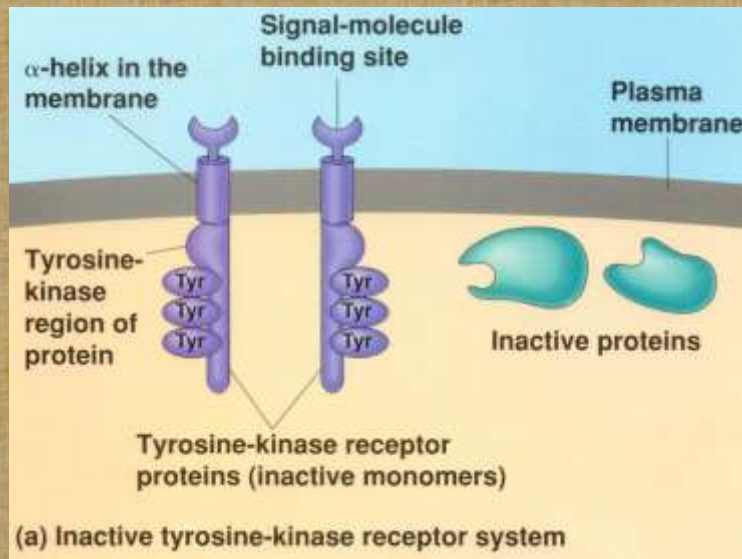
Zoya Maslak, Yuri Rashkin - The G Protein Story.flv
<http://www.youtube.com/watch?v=K7WSMybZeA8>

Major Receptor Families

3. Kinase-linked receptors

- Cytosolic enzyme activity as integral structure or function
- Most common tyrosine kinase activity (Kinase = Phosphate)
- Addition of phosphate changes 3D structure of protein

✦ Insulin



Major Receptor Families

4. Nuclear receptors

- TWO main categories
 - ✦ Those present in cytoplasm migrate to the nucleus eg. Steroid hormones
 - ✦ Present in nucleus – ligands usually lipids
- Binds to specific DNA sequences resulting in regulating gene sequences – protein synthesis
- Longer time course of action

Topics of Discussion

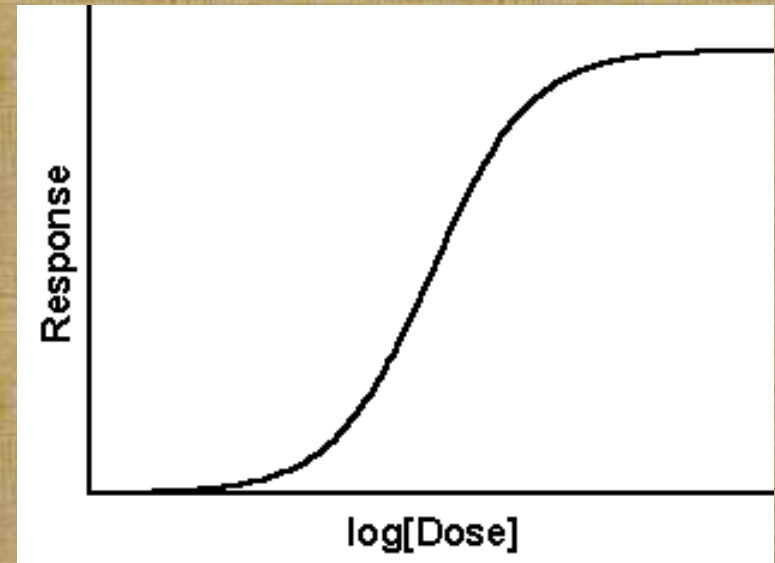
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Drug Dose-Response Relationship

- Graded dose-response relations
 - Drug-Receptor binding
 - Relationship of binding to effect
 - Efficacy
- Nature of interactions
 - Agonists
 - Antagonists
 - Functional antagonism
 - Partial agonists

Drug-receptor Binding

- Effect of dose on the magnitude of drug binding
- Relationship of binding to effect assumes
 - Magnitude proportional to receptors bound
 - Maximum efficacy when all receptors bound



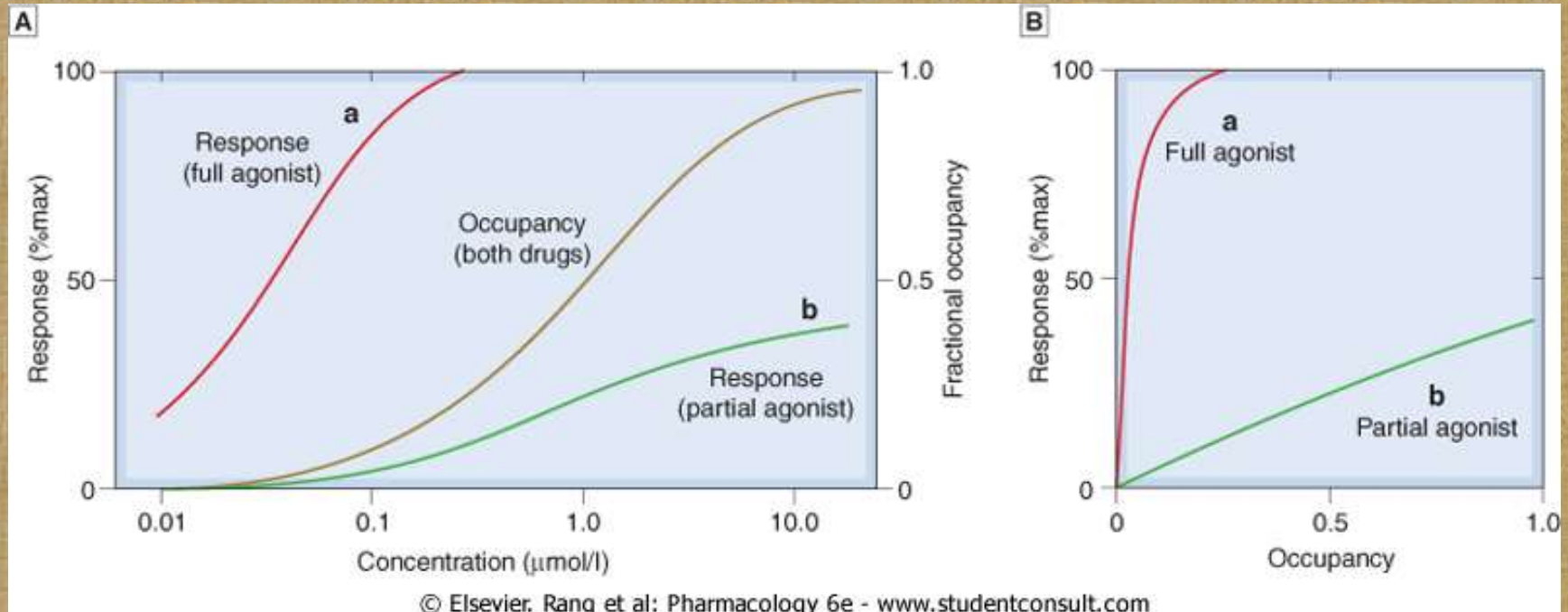
Efficacy

- Efficiency is dependent on number of drug-receptor complexes formed and corresponding cellular response

Nature of Interactions

- Agonist
 - If a drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand
- Partial agonist
 - Has intrinsic activity less than that of a full agonist

Theoretical occupancy and response curves for full vs partial agonists



The occupancy curve is for both drugs, the response curves a and b are for full and partial agonist, respectively. The relationship between response and occupancy for full and partial agonist, corresponding to the response curves in A. Note that curve a produces maximal response at about 20% occupancy, while curve b produces only a submaximal response even at 100% occupancy.

Nature of Interactions

- Antagonist
 - Drugs that decrease the actions of the endogenous ligand.
 - ✦ Reversible vs Irreversible
- Functional antagonism (physiologic antagonism)
 - Antagonist binds completely separate receptor initiating effects functionally opposite of the agonist
 - ✦ Epinephrine binding to (β_2 adrenergic receptor) reversing Histamine-induced bronchoconstriction (H_1 receptor)

Body adapts to drugs

- Change in receptors
 - Refractory period after effect of first dose - Desensitisation
- Loss or addition of receptors
 - Internalization of receptors due to prolonged exposure to agonist
- Exhaustion of mediators
 - Amphetamine release catecholamine – stores depleted
- Physiological adaptation

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Therapeutic Index

- Therapeutic index is the ratio of the dose that produces toxicity : dose for clinically desired effective response (50% of population)

$$\text{Therapeutic Index} = \text{TD}_{50} / \text{ED}_{50}$$

Summary

- Drugs only modify underlying biochemical and physiological processes, they do not create effects de novo (a new)
- 4 ways drugs and receptors interact - KING
- Dose-Response Curve
 - Nature of Interactions
 - Body adapts to drug
- Therapeutic Index

References

- Howland et al (2006) Lippincott's Pharmacology 3rd Ed.
- Rang et al (2007) Rang & Dale's Pharmacology 6th Ed.