PHARMACODYNAMICS-I

DRUG RECEPTORS & SIGNALING MECHANISMS

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ilos *By the end of this lecture Student should be able to :*

- **Define the drug receptor, types, location and**

mechanism of receptor regulation.

- **Enlist the transmembrane signaling**

methods by which drug receptor

interactions exert their effects.

What is Pharmacodynamics ?

Pharmacodynamics is a branch of pharmacology that deals with the study of the biochemical and physiological effects of drugs and their mechanisms of action.

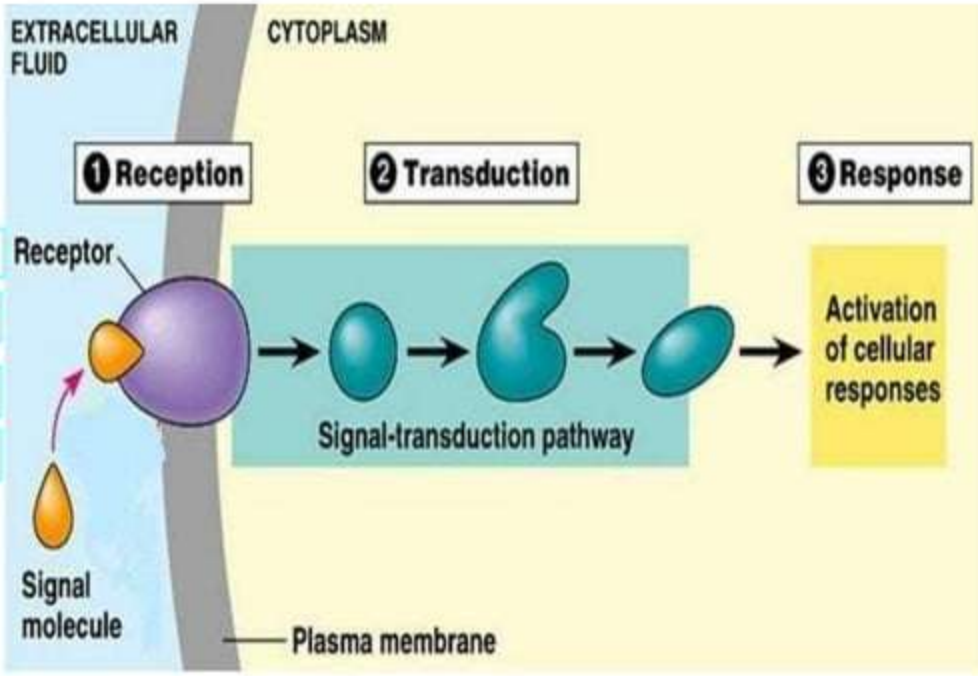
A RECEPTOR

Recognition

Reception

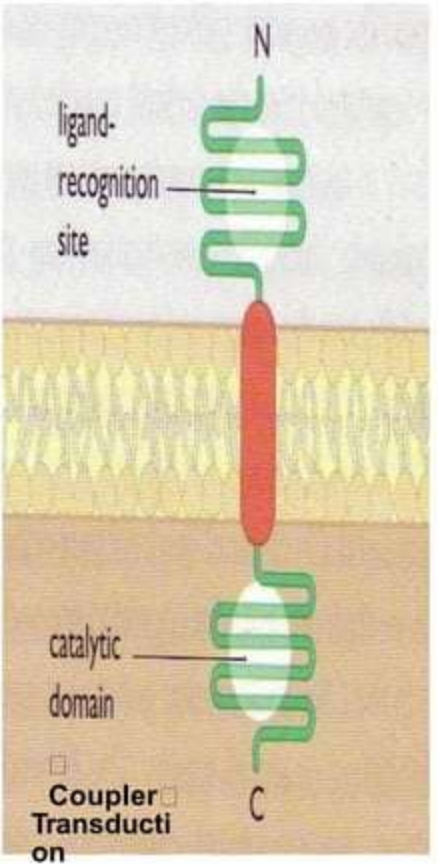
Transduction

Response



A RECEPTOR structure

- Ligand recognition site
- Inner catalytic domain



RECEPTOR FAMILIES

Type I (Ion Channel-Linked receptors)

Type II (G-Protein coupled receptors)

Type III (Enzyme-Linked receptors)

Type IV (Receptors linked to gene transcription)

RECEPTOR FAMILIES

	Type I	Type II	Type III	Type IV
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors **Adrenergic receptors**	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

TYPE I : Ion Channel-Linked receptors Ligand gated ion channels Ionotropic receptors

- Located at cell membrane
- Directly activated by ligand binding
- Directly related to ion channels.
- Involved in very fast synaptic transmission.
- Response occurs in milliseconds.

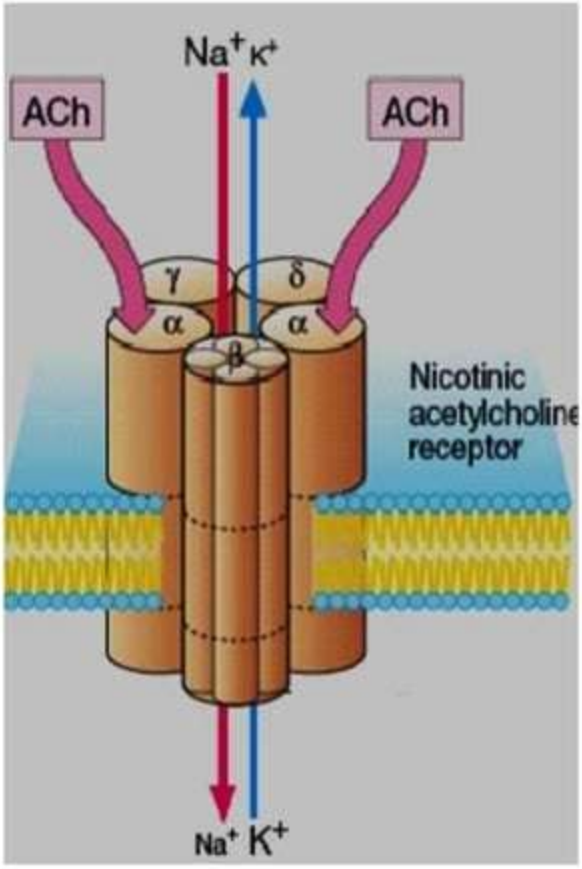
1 Channel-Linked

Ionotropic

Receptor Ligand-

Gated-Ion Channel

e.g. nicotinic receptors that are activated by occupancy of a ligand as acetylcholine.



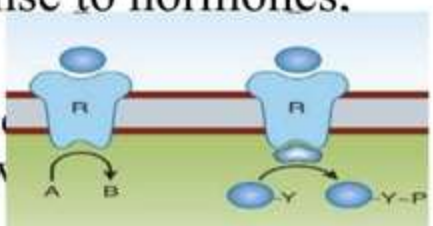
Type II: G-Protein coupled receptors Metabotropic Receptor

- The largest family that accounts for many known drug targets
- Located at cell membrane
- Coupled to intracellular effectors via **G-protein**
- Response through ion channels or enzymes.
- Involved in rapid transduction
- Response occurs in seconds.
- **E.g. Muscarinic receptors of Ach**

Type III (Enzyme-Linked receptors)

(Tyrosine Kinase-linked receptor)

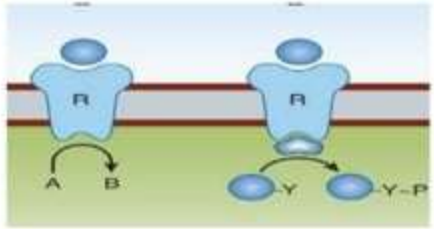
- Located at cell membrane
- Linked to enzyme (with intrinsic enzymatic activity)
- Response occurs in minutes to hours.
- Involved in response to hormones, growth factors.
- They control many c
  metabolism and grow



Type III (Enzyme-Linked receptors) (Tyrosine Kinase-linked receptor)

- **Activation of Type III receptors results in**
  - Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

E.g. Insulin receptors

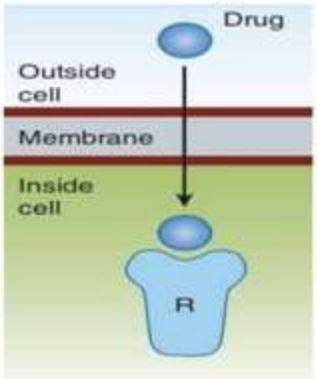


Type IV: Nuclear receptors

Gene transcription

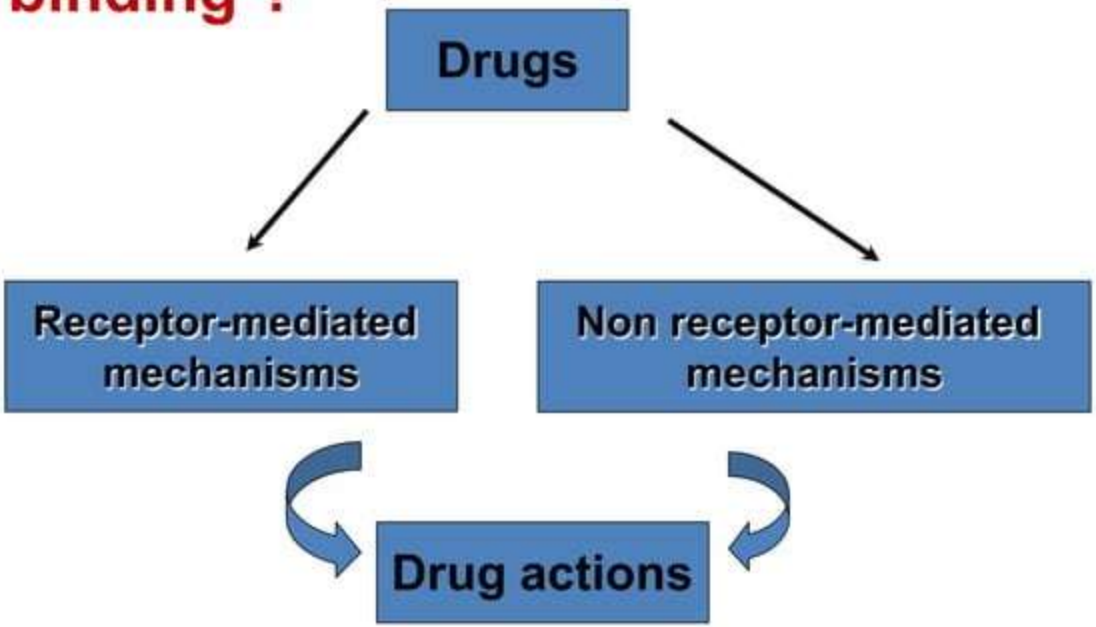
receptors

- Located intracellularly
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.



What are the mechanisms of drug action?

How drugs produce action? What are targets for drug binding ?



What are the mechanisms of drug action?

Drugs can produce their actions by one of the following mechanisms:

1) **Receptor-mediated mechanisms (Binding with biomolecules):**
   - Receptors =Biomolecules = Targets
   - Targets are mostly **protein in nature**.

1) **Non receptor-mediated mechanisms**
   Physiochemical properties of drugs.

Non receptor–mediated mechanisms

Drugs can produce actions by:

Chemical action

- Neutralization of gastric acidity by antacids.

Physical action

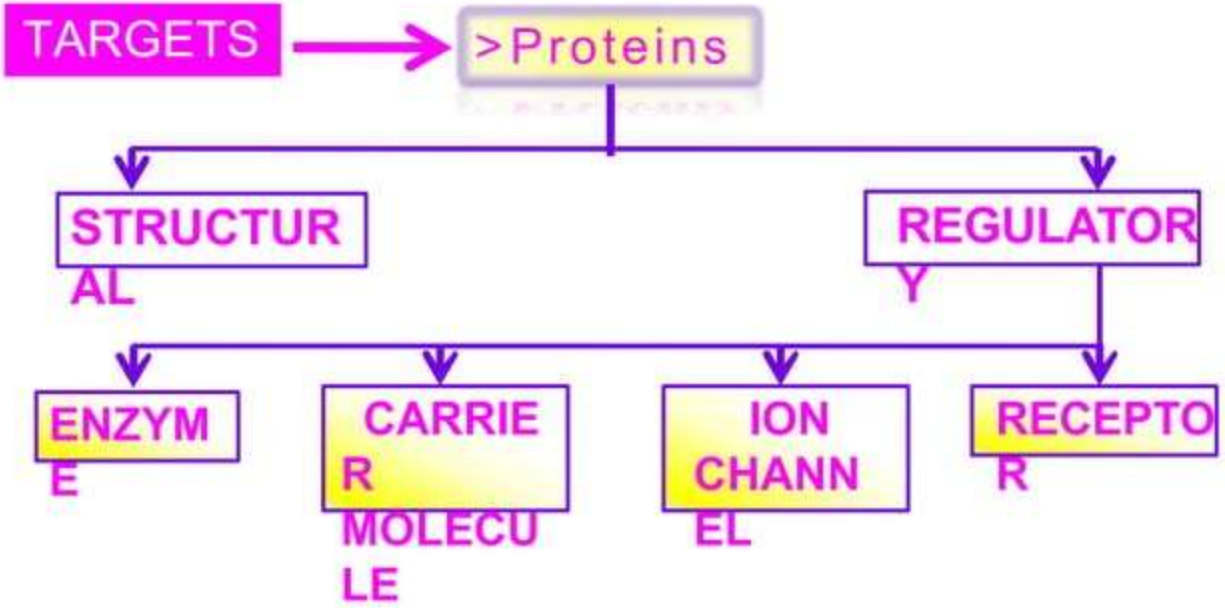
- Osmotic diuretics.
- Purgatives used in treatment of constipation e.g. MgSO4

Receptor–mediated mechanisms

Drugs can produce actions by binding with biomolecules (Protein Targets)

Protein targets for drug binding

- Structural protein
- Regulatory proteins
  - Physiological receptors
  - Enzymes
  - Ion channels
  - Carriers


TARGETS
>Proteins
STRUCTURAL
REGULATORY
ENZYME
CARRIER MOLECULE
ION CHANNEL
RECEPTOR

Receptors

Is a special target macromolecule that binds the drug and mediates its pharmacological actions.

Where are receptors located?

- Cell membrane.
- Cytoplasm.
- Nucleus.

Enzymes

- The drug competes with the natural endogenous substrate for the enzyme.

- E.g. Anticholinesterases inhibit acetylcholinesterase thus producing cholinomimetic action.

- Neostigmine **reversibly** compete with ACH for acetyl cholinesterase enzyme at motor end plate (neuromuscular junction).
- Organophosphates **irreversibly** competes with ACH for acetyl cholinesterase enzyme.

Ion channels

- Drugs bind to alter channel function **(by opening or blockade).**
- Channels are responsible for influx or outflux of ions through cell membranes.
- They are activated by alteration in action potential.

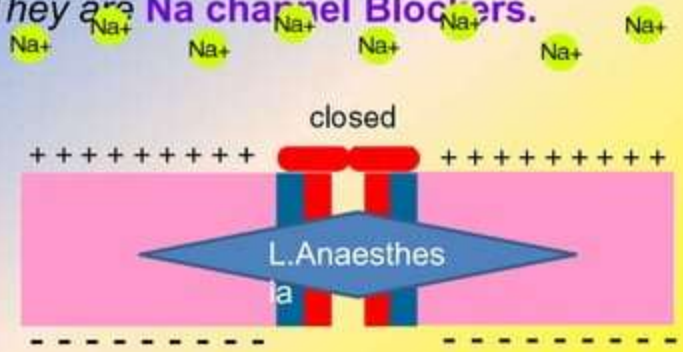
Ion channels

e.g. local anesthetics:

act by blocking sodium (Na+) influx through Na channel in nerve fibers (**Na channel blockers).**

TARGETS → >Proteins → REGULATORY → ION CHANNEL

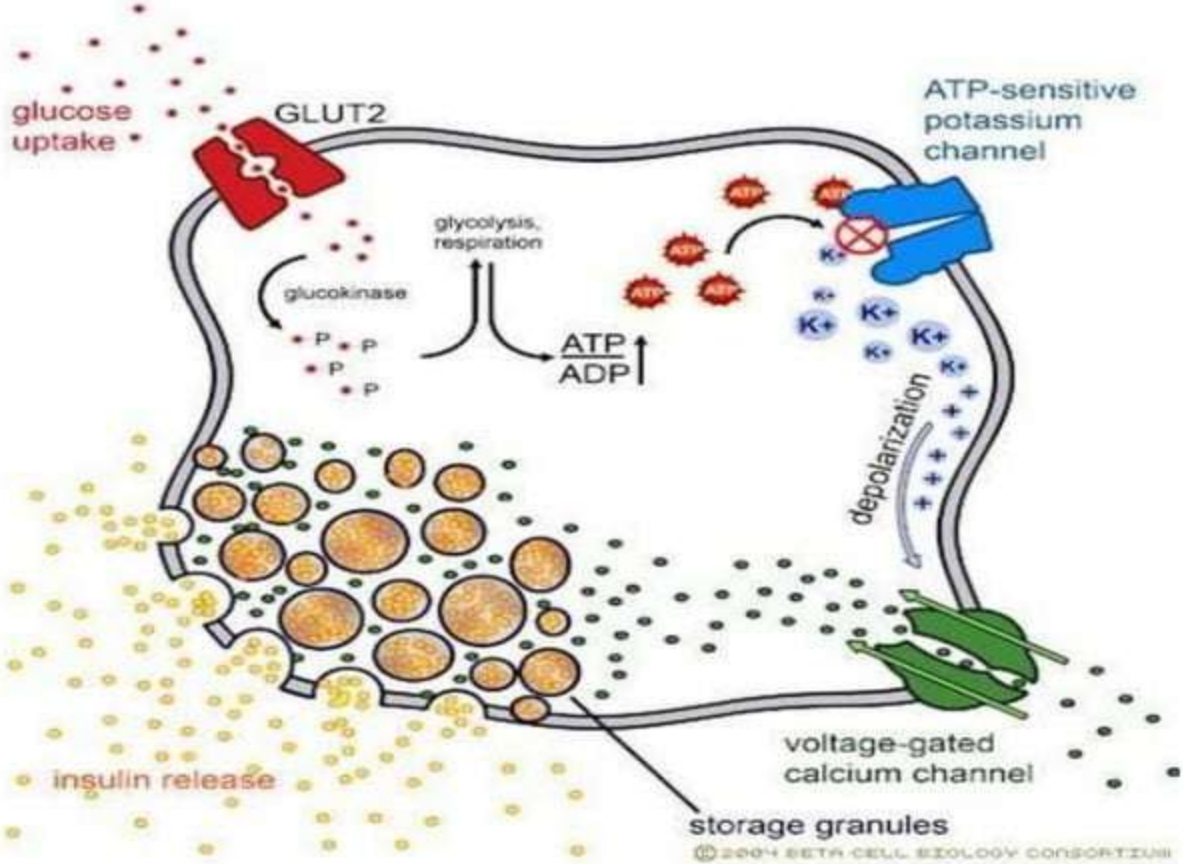
Local Anesthetics *block Na influx through* **Na channel**
in nerve fibers. They are **Na channel Blockers.**



Ion channels

- **e.g. Sulfonylurea drugs (antidiabetic drugs):**

  block potassium channels in pancreatic beta cells resulting in depolarization and opening of calcium channels and insulin secretion.


glucose uptake
GLUT2
ATP-sensitive potassium channel
glycolysis, respiration
glucokinase
ATP
ADP
depolarization
voltage-gated calcium channel
insulin release
storage granules
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Carrier molecules

- Drugs bind to such molecules to alter their transport ability.
- Responsible for transport of ions and small organic molecules between intracellular compartments, through cell membranes or in extracellular fluids.
- e.g. **Na pump (**Na+/K+ ATPase) blocked by digoxin.
- e.g. **dopamine transporter** blocked by cocaine.

Carrier molecules

Digoxin:

blocks Na efflux via **Na+/K+ pump** or **sodium- potassium pump (Na+/K+-ATPase**); used in the treatment of heart failure.

Cocaine:

- blocks transport or reuptake of (**catecholamines mainly dopamine**) at synaptic cleft.
- The dopamine transporter can no longer perform its reuptake function, and thus

What are the binding Forces between drugs and receptors?

- Ionic bond.
- Van-Dar-Waal.
- Hydrogen bond.
- Covalent bond.

Affinity

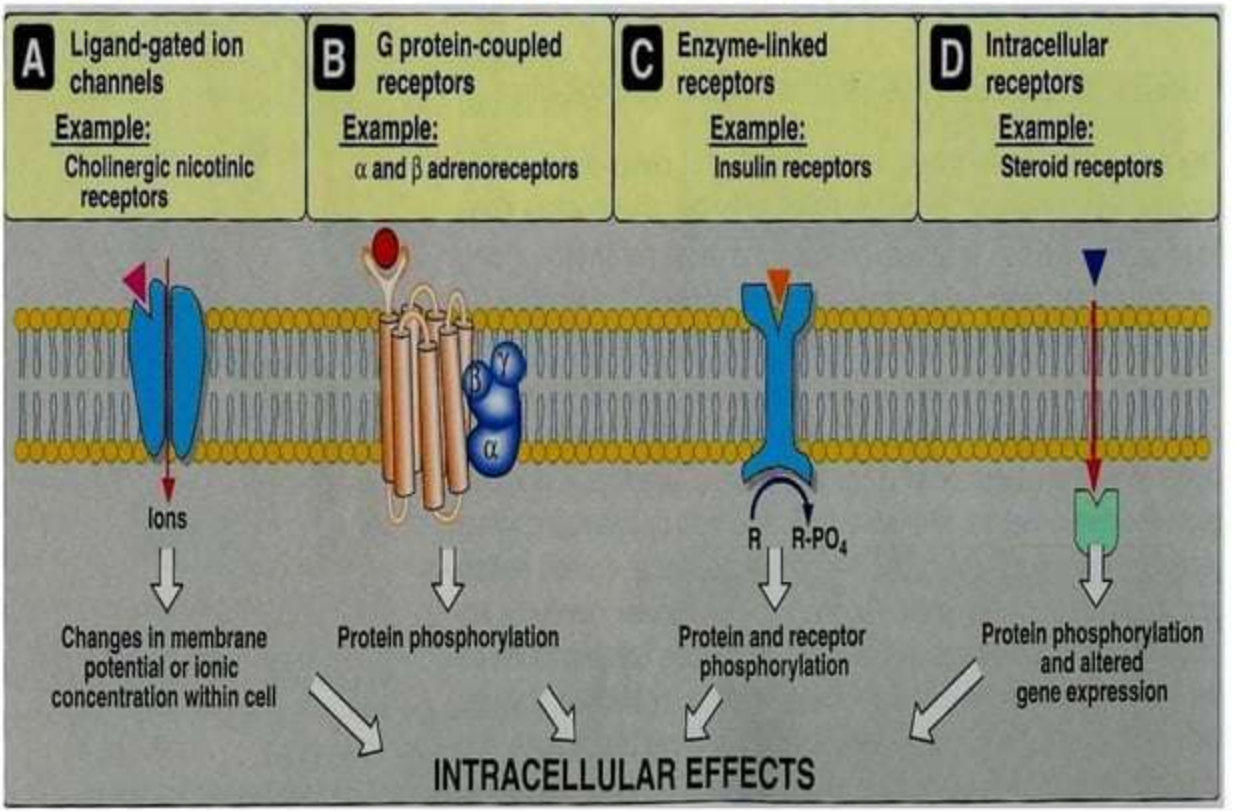
Ability of a drug to combine with the receptor.

D + R → D-R complex → Effect.

Efficacy (Intrinsic Activity)

- Capacity of a drug receptor complex (D-R) to produce an action.
- is the maximal response produced by a drug (E max).

SIGNALING MECHANISMS



What is Agonist?

What is full Agonist?

What is Partial Agonist?

What is Antagonist?

What are the types of Antagonist?

References:

1. B G Katzung. Basic and clinical pharmacology, 14th edition pp 20-40
2. Lippincott illustrated reviews pharmacology, 7th edition pp 23-36
3. Katzung and Trevor's pharmacology examination and board review pp 16-25

Thank you

Adapt it with your needs and it will capture all the audience attention.