PHARMACODYNAMICS I

MECHANISMS OF DRUG ACTION

PROF. HANAN HAGAR

ILOS

- Identify different targets of drug action

Differentiate between their patterns of action; agonism versus antagonism

Elaborate on drug binding to receptors

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.

What are the mechanisms of drug action?

Drugs can produce their actions by:

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

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

What are the mechanisms of drug action?

Binding with biomolecules (Targets)

Protein targets for drug binding

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

Non receptor–mediated mechanisms

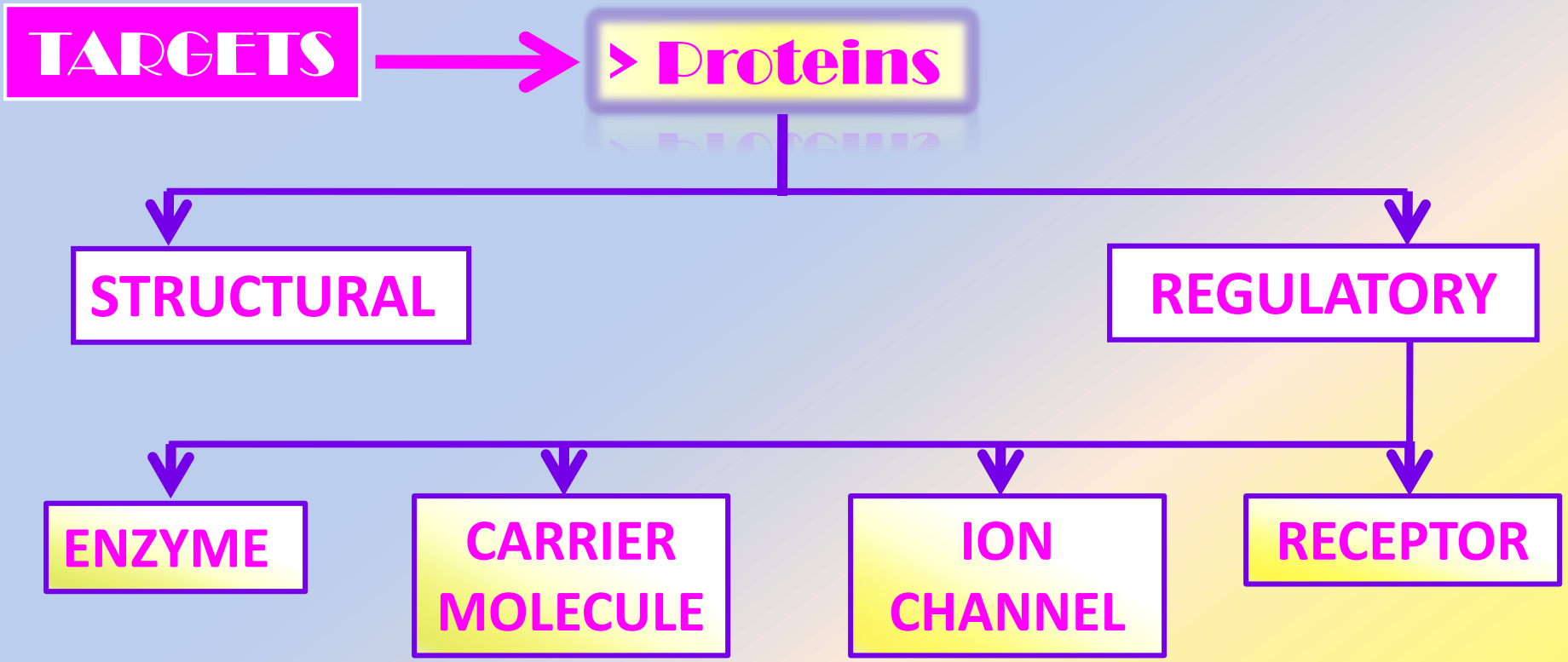
Chemical action

– Neutralization of gastric acidity by antacids.

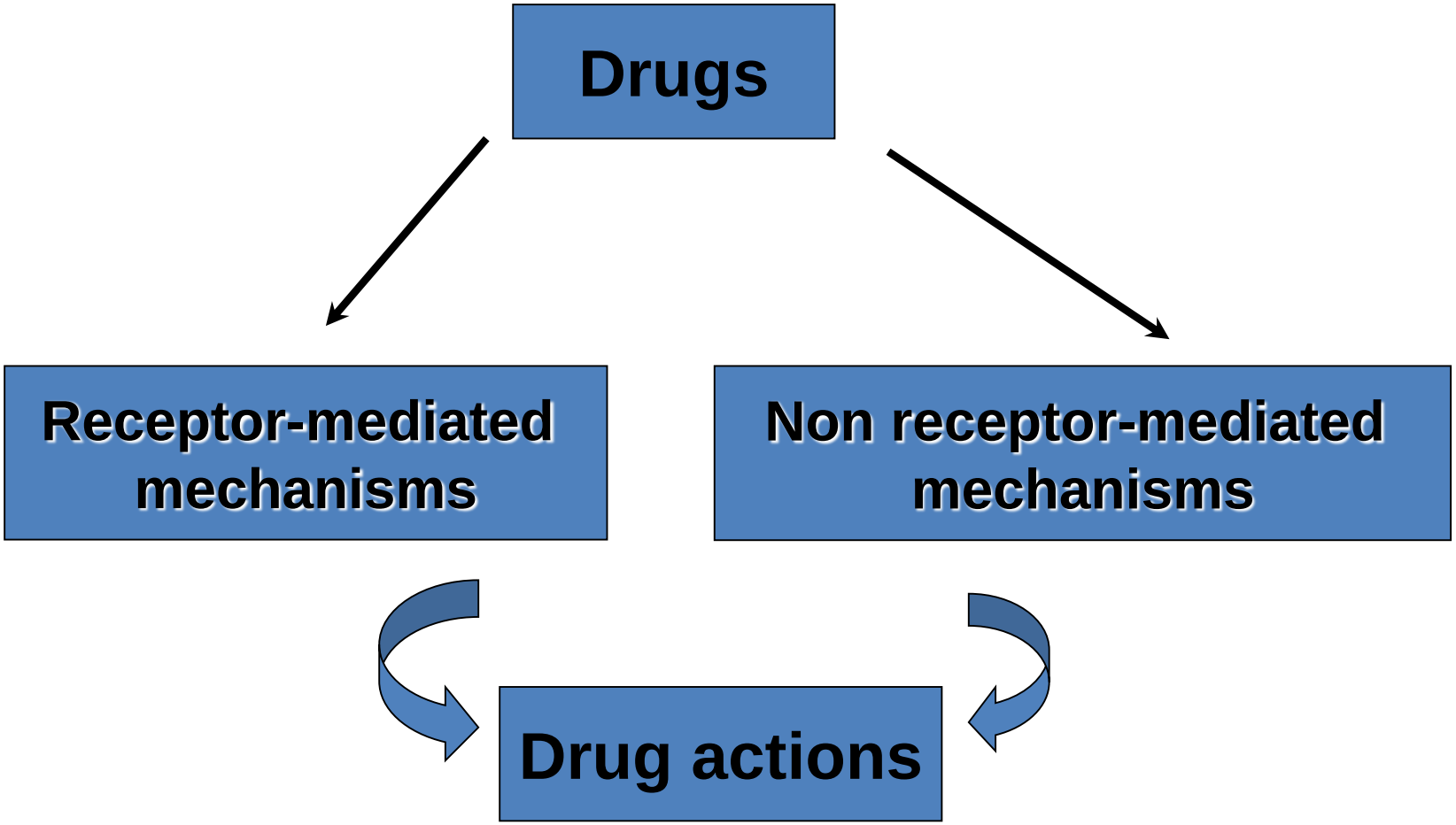
Physical action

– Osmotic diuretics.

– Purgatives used in treatment of constipation e.g. MgSO4


TARGETS
> Proteins
STRUCTURAL
REGULATORY
ENZYME
CARRIER MOLECULE
ION CHANNEL
RECEPTOR

What are targets for drug binding ?



Receptors

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

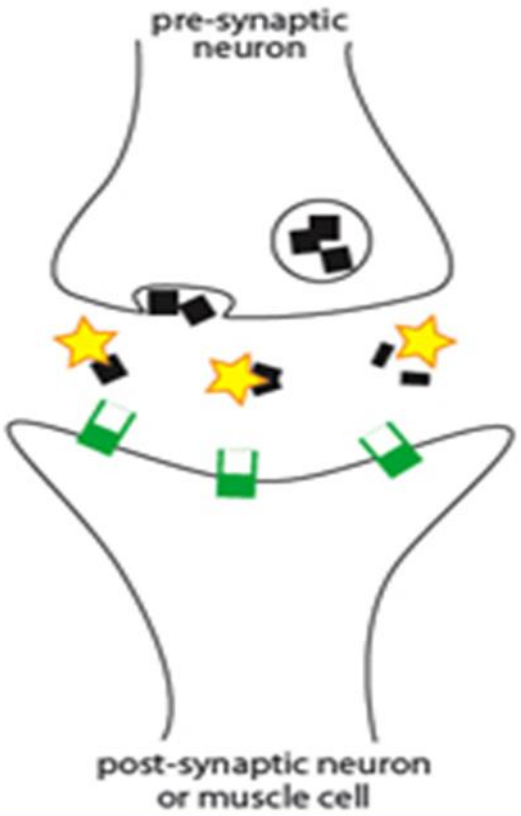
Where?

- Cell membrane.
- Nucleus.
- Cytoplasm.

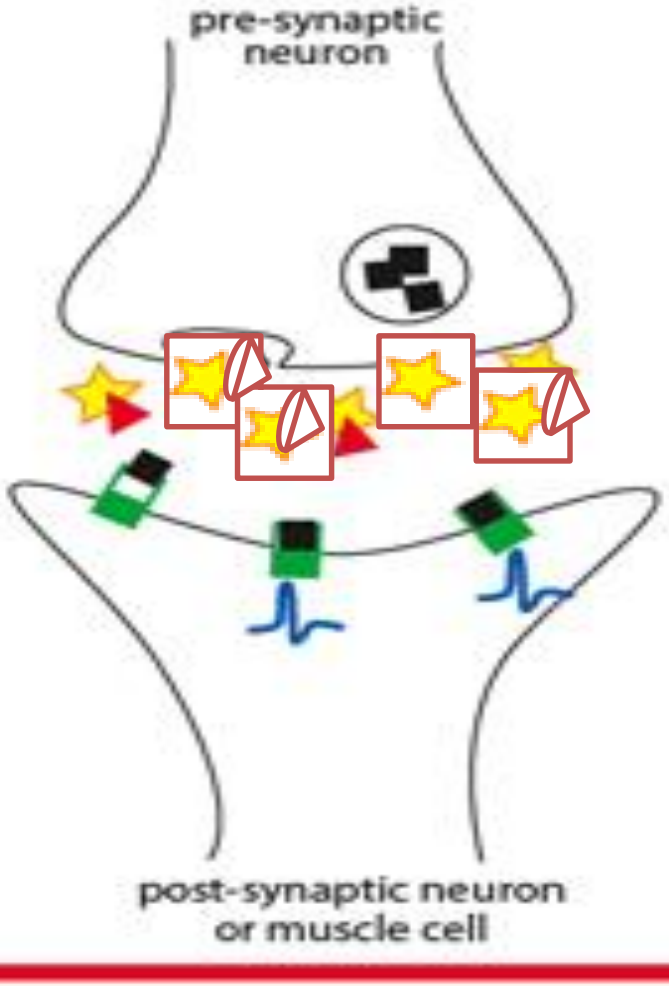
Enzymes

- The drug competes with the natural endogenous substrate for the enzyme.
- E.g. Anticholinesterases.
- Neostigmine **reversibly** compete with ACH for cholinesterase at motor end plate (neuromuscular junction.
- Organophosphates **irreversibly** competes with ACH for cholinesterase.

ACh Esterase STOPS signaling process



- ACh
- ACh Receptor
- Signal transmission
- ACh Esterase



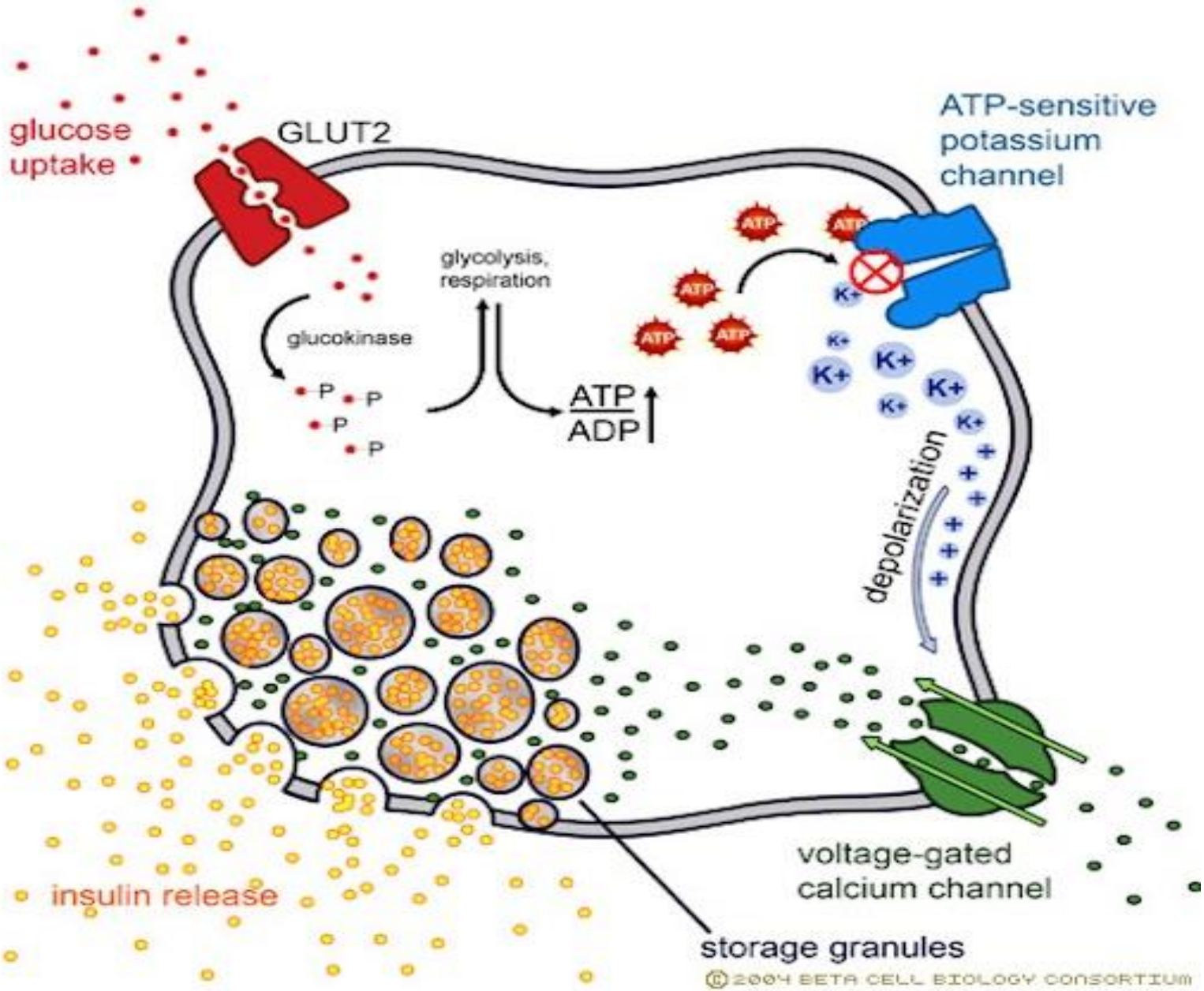
- ACh
- ACh Receptor
- Signal transmission
- ACh Esterase

Ion channels

- Drugs bind to alter channel function (by blockade or opening).
- Channels are responsible for influx or out-flux of ions through cell membranes.
- They are activated by alteration in action potential.
- e.g. local anesthetics: block Na influx through Na channel in nerve fibers (Na channel blockers).

Ion channels

- e.g. Sulfonylurea drugs (antidiabetic drugs): block K^+ outflux via the K channels in pancreatic beta cells resulting in 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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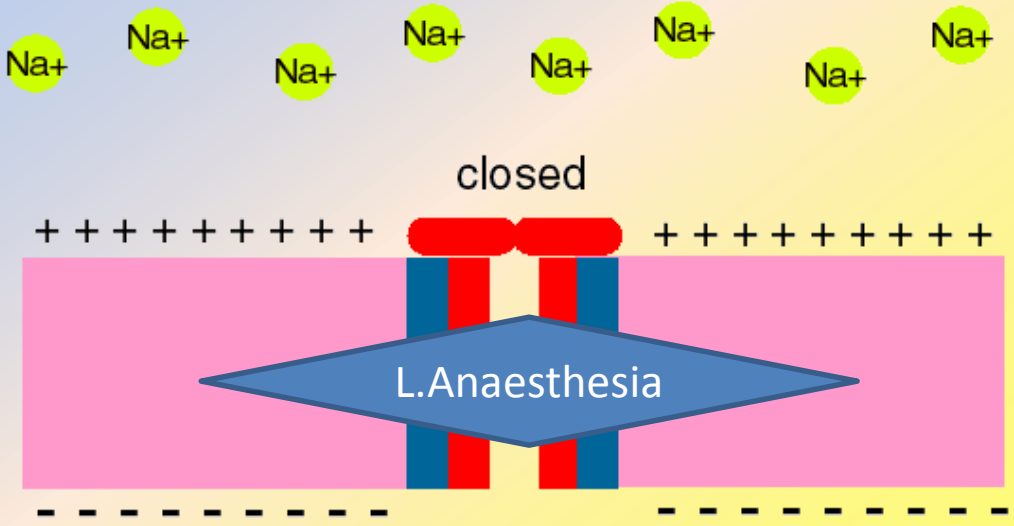
TARGETS → **> Proteins** — **REGULATORY**

ION CHANNEL

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



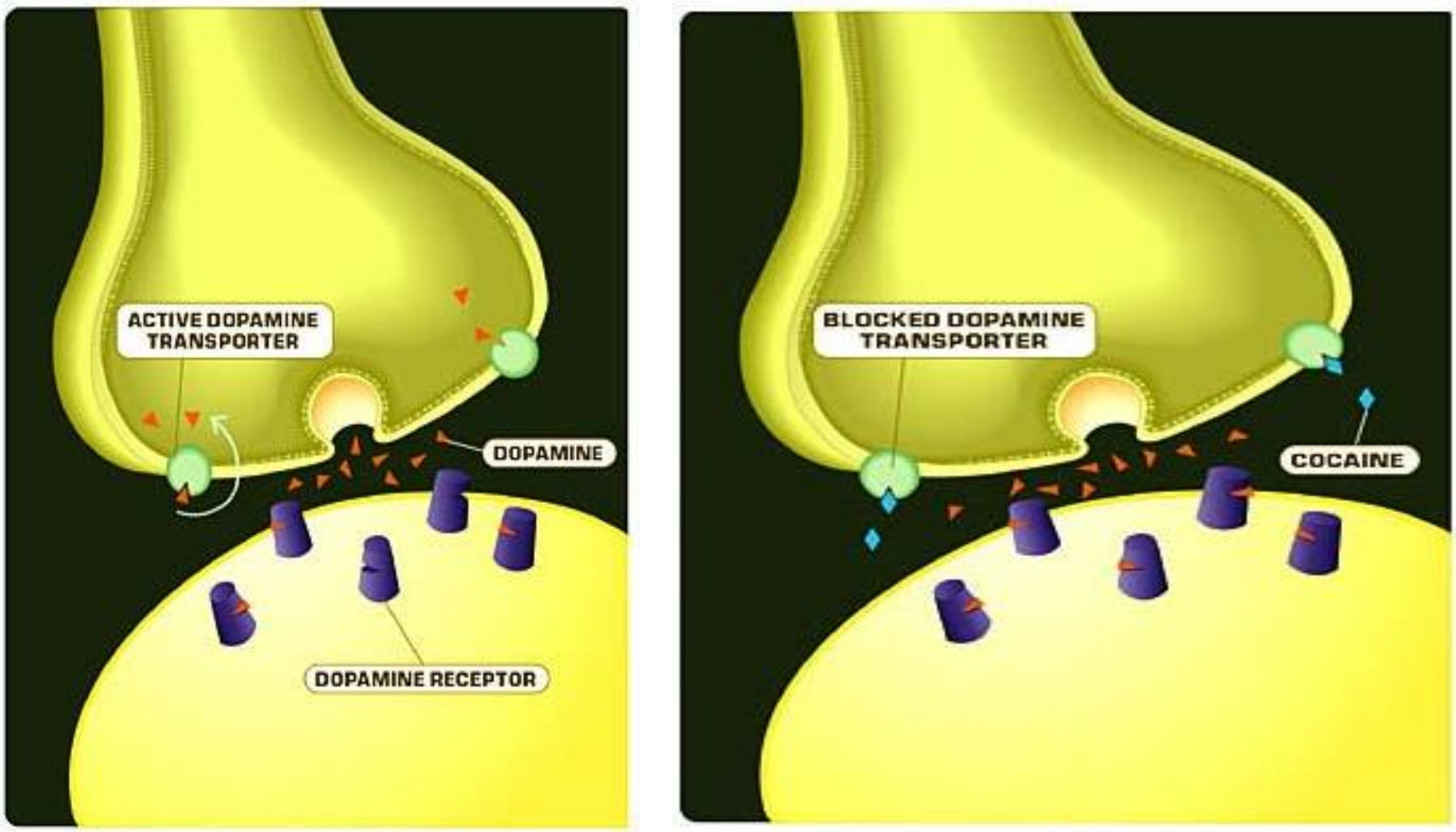
Carrier molecules

- The drug binds to such molecules altering 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+,K+-ATPase inhibitor
- **Digoxin** that block Na efflux via Na pump; used in treatment of heart failure.

Carrier molecules

- **Digoxin:** blocks Na efflux via **Na pump**; used in treatment of heart failure.
- **Cocaine:** blocks transport or reuptake of **catecholamines** (dopamine) at synaptic cleft
- The dopamine transporter can no longer perform its reuptake function, and thus dopamine accumulates in the synaptic cleft.

Effect of cocaine

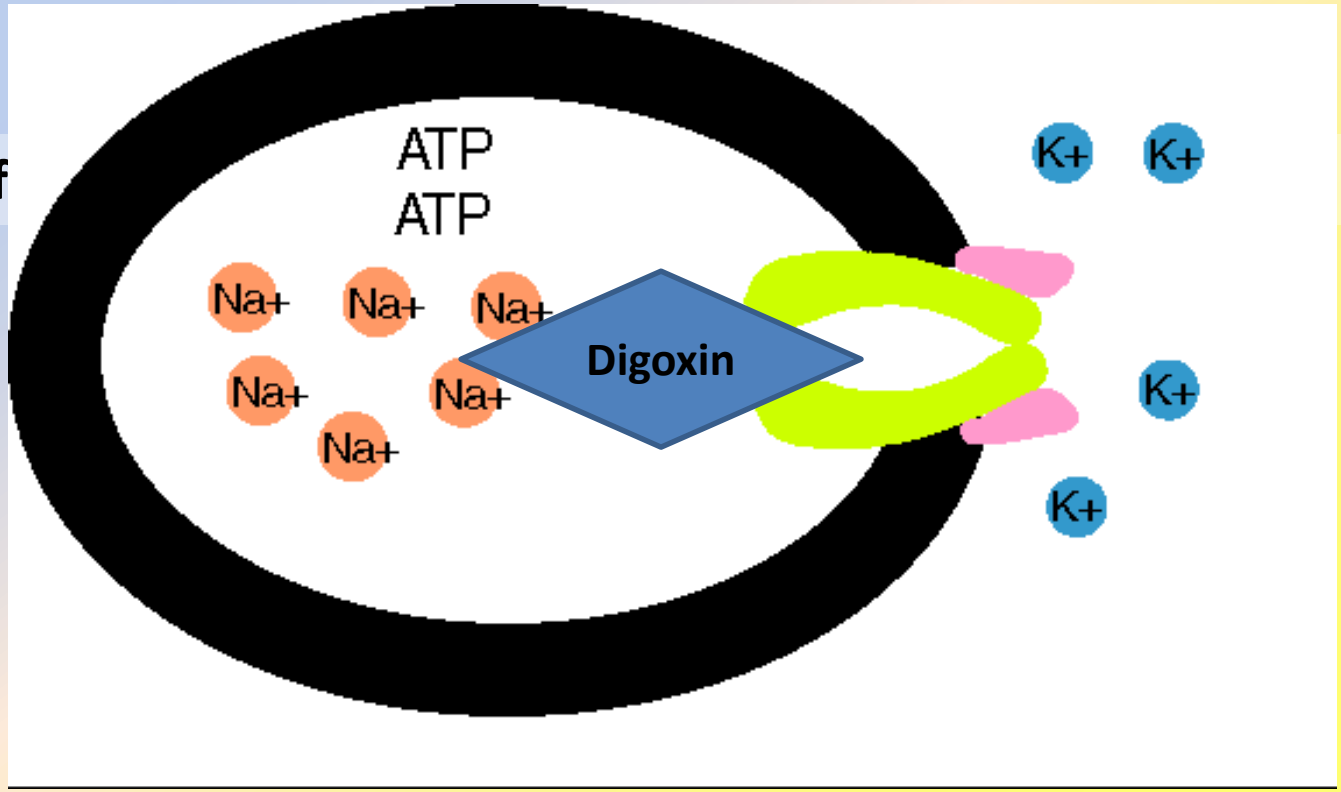


TARGETS → > Proteins

REGULATORY

CARRIER MOLECULE

Digoxin blocks eff



Structural proteins

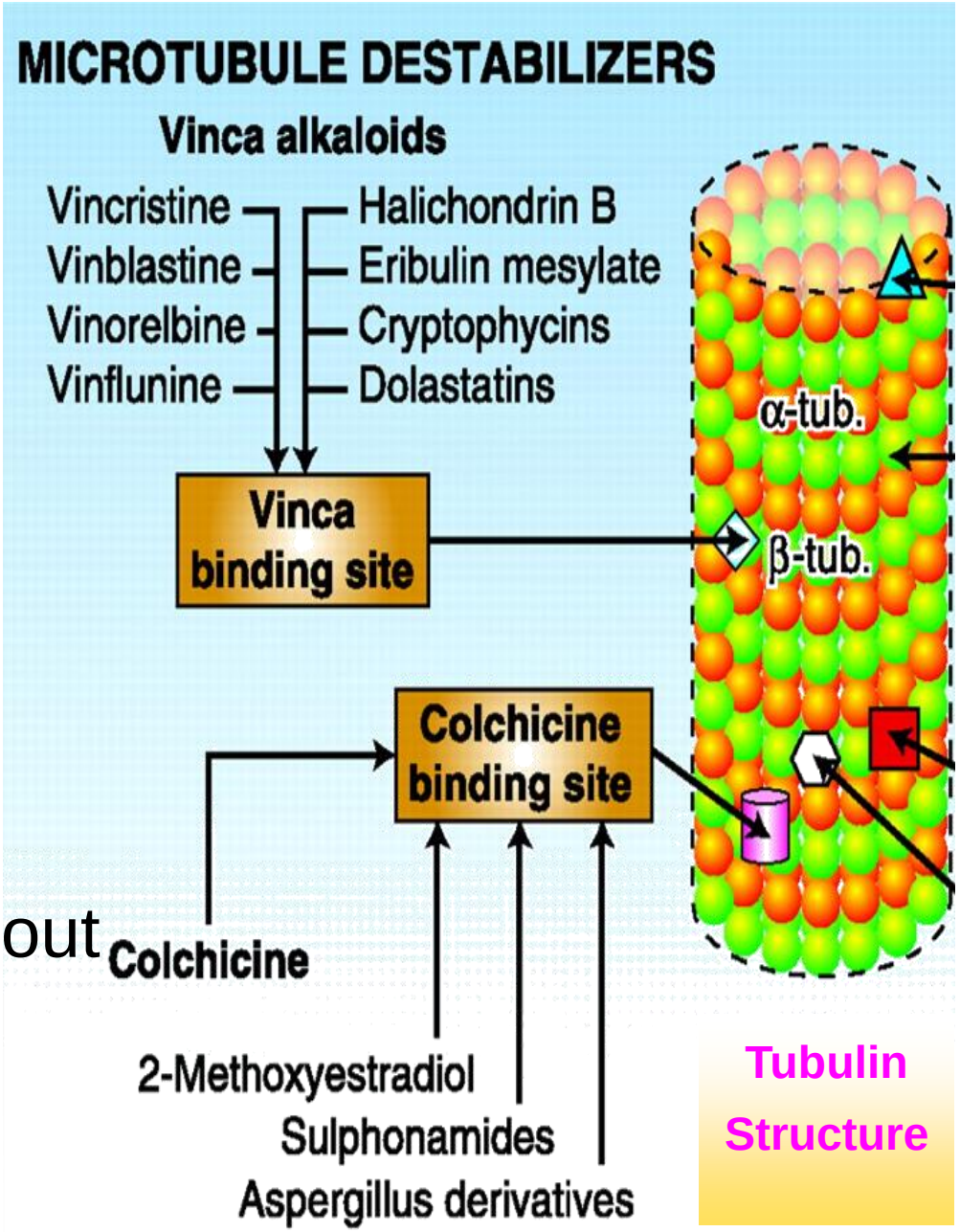
e.g. tubulin is target for:

Vincristine

- anticancer agent

Colchicine

- used in treatment of gout



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).**

Agonist

is a drug that combines with receptor and elicit a response (has affinity and efficacy).

Antagonist

is a drug that combines with a receptor without producing responses. It blocks the action of the agonist (has affinity but no or zero efficacy).

e.g. atropine

Agonist and Antagonist

Agonist

Full agonist.

Partial agonist.

Full Agonist

A drug that combines with its specific receptor to produce maximal effect by increasing its concentration (affinity & high efficacy).

e.g. acetylcholine (Ach).

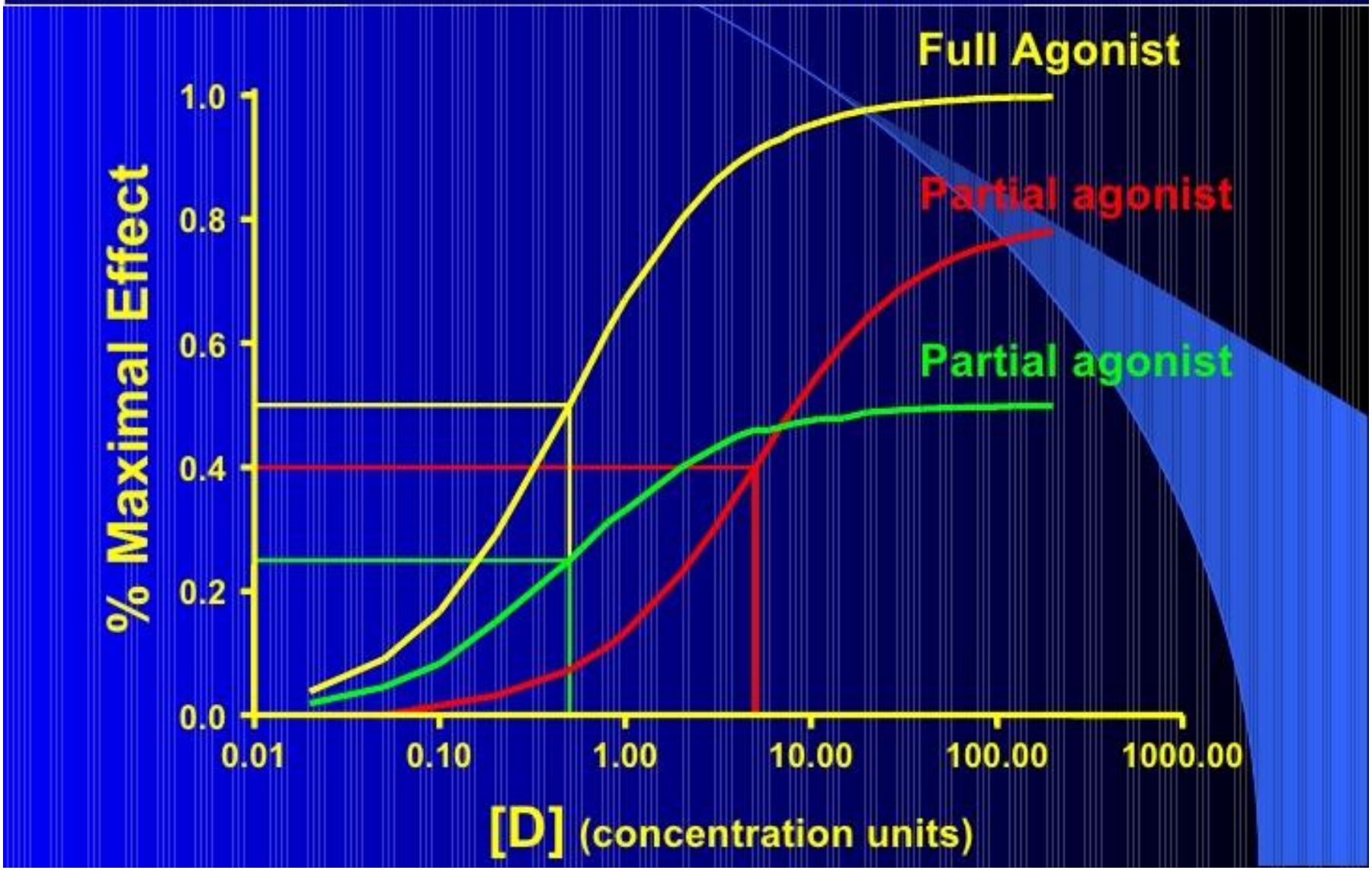
Partial Agonist

combines with its receptor & evokes a response as a full agonist but produces submaximal effect regardless of concentration (affinity & partial efficacy).

- e.g. pindolol
- a beta blocker which is a **partial agonist**, produces less decrease in heart rate than pure antagonists such as propranolol.

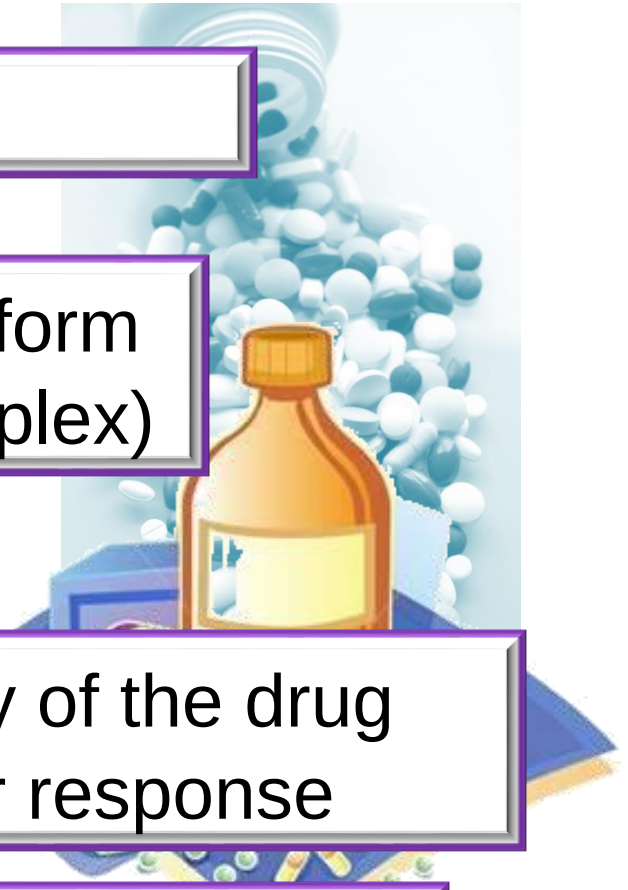
PARTIAL AGONISTS - EFFICACY

Even though drugs may occupy the same # of receptors, the magnitude of their effects may differ.



TERMS DEFINITIONS

Affinity is the capacity of a drug to form a complex with the receptor(DR complex)

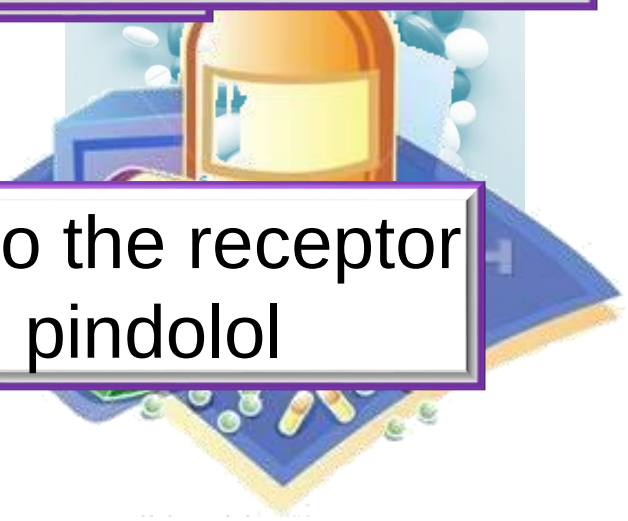


Efficacy(Intrinsic activity) the ability of the drug once bound to the receptor to trigger response

The value of intrinsic activity ranges from 0 to 1

TERMS DEFINITIONS

Full agonist having a full affinity to the receptor and a maximal intrinsic activity (1) e.g. acetylcholine



Partial agonist having a full affinity to the receptor but with low intrinsic activity (<1) e.g. pindolol

Antagonist having full affinity to the receptor but no intrinsic activity(0) e.g. atropine

GLUCOOK

PHARMACOLOGY