Molecular Mechanism of Drug Action

Lecture no. 5

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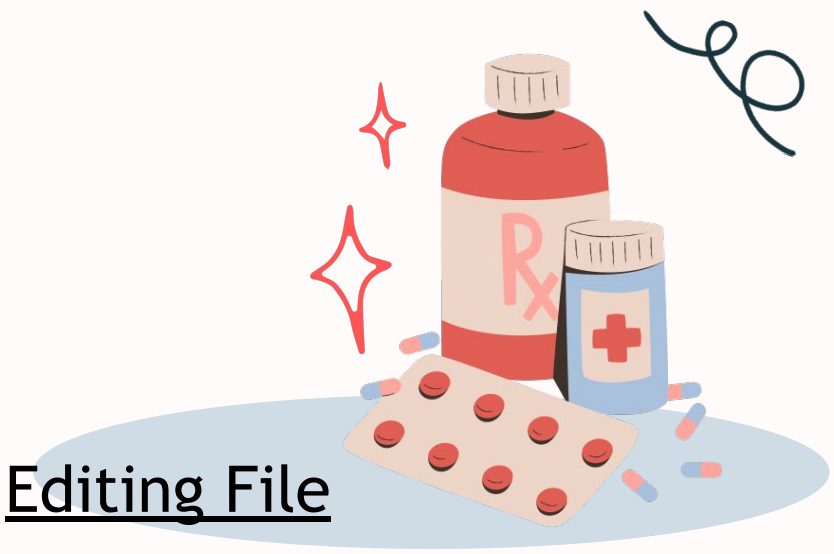

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Objectives

- Identifying different targets of drug action .
- Differentiate between their patterns of action; agonism vs 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.

Mechanisms of Drug Action

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

Receptor-Mediated Mechanisms (Binding with biomolecules)

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

(Receptors= Biomolecules =Targets)

- Targets are mostly protein in nature

Protein targets for drug binding :

- Physiological receptors
- Enzymes
- Ion channels
- Carriers
- structural proteins

Non Receptor-Mediated Mechanisms

➔ Physical / chemical properties of drugs.

Drugs can produce actions by :

- **Chemical actions:**

Neutralization (معادلة) of gastric acidity (حموضة المعدة) by antacids(magnesium milk).
acid+base=neutral water

- **Physical actions:**

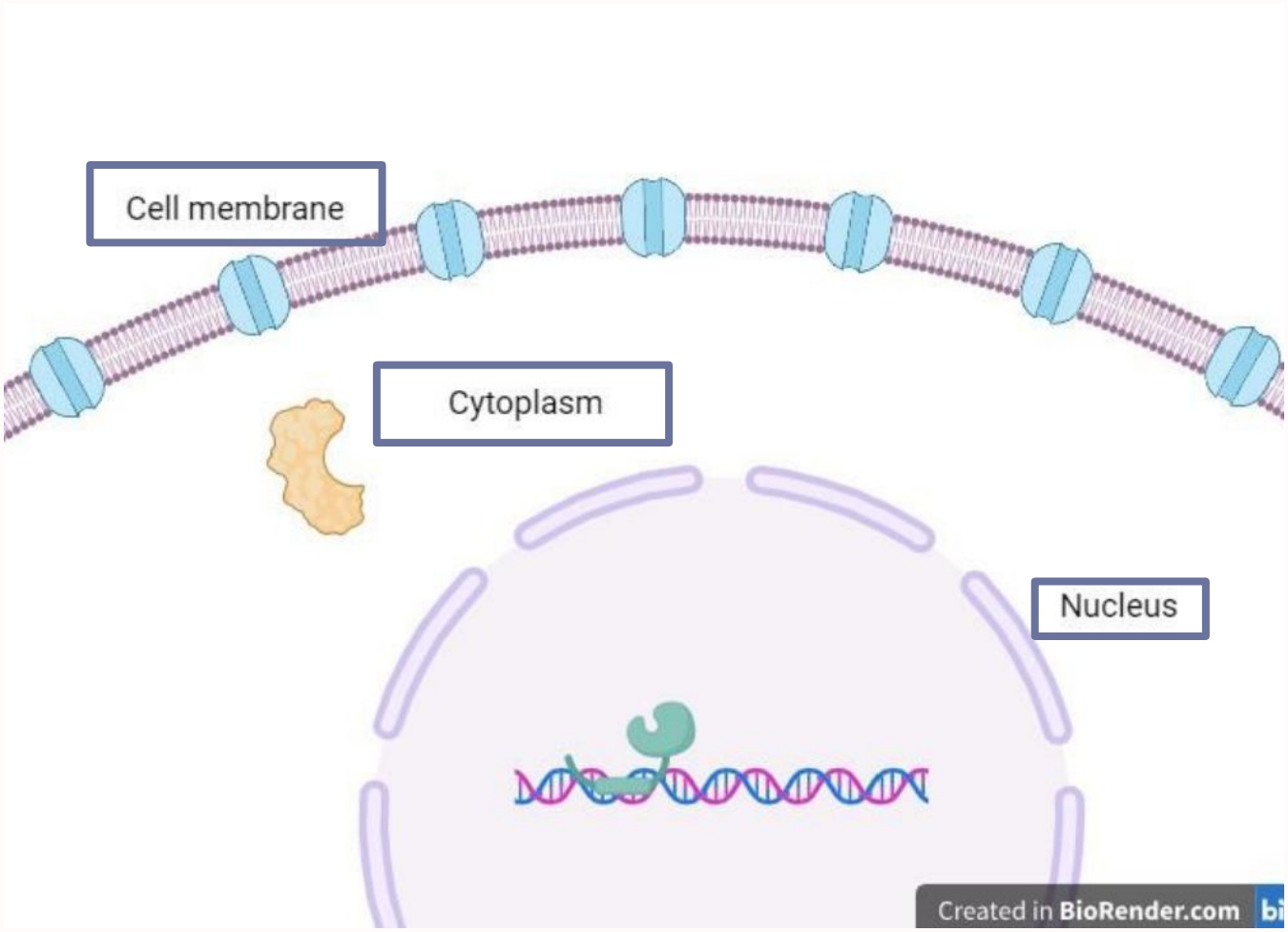
-Osmotic diuretics e.g. Mannitol.

-Purgatives (laxatives) used in the treatment of constipation e.g. $MgSO_4$.

What is a Receptor?

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

Where it is Located?



Targets for Drug Binding:

Receptor Mediated Mechanisms

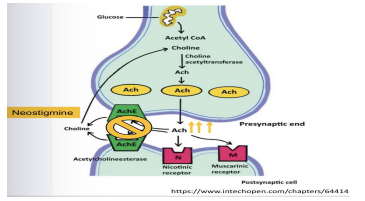
Protein targets for drug binding

Enzymes

The drug competes with the natural **endogenous** substrate for the enzyme.(إلهاء الإنزيم عن القيام بالوظيفة)

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

➔ **Neostigmine** compete with ACH for acetylcholinesterase enzymes at motor end plate (neuromuscular junction) .



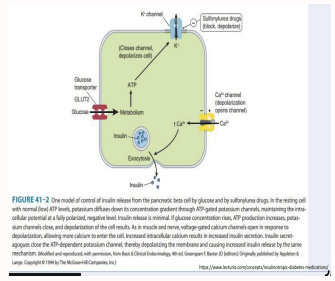
Ion channels (fastest)

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

E.g. Sulfonylurea drugs (anti-diabetic drugs) pic is in girls' slides'

e.g glipizide

- Block K+ outflux via the K+ channels in pancreatic *beta* cells → depolarisation and opening of Ca+ channels and insulin secretion.



Carrier molecules

-Drugs bind to such molecules to alter their transport ability.

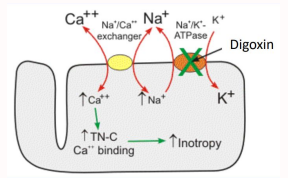
-Responsible for transport of ions and small organic molecules between intracellular compartments, through cell membranes or in extracellular fluids.

Examples:
- **Na+ pump (Na+/K+ ATPase)** blocked by digoxin
- **Dopamine** transporter blocked by cocaine

Digoxin

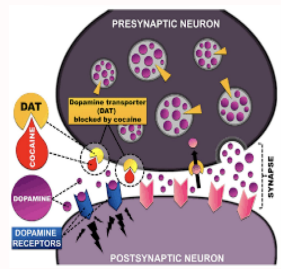
- Blocks Na+ efflux via Na+/k+ pump (Na+ / K+ -ATPase) → **high [Na]ic** and **less export of Ca+** → **stronger cardiac contraction** (Ca is imp. for contraction)

*used in the treatment of heart failure



Cocaine

-Blocks transport or reuptake of (catecholamines mainly dopamine) at synaptic cleft.
-inhibit dopamine reuptake via [DAT] → dopamine accumulates in the synaptic cleft → ***Euphoria***



Structural Proteins

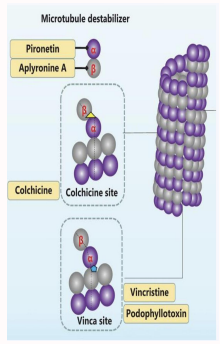
E.g.Tubulin is the required for microtubules formation (cytoskeleton).

Vincristine

Anticancer drug that kills cancerous cells by Inhibiting :
- microtubule formation - cell division

Colchicine

used in treatment of gout(النقرس) and FMF(حمى البحر المتوسط) .
binds to tubulin —>
- inhibits microtubule formation
- preventing neutrophil motility
- decreasing inflammation



Physiological receptors

are special target macromolecules that binds the drug and mediates its pharmacological actions

Located in:
- Cell Membrane
- Cytoplasm
- Nucleus

Drug - Receptor Interactions

Lock & Key Hypothesis

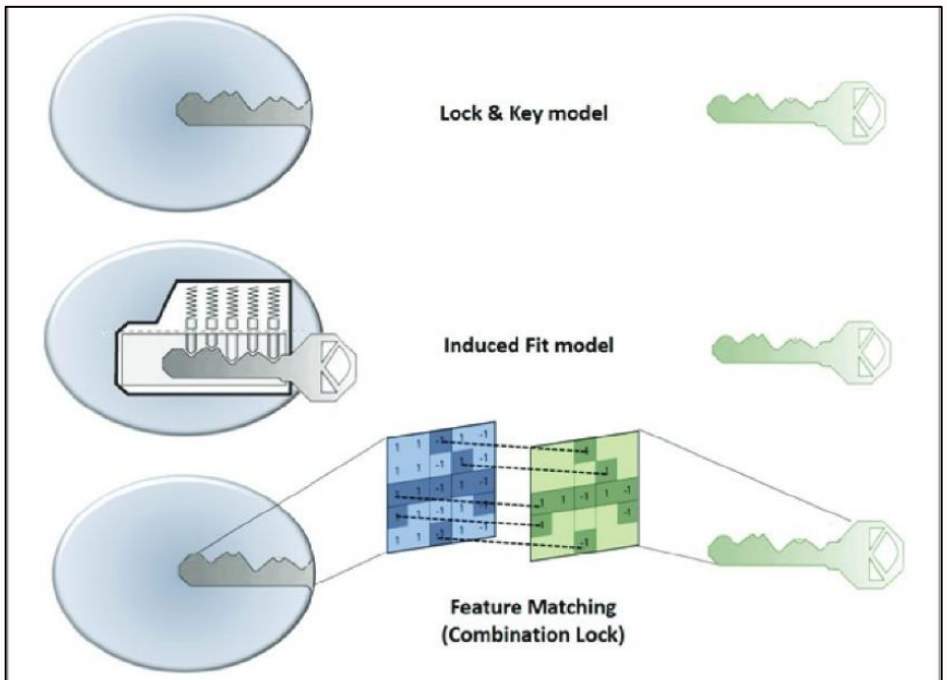
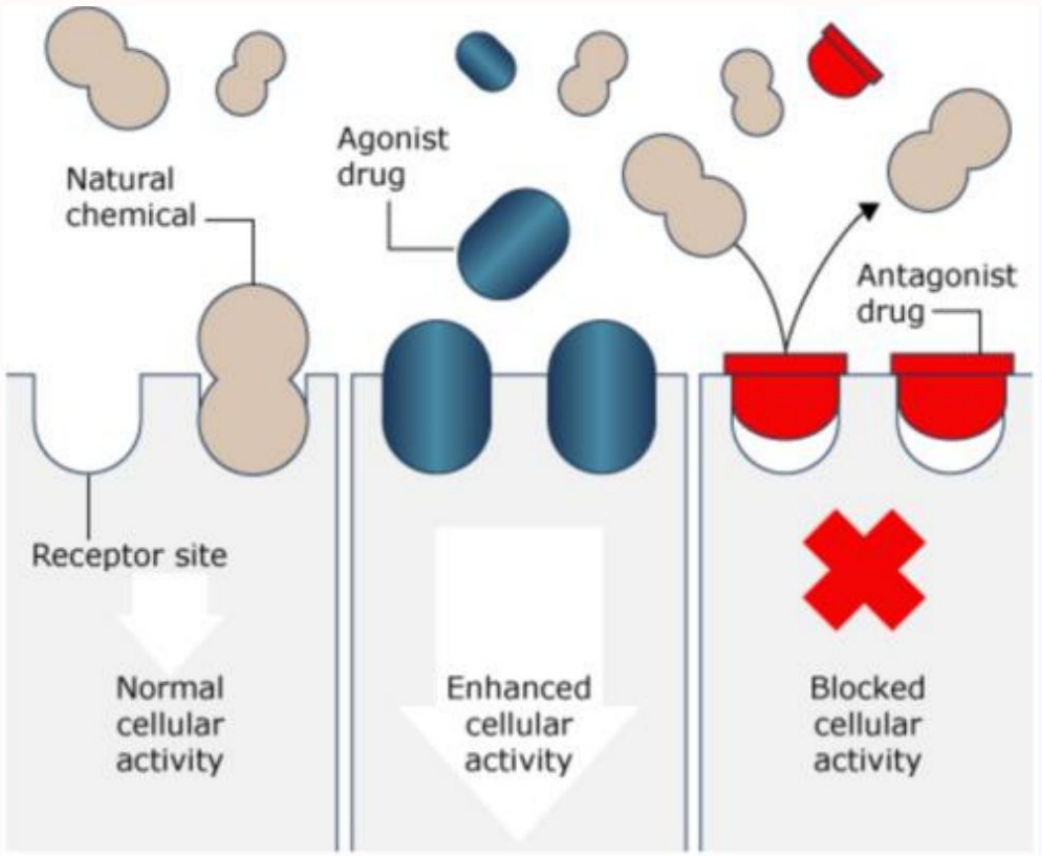
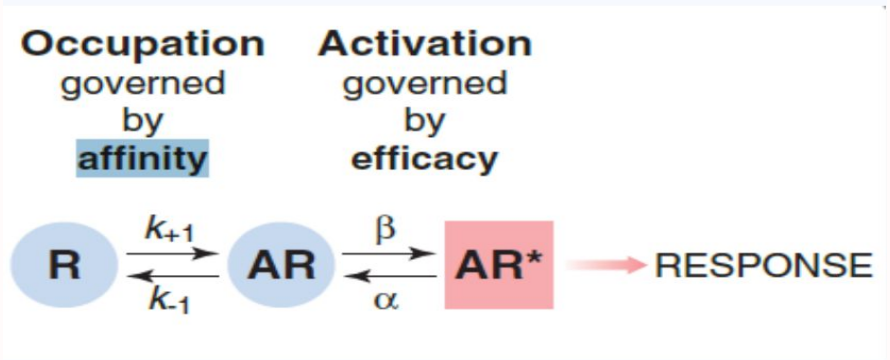


Figure 1: Illustration of 'Lock and Key' (top), Induced fit (middle) and Combination Lock (bottom) model of protein-ligand binding interaction.



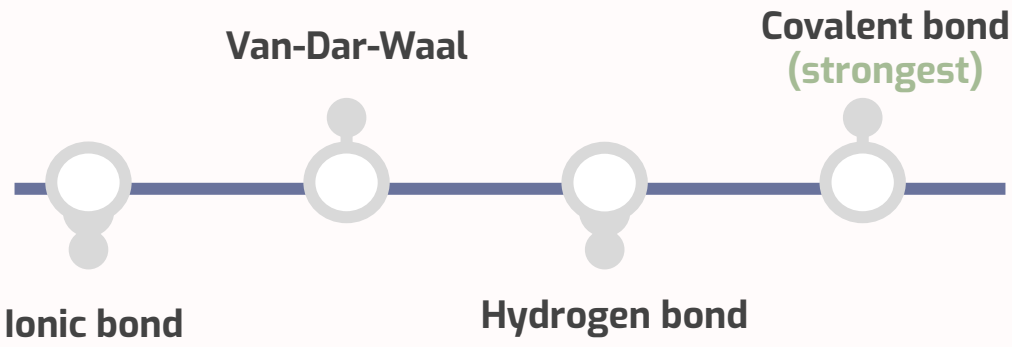
Extra info for understanding(found in next lecture)

Affinity	Efficacy
- Ability of a drug <u>to combine</u> with the receptor **OR** The capacity of a drug <u>to form a complex with the receptor</u> (DR complex). - Affinity ↑ drug selectivity ↑	- Capacity of a drug-receptor complex (D-R) <u>to produce an action</u> **OR** the ability of the drug once bound to the receptor <u>to trigger a response</u>.



R: Receptor, **A:** Drug, **AR*:** Drug-receptor complex

Binding Forces Between Drugs And Receptors



Drug-receptor Interactions

Agonist

- A drug that combines with receptor and elicits a response.

- It has **Affinity** and **Efficacy**.

- It has three types:

  - Full Agonist
  - Partial Agonist
  - Inverse Agonist

Antagonist

- A drug that decrease or the complete abolishment of the effect of one drug in the presence of another.

- A drug that combines with a receptor without producing responses.

- It blocks the action of the agonist.

- It has **affinity BUT NO efficacy** or zero efficacy.

- It has similar chemical structure to an agonist.

- Example: **atropine** blocks the action of Ach on muscarinic receptors.

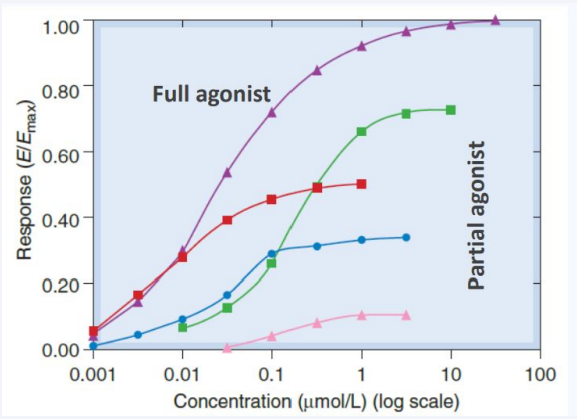
Drug-receptor Interactions - Agonist

Full Agonist

- A drug that combines with its specific receptor to produce maximal effect by **increasing** its concentration.

- It has Affinity & high Efficacy.

- e.g. acetylcholine (Ach) on **muscarinic** receptors.



Partial Agonist

- Combines with its receptor and evokes a response (submaximal effect) regardless of its concentration.

- It has Affinity & partial Efficacy.

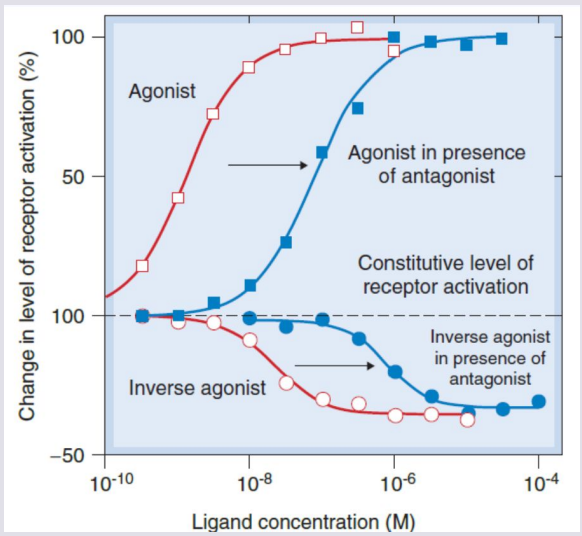
- Even though the drugs may combine with the same number of receptors, the magnitude they can produce may differ.

- e.g. Pindolol

- A **β blocker**, which is a partial agonist, produces less decrease in heart rate than pure antagonists such as propranolol.

Inverse agonist

- A drug that binds to the agonist binding site in the receptor and produces the opposite effect by suppressing spontaneous receptor signaling (intrinsic or constitutive activity).



Intrinsic activity:

In Females' Slides!!

The receptor by its own flipped between active and inactive status to produce a basal activity.

Drug-receptor Interactions - Antagonist

Chemical | Physical | Physiological | Pharmacokinetics | Pharmacodynamics

- Pharmacodynamics
  - Competitive
    - Irreversible
    - Reversible ⇄
  - Non-Competitive

Chemical

- Two drugs react chemically resulting in loss of activity of active drug [**No receptors are involved**].
  - **Dimercaprol** used as antidote - reduces heavy metal toxicity [**lead**]

Physical

- Inhibition by physical properties of another drug
  - **Activated charcoal** adsorbs ≠absorb poisons.

Physiological

- Two drugs a**ct on different receptors to produce opposing actions** in body, so tend to cancel each other's effect.
  - **Histamine** [Vasodilatation (↓ BP) & bronchoconstriction] and **Adrenaline** [Vasoconstriction (↑ BP) & bronchodilation].
  - **Adrenaline** is used in anaphylactic shock.

Pharmacokinetic

- The antagonist effectively **reduces the concentration** of the active drug at the site of action.
  - **Phenobarbitone** accelerates hepatic metabolism **warfarin**.(meaning warfarin will be broken down more easily so patient won't benefit from it)

Reversible Competitive Antagonist

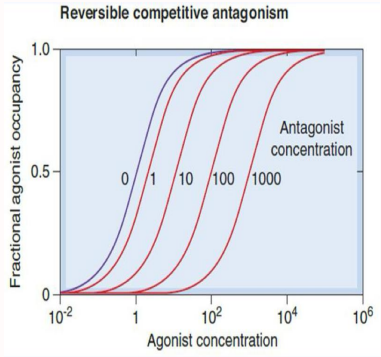
- Antagonist **readily dissociates** from the binding site of the agonist to the receptor

- Antagonism can be overcome <u>by increasing the concentration of agonists</u>, e.g. **Atropine and Ach.**

- Two drugs compete for the **same receptor** (only one is bound).

- The antagonist partially or completely prevents the pharmacological effect of the agonist.

- **Parallel shift** of the D-R curve to the right, <u>without</u> any <u>change</u> in <u>slope or maximum</u>.



Irreversible competitive Antagonist

- Antagonists form **stable, permanent/near permanent chemical bonds** with receptors.

- Inactivation lasts for duration of **receptor turnover** or its **de- novo synthesis** → explains its longevity of action.

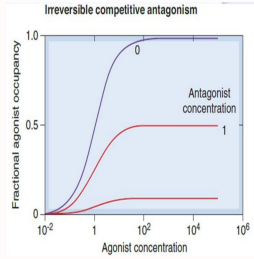
- Two drugs compete for the **<u>same receptor.</u>**

- The original response of the agonist **<u>can not be overcome by increasing the dose.</u>**

- <u>No parallel shift of D-R curve.</u>

- A **decrease in slope** and a **reduced maximal response** are obtained.

- E.g. **Phenoxybenzamine & Noradrenaline**



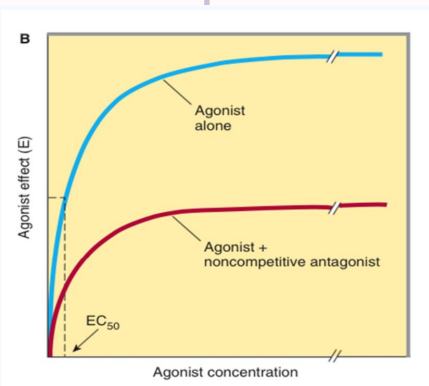
Non-Competitive Antagonist

- Agonist and Antagonist can be **bound simultaneously.**

- Antagonist blocks at some point the chain of events that ignite the response of the agonist.

- Antagonism **cannot be overcome by increasing the concentration of agonists.**

- e.g. **verapamil and noradrenaline**



Summary

Team 443:

Drug	Mechanism of Action
Antacids	Neutralization of gastric acidity
Neostigmine (reversible cholinesterase inhibitor)	competes with ACh for acetylcholinesterase enzyme at motor end plate (neuromuscular junction).
Sulphonylurea (anti diabetic)	block K+ outflux via the K channels in pancreatic beta cells resulting in opening of calcium channels and insulin secretion.
Digoxin (drug of heart failure)	blocks Na efflux via Na/K pump
Cocaine	blocks transport or reuptake of catecholamines (dopamine) at synaptic cleft causing euphoria
Vincristine	Anticancer agent
Colchicine	Drug for gout treatment

MCQs

Q1. Drug Receptors are ?			
a) micromolecules	b) macromolecules	c) none	d) both

Q2. Insulin is secreted when:			
a) Ca++ channel opens	b) K+ channel opens	c) K+ channel closes	d) a and c

Q3. The Study of biochemical and physiological effects of drugs and their mechanism of action, referred to:			
a) Pharmacodynamics	b) Pharmacokinetics	c) Pharmacology	d) None

Q4. Ability of a drug to combine with the receptor is?			
a) Affinity	b) Efficacy	c) Agonist	d) Antagonist

Q5. Sulfonylurea drugs is a treatment for?			
a) heart failure	b) cancer	c) gout	d) diabetes

Answers:

1) B
2) D
3) A
4) A
5) D

Compare between agonist and antagonist:

Slide 7

Where are receptors located?

cell membrane , cytoplasm and nucleus .

SAQS

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