Pharmacology
Team 437

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Mechanism Of Drug Action

Objectives:

- Identify different targets of drug action.
- Differentiate between their patterns of action;agonism versus antagonism.
- Elaborate on drug binding to receptors.

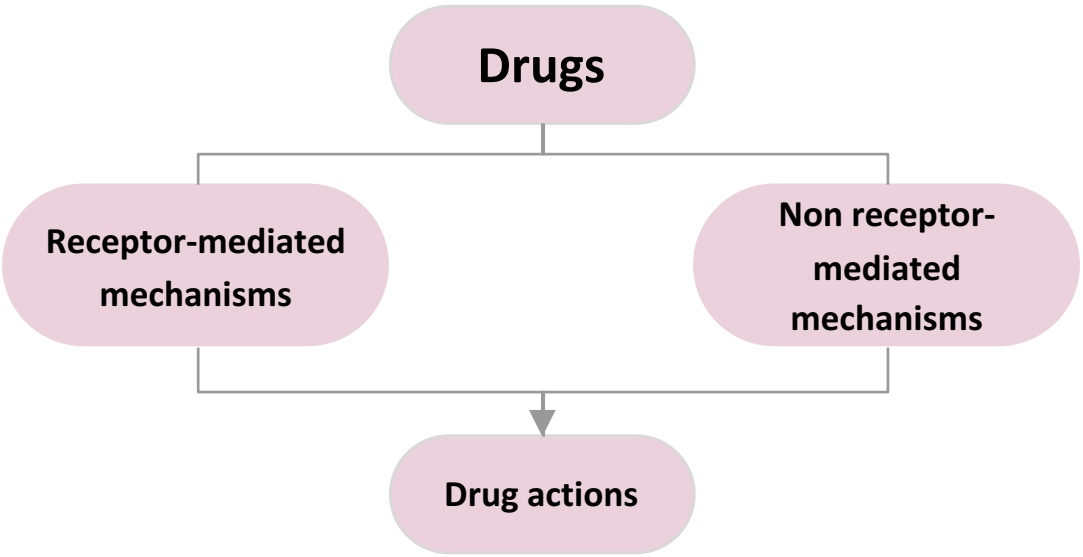
Titles Very important Terms Extra informations

Success Doesn't Come To You, You Go To It!

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 targets for drug binding?



What are the mechanisms of drug action?

Drugs can produce their actions by:

Binding with biomolecules (Targets) (Receptor-mediated mechanisms)	Non receptor-mediated mechanisms
• Biomolecules = Targets = Receptors • **Mostly protein** in nature (protein target).	**Physiochemical** properties of drugs.

Protein targets for drug binding:
• **Structural protein** (eg. cytoskeleton and microtubules)
• **Regulatory proteins:**
  ○ Physiological receptors (eg. nicotinic, muscarinic)
  ○ Enzymes
  ○ Ion channels
	Chemical action
	– Neutralization of gastric acidity by antacids. (antacids are bases)
	Physical action
	– Osmotic diuretics (drugs withdraw water so increases urine volume eg. mannitol)
	– Purgatives used in treatment of constipation e.g. MgSO4 *MgSO4 ليش؟ GIT يشد المويه في
	It gives softness for stool when we have a patient with constipation *
	*MgSO4 يدخل يسحب المويه ويطلع زي ماهو ما ما يتأثر ، فقط وظيفته يزيد المويةintestine.

Receptor-mediated mechanisms

Receptors: A Special target macromolecule that bind the drug and mediates its pharmacological actions.

Where are receptors located ? Cell membrane, Cytoplasm, Nucleus

Receptor-mediated mechanisms

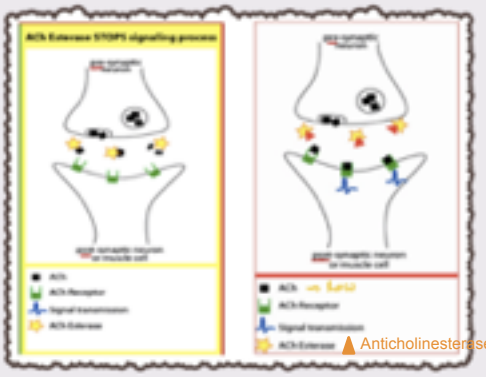
- **Regulatory proteins**: Receptors, Enzymes, Ion channels, Carrier molecules
- **Structural proteins**

1-Enzymes

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

E.g. **Anticholinesterases** *inhibits the action of acetylcholinesterases

- Reversible — Neostigmine — *4 hours
  - Compete with **ACH** for acetyl cholinesterase enzyme at motor end plate (**neuromuscular junction**)
  - *Neuromuscular junction= nicotinic receptor
  - *ACH الطبيعي يجلس دقيقتين ويكسره الانزايم واحنا نبيه يجلس فترة أطول فنستعمل Neostigmine اللي تركيبه يشبه الاسيتيل كولين ، ليش؟ عشان يلعب عالانزايم ويمسكه الانزايم بدال الاستيل كولين فبالتالي راح يجلس فترة أطول بالجسم، بدل دقيقتين راح يجلس ٤ ساعات ، ولأنه reversible بينفك بعد ٤ساعات ويتكسر الاستيل كولين.
- Irreversible — Organophosphates — *1 week
  - Compete with **ACH** for acetyl cholinesterase enzyme.
  - *less enzyme activity on ACh → less ACh broken down, thus it can work for longer periods of time.
  - * هنا راح يصير نفس اللي صار مع Neostigmine الفرق انه راح يجلس فترة أطول توصل لأسبوع ، ليش؟ لأنه irreversible حيمسك الانزايم **وماحيسيبه



2-Ion channels

Drugs bind to alter channel function (by opening or blockade).

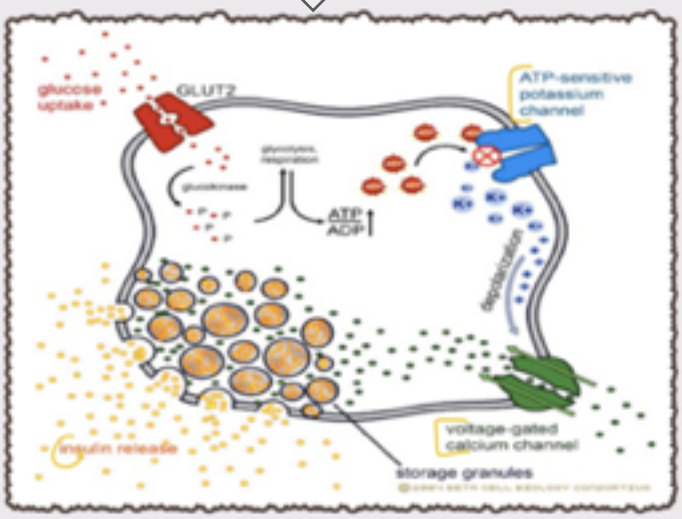
Channels are responsible for influx or out-flux of ions through cell membranes.

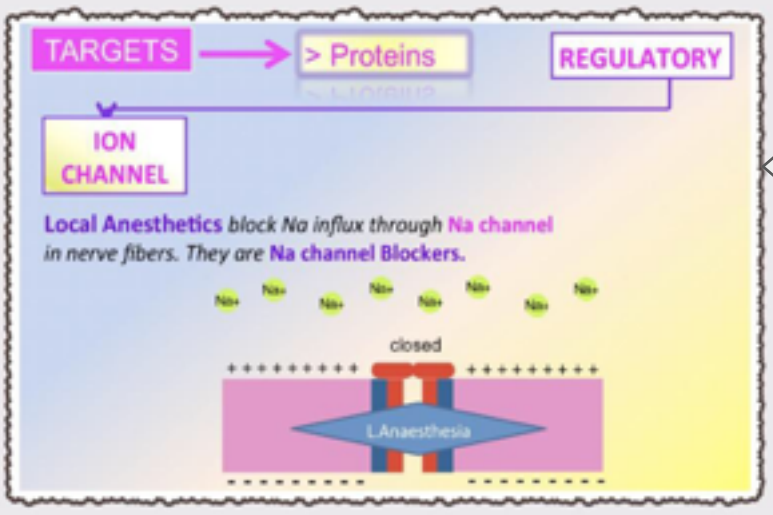
They are activated by alteration in action potential.

* تقفل الاحساس في المكان اللي حقنتها فيه Local anesthetics فالمكان راح يتخدر action potential=sensation في المكان مارح يكون فيه pain مهما اعمل NA channel لما أقفل

- E.g. 1- **Local anesthetics** — Block sodium (Na+) influx through Na channel in nerve fibers (**Na channel blockers**)
- E.g. 2- **Sulfonylurea drugs** (antidiabetic drugs) — Block potassium channels in pancreatic beta cells resulting in depolarization and opening of calcium channels and insulin secretion.

البنكرياس عندهم لما يشتغل بس مو بكفاءة عالية مرضى السكري type 2 فنعطيهم أدوية orally *antidiabetic drugs* تروح تسوي بلوك لقنوات البوتاسيوم فعطول قنوات الكالسيوم راح تنفتح وتدخل كالسيوم فيصير exocytosis فيصير secretion للأنسولين .





Continue: Receptor-mediated mechanisms

Receptor-mediated mechanisms

- Regulatory proteins
- Structural proteins

3-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. 1- **Na pump** (Na+/K+ ATPase) blocked by **Digoxin**.

Digoxin

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

E.g. 2- **Dopamine transporter** blocked by **Cocaine**.

Cocaine

Blocks transport or reuptake of (**catecholamines mainly dopamine**) at synaptic cleft.

The dopamine transporter can no longer perform its reuptake function, and thus **dopamine** accumulates in the **synaptic cleft** producing **euphoria**.

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

Tubulin is target for drugs as **anticancer** and **anti gout** drugs.

Vincristine (anticancer drug)

Kill cancerous cells by inhibiting microtubule formation and cell division.

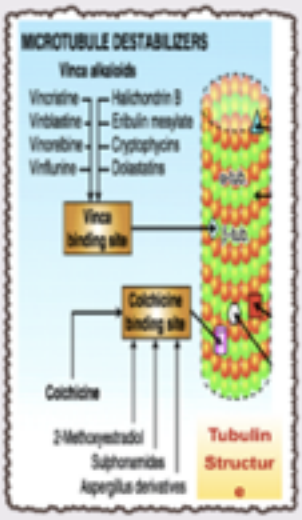
Vincristine kills the cancer cells,how? It inhibits the microtubules formation, how? يمسك بالتيوبيولين ويثبط تصنيع المايكروتيوبيولز ، ولما مايكون فيه مايكروتيوبيولز مارح تنقسم الخلايا فالكانسر مارح يزيد لأن الخلايا مارح تتكاثر

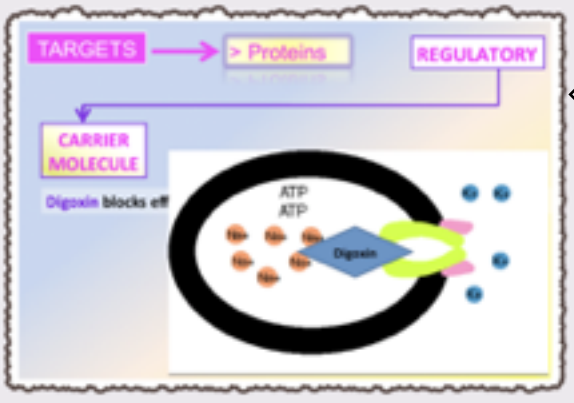
Colchicine (anti gout drug)

Used in treatment of gout.

Binds to tubulin and inhibits preventing neutrophil motility and decreasing inflammation.

Colchicine will decrease the inflammation by inhibiting the migration of neutrophils.. حركة النيوتروفيلس تعتمد عالسايتوسكيلتون وبهالحالة نبي نوقف الانفلاميشن مانبي النيوتروفيلس تجي للمكان فنوقف السبب اللي يخليها تتحرك وتوصل

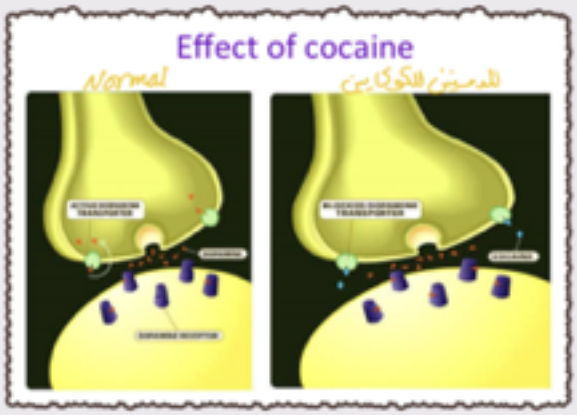




When the pump blocked by Digoxin it will cause more Ca inside the cell, then the contraction of these weak muscles will increase, then the pumping of blood will increase.

Binding forces between drugs and receptors :

- Ionic bond.
- Van-Dar-Waal.
- Hydrogen bond.
- Covalent bond. (The strongest, irreversible)



In the normal, the dopamine leave the neuron and some of the dopamine binds with the receptor (the Purple in the picture) and produce effect, and some of the dopamine will reuptake by the transporter (the green in the picture) . If the patient uses cocaine the cocaine will inhibit the transporter so the dopamine will not reuptake and all the receptors will be bind with dopamine which will give high dopamine effect.*436

Terms & Definitions

THE TERM	Definition	Other Definition	Explanation
Affinity	Ability of a drug to combine with the receptor. *binding ability	It's the capacity of a drug to form a complex with the receptors (DR complex)	D + R >> D - R Complex >> The Effect *D = drug , R = receptor
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).	-the ability of the drug once bound to the receptor to trigger response	-The value of intrinsic activity (efficacy) Ranges from 0 to 1 (the intrinsic activity of antagonist drugs is 0 e.g. atropine)
Agonist	is a drug that combines with receptor and elicit a response (has affinity and efficacy). e.g. acetylcholine (Ach) effect on muscarinic receptors.	---	كأنها قفل ومفتاحين، كل المفتاحين لهم نفس الشكل، لكن واحد هو المفتاح الأصلي والثاني مو المفتاح الأصلي، كلهم بيدخلون بفتحة القفل لكن الأصلي راح يفتح القفل واللي مو أصلي ما راح يفتح القفل لكن بيمنع المفتاح الأصلي من إنه يدخل بالقفل ويفتحه 463*
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 block the action of Ach on muscarinic receptors.	-having full affinity to the receptor but no intrinsic activity(0) e.g. atropine	
Full agonist	having a full affinity to the receptor and Affinity is the capacity of a drug to form 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	---	---

Agonist

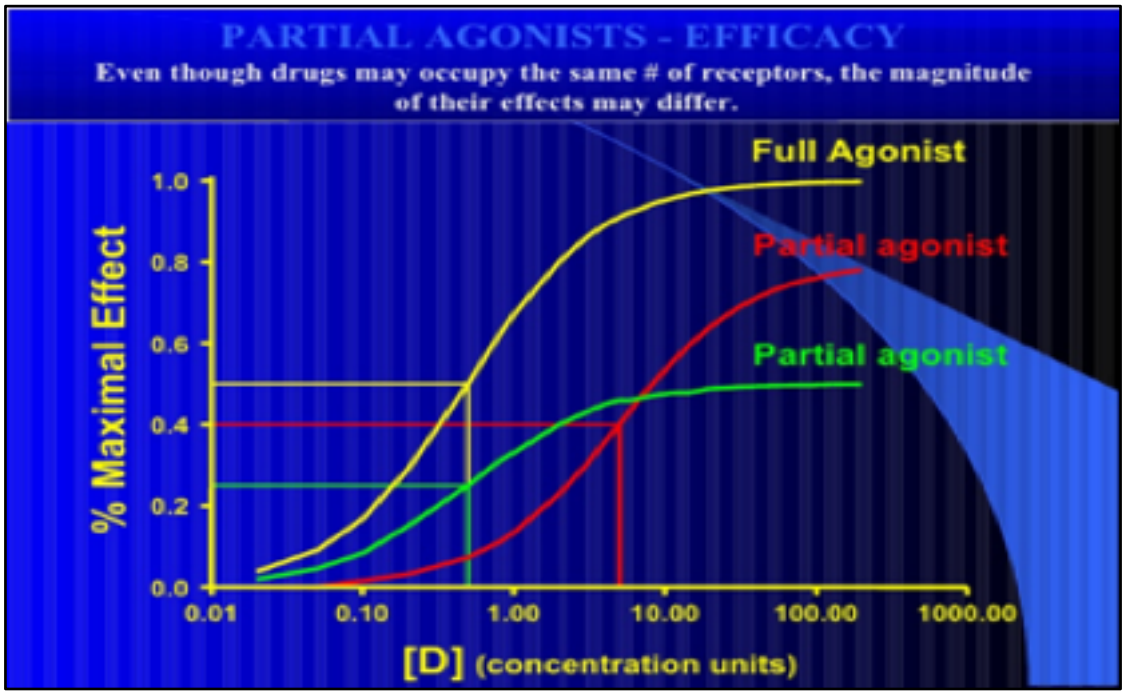
Full Agonist

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

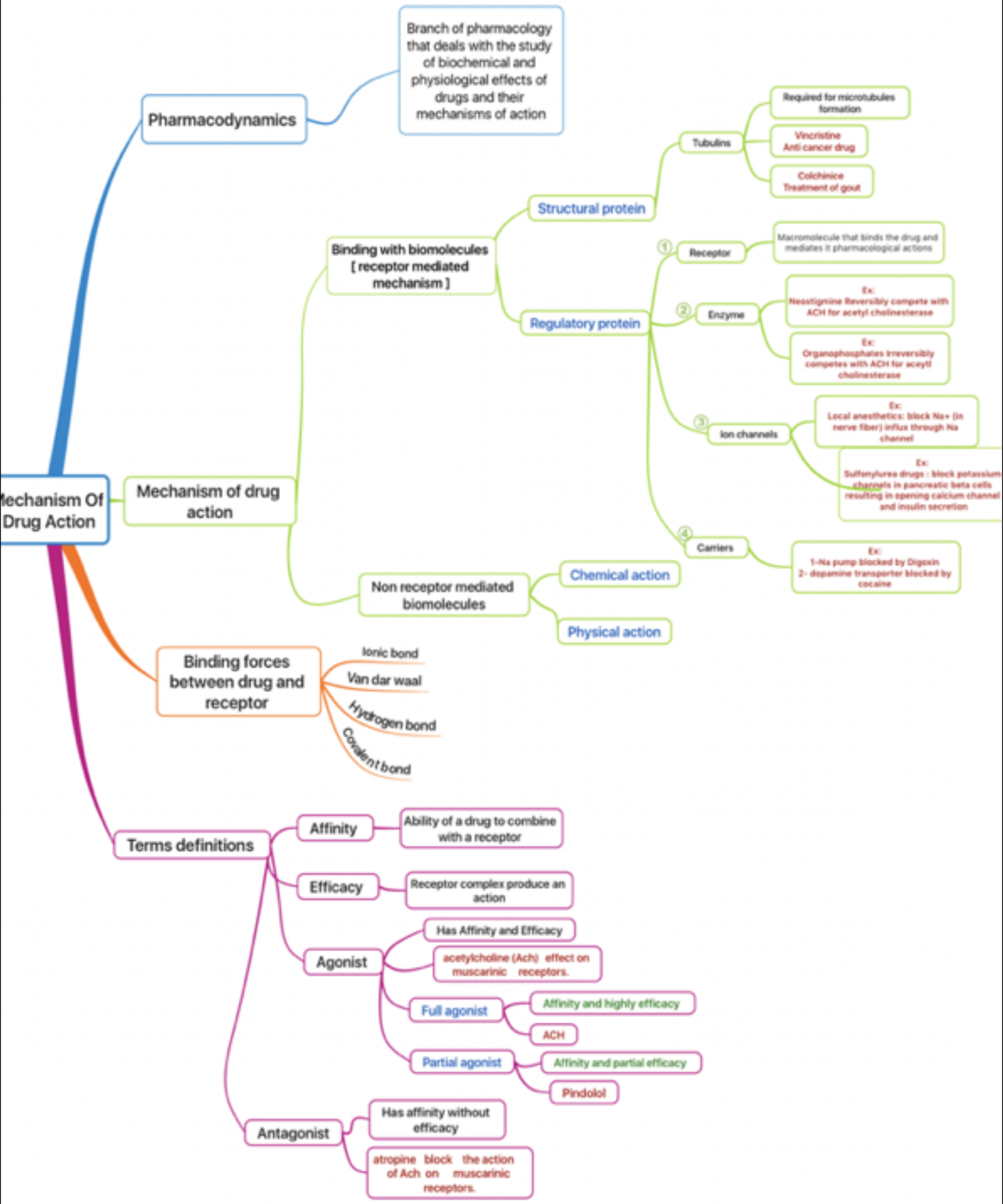
Partial Agonist

-combines with its receptor and 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.



Summary


Mechanism Of Drug Action
Pharmacodynamics
Branch of pharmacology that deals with the study of biochemical and physiological effects of drugs and their mechanisms of action
Mechanism of drug action
Binding with biomolecules [receptor mediated mechanism]
Structural protein
Tubulins
Required for microtubules formation
Vincristine Anti cancer drug
Colchinice Treatment of gout
Regulatory protein
1 Receptor
Macromolecule that binds the drug and mediates it pharmacological actions
2 Enzyme
Ex: Neostigmine Reversibly compete with ACH for acetyl cholinesterase
Ex: Organophosphates Irreversibly competes with ACH for aceytl cholinesterase
3 Ion channels
Ex: Local anesthetics: block Na+ (in nerve fiber) influx through Na channel
Ex: Sulfonylurea drugs : block potassium channels in pancreatic beta cells resulting in opening calcium channel and insulin secretion
4 Carriers
Ex: 1-Na pump blocked by Digoxin 2- dopamine transporter blocked by cocaine
Non receptor mediated biomolecules
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Binding forces between drug and receptor
Ionic bond
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Terms definitions
Affinity
Ability of a drug to combine with a receptor
Efficacy
Receptor complex produce an action
Agonist
Has Affinity and Efficacy
acetylcholine (Ach) effect on muscarinic receptors.
Full agonist
Affinity and highly efficacy
ACH
Partial agonist
Affinity and partial efficacy
Pindolol
Antagonist
Has affinity without efficacy
atropine block the action of Ach on muscarinic receptors.

MCQs

1-Neostigmine ..... compete with ACH:

A- reversibly
B- irreversibly
C-A&B
D-neither A or B

2/Organophosphates .....competes with ACH:

A- reversibly
B- irreversibly
C-A&B
D-neither A or B

3- the strongest bond is

A- Ionic bond
B- Van-Dar-Waal
C- Covalent bond
D- Hydrogen bond

4-Ability of a drug to combine with the receptor is called:

A- Efficacy
B-Affinity
C-Agonist
D-Antagonist

5-Which of the following is correct :

A- agonist has affinity only
B- agonist has affinity and efficacy
C- antagonist has affinity and efficacy
D-antagonist has efficacy only

6-A drug that combines with its specific receptor to produce maximal effect by increasing its concentration is called:

A-partial antagonist
B-partial agonist
C-full agonist
D-full antagonist

7-combines with its receptor & evokes a response as a full agonist but produces submaximal effect regardless of concentration:

A-partial antagonist
B-partial agonist
C-full agonist
D-full antagonist

Useful video
https://youtu.be/s0ubal521xI

Answers

1-A 2-B 3-C 4-B 5-B 6-C 7-B

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