PHARMACOLOGY

Modified no.7

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Pharmacodynamaics

- What the drug does to the body

Pharmacodynamaics

(MOA) Means mechanism of action
Drugs could either act through receptor or non-receptor mechanisms

1. Non-receptor mechanisms:

a. Physicochemical mechanisms:

- Osmotic diuretics —> Urea, Mnnitol
- Osmotic cathartics —> Lactulose
- Neutralizing effects —> Antacids
- Detergent effect —> Disinfectants, Oxidizing agents (anti bacterial or anti viral agents)
- ↓ excitability of membranes (stabilize cell membranes) Local anesthetics

Diuretics: drugs that increase urine output

Cathartics : laxatives, they reabsorb water into the intestinal lumin

Osmotic diuretics >>>>>>drugs which increase urine amount

They are taken orally and when they reach the kidney ,they will elevate the osmotic pressure within kidney tubules ,so water will move from the surrounding tissues into the kidney lumen and it will be excreted in urine

As the result ,we can use this drugs in case of excess water

Osmotic cathartics :they taken orally and elevate osmotic pressure within the intestinal lumen ,after that they will inhibit absorption water from lumen into intestinal cells or they draw water from salivating tissues into lumen of intestine ,each of these two options will lead to diarrhea effect

At the result ,we can use this drug in case of constipation

Neutralizing effects : for example, when we found hyperacidity in the stomach ,we will deal with this case by using antacid drugs

b. Interaction of drug with small molecules or ions:

- EDTA binds Pb^{++} with high affinity → ↑ exc.

Used in case of lead (Pb) poisoning

Penicillamine binds Cu^{++} → ↑ exc.

Dimercaprol (PAL); chelates arsenic, mercury, gold, bismuth

These drugs will use the mechanism of chelation which will make a detoxifying effect

c. Incorporation of drug into macromolecules:

Some of which are used as drug for cancer cells

Antimetabolites e.g. **5-bromouracil** is similar in its structure to thymine (replaces thymine during DNA synthesis → ↑ chromosomal breakage → ↑ anti-cancerous effect).
5-fluorouracil replaces uracil during RNA synthesis → faulty protein synthesis.
Ethionine replaces the a.a methionine → faulty protein

d. Enzyme inhibition (some consider enzymes being receptors to drugs):

Cyclooxygenase inhibitors NSAID's

Anti inflammatory effect

Cholinesterase inhibitors Neostigmine

Decarboxylase inhibitors Carbidopa

Bacterial dihydrofolate reductase inhibitor —> ex: Trimethoprim...etc

- The targeted enzymes might be in a certain microorganism in the body and not necessarily a human enzyme

- Enzyme inhibition drugs are considered as **non-receptor mediated** drugs

2. Receptor-mediated effects:

D + R ⇌ DR complex → response

Receptor: macromolecule or the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects

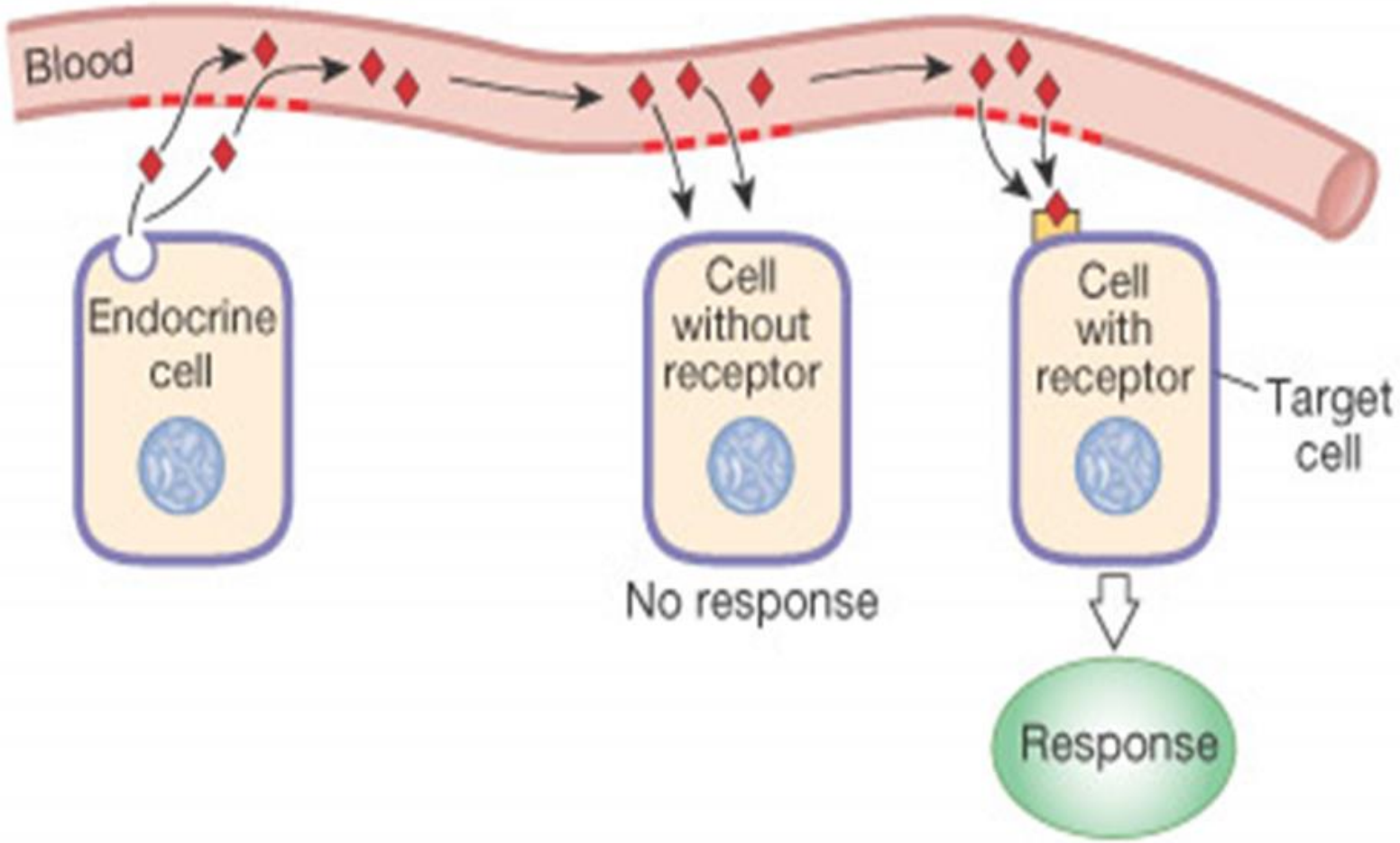
Receptors

- Found in target cells or tissues
- Determine the dose or concentration of drug required to form a significant no. of drug-receptor complexes
- No. of receptors may limit maximal effect a drug may produce
- Mediate effects of agonists and antagonists
- Responsible for selectivity of drug action

- Size, shape, electrical charge of drug determines binding to a receptor
- Changes in a drug's chemical structure can alter the affinity for the receptor where therapeutic and toxic effects may be altered

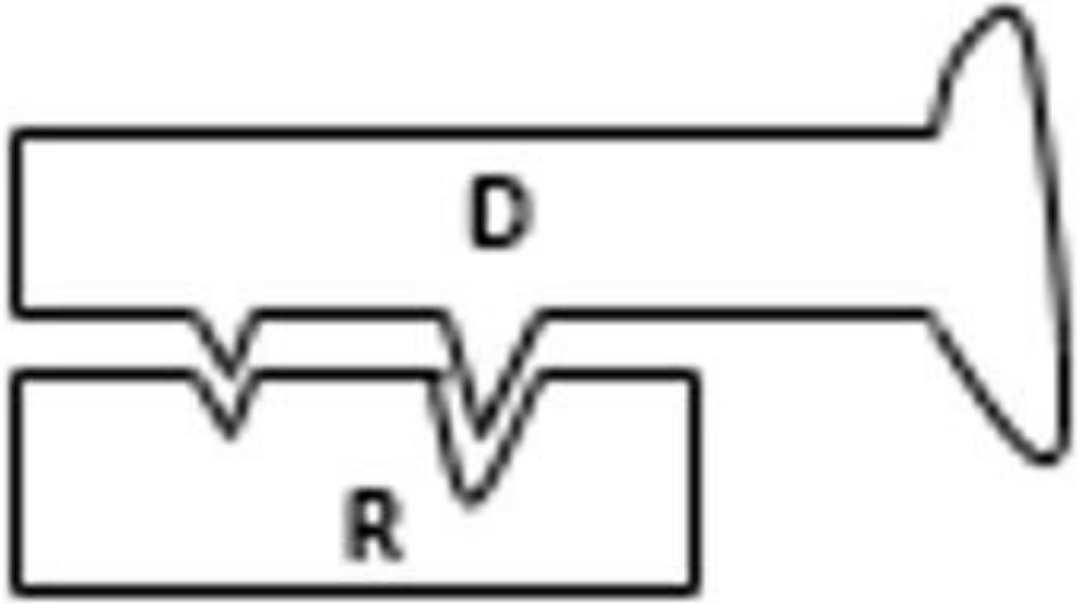
Drug moves into the target cell and interact with its receptor ,then the drug-receptor complex will be formed ,followed by number of interactions that happen inside the cell ,and finally produce the response

(a) Hormones are secreted by endocrine glands or cells into the blood. Only target cells with receptors for the hormone will respond to the signal.



Rational Drug Design

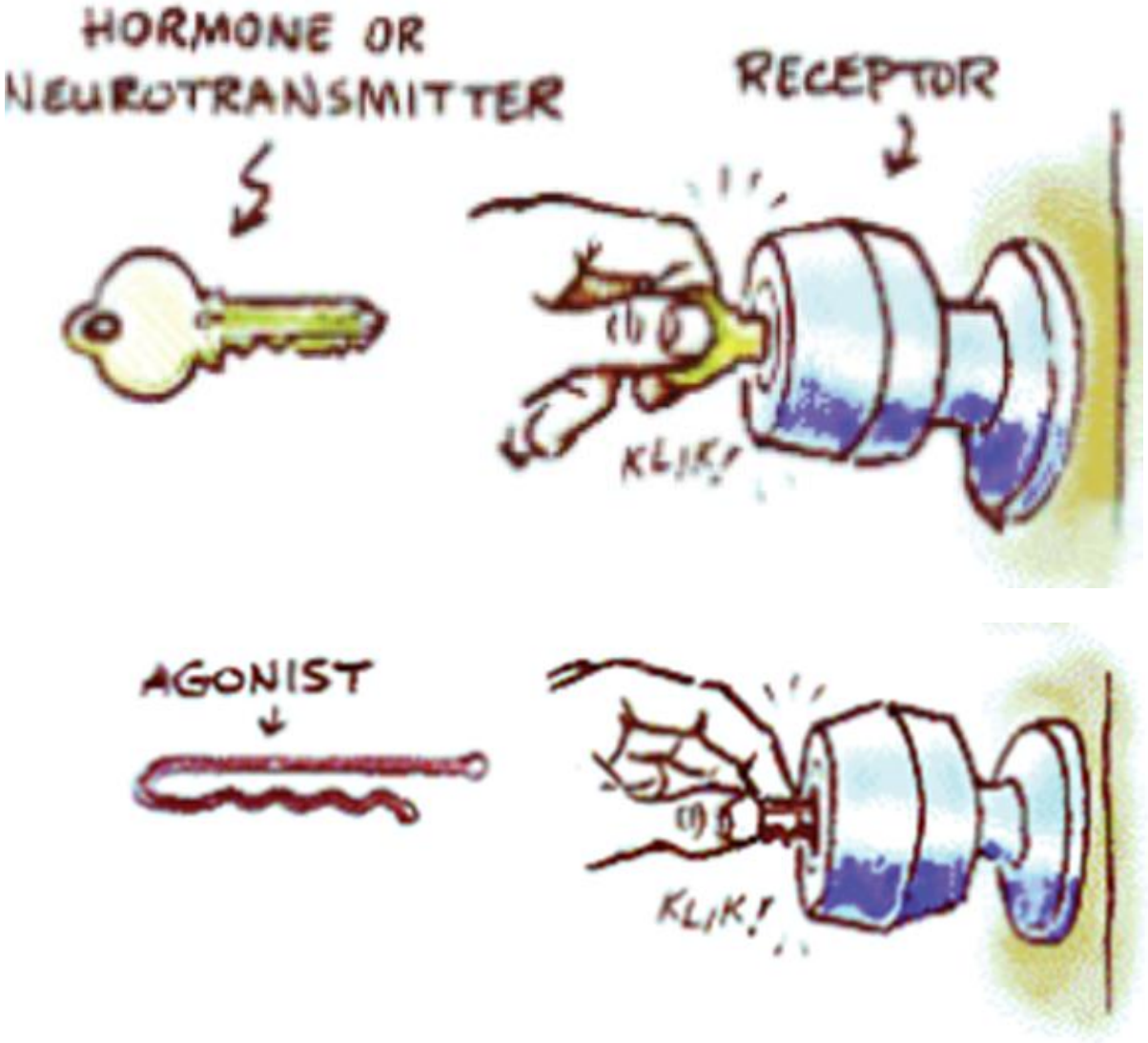
- Drugs are designed based on the structure of the receptor site
- Computers help us do this (match drug to receptor site to increase selectivity)



We have a lot of theories that explain the interaction drug with receptor ,but the best one is lock and key theory

The theory states the the drug structure should be complementary to the receptor

Lock and key theory


HORMONE OR
NEUROTRANSMITTER
RECEPTOR
KLIK!
AGONIST
KLIK!

Binding of D to R requires that:

- Both D and R should be close enough to each others
- The R has to be complementary in it's chemical structure to the D
- Binding of the D to the R should be reversible

The interaction of D with R depends on:

- Chemical structure of D and R
- Sites of loss
  e.g. proteins (plasma albumin); nucleic acids; melanin; glycosaminoglycans...etc)
- Intermolecular binding forces

Not all the bioavailability fraction of the dose that reach circulation will reach the site of action ,the drug may interact with plasma proteins and nucleic acids for example

Binding forces between D & R:

- Van der Waals:

No energy needed here to break it down

The weakest bond N…..N

The commonest (most universal) bond between the D & R

Close approximation between the D & R is required

The R chemical structure should be complementary to the D

- Hydrogen bond:

Stronger than Van der Waals

Reversible

No energy needed here to break it down

Occurs when a hydrogen connects 2 oxygens or 2 nitrogens

-O H……O=

-N H……N=

One from receptor and one from drug

- Ionic bond:

Stronger than hydrogen bond

Reversible

Occurs between ions of different charges

No energy needed here to break it down

Na^{+}-….. -Cl^{-}

- Covalent bond:

Irreversible bond

The least common bond between the D & its receptor

The strongest bond; energy is required to break it down

Occurs when the D and the R share a pair of electrons

Drug may interact with receptor by more than one force

Three aspects of drug-receptor function:

1. Receptors determine the quantitative relation between drug concentration and response

- This is based on receptor's affinity to bind and it's abundance in target cells or tissues
- Drug response depends on:
- **Affinity of drug for receptor**
- **Drug's efficacy (degree to which a drug is able to induce maximal effects)**

2. Receptors (as complex molecules) function as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs

3. Receptors determine the therapeutic and toxic effects of drugs in patients

The end of lecture 7