Pharmacology

Subject :

Lec no : 8

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وَقُل رَّبِّ زِدْنِي عِلْمًا

للوصول الى guidance الفارما و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

PHARMACODYNAMICS

Types of Drug Action:

- **Local or topical action**: drugs act on site of application e.g. ointment or eye drops.
- **Systemic or general action:** the drug acts after administration and distribution by circulation to various tissues. e.g. Aspirin
- **Reflex or remote action**: the drug acts locally at one site to produce reflex action elsewhere. e.g. Ammonia inhalation → irritation of nose → reflex stimulation of respiration

Mechanism (Mode) of Action of Drugs

- Drugs can induce a tissue response, initially through:

I. Body control systems (the regulatory proteins): involving interactions with:

(1) Receptors (2) Ion channels

(3) Enzymes (4) Carrier molecules

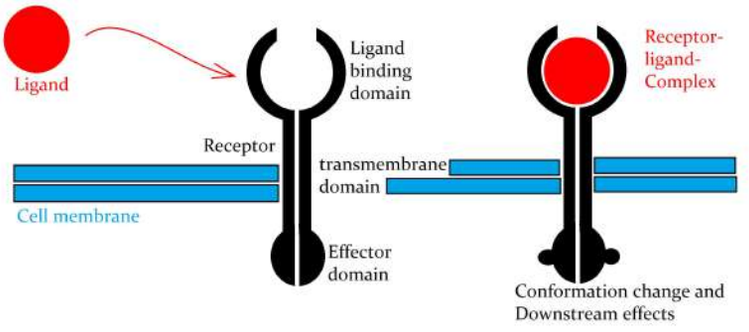
II. Other mechanisms:

(5) Subcellular structures (6) Genetic apparatus

(7) Physical mechanisms (8) Chemical mechanisms

1) Receptor-Mediated Mechanisms

- **Receptors** are specific cellular macromolecules (usually proteins) that interact with a ligand (**binding**) to produce a response.
- **Ligand:** any molecule that can combine with the receptor. A ligand that activates receptor is called **agonist**. A ligand that blocks the receptor is called **antagonist**



الـ R عم تحكيلها plasma membrane وهيك منها في السيتو بلازم

أو

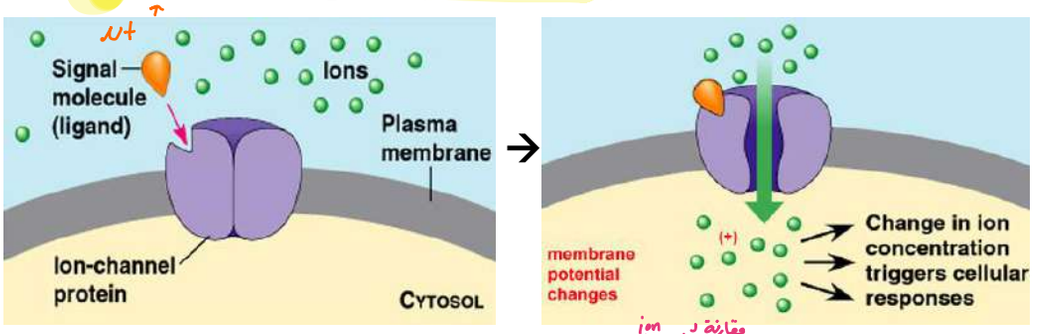
الإشارة الخلوية إزاي بتنتقل ؟ / كيفية انتقالها ؟ ←

Types of receptors (signaling mechanisms or signal transduction):

1. Ligand-gated ion channels: (for fast neurotransmitters)

- Receptors are ion-selective channels in the plasma membrane.
  - Binding of agonist to the extracellular part of receptor → opening of the channel → alteration in membrane potential or change in intracellular ion concentration → change in cell activity,
  - e.g. $GABA_A$ receptors (Cl^- channels). → inhibator of CNS.

مثلاً: من ① لزيادة الـ (-) داخل الـ cell شو بيصير ← depolarization
لزيادة أكتر الـ (-) ← hyperpolarization



مقارنة بـ ion channel

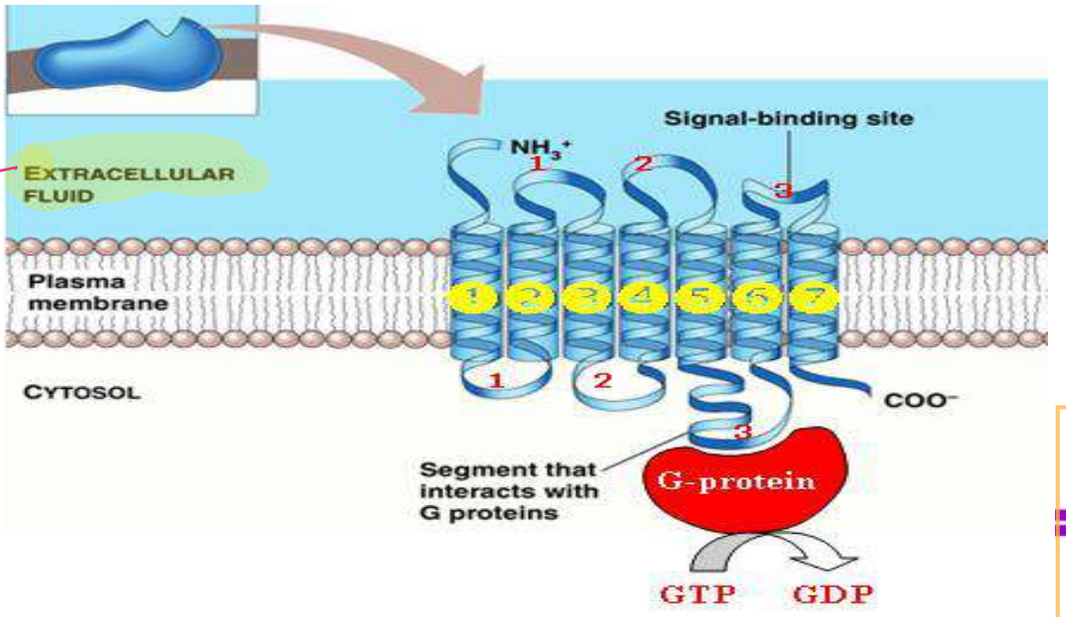
2. G protein-Coupled Receptors (for slow neurotransmitters)

مشهور جداً

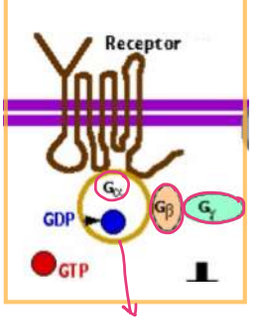
- Receptor consists of 7 transmembrane subunits which are linked to G proteins.

حوالي عبارة عن ← 7 peptide chain of a.a

- The G protein is a trimer (α, β and γ).
- Agonist binding → dissociation of α subunit which **regulates** activity of several effectors.



جوا ← الـ cell



لما يصير activation بتنفعل (α)

* Types of G Proteins

second messenger

a. G_s (stimulatory) → increased cAMP → activation of specific proteins.

b. G_i (inhibitory) → decreased cAMP → inhibition of specific proteins.

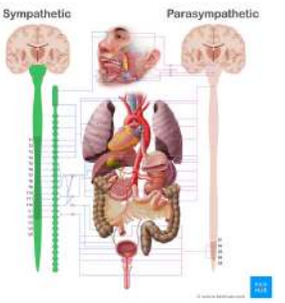
c. G_q (query) → increased DAG (diacylglycerol) and IP_3 (inositol triphosphate) → increased intracellular Ca^{++} and activate PKC (protein kinase C)

sympathetic nervous system →

- Examples: β-adrenergic receptors linked to G_s protein

  α_2- adrenergic receptors linked to G_i protein

  α_1- adrenergic receptors linked to G_q protein



3. Receptors *linked to* Tyrosine Kinase (RTKs)

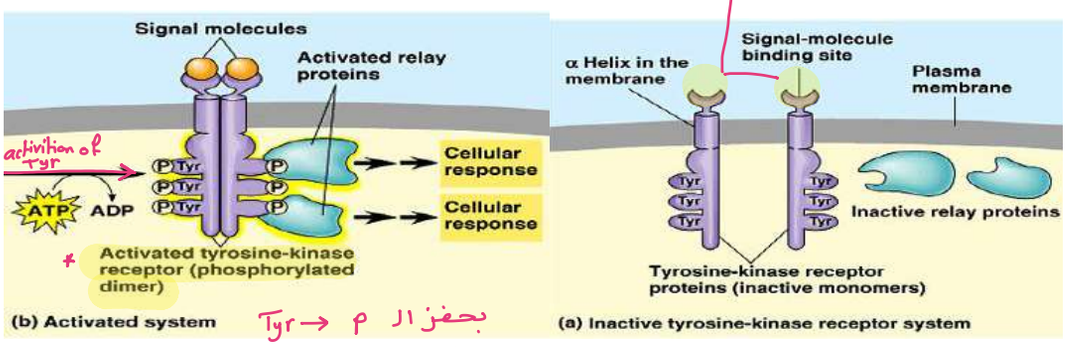
- The receptor is formed of two domains:

  a. An extracellular domain, to which the agonist binds.

  b. An intracellular domain, which is a tyrosine kinase enzyme (effector).

  c. A transmembrane segment connecting two domains.

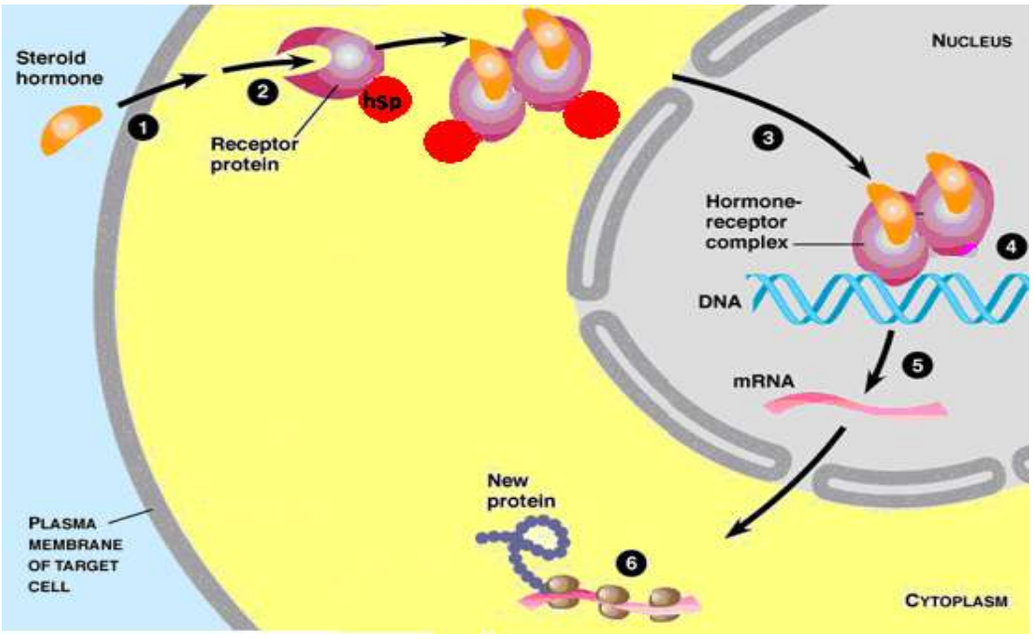
- **e.g. insulin receptors**



4. Intracellular (DNA-linked) receptors (very slow)

- The ligand enter the target cell and combine with intracellular receptor proteins → complex → acts on nuclear DNA → modify transcription of the nearby gene → modify protein production → changes in the structure or function of the target tissue.

- Examples: receptors for **corticosteroids, sex hormones, thyroid hormones and vitamin D**



5. Nitric Oxide (NO) Receptors:

- NO receptors are protein receptors inside the cell. Binding of NO receptors → formation of a "second messenger" within the cell.
- The most common: NO activates guanylyl cyclase enzyme → cyclic GMP (cGMP).
- NO receptors are activated by many drugs that increase NO level e.g. **nitroglycerine**.

Biological response to drug-receptor binding:

$$\text{Drug (D)} + \text{Receptor (R)} \underset{\text{Kd}}{\overset{\text{Affinity } K_a}{\rightleftharpoons}} \text{D/R complex} \xrightarrow{\text{Efficacy}} \text{Response}$$

- **Affinity**: ability of drug to bind with the receptor to form D/R complex.
- **Efficacy:** ability of D/R complex to evoke a response.
- K_a is the association constant
- K_d is the dissociation constant

- When a drug combines with a receptor, this may lead to:

1- Agonist effect or 2- Antagonist effect or 3- Partial agonist effect

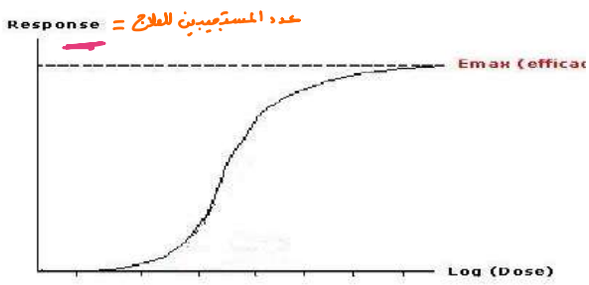
1. Agonist effect:

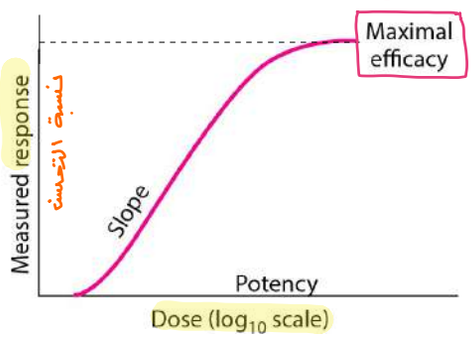
- Agonist has (1.) **Affinity** (2.) **High Efficacy** (3.) **Rapid rate** of ass. & diss.
- Theories for drug-receptor interaction:

1. **Receptor occupation theory:** response (efficacy) depends on **number** of occupied receptors
   - When maximum effect is reached, still some receptors remain free **(spare receptors)**
2. **Rate theory:** response (efficacy) depends on rate of association (K_a) and rate of dissociation (K_d)

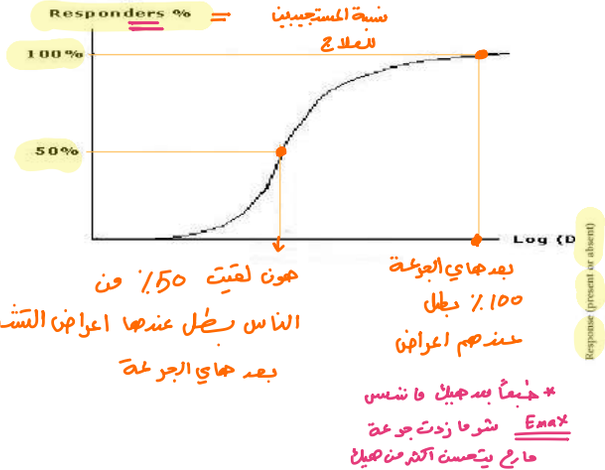
- Response will never exceed a certain limit whatever the drug concentration. This is termed E_{max} i.e. the maximal response or effect
- e.g. - **acetylcholine (Ach) activates nicotinic receptors → skeletal muscle contraction.**
  - **adrenaline activates beta adrenoceptors → increased HR**
- They are 2 types of drug responses:

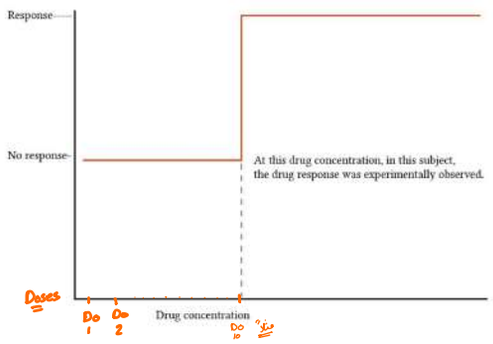
1. **Graded dose-response**: the response increases by increasing the agonist **e.g.** increases of heart rate against different doses of adrenaline.





2. **Quantal dose-response** : the response is all or none **e.g.** the % of epileptic patients who are treated by different doses of an antiepileptic drug



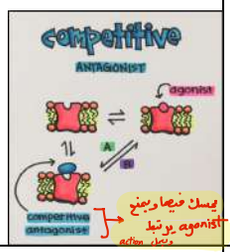
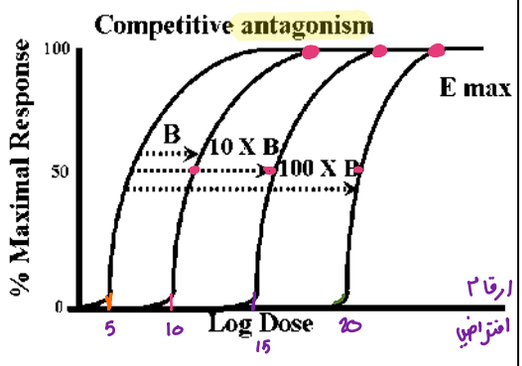
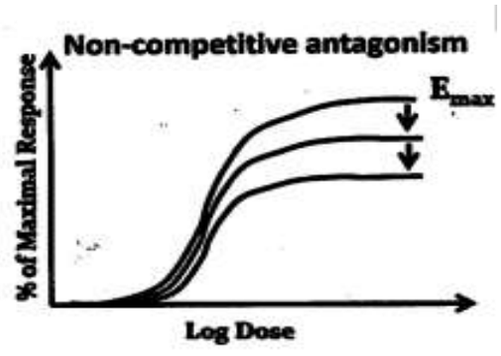


response ← ما بيعمل ← it's self ← يعني ← No Efficacy
action ← لكن الـ response داخل جسم الحيوان كيف بيبين ؟ بيمنع الـ
تاع الـ agonist إلي موجود داخل الـ Tissue
يمكن يكون hormone / chemical substance / ... NT ← [بس امنع الـ action تبعو بيلش
حدا الـ effect أو الـ response .

2. Antagonist effect:

the different

- Antagonist has: **1. Affinity** 2. **No Efficacy** **3. Slow Rate** of ass. & diss.
  - Types of **receptor (pharmacological) antagonists:**

1- Competitive Antagonist	2- Noncompetitive Antagonist
• Antagonist ***competes with the agonist*** for the ***same recognition site*** of the receptor. 	• Antagonist ***binds irreversibly with recognition site*** of the receptor ***or to an allosteric site*** (a site away from recognition site) to prevent binding of agonist with receptor or prevent activation of receptor by agonist
• ***Duration*** of antagonism depends on the relative ***plasma concentrations of agonist and antagonist.***	• ***Duration*** of antagonism depends on ***synthesis of new receptors***
• Antagonist can be ***Displaced*** by excess agonist ***(surmountable)***	• Antagonist can ***Not*** be Displaced by agonist ***(non-surmountable)***
• Causes ***parallel shift to the right*** in the log dose-response curve i.e. ***No change in E_{max} but ↓↓ in potency (↑↑ in ED_{50})***	• Causes ***downward shift*** in the log dose-response curve with ↓↓ ***in E_{max} , but No change in potency (ED_{50})***
	
• Examples: **Atropine** (muscarinic blocker)	• Example: **Phenoxybenzamine** (α – blocker)