
النادي الطبي
Pharmacology
Subject : Pharmacology
Lec no : Lecture " 8 "
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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

Act on DNA

Any molecule bind withe receptor is ligand

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**

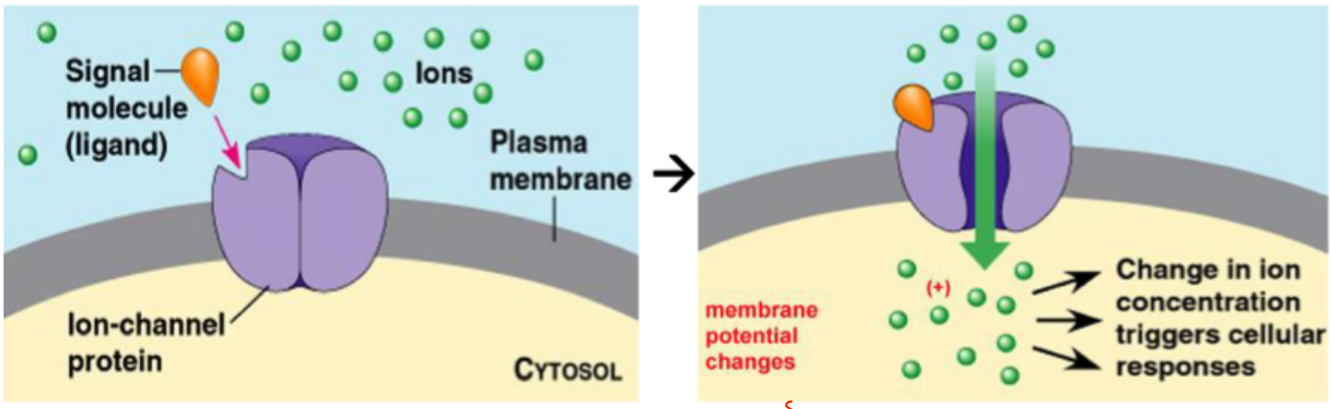
هون ligand هي اي molecule ممكن يربط بال reseptor وممكن يكون agonist او antagonist

Agonist:ligand that activates the receptor
Antagonist:ligand that blocks the receptor

هسا بدنا نحكي عن انواع

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).**



هاض reseptor بتكون من جزاين ١) extracellular part بربط فيه ligand

2) intracellular part

لما يربط ligand بال extracellular part بعمل تغير بال intracellular part

يؤدي إلى فتح ودخول الأيونات

مثال GABA$_A$ reseptors

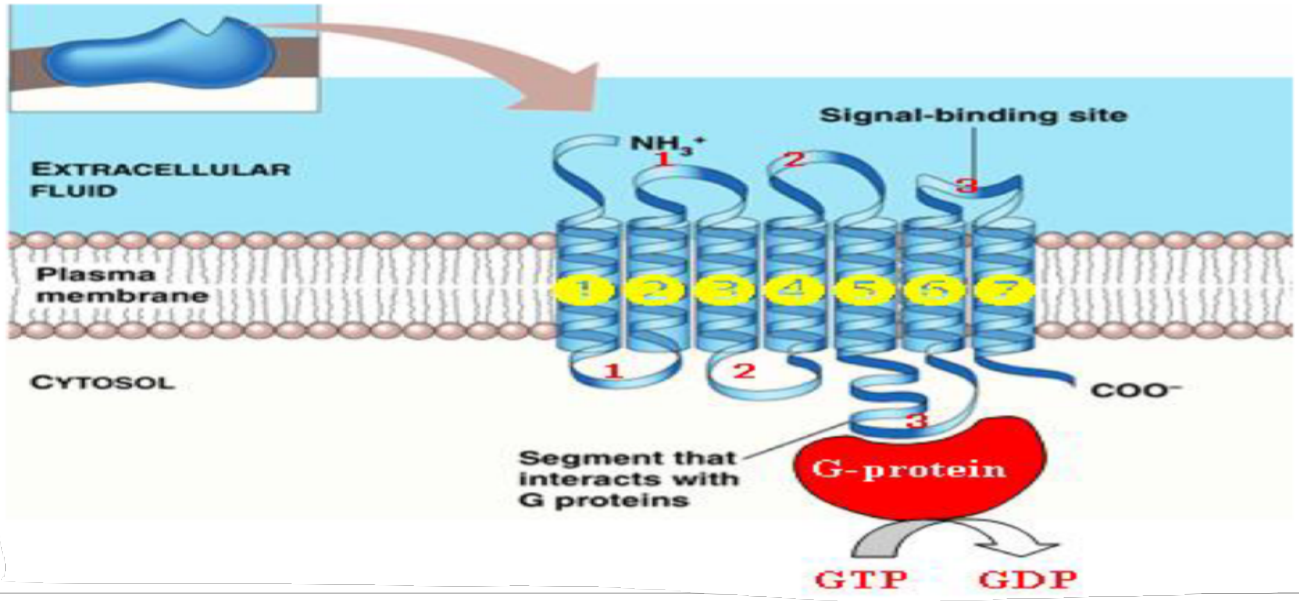
هاي الـ reseptors ترتبط فيها GABA$_A$ neurotransmitter وتؤدي إلى

دخول ايونات الكلور إلى داخل الخلية وتعمل Hyperpolarization

وبالتالي تعمل inhibition of action potential

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

- Receptor consists of 7 transmembrane subunits which are linked to G proteins.
- The G protein is a trimer (α, β and γ).
- Agonist binding → dissociation of α subunit which **regulates** activity of several effectors.



Alpha α 1 ∴ 3 subunits تتكون من G-protein complex هون فيه
beta β 2
gama γ 3

لما يرتبط ligand بالـ reseptor يؤدي إلى فك الـ α subunit

وتروح ترتبط بـ adenyl cylase onzyme وتحول ATP → CAMP

وتؤدي إلى سلسلة تفاعلات داخل الخلية.

Types of G Proteins

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)

- Examples: β-adrenergic receptors linked to G_s protein

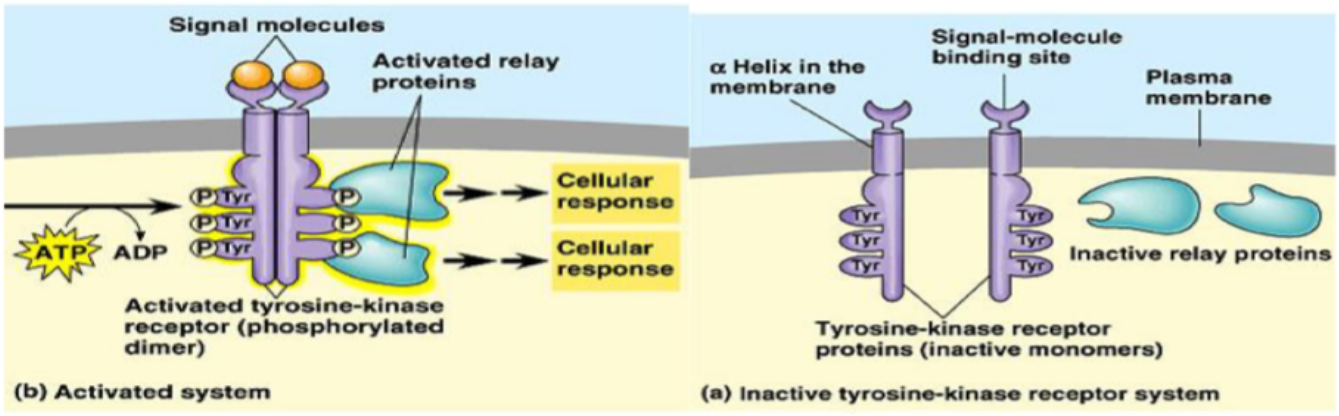
α_2- adrenergic receptors linked to G_i protein

α_1- adrenergic receptors linked to G_q protein

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

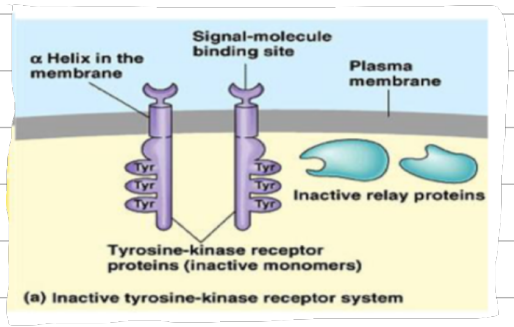
- The receptor is formed of two domains:
  a. An extracellular domain, to which the agonist binds.
  b. An intracellular domain, which is a tyrosine kinase enzyme (effector).
  c. A transmembrane segment connecting two domains.

- e.g. insulin receptors



Agonist binds with it ← extracellular domains
Consist of Tyrosine Kinase ← intracellular domain (2

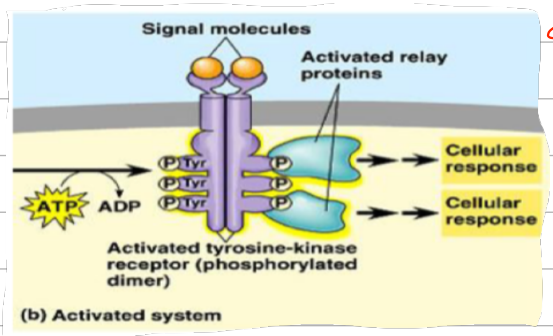
هاذ الـ Receptor بتكون من جزأين :-



طريقة العمل :-

هو بكونوا 2 monomers منفصلين عن بعض

لما يربط agonist بالـ receptor بقربوا على بعض وبربطوا مع بعض بعدين بعملوا activate لبروتين ويصير cellular response.



مثال عليه :- هرمون الأنسولين

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

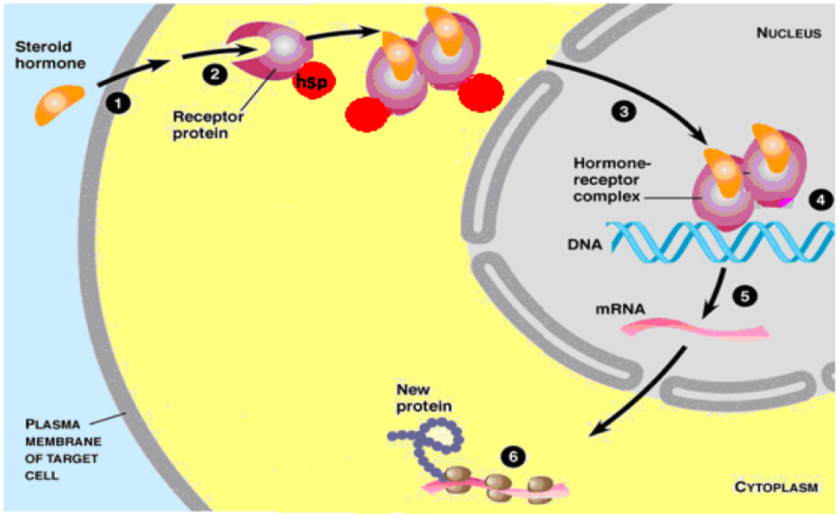
- The ligand enter the target cell and combine with intracellular receptor proteins → complex → acts on nuclear DNA → modify transcription of the nearby gene → modify protein production → changes in the structure or function of the target tissue.
- Examples: receptors for **corticosteroids**, **sex hormones**, **thyroid hormones** and **vitamin D**

هون بكون الـ Receptor داخل الخلية عكس اللي اخذناهم فوق اللي كان فيهم الـ Receptor على سطح الخلية.

طريقة العمل: بدخل ligand من cell membrane (عشان هيك ligand بكون lipophilic)

وبرتبط بالـ Receptor ويصير Cellular response واللي هو تغير في DNA ويؤدي إلى صناعة بروتين جديد يغير في وظائف الخلية.

* هاد النوع من الـ Receptors بطول ليصير فيه response بسبب تغير DNA



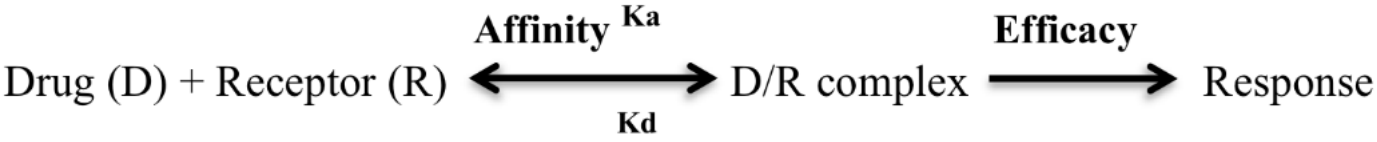
5. Nitric Oxide (NO) Receptors:

- 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**.

هو به Nitric Oxide is ligand وبكو به الـ Reseptor داخل الخلية
وبعمل على مبدأ Second messengar

مثال دواء nitroglycerine يعطى لمرضى الذبحة الصدرية
بعمل Vasodilation فبتصير كمية الدم اكبر بالشريان فبتروح الجهد
اللي بيبذلو القلب لضخ الدم للأعضاء.

Biological response to drug-receptor binding:



- **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

} معدل ربط الدواء وفكوا من receptor

↳ اثارة

* هسا لما الدواء يربط بال receptor يا إما يكون :-

1. Agonist effect: → Activates receptor

- Agonist has **1. Affinity** **2. High Efficacy** **3. Rapid rate** of ass. & diss.
- Theories for drug-receptor interaction: هاي نظريات ربط الدواء مع الreceptors

1. **Receptor occupation theory:** response (efficacy) depends on **number** of occupied receptors اول نظرية انو تاثير الدواء بعتمد على عدد الreseptors اللي ربط معهم

- increase affinity
- // sensitivity of tissues to small amounts of drugs

* - When maximum effect is reached, still some receptors remain free **(spare receptors)** انو لما الدواء يوصل لاقصى تاثير بكون لسا فيه reseptors فاضية اسمها spare receptors

2. **Rate theory:** response (efficacy) depends on rate of association (K_a) and rate of dissociation (K_d) ثاني نظرية تحكي انو تاثير الدواء بعتمد على سرعة ربط وفك الدواء من الreseptore

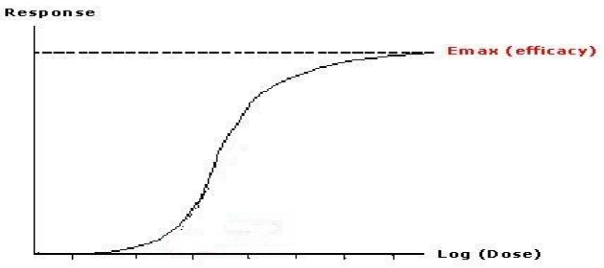
* - Response will never exceed a certain limit whatever the drug concentration. This is termed E_{max} i.e. the maximal response or effect
- e.g. **- acetylcholine (Ach) activates nicotinic receptors → skeletal muscle contraction.**

- 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.

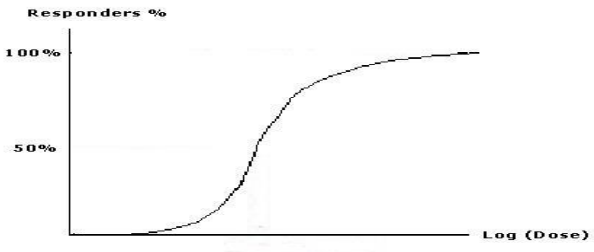
اول نوع من response of drugs
انو كل ما نزيد الجرعة بزيد تاثير الدواء
لكن هاض الحكي مش مستمر بوقف عند حد معين عندو قد ما نزيد الجرعة ما رح يزيد تاثير الدواء
اقصى تاثير للدواء اسمو Emax



potency
The dose that cause 50% response

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

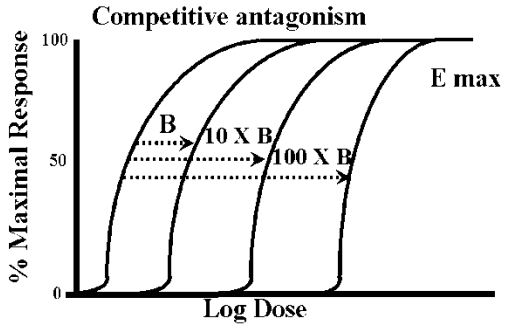
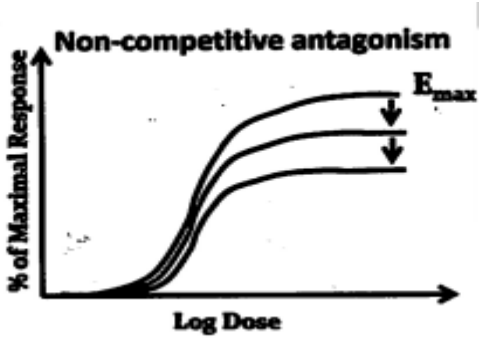
ثاني نوع بعتمد على نسبة الاشخاص اللي تعالجوا من الدواء عند جرعة معينة
يعني لما احكيلك انو عند الجرعة 5gm بكون تاثير الدواء 5% هاي النسبة معناها انو 5% من الاشخاص عند هاي الجرعة كان للدواء تاثير عليهم وتعالجو



هاي معناها مش انو الدواء ما الو response
معناها انو الدواء بربط بالreseptor ويمنع الادوية الثانية
انها تاثر على الreseptor وبالتالي تثبيط باقي الادوية

2. Antagonist effect:

- 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.*** • Antagonist can be ***Displaced*** by excess agonist ***(surmountable)***	• ***Duration*** of antagonism depends on ***synthesis of new receptors*** • 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)

Competitive Antagonist:-

* Here Antagonist competes with agonist for same site of binding on reseptor

يعني الـ Antagonist بكون نفس التركيب الكيميائي لـ Agonist فبصير بنافسو على مكان الربط ويربط محله ويمنعوا من الربط على reseptor

* To unbind antagonist from receptor you can increase the dosage of drug, the drug will replace the antagonist

* Here there is no change in Emax, but Potency will be increased.

↳ The dosage need to reach 50% of response of drug (ED_{50})