Pharmacology

Subject : PHARMACODYNAMICS

Lec no :8

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وقل رب زدني علماً

للوصول الى guidance الفارما و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

قبل ما نبلش المحاضرة... عشان أنا كتير منيحة الله يرضى عني😇😂
قررت أخليكم تكسبو أجر كبير بكل سهولة... شفتو محسني😌😂
طب شو هو الأجر وكيف يا لانا المتواضعة؟🤦🏻‍♀️😁
الأجر يا حلوين أنه تتبرعو برصيد الطباعة تبعكم اذا ما بتحتاجوه لطلاب بحاجته (قلتلكم اجر بسهولة)🤍💜
طيب شو لازم نعمل؟
أول شي لازم تفوتو ع بوابتكم ومن عند خدمات أخرى __ رصيد الطباعة
هلأ من هي الخطوة بس بدي تتأكدو انو رصيدكم موجود ولا خالص لو اعطاك (لا يوجد اي حركات طباعة حاليا) معناها الرصيد موجود وفيكم تتبرعو فيه
طيب تمام وكيف نتبرع؟
من بوبابتكم ومن عند خدمات أخرى __ الدخول لشبكة الانترنت (المختبرات واللاسلكية) بتاخدوا اسم المستخدم (والي هو رقمكم الجامعي) وبتنسخوا كلمة السر
واخر شي بتدخلو على QR code الي تحت👇 بتعبو فورم التبرع بالرصيد وبس.
سهلة القصة والله وفيها اجر كبير (اجر ع كل نقطة وحرف وكلمة انطبعت من رصيدك لشخص محتاج واجر بكل حرف اندرس من الورق الي انطبع برصيدك الي انت اصلا ما بتستخدمه).

موضوع جديد ؛ خعتمد ألوان جديدة

PHARMACODYNAMICS تأثير الدواء على الجسم

Types of Drug Action:

- **Local or topical action**: drugs act on site of application e.g. ointment or eye drops. مكان ما بتحط الدواء بشتغل
- **Systemic or general action:** the drug acts after administration and distribution by circulation to various tissues. e.g. Aspirin

absorption +

- **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

يعني حطيت الدواء بمكان وعمل reflex واشتغل بمكان آخر، وموعبر Circulation

وما حصل اله Absorption

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: acting on Cells components.

(5) Subcellular structures **(6) Genetic apparatus**

(7) Physical mechanisms **(8) Chemical mechanisms**

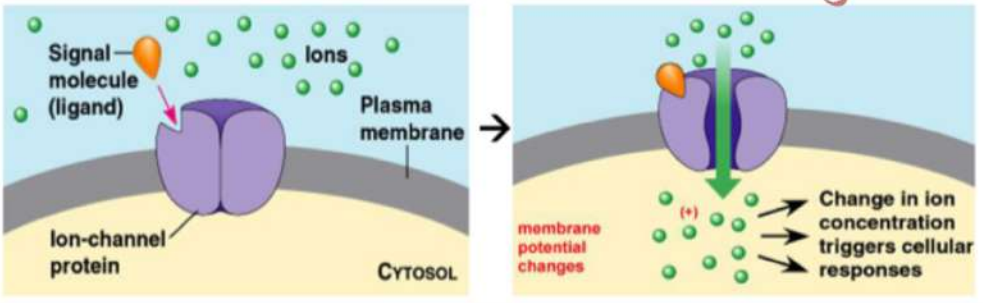
1) Receptor-Mediated Mechanisms

- **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** *Ligand could be a drug, transmitter, hormone.

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).** : γaminobutyric acid

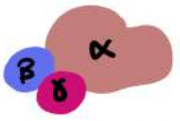


توضيح للمثال: الـ ion channel عبارة عن Cl^- ، الـ $GABA_A$ لما ترتبط براي القناة حتبدأ أيونات Cl^- تدخل للداخل ، $GABA_A$ زاد عنا السالبية داخل الخلية ← Hyperpolarization

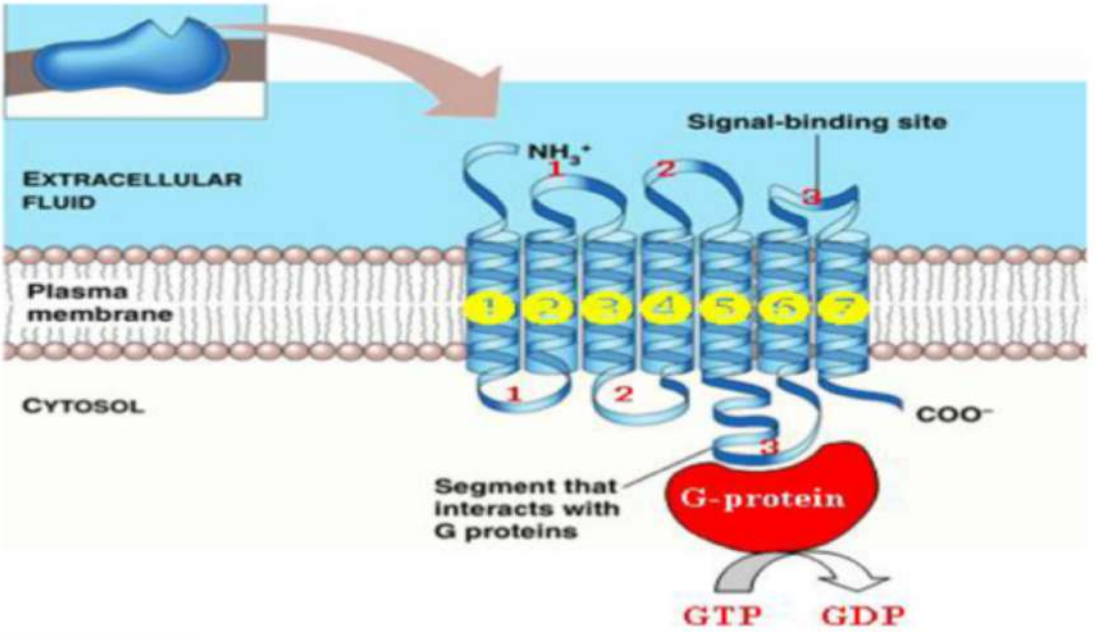
↳ inhibition to CNS .

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.



Types of G Proteins

☆Smooth muscle in blood vessels → C+ → relaxation → Vasodilation

☆لما يزيد بالقلب رح يزيد دخول C+ ف رح يزيد ال contractivity

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) → Muscle contraction / vasoconstriction.

- 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

Alpha-adrenergic receptors play an important role in the regulation of blood pressure (BP).

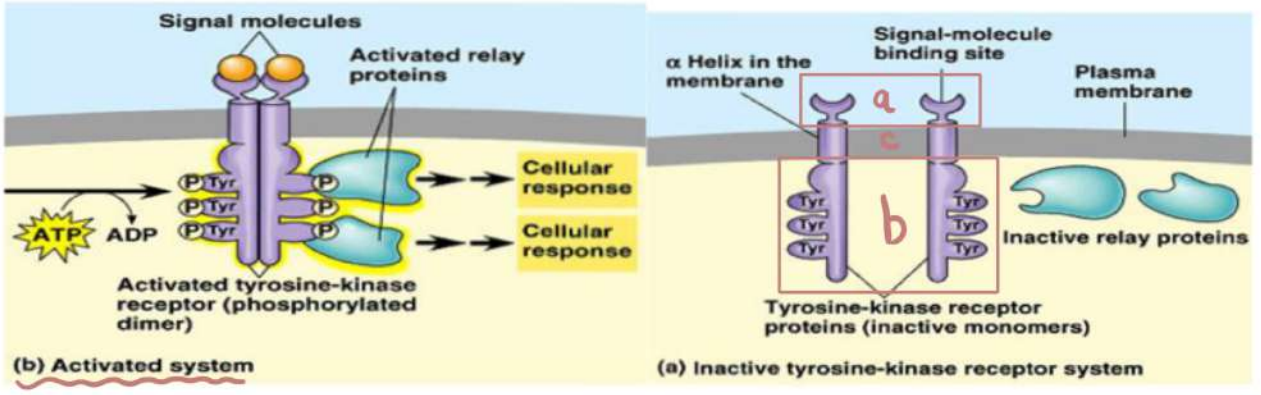
Alpha 2 receptors : inhibit the release of norepinephrine and other neurotransmitters in both the central and peripheral nervous systems.

Alpha 1 receptors : are the classic postsynaptic alpha receptors and are found on vascular smooth muscle. They determine both arteriolar resistance and venous capacitance, and thus BP, pupil dilation

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.

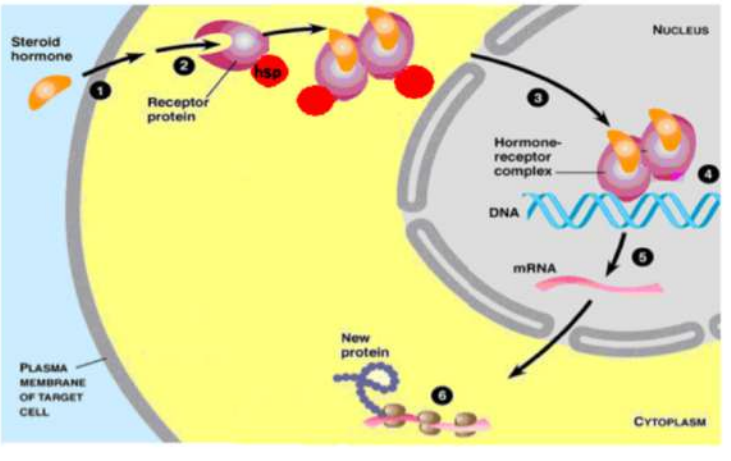
- e.g. insulin receptors



بيجي الإنسلوين بمسك بالEC domain ، فالجزيئين بالIC domain بتحدوا مع بعض و بكونوا dimer ، اللي حيعمل activation لـ Cellular response زي دخول الـ Glucose

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

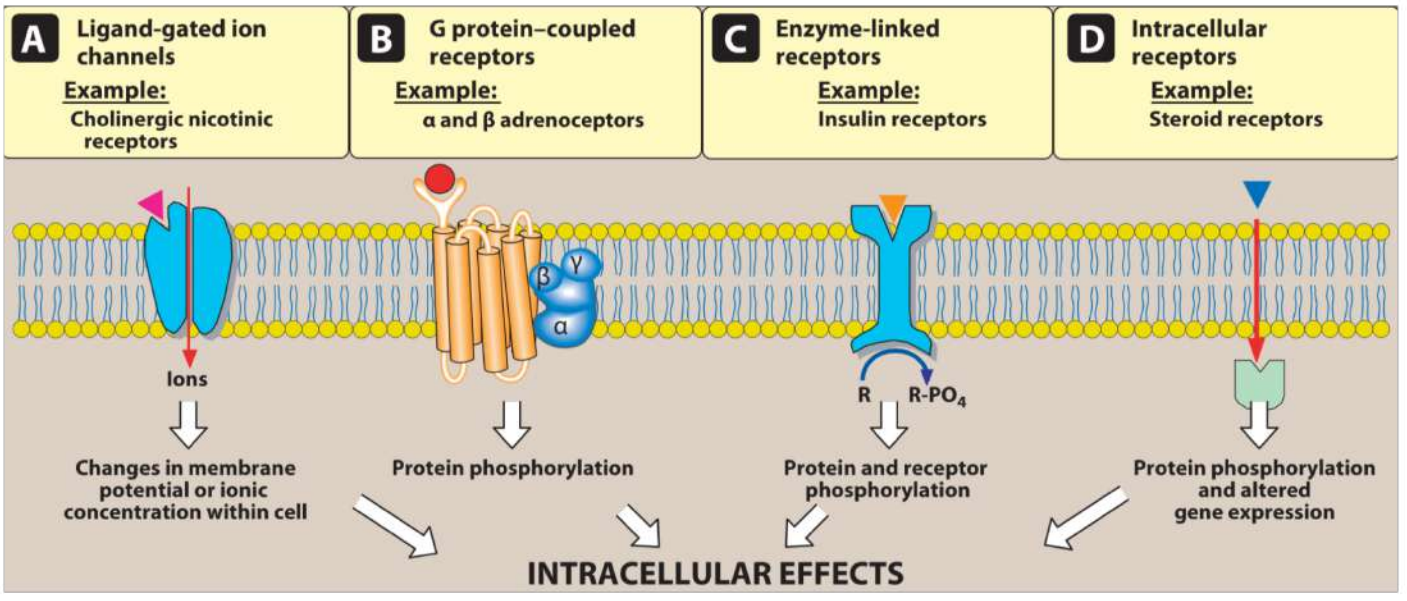
- The ligand enter the target cell and combine with intracellular receptor proteins → complex → acts on nuclear DNA → modify transcription of the nearby gene → modify protein production → changes in the structure or function of the target tissue.
- Examples: receptors for **corticosteroids, sex hormones, 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). in G-protein → cAMP
- NO receptors are activated by many drugs that increase NO level e.g. **nitroglycerine**.

Nitroglycerin sublingual tablets are used to treat episodes of angina (chest pain) in people who have coronary artery disease



أي drug بده يرتبط بـ receptor
لازم يكون عنده :-

Biological response to drug-receptor binding:

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

- **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 ,Rate of Binding.
- 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:

High response ↑

- 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)**

Spare receptors : are receptors that exist in excess of those required to produce a full effect. The presence of these receptors increases the potency of an AGONIST.

  2. **Rate theory:** response (efficacy) depends on rate ① of association (K_a) ② and rate of dissociation (K_d) (علاقة طردية)

- Response will never exceed a certain limit whatever the drug concentration. This is termed E_{max} i.e. the maximal response or effect مش dose
- e.g. - **acetylcholine (Ach) activates nicotinic receptors → skeletal muscle contraction.**
  - **adrenaline activates beta adrenoceptors → increased HR** [Heart Beat]

Maximal efficacy of a drug (Emax) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug.

هون بيجي molecule بيرتبط مع الـ receptor وبيشتغل عليه وبعدين بينفك عنه وبيجي تاني بيرتبط مع الـ receptor وبيشتغل عليه وهكذا فهيك بزيد الـ response عندي

- They are 2 types of drug responses:

أنواع response :-

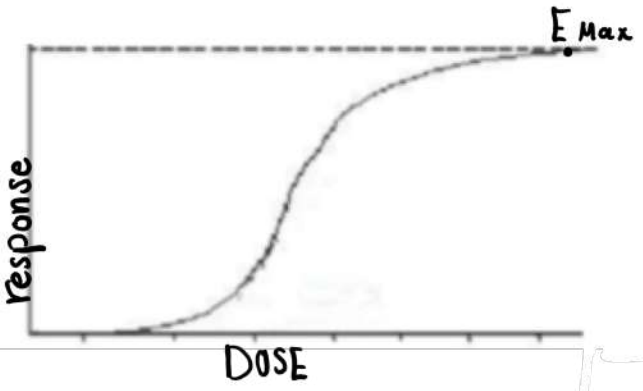
1. **Graded dose-response**: the response increases by increasing the agonist

   e.g. increases of heart rate against different doses of adrenaline.

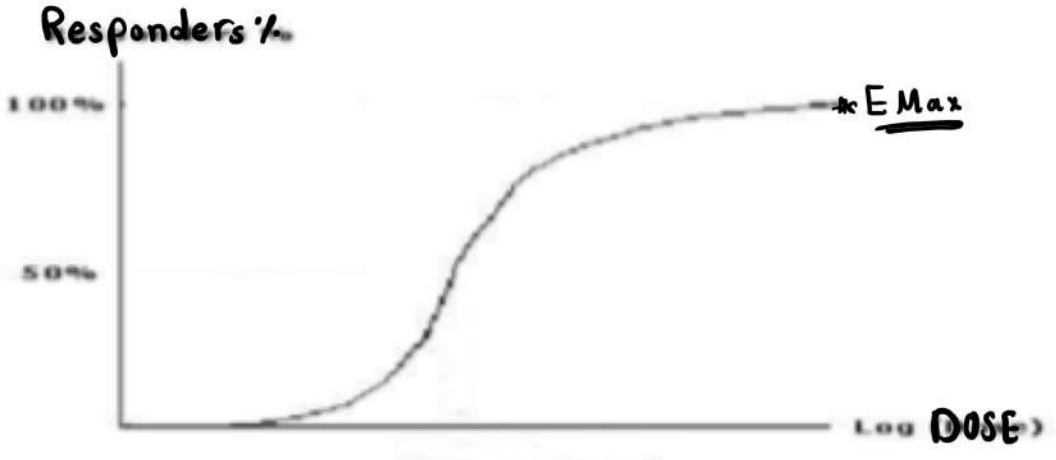
I can measure the response.

Example, Heart rate, Blood pressure, vital signs...

لو قررنا نعمل تجربة، و بهاي التجربة اعطينا المرضى دواء بزيد ال HR، حنشوف بعد كل جرعة من الدواء كم الHR حيزيد و نمثله بالجدول البياني الي عاليمين حيتكون Curve لغاية ما نوصل للEMAX و هاد الشكل بنحكيله Graded dose-response يعني بنقدر نقيس تأثير الجرعة عالمريض و كل ما ازيد الdose بزيد ال response لحد معين



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



هسا هاي مبدأها All or Non ، يعني احتمالين فقط يا حيكون في response او ما في response

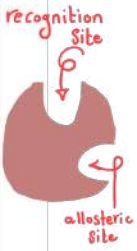
جبت المرضى و بدأت اعطيهم جرعة المرة الاولى ، عفرض 10% منهم اعطوا response و الباقي لا و لما اجيت اعطي الجرعة الثانية 20%منهم اعطوا response وهكذا لغاية ما وصلنا انه بعدد معين من الجرعات كل المرضى صار عندهم response بالتمثيل البياني ما بحط الresponse انما بحط number of responder عدد المستجابين من الdose

أنصح فيه و بشدة 👏🔥 احضروه و راجعوا المحاضرة الاولى مع فهم المحاضرة الثانية ثم اقرأوا التفريغ
عبدالمتعال مرتب الافكار بطريقة أفضل حسيت

2. Antagonist effect:

حيعمل effect عبارته يمنع الـ response
E Max

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

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*** (1) of the receptor ***or to an allosteric site*** (2) (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.*** الي كميته أكبر هو الي بيمسك بال receptor وبعطي effect • Antagonist can be ***Displaced*** by excess agonist ***(surmountable)***	• ***Duration*** of antagonism depends on ***synthesis of new receptors*** ← الارتباط irreversible • Antagonist can ***Not*** be Displaced by agonist ***(non-surmountable)***

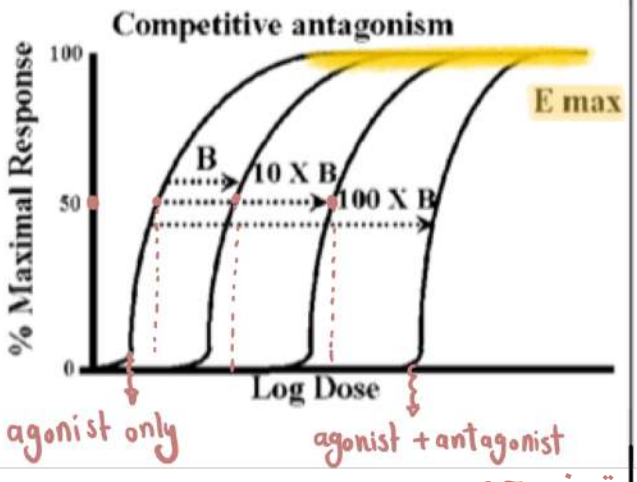
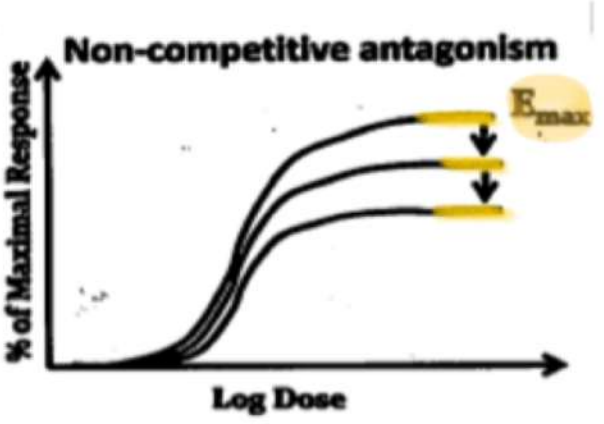
- Surmountable : Displacement قابل انه يصيرله ازاحه أو

• Examples: **Atropine** (muscarinic blocker)	• Example: **Phenoxybenzamine** (α – blocker)

*Atropine is a competitive antagonist of the actions of acetylcholine and other muscarinic agonists. Atropine competes for a common binding site on all muscarinic receptor. Cardiac muscle muscarinic receptors are blocked.

*Phenoxybenzamine is an irreversible, noncompetitive blocker of α-adrenergic receptors. It forms a covalent link with the α receptor.

مهم

• 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})***
	

توضيح :

١. ضفت دواء س الي يعتبر Agonist و ضليت ازيد من الجرعة لحتى وصلت للEmax

٢. ضفت دواء ص الي يعتبر antagonist مع دواء س الي يعتبر agonist ، فلاحظت ضليت ازيد كمية من الجرعة اكبر من التجربة الاولى لحتى اوصل Emax

باختصار:

الcompetitive antagonist بقلل ال potency تبعت الagonist ، بدليل انه وصلنا للEmax بجرعات اكبر + الEC50 تبعته بتكون أكبر

ال non competetive بخلي الreceptors غير صالحة للأبد فحتى لما ازورد الجرعات حتضل الpotency ثابته

ولكن الي يختلف انه كل ما ازود جرعة دواء الEmax بتختلف معاه

*The Emax, maximum efficacy of the agonist which in the presence of a competitive antagonist remains unchanged

*The EC50, concentration required to achieve 50% of the maximal effect, which in the presence of a competitive antagonist will increase.

Quiz Time ⏰👏

1) Which of the following best describes how a drug that acts as an agonist at the A subtype of GABA receptors affects signal transduction in a neuron?

A. Activation of this receptor subtype alters transcription of DNA in the nucleus of the neuron.

B. Activation of this receptor subtype opens ion chan- nels that allow sodium to enter cells and increases the chance of generating an action potential.

C. Activation of this receptor subtype opens ion chan- nels that allow chloride to enter cells and decreases the chance of generating an action potential.

D. Activation of this receptor subtype results in G protein activation and increased intracellular second mes- senger levels.

2) In the presence of propranolol, a higher concentration of epinephrine is required to elicit full antiasthmatic activity. Propranolol has no effect on asthma symptoms. Which is correct regarding these medications?

A. Epinephrine is less efficacious than is propranolol.

B. Epinephrine is a full agonist, and propranolol is a partial agonist.

C. Epinephrine is an agonist, and propranolol is a competitive antagonist.

D. Epinephrine is an agonist, and propranolol is a non-competitive antagonist.

3) The neurotransmitters, nor-adrenaline, adrenaline, and dopamine act through which of the following receptors ?

A. Single pass transmembrane receptors.

B. Four pass transmembrane receptors.

C. Seven pass transmembrane receptors.

D. Ligind gated receptors

4) which of the following statements best describes the mechanism of action of insulin on target cells?

A. Insulin binds to cytoplasmic receptor molecules and is transferred as a hormone receptor complex to the nucleus where it acts to modulate gene expression

B. insulin binds to receptor molecules on the outer suface of the plasma membrane and hormone receptor complex activates adenylate cyclase through the Gs protein .

C.insulin binds to a transmembrane receptor at the outer suface of the plasma membrane which will activates the tryosine kinase that is cytosolic domin of the receptor.

D. Insulin enters the cell and cause the release of calcium ions from intracellular stores

– و ما الذي يدفعگ للمحاولة ؟!

إيماني الشديد بأن القاع ليس لي . .