PASSION BATCH
SECOND YEAR

PHARMACOLOGY

Lecture 8

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ملاحظة : التفريغ شامل السلايدز

Pharmacodynamics:

- Pharmacodynamics: is the effect of the drug on the body and It is the mechanism by which the drug exerts its effects.

That can't be haphazardly!

يعني مثلاً مش أي دواء بالصدفة بيعمل تقليل للضغط . أكيد في (target tissue) أو (final destination)

وهاد الدواء رح يتم نقله لهي ال destination

- Each drug has its own **<u>mechanism of action</u>** (MOA)

That's mean what is the target? And how the drug exerts its effect?

To understand MOA in a right way we have to know what the target is.

هلا الدواء ممكن يكون بال

Plasma or intracellular fluid or in interstitial fluid.

طيب مع مين رح يرتبط لحتى يعملaction ؟؟

- That will happen by two ways:

1. nonspecific mechanisms of drug action (effect):
    - not all drugs act by receptors - the mechanism of action is mediated by the chemical or physicochemical properties of a drugs(it acts locally).
    - e.g., antacids chemically neutralize excess gastric acid

مثال: مضاد الحموضة بيعتمد على مبدأ

Acid + base = salt + water

يعني لو كان عندي حموضة بالمعدة الحل رح يكون كالتالي:

I will take a weak basic drug then it will be changed into salt that will decrease the acidity of the stomach.

انحلت المشكلة والدواء عمل ال action المطلوب بدون الحاجة لأي receptor أو enzyme أو target tissue الخ ...

2. specific mechanisms of drug action (effect)
    - Drug interacts with specific target macromolecule (receptor)
    - Interaction with various target sites: Receptors or inhibitors for transport systems (carrier) or enzymes**.**
    - 99.9% of drugs have a specific mechanism of action.

- Specific Targets For Drug Action :
    1. Receptors : it can be located inside or outside the cell
    2. Ion Channels : e.g. Na^+- k^+ channel or Na^+-K^+
        - It plays the major rule in polarization and depolarization in nerve cells and muscles relaxation.
        - Also, in the cases of Anesthesia we block these channels.

لانه لما نسكر القناة رح يصير highly repolarized وما يخلله صودوم كافي بالتالي ببطل يحس بال new impulses

3. Enzymes : e.g. angiotensin converting enzyme
   What will happen if we inhibit this enzyme?

   رح يصير عكس كل شي بيعمله ال angiotensin 2 يعني رح يصير

   Vasodilation and sodium and water will not be returned to the blood stream.
4. Carrier Molecules: transporter for absorption or elimination.

بعد ما حكينا الطرق الي بصير من خلالها ال MOA بدنا نجاوب ليش مهم نعرف ال MOA كيف بتصير شو الفائدة من انه أنا كطبيب لازم أعرف شو الآلية ؟

لانه في كتير أدوية بتتعارض مع بعض ، مشان هيك بتساعدني لحتى أعرف اذا رح يصير drug-drug interaction

- Critical thinking ☺ … try to answer these questions:

1. What will happen if you give two drugs have the same MOA and the same receptors?
2. What will happen if you give 2 drugs have oppose MOA?

مثلاً واحد بيفتح القناة و واحد بسكرها

3. What will happen if you give 2 drugs have different MOA but the final destination?

مثال : بدي أقلل الضغط أخدت دواء 1 يقلل من the volume of blood بالتالي يقلل الضغط

و أخدت معه دواء 2 عمل vasodilation وبرضه قلل الضغط شو النتيجة ؟ هل دائماً رح تكون ? bad or not برضه فكر بالجواب ☺

In general we can know from MOA if this compound is synergism, antagonism or additive.

- **Receptors :**
  - Receptor: specialized <u>macromolecule</u> (protein) present on the cell surface or intracellular that binds a drug and mediates its pharmacological action.

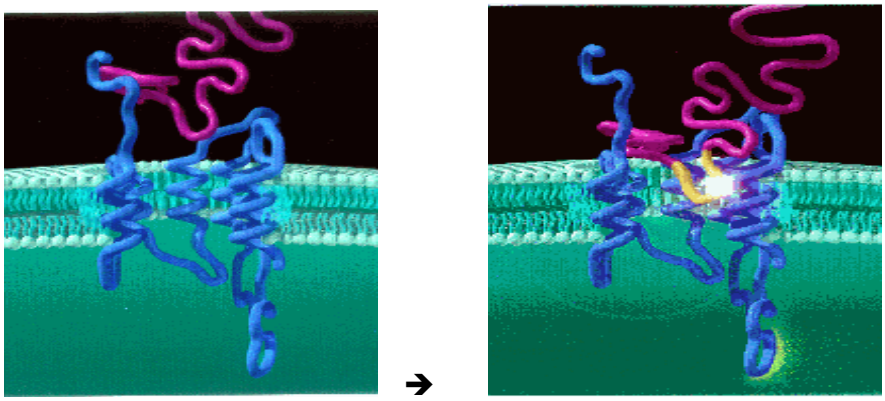
يعني ال receptors اما بتكون داخل الخلية أو embedded in the membrane

شو يعني embedded؟ يعني جزء منه موجود بال membrane وجزء طالع لل outside

  - Lock and key or induced-fit models:

    - Drug acts as key, receptor as lock, and combination yields response

    - Dynamic and flexible interaction



شرح للصورة :

هلا بدي أتخيل انه هي خلية كاملة وفي جزء من ال receptor طالع لل outsideوجزء موجود بالداخل اذن :

These receptors if it outside the cell (mostly outside) the drug doesn't need to enter the cell it just bind to these receptors and the action will enter ➔ how? Because there are messenger inside and outside the cell that is mean not all drug have to enter the cell (the drugs that can enter the cell have a unique

features like small molecular size and high lipophilicity (few drugs)).

تمام هلا لاحظ بالصورة التانية بعد ما ارتبط الدواء شو صار بشكل ال receptor
تغير شكله , صار conformational change (twisted shape)
هلا لما يتغير شكل الل(receptor) رح يعمل signaling ويبعت اشارات لل second messenger
ملاحظة لطيفة :
دائماً داخل الخلية بكون في عندي شي اسمه second messenger ممكن يكون :

Enzymes, phosphorylation, calcium influx and triphosphate .

The function of the second messenger is to stimulate the next steps.

- **Drug + Receptor ↔ Drug-receptor complex → Biologic effect:**
  - The formation of the drug-receptor complex ⇒ biologic response(makes the action)
  - The magnitude of the response is <u>proportional</u> to the number of drug-receptor complexes.
    The more <u>number</u> of drug-receptor complex the more the <u>action</u> but that means at a certain limit there is saturation. (Any more increment in dose no increase in response because we reached the saturation point)

- Receptor not only has the ability to recognize a ligand (drug), but can also transduce this binding into a response by causing a conformational change or a biochemical effect.
- Relationship between pharmacokinetic and pharmacodynamics :
  If we give a Subtherapeutic dose the drug will not act because when it bind to receptors It's not enough to exert the action.
  If we give an over dose More receptors were stimulated then you will get more action (toxicity).

مثال : أعطيت دواء للقلب والجرعة كانت زائدة فهون بدل ما أرفع ال heart rate شوي رفعته كتير بالتالي صار عند المريض taquicardia .

- Receptors exist in two states:
  1. Inactive (R) state
  2. Active (R*) state

The receptors are located in our bodies inside the cell or outside the cell (mostly) in its inactive form … once the drug or ligand (we say ligand because it can be either drug or endogenous) bind to it, it converts it into active form and we call it: Active binding

مو بالضرورة تكون agonist ممكن تكون antagonist كمان

Agonists: Drugs that bind to the receptor and do the action that the endogenous do.
Antagonists: Drugs that combine with receptors, block it and then do the opposite action that the endogenous do

- Two main types of receptor ligands are:
    1. Agonists = Drugs that bind to the receptor and activate them to produce a response
    2. Antagonists = Drugs that combine with receptors, but do not activate them.

- Antagonists reduce the probability of the agonist combining with the receptor and so reduce or block its action.

مثال لتوضيح الفكرة : هلا ال receptors موجودة بجسمي لترتبط مع ال neurotransmitters مو مشان الدواء مثال على ذلك :

- Alpha receptors → epinephrine

- AM receptors → acetylcholine

لو عملت دواء بيشبه ال epinephrine بالشكل بيقدر يرتبط بالألفا ريسيبتورز وهاد معناه Agonists ولكن اذا عملت دواء غير مناسب لل receptor بيرتبط لكن ما بيشتغل هاد اسمه Antagonists

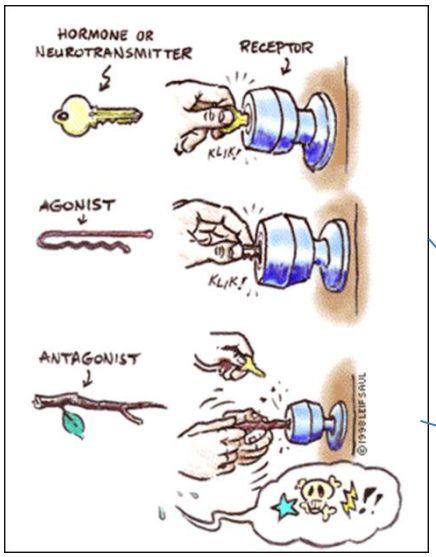
E.g. Beta 1 receptor which is located in the heart:

When adrenalin attached to it →increases the heart rate by chronotropic also increase the contractility by inotropic → increase blood pressure.

مستحيل أعطي هاد الدواء الا بحالة ال emergency مريض دخل collapse الضغط عنده أقل من 60 مباشرة بعطيه adrenalin بيرتبط بال receptor ك agonist
طيب عكس الحالة الي فوق : لو حدا عنده arrhythmia ال heart rate عالي وضغطه مرتفع شو ممكن أعطيه ؟

Beta1 blocker or beta 1 antagonistic → it will decrease blood pressure and the heart rate

- Agonism and Antagonism:



(Direct ant/agonists)

Agonists facilitate receptor response

Antagonists inhibit receptor response

شرح الدكتورة : تخيل receptor مثل قفل اله مفتاح محدد وهاد المفتاح عندنا هو ال drug

And the drug can bind to this receptor because it's shape is fit to it

لكن لو حاولت وضع الخشبة رح تعلق بالداخل واحتمال تنكسر بكل الحالات ما رح تفتح الباب

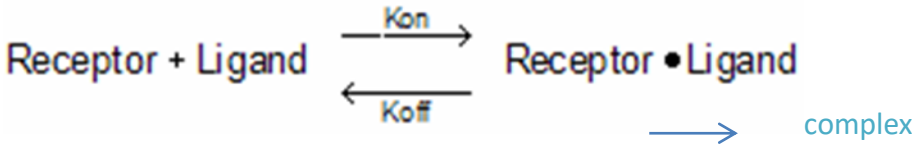
That is mean antagonist has two types:

1. Reversible : دخلت الخشبة جوا القفل لكن ما انكسرت وقدرت أطلعها و أصلح الخطأ
2. Irreversible: انكسرت بالداخل وسكرت القفل

معظم ال receptors الي بصيرلهم antagonistic بيكونوا reversible

- **Law of Mass Action**:(a model to explain ligand-receptor binding)

  - When a drug combines with a receptor, it does so at a rate which is dependent on the concentration of the drug and of the receptor
  - Assumes it's a reversible reaction



  - Ligand means drug
  - On = association , off = dissociation
  - Equilibrium dissociation (Kd) and association/affinity (Ka) constants

أي دواء بصيرله termination بيخضع لهي المعادلة :

This equilibrium make the drug at certain concentration bind and do the action after that → the concentration of the complex increase → and this will push the action to the left side →causing dissociation →elimination of drug after doing the action.

لما يرتبط ال drug مع ال receptor بيكون ال complex ولكنه ما رح يستمر لفترة طويلة متل ال adrenalin شغله ما بيتعدى الدقيقة لانه بصيرله dissociation بسرعة

هلا كل ما زاد تركيز الدوا رح تزيد سرعة انتاج ال complex ويتجه التفاعل لجهة اليمين. بعد ما يخلص شغله بصيرله dissociation(لانه ما بدي يصير long term action).

- drug-receptor interaction

  - Affinity: Tendency of a drug to bind with a receptor.
  - Or tendency of drug to bind depending on its structure.

يعني مثلاً ليش الدواء راح على alpha receptor مو على beta

  - Why is it important to know about affinity? Because you may deal with two drugs which have the same receptors so the higher affinity the more likely to bind the receptor.

  - Selectivity : <u>specific affinity</u> for certain receptors (vs. others)
  - Choosing the suitable receptor

يعني بدي أروح على B1-receptor or B2-receptor

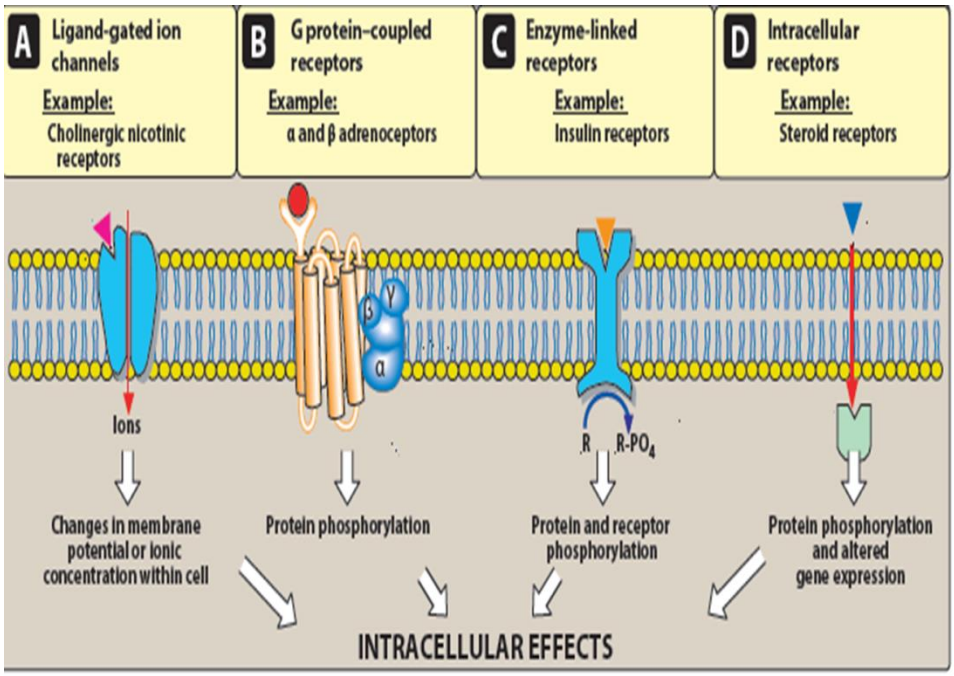
  - The drug that acts on receptors is very specific → so that the side effects are limited.
  - The more specific the less side effects

كيف ؟ لانه سواء راح عالكبد أو الكلى أو أي مكن بالجسم وما لقى receptors ما بصير شي

- **Major Receptor Families**

Receptors divided into four families:

1. ligand-gated ion channels(extracellular)
2. G protein-coupled receptors (extracellular)
3. enzyme-Linked receptors(extracellular)
4. Intracellular receptors. (intracellular)
   Note: steroid drugs can enter the cell and attach to intracellular receptors.



A) Ligand gated ➔ the receptor is attached to ion channel... When the drug bind to the receptor this leads to open the channel (the ion channel considers as a second messenger). An example of a drug that

attached to these types of receptors is digoxin. It has a specific receptor on the ion channels not like nerves.

كيف بيختلف ؟ بإنه كل ال nerve بصيرله depolarization ويمتلك قنوات محددة مو ligand gated ion cannels

Another example: Cholinergic

أدوية بتشتغل على ال muscarinic receptors وهم receptors الهم علاقة بال parasympathetic and nicotinic receptors

B) G protein-coupled receptors:

- They are receptors have 7 subunits and these subunits attached to 3 other subunits called (alpha, beta and gamma) subunits.

- When the drug attached to the receptor it leads to conformational change ➔ and this stimulates a second messenger

- This type of receptors is important when we talk about alpha and beta receptors (ANS receptors).

C) enzyme-Linked receptors

- here the drug doesn't attached to the enzyme like angiotensin converting enzyme …

- In these receptors the drug attached to a receptor and then the receptor stimulates <u>enzyme inside the cell</u> like <u>kinase enzyme</u>.

- An example of these receptors is insulin receptors.

D) Intracellular receptors

- These types of receptors don't work if the drug doesn't enter the cell because they are located inside the cell … that is mean the drug should has a specific features to reach the receptors.

- One example of these receptors is steroids receptors.

هلأ رح نحكي عن كل وحدة منهم بالتفصيل الممل : ☺

- **Ligand-gated ion channels:**
  - Called ionotropic receptors.(because it's attached to ion channel).

  - Responsible for regulation of the flow of ions across cell membranes (stimulates influx and out flux for ions like Ca^{+2})

  - Ligand binding and channel opening occur on milliseconds. So, response to these receptors is very rapid**.** Why? Because it doesn't need second messenger, stimulating enzymes or producing proteins.يعني فقط بتتطلب فتح القنوات ليظهر تأثير الدواء الي أعطيناه

  - Mediate many functions, including neurotransmission, cardiac conduction, and muscle contraction.
  - Examples:
    - ✓ Acetylcholine binds with nicotinic receptor _ **sodium influx**-contraction in skeletal muscle (neuromuscular junction). (there is no drug called acetylcholine because this endogenous acts within seconds)
      لو يصنعوا متله رح يتحطم من خلال phosphor acetyl cholinesterase
    - ✓ Benzodiazepines – bind with gamma-amino butyric acid type (GABA) receptor – **Chloride influx**-

hyperpolarization. (used to make a sedition states in depression disease and psychosis)

بيشتغل على مكان اسمه GABA (neurotransmitters) موجودة في الدماغ عبارة عن inhibitor بيعمل chloride influx

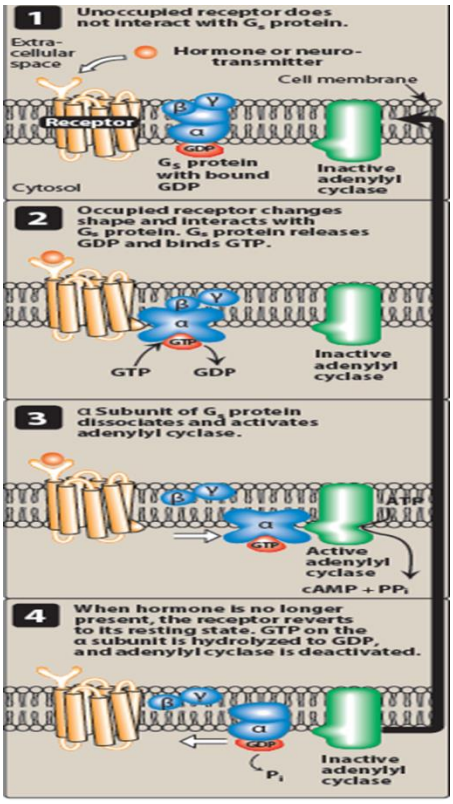
من الأمثلة على ال benzodiazepines دواء اسمه valium يستخدم كمنوم

- ✓ Digoxin: with **sodium-potassium ATPase influx** leads to enter the calcium into the muscle then contraction.

هلا الفكرة انه هو ما بخلي البوتاسيوم يطلع وبيسكر القناة فهاد الشي بيخلي الكالسيوم يدخل على الخلية العضلية ويعمل contraction لهيك بنستخد هاد الدواء لما بدنا نزيد ال contractility of the heart

حكت الدكتورة انه المهم نعرفه من الأمثلة الي فوق هو انه كل دواء منهم بيشتغل على ion channel خاصة فيه شو رح يصير لما تفتح هي القناة أو تسكروعملتلكم ال action تبع كل وحدة ب bold font

- G-protein-coupled receptors:
  - Also called <u>metabotropic receptors</u>.
  - Single peptide with seven membrane-spanning regions, these receptors is linked to a G protein.
  - One of the intracellular loops is larger than the others and interacts with the G-protein.
  - The G-protein = membrane protein comprising three subunits (α,β,γ), the α-subunit binds GTP, possessing GTPase activity.



- Binding of the ligand to the extracellular region of the receptor activates the G protein and leads to conformational change in alpha subunit → then GDP which is located on this unit replaces into GTP by phospholaration → GTP molecule now has energy → this energy cause alpha subunit to attach with adenylyl cyclase enzyme and stimulates it → this enzyme increase production of cAMP
- All drugs are sharing the same previous steps … after that each drug has a specific proses to continue.
- Dissociation of the G protein ⇒ both the α-GTP subunit and the β,γ subunit interact with other cellular effectors – so

called second messengers (responsible for further actions in the cell).

- The second messenger involved in this process are :
  1. GDP
  2. adenylyl cyclase enzyme
  3. cAMP (the main second messenger) لانه هو الي رح يشتغل الخطوات القادمة يعني لو زادت ال cAMP رح يزيد ال action ولو قلت رح يقل ال action .

- **Trans membrane G-protein-coupled receptors**

Second messengers : if I want to know the effect of drug I have to know how many second messenger are there (in the cell) .

لانه ممكن أعطي 2 drugs واحد منهم بيعمل على تثبيط ال cAMP وبالتالي يأثر على عمل الدواء الآخر

Examples of the second messenger:

- Activation of adenylyl cyclase by a-GTP subunits ⇒ production of **cAMP** that regulates protein phosphorylation.
- G proteins also activate phospholipase C –(degradation of phospholipids) responsible for the generation of 2 other second messengers :
- **inositol triphosphate [IP_3] :** increases free cytosolic Ca^{2+} (Ca^{+2} influx) by releasing Ca^{2+} from intracellular compartments (ER) — cause contraction, secretion of certain compound like hormones , enzyme activation and membrane hyperpolarization
- **diacylglycerol (DAG)** activates protein kinase C

Responses: several seconds to minutes

يعني أطول من الوقت الي بتحتاجه ال ion channels لانه بيحتاج تحفيز سلسلة من ال second messenger

هلا من كل المصايب الي فوق لازم تعرف بشكل أساسي انه ال G protein is embedded in the membrane اله طرف من فوق وطرف من تحت بيحفز second messenger الي ممكن يكونوا :

CAMP or inositol triphosphate [IP_3] or diacylglycerol (DAG)

لانه هم الي مسؤولين عن ال final action تركيزهم هو الي رح يأثر .

Examples:

- Muscarinic receptor

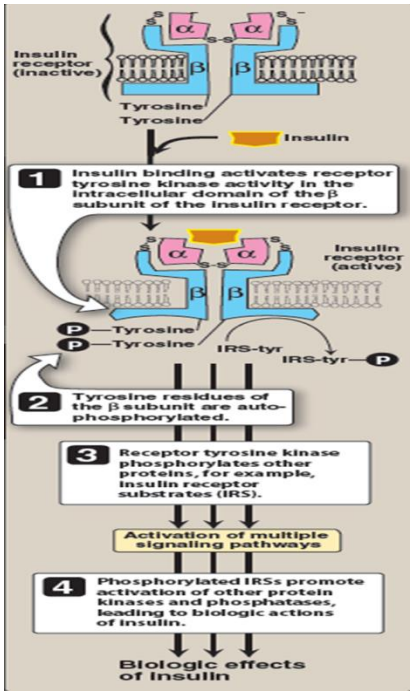
ملاحظ مهمة و ممكن نتخربط اذا ما عرفناها : هلا ال receptors الي الها علاقة بال muscles نوعين وحدة موجودة بال neuromuscular junction ووحدة على نهاية ال parasympathetic الي بنحكي عنه هون هو الي اله علاقة بال parasympathetic

- Adreno-receptors (alpha and beta receptor)
- Neuropeptide receptors.

- enzyme-Linked receptors: **(Kinase-linked receptors):**
    - Cytosolic enzyme activity is an integral component of the receptor structure or function.
    - Binding of a ligand to an extracellular domain $\Rightarrow$ activation or inhibition of this cytosolic enzyme activity.
    - Duration of responses **- minutes to hours**.
    - The most common - with a tyrosine kinase activity as part of their structure.

- Binding of a ligand activates the kinase ⇒ phosphorylation of tyrosine residues of specific proteins.
- The most common enzyme-linked receptors:
  - **epidermal growth factor**
  - **insulin**

Example: Insulin receptor



- insulin is released from pancreatic Langerhans cells
- when insulin binds to receptors (alpha and beta receptors) on our functional cells (mostly in adipose tissue and the liver), it stimulates a free cytosolic second enzyme called tyrosine to bind with it (the receptor) →that causes activation of the enzyme→ tyrosine kinase activity causes auto phosphorylation of the receptor itself.

- In turn, the phosphorylated receptor phosphorylates target molecules-insulin-receptor substrate peptides- (IRS) that subsequently activate other important cellular signals (e.g., IP_3, and the mitogen-activated protein kinase system.

- The last step in this process is opining glucose channels in the cells (in the liver starting making glycogen)

يعني ال action بيختلف حسب مكان ارتباط الانسولين

- This process needs long time because the tyrosine enzyme is free in the cytosol.

- **Intracellular receptors (nuclear receptors)**
    - The receptor is intracellular ⇒ ligand must enter the cell to interact with the receptor.
    - Particles should have a very small molecular weight and lipophilic and have a receptors inside the cell if there is no receptors there will be no action.
    - One important example of these drugs is steroids (steroidal structure like sex hormones) female : estrogen and progesterone , male: testosterone
    - Testosterone is used to treat breast cancer

    - Some are actually located in the cytosol rather than the nuclear compartment, e.g., steroid and thyroid hormones, vitamin D, certain lipid-Lowering and antidiabetic drugs.

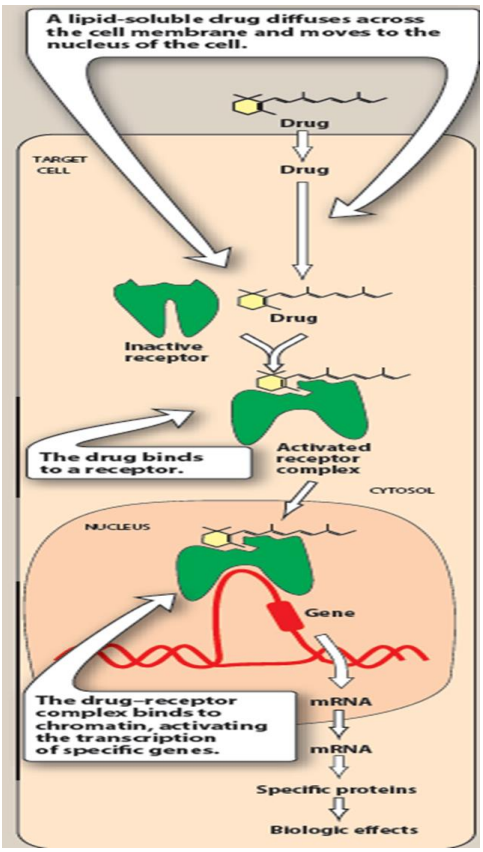
- Activated ligand-receptor complex migrates to the nucleus, where it binds to DNA sequences ⇒ regulation of gene expression.

- The time course of activation and response of these receptors is much longer, cellular responses delayed (30 minutes or more), and the duration of the response (hours to days) is much greater than in other receptors.

- To understand the point above take glucocorticostroieds as an example:

- It has a long duration and delayed onset of action needs to enter the cell and make a genetic mutation to synthesis certain protein muscles.
  So it needs a long time

مشان هيك بيحكوا ما توقف الكورتزون فجأة لانه الآكشن تبعه بيطول لحتى يحدث gene formation على ال بيشتغل انه بسبب كورتزون بياخدوا الي انه ثانية وملاظة
بنلاحظ انه شكل ظهرهم متل ال hump



شرح للرسمة :

هلا هاد الدواء عبارة عن chain متصل فيها حلقة بنزين يعني has a steroidal structure

و معروف انه كل ما كانت ال alkyl group أطول رح تزيد ال lipophilicity بالتالي رح يدخل بسهولة على الخلية

الي لونه أخضر هو inactive receptor بس يرتبط بال drug رح يصير active ويدخل ال complex على النواة وبعديها بصير DNA transcription and mutation وبعديها نعمل mRNA بيصنع بروتين جديد من خلال الرايبوسم