SHEET NO.

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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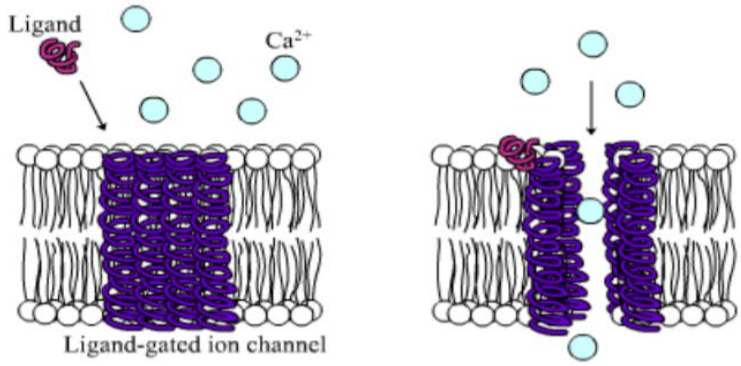
Before you start ,see the last page

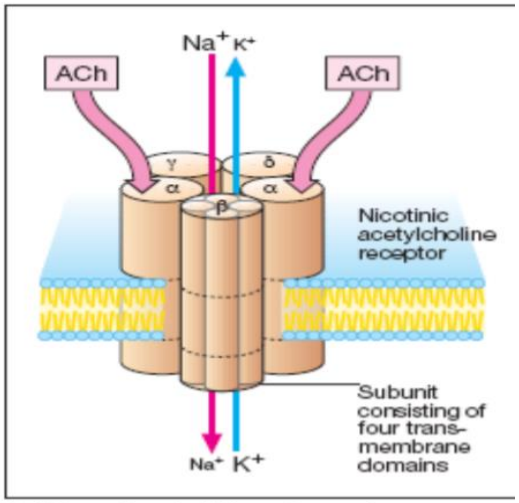
Major receptor families

1. **Ligand-gated ion channels (it is too fast. If it was taken**
   a. **-intravenously →too fast .**
   b. **-orally → just need time for the drug to reach the cell)**
2. **G protein-coupled receptors (fast)**
3. **Enzyme-linked receptors (fast)**
4. **Intercellular receptors (slow)**

Ligand-gated ion channels

Responsible for regulation of the flow of ions channels across cell membranes.
• Regulated by binding of a ligand to the channels.
• The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle .resulting contractibility .
Ligand gated ion channel are channels that have receptors which control the opening/ closing the channel and regulate to the action potential and contractibility of muscles.





B. Ligand-gated ion channel

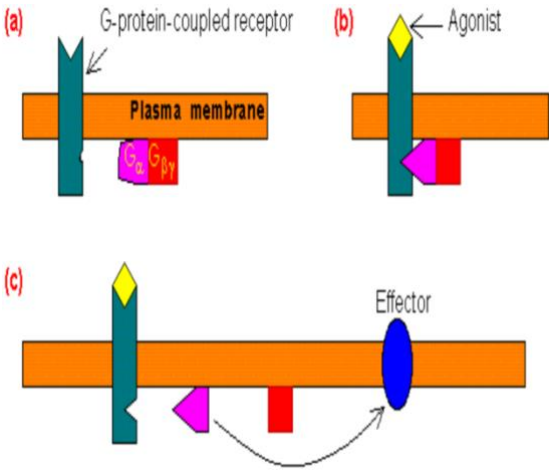
G protein-coupled receptors

the outer side → is the receptor .
the inner side →is linked with G-protein(GTP binding protein).

- when the drug or the endogenous(from the body) ligand bind such as noradrenaline which bind to beta1 receptor →induce dimerization process → induce signaling by g-protein (called GTP dependent signaling)

• Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.

• Some hormones peptide receptors and neurotransmitter
receptors (e.g., adrenergic and moscarinic receptors depend on the G proteins) mediate their action on cells.



Enzyme-linked receptors

• Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme.
• The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein.
• The addition of phosphate group can modify the three dimensional structure of the target protein, and so resulting in molecular switch.
Insulin bind with the channel from the outside (receptor region)→cause the tyrosine kinase activation(phosphorylation)→ changing of the 3-D structure of the bound proteins →starting signaling pathway through the cell →ending up with biological activity (which we call **transduction**).

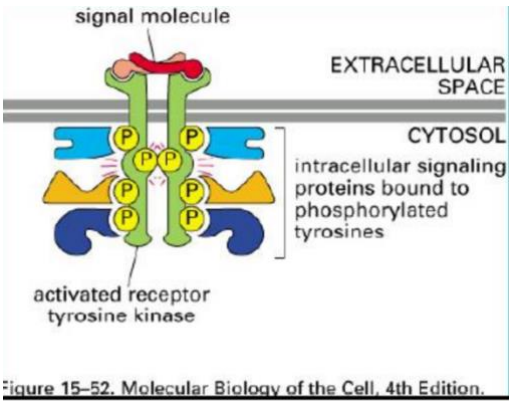
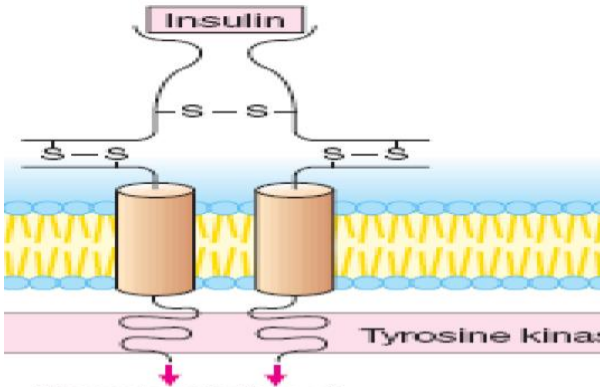
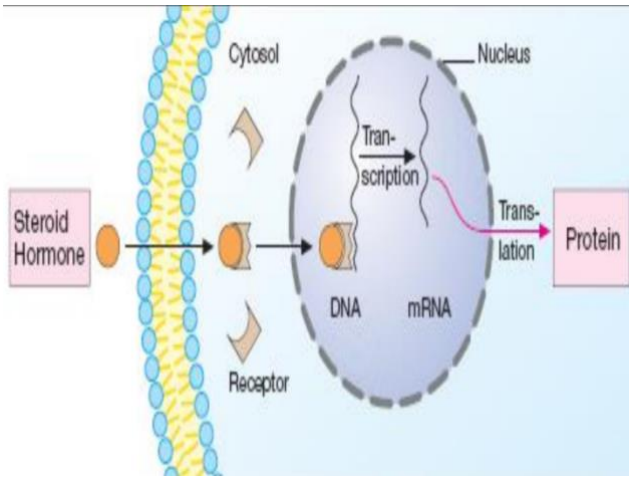


Figure 15–52. Molecular Biology of the Cell, 4th Edition.



Intercellular receptors (important)

• In this family the ligand must diffuse into the cell to interact with the receptors.
• Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.
• The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.



Steroid hormones cross the membrane because they are hydrophobic easily and bind with specific receptor in the cytosol → the hormone –receptor compound go to DNA inside the nucleus to do gene expression which is transcription and translation processes (response occur).

Notes:

-intracellular receptor may be mRNA(not a must to be protein)which gets outside the nucleus just after the transcription .
-The drug may also be a sequence of nucleotides that bind to mRNA(nucleotides drugs binds with nucleotides receptors). Then ,it will continue the underlined pathway.

-If drug's nucleotides are small(around 20 nucleotide called microRNA<<by the way, it is covered by the liposomes which will enter the cell through endocytosis>>),its receptor may be the mRNA(or may be the DNA itself)which is still in the nucleus and inhibit it there.

-it is a slow process because the drug will make changes within the transcription of the protein (response)→this will increase /decrease of the protein level → this process stabilization depends on protein half time, so it takes hours or even days .

Receptor properties

differentiated activity of the target cell.

The activity depend on the target cell.

Example: adrenergic receptors

- enhances cardiac contractility
- relaxation of smooth muscle cells

Adrenaline

The same receptor in smooth muscles →will bind with beta receptor →more release of calcium ions →more abundant ions between myosin fibers →relaxation of the muscle

The receptor of it in Cardiac muscles →will bind in beta1 receptor bound with G-coupling protein→more release of the calcium ions →more contractility of cardiac muscles which is the inotropic and chronotropic effect .

The idea here is that the receptor and the substance are identical but the reaction depends on the tissue . cardiac tissue has different response of smooth muscles

Extra info:

Stimulation of the Beta1-adrenergic receptors in the heart results in positive inotropic (increases contractility), chronotropic (increases heart rate), dromotropic (increases rat of conduction through AV node) and lusitropic (increases relaxation of myocardium during diastole) effects.

The capacity of significantly **amplify physiological signal** .(exaggeration of the response)

If I give a patient 1 molecule of cortisone .This doesn't mean that the expression of the gen will increase by 1 .However, it means that the expression of it will increase by 1000.

Example :

Heparin bind with receptor in the blood called antithrombin3

The normal activity of antithrombin3 is 1

When it bind with heparin the activity becomes 1000.

Dose response relationships

• Graduate dose-response relations :

As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax. (Example =800mg)

Example : profin drug

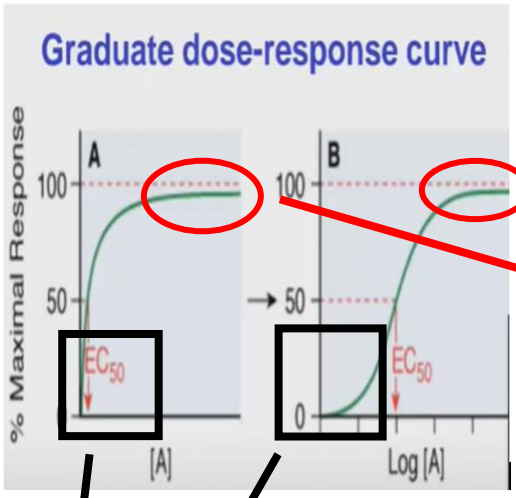
200mg→ analgesic activity for mild pain
400mg→moderate pain
600mg→moderate to severe pain
800mg→sever pain
1000mg/2000mg→will not give additional biological effect and will give the same biological effect of 800mg dose. However, it will increase in side effect and increase in the toxicity.

What can I do if the patient still in pain?
simply change the drug.

In the Emax we reached the saturation state , any increase of the concentration will not be effective .

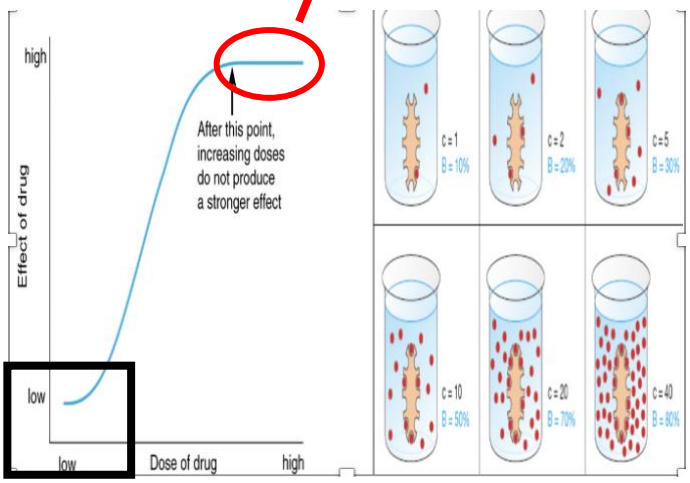
A :Hyperbolic curve
not preferred in studying
not that accurate
[A] is the concentration of the drug

B: Sigmoidal curve of Graduate dose-response curve(more accurate)because it is more linear (the higher the dose , the high the effect)



Emax(plateu)

Lacking area; lack of effect with the concentration increase.



VERY IMPORTANT TOPIC.

• Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed(عدد المستقبلات التي يرتبط بها الدواء), and also on the efficiency of the of coupling of receptor activation to cellular responses.

k1 :measurement of the drug-receptor association constant .

the higher the k1→ the stronger the amplification of physiological effect is.

The lower the k1 →loose amplification of physiological effect

• Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of.

morphine has higher efficacy because it binds stronger to the same receptor(K1 of morphine>K1of aspirin)

The same receptor may have many Emax depending on the drug that bound to it .

Different receptors also have different Emax too.

Sheet notes

Slides information

Professor notes

The professor recommend to read more about spare receptors which are the empty receptors during saturation (it is a logic not to have empty receptors when there is a saturation of the drug).

I recommend you to watch the lecture, it is entertaining .