RECEPTORS & Intracellecular signaling Molecules

Pharmacology

By: ZAKIRULLAH Yousufzai

Ligands: Substance which bind with receptor.

e.g: ① Hormones
② Neurotransmitters
③ Drugs
④ Toxins
⑤ chemical substances

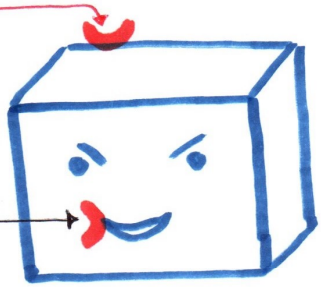
Receptor: Receptor are Macromolecules to which ligand binds.

* If ligand binds to a substance which does not cause any biological function, such substance are not called receptor: e.g: plasma protein

There are two main groups of Receptors

① Large molecular wt OR high Polar e.g (Peptides)

② Small molecular wt OR highly Lipid soluble



* Those molecules which are large and highly Polar, Can't pass through membrane, so They act on membrane, so this is called Cell surface receptor.
* Those molecules which are small & highly lipid soluble their receptors are present inside the cell.

RECEPTORS

Cell surface receptor

Peptide hormone (Large molecules)
- Insulin
- GH
- prolactin
- FSH
- LH
- TSH
- etc....

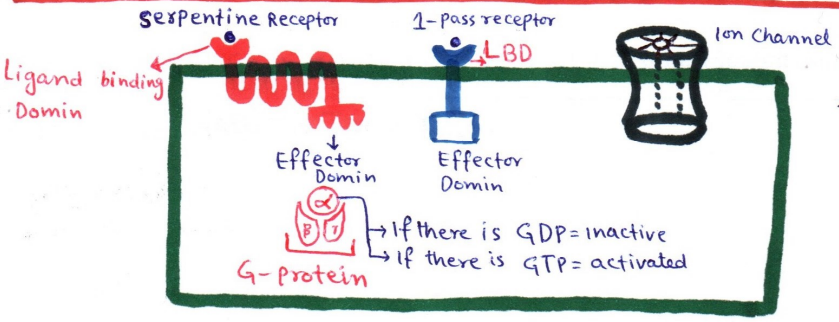
Catecolamin (high Polar)
- Epinephrin
- Nor Epinephrin
- Dopamin
- Ach
- 5OHT
- Histamin
- Prostaglandine
- etc.....

Receptor within cell

Steroid hormones like: (high Lipid soluble)
- Testosteron
- Progesteron
- estrogen
- Aldosteron
- Glucocorticoid
- Vit-D

Small molecular weight
- T_3, T_4
- Retinoid

Receptors which are Expressed on the surface of cell



* serpentine means "SNAKE") b/c This receptor is like snake.

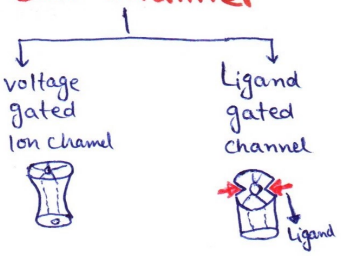
Serpentine receptor

Catecholamines
Ach
Prostaglandine
Histamine
STh
TSH

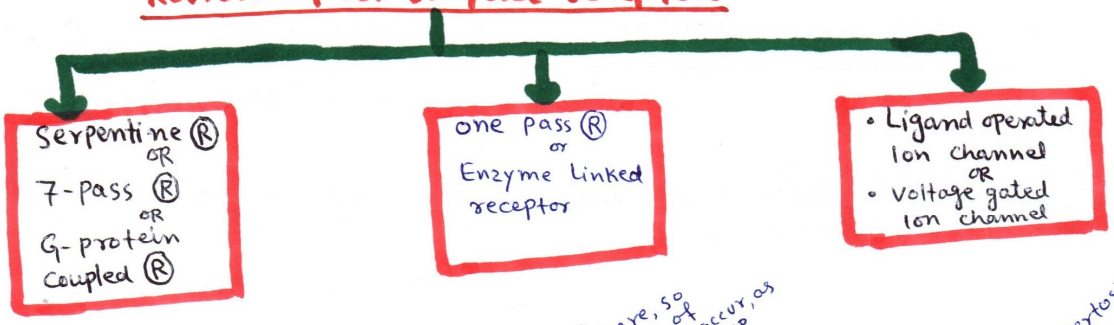
1-pass receptor

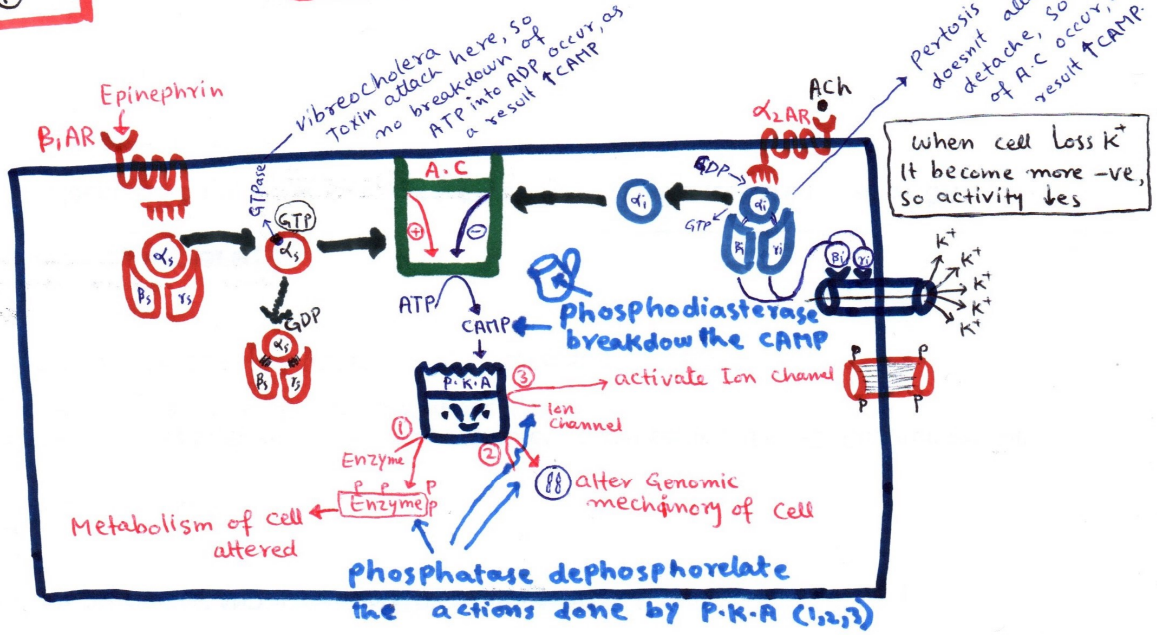
Inner domin of 1-pass receptor is usually Enzyme so it is also Called: (Enzyme linked receptor)

Ion channel



Review of cell surface receptors





when α sub unit stimulate the A.C (Adenyl cyclase), so the GTP break down into GDP.

* when α unit remain with GDP (less energy), it attached to β & γ unit again.
* when α unit gain GTP, it detaches from β & γ units & activate A.C

- Ligand is called 1st messenger to cell
- cAMP is called 2nd messenger to cell
- G-protein is called Biological switcher

this whole system is called Biological amplifier system.

Epinephrine & Ach are countering each other.

* Epinephrine ⟶ ↑ cAMP
* Ach ⟶ ↓ cAMP

GTpase is an internal enzyme of α subunit, so when α unit stimulate the AC, then this GTpase breakdown GTP into GDP.

phosphodiasterase breakdown the cAMP.

* Tea, Cocacola, Pepsi..... Inhibit the phosphodiesterase, so the activity of cAMP increase up in the cell.

phosphatase inhibit the phosphorylated substances, which were phosphorylated by P.K.A.

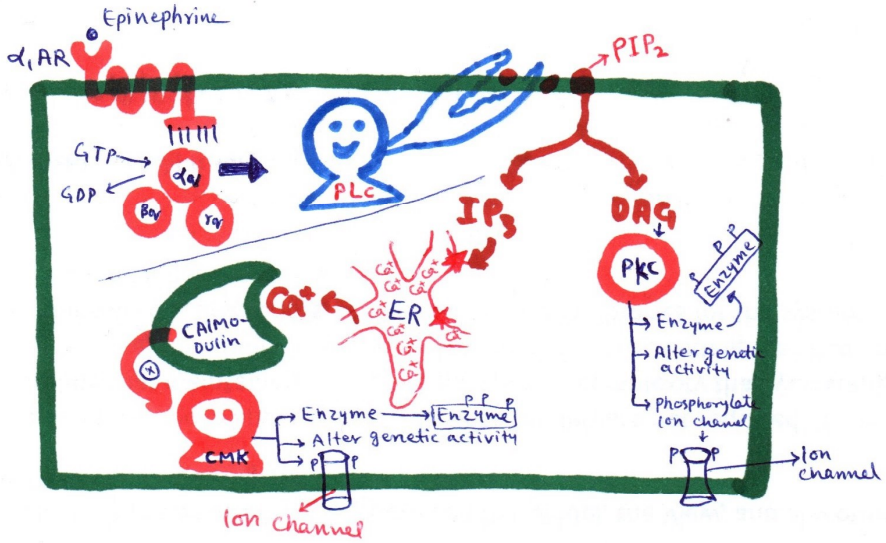
* In these above example we see at every step there is balance system going on in the body.

Pertosis → Toxin → Gi protein (αi, βi & γi fuse with each other)

so G-protein not detach from each other to produce effect on A.C.

when Pertosis (Microbe) produce Toxin in respiratory system, Toxin is taken by respiratory cell & α, β, & γ will undergo ribosylation process, they are put togather & not dissosiated, so Gi protein remain off OFF is of forever. & the cAMP action enhanced & not inhibited.

Vibrio cholera → Cholera Toxin → goes into GIT cells, & inhibit the intrinsic GTPase of G_s protein, so the ATP doesn't breakdown from α_s unit, so it stimulate A.C for more time, so we say ON is ON Forever. & the action of cAMP increase ⟶ Diarrhea occur.



Calmodulin → protein which can be modulated by Ca^{+}; & form Ca^{+}-calmodulin complex which activiate CMK → which has 3-actions.

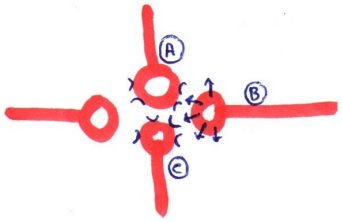
① cholinergic → Nicotinic ® → Muscarinic ®

② Adrenergic → α_1 AR → IP_3 → ↑Ca^{+} → CaMK; DAG → PLC
→ α_2 AR → Gi → ↓cAMP ⊕ β_i, γ_i → K^{+} efflux
→ β_1, β_2, β_3 → ↑A.C → ↑cAMP → P.K.A ↑

③ Dopaminergic → D_1 → G_s → ↑cAMP
→ D_2 → Gi → ↓cAMP

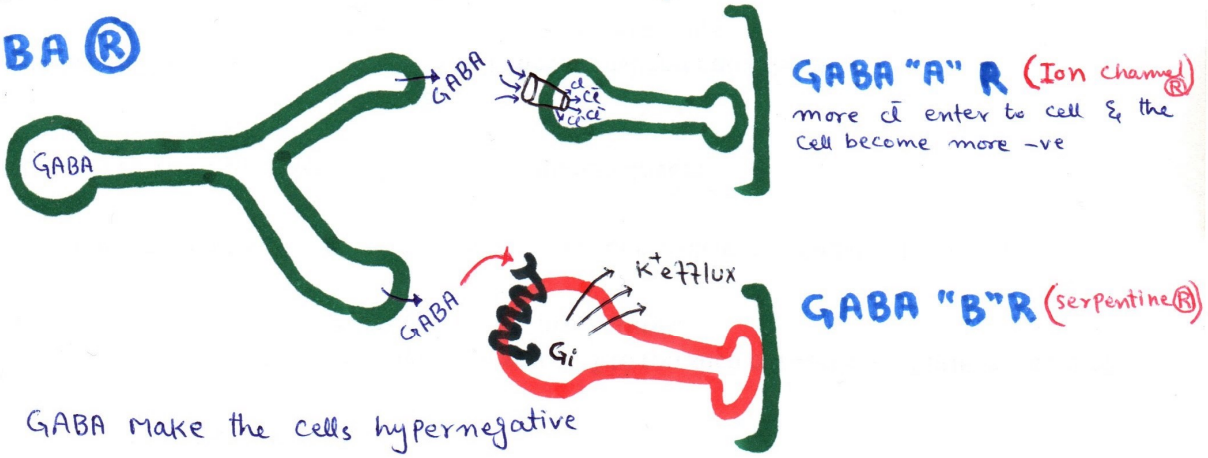
* Muscarinic receptor Antagonist.
① ATRopin ② Scopolamine ③ Pirenziphene
* Drugs which block α_1 receptor.
① Phentolamine → (α_1AR, α_2AR) ② Phenoxybenzamine ③ Prazosin (α_1AR) ④ Terazosine (α_1AR)
* Drugs which block α_2 receptor.
① Yohimbin
* Drugs which block β-receptors.
① Propranolol ② Metoprolol ③ Acebutolol ④ Esmolol ⑤ Atenolol ⑥ Timolol

④ Purinergic ® → A TYPE (serpentine) sensitive to Adenosine
→ B TYPE → sensitive to ATP



If for example B neuron has high metabolic rate, and large amount of ATP is utilized & release adenosine. This adenosine diffuse acts on nearby cells Adenosine receptor & show that metabolism of a cell is high

⑤ GABA ®



GABA "A" R (Ion channel ®) more Cl⁻ enter to cell & the cell become more -ve

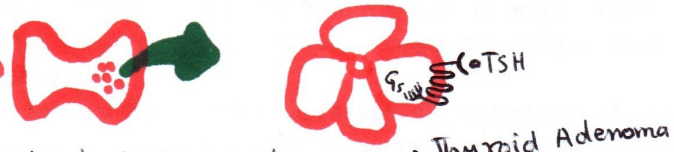
GABA "B" R (serpentine ®)

GABA make the cells hypernegative

→ Drugs which stimulate GABA "A" receptor.
① Benzodiazepine ② Barbiturates

→ Effect of drugs on GABA "B" receptor.
① Baclofan → agonist of GABA-B
② Saclofan → antagonist of GABA-B

⑥ TSH ®



Mutant TSH receptor → Thyroid Adenoma

⑦ LH-®
If this receptor is non functional, it lead to precocious puberty (puberty at age 6Y)

⑧ ACTH ® (serpentine)
If there is defective gene for this receptor it lead to:
"Familial Glucocorticoid deficiency"

⑨ Receptor for Rhodopsin:
If this receptor is defective, it can lead to "Retinitis pigmentosa".

⑩ **Neuropeptide** (R) → (serpentine)

Vasopressin (ADH) → V_1 (Receptor present in vascular system)
→ V_2 (receptor present in Cortical collecting Tubule)

If V_2 is defective Person sutter of X-linked Diabetic insipidus.

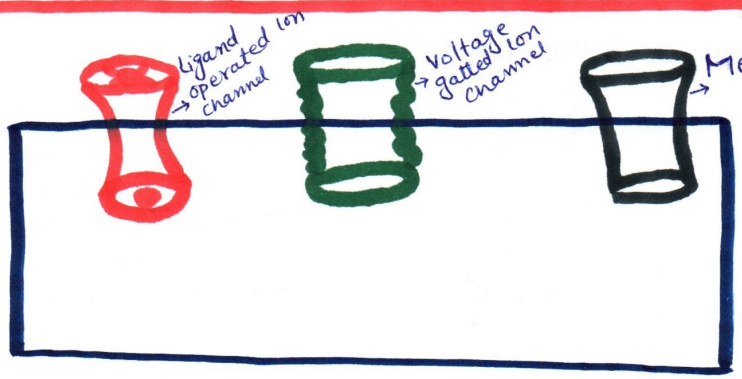
⑪ **Ang II** (R) present in arteries, veins zona glomerulosa of adrenal gland
↳ ⌇⌇

⑫ **OPIATES:** ⌇⌇ e.g → Endorphin
→ Enkephalin

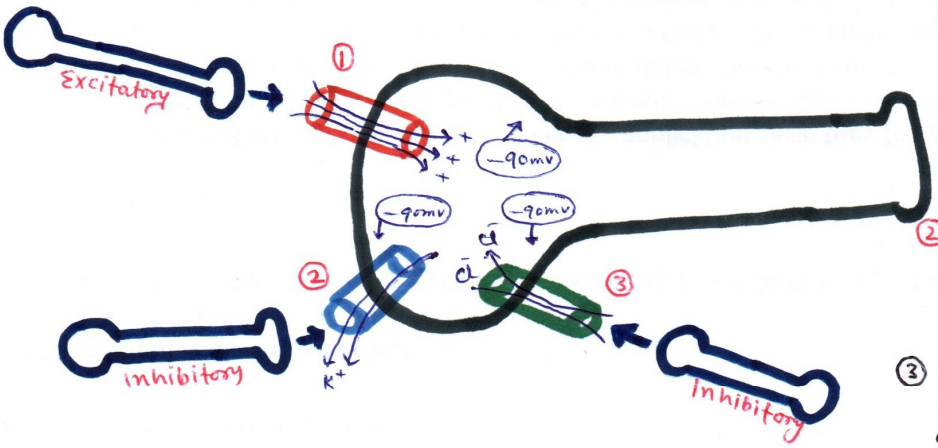
⑬ **VIP (vasoactive intestinal peptidase)** → ⌇⌇

⑭ **oxytocin** → ⌇⌇

ION CHANNEL LINKED RECEPTORS



Ligand operated Ion-channel can be stimulated by:
① Neurotransmitter
② Hormones
③ Chemicals



① when cations move in, cell become electro+ve & RMP goes to threshold, & cell Excited

② when cell loss more K^+, cell become electro-ve, & hyperpolarized

③ when more -ve ions (Cl^-) enter to cell, cell become electro-ve.

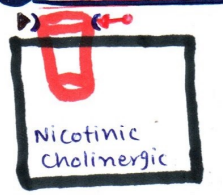
Ligand gated Ion channel

Excitatory Transmitter gated Ion channel

Let suppose
Ach = ⟵
Nicotine = ◀
Muscarine = ●

e.g

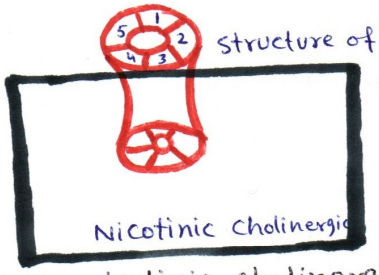
① Nicotinic Cholinergic Ⓡ



Nicotinic cholinergic Ⓡ is basically Ion channel

These receptor Can bind with:
→ Acetylcholine
→ Nicotine

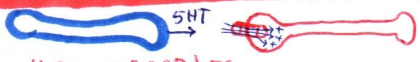
Muscarinic cholinergic Ⓡ are basically serpentine this receptor can bind with:
→ Acetylcholine
→ MUSCARINE



Structure of Ion channel
↓
Made from 5-peptide proteins

* one nicotinic cholinergic Ⓡ Can bind with two Ach.
* This channel also cause inside movement of: → Na^+, → Ca^+ & small amount K^+ efflux occur.
* Antagonist of this receptor:
① Tubocurare ② α-Bungarotoxin

② 5 HT-3 Ⓡ

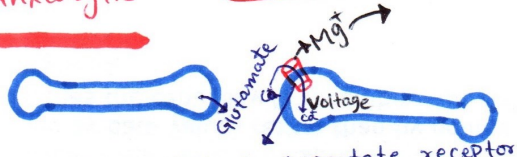


Antagonist of this receptor
① Antiemetic ② Antipsychotic ③ Anxiolytic

③ Glutamate Ⓡ

this type of receptor need doubble stimulation: ie ligand (Glutamate) from outside & voltage from inside.

Normally Mg^+ bind to this receptor, when the receptor are stimulated Mg^+ will move away from receptor & Ca^+ goes in.



N-Methyl-D-Aspartate receptor (NMDA-R)

Antagonist of NMDA R
① Phencyclidin ② Diazocilpin] anti hallucinic drugs.

* if NMDA-R are over stimulated it cause degenerative changes, by Ca^+ intoxication
* Glutamate help in long term memory

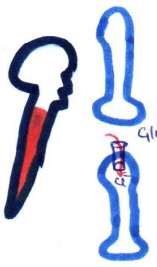
Inhibitory transmiter gated Ion channel

GABA
for whole CNS

Cell become hyperpolarized

* GABA Agonist
  - Benzodiazepin ↑ frequency of opening of this channel
  - Barbiturate ↳ ↑ duration of open of this channel
  - Steroid Metabolite
* GABA ANTAGONIST
  - picrotoxin
  - Biculine
  - penicillin

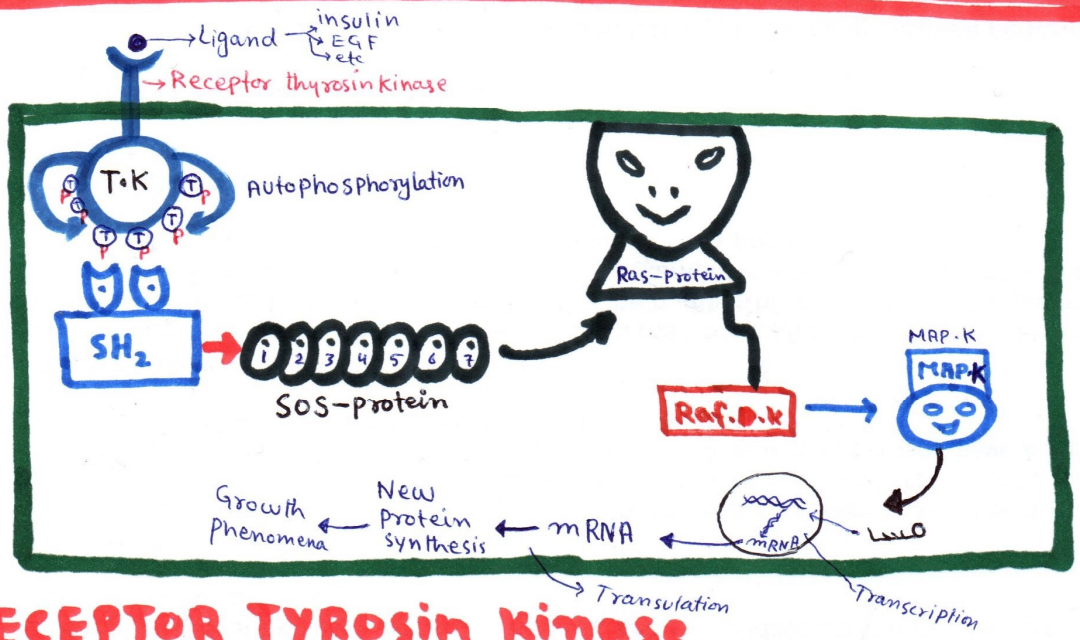
GLYCIN
only for spinal Cord



Excitatory Transmitter Ion channel
① → Nicotinic cholinergic Ⓡ
② → 5 HT-3 Ⓡ
③ → Glutamate Ⓡ

ENZYME LINKED SINGIE PASS RECEPTOR

hav 5 TYPES



1) RECEPTOR TYROSIN KINASE:

① Insulin ② Epidermal Growth Factor (EGF) ③ Nerve growth Factor (NGF) ④ Platlet growth factor ⑤ Vascular Endothelial growth factor ⑥ Plasma growth factors ⑦ Fibroblast growth factors, are bind as a ligand to this receptor.

This enzyme (T·K) have intrinsic tyrosin kinase activity, which cause phosphorylation of its own tyrosine residue this process is called "AUTOPHOSPHORYLATION".

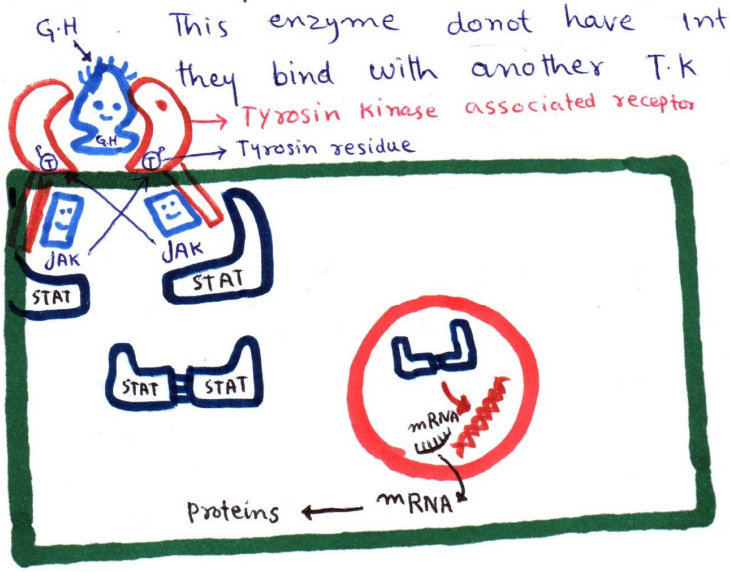
Sulfhydral protein which has two sulfhydral domin, comes & bind only with phosphorylated tyrosin residue, then sulfhydral protein themselve activated; and activate another protein called "SOS Protein" (Son of seven protein) they are going to activate another protein called "Ras-protein" which is a monomeric G-protein. Ras protein loose GDP & gain GTP, & become activated, Activated ras protein activate "RAF protein Kinase". the Raf protein activate "MAP-K" (Mitogen activating protein) kinase. This MAP·Kinase cause phosphorylation of Transcription factor, phosphorylated Transcription factor pass from nuclus, & initiate Transcription, so mRNA formed → Protein → Growth phenomena

① Ligand → ② T·K → ③ Autophosphorylation → ④ Sulfhydral protein → ⑤ Sos protein → ⑥ Ras protein → ⑦ Raf·P·K → ⑧ MAP. Kinase → ⑨ Gene regulated elements → ⑩ Transcription → ⑪ mRNA → ⑫ transulated to protein ⑬ Growth phenomena.

(2) Tyrosine kinase associated receptor (TKAR)

Bind with ligand & ligand cause dimerization of receptor.

This enzyme donot have intrinsic Tyrosine kinase activity but they bind with another T.K called JAK (Janus kinase).



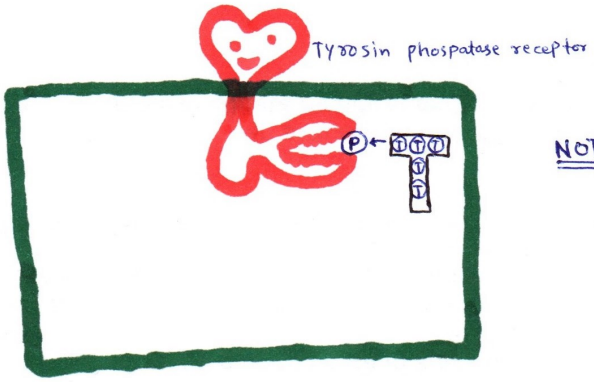
Jak cause cross phosphorylation of tyrosin residue.

Phosphorylated tyrosin bind with another protein called "STAT" (signal Transducer activation of Transcription). STAT than separated from Tyrosine residue & crosslink with each other & Translocated to nuclus.

Ligands which use this pathway are:
(1) Prolactin (2) IL-2 (3) cytokines (4) T-cell receptor (5) B-cell receptor

(3) Tyrosin phosphatase receptor

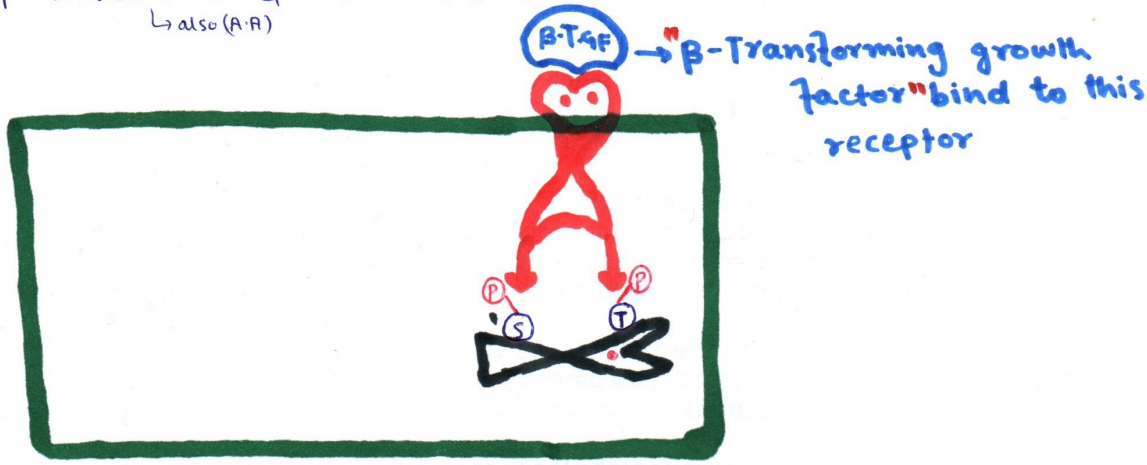
This receptor are dephosphorylating the Tyrosine residue.



NOTE: This Enzyme cause dephosporylation of Tyrosine residue

④ serine Threonin kinase receptor

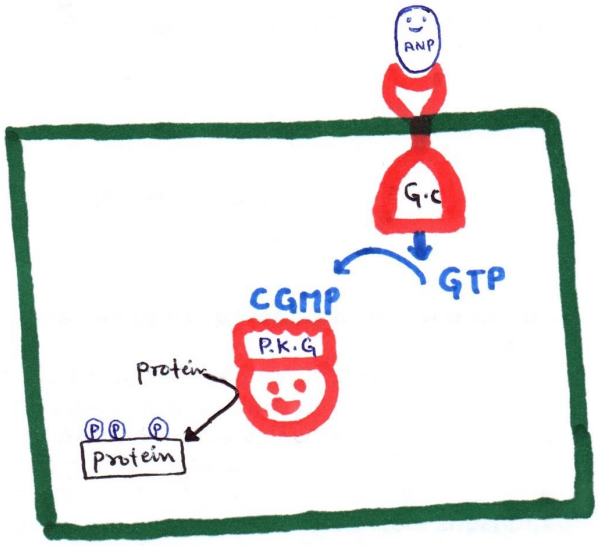
This receptor cause to load to phosphorylation of threonine & serine (A.A)
↳ also (A.A)



⑤ one pass Guanyl cyclase receptor

When ANP (Atrial natriuretic peptide) bind with this receptor, the Guanyl cyclase part of receptor Convert GTP into ⟶ CGMP.

* The CGMP activate "Protein Kinase G" which phosphorelate certain proteins.

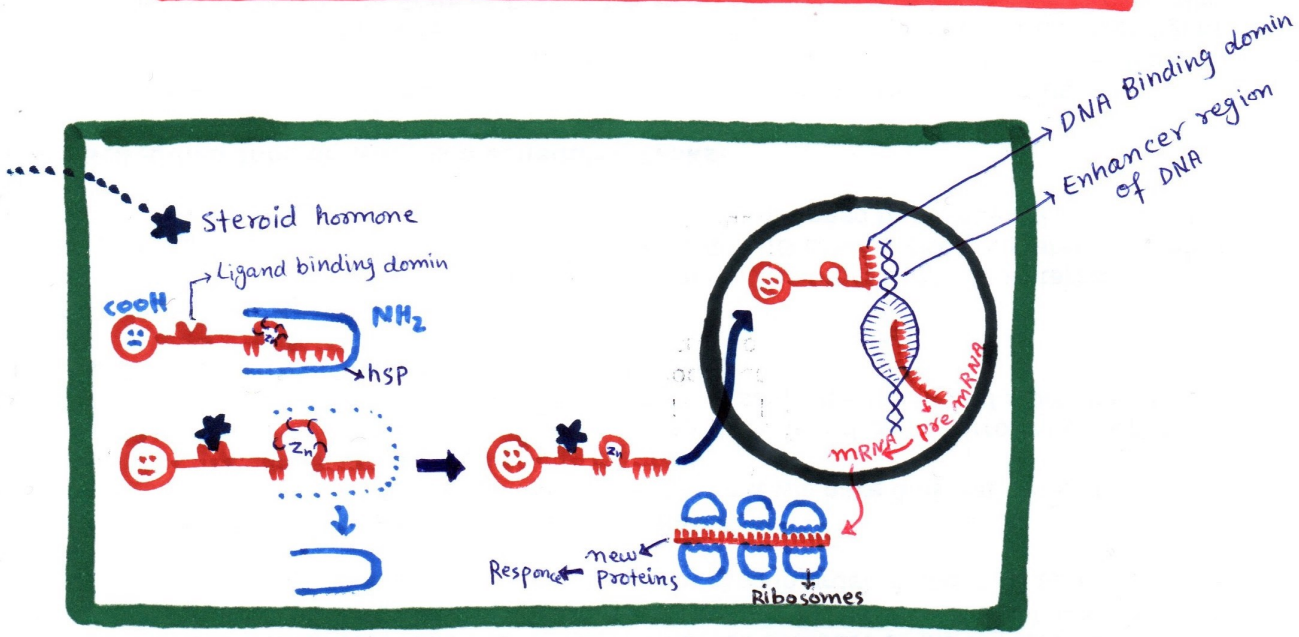


There are two types of Guanylyl cyclase receptors:

⇒ * one is the part of Guanyl cyclase receptor &

⇒ * other type is cytosolic, they are activated by Nitric oxide (NO) & this Guanyl cyclase cause conversion of GTP ⟶ into CGMP, but this is different from one pass receptor.

INTRACELLECULAR RECEPTORS



Before Ligand binding with receptor, the "DNA binding domin" is covered by HSP"(Heat shock protein)"
when Ligand bind to receptor, the hsp are removed & DNA binding domin become Exposed & activated.

This receptor is than transfered to nuclus, within the DNA binding domin binds to a specific region of DNA which is called "Enhancer region of DNA", and DNA start opening, & a pre mRNA are formed, than mRNA, the mRNA are transported to Ribosome, & new protein are made from it, & do its action.

In DNA binding Domain, there is Zinc molecule, attached to 4- Liceine crosslinked.

This is a delayed process to ligand it takes 30min ⟶ 1hr

NOTE

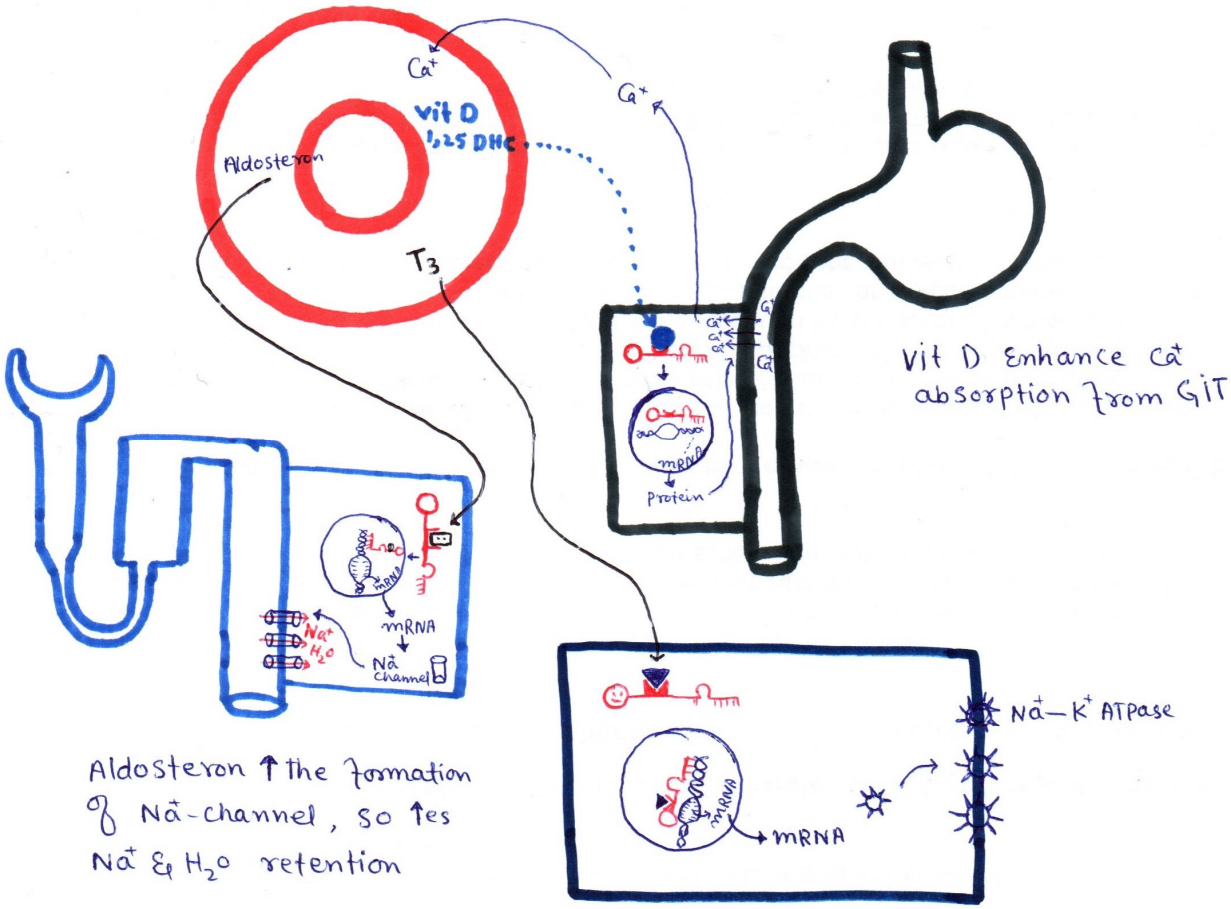
Intracytoplasmic receptors
*STD ⇒ steroid, T_3, T_4, Vit D

Receptors within the nucleus
Retinoids, T_3

Ligands

- Steroids
  - Estrogen
  - progesteron
  - Testesterone
  - Aldosteron
  - Glucocorticoids
  - ....> vit D
- T_3, T_4
- Retinoids

EXAMPLES

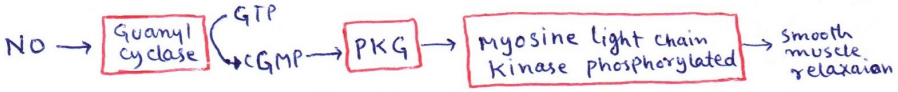


Function of other intracellecular

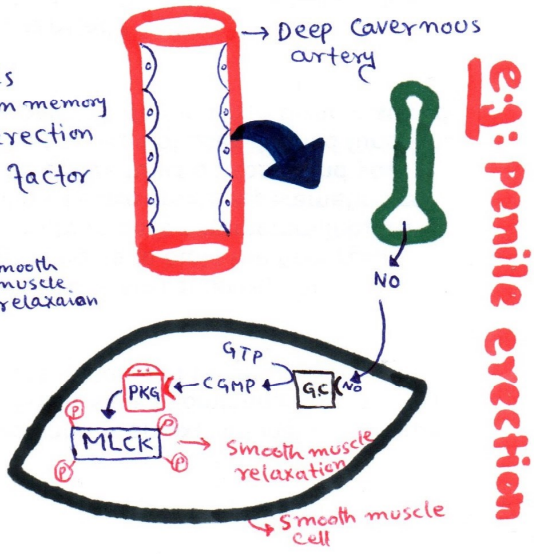
For example Ligand = NO (nitric oxide) a gas, with half lif of 5sec.

it is produced by:

- Macrophage → bactericidal, tumericidal, chemicals
- Neurons → Neurotransmitters → CNS → short term memory; PNS → Penile erection
- Endothelial cells → Endothelial derived releasing factor



MLCK are when phosphorylated, they become inactive, so it fail to cause phosphorylation of contractile protein, as a result smooth muscle relaxes & lead to arteriodialation.



e.g: Penile erection

How NO are Produced in the body :

Arginine —(NO Synthetase)→ citrulline + NO

When "nitric oxide synthetase act on the arginine, from it "citrulline" and Nitric oxide come.

NO also present in:

1. GTN (Glycerile Tri Nitrate)
2. Isosorbide dinitrate
3. Isosorbide Mononitrate
4. Nitroprusside

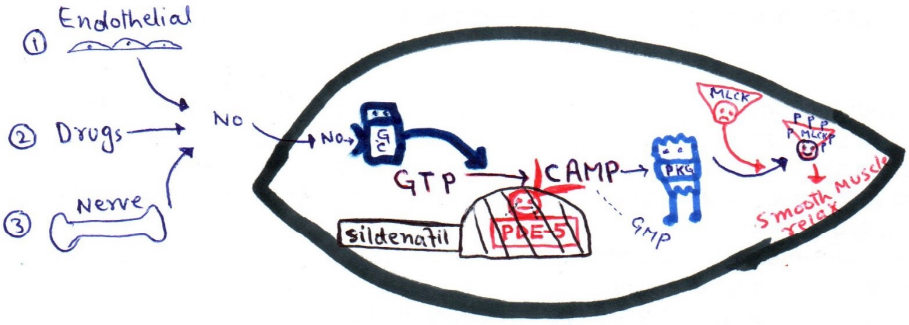
Smooth muscles around the deep Cavernous artery of penis & sinosides of Corpora Cavernosa of penis take nitric oxide & Muscle will dialate, & blood flow to penis increase & erection occur.

SILDENAFIL → VIAGRA

Sildenafil is active ingredient in viagra.

Sildenafil are binds to PDE-5 (Phospho di esterase-5) & inhibit them, so the destruction of CGMP not occur, which cause smooth muscle relaxation in penis Muscle, b/c no activation of contractile units.

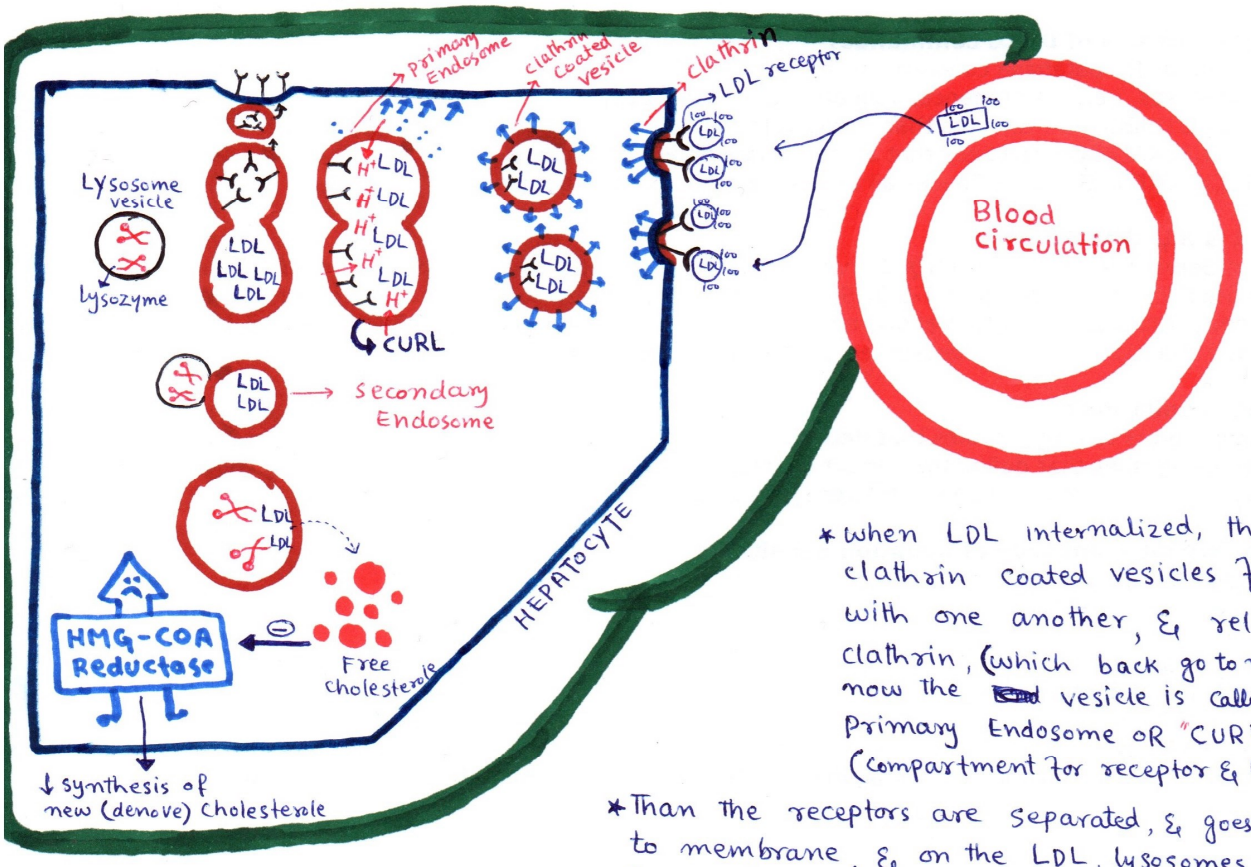
CGMP —(Phosphodiesterase-5)→ GMP



Receptor Mediated Endocytosis

In Endocytosis certain substances are internalized into cell. This is an active transport Mechanism.

e.g Endocytosis of LDL by hepatocytes.



* when LDL internalized, the clathrin coated vesicles fuses with one another, & release clathrin, (which back go to membrane) now the vesicle is called Primary Endosome or "CURL" (compartment for receptor & ligand)

* Than the receptors are separated, & goes back to membrane, & on the LDL, lysosomes attack & called "Secondary Endosome".

* The lysozyme release Free cholesterole from LDL, the Free cholesterole inhibit HMG-CoA Reductase.

The HMG-CoA Reductase makes new cholesteroles. So when there is high LDL the, HMG-CoA strongly inhibited, when the LDL is low the HMG-CoA not inhibited & more cholesterole are formed: so the Liver controle Cholesterole level in blood.

Familial Hypercholesteremia: In a family blood Cholesterole lever ↑es, lead to atherosclerosis, and at age aroun 20y MI occurs, problem is with this receptor.

① Reeceptor Mutant & does not bind to LDL.

② Receptor bind to LDL But doesnit trigger Endocytosis.

so the end result is to fail the whole process, & there is no inhibition of HMG-CoA-reductase, & ↑es blood cholesterole, & person develop FHC.

End of Receptor & Intracellecular molecule

By: Zakiyullah Yousufzai 14