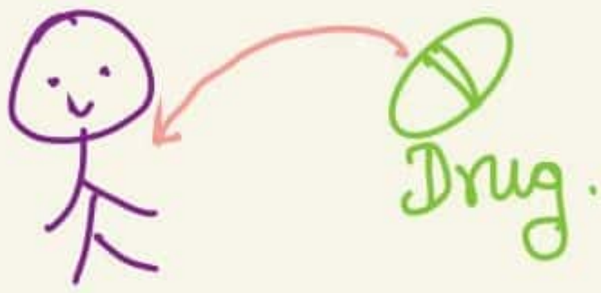
PHarmacodynamic

DEPTH OF BIOLOGY



what does drug do to the body

When We take Medicine ⇒

- Desirable effect.
- Undesirable effect.
  - Side effect
  - Toxic effect
  - Adverse effect.

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#Both desirable & Undesirable effect called PHarmacodynamic effect.

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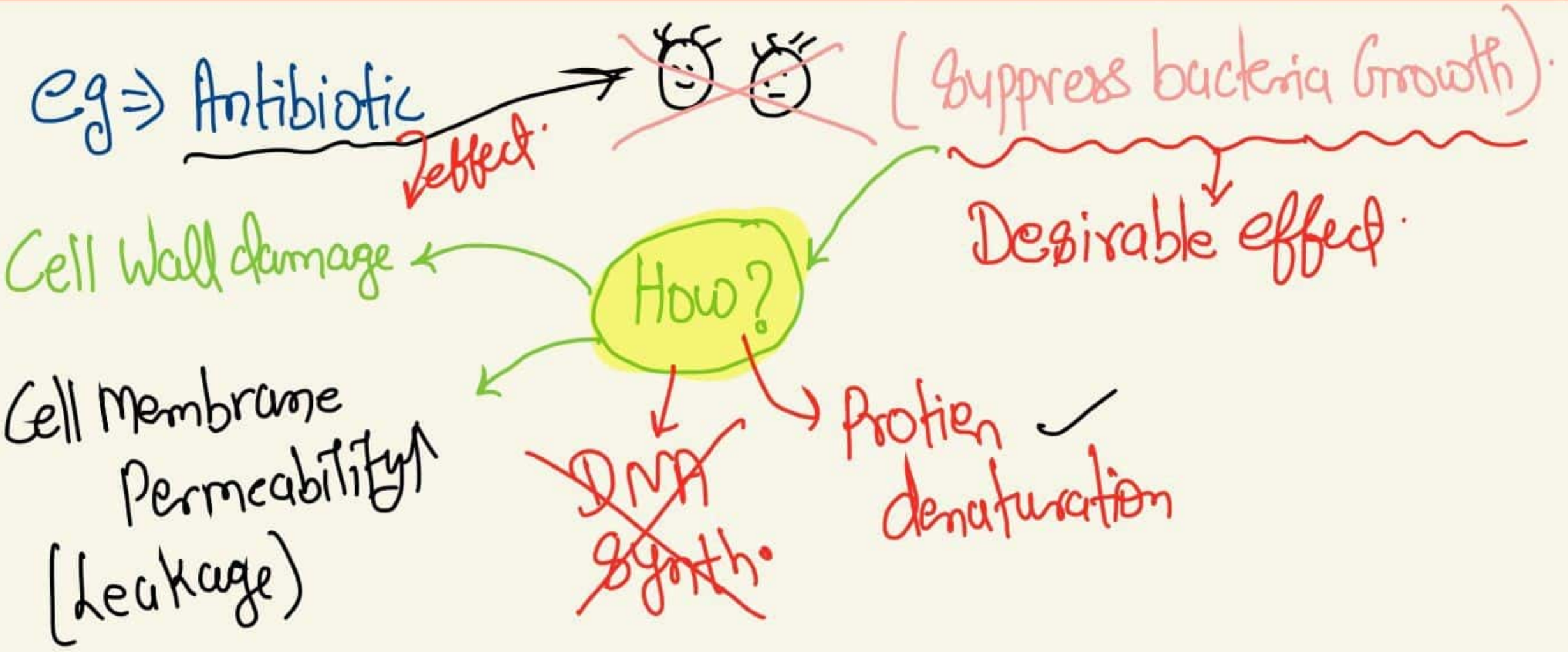

Principle of drug Action.

Drug → do not Impart any New function to any system

→ They only alter/change the pace of Ongoing Activity.

Principles of drug Action ⇒

(a) Stimulation (b) Depression (c) Replacement.

Enhancement (↑) of Activity.

eg → Caffeine

↓

CNS Stimulant.

Pilocarpine → Saliva Secretion ↑

(b) Depression or Supression

eg ⇒ Barbiturates

↓

CNS depresant

(c) Replacement.

↓ Iodine = Goitre

↓ Dopamine → Parkinson

↓ Insulin = Diabetes

↓

So, replace I2, Insulin & Dopamine.

Other Example → Fe↓

↓

Fe defic. Anemia.

Excessive stimulation is followed by depression.

(d) Irritation ⇒ Mean Uncomfortable होना

↓ DEPTH OF BIOLOGY

Lead to supression of Main surrounding Activity.

eg⇒ Balm.

☆ Excessive Use of Irritant ⇒ Cause Inflammation.

(e) Cytotoxic Action → Kill those particular cell which Harms our body

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eg→ Cancer Cell

Mechanism of Drug Action

Drug → Pharmacological Action.

↓

Mechanism ?

(How, where).

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① Enzyme → (Enzyme Substrate Complex).

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(S) → Enzyme → Binding site [Lock & Key].

⇓ Enzyme-substrate Complex.

Product form → Give Pharmaco. Action.

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Enz. Inhibitor → Competetive
→ Non-Competetive

② Ion Channel ⇒
- ⓐ Ligand Gated Ion Channel
- ⓑ Voltage (Conc.) Gated Ion Channel
- ⓒ G-protion regulated.

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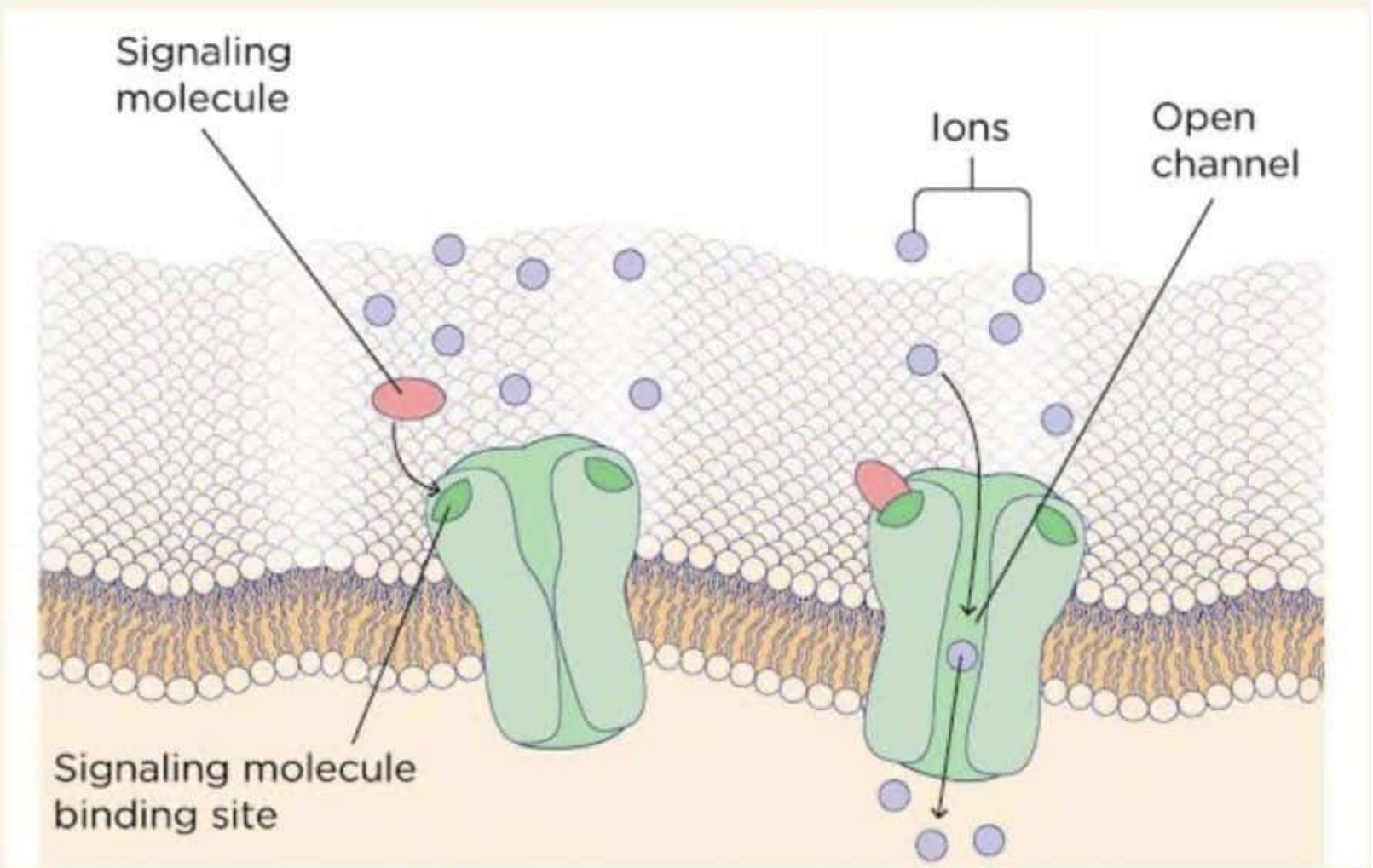

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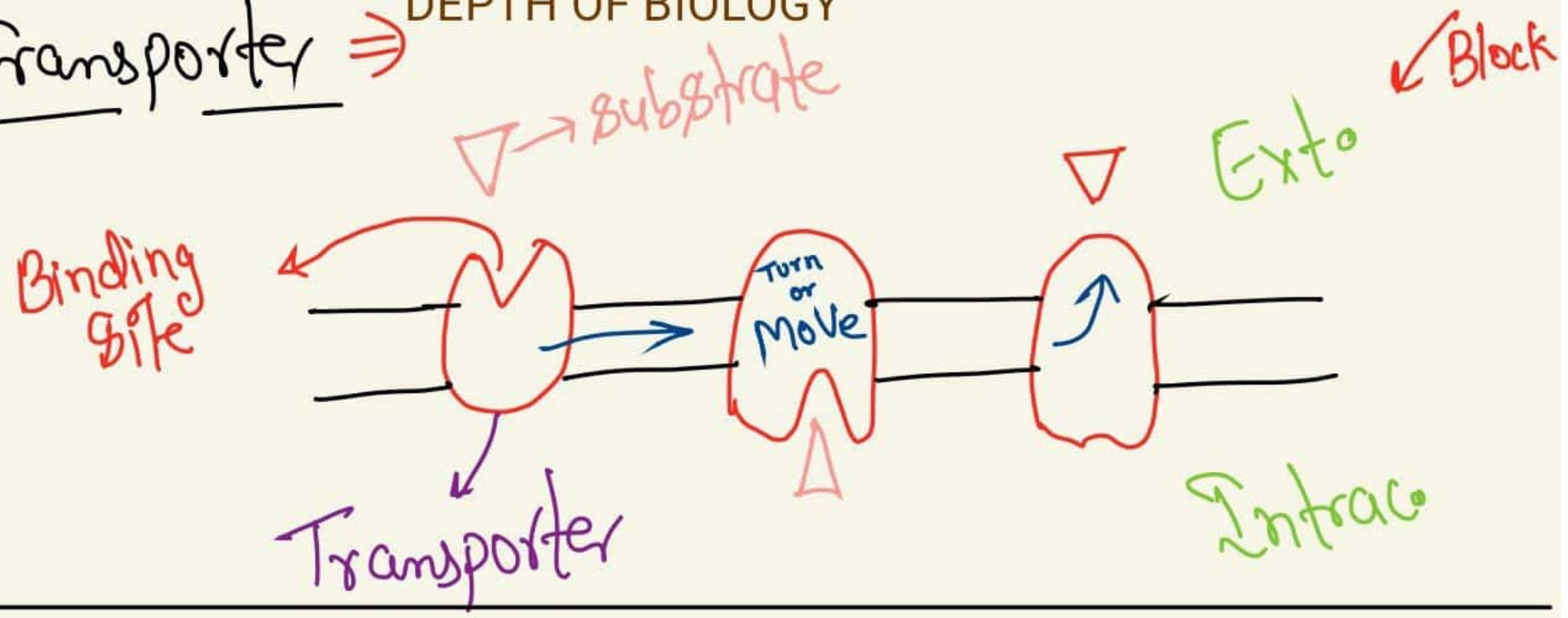
③ Transporter ⇒



④ Receptor → Identify the signal.

block by Inhibitor

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Receptor Theory & Classification of (R)

① Lock & Key Theory.

Lock → Receptor

Key → Drug.

⇒ Drug – receptor complex.

⇓

Pdt. formed

⇓

Pharmacological Action.

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(2) Rate - Theory ⇒

Drug + Receptor

⇓

Association ⇒ Pharmaco. Action ↑

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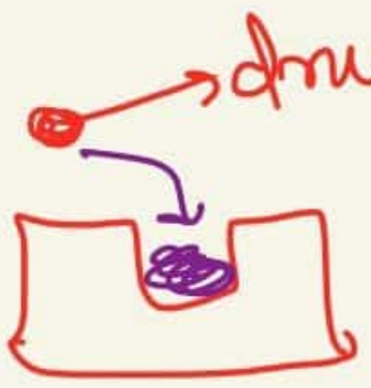
Receptor → Drug release

⇓

Then called dissociation

(3) Occupation Theory → The portion occupied by drug on Receptor



⇒ More portion occupied

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→ More will be the Pharmaco Action.

---

(4) Two - State Model

Resting

Activated

DEPTH OF BIOLOGY

Drug + Receptor

⇓

Affinity ↑ (D-R)

⇓

Action ↑.

⇒ Partial ⇒ D-R (Affinity ↓).

Agonist.

Fully Agonist.

on the basis of ⇒

Classification of Receptor

① Pharmacological Criteria ⇒

Potency of Agonist & Antagonist.

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This is Used to explain ⇒ M & Nicotinic (R). [Cholinergic]

? ⇒ α, β [Adrenergic]

? ⇒ Agonist ⇒?

⇒ Antagono ⇒?

---

② Tissue Distribution → Receptor distributed on diff. Organ.

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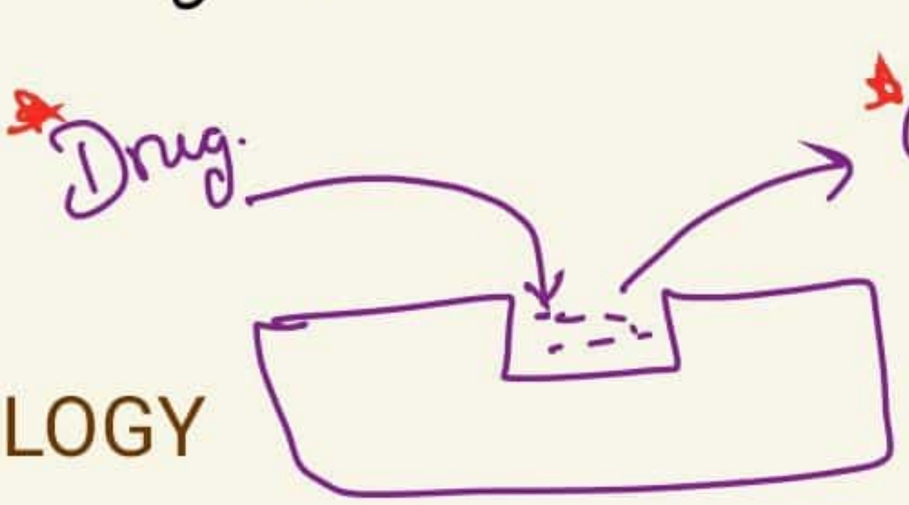
example ⇒ Cardiac β Adrenergic Receptor = β_1

Bronchial ——————— = β_2.

DEPTH OF BIOLOGY

(3) Ligand - Binding ⇒ DEPTH OF BIOLOGY

Measurment of specific binding of radio-labell Ligand to Specific Cellular fragment. [In Vitro].



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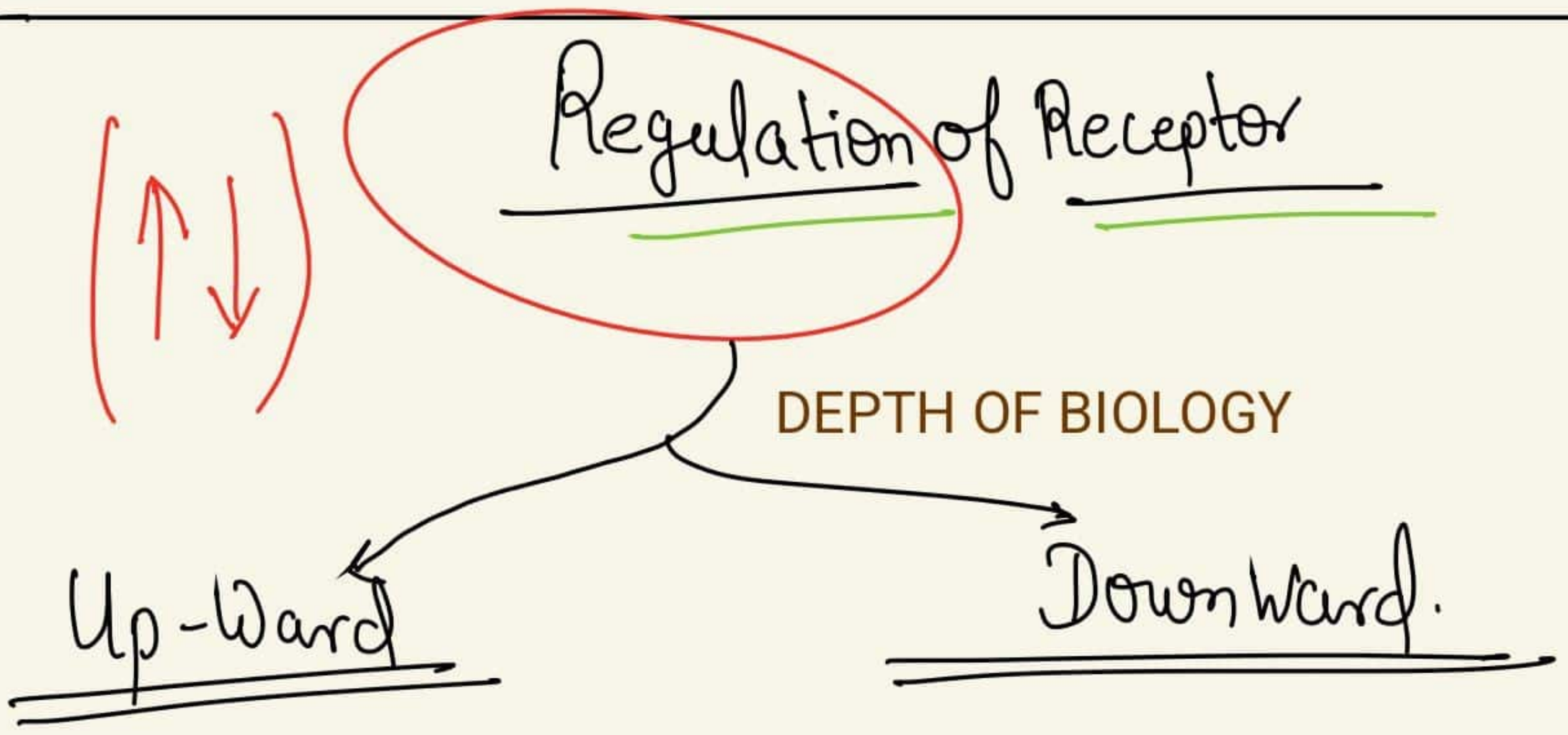
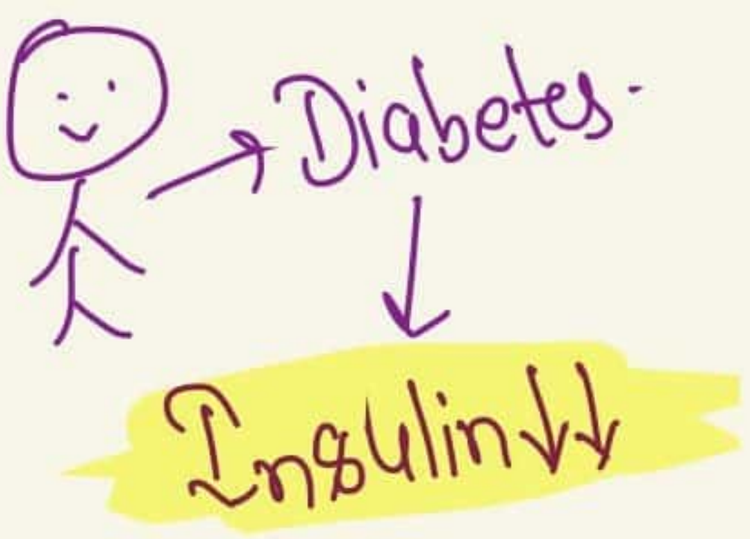
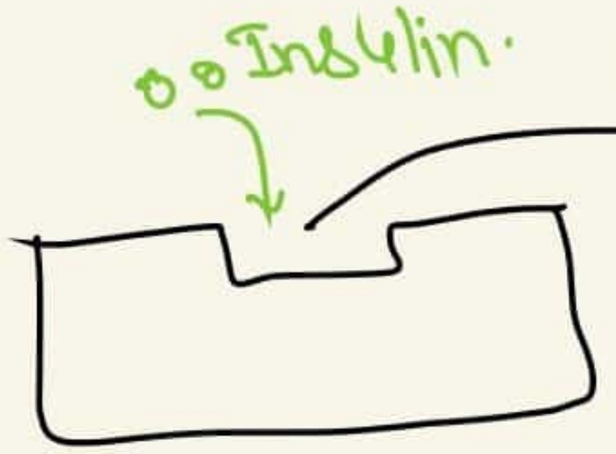
(5) Transducer pathway. → Mechanism through which drug bind on Receptor.

Eg → GPCR







Receptor

↓

Sensitivity ↑↑↑

↓

Action↑

Receptor Sensitivity (↑)se

To Maintain Homeostasis.

✡ In Case of Up-ward regulation

→ ↑se Sensitivity of (R)

DEPTH OF BIOLOGY

→ Number of (R)↑↑

→ Activation of Inactive (R)

---

(2) Downward Regulation →

→ Hormone↑

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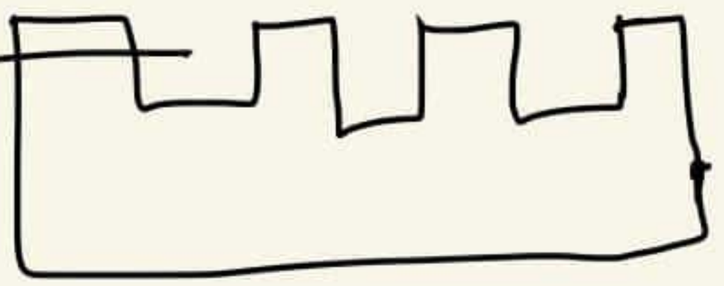
Inactivate (R)

No. of (R)↓↓

Sensitivity↓↓

Receptor



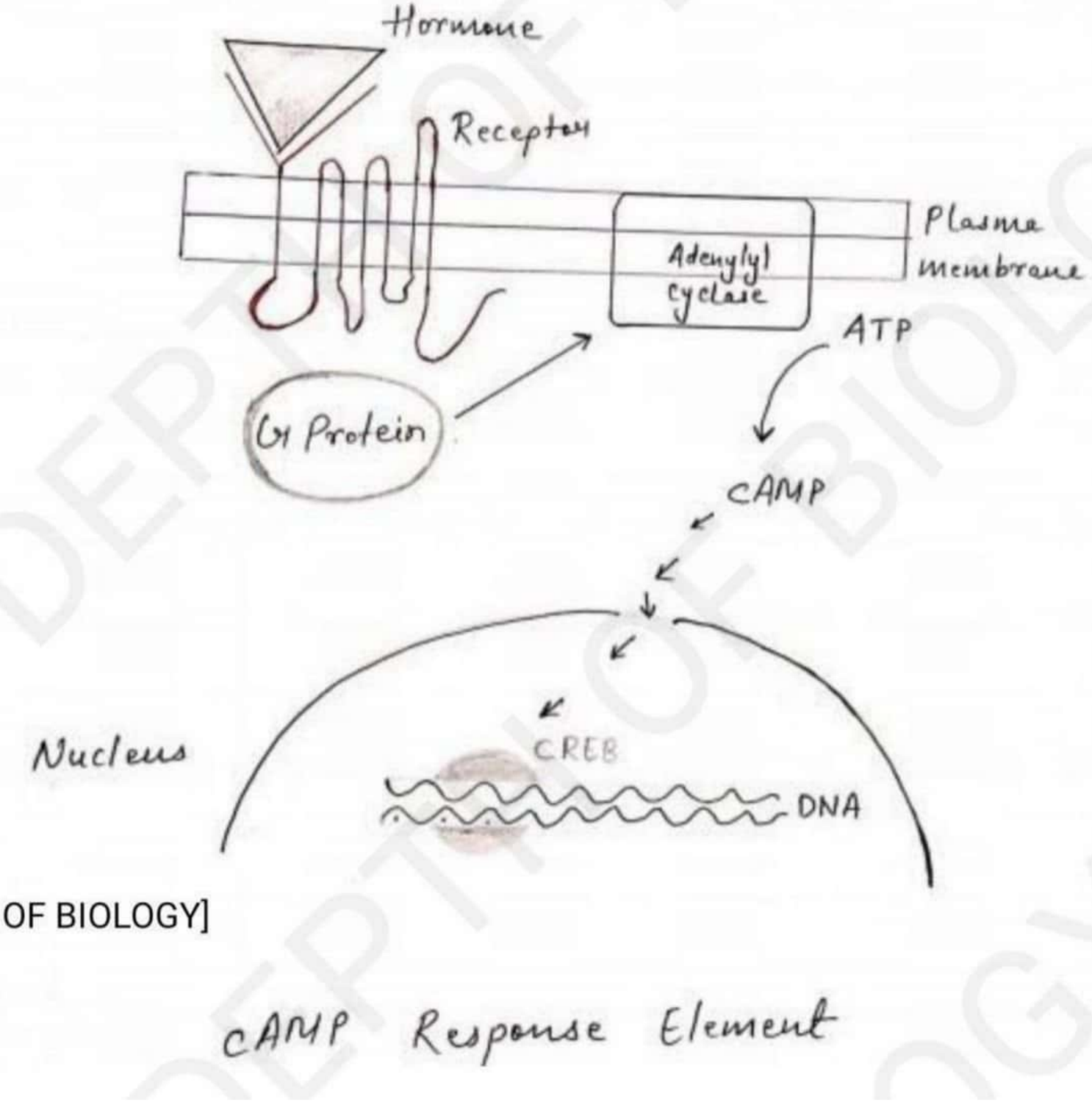
Drug - Receptor Interaction

Agonist + (R) ⇒ full action

Partial agonist + (R) ⇒ Less Action.

Inverse Ag. + (R) ⇒ opp. response.

Antag. + (R) ⇒ No response (block).



[DEPTH OF BIOLOGY]

SIGNAL TRANSDUCTION MECHANISM

- Mechanism pathway by which receptor`s activation is linked to response [DEPTH OF BIOLOGY]
- Ex: M Cholingenic receptor acts thrugh G-protein while N cholingelic receptor gates influx of Na+ ions

etc

[DEPTH OF BIOLOGY]

GROUPING OF TRANSDUCER MECHANISM

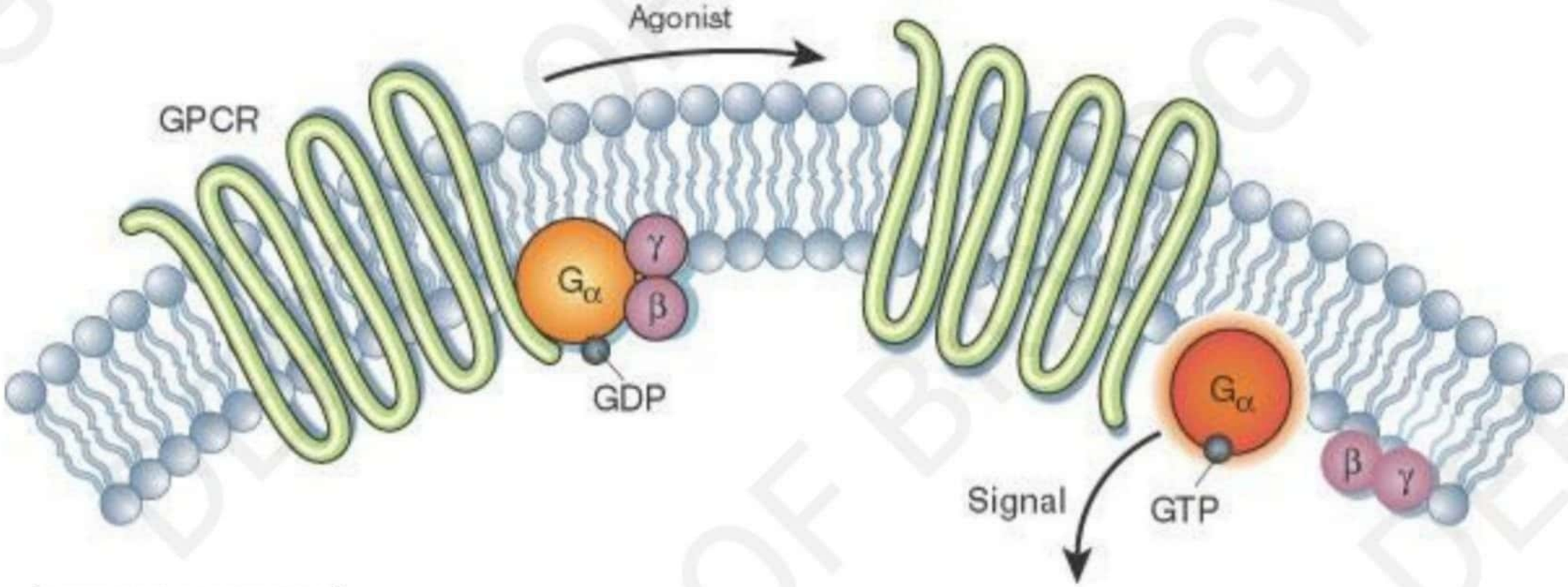
1) G-protein receptor
2) Ion channel receptor

3) Trans-membrane enzyme linked receptor
4) Trans-membrane JAK- STAT binding receptor
5) Receptor that regulate transcription factor

GPCR G-PROTEIN COUPLE RECEPTOR

- G- protein : guanine nucleotide-binding proteins
- Cell surface receptors [DEPTH OF BIOLOGY]
- Also known as- hepta helical receptor, 7 trans membrane receptor , metabotropic receptor
- Consitute large protein family of receptor that sense molecules [ligands] outside the cell [extracellular] & activate inside transduction pathway and give responses

[DEPTH OF BIOLOGY]



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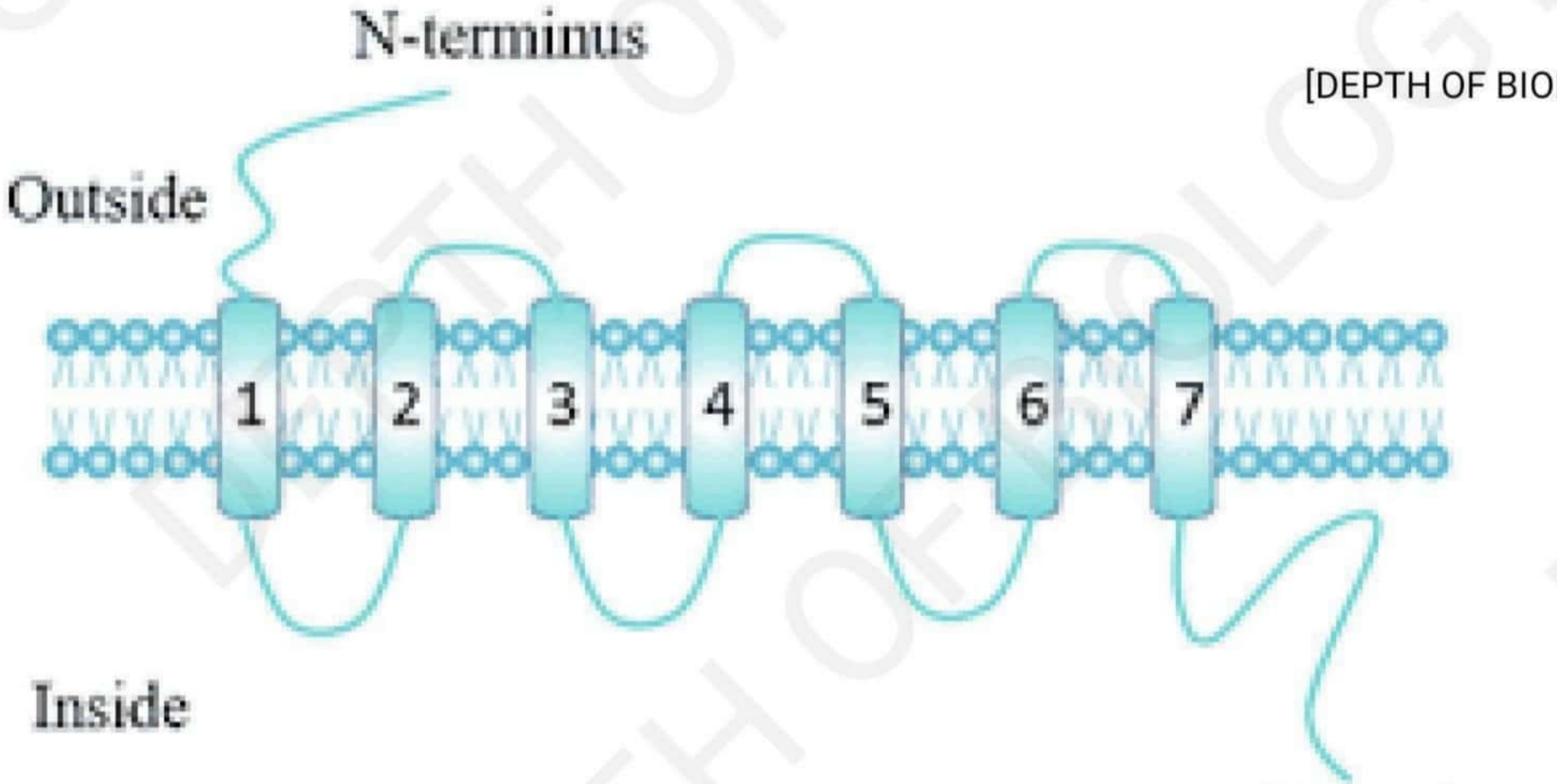


- Has 7 alpha helical membranes which contains 3 intra and 3 extracellular loops
- Triemeric complex form [α, β and γ] of G-protein in which GDP is attacked on α .

MECHANISM

[DEPTH OF BIOLOGY]

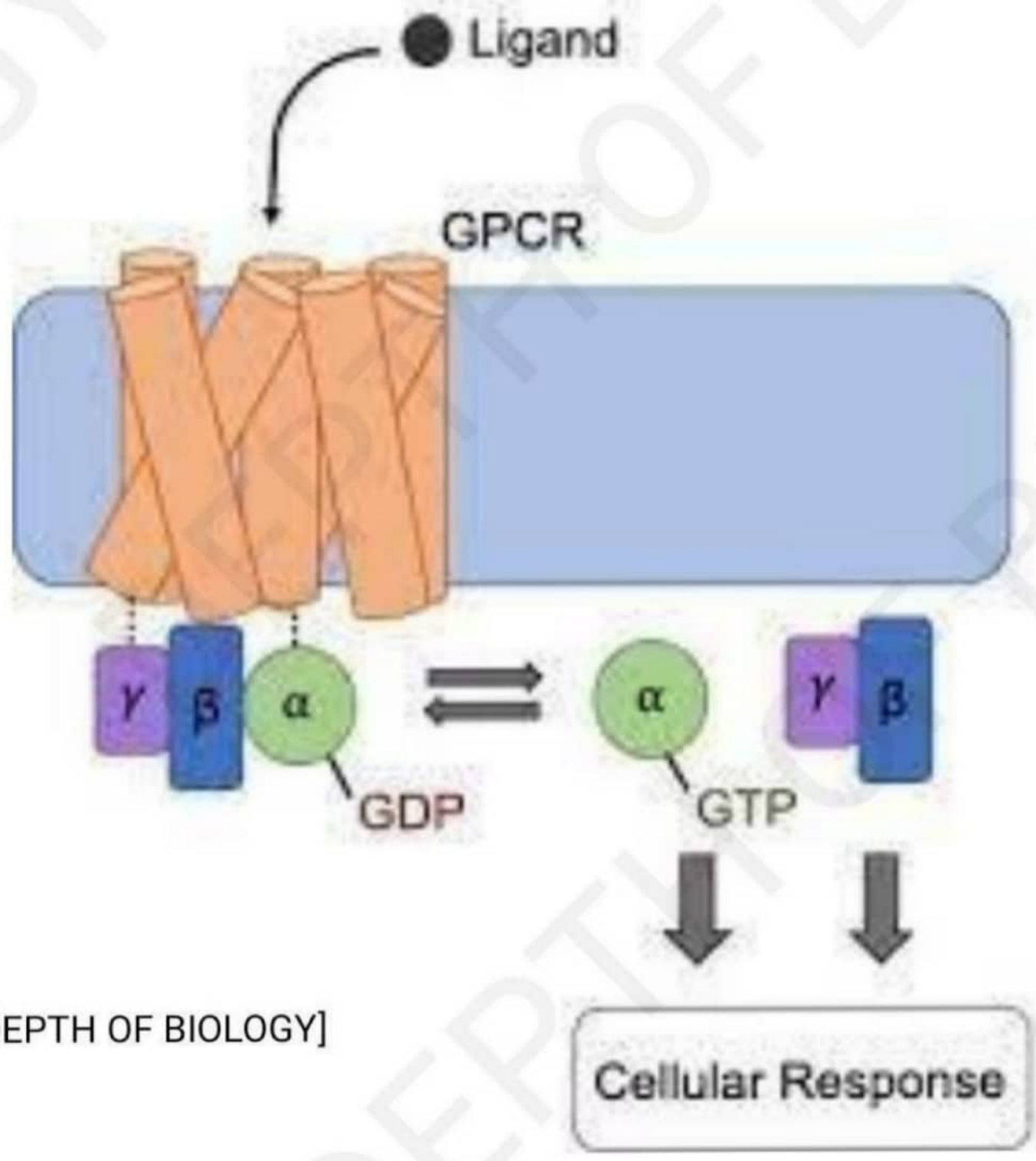
Drugs bind with receptor

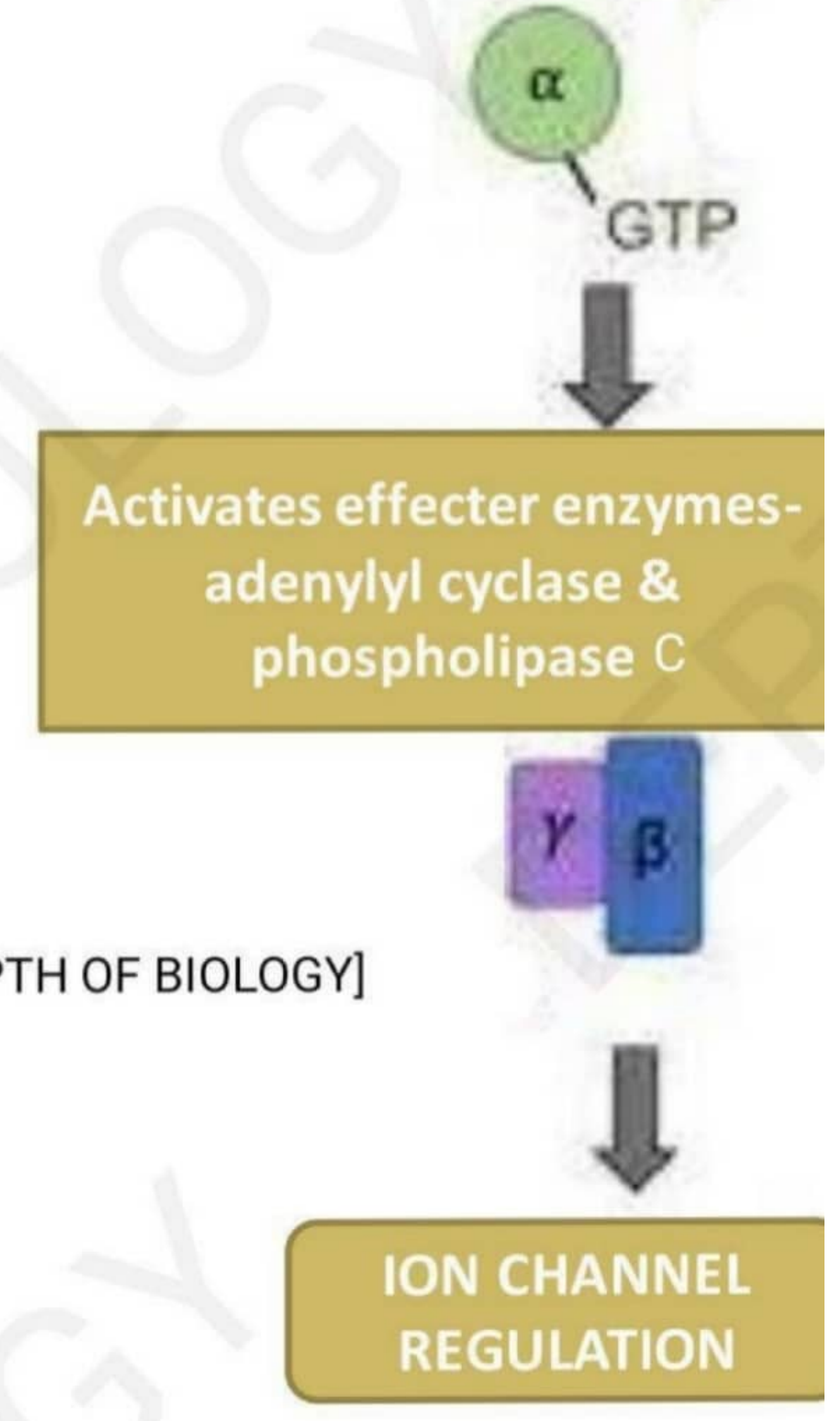
Current flow through loops

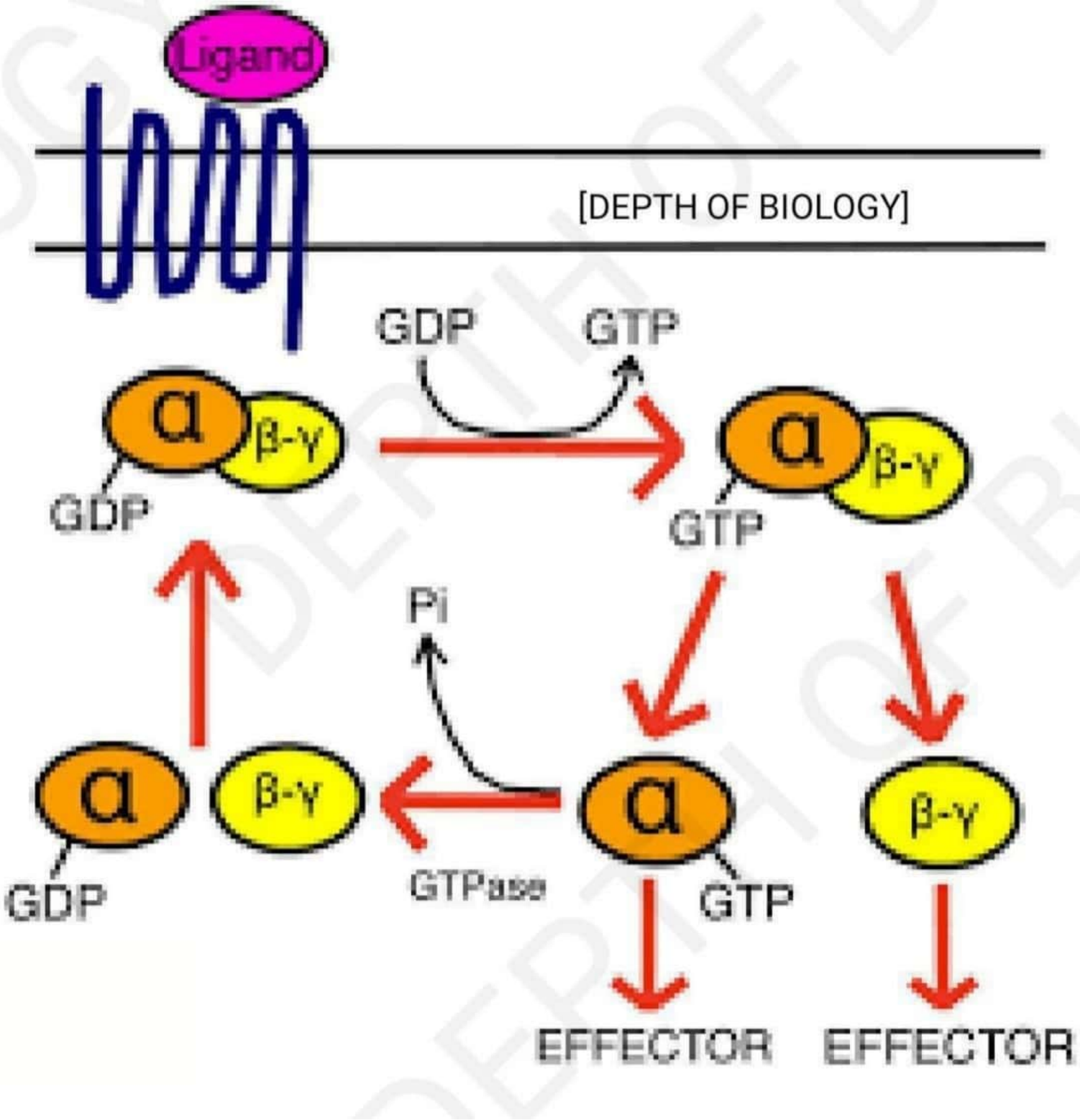
G-protein activate

[DEPTH OF BIOLOGY]

GDP replaced by GTP → breakdown of trimers







TYPES

1. Gs- adenylyl cyclase action, Ca2+ channel opening
2. Gi- adenylyl cyclase inhibition, K+ channel opening
3. G0- Ca2+ channel inhibition [DEPTH OF BIOLOGY]
4. Gq- phospholipase activation

GPCR produce their action via 3 pathways

A. cAMP pathway
B. IP3- DAG [phospholipase c]
C. Channel regulation [DEPTH OF BIOLOGY]

CYCLIC AMP PATHWAY

- Activation by Gs & inhibition by Gi
- Atp is converted into by adenylyl cyclase, it further activates protein kinase enzyme Pka
- The function of many enzymes get altereted by phosphorylation

[DEPTH OF BIOLOGY]

[DEPTH OF BIOLOGY]

FUNCTION

- Cardia contractivity increased [DEPTH OF BIOLOGY]
- Relaxation in smooth muscles
- Lipolysis, glycogenolysis, release of hormones etc.
- Opening of Ca2+ channel in heart brain & kidney [DEPTH OF BIOLOGY]

IP3- DAG pathway

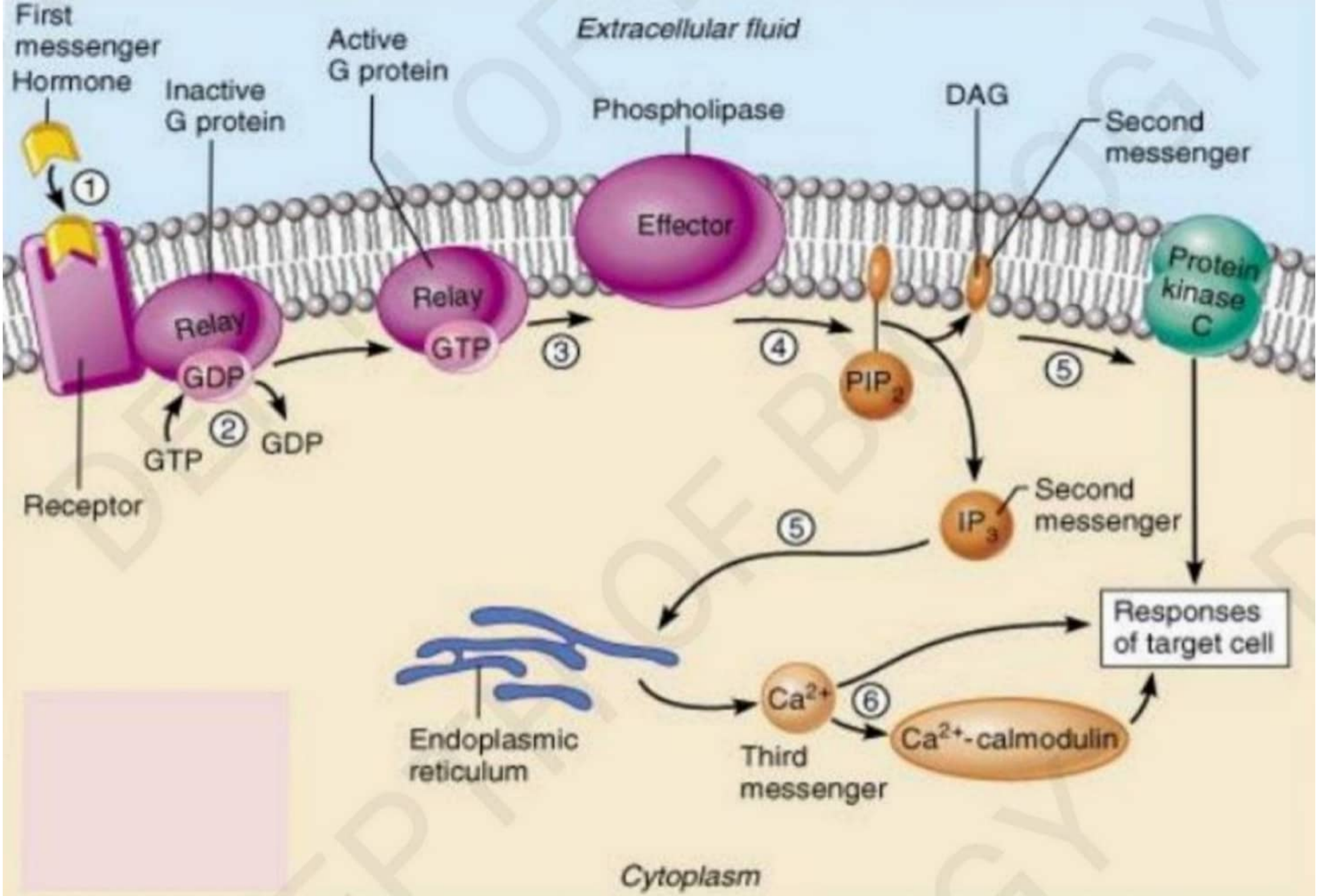
FUNCTION- [DEPTH OF BIOLOGY]

Contraction, secretion, intracellular movement & membrane function.

CHANNEL REGULATION

- Does not requires secondary messenger and is activated by Gs, Gi, Go
- Gs open Ca2+ channel in myocardium
- Gi and Go open K+ channel in heart & smooth muscles

[DEPTH OF BIOLOGY]



Dag and ip3 both activate protein kinase C

Four forms of intercellular signaling

[DEPTH OF BIOLOGY]

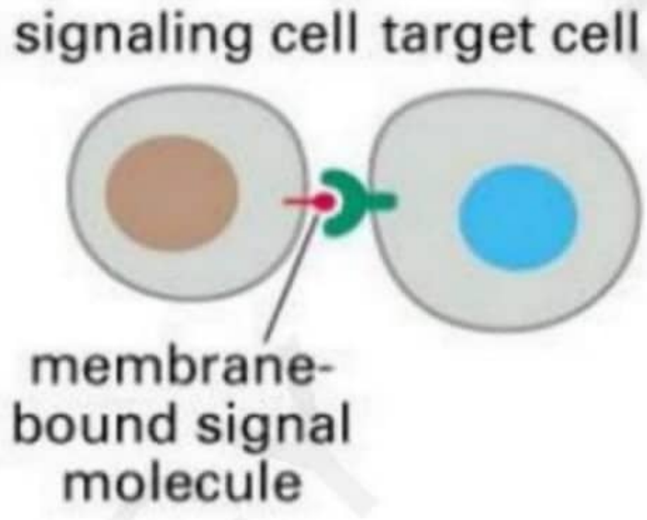
- Cells usually communicate with each other through **extracellular messenger molecules.**

1. Contact dependent signaling

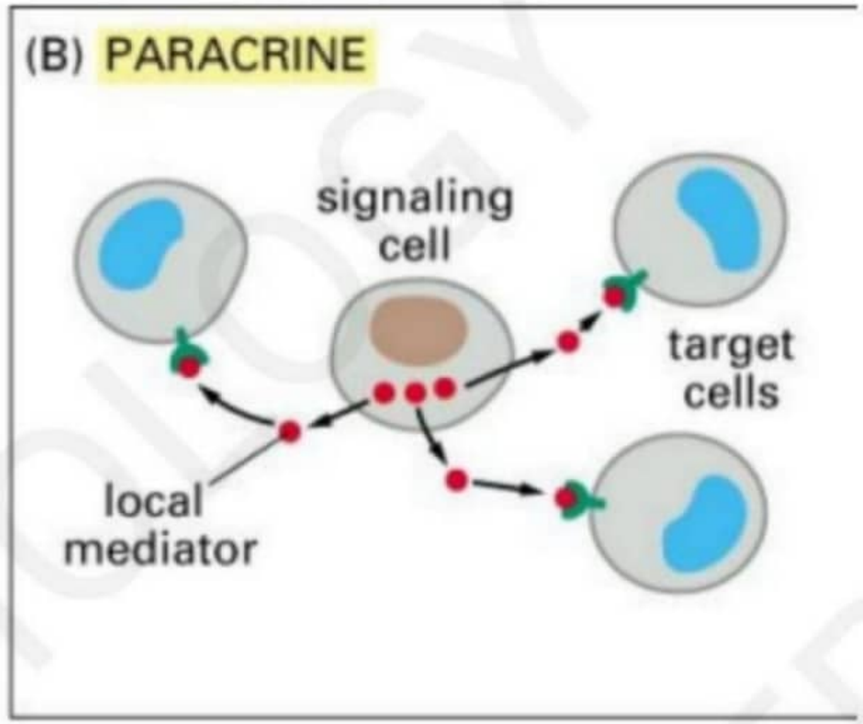
requires cells to be in direct membrane-membrane contact. This is important during development and in immune responses.

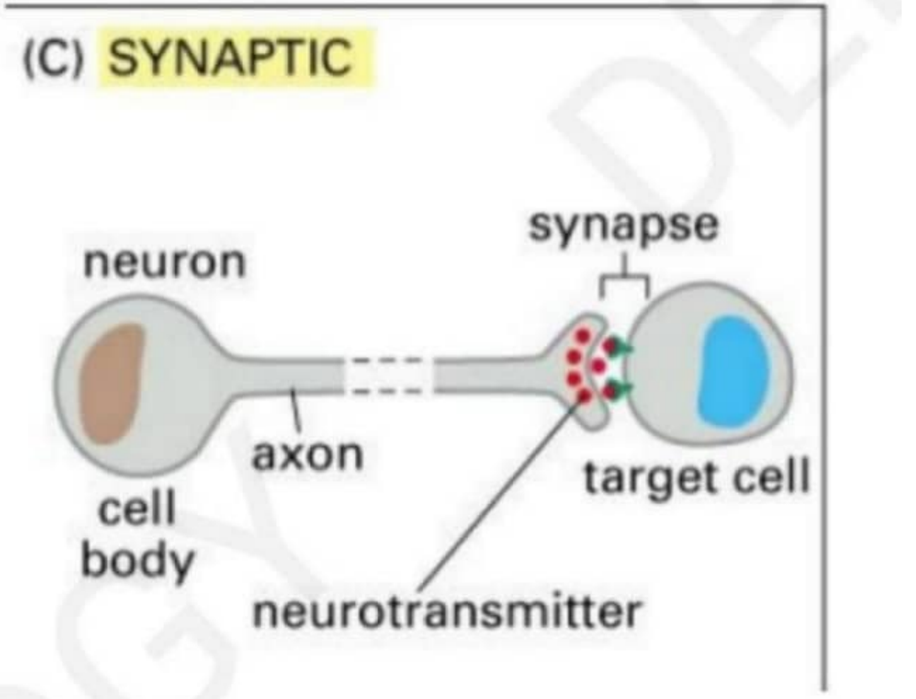
[DEPTH OF BIOLOGY]

(A) CONTACT-DEPENDENT

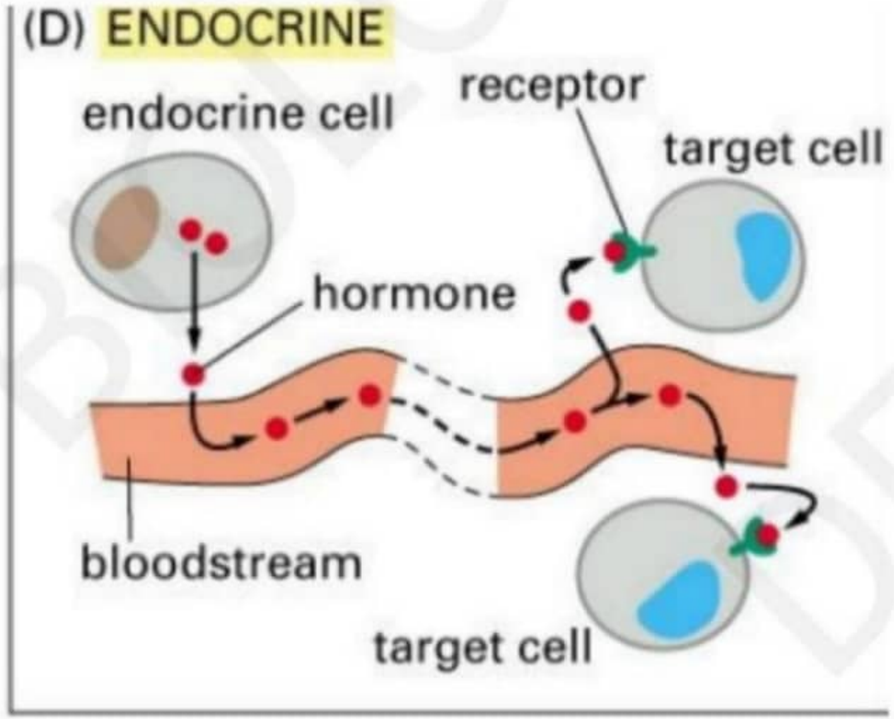


- 2. paracrine signaling depends on local mediators that are released into the extracellular space and act on neighbouring cells. E.g. nerve-muscle
- 3. synaptic signaling is performed by neurons that transmit signals electrically along their axons and release neurotransmitters at synapses.





- 4. endocrine signaling depends on endocrine cells, which secrete hormones into the bloodstream for distribution throughout the body [DEPTH OF BIOLOGY]



(2) Ion-Channel Receptor. or Ligand Gated Ion Channel

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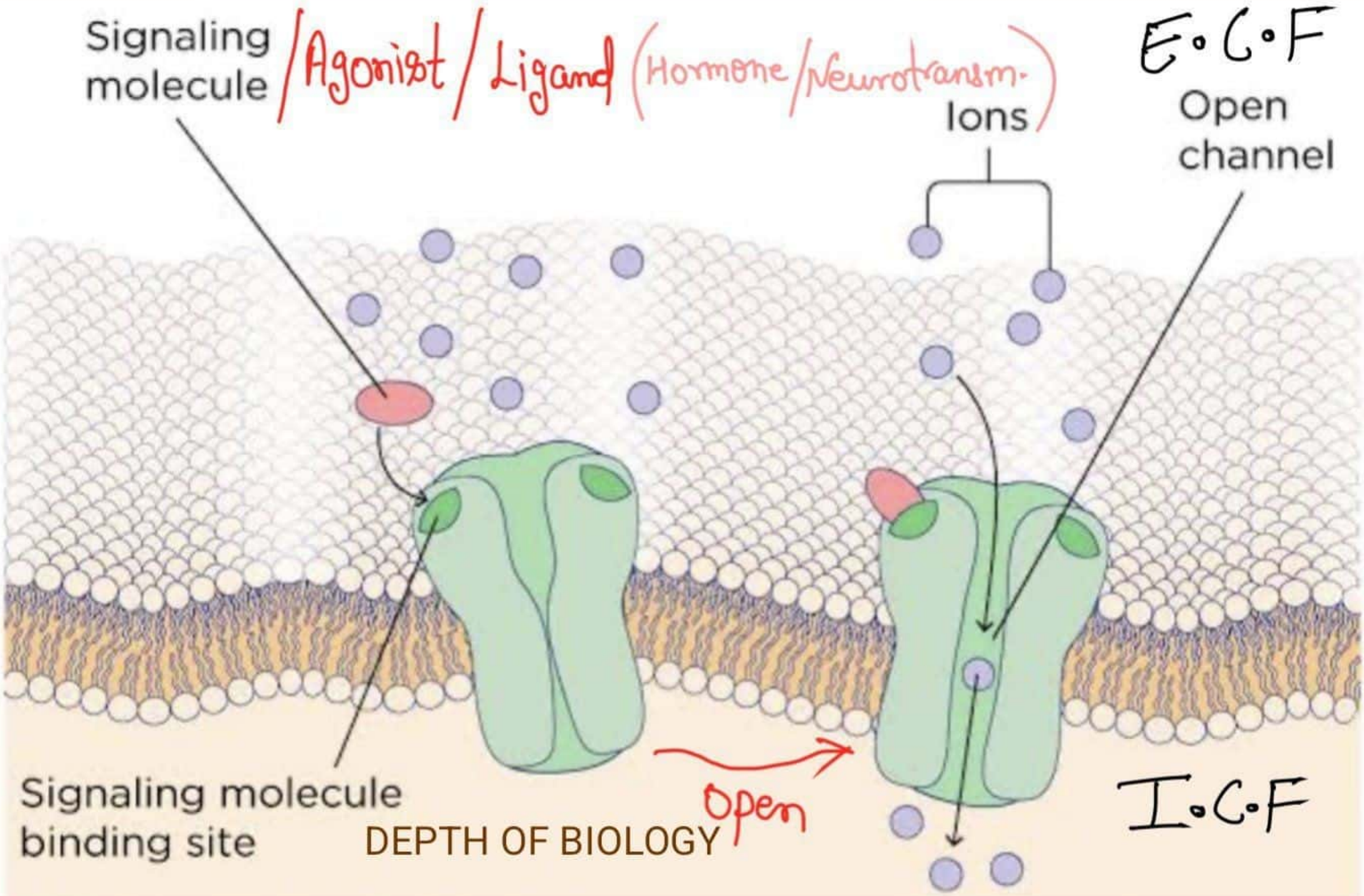
Na^+, K^+, Ca^{+2}, Cl^-



$Ca^{+2}\uparrow\uparrow \Rightarrow$ Contraction.

Points ⇒ (1) It is Cell Surface Receptor.

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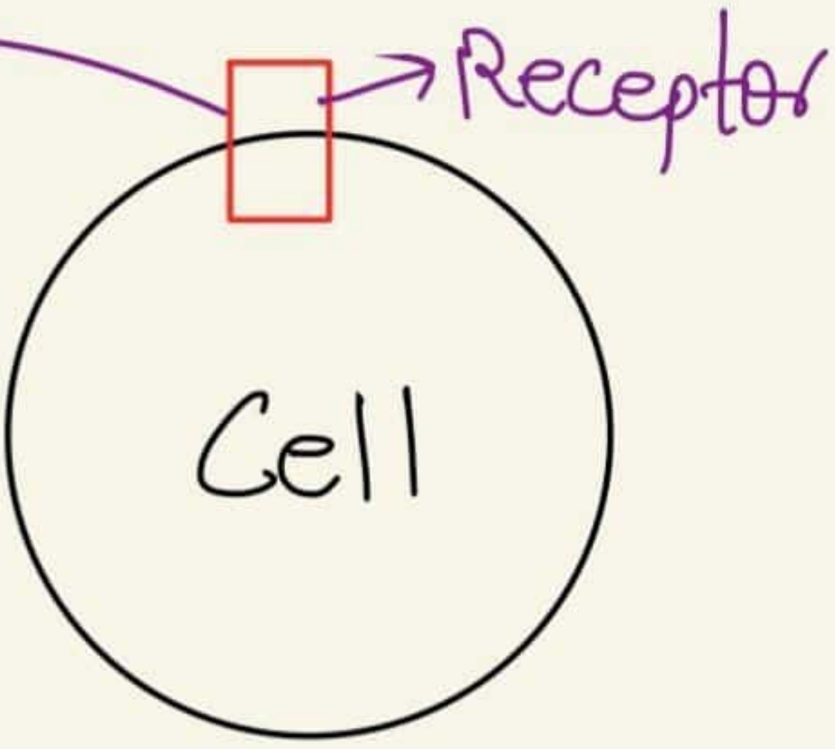
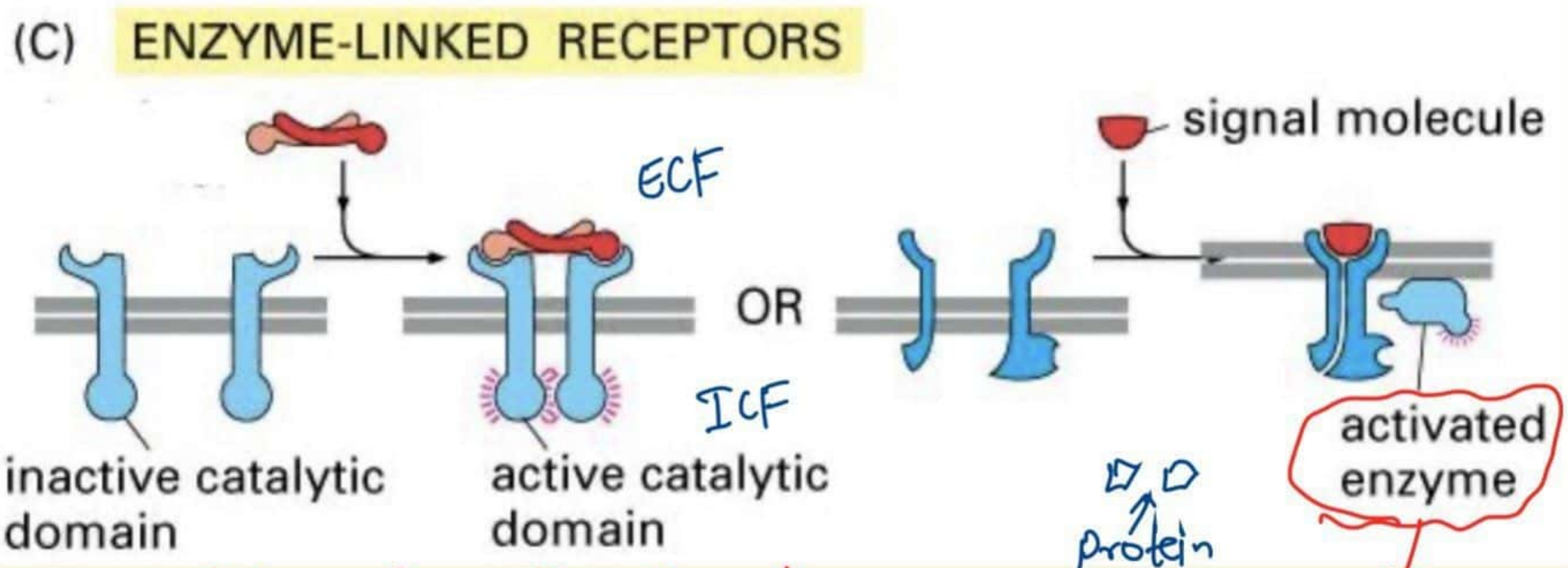
(3) ☆ Transmembrane Enzyme Linked (R)

(1) It is a plasma Membrane (R).

(2) Single Transmembrane Chain.





Agonist bind with Receptor.

⇓

Agonist – Receptor Complex formed.

eg = Peptide Hormone

Activation of Receptor.

⇓

Now, after this binding Inactive Catalytic domain

⇓

Become Active.

Or, we can say Monomer form Dimer after agonist bind with (R).

⇓

Lead to Activation of Enzyme.

& Some, Protein also activated which is already (+)ve in ICF.

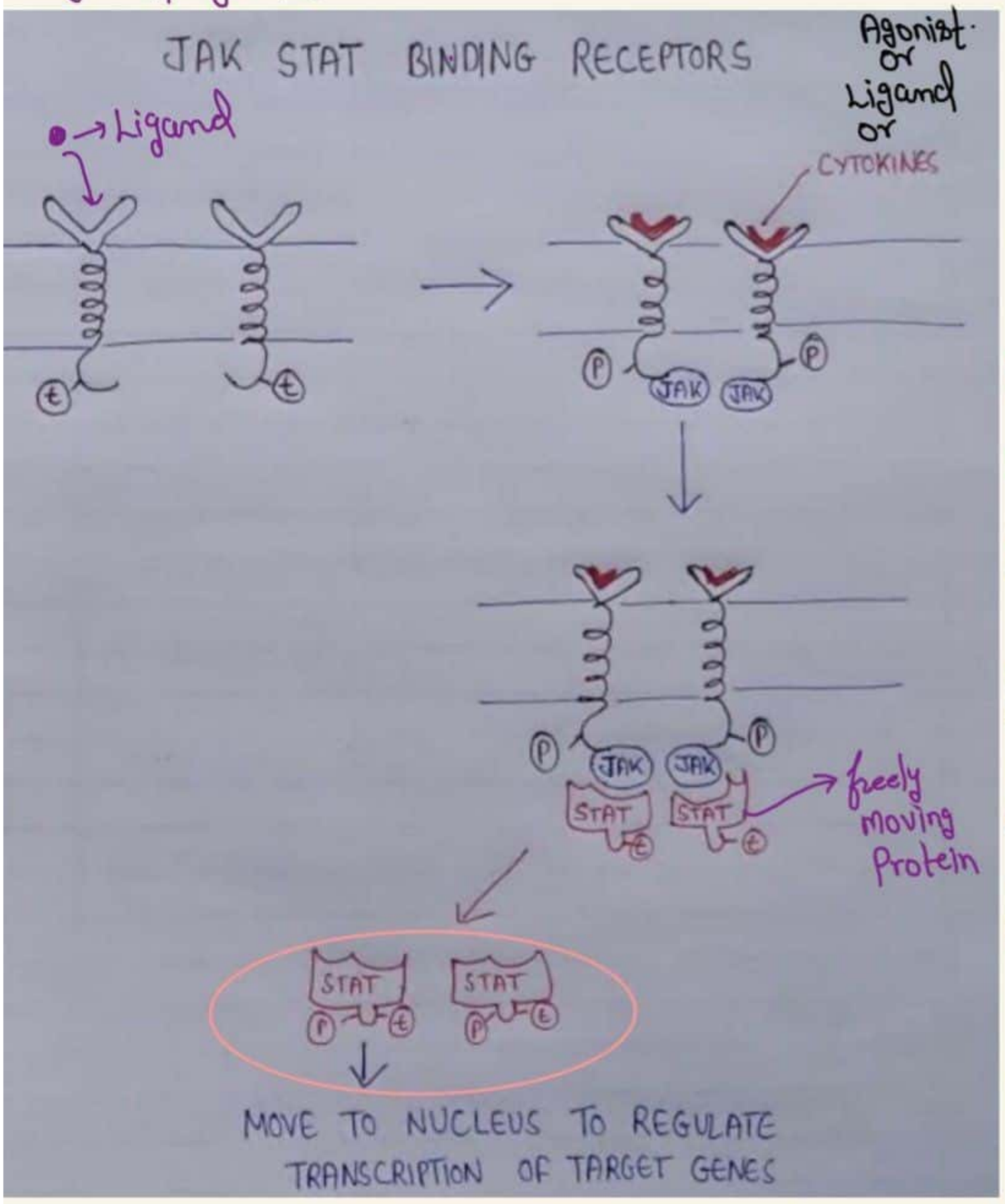
⇓

Response / Cellular response.

4

Transmembrane JAK-STAT Binding.

Ligand/Agonist.



When Ligand bind with ®

⇓

Ligand-Receptor Complex formed.

⇓

Lead to Activation of ®.

⇓

Due to this Activation Monomer form Dimer & JAK [enzyme] bind with ®.

⇓

Leads to Phosphorylation.

⇓

After this [STAT] bind with [JAK] & [STAT] also Undergo Phosphorylation

⇓

After this [STAT] form dimer

⇓

This Dimer of [STAT] protein

⇓

Goes into Nucles.

⇓

DEPTH OF BIOLOGY

⇓

& regulate Transcription.

⇓

Biological response.

(5) Receptor Regulating Gene Expression

[Transcription Factor].

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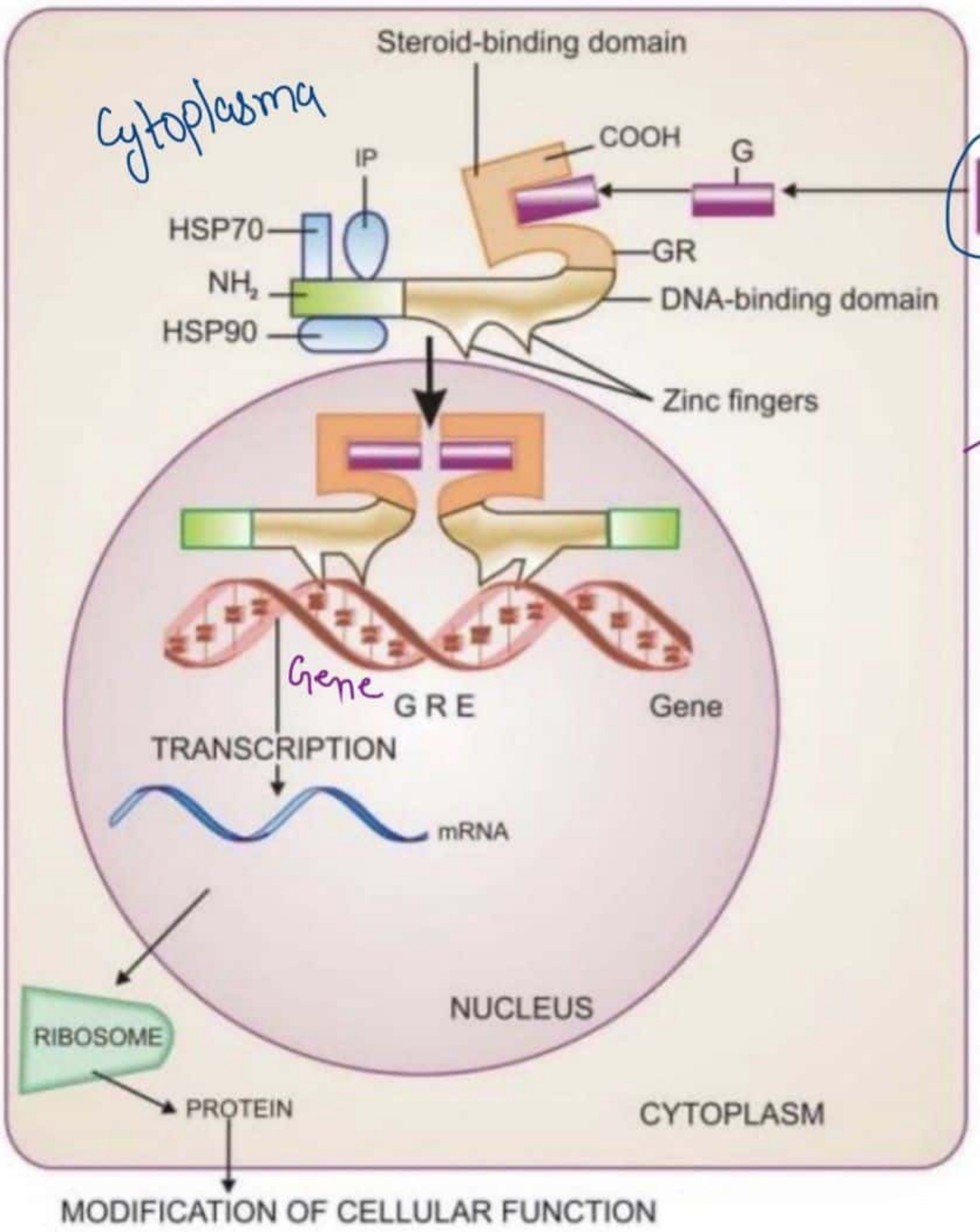


→ Must be Lipophilic in Nature

→ Cell Memb.
[Lipid + PHospho].

DEPTH OF BIOLOGY

⇒ Here HSP90 (Ant

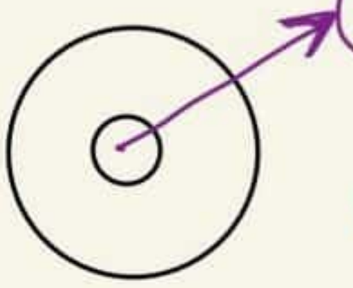
⇓

When Agonist bind with binding site.

then it Can Enter into Nucleus.

But in Case If Agonist Can't bind then HSP90 inhibit the entry of binding site Into the Nucleus.

(1) Intracellular receptor.



(Ant inside the Cell.

DEPTH OF BIOLOGY

Agonist bind on binding site.

Lipophilic

DEPTH OF BIOLOGY

Lead to removal of HSP90

It form dimer.

After formation of dimer it enter into Nucleus.

DEPTH OF BIOLOGY

With the Help of Znfinger it bind on Gene.

formation of m-RNA

Cytoplasm

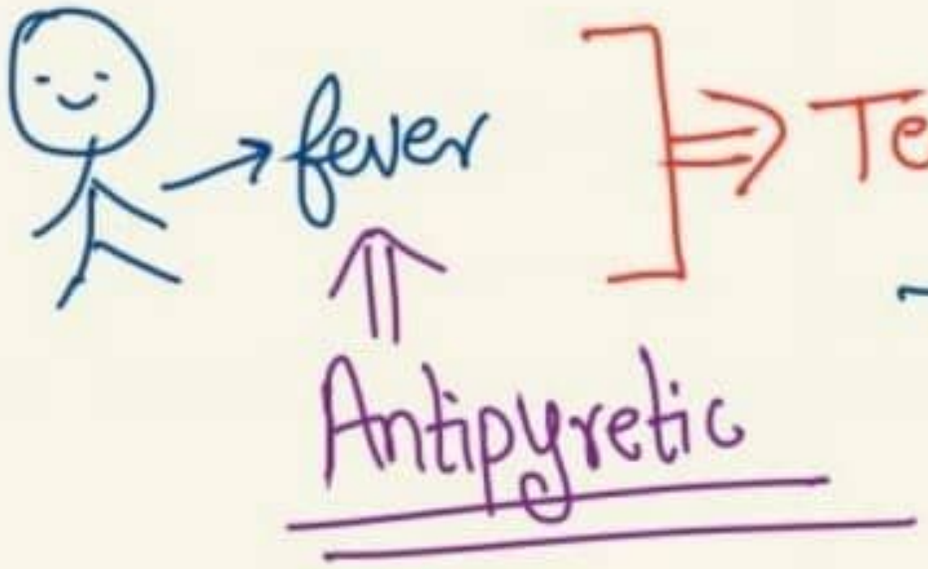
Ribosome

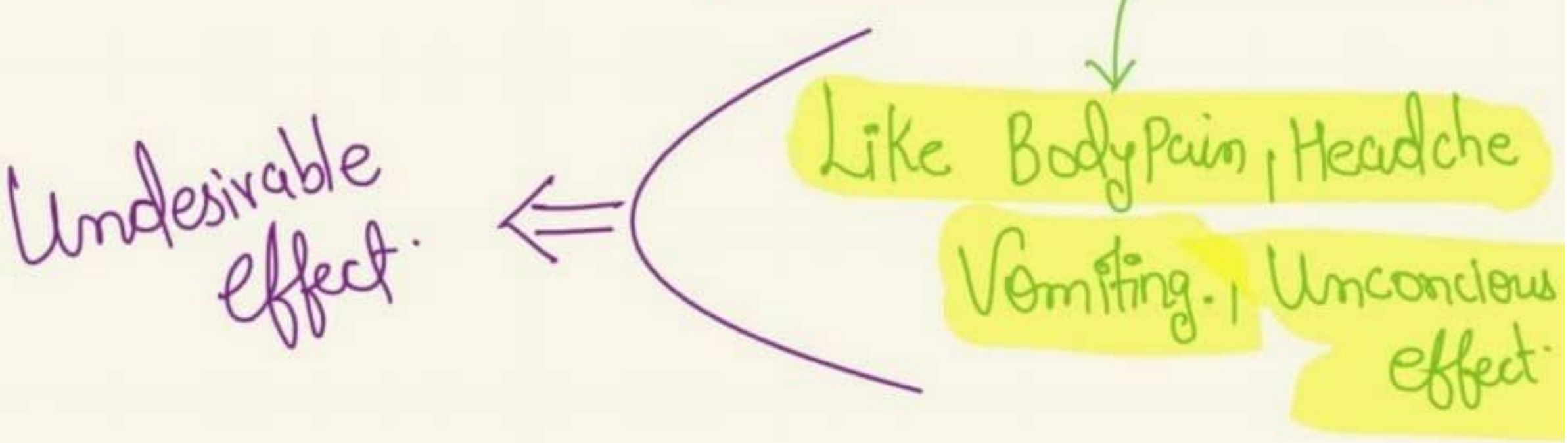
Protein formed

DEPTH OF BIOLOGY

Modification of Cellular function

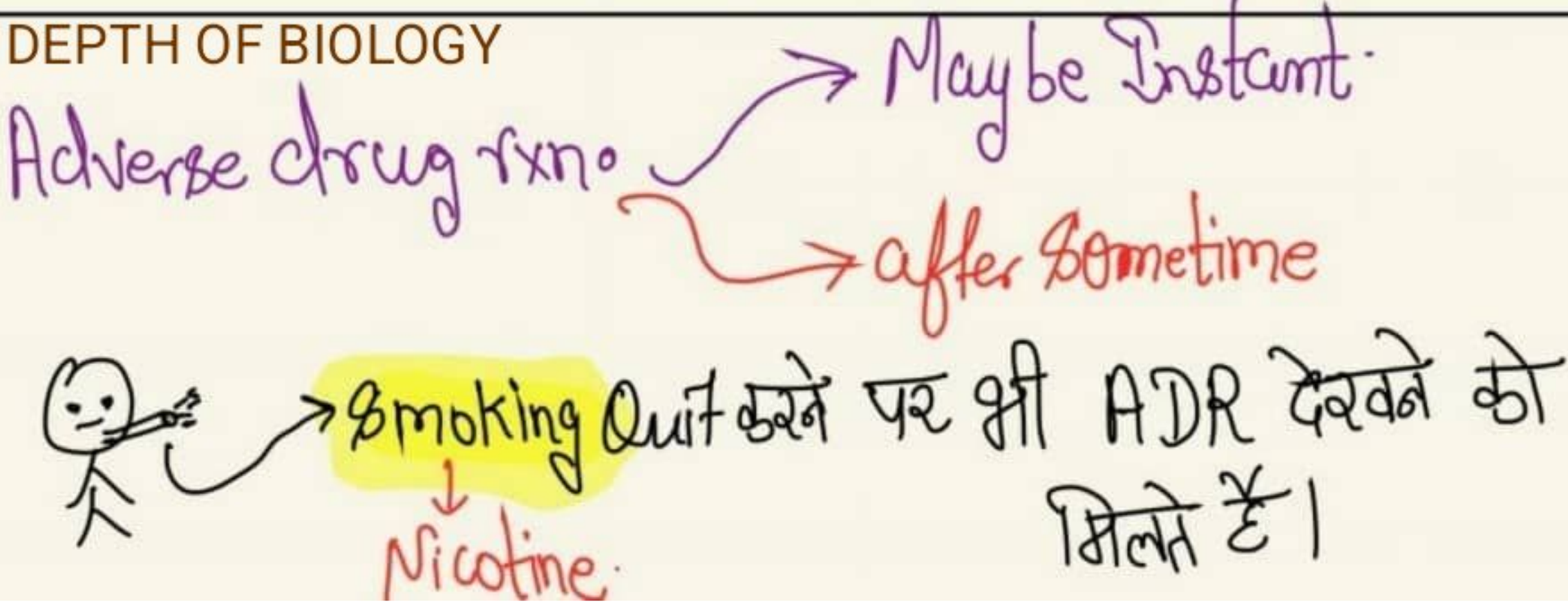
Adverse drug reaction.





⇒ Undesirable effect of drug in our body (Unwanted)

Harmful & even fatal too-
जानलेवा



• Causes of Adverse effect ⇒

① Overdose ② Idiosyncrasy ③ Allergies from Particular Medicine

④ Expiry Tablet.

Idiosyncrasy ↓ Particular person को Problem आ रही किसी drug से

• Types

ADR → 6-Types.

Type-A Type-B Type-C Type-D Type-E Type-F

⇓

also Known as → overdose Augmented reaction

→ minimise by dose adjusment

Type-A → More Common, Mostly Preventable
→ Predictable, Reversible.

eg ⇒ Insulin ↑↑↑ → Hypoglycemia.

② Type-B → This type of rxn occur suddenly With Unknown reason.

Include Allergy & Idiosyncrasy.

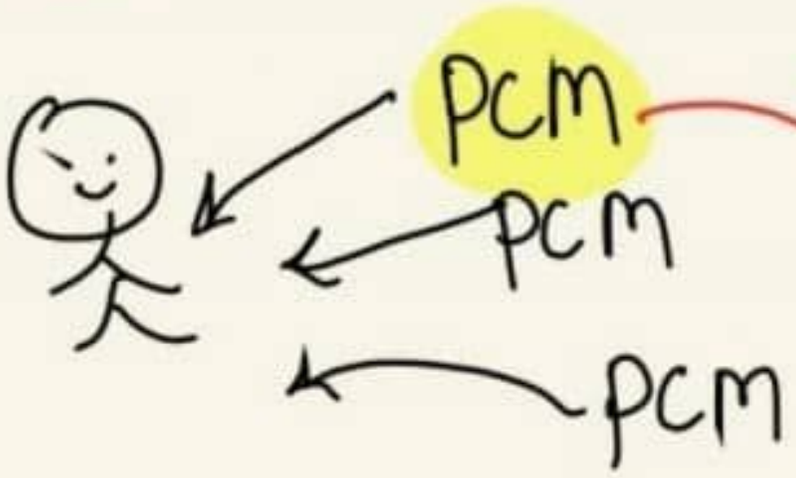
⇒ ☆ Less Common.
⇒ Non-dose related.
⇒ Unpredictable.

Example → Idiosyncrasy (In some people).

③ Type-C ⇒ → Continous.

Nicotine & Alcohol → Continous Use for long time → Lead to Adverse rxn.

④ Type - D → Delayed.



→ effect of drug delayed after Prolonged Use of Medicatio

eg → Carcinogenesis , Teratogenicity.

↓ Cause Cancer

↳ during Pregnancy.

⑤ Type - E (End of Use) ⇒

Suddenly Stop of Use of any drug ⇒ Lead to Harmful effect

eg ⇒ Angina after Atenolol.

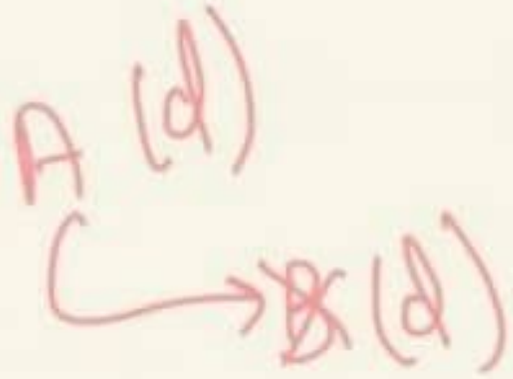
⑥ Type – F (failure of Efficacy) ⇒

Drug ⊕ (failed to show their efficacy)

↓

drug fail to share it's Own response.

eg → Antagonism



Prevention

☆ Avoid Inappropiate Use of drug.

① Minimize but Not Eliminated.

② Avoid Expired drug Use.

③ Check History of Allergic disease.

④ Medication Consider Previous History of drug rxn.

⑤ Check Drug Interaction Possibility.

• Drug Interaction.

Drug Interact with (G.I.T food, or another drug).

Drug-Drug, Drug-food, Drug-other substance Interaction

---

① This Interaction affect ⇓ ADME (PHarmacoKinetic).
→ type of drug Interaction

② If drug action is change (↑)(↓)
(PHarmacodynamic type of drug Interaction)

Drug Interaction → Kind of Interaction in which one drug can affect the Action/Potency availibility of another drug.

Drug-Interaction

→ Harmful.

→ Benificial

⇒ Hydralazine + Propanolol → Combination से Efficacy(↑)

⇓

AntiHypertensive

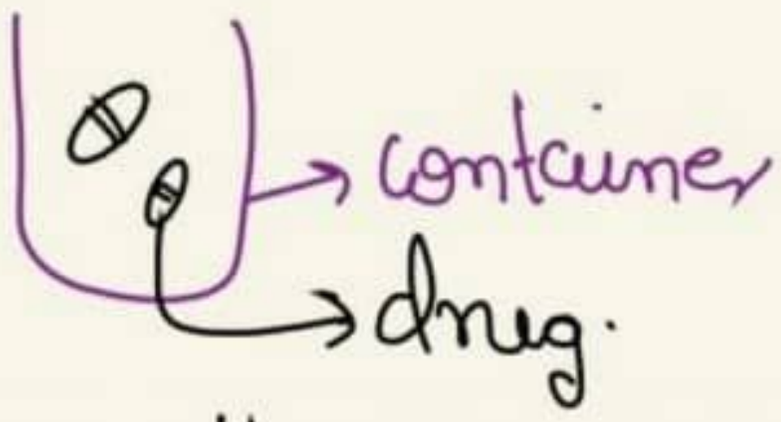
Iron Salt + Tetracycline

drug Absorb ← Insolub. Salt Formed

Drug Interaction Site

In-Vitro

Outside the Cell



2 drug Mixed in Container → Lead to Interaction

Poisonous.

eg ⇒ Penicillin & Gentamycin.

In-Vivo.

Inside the Cell

→ Drug - Drug.

→ Drug - G.I.T food.

⇒ This Interaction affect the Binding, PH, Absorb., Dist., Metabo., Excretion.

PHarmacokinetic type of drug Interaction.

① Absorbtion

Binding → Iron & Antacid

↓

form Complex

Absorb.

→ Anti-Coagulant work On Acidic pH but Antacid Increase the pH.

Distribution → Drug Movment. (D-Protein Complex).

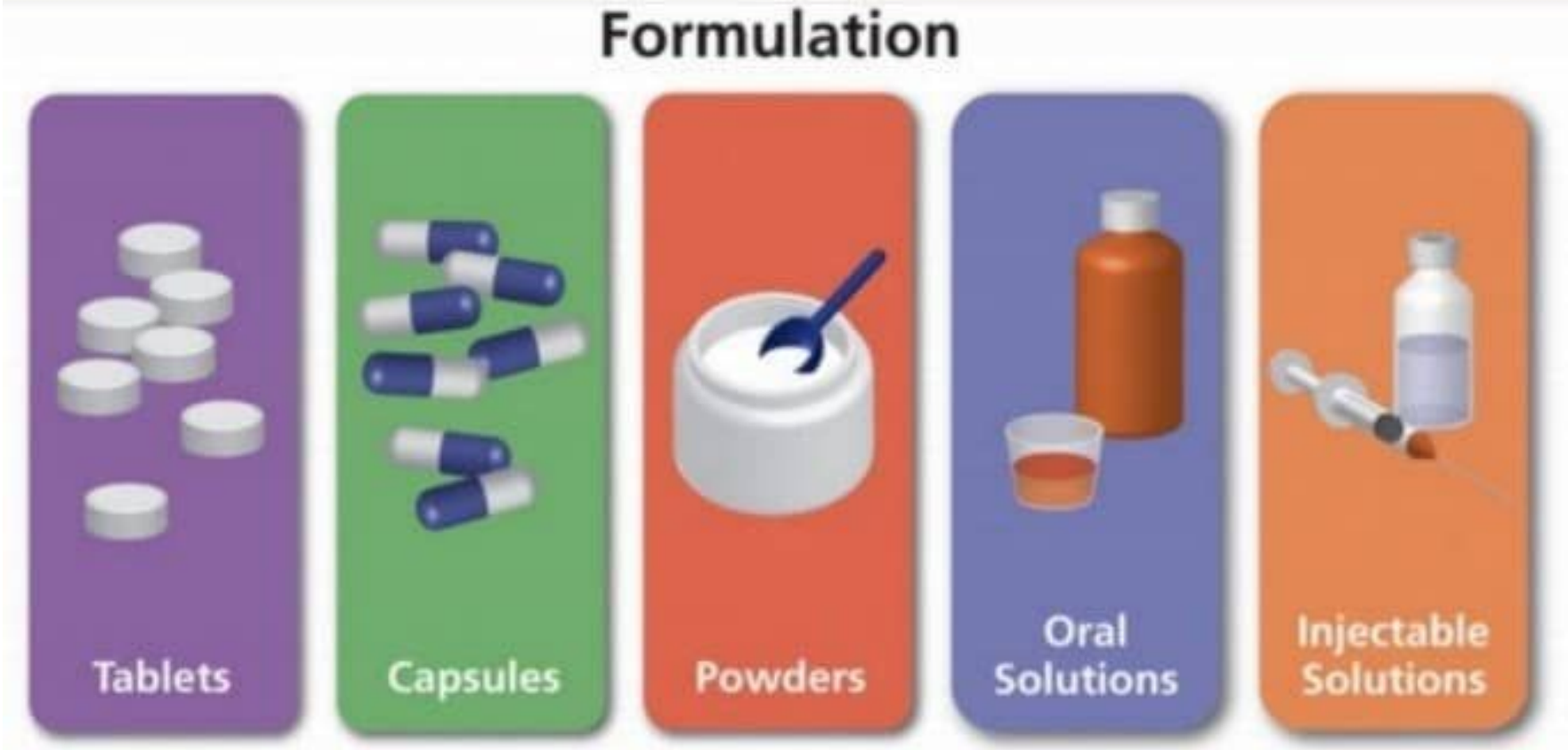
eg ⇒ Warfarin is displace by Phenylbutazone

Metabolism → Inducer & Enzyme Inhibitor.

Elimination → duration of Action(↑). → It cross Therapeutic Window.

→ Elimination ↓.

- Drug devlopment & discovery Phases.



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Drug devlopment divided into 2 Stage.

Conceptual Stage

① Max. Efficacy of drug.
② Min./Less Side effect of drug.
③ Drug ने Change करके देखना

Devlopmental Stage.

Chemical Constituent से
Or
Active Constituent से

④ Dosage form कौनसा बनना चाहिये

⑤ Active const. with Minim. Sideeffect is Used.

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Developmental Stage → Screening Techq. & Separate.

- HPLC
- TLC
- Gas Chromatography

Developmental

Steps

① Synthesis / Isolation of Compounds. [1–2 Year] ☆

Old Chemical Constituent से → New Chemical Constituent derived.

Old Chemical Const.

→ Side effects ↑↑ → Alternate.

→ Less Side effect.

To Know this effect.

↓

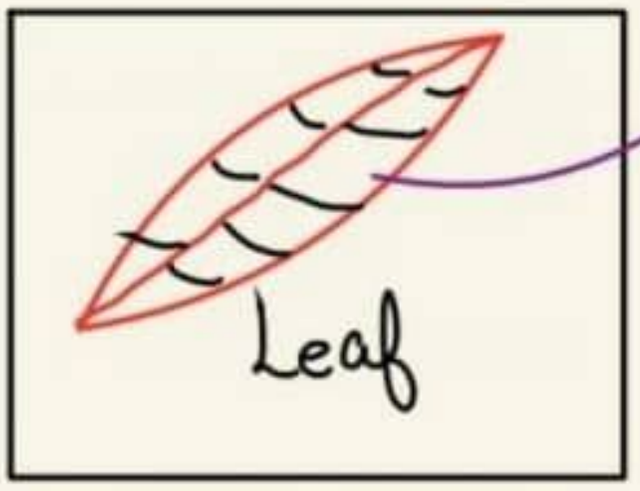
We Need to know drug effects

Like Additive, Synergism, Supraadditive

Antagonistic effect, Drug-Drug Interaction

Drug-food Interaction.

Isolation → Separate Chemical Constituents in Individual form.



Isolation → proper (In pure form).

(2) Pre-Clinical Studies. →

Here we study about.

Before ⇓

*2-4 Years

To check desirable effect, Undesirable effect or Lethal effect Before Prescribed for Human being.

1. Screening.
2. Evaluation.
3. PHarmacoKinetic
4. Short term Toxicity Studies.

(1) Screening →

- depend upon Need & Drug Profile
- dose/drug Screenout who have High Therapeutic effect.
- On the basis of Toxicity We can Screenout.

(2) Evaluation → Given drug का Given Concn. पर क्या effect है Animal पर वो check करना

(3) Pharmacokinetic → ADME

↓

We Have to check that drug is proper Absorb, D, M, E out or Not.

Absorb ↓ X

D ↓ X

M ↓ X

E ↓ Accumulation

(4) Short-Term Toxicity Effect ⇒ We have to do Proper study about Toxicity of drug.

This pre-Clinical trial perform on Animals (Mice).

⇓

& determine LD_{50}

③ Pre-Clinical Trial

↓ Permission [3-6 Month] → We Have to submit Proper document that our drug is Pass Pre-clinical Trial phase.

Clinical Trial.

④ Clinical Studies → Here we Check drug effectivness.

↘ Drug Potency

→ Side effect of drug.

Phase-I , Phase-II , Phase-III , Long term Toxicity Studies.

[3-10 Year].

⑤ Review & Grant of Marketing. ⇒ (1/2 Year to 2 Year)

⑥ Post-Marketing Surveillance → study. ⇒

Nature , Geography , Genetic Sequence → maybe possible after Launching a drug it Cause side effect

→ Approx 5 compounds send in Clinical trials.

2) Clinical trials :- In this phase, drug is given to humans.

Phases - Phase I - Phase II
- Phase III - Phase IV

a) Phase-I ÷ In this, drug is tested on 20-80 healthy volunteer.

→ This is done to check the safety and toxicity of drug.

→ Study of Pharmacokinetics, Pharmacodynamics, pharmacological effect, tolerability, side effects and toxicity at different doses is purpose of this phase.

b) Phase-II → In this phase, approx 100-500 patients are selected with that targeted disease. Then drug is tested on patients

→ This phase is to check efficacy and side effect of drug

→ Purpose - finding dose range (1)
- effectiveness for treatment
- maximum tolerated dose (2)

→ Approx 33% of drugs passed this phase.

c) Phase-III :- In this phase, approx 1000-5000 patients selected with targeted disease.

→ length of this phase - 1-4 yrs.

→ Purpose - long term safety
- Tolerability - common side effect
- Drug interaction
- safety & efficacy

* After completing phase-III, drug goes for approval of Food and Drug Administration (FDA). After this approval, drug is launched in market.

d) Phase-IV - (Post Marketing therapeutic use)

→ In this, when drug is launched in market, then data is collected that drug is safe or not.

Purpose - Collect Information of long term safety

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* Pharmacovigilance :-

Pharmaco - drug
Vigilance - keep watching

→ It is branch of clinical pharmacy, involving study of early detection of drug-induced unknown adverse effects and their risk factors.

→ It is the part of pharmacoepidemiology that involves the study of pharmacokinetic and pharmacodynamic features of a drug which is already present in market.

→ The main purpose of pharmacovigilance is to reduce the drug related harm to patients

→ To improve patient care and safety in relation to the use of medicine.

→ To improve public health and safety in relation to use of medicine

→ If patient have any problem with any drug, patient informed the physician & fill a yellow form. It contain -

Broand name, manufacturer, Batch no., Expiry date, Dose used, route of admin&., reason for prescription, date etc.

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