Paper Code:-402 Cytology & Molecular Biology of Plants

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Signal Transduction (Unit-V)

* Any process occurring within cells that convert one kind of signal into another type. It is also known as cell signaling in which the transmission of molecular signals from cell's exterior to its interior.

* Signals received by cells must be transmitted effectively into the cell to ensure an appropriate response. This is initiated by cell surface receptor which triggers a biochemical chain of events inside the cell, creating a response.

* It is also defined as the ability of a cell to change behavior in response to a receptor-ligand interaction.

* In cell signaling, ligand is the primary messenger. As the result of binding the receptor, second messengers are produced within the target cell.

* Second messengers relay the signal from one location to another (plasma membrane to nucleus) leading cascade of events within a cell

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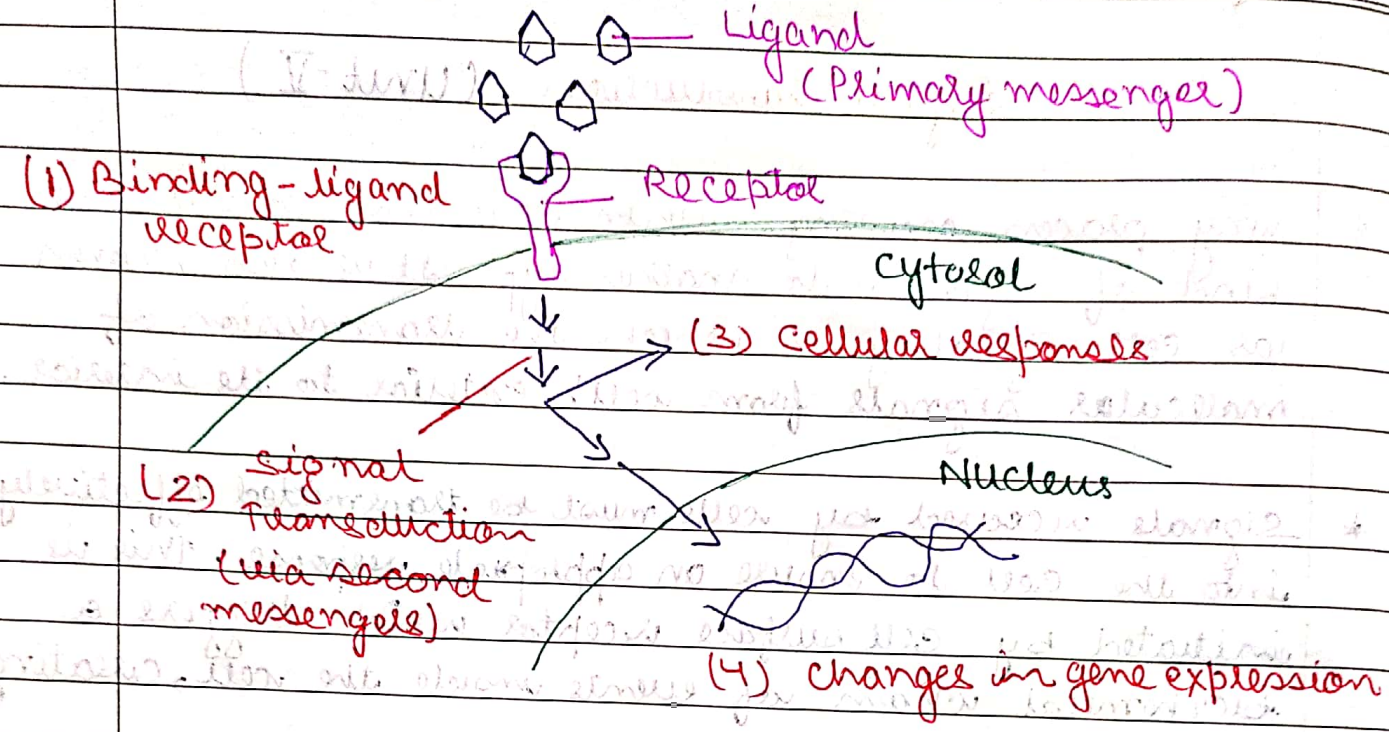

* Messenger molecule may be amino acicle, peptides, protein, lipicle & nucleoside.

* Messengers are of two type.

1) Hydrophillic messengers - It binds to cell membrane receptors

2) Hydrophobic messengers - It binds to intracellular receptors which regulate expression of specific genes.

* A ligand binds its receptor through a number of specific weak non-covalent bond by fitting into a specific binding site

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* Even low concentration of ligand will result in binding of most of the congnate receptors, the receptor affinity is considered to be high. Low receptor affinity occurs when a high concentration of the ligand is required for most receptors to be occupied.

* with prolong exposure to a ligand cells often become desensitized

* Desensitization of the cell to a ligand depends upon receptor down regulation.

Receptors

* Receptor can be roughly divided into major classes:-

- Intracellular & Extracellular receptors

1) * Extracellular receptor are integral transmembrane proteins and make up of most receptors.

* They span the plasma membrane of the cell, with one part of the receptor on the outside of the cell & other one the inside.

* Signal transduction occurs as a result of a ligand binding to the outside region of the receptor

* Various extracellular receptors are G-protein coupled receptors, Receptor with Kinase activity, integrin receptor, and ligand gated ion channel receptor.

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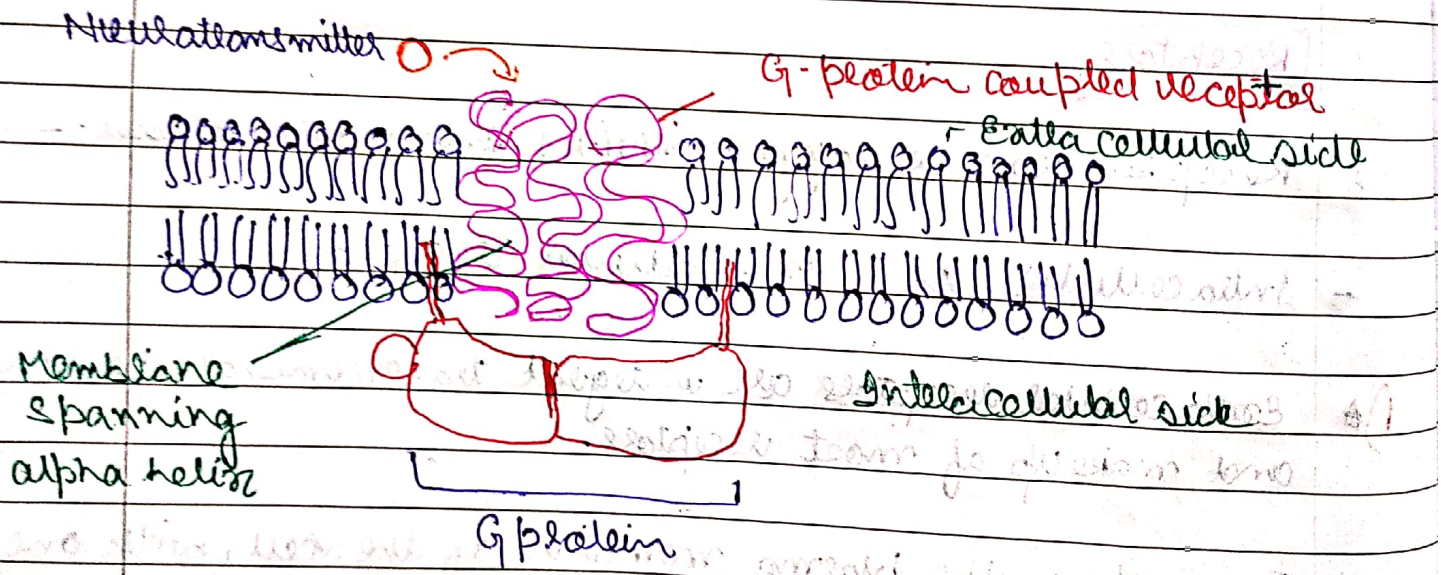
1. G protein-coupled receptors

* It is also known as seven transmembrane domain receptors and G protein-linked receptors

* These constitute a large protein family of receptors that sense molecule outside the cell and activate inside signal transduction pathway ultimately cellular response

* Coupling with G protein, they all called 7-transmembrane receptors because they pass through the cell membrane seven times.



* G protein acts as a molecular switches inside cells and are involved in transmitting signals from a variety of stimuli outside a cell to its interior

* When they are bound to GTP, they are 'on' and when they are bound to GDP they are 'off'.

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* G-proteins belongs to the larger group of enzymes called GTPase.

* There are 2 classes of G-protein

1) The first function as monomeric small GTPase

2) The second form & function as heterotrimeric G-protein complexes

* heterotrimeric class is made up of α, β & γ subunits. The β & γ subunits can form a stable dimeric complex refferred to as beta-gamma complex while alpha subunit dissociates on activation.

Mechanism

* It is known that in the inactive state, the GPCR is bound to a heterotrimeric G protein complex

* Binding of an agonist to the GPCR results in a conformation changes in the receptor that is transmitted to the bound G_α subunit of the heterotrimeric G protein.

* The activated G_α subunit exchange GTP in place of GDP which in turn triggers the dissociation of G_α subunit from the $G_{\beta\gamma}$ dimer & forms from the receptor.

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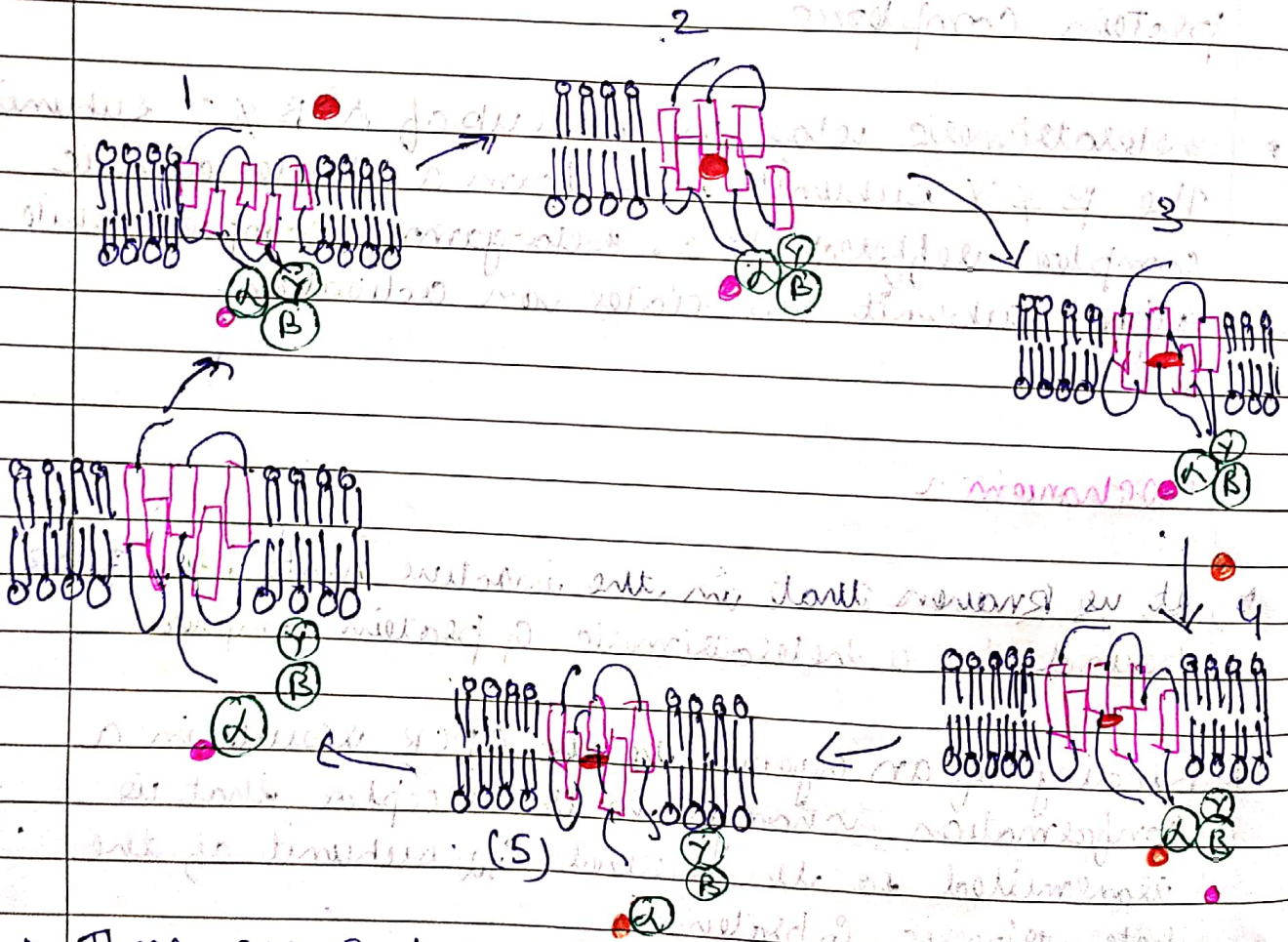
* The dissociated G_{α} & $G_{\beta\gamma}$ subunits interacts with other intracellular proteins to continue the signal transduction cascade

* The full GPCR is able to rebind to another heterotrimeric G protein to form a new complex that is ready to initiate another round of signal transduction



* There are 2 principle signal transduction pathways involving G protein coupled receptors

1) the cAMP signal pathway
2) the phosphatidylinositol pathway

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cAMP-Dependent Pathway

* It is also known as adenyl cyclase pathway
* In a cAMP-dependent pathway, the activated G_s alpha subunit binds to and activates an enzyme called adenylyl cyclase, which in turn catalysed the conversion of ATP into cyclic adenosine monophosphate.
* Increase in concentration of the second messenger cAMP may lead to the activation of

-> cyclic nucleotide-gated ion channels

-> Exchange proteins activated by cAMP such as RAPGEF3

- Popeye domain containing proteins (Popdc)
- an enzyme called protein kinase A (PKA)

* The PKA enzyme is known as cAMP-dependent enzyme because it gets activated only if cAMP present. once PKA is activated, it phosphorylated a number of other proteins.
* Cholera toxin, caffeine and pertussis toxin increase cAMP levels.
* The G_s alpha subunit slowly catalyzed the hydrolysis of GTP to GDP, which in turn deactivated the G_s protein, shutting off the cAMP pathway.

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A The pathway may also be deactivated downstream by directly inhibiting adenylyl cyclase.

A Molecule that inhibit cAMP pathway include

a) cAMP phosphodiesterase dephosphorylated cAMP into AMP reducing the cAMP levels.

b) G_i Protein that inhibit adenylyl cyclase reducing cAMP levels.

B) Phosphatidylinositol signal Pathway

A In the phosphatidylinositol pathway, the extracellular signal molecule binds with the G-protein receptor on the cell surface and activates phospholipase C, which is located on the plasma membrane

PIP_2 Phosphatidylinositol 4,5 diphosphate

↓ Phospholipase C

IP3 Inositol 1,4,5 triphosphate

DAG Diacylglycerol

A IP3 binds with IP3 receptor in the membrane of the smooth endoplasmic reticulum & mitochondria to open Ca^{++} channel

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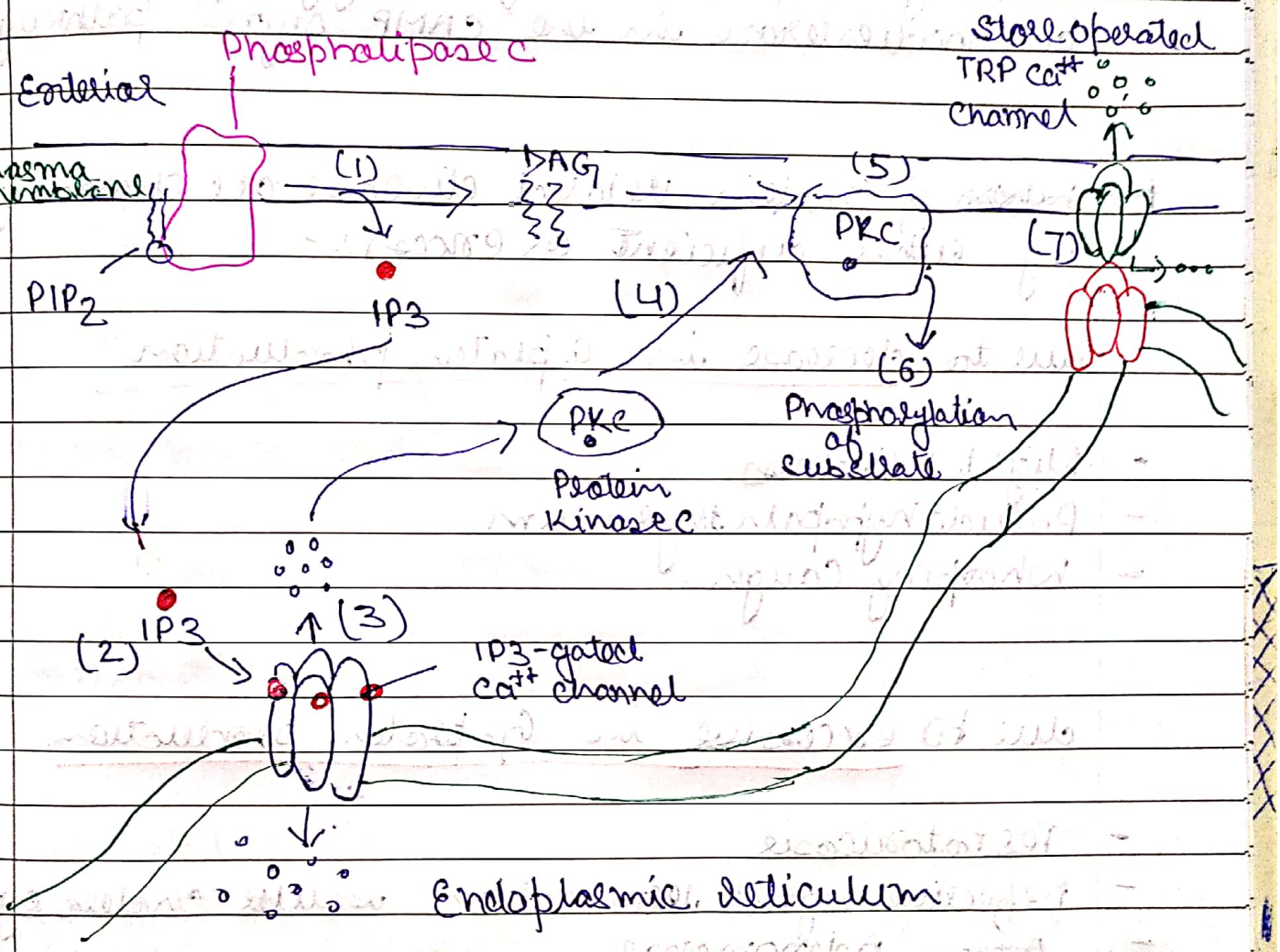
▷ DAG helps activate protein kinase C, which phosphorylate many other proteins, changing their catalytic activities leading to cellular responses.



▷ Ca^{2+} co-operates with DAG in activating PKC & can activate the CaM Kinase pathway in which calcium modulated protein calmodulin (CaM) binds Ca^{++}, undergoes a change in conformation and activates CaM kinase

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* The kinase then phosphorylates target enzyme, regulating their activities. The 2 signal pathway are connected together by Ca^{++}-CaM, which is also regulatory subunit of adenylyl cyclase & phosphodiesterase in the cAMP signal pathway.

* ~~Various~~ G protein related disease are characterized by either deficient or excess :-

due to decrease in G protein production

- Night blindness
- Pseudohypoparathyroidism
- Whooping cough.

due to excessive in G-protein production

- Testatoriosis
- Defective signal termination results cholera like symptoms.
- ~~Adeno~~ Adenomonas
- Mc Cune - Albright Syndrome

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Intracellular receptors

- They all located inside the cell rather than on its cell membrane
- Classic hormones that use intracellular receptors include thyroid & steroid hormones
- Class of nuclear receptors located in the cell nucleus & cytoplasm
- IP3 receptor located on the endoplasmic reticulum
- The ligand that bind to them are usually
- Intracellular second messenger like Inositol triphosphate
- Intracellular lipophilic hormones like steroid hormones
- Activated nuclear receptors attach to the DNA at receptor specific hormone-responsive element sequences located in promoter region of the genes activated by the hormone receptor complex
- Due to their enabling gene transcription, they are alternatively called inductors of gene expression.
- All hormones that act by regulating gene expression have 2 consequences

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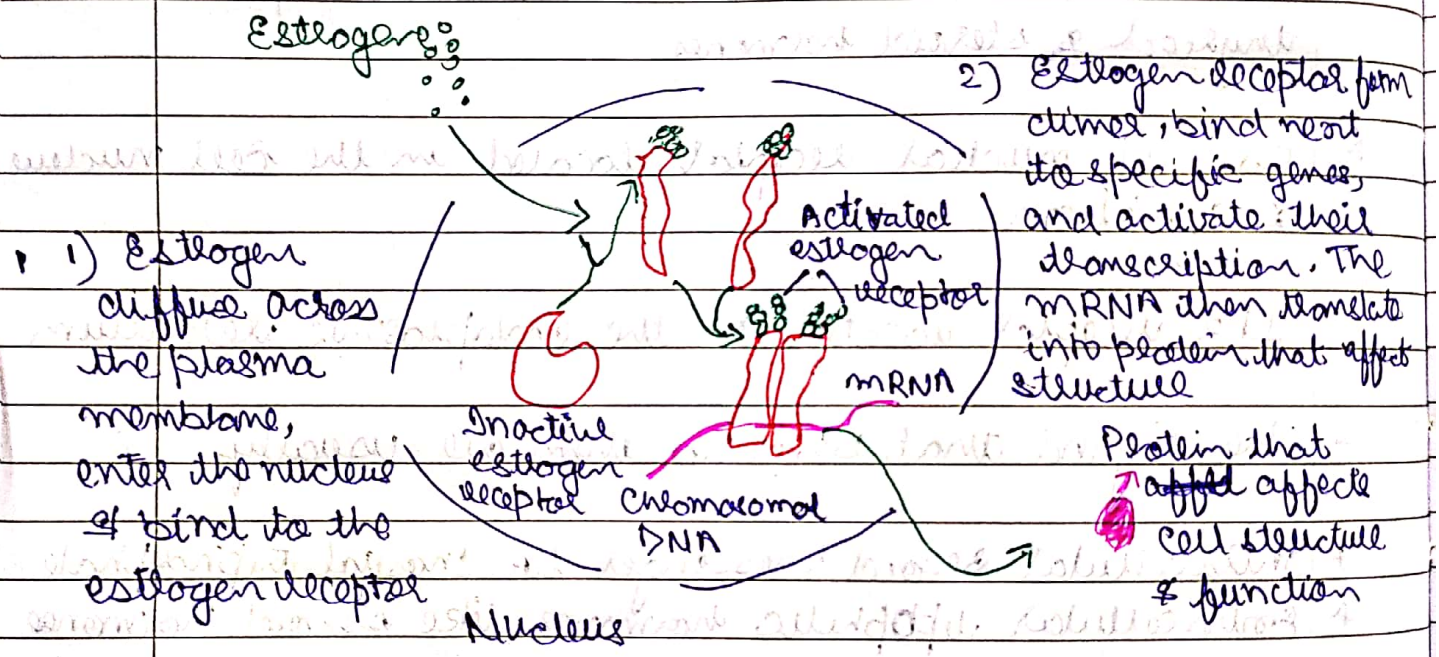
1) their effect are produced after a characteristically long period of time

2) their effect persist for another long period of time even after their concentration has been reduced to zero.



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