GENERAL MEDICINE 1

Marrow SS Medicine

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General Medicine

Volume - 1

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CLASSIFICATIONS OF HORMONES

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Classification based on structure

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Derivatives :

Amino acid derivatives :

1. Tyrosine :

- T_3, T_4.
- Catecholamines : produced by adrenal medulla, most abundant in order of adrenaline (Epinephrine) > Nor-adrenalin (Nor-epinephrine) > Dopamine.

2. Tryptophan :

Serotonin & melatonin (Centrally acting neurotransmitters and peripherally acting hormones).

Serotonin :

- It is one of the hormones of happiness.
- Decreased serotonin linked to depression, anxiety & panic.
- It is produced on exposure to sunlight → Retinal ganglionic cells stimulated → Activate raphe nuclei in brain stem → Release of serotonin (High activity levels).
- It is part of sleep wake cycle.
- At around 9:30 pm → Serotonin stimulates → Pineal gland → melatonin released (Causes sleep) → Highest at 2-4 am, decreases by 7 : 30 am → Serotonin dominant hormone during the day (Same cycle repeats everyday).
- Abundant amount of serotonin is produced by GIT (Enterochromaffin cells).
- Note : 4 happy hormones : Dopamine, oxytocin, serotonin & endorphin.

Vitamin derivatives : A & D.

Peptide hormones :

- Small peptides (< 50 AA) : Hypothalamic hormones, posterior pituitary hormones, ACTH.
- Large peptides (> 50 AA) : Anterior pituitary hormones : Prolactin (199 AA), GH (191 AA), Insulin, Parathormone and renin.

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Glycoprotein hormones (>200 AA) :

- Lots of protein + less carbohydrates
- Examples : Thyroid Stimulating Hormone, Follicule Stimulating Hormone, Luteinizing Hormone.
- α subunit is common to all.
- β subunit is the differentiating factor.

Steroid hormones :

Adrenal cortical hormones :

- mineralocorticoid : Aldosterone.
- Glucocorticoids : Cortisol.
- Sex steroids/adrenal androgens : DHEAS (Dihydro Epiandrosterone sulphate), Androstenedione.
- Gonadal hormones : Oestrogen, progesterone, testosterone.

Classification based on mechanism of action

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Classification :

- Group 1 hormones : They have intracellular receptors.
- Group 2 hormones : They have cell membrane (Extracellular receptors).

Group 1 hormones :

- Lipophilic.
- Require transport proteins.
- Long T1/2.
- Receptor hormone complex : Effects are mediated through gene transcription (Rarely transport channels).

Types :

- Cytoplasmic receptors/type 1 receptor : Steroid hormones.
- Nuclear receptors/type 2 receptors : Vitamin A & D, T3 & T4.

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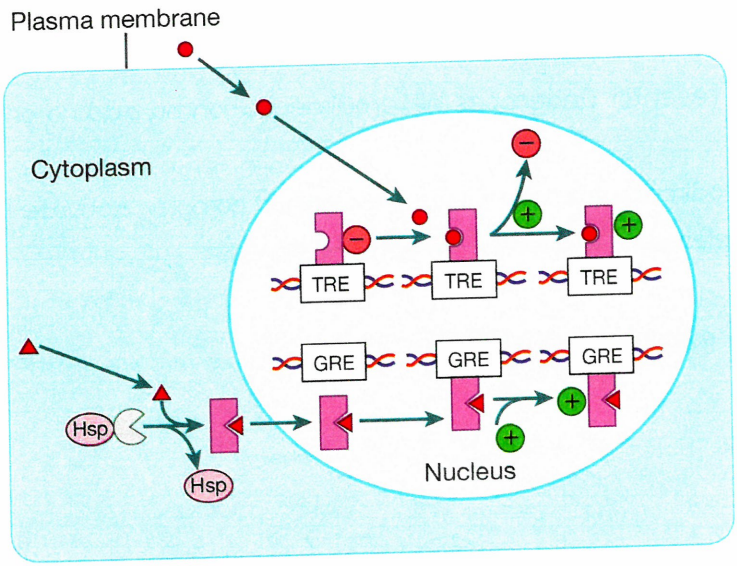
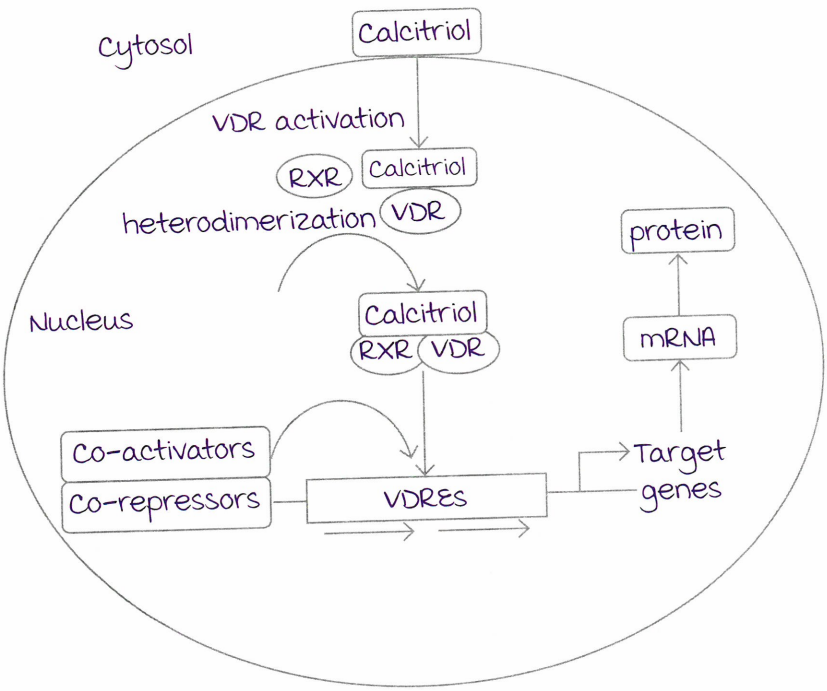


Steroid hormone receptor

- In the inactive state : Steroid receptor (Homodimer) is bound to HSP (Heat Shock Protein)-90/chaperones.
- Once ligand (Steroid hormones) arrives, steroid receptor changes configuration.
- HSP is released.
- And receptor hormone complex is formed and it migrates to nucleus.
- Binds to DNA at Glucocorticoid Response Element (GRE).
- End result is gene transcription.

mechanism of action of calcitriol :



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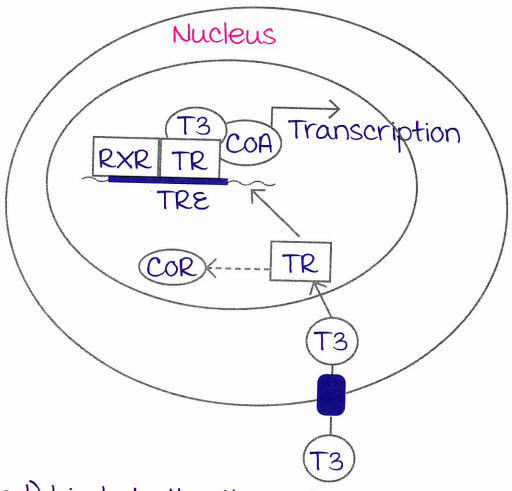
- Calcitriol (1,25 OH2 D3) : active form of vitamin D3 binds to vitamin D receptor in nucleus.
- Vitamin D receptor undergoes heterodimerisation by adding on retinoic acid receptor.
- The heterodimer receptor & ligand (calcitriol) complex activate vitamin D response element (VDRE) → gene transcription.

mechanism of action of thyroid hormones :



- T3 (ligand) binds to the thyroid receptor in the nucleus.
- In the thyroid receptor, there is the dissociation of the co - repressor.
- The thyroid receptor binds to retinoic acid receptor to form a heterodimer and activate Thyroid Response Element (TRE).
- Then gene transcription occurs.

Group 1	Type 1 receptor	Type 2 receptor
Type	Homodimer	Heterodimer
Location	Cytoplasm	Nucleus
mechanism	migration to the nucleus & direct gene transcription.	Dissociation of co repressor & hetero dimerisation & then gene transcription.
Examples	Steroid	T3, T4, Vitamin A & D.

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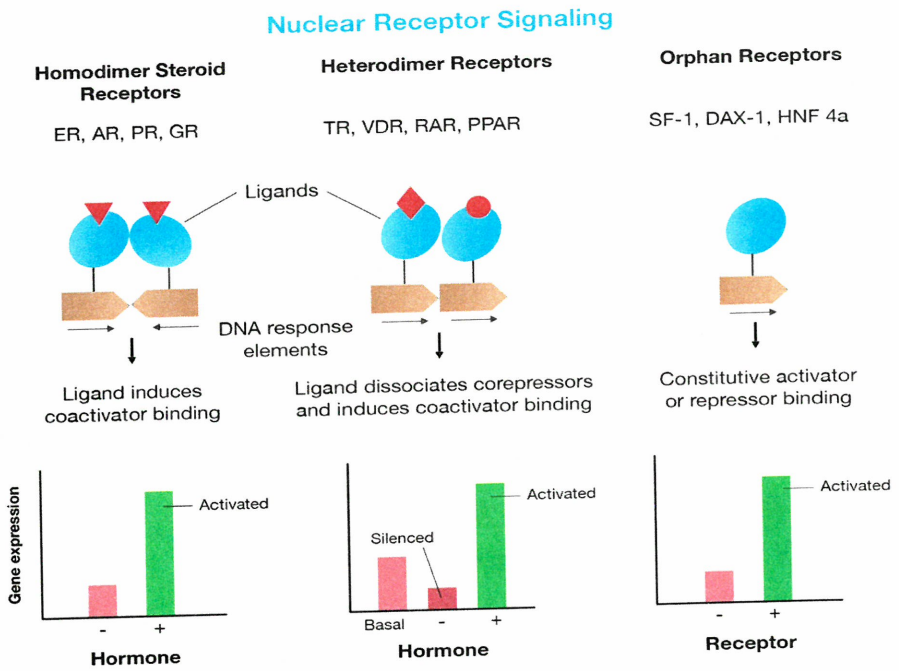

Other Heterodimer receptors :

PPAR (peroxisome proliferator activator receptor) :

PPAR α : Agonist is clofibrate (used when triglycerides > 440 mg/dL).

PPAR γ : Agonist is pioglitazone (thiazolidinediones) (associated with Carcinoma bladder).

Dual PPAR α and γ agonists : Saroglitazal is DOC for diabetic dyslipidaemia (acts against oxidised LDL & increases HDL).

Orphan receptors :

No ligand is required.

It is constitutive.

Example :

- SF-1
- DAX-1

} Required for gonadotroph cell development

- HNF-4α (MODY-1)

Group 2 hormones

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General features of hormone classes :

	Group I	Group II
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-time	Long (hours to days)	Short (minutes)

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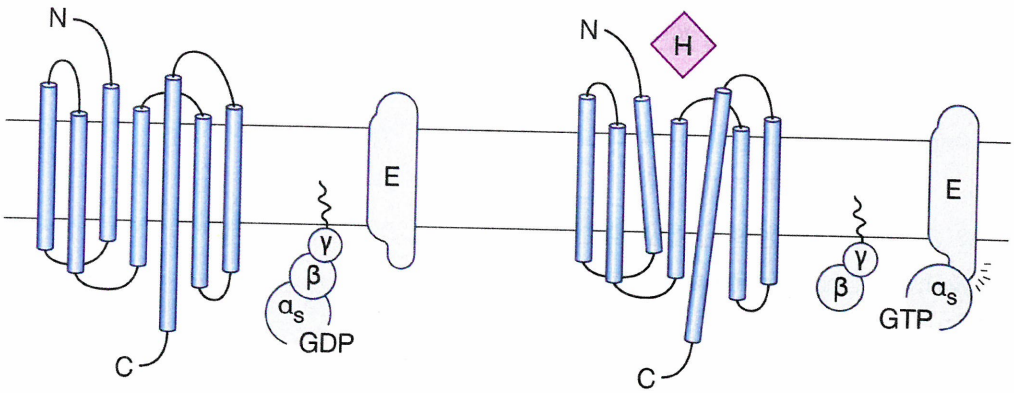
Signals are generated by second messengers. They are responsible for protein modification or translocation followed by transport channel regulation.

Receptors :

- G-protein coupled receptor (GPCR).
- Tyrosine Kinase receptor.
- JAK (Janus Kinase or cytokine) receptor.
- Serine threonine Kinase receptor.

Hormones acting via GPCR :

- It is called as transmembrane receptor.
- They have 7 membrane spanning domains.
- It has α, β, γ subunits bound to GDP in inactive form.
- When hormone binds to receptor; GDP → GTP.
- Alpha subunit & GTP dissociate from complex & bind to the effector.



No hormone: inactive effector

Bound hormone (H): active effector

Effector is 2nd messengers; It can be,

- cAMP (G_s: stimulatory or G_i: Inhibitory).
- IP3/DAG (G_q).
- cGMP (transducin mediated G_t).

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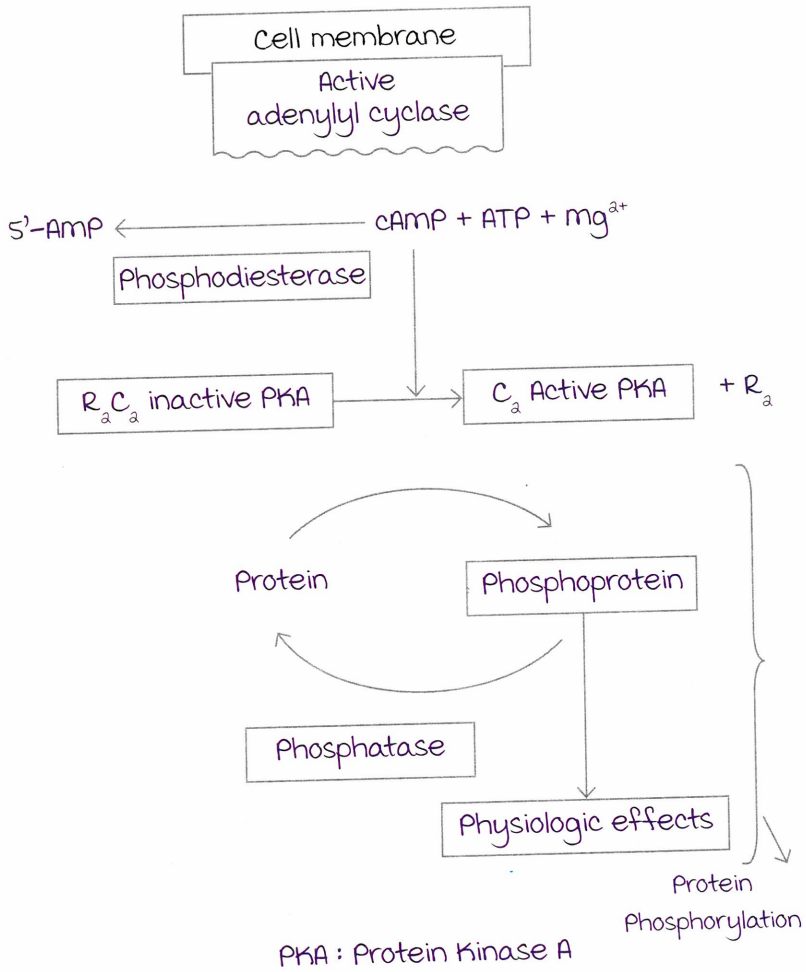
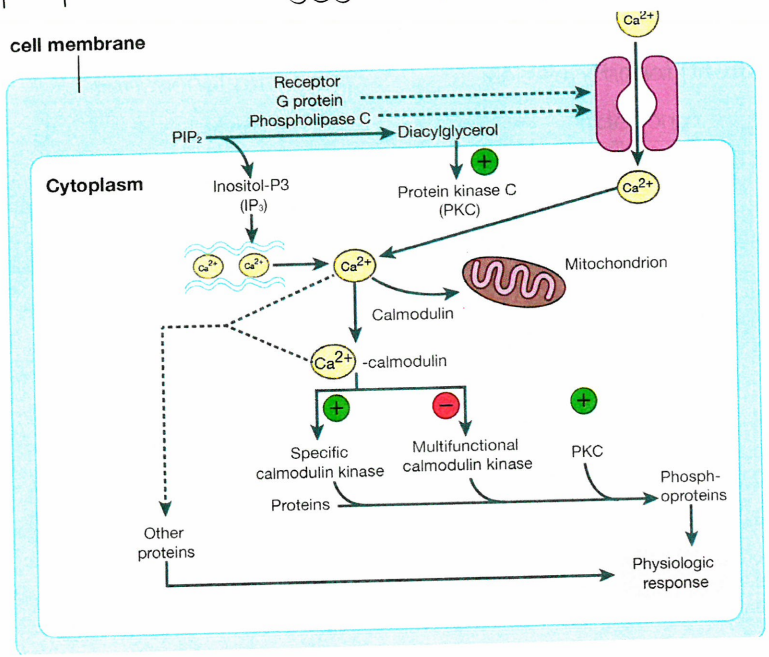
cGMP pathway :

Vasodilators like NO and ANF act via this pathway.



IP3 (inositol triphosphate)/DAG (diacylglycerol) pathway :



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Broad terminology : vasoconstrictors : IP3 pathway, vasodilators : cGMP pathway.

	cAMP	IP3/DAG/Ca^{2+}
Hypothalamus	CRH	TRH, GnRH
Pituitary	ACTH, FSH, LH, TSH + V2 (ADH)	Oxytocin V1, V3 (ADH)
Vasoconstrictors	-	AT-II, Substance P
Pancreas	Glucagon, Somatostain (Gi)	-
GIT	Secretin	CCK, Gastrin
ANS	α 2(Gi), Beta	α 1, Muscarinic Ach
Miscellaneous	PTH, Calcitonin	-

Most potent vasoconstrictor is urotensin.

Subclassification of Group II A Hormones :

Hormones that inhibit adenylyl cyclase (Ha)
Acetylcholine
α-2-adrenergics
Angiotensin II
Somatostatin

Acetyl choline and angiotensin II decrease cAMP, but their hormonal actions are due to IP3/DAG pathway.

α-2 adrenergics and Somatostatin hormonal action mediated by ↓ in cAMP.

Tyrosine kinase pathway

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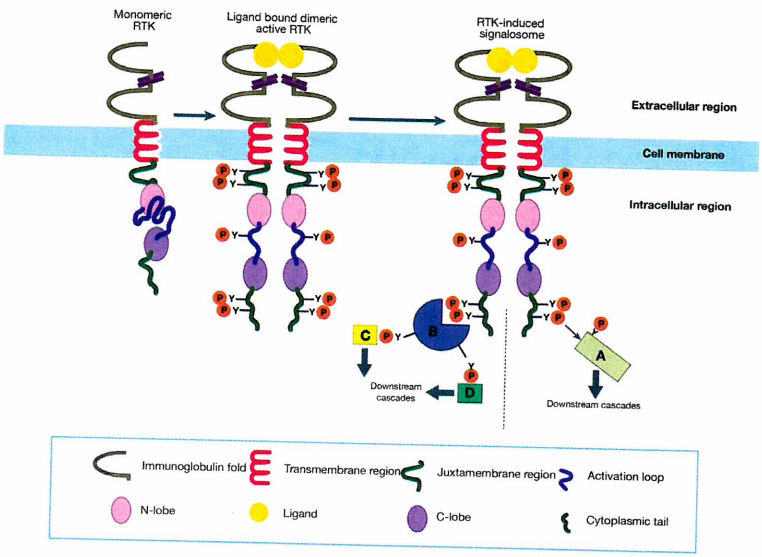
Insulin, Insulin like Growth Factor, Nerve growth factor, Epidermal growth factor, Fibroblast growth factor, TGF α.



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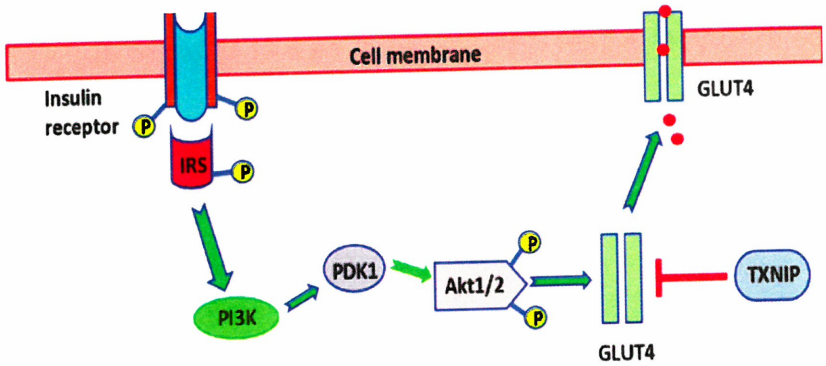
Inactive tyrosine kinase receptor (monomeric state) → Ligand binding → Intracellular dimerisation of receptor → Receptor autophosphorylation → Activate signalling molecules.

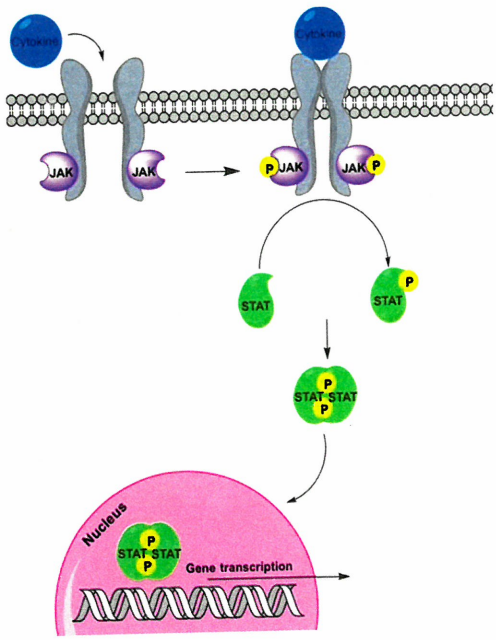
mechanism of action of insulin :



Insulin receptor substrate undergoes phosphorylation → Phosphoinositide 3- kinase (PI3K) /Akt 1/2 activated → Activates GLUT 4 → Glucose uptake.

GLUT 4 : seen in Heart, skeletal muscles, Adipose tissue.

JAK stat pathway :



- Phosphorylation of STAT proteins seen.
- GH (Growth hormone), prolactin (Twin hormones) and EPO (erythropoeitin) act via this pathway.

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Serine-threonine kinase pathway

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Inhibin, Bone morphogenic Protein -7, activin, TGF-beta (most potent fibrogenic cytokine).

Smad proteins activate the pathway.

Exception : TGF-beta → Serine Threonine Kinase pathway.

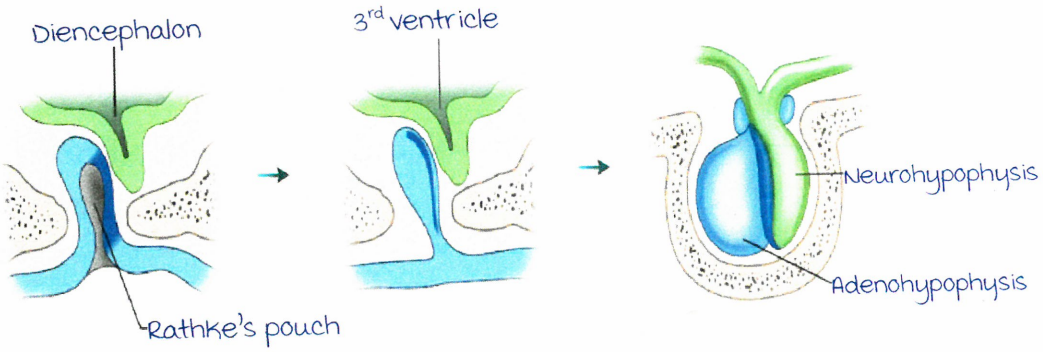
All other growth factors + TGF alpha → Tyrosine Kinase pathway.

BASICS OF PITUITARY GLAND

master gland of the endocrine system (regulates everything).
Size = 600 mg, enlarges itself to 1 g during pregnancy.
Divided into :

- Anterior pituitary gland.
- Posterior pituitary gland.

	Anterior pituitary gland	Posterior pituitary gland
Developed from	Rathke's pouch (upgrowth from the roof of the oral cavity)	Downgrowth from the floor of the 3rd ventricle
Derivative of	Surface ectoderm	Neuroectoderm



Congenital hypopituitarism :

- m/c cause : Pituitary Dysplasia.
- Pituitary dysplasia → Anterior pituitary hormones not produced, posterior pituitary gland is intact.

Clinical features :

- Midline cranio-facial abnormalities (Single central incisor, cleft lip etc)
- Anterior pituitary formed from → Rathke's pouch → Located in the nasopharynx → From there cells migrate across the midline → reach the pituitary. Because of this migration, pituitary dysplasia causes midline cranio-facial abnormalities.

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Anterior pituitary

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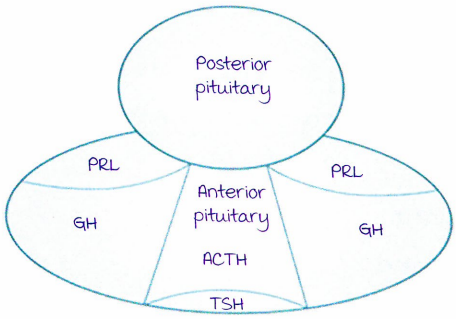

Cells	Development	Hormones produced	Amount of cells seen	Notes	Produced from which part
Somatotrophs	12 weeks	Growth Hormones (Polypeptide hormones)	most abundant cells (50%)	(191 amino acids)	Produced from lateral portion of anterior pituitary
Lactotrophs	Last cells to develop (24 weeks of intrauterine life)	Prolactin (Polypeptide hormones)	15% of cells in anterior pituitary	(199 amino acids)	Produced from lateral portion of anterior pituitary
Corticotrophs	Earliest cells to develop (6 weeks of intrauterine life) intrauterine life)	POMC (Pro opiomelanocorticotropic hormone		POMC = ACTH + MSH + Beta-lipotrophins (endorphins are dervied from them)	Produced from central portion of anterior pituitary
Gonadotrophs	12 weeks	FSH, LH	15% of cells in anterior pituitary		Scattered throughout the pituitary
Thyrotrophs	12 weeks	TSH	5% of cells (least)		Produced from central portion of anterior pituitary

Note : 4 hormones of happiness :

- Dopamine (hormone of pleasure).
- Oxytocin (hormone of love).
- Serotonin (hormone of mood stabilization).
- Endorphins (natural pain Killer) (Endorphins inhibit μ-receptor → Decreased substance P → Decreased pain.)