HARRISON'S BASED GENERAL MEDICINE

PART 1

CONTENT

ENDOCRINOLOGY & METABOLISM

CLASSIFICATION OF HORMONES

Classification based on structure 00:00:50

Amino acid derivatives :

1. Tyrosine : T_3, T_4, catecholamines.
   Produced by adrenal medulla : most abundant in order of adrenaline > NE > dopamine.
2. Tryptophan : Serotonin, melatonin (centrally acting neurotransmitters and peripherally acting hormones).
   Serotonin :
   It is one of the hormones of happiness.
   It is produced by raphe nuclei by retinal (ganglionic cells) stimulus.
   It is part of sleep wake cycle.
   By around 9:30 pm, serotonin stimulates pineal gland and produce melatonin (highest : 2-4 am, decreased : 7:30 am).
   Abundant amount of serotonin is produced by GIT (enterochromaffin cells)

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, PTH and renin.

Glycoprotein hormones (protein + carbohydrates) :
TSH, FSH/LH (>200 AA).
Alpha subunit is common among them.

Steroid hormones :

- Adrenal cortical hormones :
  mineralocorticoid : Aldosterone.

Glucocorticoids : Cortisol.

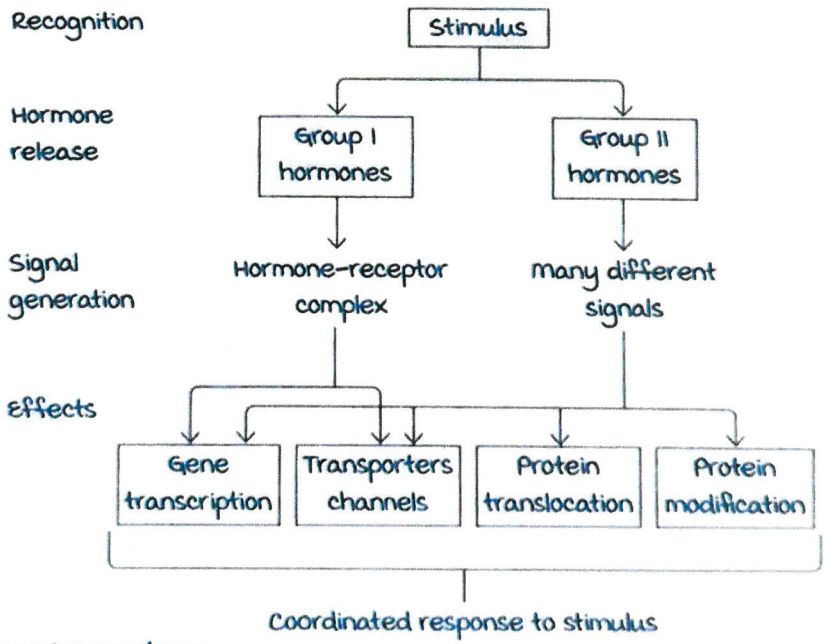
- Sex steroids/adrenal androgens: DHEAS, androstenedione.
  Sex hormones : Oestrogen, progesterone, testosterone.

Classification based on mechanism of action 00:14:44

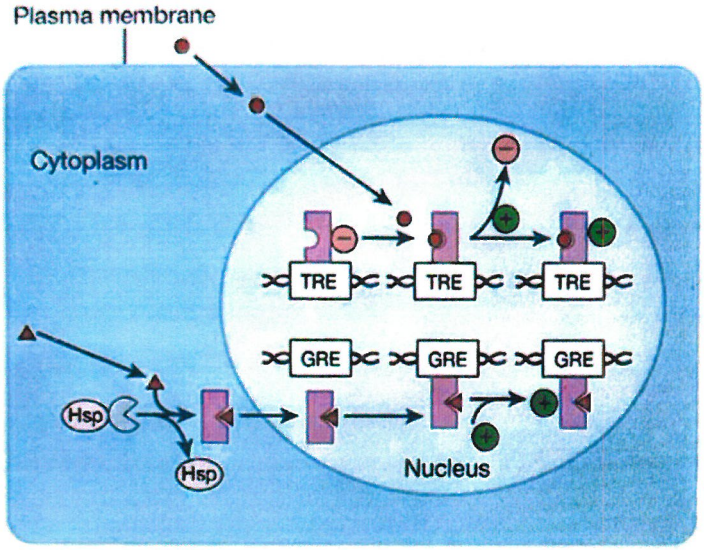
Group I hormones : They have intracellular receptors.
2 types :

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

Group 2 hormones : They have cell membrane (extracellular receptors).
Receptor hormone complex : Effects are mediated through gene transcription.



Type I receptor :
Regulation of gene expression glucorticoids.
Homodimer receptors (receptor in cytoplasm) : Steroid hormones. There is no corepressor.
Heterodimer receptors (receptor in nucleus) : T3, T4, Vitamin D & A. There is a corepressor.



In the inactive state : Steroid receptor (homodimer) is bound to HSP-90 (chaperones).

Once ligand (steroid hormones) arrives, steroid receptor changes configuration.

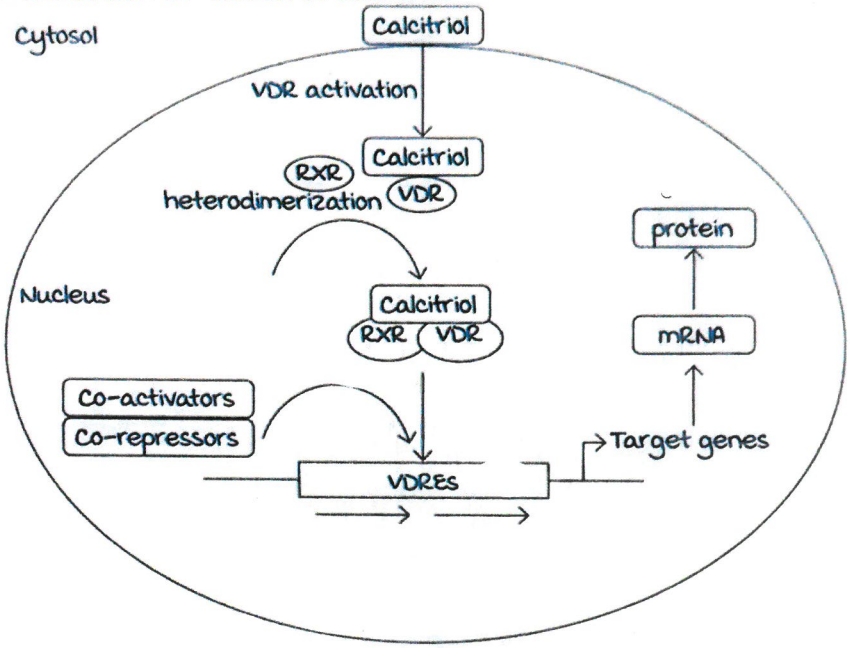
HSP is released.

And receptor hormone complex is formed and it migrates to nucleus.

Binds to DNA at glucocorticoid response element (GRE).

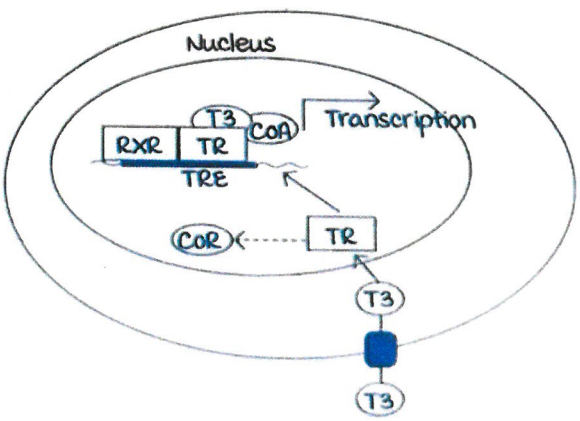
End result is gene transcription.

mechanism of action of calcitriol :



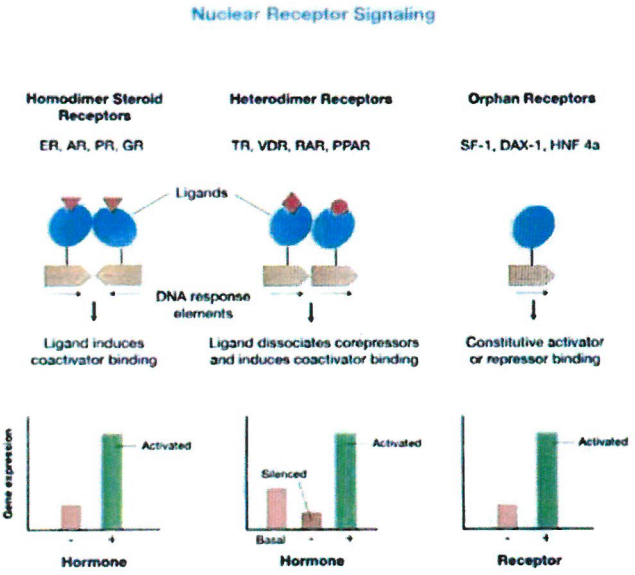
Vitamin D receptor (VDR) action at target cells. Intracellular calcitriol (1,25(OH)2D] binds to the VDR.
It causes its dimerization with the retinoid X receptor (RXR).
The ligand-bound VDR-RXR complex binds to structurally distinct vitamin D response elements (VDREs) in multiple, widely spaced vitamin D-responsive regions, and this causes a modification in the recruitment of co-activators or co-repressors, which leads to transcriptional regulation of gene expression

mechanism of action of thyroid hormones :



Thyroid hormone receptor-mediated transcription.
T3 enters the target cell through membrane transport.
T3 enters the nucleus and binds to the thyroid hormone receptor (TR).

TR then releases the co-repressor (CoR), dimerizes with the retinoid x receptor (RXR), and recruits the co-activator (COA) complex.
This complex binds the T3 response element to activate transcription.



PPAR (peroxisome proliferator activator receptor) :
PPAR α : Agonist is clofibrate (TGs > 400 mg/dL).
PPAR γ : Agonist is pioglitazone (thiazolidinediones) (associated with Ca bladder).
Dual PPAR α and γ agonists : Saroglitazal is DOC for diabetic dyslipidaemia.

Orphan receptors :
No ligand is received.
It is constitutive.

Example :

- SF-1
- DAX-1

  } Required for gonadotroph cell development

- HNF-4a (MODY-1)

Group 2 hormones

00:36:24

They have cell membrane (extracellular) receptors.

General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-time	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
mediator	Receptor - hormone complex	cAMP, cGMP, Ca^{2+}, metabolites of complex phosphinositols, kinase cascades

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

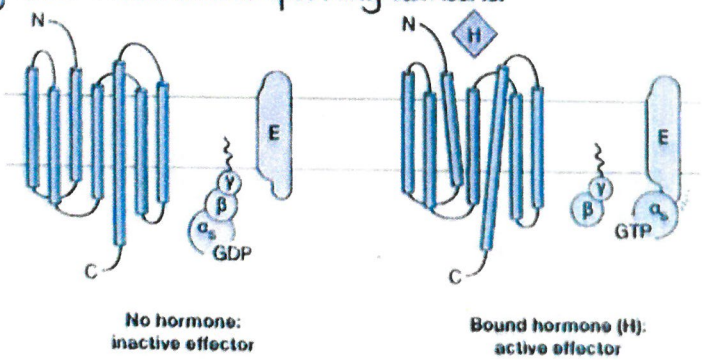
Receptors :

- G-protein coupled receptor.
- Tyrosine kinase receptor.
- JAK (Janus kinase or cytosine kinase) receptor.
- Serine threonine kinase receptor.

Hormones acting via GPCR :

It is called as transmembrane receptor.

They have 7 membrane spanning domains.



Receptors that couple to effectors through proteins (GPCR) typically have seven membrane-spanning domains. In the absence of hormone (left), the heterotrimeric G-protein complex (alpha, beta, gamma) la in an inactive quantino diphosphate (GDP)-bound form and is probably not associated with the receptor This complex is anchored to the plasma membrane through prenylated groups on the Dy subunits (wavy lines) and perhaps by myristoylated groups on a subunits (not shown). On binding of the hormone to the receptor, there is a presumed conformational change of the receptor -as indicated by the tited membrane-spanning domains and activation of the G-protein comples. The results from the exchange of GDP with guanonane triphosphate (GTP) on the a subunit, after which a and by dissociate. The subunit binds to and activate the effector (E). E can be adenytyl cyclase Ca2+, Na+, or Cl- channels

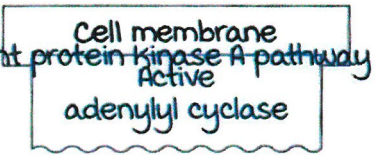
Effector is 2nd messengers.

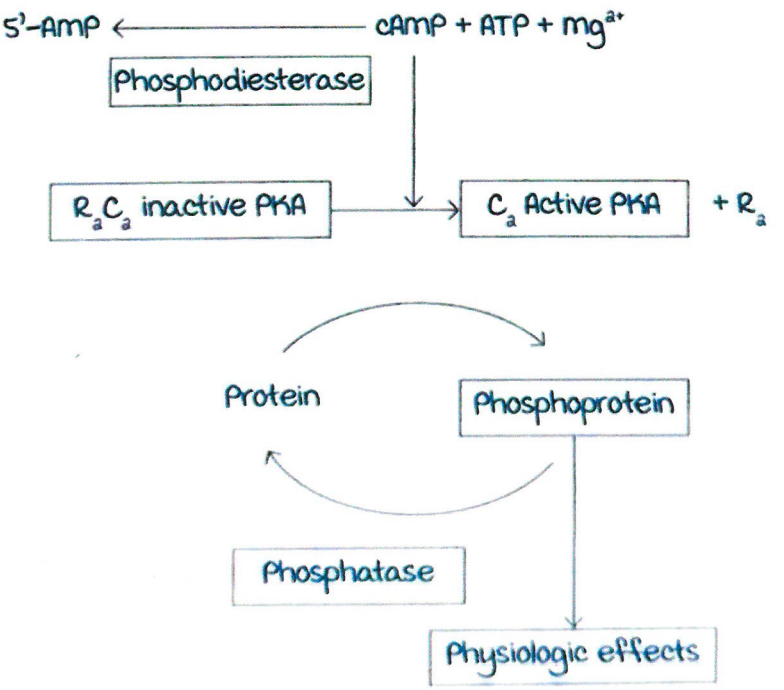
It can be,

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

cGMP pathway : Vasodilators like NO and ANF act via this pathway.

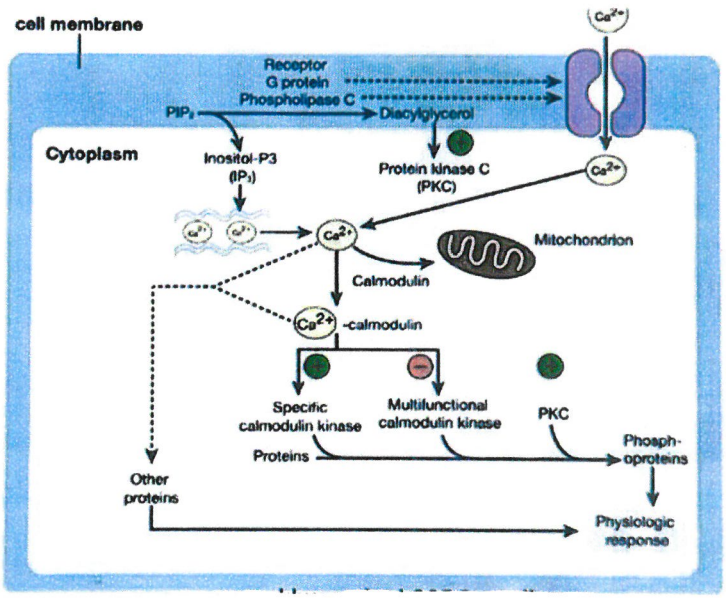
cAMP dependant protein kinase A pathway :





cAMP : Hypothalamic hormones (CRH) , TSH , FSH , LH , ACTH
V2 receptor of vasopressin,
Glucagon, Somatostatin, Secretin
Alpha 2 and beta blockers
PTH, calcitonin

IP3/DAG pathway : Vasoconstrictors.
Hypothalamic hormones (TRH & GnRH).
Vasopressin V1 & V3 receptors, oxytocin.
CCK, gastrin.
Alpha 1 & Ach receptors.



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

most potent vasoconstrictor is urotensin.

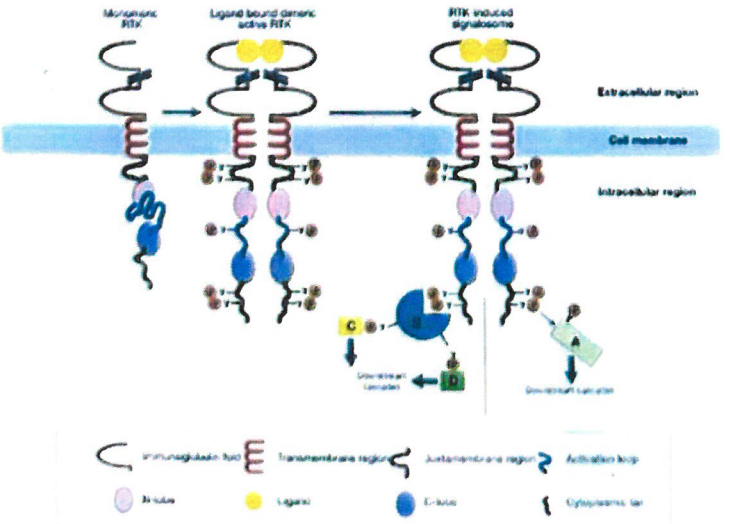
Subclassification of Group II A Hormones

Hormones that stimulate adenylyl cyclase (H2)	Hormones that inhibit adenylyl cyclase (H2)
ACTH	Acetylcholine
ADH	Alpha-2-adrenergics
Beta-adrenergics	Angiotensin II
Calcitonin	Somatostatin
CRH	
FSH	
Glucagon	
hCG	
LH	
LPH	
MSH	
PTH	
TSH	

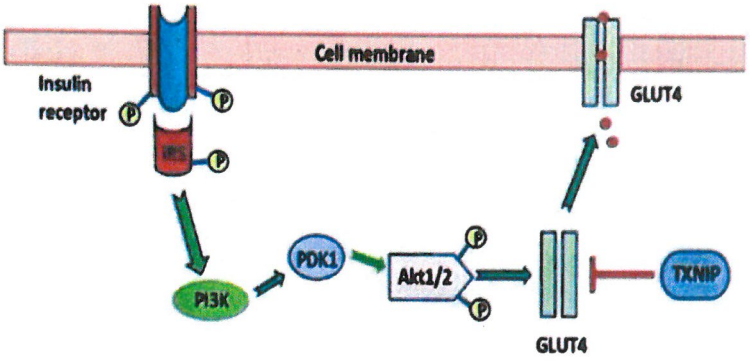
Ach and angiotensin II decrease cAMP, but their hormonal actions are due to IP3/DAG pathway.

Tyrosine kinase pathway 00:52:05

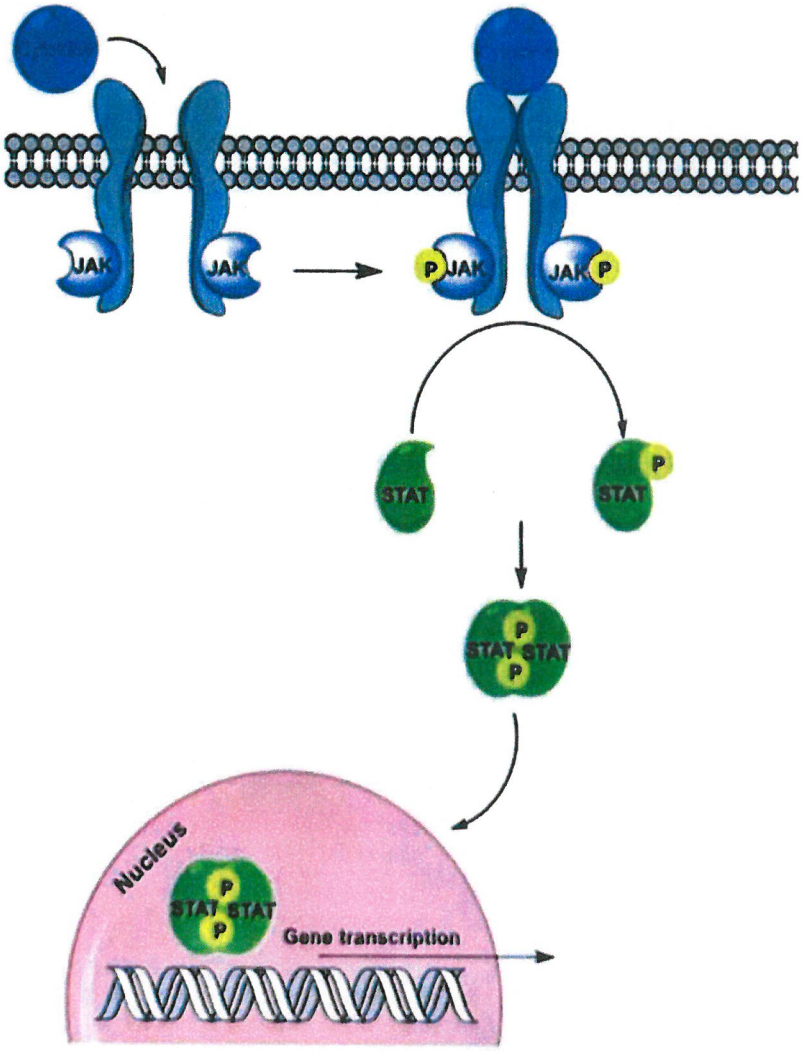
Insulin, IGF, NGF, EGF, FGF, TGF alpha.



mechanism of action of insulin :



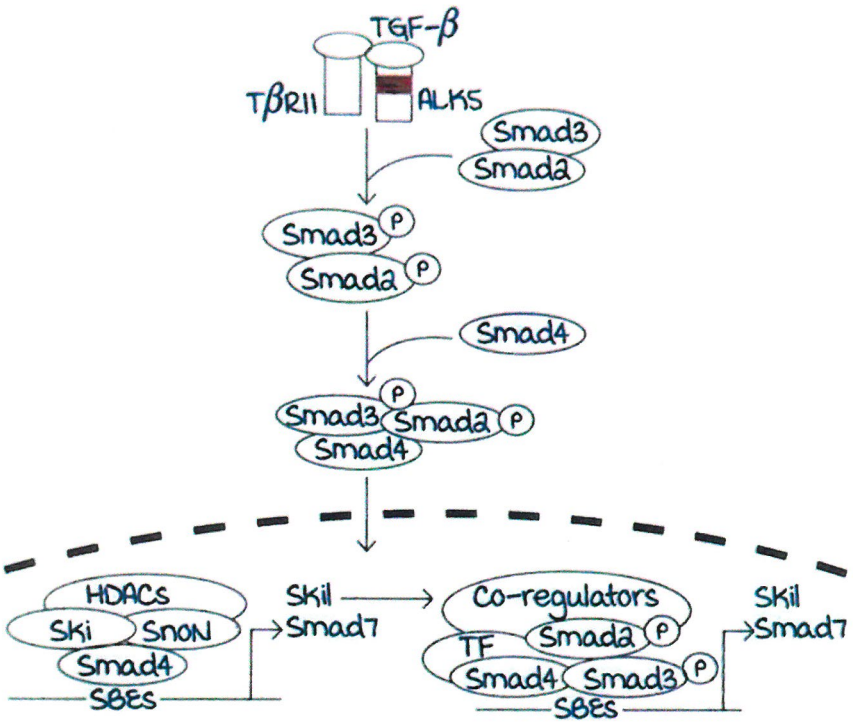
JAK stat pathway :



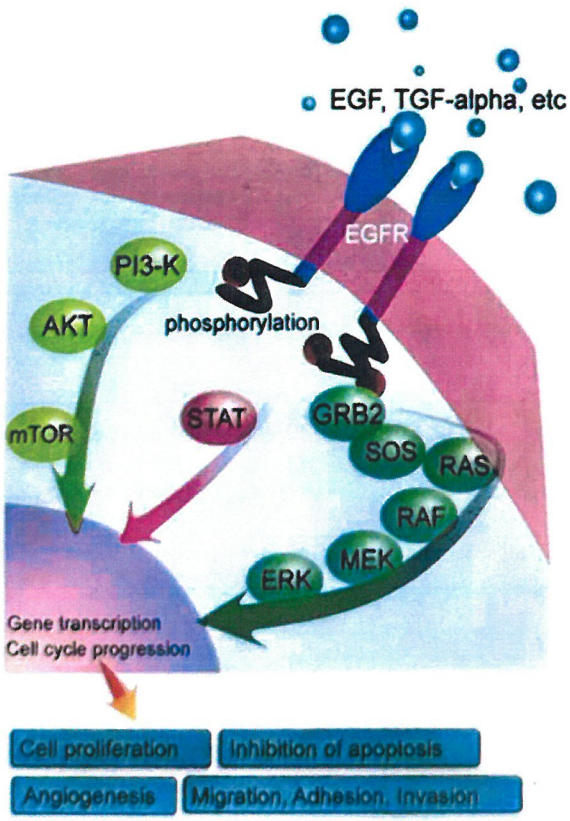
Phosphorylation of STAT proteins seen.

GH, prolactin (twin hormones) and EPO act via this pathway.

Inhibin, BMP-7, activin, TGF-beta.



TGF :



BASICS OF PITUITARY GLAND

master gland of the endocrine orchestra (regulates everything).

Size = 600 mg, enlarges itself to 1 g during pregnancy.

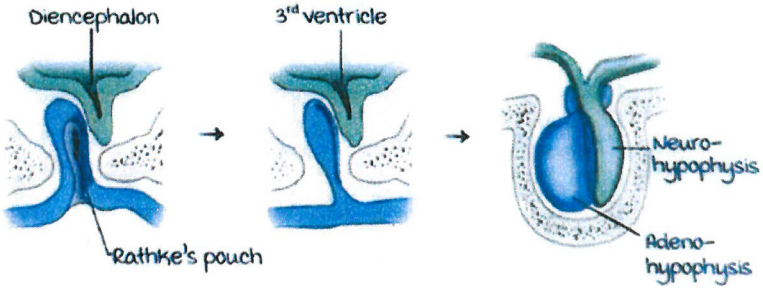
Divided into :

- Anterior pituitary gland
- Posterior pituitary gland

Development

00:01:07

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



Congenital hypopituitarism :

m/c cause : Pituitary Dysplasia.

Pituitary dysplasia ☒ Anterior pituitary hormones only not produced, posterior pituitary gland is intact.

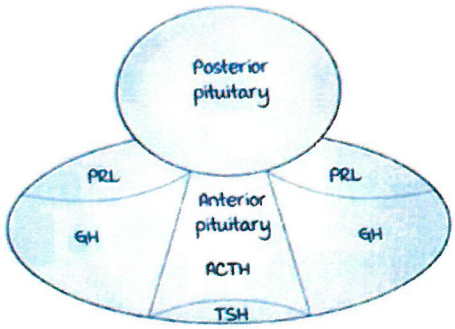
Clinical features :

- Midline cranio-facial abnormalities (single central incisor, cleft lip etc)

  (Anterior pituitary is formed from Rathke's pouch, which is located in the nasopharynx. From there, cells migrate across the midline to reach the pituitary, in the brain. Because of this migration, pituitary dysplasia causes midline cranio-facial abnormalities)

ANTERIOR PITUITARY

00:6:14



Distribution and percentage of anterior pituitary cell subtypes, horizontal view. Gonadotroph cells are scattered throughout the anterior pituitary and constitute ~10% of cells. PRL, prolactin secreting cells (15%); GH, growth-hormone-secreting cells (50%: ACTH, adrenocorticotropin-secreting cells (15%): TSH, thyrotropin-secreting cells (5%).

Cells	Extra	Hormones produced	Amount of cells seen	Notes	Produced from which part
Somatotrophs		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)	
Corticotrophs	Earliest cells to develop (6 weeks of intrauterine life) intrauterine life)	POMC (Pro opiomel-anocorticotropic hormone		POMC = ACTH + MSH + Beta-lipotrophins (endorphins are dervied)	Produced from central portion of anterior pituitary
Gonadotrophs		FSH, LH	15% of cells in anterior pituitary		Scattered throughout the pituitary
Thyrotrophs		TSH	5% of cells (least)		Produced from central portion of anterior pituitary

ACTH increase ☒ MSH receptor binds ☒ increased MSH ☒ Hyperpigmentation in increased ACTH situations.

4 hormones of happiness :

1. Dopamine (hormone of pleasure).
2. Oxytocin (hormone of love).
3. Serotonin (hormone of mood stabilization).
4. Endorphins (natural pain killer) (Endorphins inhibit U-receptor ⊠ Decreased substance P ⊠ Decreased pain.)

Acidophilic and basophilic hormones 00:15:12

Acidophilic	Basophilic
Growth Hormone	ACTH
Prolactin	FSH, LH
	TSH

Transcription factors required for pituitary development :
m/c cause of congenital hypopituitarism is Pituitary dysplasia, which is due to loss of function of transcriptional factors :

1. PROP 1 regulates the development of :
   - GH producing cells.
   - Prolactin producing cells.
   - TSH producing cells.
   - ACTH producing cells.

2. PIT 1 :

   Specific transcriptional factors for growth of :

   1. Corticotroph ⊠ t-pit.
   2. Gonadotroph ⊠ GATA-3 (proteins released by GATA 3 are SF-1 and DAX-1).

Cell	Corticotrope	Somatotrope	Lactotrope	Thyrotrope	Gonadotrope
Tissue specific transcription factor	T-pit	Prop-1, Pit-1	Prop-1, Pit-1	Prop-1, Pit-1, TEF	SF1, DAX-1
Fetal appearance	6 weeks	8 weeks	12 weeks	12 weeks	12 weeks
Hormone	POMC	GH	PRL	TSH	FSH, LH
Protein	Polypeptide	Polypeptide	Polypeptide	Glycoprotein - alpha, beta subunits	Glycoprotein - alpha, beta subunits
Amino acids	266 (ACTH 1-39)	191	199	211	210, 204
Stimulators	CRH, AVP, gp-130 cytokines	GHRH, ghrelin	Estrogen, TRH, VP	TRH	GnRH, activins, estrogens
Inhibitors	Glucocorticoid	Somatostatin IGF-1	Dopamine	T3, T4, dopamine, somatostatin, glucocortic-oids	Sex steroids, inhibin
Target gland	Adrenal	Liver, bone, other tissues	Breast other tissues	Thyroid	Ovary, testis
Trophic effect	Steroid production	IGF1 production, growth induction, insulin antagonism	milk production	T4 synthesis and secretion	Sex steroid production, follicle growth germ cell maturation

Anterior pituitary hormone expression and regulation

Fetal appearance	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Hormone	FSH, CH	TSH	PRL	GH	POMC
Chromosomal gene locus	☒-11p, ☒-19q	a-6q, ☒-1p	6	17q	2p
Protein	Glycoprotein a,☒ subunits	Glycoprotein a,☒ subunits	Polypeptide	Polypeptide	Polypeptide
Amino acids	210,204	211	199	191	266 (ACTH 1-39)
Stimulators	GnRH, estrogen	TRH	Estrogen, TRH	GHRH, GHS	CRH, AVP, gp-130 cytokines
Inhibitors	Sex steroids, inhibition	T3, T4, dopamine, somatostatin, glucocorticoids	Dopamine	Somato-statin, IGF activins	Glucocorticoids
Target gland	Ovary, testis	Thyroid	Breast, other tissues	Liver, bones, other tissues	Adrenal