GENERAL MEDICINE

PART-1

CONTENT

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.

Active space

Glucocorticoids : Cortisol.

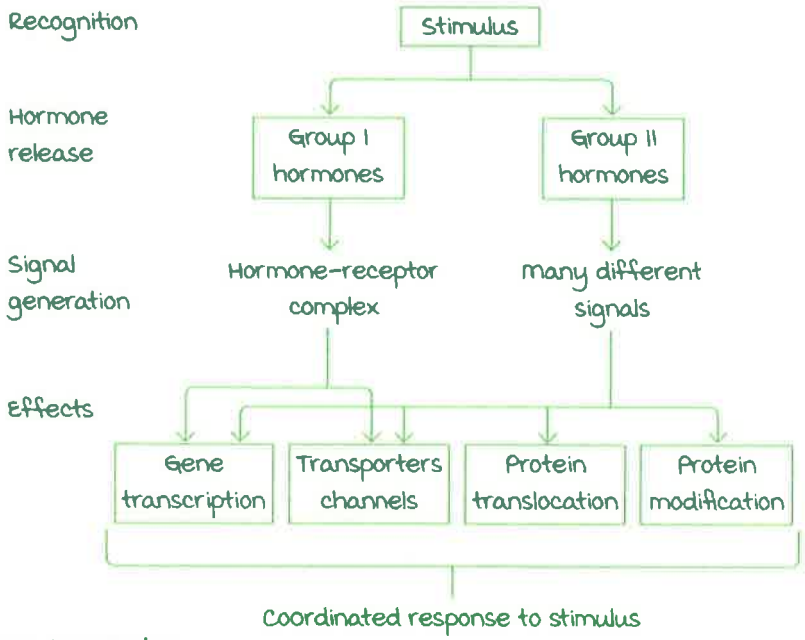
- Sex steroids/adrenal androgens : DHEAS, androstenedione.
  Sex hormones : Oestrogen, progesterone, testosterone.

Classification based on mechanism of action 00:14:44

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

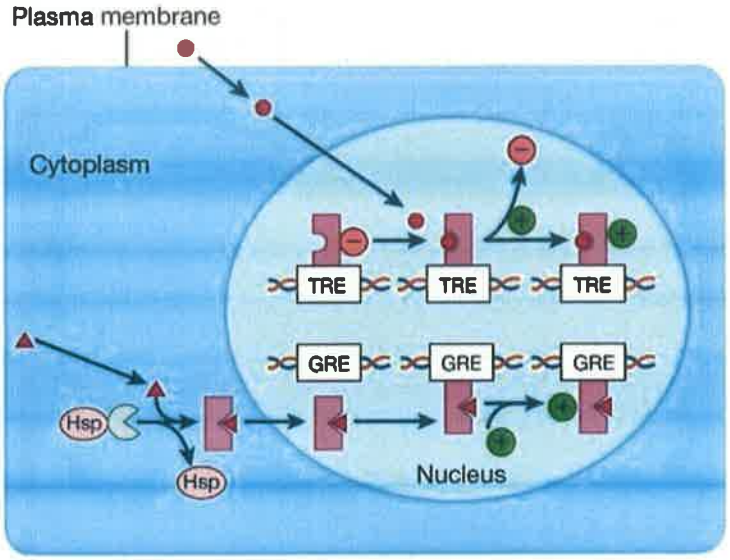
- Cytoplasmic receptors/type I hormones : Steroid hormones.
- Nuclear receptors/type 2 hormones : Vitamin A & D, T3 & T4.

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.

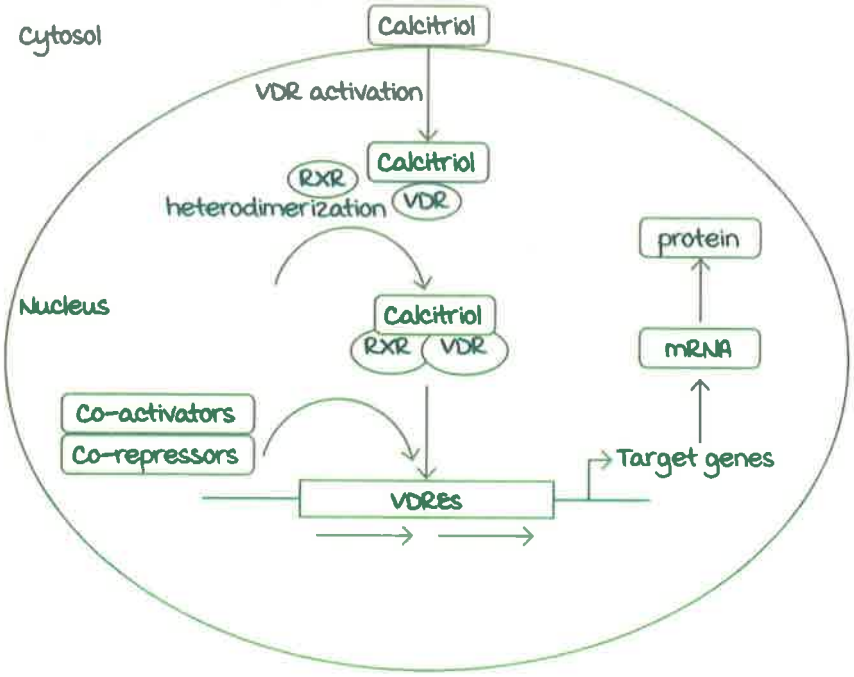
Active space



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.

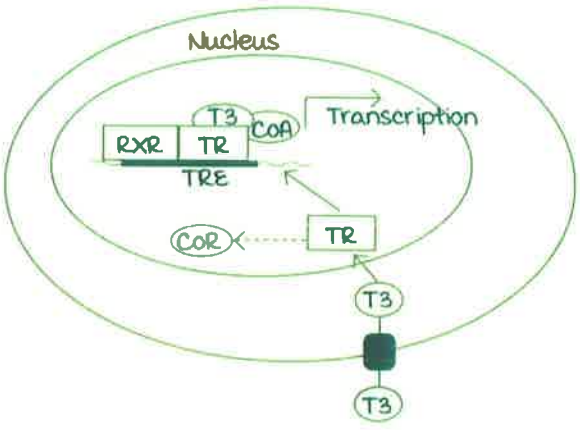
Active space

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

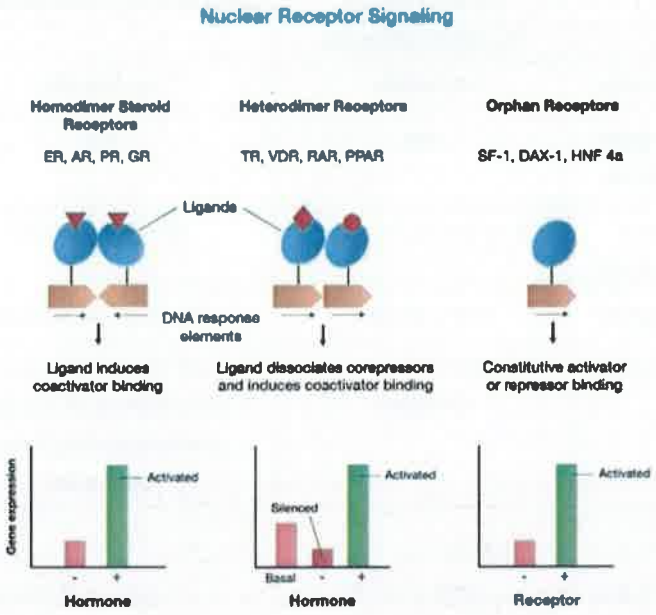
mechanism of action of thyroid hormones :



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).

Active space

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)

Active space

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.

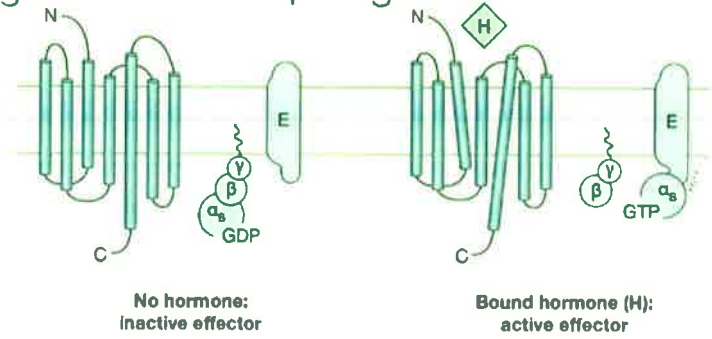
Receptor

- 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.



No hormone: inactive effector

Bound hormone (H): active effector

Active space

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 Ca^{2+}, Na^{+}, or Cl^{-} channels

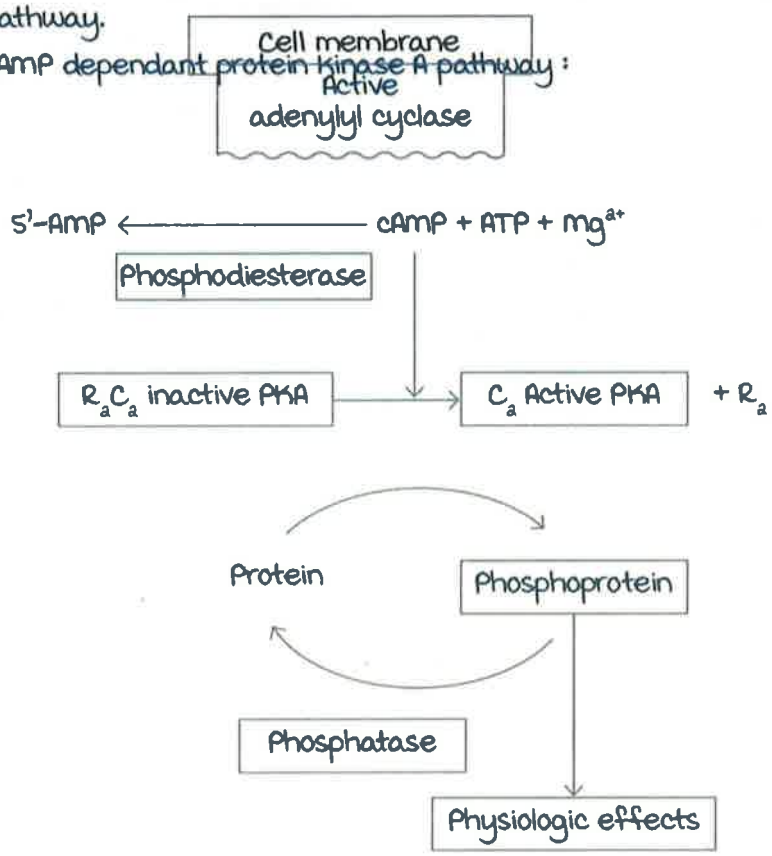
Effector is 2nd messengers.

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.

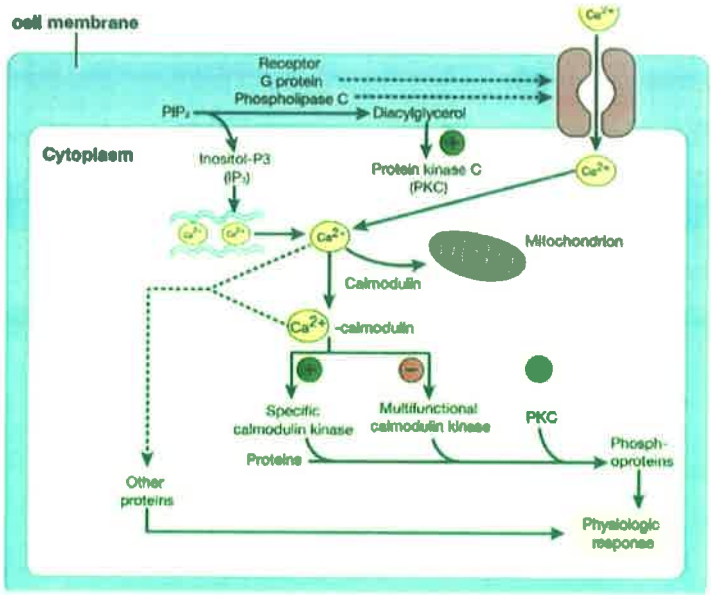
cAMP dependant protein kinase A pathway :



Active space

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	-

Active space

most potent vasoconstrictor is urotensin.

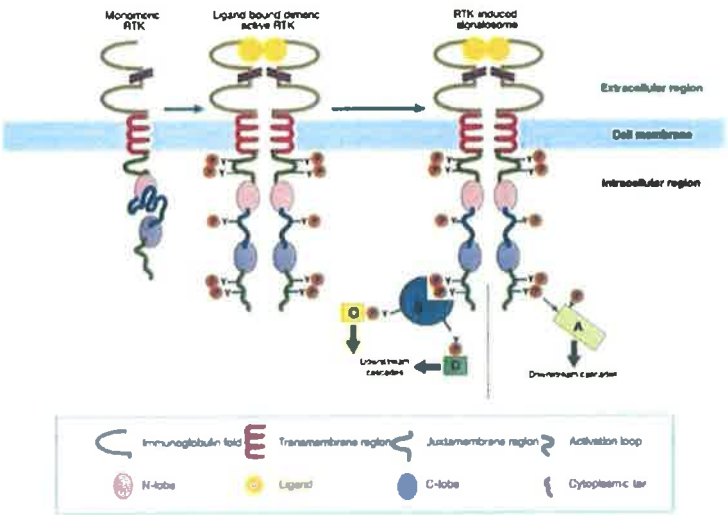
Subclassification of Group II A Hormones

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.

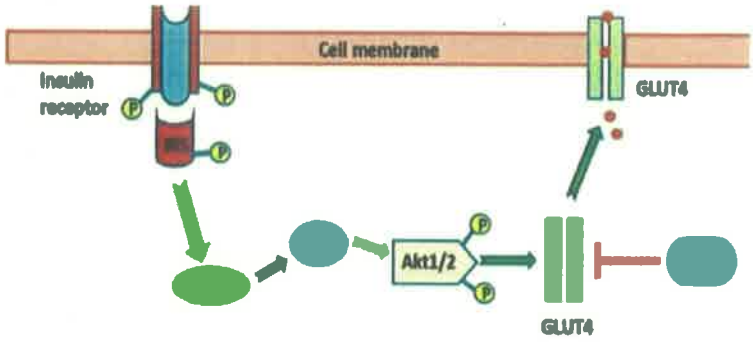
Tyrosine kinase pathway 00:52:05

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

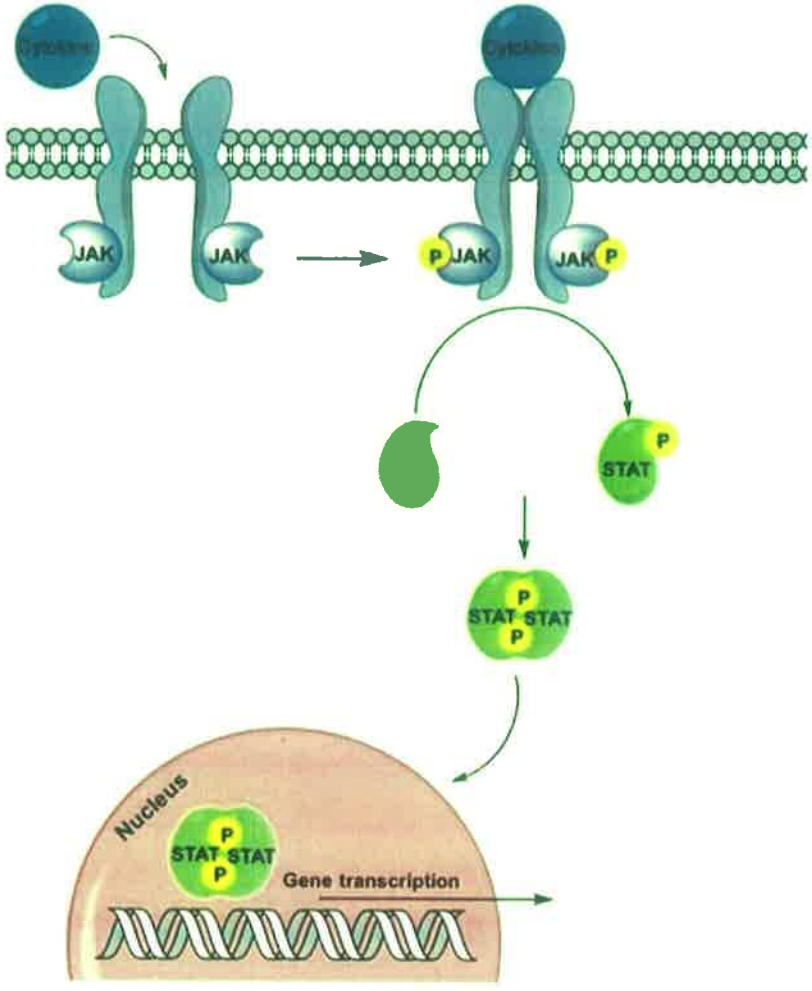


Active space

Mechanism of action of insulin :



JAK stat pathway :



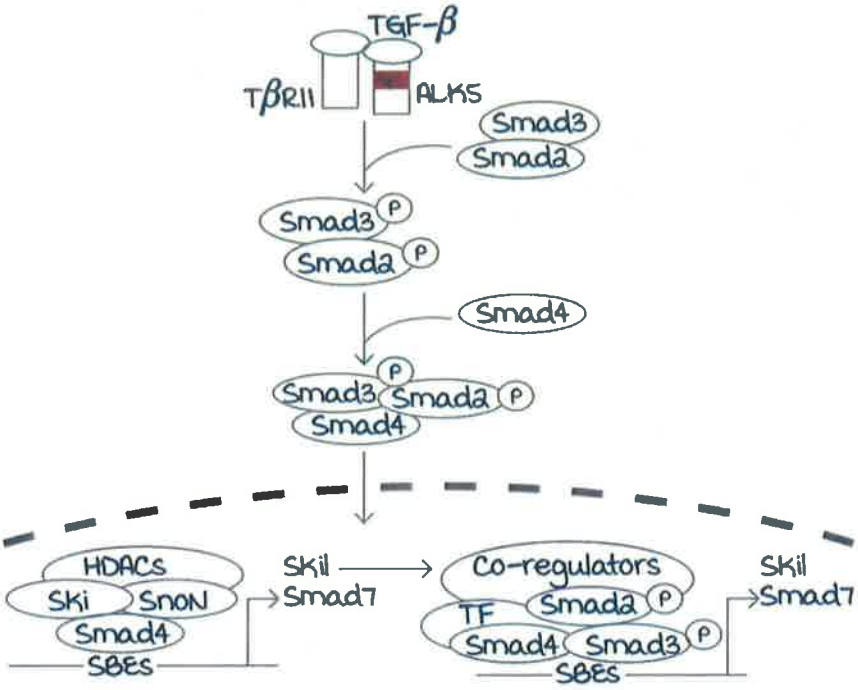
Phosphorylation of STAT proteins seen.

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

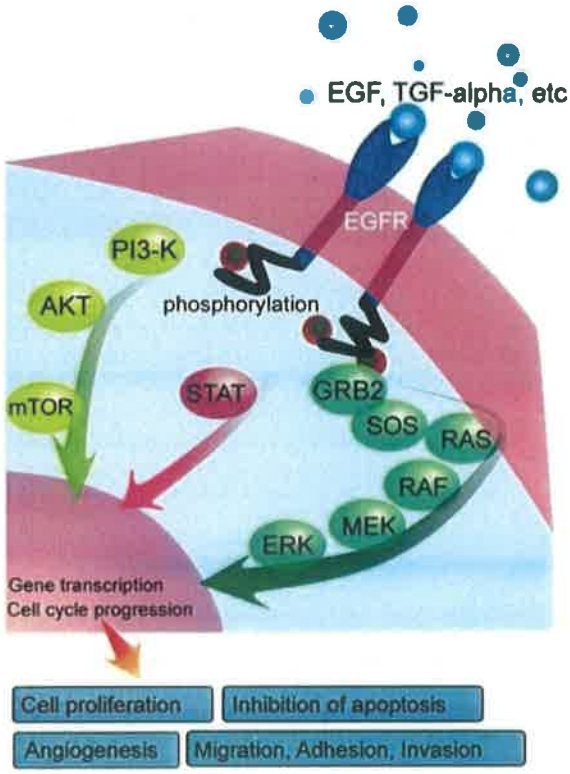
Active space

Serine-threonine kinase pathway 00:56:40

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



TGF:



Active space

BASICS OF PITUITARY GLAND

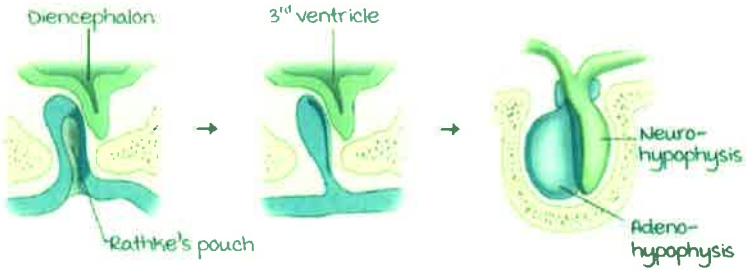
Master gland of the endocrine orchestra (regulates everything).
Size = 600 mg, enlarges itself to 1 g during pregnancy.
Divided into :

- 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 :

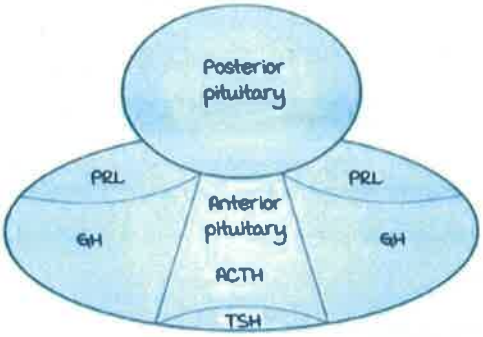
- Midline cranio-facial abnormalities (single central incisor, cleft lip etc)
  (Anterior pituitary is formed from Rathke's pouch, which is located in the nasopharynx. From there, cells migrate across the midline to reach the pituitary, in the brain. Because of this migration, pituitary dysplasia causes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

Active space

Feedback

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-socroting colls (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.

Active space

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

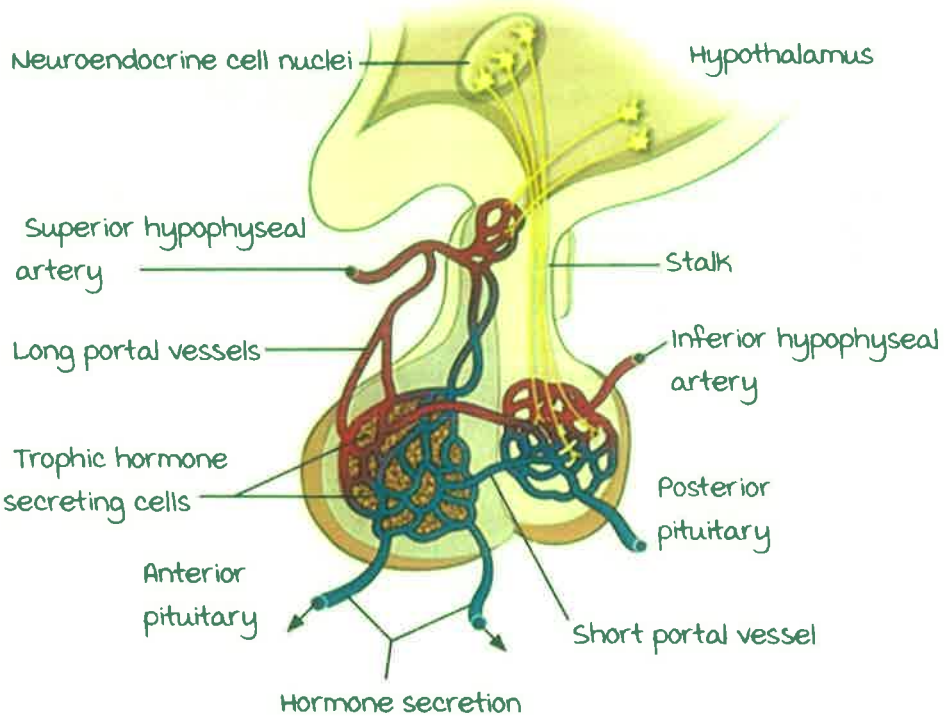
Fetal appearance	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Hormone	FSH, CH	TSH	PRL	GH	POMC
Chromosomal gene locus	☒-11p, ☒-19q	a-6q, ☒-1p	6	17q	2p
Protein	Glycoprotein a,☒ subunits	Glycoprotein a,☒ subunits	Polypeptide	Polypeptide	Polypeptide
Amino acids	210,204	211	199	191	266 (ACTH 1-39)
Stimulators	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

Active space

Trophic effect	Sex steroid Follicle growth Germ cell maturation M=5-20 IU/L F(basal) 5-20 IU/L	T4 synthesis and secretion	milk production	IGF-1 production, growth induction, insulin antagonism	Steroid production
Normal range	M-5-a IU/L F(basal) 5-20 IU/L	0.1-5 mU/L	M<15; F<20	<0,5⊠g/L	ACTH, 4-22 pg/L

Relationship between hypothalamus and the anterior pituitary : Hypothalamo-hypophyseal trophic relationship.

- Superior Hypophyseal artery ⊠ Joins with hypothalamo-hypophyseal portal system (between the hypothalamus and adenohypophysis), where the hypothalamus releases the growth factors.
- This release of growth factors stimulates the anterior pituitary gland to release hormones.



Active space

Hypothalamus	Anterior pituitary
GHRH	Somatotrophs
CRH	Corticotrophs
TRH	Thyrotrophs
GnRH	Gonadotrophs

- Except Dopamine , through the tubulo-infundibular pathway ☒ inhibits prolactin (PRIH/PRIF : Prolactin Release Inhibiting Hormone/Factor).
- Therefore all the hormones except prolactin is under stimulatory control.

Neurohypophyseal relationship 00:23:02

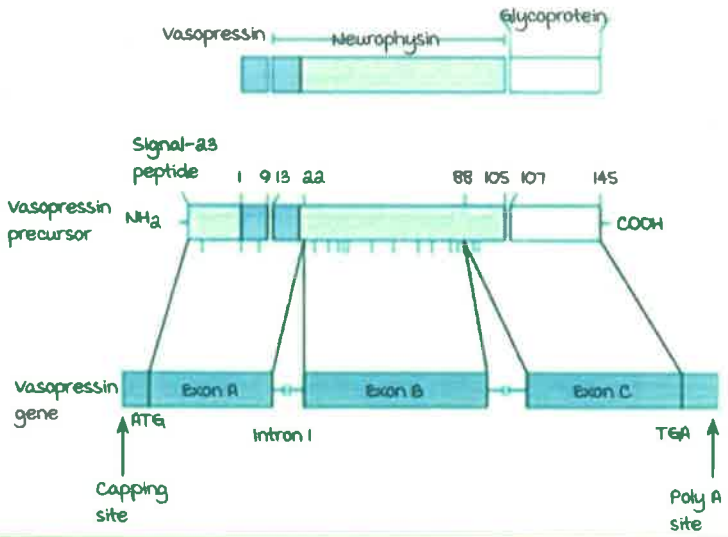
- Relationship sustained via axons.
- In the hypothalamus :

Magnocellular Neurons (in Supraoptic nucleus and Paraventricular nucleus of Hypothalamus) ☒ produces pro-vasopressin.

Neurons in Periventricular nucleus of hypothamus ☒ produces oxytocin.

- These hormones are released and travel via axons (pituitary stalk)☒ Provasopressin is cleaved ☒ Vasopressin (ADH/AVP) + Neurophysin + Co-peptin formed.
- Hormones are stored in the posterior pituitary gland.

The arginine vasopressin (AVP) gene and its protein products



The three exons encode a 145 amino acid prohormone with an NH-terminal signal peptide. The prohormone is packaged into neurosecretory granules of magnocellular neurons. During axonal transport of the granules from the hypothalamus to the posterior pituitary, enzymatic cleavage of the prohormone generates the final products, AVP, neurophysin and a COOH-terminal glycoprotein called copeptin. When afferent stimulation depolarizes the AVP containing neurons, the three products are released into capillaries of the posterior pituitary in equimolar amounts.

Inferior hypophyseal artery supplies to posterior pituitary gland.

m/C manifestation of pituitary metastases : Posterior pituitary mostly affected (since it has direct blood supply through inferior hypophyseal artery) ☒ Leads to ADH insufficiency ☒ Diabetes insipidus.
Classical malignancy to metastazise to pituitary : Ca breast.

Pituitary adenoma

00:29:04

- Macroadenoma > 1 cm.
- Microadenoma < 1 cm.

Functional pituitary adenomas secrete hormones.

- Prolactin secreting tumors > GH secreting tumors > ACTH secreting tumors.
- FSH, LH, TSH secreting tumors (very rare).

Active space

Clinical features :

1. Functional (hormonal effects).
2. Mass effects (tumor compresses something ☒ symptoms.)
3. ± stalk effects

Non Functional pituitary adenomas – no hormonal component.

- Craniopharyngioma.
- Rathke cell cyst.
- Eosiniphilic Granuloma.
- Langerhans cell histiocytosis.

Clinical features :

1. Mass effects (tumor compresses something ☒ symptoms.)
2. ± stalk effects

Anatomical relations of pituitary :

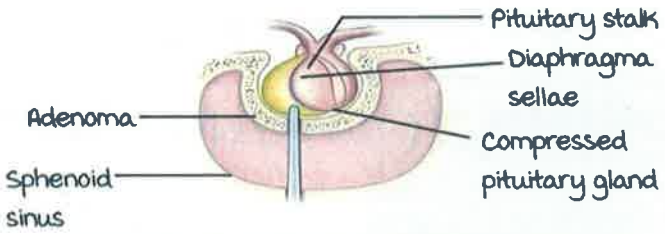
Pituitary is situated in a bony cage, called sella turcica.

Site of Expansion of any tumor :

Ventral (least resistance) > Lateral.

Posterior relation : Sphenoid sinus

Therefore, any removal of tumor, surgery (resection) is done through trans-sphenoidal route.



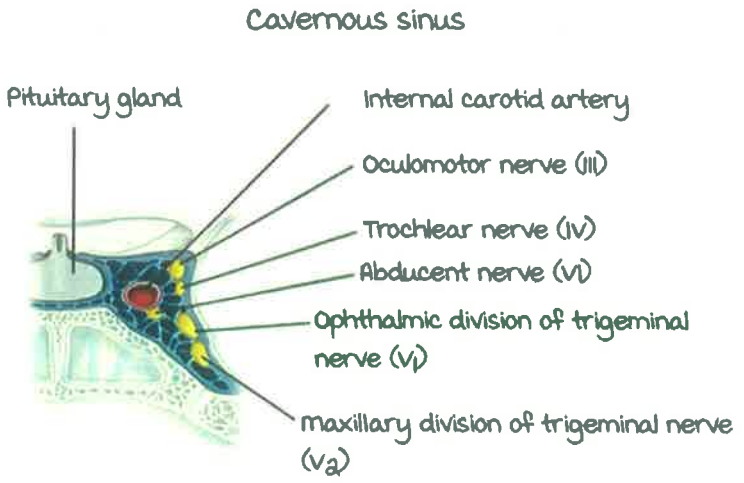
Trans-sphenoidal resection of pituitary adenoma.

Lateral relation : Cavernous sinus.

Clinical manifestations :

- Initially, centre affected : ICA + 6th nerve ☒ LR palsy (abduction palsy), encasement of ICA may be seen without clinical manifestations.
- Wall : 3,4,5-1 and 5-2 cranial nerves ☒ multiple cranial nerve palsies.
- Temporal lobe may be affected last.

Active space



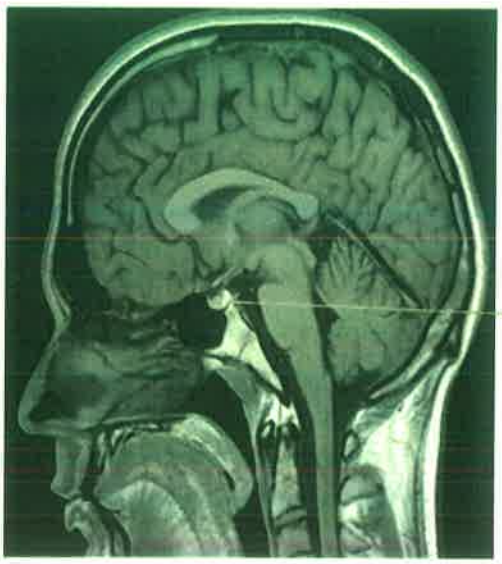
Ventral enlargement of tumor

00:37:50

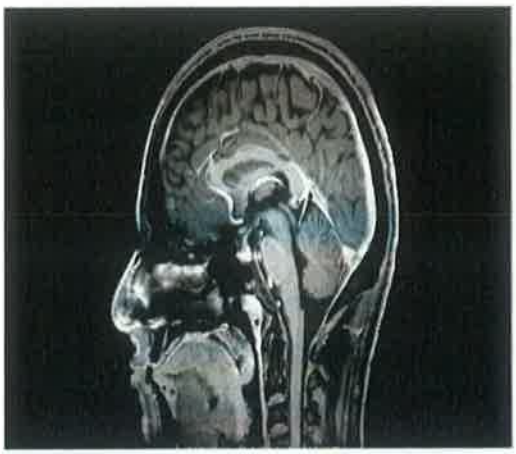
Through the layer of dura (diaphragma sella) ⊠ stalk is compressed ⊠ Stalk effects.

Stalk effects : Hypothalamo-hypophyseal portal system (via blood) + Neurohypophyseal system (via axons) are affected as blood and axons travel via the stalk ⊠ Connections are lost ⊠ No more trophic factors released from the portal system and posterior pituitary ⊠ All hormones decreased, except prolactin ⊠ Hyperprolactinemia.

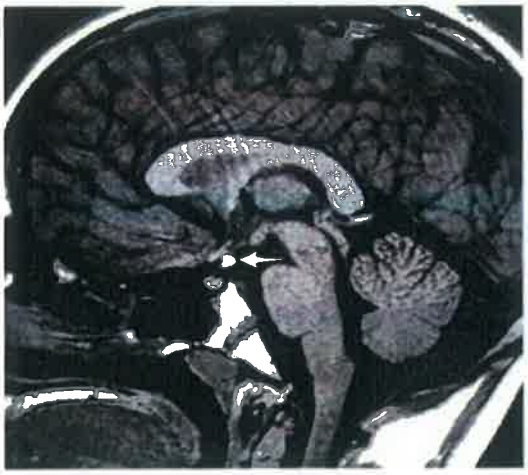
When further expands ⊠ Optic chisma compressed ⊠ Bitemporal or heteronymous hemianopia.



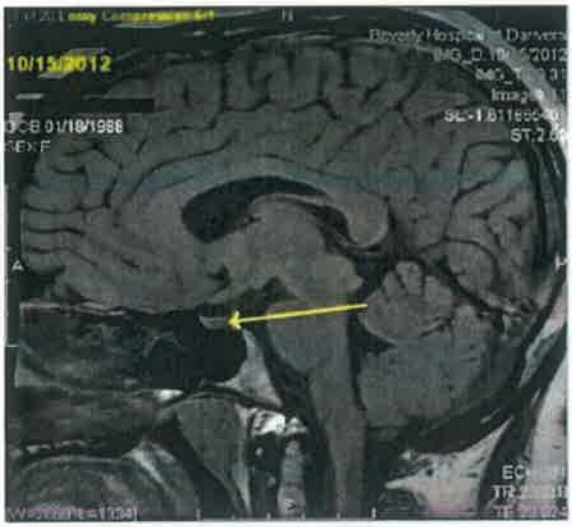
Active space



T1 saggital view post contrast : Pituitary will uniformly take up the contrast.



Ectopic posterior pituitary gland.



Absence of bright spot : Central Diabetes insipidus

Active space

PROLACTIN

Prolactin

00:00:27

- Polypeptide hormone.
- From lactotroph cells in the periphery of anterior pituitary.
- Constitutes 199 amino acids.
- Acts via JAK-STAT pathway.
- Inhibited by dopamine from hypothalamus.
- Major sources of production are CNS, placenta and uterus.
- Increases during REM phase of sleep.
- Stimulators of prolactin : Estrogen, TRH, VIP, oxytocin.

Function of prolactin :
Induces and maintains lactation in a fully developed breast primed by estrogen and progesterone.

Clinical scenario : A 24yr old female C/O oligomenorrhea, amenorrhea for 1 year.
USG abdomen and pelvis was normal. TFT was normal. No other significant findings.
Fasting prolactin assay (enzyme immunoassay) was 195 mcg/l (normal range : < 25 ng/mL or mcg/L).
She was suggested to do MRI by her family member. Is MRI a requirement in this scenario?
Solution : No.

Prolactin value > 100 mcg/L : Adenoma very likely.
> 200 mcg/L : Adenoma almost certain.
But there were no symptoms suggestive of hormone excess other than menstrual irregularity. No symptoms pointing towards pituitary stalk compression/mass.

Active space

Mostly asymptomatic patient with disproportionate prolactin values.
Do macro prolactin assay (macroprolactin : Inactive prolactin).
Many reproductive age females have anti-prolactin antibodies.
Prolactin-anti prolactin complexes are called macro prolactin (misinterpreted as prolactin on EIA/enzyme immunoassay).

Bioactive form of prolactin (present in blood) is 23Kd little prolactin/micro prolactin.
Macroprolactin levels are checked by gel filtration chromatography.
Elevated macroprolactin level is insignificant and no further evaluation is required.

Hyperprolactinemia 00:08:22

Normal : 25 mcg/L.
Physiological < 40 mcg/L :

1. Pregnancy (upto 180 mcg/L is normal).
2. Lactation.
3. REM sleep.
4. Stress.
5. Chest wall stimulation.

Pathological : 40-100 mcg/L.
Commonest cause is drugs/medications.
Dopamine antagonists by inhibiting tubulo-infundibular pathway.

- Typical antipsychotics.
- Risperidone (only atypical antipsychotic).

Risperidone can increase prolactin levels > 200 mcg/L.

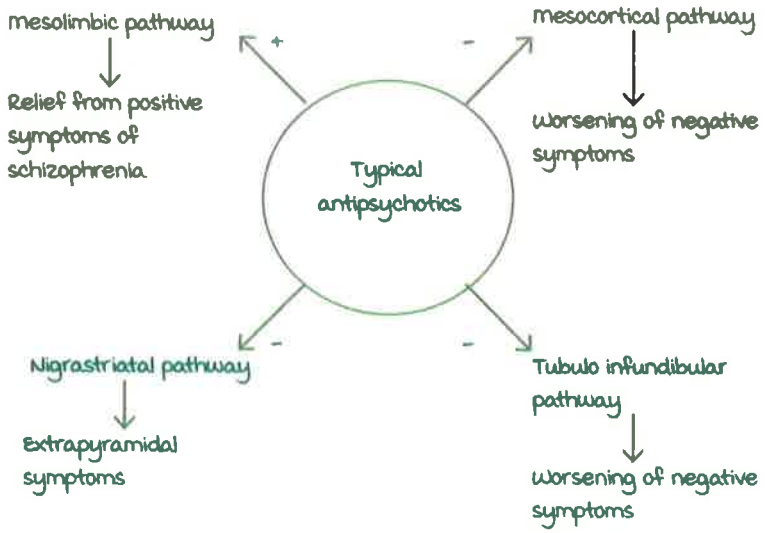
Dopamine regulation :
Dopamine is regulated by 4 pathways viz.,

1. Mesolimbic pathway.
2. Mesocortical pathway.
3. Nigrastriatal pathway.
4. Tubulo-infundibular pathway.

Active space

Feedback

5. CTZ outside BBB.



Atypical antipsychotics decreases negative symptoms, does not cause EPS and galactorrhea.

Other drugs :
TCA/SSRIs, opiates, verapamil, H2 blockers, α methyl dopa.
Prolactin levels comes back to normal 72 hours (3days) after stopping the drug.

D_2 receptor blocking anti emetics

00:16:35

metoclopramide	Domperidone
Crosses BBB	Does not cross BBB
Affects all CNS pathways (dopamine regulating pathways)	Acts only on CTZ
Can cause hyper prolactinemia	No hyper prolactinemia

Causes other than drugs (prolactin 40-100 mcg/L) :
CKD, CLD, primary hypothyroidism (TRH overactivity), PCOS.
Prolactin > 100 mcg/L in the absence of macro prolactin likely to be a tumour.

Active space

Prolactinoma 00:21:59

Serum prolactin level > 200 mcg/L.
Most common pituitary adenoma (α subunit of FSH secreting tumour > prolactinoma, though clinically irrelevant).
Clinically relevant tumours : Prolactinoma > GH secreting adenoma > ACTH secreting adenoma.

Prolactinoma < 1 cm (majority) called microadenoma.
1 – 4 cm called **macroadenoma.**
> 4 cm called **giant prolactinoma.**

Fasting prolactin level corresponds to the size of the tumour.

Prolactin secreting microadenoma follows 20 : 1 female to male ratio.
20–40yrs females.
Genetic causes (MEN-1 syndrome, McCune Albright syndrome, Carney complex) in <20 yr old females.
Macroadenomas 1 : 1 male–female ratio.

Clinical presentation in females :

- most commonly with galactorrhea/amenorrhea syndrome in the reproductive age.
- Secondary amenorrhea (UPT, TFT, prolactin levels).
- Hypogonadism/luteolysis features like menstrual irregularities, amenorrhea, dryness, hot flushes (prolactin suppresses HPG axis).

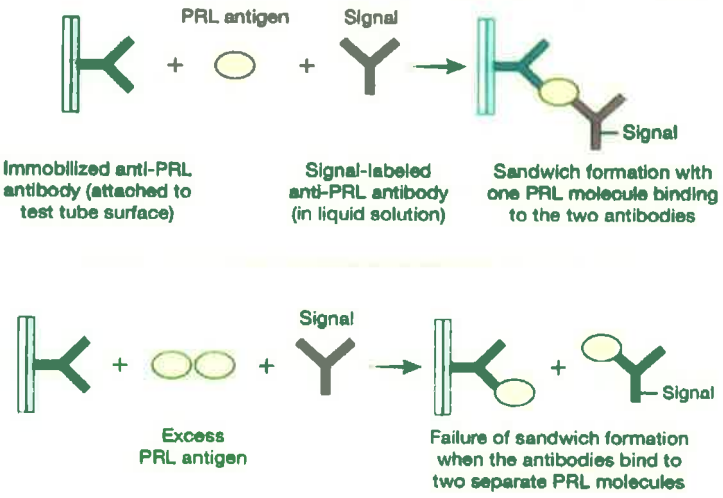
Presentation in males 00:29:58

Loss of libido, erectile dysfunction, gynecomastia. Overlooked most of the time.
Hence, males mostly present late with mass effects (headache and ICT symptoms, vision abnormality, 6th nerve palsy etc).
Osteopenia/osteoporosis of spine, insulin resistance are common to both males and females.

Active space

Feedback

Clinical scenario :
MRI of a patient shows 3cm pituitary adenoma. Prolactin level measures 80 mcg/L.
This is called hook effect.



Solid phase antibody + Prolactin antigen + Liquid phase antibody : Sandwich formation.
In presence of excess prolactin, antigens bind independently to solid and liquid phase antibodies (no sandwich formation).

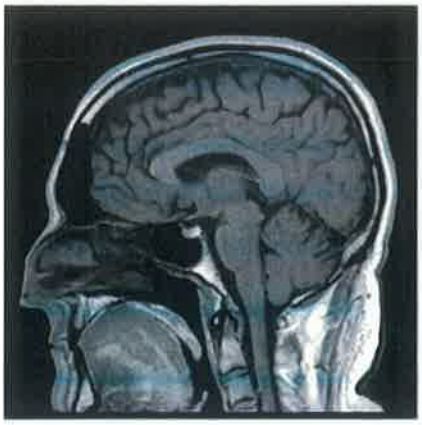
If serum prolactin values are not corresponding to patient symptoms/radiological findings, repeat in serial dilution.

45% of patients with macroprolactinomas have deficiency of other hormones : Stalk effect.
35% of patients with macroprolactinomas have visual field effects : mass effect.

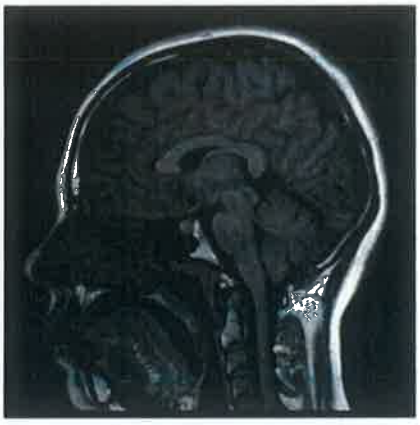
Investigation of choice : Contrast enhanced (gadolinium) MRI.

Active space

MRI Brain 00:36:00



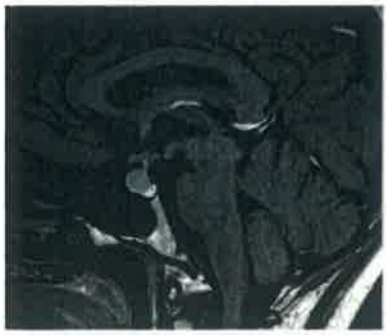
T1 Pre contrast : Normal pituitary.



T1 post contrast : Normal pituitary.

Points in favour of diagnosing microadenoma on MRI :

- Isointense in T1. Pituitary itself is hyperintense on T2.
- Asymmetry of the gland.
- Stalk deviation.
- Depression of sella floor.



Pre contrast pituitary adenoma

Post contrast pituitary adenoma

Adenoma will appear black as it does not take up the contrast (poor vascularity).

Treatment of pituitary adenoma 00:39:19

- Symptomatic patients.
- Asymptomatic with macroadenoma.
- Enlarging microadenoma.

Active space

Feedback

Follow up asymptomatic microadenoma patients every 3 months.
No role for surgery in primary management of prolactinoma.

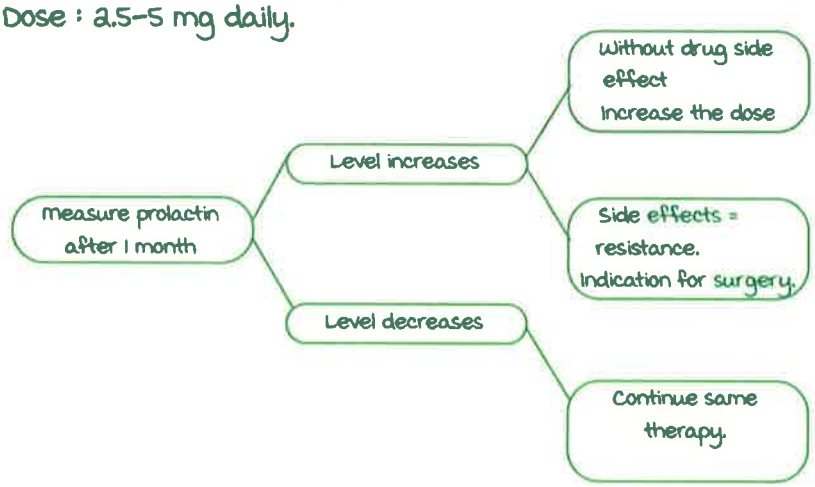
Medical managementis with dopamine agonists :

1. Cabergoline (drug of choice) :

Longer $^1/_2$ life, less side effects (vomiting, postural hypotension, dizziness), weekly dosage.
Dose : 0.25 mg twice a week.

2. Bromocriptine :

Used in pregnant females. Lack of study on efficacy of cabergoline in pregnancy.
Dose : 2.5-5 mg daily.



Maximum dose of cabergoline is 2 mg/week.
>2 mg/week : Valvular heart disease (TR), lung fibrosis.
Stop 7 days prior to lactation.

Surgical indications in prolactinoma 00:46:18

- Drug resistance.
- Non shrinkage of tumour on MRI taken after 3-6 months.
- Persistent visual field defects.
- Pituitary bleeding (unstable apoplexy).
- Pregnancy.

Active space

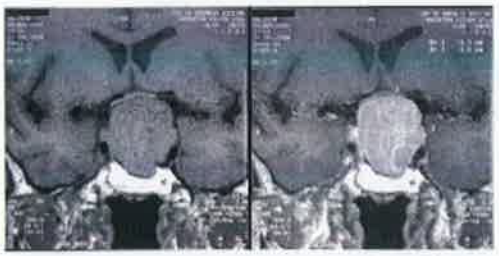
eedback

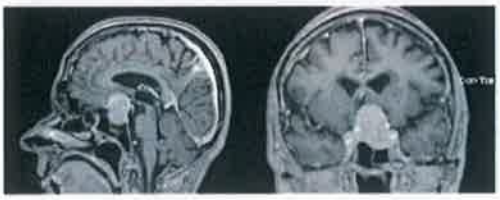
Patient unfit for surgery : Radiotherapy.
Ki-67 marker for malignant prolactinoma (very rare).

MRI images :

T1 weighted Pre contrast microadenoma.

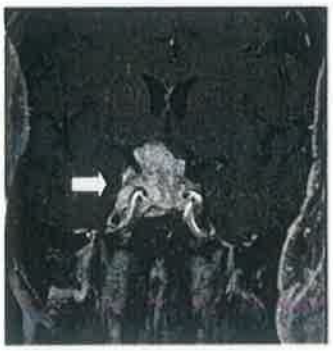
T1 weighted Post contrast macroadenoma.





Heterogenous tumour.
Solid (white) and cystic (dark) components.

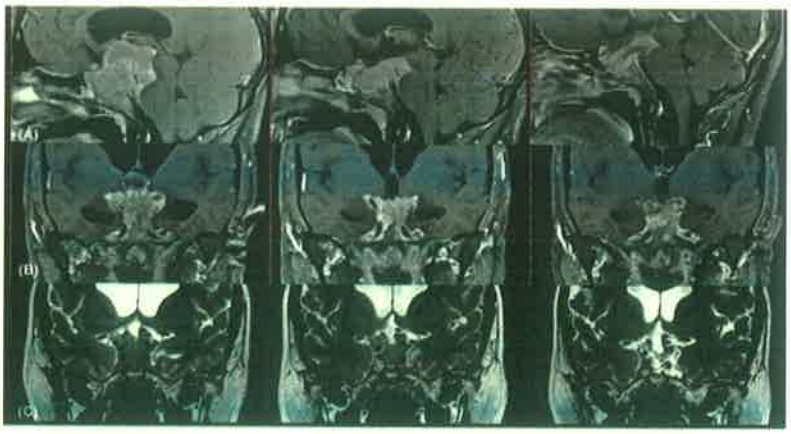
Heterogenous tumour : Macroadenoma.



Coronal image showed an enhancing, lobulated mass in the sella arising from the pituitary enveloping the right carotid siphon, right cavernous sinus, optic chiasm and right optic nerve. The parenchyma was otherwise normal.

Active space

eedback



At diagnosis 2 months 8 months

Figure 1 : Radiological images showing remarkable therapeutic response with cabergoline in young man with hydrocephalus and intracranial hypertension for giant prolactinoma as first clinical manifestation of multiple endocrine neoplasia type 1.
(A) Magnetic resonance imaging in T1 with gadolinium, sagittal section ;
(B) MRI in T1 with gadolinium ;
(C) MRI inT2 with gadolinium, coronal section.
Left images show the solid-cystic sellar and parasellar tumoral mass identified at diagnosis, with invasion of cavernous sinus, midbrain and third ventricle, occluded foramen of Monro and moderate to severe supratentorial obstructive hydrocephalus.
Central images obtained 2 months after the beginning of cabergoline shows significant reduction of the tumor.
Right images, with 8 months of cabergoline reveal a notable tumoral shrinkage and necrosis of the tumour.

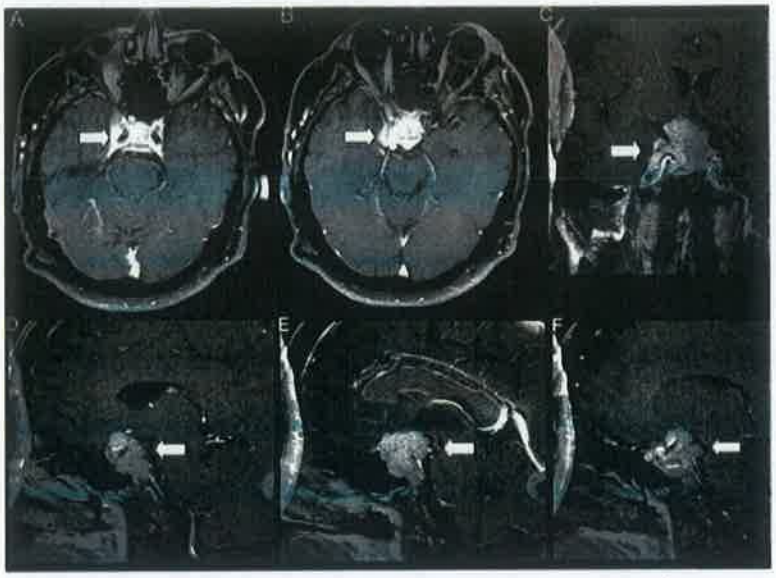
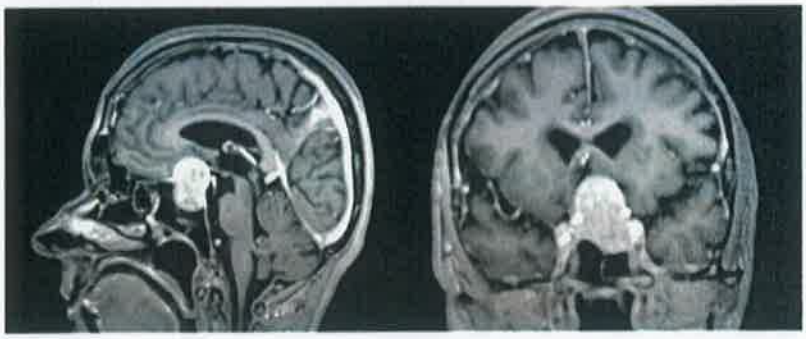


Figure 1 : Contrast enhanced brain magnetic resonance imaging (MRI) on presentation.
Axial (A,B), Coronal (C) and sagittal (D, E and F) images showed an enhancing, lobulated mass in the sella arising from the pituitary enveloping the right carotid siphon, right cavernous sinus, optic chiasm and right optic nerve. The parenchyma was otherwise normal.



Heterogenous tumour (macroadenoma) with both solid and cystic components.

Active space

GROWTH HORMONE

Introduction

00:00:33

- It is a Polypeptide hormone with 191 amino acids.
- Produced by somatotrophs (acidophilic cells) in the anterior pituitary. most abundant >50% and situated laterally.
- GH and Prolactin act via the JAK STAT pathway : Twin hormones.
- Has both direct actions and through a mediator, Insulin like Growth Factor (IGF-1 & 2). IGF mostly responsible for peripheral actions of GH.
- measurement of GH : Direct GH assay is difficult as it is released in a pulsatile manner and has a $T_{1/2}$ of 5 to 20 min.
- Best method to measure growth hormone levels : measure IGF. IGF binds to IGF binding protein (IGFBP-3). IGF + IGFBP-3 has T1/2 of 12 to 15 hours.
- Increases during phase 2 & 4 NREM sleep (Prolactin : REM sleep).

Stimulators	Inhibitors
Hypoglycemia. Growth hormone releasing hormone (GHRH). Ghrelin.	Somatostatin(most powerful). Aging. Obesity. Hypocaloric state/ extreme malnutrition. cause GH resistance.

All hormones of the anterior pituitary are positively regulated except for Prolactin.

Paradoxical GH release by TRH.

- TRH stimulates lactotrophs → Prolactin. Has no action on somatotrophs.
- In Somatotrophic/ GH secreting adenoma : TRH stimulates GH production.

Active space

edback

IGF :

IGF includes IGF-1 & IGF-2. Most abundant IGFBP is IGFBP-3.

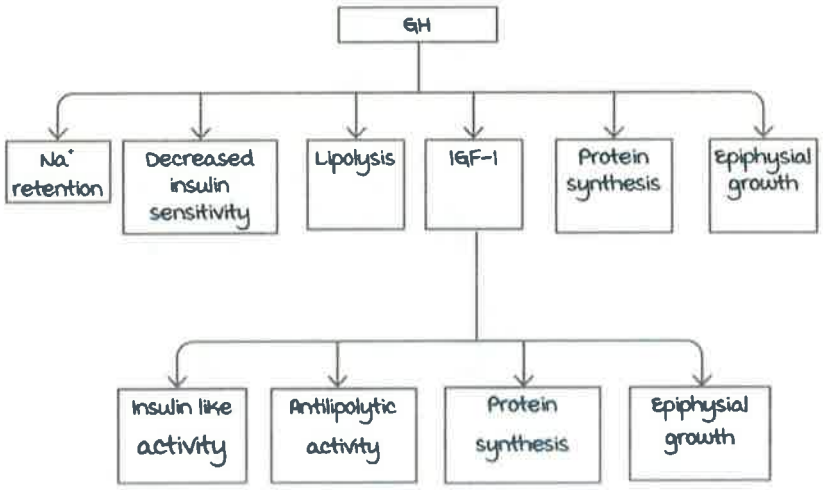
Intrauterine growth is purely under control of IGF-2 only. So, child with GH deficiency at birth will have normal length.

Other hormones that increase IGF release from liver : Thyroid hormone, Testosterone, Insulin.

	Insulin	IGF-I	IGF-II
Other names		Somatomedin C	Multiplication stimulating activity (MSA)
Number of amino acids	51	70	67
Source	Pancreatic B cells	Liver and other tissues	Diverse tissues
Level regulated by	Glucose	Growth hormone after birth, nutritional status unknown	Unknown
Plasma levels	0.3 to 2 ng/mL	10 to 700 ng/mL; peaks at puberty	300 to 800 ng/mL
Plasma binding proteins	No	Yes	Yes
Major physiologic role	Control of metabolism	Skeletal and cartilage growth	Growth during fetal development

Actions of GH and IGF

00:08:32



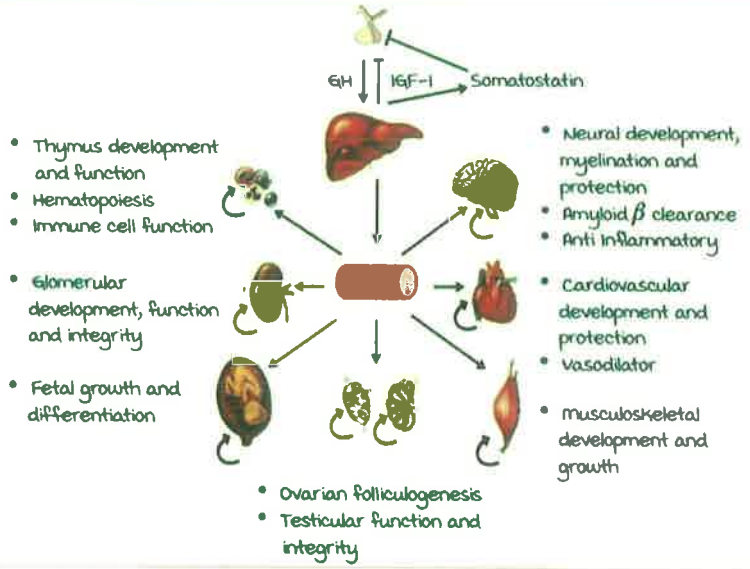
Active space

Action.	GH.	IGF.
Bone.	Increases osteoblastic activity and epiphyseal growth.	Increases osteoblastic activity an epiphyseal growth.
Protein Synthesis.	Increased.	Increased.
	Muscle anabolism : Increases lean muscle mass	
Carbohydrate metabolism.	Diabetogenic.	Anti diabetic/ Insulin like activity.
Fat metabolism.	Lipolysis causes Increased FFA resulting in Increased glucose output via gluconeogenesis; As Carnitine is not expressed, excess FFA cannot enter mitochondria so it forms fatty acyl CoA causing Insulin resistance.	Anti lipolytic.
Salt & water retention	Present.	Absent.

GH actions independent of IGF-1 : BEAMS.
Bone action.
Epiphyseal growth.
Adipose tissue : Increases lipolysis.
Muscle protein synthesis.
Salt and water retention.

Other actions of IGF -1

00:14:42



Active space

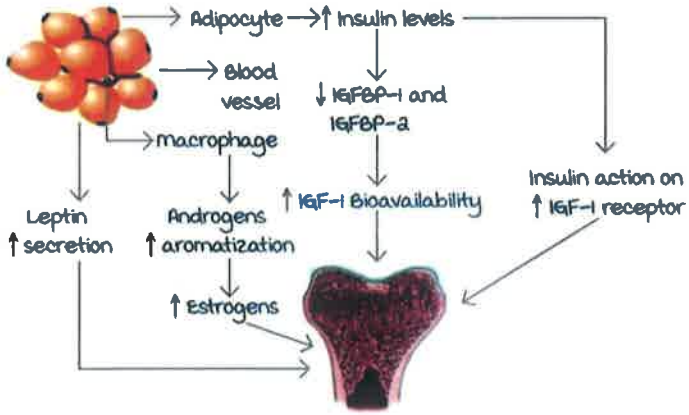
Feedback

Also involved in prolonging longevity : Facilitates Genetic stability, stress resistance, telomere shortening.

Causes of Acromegaly

Lifelong physiological properties of IGF-I	Growth	Bone metabolism	Lipid and glucose metabolism	Neuroprotection
	Neurogenesis and synaptogenesis	Anabolizing	Antioxidant and antiinflammatory	Antiapoptotic
	Genital development	Proliferative	Hepato- and cardioprotection	Mitochondrial protection
Processes involved in longevity	Genetic stability	Stress resistance	Metabolic control	Telomere shortening

Obese children have low GH but accelerated growth velocity.



Laron Dwarfism : Mutation of GH receptor. GH cannot exert its effects.

Very high GH levels, but very low IGF-1 & IGF- BP levels.

Laron Dwarfism

FSH, LH, TSH, Prolactin levels can be measured directly. ACTH and GH cannot be measured directly.

Active space

Feedback

Provocative tests for GH :

1. Insulin tolerance test : Give 0.1 U /Kg of insulin IV to the patient, usually 6U. Glucose levels every 15 minutes for 1 hour. Glucose levels start falling and GH levels start rising >3 µ g/L. Done by trained personnel since it can lead to hypoglycemia.
2. L-dopa, Arginine, Glucagon, clonidine, GHRH tests are easier & done as alternate methods. In India, Arginine and glucagon methods are commonly used.
3. Glucagon method : 0.03mg/Kg IM/ SC and observe glucose levels.
4. GHRH method : 1 µ g/Kg IV and response recorded.

GH Provocative test	Drug administration	Blood samples	GH peak	Side effects
insulin Tolerance Test (ITT) iv	0.05 to 0.1 u/kg	0 (baseline), 15, 30, 45,60, 15 to 30 minutes after the and 90 minutes.	15 to 30 minutes after the glucose nadir	Hypoglycaemia
L-dopa, iv.				Nausea, emesis and headache
Arginine HCl, iv (over a 30-minute period)	0.5 mg/kg (max 40 mg)	0 (baseline), 30, 60, 90 and 120 minutes.	60 minutes after starting arginine infusion.	Nausea and vomiting. Contraindicated in severe Kidney or liver disease.
Glucagon, im or s.c.	0.03 mg/kg max 1 mg)	0 (baseline), 30, 60, 90 and 120, 150 and 180 minutes	2 hours after glucagon injection	Nausea and vomiting
Propranolol (oraly) + exercise	0.5 mg/kg (max 40 mg)	0,90 (20 minutes of intense exercise) 120, 150 minutes	120 to 150 minutes	Hypoglycaemia, contraindicated in asthma or cardiac pathology
Clonidine, iv	0.15 mg/m^2	0 (baseline) 30, 60, 90 minutes	60 minutes after Clonidine administration	Decrease in blood pressure and drowsines for several hours
GHRH, iv	1 mcg/kg	0(baseline), 15, 30, 45, 60, 90 and 120 minutes	60 minutes after GHRH administration	Fainting or feeling light-headed
i.v., intravenously				
im., intramusculary				
S.C., subcutaneously				

Active space

Feedback

Acromegaly

00:20:42

Adenoma that produces excess GH or excess GHRH

↓ ↓

pituitary or ectopic hypothalamus or ectopic.

MC cause (98%) of acromegaly is GH secreting pituitary adenoma. 20% have increased Prolactin (twin hormones : somato-mammotrophic adenomas).

Acromegaly.	Prolactinoma.
Macro adenomas.	Micro adenomas.
Males> females.	Females > Males.
2nd MC pituitary adenoma.	MC pituitary adenoma.

	Prevalence, %
Excess Growth Hormone Secretion	
Pituitary	98
Densely or sparsely granulated Growth hormone (GH) cell adenoma	60
Mixed GH cell and Prolactin (PRL) cell adenoma	25
Mammosomatotrope cell adenoma	10
Plurihormonal adenoma	
GH cell carcinoma or metastases	
Multiple endocrine neoplasia I (GH cell adenoma)	
McCune Albright syndrome	
Ectopic sphenoid or parapharyngeal sinus pituitary adenoma	
Extrapituitary tumor	
Pancreatic islet cell tumor	<1

Active space

Feedback

Lymphoma	
Excess Growth Hormone-Releasing Hormone Secretion	
Central	<1
Hypothalamic hamartoma, choristoma, ganglioneuroma	<1
Peripheral	<1
Bronchial carcinoid, pancreatic islet cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma	

Most common tumors :

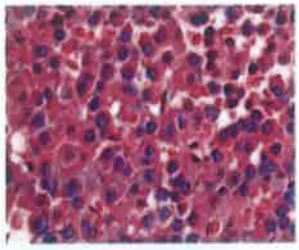
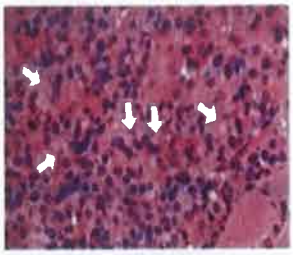
Most common	Tumors
Ectopic GH secreting tumor.	Pancreatic islet cell tumor. <20 years, consider MEN-1 Syndrome. mc Cune Albright Syndrome .Carney complex.
GHRH secreting tumor.	Hamartoma.
Ectopic GHRH secreting tumor	Bronchial carcinoid. Small cell lung cancer. Medullary carcinoma of the thyroid.

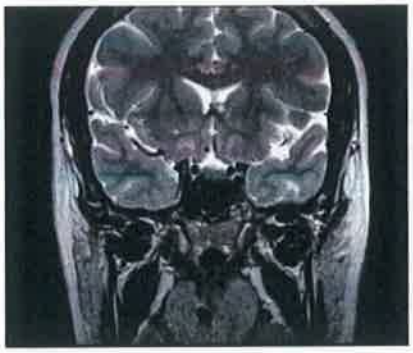
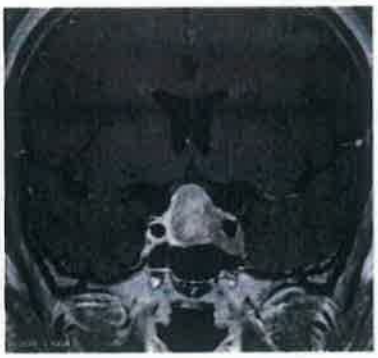
GH secreting adenomas :

- Macroadenomas.
- M > F.
- Associated with increased prolactin levels in 20% of patients as they are somatomammotrophic adenomas.

Active space

Two types :

Densely granulated.	Sparsely granulated.
Better prognosis. 	Poor prognosis due to high growth rate & rapidly progressive. 

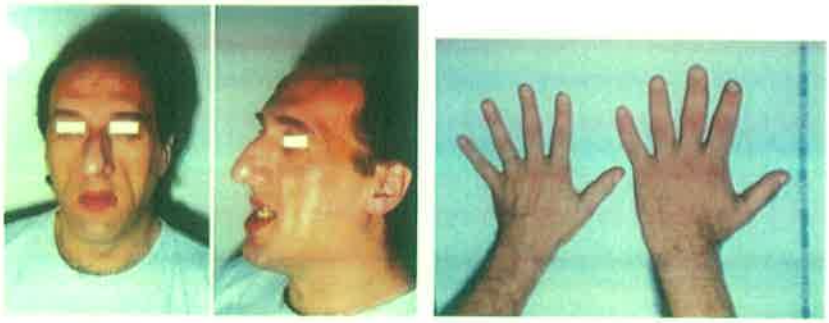
Large heterogenous mass (T1 & T2 images) showing macroadenoma.

Gigantism vs. Acromegaly 00:27:16

GH excess before epiphyseal fusion is called gigantism. After fusion of epiphysis, peripheral/ acral enlargement called Acromegaly. There is enlargement of lips, nose, hands, feet, internal organs except brain.

Symptoms of Acromegaly :
Acromegalic facies/ Coarse facial features: Thick lips, prominent supra orbital ridge, deepening of furrows, frontal bossing, prognathism , jaw malocclusion , macroglossia.
These changes happen over a prolonged period and is not easily noticeable.

Active space



Mass effect : Headache, visual impairment.

Stalk effect :

Pan hypopituitarism except prolactin (hyperprolactinemia) will be present.

Soft tissue swelling.

Large hands and feet.

Obesity.
Hypothyroidism.
Phenytoin.
2 tumors
Insulinoma.

Pseudo acromegaly : Acromegaly like IGF-facies present.

Features of Acromegaly :

Organ system.	Feature.
Nerve.	Entrapment neuropathy. E.g., Carpal tunnel syndrome.

Active space

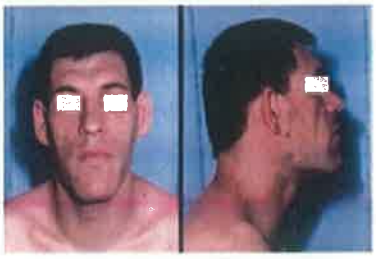
Feedback

Muscle.	Myopathy due to hypertrophied Type I fibers and atrophied type 2 fibers.
RS.	Obstructive Sleep Apnea Syndrome and its complications including pulmonary Hypertension.
CVS.	MC cause of death. Asymmetrical LVH, CAD, HFpEF.
GIT.	Nonmalignant colonic polyposis.
Ophthalmic.	Angle closure glaucoma.
Skin.	Acanthosis nigricans due to insulin resistance. Hyperhidrosis/ Extreme sweating.Seborrhea. Warm hands. Hirsutism.
Thyroid.	Goiter due to IGF-I.
Elevated Aldosterone.	Salt and water retention.
Female.	Oligomenorrhoea.

McCune Albright syndrome 00:34:38

Asymmetrical facies due to fibrous dysplasia.

Characterized by Café au lait spots + Polyostotic fibrous dysplasia + Precocious puberty + Tumors (GH secreting/ Prolactinoma).

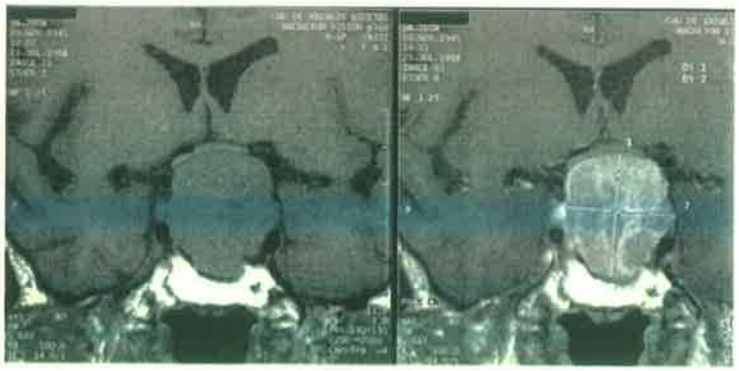


Coarse facial features

Asymmetrical facies

Active space

Feedback



Macroadenoma

Metabolic changes in acromegaly :

- Hypertriglyceridemia.
- Hyperglycemia with insulin resistance.
- Tumor produces 1α Hydroxylase → Increased 1,25 $(OH)_2D_3$ → Hypercalcemia & Hyperphosphatemia.
- Hypercalcemia → Hypercalciuria and stones.

DOSA features : Diabetes, OSAS, Seborrhea, Arthralgia indicate activity of rapidly progressing tumor.

Clinical Features of Acromegaly
Local Tumor Effects Pituitary enlargement Visual field defects Cranial nerve palsy Headache
Somatic Effects Acral Enlargement Thickening of soft tissues in hands and feet
Musculoskeletal Gigantism Prognathism Jaw malocclusion Arthralgias and arthritis Carpal tunnel syndrome Acroparesthesia Proximal myopathy Hypertrophy of frontal bones

Active space

Skin
Hyperhidrosis
Oily
Skin tags

Clinical Features of Acromegaly : continued
Carbohydrates
Impaired glucose tolerance
Insulin resistance hyperinsulinemia
Diabetes mellitus
Lipids
Hypertriglyceridemia
Minerals
Hypercalciuria, increased 1,25-dihydroxy vitamin D3 Urinary hydroxyproline
Electrolytes
Low renin
Increased aldosterone
Thyroid
Low thyroxine-binding globulin
Goiter

Colon
Polyps
Cardiovascular
Left ventricular hypetrophy
Asymmetric septal hypertrophy
Cardiomyopathy
Hypertension
Congestive heart failure
Pulmonary
Sleep disturbances
Sleep apnea-central and obstructive
Narcolepsy

Active space

Visceromegaly Tongue Thyroid Salivary glandn Liver Spleen Kidney Prostate
Endocrine , metabolic Effects Reproductive menstrual abnormalities
Galactorrhea Decreased libido, impotence, low sex hormone-blinding globulin
multiple Endocrine Neoplasia Type I (MEN I) Hyperparathyroidism Pancreatic islet cell tumors

Diagnosis :
Screening test : IGF-I levels.
Confirmatory test : Glucose suppression test. Give 75g oral glucose and check GH level after 1 hour. Hyperglycemia should normally suppress GH levels (via Somatostatin/Cholinergic pathway) to < 1ng/mL Failure of suppression is confirmatory.
GH > 40ng/mL concludes poor prognosis.
If GH is not suppressed, proceed to imaging.
Investigation of choice : Gadolinium enhanced MRI showing macroadenoma.
Pituitary Function tests.

Management 00:41:09

Treatment of choice :
Transsphenoidal Resection : 80% success rate in microadenomas and 50% success rate in macroadenoma.

Active space