ANTERIOR PITUITARY HORMONES

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Relationship between hypothalamus & pituitary gland

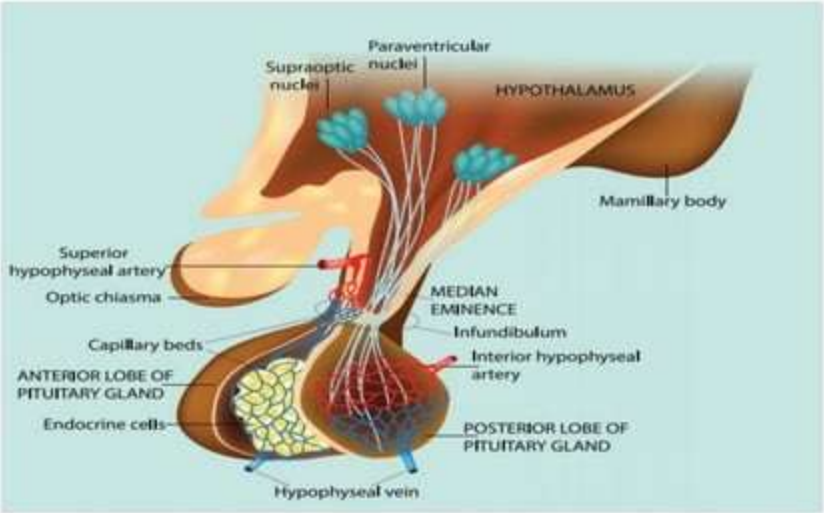
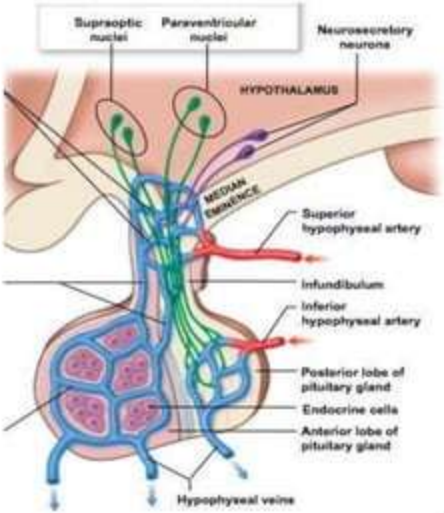
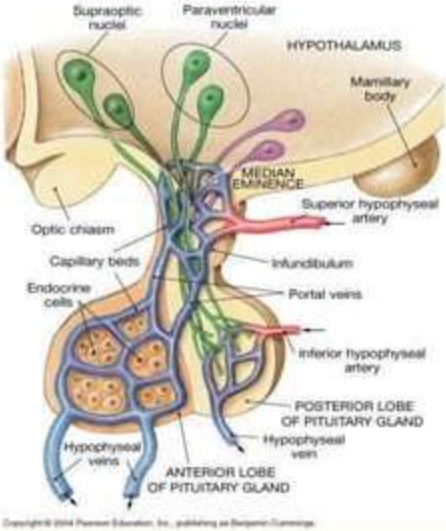


Figure.11. 2 Hypothalamus and pituitary gland


Supraoptic nuclei
Paraventricular nuclei
Neurosecretory neurons
HYPOTHALAMUS
MEDIAN EMINENCE
Superior hypophyseal artery
Infundibulum
Inferior hypophyseal artery
Posterior lobe of pituitary gland
Endocrine cells
Anterior lobe of pituitary gland
Hypophyseal veins

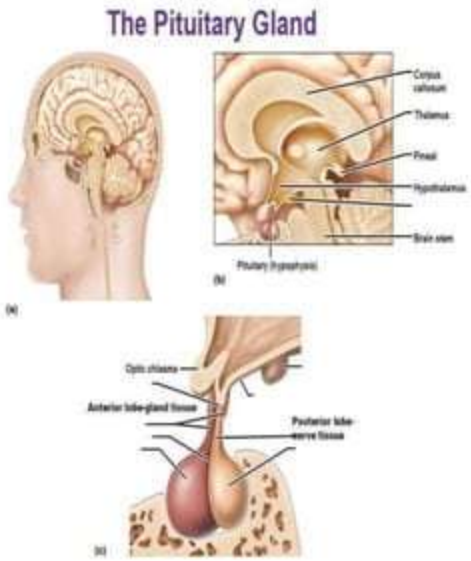

Supraoptic nuclei
Paraventricular nuclei
HYPOTHALAMUS
Mamillary body
MEDIAN EMINENCE
Superior hypophyseal artery
Optic chiasm
Capillary beds
Infundibulum
Endocrine cells
Portal veins
Inferior hypophyseal artery
POSTERIOR LOBE OF PITUITARY GLAND
Hypophyseal vein
Hypophyseal veins
ANTERIOR LOBE OF PITUITARY GLAND

Hormones of Hypothalamus

Releasing hormones	Inhibiting hormones
Thyrotropic releasing hormone (TRH)	-
Corticotropin releasing hormone (CRH)	-
Growth hormone releasing hormone (Gh-RH) / Somatotropin releasing hormone (SRH)	Growth hormone release inhibitory hormone (GhRIH)
Gonadotropin releasing hormone (GnRh)	-
Prolactin releasing hormone (PRH)	Prolactin release inhibitory hormone (PRIH)
Melanocyte Stimulating hormone releasing hormone (MSH-RH)	Melanocyte Stimulating hormone –inhibiting hormone (MSH-IH)

Pituitary Gland (Hypophysis)

- Located at the base of brain or just below the hypothalamus
- It is also known as the "**master gland**"
- It is a master in controlling other glands of the body (thyroid, adrenal glands, and gonads
- It is consists of **anterior pituitary** and **posterior pituitary** glands.



Anterior Pituitary Gland/ Adenohypophysis /pars anterior

Types of endocrine cells in Ant. Pituitary:

- Thyrotropes (TSH)
- Corticotropes (ACTH)
- Somatotropes (GH)
- Gonadotropes (LH and FSH)
- Lactotropes (PRL)

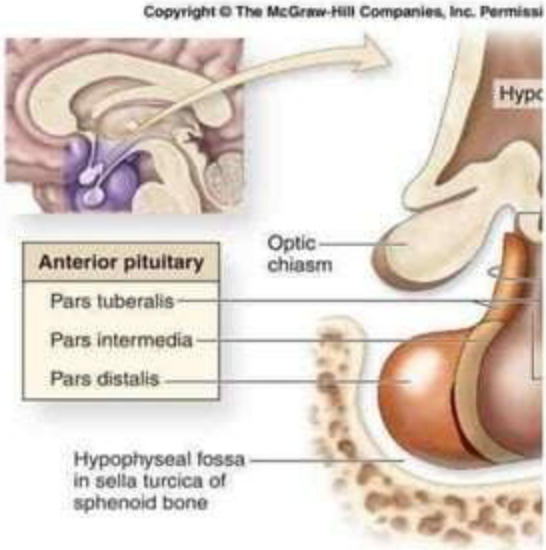
- Hormones secreted by the **anterior pituitary** are **trophic hormones**
- **Trophic** : Greek: trophe, "nourishment"
- *Trophic hormones* directly affect growth either as hyperplasia or hypertrophy on the tissue it is stimulating.
  - Act directly on target tissues or other endocrine glands to release hormones, causing numerous cascading physiological responses

Anterior Pituitary Glands

It has three region :

1. **Pars distalis** – It is the largest and vascular lobe, it is the major secretory of the gland
2. **Pars intermedia** – it is located between the pars distalis and posterior gland,

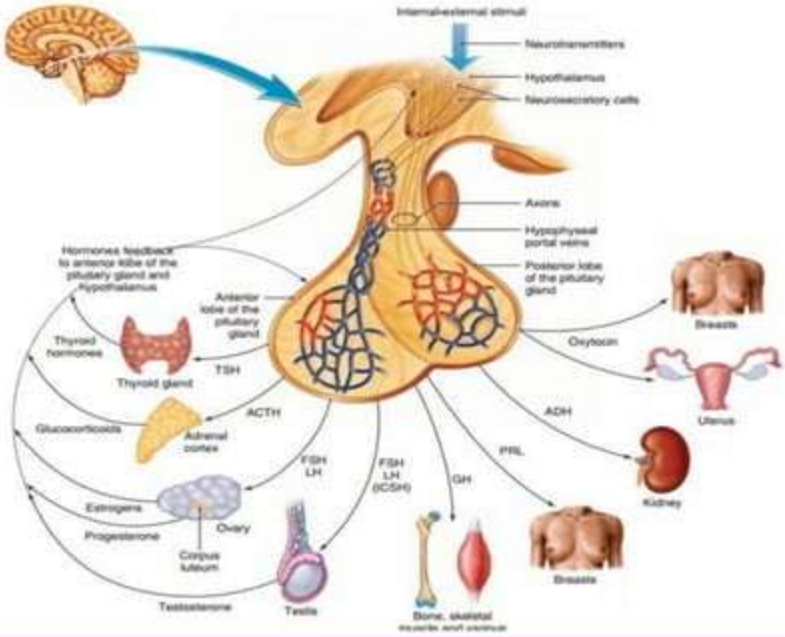
   As the boundary between anterior and posterior gland (it is very small and indistinct to humans)
3. **Pars tuberalis** – it joins the pituitary stalk arising from the posterior gland



Anterior pituitary hormone is produced by a separate **group of cells**

- The **acidophils:**
  - Somatotropes -- GH; or
  - Lactotropes --- Prolactin.
- The **basophils**:
  - Gonadotropes -- FSH and LH;
  - Thyrotropes -- TSH; and
  - Corticotrope-lipotropes -- ACTH.
    - also produce two melanocyte stimulating hormones (MSHs) and two lipotropins, but these are probably not important in man.

Hormones released by Anterior Pituitary Gland



Hormones of Anterior pituitary gland

- **Thyroid Stimulating Hormone** (TSH)
- **Adrenocorticotropic Hormone** (ACTH)
- **Growth Hormone** (GH)
- **Luteinizing Hormone** (LH) and Follicle Stimulating Hormone (FSH)
- **Prolactin** (PRL)
- **Melanocyte-Stimulating Hormone** (MSH)
  - Regulates the production of melanin, a dark pigment, by melanocytes in the skin.
  - Increased melanin production produces pigmentation or tanning of the skin; in certain conditions excessive production of melanocyte-stimulating hormone can cause darkening of the skin.

1. THYROID STIMULATING HORMONE (TSH / Thyrotropin)

- Glycoprotein with a 210 amino acid, two chain glycoprotein (22% sugar), MW 30000
- Acts on the thyroid gland to secrete and release thyroxine (T4) and triiodothyronine (T3)

Functions:

- Induces hyperplasia & hypertrophy of thyroid follicles; increases blood supply to the gland.
- Promotes trapping of iodide into thyroid by increasing Na+: Iodide symporter (NIS).
- Promotes organification of trapped iodine & its incorporation into T3 & T4 by increasing peroxidase activity.
- Enhances endocytotic uptake of thyroid colloid by the follicular cells & proteolysis of thyroglobulin to release more of T3 and T4.

TSH Receptors: GPCR

- Gs protein: adenylyl cyclase-cAMP
- Gq protein: in humans high TSH levels: PIP2 hydrolysis: increase in cytosolic Ca_{2+} and protein kinase C activation: generation of H_2O_2 needed for oxidation of iodide and iodination of tyrosil residues

- **Regulation**: controlled by hypothalamus through
  - Release: TRH
  - Inhibition: Somatostatin , Dopamine

- **TRH receptor** on pituitary thyrotrope cells is a GPCR which is linked to Gq protein; activates PLC–IP3/DAG–cytosolic Ca2+ pathway to enhance TSH synthesis and release

Diseases

- **Hypothroidism**
- **Hyperthyroidism**
- **Myxedema**: Elevated TSH levels due to deficient feedback inhibition
- **Graves' disease**: Due to an immunoglobulin of the IgG class which attaches to the thyroid cells and stimulates them in the same way as TSH. Low TSH levels.

Uses

- Thyrotropin has no therapeutic use.
- Thyroxine is the drug of choice even when hypothyroidism is due to TSH deficiency.
- Diagnostic application: to differentiate myxoedema due to pituitary dysfunction from primary thyroid disease.

2. ADRENOCORTICOTROPIC HORMONE (ACTH, CORTICOTROPIN)

- It is a 39 amino acid single chain peptide, MW 4500, derived from a larger peptide *pro-opiomelanocortin* (MW 30,000) which also gives rise to endorphins, two lipotropins and two MSHs
- **Functions**
  - Promotes steroidogenesis in adrenal cortex by stimulating cAMP formation in cortical cells: rapidly increases availability of cholesterol
    - Cholesterol is precursor for Glucocorticoids, mineralocorticoids & some sex hormones.
    - The adrenal glands are also responsible for the body's fight or flight response.

Regulation of secretion

- Hypothalamus regulates ACTH release from pituitary through corticotropin-releasing hormone (CRH).
- CRH receptor on corticotropes is also a GPCR which increases ACTH synthesis as well as release by raising cytosolic cAMP.
- Peak plasma levels of ACTH occur in the early morning, decrease during day and are lowest at midnight
- stressful stimuli, e.g. trauma, surgery, severe pain, anxiety, fear, blood loss, exposure to cold, etc. generate neural impulses --- rise in ACTH secretion continues despite high plasma level of cortisol induced by it.
- Arginine vasopressin (AVP) enhances the action of CRH on corticotropes and augments ACTH release

Diseases:

- **Excess ACTH**: Cushing's syndrome
- **Hypocorticism**: due to low ACTH production: may be due to the use of pharmacological doses of glucocorticoids in nonendocrine diseases

Uses:

- Used primarily for the diagnosis of disorders of pituitary adrenal axis.

  Injected i.v. 25 IU causes increase in plasma cortisol if the adrenals are functional. Direct assay of plasma ACTH level is now preferred.

- ACTH does not offer any advantage over corticosteroids and is more inconvenient, expensive as well as less predictable

3. Growth Hormone (GH)

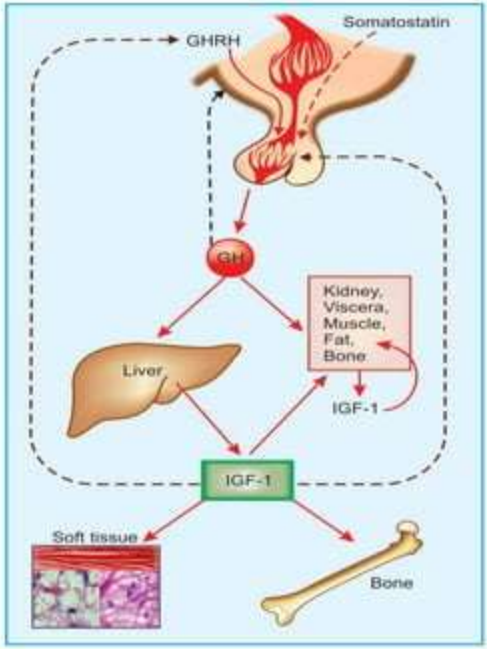
NORDITROPIN 5, 10, 15 mg inj,
HUMATROPE 6 mg, 12 mg cartridges,
1.33 and 5.33 mg vials.

- It is a 191 amino acid, single chain peptide of MW 22000.
- **Functions**:
  - Promotes growth of bones and all other organs by inducing hyperplasia
  - Promotes retention of nitrogen, calcium and other tissue constituents
  - +ve nitrogen balance results from increased uptake of AA by tissues and their synthesis into proteins
  - Promotes utilization of fat and spares carbohydrates: uptake of glucose by muscles is reduced while its output from liver is enhanced; fat is broken down.
  - Induces lipolysis in adipose tissue, gluconeogenesis and glycogenolysis in liver and decreased glucose utilization by muscles. These effects are opposite to those of IGF-1 and insulin.

- *The growth of brain and eye is independent of GH.*

Receptors:
GH acts on cell surface JAK-STAT binding protein kinase receptors

Somatomedins/ insulin-like growth factors:
Promote growth, retain nitrogen, & some metabolic actions



Action of growth hormone (GH) and regulation of its secretion
GHRH—Growth hormone releasing hormone;
IGF-1: Insulin like growth factor-1;
Stimulation (——→); Inhibition (- - - →)

Regulation :

- The hypothalamus produces GH releasing (GHRH) as well as release inhibitory (*somatostatin*) hormones. Both are peptides.
  - *Somatostatin* is also produced by D cells of islets of Langerhans in the pancreas & by few other tissues.
  - Receptors for GHRH and somatostatin are G protein coupled receptors (GPCRs) which enhance or inhibit GH secretion by increasing or decreasing cAMP formation respectively in pituitary somatotropes.
  - Somatostatin has also been shown to inhibit Ca2+ channels and open K+ channels.
- Release of GH—fasting, hypoglycaemia, exercise, stress and i.v. infusion of arginine.
  - Dopaminergic agents cause a brief increase in GH release in normal subjects but paradoxically depress it in acromegalics.
- Inhibition of GH secretion: by rise in plasma free fatty acid levels & high doses of glucocorticoids.
  - IGF-1 causes feedback inhibition of GH secretion

Diseases:

- Gigantism: Excess production of GH in childhood
- Acromegaly : Excess production of GH in adults.
- Pituitary dwarfism: Hyposecretion of GH in children
- Adult GH deficiency: Rare: low muscle and bone mass, lethargy, decreased work capacity, hyperlipidaemia and increased cardiovascular risk.

Uses:

- Pituitary dwarfism: 0.03–0.06 mg/kg daily in the evening or on alternate days, upto the age of 20 years or more
- hGH produced by recombinant DNA technique (*rhGH*) *somatropin* (191AA): also be used in *Turner's syndrome* and in children with *renal failure.*
- Children with *constitutional short stature* (only if epiphyses are open)
- Adult GH deficient patients: rHGH 150–300 μg/day s.c. initially
- *Catabolic states* like severe burns, bedridden patients, chronic renal failure, osteoporosis, etc
- approved for *AIDS related wasting*: higher dose (0.05–0.1 mg/kg/day)
- It is one of the drugs included in 'dope testing'.

- **Adverse effects:**
  - Low immunogenicity: no allergic reactions
  - Pain at injection site, lipodystrophy, glucose intolerance, hypothyroidism (due to unmasking of TSH deficiency), salt and water retention, hand stiffness, myalgia, headache are the possible adverse effects.
  - Rise in intracranial tension occurs in few cases.

GH Inhibitors
Somatostatin

STILMEN, SOMATOSAN, SOMASTAT
250 µg and 3 mg amps.

- 14 amino acid peptide: inhibits the secretion of GH, prolactin, & TSH by pituitary; insulin and glucagon by pancreas, and of almost all gastrointestinal secretions including that of gastrin and HCl.
- **Side effects**: steatorrhoea, diarrhoea, hypochlorhydria, dyspepsia and nausea, constricts splanchnic, hepatic and renal blood vessels.
- **Uses**: The decreased G.I. mucosal blood flow – used for controlling bleeding esophageal varices and bleeding peptic ulcer (octreotide is preferred -longer duration of action).
- Antisecretory action: pancreatic, biliary or intestinal fistulae; also to reduce complications after pancreatic surgery.
- As an adjuvant value in diabetic ketoacidosis (by inhibiting glucagon and GH secretion).
- Use in acromegaly is limited due to short duration of action (t½ 2–3 min), lack of specificity for inhibiting only GH secretion and GH rebound on discontinuation.
  - Surgical removal of pituitary adenomas is the preferred treatment modality,
  - Somatostatin analogues are used.
- **Dose**: (for upper g.i.bleeding) 250 µg slow i.v. injection over 3 min followed by 3 mg i.v. infusion over 12 hours.

SANDOSTATIN, OCTRIDE 50 µg, 100 µg in 1 ml amps.
SANDOSTATIN LAR (microsphere formulation) 20 mg/5 ml inj.

Octreotide

- Synthetic octapeptide: surrogate of somatostatin
- 40 times more potent; longer acting (t½ ~90 min), but only a weak inhibitor of insulin secretion.
- Preferred over somatostatin for acromegaly and secretory diarrhoeas due to carcinoid, AIDS, cancer chemotherapy or diabetes. Suppresses hormones enhancing intestinal mucosal secretion.
- **Dose**: Initially 50–100 µg s.c. twice daily, increased upto 200 µg TDS;

  For acromegaly: 10-30 mg i.m. of microsphere formulation every 4 weeks.
- **Adverse effects**: abdominal pain, nausea, steatorrhoea, diarrhoea, and gall stones (due to biliary stasis).
- Octreotide (100 µg i.v. followed by 25–50 µg/hr) reduces hepatic blood flow and helps stop esophageal variceal bleeding.

- **Lanreotide:** long-acting analogue of somatostatin,
  - Very similar in actions and specificity to octreotide
  - Duration of action: 10–15 days after i.m. injection
  - **Use**: pharmacotherapy of acromegaly.
- **Pegvisomant:** This polyethylene glycol complexed mutant GH
  - Binds to the GH receptor but does not trigger signal transduction:
  - Acts as a **GH antagonist**.
  - **Use**: acromegaly due to small pituitary adenomas.

4. Prolactin (PRL)

- 199 amino acid, single chain peptide of MW 23000; quite similar chemically to GH.
- Originally described as the hormone causing secretion of milk from crop glands of pigeon

Function:

- Causes growth and development of breast during pregnancy along with estrogens, progesterone
- Promotes proliferation of ductal as well as acinar cells in the breast
- Induces synthesis of milk proteins and lactose

- Prolactin suppresses hypothalamo-pituitary-gonadal axis by inhibiting GnRH release.
- Continued high level of prolactin during breastfeeding is responsible for lactational amenorrhoea, inhibition of ovulation and infertility for several months postpartum.
- Prolactin may affect immune response through action on T-lymphocytes.
- **Receptor**:
  - A specific prolactin receptor is expressed on the surface of target cells, which is structurally and functionally analogous to GH receptor: action is exerted by transmembrane activation of JAK—cytoplasmic tyrosine protein kinases and STAT.
  - Placental lactogen and GH also bind to prolactin receptor and exert similar effects, but prolactin does not bind to GH receptor

- **Regulation of secretion**:
- Prolactin is under predominant inhibitory control of hypothalamus through PRIH which is dopamine that acts on pituitary lactotrope D2 receptor. Dopaminergic agonists (DA, bromocriptine, cabergoline) decrease plasma prolactin levels, while dopaminergic antagonists (chlorpromazine, haloperidol, metoclopramide) and DA depleter (reserpine) cause hyperprolactinemia.
- Though TRH, prolactin releasing peptide and VIP can stimulate prolactin secretion, no specific prolactin releasing factor has been identified. Endogenous opioid peptides may also be involved in regulating prolactin secretion, but no feedback regulation by any peripheral hormone is known.
- Prolactin levels in blood are low in childhood, increase in girls at puberty and are higher in adult females than in males.
- A progressive increase occurs during pregnancy, peaking at term. Subsequently, high prolactin secretion is maintained by suckling: it falls if breast feeding is discontinued. Stress, exertion and hypoglycaemia also stimulate prolactin release

Diseases:

- Hyperprolactinaemia is responsible for the galactorrhoea– amenorrhoea–infertility syndrome in women. In males it causes loss of libido and depressed fertility. The causes of hyperprolactinaemia are:

(i) Disorders of hypothalamus removing the inhibitory control over pituitary.

(ii) Antidopaminergic and DA depleting drugs —these are a frequent cause now.

(iii) Prolactin secreting tumours—these may be microprolactinomas or macroprolactinomas.

(iv) Hypothyroidism with high TRH levels—also increases prolactin secretion.

Uses: No clinical uses

PROCTINAL, PARLODEL, SICRIPTIN, BROMOGEN 1.25mg, 2.5 mg tabs.

Prolactin inhibitors

- **Bromocriptine**
- Synthetic ergot derivative 2-bromo- ergocryptine is a potent dopamine agonist
- It has greater action on D2 receptors,
  - At certain dopamine sites in the brain it acts as a partial agonist or antagonist of D1 receptor.
  - It is also a weak adrenergic blocker but not an oxytocic.

Actions

1. Decreases prolactin release from pituitary by activating dopaminergic receptors on lactotrope cells: is a strong antigalactopoietic.

2. Increases GH release in normal individuals, but decreases the same from pituitary tumours that cause acromegaly.

3. Has levodopa like actions in CNS—antiparkinsonian and behavioral effects.

4. Produces nausea and vomiting by stimulating dopaminergic receptors in the CTZ.

5. Hypotension—due to central suppression of postural reflexes and weak peripheral a adrenergic blockade.

Pharmacokinetics: Only 1/3 of an oral dose of bromocriptine is absorbed; bioavailability is further lowered by high first pass metabolism in liver.
Has higher oral: parenteral activity ratio than ergotamine.
Metabolites are excreted mainly in bile. Its plasma t½ is 3–6 hours.

Uses: Bromocriptine should always be started at a low dose, 1.25 mg BD and then gradually increased till response occurs otherwise side effects become limiting.

1. **Hyperprolactinemia** due to microprolactinomas causing galactorrhoea, amenorrhoea and infertility in women; gynaecomastia, impotence and sterility in men. Bromocriptine and cabergoline are the first line drug for most cases.

2. **Acromegaly** due to small pituitary tumours and inoperable cases. Relatively higher doses are required (5–20 mg/day) and it is less effective than octreotide/lanreotide. Oral administration and lower cost are the advantages..

3. **Parkinsonism** Bromocriptine, if used alone, is effective only at high doses (20–80 mg/day) which produce marked side effects. Sae effect as levodopa.

Now recommended in low dose only, as an adjunct to levodopa in patients not adequately benefited and in those showing marked 'on-off' effect.

4. **Diabetes mellitus (DM)** A new use of bromocriptine based on its dopamine D2 agonistic action in the hypothalamus has been found in type 2 DM, and it has been approved by US-FDA as an adjunctive drug.

5. **Hepatic coma**: Bromocriptine may cause arousal.

6. Bromocriptine suppresses lactation and breast engorgement in case of neonatal death, but is not recommended due to unfavourable risk: benefit ratio.

Side effects: frequent and dose related.

- **Early**: Nausea, vomiting, constipation, nasal blockage.

  Postural hypotension may be marked at initiation of therapy—syncope may occur if starting dose is high.

  Hypotension : in patients taking antihypertensives.

- **Late**: Behavioral alterations, mental confusion, hallucinations, psychosis—are more prominent than with levodopa. Abnormal movements, livedo reticularis.

CABERLIN 0.5 mg tab,
CAMFORTE 0.5, 1 mg tabs.

Cabergoline

- A newer D2 agonist; more potent;
- More D2 selective and longer acting ($t_{1/2}$ > 60 hours) than bromocriptine; needs to be given only twice weekly.
- Incidence of nausea and vomiting is also lower;
- Useful for patients intolerant to bromocriptine.
- Preferred for treatment of hyperprolactinemia and acromegaly.
- Some patients who achieve total regression of prolactinoma and normalization of prolactin levels can stop cabergoline without recurrence.
- **Dose**: Start with 0.25 mg twice weekly;
  if needed increase after every 4–8 weeks to max. of 1 mg twice weekly.

5. Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

- Control the production of sex hormones (estrogen and testosterone) and sperm and egg maturation and release.

Anterior pituitary hormones

Hormone	Target cell(s)	Action
Thyroid-stimulating hormone (TSH)	Thyroid gland	Stim. thyroid growth and hormone secretion (metabolism)
Adrenocorticotropic hormone (ACTH)	Adrenal cortex Pancreas (insulin release)	Reg. Stress response Stim. Ad. cortex to secrete glucocorticoids (glucose, fat and protein metabolism)
Follicle-stimulating hormone (FSH)	Ovaries, testes (A gonadotropin)	Stim egg dev. Stim. Sperm prod.
Luteinizing hormone (LH)	Ovaries, testes (a gonadotropin) Peak at mid-menstrual cycle	Stim. Egg release & corpus luteum to release progesterone Stim. Interstitial testicular cells to release testosterone

Anterior pituitary hormones

Hormone	Target cell(s)	Action
Prolactin (PRL)	Mammary glands Testes	Stim. milk synthesis after birth Sensitizes testes to testosterone (permissive)
Growth Hormone (GH) or Somatotropin	Many Esp. liver Secreted mainly at night	Stim. Hyperplasia (growth by mitosis) and hypertrophy (growth by increase in cell size) of tissues Increases fatty acid metabolism, decreases muscle uptake of glucose Liver: stim. Somatomedins production (insulin-like growth factors, IGF); this stim. fat, cartilage, bone, tissue Bone growth at epiphyseal plates

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