SNS COLLEGE OF ALLIED HEALTH SCIENCES

SNS Kalvi Nagar, Coimbatore - 35

Affiliated to Dr MGR Medical University, Chennai

DEPARTMENT OF CARDIO PULMONARY PERFUSION CARE TECHNOLOGY

COURSE NAME : Pharmacology Pathology and Clinical Microbiology

II nd YEAR

TOPIC : ANTERIOR PITUITARY HORMONES: ANALOGUES AND INHIBITORS

Hormone:

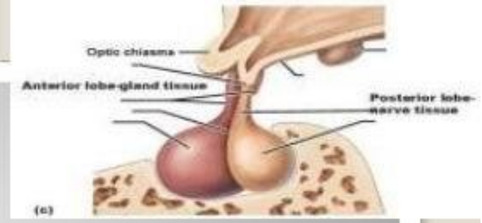
(Greek word, Hormaein- to stir up) “It is a substance of intense biological activity that is produced by specific cells in the body and is transported through circulation to acts on its target cell.”

Hormones are secreted from the endocrine glands in the body.

Hormones regulate body functions to bring about a programmed pattern of life events and maintain homeostasis in the face of markedly
variable external/internal environment.

Also called as signalling molecules.

Pituitary gland:



Anterior & Posterior lobe of Pituitary gland receives separate neuronal inputs form hypothalamus.

A)Anterior gland: (Master endocrine Gland) ; Which secrets;

- Growth hormone (GH),
- Prolactine (Prl),
- Adrenocorticotropic hormone (ACTH, Corticotropin),
- Thyroid stimulating hormone (TSH, Thyrotropin),
- Gonadotropins- Follicle stimulating hormone (FSH) & Luteinizing hormone (LH).

B) Posterior gland: Which secrets;

- Oxytocin,
- Antidiuretic hoemone (ADH, Vasopressin)

Anterior Pituitary gland (Adenohypophysis):

Also called as master endocrine gland.

Release various peptide hormones which act on extracellular receptors located on their target cells.

Their secretion is controlled by the hypothalamus through releasing and release-inhibitory hormones.

Each anterior pituitary hormone is produced by a separate group of cells, depend on their staining characteristic (acidophilic or basophilic).

Acidophils: Somatotropes (GH),
Lactotropes (Prolatine).

Basophils: Gonadotropes (FSH & LH),
Thyrotropes (TSH),
Corticotrope-lipo-tropes (ACTH).

(Produce two melariocyte stimulating hormones (MSHS) and two lipotropins, but these probably not important in man.)

A) Growth hormone (GH)

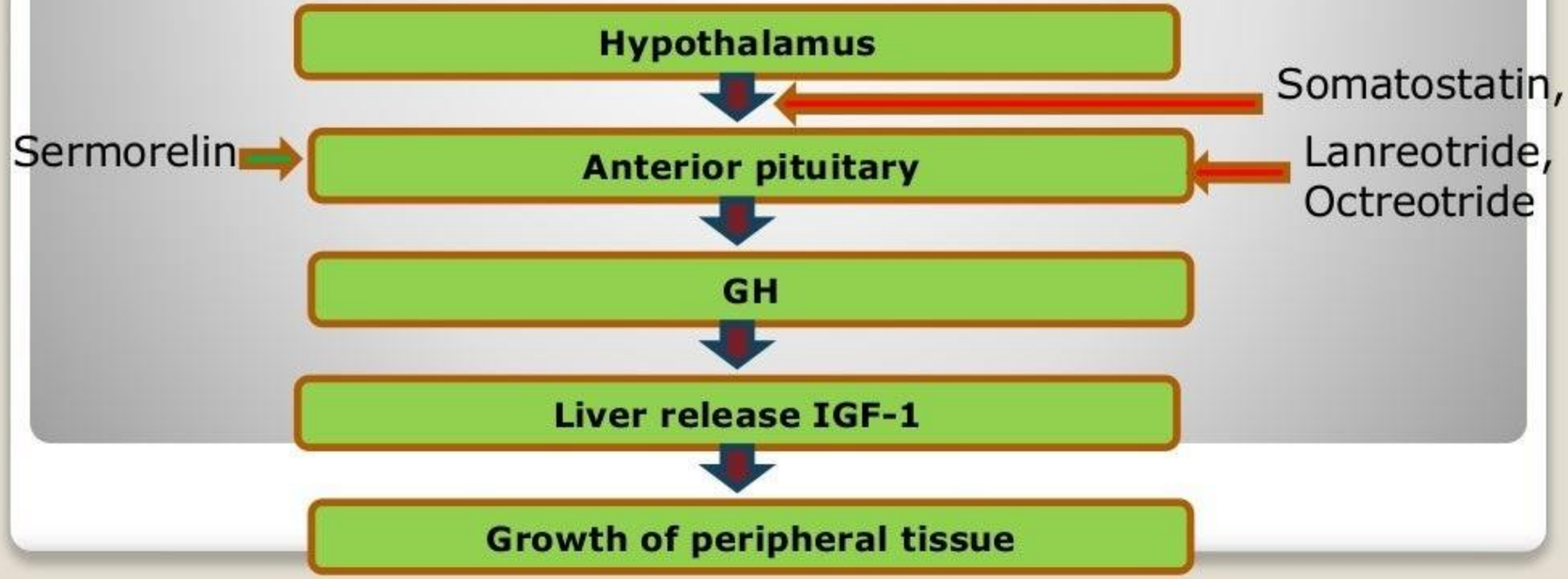
It is secreted by somatotroph cells which contains 191 amino acids, single chain peptide have molecular weight 22000.

Secretion of GH is more in newborn which subsequently decreases at age 4 years that level maintained until after puberty after which further decreases.

Regulation of secretion:

Secretion regulated by hypothalamic GHRF & modulated by somatostatin.

Insulin like growth factor-1 has inhibitory effect on GH.



Physiological role:

Main effect of GH to promotes growth by inducing hyperplasia.

But GH is not responsible for growth of brain and eye.

It promotes retention of nitrogen and other tissue constituents- More protoplasm is formed- increased uptake of amino acids by tissues and their synthesis into proteins.

GH promotes utilization of fat and spares carbohydrates;

- Reduce uptake of glucose by muscles but output from liver is enhanced.
- Induce lipolysis in adipose tissue.

GH mediates some anabolic effects on skeletal muscle & cartilage at epiphyses of long bone and hence promotes bone growth.

Pathological role:

Deficiency of GH (Lack of GHRF): resulting in Pituitary dwarfism.

GH used in treatment of Turner's syndrome (chromosomal disorder), chronic renal insufficiency in children.

hGH is also used illegally by athletes to increase muscle mass.

Excessive production of GH: resulting in gigantism (Children) & acromegaly (adults).

in adults, benign pituitary tumour resulting excessive production of GH. Causes enlargement of facial structures and of the hands and feet.

Preparations/ Dosing:

For treatment of pituitary dwarfism-0.03-0.07 mg/kg (0.06-0.16 Units/ kg) i.m. or s.c. 3 times a week upto the age of 20-25 years is given.

Treatment of excess GH secretion is with dopamine agonist bromocriptine and octreotide is advised.

Pegvisomant, a modified hormone prepared by recombinant technology selective antagonist of growth.

Adverse drug reaction:

- Allergic reaction.
- Pain at injection site.
- Lipodystrophy (abnormal distribution of fat in the body).
- Glucose intolerance.
- Hypothyroidism.
- Salt and water retention.
- Hand stiffness & myalgia.
- Raise in intracranial tension.

Growth hormone (GH) inhibitor:

Drug Name	Points	Uses
1. Somatostatin	It is 14 amino acid peptide inhibits secretion of GH, TSH & prolactin. Also other secretion like insulin & glucagon (Pancreatic secretion), Gastrin & HCL (GI secretion). **Adverse drug reaction:** Diarrhoea, hypochlorhydria, dyspepsia and nausea.	It constricts splanchnic, hepatic and renal blood vessels so used in treatment of GI mucosal blood flow bleeding oesophageal varices and bleeding peptic ulcer. Its anti-secretory action is beneficial in pancreatic, biliary or intestinal fistulae. It reduces complications after pancreatic surgery. It also has adjuvant value in diabetic ketoacidosis (by inhibiting glucagon and GH secretion).
2. Octreotide	This synthetic octapeptide somatostatin is 40 times more potent in suppressing GH secretion and longer acting. **Adverse drug reaction:** Abdominal pain, nausea, steatorrhoea, diarrhoea, and gall stones (due to biliary stasis).	It is preferred in condition like acromegaly and seretory diarrhoeas associated with carcinoid, AIIDS, cancer chemotherapy or diabetes.
3. Pegvisomant:	This is Polyethylene complex GH bind to GH receptor and prevent action of GH by antagonizing the receptor.	

B) Prolactin

It is 199 amino acid, Single chain peptide having MW 23000, similar to GH.

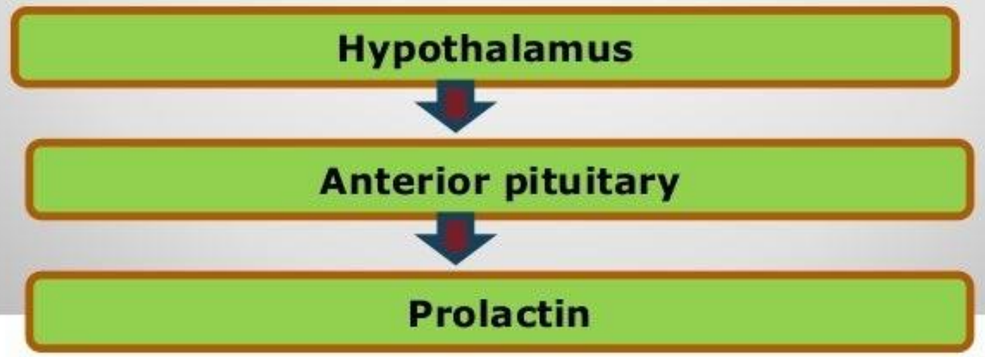
This hormone responsible for secretion of milk from crop glands of pigeon.

Prolactin secreted from cell lactotroph/ mammotroph cells action of Prolactin increased by influence of oestrogen.

Regulation of secretion: Release takes place after stimulation like;

Suckling, sound of hungry pups.

Inhibition by dopamine.



Physiological role:

Prolactin receptor are not only found in the mammary gland but are widely distributed throughout the body, including the brain, ovary, heart and lungs.

Along with estrogens, progesterone and several other hormones, causes growth and development of breast during pregnancy.

It causes proliferation of ductal as well as acinar cells in the breast and induces synthesis of milk proteins and lactose.

Pathological role:

- Hyper prolactinaemia is responsible for the galactorrhoea amenorrhoea infertility syndrome. In males it causes loss of libido and depressed fertility.
- Disorders of hypothalamus decreases inhibitory control over pituitary.
- Antidopaminergic and DA depleting drugs causes hyper prolactinaemia
- Prolactin secreting tumours-these may be microprolactinomas or macroprolactinomas.

Prolactin inhibitor:

Ex- Bromocriptine, Cabergoline.

a) Bromocriptine: synthetic ergot derivative 2-bromo-aergocryptine is a potent dopamine agonist weak a adrenergic blocker .

b) Cabergoline: It is a newer D2 agonist; more potent; more D2 selective and longer acting (t½> 60 days) than bromocriptine less side effects than bromocriptine.

Actions:

Activating dopaminergic receptors and decreases Prolactin release.

In normal individuals increases GH release but decreases the same from pituitary tumours that cause acromegaly.

It has levodopa like actions in CNS-antiparkinsonian and behavioural effects produces nausea and vomiting by stimulating dopaminergic receptor in CTZ.

Hypotension due to central suppression of postural refluxes & weak adrenergic blocker.

Decreases GI motility.

Uses: In treatment of conditions like;

Hyperprolactinemia: In women it shows galactorrhoea, amenorrhoea and infertility & men gynaecomastia, impotence and sterility.

lower doses (bromocriptine 2.5-10 mg/ day or cabergoline 0.25-1.0 mg twice weekly) are effective.

Acromegaly (Due to small pituitary tumours) : Slightly higher doses of bromocriptine required (5-20 mg/day) .

Parkinsonism: Bromocriptine effective only at high doses (20-80 mg/day)and response is similar to that of levodopa .

Adverse drug reaction:

Nausea, vomiting, constipation, nasal blockage.

Postural hypotension in patients taking antihypertensives.

Late: Behavioral alterations, mental confusion, hallucinations, psychosis and Abnormal movements

C) Adrenocorticotrophic Hormone (ACTH, also adrenocorticotropin, corticotropin)

Adrenocorticotrophic hormone (ACTH, corticotrophin) is the anterior pituitary secretion that controls the synthesis and release of the glucocorticoids of the adrenal cortex .

It is a 39-residue peptide derived from the precursor pro opiomelanocortin

The principal effects are increased production and release of cortisol by the cortex of the adrenal gland.

Regulation of secretion:

Hypothalamus

↓ Corticotropin releaseing hormone

Anterior pituitary corticotropes

↓ removal of the signal peptide during translation

pre-pro-opiomelanocortin

↓

ACTH

Physiological role:

- ACTH plays a role in glucose metabolism and immune function.
- The circadian rhythm influences cortisol secretion. The highest levels of cortisol are seen in the early morning, and the lowest levels are in the evening. This concept is important for diagnostic testing.
- Promotes sterodogenesis in adrenal cortex by stimulating CAMP supply formation in cortical cells.

Pathological role:

Hypofunctioning or hyperfunctioning of pituitary gland resulting resulting in pathological consequences;

Addison Disease (autoimmune destruction of adrenal cortex causes decreases level of Adrenocorticotrophic Hormone)

Cushing's disease (Increased ACTH caused by a non-cancerous tumour called an adenoma located in the pituitary gland produces hyperfunctioning of gland)

Uses:

- ACTH is used for the diagnosis of disorders of pituitary adrenal axis. When it will injected i.v. 25 IU causes increase in plasma cortisol if the adrenals are functional.
- Direct assay of plasma ACTH level is now preferred.
- For therapeutic purposes, ACTH does not offer any advantage over corticosteroids and is more inconvenient, expensive ,less predictable.

Thyroid stimulating hormone (TSH, Thyrotropin)

- It is a 210 amino acid, two chain glycoprotein (22% sugar), MW 30000.

Physiological function:

TSH stimulates thyroid to synthesize and secrete thyroxine (T) and triiodothyronine (T) shows action like:

- Induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland.
- Promotes processes helpful for synthesis of thyroid hormones.

Pathological role:

Hypo-or hyperthyroidism are due to inappropriate TSH secretion.

Uses:

Thyrotropin has no therapeutic use only used for diagnosis purpose of myxoedema.

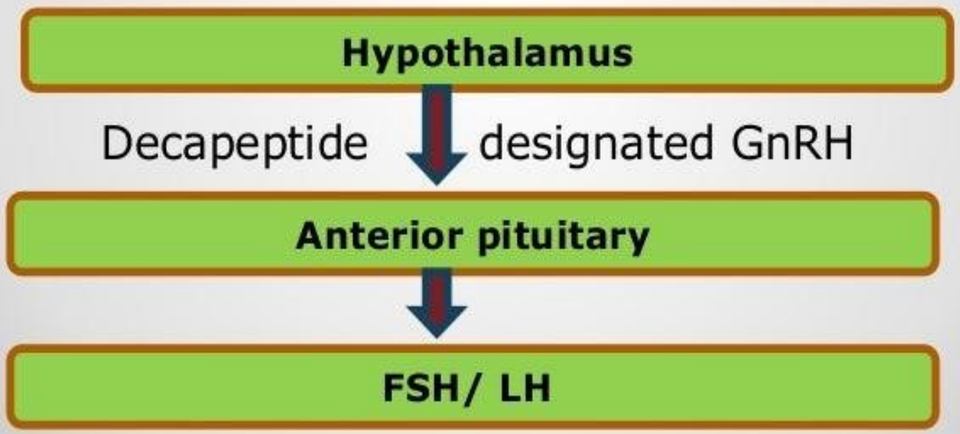
Gonadotropins-

Follicle stimulating hormone (FSH) & Luteinizing hormone (LH):

Both are glycoproteins containing 23-28% sugar and consist of two peptide chains having a total of 207 amino acid residues.

Having molecular weight FSH-32,000 while LH- 30,000.

Regulation of secretion:



Physiological function:

Both hormones promote gametogenesis and secretion of gonadal hormones.

FSH- In female it induces follicular grow causes development of ovum and secretion of estrogens.

In male supports spermatogenesis and has trophic influence on seminiferous tubules.

LH- In female induces preovulatory swelling of the ripe graafian follicle and triggers ovulation. Also responsible for progesterone secretion.

In male stimulate testosterone secretion.

Pathological role:

Hypo secretion of gonadotrophins resulting delayed puberty precocious puberty both in girls and boys. Also amenorrhoea and sterility in women; oligozoospermia, impotence and infertility in men.

Excess production of gonadotrophins causes polycystic ovaries.

Uses:

1. Amenorrhea & infertility:

When deficient production of gonadotrophins resulting in nonovulation. Which is treated with 1 injection of menotropins. (75 IU FSH & LH)

I/m daily for 10 days causes ovulation. 75% women conceive but high chances of abortion & multiple pregnancy. Not produce teratogenic effect.

2. Hypogonadotrophic hypogonadism in males:

In treatment of delayed puberty or defective spermatogenesis oligozoospermia, male sterility, treatment start with 1000-4000 IU of HCG i.m. 2-3 times. After 3-4 months add FSH 75 IU +LH 75 IU.

3. Cryptorchism:

undescended testes (one or both of the male testes have not passed down into the scrotal sac) can infertility and predispose to testicular cancer.

HCG can be tried between the age of 1-7 years if there is no anatomical obstruction.

4. To aid in vitro fertilization Menotropins:

used to induce simultaneous maturation of several ova and to precisely time ovulation so as to facilitate their harvesting for in vitro fertilization.

Adverse effects and precautions:

- Ovarian hyperstimulation (polycystic ovary, pain in lower abdomen and even ovarian bleeding and Shock).
- Precocious puberty (child's body begins changing into that of an adult).
- Allergic reactions.
- Hormone dependent malignancies (prostate, breast).
- Edema, headache, mood changes.

Gonadotropin Releasing Hormone (GnRH): Gonadorelin / Agonist:

- GnRH injected i.v. (100 μg) induces prompt release of LH and FSH but causes rapid enzymatic degradation so shorter plasma t½ (4–8 min)
- Used for testing pituitary gonadal axis in male as well as female hypogonadism.
- Example of Superactive / long-acting GnRH agonists are Nafarelin Goserelin ,Triptorelin & Leuprolide.

Advantage of synthetic analogues are :

- 15-150 times more potent than natural GnRH.
- High affinity for GnRH receptor.
- resistance to enzymatic hydrolysis so longer acting having half life t½ 2–6 hours.
- Used as nasal spray or injected s.c.
- Long-acting preparations for once a month reversible pharmacological oophorectomy/ orchidectomy is being used in precocious puberty, prostatic
- carcinoma, endometriosis, premenopausal breast cancer, uterine leiomyoma, polycystic ovarian disease and to assist induced ovulation.

Sr. No.	Drug Name	Points
1.	Nafarelin	•150 times more potent than native GnRH. • Used as intranasal spray having bioavailability 4–5%. • Plasma t½ is 2–3 hours. •Used in treatment of Assisted reproduction, Uterine fibroids, Endometriosis & Central precocious puberty. Adverse effects: Hot flashes, loss of libido, vaginal dryness, osteoporosis, emotional lability.
2.	Goserelin	Used as a depot s.c./i.m. Injection. Used for endogenous Gn suppression before ovulation induction, as well as for endometriosis, carcinoma prostate.

Sr. No.	Drug Name	Points
3.	Triptorelin	Used as regular release daily s.c. Injection for treatment of female infertility. Depot i.m. monthly injection in the treatment of carcinoma prostate, endometriosis, precocious puberty and uterine leiomyoma. Long term treatment not advised because it resulting in to osteoporosis.
4.	Leuprolide.	injected s.c./i.m. daily or as a depot injection once a month for palliation of carcinoma prostate

- **GnRH antagonists**
- Substituted GnRH analogues act as GnRH receptor antagonists. They inhibit Gn secretion without causing initial stimulation.
- The early GnRH antagonists causes histamine release. Later agents like ganirelix and cetrorelix have low histamine releasing potential so clinically used as s.c. inj. for inhibiting LH and in women undergoing in vitro fertilization.

Advantages over long-acting GnRH agonists include:

- They produce quick Gn suppression by competitive antagonism , so started only from 6th day of ovarian hyperstimulation.
- They carry a lower risk of ovarian hyperstimulation syndrome.
- They achieve more complete suppression of endogenous Gn secretion.
- However, pregnancy rates are similar or may even be lower

THANK YOU