Lec. 4: Hypothalamic and Pituitary hormons

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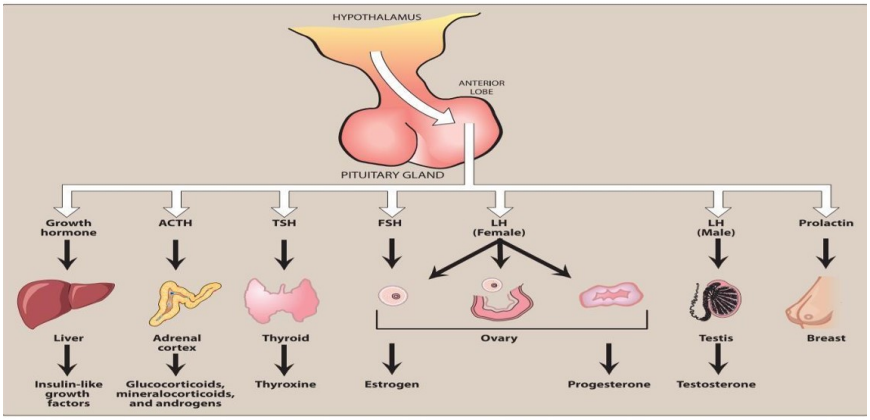
- The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body.
- Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months.
- [Note: Nerve impulses generally act within milliseconds.]
- An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland.

HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

- The hormones secreted by the hypothalamus and the pituitary are peptides or glycoproteins that act by binding to specific receptor sites on target tissues.
- The hormones of the anterior pituitary are regulated by neuropeptides that are called either "releasing" or "inhibiting" factors or hormones.
- These are produced in the hypothalamus, and they reach the pituitary by the hypophyseal portal system.



- The interaction of the releasing hormones with receptors results in the activation of genes that promote the synthesis of protein precursors.
- The protein precursors then undergo posttranslational modification to produce hormones, which are released into the circulation.
- Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary.

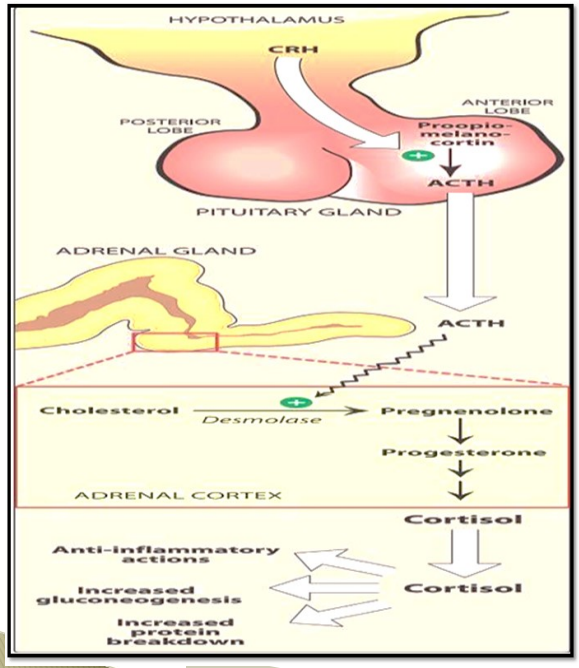
- Pituitary hormone preparations are currently used for specific hormonal deficiencies, although most of the agents have limited therapeutic applications.
- Hormones of the anterior pituitary are administered intramuscularly (IM), subcutaneously, or intranasally because their peptidyl nature makes them susceptible to destruction by proteolytic enzymes of the digestive tract.

A. Adrenocorticotropic hormone (corticotropin)

- A. Adrenocorticotropic hormone (corticotropin= ACTH):

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide proopiomelanocortin by the pituitary.

- Adrenocorticotropic hormone (ACTH) or corticotropin is a product of the posttranslational processing of this precursor polypeptide.
- [Note: CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH- producing cells.]
- Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring in early morning and the lowest in late evening.
- Stress stimulates its secretion, whereas cortisol acting via negative feedback



- **1. Mechanism of action:**

ACTH binds to receptors on the surface of the adrenal cortex, thereby activating G protein-coupled processes that ultimately stimulate the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone).

This pathway ends with the synthesis and release of adrenocorticosteroids and the adrenal androgens.

2. Therapeutic uses:

The availability of synthetic adrenocorticosteroids with specific properties has limited the use of corticotropin mainly to serving as a diagnostic tool for differentiating between:

- Primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary).
- Therapeutic corticotropin preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, cosyntropin, is preferred for the diagnosis of adrenal insufficiency.
- ACTH is also used in the treatment of : infantile spasms and multiple sclerosis.

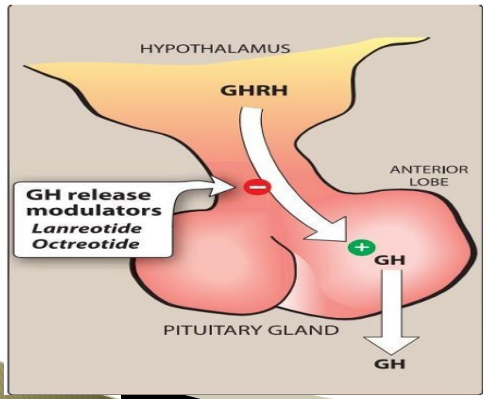
- 3. Adverse effects:

Short-term use of ACTH for diagnostic purposes is usually well tolerated.

With longer use, toxicities are similar to glucocorticoids and include hypertension, peripheral edema, hypokalemia, emotional disturbances, and increased risk of infection.

B. Growth hormone (somatotropin)

- Growth hormone (somatotropin): Somatotropin is released by the anterior pituitary in response to growth hormone (GH)–releasing hormone (GHRH).



- Conversely, secretion of GH is inhibited by the hormone somatostatin.
- GH is released in a pulsatile manner, with the highest levels occurring during sleep.
- With increasing age, GH secretion decreases, accompanied by a decrease in lean muscle mass.
- Somatotropin influences a wide variety of biochemical processes (for example, cell proliferation and bone growth).
- Synthetic human GH (somatropin) is produced using recombinant DNA technology.

- Mechanism of action:
- Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins–insulin-like growth factors 1 and 2 (IGF-1 and IGF-2).
- GH is a large peptide, the exogenous one, synthesized by gene technology and used as injection; the animal one is ineffective for human.
- Over secretion of GH before puberty causes Gigantism Over secretion of GH after puberty causes Acromegaly Reduced secretion of GH causes Dwarfism.

- GH has the following functions:

1- Glycogenolysis (catabolism of glycogen)→↑ blood sugar.

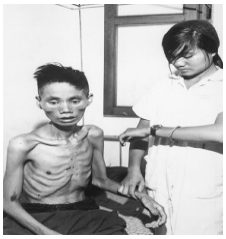
2- Lipolysis (catabolism of lipid).

3- protein synthesis.

4- Increase the no. of cells and their density including bone and cartilage.

- Therapeutic uses:

Somatropin is used in the treatment of:



1- GH deficiency.

2- Growth failure in children.

3- treatment of HIV patients with cachexia.

4- GH replacement in adults with confirmed deficiency.

- The synthetic GH (somatrem has longer t1/2 =25 min than natural GH.
- This drug is given to dwarf patients before puberty because after puberty the closure of long bones epiphysis occur, so administration of GH after puberty causes acromegaly, which characterized by thick skin & bone ,large nose and lower jaw and extremities specially fingers.

- Adverse effects:

Adverse effects of somatropin include pain at the injection site, edema, arthralgias, myalgias, nausea, and an increased risk of diabetes.

Somatropin should not be used in pediatric patients with closed epiphyses, patients with diabetic retinopathy, or obese patients with Prader–Willi syndrome.

C. Somatostatin (growth hormone–inhibiting hormone)

- In the pituitary, somatostatin binds to receptors that suppress GH and thyroid-stimulating hormone (TSH) release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide found in neurons throughout the body as well as in the intestine, stomach, and pancreas. Somatostatin not only inhibits release of GH but also insulin, glucagon, and gastrin.

- Octreotide and lanreotide are synthetic analogs of somatostatin with longer half- lives.
- Depot formulations of these agents allow for administration every 4 weeks.
- They have found use in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors.
- An intravenous infusion of octreotide is also used for the treatment of bleeding esophageal varices.
- Adverse effects of octreotide include bradycardia, diarrhea, abdominal pain, flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-

D. Gonadotropins

- The gonadotropins (FSH and LH) are produced in the anterior pituitary.
- The regulation of gonadal steroid hormones depends on these agents.
- They used in the treatment of infertility.
- Menotropins (also known as human menopausal gonadotropins or hMG) are obtained from urine of postmenopausal women and marketed under trade name (pergonal ®) and contain both FSH and LH.

- Urofollitropin is FSH obtained from postmenopausal women and is devoid of LH.
- Follitropin alfa and follitropin beta are human FSH products manufactured using recombinant DNA technology.
- Human chorionic gonadotropin (hCG) is a placental hormone that is excreted in urine of pregnant women isolated and marketed under trade name (pregenyl ®).
- The effects of hCG and choriogonadotropin alfa (made using recombinant DNA technology) are essentially identical to those of LH.

- Both preparations administered as IM injection as follow:

1- For infertile women:

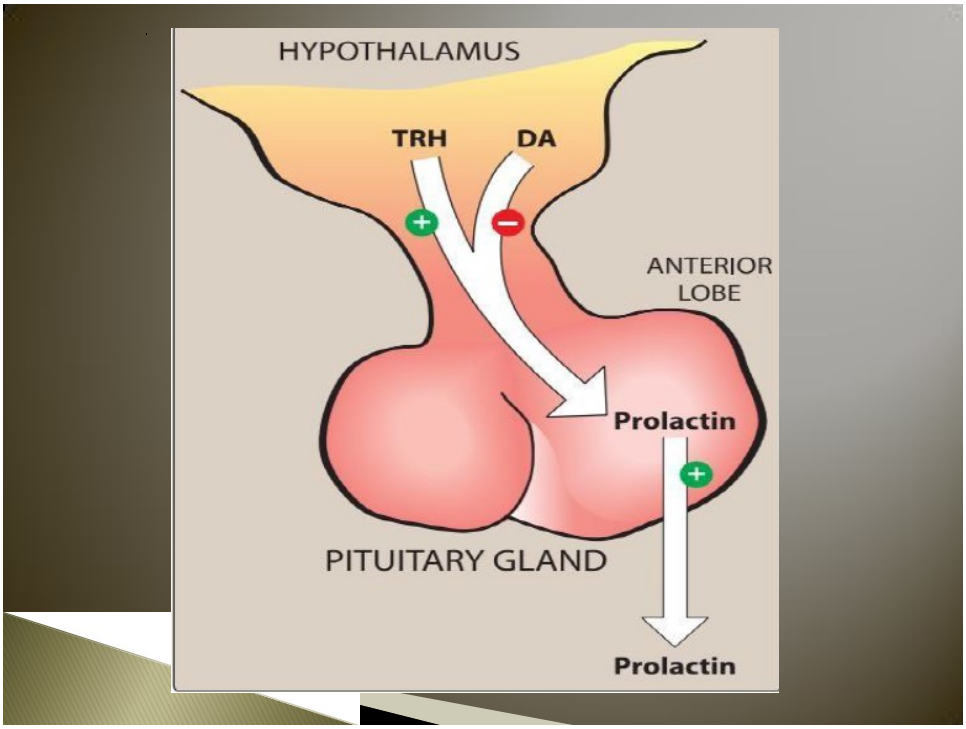
- Give menotropin at 5-12 days of menstrual cycle (for growth and maturation of follicals) followed by HCG at day 13-15 from period for ovulation.

2- For infertile men:

- Give HCG for maturation of external sexual organs followed by menotropin for induction of spermatogenesis.
- Adverse effects include ovarian enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening. Multiple births can occur.

E. Prolactin

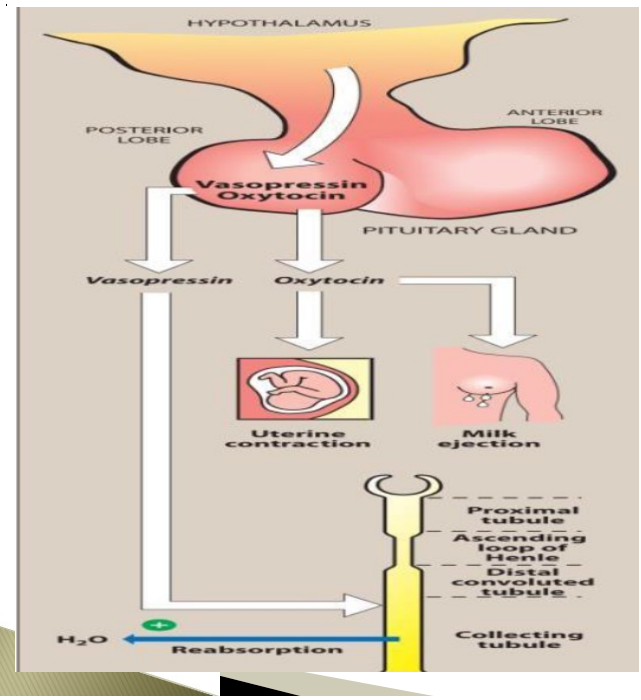
- Prolactin is a peptide hormone secreted by the anterior pituitary.
- Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function.
- Thyrotropin releasing hormone (TRH) stimulates the release of prolactin, and secretion is inhibited by dopamine acting at D2 receptors.
- [Note: Drugs that act as dopamine antagonists (for example, metoclopramide and some antipsychotics) can increase the secretion of prolactin.]



- Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D2 receptor agonists, such as bromocriptine and cabergoline.
- Both of these agents also find use in the treatment of pituitary microadenomas.
- Bromocriptine is also indicated for treatment of type 2 diabetes.
- Among their adverse effects are nausea, headache and, less frequently, psychosis.

HORMONES OF THE POSTERIOR PITUITARY

- In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, vasopressin and oxytocin, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition.
- Both hormones are administered intravenously and have very short half-lives.



A. Oxytocin:

- Oxytocin is used in obstetrics to stimulate uterine contraction and induce labor.
- Oxytocin also causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.
- Although toxicities are uncommon with proper drug use, hypertension, uterine rupture, water retention, and fetal death may occur.
- Its antidiuretic and pressor activities are much less than those of vasopressin.

B. Vasopressin:

- Vasopressin (antidiuretic hormone) is structurally related to oxytocin.
- Vasopressin has both antidiuretic and vasopressor effects.
- In the kidney, it binds to the V2 receptor to increase water permeability and reabsorption in the collecting tubules.
- Thus, the major use of vasopressin is to treat diabetes insipidus.
- It also finds use in septic shock and in controlling bleeding due to esophageal varices.

- Other effects of vasopressin are mediated by the V1 receptor, which is found in the liver, vascular smooth muscle (where it causes constriction), and other tissues.
- The major toxicities of vasopressin are water intoxication and hyponatremia. Abdominal pain, tremor, and vertigo can also occur.

- Desmopressin, an analog of vasopressin, has minimal activity at the V1 receptor, making it largely free of pressor effects.
- This analog is longer acting than vasopressin and is preferred for the treatment of diabetes insipidus and nocturnal enuresis.
- For these indications, desmopressin is administered intranasally or orally.
- [Note: The nasal spray should not be used for enuresis due to reports of seizures in children using this formulation.]
- Local irritation may occur with the nasal spray.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