

Endocrine system

- Pituitary & hypothalamus control the neuroendocrine system (which coordinates body functions) by transmitting messages between individual cells & tissues.
- The nervous system communicates locally by electrical impulses & neurotransmitters directed through neurons to other neurons or to specific target organs, such as muscle or glands. Nerve impulses generally act within milliseconds.
- The endocrine system releases hormones (chemical messengers) into the bloodstream, from which they reach their target cells.
- Response time to hormones (seconds - days, or longer) is much than that of nerve impulses

Note: response to hormones may last for weeks or months.

- In several instances, the release of hormones is stimulated or inhibited by the nervous system, & some hormones (Hs) can stimulate or inhibit nerve impulses.

Hypothalamic & anterior pituitary hormones

- Peptides or low-molecular-weight proteins.
- Bind to specific receptor sites.
- Hypothalamus produced neuropeptides (releasing or inhibiting factors or Hs), which regulate the anterior pituitary Hs.

Note: hypothalamic-releasing hormones (RHs) are primarily used for diagnostic purposes (to determine pituitary insufficiency).

- Interaction of the RHs with their receptors results in the activation of genes that promote the synthesis of protein precursors which then undergo post-translational modification to produce Hs which are released into the circulation.

Note: hypothalamus also synthesizes the precursor proteins of the Hs vasopressin & oxytocin, which are transported to the posterior pituitary, where they are stored until released (anterior pituitary Hs are not stored in granules prior to release).

- Anterior & posterior pituitary Hs are administered either IM, SC, or intranasally, but not orally (destroyed by the proteolytic enzymes of the digestive tract).

Adrenocorticotrophic hormone (ACTH) or corticotropin

- Synthesized & released under the influence of CRH.

Note: CRH is used diagnostically to differentiate between Cushing syndrome & ectopic ACTH-producing cells.

- Normally, the ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM & the lowest in the late evening.
- Stress stimulates ACTH secretion, whereas cortisol suppresses ACTH release via negative feedback.

Mechanism of action:

ACTH binds to its receptors (on the cell surfaces of adrenal cortex) → activate G protein → ↑ cAMP → stimulates conversion of cholesterol to pregnenolone (the rate-limiting step in the adrenocorticosteroid synthesis) → synthesis & release of the adrenocorticosteroids & adrenal androgens.

Therapeutic uses:

- ACTH (**corticotrophin**) preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH.
- The availability of synthetic adrenocorticosteroids limited the use of **corticotrophin** mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) & secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary).

Cosyntropin

A synthetic human ACTH, it is preferred for the diagnosis of adrenal insufficiency.

- ACTH is used in the treatment of multiple sclerosis & infantile spasm (West syndrome).

Adverse effects:

- Toxicities are similar to those of glucocorticoids (osteoporosis, HT, peripheral edema, hypokalemia emotional disturbances & increased risk of infection).
- Abs can form against ACTH from animal origin.

Growth hormone (GH) or Somatotropin

- Large polypeptide released by the anterior pituitary in response to GH -RH (from hypothalamus).
- **Somatostatin** (from hypothalamus), inhibits GH secretion.

GH is released in a pulsatile manner (highest levels occurring during sleep).

- With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass.

Human GH is produced synthetically by using recombinant DNA technology.

- GH from animal sources is ineffective in humans.

Somatotropin influences a wide variety of biochemical processes; eg. through stimulation of protein synthetic processes, cell proliferation & bone growth are promoted.

Mechanism of action:

- Many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins—insulin-like growth factors I & II (IGF-I and IGF-II).

Note: In acromegaly, IGF-I levels are consistently high, reflecting elevated GH.

Therapeutic uses:

- GH deficiency in children due to hypopituitarism.
- GH has been abused by some athletes (it increases lean body mass, bone density & skin thickness, while decreases adipose tissue mass), but it is not approved for this purpose & diabetes have developed in some who have taken it.

Somatrem

- A **somatotropin** equivalent drug, although the half-lives of both drug are short (≈ 25 minutes), they induce the release from the liver of IGF-1 (somatomedin C) which is responsible for subsequent GH-like actions.
- **Somatotropin** & **Somatrem** should not be used in individual with closed epiphyses or an enlarging intracranial mass.

Growth hormone-inhibiting hormone (Somatostatin)

- Small polypeptide found also in neurons through out the body, intestine & pancreas.
- Binds to distinct receptors (SSTR2 & SSTR5) in the pituitary, suppressing GH & TSH release.
- It is not only inhibits the release of GH but, also that of insulin, glucagons & gastrin.

Octreotide

- A synthetic octapeptide analog of **somatostatin** with longer half-life & a depot form is also available.

- Both agents suppress GH & IGF-1 for 12 hours & 6 weeks respectively.

Both are used in treatment of acromegaly caused by hormone-secreting tumors & in secondary diarrhea associated with tumors producing vasoactive intestinal peptide (VIPomas).

- **Octreotide** adverse effects include flatulence, nausea & steatorrhea. Gallbladder emptying is delayed & asymptomatic cholesterol gallstones can occur with long-term treatment.

Pegvisomant

An analog of human GH used in the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention, it acts as an GH receptor blocker & result in the normalization of IGF-I levels.

Gonadotropins – releasing hormones (GnRH) / luteinizing hormone - releasing hormones (LHRH)

- GnRH also called gonadorelin.
- Decapeptide obtained from the hypothalamus.
- Its pulsatile secretion is essential for the release of FSH & LH from the pituitary.
- Its continuous administration inhibits gonadotropin release.
- GnRH is used in treatment of hypogonadism.
- Leuprolide, goserelin, nafarelin & histrelin are synthetic analogs act as agonists at GnRH receptors, they are effective in treatment of prostatic cancer, endometriosis & precocious puberty.
- Gonadorelin adverse effects include hypersensitivity, dermatitis & headache.
- In women the GnRH analogs may cause hot flushes, sweating & diminished libido, depression & ovarian cysts.
- Contraindicated in pregnancy & breast-feeding.
- In men, they initially cause a rise in testosterone that can result in bone pain, hot flushes, edema, gynecomastia & diminished libido.

Gonadotropins: Human menopausal gonadotropin (hMG), follicle- stimulating hormone (FSH) & human chorionic gonadotropin (hCG)

- Glycoproteins that are produced in the anterior pituitary.
- They regulate the gonadal steroid hormones.
- Used in the treatment of infertility in men and women.

Menotropins (human menopausal gonadotropins" hMG ")

- Obtained from the urine of postmenopausal women.
- Contain both FSH & LH.

Human chorionic gonadotropin (hCG)

- Placental hormone structurally related to LH.
- Excreted in the urine.

Urofollitropin

FSH obtained from postmenopausal women & is devoid of LH.

Follitropin beta

- Human FSH manufactured by recombinant DNA technology.

All of these hormones are injected via the IM or SC route.

- hMG or FSH injection over a period of 5 to 12 days causes ovarian follicular growth & maturation, & with subsequent injection of hCG, ovulation occurs.
- hCG treatment in men (who are lacking gonadotropins), causes external sexual maturation, & with the subsequent injection of **hMG** or **follitropin**, spermatogenesis occurs.
- In females adverse effects include ovarian enlargement and possible hypovolemia multiple births are not uncommon.

- Men may develop gynecomastia.

Prolactin (PRL)

- Peptide hormone secreted by the anterior pituitary.
- Its secretion is inhibited by dopamine acting at D2 receptors.
- It stimulates & maintains lactation.
- It decreases sexual drive & reproductive function.
- Hyperprolactinemia (galactorrhea & hypogonadism), is usually treated with D2 receptor agonists eg. **bromocriptine** & **cabergoline**. Both of these agents also find use in the treatment of pituitary microadenomas, macroprolactinomas & hyperprolactinemia, their adverse effects include nausea, headache & sometimes, psychiatric problems.

Posterior pituitary hormones

- **Vasopressin & oxytocin**, they are not regulated by RHs.
- Synthesized in the hypothalamus, transported to the posterior pituitary, & released in response to specific physiologic signals, such as high plasma osmolarity or parturition.
- Both Hs are nonapeptide & have very short half-lives.
- Given parenterally (susceptible to proteolytic cleavage).

Oxytocin

- Extracted from animal posterior pituitaries, is now chemically synthesized.
- It is employed to stimulate uterine contraction to induce or reinforce labor.
- Given as IV injection for labor induction & as nasal spray to induce milk ejection.
- Although toxicities are uncommon when the drug is used properly, HT, uterine rupture, water retention, & fetal death have been reported.

Note: Oxytocin is contraindicated in abnormal fetal presentation, fetal distress, and premature births.

- Its antidiuretic & pressor activities are very much lower than those of vasopressin.

Vasopressin (antidiuretic hormone "ADH")

- Structurally related to oxytocin.
- The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries.
- Has both antidiuretic & vasopressor effects.
- Binds to the V2 receptor in the kidney, increasing water permeability & reabsorption in the collecting tubules.
- Its major use is to treat diabetes insipidus.
- Also used in the management of cardiac arrest & in controlling bleeding due to esophageal varices or colonic diverticula.

- Other effects of vasopressin are mediated by the V1 receptor, which is found in liver, vascular smooth muscle (where it causes constriction), & other tissues.
- Major toxicities are water intoxication & hyponatremia. Headache, bronchoconstriction & tremor can also occur.
- Used cautiously in patients with coronary artery disease, epilepsy & asthma.

Desmopressin

- A modified vasopressin, that has minimal activity at the V1 receptor, thus it is largely free of pressor effect.
- Preferred for diabetes insipidus & nocturnal enuresis.
- It is longer-acting than vasopressin.
- Administered intranasally, however local irritation may occur.

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