College of Pharmacy

Fifth Stage

Clinical Chemistry

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Lectutre 1

The Hypothalamus and Pituitary Gland

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The hypothalamus

It is a structure in the brain that concerned mainly with homeostasis of the body. It regulates many functions of the body like endocrine functions, visceral functions, metabolic activities, hunger, thirst, sleep, wakefulness, emotion, sexual function, etc.

The hypothalamus produces two groups of hormones that are associated with posterior and anterior pituitary:

The **first group** includes peptides that travel down to the posterior pituitary through **nerve fibers** where they are stored there. These hormones are:

1.Arginine-vasopressin or known as antidiuretic hormone (ADH)

2. Oxytocin: a hormone similar in structure to ADH, controls ejection of milk from lactating breast. It is also initiates uterine contraction during labour.

The **second group** includes small molecules called regulatory hormones that produced in hypothalamus and are transported through blood network to anterior pituitary (to stimulate or inhibit the secretion of anterior lobe hormones).These hormones are:

Releasing hormones (RH), and releasing hormones-inhibitory hormones (RHIH).

The pituitary gland

The pituitary is a small gland found inside the skull just below the brain and above the nasal passages. The pituitary gland is connected directly to part of the brain called the hypothalamus. The hypothalamus releases hormones into tiny blood vessels directly connected to the pituitary gland. These cause the pituitary gland to make its own hormones. **The pituitary is considered the "master control gland"** because the hormones it makes control the levels of hormones made by most other endocrine glands in the body. The pituitary gland has two parts, the anterior and posterior pituitary part, each of which has distinct functions.

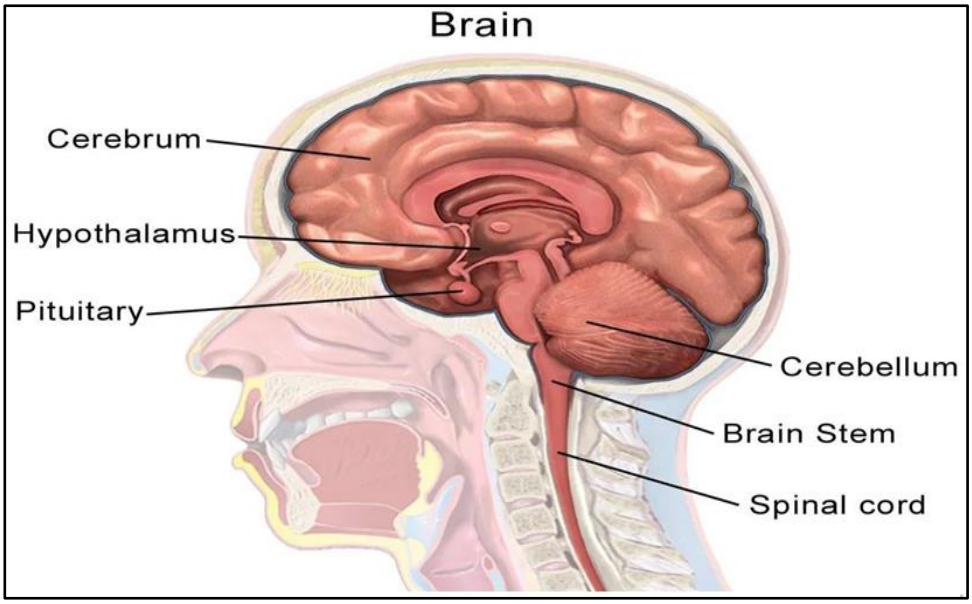

Figure (1) The locations of hypothalamus and pituitary gland

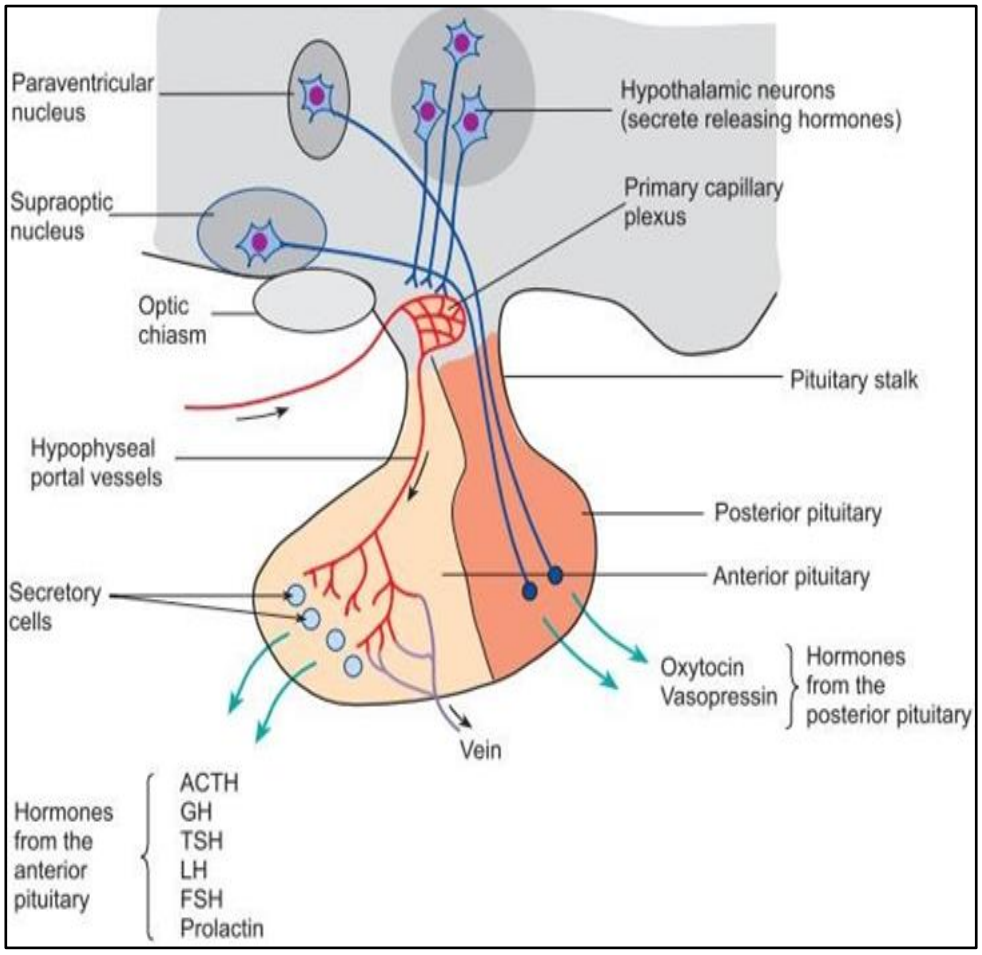

Figure (2) The connection between hypothalamus and pituitary gland

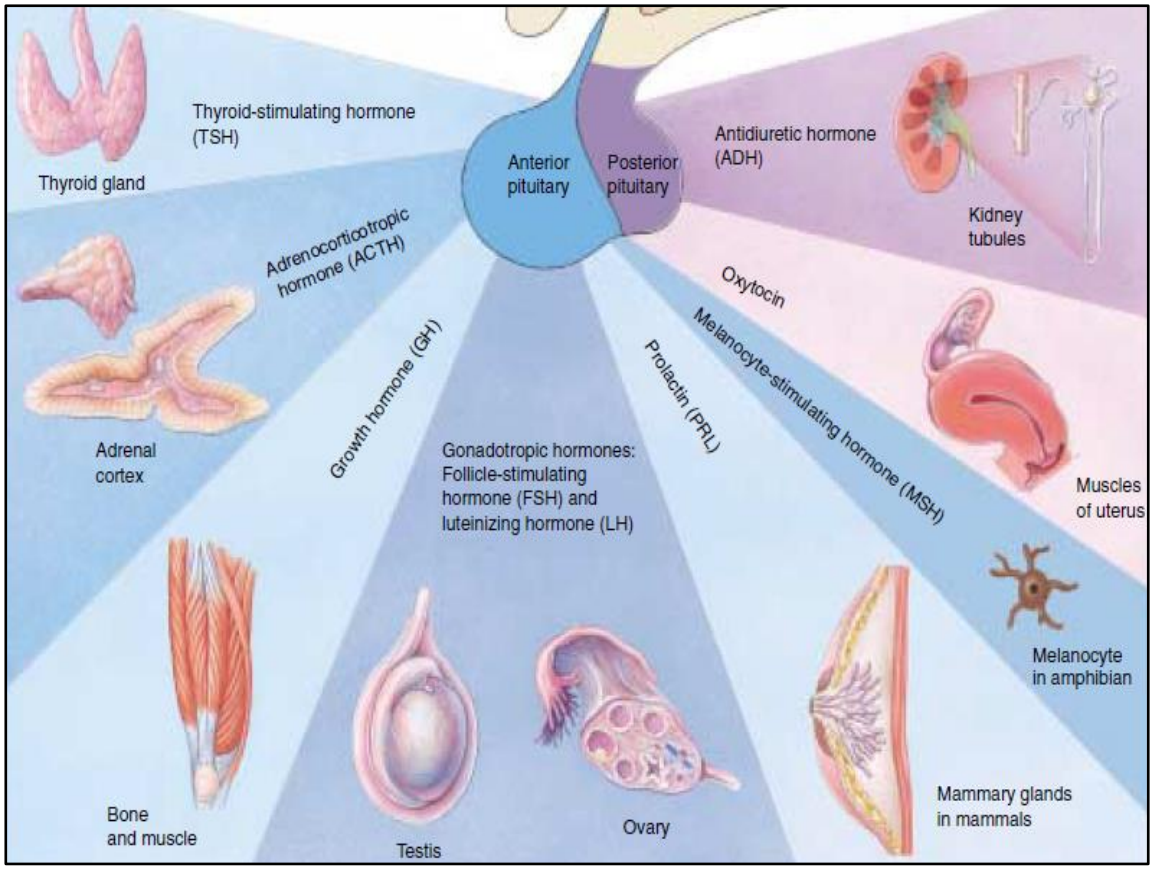

Figure (3) Effects of pituitary gland on various organs

Anterior pituitary hormones

The cells of the anterior pituitary lobe can be classified simply by their staining reactions as **acidophils**, **basophils** and **chromophobes**.

1. Acidophils include two types of cells:

A. Somatotrophs, which secrete **growth hormone GH (somatotrophin)**. This hormone, is a polypeptide hormone. The GH stimulates long bone and soft tissue growth. The GH also exerts complex actions on metabolism (amino acid, fatty acid, glucose). Secretion is **increased** via the hypothalamus by **hypoglycaemia**, **stress** and **exercise**. Hypothalamic factors that regulate GH release are growth hormone releasing hormone **(GHRH)** which stimulates and **somatostatin** which inhibits GH release. Systemic control is via negative feedback by GH at the hypothalamus. The GH insufficiency causes short stature (**dwarfism**); GH excess causes **gigantism** in

children, **acromegaly** in adults.

B. Lactotrophs, which secrete **prolactin**. This hormone, is a polypeptide hormone. Prolactin stimulates the development and growth of secretory alveoli in the breast and milk production. Prolactin also inhibits the reproductive system at the level of the gonads and pituitary (causes 'lactational amenorrhoea' in women after delivery of baby). Secretion of prolactin is increased by **suckling**. Prolactin is the only pituitary hormone inhibited by **dopamine** from the hypothalamus. Hypersecretion of prolactin can causes **galactorrhoea**, **infertility** and **amenorrhoea**. Hyposecretion of prolactin can cause lactation failure.

2. Basophils include three types of cells:

A. Corticotrophs synthesize a large polypeptide **[**pro-opiomelanocortin (**POMC**)**]**, which is a **precursor** of adrenocorticotrophic hormone (**ACTH**; corticotrophin), melanocyte stimulating hormone (**MSH**) and **β-lipotrophin**.

The **ACTH** stimulates the synthesis and secretion of steroids, from the adrenal cortex and maintains adrenal cortical growth. Secretion of ACTH is increased by **stress**. Secretion is pulsatile with a **diurnal rhythm**. Release of ACTH is stimulated by corticotrophin releasing hormone (**CRH**) from the hypothalamus. The ACTH release is inhibited by **glucocorticoid negative feedback.** Excess ACTH from **pituitary tumours** causes excess glucocorticoid secretion **Cushing's disease;** deficiency of ACTH causes glucocorticoid deficiency.

The **MSH** is also cleaved from POMC and is released by corticotrophs. The MSH stimulates pigmentation of skin via actions on melanocytes of the epidermis to produce more melanin.

β-Lipotrophin is inactive until rapidly converted to **endorphins**. These are **neurotransmitters** which, because they have opiate-like effects, help control pain.

B. Gonadotrophs: secrete the gonadotrophins [follicle stimulating hormone (**FSH**) and luteinizing hormone (**LH**)], which act on the gonads. Gonadotrophins are glycoprotein hormones made up of an **α** and a **β** subunit; the α subunit is common with that in TSH, the β subunits are specific to LH and FSH. The β subunit is important for **receptor recognition** and therefore in **specific biological activity**. The LH and FSH control growth and development of **germ cells** of gonads, also control the synthesis and secretion of **sex hormones** (testosterone, oestrogen and progesterone) of gonads. The LH and FSH release is stimulated by gonadotrophin releasing hormone (**GnRH**) during reproductive life. The LH and FSH release is inhibited by sex steroid by **negative feedback**. Deficiencies of LH and FSH causes infertility in adult life and lack of sexual maturation in children. Excess LH and FSH secretion cause precocious puberty.

C. Thyrotrophs: secrete TSH (thyrotrophin), which acts on the thyroid gland. The TSH is glycoprotein hormone made of α and β subunits; the β subunit is specific to TSH, the α subunit is shared with LH and FSH. The TSH acts in the **thyroid**: it stimulates **thyroid hormones (T_3 and T_4)** production; increases **iodine uptake** by the thyroid (required for thyroid hormone production) and stimulates **thyroid growth**. The TSH release is stimulated by thyrotrophin releasing hormone (**TRH**) from the hypothalamus. Secretion of TRH is stimulated by **stress** via the CNS. The TSH is released in pulses with a **diurnal rhythm**. The TSH release is inhibited by T_3 & T_4 **negative feedback**.

3. Chromophobes, once thought to be inactive, do contain secretory granules. Chromophobe adenomas often secrete hormones, particularly prolactin.

Posterior pituitary hormones

Two **structurally similar** peptide hormones, antidiuretic hormone (**ADH**) also called vasopressin or arginine vasopressin (**AVP**) and **oxytocin**, are synthesized in the

hypothalamus and transported to pituitary by specific carrier proteins **neurophysins**. The hormones are **stored** in the posterior pituitary gland and are released independently of each other into the bloodstream under hypothalamic control.

1. Antidiuretic hormone (arginine vasopressin) is a peptide of nine amino acids. It enhances water reabsorption from the collecting ducts in the kidney. The increase plasma osmolality stimulate **hypothalamic osmoreceptors** for secretion of ADH. The increase plasma ADH enhances water reabsorption from the collecting ducts in the kidney to normalized the osmolality of plasma. The defect in ADH lead to **diabetes insipidus** (**hypothalamic** or cranial and **renal** or nephrogenic diabetes insipidus) due, respectively to lack of ADH production and action.

2. Oxytocin: It controls the **ejection of milk** from the lactating breast and may possess a role in **initiating uterine contractions**, although normal labour can proceed in its absence. It may be used therapeutically to induce **labour**. The synthetic oxytocin generic names are (Pitocin®, Syntocinon®).

Control of pituitary hormones secretion

1. **Extra hypothalamic neural stimuli** modify, and at times override, other control mechanisms. Physical or emotional **stress** and **mental illness** may give similar findings to, and even precipitate, endocrine disease.

2. **Feedback control** is mediated by the concentrations of circulating target cell hormones; a rising concentration usually suppresses trophic hormone secretion. This negative feedback may directly suppresses hypothalamic hormone secretion or may modify its effect on pituitary cells (**long feedback loop**). The secretion of hypothalamic hormones may also be suppressed by rising concentrations of pituitary hormone in a **short feedback loop**.

3. **Inherent rhythms:** hypothalamic, and consequently pituitary, hormones are released intermittently, either in pulses or in a regular circadian rhythm.

4. **Drugs** may also stimulate or block the action of neurotransmitters, such as certain neuroleptic drugs, such as chlorpromazine and haloperidol, interfere with the action of dopamine. This results in reduced GH secretion (reduced effect of releasing factor) and increased prolactin secretion (reduced inhibition). Bromocriptine, which has a dopamine-like action, and levodopa, which is converted to dopamine, decrease prolactin secretion.

Hypopituitarism

Hypopituitarism is a syndrome of **deficiency** of pituitary hormone production that may result from disorders of the hypothalamus, pituitary or surrounding structures. Clinical features of deficiency are usually absent until about 70 per cent of the gland has been destroyed, unless there is associated hyperprolactinaemia, when amenorrhoea and infertility may be early symptoms. **Panhypopituitarism** alludes to the involvement of **all** pituitary hormones; alternatively, only **one or more** may be involved, as in **partial hypopituitarism**. Although isolated hormone deficiency, particularly of GH, may occur, several hormones are usually involved. **The causes of hypopituitarism** include tumours, infections (tuberculosis, meningitis and syphilis), infiltrations, head injury and etc.

Consequences of pituitary hormone deficiencies

Progressive pituitary damage usually presents with evidence of deficiencies of **gonadotrophins** and **GH**. Plasma ACTH and/or TSH concentrations may remain normal, or become deficient months or even years later. The clinical and biochemical consequences of the target-gland failure include the following:

1. **Growth retardation in children**: This may be due to **deficiency of GH**.
2. **Secondary hypogonadism**: This is due to **gonadotrophin deficiency**, presenting as amenorrhoea, infertility and atrophy of secondary sexual characteristics with loss of axillary and pubic hair and impotence or loss of libido. Puberty is delayed in children.

3. **Secondary adrenocortical hypofunction (ACTH deficiency)**: Cortisol is necessary for the maintenance of normal blood pressure. Hypotension may be associated with ACTH deficiency. Cortisol and/or GH deficiency may cause increased insulin sensitivity with fasting hypoglycaemia.

4. **Secondary hypothyroidism (TSH deficiency)**: This may sometimes be clinically indistinguishable from primary hypothyroidism.

5. **Prolactin deficiency**: Associated with failure to lactate, this may occur after post-partum pituitary infarction (Sheehan's syndrome). However, in hypopituitarism due to a tumour, plasma prolactin concentrations are often raised and may cause galactorrhoea.

Investigation of suspected hypopituitarism

Deficiency of pituitary hormones causes hypofunction of the target endocrine glands. Investigation aims to confirm such deficiency, to exclude disease of the target gland and then to test pituitary hormone secretion after maximal stimulation of the gland.

Measurement should be made of the plasma concentrations of:

- LH, FSH and oestradiol (female) or testosterone (male)
- Total or free T_4 and TSH
- Prolactin
- Cortisol at 09.00 h, to assess the risk of adrenocortical insufficiency

If the plasma concentration of the target gland hormone is low and the concentration of trophic hormone is raised, the affected target gland should be investigated. Conversely, if the plasma concentrations of **both** the target gland and trophic hormones are low or low-normal, consider a pituitary stimulation test.

Investigation of the pituitary region using radiological techniques such as CT or MRI scanning may help elucidate a cause of the hypopituitarism. Sometime the combined pituitary stimulation tests (insulin or glucagon plus TRH and GnRH given as one test), is used to evaluate pituitary hormones.

Insulin stimulation test

This test is potentially dangerous and must be done under direct medical supervision.

Indications of the insulin stimulation test may include:

1. Assessment of GH in growth deficiency.
2. Assessment of ACTH/cortisol reserve.
3. Differentiation of Cushing's syndrome from pseudo-Cushing's syndrome, for example depression or alcohol excess.

After an overnight fast, insert an indwelling intravenous cannula. After at least 30 minutes, take basal samples at time 0 minute for cortisol, GH and glucose. Inject soluble insulin in a dose sufficient to lower plasma glucose concentrations to less than 2.5 mmol/L and evoke symptomatic hypoglycaemia. Take blood samples at 30, 45, 60, 90 and 120 minutes after the injections for cortisol, GH and glucose assays.

If hypoglycaemia has been adequate, plasma cortisol concentrations should rise by more than 200 nmol/L and exceed 580 nmol/L, and an adequate GH response occurs with an absolute response of greater than 20 mU/L (7 µg/L).

Glucagon stimulation test

This test is useful if the insulin hypoglycaemic test is contraindicated. However, it is essential that the test is carried out in a specialist unit by experienced staff. The basic principle is that glucagon stimulates GH and ACTH release probably via a hypothalamic route.

Patients should fast overnight. Insert an indwelling intravenous cannula. For adults, 1 mg of glucagon is injected subcutaneously at 09.00 hour. Blood samples are taken at 0, 90, 120, 150, 180, 210 and 240 min for cortisol and GH.

Plasma cortisol should normally rise by at least 200 nmol/L to more than 580 nmol/L, and an adequate GH response occurs with an absolute response of greater than 20 mU/L (7 µg/L).