Pituitary Gland or Hypophysis

The pituitary gland is located in the Sella turcica and attaches to the hypothalamus via a stalk like structure (infundibulum).

In humans, the pituitary gland has two anatomical portions that are functionally separate:

- **posterior lobe (posterior pituitary gland or PPG)**
  - contains mostly nerves; the cell bodies of the nerves are located in the hypothalamus
    - supraoptic nuclei of HT produce ADH
    - paraventricular nuclei of HT produce oxytocin
  - both hormones are directed towards the ends of the nerves into the posterior lobe where they are stored and released when the neurons fire (hypothalamic-hypophyseal tract)
  - posterior lobe with H-H tract in infundibulum = neurohypophysis
  - an inferior hypophyseal artery and vein supply and drain the posterior lobe

- **anterior lobe or adenohypophysis**
  - contains mostly glandular tissue; no neural connection with the HT
  - 6 distinct hormones are produced in the adenohypophysis and are induced/inhibited to be released by specific releasing/inhibiting hormones produced in the HT
    - connection between HT and adenohypophysis is by means of a capillary network
      - a superior hypophyseal artery enters at the base of the HT
      - this flows into a primary capillary plexus at the base of HT and around the infundibulum
      - blood passes downwards via a hypophyseal portal vein
      - flows into a secondary capillary plexus which forms around the anterior pituitary gland
      - blood leaves the adenohypophysis by means of an inferior hypophyseal venule

All hypothalamic hormones are amino-acid based hormones!
PPG Hormones

1. AntiDiuretic Hormone or ADH

- Physiological effect is to decrease the urine output and urine production
- ADH causes the kidneys to remove water from the urine that is being formed in the nephrons of the kidneys; this water is redirected into the blood
- In absence of ADH, urine output increases about 10 fold from 1 - 2 liters a day to 22 liters a day
- Since ADH promotes water return to the blood, it regulates blood volume and the state of dehydration of our body
- ADH production is of homeostatic importance and regulation is by means of negative feedback
- Increased state of Dehydration promotes increased production of ADH
  - Hypothalamus nuclei have osmo-receptors that detect changes in blood osmolarity
  - Increased state of Dehydration means less fluid and results in increased "particles" per volume unit.
  - This increased blood osmolarity is picked up by the specific cells in hypothalamus and results in the release of ADH from the PPG into the blood
  - ADH travels via the blood stream to the target organ (being the kidney), where it promotes water retention
- Blood volume loss (bleeding, diarrhea, sweating..) results in ADH production increase (and thus less urine production)
- Blood volume loss, besides resulting in dehydration, also results in blood pressure drops
  - ADH counteracts this as well by causing arterioles to constrict which raises blood pressure (another homeostatic effect)
- Alcohol inhibits ADH secretion. So, what happens when you drink too much alcohol?

Clinical Applications of ADH

Diabetes insipidus
- results from hyosecretion of ADH (damage to PPG or nonfunctional ADH receptors)
- Symptoms: excretion of large amounts of urine, dehydration, thirst
2. **Oxytocin**

- Major function in the female, less important in the male
- Enhances smooth muscle contraction in the uterus during labor
  - stretching of cervix during delivery stimulates stretch receptors of the uterus
  - receptors signal HT to release more oxytocin resulting in a positive feedback
- Enhances milk ejaculation by mammary glands
- Apparently also seems to play a role in sexual arousal (sometimes called the 'cuddle' hormone)
- The following provide some interesting links to read about for you curious ones
  - The Hormone of Love ([http://www.oxytocin.org/oxytoc/index.html](http://www.oxytocin.org/oxytoc/index.html))
  - The Cuddle Hormone ([http://oxytocin.org/cuddle-hormone/index.html](http://oxytocin.org/cuddle-hormone/index.html))

This figure below shows the minor differences between the two hormones. They are both nano-peptides but differ in only 2 of the nine amino acids

**Oxytocin**

Cys - Tyr - **Ile** - Gln - Asn - Cys - Pro - Leu - Gly - NH₂

\[ \text{SS} \]

**ADH (vasopressin)**

Cys - Tyr - **Phe** - Gln - Asn - Cys - Pro - **Arg** - Gly - NH₂

\[ \text{SS} \]
Anterior Pituitary Gland or AdenoHypophysis

- Contains mostly glandular tissue; no neural connection with the HT
- 6 distinct hormones are produced in the adenohypophysis and are induced/inhibited to be released by specific releasing/inhibiting hormones produced in the HT
- All hormones are amino-acid based hormones

- Glandular part of the adenohypophysis makes up 75% of total Pituitary Gland
- Secretes hormones that regulate a wide range of bodily activities
- There are eight hormones produced in the APG and six hormones are well characterized
  - **Growth Hormone (GH) (also called somatotropin)**
  - **Thyroid stimulating hormone (TSH) (thyrotropin)**
  - **Adrenocorticotropic hormone (ACTH) (corticotropin)**
  - **Follicle stimulating hormone (FSH)**
  - **Luteinizing hormone (LH)**
  - **Prolactin (PrL)**

- Five of the 6 hormones mentioned above (TSH, ACTH, FSH, LH) are **tropic hormones**; this means that they regulate the secretory activity of other endocrine glands
  - TSH stimulates the thyroid gland to make thyroid hormones
  - ACTH stimulates the adrenal glands
  - FSH and LH (the gonadotropic hormones) stimulate the gonades
  - GH induces the liver to secrete a growth promoting peptide hormones known as insulin like growth factor I (such as IGF-I)

- Only ACTH and TSH are pure tropic hormones. The other three also regulate growth and development and metabolism

- Four distinct cell types within the APG produce tropic hormones
  - **Thyrotropes**: endocrine cells that produce TSH
  - **Corticotropes**: endocrine cells that produce ACTH
  - **Gonadotropes**: endocrine cells that produce FSH and LH
  - **Somatotropes**: produce GH

- Only PL, exert its effect on non endocrine target cells (breast cells) and is made in another cell type (Lactotropes)
- All these hormones except GH (of which the mechanisms is not known) work via the cAMP mechanism

**Hypothalamus Hormones (hypophysiotropic hormones)**

- Release of APG hormones is stimulated (or inhibited) by releasing (inhibiting) hormones from the HT: these are also called the **hypo-physiotropic** hormones
- There are 5 releasing and 2 inhibiting hormones that originate in the HT. These regulatory hormones from the HT reach the adenohypophysis by means of the blood vessels and the capillary plexi mentioned earlier
Major hypophysiotropic hormones

- Corticotropin releasing hormone (CRH) : stimulates secretion of ACTH
- Thyrotropin Releasing Hormone (TRH) : stimulates secretion of TSH
- Growth hormone Releasing Hormone (GHRH) : stimulates secretion of GH
- Growth hormone Inhibiting Hormone (GHIH or somatostatin) : inhibits the secretion of GH
- Gonadotropin Releasing Hormone (GnRH) : stimulates secretion of LH and FSH
- Prolactin Releasing Hormone (PRH)
- Prolactin Inhibiting hormone (PIH)

**An overview of some important APG hormones**

1. **Prolactin (PRL)**
   - Is important in production of milk in mammary glands
   - Target cells are the milk producing alveolar cells of the breasts
   - Suckling by the baby results in a 10-fold rise in plasma PRL in the mother
   - Nursing and suckling thus results in parallel increases in blood plasma levels for PRL and Oxytocin
   - Control of PRL release is under the influence of oxytocin, PIH and PRL

The figure below shows for example the events that happen right before and after delivery. The drop in estrogen and progesterone after delivery results in an upswing in oxytocin, which in turns has an effect on Prolactin. After that each suckling and nursing period results in periodic up and down swing in oxytocin, paralleled by prolactin.

The main event is that normally PIH is active in a ‘normal’ female, preventing prolactin from doing its job. However, the increase in oxytocin following delivery, stops PIH release and promotes PRH. The latter will stimulate the APG to release PrL and this will stimulate the alveolar cells of the breasts to produce milk.

(see scheme in PPT presentation)
2. Thyroid Gland and Regulation

1. The Thyroid Gland (Fig. 16-8)

- located below the larynx with right and left lobes on either side of trachea
- connected by tissue mass called isthmus in front of trachea
- largest single endocrine gland in body with many blood vessels

- the gland is composed of spherical thyroid follicles
- the walls of these follicles are made from simple cuboidal epithelium cell = follicular cells
- follicular cells produce thyroglobulin and secrete it into the inside of the spheres, the lumen of the follicle, which is filled with colloid.
- thyroglobulin is a precursor of thyroid hormones and complexes with Iodine
- in-between the follicles are other cells called parafollicular cells; they produce calcitonin

2. Formation, Storage, Release of Thyroid Hormones (if 16-9)

Formation requires both tyrosine and iodine. Tyrosine is usually abundant but iodine could be rate limiting.

Step 1. Iodide trapping

- thyroid follicles trap iodide (I⁻) by actively transporting it from blood to the cytoplasm of follicular cell
- Iodide concentration is here 30-40 x higher than blood (most of body iodide is in thyroid gland)

Step 2. Synthesis of Thyroglobulin

- TGB is formed on rough ER
- it is a high molecular protein containing ~5000 AA of which 70 to 100 are tyrosine
- in Golgi apparatus, TGB is modified, sugar residues are added, molecule packed in vesicles and secreted into the lumen of the follicle (thus into the colloid)

Step 3. Oxidation of Iodide to Iodine

- Negative charged I⁻ cannot bind to tyrosine
- Peroxidase enzyme oxidizes I⁻  (2 I⁻       I₂)

Step 4a. Iodination of Tyrosine

- in the lumen, iodine attaches to the tyrosine AA's on TGB molecule catalyzed by specific enzymes
- binding of one atom of iodine yields mono-iodotyrosine (MIT)
- binding of two atoms of iodine yields di-iodotyrosine T₂ (DIT)

Step 4b. Coupling of MIT and DIT

- Some of the iodinated tyrosines couple via unknown or disputed mechanisms
- Two DIT's join to form one tetralodothyronine or Thyroxine (T₄) molecule
- One MIT joins with one DIT to form a trilodothyronine or T₃ molecule
- The formed hormones remain attached within the TGB molecule

Step 5. Colloid endocytosis

- Droplets of colloid, containing thyroglobulin, re-enter the follicular cells by pinocytosis and merge with lysosomes
- The lysosomes break down the thyroglobulin into its individual amino acids, liberating the T₄ and T₃ hormones

Step 6. Hormones diffuse into circulation
3. **The Thyroid hormones**

- the 2 important thyroid hormones are thus T4 (Thyroxine) and T3 (Triiodothyronine)
- Thyroxine is the most common released form but T3 is the most potent form

Thyroid hormones have an effect on all cell types except the thyroid gland itself, adult testes, uterus, spleen, brain.

**Actions of these hormones are**

- To increase metabolic rate
  - stimulate protein synthesis, increase lipolysis (fat break down), increase glucose use
  - results in more ATP use by cells, more O2 usage, heat release
  - helps in thermoregulation (= calorigenic effect of thyroid hormones)
  - mammals without thyroid gland do not survive in freezing temperatures
- Effect the Cardiovascular system
  - Results in up-regulation of beta receptors (permissive action of T4/T3)
  - thus enhances action of catecholamines (NE, EpiN)
  - hyperthyroidism thus results is increased HR, BP, forceful heartbeat, nervousness
- Accelerate body growth (because T3 and T4 induce the release of the growth hormone) and growth of nerve tissues

4. **Transport and Regulation**

- Since T4 and T3 are lipid soluble they don't dissolve well in blood
- They bind to a transport protein called Thyroxine-binding protein
- Although more T4 is present than T3, the potency of T3 is much higher

Production and release of Thyroid hormones is regulated by two means

- levels of iodine in the gland
- negative feedback involving HT and APG

**Thyroid Stimulating Hormone (TSH) and Thyrotropin Releasing hormone (TRH)**

- TSH is also called Thyrotropin and is released from thyrotrope cells in APG
- Functions to stimulate the normal development and secretory activity of the thyroid gland

- Secretion of TSH is regulated by
  - Thyrotropin-Releasing hormone (TRH) : produced by the Hypothalamus
  - Low blood levels of Thyroid hormones stimulate release of both TRH and TSH
5. Clinical Applications

**Hyposecretion** of TH during fetal life or infancy

- results in [cretinism](#)
- child exhibits dwarfism (skeleton fails to grow)
- mentally retarded (fewer neurons, defective myelination)
- delayed sexual development
- can be prevented by oral thyroid replacement therapy

**Hypothyroidism** in adults results in the syndrome of [Myxedema](#)

- edema with swollen facial tissue
- diminished Basal Metabolic rate (BMR) (sensitive to cold)
- slow Heart Rate, muscular weakness
- no mental retardation but less alert (more common in females)
- may result from thyroid gland defect, inadequate TRH, TSH release, or due to a thyroid removal

If Myxedema results from an absence of iodine

- follicle cells produce colloid but cannot make functional hormones
- APG keeps making TSH to stimulate thyroid gland to make more hormone
- This constant stimulation cause the thyroid gland to enlarges (goiter)
Hachimodo’s disease is a form of Hypothyroidism; it is an autoimmune disease in which antibodies destroy the complete Thyroid gland. It manifests itself between 30-40 years old and is more common in women than men.

Hypersecretion of Thyroid hormones

- increases oxygen use by tissues
- elevated heat production (wasting of energy, resulting in thinning)
- increased food intake
- sweating, nervousness

Most common form of Hyperthyroidism is Graves Disease. It is also an autoimmune disorder where antibodies mimic the action of TSH without the regulatory feedback action. The antibodies stimulate the TSH receptor on the thyroid gland continuously. Since there is no feedback mechanism to turn the antibodies off (normally TSH is turned off by T3 and T4), the thyroid gland continues to secrete and grow (also results in a goiter).