The Pituitary Gland

- Also called hypophysis
- Lies within sella turcica
- Hangs inferior to hypothalamus and between optic chiasma and mamillary bodies
- Connected to the hypothalamus by infundibulum
The hypothalamus and the posterior pituitary gland are derived from embryonic brain tissues.

The posterior pituitary gland is a down-growth of hypothalamic neural tissue.

The anterior pituitary gland arises from tissue in the roof of the mouth (oral mucosa).
Pituitary Gland or Hypophysis

- Pituitary gland – two-lobed organ that secretes nine major hormones

- Neuro-hypophysis: posterior lobe and contains un-myelinated axons from the hypothalamus
  - Receives, stores, and releases hormones from the hypothalamus

- Adeno-hypophysis: anterior lobe, made up of glandular tissue
  - Synthesizes and secretes a number of hormones
  - There is no direct neural connection between APG and HT.

Anterior lobe (anterior pituitary gland or APG)

- Also called the adeno-hypophysis

- Has 3 distinct regions
  - Pars distalis
  - Pars tuberalis
  - Pars intermedia

- Contains mostly glandular tissue

- There is no neural connection with the HT
Anterior pituitary gland

- 6 distinct hormones are produced in the adenohypophysis

- The secretion of these hormones is controlled by specific releasing and inhibiting hormones produced in the HT = **tropic hormones**

- This requires an intricate network of blood vessels and capillaries to direct the hypothalamic hormones to APG cells

- There are thus two capillary beds connected via portal vessels!

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Hypophyseal Portal System

These portal vessels, which deliver hypothalamic hormones to the pituitary, are unusual in that they connect two capillary beds.

This system is called the hypophyseal portal system and is fed by the **superior hypophyseal artery**.
Posterior pituitary gland or PPG

- Contains mostly nerves
- The cell bodies of the nerves are located in the hypothalamus
- Axons extend into the PPG
- Hormones are directed to the axon terminals and secreted by nerve stimuli. Thus, other names for the PPG are
  - Pars Nervosa
  - Neuro-hypophysis
- An inferior hypophyseal artery and vein supply and drain the posterior lobe

Hormones of the posterior pituitary gland

Only two hormones are released by the PPG

- Oxytocin
- Anti-diuretic Hormone (ADH)

The hormones are produced by neuronal cell bodies, located in the Hypothalamus and directed via neurons of the hypothalamic-hypophyseal tract to the capillary bed of the PPG.

(why is it called a tract?)
Those neuronal cell bodies in the HT are:

- **Supraoptic nuclei**
  - these produce ADH

- **Paraventricular nuclei**
  - these produce Oxytocin

**AntiDiuretic Hormone or ADH (Vasopressin)**

- 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 and re-direct it into the bloodstream.
- Since ADH promotes water return to the blood, it regulates **blood volume** and the **state of dehydration** of our body
- ADH production is thus of homeostatic importance and regulation is by means of negative feedback
Hypothalamic 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 = osmolarity.

This increased blood osmolarity is sensed by the osmo-receptors 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 (the kidney), where it promotes water retention.

less urine production
Feedback Regulation of Kidneys

Release of ADH is directly correlated to the degree of dehydration (blood osmolarity)

- normal blood osmolarity = 285 mOsm
- above that = indicates dehydration

Factors that release ADH

- Dehydration
  - excessive sweating
  - not enough water intake
  - diarrhea
- Low blood pressure
  - blood loss

Factors that inhibit ADH release

- Osmolarity below 280 Osm
  - over-hydration
- Alcohol
  - inhibits ADH secretion
Diabetes insipidus

- Results from hypo-secretion of ADH or hypo-responsiveness
  - damage to PPG or nonfunctional ADH receptors
- Symptoms: excretion of large amounts of urine, dehydration, thirst
- Normal urine volume ~ 1 to 1.5 L / day
- With no ADH present: urine volume ~ 24 L / day

Clinical Correlation

Oxytocin

Major function in the female, less important in the male

- Enhances smooth muscle contraction in the uterus during labor
- It is one of the few positive feedback mechanisms
  - stretching of cervix during delivery stimulates stretch receptors in the uterine wall
  - receptors signal HT to release more oxytocin
  - results in more contractions and movement of baby through the birth canal, additional stretching
- Additional “help” is provided by release of local prostaglandins.
Oxytocin

- Fetus drops lower in uterus
- Cervical stretch
- Oxytocin from posterior pituitary
  - Uterine contractions
  - Prostaglandins from uterine wall

Oxytocin Also Enhances milk ejaculation by mammary glands after childbirth

ProLactin, an APG hormone, is responsible for milk production and secretion. (see later)
Research links oxytocin with socio-sexual behaviors

The Hormone Involved In Reproduction May Have a Role In The Maintenance Of Relationships!

Oxytocin makes you wanna cuddle

Oxytocin makes you want to cuddle, touch, be close and affectionate towards another human being.

ADH and Oxytocin are Peptide Hormones

**Oxytocin**

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

S-S

**ADH (vasopressin)**

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

S-S

Knowing this, how do these hormones work?
Hormones of the Anterior Pituitary Gland

- Adeno-hypophysis contains mostly glandular tissue (75% of APG is glandular tissue).
- There is no neural connection with the HT.
- 6 distinct hormones are produced in the adenohypophysis.
- All hormones are amino-acid based hormones.

Hormones of the APG are

- Growth Hormone (GH) (also called somatotropin)
- Thyroid stimulating hormone (TSH) (thyrotropin)
- Adrenocorticotropic hormone (ACTH) (corticotropin)
- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin (PRL)
**Hormones of the Anterior Pituitary Gland**

**Hormone from the pars intermedia**

- In addition, Melanocyte Stimulating Hormone (MSH) has been isolated from the pituitary pars intermedia region.
- It functions to stimulate melanin synthesis in the epidermis
- It is not active in normal adults

---

**Hormones of the Anterior Pituitary Gland**

All except Prolactin are **tropic hormones**

- 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 hormone known as insulin like growth factor I (IGF-I and II)

Only ACTH and TSH are pure tropic hormones. The other three also regulate growth, development and metabolism.
Hormones of the Anterior Pituitary Gland

Five 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 PRL, exert its effect on non endocrine target cells (breast cells); it is made in another cell type (**Lactotropes**) 

Most of these hormones activate receptors linked to the cAMP mechanism
Hypothalamus Hormones

- Also called the hypophysiotropic hormones
- They stimulate or inhibit the Release of APG hormones
- They are thus referred to as Releasing Hormones or Inhibiting Hormones
- There are 5 releasing and 2 inhibiting hormones that originate in the HT.
- These regulatory hormones from the HT reach the APG by means of the blood vessels and the capillary plexi mentioned earlier.

Hypothalamus Hormones

The hypothalamic hormones are produced by specific HT neurons and released at axon terminals.

These axon terminals end in upper part of infundibulum

Upper capillary bed carries hormones to the other capillary bed in the APG via portal vessels as discussed earlier.
Hypothalamus Hormones

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

All are small peptide hormones

The releasing and inhibiting hormones from the hypothalamus regulate secretion by negative feedback mechanisms.

Short- and long-loop feedback relationships between hypothalamic, pituitary, and third-gland hormones are shown in the diagram.

It demonstrates the importance of homeostatic regulation of hormone synthesis and secretion.
Figure 18-8a Feedback Control of Endocrine Secretion

<table>
<thead>
<tr>
<th>Releasing hormone (RH)</th>
<th>Hormone 1 (from pituitary)</th>
<th>Endocrine target organ</th>
<th>Hormone 2 (from target organ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH</td>
<td>TSH</td>
<td>Thyroid gland</td>
<td>Thyroid hormones</td>
</tr>
<tr>
<td>CRH</td>
<td>ACTH</td>
<td>Adrenal cortex</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>GnRH</td>
<td>FSH</td>
<td>Ovaries</td>
<td>Inhibin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estrogens</td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>Ovaries</td>
<td>Progesterone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testes</td>
<td>Androgens</td>
</tr>
</tbody>
</table>

Negative feedback

Hypothalamus

Pituitary gland

Anterior lobe

Hormone 1

Endocrine organ

Hormone 2

Target cells

KEY

→ Stimulation

∥ Inhibition

Function and Action of 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
- Oxytocin is important for milk ejaculation (smooth muscle control milk ducts), while prolactin is important for milk production by the alveolar cells.
PROLACTIN (PRL)

- Suckling, child’s cry results in stimulation of oxytocin release and inhibition of Prolactin Inhibiting and Hormone

- Nursing and suckling thus results in parallel increases in blood plasma levels for PRL and Oxytocin

Effect of the PTH2R antagonist (blocks the prolactin receptor) on the suckling-induced prolactin release.
**Thyroid Gland and Thyroid Hormones**

The thyroid gland straddles the windpipe, just below the voicebox in the neck.

The thyroid consists of two lobes connected by narrow isthmus.

The thyroid is made from many thyroid follicles, each made from follicular cells. They work interactively to form and package the thyroid hormones.
**Thyroid Gland and Hormones**

**Thyroid follicles**
- Are hollow spheres lined by cuboidal epithelium
- The cuboidal cells (follicular cells) surround **follicle cavity** that contains a viscous **colloid**
- Surrounded by network of capillaries that
  - Deliver nutrients and regulatory hormone
  - Accept secretory products and metabolic wastes

In-between the thyroid follicles are other cells called the **para-follicular cells** (also called the C-cells)
They produce the **calcitonin** hormone.

---

**Thyroid Gland and Hormones**

<table>
<thead>
<tr>
<th>Follicular cells</th>
<th>Para follicular cells (called C-cells)</th>
</tr>
</thead>
</table>

![Image of thyroid follicles](image_url)
Thyroid Gland and Hormones

Histological details of the thyroid gland showing thyroid follicles and both of the cell types in the follicular epithelium ATLAS: Plate 18c

Thyroid Hormones Synthesis

Thyroid hormones are synthesized in the colloid. Ingredients for synthesis are collected from the blood stream into the follicular cells.

**Tyrosine**
- synthesized in sufficient amounts by the body
- taken up in the Follicular cells
- assembled into a larger protein molecule called *Thyroglobulin (via ER and Golgi)*

**Iodide**
- we need about 1mg /week
- taken up in the Follicular cells as Iodide by powerful pumps (called *iodide traps*)
- concentration within follicular cells is 30 x higher than blood
- within the follicular cells, it becomes oxidized to iodine (I\(_2\))
Thyroid Hormone Synthesis

- Thyroglobulin and iodine are moved into the colloid
- Thyroglobulin is a very large protein of about 335,000 MW and contains 70 tyrosine a.a.
- Iodine binds to the tyrosines of the Thyroglobulin in a specific manner = iodination

\[
\begin{align*}
I_2 + \text{Tyrosine} & \rightarrow \text{Mono-iodo-tyrosine (MIT)} \\
2I_2 + \text{Tyrosine} & \rightarrow \text{Di-iodo-tyrosine (DIT)} \\
\text{MIT} + \text{DIT} & \rightarrow \text{Tri-iodo-tyrosine (T}_3) \\
\text{MIT} + \text{DIT} & \rightarrow \text{Tetra-iodo-tyrosine or Thyroxine (T}_4)
\end{align*}
\]
• The thyroglobulin enters back into the follicular cells via endocytosis

• The vesicles fuse with lysosomes and the thyroglobulin is broken down, releasing $T_3$ and $T_4$.

$T_3$ and $T_4$ are the active Thyroid hormones

• Since $T_3$ and $T_4$ are hydrophobic, they diffuse right through the cell membranes into the bloodstream

• In plasma, they bind to Tyroxine-binding protein produced by the liver, and which functions as a carrier protein.

Thyroid Hormones

More $T_4$ is secreted than $T_3$ but $T_3$ is more potent

$T_4$ is converted to $T_3$ after passage through liver and kidney

Enough iodinated Thyroglobulin is stored to last for months

Thyroid problems may thus go unnoticed for months
Thyroid Hormone Action

- Thyroid Hormones
  - Enter target cells by transport systems
  - Affect most cells in body
  - Bind to receptors in:
    1. Cytoplasm
    2. Surfaces of mitochondria
    3. Nucleus
  - In children, essential to normal development of:
    - Skeletal, muscular, and nervous systems
### Thyroid Hormone Action

**Increases metabolic rate**
- stimulate protein synthesis
- increase lipolysis (fat break down)
- increase glucose use
- increases overall metabolic rate
  - increased $O_2$ uptake and energy expenditure
  - increased heat production = calorigenic effect

**Effect on Cardiovascular system**
- increased metabolism and $O_2$ usage causes vasodilation and increased blood flow
- increases heart responsiveness to catecholamines
  - due to upregulation of beta receptors
  - increased heart rate, contractile force

### Thyroid Hormone Action

**Effect on growth and nervous system**

Thyroid hormones are important for normal growth
- thyroid hormones stimulate growth hormone release

Thyroid hormones are important for normal development of nervous system (myelination etc.)

**Effect on muscular system**

Makes muscle contract with vigor
- too much results in muscle tremors
- not enough results in sluggish muscles
Control of Thyroid Hormones

TSH or Thyrotropin (from APG)
- Works on Thyroid gland
- Stimulates growth of follicles
- Stimulates all aspects of hormone formation

Thyrotropin Releasing Hormone (from HT)
- Works on Thyrotrope cells of APG
- Induces the release of TSH

Negative feedback by Thyroid Hormones
- Too much T3, T4 in blood inhibits TSH release and a minor effect on inhibition of TRH
- Not enough takes away the inhibition and TSH starts working again

Control of Thyroid Hormones

- Thus TRH ‘turns on’ the output of Thyroid Hormone via TSH, while the output itself, the Thyroid Hormones, ‘turn off’ the output.

- The Hypothalamic-pituitary-Thyroid axis represents a typical negative feedback system.

- Thyroid hormone output is as such neatly regulated and wide swings in hormone level rarely occur

- A typical trigger for additional hormone output is
  - exposure to cold
  - pregnancy
  - hypoglycemia
Abnormalities in Thyroid Hormones

**Hyposecretion** of TH during fetal life or infancy
- results in [cretinism](#)
- child exhibits dwarfism (skeleton fails to grow)
- mentally retarded (fewer neurons, defective myelination)
- retarded 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 HeartRate, 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

Abnormalities in Thyroid Hormones

- Myxedema can 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)

**Hashimoto’s disease**
- auto-immune disease where antibodies attack and destroy the thyroid gland
- Occurs around 30 - 40 year olds and more 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 is an autoimmune disorder where antibodies mimics the action of TSH without the regulating feedback action

Results in a continuous stimulation of thyroid gland to secrete and grow (goiter) = Graves Disease

Abnormalities in Thyroid Hormones

Goiter at advanced stage

Exophthalmos (Graves’ disease)