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 Anterior Pituitary Gland

<table>
<thead>
<tr>
<th>Hormones of the APG are</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Growth Hormone (GH) (also called somatotropin)</td>
</tr>
<tr>
<td>• Thyroid stimulating hormone (TSH) (thyrotropin)</td>
</tr>
<tr>
<td>• Adrenocorticotropic hormone (ACTH) (corticotropin)</td>
</tr>
<tr>
<td>• Follicle stimulating hormone (FSH)</td>
</tr>
<tr>
<td>• Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>• Prolactin (PRL)</td>
</tr>
</tbody>
</table>

### Hormones from the pars intermedia

<table>
<thead>
<tr>
<th>Hormone from the pars intermedia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In addition, Melanocyte Stimulating Hormone (MSH) has been isolated from the pituitary pars intermedia region.</td>
</tr>
<tr>
<td>• It functions to stimulate melanin synthesis in the epidermis</td>
</tr>
<tr>
<td>• It is not active in normal adults</td>
</tr>
</tbody>
</table>
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 gonads
- 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.
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.
Dopamine serves as the major prolactin-inhibiting factor or brake on prolactin secretion.

Dopamine is secreted into portal blood by hypothalamic neurons, binds to receptors on lactotrophs, and inhibits both the synthesis and secretion of prolactin.

Agents and drugs that interfere with dopamine secretion or receptor binding lead to enhanced secretion of prolactin.

Prolactin secretion is positively regulated by several hormones.

Estrogens provide a well-studied positive control over Prolactin synthesis and secretion.

The increasing blood concentrations of estrogen during late pregnancy appear responsible for the elevated levels of Prolactin that are necessary to prepare the mammary gland for lactation at the end of gestation.
One of the important roles of PRL is thus 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 to 20-fold rise in plasma PRL in the mother

Oxytocin is important for milk ejaculation (via smooth muscle control of 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 Hormone (= Dopamine)

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.

Cservenák M et al. Endocrinology 2010;151:5830-5840

PROLACTIN (PRL)

Pre-childbirth

HT

PIH

PPG

APG

PRL

Breast Alveolar cells

Childbirth

HT

PH

PRH

Oxytocin

PPG

APG

PRL

Breast Alveolar cells
Prolactin has many other functions, some of which are still unclear.

- Prolactin is necessary for normal breast development in females.
- It has also been found that compared to un-mated males, fathers and expectant fathers have increased prolactin concentrations.
- Prolactin levels peak during REM sleep, and in the early morning.
- Hypersecretion of prolactin is more common than hyposecretion; hypersecretion affects other hormones and may result in infertility in females as well as impotence in males.
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 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.
Para follicular cells (called C-cells)

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

\[
I_2 + \text{Tyrosine} \rightarrow \text{Mono-iodo-tyrosine (MIT)}
\]

\[
2I_2 + \text{Tyrosine} \rightarrow \text{Di-iodo-tyrosine (DIT)}
\]

\[
\text{MIT} + \text{DIT} \rightarrow \text{Tri-iodo-tyrosine ($T_3$)}
\]

\[
\text{MIT} + \text{DIT} \rightarrow \text{Tetra-iodo-tyrosine or Thyroxine ($T_4$)}
\]
Thyroid Hormone Synthesis

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 $T_4$.

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.
More T4 is secreted than T3 but T3 is more potent

T4 is converted to T3 after passage through liver and kidney

Thyroid problems may thus go unnoticed for months

Enough iodinated Thyroglobulin is stored to last for months

Thyroid may thus go unnoticed for months

**Figure 16.9**

Thyroid Hormones

- Iodine is actively transported into thyroid follicle cells and oxidized by thyroid peroxidase.
- Thyroglobulin is synthesized in the thyroid follicle cell.
- Lysoosomal enzymes cleave T4 and T3 from thyroglobulin colloid and hormones diffuse from follicle cell into bloodstream.
- Iodinated tyrosines are linked together to form T3 and T4.
- Thyroglobulin is endocytosed and combined with a lysosome.
- Iodine is attached to tyrosines in colloid, forming DIT and MIT.
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

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**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 Thyrotrpoe 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

Abnormalities in Thyroid Hormones

**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)