Endocrinology

Posterior pituitary and Anterior pituitary hormones

**Posterior Pituitary hormones**

1) **ADH** – Antidiuretic hormone – “Vasopressin” – made in the SON
   - Responsible for regulation of blood pressure by its action on the collecting duct of the kidney tubule.

2) **Oxytocin** – made in the PVN
   - At the onset of labor, stimulates the contraction of the uterine smooth muscle in delivery of baby.
   - Milk let-down. Promotes ejection of milk from mammary glands during breast feeding.
   - Suckling of infant sends impulses to mom’s hypothalamus causing oxytocin to be released which stimulates milk let down (unconditioned response). Baby’s cry can cause secretion of oxytocin (conditioned response).
   - Sperm transport. Sexual intercourse stimulates vagina and sends signal to hypothalamus to ↑ oxytocin secretion which causes contraction of uterus to help in sperm transportation.

**Regulation of Posterior pituitary hormones and Hypothalamus**

- The hypothalamus and neurohypophysis form a neuroendocrine system that consists of neurosecretory neurons whose cell bodies lie in 2 well-defined clusters in the hypothalamus (SON and PVN) whose axons pass down through the connecting stalk to terminate on capillaries in posterior pituitary. **Neurohypophysis does not synthesize but stores hormones.**

**Anterior Pituitary Hormones**

- 1) **FSH** – follicle stimulating hormone –
  - Female – maturation of ova
  - Male – sperm formation within seminiferous tubules – spermatogenesis

- 2) **LH** – luteinizing hormone –
  - Female – formation of corpus luteum; produces progesterone
  - Male – testosterone secretion from interstitial cells of Leydig

- 3) **ACTH** – adrenocorticotropic hormone –
  - Maintains adrenal cortex of the adrenal gland in secretory state particularly the zona fasciculata (produces cortisol).

- 4) **TSH** – thyroid stimulating hormone
  - Responsible for growth and maturation of thyroid tissue; keeps in secretory state.

- 5) **Prolactin** – PRL - female – causes secretion of milk into alveoli sacs of the mammary gland, not nipple release

- 6) **HGH** – human growth hormone – STH – somatotrophic hormone –
  - Stimulates body growth in several different tissues.

**Regulation of Adenohypophysis and Hypothalamus**

The hypothalamus is connected to the pituitary by a hypophyseal stalk.

Secretion of the anterior pituitary hormones is controlled by hormones or factors called releasing hormones or inhibitory hormones secreted within the hypothalamus and then conducted down to the adenohypophysis through minute blood vessels called the hypothalamic-hypophyseal portal vessels. These releasing hormones act on glandular cells within the adenohypophysis to control their secretion.

Let’s now look at the types of glandular cells found within the anterior pituitary from which these hormones are released.
Anterior pituitary cell types

Anterior pituitary contains several types of secretory cells, usually one type for each hormone formed in that gland.

1) Somatotropes – 40 – 50% - HGH
2) Mammatropes (Lactotropes) – 10 – 15% - PRL
3) Corticotropes – 15 – 20% - ACTH and MSH
4) Thyrotropes – 3 – 5% - TSH
5) Gonadotropes – 10 – 15% - FSH and LH

Anterior pituitary cell types and actions of each hormone released

Thyroid Biochemistry and Physiology

The thyroid gland has 2 lobes of endocrine tissue joined in the middle by a narrow portion of the gland called the isthmus. Looks similar to a bow tie. The gland is located immediately below the larynx on the ventral surface anterior to the trachea.

If we took a cross section of each lobe, would find major thyroid secretory cells arranged in a hollow sphere called a follicle. The follicle is the functional and structural unit of the thyroid so secretory cells are called follicular cells. Follicles are lined by a single layer of epithelium which can change shape based on cells’ activity. So follicles are rings of follicular cells enclosing an inner lumen of a secretory substance called colloid.

Colloid acts as a storage site for thyroid hormones. The chief constituent is thyroglobulin – a large glycoprotein of MW 660,000. It contains thyroid hormones in various stages of synthesis.

Tyrosine is major substrate to form thyroid hormones within the molecule thyroglobulin.

Epithelium of thyroid gland is one cell thick but the morphology varies with the activity of the gland once under the influence of TSH.

a) flattened squamous epi – inactive gland
b) cuboidal or columnar epi – active gland (after TSH has bound)

Follicular cells make 2 iodine-containing hormones which are derived from the amino acid tyrosine:

1) tetraiodothyronine – T4 – thyroxine – 80%
2) triiodothyronine – T3 – 20%

All of the steps in the synthesis of hormones occur on the thyroglobulin (TGB) molecule in colloid of the follicle.

T1 and T2 denotes the number of iodine atoms in each hormone. These 2 collectively are called thyroid hormone. Important in the overall regulation of basal metabolism. Too much is a fast metabolism and too little represents a slow metabolism of your tissues.

Much more T4 is produced than T3 or 4x amount of T4 is made than T3 but T3 has 20x the biological activity.

So now let’s look at the formation of thyroid hormones

Thyroid hormones synthesis

Steps in formation of Hormones:
1) Iodide trapping
2) Synthesis of TGB
3) Oxidation of iodide
4) Iodination of tyrosine
5) Coupling of T1 and T2
6) Pinocytosis and digestion of colloid
7) Secretion of thyroid hormones
8) Transport to blood

I = Iodide
I1 = Iodine
TGB = thyroglobulin
TBG = Thyroxine-binding globulin
1) Iodide Trapping — To start, need organic iodine (I₂) from the diet intake. After ingestion, it is converted in the GI tract to iodide (I⁻) and then absorbed into the blood from the intestine. Iodine is captured from the blood by a very active “iodide pump” or “iodide trapping” mechanism. Energy-requiring carrier protein in outer membranes of follicular cells move the iodide against a concentration gradient. It can move from areas of lesser concentration to areas of greater concentration up to 48x higher. This is the only purpose for iodine in the body!!!

2) Synthesis of TGB — This occurs within the follicular cell on the rough endoplasmic reticulum as are proteins within cells. It is then passed on to the Golgi complex and pinched off into secretory vesicles to be dumped into the colloid to stay within the cell.

3) Oxidation of Iodide — The oxidative enzymes to convert Iodine to Iodide are located at the luminal border of colloid. Peroxidase is the converting enzyme.

4) Iodination of tyrosine — Once oxidized, I⁻ is quickly snatched up by a tyrosyl residue in the TGB. Tyrosyl represents the form of the amino acid, tyrosine, found in TGB. Also referred to as Organisation of Thyroglobulin. So the following will be formed as a result:
   a) Tyr + I⁻ → Monoiodotyrosine (MIT, T₁)
   b) M.I.T. + I⁻ → Diiodotyrosine (DIT, T₂)
   c) M.I.T. + D.I.T. → T₃
   d) M.I.T. + D.I.T. → T₄

5) Coupling of T₁ and T₂ — Now coupling of these products will form T₃ and T₄. But not all combinations are possible or active molecules:
   Can have: MIT + DIT → T₃
   or
   DIT + DIT → T₄
   but not 2 MITS. Molecules of MIT and DIT alone are considered inactive. Each thyroglobulin molecule produces 5–6 thyroxine molecules. So all of the products are still attached to the thyroglobulin in colloid. This is where the thyroid hormones remained stored until they split off of the protein TBG. Enough stored for 2–3 months.

6) Pinocytosis and Digestion of Colloid — So now follicular cells send out pseudopod extensions around small portions of colloid to form pinocytotic vesicles. They essentially “bite” off a chunk of colloid and break down the TGB into components. The tyrosines in the follicular cell attach to the pinocytotic vesicles and then release enzymes to digest the TGB molecule.

7) Secretion of Thyroid hormones — Now the T₃ and T₄ are free and can freely pass out of outer membranes of follicular cells and into the blood. MIT and DIT released do not go to the blood. Instead there is an active “iodide pump” or “iodide trapping” mechanism. Energy-requiring carrier protein in outer membranes of follicular cells move the iodide against a concentration gradient. Most of what is released is T₄, but it is converted to T₃ or more biologically active at the cell level. Much more potent as T₃ or more biologically active at the cell level.

8) Transport in blood — Once released and before it enters tissues, it doesn’t stay free. It immediately binds in the blood to binding plasma proteins. Three proteins exist that it can bind to:
   a) Thyroxine-binding globulin (55% circ. T₄ and 65% circ. T₃)
   b) Thyroxine-binding albumin (10% T₄ and 35% T₃)
   c) Thyroxine-binding prealbumin (35% T₄)

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99% T₃ and 99.9%T₄ is bound in blood. The rest is free and if free, it is available to be used by the tissues at the cell level. As it is used, more is freed. It is released to the tissues slowly.

Regulation of Thyroid secretion —

Classic negative feedback that is used to illustrate negative feedback.

\[ \text{TRH} \rightarrow \text{TSH} \rightarrow \text{Thyroid hormones released} \rightarrow \text{T₃, T₄ released back to blood} \]

Actions of TSH —

a) Enhances action of the iodide pump to go against concentration gradient.
   b) Increases the size of the epith. Cells so go from squamous to columnar
   c) ↑ rate of iodination of Tyr and oxidation of I⁻.
   d) ↑ rate of absorption of CHO at gut
   e) ↓ rate of oxidation of I⁻ and oxidation of Tyr
   f) ↑ rate of chewing up of TGB

Effects of free T₃/T₄:

1) Calorigenesis — (or heat-producing effect or metabolic effect)
   Increased heat due to the effect on the tricarboxylic cycle (TCA) or e- transport system. Increased Oxygen consumption to do so but some tissues do not exhibit a calorigenic effect: 1) brain 2) testes 3) retina.
   Hypothyroid — 2-fold increase in metabolic rate. Hypothyroid — 40 – 50% decrease in metabolic rate.

2) ↑ Protein synthesis — need optimal amounts of thyroid hormones for this but alternatively very high doses can cause protein degradation. If thyroidectomize, will inhibit protein synthesis or if deficient in child, will stunt his growth.

3) ↑ Carbohydrate (CHO) metabolism — all aspects of CHO metabolism enhanced:
   a) ↑ rate of absorption of CHO at gut
   b) ↓ insulin secretion
   c) ↑ glucose uptake at the cell level (rapid)
   d) ↑ glycogenolysis — increases glucose in blood
   e) ↑ gluconeogenesis — formation of new CHO
4) Effects on Lipids – increase lipolysis in the blood so increases free fatty acids in the blood to be used for energy. (If hyperthyroid, skinny, will decrease fat stores; the opposite is also true.)

5) Effects on CNS –
   a) Hormones have a sympathomimetic effect by ↑ tissue responsiveness to catecholamines (epinephrine and norepinephrine). Will increase HR as well.
   b) Normal development of NS, especially CNS (brain); Shows large effect in children without thyroid at birth.
   c) Maintains proper function of neurons and action potentials – seen as behavioral changes.
   d) Proper conduction speed of action potentials:
      Hyperthyroid – rapid cerebration – process too quickly.
      Hypothyroid – lethargic, slow to think or can’t.

6) Sexual function –
   a) Proper development of sexual functions
   b) Proper function of sexual functions

Pathologies of Thyroid

A) Hypothyroidism
   1) Primary – most common; failure is of thyroid gland itself. Due to thyroidectomy, radiation, active F131 and F135
   2) Secondary – to hypothalamic or anterior pituitary failure so see decrease in or deficiency of TRH or TSH.
   3) Tertiary or Lack of iodine in the diet.

Symptoms: Overall related to reduction in metabolic activity so will see:
   a) decrease in Basal metabolic rate
   b) decrease in calorigenic effect (poor resistance to cold)
   c) increase in weight gain (not burning fuels at normal rate)
   d) easily fatigued (no energy production)
   e) slow, weak pulse (decrease in rate and strength of cardiac function)
   f) slow reflexes and slow mentation (effect on nervous system)
   g) increase infiltration of interstitial spaces of skin with mucopolysaccharides. Shows as edematous appearance in face, hands, feet and called myxedema – hypothyroidism in an adult.

Cretinism – hypothyroidism from birth to childhood. Symptoms are:
   dwarfism, mental retardation (slow brain development and NS) -can correct with replacement therapy if immediate but after several months nonreversible.

Treatment:
   Can correct hypothyroidism with exogenous thyroid hormone, Synthroid, but if it is merely diet lacking in iodine, can simply increase the amount in the diet through salt or seafood which are rich in iodine.

Others beside Synthroid are
Levothyroxine, Thyroid USP.

Hyperthyroidism –
   Most common cause is an autoimmune disorder called Grave’s disease. The body erroneously produces a mimic for TSH called TSI (Thyroid stimulating immunoglobulin). TSI is actually an antibody that binds to TSH receptors on thyroid cells. As it binds it stimulates both secretion and growth of the thyroid gland like TSH does but is not subject to negative feedback like TSH.

Therefore, ↑ levels of T4 and T3 do not inhibit TSI release so thyroid growth and secretion continue unchecked.

The antibody is called LATS - long acting thyroid stimulator so get hypertrophy of the gland. The thyroid gland enlarges! This enlarged gland is called a goiter. Since it continues to produce T4 and T3, it is called a productive goiter.

Graves’ Disease and goiter

Non productive goiter -
   is a goiter produced in Hypothyroidism. Occurs if:
   1) the primary reason is if thyroid gland fails or
   2) if there is not enough iodine in the diet.

In other words, as TSH↑, the gland grows larger and develops but no T4 or T3 can be produced.

So the negative feedback keeps stimulating the hypothalamus to produce TSH which in turn keeps the adenohypophysis producing TSH which binds to cells of the thyroid gland.

Summary of Goiter profiles:
Productive goiter - hyperthyroid, ↑TSH, (Graves) ↑T4, ↑T3
Nonproductive goiter - hypothyroid, ↑TSH, ↓T4, ↓T3

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