

# **ENDOCRINE SYSTEM**

## **PHYSIOLOGY:**

### **PART I**

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# HORMONES: CATEGORIES, CLASSIFICATION AND EXAMPLES

‡Note: the examples given in this table are not all-inclusive

HORMONE CATEGORY	CLASSIFICATION [EXAMPLES]
<b>Tyrosine Derivatives</b>	<b>1.Thyroid</b> <b>2.Catecholamines</b>
<b>Lipid-Fat Soluble Hormones</b>	<b>1.Steroids</b> <b>2.Secosteroids</b> <b>3.Icosanoids</b>
<b>Peptide Hormones</b>	<b>1.Hypothalamic Releasing-Inhibiting Hormones</b> <b>2.Posterior Pituitary</b> <b>3.Pancreas, Gut</b> <b>4.Thyroid</b> <b>5.Anterior Pituitary</b> <b>6.Growth Factors</b>
<b>Proteins</b>	<b>1.Anterior Pituitary</b> <b>2.Parathyroid</b>
<b>Glycoproteins</b>	<b>1. Anterior Pituitary</b> <b>2. Placenta</b>

# HORMONES: CATEGORIES, CLASSIFICATION AND EXAMPLES

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HORMONE CATEGORY	CLASSIFICATION [EXAMPLES]
<b>Tyrosine Derivatives</b> [biogenic amines]	<p><b>1.Thyroid</b> [T3, rT3, T4, iodinated tyrosines]</p> <p><b>2.Catecholamines</b> [dopamine, norepinephrine, epinephrine]</p>
<b>Lipid-Fat Soluble Hormones</b>	<p><b>1.Steroids</b> [estrogens, progesterone, cortisol, aldosterone, androgens (testosterone)]</p> <p><b>2.Secosteroids</b> [Vitamin D3]</p> <p><b>3.Icosanoids</b> [prostaglandins, thromboxanes, leukotrienes]</p>
<b>Peptide Hormones</b>	<p><b>1.Hypothalamic Releasing-Inhibiting Hormones</b> [TRH, GnRH, GHIH, PIF, GHRH, CRH]</p> <p><b>2.Posterior Pituitary</b> [oxytocin, vasopressin]</p> <p><b>3.Pancreas, Gut</b> [insulin, glucagon]</p> <p><b>4.Thyroid</b> [calcitonin]</p> <p><b>5.Anterior Pituitary</b> [ACTH, MSH, LPH, endorphins, enkephlins]</p> <p><b>6.Growth Factors</b></p>
<b>Proteins</b>	<p><b>1.Anterior Pituitary</b> [GH, POMC, PRL, hPL]</p> <p><b>2.Parathyroid</b> [PTH]</p>
<b>Glycoproteins</b>	<p><b>1.Anterior Pituitary</b> [FSH, LH, TSH]</p> <p><b>2.Placenta</b> [hCG]</p>

# THE HORMONES

Classification

Function

Feedback Mechanisms

Transport

Receptor Binding

## **HYPOTHALAMUS**

THYROID RELEASING HORMONE (**TRH**)

CORTICOTROPIN RELEASING HORMONE (**CRH**)

GONADOTROPIN RELEASING HORMONE (**GnRH**)

GROWTH HORMONE RELEASING HORMONE (**GHRH**)

SOMATOSTATIN (**GHIH**, SOMATOTROPIN)

PROLACTIN RELEASING HORMONE (**PRH**)

PROLACTIN INHIBITING HORMONE (**PIH**)

## **ANTERIOR PITUITARY GLAND**

LEUTINIZING HORMONE (**LH**)

FOLLICLE STIMULATING HORMONE (**FSH**)

THYROID STIMULATING HORMONE (**TSH**)

PROOPIOMELANOCORTIN (+ACTH) **POMC**

GROWTH HORMONE (**GH**)

PROLACTIN (**PRL**)

# THE HORMONES (Cont'd)

## POSTERIOR PITUITARY GLAND

ANTIDIURETIC HORMONE (**ADH**) or (**VASOPRESSIN**)\*  
OXYTOCIN\* (**OXY**)

## THYROID GLAND

TRI-/TETRAIODOTHYRONINE (**T3, T4, rT3**)  
CALCITONIN (**CT**)

## PARATHYROID GLANDS

PARATHYROID HORMONE (**PTH**)

## PANCREAS

INSULIN  
GLUCAGON

## ADIPOSE TISSUE

LEPTIN

\*Synthesized in the hypothalamus, released by the posterior pituitary

# THE HORMONES (Cont'd)

## ADRENAL GLANDS

### ADRENAL CORTEX:

GLUCOCORTICOIDS (CORTICOSTEROIDS,  
CORTISOL)

ANDROGENS (ANDROSTERONE,  
TESTOSTERONE, DIHYDROTESTOSTERONE)

MINERALOCORTICOIDS  
(ALDOSTERONE)

### ADRENAL MEDULLA:

EPINEPHRINE (E)  
NOREPINEPHRINE (NE)  
DOPAMINE (DA)

## KIDNEYS

ERYTHROPOIETIN  
1,25-DIHYDROXY VITAMIN D3  
RENIN

## CALCIUM AND PHOSPHATE

BONE

# The Anterior Pituitary

The **pituitary gland** (*hypophysis*) has traditionally been called the "master gland" by virtue of its main regulator: the hypothalamus, which receives input from virtually all other areas of the central nervous system (CNS) .

The **hypothalamus** regulates the activities of both the lobes of the pituitary (the anterior pituitary or *adenohypophysis* and the posterior pituitary or *neurohypophysis*,). The anterior lobe (80% of the pituitary gland by weight) is the larger of the two .

The hypothalamus regulates the anterior pituitary directly by delivering neurohormones through a portal vascular system, and indirectly by regulating the synthesis and secretion of its six major hormones.

**There is no direct neural connection between the hypothalamus and the anterior pituitary.**

Targets for regulation by the pituitary hormones include peripheral organs, glands, tissues and metabolic functions.

# The Posterior Pituitary

**The posterior pituitary contains axons that actually originate in neuronal cell bodies located in the hypothalamus.**

**Notably, these axons are storage sites for peptide hormones that are associated with the posterior pituitary: oxytocin and vasopressin.**

**Oxytocin and vasopressin are synthesized in the hypothalamus but released into circulation from the posterior pituitary.** These posterior pituitary hormones then act on peripheral organs and functions.

**Target organs for oxytocin include the uterus, where it can cause uterine contractions (i.e. during parturition), and the mammary gland, where it can stimulate milk ejection (i.e. the 'let-down' response during lactation).**

**Vasopressin (also known as ADH or antidiuretic hormone) is involved in regulating water balance (see Renal Physiology section).**

## ----- Hypothalamic-Pituitary Hormone Regulation

Most of the hormones produced by the hypothalamus and pituitary are released in a **pulsatile or burstlike fashion.**

In addition, certain hormones (eg, adrenocorticotrophic hormone [ACTH], growth hormone [GH], and prolactin [PRL]) have definite **circadian or diurnal** rhythms with increased secretion during specific hours of the day or during specific parts of the sleep-wake cycle.

Other hormones (eg, luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) have monthly rhythms (in premenopausal women) with circadian rhythms superimposed upon them.

**Six physiologically important neurohormones have been identified in the hypothalamus.** Except for the biogenic amine dopamine, all are small **peptides.** (Many are produced in other parts of the body as well, where they function in local paracrine systems, especially in the GI tract.)

## Hypothalamic-Pituitary Hormones: Regulation and Characteristics

The hypothalamus exerts positive regulation over most of the anterior pituitary hormones. Prolactin, which is under inhibitory control by the hypothalamus, is the exception.

Thyrotropin-releasing hormone (TRH) stimulates the synthesis and secretion of thyroid-stimulating hormone (TSH) by cells in the anterior pituitary called “thyrotrophs”.

Under pathologic conditions, TRH may also stimulate the production and release of other hormones from the anterior pituitary, like PRL from the “lactotrophs”, and GH from the “somatotrophs”.

Gonadotropin-releasing hormone (GnRH) stimulates secretion of LH and FSH.

When GnRH is administered in a pulsatile fashion, the secretion of gonadotropin hormones (LH and FSH) is stimulated and maintained.

When GnRH is administered by **continuous infusion**, the initial stimulation of LH and FSH secretion become **inhibited**.

This is because sustained GnRH levels are able to feedback negatively on the gonadotropin-producing cells of the anterior pituitary.

Chronically high levels of GnRH bind and down-regulate GnRH receptors located on the gonadotroph cells of the anterior pituitary gland.

This observation led to the development of long-acting GnRH agonists, GnRH analogs, and other pharmaceuticals that are used clinically to:

- ★ inhibit androgen secretion in men with hormone-dependent prostate cancer;
- ★ suppress ovarian steroid secretion in women with endometriosis and uterine leiomyomas;
- ★ induce medical castration when warranted;
- ★ delay gonadal steroid secretion in cases of precocious puberty

**Dopamine, from the hypothalamus, is the major regulator of prolactin and it acts by inhibiting PRL synthesis and release.**

**When the stalk which connects the pituitary to the hypothalamus is severed, prolactin secretion increases dramatically, while the secretion of all other anterior pituitary hormones decreases.**

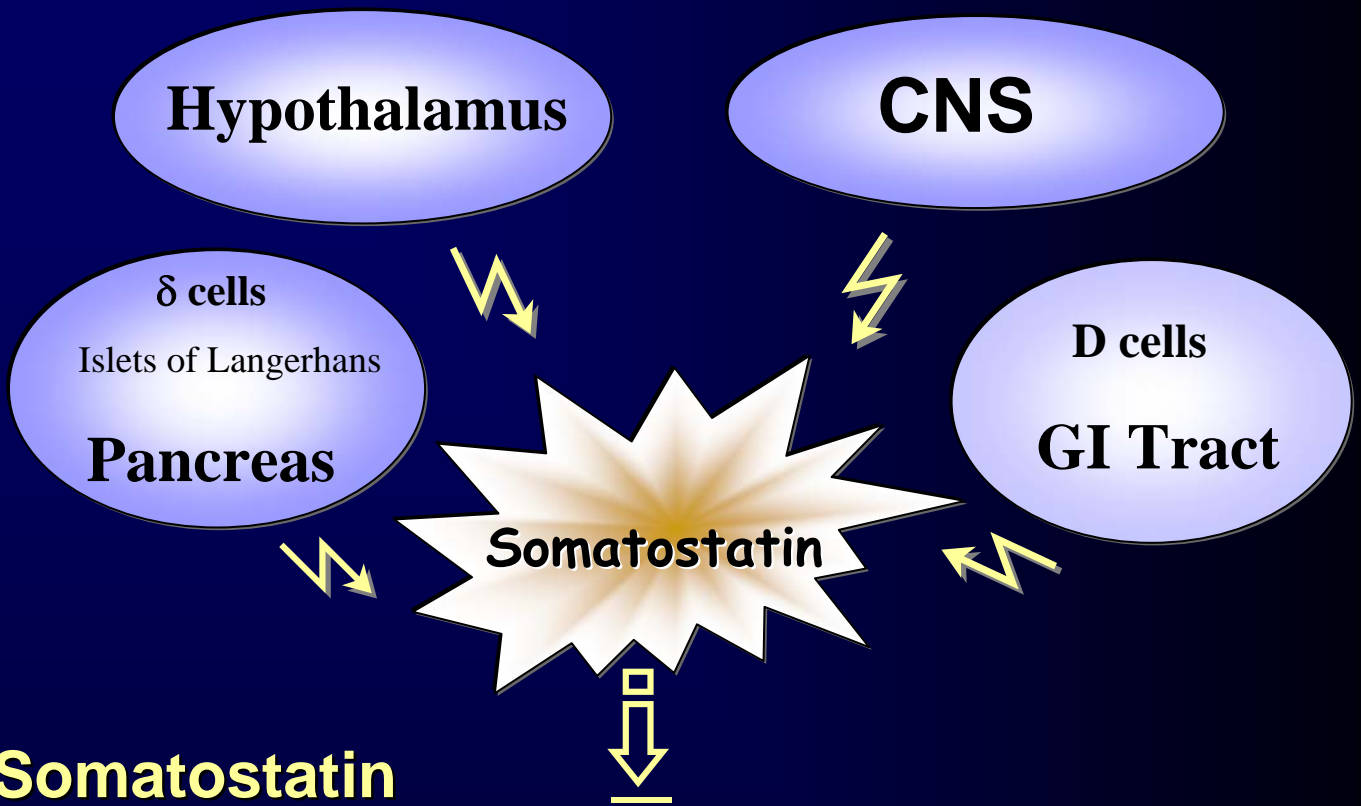
**GH release from the anterior pituitary is stimulated by GHRH (growth hormone-releasing hormone) and inhibited by somatostatin from the hypothalamus (also known as GHIH or somatotropin).**

**The rate of GH production depends on the balance between these two regulators.**

**Somatostatin can also inhibit the secretion of TSH (from the anterior pituitary) and insulin from the endocrine pancreas.**

**Corticotropin-releasing hormone (CRH) stimulates release of ACTH from the pituitary.**

**SOMATOSTATIN** is made in the: Hypothalamus, Central Nervous System, Pancreas, and GI Tract



**Somatostatin**

**inhibits** the secretion of several hormones including:

- **INSULIN**
- **GLUCAGON**
- **GH**
- **VIP**
- **GASTRIN**
- **TSH**

# GLUCAGON

- **Glucagon is a 31 amino acid peptide hormone that is synthesized by the  $\alpha$  cells of the pancreatic islets.**
- **The main activators of glucagon secretion are the amino acids released by the digestion of a protein meal.**
- **The main target organ for glucagon's actions is the liver.**
- **Glucagon is involved in regulating carbohydrate and lipid metabolism.**

In the liver, **GLUCAGON** promotes:

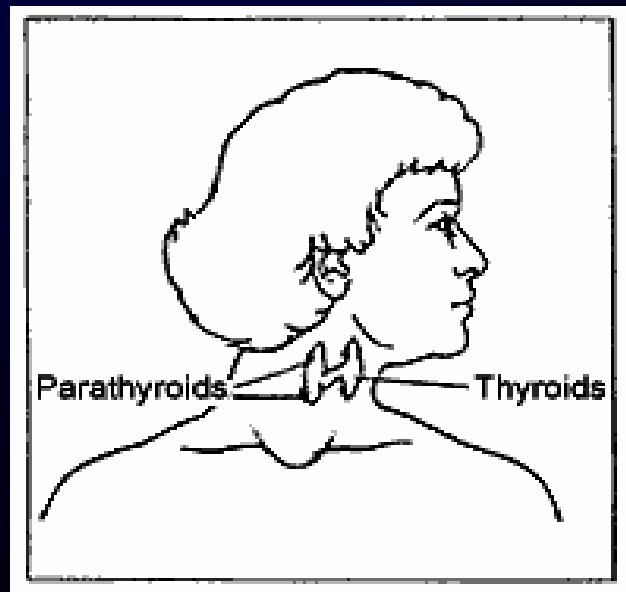
- the break down of glycogen (glycogenolysis),
- the synthesis of glucose (gluconeogenesis), and
- the formation of ketone bodies (ketogenesis)
- **GLUCAGON** *may* antagonize the actions of insulin.
- Both glucagon and insulin are vital to fuel homeostasis.
- During fasting, insulin levels fall and glucagon levels rise.

# PTH, VITAMIN D, and CT

## Parathyroid Hormone (PTH)

PTH is a protein synthesized by the **chief cells** of the parathyroid glands. In humans, there are four parathyroid glands contained within the capsule of the thyroid gland.

PTH levels are **regulated mainly by the calcium ion concentrations** of the extracellular fluids. High blood calcium levels lower the rate of PTH synthesis, whereas low blood calcium levels stimulate PTH synthesis.



# Positive regulators of PTH secretion:

- **Low  $[Ca^{++}]^a$**
- **High [phosphate]<sup>a</sup>**
- **Glucocorticoids (cortisol)**
- **Growth Hormone**
- **cAMP, cAMP analogues, activators of adenylate cyclase (such as epinephrine, dopamine, isoproterenol)**
- **Estradiol**
- **Low vitamin D, calciferol levels**
- **Low 1- $\alpha$ -hydroxylase activity**

<sup>a</sup> *extracellular fluids*

**Normally PTH functions to increase plasma  $[Ca^{++}]$  and decrease plasma  $[PO_4]$  this latter occurs by increasing urinary phosphate excretion.**

**Hypercalcemia is defined as plasma  $[Ca^{++}] \geq 11$  mg/dl\***

**Normal blood calcium levels are between 9 and 10.5 mg/dl.**

**Chronically elevated PTH is seen in those with hyperparathyroidism.**

**The hallmark of hyperparathyroidism is elevated blood calcium or hypercalcemia.**

**The high blood calcium levels present in hyperparathyroidism often give rise to kidney stones.**

**– why is this so?**

\*note blood calcium levels  $\leq 5$  mg/dl lead tetany



## THIS RESULTS IN:

PLASMA CALCIUM LEVELS THAT BECOME SO HIGH THAT THEY **spill out into the urine**, exceeding the maximum GFR for  $\text{Ca}^{++}$ .

**This causes the GFR [ $\text{Ca}^{++}$ ] to  $\uparrow$** , thus decreasing further renal tubular calcium reabsorption.

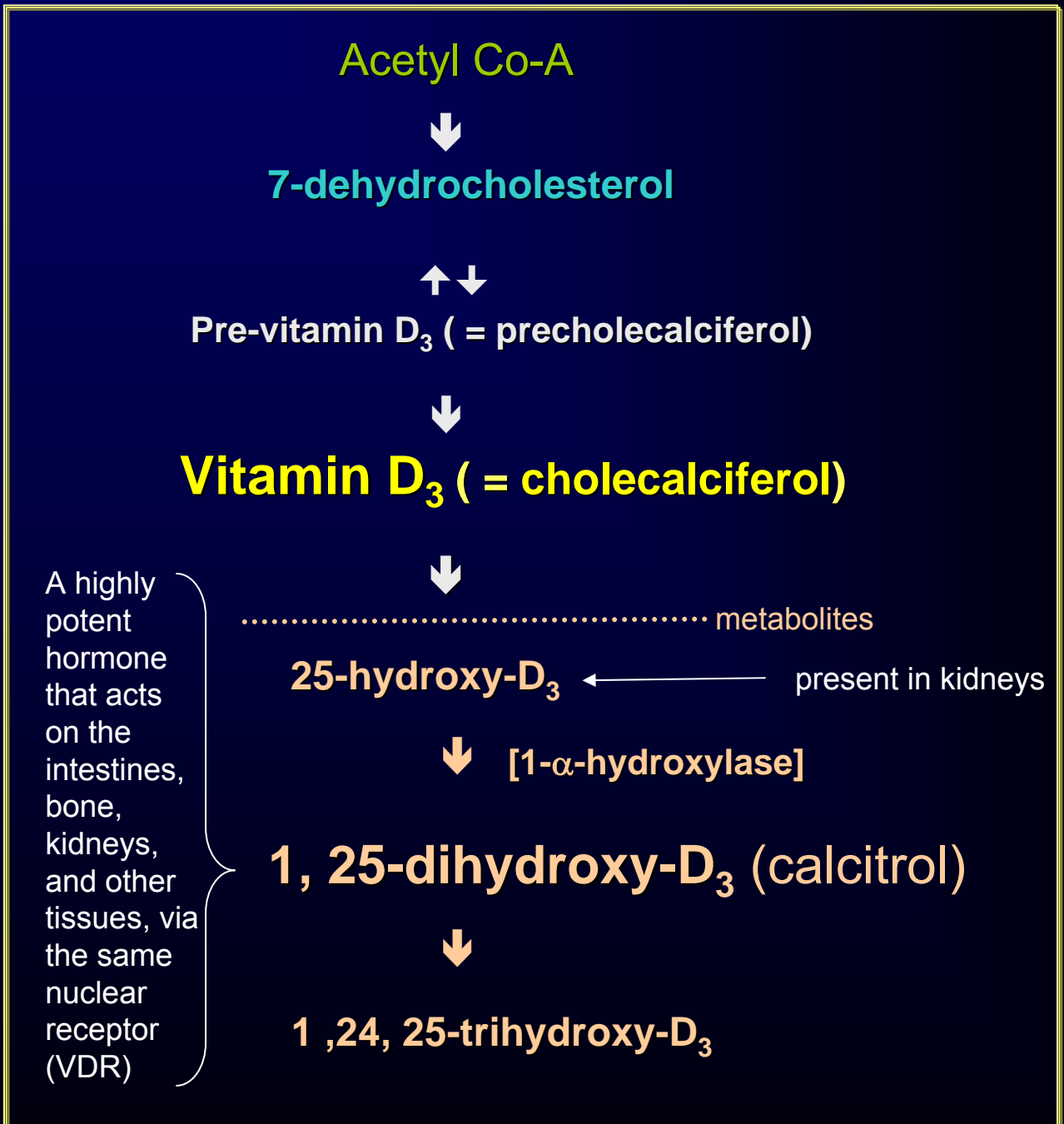
When urinary  $\text{PO}_4$  and  $\text{Ca}^{++}$  are both elevated, **the urine becomes supersaturated**.

As a consequence,  $\text{PO}_4$  and  $\text{Ca}^{++}$  can precipitate out, **forming 'stones'\*\***.

*[\*\*This is referred to as: nephrocalcinosis or urolithiasis].*

# VITAMIN D

Vitamin D<sub>3</sub> (= Cholecalciferol) is a secosteroid (meaning one of the rings is opened) which can be obtained from the diet or synthesized in the skin\* when sunlight is present.



**\*7-dehydrocholesterol** is the precursor of **Vitamin D<sub>3</sub>** that undergoes a photolytic reaction in the skin.

**7-dehydrocholesterol** can be synthesized from **Acetyl CoA** or obtained in the diet.

Food sources such as fish oil (i.e. cod liver oil) and egg yolks naturally contain significant amounts of vitamin D and/or its precursors, and milk is artificially supplemented with it.

1 gram of oil from the liver of a tuna or mackerel supplies 1000 times the daily requirement

Vitamin D<sub>3</sub> levels undergo seasonal variations too, being highest in the summer or when the number of daylight hours is increased, and lowest in the winter.

# THE THYROID HORMONES

The follicular cells of the thyroid gland produce and secrete thyroid hormones, mainly thyroxine or T4 [80%], and triiodothyronine or T3 [20%].

Note that the relative concentrations of these hormones may vary with disease and nutritional deficiencies.

T3 is the biologically active form. Its activities are mediated by binding to the thyroid hormone receptor: TR

Most T3 in circulation derives from peripheral T4 to T3 conversion although intrathyroidal T4 to T3 conversion also takes place within the thyroid gland itself.

Nearly all of the T3 and T4 that are in circulation are bound to proteins [i.e. thyroid binding globulin, TBG] and only 0.02 to 0.03% is free (and thus active).

# THE THYROID HORMONES

**Estrogens (pregnancy-level estrogens, estrogen-containing medications) cause TBG concentrations to increase (less free hormone is available).**

**Hypothyroid patients receiving estrogen replacement therapy may need higher T4 doses, for example androgens, glucocorticoids, and malnutrition cause TBG concentrations to decrease.**

**Glucocorticoids inhibit pulsatile TSH secretion.**

**Dopamine and retinoids decrease TSH. Some selective **serotonin reuptake inhibitors** [SSRIs] accelerate T4 metabolism thereby lowering T4 levels in circulation.**

**Some drugs, like **Dilantin (phenytoin)** and **Aspirin (salicylates)** cause T3- and T4-TBG binding to decrease.**

# THE THYROID HORMONES

The thyroid gland has the unique ability to concentrate iodine.

This is made possible by the presence of a symporter called the **sodium-iodide symporter** or **NIS**.

The **NIS** is able to concentrate iodide to levels which are 40- to 60 times greater in the colloid (present inside of the follicular cells of the thyroid gland) than the levels found outside, in the serum.

The **NIS** gene is regulated by **TSH** (or thyrotropin).

**Thyroglobulin (TG)** is the precursor for all **thyroid hormones**. It is a protein that contains 140 tyrosine residues. These tyrosines are iodinated and coupled to form thyroid hormones.

## THE THYROID HORMONES

Iodine is added to tyrosine residues in the thyroid colloid forming either monoiodotyrosines [MIT] or 3,5-diiodotyrosines [DIT].

★ Thyroid peroxidase catalyzes the coupling between them such that:

**one MIT and one DIT combine to form T3; and, two DITs [DIT and DIT] are coupled to form T4.**

TSH stimulates a cleavage process allowing some of the T4 and T3 to be released into the bloodstream.

Thyroid hormone metabolism can follow different pathways. In the predominant metabolic pathway the progressive deiodination of T4 to T3 or to rT3, and then to T2, T1, and T0 occurs.

★ T4 is first deiodinated to form T3 or reverse T3, rT3. The enzyme **5'-monodeiodinase converts T4 into T3**, whereas the **5-monodeiodinase enzyme converts T4 into rT3**.

★ The T3 that is formed by the peripheral monodeiodination of T4 is the biologically active form.

# THE THYROID HORMONES

★ By contrast, **rT3 is inactive.**

★ This means that the initial deiodination step, and the factors that determine it, have the capacity to form a potent compound: **T3 OR an inactive one: rT3.**

During fasting, starvation, or significant illness, the activity of the 5'-monodeiodinase enzyme is lower, T3 conversion from T4 decreases, and the basal metabolic rate slows down.

## TERMS and ABBREVIATIONS

thyroxine = **T4**;

iodide = **I<sup>-</sup>**

triiodothyronine = **T3**;

reverse T3 = **rT3**

thyroid binding globulin = **TBG**;

thyroglobulin = **TG**

monoiodotyrosines = **MIT**;

3,5-diiodotyrosines = **DIT**

sodium-iodide symporter = **NIS**

thyroid stimulating hormone = **TSH** ≡ thyrotropin

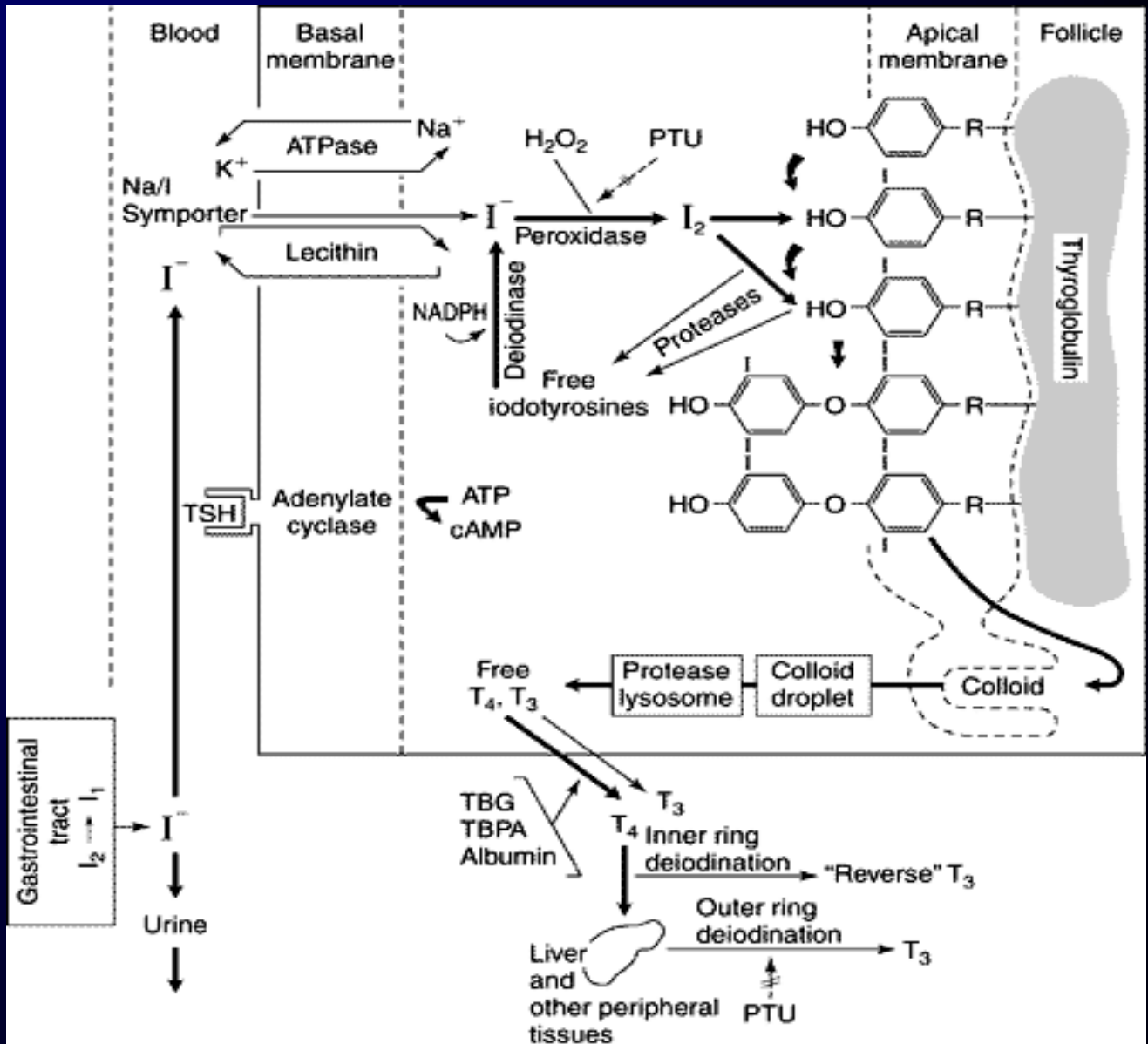
thyroid peroxidase;

thyroid follicular cells;

colloid

# THE THYROID HORMONES

## Biosynthesis of thyroid hormones.



ATP = adenosine triphosphate; cAMP = adenosine 3':5'-cyclic phosphate; I = iodide; NADPH = the reduced form of nicotinamide-adenine dinucleotide phosphate; PTU = propylthiouracil;  $T_3$  = triiodothyronine;  $T_4$  = thyroxine; TBG = thyroxine-binding globulin; TBPA = thyroxine-binding prealbumin (transthyretin); TSH = thyroid-stimulating hormone.