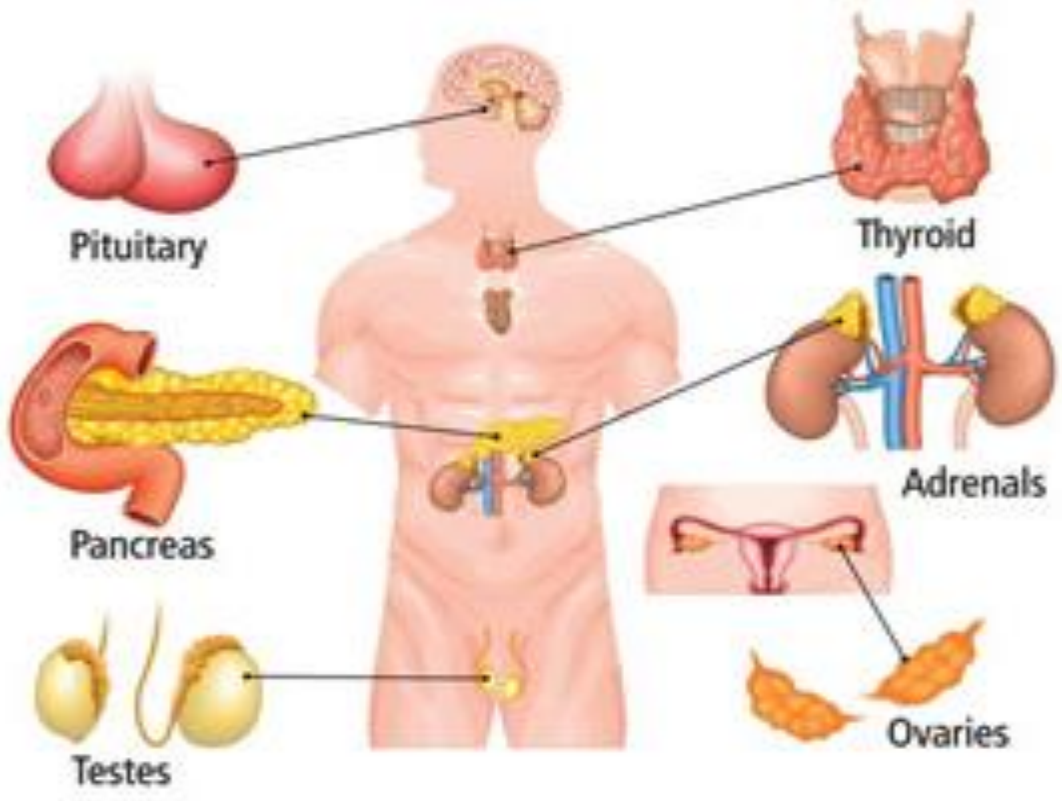
ENDOCRINE SYSTEM

Glandular structures secretes **Hormones** directly into the blood stream which delivers them at distant target sites



Major functions of hormones

- Regulation of energy storage, production, and utilization
- Facilitation of growth and development;
- Maturation and function of the reproductive system.

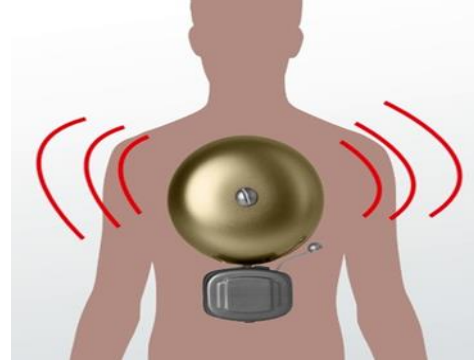
Hormones

divided into **2** classes:

- Hormones that act predominantly via **nuclear receptors** (e.g., steroid hormones, thyroid hormone, and vitamin D).
- Hormones that typically act via **membrane receptors** (e.g., peptide and amino acid hormones)

Hypothalamic & Pituitary Hormones

Overview



- **Hypothalamus** is detection center in brain

BODY HOMEOSTASIS

Long response

Endocrine system

e.g. growth & reproduction

Chemical messenger

HORMONES

Fast response

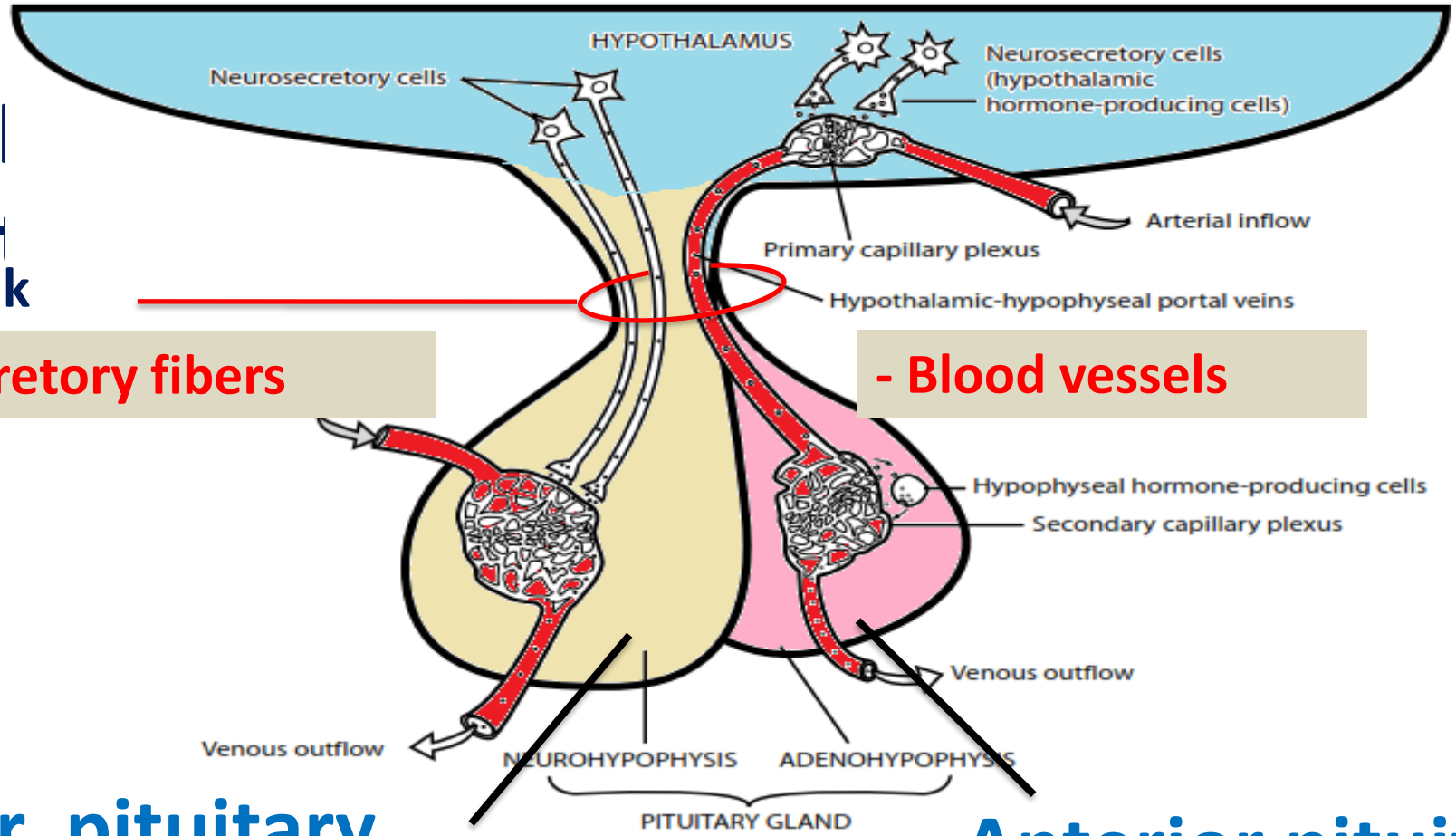
AUTONOMIC NS

e.g Muscle contraction

Hypothalamus control endocrine system via inhibition or stimulation of

Pituitary Gland

Pituitary gland



Pituitary stalk

- Neurosecretory fibers

- Blood vessels

Posterior pituitary

neurohypophysis

master gland

Anterior pituitary

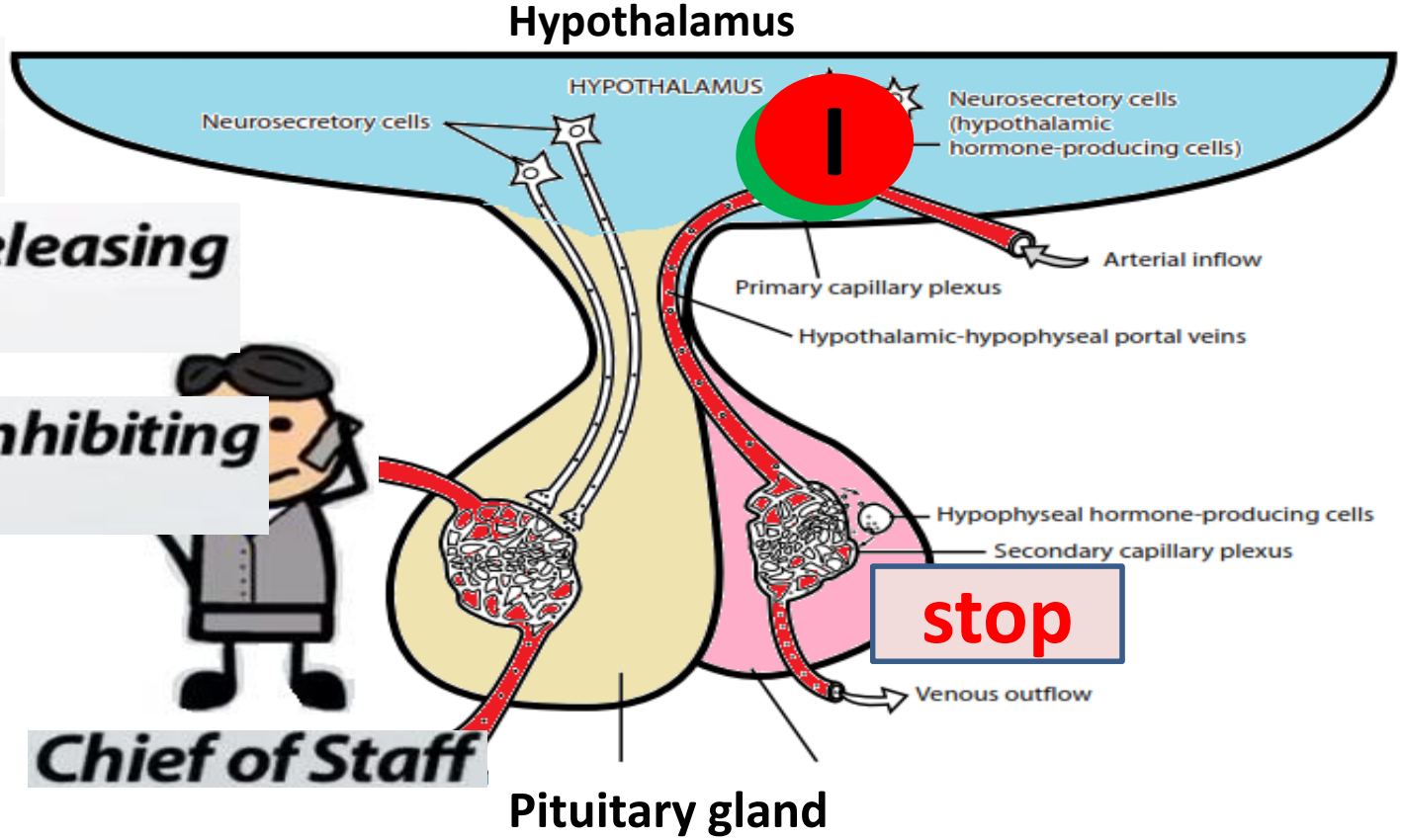
adenohypophysis

Anterior lobe

hypothalamus communicates with the **Anterior portion** by **hormonal messages, thru Portal system, which tell the anterior pituitary to start or stop an action.**

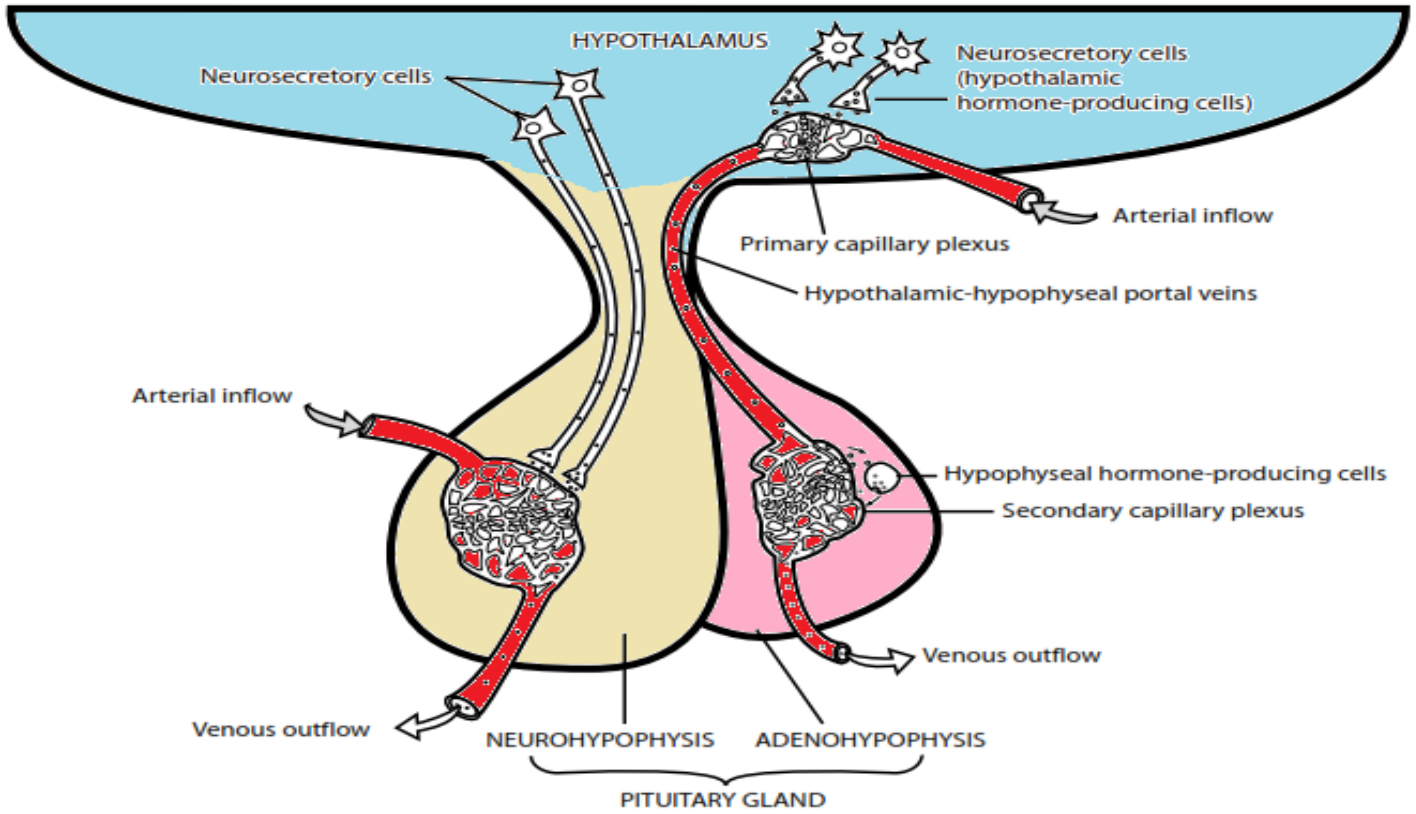
R hypothalamic releasing hormones

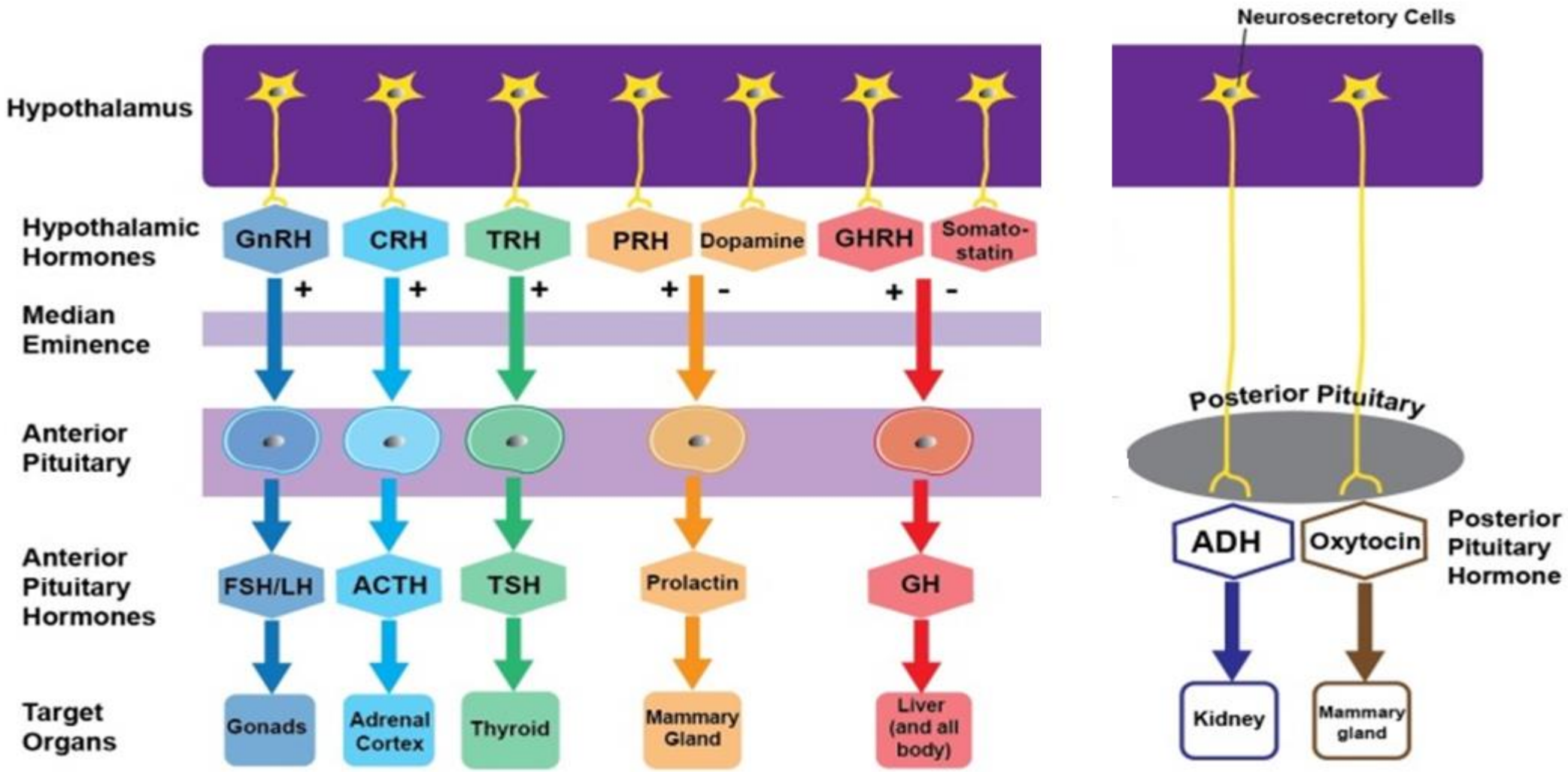
I hypothalamic inhibiting hormones



Posterior lobe

Posterior lobe hormones are synthesized in the hypothalamus and transported via the neurosecretory fibers to the posterior lobe & then to circulation (ADH, Oxytocine)




Hypothalamus
Hypothalamic Hormones
GnRH
CRH
TRH
PRH
Dopamine
GHRH
Somato-statin
+
+
+
+
-
+
-
Median Eminence
Anterior Pituitary
Anterior Pituitary Hormones
FSH/LH
ACTH
TSH
Prolactin
GH
Target Organs
Gonads
Adrenal Cortex
Thyroid
Mammary Gland
Liver (and all body)
Neurosecretory Cells
Posterior Pituitary
ADH
Oxytocin
Posterior Pituitary Hormone
Kidney
Mammary gland

Pharmacologic applications

- Drugs mimic or block the effects of hypothalamic - Pituitary hormones have pharmacologic applications in 3 primary areas:

✓ **Replacement** therapy for hormone deficiency states.

✓ **Antagonists** for diseases caused by excess production of pituitary hormones.

✓ **Diagnostic** tools for identifying several endocrine abnormalities

Hypothalamic Hormones

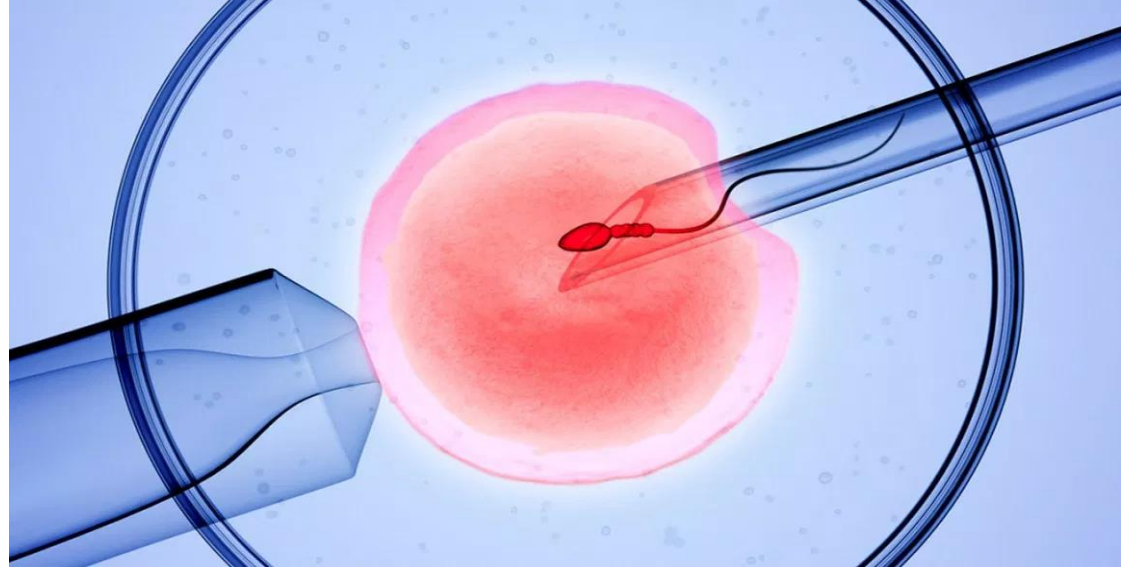
Hormones	Clinical application
Corticotropin releasing hormone (CRH) **Stimulate ACTH from anterior pit. gland**	**diagnostic use.** ↑ secretion of ACTH in Cushing's disease 2nd to pituitary ACTH-secreting adenoma (i.e. pituitary tumors are responsive to exogenous CRH, whereas ectopic and adrenal tumors are not.)
Thyrotrophin releasing hormone (TRH) **Stimulate TSH from anterior pit. gland**	**diagnostic use**. Given i.v in normal subjects causes ↑ in plasma TSH concentration, whereas in patients with hyperthyroidism there is a blunted response because the raised blood thyroxin concentration has -ve feedback effect on the anterior pituitary.

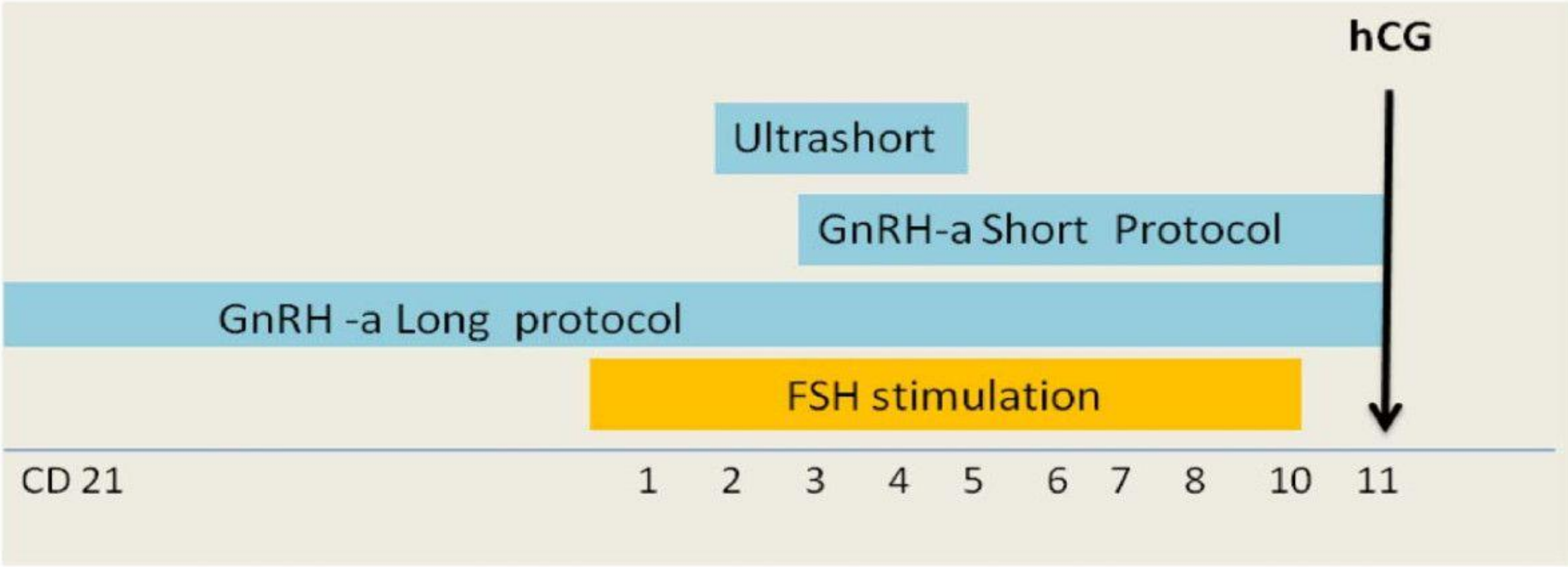
Hormones	Clinical application
Growth hormone releasing hormone (GHRH) **Stimulate GH release from anterior pit. Gland**	**diagnostic use**. for growth hormone secretion from the pituitary
Growth hormone inhibiting hormone (somatostatin) • **inhibit GH release from anterior pit. Gland**	**Octreotide** is a synthetic analogue of somatostatin, longer action (t½ 1.5 h). S.C two or three times daily. Used in **acromegaly**

Hormones	Clinical application
Gonadotrophin releasing hormone (GnRH) **Stimulate LH & FSH from anterior pit. Gland**	induce spermatogenesis and fertility. **Pulsatile** administration via a a mini-pump evokes secretion of LH and FSH and is used to treat infertility. But **continuous** use evokes tachyphylaxis owing to gonadal secretions are reduced
● GnRH ANALOGS **Leuprolide, Goserline**	**prolonged continuous** administration → Ovarian suppression used in controlled ovarian hyperstimulation → Testosterone suppression used in advanced prostate cancer
● GnRH RECEPTOR ANTAGONISTS **Cetrorelix, Ganirelix**	**Blocks GnRH receptors ,** → used for controlled ovarian hyperstimulation → Used for for advanced prostate cancer

IVF

(In vitro fertilization)
Protocol





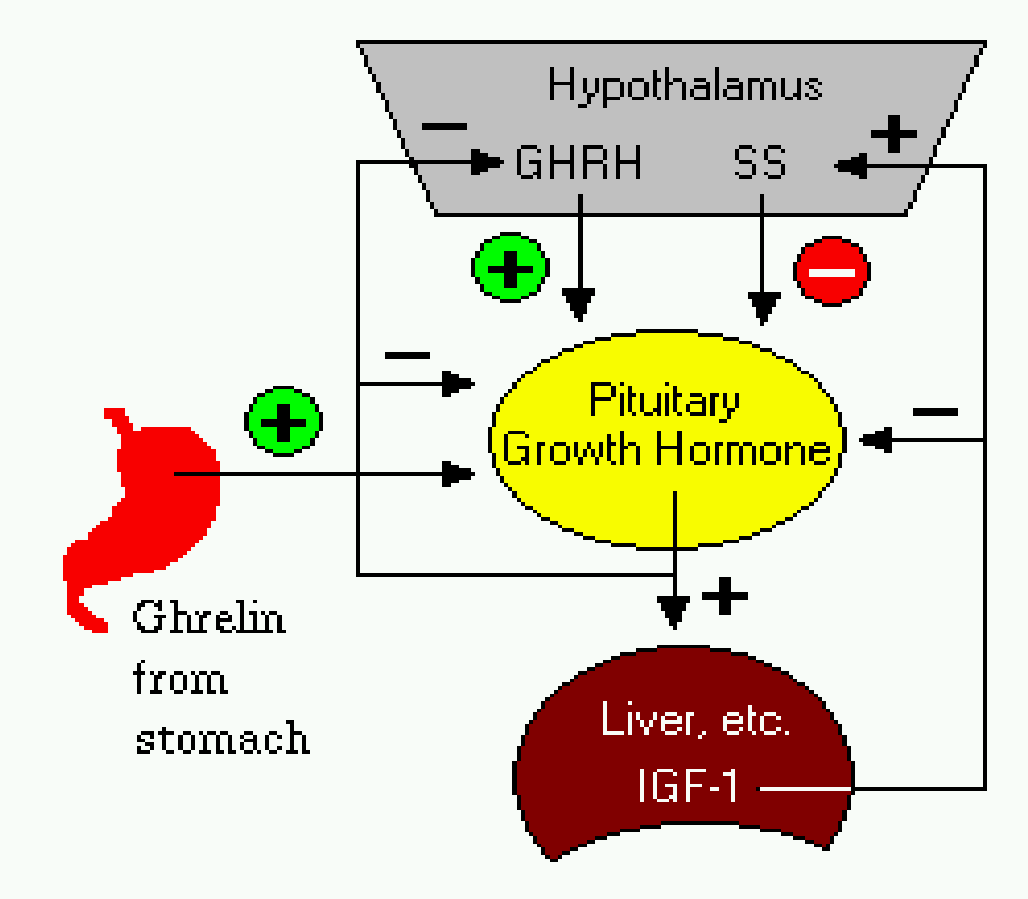
Hormones	Clinical application
Prolactin releasing hormone (PRH) **Stimulate prolactin from anterior pit. Gland**	!!!!!!!!!!!!!!!!!!!!!!!
Bromocriptine, Cabergoline (D2 agonist)	Inhibit prolactin secretion, used in Hyperprolactinemia, which is associated with galactorrhea and hypogonadism

Anterior Pituitary Hormones

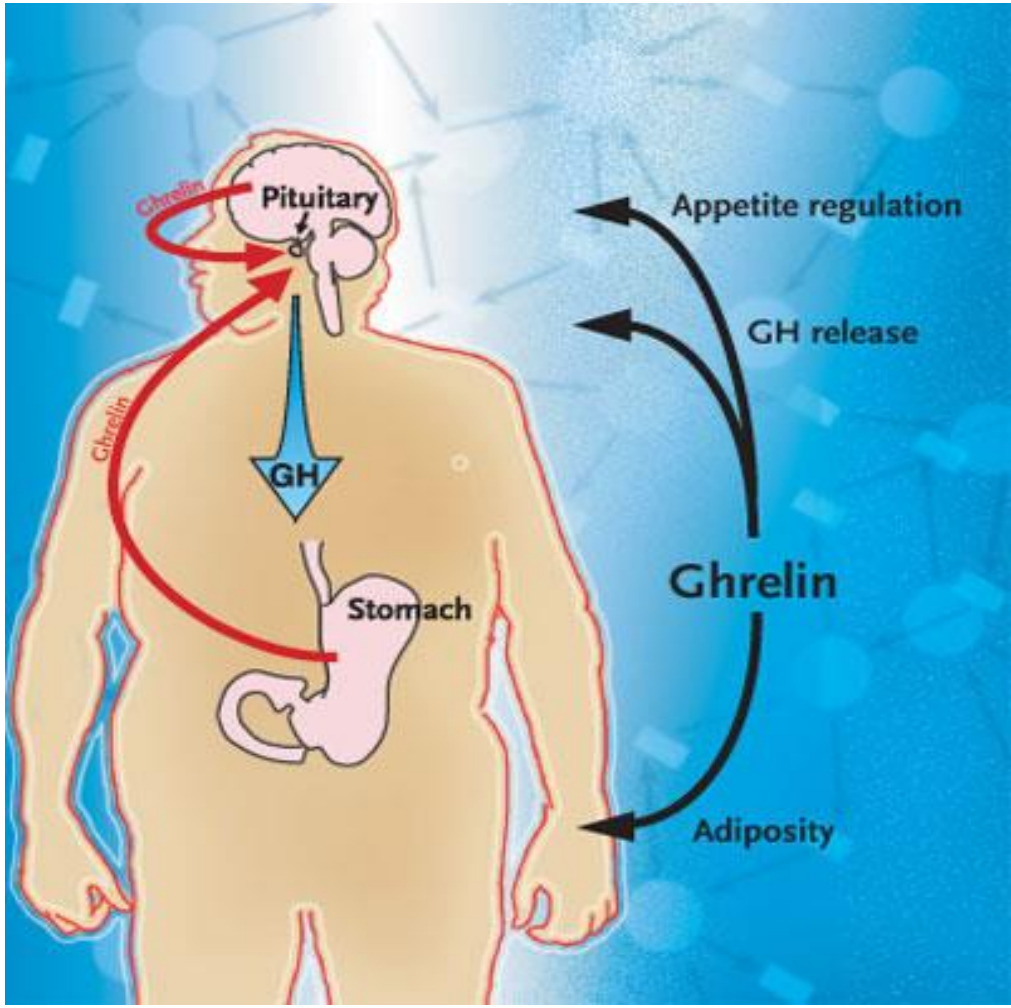
Hormones released from **ANTERIOR lobe** by Hypothalamic releasing hormones

1.Growth Hormone

- GH (somatotropin) a **peptide** hormone
- GH is secreted by anterior pituitary cells called somatotrophs, which release between 1-2mg each day. GH levels rise progressively during childhood and peak during the growth spurt that occurs in puberty.
- GH stimulated by **GHRH & by Ghrelin hormone.**
- GH inhibited by **Somatostatine** hormone
- GH stimulate longitudinal growth of bones & increases muscle mass, thru induction of IGF-1



- Ghrelin hormone released from <u>hypothalamus</u> stimulate GH.
- also Ghrelin released from <u>fundus of stomach</u> during fasting to stimulates appetite and increases food intake, apparently by central actions on NPY.



Disease States

- *Growth hormone* **deficiency or excess** [lesions in either the hypothalamus, the pituitary or in target cells]

➢ ***GH deficiency***

→ *growth retardation &* dwarfism *(childhood)*

Disease States

➢ *GH excess*

childhood before union of epiphysis in long bone)

overgrowth of muscles → *Gigantism*

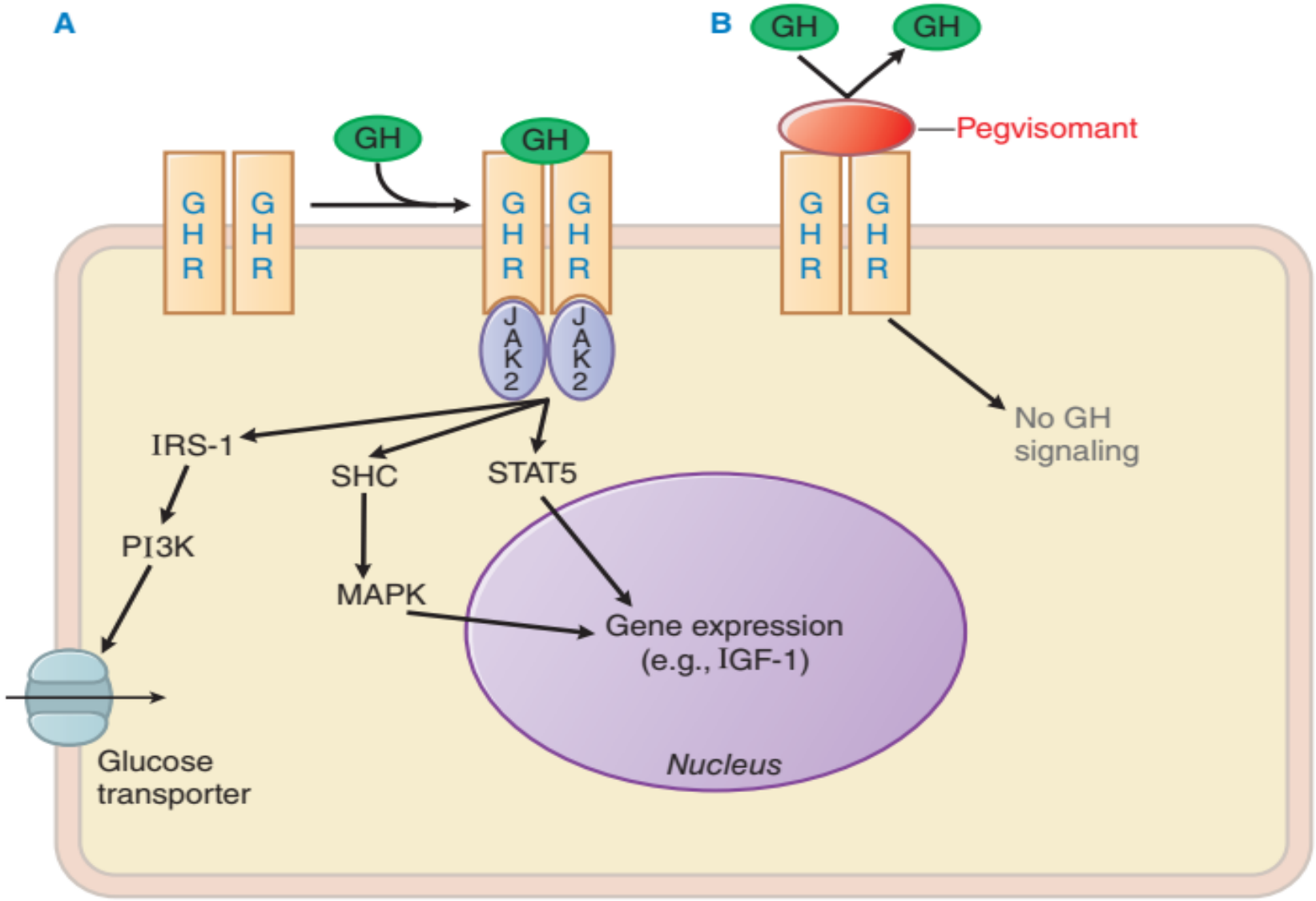
adulthood bone become thicker, Ptn. become diabetic

→ *Acromegaly*

Acromegaly

Gigantism and dwarfism

Drug	Clinical application
GH AGONIST **Mecasermin** **(IGF-I agonist)**	**Replacement in IGF-I deficiency that is not responsive to exogenous GH**
GH ANTAGONIST • **Octreotide** **(Somatostatin Analogue)** • **Pegvisomant** **(GH Rc antagonist)**	• **Acromegaly** • **Carcinoid tumors [**neuroendocrine **tumors]**

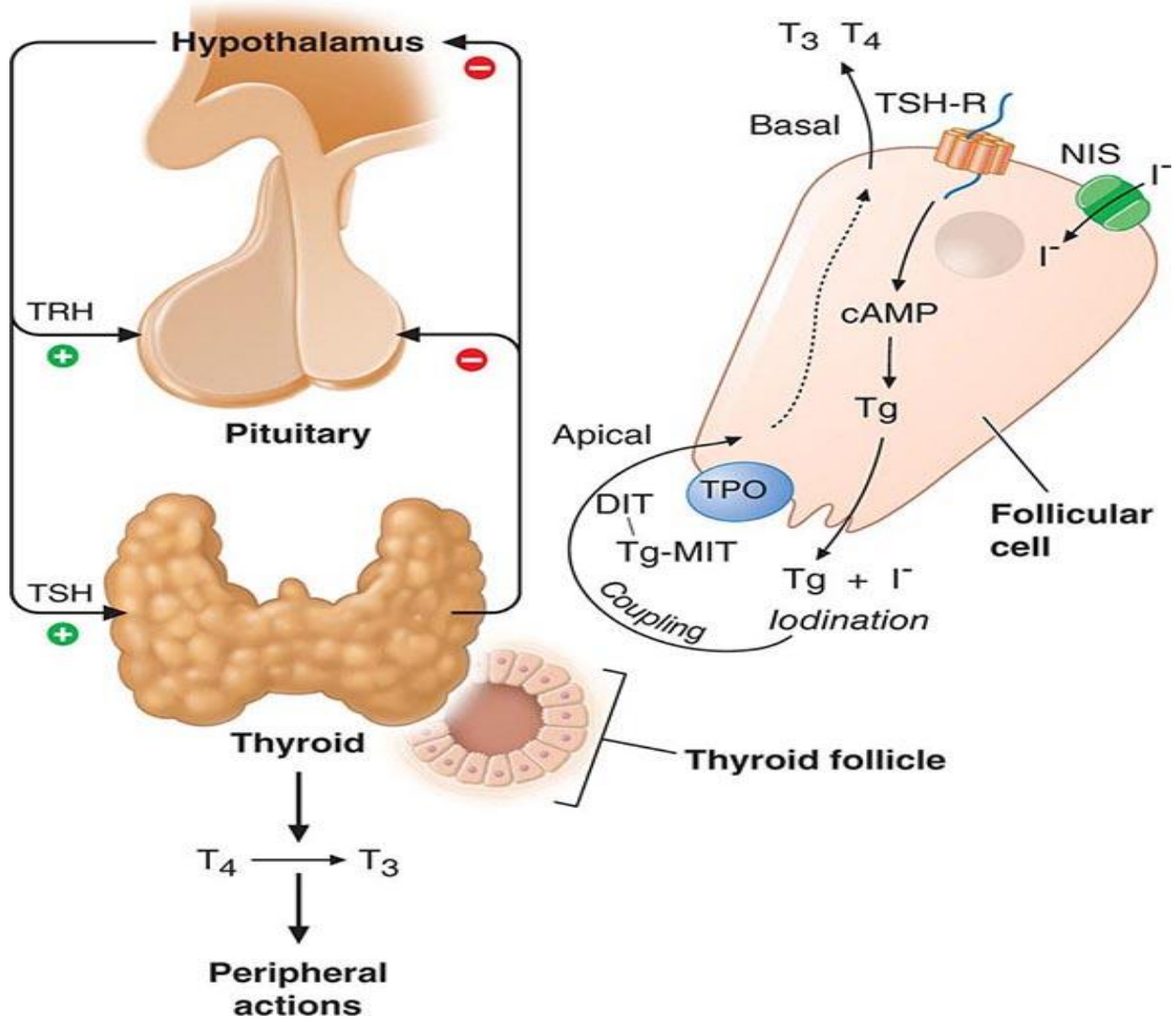

A
B
GH
GH
GH
GH
Pegvisomant
GHR
GHR
GHR
GHR
GHR
GHR
JAK2
JAK2
No GH signaling
IRS-1
SHC
STAT5
PI3K
MAPK
Gene expression (e.g., IGF-1)
Nucleus
Glucose transporter

2. Thyroid stimulating hormone TSH

- A glycoprotein of anterior pituitary, controls synthesis and release of thyroid hormone from the gland.
- TSH used as **Diagnostic** to evaluate thyroid function

- TSH stimulated by TRH & inhibited by –ve feed back

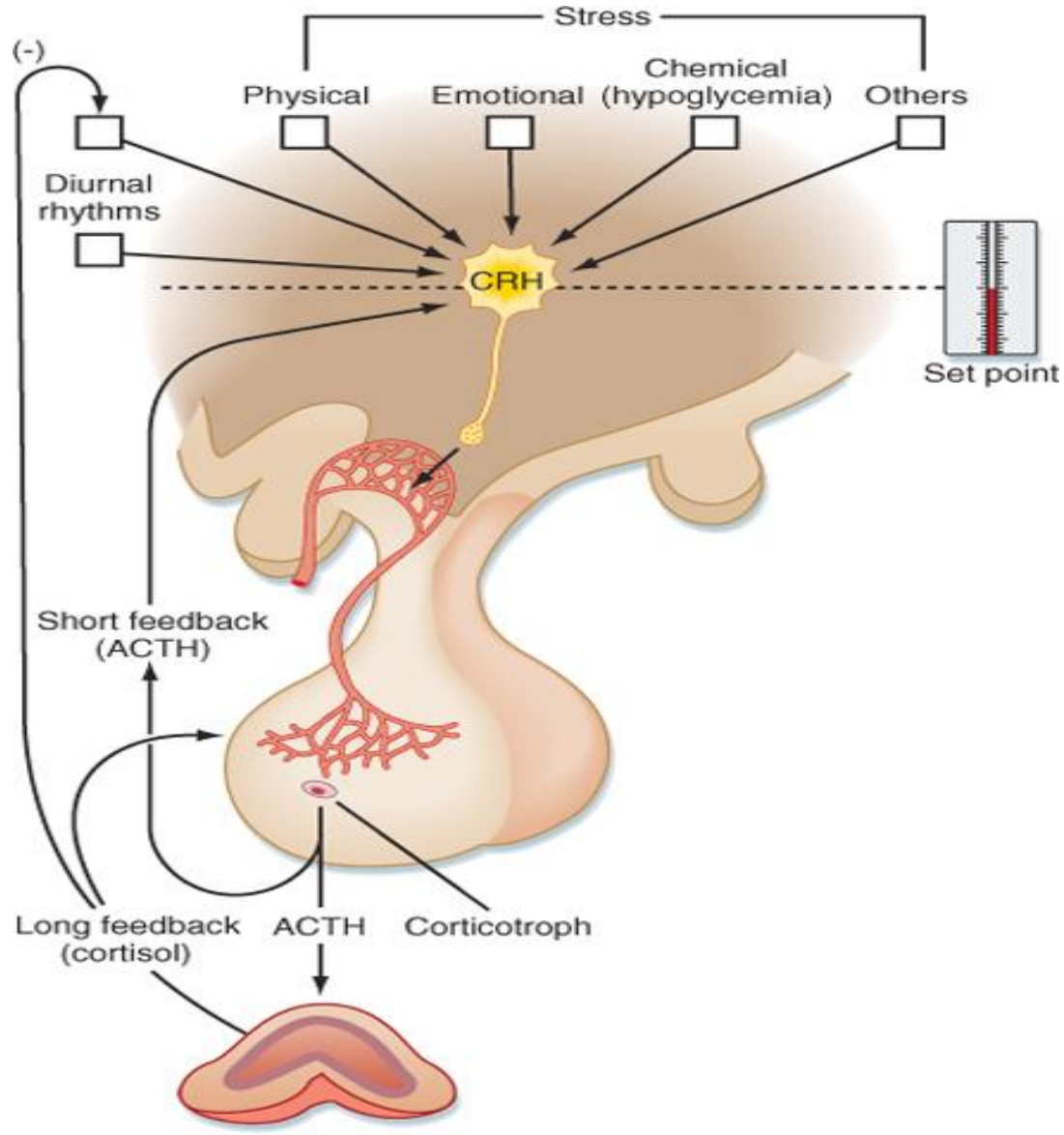
- TSH act on cell membrane receptor on thyroid follicle



3. Adrenocorticotropine (ACTH)

- secreted in **intermittent pulses** thru a day , high in the morning & fall throughout the day.
- This is called a **diurnal rhythm.**

- Secretion of ACTH is controlled by CRH & inhibited by –ve feed back mechanism.



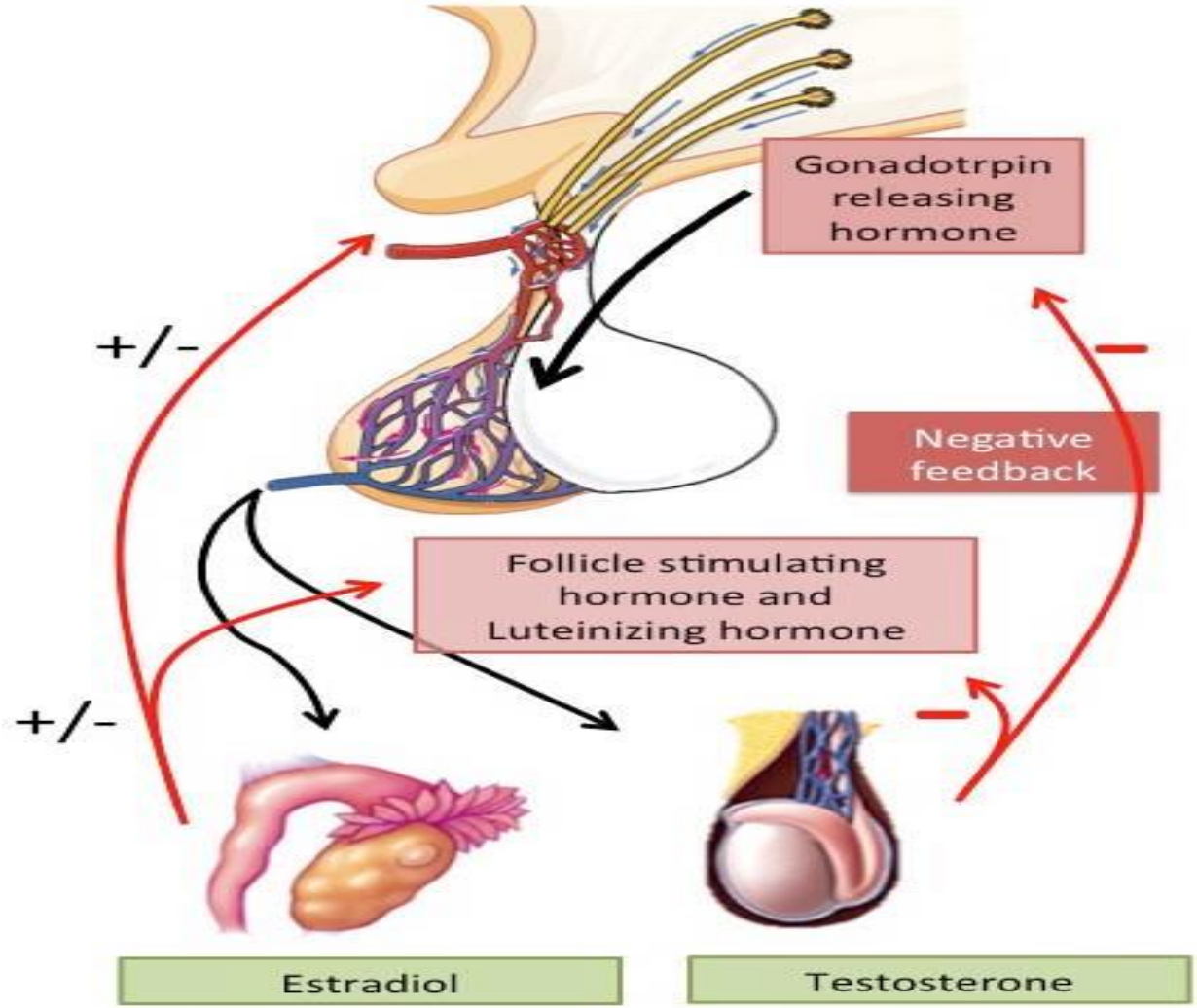
Synthetic analogue of ACTH

Cosyntropin

uses

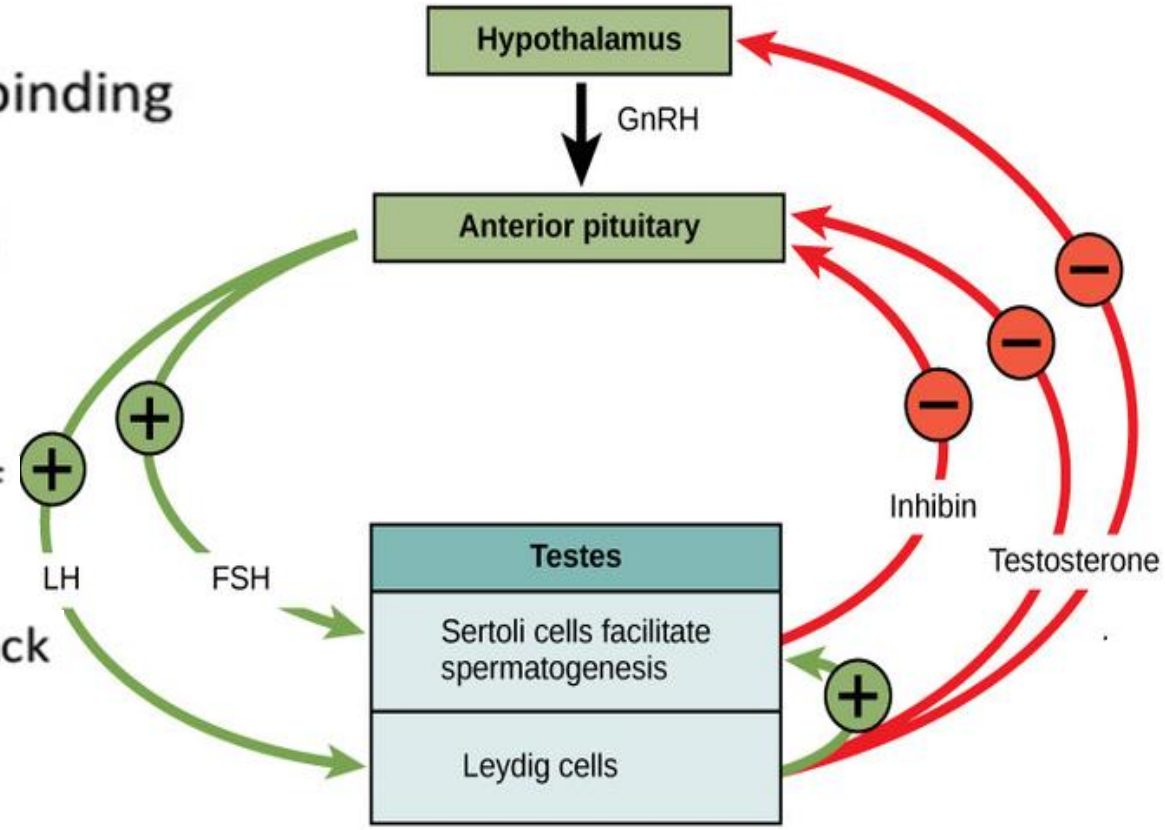
- **Diagnostic for 1 or 2nd adrenal insufficiency**
- **Infantile spasm (epilepsy) with Vigabatrin**

4. Gonadotropin **(LH ; FSH)**

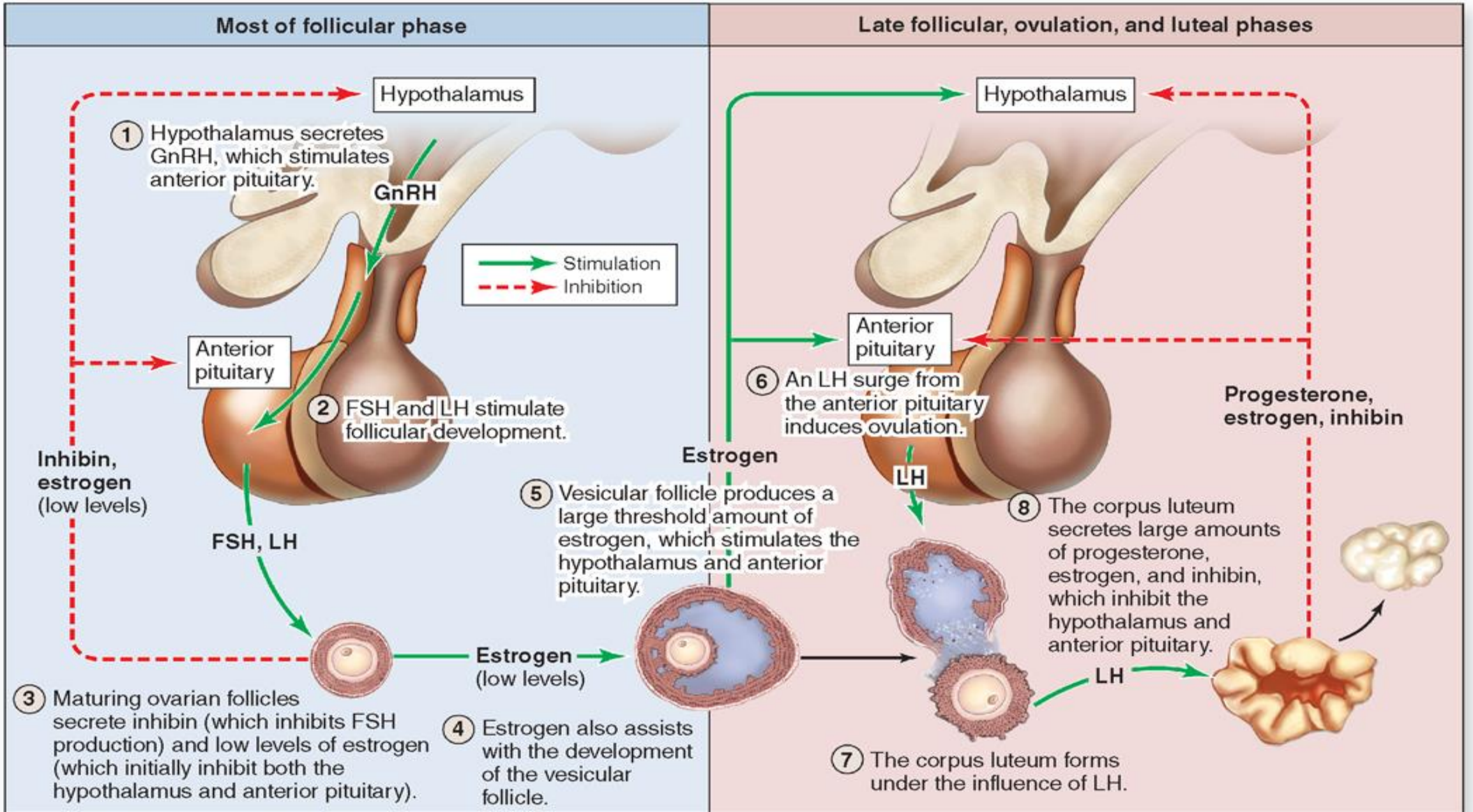


In male

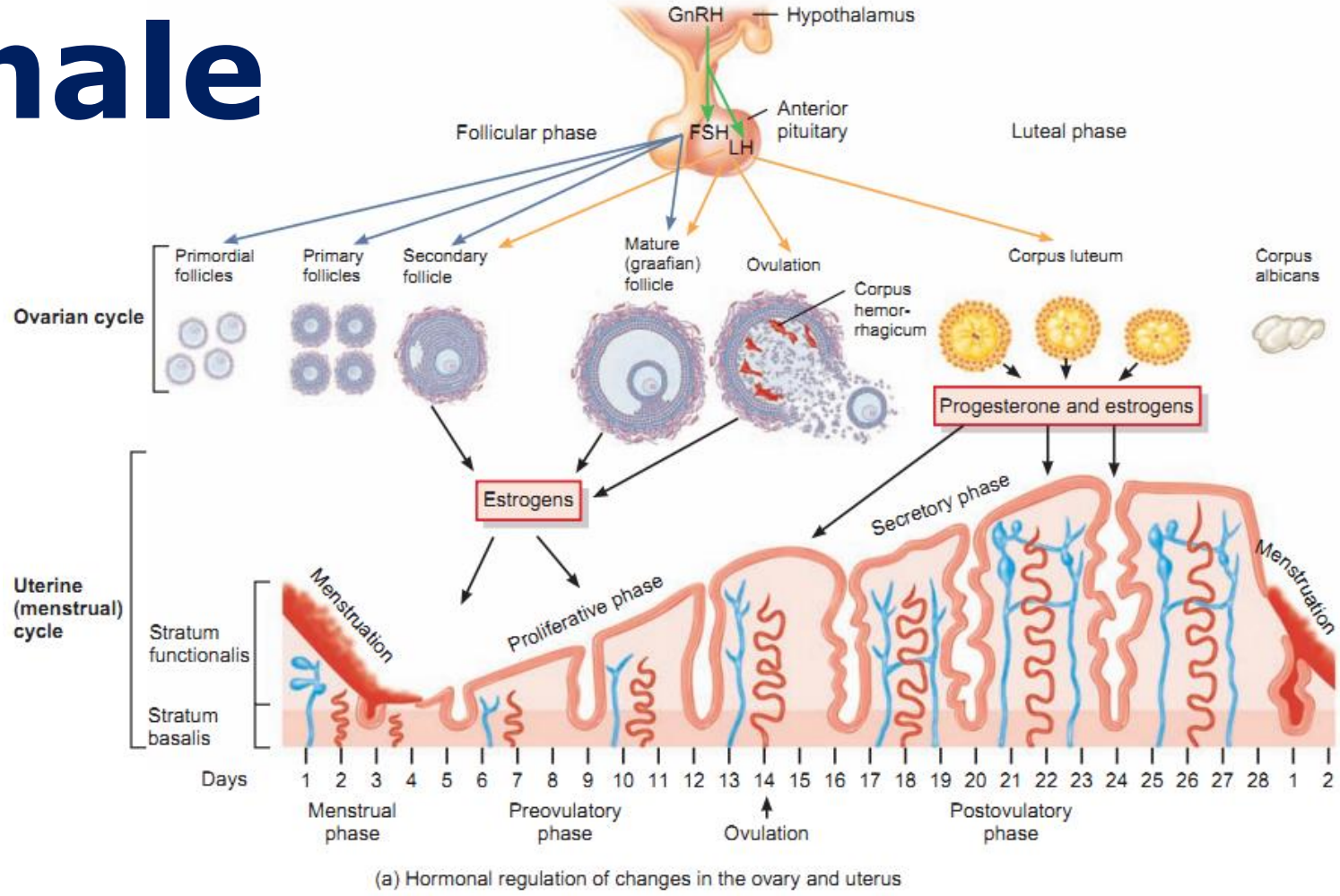
- **GnRH (hypothalamus) → FSH & LH (APG) → testosterone and androgens (testes)**
- FSH → sustentocytes release androgen-binding protein (ABP) → ↑ testosterone near spermatogenic cells → spermatogenesis
- LH → Leydig cells → testosterone → spermatogenesis
- Testosterone → negative feedback regulation of GnRH and gonadotropins
- **High sperm count → inhibin** → negative feedback regulation of GnRH and FSH



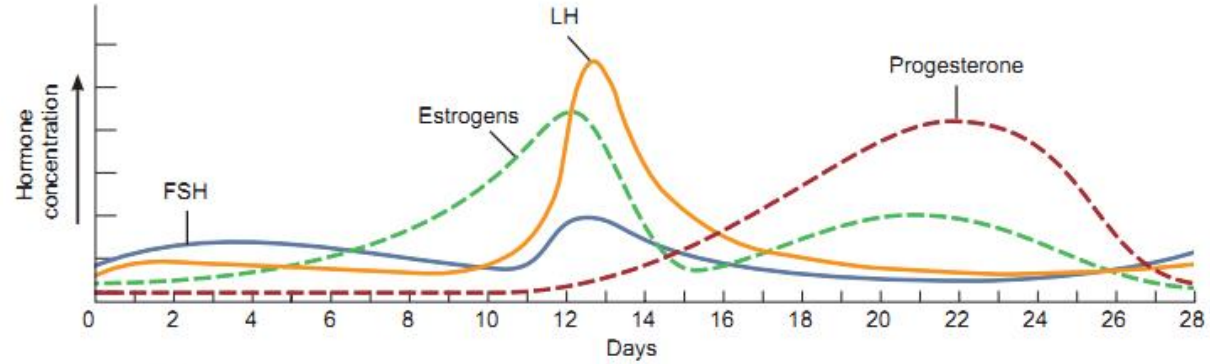
In Female


Most of follicular phase
Late follicular, ovulation, and luteal phases
Hypothalamus
1 Hypothalamus secretes GnRH, which stimulates anterior pituitary.
GnRH
Stimulation
Inhibition
Anterior pituitary
2 FSH and LH stimulate follicular development.
Inhibin, estrogen (low levels)
FSH, LH
3 Maturing ovarian follicles secrete inhibin (which inhibits FSH production) and low levels of estrogen (which initially inhibit both the hypothalamus and anterior pituitary).
Estrogen (low levels)
4 Estrogen also assists with the development of the vesicular follicle.
5 Vesicular follicle produces a large threshold amount of estrogen, which stimulates the hypothalamus and anterior pituitary.
Estrogen
Hypothalamus
Anterior pituitary
6 An LH surge from the anterior pituitary induces ovulation.
LH
7 The corpus luteum forms under the influence of LH.
8 The corpus luteum secretes large amounts of progesterone, estrogen, and inhibin, which inhibit the hypothalamus and anterior pituitary.
Progesterone, estrogen, inhibin
LH

In Female



(a) Hormonal regulation of changes in the ovary and uterus



Estrogen

Hypothalamus

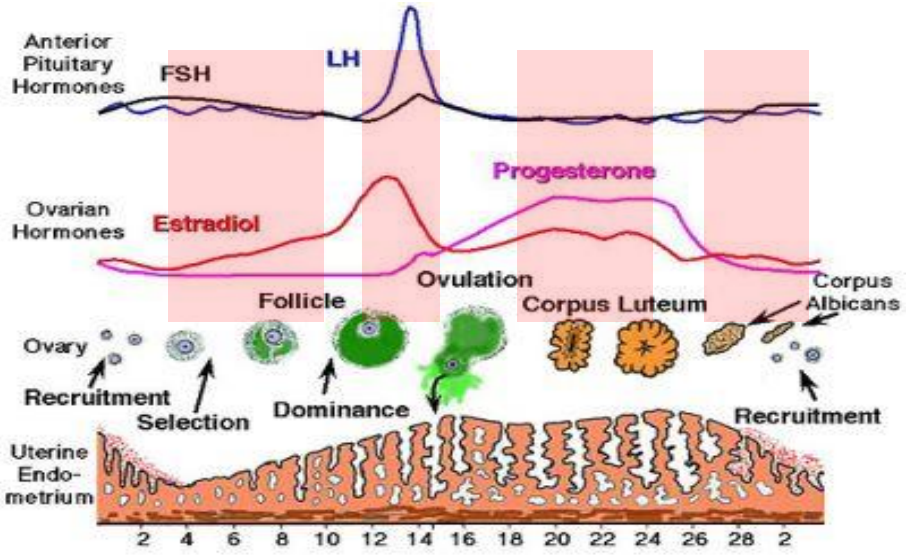
GnRH

AP

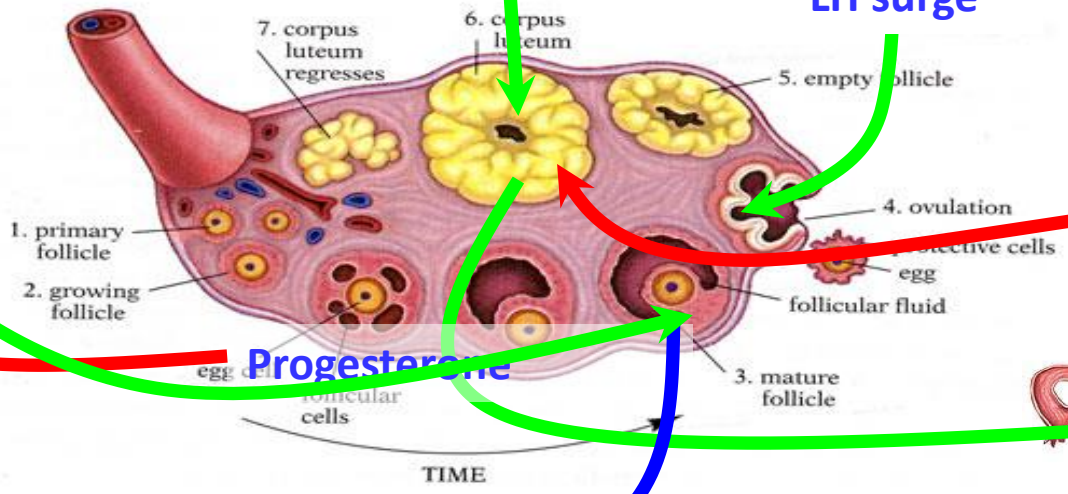
FSH

LH

Ir

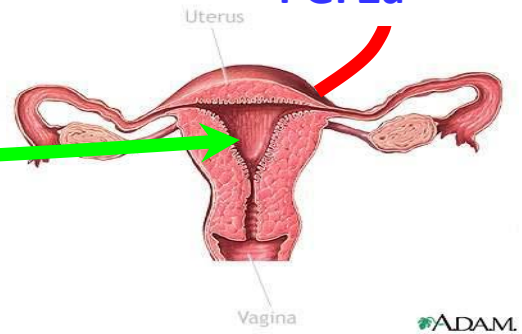


LH surge



Progesterone

PGF2a



Estrogens

Synthetic analogues of Gonadotropins

1- **Urofollitropin**: **Human FSH**

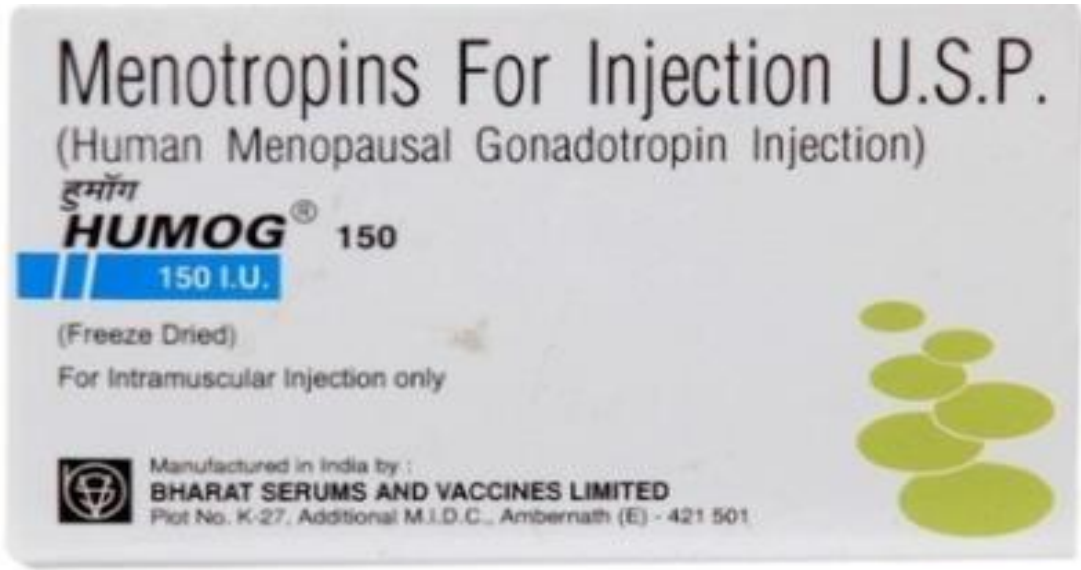
(from urine of postmenopausal women)

used in fertility problem cause the ovaries to produce eggs.

Mostly used in combination with HCG

2- **Menotropins** (hMG): (from urine of postmenopausal women), **contains both FSH and LH activity.**

Mostly used in combination with HCG



3- **Human chorionic gonadotropin (hCG) :**

Agonist at LH receptors

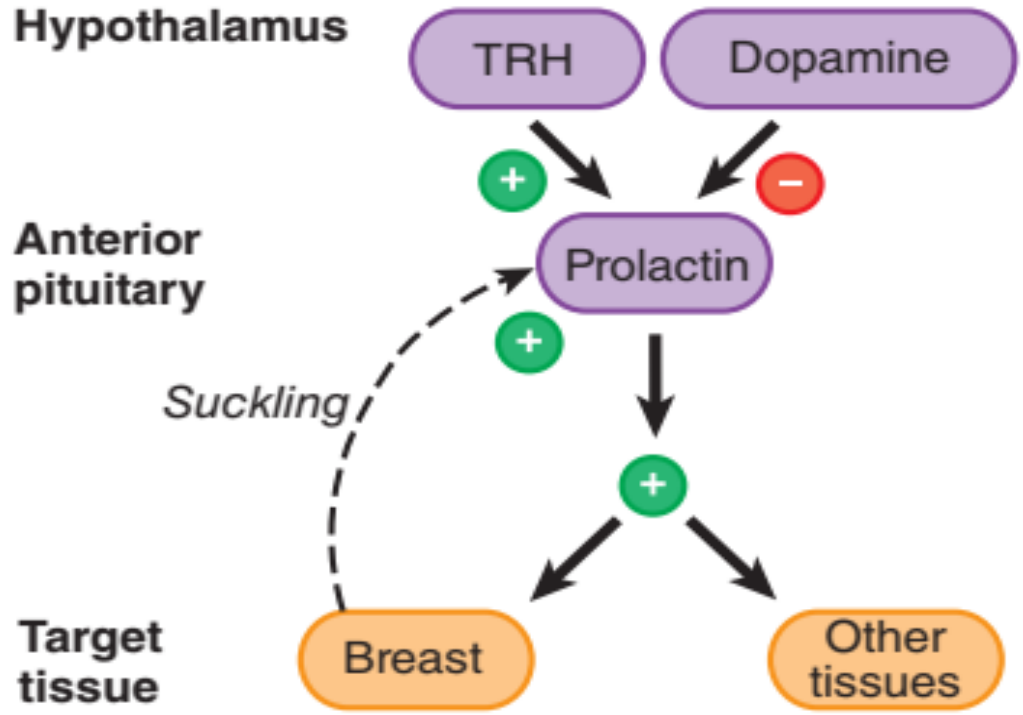
- It produced during pregnancy formed in the placenta, which nourishes the fertilized egg and becomes attached to the uterine wall.

- It used to cause **ovulation**

  Also increase **sperm count** in men.

5. Prolactin PRL

- **Peptide hormone** secreted by anterior pituitary & is critical for **lactation** and **breast development** in women.
- **TRH** and **hypothalamic VIP** have PRL-releasing properties while **DA** **inhibit PRL secretion**



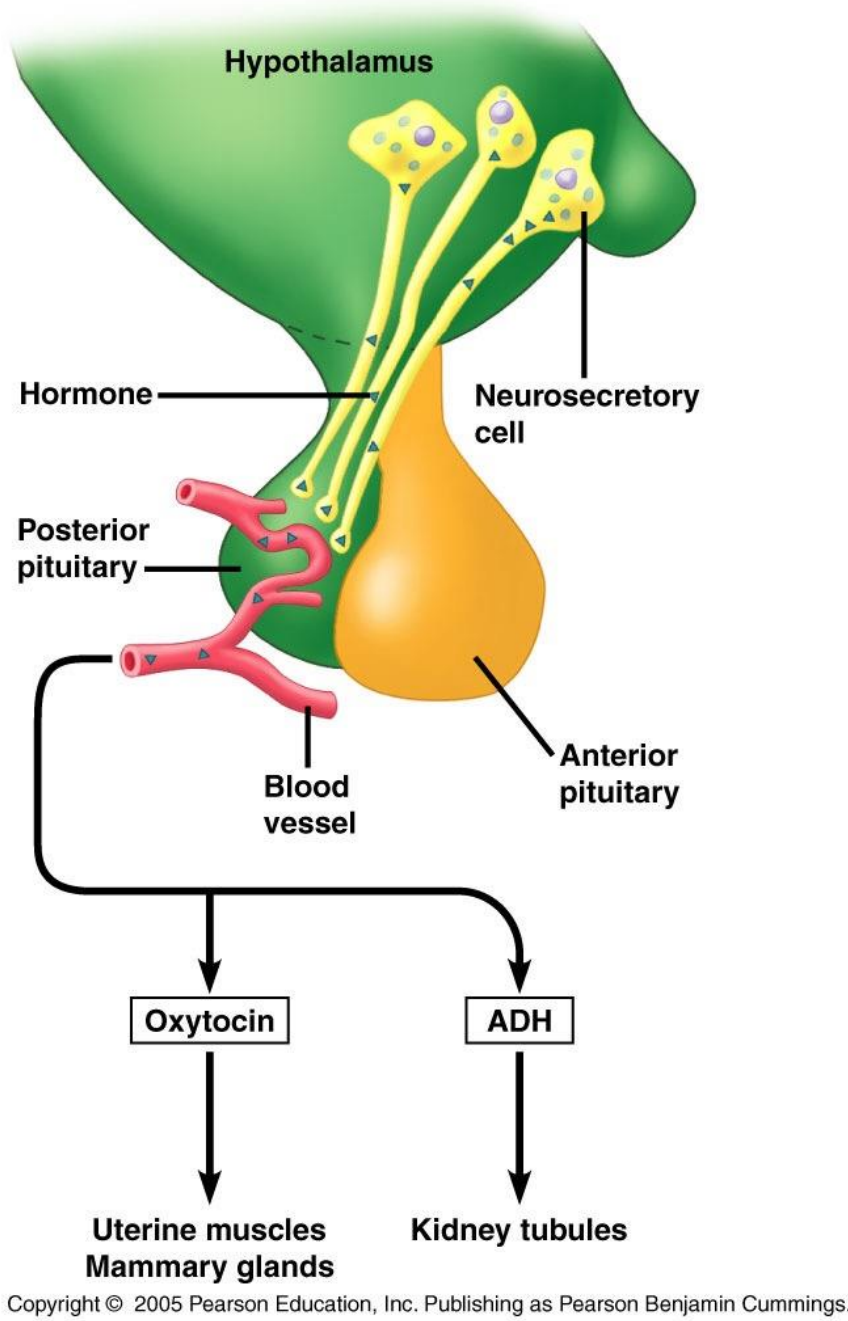
Dopamine Receptor Agonists

Bromocriptine, Cabergoline, & Quinagolide

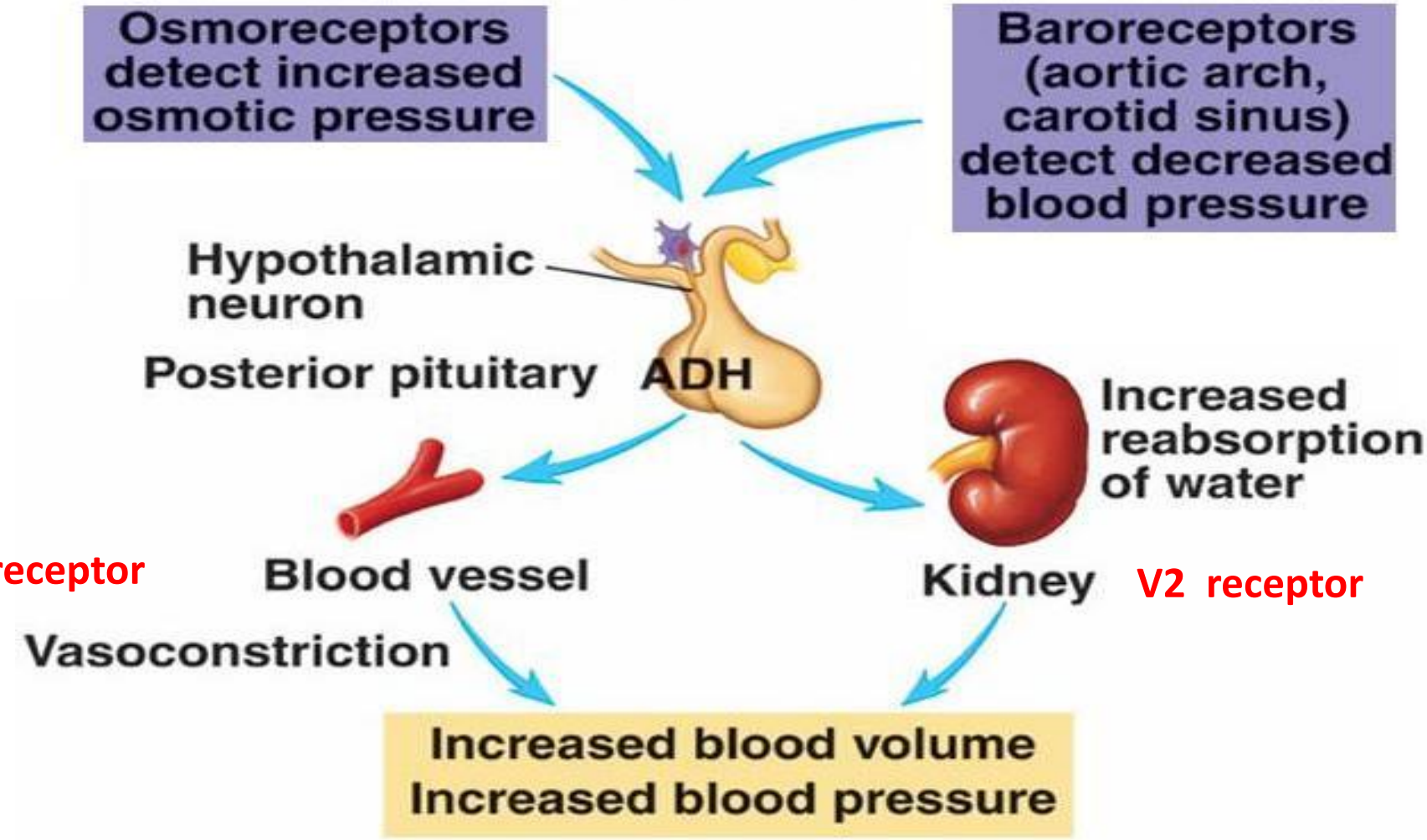
effectively reduce PRL levels, → relieving the inhibitory effect of hyperprolactinemia on ovulation and permitting most patients with prolactinomas to become pregnant.

Posterior Pituitary Hormones

Hormones synthesized by Hypothalamus & then transported thru neurosecretory fibers to **POSTERIOR lobe** where they stored until release.



1. Antidiuretic Hormone ADH (Vasopressin)



Synthetic analogues of ADH

- Desmopressin

used for control increased thirst and too much urination due to brain surgery or neurogenic diabetic inspidus.

ADH receptor blocker

- **Conivaptan** **V1 and V2 receptors.**
- **Tolvaptan** **has a 30-fold higher affinity for V2 than for V1 receptors.**

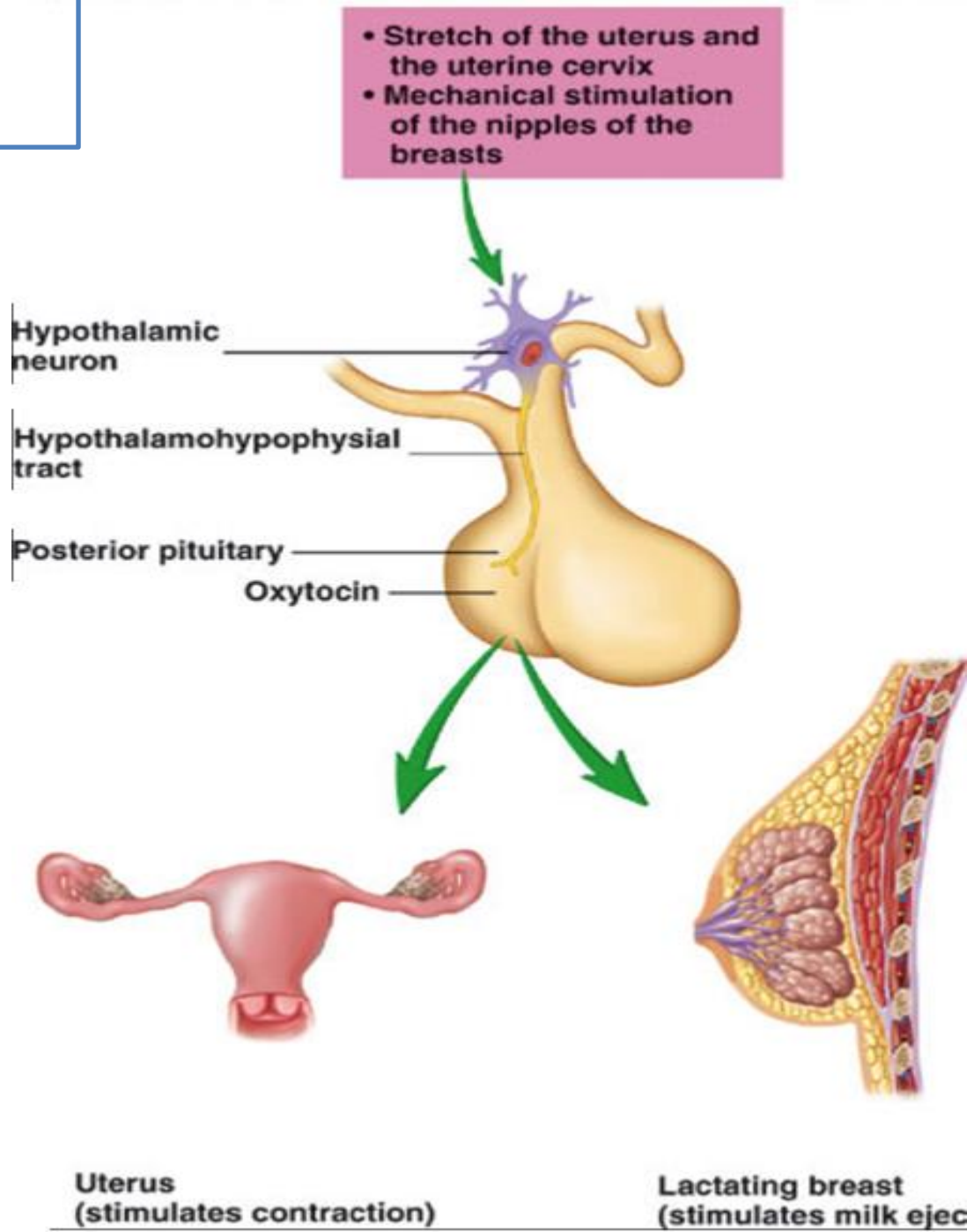
used in hyponatremia (low sodium level) & Heart failure.

Oxytocine

- they stored in **POSTERIOR lobe** until release **(by stretch of uterus or suckling of nipples)**.

Breast: contraction of myoepithelial cells in breast causing ejection of milk from breast alveoli & ducts to nipple

Uterus : contraction of uterus during labour



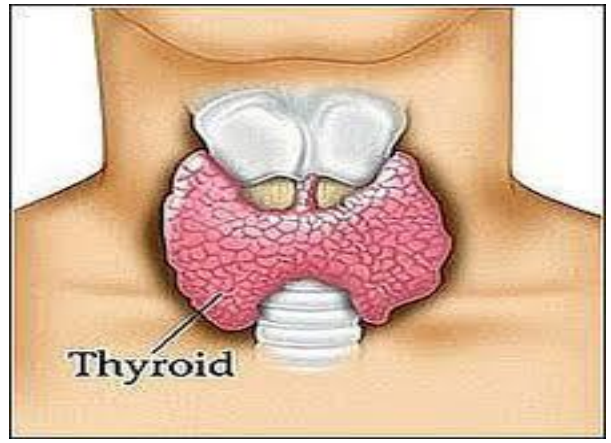
Synthetic analogues of Oxytocin

- Oxytocin injection

<u>induce labor</u> for conditions requiring early vaginal delivery such as Rh problems, maternal diabetes, preeclampsia, or ruptured membranes.

Thyroid & Antithyroid Drug

Thyroid gland

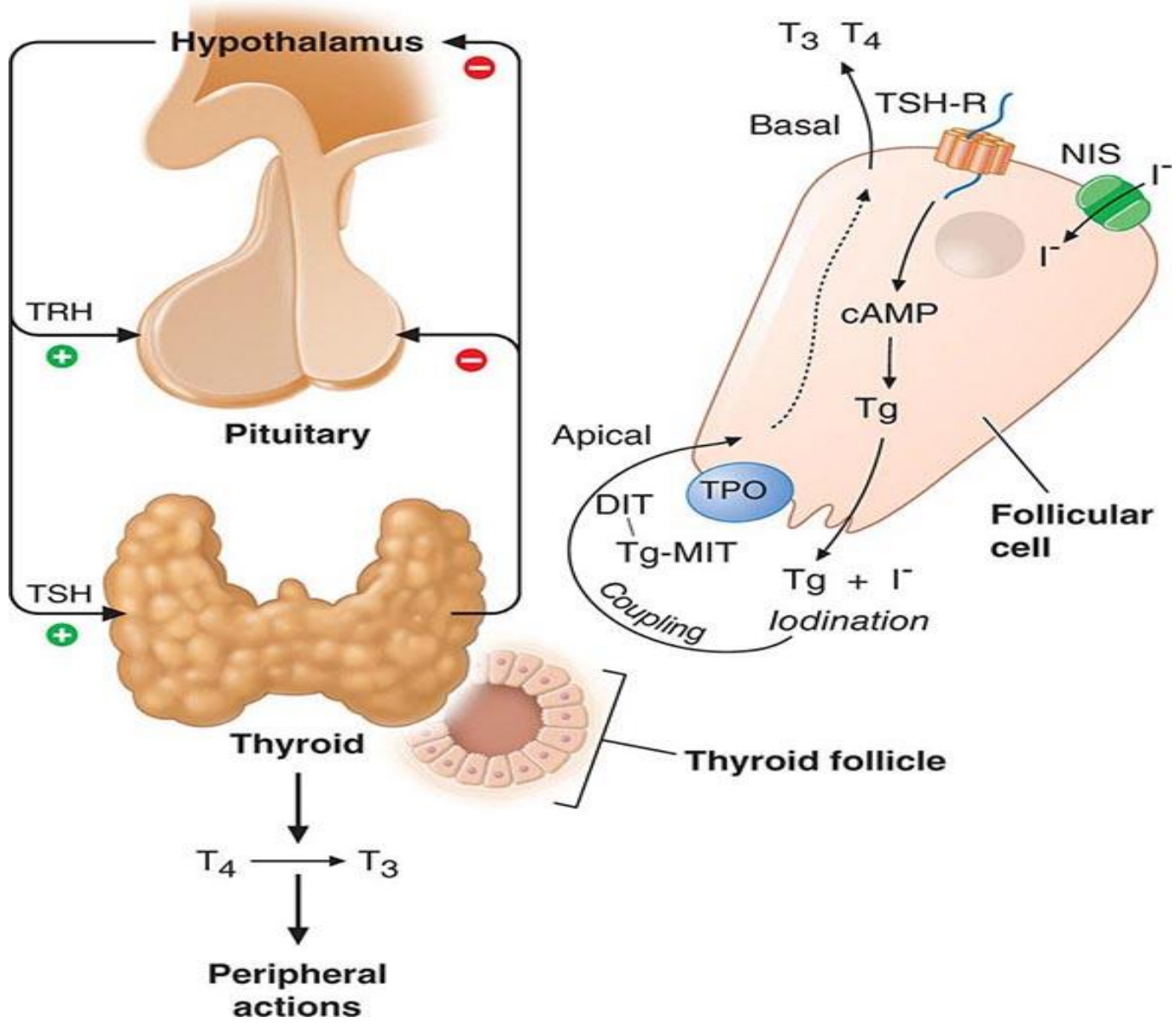


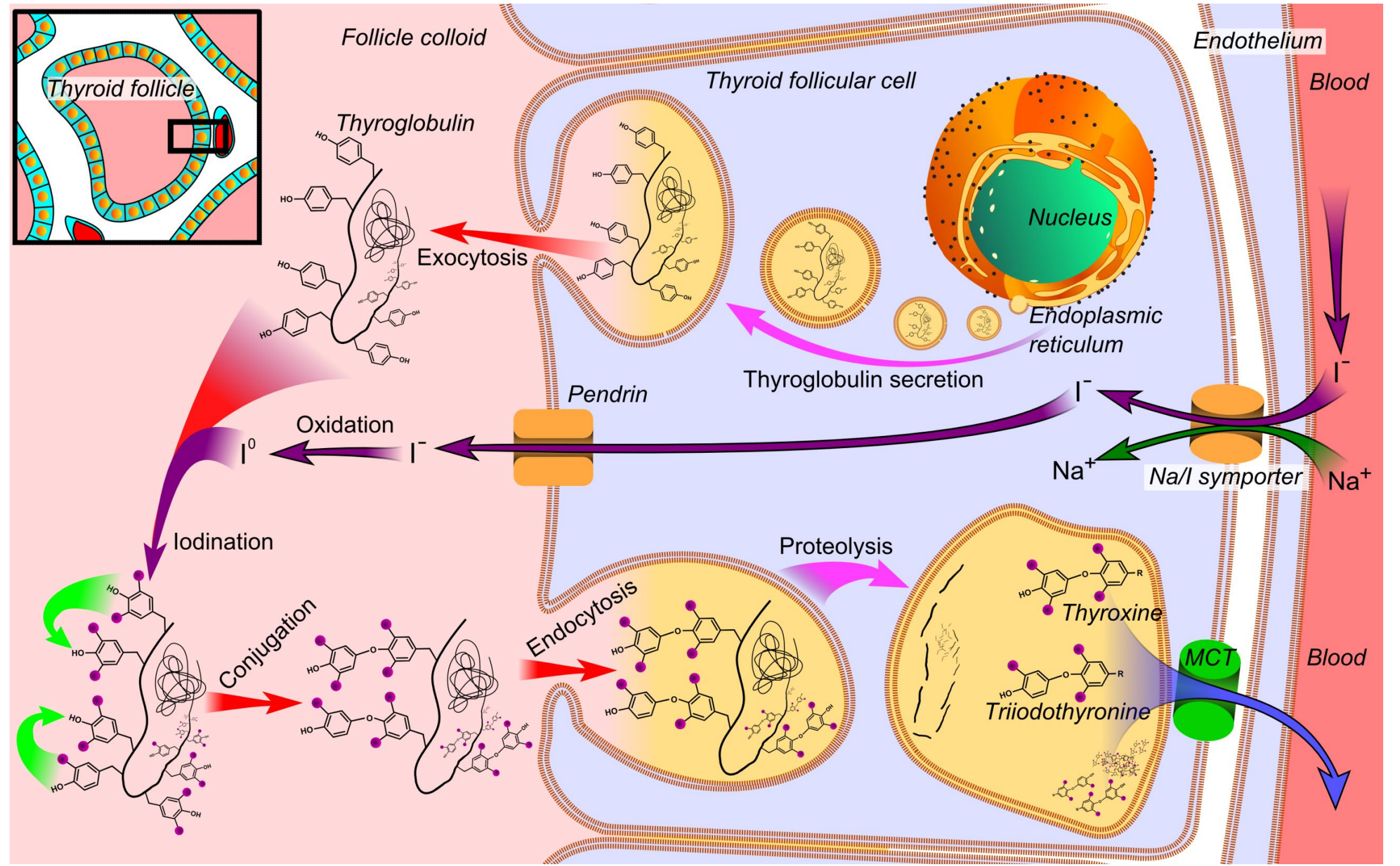
- Thyroid gland secretes 3 main hormones: ***thyroxin*** ***(T_4)***, ***triiodothyronine*** ***(T_3)*** **and** ***calcitonin*****.**
- T_4 and T_3 are critically important for **normal growth and development and for energy metabolism**

Hypothalamic-Pituitary-Thyroid axis

- TRH >>> TSH stimulate adenylyl cyclase >> synthesis and release of T4 and T3.

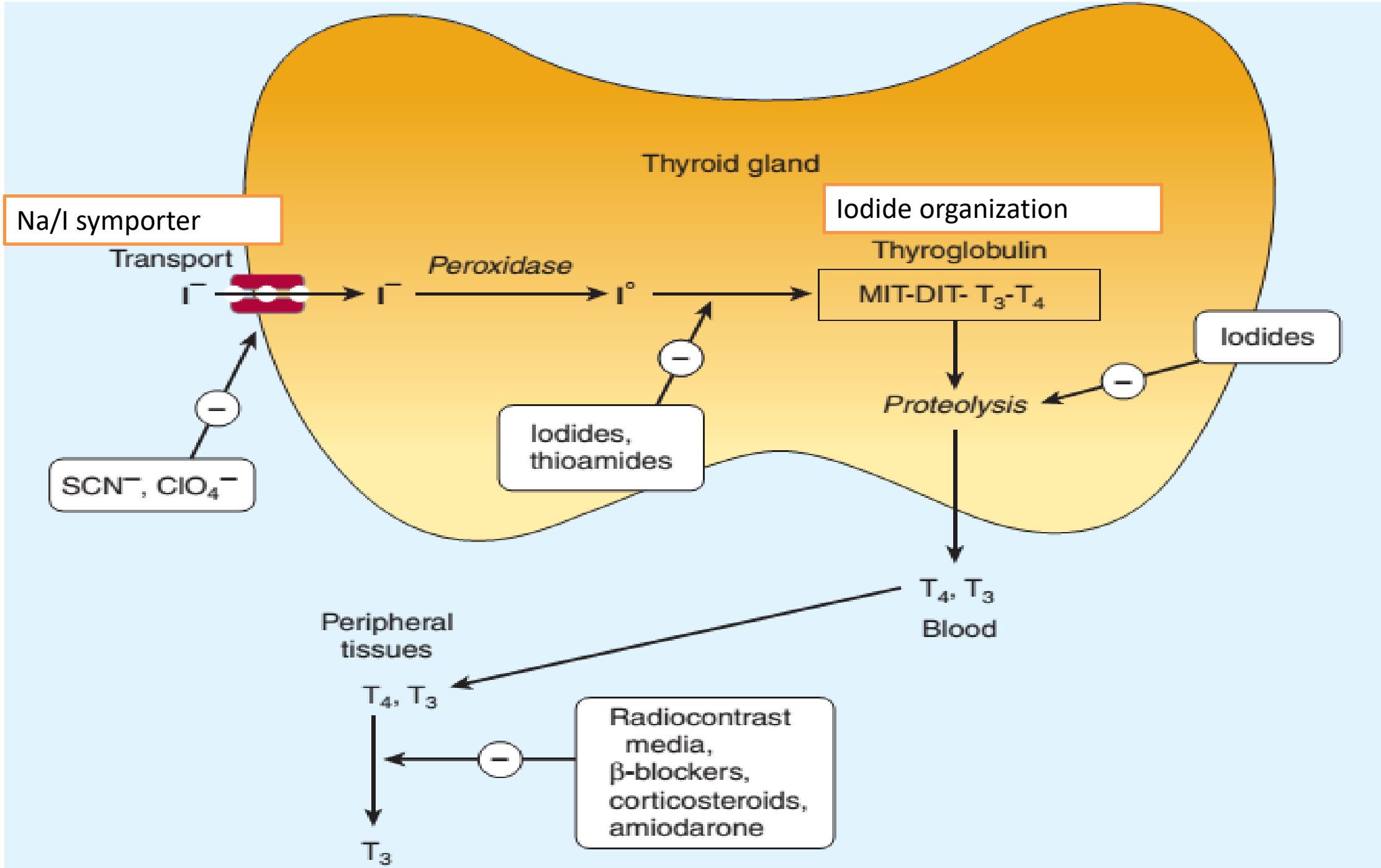
- Regulated by :
  - **negative feedback** fashion to block the action of TRH.
  - **large doses of iodine.**



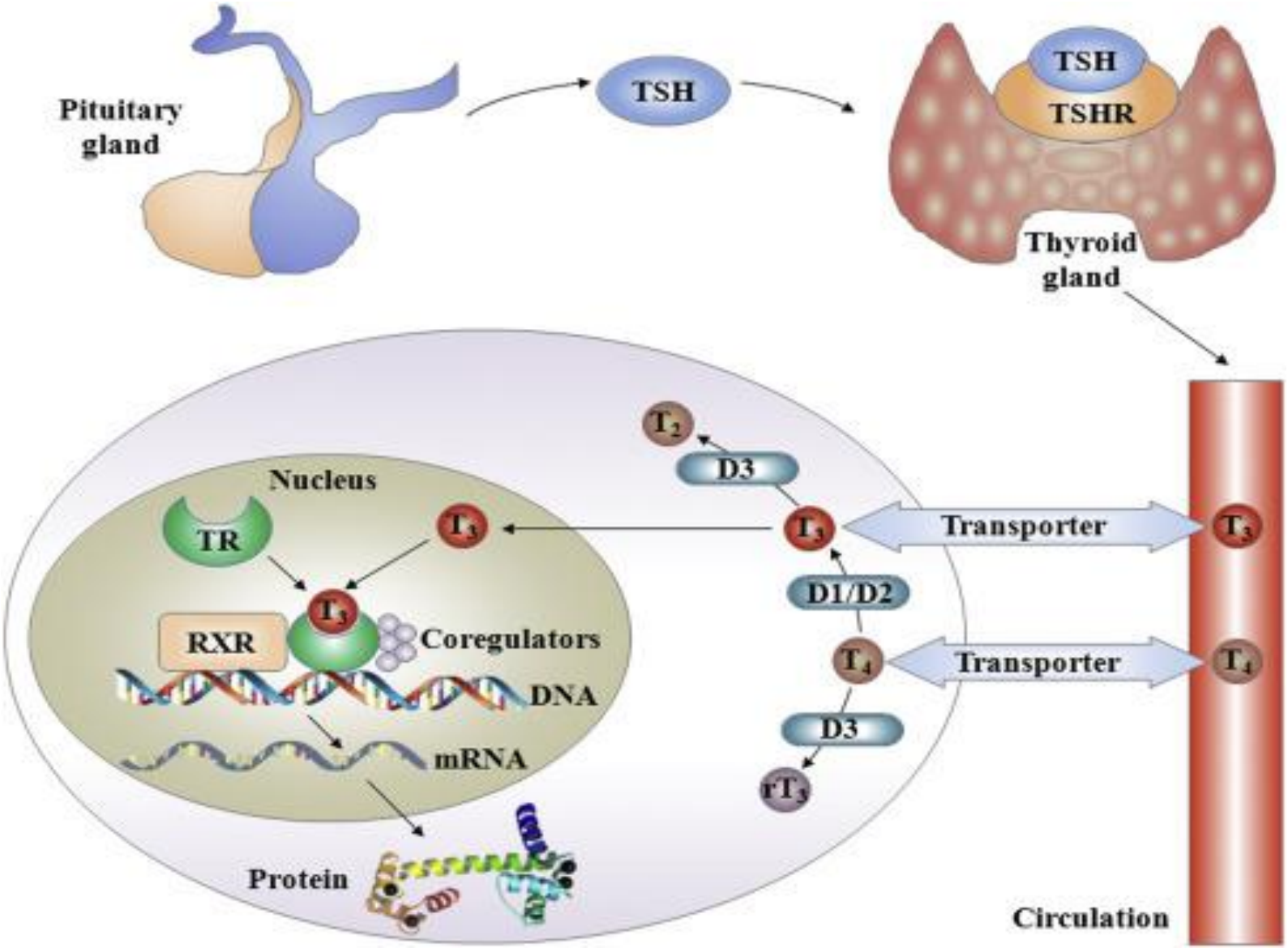

Thyroid follicle
Follicle colloid
Thyroid follicular cell
Endothelium
Blood
Thyroglobulin
Exocytosis
Nucleus
Endoplasmic reticulum
Thyroglobulin secretion
Pendrin
Oxidation
I^0
I^-
I^-
I^-
Na^+
Na^+
Na/I symporter
Iodination
Conjugation
Endocytosis
Proteolysis
Thyroxine
Triiodothyronine
MCT
Blood

Iodine metabolism

- Food contain mainly organic iodine (*not absorbed*) ;
- in GIT : organic iodine → inorganic iodide (*well absorbed*). 50% of circulating Iodide is trapped & concentrated in thyroid gland & 50% is excreted in urine.


Thyroid gland
Na/I symporter
Transport
I^-
I^-
Peroxidase
I°
Iodide organization
Thyroglobulin
MIT-DIT- T_3-T_4
Iodides
Proteolysis
Iodides, thioamides
SCN^-, ClO_4^-
T_4, T_3
Blood
Peripheral tissues
T_4, T_3
Radiocontrast media, β-blockers, corticosteroids, amiodarone
T_3

Thyroid hormone action



Thyroid hormone

- **Mechanism of action:**

  they **enter the cell & bind to intracellular thyroid receptors** in nucleus affect DNA transcription & synthesis of mRNA.

- **Actions of thyroid hormone:**

  1- **Thermogenic & Caloroginic effect**: → ↑ BMR & O2 consumption.

  2- **Metabolic effect:** a. CHO: ↑ glucose absorption.

  b. Fat: Lipolysis

  c. Protien: Catabolic effect

  d. Cholesterol: hypocholesteremia !!!

  3- **Growth:** Important for physical, mental

  4- **ANS:** supersenstivity of Adrenergic receptors

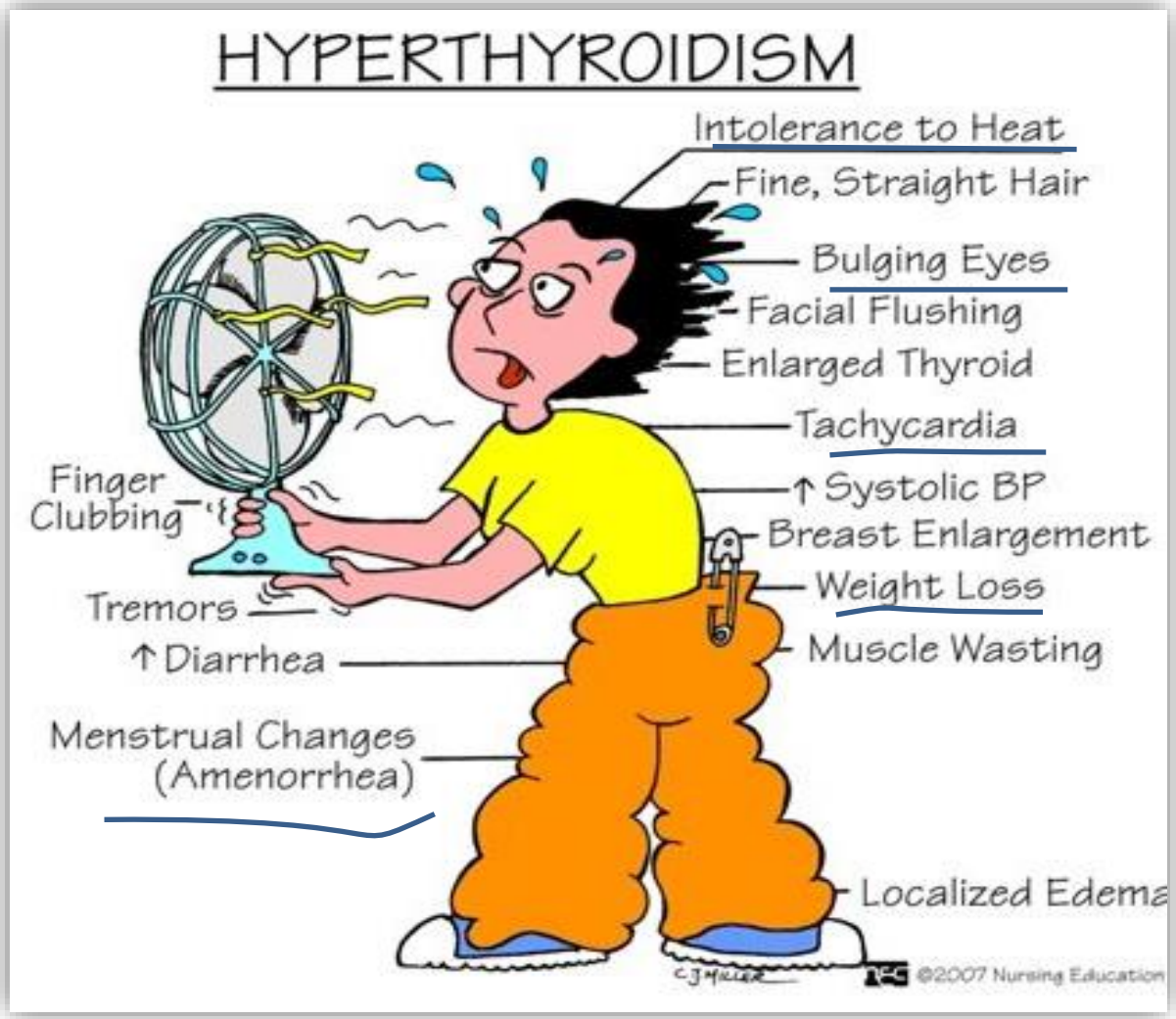
  5- **CVS:** Cardiac stimulation

  6- **GIT:** increase appetite & motility.

HYPERTHYROIDISM

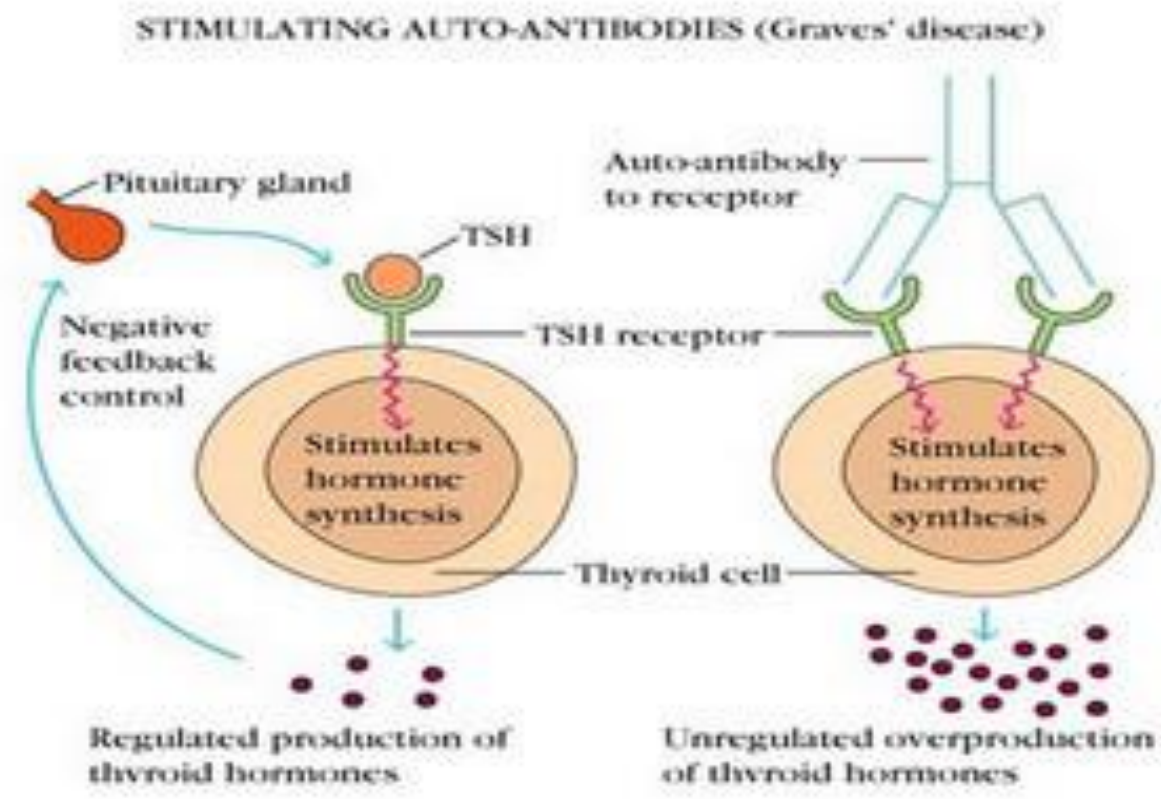
- **Thyrotoxicosis**: excessive activity of the thyroid hormones.
- **Laboratory Dx:**

- T3, T4 are elevated and TSH is suppressed **(more sensitive)**. .
  - Measurement of TRAb (TSH receptor antibody) in serum a value in diagnosis of Grave`s disease
  - Thyroid scan



The most common forms of hyperthyroidism are:

① diffuse toxic goiter (also called Graves' disease) an autoimmune disease. Management Mostly by drug



② toxic nodular goiter: benign neoplasm or adenoma. Management Mostly by surgical

HYPOTHYROIDISM

- A decreased activity of the thyroid manifested by a reversible slowing down of all body functions.
  - in fetus → Cretinism (dwarfism & mental retardation)
- Laboratory Dx.:

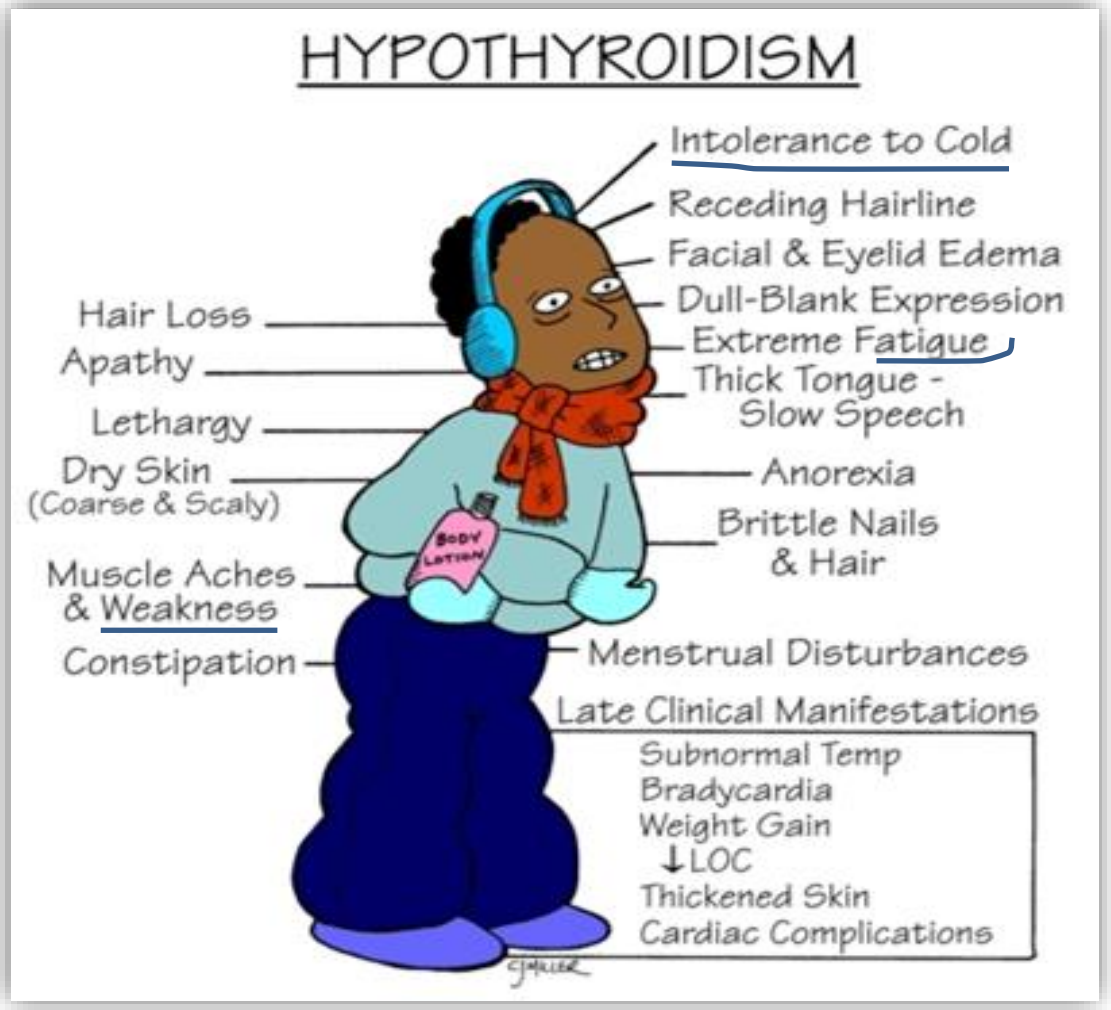
by the combination of a low free thyroxin and **elevated serum TSH (more sensitive)**.

- **Common cause of hypothyroidism**

is probably Hashimoto's thyroiditis, an immunologic disorder.

- **Management (replacement)**

The most satisfactory preparation is **levothyroxine.**



Management of Hyperthyroidism

- **Surgically**: used only when compression of the trachea
- **Pharmacologically**: antithyroid drugs

  1 -Thioamides

  2- Ionic inhibitors (old drugs)

  3- Iodide

  4- Radio active iodine

  5- β- blockers (Propranolol)

Thioamides

- Methimazole , Carbimazole & propylthiouracil
- **Mechanism of action:**

  ↓ synthesis of thyroid h. via inhibit oxidation of Iodide & inhibit Organification & coupling. click
- The effect appear after **3-6 weeks** till depletion of stores.
- Methimazole is **preferable** to propylthiouracil **(except in pregnancy and thyroid storm)** because it has a lower risk of liver injury and administered once daily.
- **protocol of ttt** : 4 weeks of high dose till euthyroid
  18 months half dose
  gradual withdrawal

Thioamides side effects

- **Agranulocytosis** (CBC must done regularly)
  ptn with Agranulocytosis → fever, sore throat
  ttt by blood transfusion + dexamethasone + filgrastim **(bone marrow stimulant)**
- increase vascularity of Gland,
- Hepatotoxicity (with Propythiouracil)
- GI disturbance.

Dr. AM Fouda *MD, PhD*

Endocrine Pharmacology - 04 - Pharmacology of thyroid gland

Ionic inhibitors

- K perchlorate, & Thiocyanate
- **Mechanism of action:**

  ↓synthesis of thyroid h. via competitive inhibition of Iodine uptake.
- **S/E:** Fatal aplastic anemia **(so not used now)**

Iodide

- Logol`s iodine & KI
- **Mechanism of action:**

1- ↓ size & vascularity of Gland & become firmer. (preop.)

2- inhibit Organification & iodine binding.

3 - at pharmacologic dose > 6mg/day inhibit hormone release thru inhibition of proteolysis click

- **Uses in**
  - Thyroid crisis (rapid onset 2-7 days)
  - Adjunctive in thyroidectomy to ↓ vascularity (before 7-14 days)
- **S/E:**
  - Iodism: conjunctivitis, metallic taste, rhinitis.
  - allergy & skin rash
  - foetal goiter

Radioactive Iodine

- I^{131}
- **Mechanism of action:**

  After oral administration , concentrated in gland & emit

  β particle and **γ rays** destruction of thyroid follicles.
- The effect appear after **2-3 months**.
- **Uses in**

  - Hyperthyroidism (old age, recurrence after surgery).
  - Cancer thyroid
- **S/E**: Hypothyroidism, malignant changes
- **CI** : in young (< 16yrs) , pregnancy & lactation.

β-Blockers

- Propranolol
- **Mechanism of action:**

1 - ↓ peripheral conversion of T_4 to more active T_3.

2 - control peripheral symptoms until effect of antithyroid appear

NB: lifesaving in Thyroid crisis.

SPECIAL PROBLEMS

Thyroid Storm

- or thyrotoxic crisis, is sudden acute exacerbation of the symptoms of thyrotoxicosis, a life threatening syndrome.

- Vigorous management is mandatory.

  - **Propranolol**, 1–2 mg slowly intravenously or 40–80 mg orally every 6 hours, is helpful to control the severe cardiovascular manifestations.

  - **propylthiouracil,** 250 mg orally / 6 hours. If the patient is unable to take propylthiouracil by mouth, a rectal formulation administered in a dosage of 400 mg / 6 hours as a retention enema. Methimazole may also be prepared for rectal administration in a dose of 60 mg daily.

  - **Hydrocortisone,** 50 mg intravenously every 6 hours, will protect the patient against shock and will block the conversion of T4 toT3.

Thyrotoxicosis during Pregnancy

- Ideally, women in the childbearing period with severe disease should have **I_{131}** or subtotal **thyroidectomy**, prior to pregnancy.

- radioiodine is **contraindicated** during pregnancy.

- **Propylthiouracil** (*fewer teratogenic risks than Methimazole*) can be given in the first trimester, and then methimazole can be given for the remainder of the pregnancy in order to avoid potential liver damage.

Myxoedema coma

A rare presentation of **hypothyroidism** in which there is:

- A depressed level of consciousness.
- Body temperature may be < 25°C.
- convulsions and cerebrospinal fluid (CSF) pressure and protein content are raised.
- ††† triiodothyronine is given as an i.v bolus of

20 ug followed by 20 ug 8hourly until there is sustained clinical improvement