Clinical endocrinology part 1

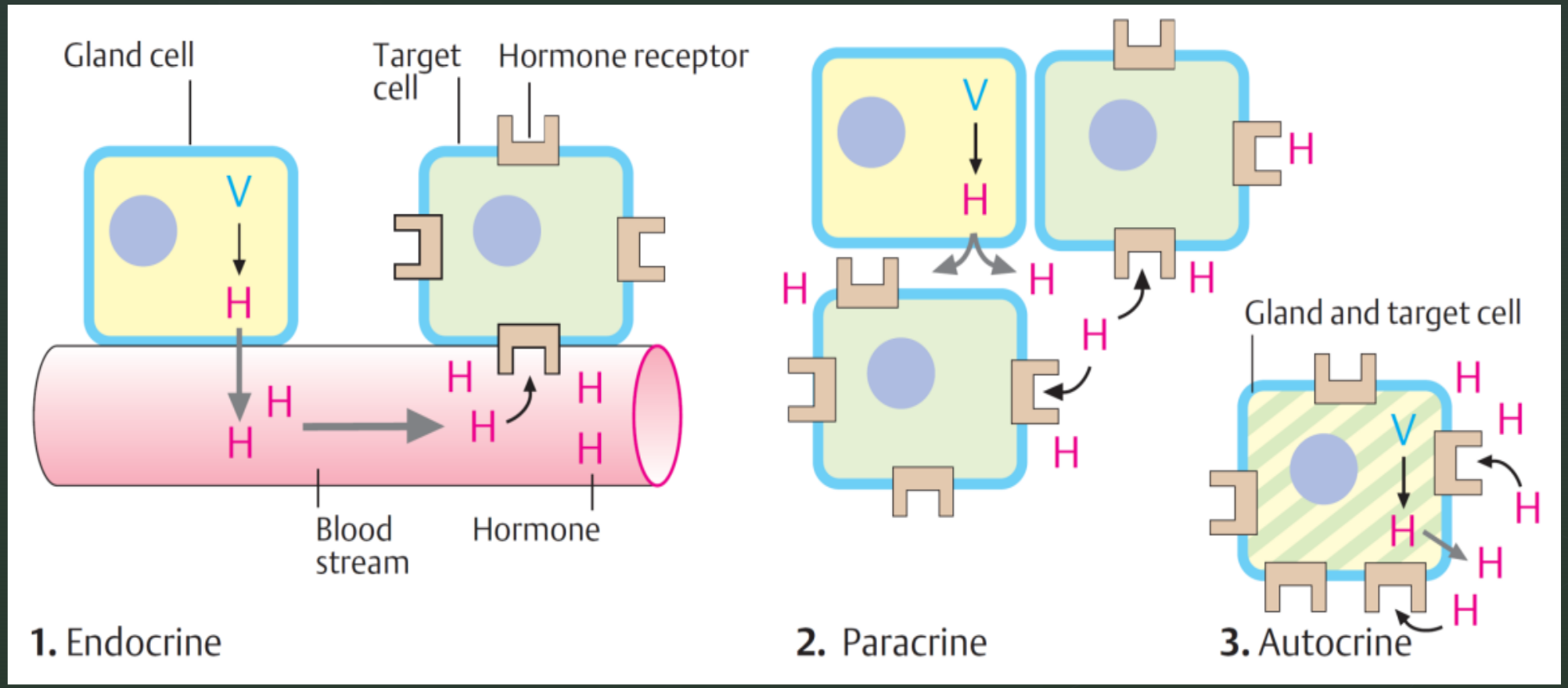
❑ Endocrine System

- - The endocrine system consists of a group of glands and organs that regulate and control various body functions by producing and secreting hormones.
- - The glands of the endocrine system do not have ducts but rather release their hormones directly into the bloodstream, so hormones are readily accessible to laboratory evaluation
- - Hormones are organic compounds secreted from the endocrine glands and circulate in the blood to act near to their site of release (local hormones) or at a distant organ.
- - Hormones cause changes in physiologic and chemical processes that help to maintain body equilibrium or homeostasis.

- Hormonal effects

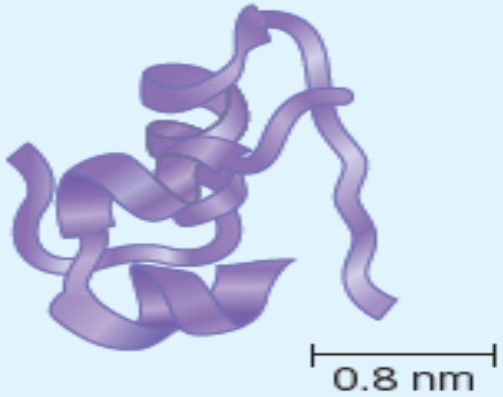
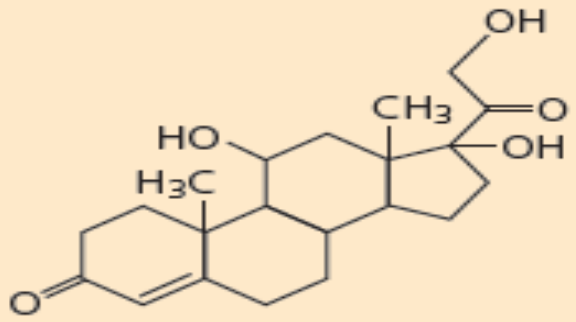
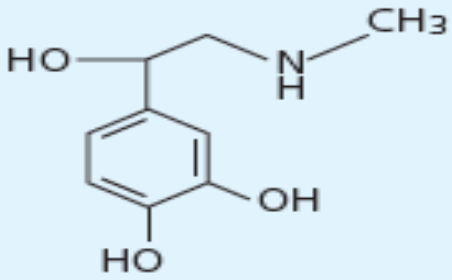
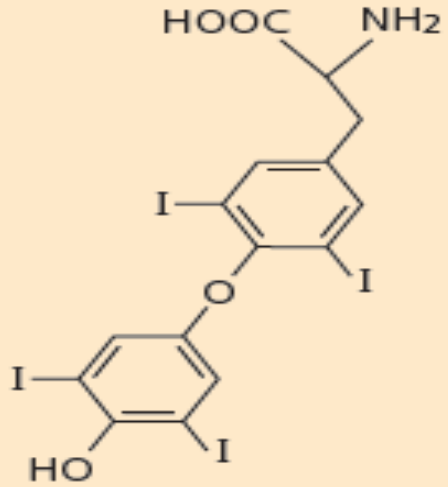
- 1) **Endocrine hormones:** they migrate from their site of synthesis to the site of action in the blood (Insulin).
- 2) **Paracrine hormones:** tissue hormones, the target cells for which are in the immediate vicinity of the glandular cells that produce them (GIT hormones)
- 3) **Autocrine hormones**: they pass their effects back to the cells that synthesize them (Prostaglandins)

Hormonal effects



Classes of Hormones

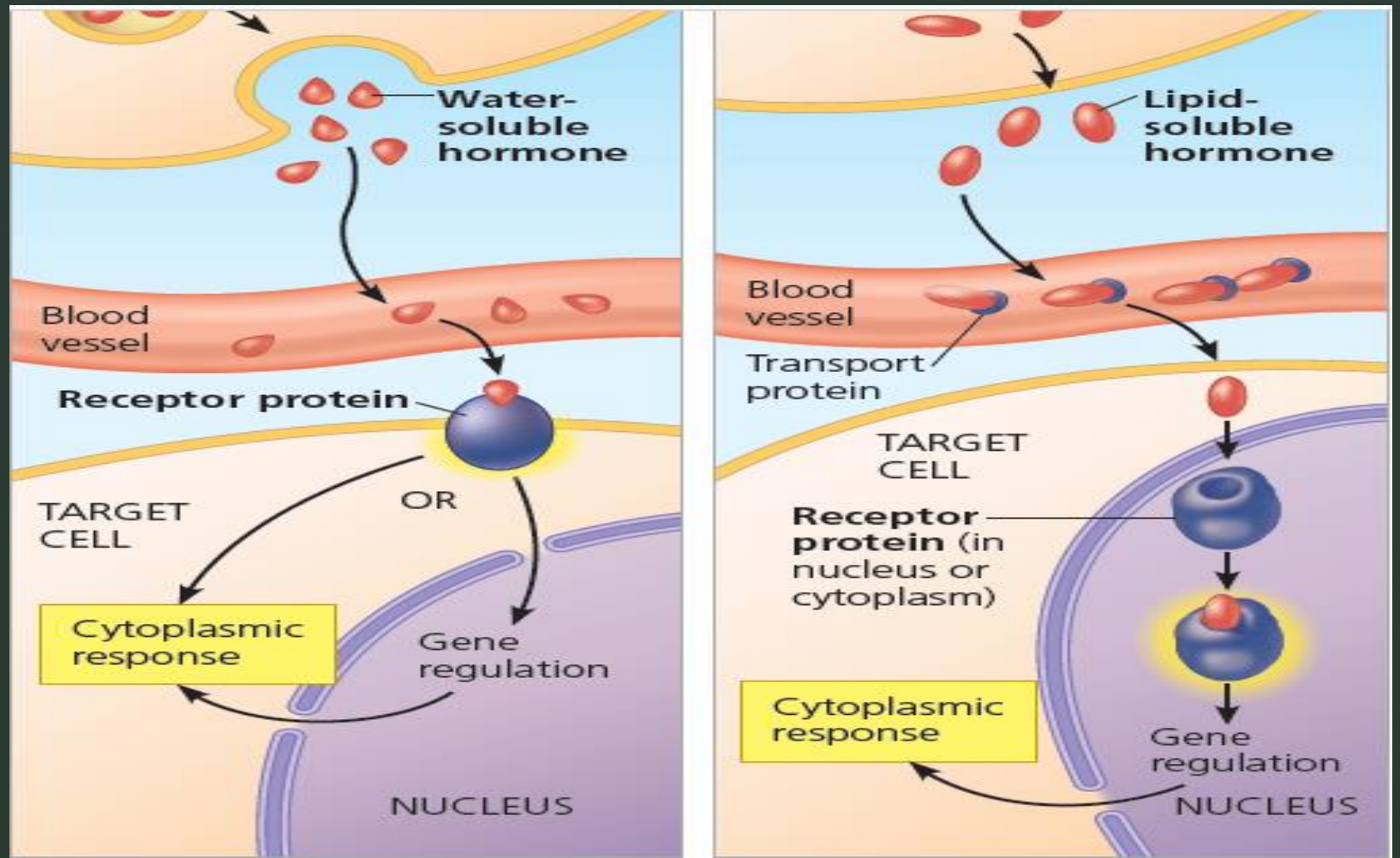
- Hormones fall into three major chemical classes: polypeptides, steroids, and amines.
- 1- The a polypeptide hormone insulin, for example, is a polypeptide that contains two chains in
- its active form.
- 2- Steroid hormones, such as cortisol, are lipids that contain four fused carbon rings; all are derived from the steroid cholesterol
- 3- amine hormones, such as Epinephrine and thyroxine are, each synthesized from a single amino acid, either tyrosine or tryptophan.

Water-soluble (hydrophilic)	Lipid-soluble (hydrophobic)
Polypeptides	**Steroids**
 Insulin	 Cortisol
Amines	
 Epinephrine	 Thyroxine

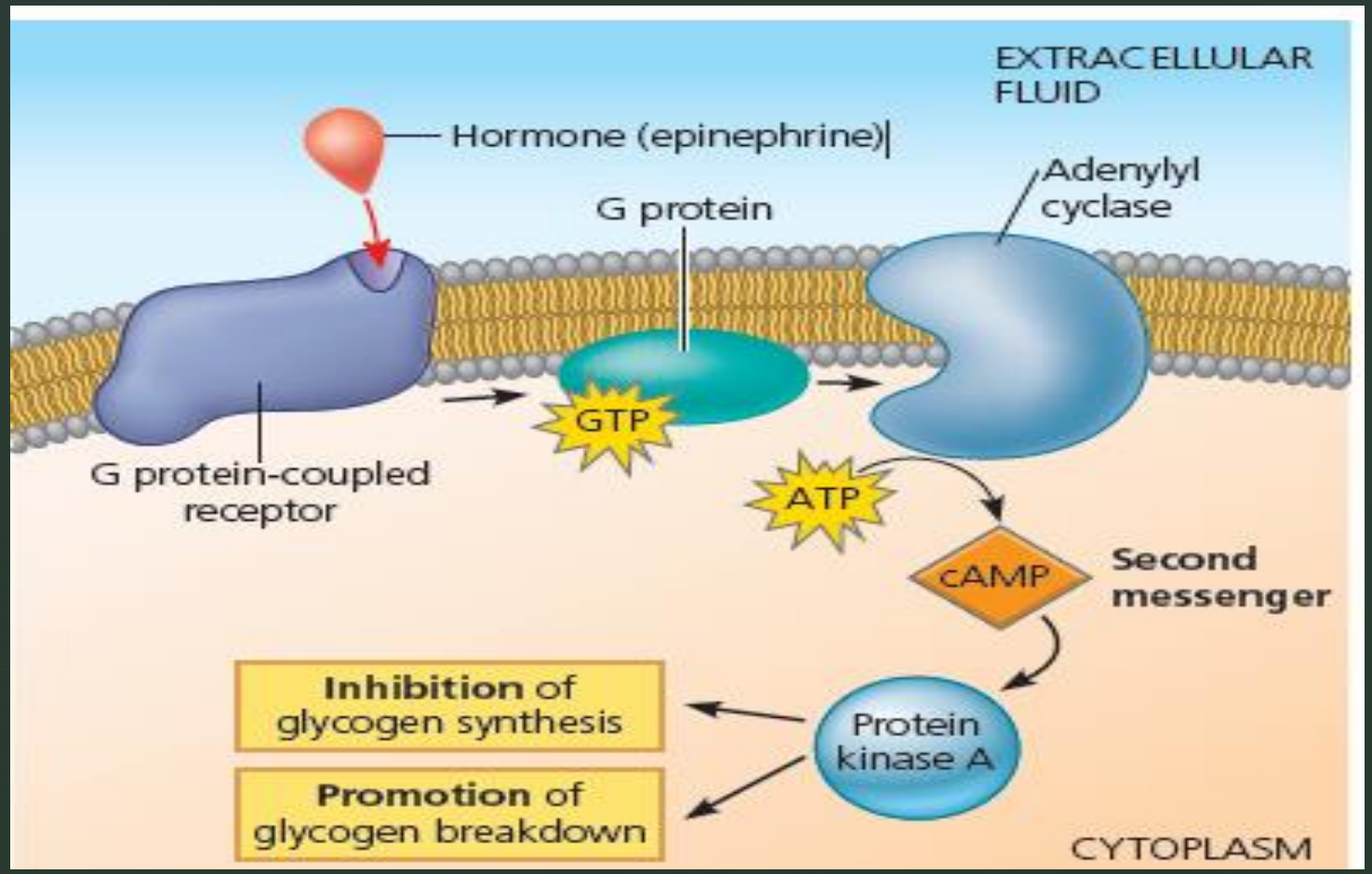
Variation in hormone receptor location

- Water-soluble and lipid-soluble hormones differ in their response pathways. One key difference is the location of the receptor proteins in target cells.
- 1- Water-soluble hormones are secreted by exocytosis and travel freely in the bloodstream. Being insoluble in lipids, they cannot diffuse through the plasma membranes of target cells. Instead, these hormones bind to cell-surface receptors, inducing changes in cytoplasmic molecules and sometimes altering gene transcription

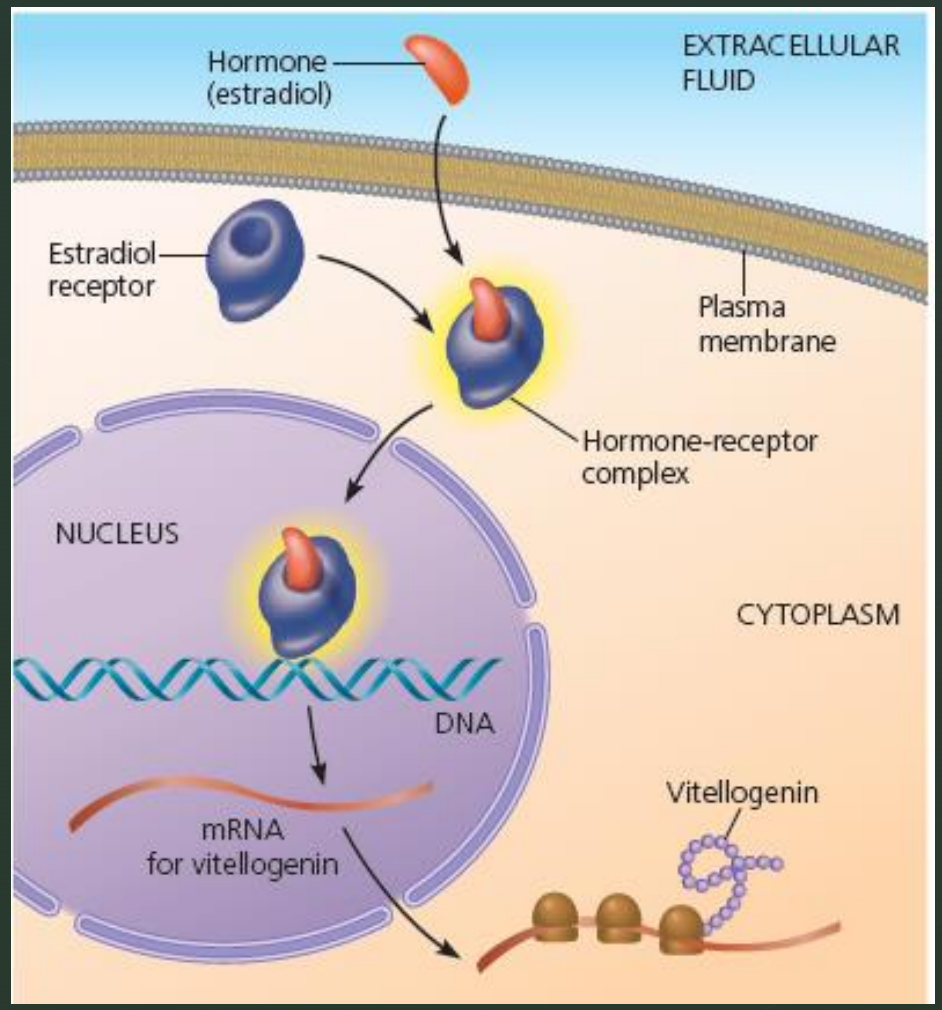
- 2- lipid-soluble hormones exit endocrine cells by diffusing out across the membranes. They then bind to transport proteins, which keep them soluble in blood. After circulating in the blood, they diffuse into target cells and typically bind to receptors in the cytoplasm or nucleus . The hormone-bound receptor then triggers changes in gene transcription.


Water-soluble hormone
Blood vessel
Receptor protein
TARGET CELL
OR
Cytoplasmic response
Gene regulation
NUCLEUS
Lipid-soluble hormone
Blood vessel
Transport protein
TARGET CELL
Receptor protein (in nucleus or cytoplasm)
Cytoplasmic response
Gene regulation
NUCLEUS

Signal transduction triggered by a cell-surface hormone receptor.

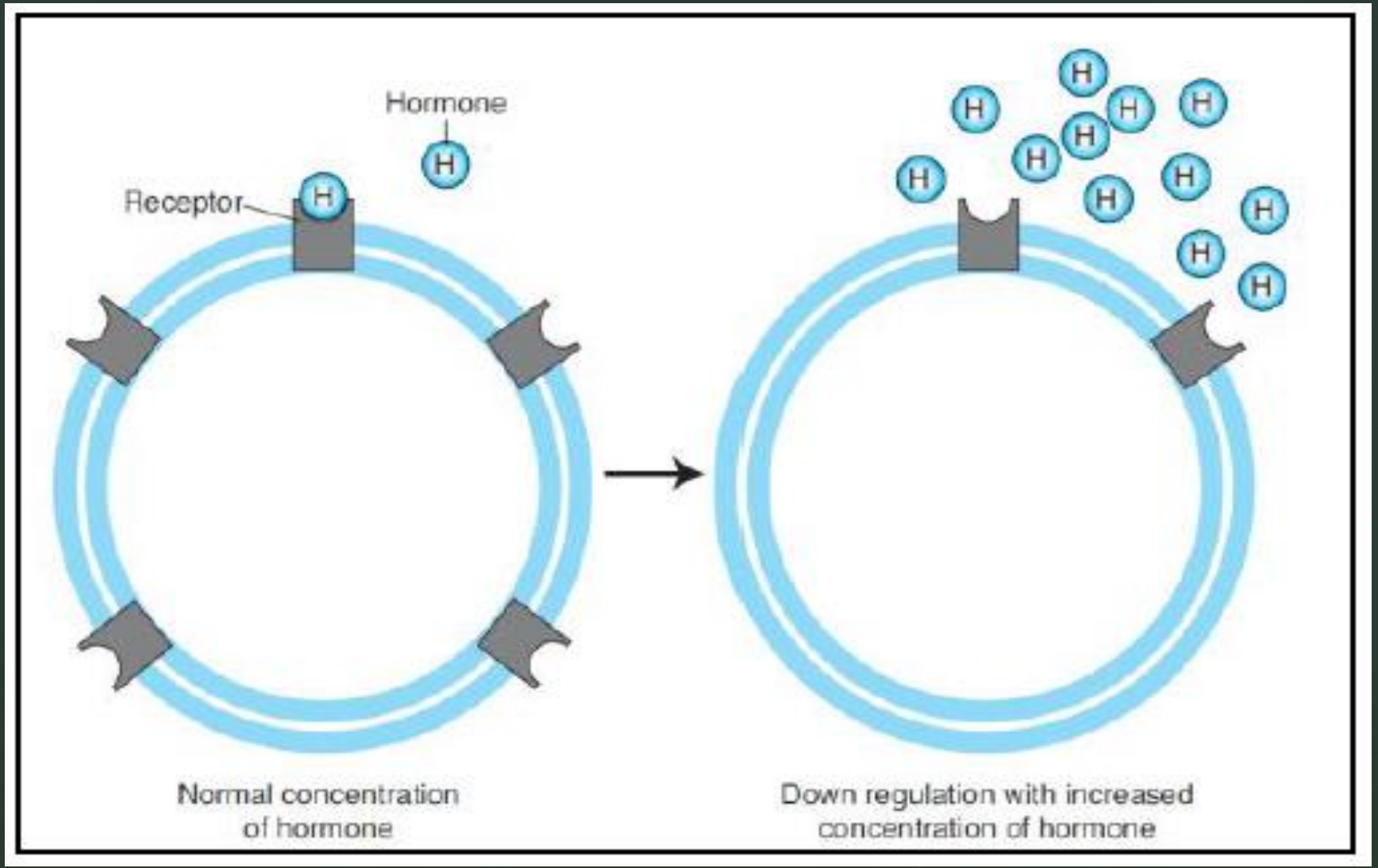


Direct regulation of gene expression by a steroid hormone receptor



Down-regulation of receptors

- - Exposure of receptors to high concentrations of hormone may decrease the number and affinity of surface receptors (down-regulation or desensitization)
- - This phenomenon is seen in obesity, where high levels of insulin occur, This results in a decreased sensitivity of cells to insulin leads to type-2 DM.

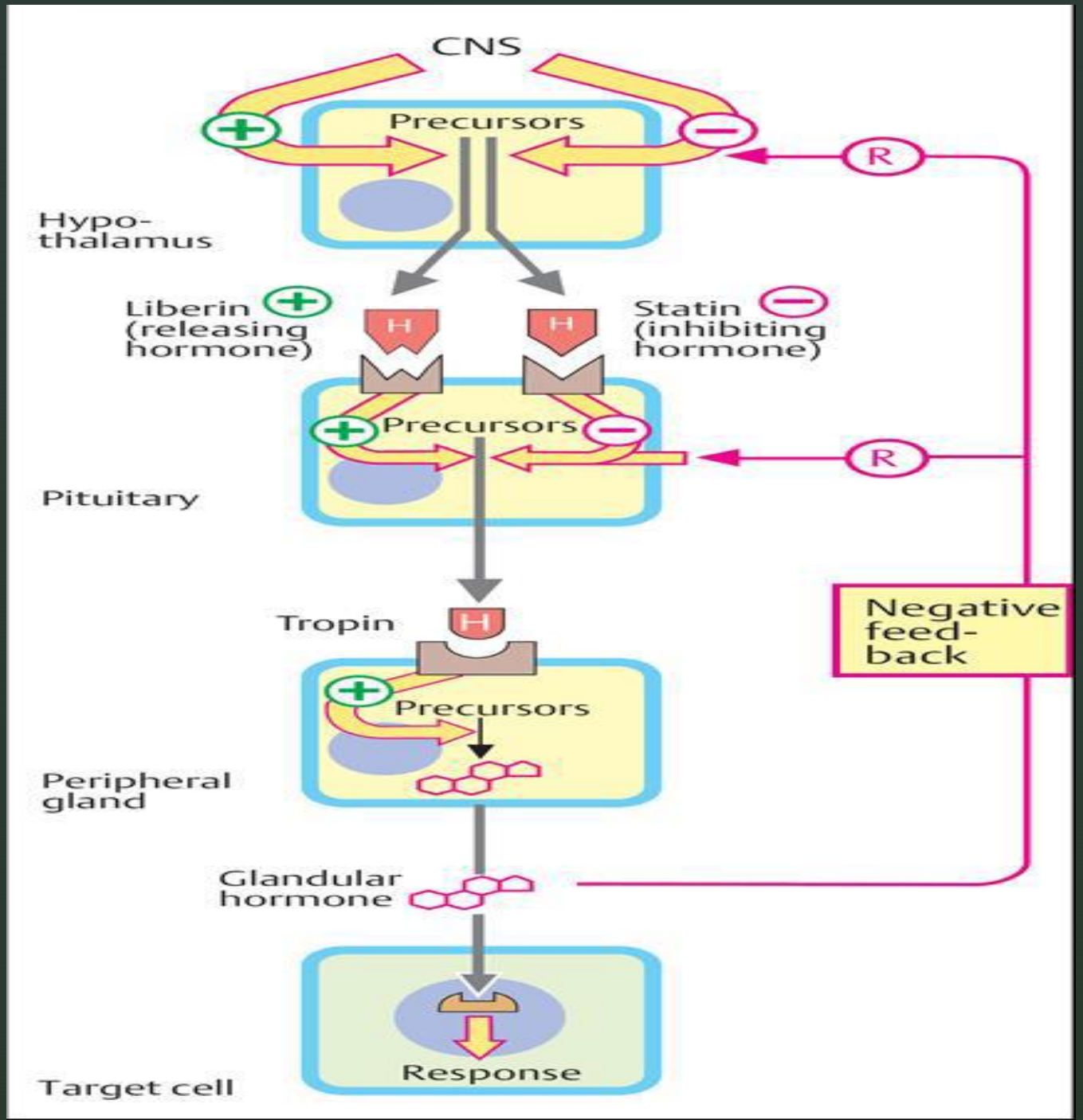

Hormone
H
Receptor
H
Normal concentration
of hormone
Down regulation with increased
concentration of hormone

❑ Regulation of hormonal secretion

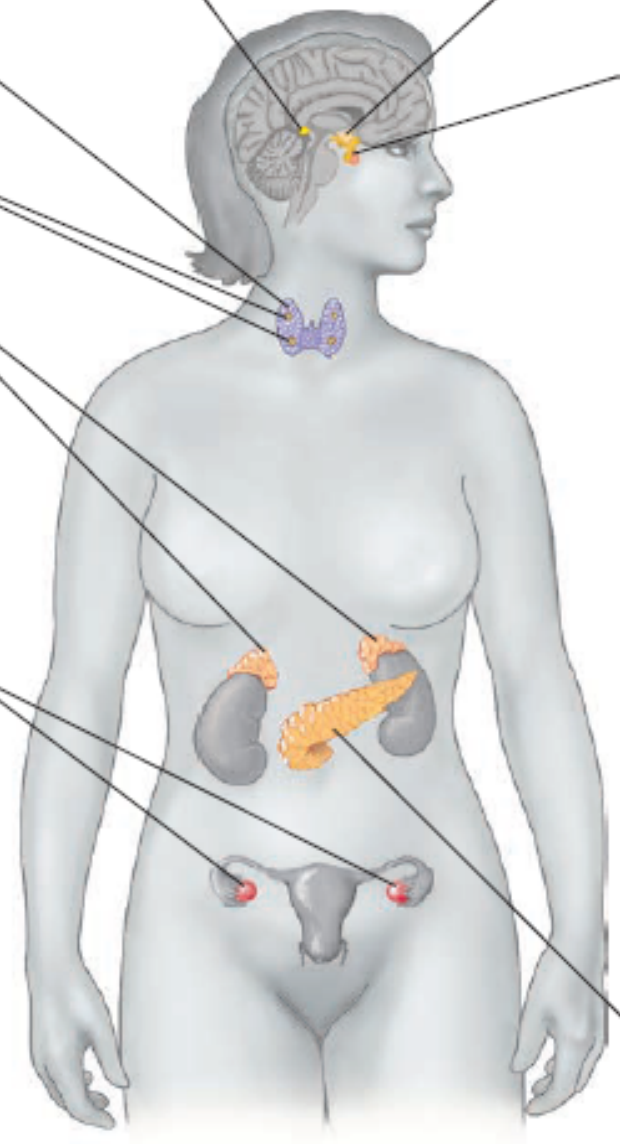
- **1) Stimulatory or inhibitory** signals such as hypothalamic factors, pituitary hormones and neurotransmitters
- **2) Circadian rhythm or diurnal variations**: such as ACTH has the peak level at 8 am while GH at has the peak level at night.
- **3)** Many hormones are released in **pulsatile** fashion such as GHRH

- **4) Feedback regulation:**
- The final secreted hormone regulates its own secretion through inhibition of the secretion of one or more of the precursor hormones
- When a peripheral hormone level is increased above threshold level, this will supress releasing of precursor hormones. When its level is decreased below threshold level, this will stimulate releasing of precursor hormones (like the thermostat that regulates the heating/cooling cycles in refrigerator).

- ▪ **Releasing hormones:** they are secreted by hypothalamus and they control the release of other hormones (tropic hormones) from the pituitary gland.
- ▪ **Tropic hormones:** they are secreted by pituitary gland (master gland) and they control the release other hormones (peripheral hormones) from endocrine glands
- ▪ **Peripheral hormones:** they are secreted by peripheral
- endocrine glands and responsible for the tissue response and feedback regulation


CNS
Precursors
R
Hypo-
thalamus
Liberin
(releasing
hormone)
H
H
Statin
(inhibiting
hormone)
Precursors
R
Pituitary
Tropin
H
Negative
feed-
back
Precursors
Peripheral
gland
Glandular
hormone
Response
Target cell

Human endocrine glands and their hormones



Thyroid gland
Thyroid hormone (T_3 and T_4): Stimulates and maintains metabolic processes
Calcitonin: Lowers blood calcium level

Parathyroid glands
Parathyroid hormone (PTH): Raises blood calcium level

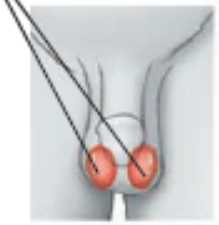
Adrenal glands (atop kidneys)

Adrenal medulla
Epinephrine and *norepinephrine*: Raise blood glucose level; increase metabolic activity; constrict or dilate blood vessels

Adrenal cortex
Glucocorticoids: Raise blood glucose level
Mineralocorticoids: Promote reabsorption of Na^+ and excretion of K^+ in kidneys

Ovaries (in females)
Estrogens:* Stimulate uterine lining growth; promote development and maintenance of female secondary sex characteristics
Progesterone:* Promotes uterine lining growth

Testes (in males)
Androgens:* Support sperm formation; promote development and maintenance of male secondary sex characteristics



*Found in both males and females, but with a major role in one sex

Pineal gland
Melatonin: Participates in regulation of biological rhythms

Hypothalamus
Hormones released from posterior pituitary (see below)
Releasing and inhibiting hormones: Regulate anterior pituitary

Pituitary gland

Posterior pituitary
Oxytocin: Stimulates contraction of uterus and mammary gland cells
Vasopressin, also called *antidiuretic hormone* (*ADH*): Promotes retention of water by kidneys; influences social behavior and bonding

Anterior pituitary
Follicle-stimulating hormone (FSH) and *luteinizing hormone (LH):* Stimulate ovaries and testes
Thyroid-stimulating hormone (TSH): Stimulates thyroid gland
Adrenocorticotropic hormone (ACTH): Stimulates adrenal cortex
Prolactin: Stimulates mammary gland growth and milk synthesis in mammals
Growth hormone (GH): Stimulates growth and metabolic functions
Melanocyte-stimulating hormone (MSH): Affects color of melanocytes, a type of skin cell

Pancreas
Insulin: Lowers blood glucose level
Glucagon: Raises blood glucose level

The Hypothalamo-Pituitary Axis

Hypothalamic hormone	Structure	Pituitary hormone that they control
Thyrotrophinreleasing hormone (TRH)	Tripeptide	Stimulates secretion of Thyroid stimulating hormone (TSH) and prolactin
Corticotrophin releasing hormone (CRH)	41 amino acids protein	Stimulates secretion of adrenocorticotrophin hormone (ACTH)
Growth hormone releasing hormone (GHRH)	44 amino acids protein	Stimulates secretion of growth hormone (GH)
Gonadotrophin releasing hormone (GnRH)	Decapeptide	Stimulates secretion of Luteinizing hormone (LH) & Follicle stimulating hormone (FSH)
Prolactin releasing hormone	Unknown structure	Stimulates the release of prolactin
Somatostatin (SST) also known as growth hormone inhibiting hormone	14 amino acids protein	Inhibits the release of GH and PRL and TSH
Prolactin release inhibiting hormone (PIH) also known as dopamine (DA)	A tyrosine derived monoamine	Inhibits the release of prolactin

❑ Disorders of the endocrine system

- **- There are two main categories of endocrine disorders “Primary and secondary”**
- **- Primary disorders** include problems with the gland itself which leads to either hyper-secretion or hypo-secretion (defects are in the peripheral gland)
- **- Secondary disorders** where the glands are functioning normally, however, the outside stimulating agents are either in excess resulting in hyper-secretion or deficient resulting in hypo-secretion (defects are in the pituitary gland or the hypothalamus)
- **-** Hyper-secretion of hormone is more difficult to treat than hypo-secretion.
- **-** Hyper-secretion is treated by gland inhibition or partial removal
- **-** Whereas hypo-secretion is treated by hormone replacement therapy.

❑ Assessment of endocrine function

- **-** There are some **difficulties** in the endocrine assessment: 1) Low concentration of hormones in blood, sometimes the hormone concentration is below the detection limit
- 2) Variability due to circadian rhythm and pulsatile fashion of release
- 3) Hormone binding to proteins (the unbound or free fraction of the hormone is the biologically active and responsible for feedback regulation

- Pitfalls in interpretations

- 1) Immunoassay interference: presence of unsuspected antibodies that can interfere with the hormone being measured
- 2) Log-linear response: dose response curve is usually not linear

Dynamic function tests (DFTs)

- Where the results of clinical assessment and baseline biochemical investigation fail to rule in or rule out a serious endocrine diagnosis, dynamic function tests may be required.
- DFTs involve either stimulating or suppressing a particular hormonal axis and observing the appropriate hormonal response
- If **deficiency** is suspected → stimulation test (by tropic hormone or physiological stress)
- If **excess** is suspected → suppression test

1) Insulin stress test: (insulin tolerance test)

- **-** For **hypopituitarism**
- **-** It measures the ability of anterior pituitary to produce **GH** and **ACTH** (cortisol is measured instead of ACTH)
- **-** Insulin is administered to produce hypoglycaemia (BGL < 2.2 mmol/L)
- **- Normal response: GH > 20 mU/L and cortisol > 550 mmol/L**

2) TRH test:

- **-** For **hypopituitarism, hypothalamic diseases,** and **less frequently thyroid gland**
- **- IV TRH then blood sampling is at 0, 20, 60 min**
- **-** Normal response is a rapid increase in both **TSH** and **prolactin**

3) GnRH test:

- **-** For **hypogonadism**
- **-** It measures the ability of anterior pituitary to produce **FSH** and **LH**
- **-** In adults, GnRH produces marked rise in **LH** and a smaller rise in **FSH.**
- **-** In children, reverse the FSH response is greater than LH.

4) OGTT with GH measurement:

- **-** Hyperglycaemia **supresses** GH secretion
- **- Normal adult OGTT supresses GH to < 2 mU/L**
- **- Acromegalic patient do not response**

5) (ACTH) test:

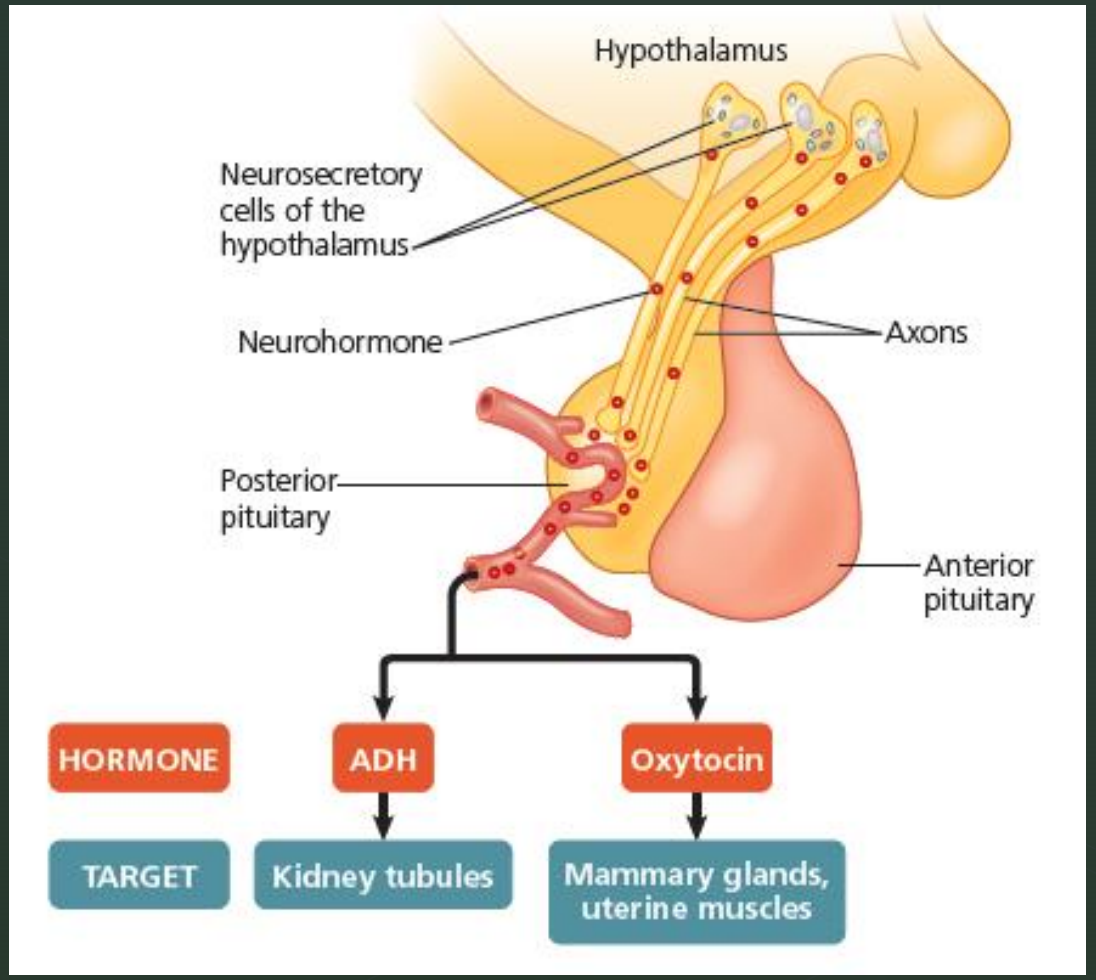
- **-** For **adrenal hypofunction**

6) Dexamethasone suppression test (DST):

- **-** For **adrenal hyperfunction**
- **-** Dexamethasone is an exogenous steroid mimics the negative feedback of endogenous glucocorticoids
- **-** For assessment of over-activity of hypothalamic-pituitary adrenal axis

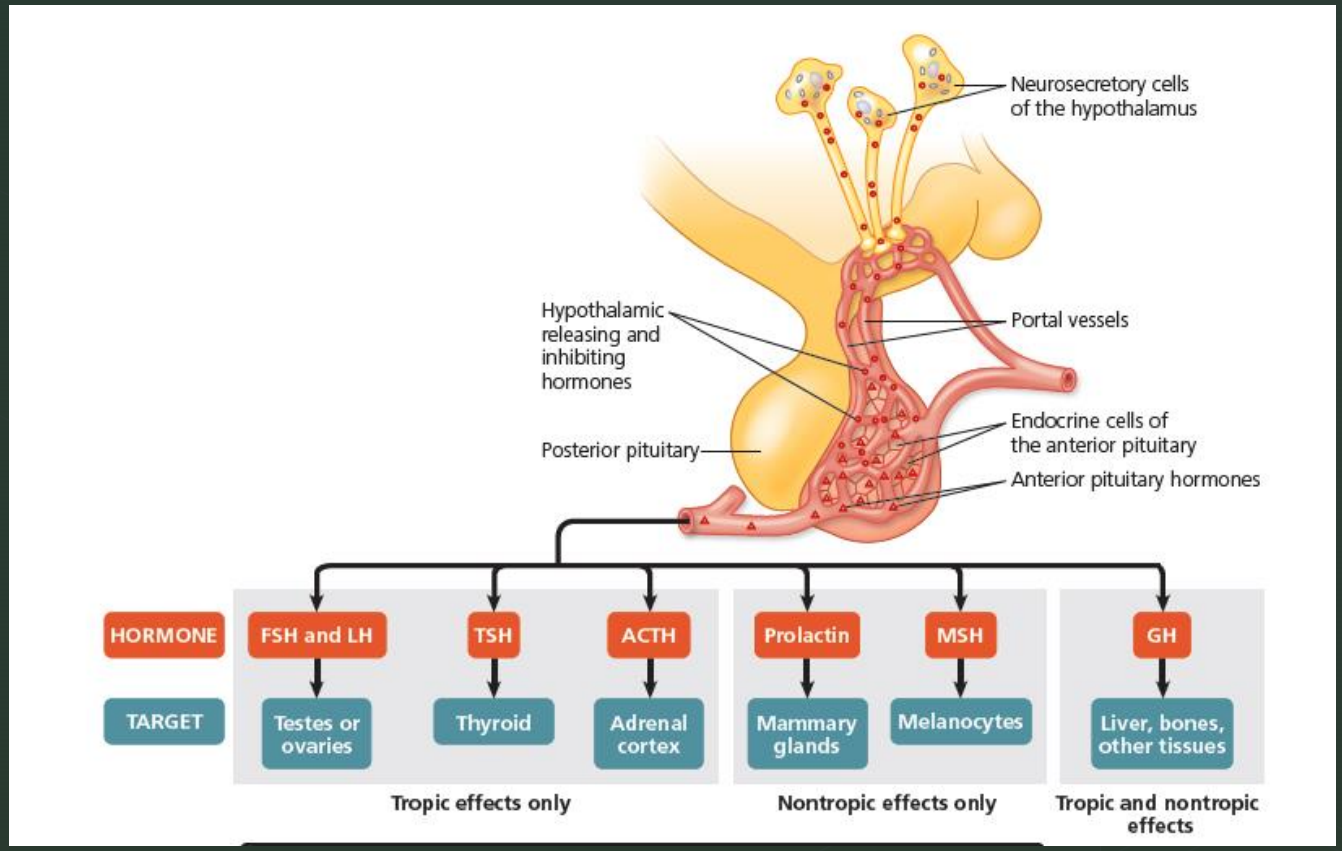
Production and release of posterior pituitary hormones

The posterior pituitary gland is an extension of the hypothalamus. Certain neurosecretory cells in the hypothalamus make antidiuretic hormone (ADH) and oxytocin, which are transported to the posterior pituitary, where they are stored. Nerve signals from the brain trigger release of these neurohormones.



Production and release of anterior pituitary hormones

The release of hormones synthesized in the anterior pituitary gland is controlled by hypothalamic releasing and inhibiting hormones. The hypothalamic hormones are secreted by neurosecretory cells and enter a capillary network within the hypothalamus. These capillaries drain into portal vessels that connect with a second capillary network in the anterior pituitary.



❑ Pituitary Gland Disorders

- **1) Hyperprolactinemia**
- **- It is a common cause of infertility in both sexes.**
- ▪ Secondary: stress, drugs (estrogens), primary hypothyroidism (prolactin is stimulated by increased TRH).
- ▪ Primary: if the secondary causes are excluded. The differential diagnosis is:
- a) Prolactinoma (Prolactin-secreting pituitary tumour)
- b) Idiopathic hypersecretion (may be due to decrease in dopamine secretion)

- **-** Dynamic prolactin test: administration of TRH, if prolactin is increased → idiopathic, if no change in prolactin → Prolactinoma)

2) Growth hormone disorders

- **- Normal growth in children can be divided into 3 stages:**
- a) Rapid growth: first 2 years the rate is affected by embryo period
- b) Steady growth: next 9 years controlled by GH
- c) Puberty growth: controlled by the sex hormones + GH

- **a) GH insufficiency: Dwarfism (**fail to grow and be short in stature)
- ▪ **Lab. diagnosis:** To prove the deficiency of GH, patient must fail to respond to two different **stimulation tests**
- 1) Injection of **exogenous insulin** to induce severs hypoglycemia, which in turn stimulates secretion of GH. This test is dangerous due to severity of the induced hypoglycemia.
- 2) Injection of **CRH** to stimulate GH secretion. This taste is safer as it is not inducing hypoglycemia.
- 3) Another test to increase GH involves **strenuous exercise**. The patient is asked to exercise for 20 min, and then a blood specimen is drawn immediately and assayed for GH level.
- 4) Sleep: rise of GH during sleep exclude GH deficiency
- 5) Urinary GH measurement may be used.

b) GH Excess:

- ▪ **Gigantism (childhood):** excessive production of GH (due to GH secreting pituitary tumour) before the fusion of **epiphyseal plates** of bones, where there is accelerated growth of the long bones.
- ▪ **Acromegaly (adulthood)**: excessive production of GH after the fusion of epiphyseal plates and the cessation of long bones growth. It is marked by enlargement of the bones of the extremities, face, and jaw.
- ▪ **Lab. diagnosis:**
- 1) OGT suppression test: acromegaly does not response to the hyperglycaemia
- 2) Serial measurements of GH. Acromegaly, plasma level is 50 ng/ml (normal adult level is 1-5 ng/ml).
- 3) Increased level of IGF-1 is diagnostic (IGF-1 is produced in response to GH)

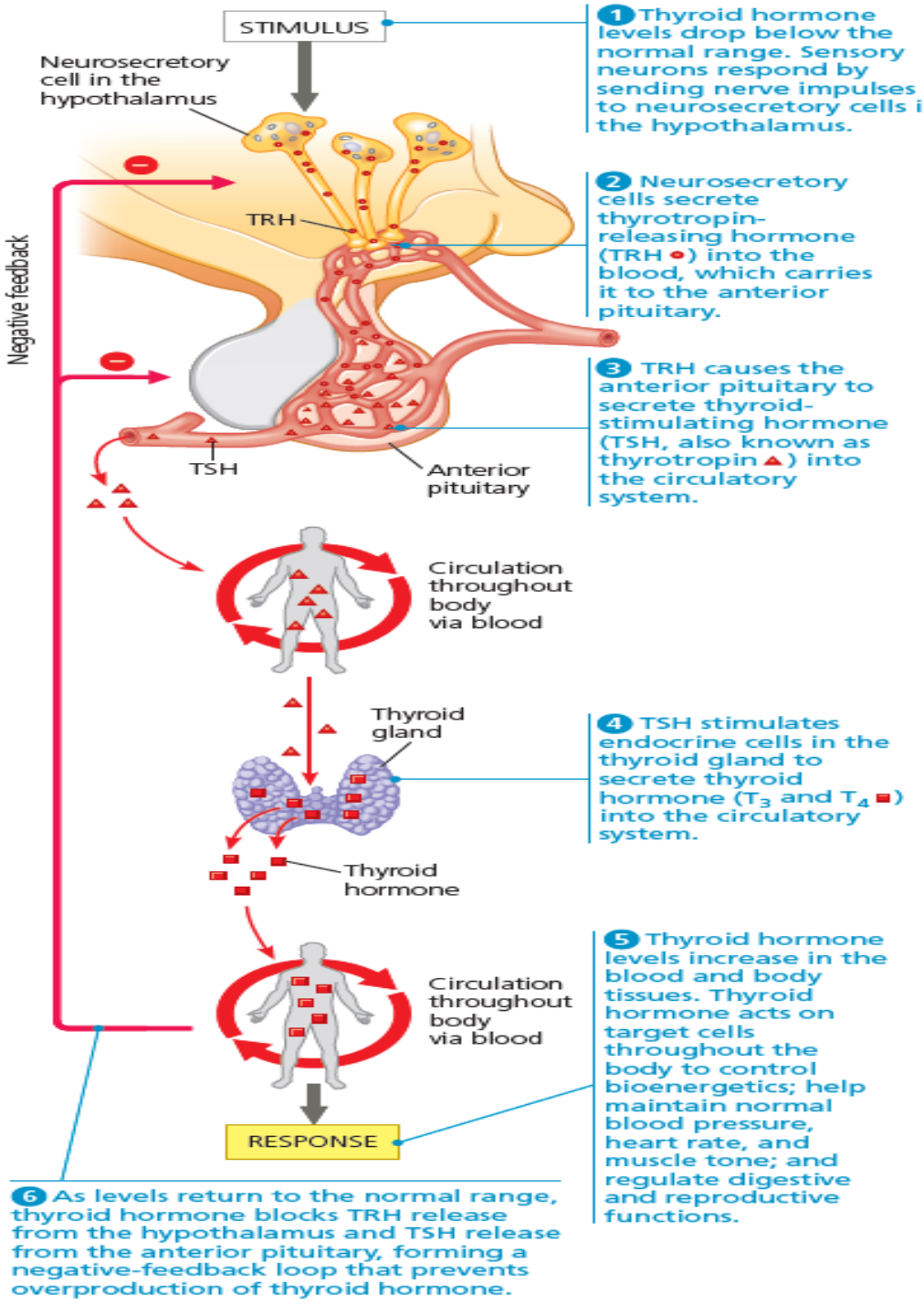
3) Diabetes insipidus

- **-** Diabetes insipidus (DI) is caused by deficiency of ADH or AVP and classified into:
- 1) Neurogenic DI: Deficiency of ADH itself
- 2) Nepherogenic DI: Failure of kidney to respond to ADH (ADH resistance)
- **-** Symptoms; polyuria (production of large amount of urine about 20 L/day), fatigue, severe dehydration, hypothermia and polydipsia (increased thirst).
- **- Lab. diagnosis**
- 1) The most valuable test for diagnosis of DI is urine and plasma osmolality
- 2) The plasma level of ADH can be determined
- 3) Stimulation test, exogenous ADH is given to the patient to test their response; a) Normal patients respond by decreasing their urine output and increasing urine osmolality.
- b) Nephrogenic DI patients will show no response.
- c) Neurogenic DI patients show increase > 10% in their urine osmolality.

Thyroid hormone

Thyroid hormone regulates bioenergetics; helps maintain normal blood pressure, heart rate, and muscle tone; and regulates digestive and reproductive functions.

As with other hormone cascade pathways, feedback regulation often occurs at multiple levels. For example, thyroid hormone exerts negative feedback on the hypothalamus and on the anterior pituitary, in each case blocking release of the hormone that promotes its production.



❑ Thyroid Function Tests

- **-** Thyroid hormones act by entering cells and binding to specific receptors in the nuclei, where they stimulate the synthesis of a variety of species of mRNA, thus stimulating the synthesis of polypeptides, including hormones and enzymes. a) Thyroid hormones are essential for normal growth and development.
- b) They increase **basal metabolic rate**.
- c) They increase heat production and oxygen consumption in most tissues through stimulation of ATPase activity.
- d) Overall, they increase the catabolism (weight loss and muscle wasting are typical features of excessive secretion of thyroid hormones).
- e) They increase the sensitivity of the CVS and CNS to catecholamines, leading to increases in heart rate and cardiac output
- **-** Most laboratories offer a standard ‘profile’ of thyroid function tests (e.g. TSH and free T4), and perform additional tests only if these results are equivocal or the clinical circumstances require it

- **a) TSH:** it is the first-line thyroid function test.
- Used for screening of congenital hypothyroidism, a condition which, unless treated within 3 months of birth, results in permanent brain damage
- Only in hypopituitarism, TSH can not be used to diagnose primary thyroid diseases
- **b) Total T4 and T3:** these tests have the major disadvantage in that it is dependent on binding protein concentration as well as thyroid activity
- **c) Fee T4 and T3:** these tests avoid the problems associated with protein binding
- **d) Antibodies:** the titre of autoantibodies to thyroid tissues may be helpful in the diagnosis and monitoring of autoimmune thyroid diseases

1) Hypothyroidism:

- - It is under-activity of the thyroid gland that leads to inadequate production of thyroid hormones. Develops slowly
- - **Cretinism** or **congenital hypothyroidism** occurs in newborn and accompanied by abnormal physical development and mental retardation. If occurs later in life it is called **myxedema**.
- ▪ Clinical features: Weight gain, Lethargy and tiredness, Cold intolerance, Dryness and coarsening of skin and hair
- ▪ Causes: most common is autoimmune destruction of the thyroid, Hashimoto's disease, surgical treatment of hyperthyroidism or iodine deficiency.

- ▪ Screening of neonatal hypothyroidism (cretinism):
- **- Frequency 1/4000 live births**
- **-** If they are diagnosed at an early age (first 3 months), replacement therapy of T4 is simple and effective, but this must be started as soon after birth as a reliable diagnosis can be made
- **-** Untreated, affected children become cretins, with very low intelligence and impaired growth and motor function.
- **-** The screening method involves measurement of TSH in a capillary blood spot from the heal at 6-8 days of age
- **- Elevated TSH in a blood spot is diagnostic of the disease**

2) Hyperthyroidism:

- - It is the over-activity of thyroid gland.
- ▪ **Thyrotoxicosis** occurs when tissues are exposed to high level of thyroid hormones from hyperthyroidism or ingestion of too much T4
- ▪ Clinical features: Weight loss despite normal appetite, Fatigue, sweating, Heat intolerance, Tachycardia, Goiter, Hand tremors.

- Causes:
- 1. Graves’ disease, an autoimmune disorder ultimately caused by auto-antibodies stimulating thyroid growth and function through their interaction with the TSH receptor on thyroid follicular, is the most common cause of hyperthyroidism
- 2. Thyroiditis
- 3. Excessive T4 ingestion

- Differential diagnosis of thyroid dysfunctions

Free T3 or T4	TSH	Disorder	Affected gland
Low	High	Primary Hypothyroidism	Thyroid gland (common)
Low	Low	Secondary Hypothyroidism	Pituitary gland (very rare)
High	Low	Primary Hyperthyroidism	Thyroid gland
High	High	Secondary Hyperthyroidism	Pituitary gland