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Endocrine System

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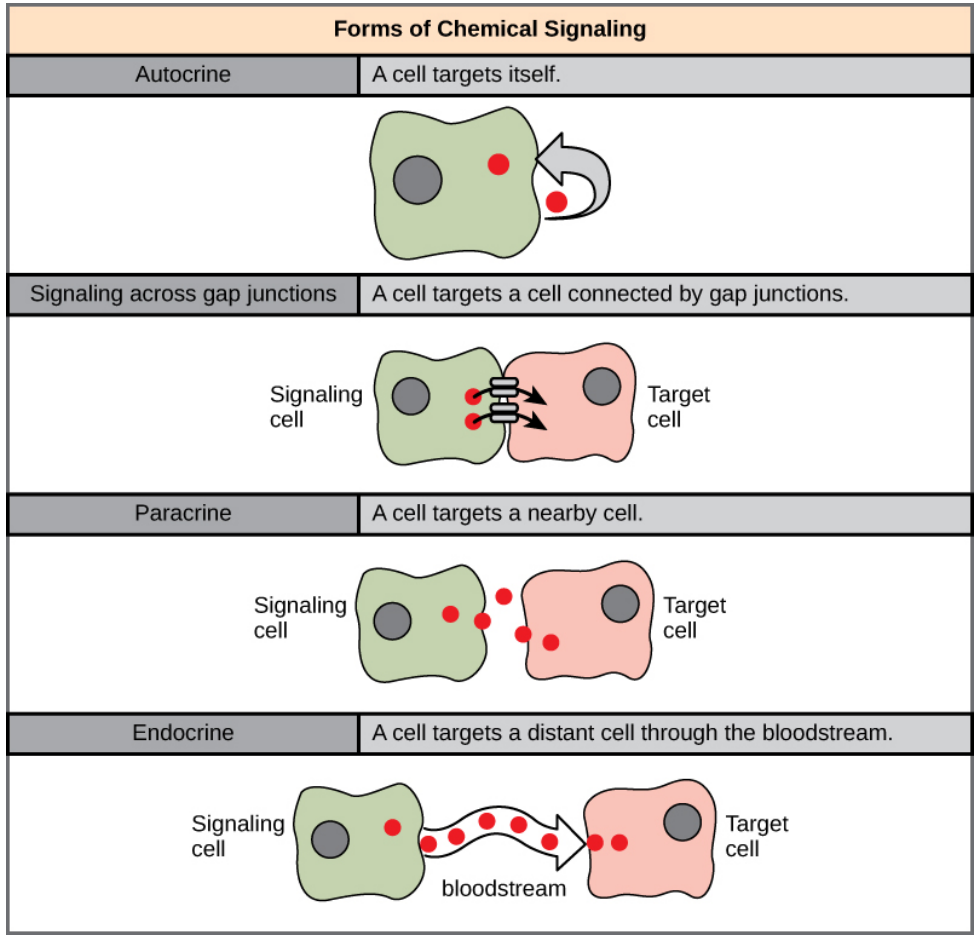
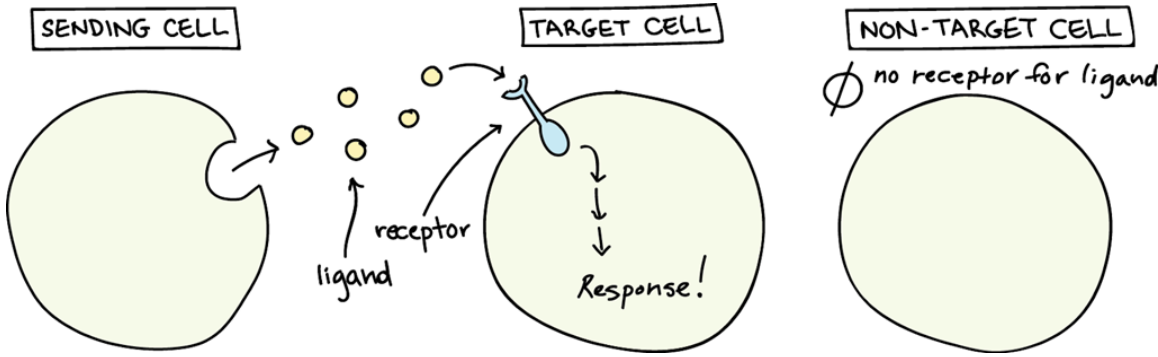
DEPARTMENT OF PHYSIOLOGY

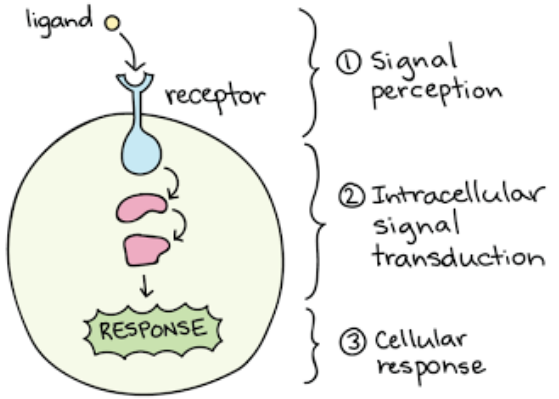
Forms of cell to cell communication!



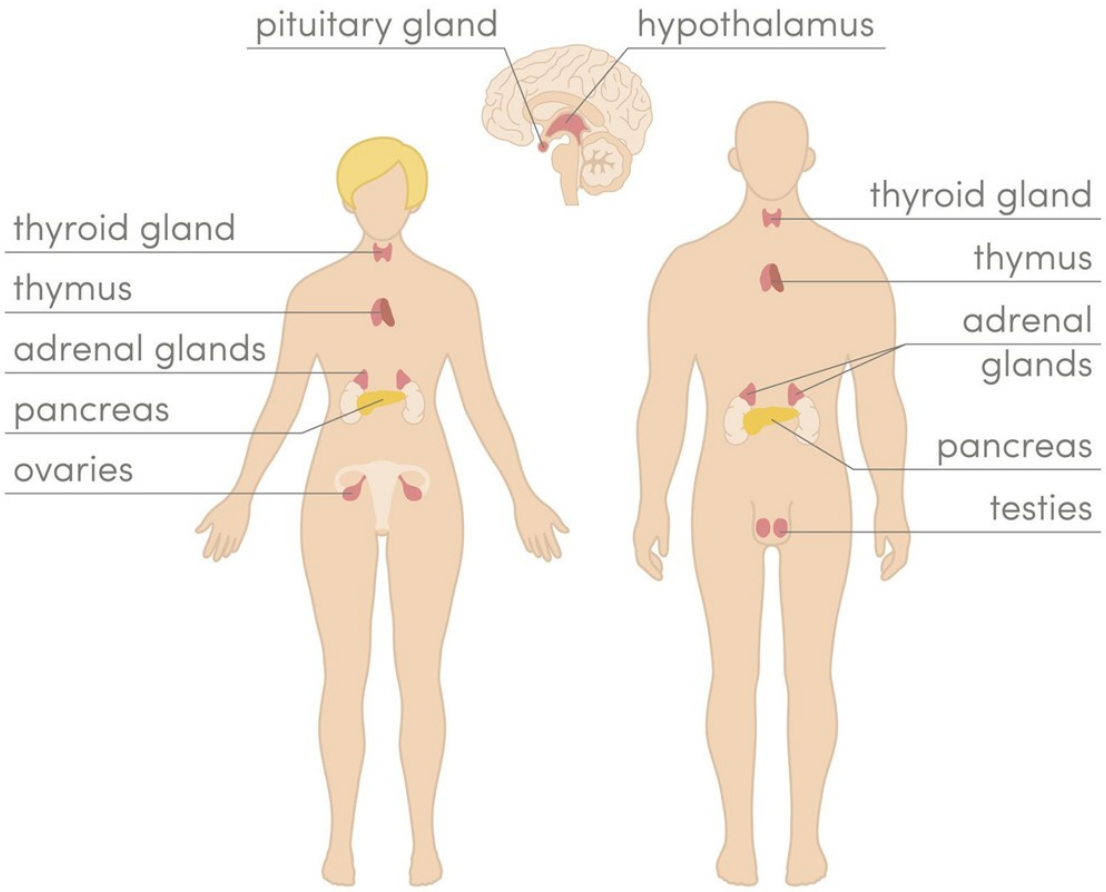
Endocrine system

- Works with Nervous system to maintain homeostasis
- **Glands** → produce specific signaling molecules (**Hormones**)
- Hormones will be released into the blood
- Bind to their specific receptor on target tissue → Physiological response !





Hormones overview



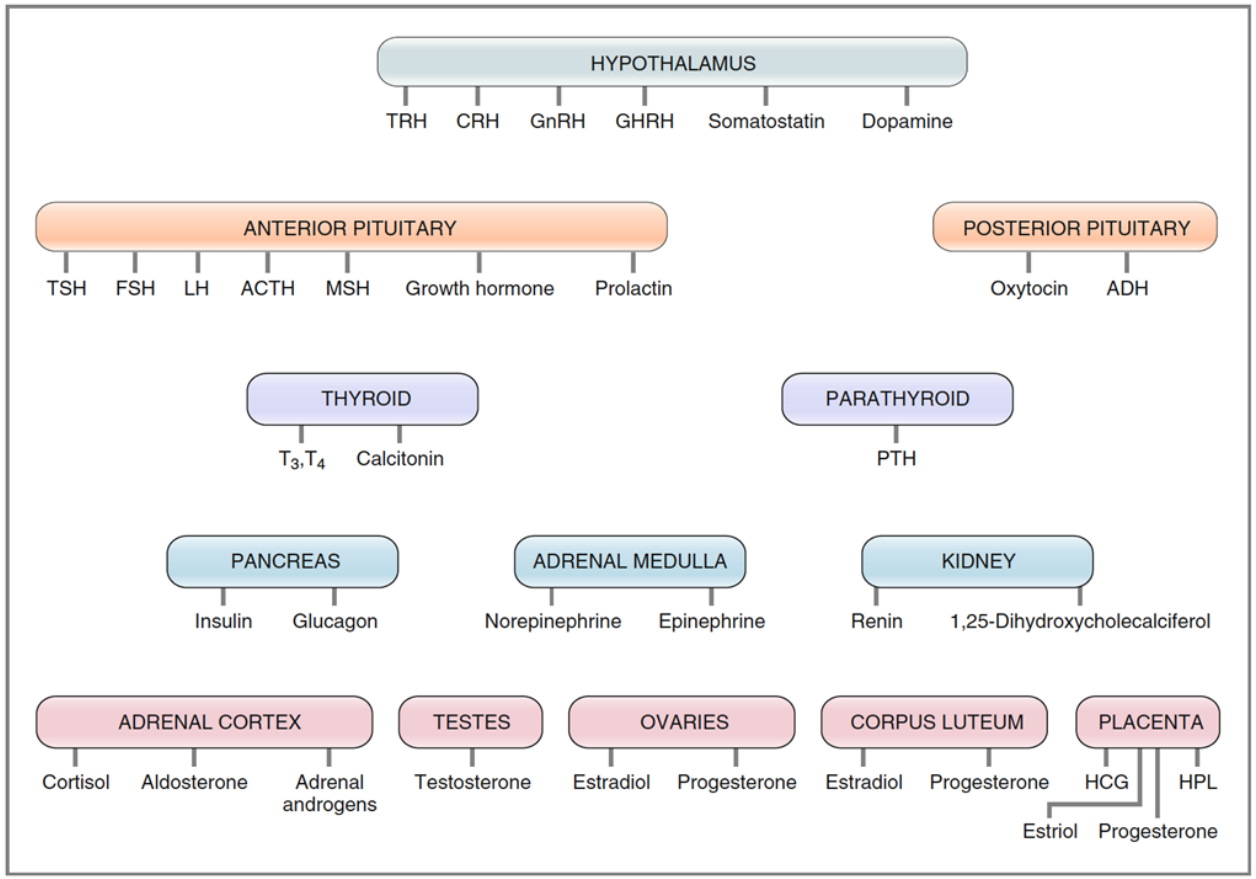
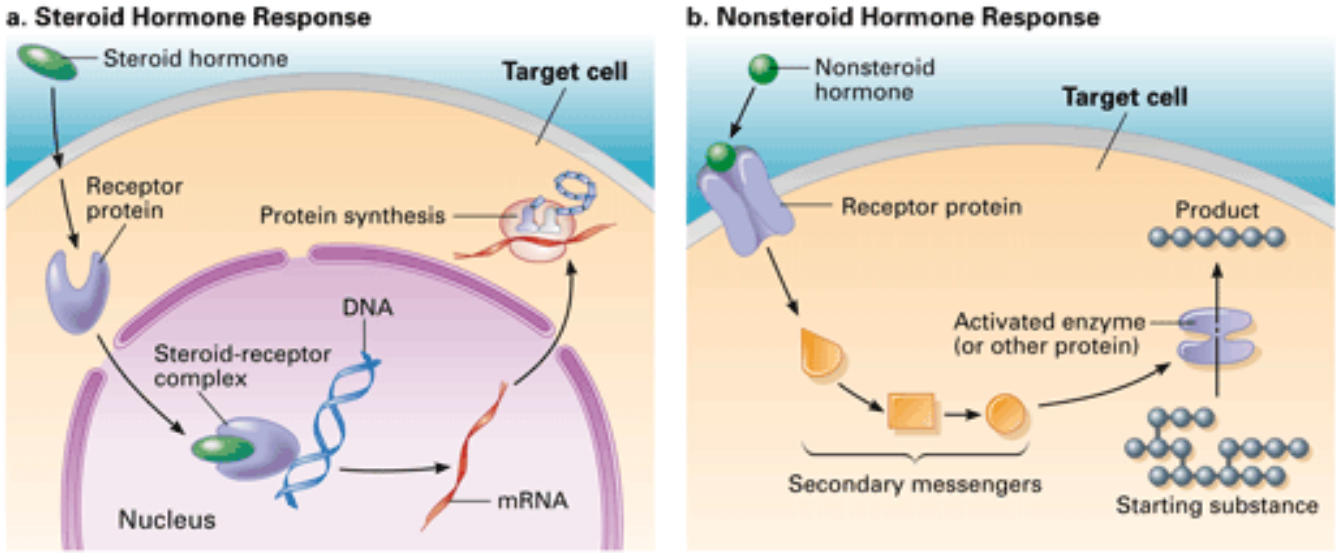
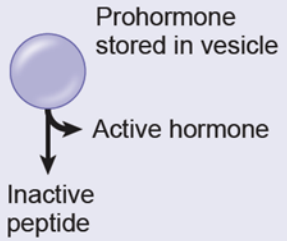


Figure 9-1 **Endocrine glands and the hormones secreted by each gland.** Refer to Table 9-1 for abbreviations used in this figure.

Hormones can be Hydrophilic or lipophilic

- **Water soluble hormones (Peptides and protein)** can not pass membrane bind to peripheral receptors on the surface of the cell , eg : G-protein-coupled receptors or Tyrosin kinases
- **Lipid soluble hormones (Steroids, Thyroid-hormones)** can pass cell membrane act on cytoplasmic or nuclear receptor to alter gene expression



	Lipid-Soluble Hormones (steroids, thyroid hormones)	**Water-Soluble Hormones** (peptides, proteins)
Receptors	Inside the cell, usually in nucleus	Outer surface of the cell membrane
Intracellular action	Stimulates synthesis of specifi new proteins	• Production of second messengers, e.g., cAMP • Insulin does not utilize cAMP, instead activates membrane-bound tyrosine kinase • Second messengers modify action of intracellular proteins (enzymes)
Storage	• Synthesized as needed • Exception: thyroid hormones	• Stored in vesicles • In some cases, prohormone stored in vesicle along with an enzyme that splits off the active hormone 
Plasma transport	• Attached to proteins that serve as carriers • Exception: adrenal androgens	Dissolved in plasma (free, unbound)
Half-life	Long (hours, days) ∝ to affinit for protein carrier	Short (minutes) ∝ to molecular weight

Protein bound and free circulating hormone

The liver produces proteins that bind lipid-soluble hormones, e.g.:

- cortisol-binding globulin
- thyroid-binding globulin
- sex hormone-binding globulin (SHBG)

Equilibrium

The lipid-soluble hormone circulating in plasma bound to protein is in equilibrium with a small amount of free hormone. It is the free form that is available to the tissues, and thus the free unbound form normally determines the plasma activity. It is the free form that also creates negative feedback. Th s equilibrium is shown in Figure X-1-2.

Role of the liver

If the liver changes its production and release of binding proteins, the circulating level of **bound hormone will change.** However, under most conditions the level of **free hormone will remain constant**.

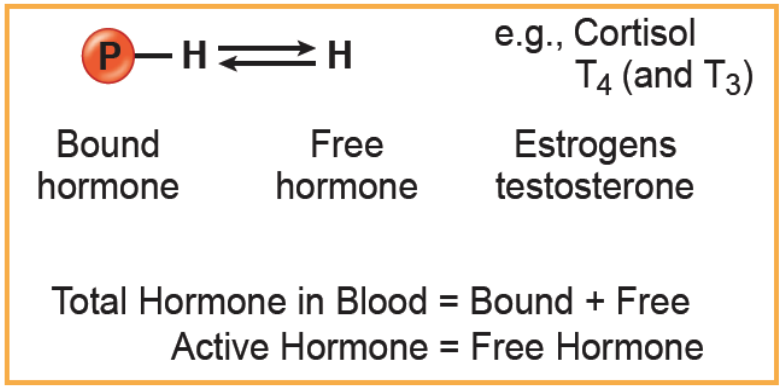


Figure X-1-2. Transport of Lipid-Soluble Hormones

Factors determining the magnitude of response in target cell

- **Concentration of circulation hormone**
- (Dose – response relation) : higher the dose higher the response
- **Number of receptors and their affinity for the hormone**

Regulation of hormone secretion

C. Regulation of hormone secretion

1. Negative feedback

- is the most commonly applied principle for regulating hormone secretion.
- is self-limiting.
- A hormone has biologic actions that, directly or indirectly, inhibit further secretion of the hormone.
- **For example,** insulin is secreted by the pancreatic beta cells in response to an increase in blood glucose. In turn, insulin causes an increase in glucose uptake into cells that results in decreased blood glucose concentration. The decrease in blood glucose concentration then decreases further secretion of insulin.

2. Positive feedback

- is rare.
- is explosive and self-reinforcing.
- A hormone has biologic actions that, directly or indirectly, cause more secretion of the hormone.
- **For example,** the surge of luteinizing hormone (LH) that occurs just before ovulation is a result of positive feedback of estrogen on the anterior pituitary. LH then acts on the ovaries and causes more secretion of estrogen.

Negative vs positive feedback

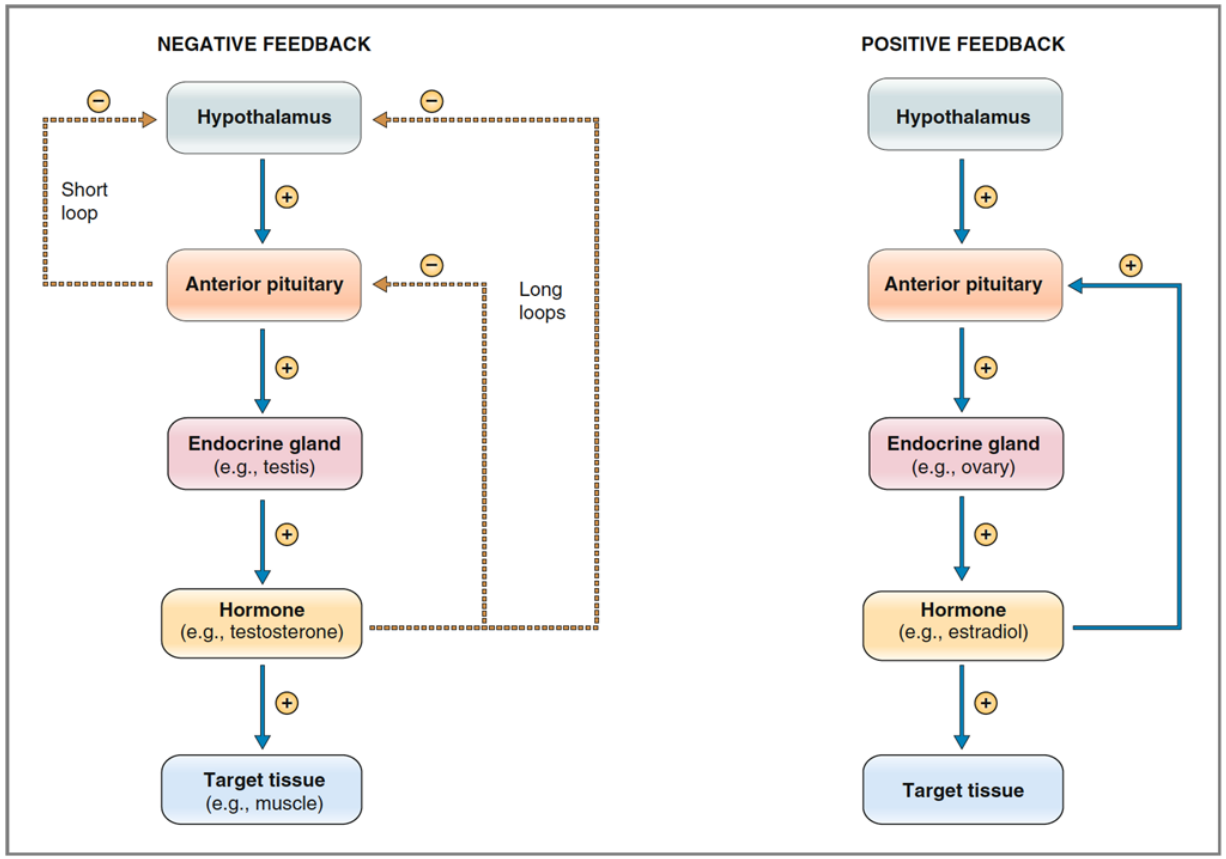


Figure 9-3 **Negative and positive feedback mechanisms.** The hypothalamic-pituitary axis is used as an example in this illustration. *Solid lines* and *plus* (+) *signs* indicate stimulation; *dashed lines* and *minus* (–) *signs* indicate inhibition.

Regulation of reception

D. Regulation of receptors

- Hormones determine the sensitivity of the target tissue by **regulating the number or sensitivity of receptors.**

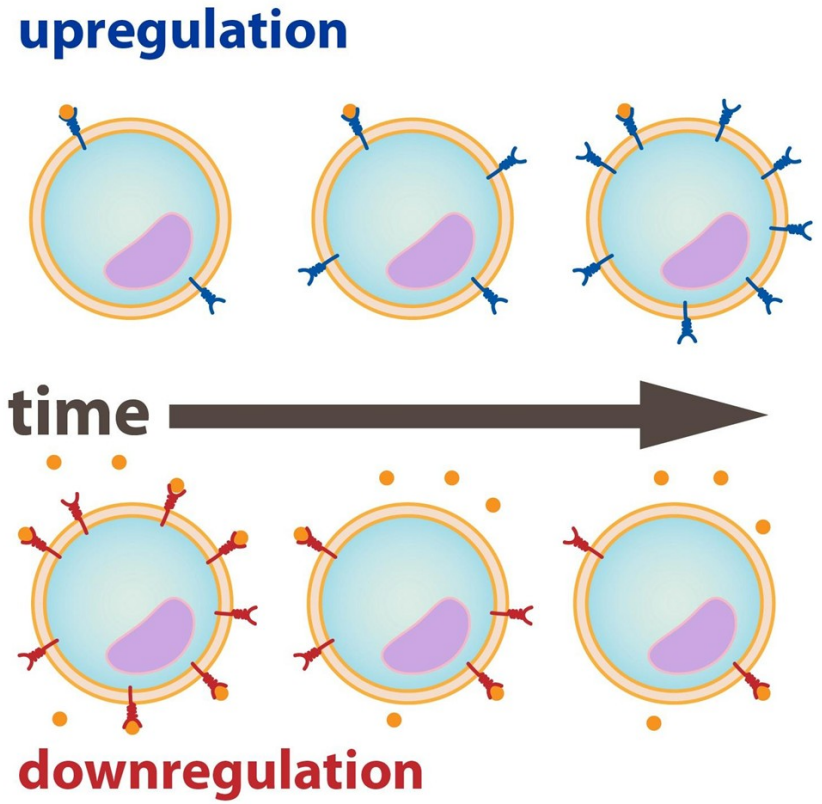
1. Down-regulation of receptors

- A hormone **decreases the number or affinity of receptors** for itself or for another hormone.
- **For example,** in the uterus, progesterone down-regulates its own receptor and the receptor for estrogen.

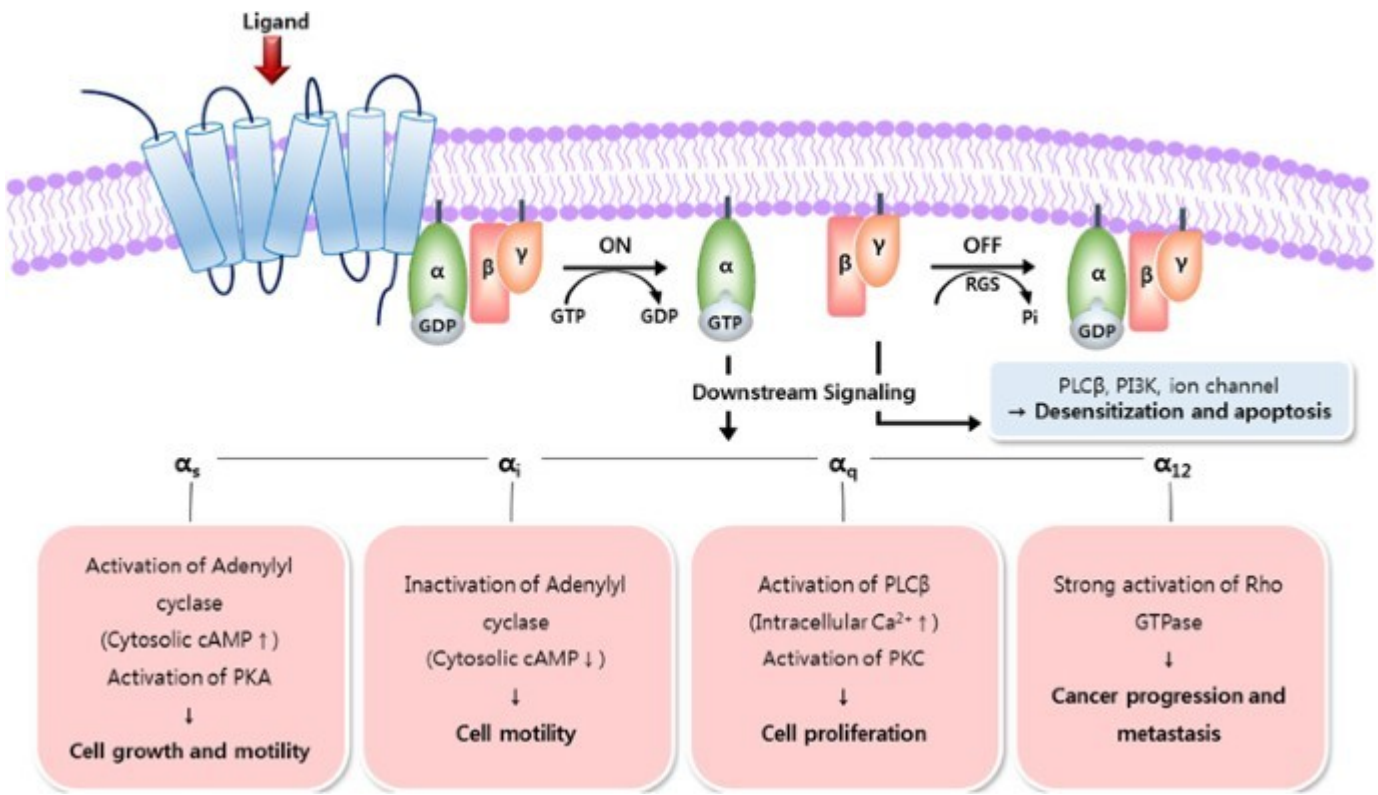
2. Up-regulation of receptors

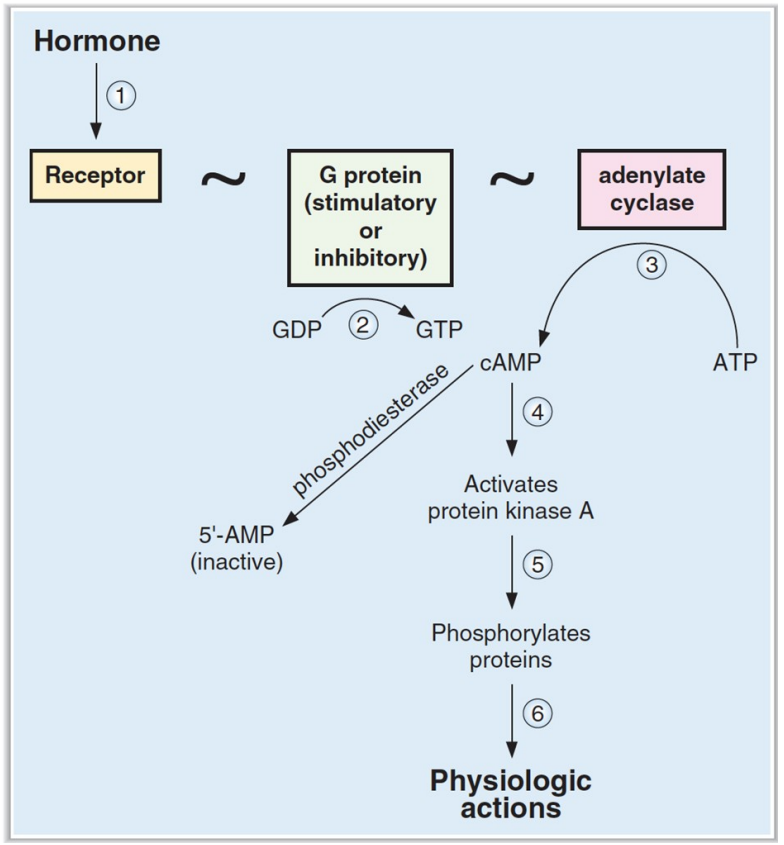
- A hormone **increases the number or affinity of receptors** for itself or for another hormone.
- **For example,** in the ovary, estrogen up-regulates its own receptor and the receptor for LH.

Cell response : receptors up/down regulation

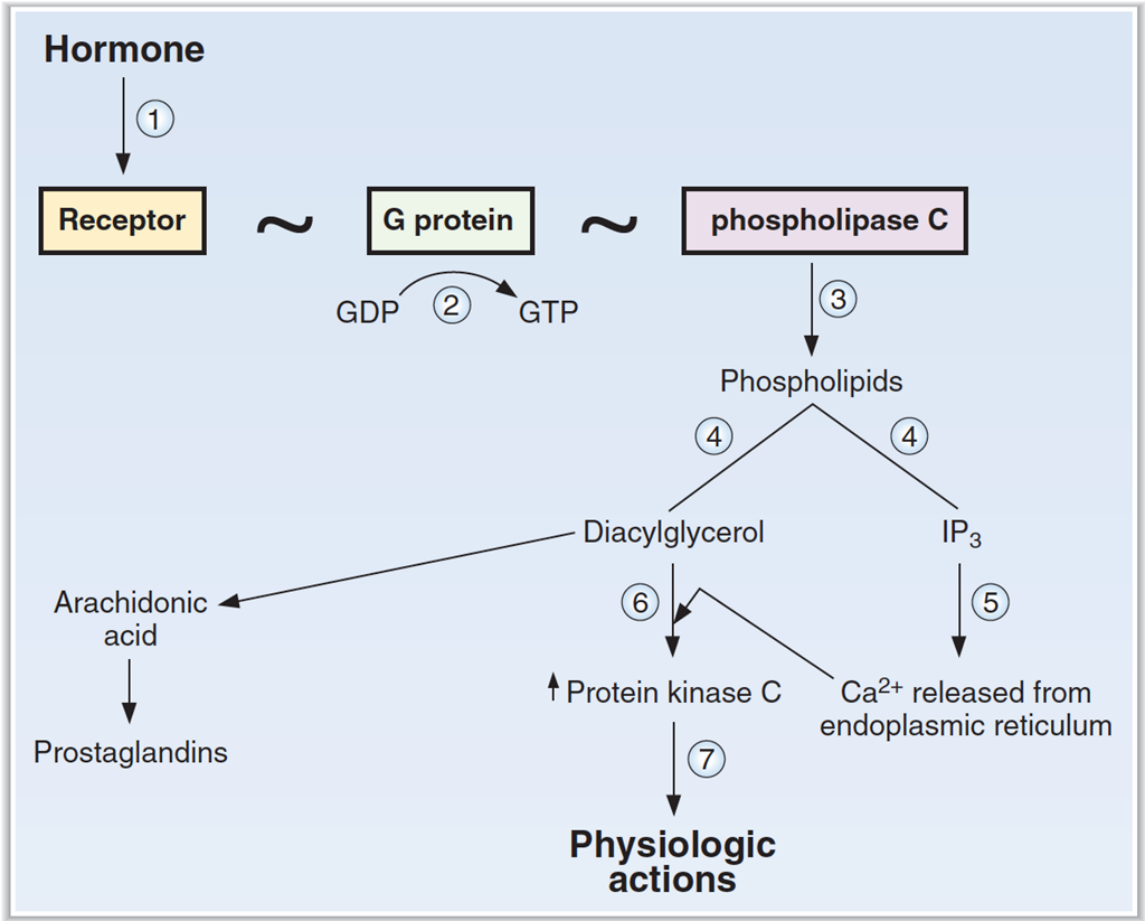


Gs/i □ cAMP □ Protein kinase A





Gq □ PL C □ DAG & IP3□ PK C



Steroid hormone cell response mechanism

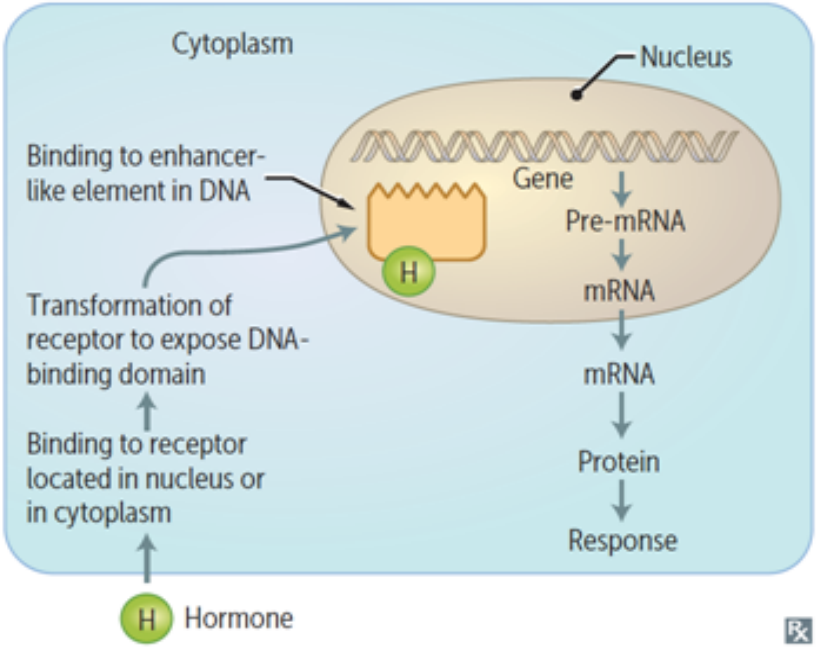
Signaling pathway of steroid hormones

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.

In men, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia.

In women, ↓ SHBG raises free testosterone → hirsutism.

OCPs, pregnancy → ↑ SHBG.



Mechanism of signal transduction (summary)

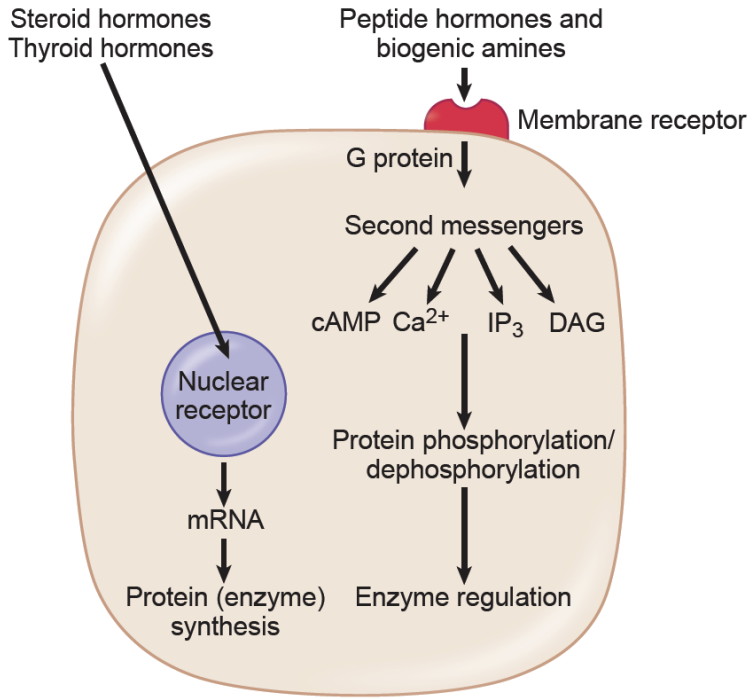
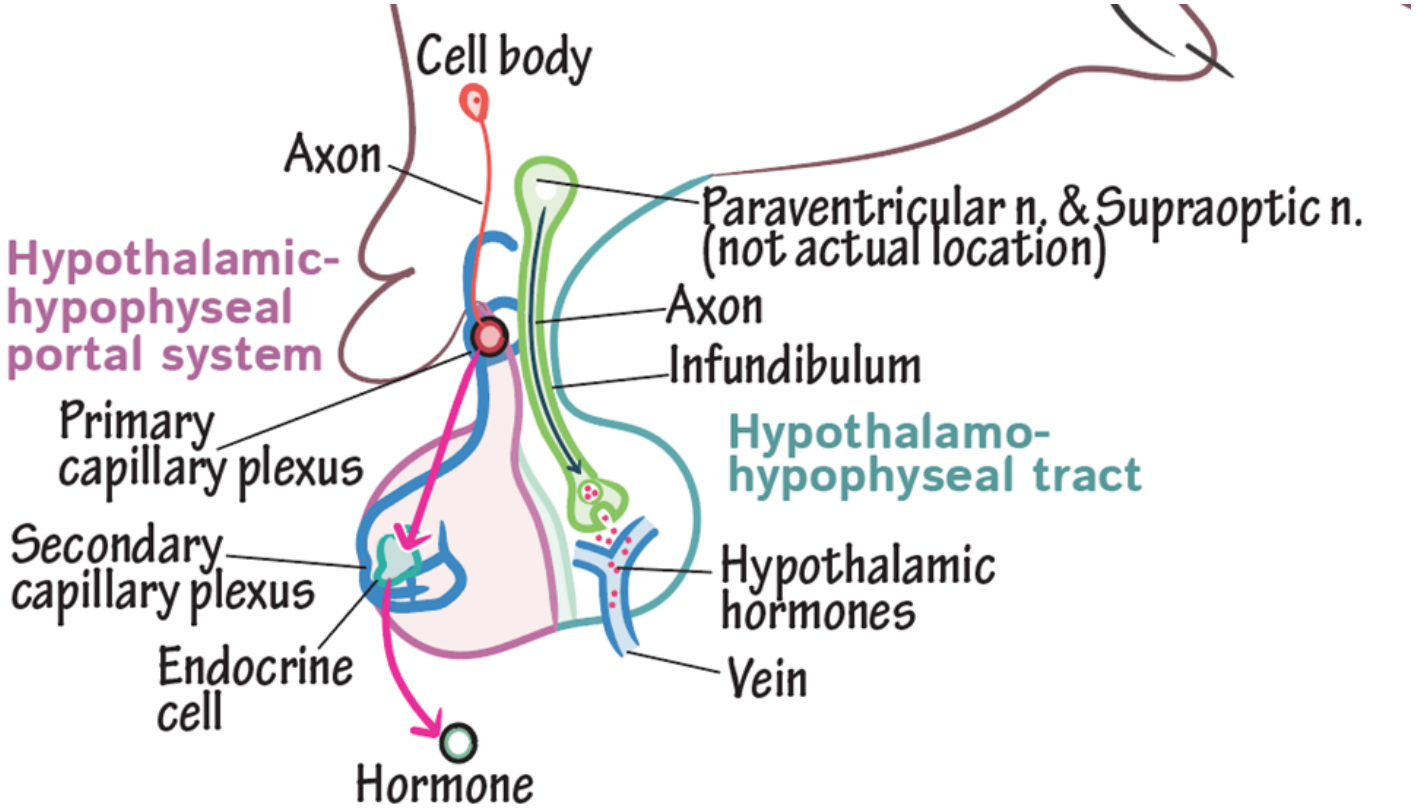


Figure X-1-1. Signal Transduction Mechanisms

Hypothalamo-Hypophysial Axis



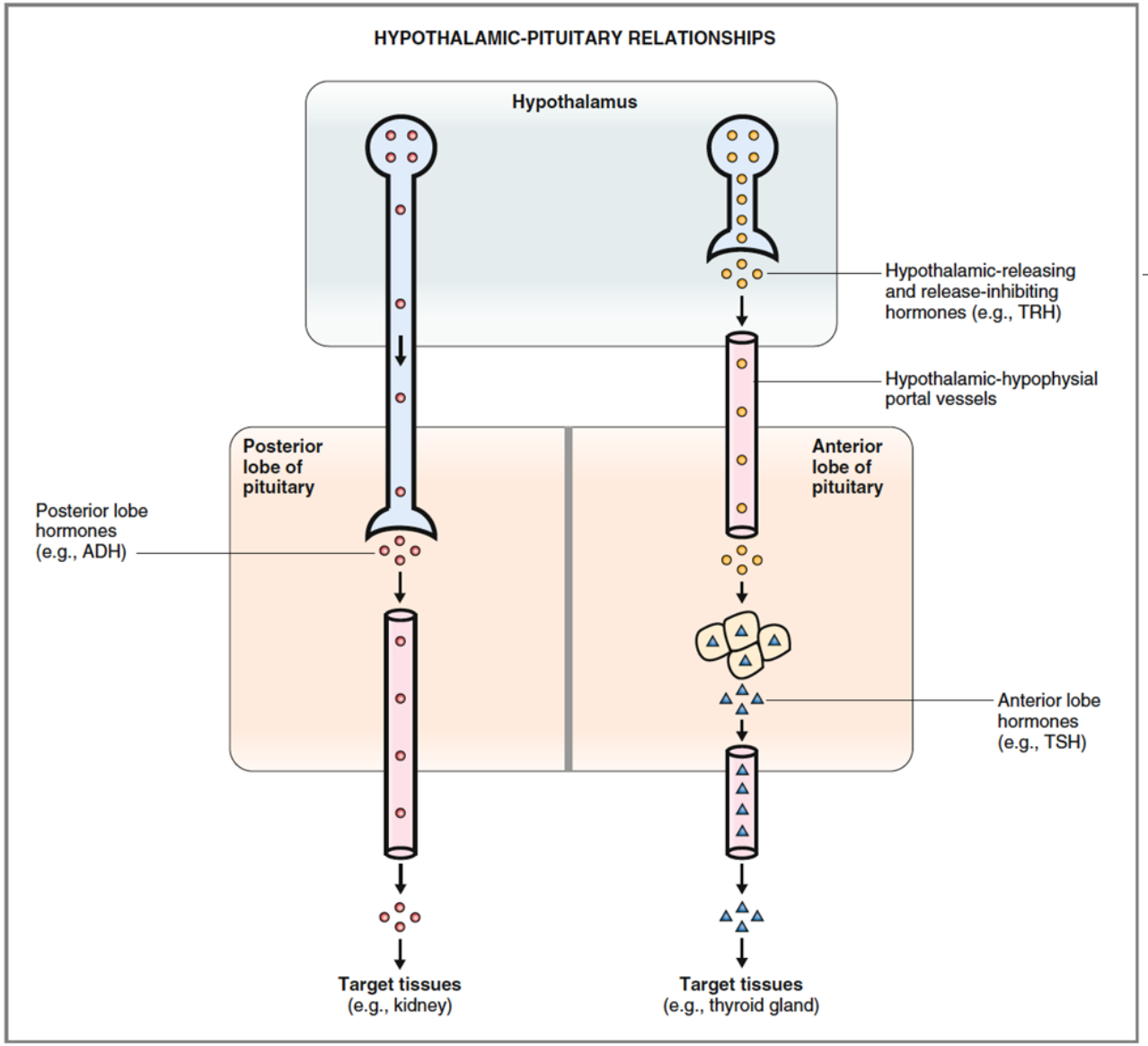
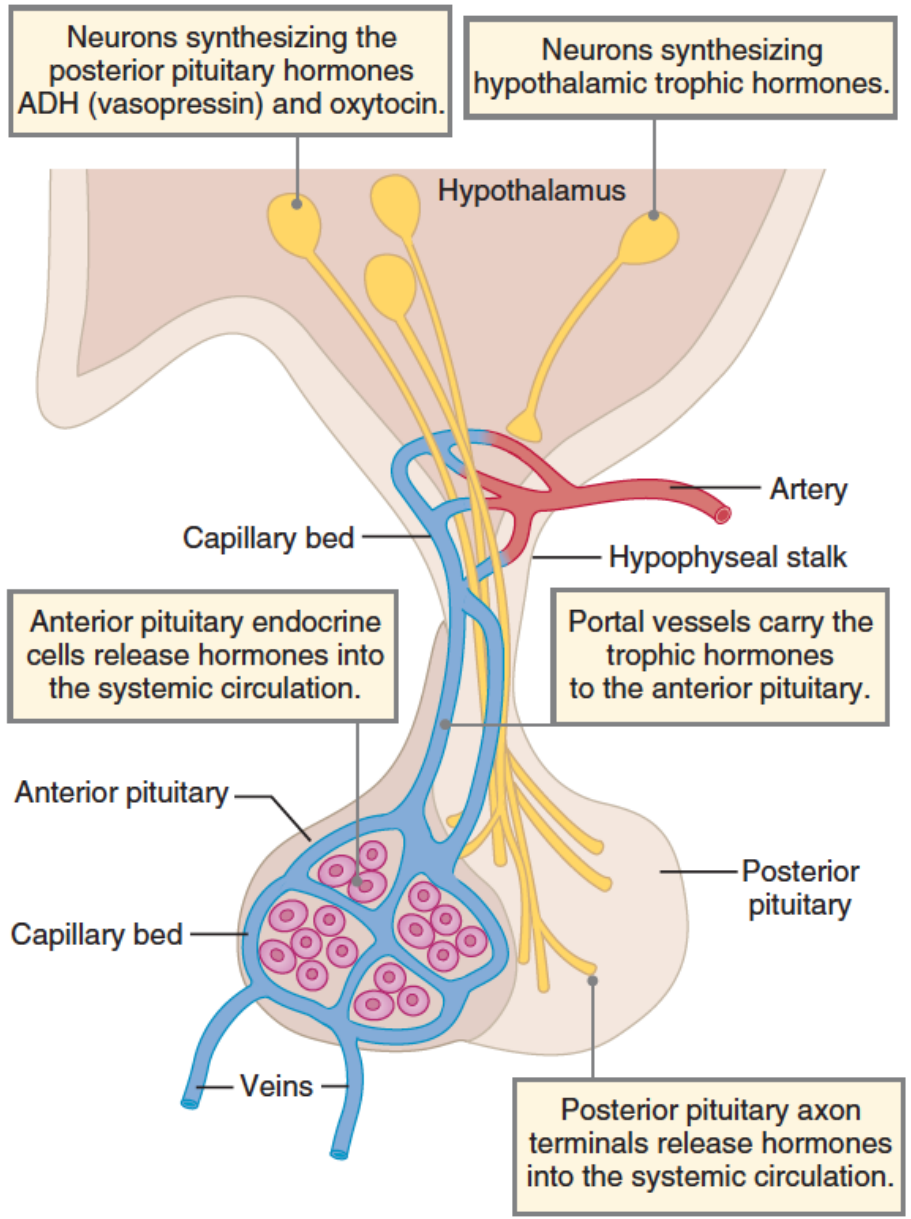


Figure 9-8 **Schematic figure showing the relationship between the hypothalamus and the posterior and anterior lobes of the pituitary gland.** *Pink circles* are posterior pituitary hormones; *yellow circles* are hypothalamic hormones; *triangles* are anterior pituitary hormones. ADH, Antidiuretic hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.



Hypothalamo pitutary hormons

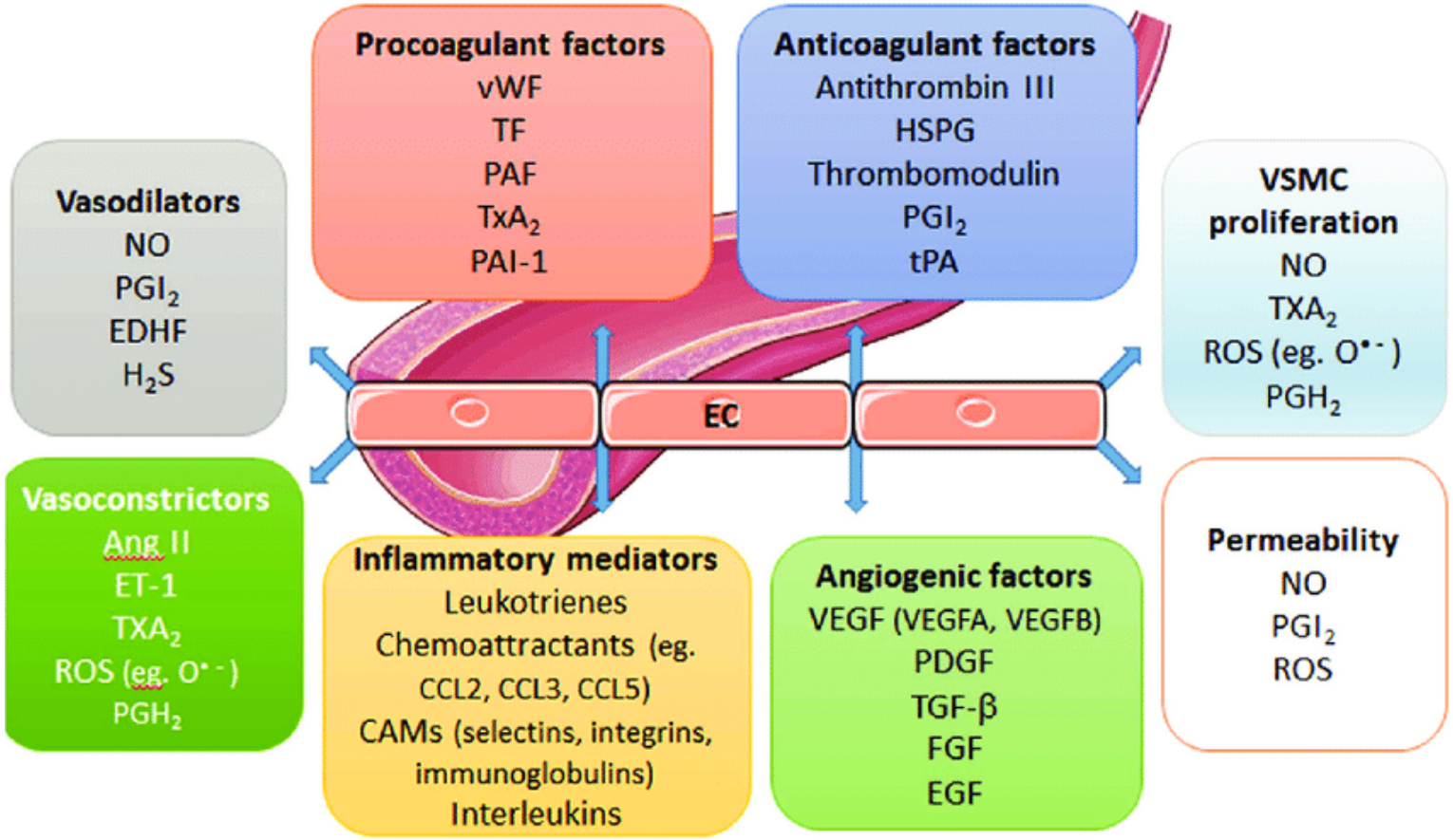
Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
CRH	↑ ACTH, MSH, β-endorphin	↓ in chronic exogenous steroid use.
Dopamine	↓ prolactin, TSH	Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia.
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy.
GnRH	↑ FSH, LH	Suppressed by hyperprolactinemia. Tonic GnRH suppresses HPG axis. Pulsatile GnRH leads to puberty, fertility.
Prolactin	↓ GnRH	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea.
Somatostatin	↓ GH, TSH	Analogs used to treat acromegaly.
TRH	↑ TSH, prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea.

Pitutary in a nutshell

Pituitary gland		
Anterior pituitary (adenohypophysis)	Secretes FSH, LH, ACTH, TSH, prolactin, GH. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch). ▪ α subunit—hormone subunit common to TSH, LH, FSH, and hCG. ▪ β subunit—determines hormone specificity.	ACTH and MSH are derivatives of proopiomelanocortin (POMC). FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH. B-FLAT: Basophils—FSH, LH, ACTH, TSH. Acidophils: GH, PRL.
Posterior pituitary (neurohypophysis)	Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.	

Vascular endothelial cell function

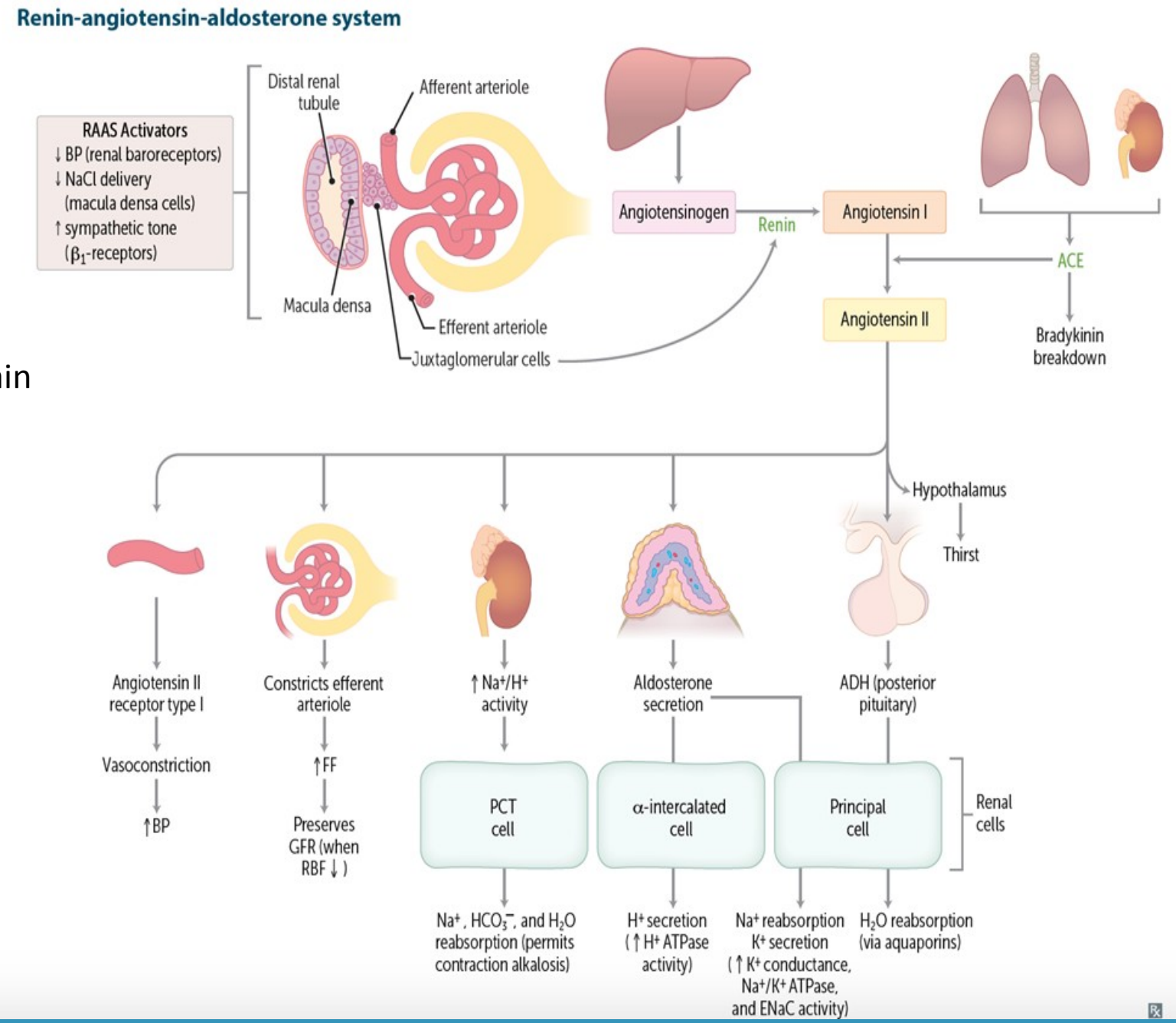


RAAS and AG II

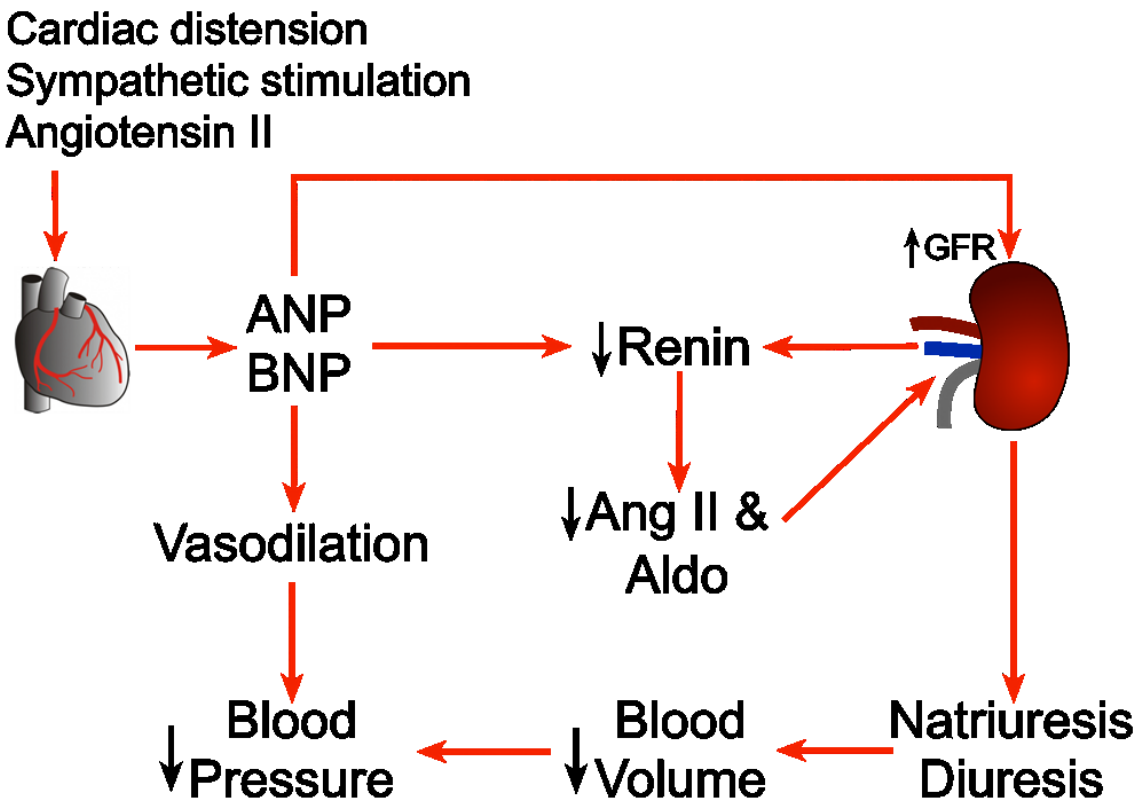
- Is activated to preserve Volume and maintain the Blood pressure

This is done by :

1. Vasoconstictrion increase TPR
2. Increasing Na+ resorbtion increase Preload increase in CO
3. Both of which increase MAP

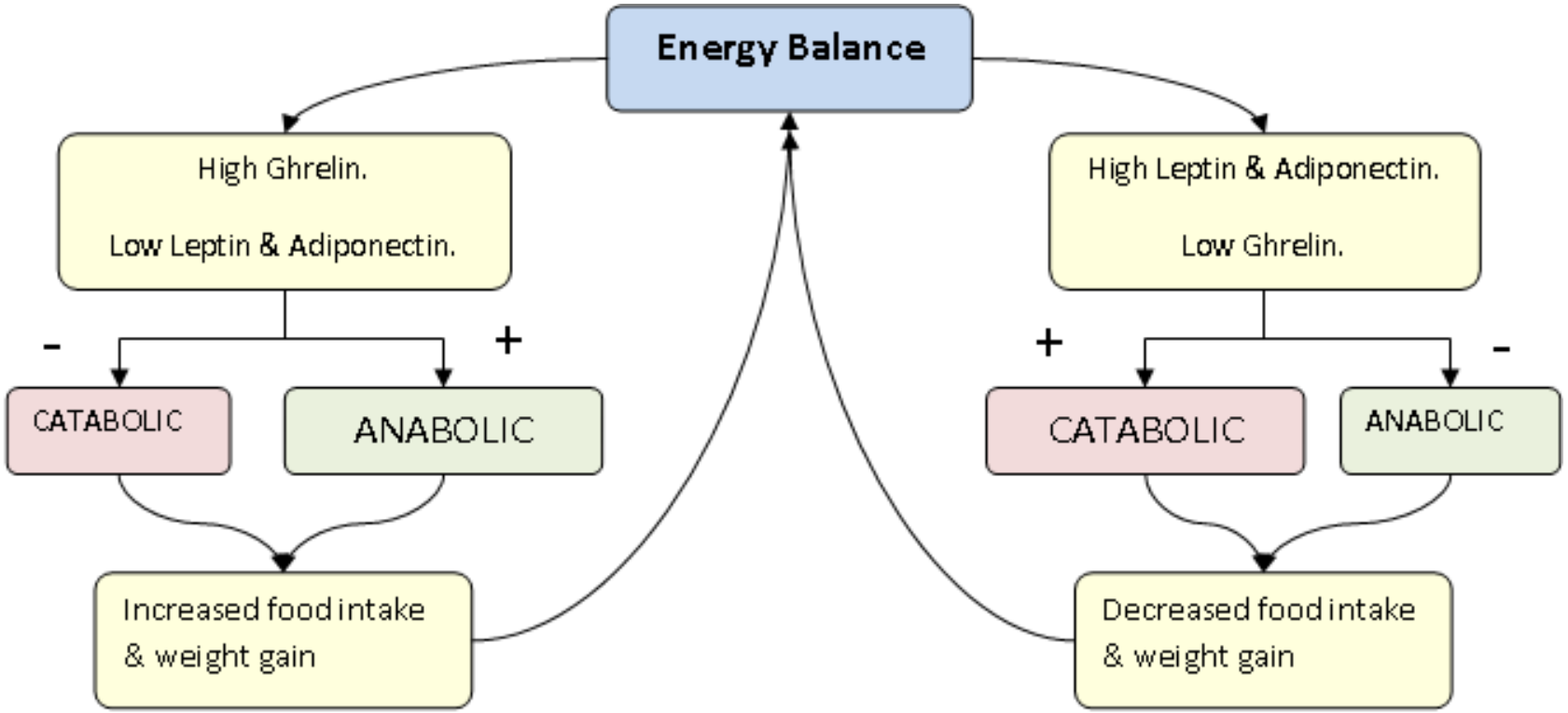


Natriuretic peptides (opposing RAAS)



Cardiovascular and Renal Actions of Natriuretic Peptides

- Natriuresis
- Diuresis
- Improve glomerular filtration rate & filtration fraction
- Inhibit renin release
  - ↓ circulating angiotensin II
  - ↓ circulating aldosterone
- Systemic vasodilation
- Arterial hypotension
- Reduced venous pressure
- Reduced pulmonary capillary wedge pressure


Energy Balance
High Ghrelin.
Low Leptin & Adiponectin.
-
+
CATABOLIC
ANABOLIC
Increased food intake
& weight gain
High Leptin & Adiponectin.
Low Ghrelin.
+
-
CATABOLIC
ANABOLIC
Decreased food intake
& weight gain

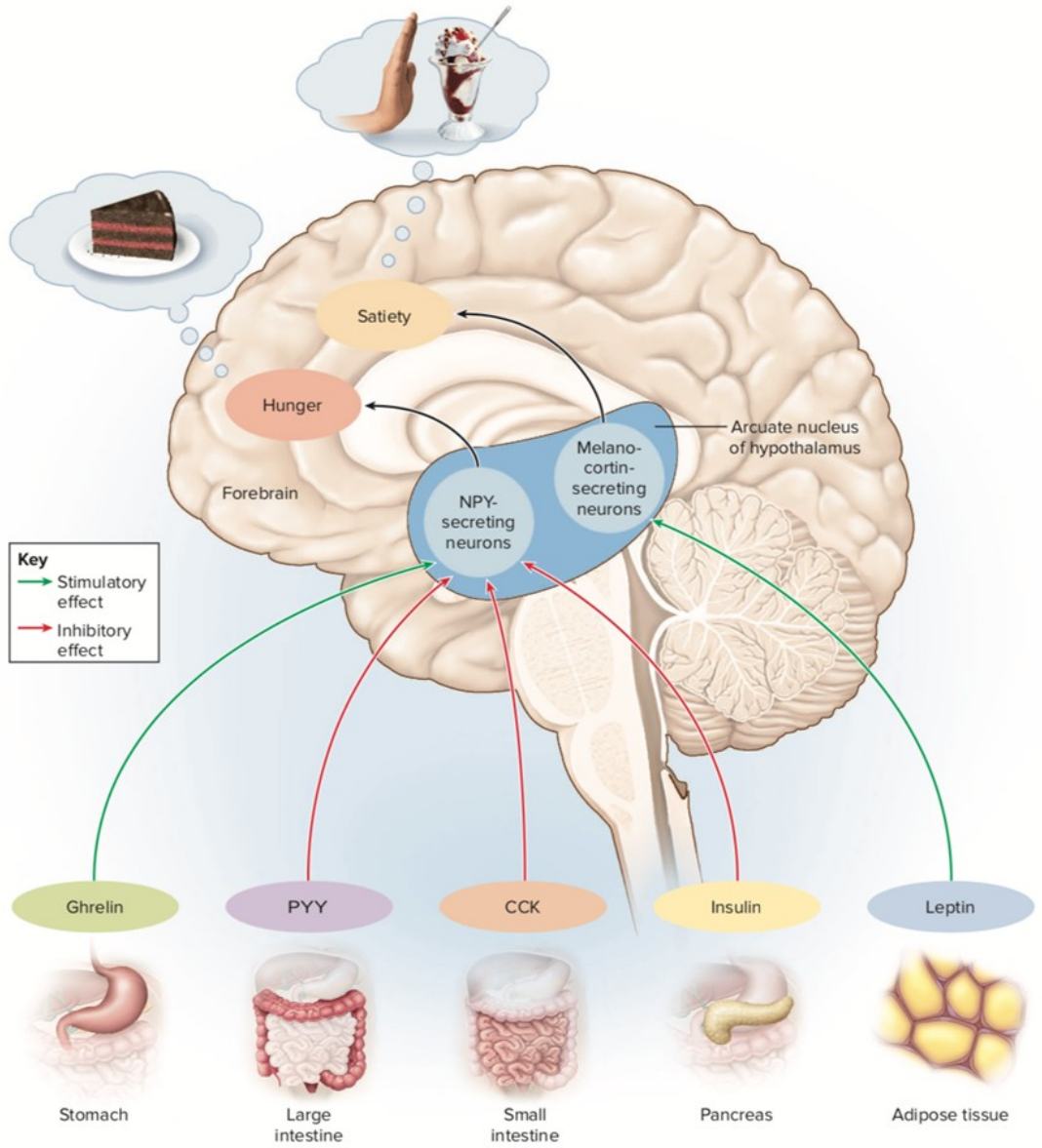
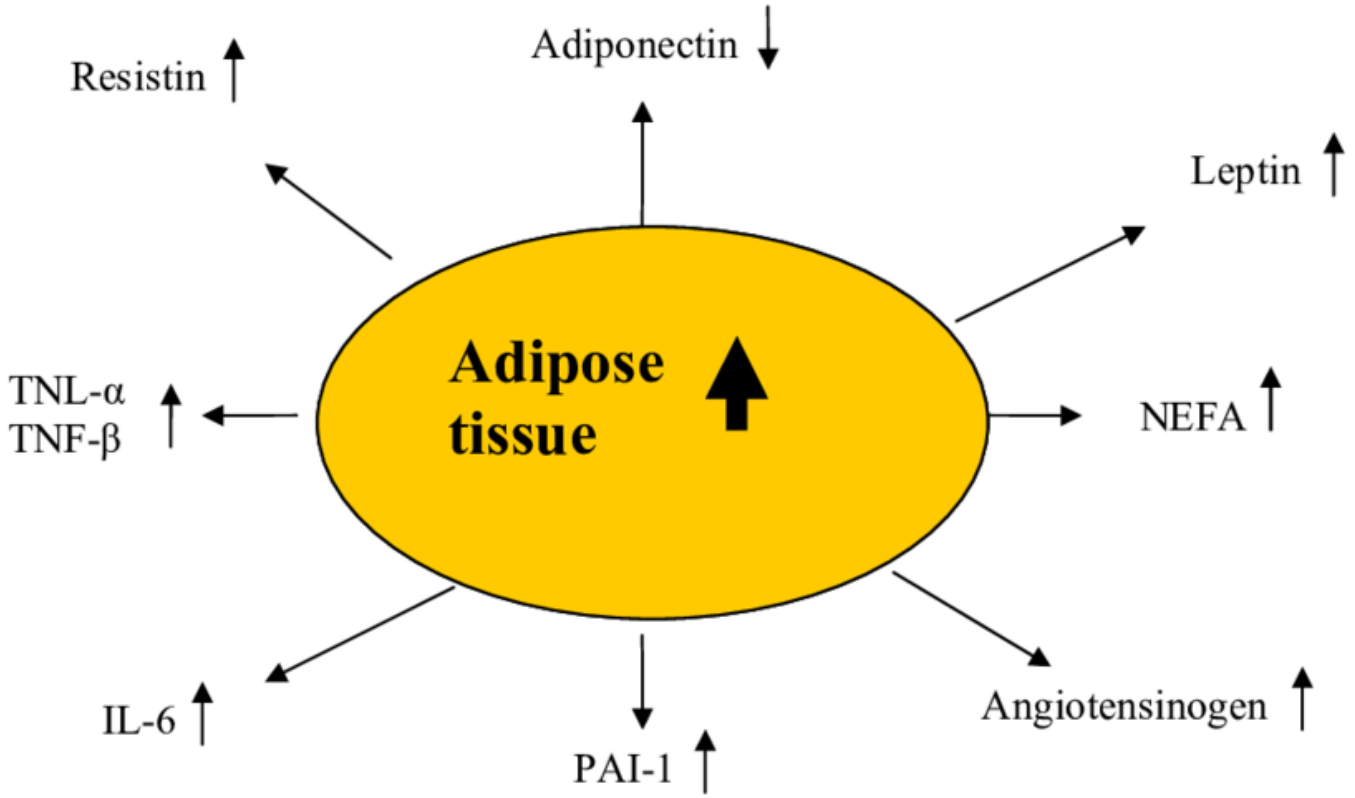


FIGURE 26.2 Principal Pathways of Appetite Regulation by Gut–Brain Peptides. Tissues and organs at the bottom of the figure are sources of peptides that stimulate or inhibit appetite-regulating neurons in the arcuate nucleus of the hypothalamus. Depending on the balance of stimulation and inhibition, those neurons secrete NPY or melanocortin to create a conscious sensation of hunger or satiety, respectively. (The arcuate nucleus is shown far larger than its real size.) (PYY = peptide YY; CCK = cholecystokinin; NPY = neuropeptide Y)

Increase in white adipose tissue and changes in related hormones



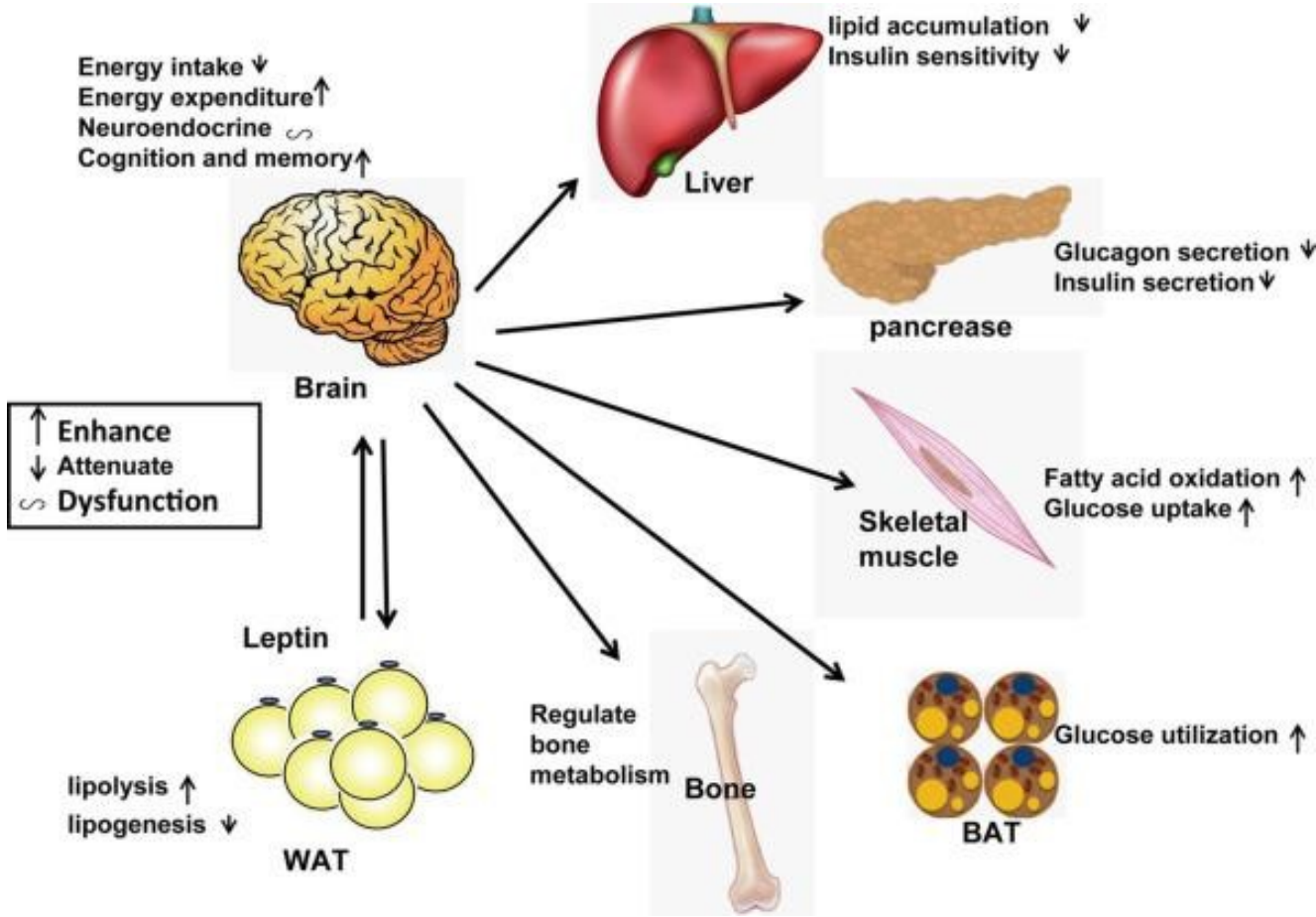
Pathophysiology of Obesity (Increase in WAT mass)

- Increase in **AGE** → increase in BP (HTN)
- Increase in **PAI-1** → inhibiting fibrinolytic system Clotting Risk of CVD
- **TNF-a & IL-1** → disruption of insulin signaling insulin resistance
- Excess **leptin** → leptin resistance obesity and insulin resistance type 2 DM
- Decrease in **adiponectin** → decrease Gluc uptake & Pro-inflammatory condition in endothelial cells → risk of type 2 diabetes & CVD respectively.
- excess **resistin** → decrease insulin mediated Glu uptake type 2 DM

Leptin as a marker of long-term energy storage and acute changes in energy intake (keeps you thin)

Factors promoting leptin secretion
Excess energy stored as fat (obesity)
Overfeeding
Glucose
Insulin
Glucocorticoids
Estrogens
Inflammatory cytokines, including Tumor Necrosis Factor-α and Interleukin-6 (acute effect)

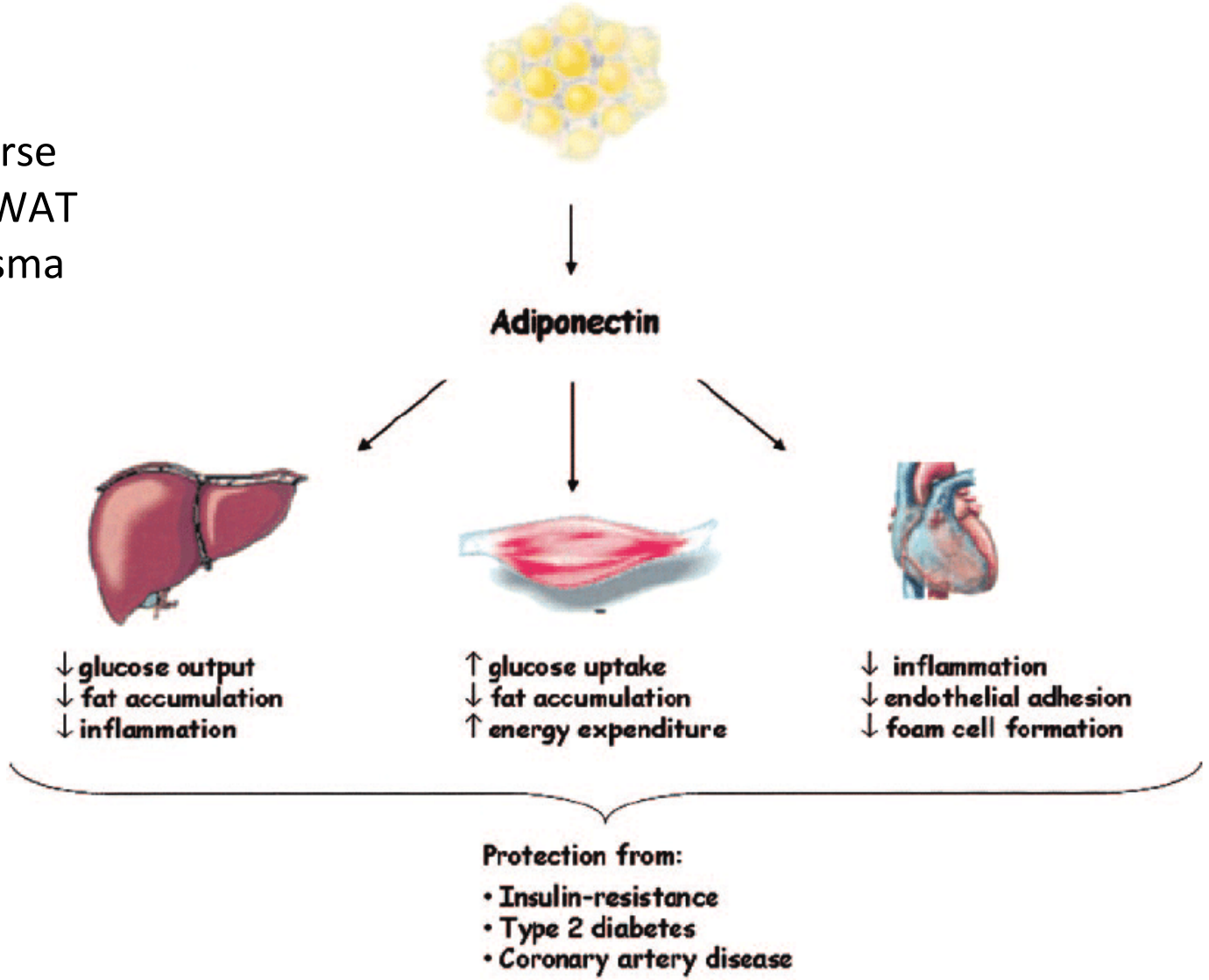
Factors inhibiting leptin secretion
Low energy states with decreased fat stores (leanness)
Fasting
Catecholamines and adrenergic agonists
Thyroid hormones
Androgens
Peroxisome Proliferator-activated Receptor-γ (PPARγ) agonists[c]
Inflammatory cytokines, including Tumor Necrosis Factor-α (prolonged effect)

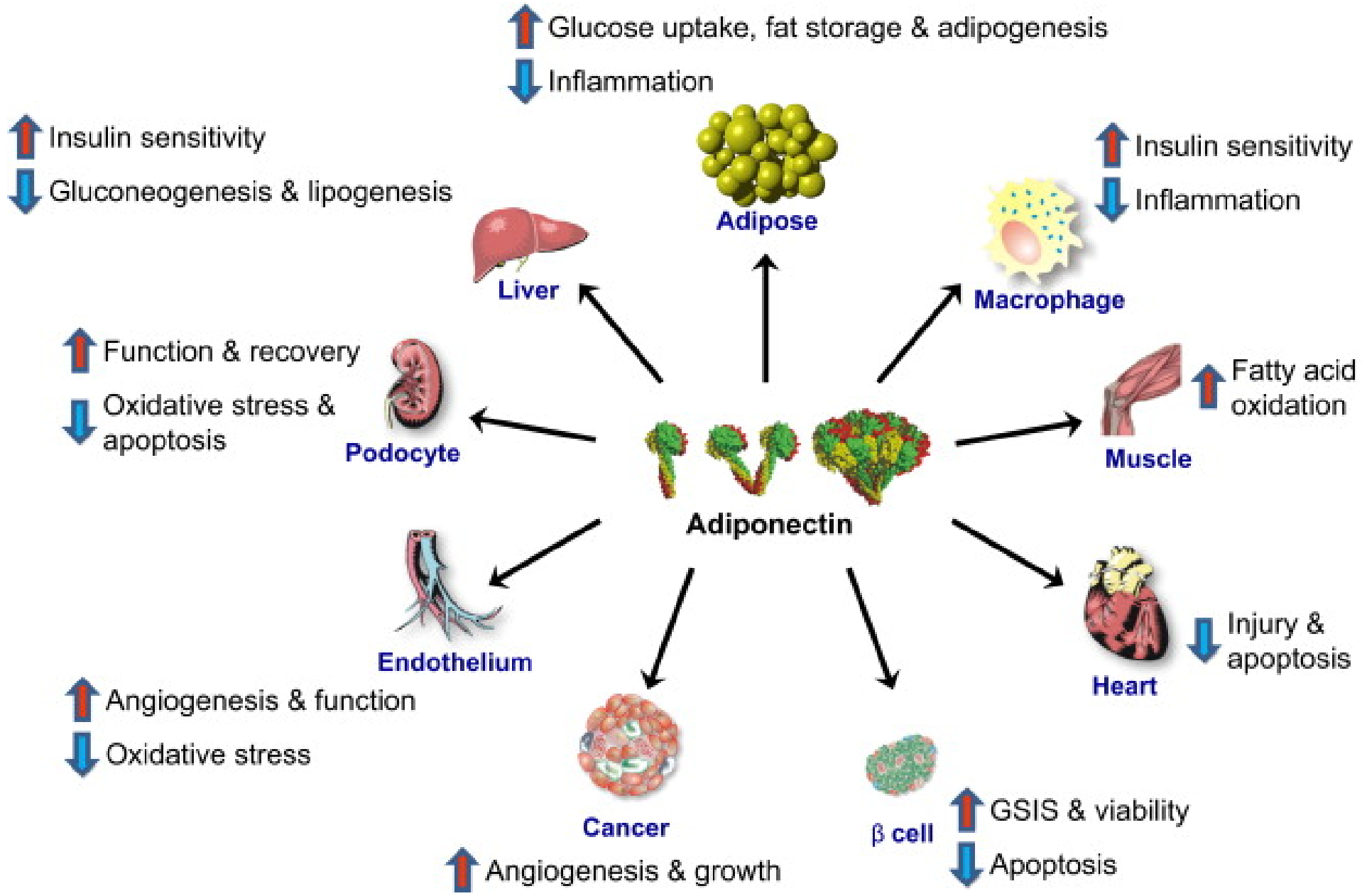


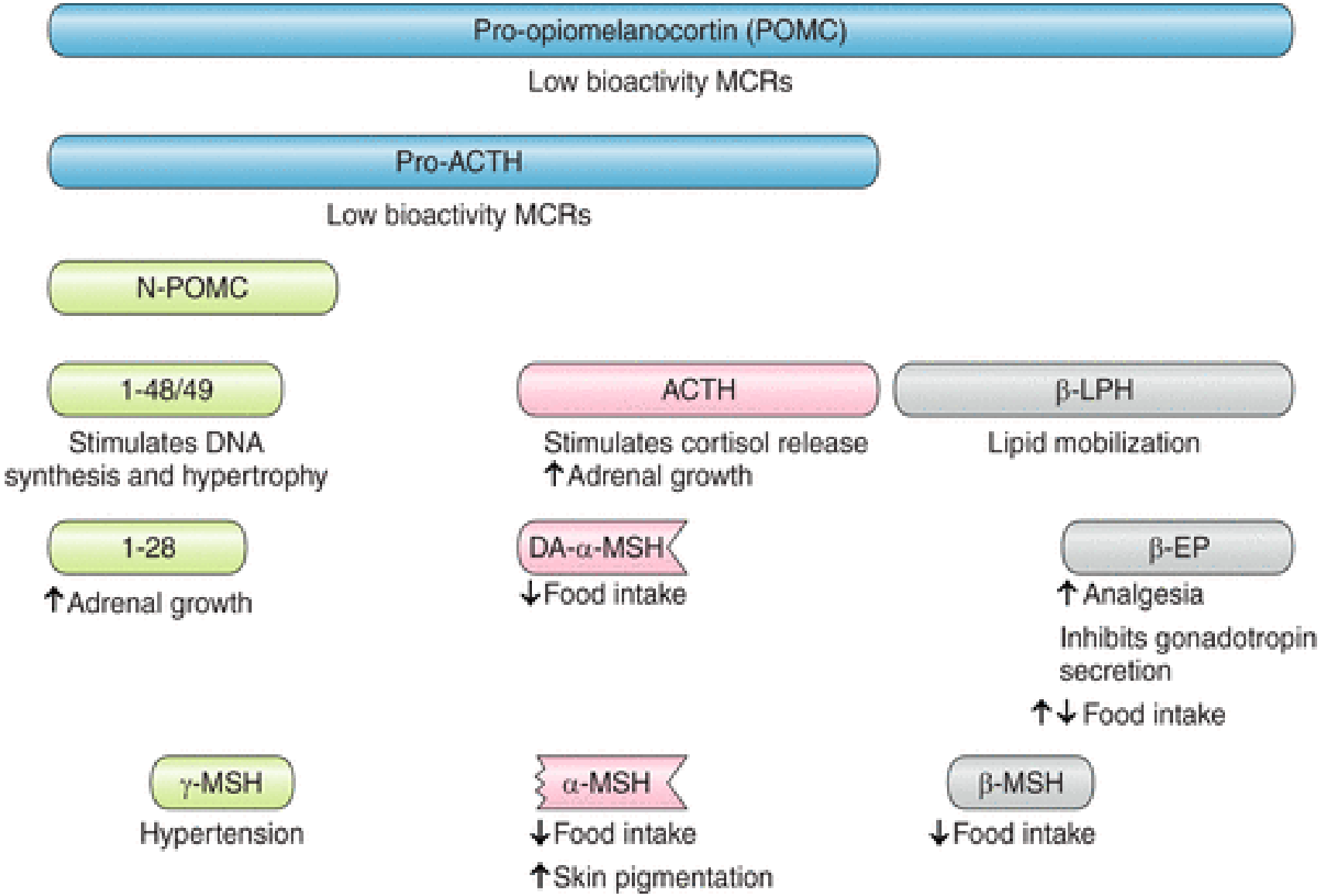
Adiponectin

Plasma adiponectin concentration has inverse correlation with body fat mass ie, the less WAT you have higher is your adiponectin plasma level

High levels of Adiponectin is beneficial and protective against Type 2 DM and CVD




Glucose uptake, fat storage & adipogenesis
Inflammation
Insulin sensitivity
Gluconeogenesis & lipogenesis
Adipose
Liver
Macrophage
Insulin sensitivity
Inflammation
Function & recovery
Oxidative stress & apoptosis
Podocyte
Adiponectin
Muscle
Fatty acid oxidation
Endothelium
Heart
Injury & apoptosis
Angiogenesis & function
Oxidative stress
Cancer
β cell
GSIS & viability
Apoptosis
Angiogenesis & growth


Pro-opiomelanocortin (POMC)
Low bioactivity MCRs
Pro-ACTH
Low bioactivity MCRs
N-POMC
1-48/49
Stimulates DNA synthesis and hypertrophy
1-28
↑Adrenal growth
ACTH
Stimulates cortisol release
↑Adrenal growth
β-LPH
Lipid mobilization
DA-α-MSH
↓Food intake
β-EP
↑Analgesia
Inhibits gonadotropin secretion
↑↓Food intake
γ-MSH
Hypertension
α-MSH
↓Food intake
↑Skin pigmentation
β-MSH
↓Food intake