Principles of Endocrinology and Hormone Action

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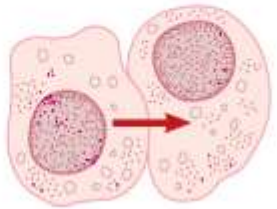
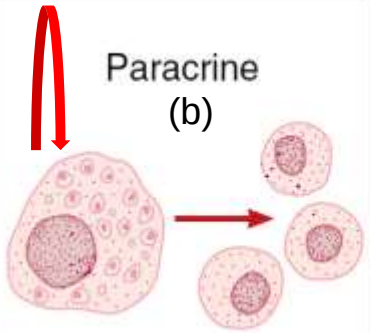
Definition and Scope of Endocrinology

- **Endocrinology** is the branch of biology and medicine concerned with the **endocrine system**, its **diseases** and the secretory products of endocrine glands known as "***hormones***"
- **Endocrine glands** are **ductless glands** of the endocrine system which **synthesize** and **secrete hormones** directly into the **blood**
- **Hormones** (from the Greek verb *hormao*, "*to set in motion*") are **signaling molecules**, produced by endocrine glands, that are **transported** through the bloodstream (often bound to a plasma protein) to target **distant organs and tissues/cells** to regulate their physiology and behavior (***endocrine effect***)
- Hormones can also act locally following secretion, either on a neighboring cell (***paracrine effect***), or on the secretory cell itself (***autocrine effect***)

Intercellular communication by chemical mediators

(a) Autocrine

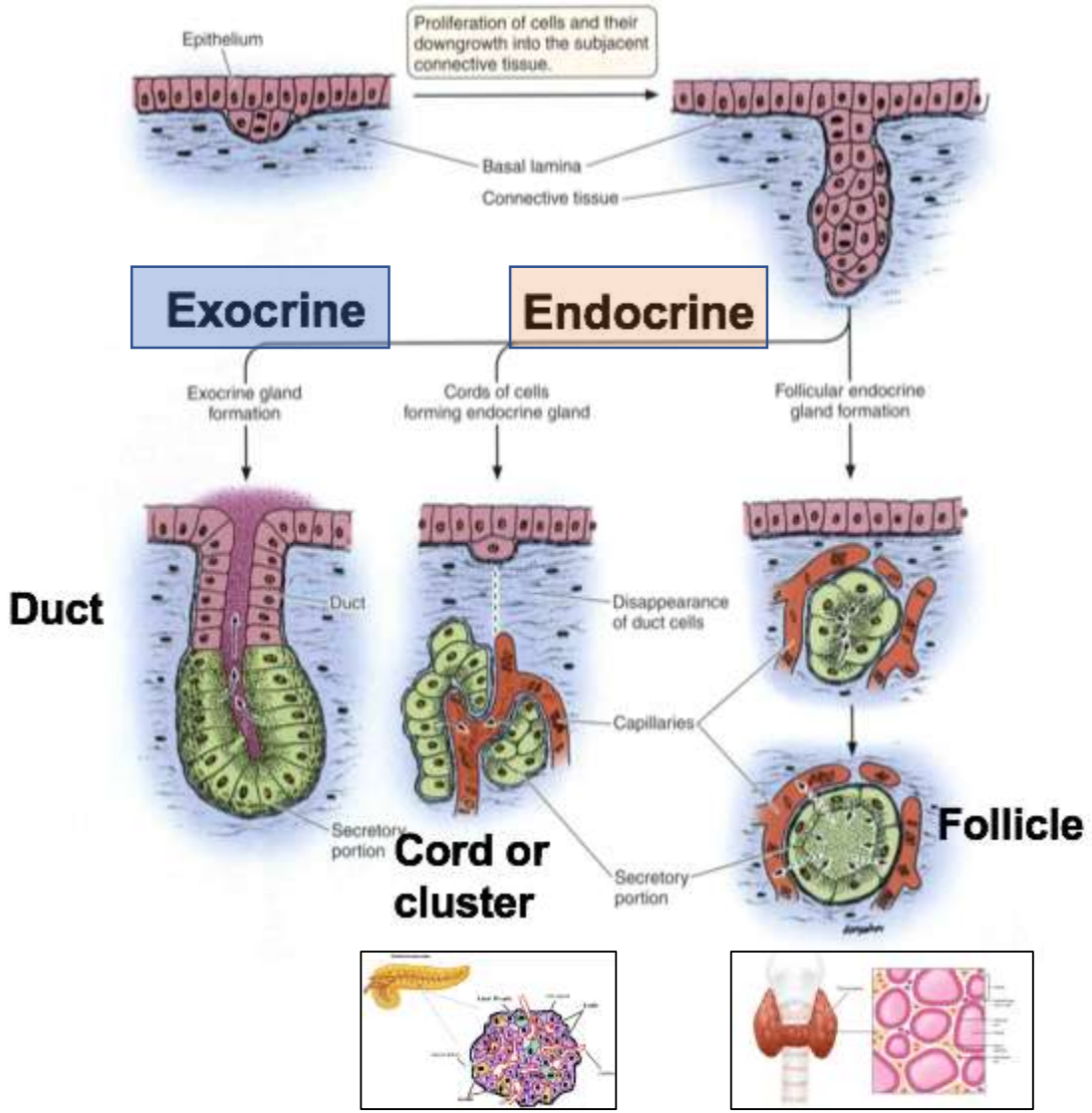
	Gap junctions	Synaptic	Paracrine (b)	Endocrine
				
Message transmission	Directly from cell to cell	Across synaptic cleft	By diffusion in interstitial fluid	By circulating body fluids
Local or general	Local	Local	Locally diffuse	General
Specificity depends on	Anatomic location	Anatomic location and receptors	Receptors	Receptors

Greenspan's, 10th Edition

Exocrine glands *vs*. Endocrine glands

Exocrine glands secrete substances through ducts onto an epithelial surface

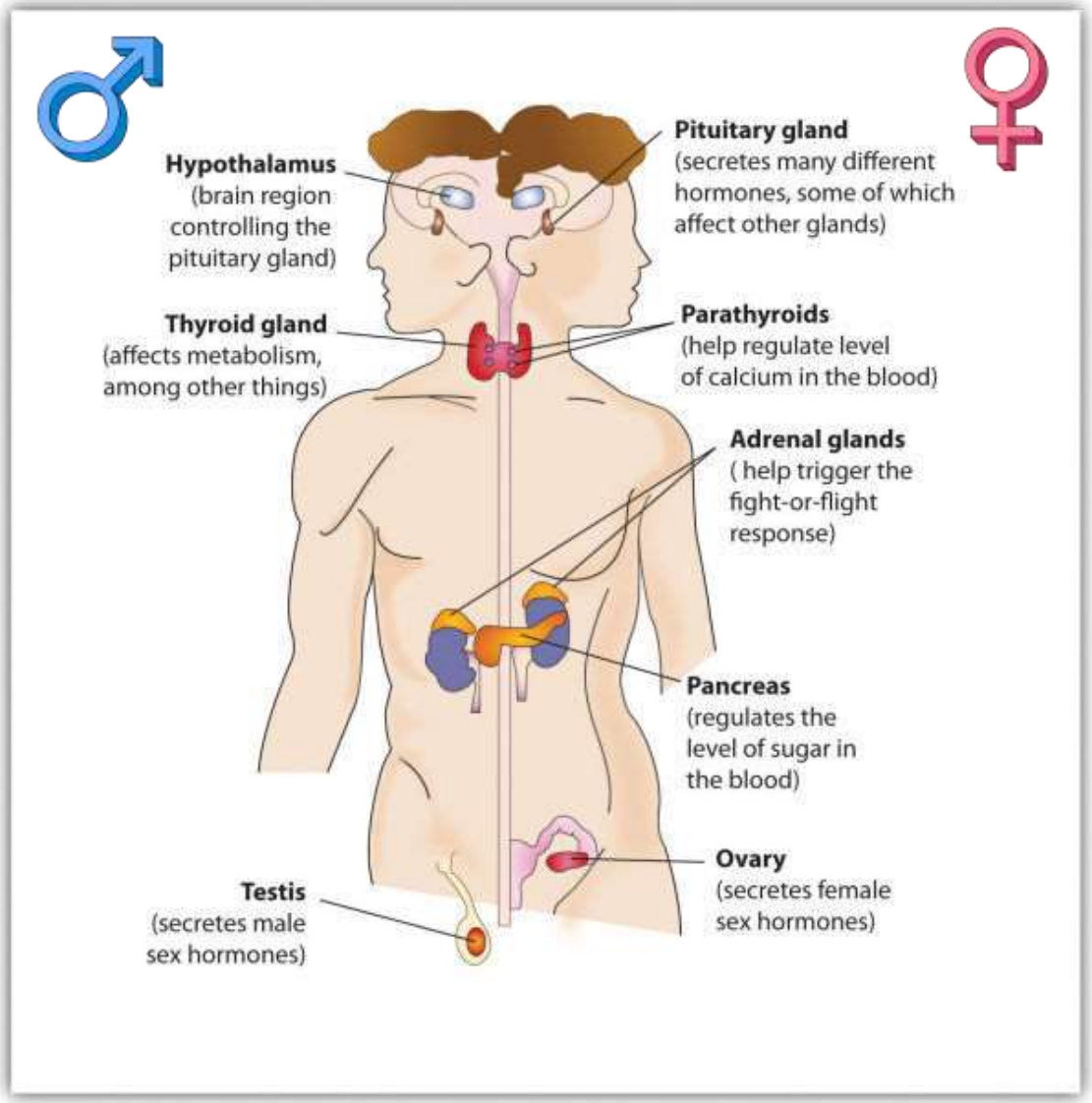
Examples:
Salivary glands
Breast
Exocrine pancreas



Endocrine glands are **ductless** glands that secrete hormones directly into the bloodstream

Examples:
Thyroid gland
Adrenal glands
Endocrine pancreas

The Endocrine System



Examples of organs with secondary endocrine functions

Organ	Examples of hormones produced by different endocrine cells
Heart	Natriuretic polypeptide hormones produced by atrial cardiomyocytes: • **Atrial natriuretic factor**, a.k.a. **Atrial natriuretic peptide** (**ANF** or **ANP**) • **Brain natriuretic peptide** (**BNP**)
Gastrointestinal tract **[Gastro-entero-pancreatic (GEP) endocrine system]**	• **Gastrin** (G cells – gastric antrum and duodenum) • **Ghrelin** (P/D1 cells – gastric fundus) • **Cholecystokinin** (CCK) (I cells – proximal small intestine) • **Somatostatin** (D cells – gastric corpus and antrum, small intestine) • **Glucose-dependent insulinotropic polypeptide (GIP)** (K cells – proximal small intestine) • **Glucagon-like peptide 1** (**GLP-1**), **GLP-2, peptide YY** (**PYY**) (L cells – distal small intestine, colon) • **Serotonin** [**5-hydroxytryptamine** (**5-HT**)] [enterochromaffin (EC) cells, a.k.a. as Kulchitsky cells – stomach, small and large intestine]
Kidneys	• **Renin** – Juxtaglomerular cells (JGCs) • **Calcitriol** [a.k.a. 1,25(OH)2D], which is hydroxylated by the enzyme 1α-hydroxylase (CYP27B1) located in the mitochondria of proximal tubules of the kidney • **Erythropoietin** (**EPO**) – Renal cortex peritubular cells
Adipose tissue	• **Adipose-derived hormones and adipokines** (e.g., leptin, adiponectin, resistin, visfatin, etc.)
Thymus	• **Thymosin** (thymosin-producing cells of the thymus)
Diffuse endocrine system (**DES**)	DES is composed of **neuroendocrine cells** scattered throughout the entire body, either isolated or grouped to form discrete aggregates, such as the neuroepithelial bodies in the bronchopulmonary tract.

Chemical Nature of Hormones

- **Large proteins, polypeptides and glycoproteins** (e.g., insulin, ACTH, GH, PRL, PTH; **glycoproteins**: FSH, LH, TSH)
- **Small neuropeptides** (e.g., GnRH, TRH, ADH, somatostatin)
- **Amino acid derivatives** (thyroid hormones, catecholamines, dopamine)
- **Steroid hormones** (e.g., cortisol, estrogen, testosterone, progesterone)
- **Vitamin derivatives** (e.g., vitamin A, vitamin D)

Principles of Hormone Action

1. Hormone biosynthesis and secretion
2. Feedback regulation
3. Hormone transport
4. Hormone-receptor binding
5. Initiation of intracellular signaling

Hormone biosynthesis and release

Protein or peptide hormones

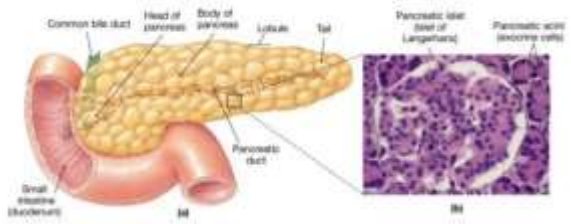
- **Increased expression of genes** encoding the hormone leads to subsequent increases in hormone synthesis.
  - Peptides, proteins, and monoamines are generally stored in **secretory granules** in endocrine cells.
  - Release of these granules is promoted by signaling events triggered by exogenous regulators termed "**secretagogues**".

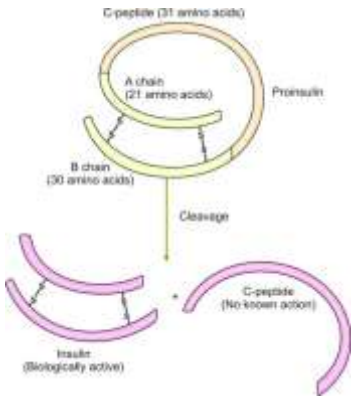
Steroid or thyroid hormones

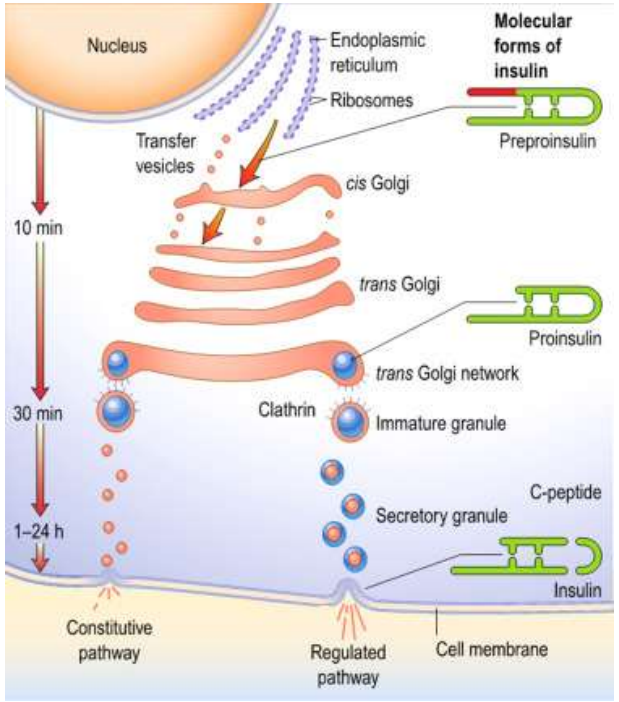
- **Increased sequestration of precursors** for hormone synthesis (e.g., cholesterol for steroid hormones or iodide for thyroid hormones) and **increased activity of enzymes** responsible for executing the individual catalytic events required for hormone production.
- Steroid hormones are not stored in secretory granules to a significant degree in the hormone-producing cells; steroid hormones usually diffuse into the bloodstream as they are synthesized.

Precursor processing: examples

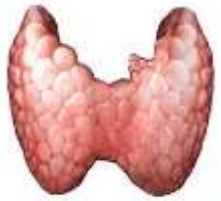
a) Pancreas

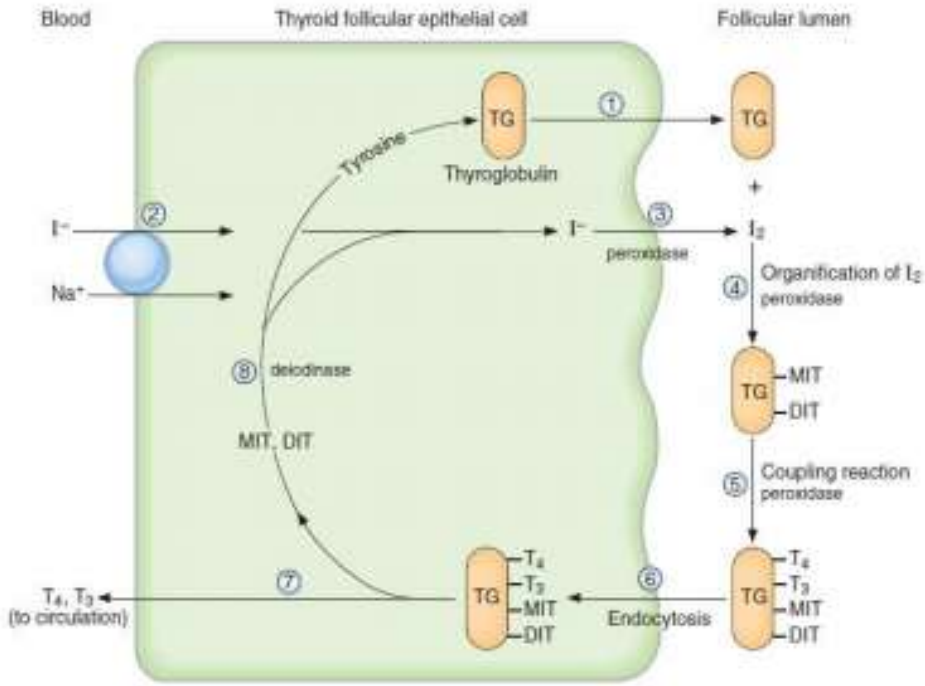






b) Thyroid

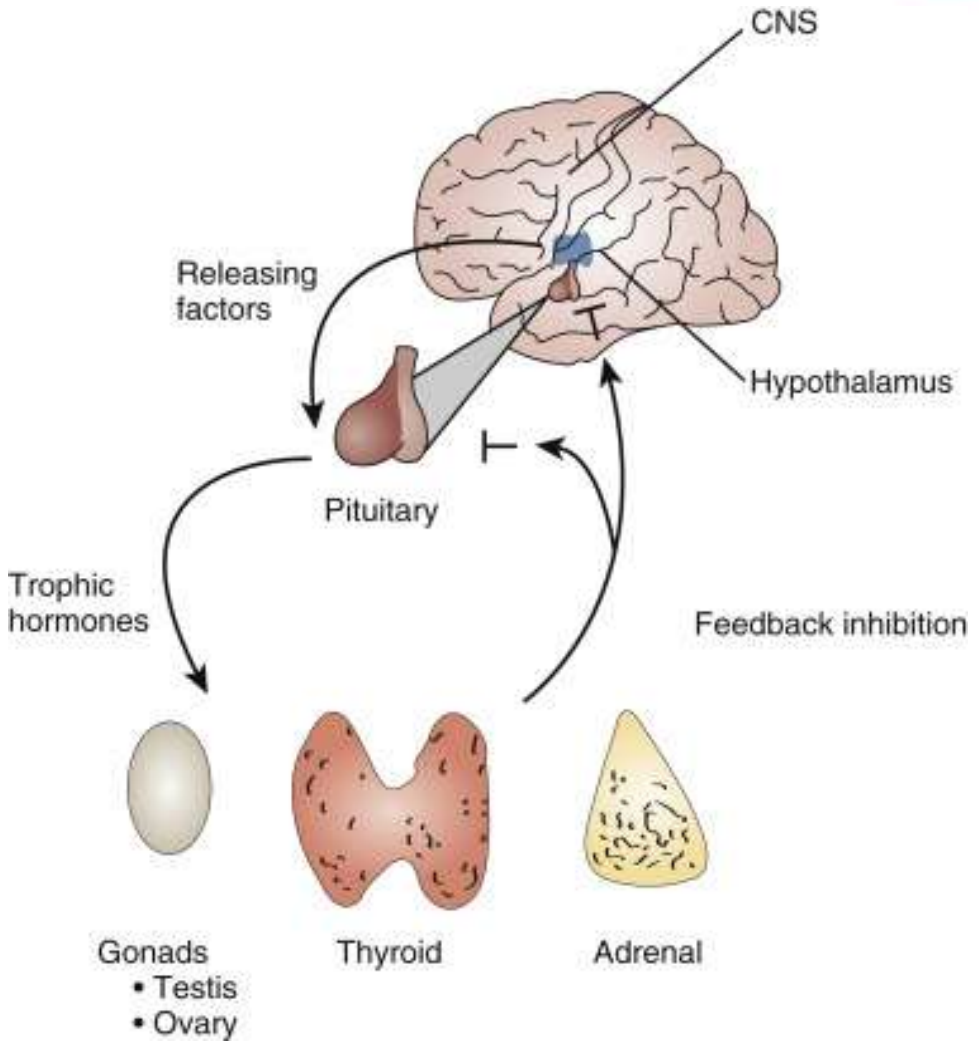




Feedback regulation

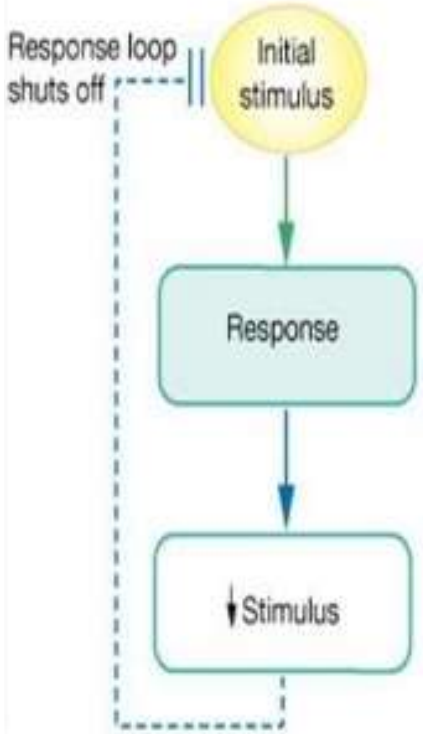
Hormones have a **particular set point** that is controlled by:

- **<u>downregulating</u> stimulatory pathways** when the set point is exceeded
- **<u>upregulating</u> stimulatory pathways** when hormone levels fall below the set point

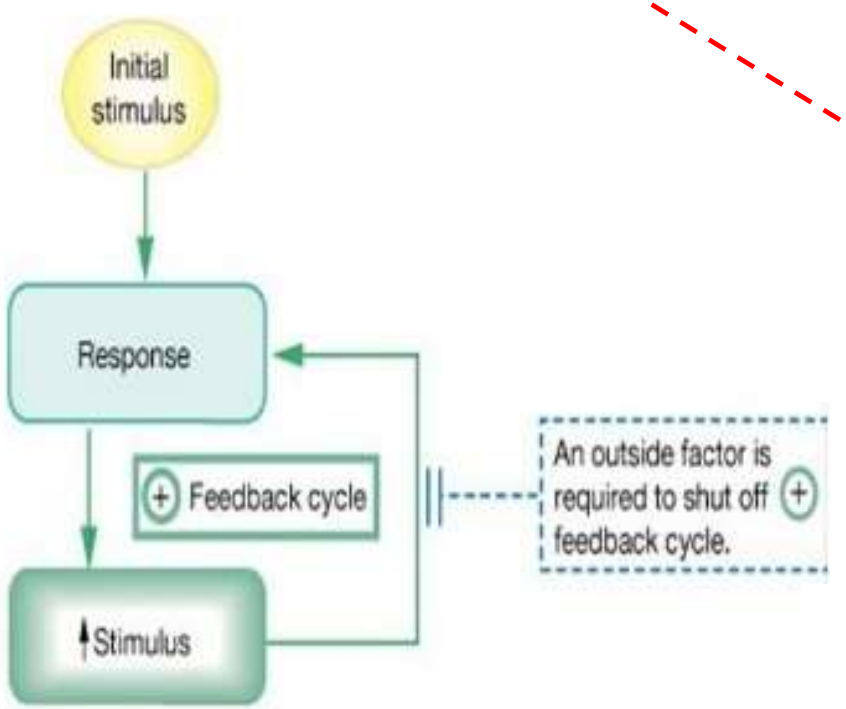


Feedback regulation

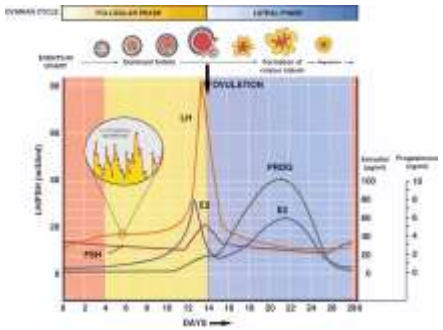
a) Negative feedback: the response counteracts the stimulus shutting off the response loop.



(b) Positive feedback: the response reinforces the stimulus sending the parameter farther from the setpoint.

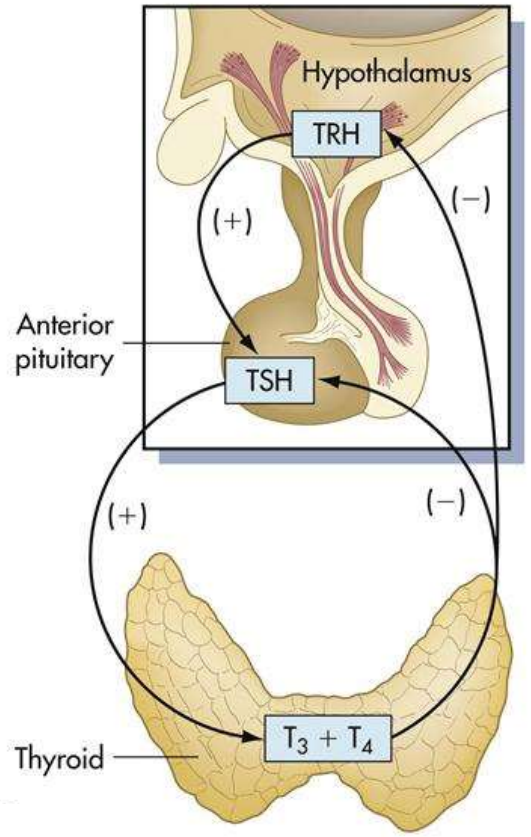


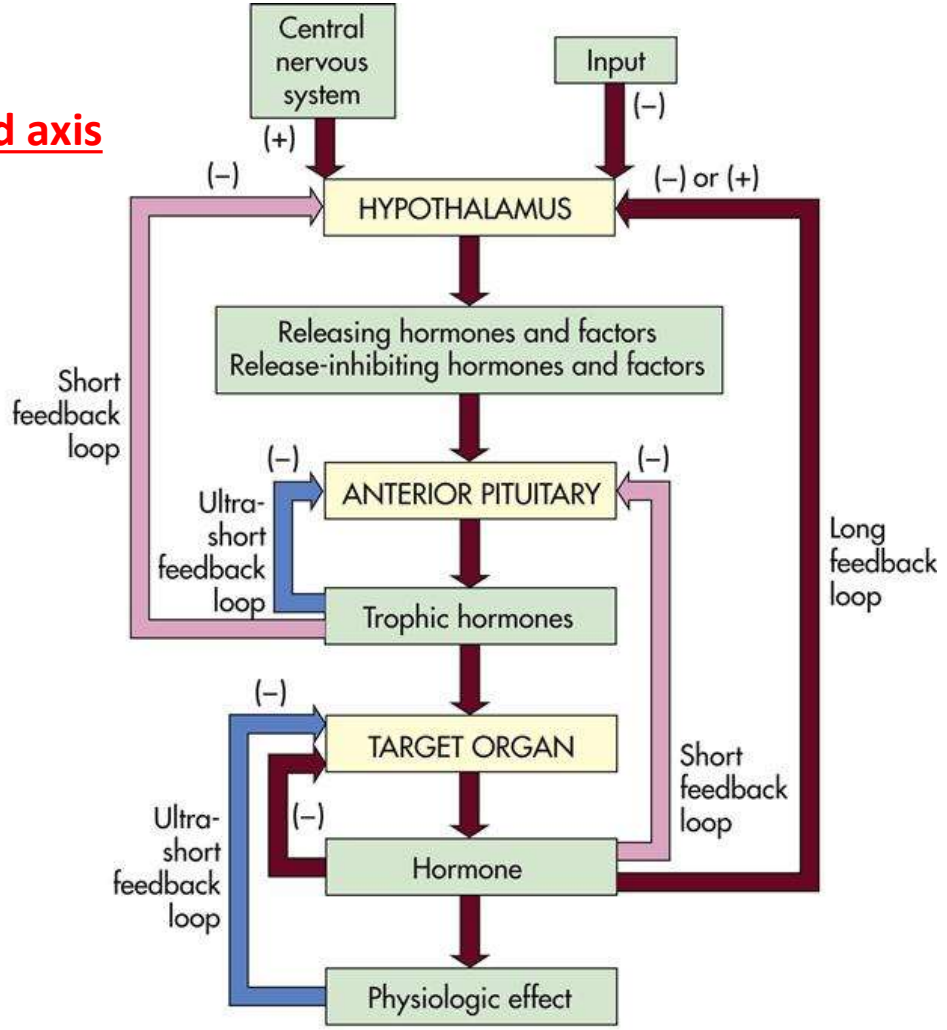
Mid-cycle estradiol-induced LH secretion



Feedback regulation: HPT axis

Hypothalamic-Pituitary-Thyroid axis



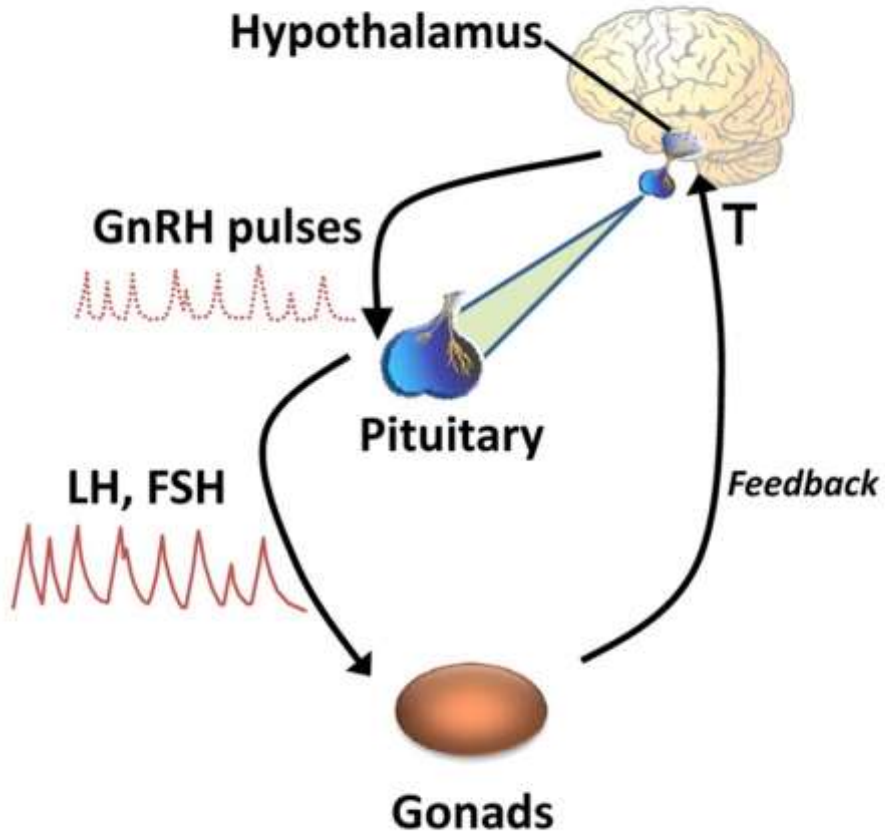


Pulsatility of hormone secretion

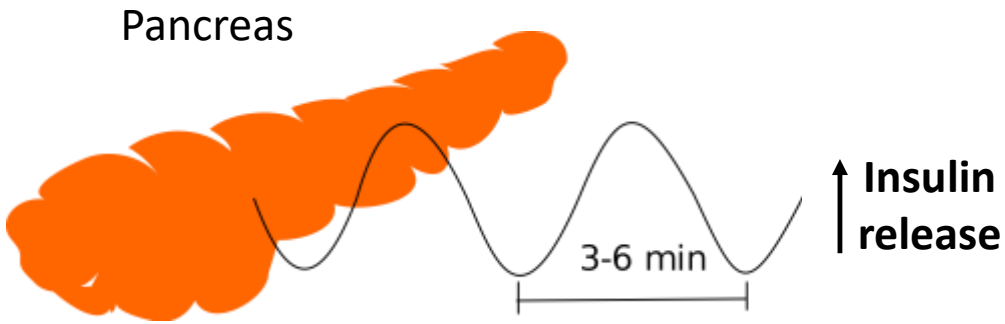
- **Several hormones are secreted in a <u>pulsatile fashion</u>** (e.g., GnRH, TRH, GH, insulin, etc.) and **<u>hormonal rhythms</u>** are used to adapt to environmental changes, such as **daily light-dark cycle**, **sleep**, **meals**, **stress** and **seasonality**.
- **Hormone rhythms** have important implications for **endocrine testing and treatment**.
- **Biomarkers to circumvent hormonal fluctuations**: 24-hour urinary free cortisol (UFC), Insulin-like Growth Factor 1 (IGF-1, a relatively stable biologic marker of GH action), etc.

Pulsatility of hormone secretion: examples

HPG axis

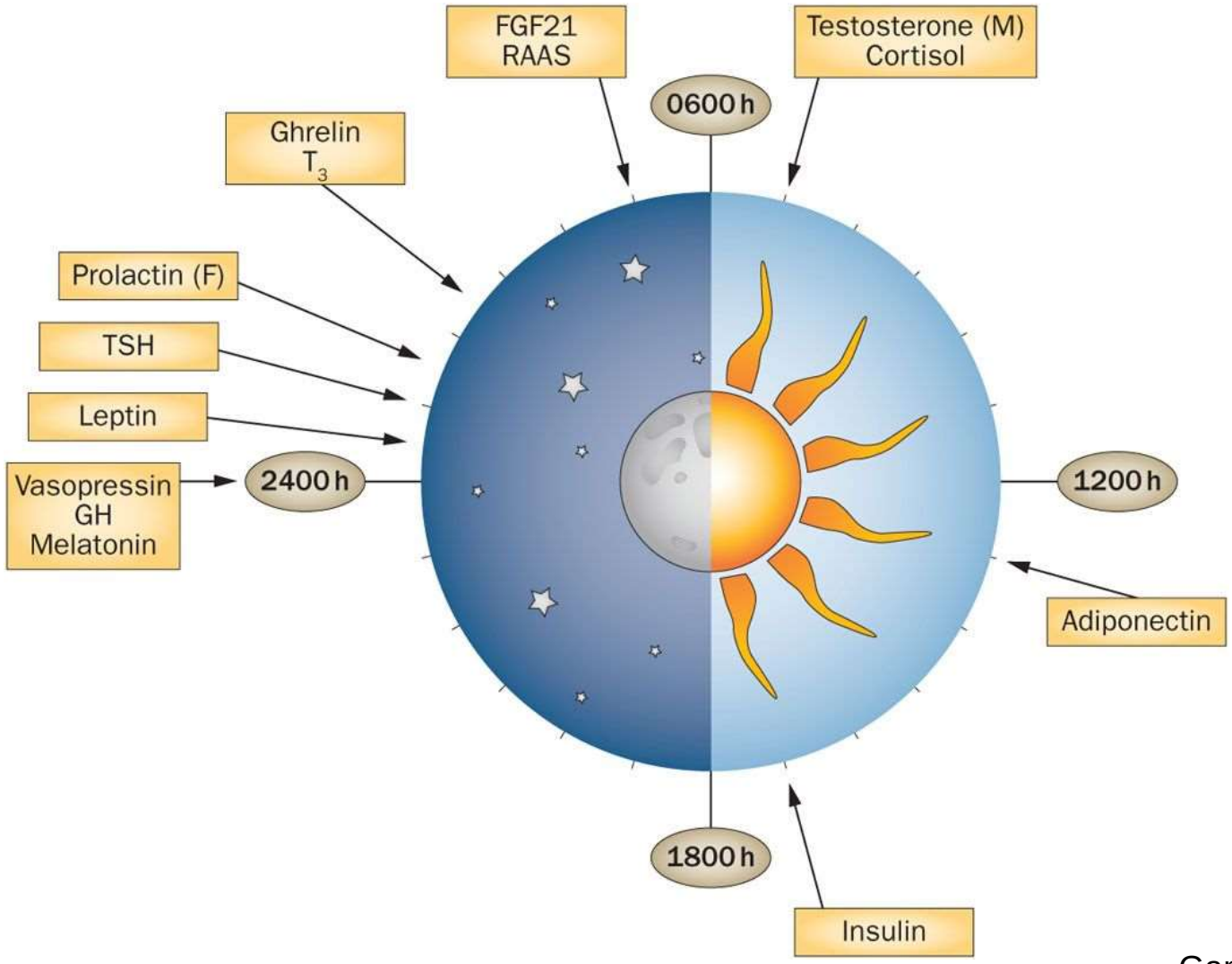


Pancreas



Jameson 2007; Hellman et al. 2007

Circadian hormone rhythms



Gamble *et al*. 2014, Nat Rev Endocrinol

Hormone transport

- Most **steroid hormones** and many **peptide hormones** circulate in association with **binding proteins**, which are globulin proteins synthesized primarily in the **liver**.

Hormone	Hormone-binding protein(s)
Cortisol	**Cortisol-binding globulin** (**CBG**) or transcortin
Sex hormones (androgens and estrogens)	**Sex hormone-binding globulin** (**SHBG**)
Thyroid hormones (T3 and T4)	• **Thyroxine-binding globulin** (**TBG**) • **Albumin** • **Thyroxine-binding prealbumin** (**TBPA**) or transthyretin (TTR)
Growth hormone (GH)	**GH-binding protein** (**GHBP**)
Insulin-like growth factors: IGF-1 and IGF-2	Multiple **IGF-binding proteins** (**IGFBPs**)

Hormone action through receptors

- **Hormones** produce their **biologic effects** through interaction with **high-affinity receptors** that are, in turn, linked to one or more effector systems within the cell.

- **Hormone receptors** can be divided broadly into **two categories**, namely:

a. **Membrane receptors** → these receptors primarily bind **peptide hormones**, **neurotransmitters** and **small molecules** that are not able to cross the plasma membrane (e.g., **catecholamines**, **dopamine**)

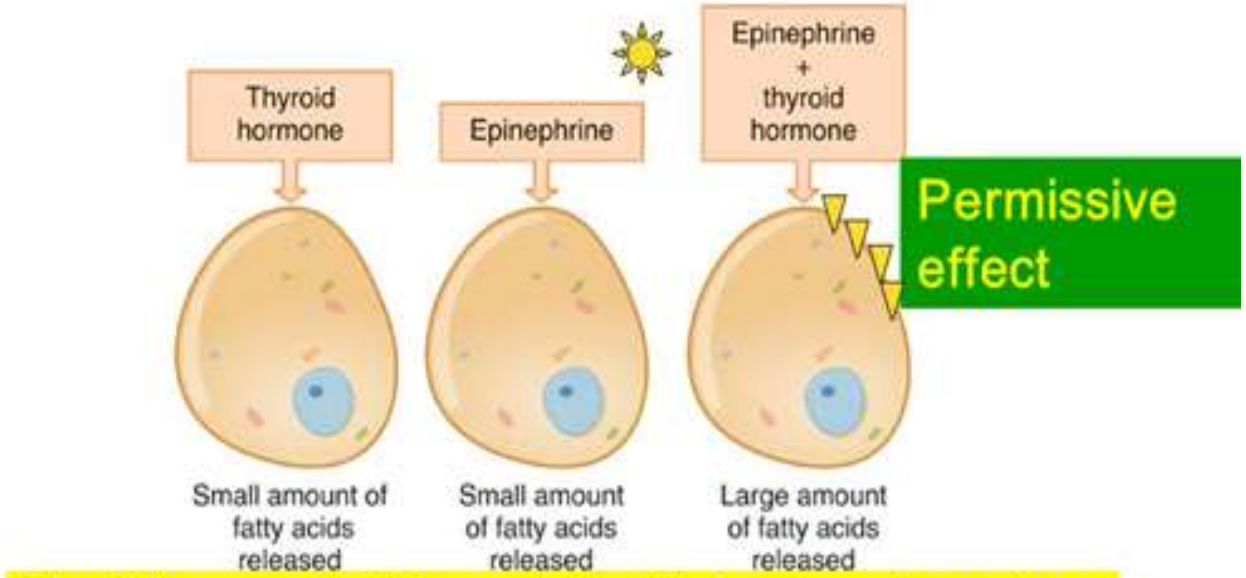
b. **Nuclear receptors** → these receptors bind **small**, **lipid-soluble molecules** that diffuse or are transported across the cell membrane (e.g., **thyroid hormone**, **steroids**, **vitamin D**)

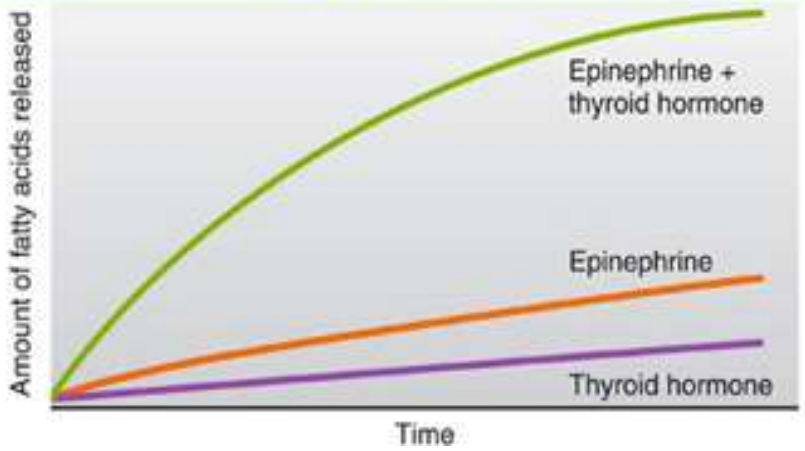
Permissiveness

Permissiveness (***permissive effect***) is a **biochemical phenomenon** in which the **presence of one hormone** is **required** in order for **another hormone to exert its full effects** on **a target cell**.

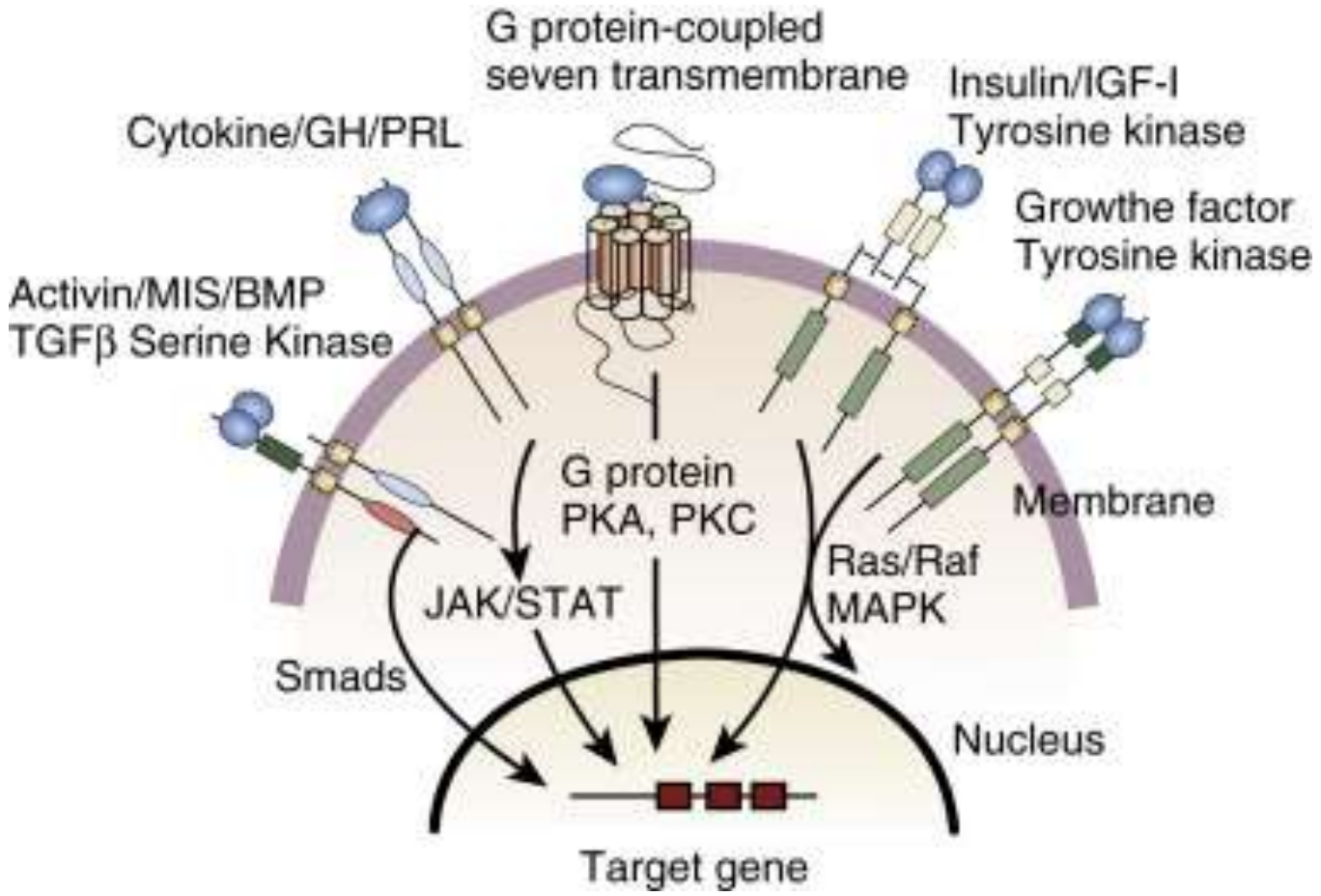
*A hormone increases another hormone's effectiveness mainly by **up-regulating the receptor** of the second hormone.

Example: thyroid hormones exert permissive effects on the actions of catecholamines by up-regulating beta-adrenergic receptors.





a) Membrane receptors



Endocrinology: Adult and Pediatric (Seventh Edition)

a) Membrane receptors

- **<u>Membrane receptors</u>** can be divided into **several major groups** on the basis of **structural similarities** and **signaling pathways:**

1. **Seven transmembrane domain G protein-coupled receptors (GPCRs)**
2. **Tyrosine kinase receptors (TKRs)**
3. **Cytokine receptor family**
4. **Transforming growth factor-beta (TGF-β) family serine kinase receptors**

a) Membrane receptors

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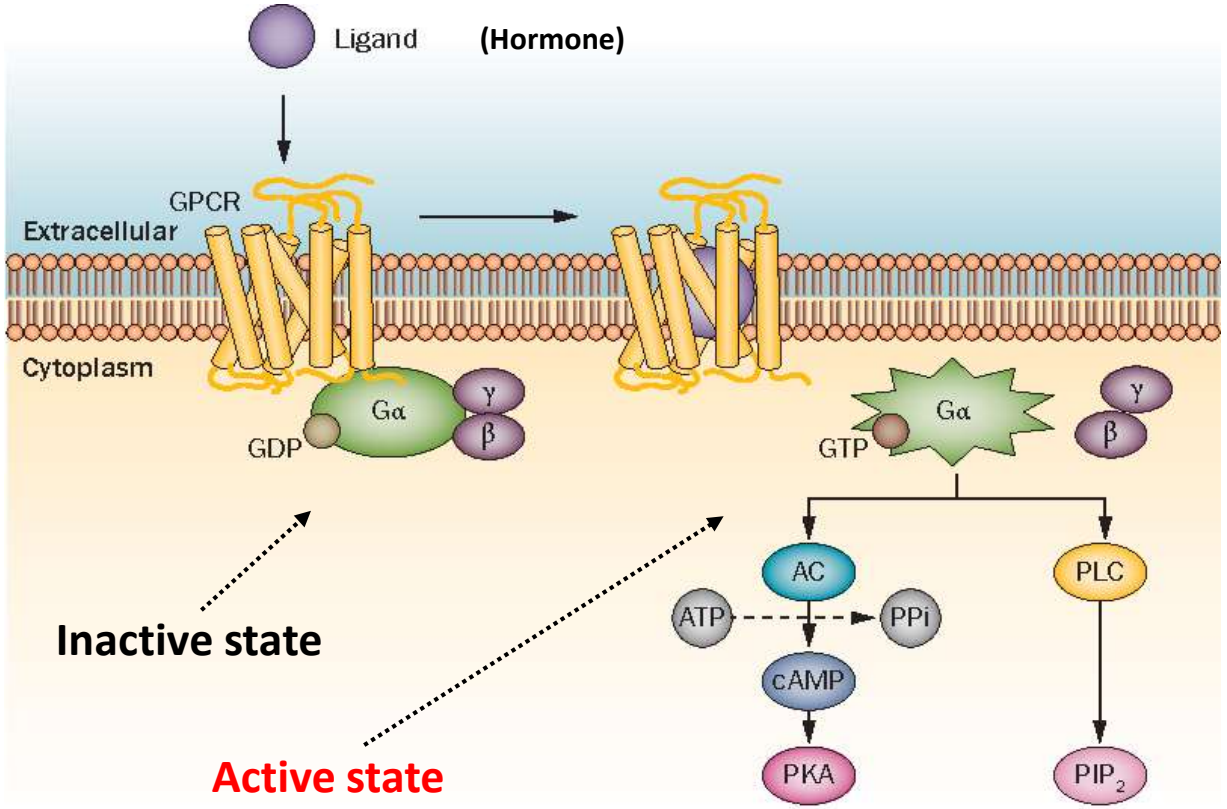
1. G protein-coupled receptors (GPCRs)



- **GPCRs** possess **seven transmembrane-spanning regions** composed of hydrophobic **α-helical domains**, that are connected by extracellular and intracellular loops.
- **G proteins** form a **heterotrimeric complex** that is composed of various **Gα** and **Gβ-γ subunits**.

GPCRs (also known as «**seven-(pass)-transmembrane domain receptors**» or «**serpentin receptors**») bind a broad array of **hormones**, including:

- **Glycoprotein polypeptide hormones**: e.g., FSH, LH, TSH
- **Polypeptide hormones**: e.g., PTH, glucagon
- **Peptide hormones**: e.g., TRH, GHRH, somatostatin (GHIH), calcitonin, vasopressin (ADH), oxytocin (OXT)
- **Catecholamines**: epinephrine, dopamine

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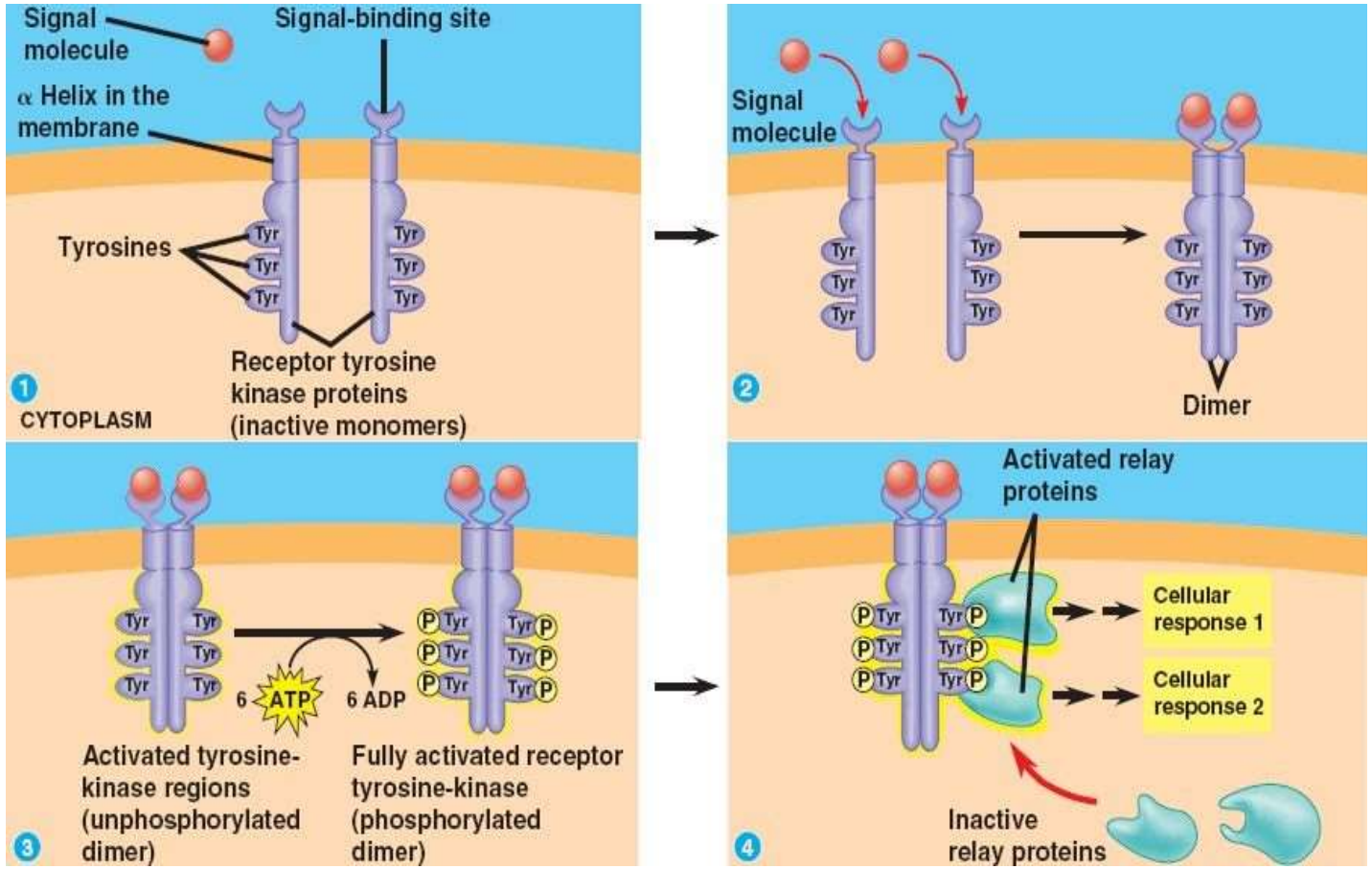
2. Tyrosine kinase receptors (TKRs)

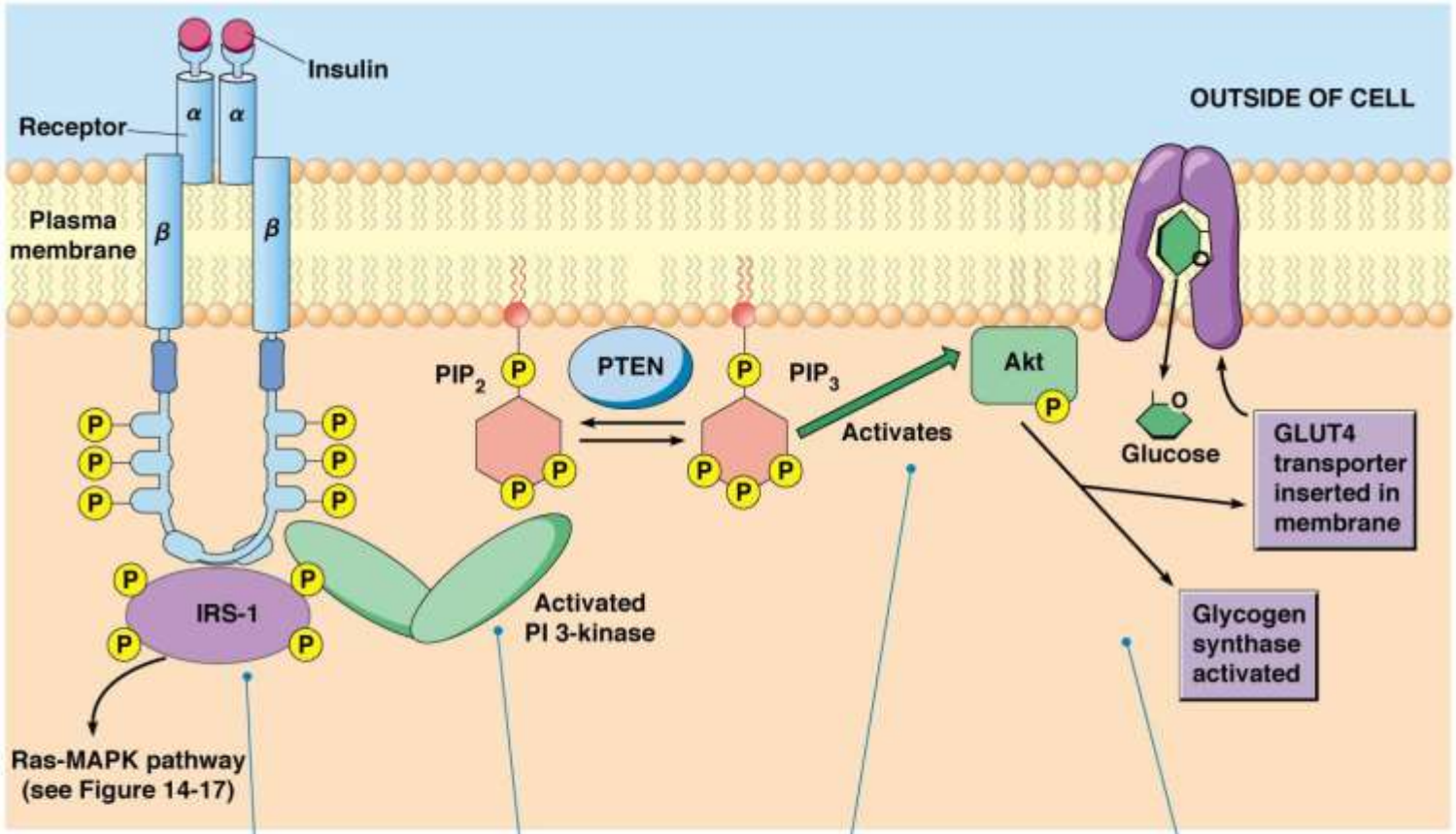


TKRs are **transmembrane**, immunoglobulin-like molecules containing an **extracellular ligand-binding region**, a **transmembrane region**, and an **intracellular tyrosine kinase region** that contains tyrosine residues whose **phosphorylation** regulates signal transduction.

Tyrosine kinase receptors (TKRs) transmit signal for **insulin** and a variety of **growth factors**, including:

- Insulin-like growth factor-1 (**IGF-1**)
- Platelet-derived growth factor (**PDGF**)
- Fibroblast growth factors (**FGFs**)
- Epidermal growth factor (**EGF**)

Insulin signal transduction pathway is linked to TKRs



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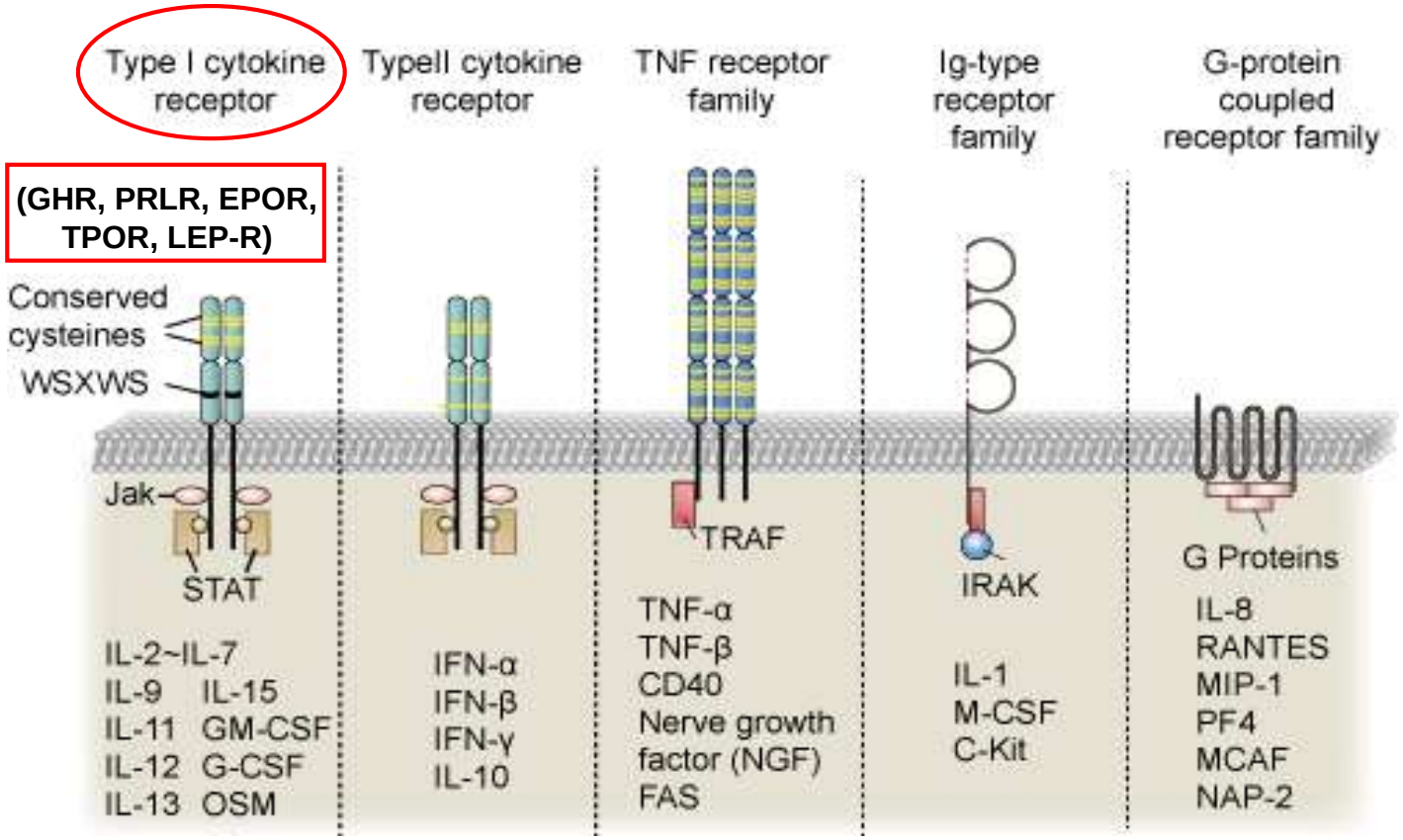
3. Cytokine receptor family



Ligand (e.g., hormone) binding induces **receptor interactions with intracellular kinases** (e.g., JAKs), which phosphorylate members of the STAT family and other signaling pathways. The activated STAT proteins translocate to the **nucleus** and **promote expression of target genes.**

- **Cytokine receptors** are classified according to their **three-dimensional structure**.
- **Growth hormone receptor** (**GHR**), **prolactin receptor** (**PRLR**), **erythropoietin receptor** (**EPOR**), **thrombopoietin receptor** (**TPOR**), **leptin receptor** (**LEP-R** or **OB-R**) belong to the **class I cytokine receptor family**, which includes more than 30 receptors.

Dehkhoda *et al*., 2018

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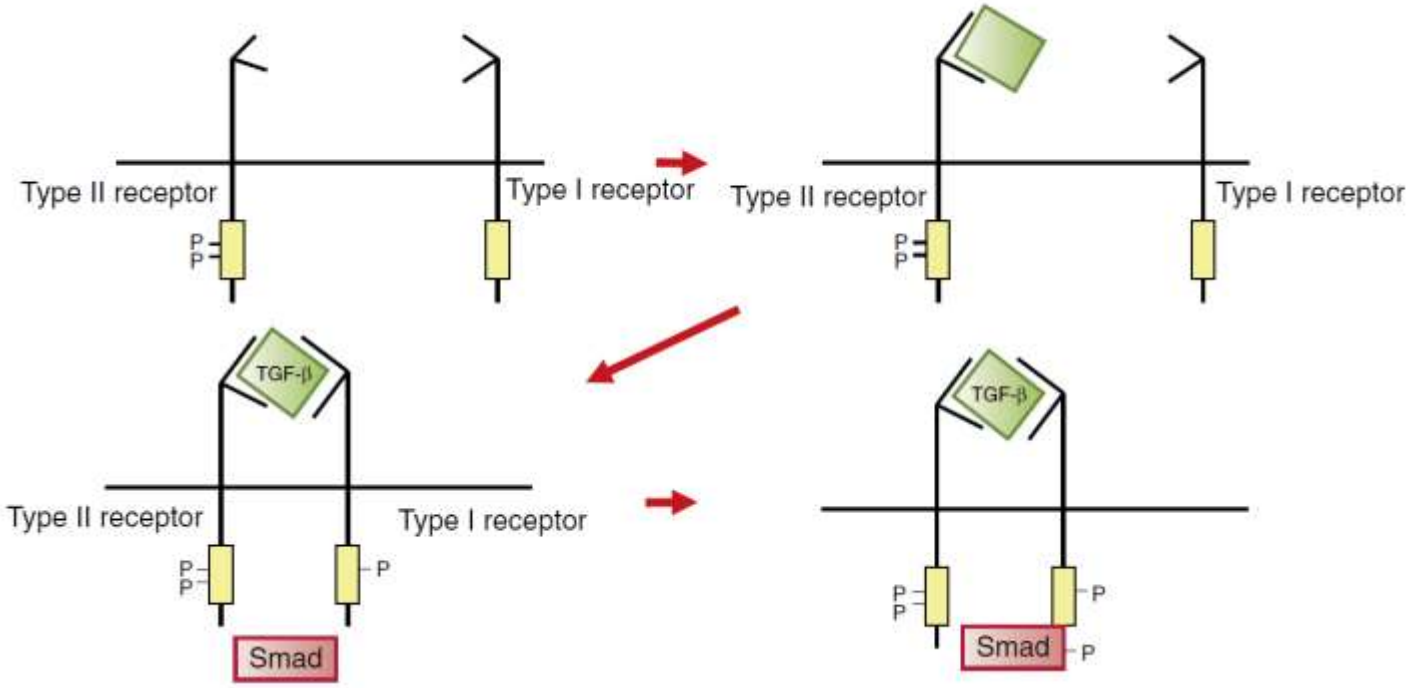


TGF-β receptors are a family of **serine/threonine kinase receptors**. These receptors bind to ligands through a **heterodimeric receptor** consisting of **two transmembrane subunits** known as **type I and type II receptors**.

A group of downstream phosphorylation targets called the **Smad proteins**, upon **phosphorylation**, migrate to the nucleus to activate and/or repress transcription of target genes.

- These receptors bind a variety of ligands, including **TGF-β**, and **hormones**, such as **inhibin**, **activin**, **anti-müllerian hormone (AMH)**, and **bone morphogenetic proteins (BMPs)**.

Greenspan's Basic and Clinical Endocrinology, Tenth Edition

b) Nuclear receptors

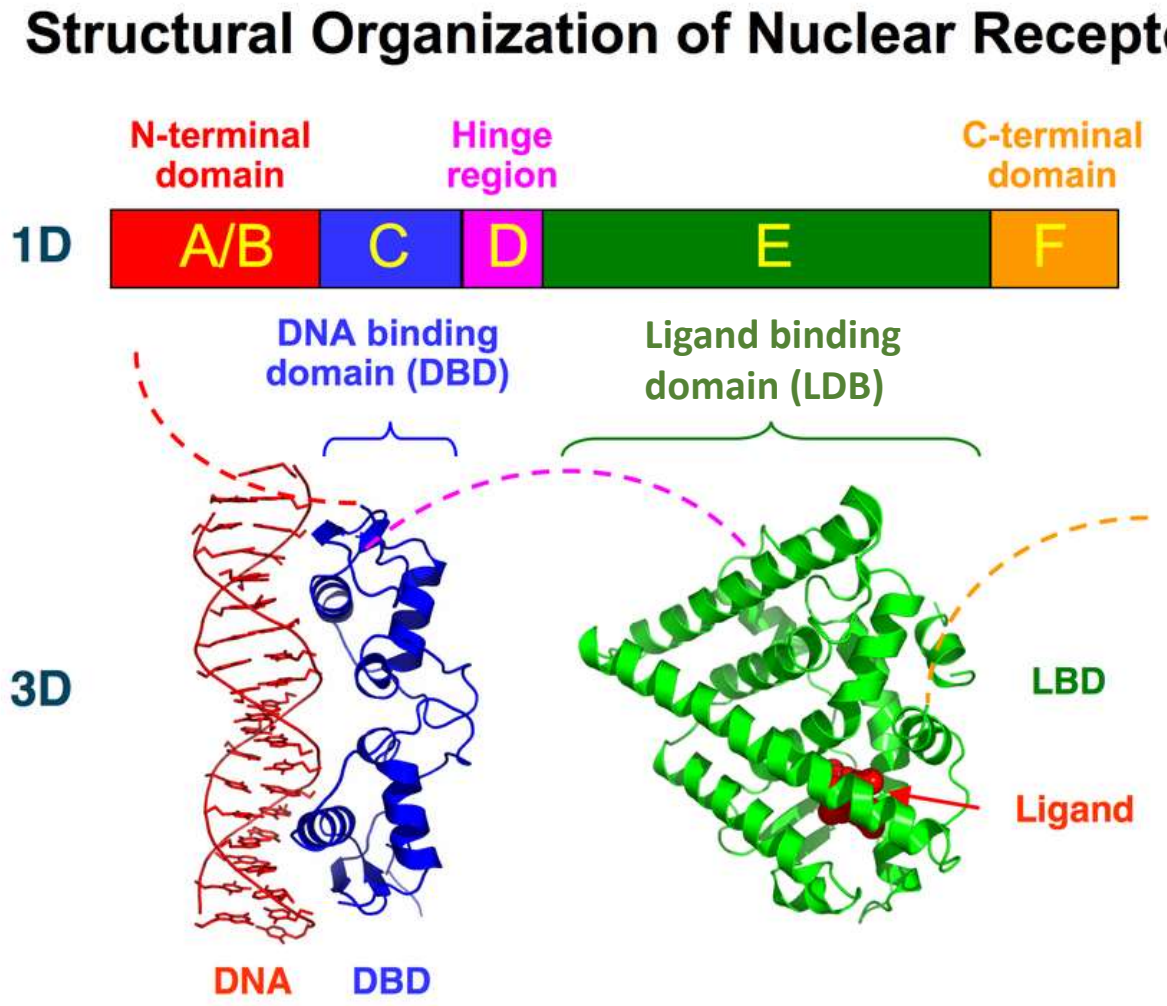
- **Nuclear receptors** are **ligand-activated transcription factors** which alter transcription of target genes by binding specific sequences of DNA known as "***Hormone Response Elements***" (**HREs**).

Nuclear receptors can be divided into **two categories** on the basis of their localization and mechanism of action:

1. **Type I nuclear receptors**: in the absence of ligand, type I nuclear receptors are complexed with heat shock proteins (HSP) in the **cytoplasm**. Hormone binding triggers dissociation of heat shock proteins (HSP), dimerization, and translocation to the nucleus. These receptors bind to HREs as **homodimers**.

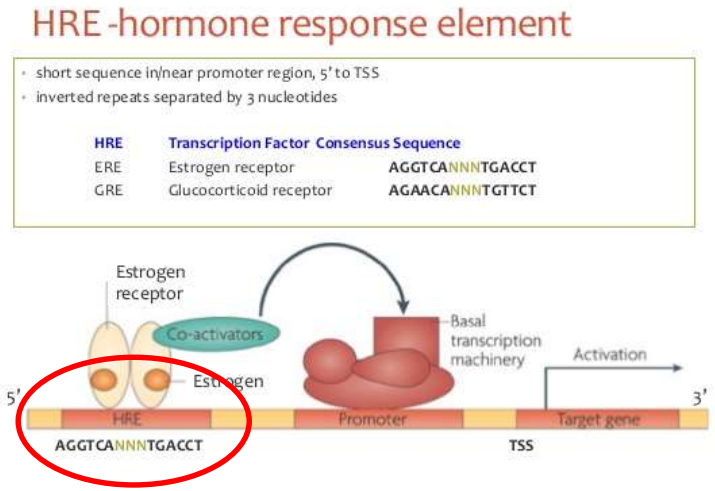
2. **Type II nuclear receptors**: unlike type I receptors, type II receptors are retained in the **nucleus** regardless of the ligand binding status and in addition bind to HREs as **heterodimers** using **retinoid X receptor (RXR)** as obligate partner. In the absence of ligand, type II nuclear receptors are often complexed with corepressor proteins.

b) Nuclear receptors



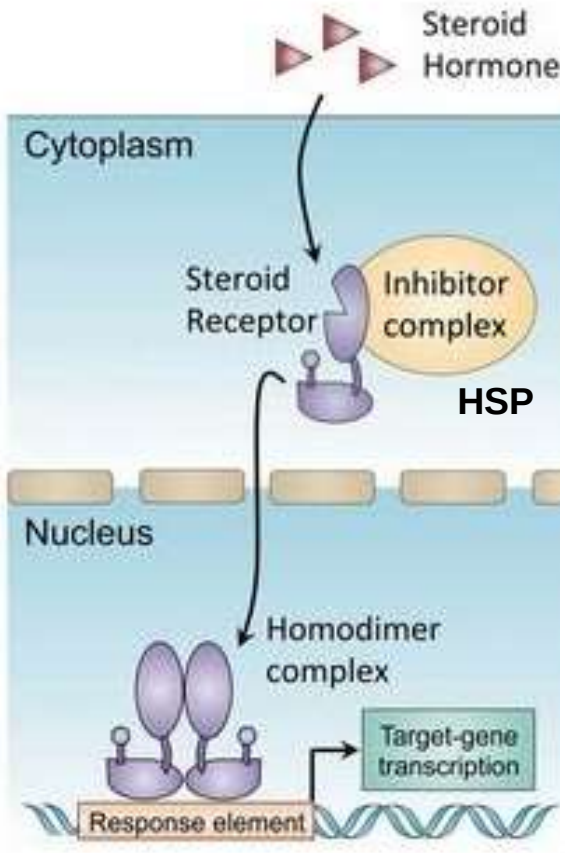
Hormone response elements (HREs)

- Glucocorticoid response element (GRE)
- Mineralocorticoid response element (MRE)
- Estrogen response element (ERE)
- Progesterone response element (PRE)
- Androgen response element (ARE)



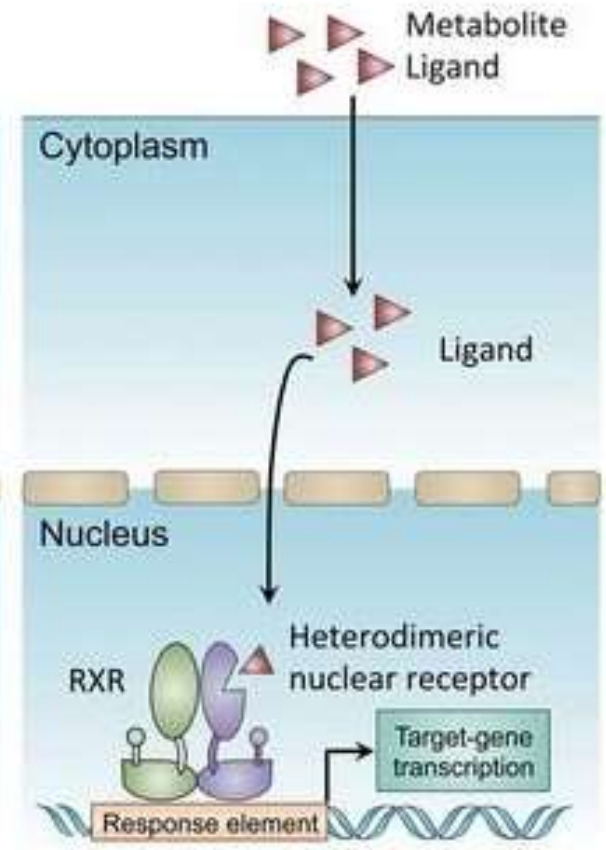
- Thyroid hormone response element (TRE)
- Vitamin D response element (VDRE)
- Retinoic acid response element (RARE)
- Retinoid X response element (RXRE)

Type I nuclear receptors



Glucocorticoid Receptor (GR)
Mineralocorticoid Receptor (MR)
Estrogen Receptors (ERs)
Progesterone Receptor (PR)
Androgen Receptor (AR)

Type II nuclear receptors



Retinoic Acid Receptor (RAR)
Retinoid X Receptor (RXR)
Vitamin D Receptor (VDR)
Thyroid Hormone Receptor (TR)

Avior *et al*., 2013

Specificity-spillover phenomenon

- **A given hormone** has a **primary affinity for its own receptor** (e.g. vitamin D for VDR), **but it may also retain an affinity for the receptor of a hormone to which it is related structurally**.
- In **some disease states**, one or more manifestations of hormonal excess may be caused by **the interaction of one hormone with the receptor for a different hormone**.
- When one receptor is activated by a signal designed for another receptor, the event is termed a "***specificity spillover***".

Fradkin et al., NEJM 1989

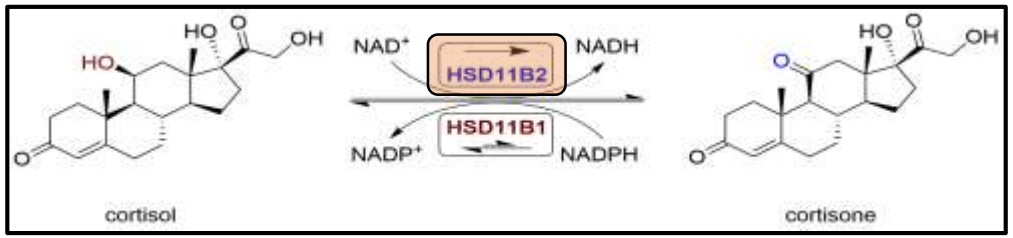
Specificity-spillover phenomenon

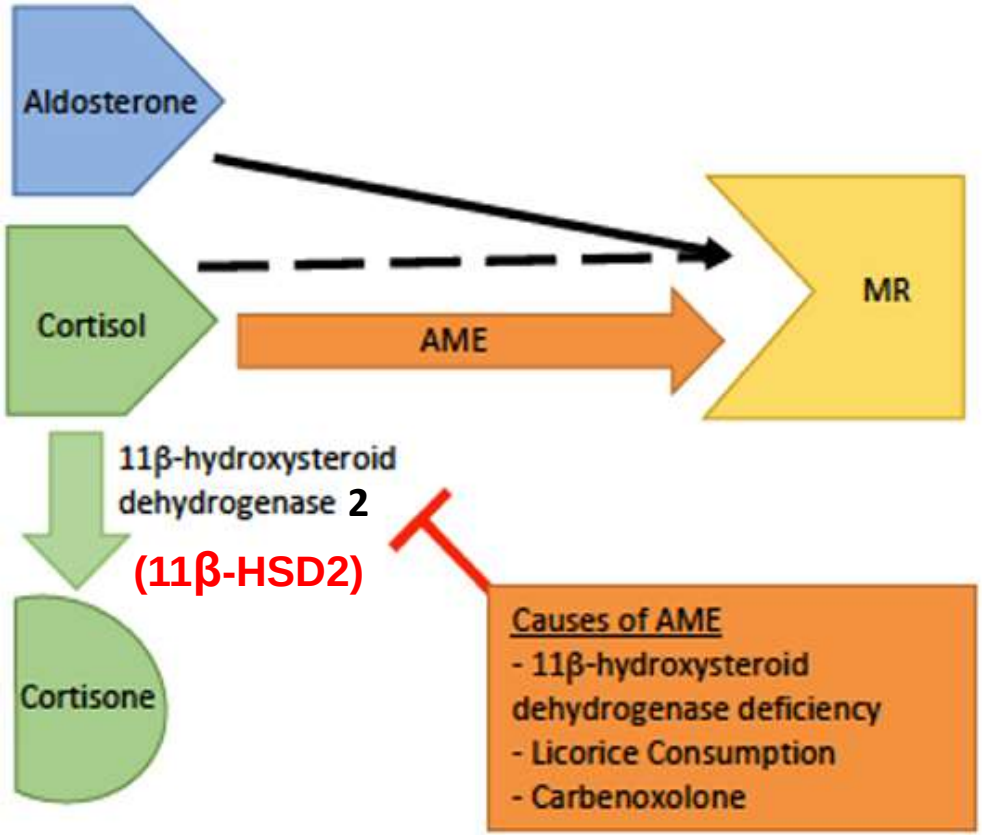
- **<u>At physiologic hormone concentrations</u>**, **the affinity for the second receptor is often low enough**, relative to the concentration of reactants, that the consequences of the spillover are negligible.

- **<u>Under pathologic conditions</u>**, when the hormone is present in excess, manifestations of disease typically result from an excessive effect mediated through the hormone's own receptor. **However, if the concentration of the hormone is sufficiently high**, **additional serious biologic effects, characteristic of a second hormone, can be mediated through an association of the first hormone with the receptor for the second hormone** (whether or not the second hormone is present).

Fradkin et al., NEJM 1989

Specificity-spillover phenomenon
Apparent mineralocorticoid excess (AME) syndrome





Raina et al., 2019

Mineralocorticoid receptor (MR) shows a high affinity for both **aldosterone** (the primary endogenous mineralocorticoid hormone) and **glucocorticoids** (GCs: cortisol and corticosterone).

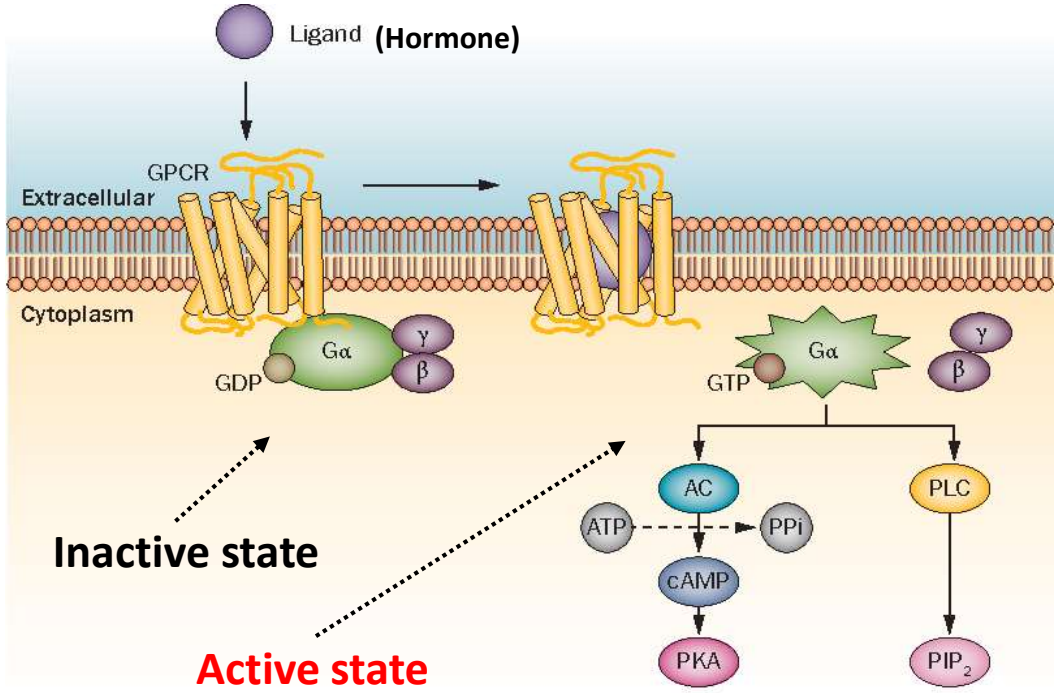
MR affinity for GCs is more than 10-fold higher than that of GR itself. In addition, **circulating GC concentration is 100- to 1,000-fold higher** with respect to that of aldosterone. Thus, **GCs can bind both to glucocorticoid receptor (GR) and MR**.

In **aldosterone-selective epithelial target tissues** (e.g. kidney, colon, salivary and sweat glands), the enzyme **11β-hydroxysteroid dehydrogenase 2** (**11β-HSD2**) catalyzes the conversion of **cortisol** to the inactive metabolite **cortisone**, thus preventing the illicit activation of MR by GCs.

GCs can, however, also bind to MR, mimicking aldosterone action if **11β-HSD2 activity is reduced** (e.g. **AME syndrome**) or **when GC concentration exceeds the capacity of 11β-HSD2 to inactivate cortisol to cortisone** (e.g. **Cushing's syndrome**), resulting in higher sodium uptake, hypertension, increased potassium excretion at the renal level and hypokalemia.

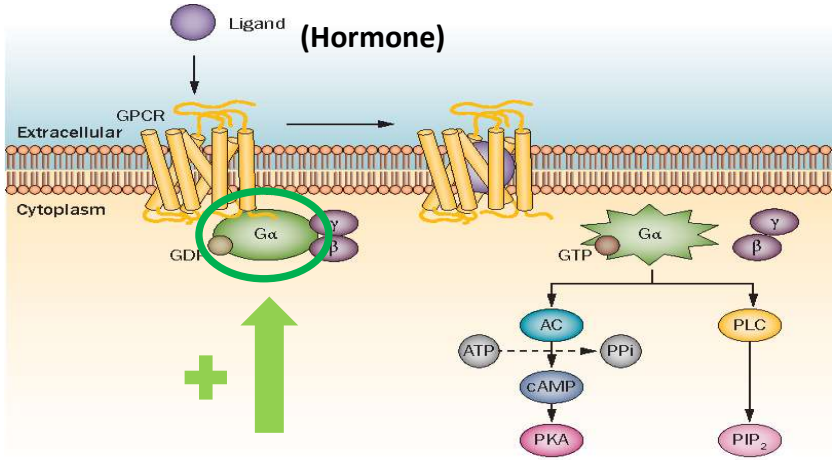
Implications for Clinical Endocrinology

GPCR-related disorders



- **Gain-of-function mutation**
- **Loss-of-function mutation**

McCune-Albright syndrome

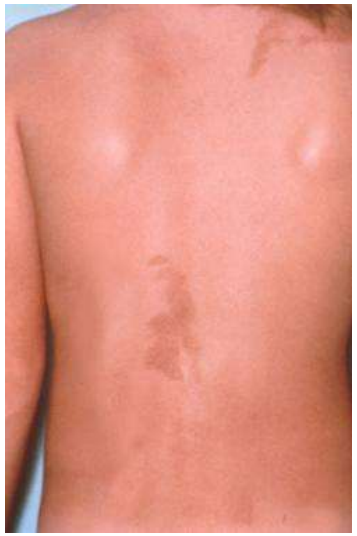


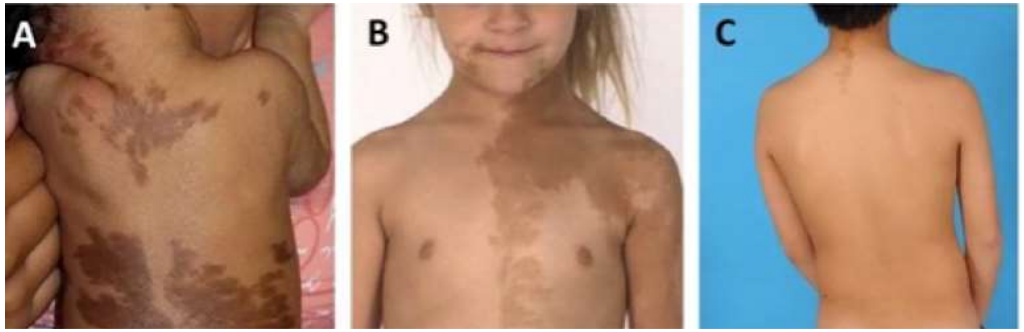
- **Gain-of-function mutation**
- Loss-of-function mutation

Syndrome arising from **somatic activating mutations** in ***GNAS* gene**, which encodes the **alpha-subunit** of the **Gs** G protein-coupled receptor, resulting in **constitutive receptor activation**.

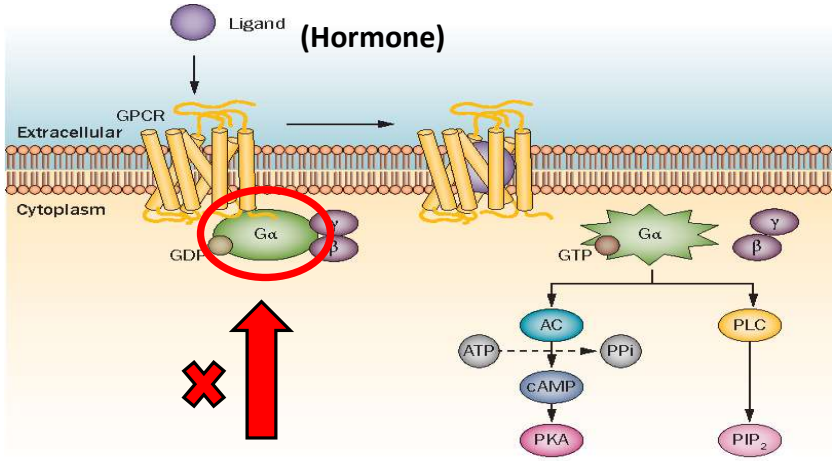
Clinical features:

- Fibrous dysplasia
- « *Café au lait* » skin pigmentation
- Precocious puberty
- Pituitary and thyroid adenomas
- Bilateral adrenal hyperplasia





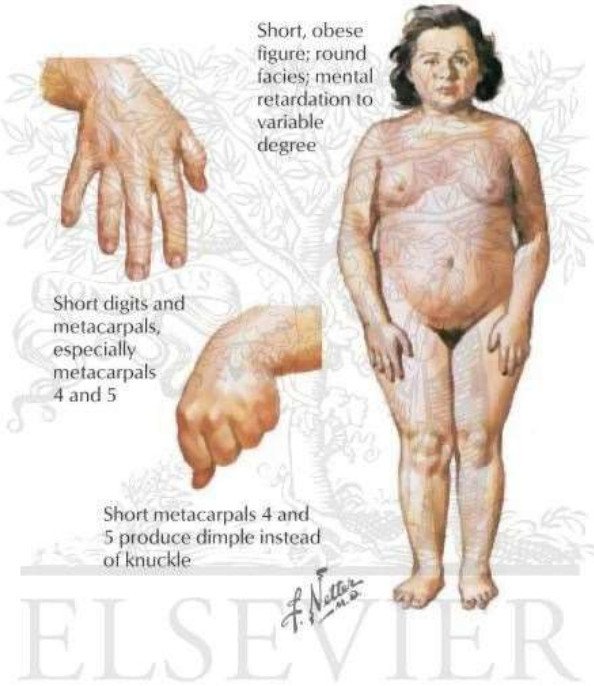
Pseudohypoparathyroidism type 1A (PHP-1a)



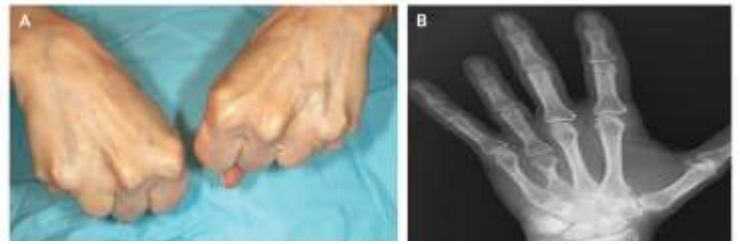
➢ Gain-of-function mutation

➢ Loss-of-function mutation

Disease caused by a **loss-of-function mutation** in ***GNAS* gene**, which encodes the **alpha-subunit** of the **Gs** G protein-coupled receptor. It is inherited in an autosomal dominant pattern and is associated with genetic imprinting (maternal origin).



Also known as
«Albright's hereditary osteodystrophy»



Clinical features:

- Resistance to PTH, hypocalcemia
- Hypogonadism and hypothyroidism
- Round face, short stature, obesity
- Mental retardation to variable degree
- Subcutaneous calcifications and hypoplasia of dental enamel
- Short digits and metacarpals, especially metacarpals 4 and 5, which produce dimple instead of knuckle

Rolla & Rodriguez-Gutierrez, NEJM 2012

Steroid and thyroid hormone receptor resistance syndromes

- **Heritable defects** caused by **mutations** in **hormone receptor genes** that prevent hormone ligand binding to hormone receptor (mutations in ligand binding domain) or alter hormone receptor-mediated transcriptional effects (mutations in DNA binding domain).

- These disorders are characterized by a **clinical phenotype suggesting hormone deficiency**, **elevated levels of the circulating hormone ligand**, and **increased** (or inappropriately detectable) **levels of the relevant trophic regulatory hormone** (e.g., ACTH, FSH, LH, or TSH).

Clinical Endocrinology

Endocrine Diseases

- Hypofunction of an endocrine gland
- Hyperfunction of an endocrine gland
- Hormone receptor defects
- Defects in second messengers and intracellular signaling

Hypofunction of an endocrine gland

Etiology

- Congenital defects in hormone synthesis
- Autoimmune destruction of the endocrine gland
- Surgical or traumatic injury to the endocrine gland
- Endocrine gland infiltration (tumors, infectious diseases, infiltrative and granulomatous disorders)

Hyperfunction of an endocrine gland

Etiology

- Hormone-secreting tumors
- Autoimmune diseases leading to hyperfunction of the endocrine gland
- Inflammatory or infectious diseases
- Iatrogenic or factitious causes
- Ectopic hormone production