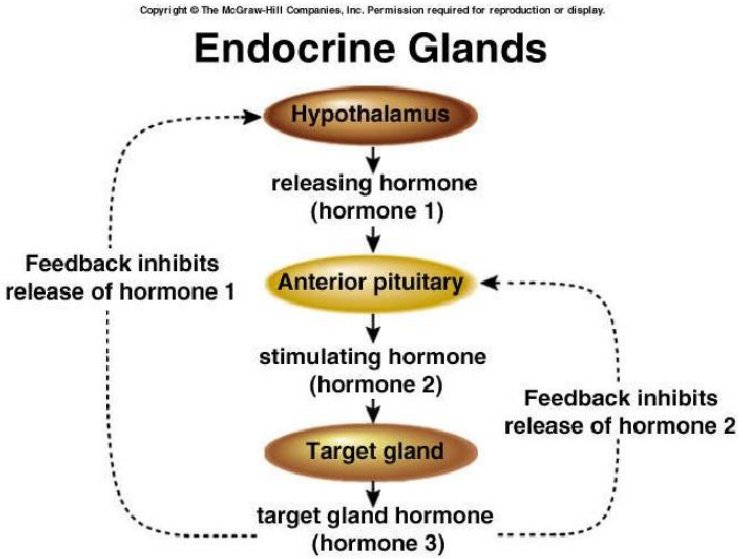
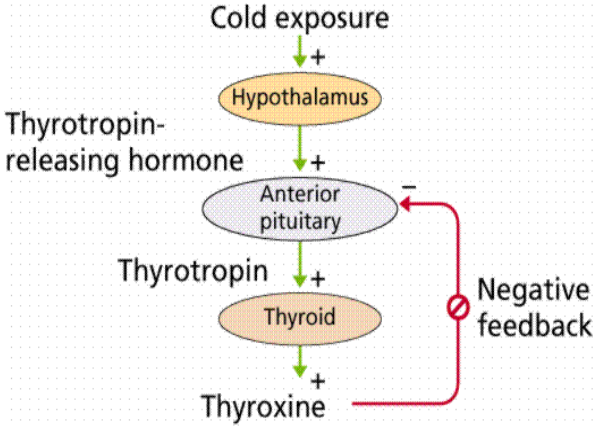
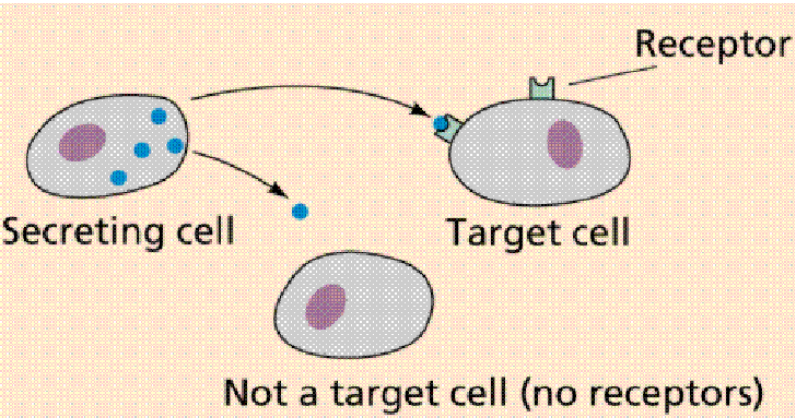
Prof. Nafez Abu Tarboush

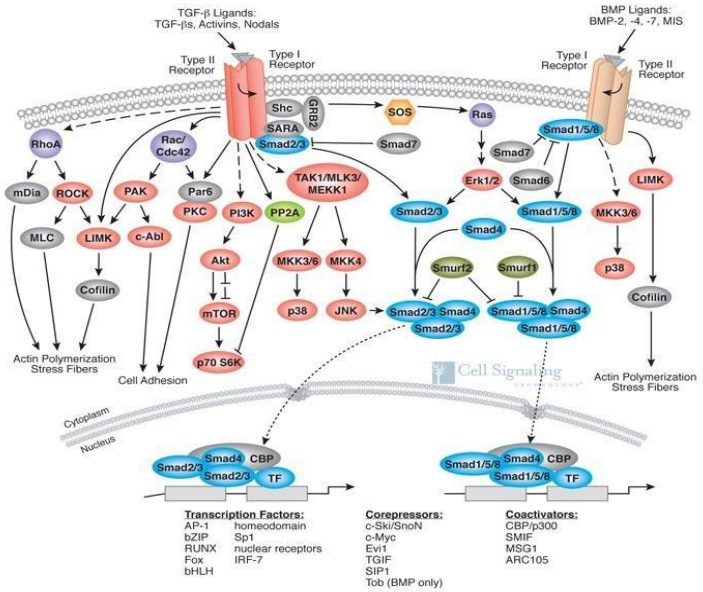
THE UNIVERSITY OF JORDAN

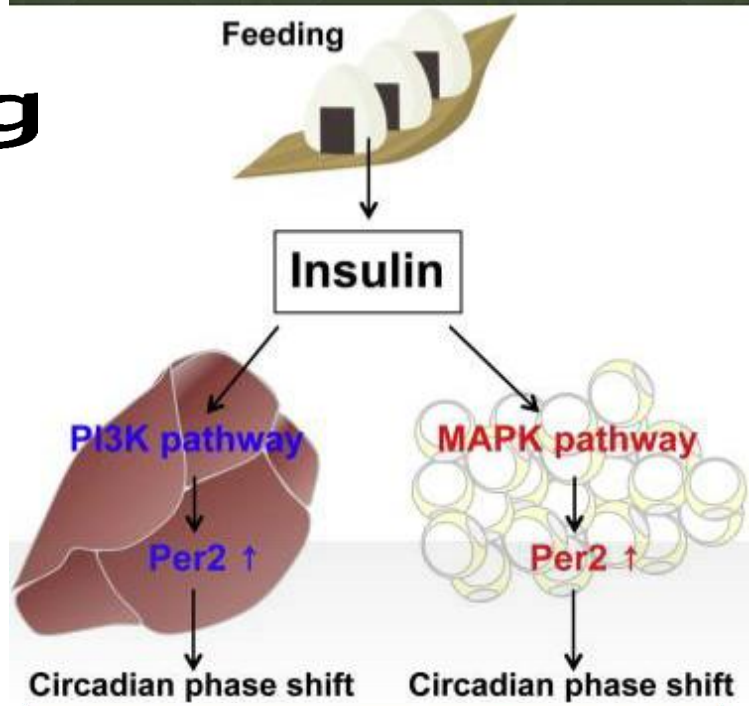
Integration of Metabolism: hormones & Cellular Signaling



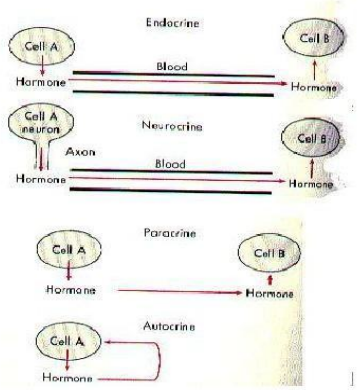








Types of cell-to-cell signaling



Endocrine Hormones: travel via bloodstream to target cells

Neurocrine hormones: released from nerve terminals

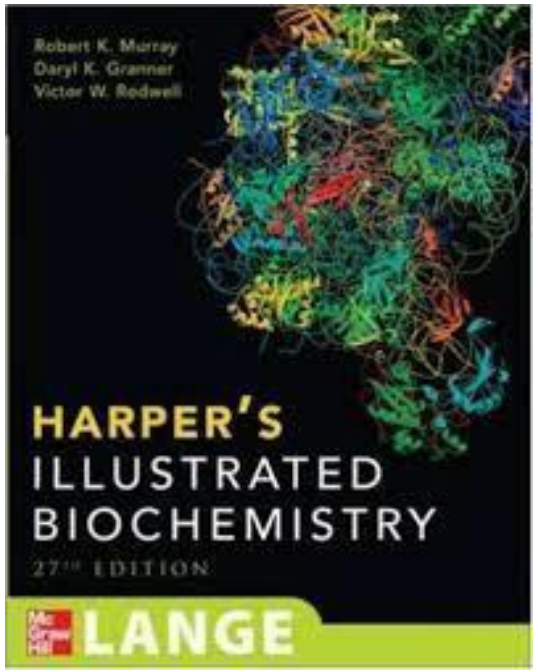
Paracrine hormones: act on adjacent cells

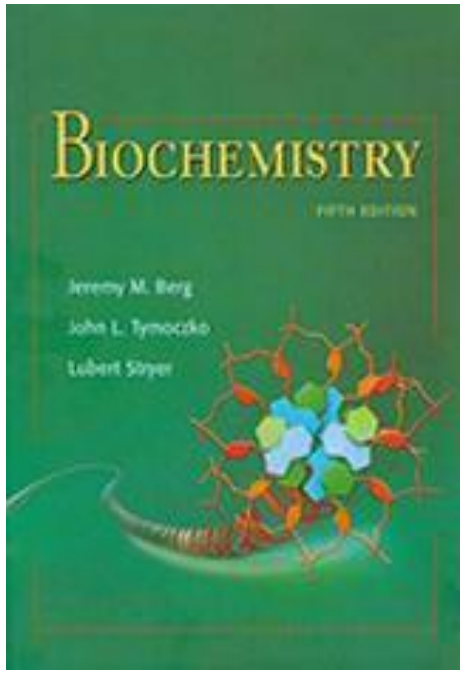
Autocrine hormones: Released and act on the cell that secreted them.

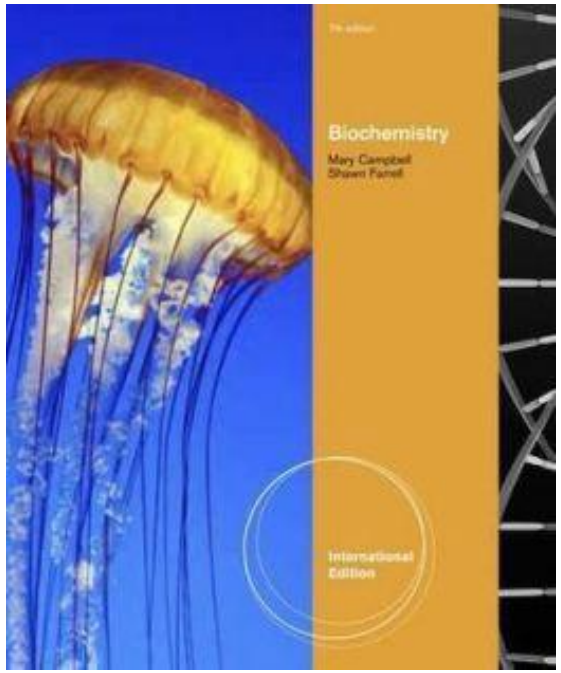
Intracrine Hormones: act within the cell that produces them.

Resources for the lectures

- Harper's Illustrated Biochemistry
- Stryer's Biochemistry
- Campbell's Biochemistry







Outline

1st lecture

- Definition
- Signaling
- Biochemical issues
- Target cell concept
- Receptor domains
- Amplification
- Regulation
- Classification
- Structure, synthesis, and degradation

2nd lecture

- Continued Structure, synthesis, and degradation
- Signal transduction
- 2nd messengers
- GPCR
- G-proteins
- Adenylate cyclase

3rd lecture

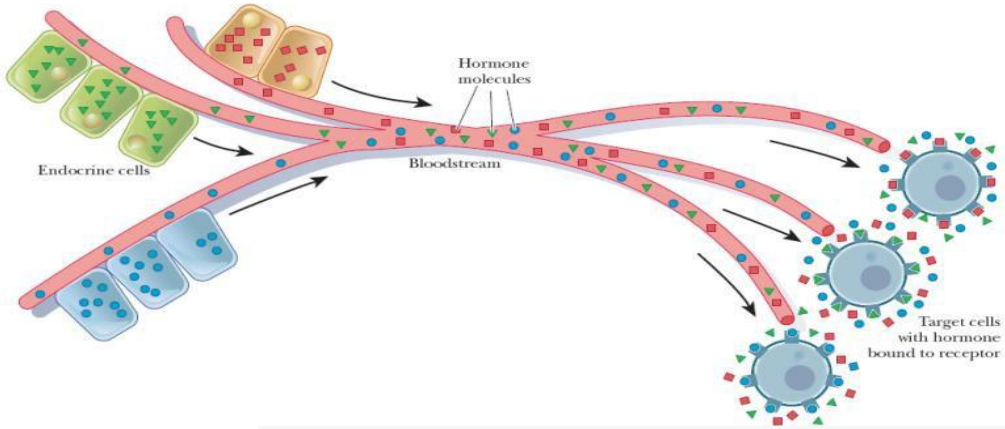
- PI cascade
- Calcium binding proteins
- RTK cascade
- Monomeric G-proteins

4th lecture (online material)

- Steroidogenesis

Hormones: The Remote Controllers

- **What are hormones**? Organic, blood, low amounts, source & target
- **Classes**:
  - Endocrine hormones
    - Distance; stability; & concentration
  - Paracrine hormones
  - Autocrine hormones



Signaling by Secreted Molecules

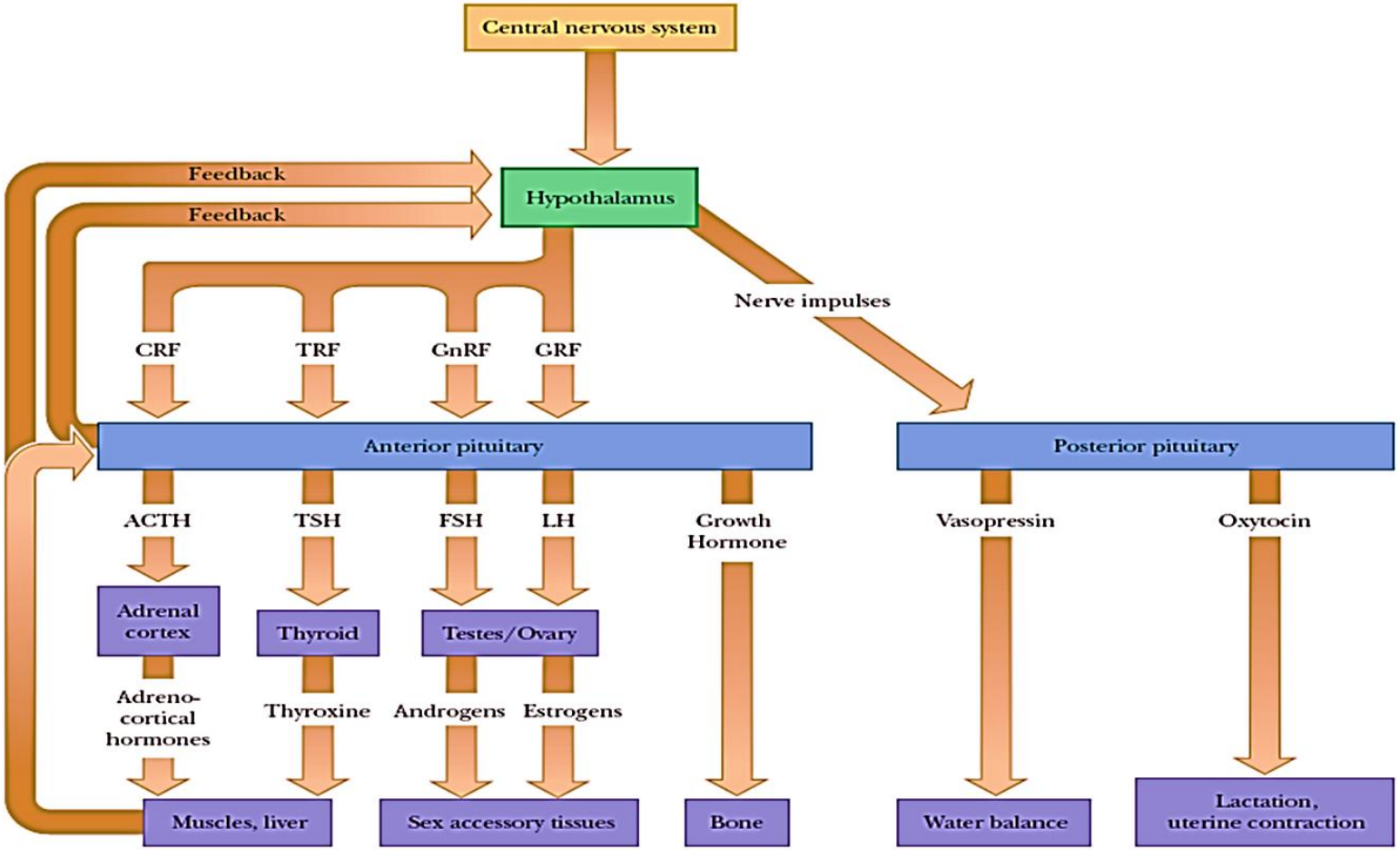
Nervous vs. endocrine

- These two systems are functionally interrelated.

✓ Both regulate human physiology

✓ The endocrine system produces a slower and more prolonged response than the nervous system.

✓ Both systems may act simultaneously on the same target cells and tissues, and some nerve cells secrete hormones.



The Target Cell Concept

- The definition of a target has been expanded to include any cell in which the hormone (ligand) binds to its receptor, regardless of the action

- **200 types** of differentiated cells in humans
- Only a few produce hormones! **(<50 known hormones)**
- All of **75 trillion cells** in a human are targets to one or more

- One hormone ⟶ several cell types
- One cell type ⟶ several hormones
- One hormone ⟶ several effects (pleiotropy).

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

Factors affect the concentration of the hormone at the target cell
✓ The rate of synthesis and secretion of the hormone
✓ The proximity of the target cell to the hormone source (dilution)
✓ The $\mathbf{K_d}$ of the hormone – receptor complex
✓ The rate of conversion of inactive form to the fully active form
✓ The rate of clearance from the plasma

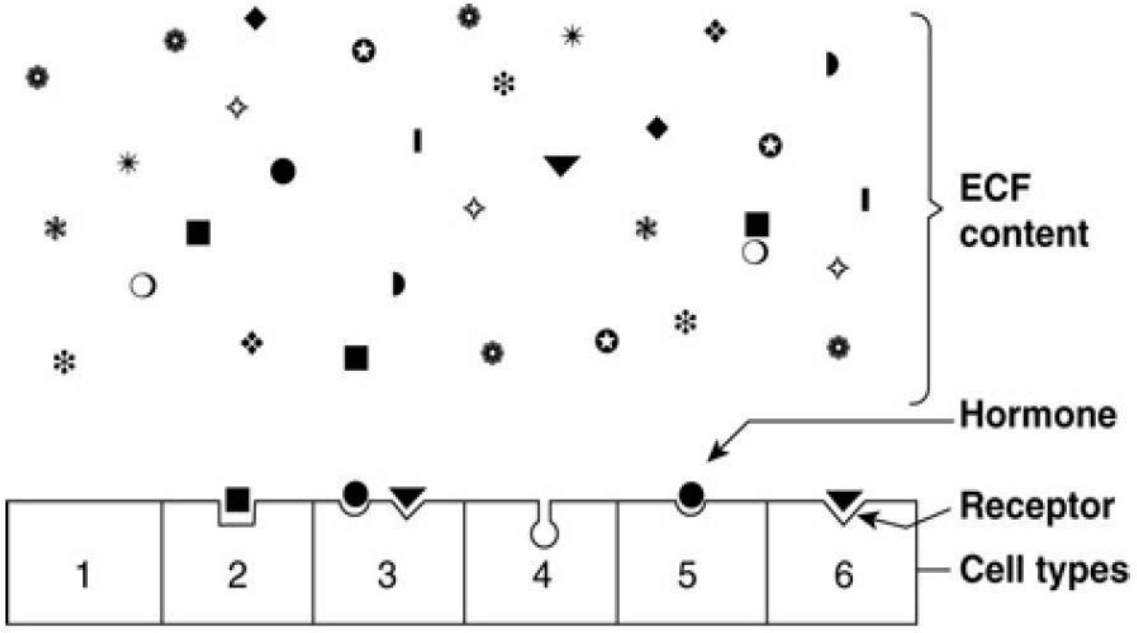
The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

Factors affecting the target cell response
✓ The number, relative activity, and state of occupancy of receptors
✓ The metabolism (activation / inactivation) of the hormone in the target cell
✓ The presence of factors within target cell necessary for the response
✓ Up- or down-regulation of the receptors upon interaction with ligand ✓ Post-receptor desensitization of the cell

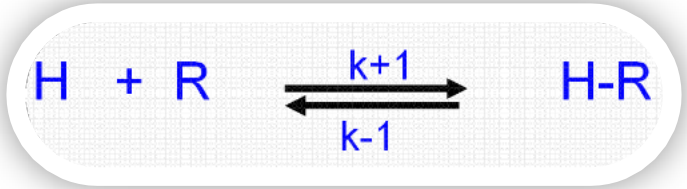
Receptors Discriminate Precisely

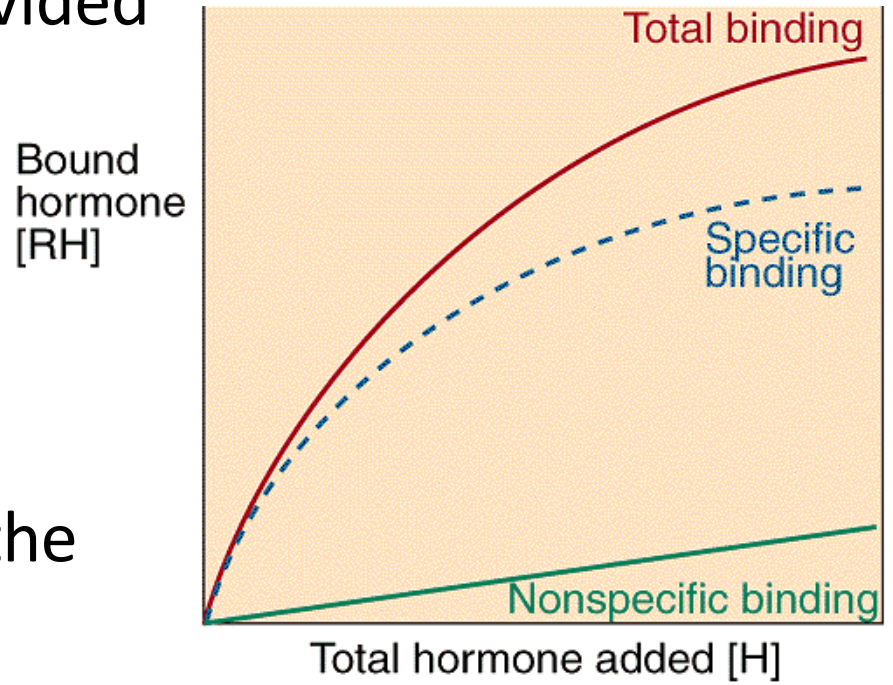
- **Major challenge**:
  - Atto- to nano-molar range (10^{-15} to 10^{-9} mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar (10^{-6} to 10^{-3} mol/L) range



Accordingly; Hormone-Receptor interactions

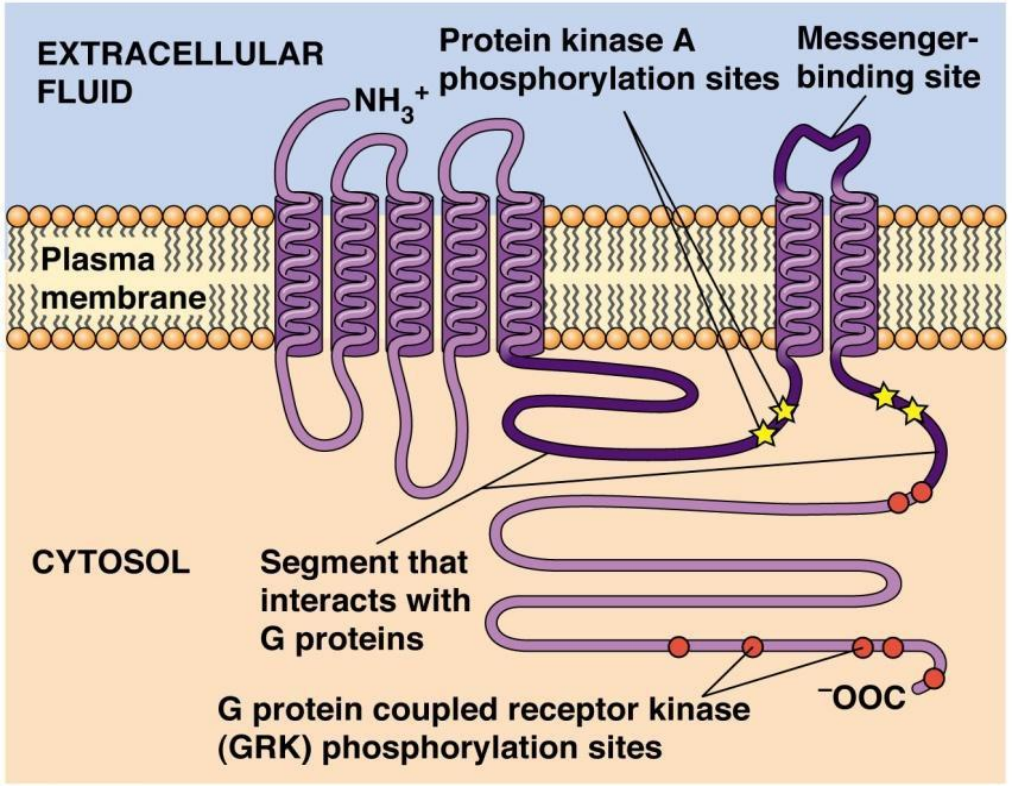
- Should be specific: displaceable by agonist or antagonist
- Should be saturable
- Should occur within the concentration range provided





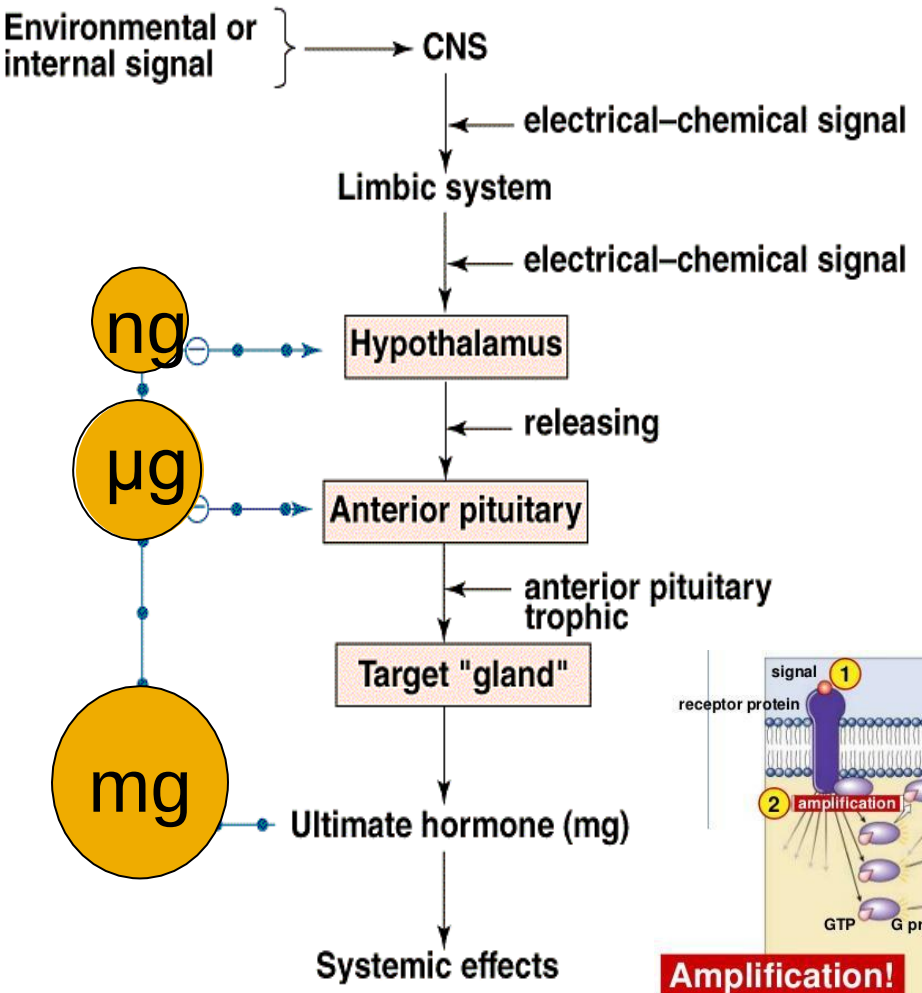
- Dissociation constant K_d
  - $K_d = \{[H] \times [R]\} / [H\text{-}R]$
- 20 X dissociation constant is enough to saturate the receptor
- $\mathbf{K_d}$ values for many hormone range from 10^{-9} to 10^{-11} M

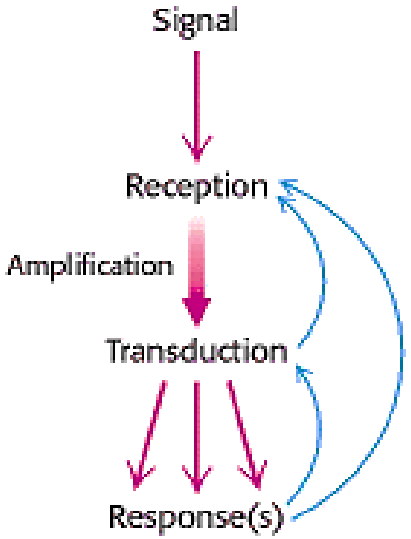
Receptor domains

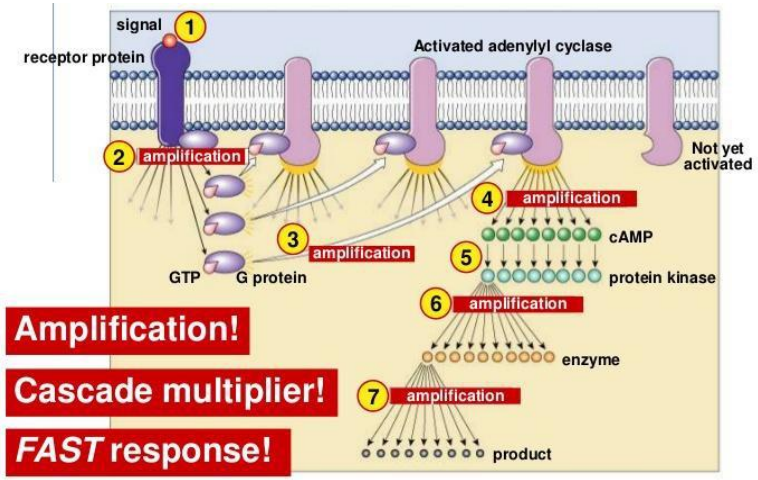


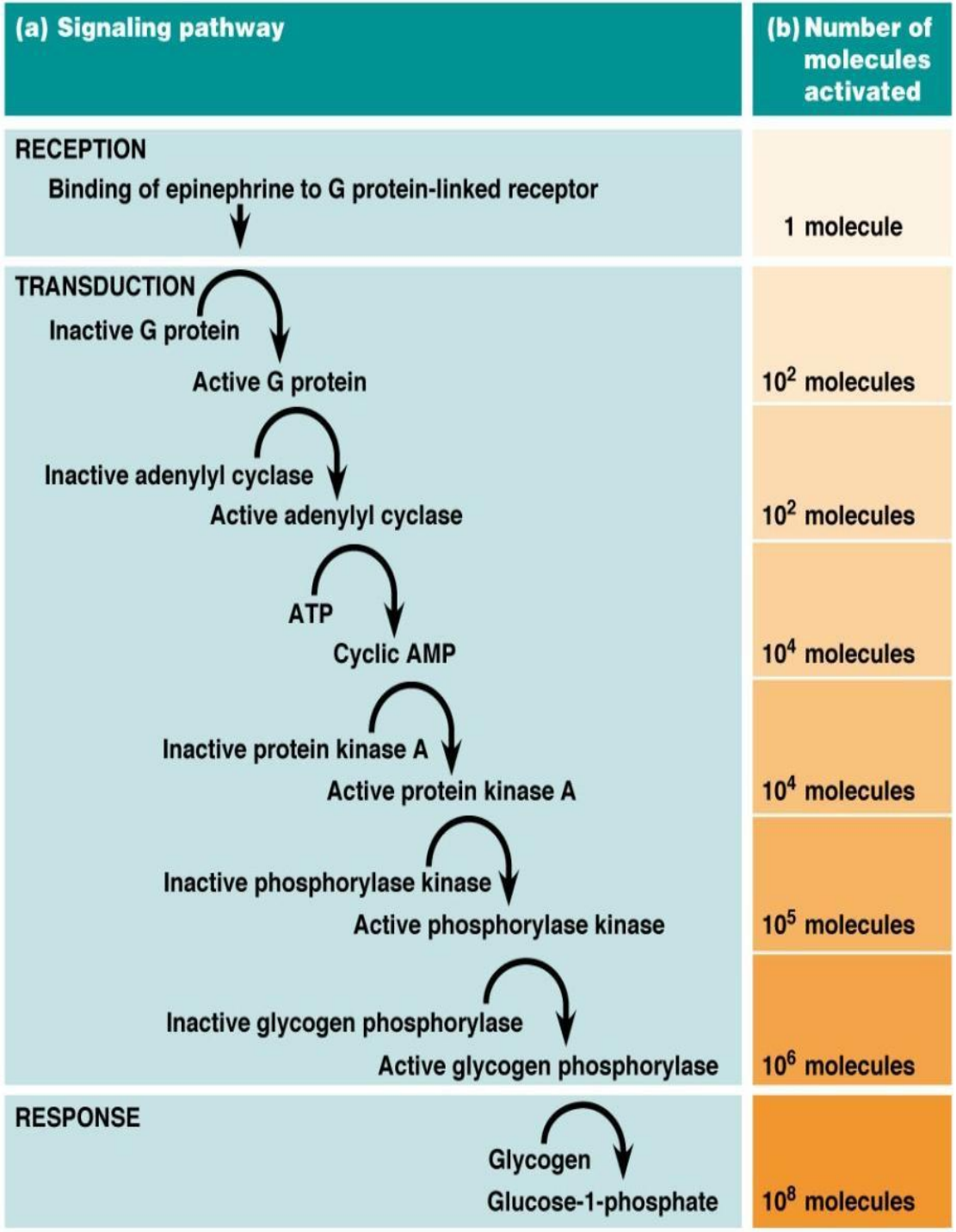
- All receptors have at least two functional domains:
  - **Recognition domain**
  - **Coupling or signal transduction domain**
- Coupling occurs in two general ways:
  - Changing the activity of an enzyme (Polypeptide & catecholamines, plasma membrane)
  - Direct (steroids, retinoids, and thyroid hormones, intracellular)
- Steroid, thyroid, and retinoid hormone receptors:
  - Hormone binding site ; DNA binding site; co-regulator proteins binding site, cellular trafficking proteins binding site
- Receptor–effector coupling provides the first step in amplification

Signal Amplification



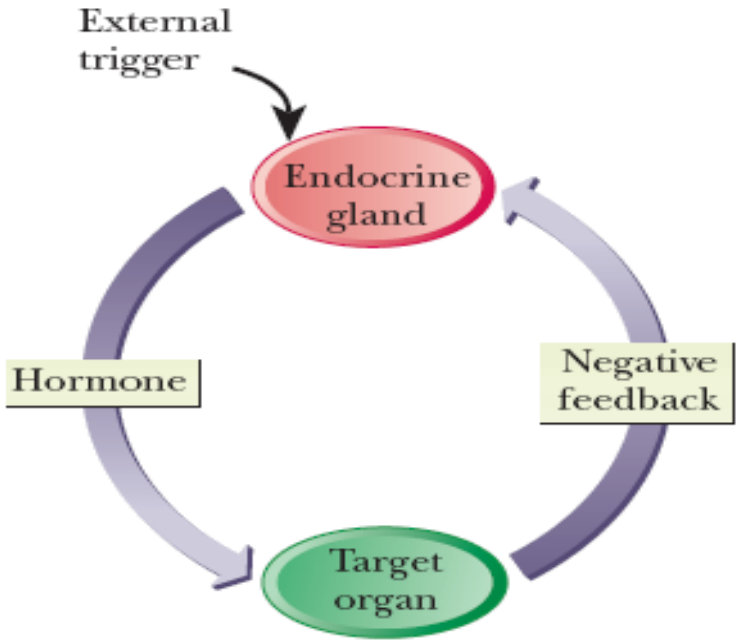


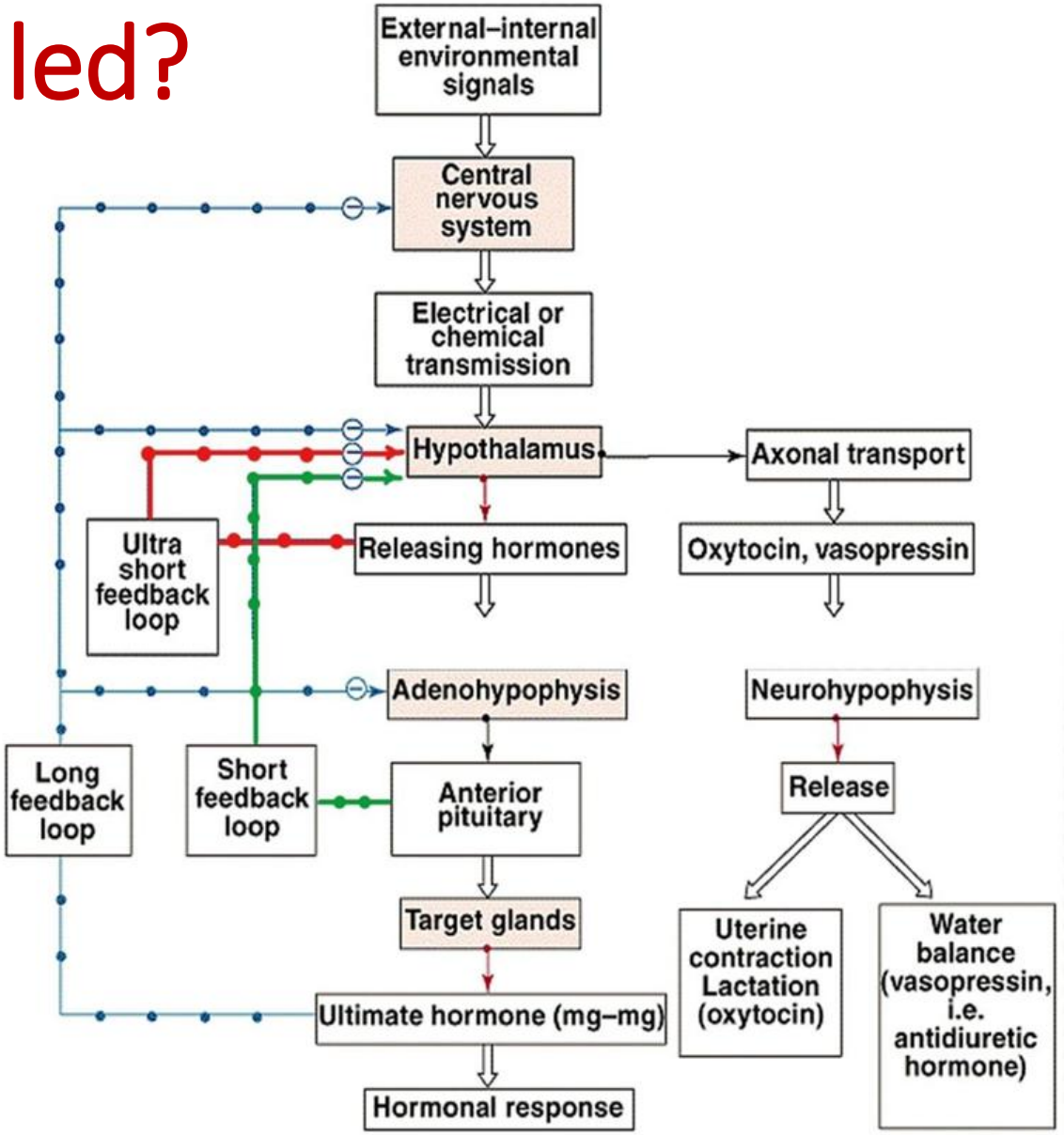




How the release is controlled?

- **Feedback inhibition**
  - **Ultrashort loop**
  - **Short loop**
  - **Long loop**





Classification of hormones

- Chemistry, solubility, receptors' location, signaling mediator

  - ✓ **Small peptides, polypeptides and proteins**
  - ✓ **Amino acid derivatives and arachidonic acid analogs**
  - ✓ **Steroids**

Classification of hormones - Chemistry

Steroids

- Cholesterol-derived
- Transported by plasma proteins or specialized carrier (protection)

Small peptides, polypeptides, and proteins

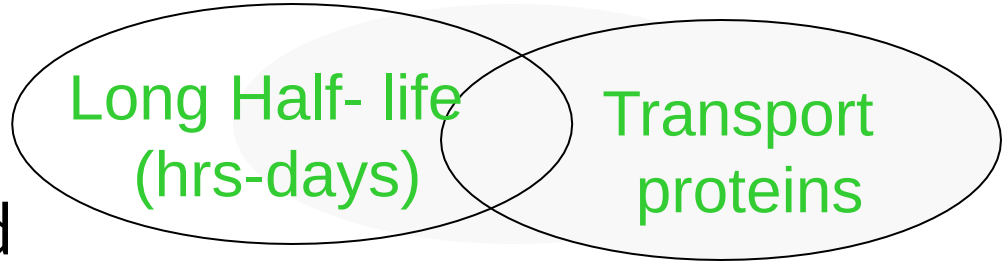
- Released and dissolve readily in blood and generally do not require special transport proteins.
- Most if not all polypeptides and proteins have specific carrier proteins

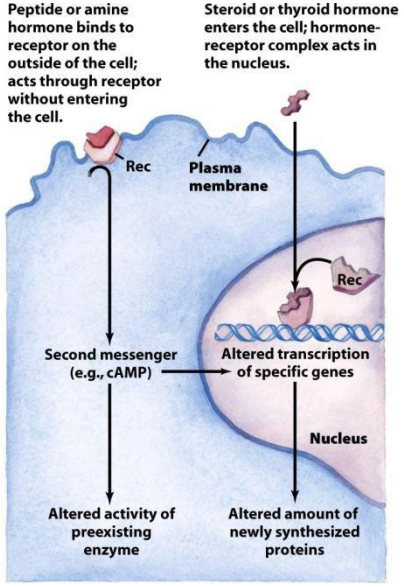
Amino acid derivatives and arachidonic acid analogs

- Catecholamines: released and dissolve readily
- Thyroid: bind transport proteins (prealbumin).

Classification of Hormones Mechanism of Action

- Hormones that bind to intracellular receptors
  - Steroids
  - Thyroid hormones
  - Calcitriol, retinoic acid



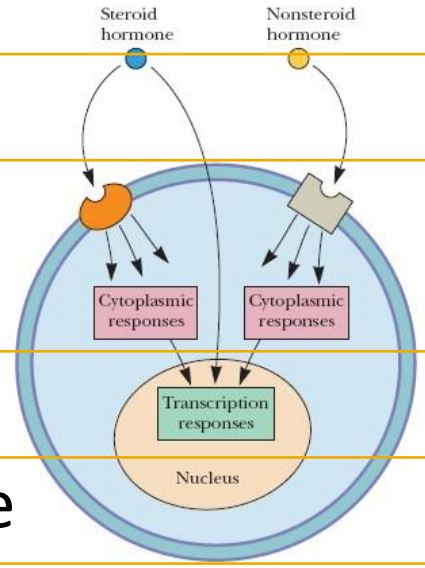


Classification of Hormones Mechanism of Action

- Hormones that bind to cell surface receptors
- (According to second messenger):
  - cAMP (β adrenergic factor, glucagon, ACTH)
  - cGMP (atrial natriuretic factor, Nitric oxide)
  - Calcium or phosphatidyl inositol (oxytocin, TRH)
  - Kinase or phosphatase cascade (insulin, GH)

General features of hormone classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor- hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols



Genomic responses vs. rapid responses

TABLE 1-1 Nuclear Receptors and Involvement in Genomic and/or Rapid Biological Responses

(Steroid receptor) & ligand	# aa Receptor	Steroid nuclear receptors & gene transcription generate genomic responses (GR)	Steroid membrane receptors generates rapid responses (RR)
(Thyroid β) T_3	461	T_3 binding to its nuclear receptor, in target cells stimulates dissociation of co-repressors, recruitment of co-activators, etc. to complete a GR.	T_3 activates PI3kinases and MAP kinase **RR** pathways which can result in glucose uptake, Ca^{2+}-ATPase, Na^+/H^+ antiporter.
(Vitamin D receptor) 1α,25$(OH)_2$- vitamin D_3	427	Both intestinal Ca^{2+} absorption & kidney Ca^{2+} reabsorption requires **GR** for production of new calcium binding proteins (CaBP).	**RR** opening of Cl^- channels in osteoblasts & keratinocytes in 20 min; insulin secretion from β-cells, MAP kinase activation in NB4 cells.
(Estrogen receptor α) Estradiol	595	ERα **GR** are required for normal ovarian function.	ERα activates PI3K and then AKt **RR** stimulates nitric oxide NO.
(Estrogen receptor β) Estradiol	530	ERβ **GR** are required for ovulation & pregnancy.	The cell membrane ERβ bound to caveola has been implicated in RR.
(Glucocorticoid receptor) Cortisol	777	Knockout (KO) of the mouse GC receptor is lethal at time of birth.	Cortisol stimulates PI3-kinase/Akt to activate in seconds NO release.
(Mineralocorticoid receptor) Aldosterone	919	MR **KO** mice die of Na^+ and H_2O deprivation.	Aldosterone activates in 3–15 minutes the **RR** of Na^+/H^+ exchange in renal cells.
(Progesterone receptor) Progesterone	933	The progesterone receptor participates in **GR** sexual differentiation determination.	Progesterone stimulates **RR** within seconds to minutes, the acrosome reaction in spermatozoa.
(Androgen receptor) Testosterone	919	**KO** of the AR male mouse causes development of female genitalia.	Activation of MAP kinase then activates the ERK pathway via **RR**.

GR = genomic responses; RR = rapid responses. RR are not dependent on genomic responses. KO = Knock-out renders affected genes inactive.