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Ligands are in green, important second messengers are in red

Steroid Hormone Receptors (no second messengers)

Androgen Estrogen Progesterone Glucocorticoids Mineralocorticoids	enter the cell cytoplasm via **simple diffusion** bind to **cytoplasmic receptors**. receptors dimerize with each other and enter the nucleus in the nucleus zinc finger regions of receptor binds to specific DNA response elements (upstream of target gene).

Thyroid hormones Vitamin A Vitamin D	enter the cell cytoplasm via **facilitated diffusion** **go directly to the nucleus** bind to **intranuclear receptors** in the nucleus zinc finger regions of receptor binds to specific DNA response elements (upstream of target gene).

Peptide Hormone G-Protein Receptors

All G-protein Receptors = 7-helix membrane-spanning domains.
Receptors are associated with G-proteins.
G proteins have 3 subunits: α, β, and γ.

The α subunit

α is linked to GDP. When peptide binds receptor, GDP is phosphorylated to GTP, and the α subunit is activated.

3 kinds of α subunits:

- α_s subunits → activate adenylatecyclase,
- α_i subunits → inhibit adenylatecyclase,
- α_q receptors → activate phospholipase C.

G proteins are named according to α subunits (G_s, G_i, or G_q)

G_q receptors:

α_1 receptors (epinephrine, norepinephrine, phenylephrine)
H_1 receptors (histamine)
V_1 receptors (vasopressin)
M_1, M_3 receptors (acetylcholine)

G_q
→ **GTP**
→ **α_q**
→ **Phospholipase C**
Phospholipase C cleaves **PIP_2** (in cell membrane) into two: IP_3 , DAG
- **IP_3** goes to IP_3 receptors on endoplasmic reticulum → release calcium into cell
- **DAG** stays in the cell membrane & binds to protein kinase C.

→ **Protein kinase C** is activated by binding DAG, and by calcium released via IP_3.
→ Protein kinase C phosphorylates a wide variety of cell proteins.

G_s receptors:

β_1 receptors (epinephrine, norepinephrine, isopreterenol, dobutamine)
β_2 receptors (epinephrine, isoproterenol, albuterol)
H_2 receptors (histamine)
D_1 receptors (dopamine)
V_2 receptors (vasopressin)
receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins

G_s
→ **GTP**
→ **α_s**
→ **adenylatecyclase**
adenylatecyclase converts ATP to **cAMP**
→ **cAMP** activates protein kinase A
→ **Protein kinase A** phosphorylates CREB (cAMP response element binding protein)
→ **CREB**-P goes in the nucleus and binds to **CRE** (cAMP response element) on target DNA via **leucine zippers**. *(The interaction of CREB-P and CRE via leucine zippers is analogous to the interaction of steroid receptors and hormone response elements via zinc fingers.)*

cAMP is deactivated by phosphodiesterase (PDE); PDE inhibitors, such as caffeine, prolong the activity of cAMP and thus enhance the actions of epinephrine, norepinephrine, etc.

G_i receptors

M_2 receptors (acetylcholine)
α_2 receptors (epinephrine, norephinephrine)
D_2 receptors (dopamine)

G_i
→ **GTP**
→ **α_i**
→ **inhibition of adenylatecyclase**
Inhibited adenylatecyclase cannot convert ATP to cAMP
→ levels of cAMP drop → ↓↓↓ protein kinase A

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cGMP Receptors (no associated G proteins)

Atrial Natriuretic Peptide	binds to ANP receptor **ANP receptor** has intrinsic **guanylate cyclase** activity → GTP to **cGMP** → **cGMP** activates **protein kinase G** → **relaxation of vascular smooth muscle**.
Nitric oxide a) from arginine via *nitric oxide synthase* in vascular endothelial cells b) from nitroprusside, nitroglycerine, or isosorbide dinitrate.	**NO diffuses across cell membranes** **NO directly activates** a **guanylate cyclase** (free-floating) → GTP to **cGMP** → **cGMP** activates **protein kinase G** → **relaxation of vascular smooth muscle**.

Receptor Tyrosine Kinases (no second messengers)

PDGF FGF EGF VEGF	receptors are **monomeric** When hormones bind, two adjacent receptors **dimerize**, → **autophosphorylate** their own C terminal tyrosine residues. → kinase cascade → proteins become sequentially activated: GRB_2, SOS, **ras**, **raf**, MEK, **MAPK**. → MAP kinases are **serine/threonine specific**

Receptor Tyrosine Kinases (no second messengers)

Insulin	receptors are **dimeric** When insulin binds → **autophosphorylation** of the receptor → **IRS** (Insulin receptor substrate) binds to the phosphorylated domains → **IRS becomes phosphorylated** Proteins with ***src*** homology (SH2) binds the IRS phosphorylated region and are activated. ➔ transport GLUT-4 (fat, muscle) to surface of cells ➔ stimulate *ras*-encoded $p21^{ras}$ G protein ➔ activating various protein phosphatases, which can terminate some of these actions and may serve to regulate insulin function.

Receptor-Associated Tyrosine Kinases

Prolactin Growth Hormone Cytokines Erythropoietin Colony-Stimulating Factor	receptors are **dimeric** and **do not have intrinsic tyrosine kinase activity** When PRL binds → tyrosine kinases are **recruited** to the receptor → the **Jak/STAT** signaling pathway is activated → activated STAT proteins travel to the nucleus and modify gene transcription This pathway is important in cell **differentiation**, **proliferation**, and **apoptosis**