Water soluble signaling molecules cannot pass through the PM, therefore their receptors are on the surface.

Kinase: an enzyme that adds a Ⓟ group to another molecule. phosphorylation activates or deactivates proteins

like protein, peptide, catechochalamine hormones & tyrosine

Pathways they use:

① Bind to open or closed chemically gated channels e.g: neurotransmitters

② Bind to GPCRs and activate 2nd messenger pathways e.g: eicosanoids + most peptide hormones

③ Bind to and activate receptor-enzyme complexes → tyrosine kinase pathway insulin + growth factors

→ JAK/STAT pathway + prolactin + immune cytokines

- Not all 2nd messenger pathways involve G-proteins
- In some cases, a hormone may stimulate more than one second messenger system in the same target tissue.

(water soluble)

Peptide & Protein Hormones

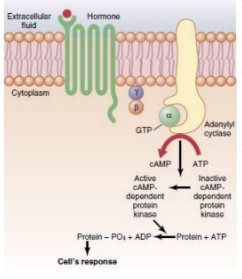
Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	▪ TRH, GnRH, CRH GHRH, Somatostatin,	Placenta	▪ HCG, HCS or HPL
Anterior pituitary	▪ ACTH, TSH, FSH, LH, PRL, GH	Kidney	▪ Renin (enzyme) ▪ Ang II (peptide)
Posterior pituitary	▪ Oxytocin, ADH	Heart	▪ ANP
Thyroid	▪ Calcitonin	G.I. tract	▪ Gastrin, CCK, Secretin, GIP, Somatostatin
Pancreas	▪ Insulin, Glucagon, Somatostatin	Adipocyte	▪ Leptin JAK/STAT
Liver	▪ Somatomedin C (IGF-1)		
Parathyroid	▪ PTH		

Amine Hormones These examples are derived from tyrosine

Gland/Tissue	Hormones
Hypothalamus	▪ Dopamine — water soluble
Thyroid	▪ T_3, T_4 — lipophilic
Adrenal medulla	▪ Epinephrine and Norepinephrine (NE, EPI)

Bind to GPCRs

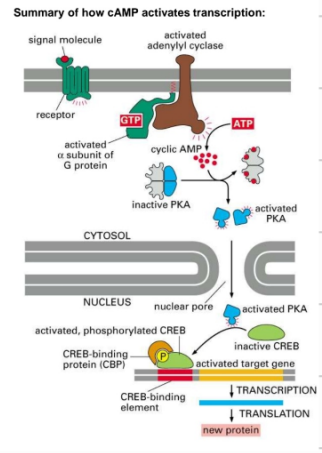
General Mechanism



1. Messenger binds to GPCR
2. Undergoes conformational changes and Ⓟ GP. (GDP that is bound to α is replaced by GTP)
3. α-subunit separates leaving $G_{\beta\gamma}$ complex, it goes to the effector protein to Ⓟ or Ⓟ it.

Ⓟ effector protein → inc in [2nd messenger] Ⓟ does the opposite

$G_{\beta\gamma}$: either: ① acts as an effector, Ⓟ or Ⓟ proteins
② inhibit adenylyl cyclase



G_s it has α_s subunit

- effector protein: adenylyl cyclase, Ⓟ it → converts ATP to cAMP
- second messenger: cAMP, activates c-AMP dependent protein kinase (PKA)

PKA Ⓟ target proteins, for example: CREB:-

PKA → nucleus → Ⓟ CREB (cAMP response element binding protein)

→ binds to CRE (cAMP response element, it's a specific regulatory DNA sequence) → transcription of this sequense

G_i it has α_i subunit
it inhibits adenylyl cyclase

Turn off of the signal ways:

① Gα hydrolyses GTP to GDP + Pi (GTPase)

② phosphodiesterases catalyse hydrolysis of cAMP → AMP

Gq

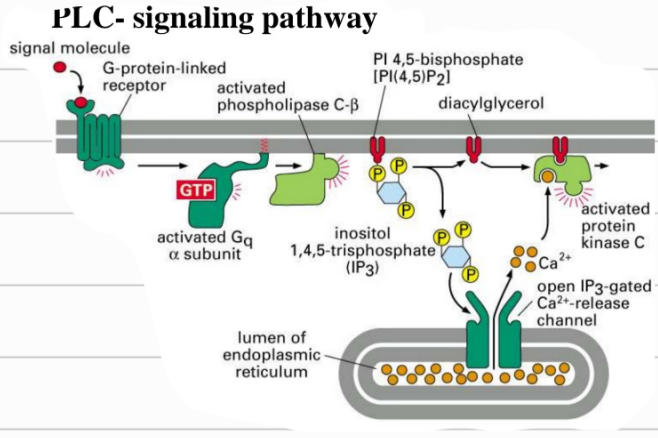
effector protein: Phospholipase C (PLC) → catalyzes breakdown of some PL. like PIP_2
- minor Phospholipid
- inner leaflet of PM
- produced by Ⓟ of phosphatadil inistol

Second messengers: IP_3 and DAG

There are 2 forms of PLC → PLC-β stim by Gq
→ PLC-γ → stim by TKRs → has SH_2 domains that allow binding to activated tyrosine kinases

IP_3: stimulates Ca^{+2} release from intracellular stores which alter activities of target proteins like PKC

DAG: remains associated with PM, stimulates PKC



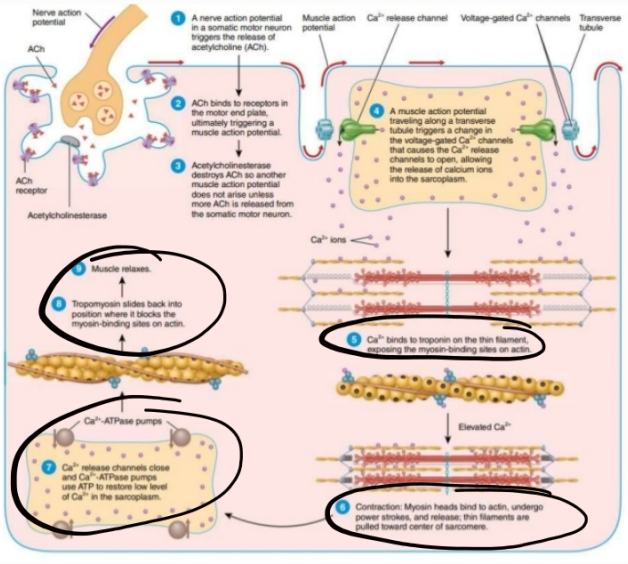
Calcium calmodulin second messenger system

- When Ca^{+2} is released from intracellular stores it binds with calmodulin
- When 3-4 Ca^{+2} bind to it, it changes it shape and ⊕ or ⊖ PKs like CaM kinases (calmodulin dependent protein kinase)
  - Ⓟ inactive proteins and bring about cellular responses

Other means by which Ca can enter the cells

*NMJ – Ach

* AP travels through transverse tubule to open VGC of Ca^{+2} in the sacroplasmic reticulum

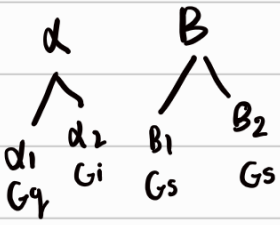


cGMP as a second messenger

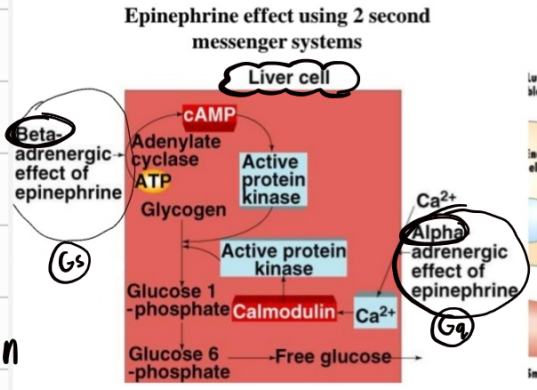
B. cGMP:

1. produced from GTP by guanylyl cyclase;
2. activates cGMP-dependent kinases or other targets
3. example: G-prot. Coupled rhodopsin photoreceptor in rod cells of retina

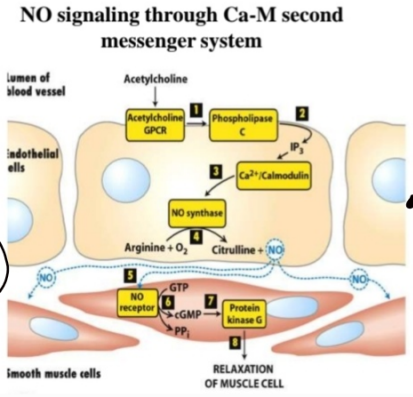
Examples of Second messenger pathways



PKA Ⓟ enzymes that turn glycogen to glucose to be released

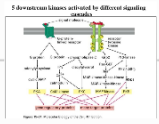


Releasing Glucose



SM Relaxation for vasodilation

- Ca^{+2} Calmodulin Ⓐ NO synthase
- NO diffuses into SM cells
- NO Ⓐ guanalylcyclase
- Protein kinase G
- Muscle relaxation



Enzyme linked hormone receptors

receptors are homodimers

Note: both these pathways involve tyrosine kinases, but
tyrosine kinase pathway → receptor itself is a tyrosine kinase
JAK stat pathway → receptor is not a kinase but associated with JAK proteins which are non receptor tyrosine kinases (separate cytosolic enzymes)

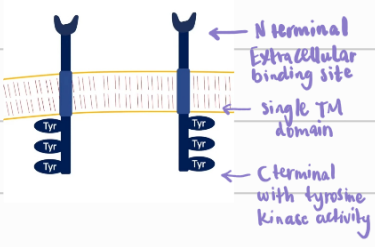
either the receptor itself is an enzyme

↓

Tyrosine kinase Pathway

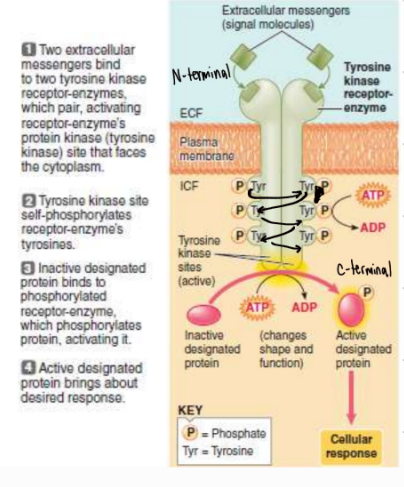
ligands examples: insulin, growth factors (EGF, NGF, PDGF)

using tyrosine kinase receptors. (Ⓟ tyrosine)



What happens:

RTKs Ⓟ eachother at tyrosine residues. Then these phosphorylated sites phosphorylate proteins that have SH2 binding domains



or the receptor & enzyme function as a unit but the receptor itself isn't an enzyme

Janus kinase

JAK / STAT Pathway

cytokines, prolactin, growth hormone

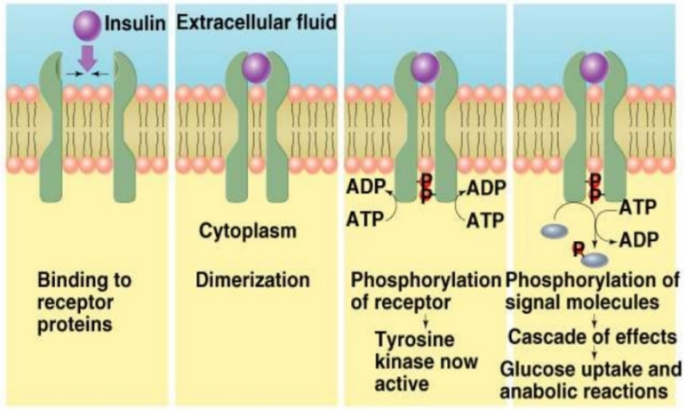
↳ transcription factors not enzymes

What happens: ① Binding of a receptor activates the JAKs (in cytosolic side of receptor) and causes dimerization

② Activated JACKs Ⓟ STATS (signal transducers and activators of transcription)

③ Ⓟ STATs move to nucleus and turn on transcription of certain genes resulting in new proteins that carry out cellular responses.

Specific example : insulin

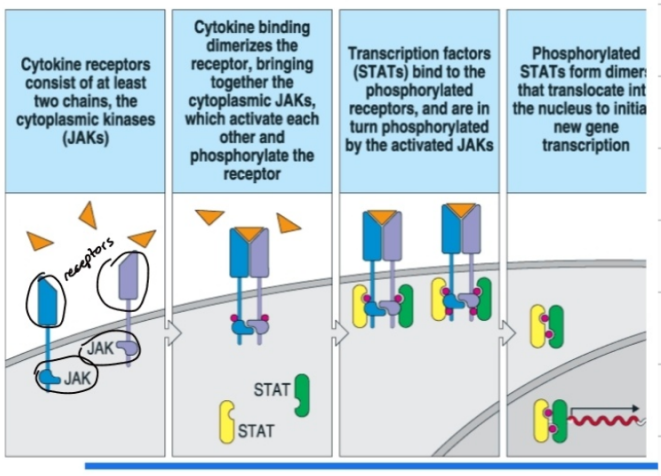


Binding of insulin ↴

- Activates signaling molecules. (get phosphorylated by RPKs)
  - Stimulate glycogen, fat and protein synthesis.
  - Stimulate insertion of GLUT-4 carrier proteins.

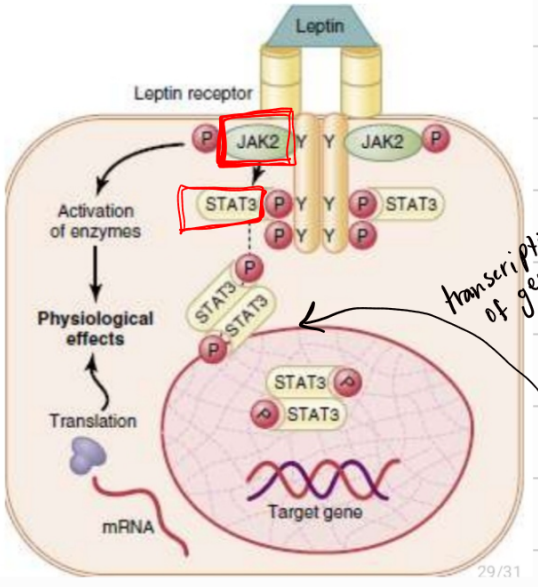
↓ Glucose transporter type 4

Specific example : cytokine



leptin

secreted by fat cells. responsible for energy balance & apetite. telling the brain when the body has enough fat



When JAK2 is activated it Ⓟ STAT3 & several other enzymes that mediate some of the most rapid effects of leptin

Table 75-3 Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (beta receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Growth hormone–releasing hormone (GHRH)
Human chorionic gonadotropin (hCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)

cAMP, Cyclic adenosine monophosphate.

Table 75-4 Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone–releasing hormone (GHRH)
Parathyroid hormone (PTH)
Oxytocin
Thyrotropin-releasing hormone (TRH)
Vasopressin (V_1 receptor, vascular smooth muscle)

Table 75-2 Hormones That Use Receptor Tyrosine Kinase Signaling

Fibroblast growth factor
Growth hormone
Hepatocyte growth factor
Insulin
Insulin-like growth factor-1
Leptin
Prolactin
Vascular endothelial growth factor