# Hydrophilic hormones and enzyme cascades

- Describe the action of GPCRs in generating second messengers, and how this alters cell behaviour.
- Describe the MAPK signal transduction pathway, and how dysregulation of this pathway relates to cancer.
- Describe the PI-3 kinase pathway as stimulated by insulin, and how it relates to the MAPK pathway.
- Describe the Smad pathway as initiated by the TGF-β receptor, and its relationship to cancer.
- Describe the JAK/STAT pathway initiated by erythropoietin, and explain how the signal is shut down in the absence of the cytokine.

## Types of hormone

**Endocrine** - released into blood

**Paracrine** - act on nearby cells (interstitial fluid)

**Juxtacrine** - bound to membrane (requires physical contact between cells) or secreted into ECM

**Autocrine** - Act on cell that released the hormone

## Types of receptor

**Ligand-gated ion channels** - signal tranduced to the cell via change in membrae potential

**Receptor enzymes** - enzymatic activity of receptor activated by hormone-binding

**Enzyme recruiting receptors** - hormone-binding induces the recruitment and activation of kinases

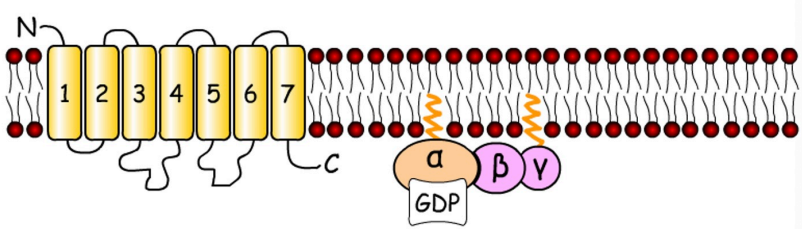
**G-protein coupled receptor (GCPR)** - hormone-binding activates GTP-binding proteins

### GPCRs

Activation mechanism:

TLDR:

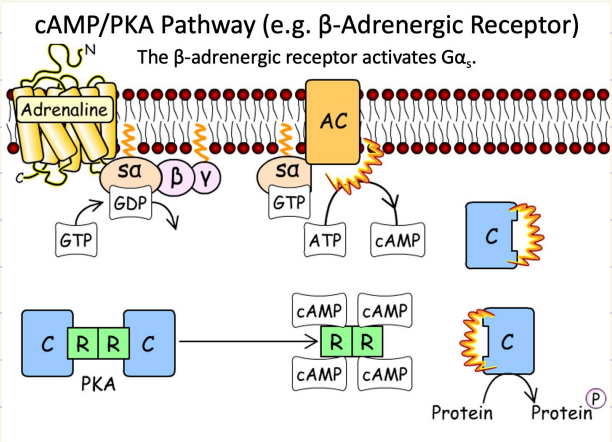
1. Hormone binds, GDP --> GTP
2. a subunit dissociates from beta & gamma
3. interacts with target enzymes
4. triggers second messenger production.




Hormone-bound receptor causes the exchange of GDP for GTP, activating the Gα subunit. The (dissociated) Gα subunit then interacts with an enzyme, until it hydrolyses the GTP to GDP, becoming inactive again (takes seconds to minutes).

### GPCR Second Messengers

- cAMP/PKA Pathway: Gαs activates adenylyl cyclase, increasing cAMP, which activates PKA. PKA phosphorylates proteins, influencing metabolism and transcription.

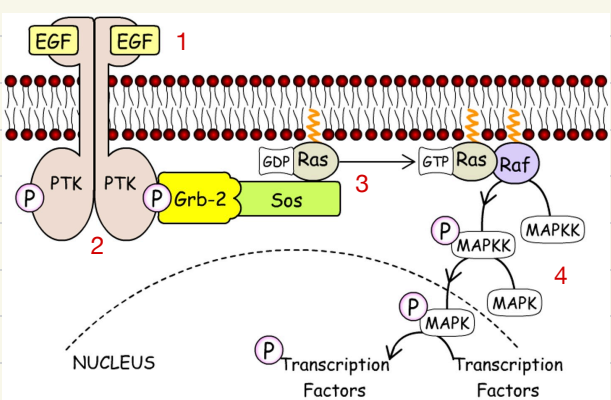



- Phospholipase C Pathway: Gαq activates phospholipase C, producing DAG and IP3, which increase [Ca++] and activate protein kinase C.

## MAPK Signal Transduction Pathway and Cancer

**Pathway Overview:**

- Activated by growth factor binding (e.g., EGF) to receptor tyrosine kinases (RTKs). 1
- Binding causes receptor dimerization and cross-phosphorylation. 2
- Adaptor proteins (Grb-2/Sos) recruit Ras, activating it via GTP exchange. 3
- Ras activates Raf → MEK → ERK, leading to transcription factor phosphorylation. 4



**Cancer Link:**

- Overexpression or mutation of EGFR or Ras can result in uncontrolled growth signals.
- EGFR overexpression in epithelial cancers can trigger signal transduction without ligand binding.
- Therapeutics like cetuximab target and block EGFR activity.

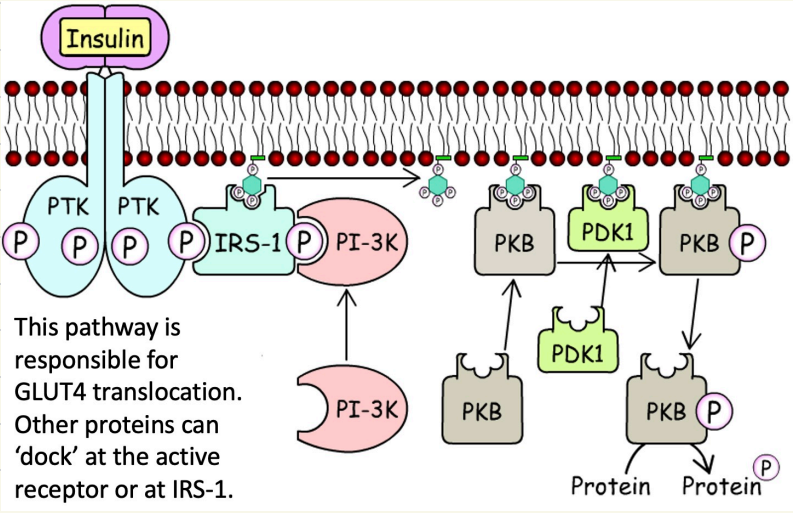
## PI-3 Kinase Pathway Stimulated by Insulin

**Pathway Overview:**

- Insulin binding to its receptor (RTK) causes cross-phosphorylation.
- IRS-1 docks at phosphorylated tyrosines, recruits PI-3K.
- PI-3K phosphorylates PIP2 → PIP3, which recruits PDK1 and PKB (Akt) to the membrane.
- PKB phosphorylates targets, regulating glucose uptake via GLUT4 and other metabolic processes.

**MAPK Link:**

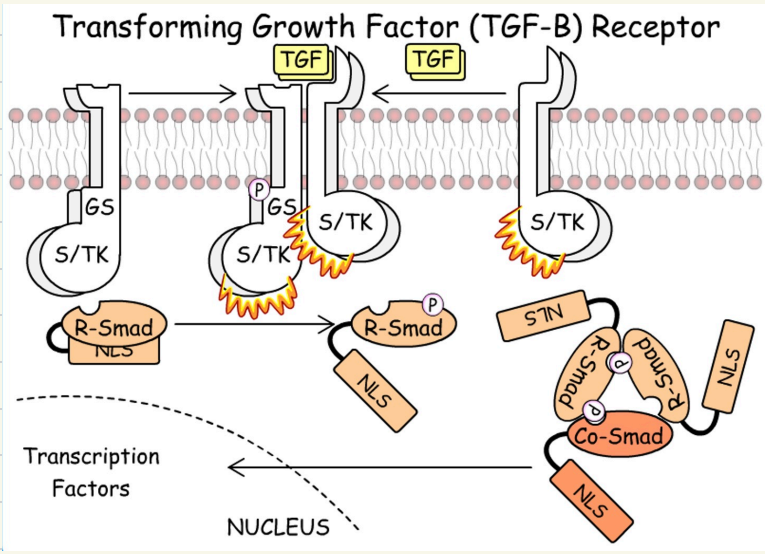
- IRS-1 can also activate Grb-2, linking the PI-3K pathway to MAPK, enabling insulin to affect growth and metabolism.



## Smad Pathway and TGF-β Receptor

**Mechanism:**

- TGF-β binds to TβR-II, recruiting and phosphorylating TβR-I.
- Activated TβR-I phosphorylates R-SMADs, which form a complex with Co-SMADs.
- SMAD complexes enter the nucleus to regulate gene expression.



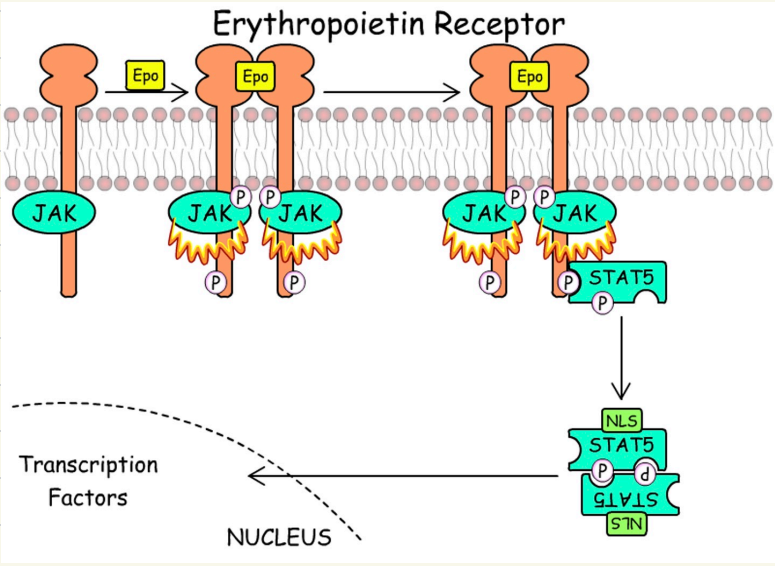

Cancer Link:

- TGF-β usually inhibits growth in cell. Loss of TGF-β receptors or SMAD mutations leads to unregulated cell growth.
- Mutations in Smad4 are common in pancreatic cancers, disabling TGF-β signaling.

## JAK/STAT Pathway Initiated by Erythropoietin

**Mechanism:**

- Erythropoietin binds to its receptor (EpoR), bringing JAK kinases into proximity for cross-phosphorylation.
- Activated JAK phosphorylates EpoR and STAT5.
- Phosphorylated STAT5 dimerizes, enters the nucleus, and promotes erythrocyte differentiation.




**Shut-Down Mechanism:**

- SHP1 phosphatase binds phosphorylated EpoR and dephosphorylates JAK, terminating the signal.
- Mutations that prevent SHP1 binding can lead to excessive red blood cell production.

# Summary

Hydrophilic hormones must bind to receptors in the plasma membrane in order to change the behaviour of proteins inside the cell.

Hormones can have a range of effects on different tissues, by stimulating different pathways, or acting on different targets.

Pathways generally act by changing the location, activity or concentration of proteins.

Dysregulation of these pathways can have serious negative effects, such as cancer or insulin resistance, or sometimes positive ones.

Understanding these pathways has resulted in successful treatments for various conditions.