# HORMONES OF THE PANCREAS

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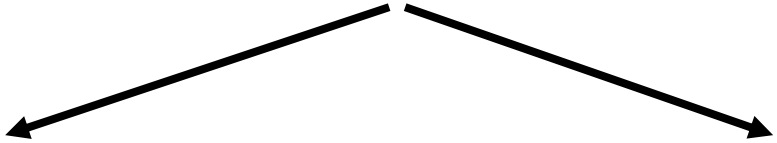
# Pancreas



## Acinar portion

Exocrine function.
Secrete enzymes & ions into duodenal lumen

## Islets of Langerhan

Endocrine function

- Insulin - β cells (60%)
- Glucagon - α cells (25%)
- Somatostatin - δ cells (10%)
- pancreatic - F cells (5%) polypeptide

# Insulin

- Secreted by β cells of islets of Langerhan
- First protein to be crystallized & sequenced
- Treatment for IDDM


Chemistry

❖ Consists of two chains

A chain – 21 AA

B chain – 30 AA

❖ Linked by 2 di-sulphide bridges-

A7-B7 & A20-B19

❖ A6-A11 intrachain disulphide bridge

❖ Forms a dimer with two zinc atoms

# Biosynthesis

Synthesized as preproinsulin.

23 AA leader sequence directs the molecule into ER for processing.

Leader sequence removed

↓

Proinsulin – continuous molecule with (N-terminal) B chain + connecting peptide + A chain (C terminal)

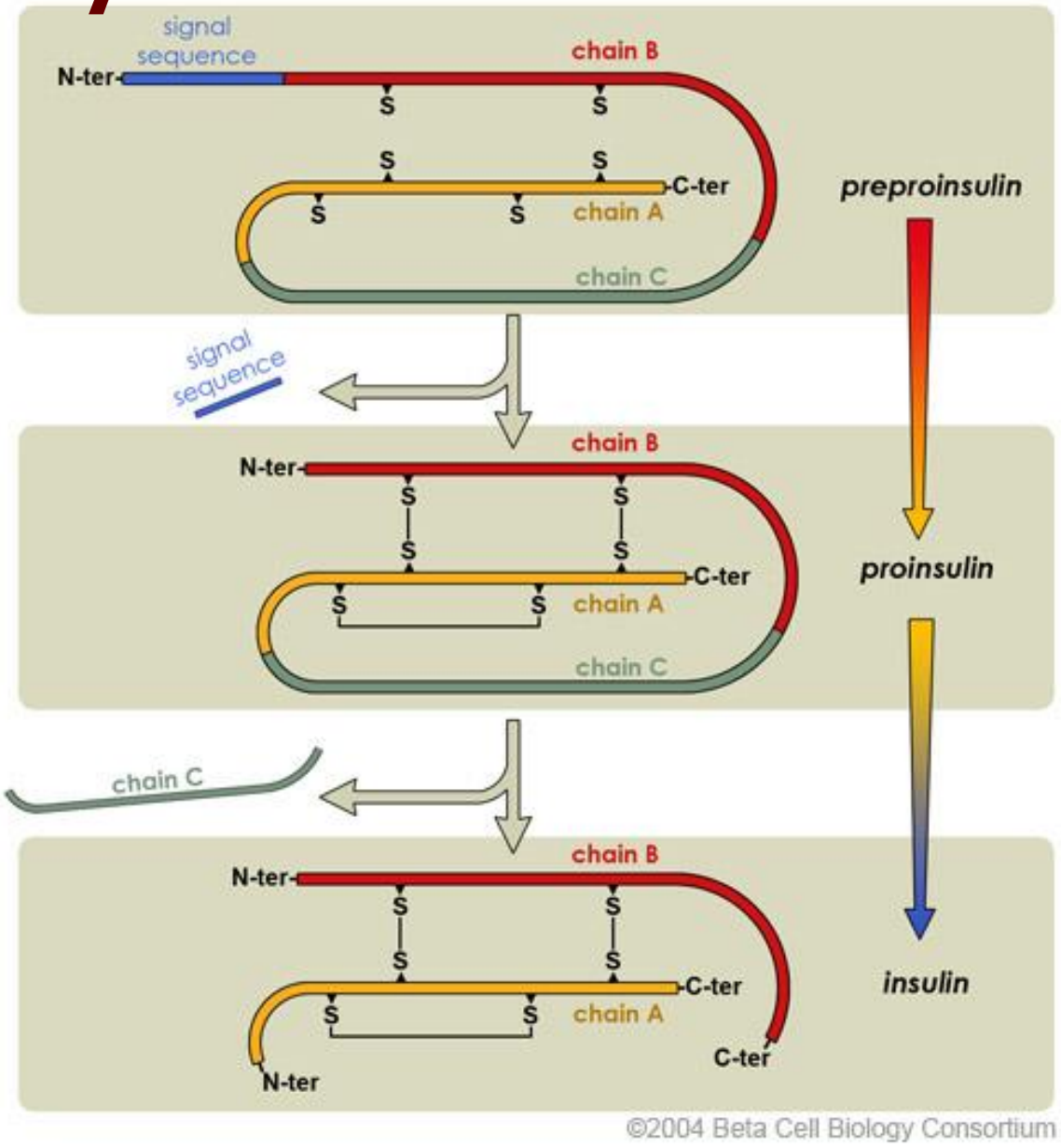
↓

Site specific peptide changes

↓

Equimolar amounts of mature insulin and C peptide

# Insulin Synthesis



# Secretion of insulin

Energy consuming process, the uptake of $Ca^{+2}$ into β cells trigger a contractile mechanism which involves the movement of insulin containing granules to the cell membrane

Mediators of insulin release

a) Blood glucose level- ↑ plasma glucose binds with receptors on β cell membrane activates the release mechanism.

b) Hormonal factors- GH, (cortisol), estrogens, progestins increase insulin secretion

c) Pharmacological agents- Drugs

eg. Sulfonylurea compounds – use in therapy of NIDDM in humans

Glucose induced insulin secretion

- Glucose enters pancreatic β cells through glucose uniporter GLUT2 and is used to produce ATP (oxidative phosphorylation)
- ATP closes ATP gated K+ channel and depolarizes the membrane
- Depolarization opens voltage gated calcium channels.
- Entry of calcium causes exocytosis of insulin containing secretory vesicles.

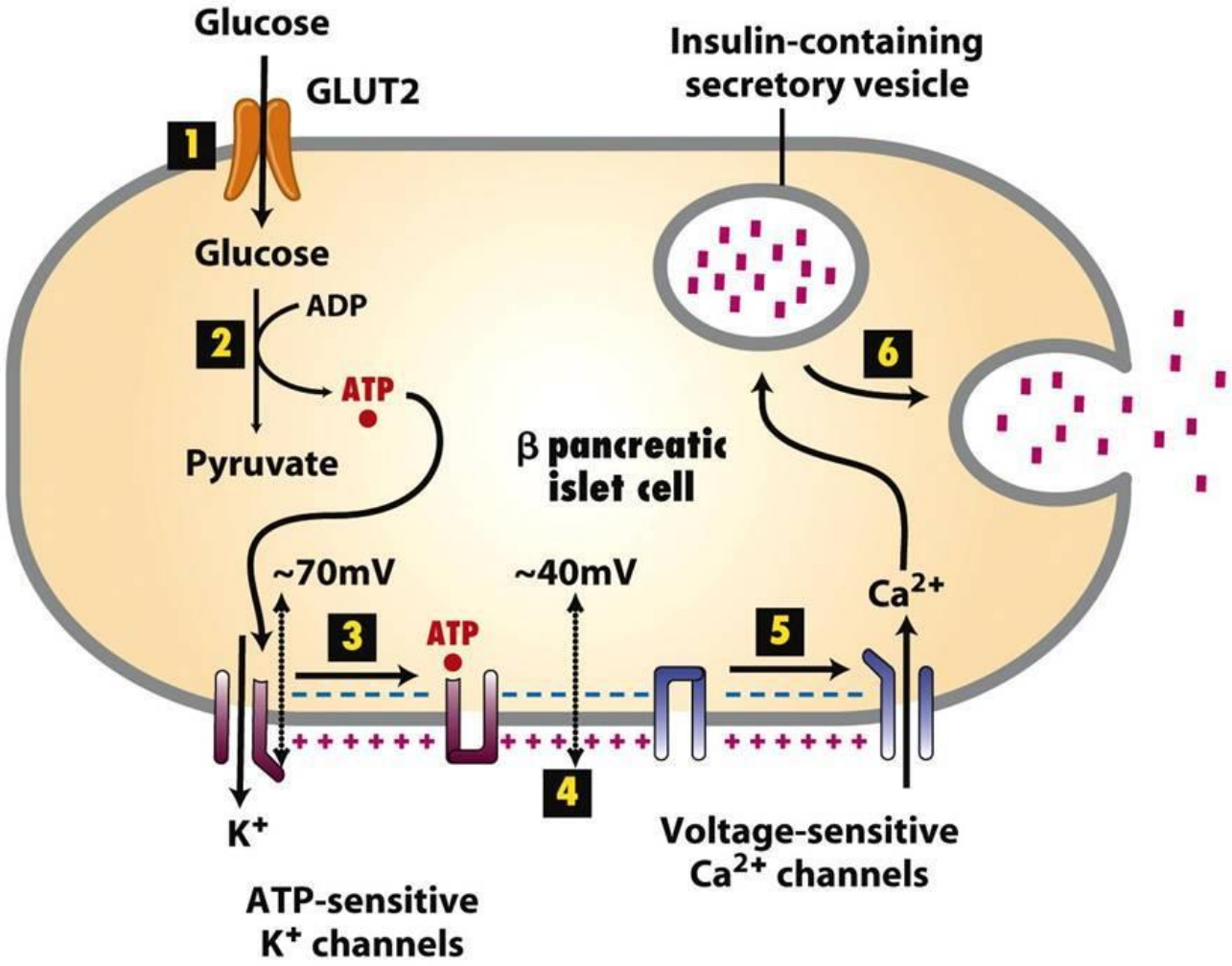



Figure 15-33
*Molecular Cell Biology, Sixth Edition*

# Metabolism of insulin

- Plasma $t_{1/2}$ = 3-5 minutes
- Major sites of metabolism are liver and kidney
- Circulates unbound to plasma proteins
- Filtered by glomeruli, reabsorbed in the proximal tubules & degraded by kidneys
- Liver metabolizes about 50% of insulin that passes through it.

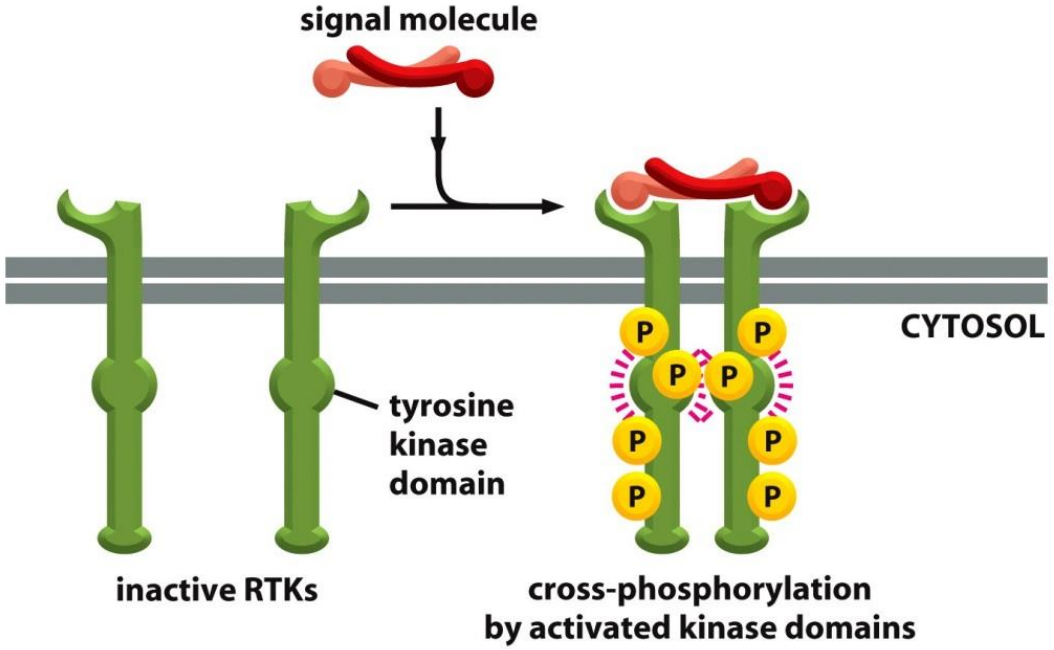
# Mechanism of action

Receptor located on cell membranes of target cells

Receptor →
- 2α subunits- extracellular contain insulin binding sites
- 2β subunits- span the membrane, transduce binding of insulin to an intracellular signal

Receptor Tyrosine Kinases (RTKs)

- Insulin receptor belongs to a family of receptors called RTKs.
- Activate intrinsic tyrosine kinase activity upon binding of hormone
- Autophosphorylation of β-subunits.




NORMAL RTK ACTIVATION

Mechanism of insulin action

(i) Insulin Receptors (IR) bind two insulin peptides with 2 α chains

- β chains auto-phosphorylate each other
- P- β subunits now active receptor tyrosine kinases (RTK)

(ii) Active RTK initiates a signal transduction cascade. RTK phosphorylates **<u>adapter proteins</u>**

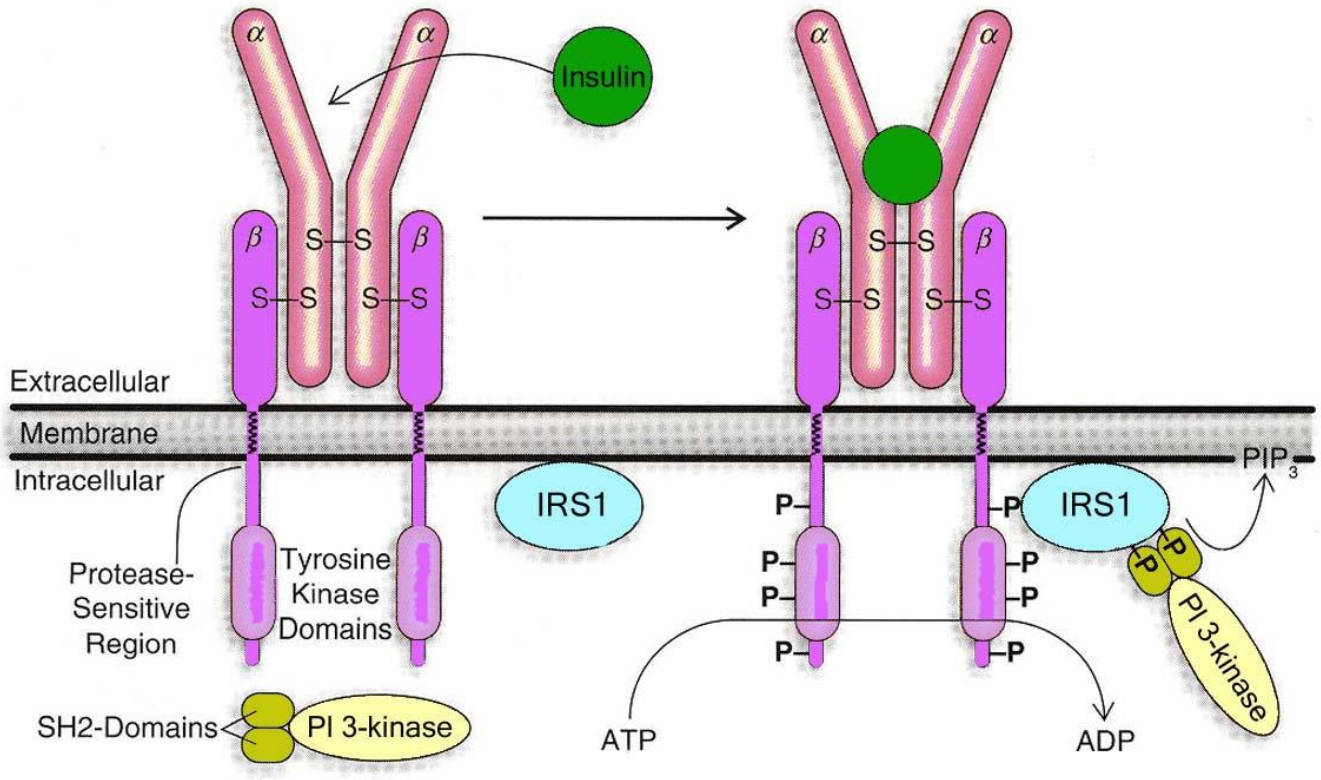
Eg: Insulin Receptor Substrates (IRS1 to IRS4)
SHC proteins

(iii) Phosphorylated tyrosines on adapter proteins serve as docking sites for proteins with SH2 domains (for *Src homology region*)

Eg. **PI 3 kinase** → activates PI3 kinase (phosphoinositide-3 kinase) pathway - **non-genomic effects**

**GRB-2** → activates ser/thr kinases and **Ras/MAPK pathway (genomic effects)**

**Figure 11.7** Diagrammatic structure of stimulation of the insulin receptor

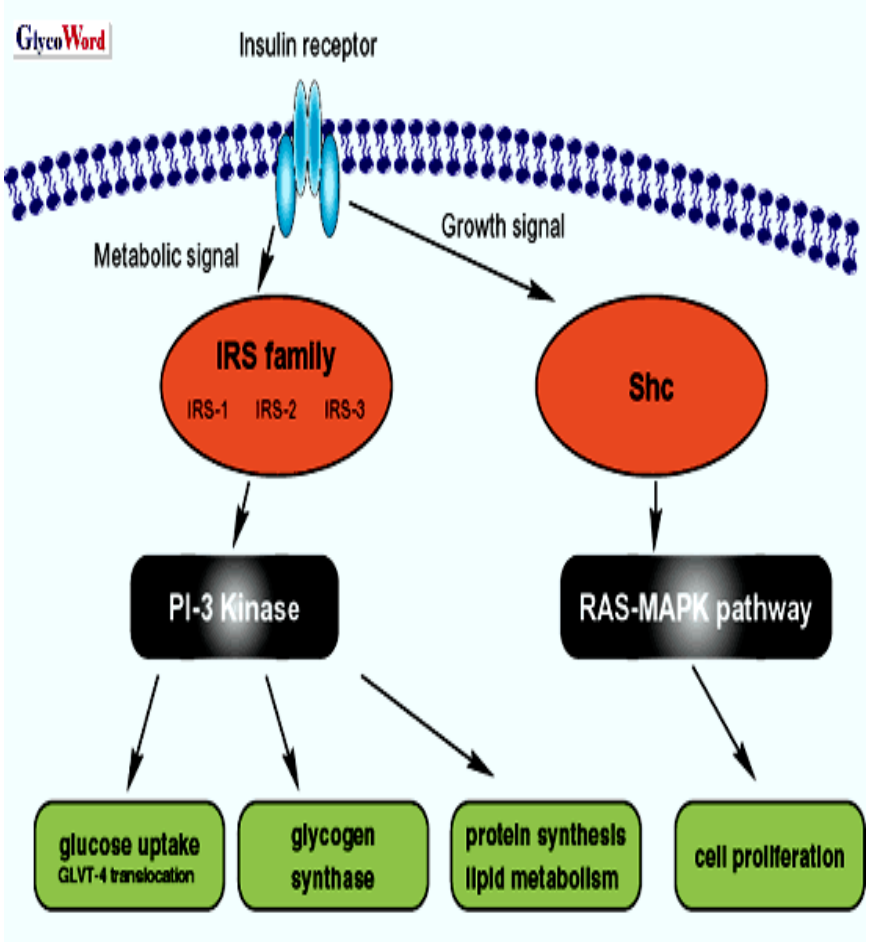


# The Insulin Signaling Network

- **Two major pathways well described.**
  - **RAS-MAPK pathway**
  - **PI 3-kinase pathway**
- **RAS-MAPK pathway**

  general signaling pathway leading to **enhanced cell growth & differentiation.**
- **PI 3-kinase pathway**

  biologic responses that are **more unique to insulin action (metabolic), cell survival.**

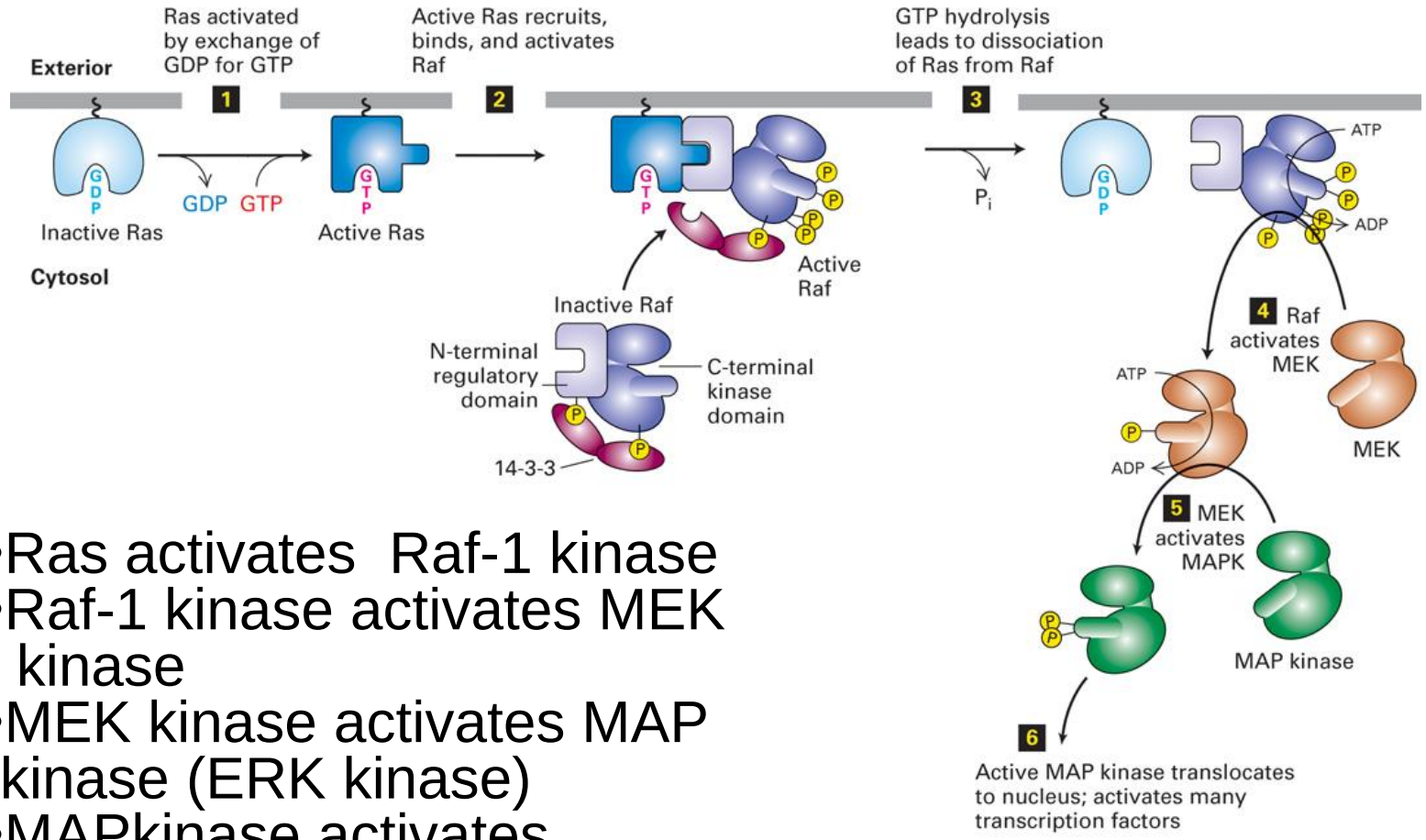


# RAS-MAPK Pathway

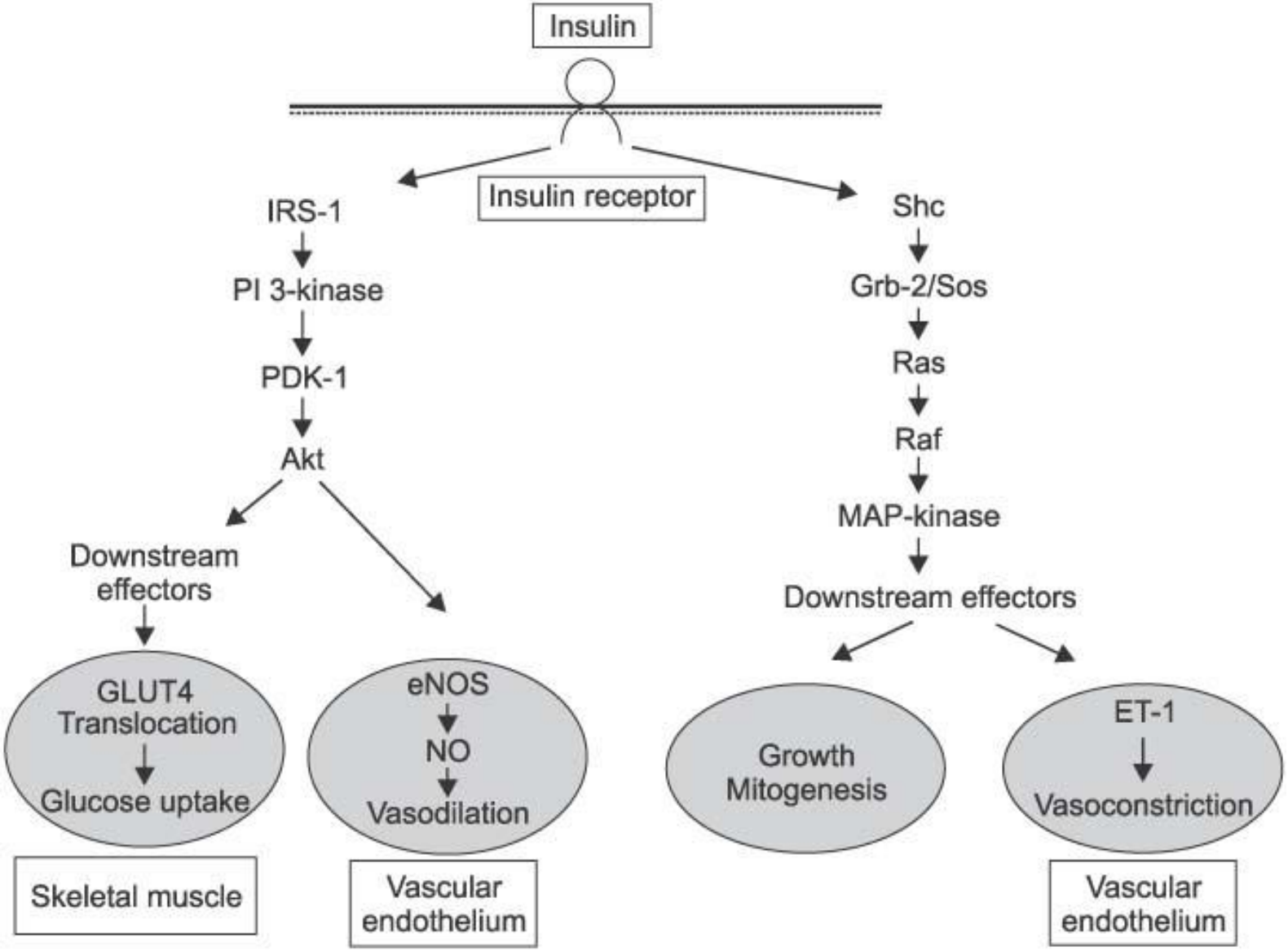
- The insulin receptor uses the Ras/MAP kinase pathway to regulate gene expression.
- RTK-Ras/MAP kinase signaling controls cell division, differentiation, and metabolism.
- Ras is a monomeric G protein which does not directly bind to receptors. Ras is activated by binding of GTP.
- Once activated, Ras propagates signaling via a kinase cascade that results in the activation of members of the MAP kinase family.

- MAP kinases phosphorylate transcription factors (TF) that regulate genes involved in the cell cycle and in differentiation.
- Mutant RTKs or Ras/MAP kinase signaling proteins are associated with nearly all cancers.
  - Ras activates  Raf-1 kinase
  - Raf-1 kinase activates MEK kinase
  - MEK kinase activates ERK kinase (MAPkinase)
  - ERK kinase activates Elk1 transcriptional activator.
  - Synthesis of new proteins

# Ras Activation of MAP Kinase




- Ras activates Raf-1 kinase
- Raf-1 kinase activates MEK kinase
- MEK kinase activates MAP kinase (ERK kinase)
- MAPkinase activates transcriptional factors.
- Synthesis of new proteins


Insulin
Insulin receptor
IRS-1
PI 3-kinase
PDK-1
Akt
Downstream effectors
GLUT4 Translocation
Glucose uptake
Skeletal muscle
eNOS
NO
Vasodilation
Vascular endothelium
Shc
Grb-2/Sos
Ras
Raf
MAP-kinase
Downstream effectors
Growth Mitogenesis
ET-1
Vasoconstriction
Vascular endothelium

# The PI 3-kinase pathway

- Central role of metabolic & growth-promoting actions of insulin

  Mediating **regulation of glucose transport via GLUT4, glycogen synthesis, protein synthesis, antilipolytic effects** of insulin, as well as cell **growth and cell survival** induced by insulin.

- P-Tyr-IRS-1 binds with PI3kinase (PI3K)
  - PI3K converts $PIP_2$ + ATP => $PIP_3$
  - $PIP_3$ activates **protein kinase B** (**PKB or AkT**) via PDK
- PKB (AkT) – metabolic effects

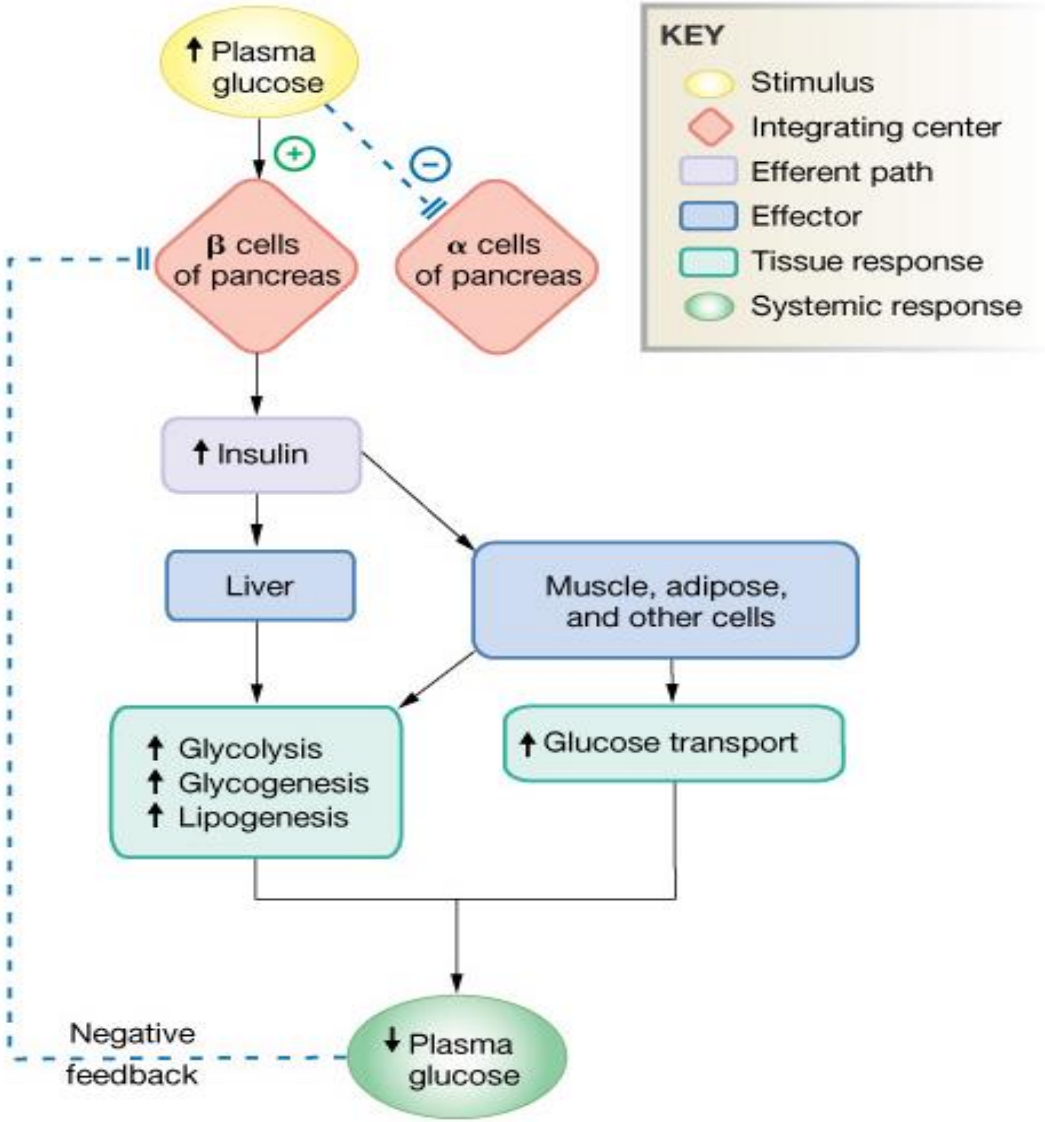
  Eg: activate glycogen synthase

  mediate translocation of GLUT4 to cell membrane for glucose uptake in adipose and muscle tissue.

**In insulin resistance –**

- Pancreas secretes insulin but it's action is impaired.
- IRS-1/ PI3 kinase pathway inhibited. This leads to-
  - (i)Decreased glucose uptake – translocation of GLUT4 to membranes impaired.
  - (ii)Reduced levels of eNOS (endothelial nitric oxide synthase) – leads to endothelial dysfunction.
  - (iii) Reduced glucose utilization – reduced glycogen, protein and fat synthesis.
- RAS/MAPK pathway unaffected. Promote pro-atherogenic and pro-inflammatory effects.

# Insulin : Metabolic effects



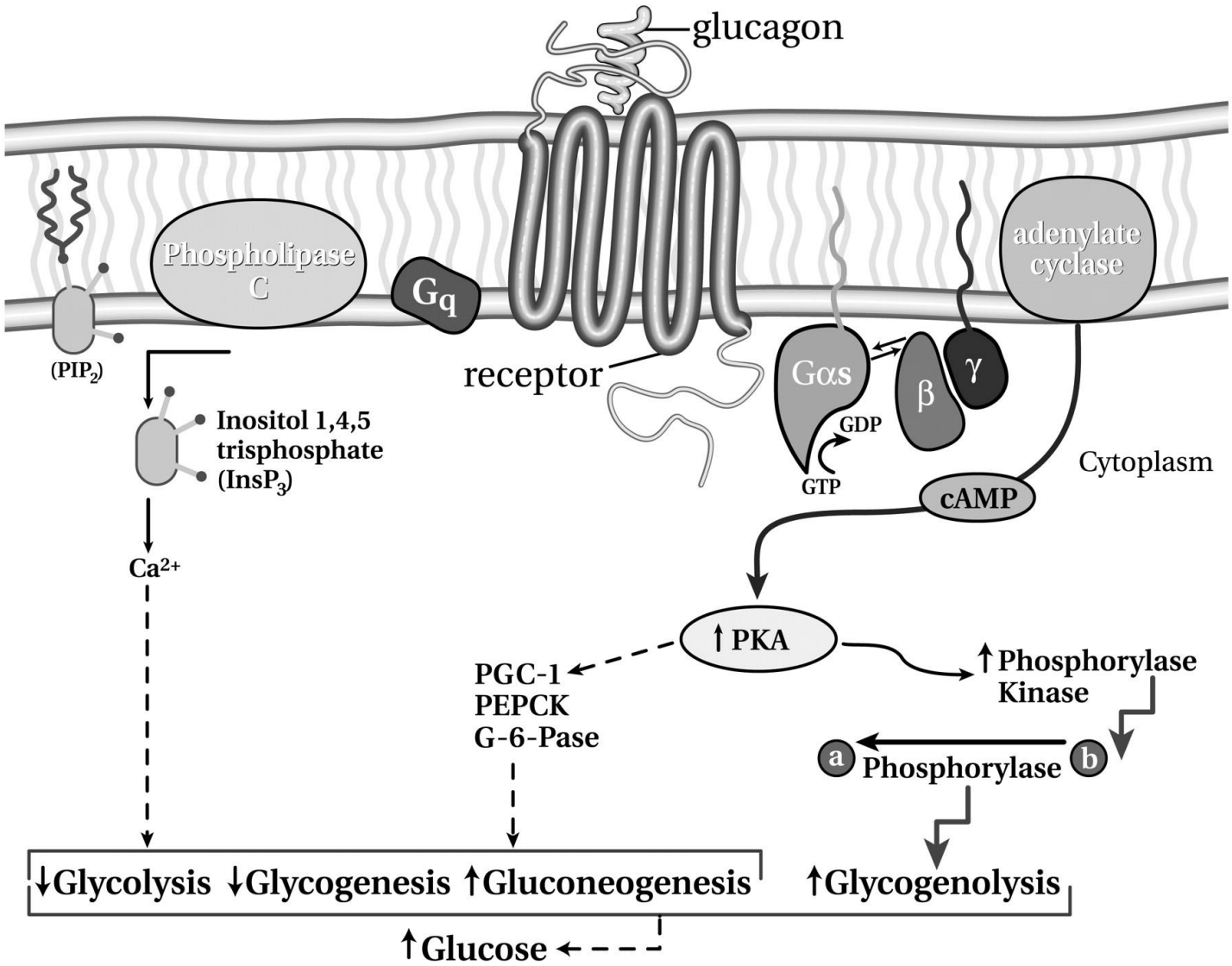
# GLUCAGON

- Synthesised in pancreatic α-cells
- Secreted in response to low plasma glucose. In plasma has a short $t_{1/2}$ ~5 mins.
- Preproglucagon (179 AA), removal of signal peptide convert to proglucagon (158 AA).
- Proglucagon (contains a glycentin-related polypeptide fragment- GRPP in the N- terminal)
- Glucagon cleaved by action of prohormone convertase in α-cells.

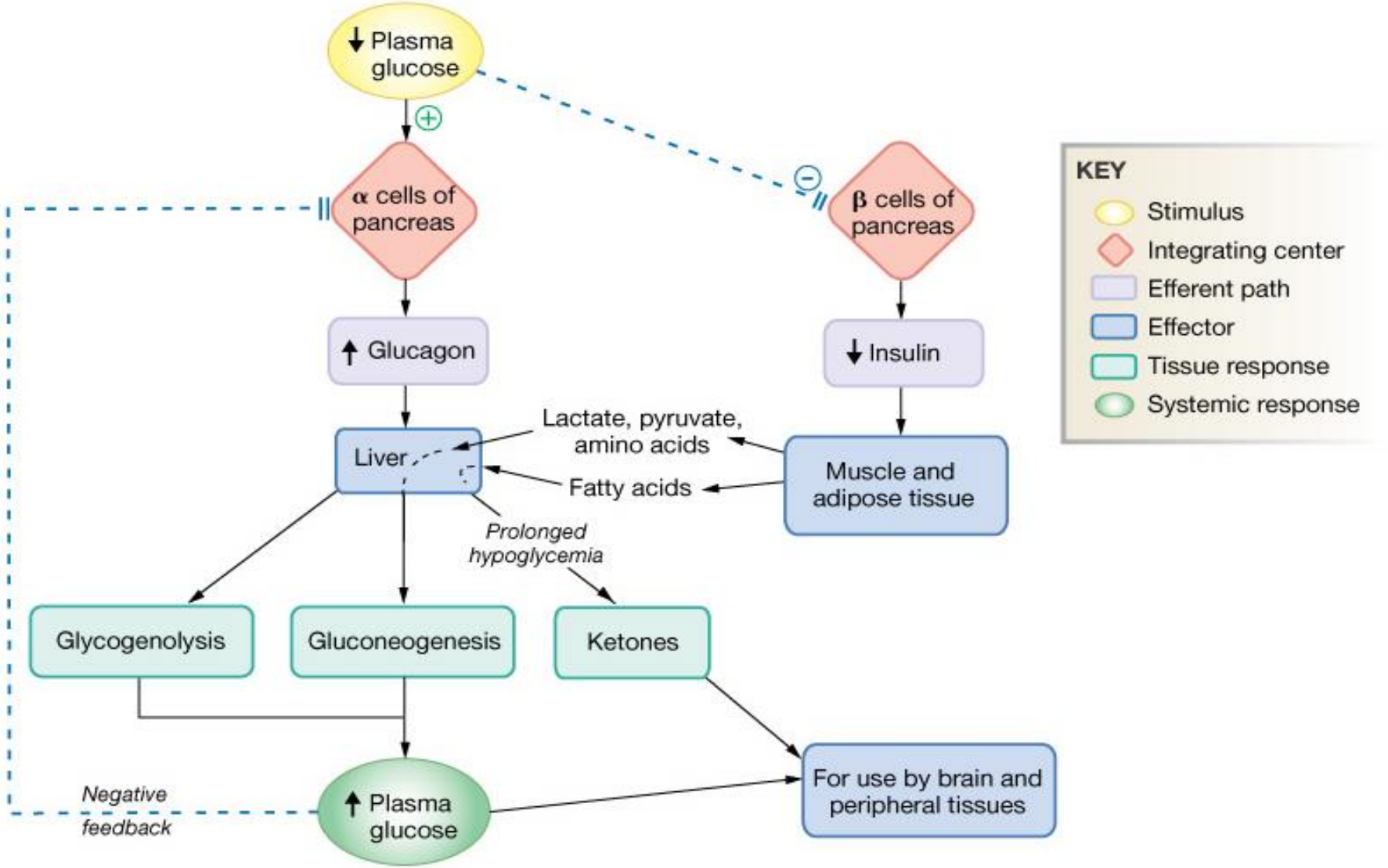
**Signal transduction by glucagon:**

- Glucagon receptor is G-protein coupled ($G_s$)
- Activate adenylyl cyclase → cAMP → activate PKA
- PKA phosphorylates enzymes on ser:
  - Activates some enzymes, inhibits others
  - Especially affects kinases, phosphatases
- cAMP rapidly degraded to AMP

- Hormone signal terminated by phosphatases remove the $PO_4$ from enzymes
- Liver is the major target organ and skeletal muscle does not have glucagon receptors.


glucagon
Phospholipase C
Gq
receptor
adenylate cyclase
(PIP2)
Inositol 1,4,5 trisphosphate (InsP3)
Gαs
GDP
GTP
β
γ
Cytoplasm
cAMP
Ca2+
↑PKA
PGC-1
PEPCK
G-6-Pase
↑Phosphorylase Kinase
a
Phosphorylase
b
↓Glycolysis ↓Glycogenesis ↑Gluconeogenesis
↑Glycogenolysis
↑Glucose

# Glucagon Action on Cells:




*THANK YOU*

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