

Cell-to-Cell Signaling

Insulin signaling



Insulin

- A hormone secreted by pancreatic β cells in response to elevated blood glucose levels
- **Increases transport of glucose to muscle and adipose tissue** (what lowers blood glucose levels)
- The **ONLY** hormone capable of lowering blood glucose



Insulin

- Required for normal growth and development
 - Lack of insulin (insulin dependent diabetes mellitus) causes wasting
 - Glucose can not effectively go to muscles (blood glucose levels are high)



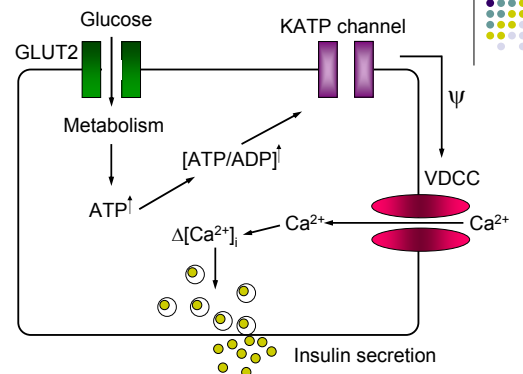
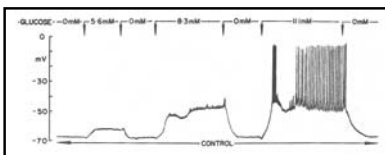
Response to elevated blood glucose levels (a meal)

- Remember there are two separate signaling events in glucose metabolism !!!
- First glucose in blood signals to pancreatic cells to secrete insulin
- Then insulin signals to target cells (liver, muscle and adipose tissue) to utilize glucose and lower blood glucose levels



Pancreatic β cells

- β cells of pancreas are excitable cells
- In low glucose they are hyperpolarized
- In high glucose they are depolarized, have action potentials and secrete insulin in the process of exocytosis



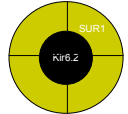
Glucose induced insulin secretion

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



Sulfonylurea receptor

- ATP gated K^+ channel can be closed by sulfonylurea (very popular anti – type 2 diabetic drug) independently of glucose level
- Depolarize the cell.....and increase insulin secretion
- works only when pancreatic cells are capable of secreting insulin, does not work in insulin dependent diabetes melitus



Sulfonylureas

KATP channel

ψ

VDCC

$\Delta[Ca^{2+}]_i$

Ca^{2+}

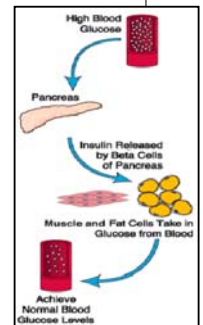
Ca^{2+}

Insulin secretion



Now insulin is secreted to blood and starts a second signaling event

- Insulin binds to insulin receptors on muscle and fat cells
- Muscle and fat cells increase glucose uptake
- This lowers blood glucose level



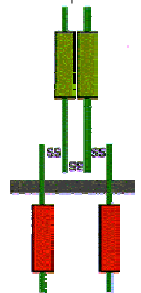
Insulin

- A dimer of two polypeptides
- Each polypeptide consists of an A and B chain of 21 and 30 aa
- Two chains are linked by a pair of S-S bonds

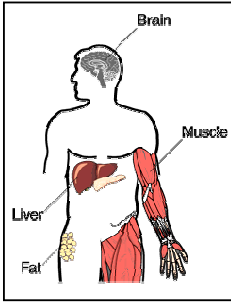


Insulin receptor

- Receptor tyrosine kinase (RTK)
- Localized to 19th chromosome in humans
- Two α and two β subunits
- Hormone binding site on α subunit
- β subunit - tyrosine kinase activity



Effectors for insulin action – don't forget about the brain



Physiological roles of insulin

- Enhances transport of glucose into the cells
- Activates glycogen synthase
- Activates glucokinase (trapping of glucose)

Physiological roles of insulin

- Enhances metabolism of sugar to glycerol
- Stimulates lipid synthesis
 - Activates of citrate lipase, acetyl-CoA carboxylase, fatty acid synthase and glycerol -3-phosphate dehydrogenase

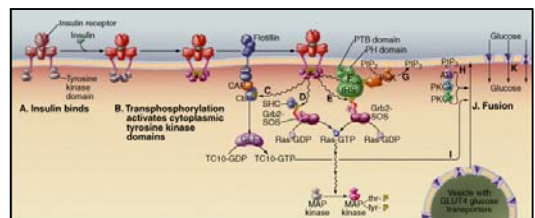
Physiological roles of insulin

- Stimulates active transport of glucose into cells
- Stimulates transport of amino acids and protein synthesis
- Stimulates K^+ uptake by cells

Insulin activates Ras dependent and Ras independent signaling

- Ras independent through activation of protein kinase B for immediate nongenomic effects
- Ras dependent – activation of mitogen activated protein kinase (MAPK) pathway for genomic effects

Insulin receptor signaling



Insulin receptor signaling

- Binding of insulin causes transphosphorylation of tyrosines on the receptor
- Phosphotyrosine residues bind IRS-1 (insulin receptor substrate – adapter protein)
- IRS1 binds PI_3 kinase through SH2 domain
- This phosphorylates PIP_2 to PIP_3
- Increased concentration of PIP_3 recruits PKB/Akt to the membrane

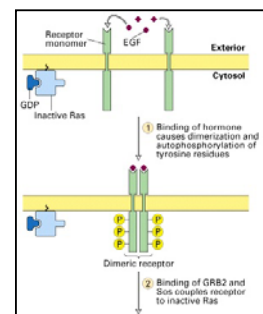
Insulin receptor signaling

- PKB is phosphorylated by two membrane associated kinases $PKC\lambda$ and ξ
- Active PKB is released into the cytosol
- Where it translocates glucose transporter GLUT4 (uniporter) to the membrane
 - Increases glucose uptake

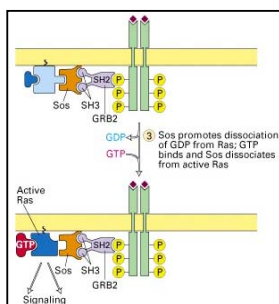
At the same time...

- Phosphorylated insulin receptor binds to adapter protein SHC and then Grb2
- Grb2 also has SH3 domains that bind and activate Sos

Linking insulin receptor to Ras



Linking insulin receptor to Ras

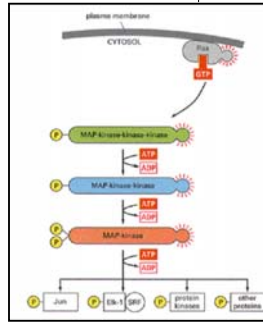


Linking insulin receptor to Ras

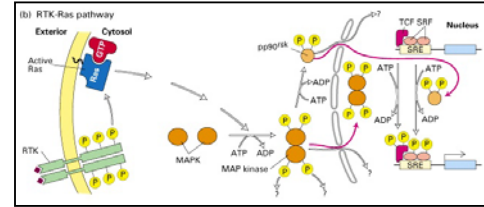
- Binding of Sos to inactive Ras causes a conformational change that permits release of GDP and binding of GTP (activation of Ras)
 - Sos is a GEF for monomeric G protein Ras
- Sos dissociates from activated Ras
- Activated Ras passes the signal to raf kinase
- Raf activates a cascade of kinases (Mitogen Activated Protein Kinase cascade)

Mitogen Activated Protein Kinases (MAP Kinases)

- Highly conserved kinase cascades
- Last kinase in the cascade has to be double phosphorylated by the kinase just above it (high specificity since it is double phosphorylation)



MAP kinase regulates the activity of transcription factors



- Active MAPK translocates to the nucleus
- Where it phosphorylates several transcription factors (and production of more GLUT4)

Insulin/GLUT4 pathway is not the only way to deliver glucose into cells

- Insulin-dependent, GLUT 4 - mediated cellular uptake of glucose into muscle and adipose tissue (40%)
- **Insulin-independent glucose disposal (60%)**
 - GLUT 1 – 3
 - GLUT 1 is responsible for “feeding” muscle during exercise (that’s how exercise lowers blood glucose levels)
 - SGLT 1 and 2 (sodium glucose symporter) intestinal epithelium, kidney