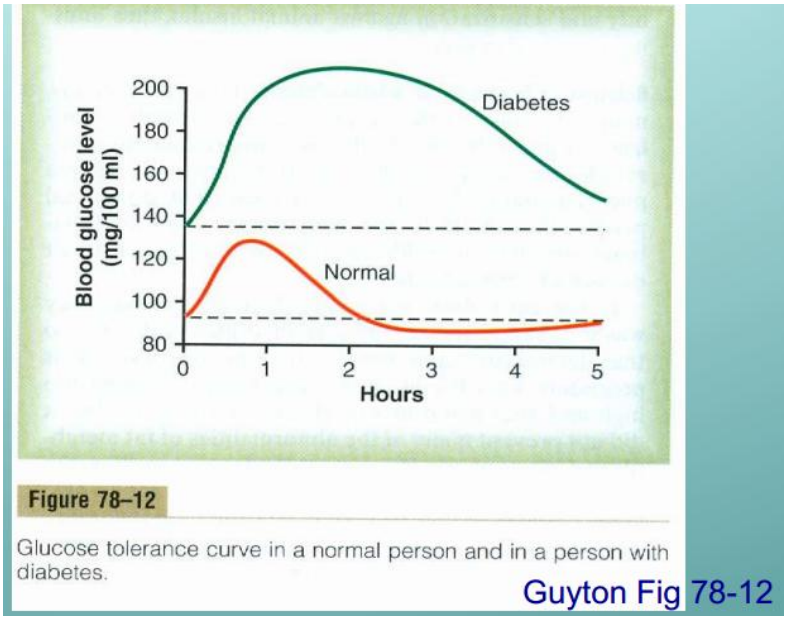
BIOM2012 Endocrinology Notes

Glucose homeostasis – body defends range of normal blood glucose levels

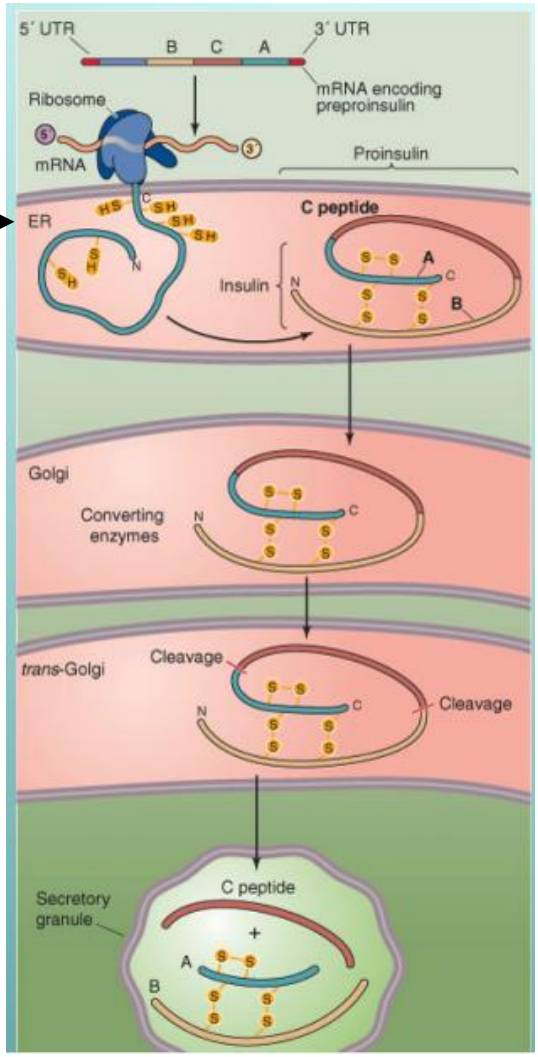
- Hyperglycaemia causes an osmotic pressure leading to cellular dehydration; whereas hypoglycaemia impairs cell function particularly in CNS and retina which depend only on glucose for energy
- Energy sources for tissues: carbs = 4.1kcal/g, lipid = 9.4kcal/g, protein=4.3kcal/g
- Glucose (carbs) – main energy source for neurons, (neurons cannot store glycogen, glia can) & adequate blood glucose levels needed for CNS function
- Glucose moves through cells through facilitated diffusion dependent on concentration gradients
  - GLUT transporters span 12 TM domains and ~500aa
  - GLUT1: all cells, (basal glucose uptake) blood brain barrier
  - **GLUT2:** pancreatic beta cells (plays role in insulin regulation) & liver (removes excess glucose from blood); insulin independent
  - GLUT3: neurons (basal glucose uptake) but in all cells
  - **GLUT4** (insulin sensitive): in muscle and fat cells, expression can be **upregulated by exercise**; amount in PM of muscle increases with exercise



- Hyperglycemia (high blood glucose levels) results in **osmotic diuresis** + other signs of diabetes
  - This is because the large increase in glucose in blood prevents the kidney's renal tubules from reabsorbing the extra glucose hence retained in the lumen, creating an osmotic pressure which retains water (as water movement follows glucose movement) in the lumen as well thus increasing urine volume
- Hypoglycaemia (low blood glucose levels) results in seizures, confusion, coma

- Pancreas – beta cells: controls insulin where insulin acts on liver, skeletal muscle and adipose tissue; anabolic & increases storage of glycogen, amino acids (proteins) and fatty acids (lipids)
    - Alpha cells control glucagon and glucagon acts on liver; impaired glucagon can be compensated (no diseased state); catabolic & mobilises glucose, amino acids and fatty acids
    - Delta cells produce somatostatin
    - Endocrine function of pancreas is located within islets of langerhans; reciprocal secretion of glucagon and insulin

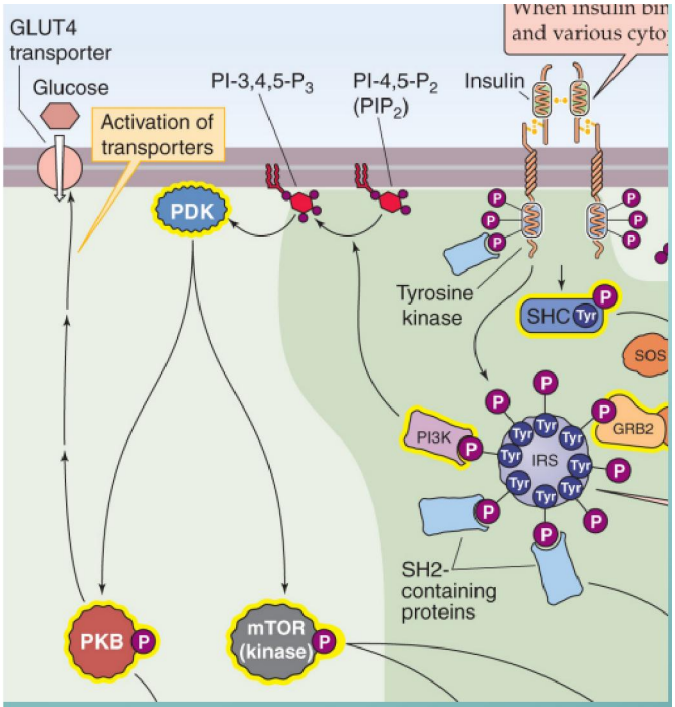
<u>Insulin synthesis in Beta cells</u> →



- Starts as insulin precursor – preproinsulin (newly synthesised polypeptide)
    - Signal peptide removed and folded after cotranslation translocation (disulfide bridges/bonds) = proinsulin consists of A, B chains and C peptide
    - C peptide (biologically inactive) removed = insulin (51aa)
    - Insulin stored in **secretory granules** and plasma half life of 5-10mins

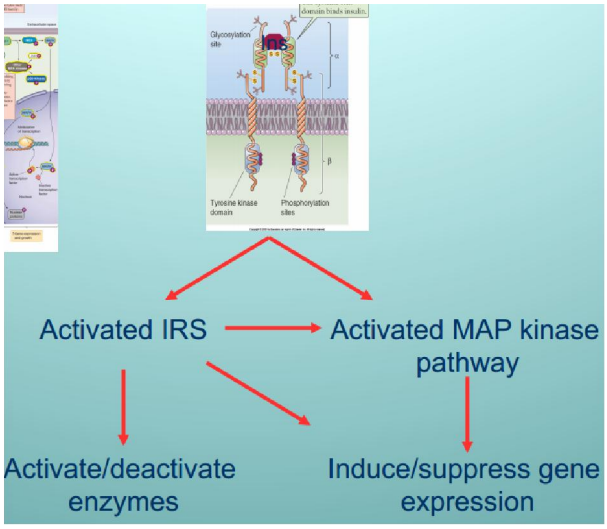
<u>Hormone actions on target cells – receptors</u>

- GPCRs: oxytocins, GHRH, somatostatin, dopamine
    - RTKs: insulin, IGF1
    - Cytokine: EPO, leptin, prolactin, GH
    - Steroid: oestrogen
- Insulin receptor – insulin binds, receptor activation/dimerisation, **autophosphorylation** on tyrosine domains (on intracellular domain of receptor), **activates tyrosine kinase** which further phosphorylates proteins that regulate target cell activity (downstream)
    - **IRS** = insulin receptor substrate bis a target for phosphorylation by tyrosine kinase
    - After IRS phosphorylation, IRS becomes a **docking site** for other

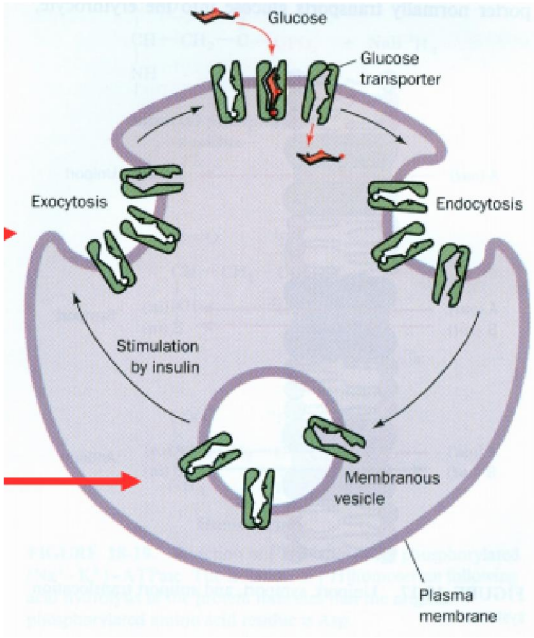


proteins (containing SH2 domain) and bind on the phosphorylated tyrosines of IRS

- After binding, PI3K is one pathway which activates PDK (PIP3 dependent protein kinase) leading to activation/phsophorylation of PKB
- After binding, other downstream pathways can also be activated

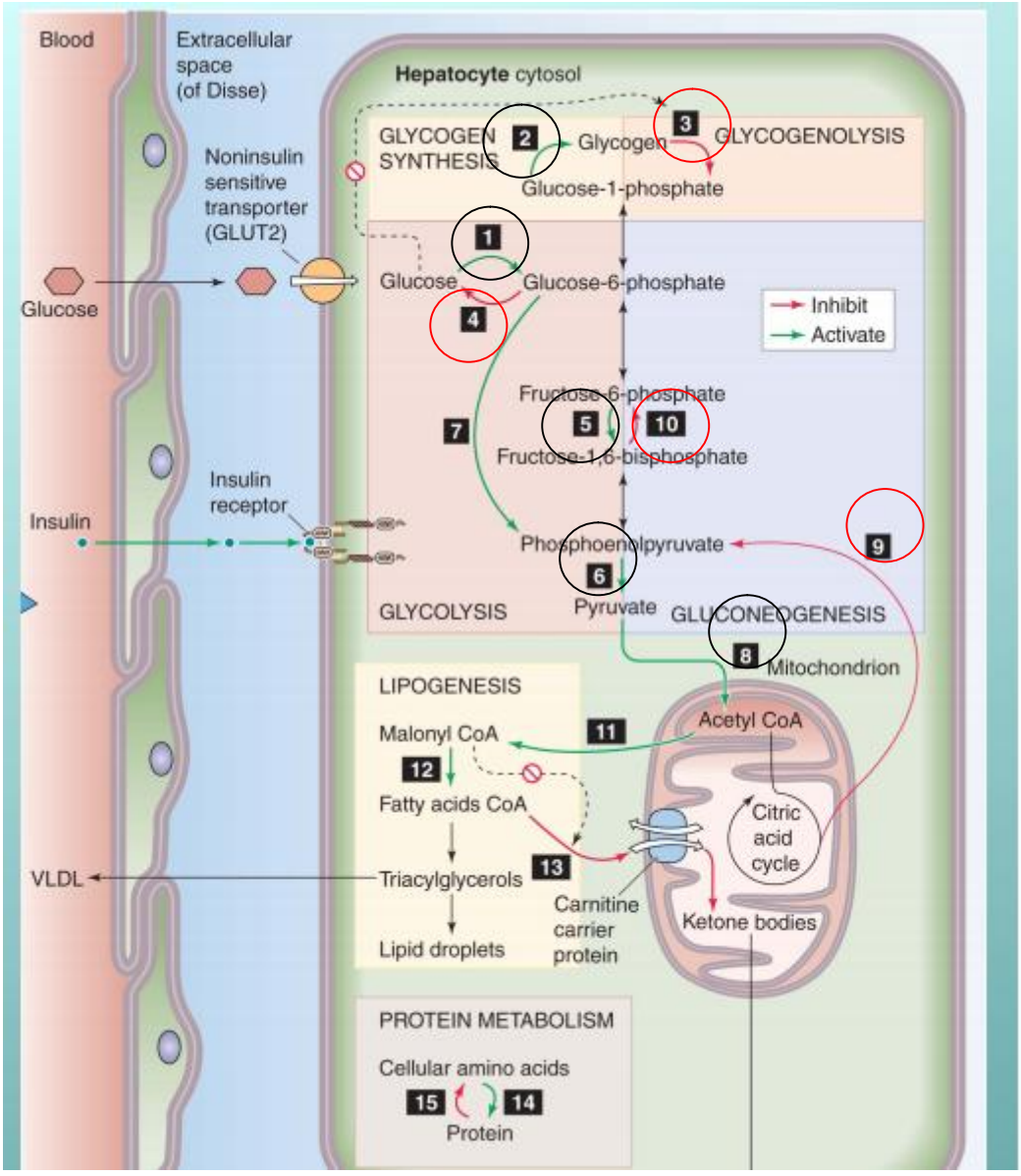


- Insulin stimulates glucose uptake by inducing **exocytosis of GLUT4** (transporters) in skeletal muscle and adipose tissue
  - Upon insulin stimulation: cytoplasmic vesicles containing GLUT4 undergo exocytosis to cell surface/membrane and transport glucose into cell
  - When insulin stimulation ends: receptors at cell PM undergo endocytosis to be recycled



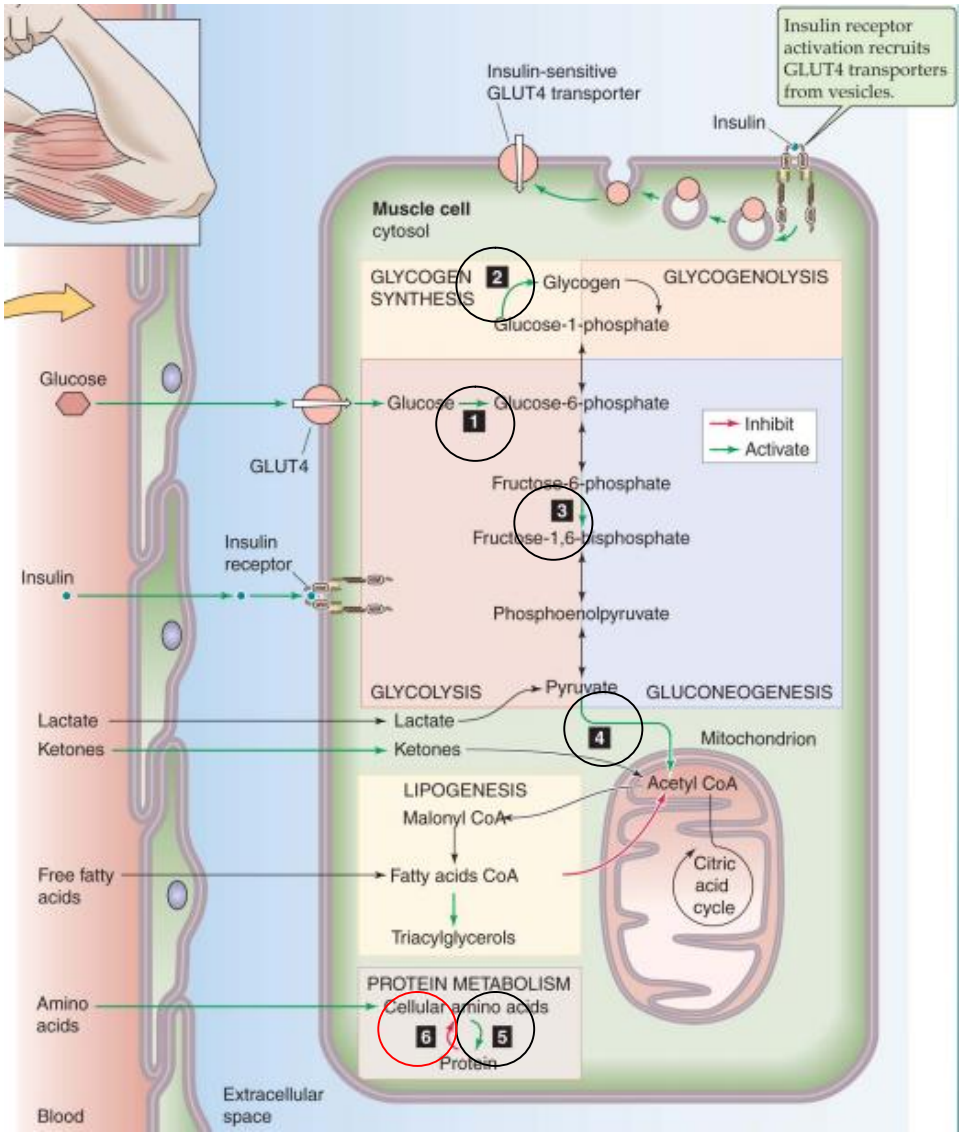
Insulin and it's effects on liver, muscle tissue & adipocytes

- Liver:
  - Promotes glycogen synthesis (glycogenesis): by enhancing glucose kinase transcription, increasing glucose kinase expression (1) and activating glycogen synthase (2)
  - Promotes glycolysis and oxidation: by increasing phosphofructokinase (5) and pyruvate kinase activity (6), stimulates pyruvate dehydrogenase (8)
  - Inhibits gluconeogenisis: by decreasing activity of PEPCK (9), FBPase (10), G6Pase (4)

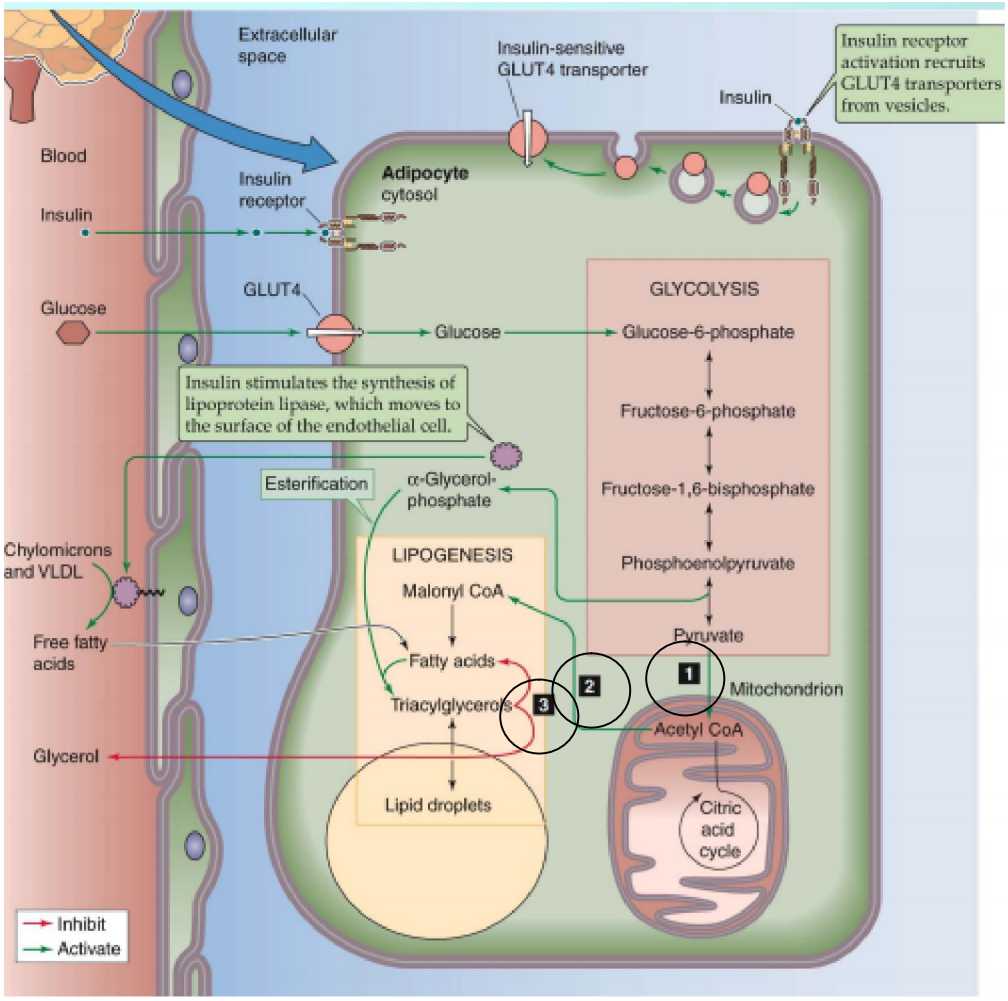


Promotes	Inhibits
Glycogen synthesis	Glycogen breakdown (glycogenolysis)
Glycolysis	Gluconeogensis
Protein synthesis	Protein breakdown
Lipid synthesis/storage	Lipid breakdown

- Muscle:
  - Promotes glucose uptake by GLUT4
  - Promotes glycogen synthesis: Increases, hexokinase activity (1) and activating glycogen synthase (2)
  - Promotes glycolysis and oxidation: increases activity of phosphofructokinase (3) and pyruvate dehydrogenase (4)
  - Promotes protein synthesis (5) and inhibits protein breakdown (6)
  - No gluconeogensis



- Adipocytes:
  - Promotes glucose uptake by GLUT4
  - Promotes glycolysis (which produces precursors for lipogenesis i.e. acetyl CoA) by stimulating pyruvate dehydrogenase (1) and acetyl CoA carboxylate (2); adipocytes store triglycerides in form of fat droplets
  - Inhibits hormone sensitive triglyceride lipase (3)
  - Promotes synthesis of LPL
  - promotes entry of fatty acids from blood into adipose



Control of insulin secretion

- high blood glucose (hyperglycemia) stimulates insulin secretion
  - concentration gradient drives glucose through GLUT2
  - glucose converted to intermediates then oxidised to ATP

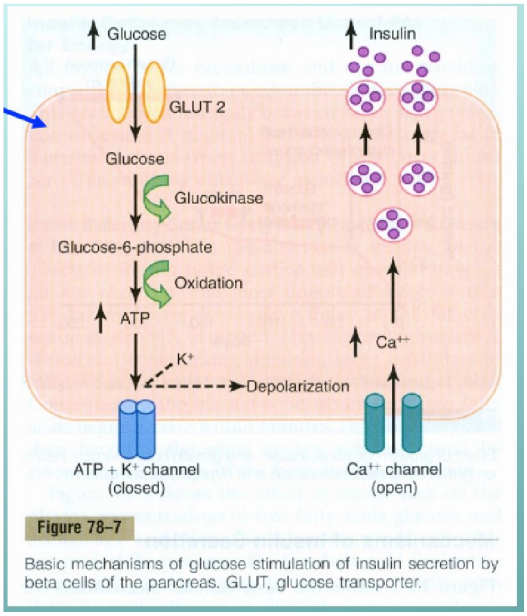


Figure 78–7

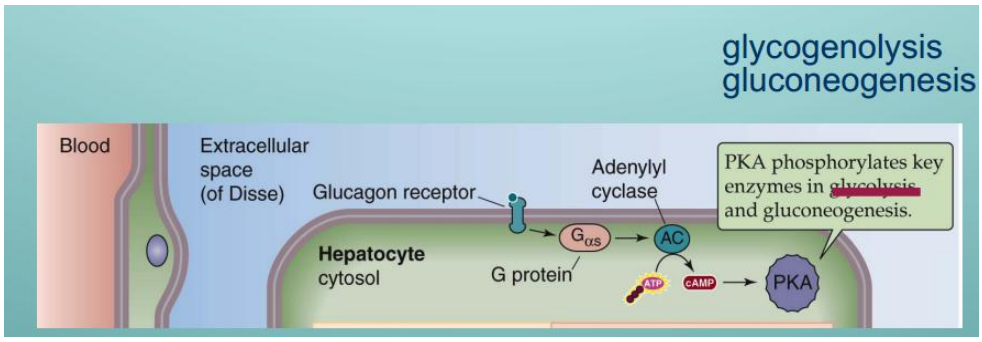
Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

- ATP induces closing of **ATP-sensitive potassium channels** and depolarisation of cell leading to opening of voltage gated calcium channels (on cell's PM) where influx of calcium causes calcium induced calcium release(on SR)
- Elevated intracellular calcium levels causes **exocytotic release of vesicles** with insulin

- Other control mechanisms include – stimulation induced by high blood amino acid (as insulin is responsible for transport of aa into tissues/storage in tissues i.e. important for utilisation of excess aa) and fatty acid levels
  - Stimulation also induced ANS (parasympathetic vagus nerve) whereas inhibited by sympathetic noradrenaline (alpha adrenoceptors)
  - Glucagon stimulates, somatostatin inhibits
  - GI hormones stimulate including: gastrin, secretin & gastric inhibitory peptide

<u>Glucagon receptor and actions</u>

- Prevents blood glucose levels form falling too low
- Functional antagonist of insulin
- Major site of action is **liver and adipose tissue**
- Stimulates catabolism to increase blood glucose levels
- 29 aa and secrets by alpha cells of islets of langerhans
- Glucagon receptor – GPCR (signals through AC, cAMP) and primarily in hepatocytes



- Actions:

Carbs	Lipids	Proteins
Inhibits glycogen synthesis	Promotes lipolysis	Inhibits hepatic portal synthesis
Promotes gylcogenolysis	Inhibits triglyceride synthesis	Promotes degradation of hepatic portal protein
Stimulates gluconeogenesis	Enhances ketogenesis	Stimulates gluconeogenesis

Overall: increase hepatic glucose production, release thus increasing blood glucose levels	Overall: increases blood fatty acids and ketone bodies	Overall: no effect on blood aa levels