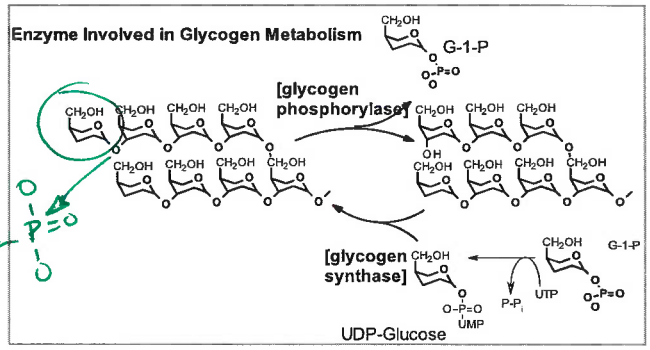
Lecture 31: Hormonal Regulation of Glucose/Glycogen Metabolism:

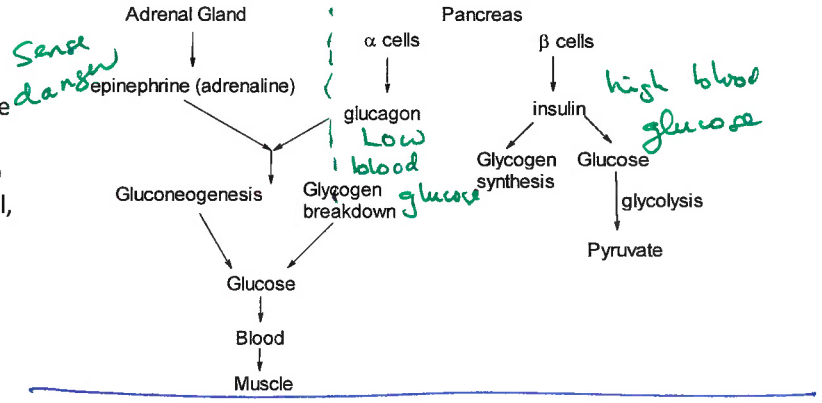
1. Regulation makes physiological sense.
2. Opposing pathways are coordinately regulated (if one is on, other is off, both can also be off).

Overview of Regulation in Liver Cell:

1. Liver responds to the energy needs of the organism, with coordinated regulation of glycolysis, gluconeogenesis, and glycogen metabolism, as follows.
   i. Low blood glucose:
   - Enzymes become phosphorylated.
     - Glycogen degraded – releasing glucose.
     - F26P levels drop, glycolysis off, gluconeogenesis on, making glucose.

   ii. High blood glucose causes:
   - Enzymes to become dephosphorylated
     - glucose stored in glycogen.
     - F26P levels become high, allowing glycolysis to oxidize glucose.
2. Glycolysis and gluconeogenesis also respond to energy needs of the cell, i.e. ATP, ADP, AMP levels, provide hormonal signals are met.





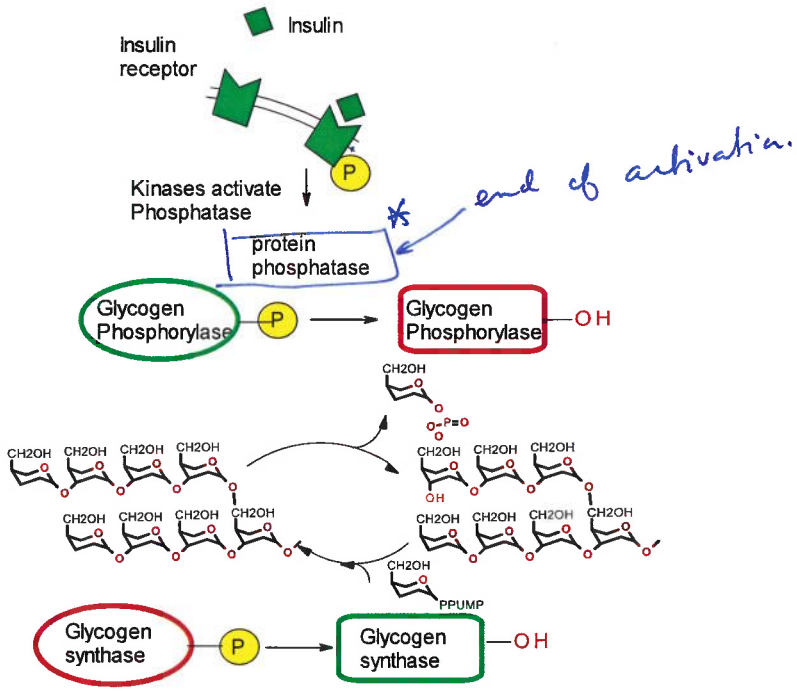
Hormonal Control of Pathways:

High Blood Sugar:

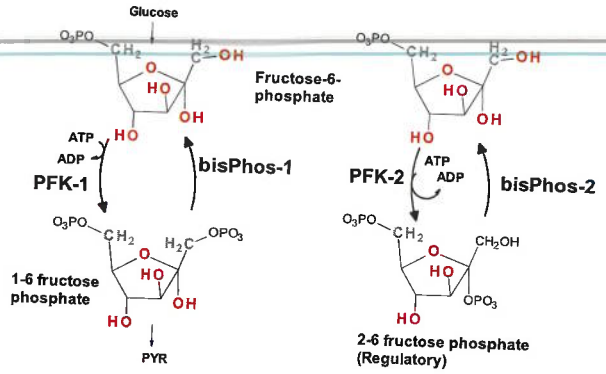
- Secretion of **insulin** from the β-cells pancreas occurs when blood glucose levels are high. This ultimately leads to the **dephosphorylation** of many enzymes. Glycogen is synthesized to store excess glucose. Glucose can be used for energy (ATP) production (if needed).

Steps:

1. Insulin released by β-cells in pancreas
2. Insulin binds to insulin receptor in cell membrane.
3. Conformational change in receptor activates tyrosine kinases as the initial signal in the cell.
4. Signal transduction pathway ultimately results in activation of protein phosphatases.
5. Many enzymes are dephosphorylated. **glycogen synthase becomes active,** leading to the synthesis of glycogen.



Hormonal Regulation of Glycolysis/Gluconeogenesis in the liver by F-2,6P Levels.



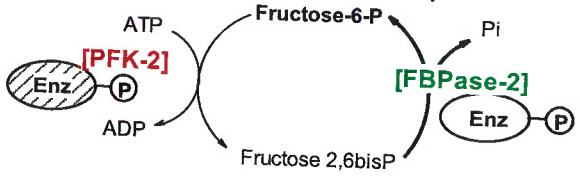
	Low blood Glucose	High blood Glucose
Protein Phosphorylation	HIGH	LOW
F2,6P levels	LOW	HIGH
Glycolysis	OFF	ON
Gluconeogenesis	ON	OFF

Chormonal control ① + energy sensing ②

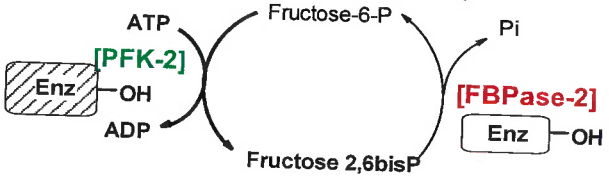
- Glycolysis/gluconeogenesis use PFK-1 and bisphosphatase 1 to interconvert F6P and F16P – most of the fructose is used in these pathways.
- F26P is made and destroyed by PFK-2 and bisphosphatase 2, small amounts are used to make F26P.

Regulation of F26P Levels by Enzyme Phosphorylation (Hormonal)

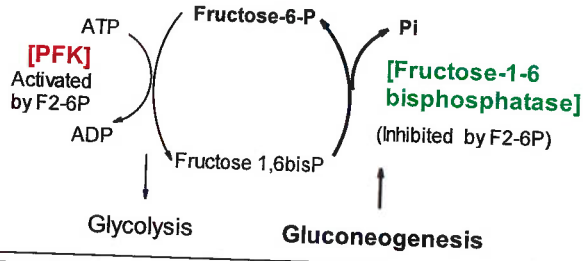
Low Blood Glucose → low F2,6P (Enzymes phosphorylated)

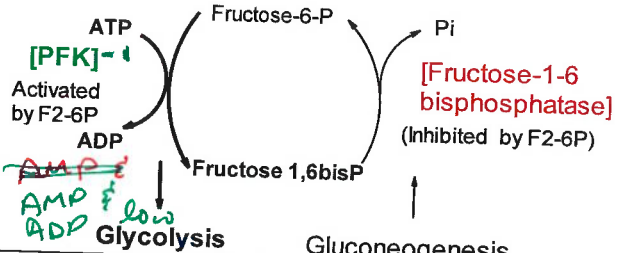


High Blood Glucose Levels → high F2,6P (Enzymes dephosphorylated)

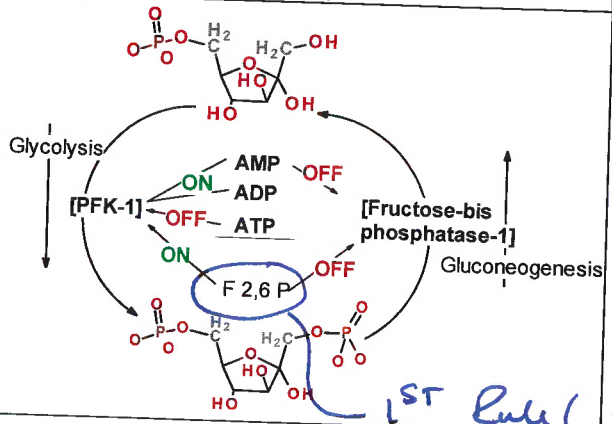


Regulation of Glycolysis and Gluconeogenesis by F26P





Regulation of PFK-1/bisPhosphatase



Key Points

Low Glucose – enzyme phosphorylation.
- F-2,6 P – levels drop
- Glycolysis off
- gluconeogenesis on, if ATP is avail.

High Glucose – enzymes dephosphorylated
- F-2,6 P – levels rise
- Glycolysis on, unless there is excess ATP
- gluconeogenesis off

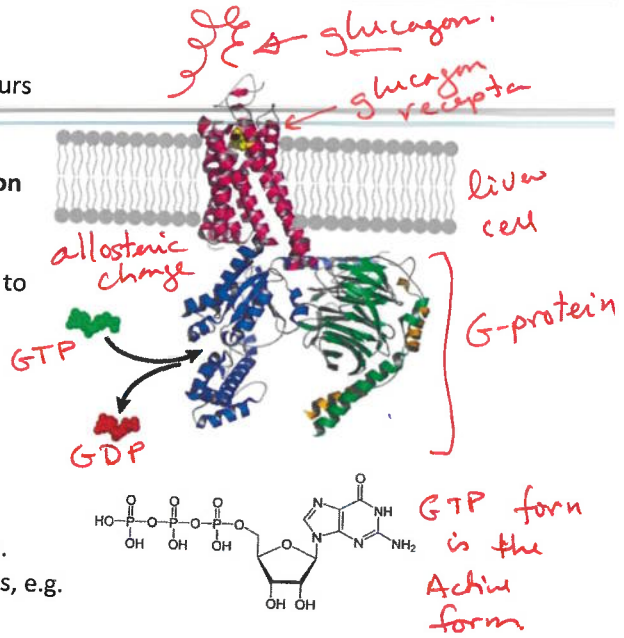
F-2,6-P levels follow blood glucose levels.

F-2,6-P is absolutely required for PFK to be on (see velocity curves, next page).

2nd Rule (energy sensing)

Low Blood Sugar or Epinephrine:

- Secretion of **epinephrine** (also known as adrenaline) occurs during dangerous situations, indicative of high energy needs. Secretion of epinephrine is under control of the central nervous system. This leads to the **phosphorylation** of many enzymes.
- Secretion of **glucagon** from the α- cells in the pancreas occurs when blood glucose levels are low. This also leads to the **phosphorylation** of many enzymes.



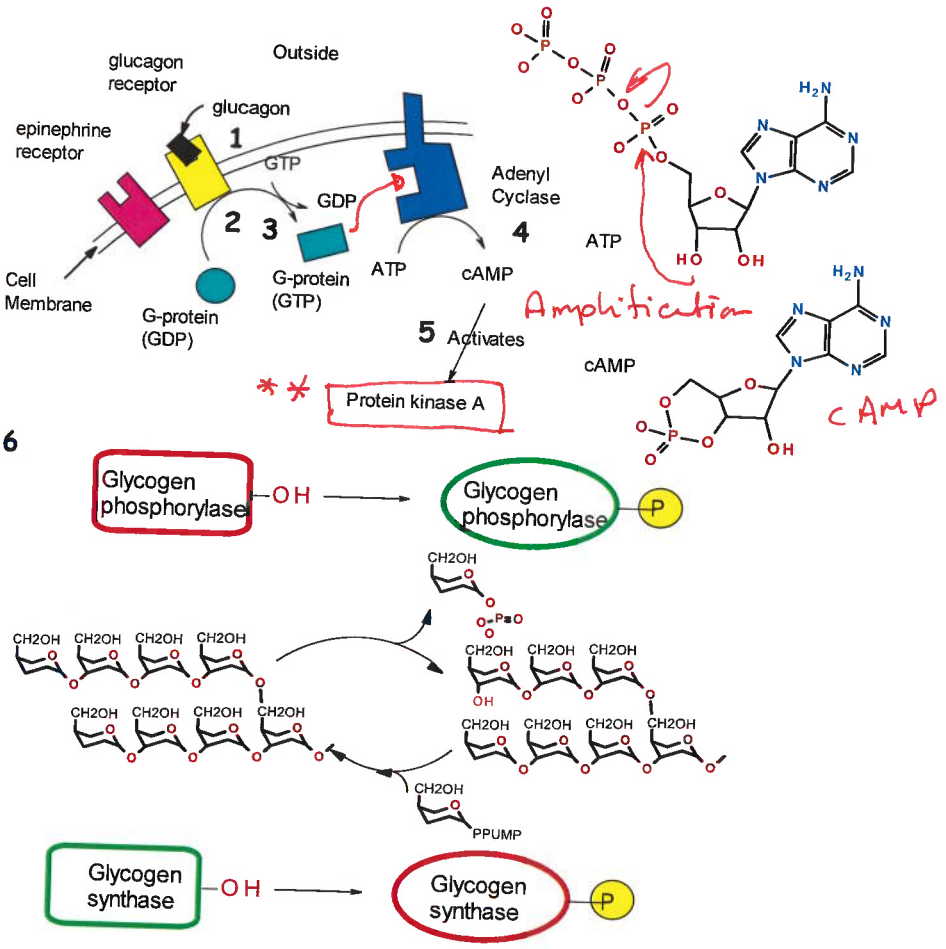
GTP form is the Active form

G-Protein Coupled Receptors:

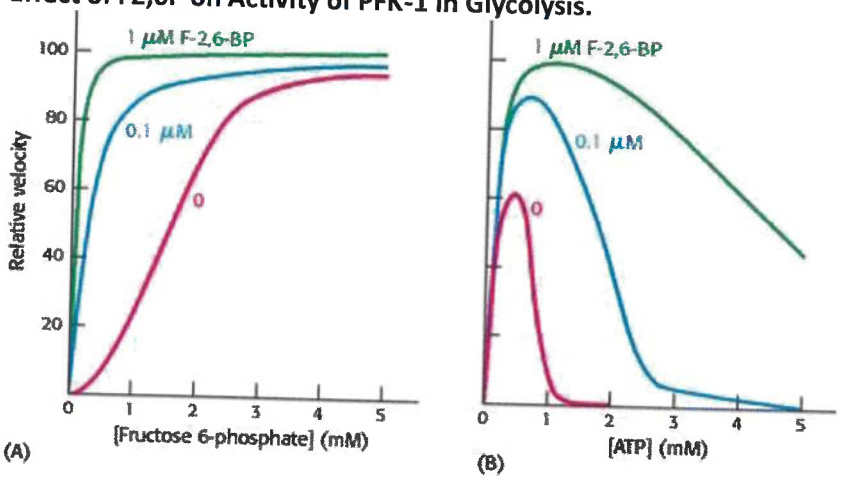
- Conformational change in receptor due to ligand binding.
- Conformation change causes exchange of GDP with GTP.
- Conformational change in G-protein due to GDP/GTP exchange, leading to activated (GTP bound) G-protein.
- Activated G-proteins will activate down-stream targets, e.g. adenyl cyclase.

Overall Process:

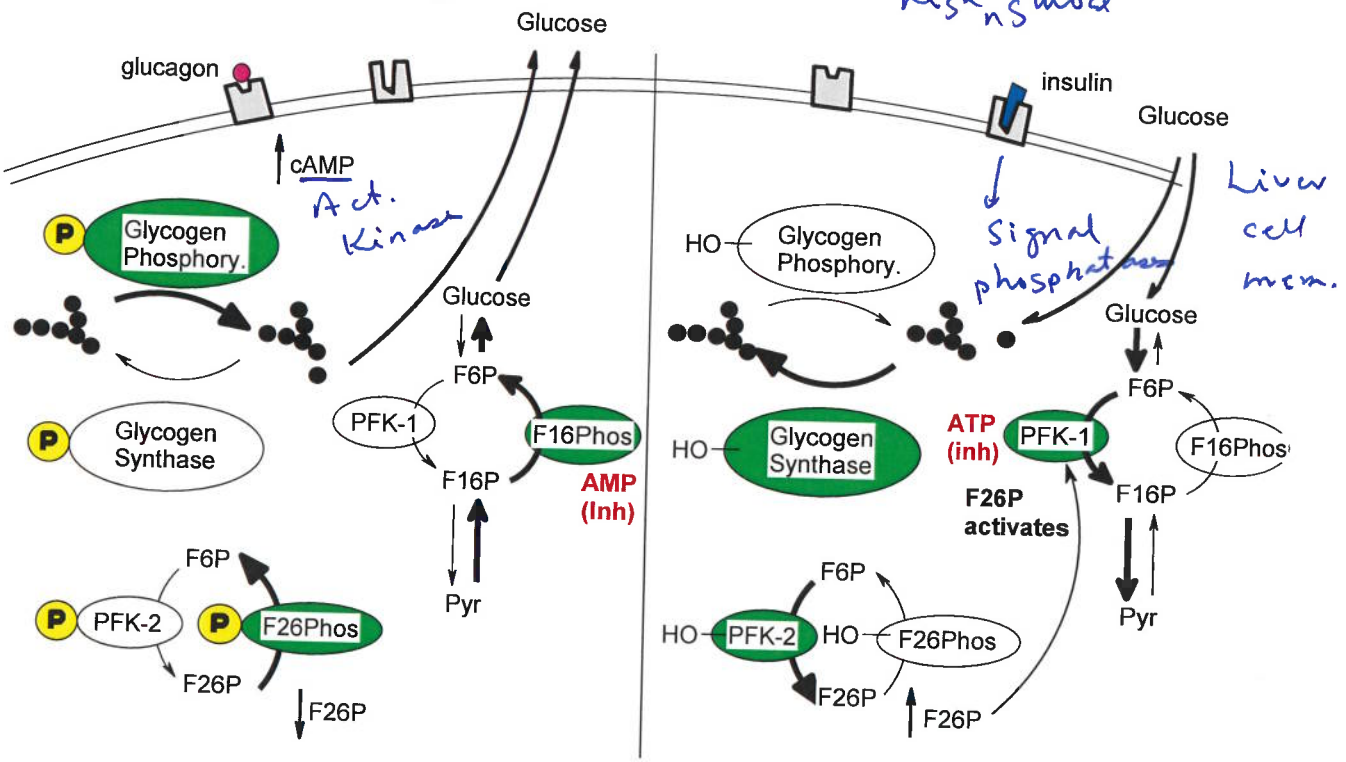
1. Glucagon and/or epinephrine bind to G-protein coupled receptors on the surface of the cell.
2. The Binding of ligand to receptor generates a binding site for G-protein/GDP complex inside the cell via allosteric changes, thus transmitting the signal across the membrane.
3. Receptor-G-protein interaction exchanges GDP for GTP, G-protein-GTP complex binds to Adenylate cyclase, activating it, also by an allosteric change.
4. Adenylate cyclase converts ATP to cAMP. cAMP is called a *'2nd messenger'*. Each receptor binding event produces 1000-2000 molecules of cAMP. G-protein/GTP complex decays to GDP complex, ending cAMP synthesis unless hormones are still present.
5. cAMP activates **protein kinase A.**
6. Protein kinase A activation results in the phosphorylation of several target enzymes, activating glycogen phosphorylase.

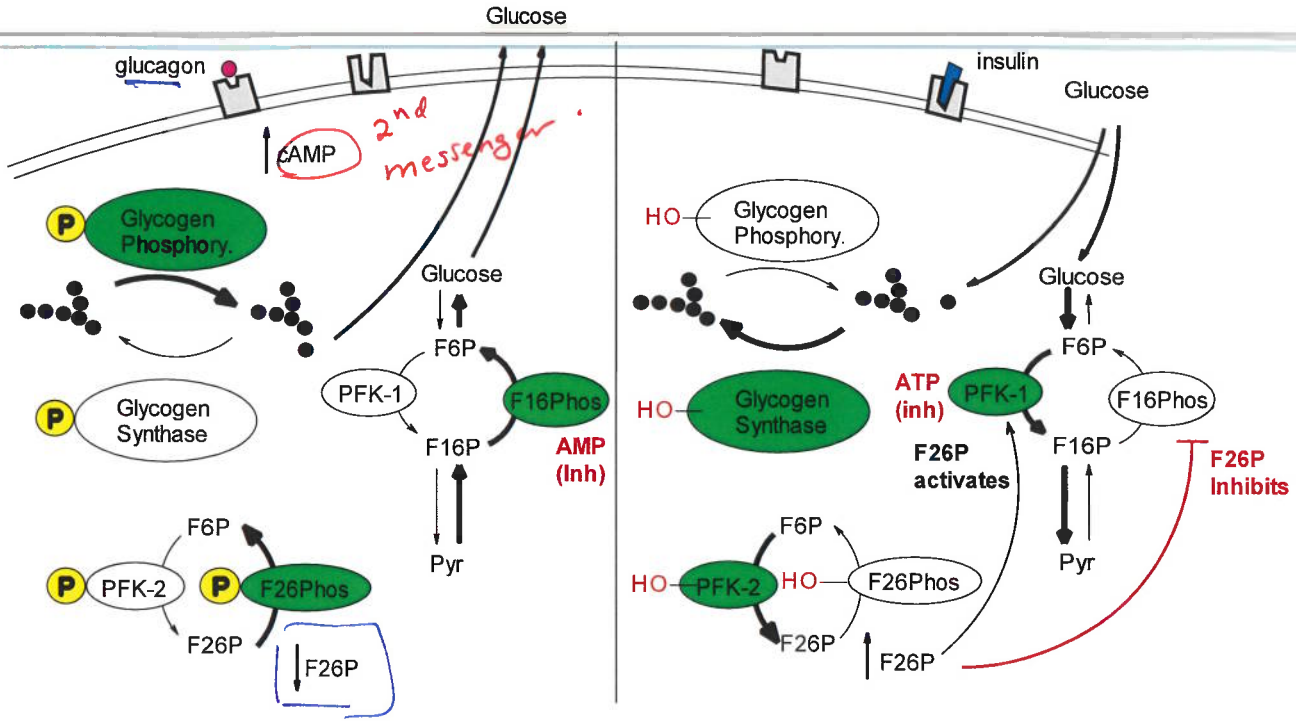


Effect of F2,6P on Activity of PFK-1 in Glycolysis.



Summary: low blood glucose





Outline the steps that would occur under the following scenario:
You haven't eaten properly today so your blood glucose level is low. However, The ATP levels in the liver are high.

low blood glucose ATP high.

1. What hormone is released? glucagon. Why?

2. How does this change the phosphorylation state of enzymes?

phosphorylation (protein kinases activated)

3. This activates glycogen phosphorylase, causing the (release/storage) of glucose from/to glycogen.

4. The levels of F26P drop because:

F26P → F6P
activated F26 phosphatase.

5. Glycolysis is _____ (on/off) because

PFK requires F26P for activity. F26P low ∴ PFK is off.

6. Gluconeogenesis is _____ (on/off) because

Potentially. ON F26P levels are low is ON because ATP is high.