Lecture 31: Hormonal Regulation of Glucose/Glycogen Metabolism (liver):

The Rules:
1. Regulation makes physiological sense.
2. Opposing pathways are coordinately regulated (if one is on, the other is off)
3. Low blood glucose:
   - Enzymes become phosphorylated.
     - F26P levels drop, glycolysis off, gluconeogenesis on, making glucose.
     - Glycogen degraded - releasing glucose.
4. High blood glucose causes:
   - Enzymes to become dephosphorylated
     - F2-6P levels become high, allowing glycolysis to oxidize glucose.
     - glucose stored in glycogen.

Hormonal Control of Pathways:
- 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.
- Secretion of insulin from the β-cells pancreas occurs when blood glucose levels are high. This leads to the dephosphorylation of the enzymes that were phosphorylated due to epinephrine or glucagon.

High Blood Sugar: Proteins dephosphorylated - Glycogen synthesized, Glucose used for energy 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.

Enzyme Involved in Glycogen Metabolism

Level of F26P controlled by hormones

LUDP-Glucose
Low Blood Sugar or Epinephrine: Proteins phosphorylated.

Review of G-Protein Coupled Receptors:
- Conformational change in receptor due to ligand binding.
- Conformational change in G-protein due to GDP/GTP Exchange, leading to activated (GTP bound) G-protein.

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 Adenylyl cyclase, activating it, also by an allosteric change.
4. Adenylyl 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 a number of target enzymes.

Caffeine: One of its many effects is to inhibit the breakdown of cAMP, enhancing sugar release from glycogen.
### Effect of Phosphorylation/Dephosphorylation on Glycogen Metabolism

<table>
<thead>
<tr>
<th>Low Glucose = Glucose Demand</th>
<th>High Glucose Levels</th>
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</thead>
<tbody>
<tr>
<td>Glycogen phosphorylase</td>
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<tr>
<td>Glycogen synthase</td>
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### Regulation of Glycolysis/Gluconeogenesis in the liver by F-2,6P Levels.

- Glycolysis/gluconeogenesis use PFK-1 and bisphosphatase 1 to interconvert F16P and F6P
- F26P is made and destroyed by PFK-2 and bisphosphatase 2.

<table>
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<th>Low Blood Glucose</th>
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<tbody>
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#### Glycolysis
- **Low Blood Glucose** → low F,2,6P (Enzymes phosphorylated)
- **High Blood Glucose Levels** → high F,2,6P (Enzymes dephosphorylated)

#### Gluconeogenesis
- **Low Blood Glucose** → low F,2,6P (Enzymes phosphorylated)
- **High Blood Glucose Levels** → high F,2,6P (Enzymes dephosphorylated)
Regulation of PFK-1/bisPhosphatase by energy sensing and F26P (hormonal control)

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.

Summary:

Glucose

Glycogen Phosphorylase

Glycogen Synthase

PFK-2

PFK-1

F26P

AMP

ATP

F6P

Pyr

AMP (inh)

ATP (inh)

Glucose

F26P

Glucagon

cAMP

insulin

Low glucose → phosphorylation

Low glucose → low F26P