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, 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.

A. 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.

B. Molecular events that lead to protein phosphorylation/dephosphorylation

Low Blood Sugar or Epinephrine: Proteins phosphorylated.
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 "second 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
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.

**High Blood Sugar:** Proteins dephosphorylated- glycogen synthesized, glycolysis (if needed). To reverse the above effects the proteins above are de-phosphorylated. Thus occurs in two steps:
1. cAMP levels drop since they are no longer elevated due to absence of glycogen and/or epinephrine. Caffeine inhibits the decay of cAMP.
2. A protein phosphatase is activated leading to loss of phosphate groups. Glycogen synthase becomes active, leading to the synthesis of glycogen.

C. Regulation by Energy sensing (AXP) and Hormones (via F-26P)

Hormonal Regulation of Glycolysis/Gluconeogenesis in the liver by F2,6P levels.

- Glycolysis/gluconeogenesis use PFK-1 and bisphosphatase 1 to interconvert F16P and F6P
- F26P is made and destroyed by PFK-2 and fructose Bisphosphatase 2.
- Fructose Bisphosphatase 2 is active when phosphorylated (low glucose), inactive when dephosphorylated (high glucose)
- PFK-2 is active when dephosphorylated (high glucose), inactive when phosphorylated. (low glucose)
F2,6 Allosteric regulation of Glycolysis and Gluconeogenesis

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

[Fructose-1-6 bisphosphatase] (inhibited by F2-6P)

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

[Fructose-1-6 bisphosphatase] (inhibited by F2-6P)

Regulation of PFK-1/bis phosphatase by energy sensing and F26P

Glycolysis

AMP

ON

OFF

[PKF-1]
Activated by F2-6P

ADP

ATP

[Fructose-bis phosphatase-1]

Gluconeogenesis

ON

OFF

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Summary:

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<tr>
<td>Glycogen breakdown</td>
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low blood sugar

Glucose

glucagon → cAMP

Glycogen Phosphor.

Glycogen Synthase

PFK-1

F6P

AMP (Inh)

F16Phos

Pyr

F26Phos

PFK-2

F6P

F26P

F16P

insulin

Glucose

Glycogen Phosphor.

Glycogen Synthase

ATP (inh) F26P activates

F16Phos

Pyr

F26Phos

F16P