**Lecture 31: Hormonal Regulation of Glucose/Glycogen [Liver]**

**Glycogen Metabolism:**

**The Rules:**

1. Regulation makes physiological sense.



2. Opposing pathways are coordinately regulated (if one is on, other is off)

3. Low blood glucose (or request for additional glucose) causes:

* Enzymes become phosphorylated via hormone signal. Directly affecting glycogen metab.
* F2-6P levels become low due to enz. Phosphorylation (F2-6P follows glucose levels), affecting glycolysis/gluconeogenesis.

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.

**Molecular events that lead to protein:**

**Phosphorylation Dephosphorylation**

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**A. 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 *'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 the following targets related to glycogen metabolism, resulting in the breakdown of glycogen to glucose-1-phosphate.

a. **glycogen synthase** (inactivating it)

b. **glycogen phosphorylase**, activating it, leading to glycogen breakdown.

**B. High Blood Sugar:** Proteins dephosphorylated -Glycogen synthesized, Glucose used for energy production (if needed).



To reverse the above effects we need to de-phosphorylate the proteins that were phosphorylated in the above reactions. 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.

**Control of Glycogen Metabolism:** Glycogen synthesis and degradation is **directly** controlled **by protein phosphorylation**.

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| **Low Glucose** | **High Glucose Levels** |
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| **A. Regulation of PFK-1/bisPhosphatase by energy sensing and F26P** | **B. Regulation of glycogen synthesis & degradation by enzyme phosphorylation.** |
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**C. Regulation of Glycolysis/Gluconeogenesis in the liver by F-2,6P Levels.**



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|  | **Low blood Glucose** | **High blood Glucose** |
| **Protein Phosphorylation** | **HIGH** | **LOW** |
| **F2,6P levels** | **LOW** | **HIGH** |
| Glycolysis |  |  |
| Gluconeogenesis |  |  |

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| **Low Blood Glucose → low F2,6P**  **(Enzymes phosphorylated)** | **High Blood Glucose Levels → high F2,6P**  **(Enzymes dephosphorylated)** |
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| **F2,6 Allosteric regulation of Glycolysis and Gluconeogenesis** | |
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F2-6P is required for glycolysis to be active in the liver. If f26P levels are low (glucose demand) the liver will not undergo glycolysis.