Lecture 31: Energy Sensing & Hormonal Regulation of Glucose/Glycogen Metabolism:

Overview:
1. Regulation makes physiological sense.
2. Opposing pathways are coordinately regulated (if one is on, other is off, both can also be off).
3. 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.
4. 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 leads to the dephosphorylation of the enzymes. Glycogen synthesized, Glucose released to the blood and 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.
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.

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.

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.

Glycogen phosphorylase

Glycogen synthase

OH

OH

P

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

<table>
<thead>
<tr>
<th></th>
<th>Low blood Glucose</th>
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</thead>
<tbody>
<tr>
<td><strong>Protein Phosphorylation</strong></td>
<td>HIGH</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>F-2,6P levels</strong></td>
<td>LOW</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Glycolysis</strong></td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td><strong>Gluconeogenesis</strong></td>
<td>ON</td>
<td>OFF</td>
</tr>
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- 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**

- ATP is hydrolyzed to produce energy for cellular activities, generating ADP + inorganic phosphate (Pi).
- ATP levels are kept relatively constant so that enzymes that require ATP can function properly; however AMP and ADP levels can change dramatically.
- ADP is converted to ATP by the enzyme adenylate kinase, producing AMP as well.
- ATP is re-synthesized from ADP by oxidation of glucose and other carbons sources.
Warm-up: You just consumed a Hershey’s kiss. The increase in glucose in your blood will cause the production of the hormone insulin from the pancreas, leading to dephosphorylation of many enzymes. This activates glycogen synthase and inhibits glycogen phosphorylase. The levels of F26P will increase allowing glycolysis to occur if the cell needs ATP.

Regulation of Glycolysis/Gluconeogenesis by Energy Sensing:
- ATP is hydrolyzed to produce energy for cellular activities, generating ADP and inorganic phosphate (P). 
- ATP levels are kept relatively constant so that enzymes that require ATP can function properly; however AMP and ADP levels can change dramatically. 
- ADP is converted to ATP by the enzyme adenylate kinase, producing AMP as well. 
- ATP is re-synthesized from ADP by oxidation of glucose and other carbon sources.

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<th>A cell has HIGH energy reserves when:</th>
<th>Glycolysis (Glucose→Pyr)</th>
<th>Gluconeogenesis (Pyr→Glucose)</th>
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<tbody>
<tr>
<td>ATP High</td>
<td></td>
<td>ON</td>
</tr>
<tr>
<td>AMP, ADP Low</td>
<td>Glycolysis (Glucose→Pyr)</td>
<td>Gluconeogenesis (Pyr→Glucose)</td>
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<td>Off</td>
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Glycolysis - Allosteric control of PKF-1 by AMP, ADP, ATP

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<tr>
<th>T-state stabilized by ATP</th>
<th>R-state stabilized by ATP</th>
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Gluconeogenesis - Control of fructose bisphosphatase-I by AMP bisphosphatase

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Regulation of PKF-1/bisPhosphatase by F26P (hormonal control) and energy sensing.

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 PKF to be on.
Summary: Liver cell

Deamond for glucose

Excess blood glucose

Hormone

Glucagon

Glucose

cAMP

Glycogen Phosphory.

Glycogen Synthase

PFK-1

F6P

AMP (inh)

Glycogen Phosphory.

Glycogen Synthase

PFK-2

F26Phos

F26Phos

F26Phos

F6P

F16Phos

F6P

F16P

F26P

Pyr

Regulation - Allosteric

i) Non-covalent (ligand)

T

E

binding site

R (Active)

ii) Covalent

T

E

ATP

Kinase

ADP

R

Phosphate

Thr

Ser

Tyr

any other

Non activated

Activated

Levels are controlled by phosphorylation and by hormones.