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Due to the overlapping nature of the material covered in Lectures 24 and 25, one study guide is provided that covers both lectures.

**Lecture 24 Glycolysis Objectives**

- List the names in order of all the glycolytic enzymes, reaction intermediates and products.
  - This includes knowing which steps utilize and produce ATP and NADH
  - You do not need to memorize structures, but you should know which intermediates have six carbons and which have three carbons. Knowing where the intermediates are in the pathway will tell you the number of carbons. Any intermediate before step 4 has six carbons and any intermediate after has three carbons.

- Explain how ATP and NADH are produced during glycolysis.

- Describe the mechanisms that regulate glycolysis, including the roles of isozymes, covalent modification, allosteric regulation, fructose 2,6-bisphosphate, and the hormones glucagon, insulin, and epinephrine.

- Discuss the mechanisms of action for each of the poisons discussed.

**Lecture 25 Gluconeogenesis Objectives:**

- Describe the role of gluconeogenesis for glucose production in the liver and kidney and its relevance to glucose homeostasis.

- Explain how the three bypass reactions in gluconeogenesis circumvent the three irreversible reaction in glycolysis.

- List in order the names of the enzymes, intermediates, and products of the three gluconeogenic bypass reactions.
  - You should know what compounds are glucogenic. Acetyl CoA is not glucogenic.

- Explain the mechanisms that regulate gluconeogenesis, including the roles of isozymes, covalent modification, fructose 2,6-bisphosphate, and the hormones glucagon, insulin, and epinephrine.
Hormonal Regulation of Glucose Metabolism

You are required to know the effects of glucagon, insulin and epinephrine on glucose metabolism.

One approach would be to learn the overall effect of the hormones on each pathway, e.g. glucagon stimulates gluconeogenesis in the liver. This knowledge should then provide a rationale for learning how the hormone has that effect, e.g. glucagon decreases fructose 2,6-bisphosphate in the liver. If you start with knowing what the outcome will be, it will be easier to understand how it happens. Remember that glucose homeostasis is really about the utilization and storage of energy.

- **Glucagon**
  - Secreted by the pancreas
  - Liver main target tissue
  - Signals low blood glucose
  - Increases cAMP by the adenylate cyclase reaction
  - Decreases fructose 2,6-bisphosphate levels
  - Decreases glycolysis and glycogen synthesis
  - Increases gluconeogenesis and glycogen degradation
  - Leads to accumulation and export of glucose

- **Insulin**
  - Secreted by the pancreas
  - Signals high blood glucose
  - Decreases cAMP by stimulating cAMP breakdown
  - In liver:
    - increases fructose 2,6-bisphosphate levels
    - increases glycolysis and glycogen synthesis
    - decreases gluconeogenesis and glycogen degradation
  - In muscle:
    - increases glucose entry into cells
    - increases glycogen synthesis
  - Increases the pentose phosphate pathway
  - Leads to reduction in glucose concentration

- **Epinephrine**
  - Muscle primary target, but can also target liver
  - Signals impending activity – “Fight or flight response”
  - Increases [cAMP] by the adenylate cyclase reaction
  - In muscle, signals for energy production:
    - stimulates glycogen degradation to glucose
    - increases fructose 2,6-bisphosphate levels which increases glycolysis
  - In liver, signals for glucose export:
    - stimulates glycogen degradation to glucose
    - decreases fructose 2,6-bisphosphate levels which decreases glycolysis and increases gluconeogenesis
Fructose 2,6-bisphosphate

- Fructose 2,6-bisphosphate is an important regulatory molecule in glycolysis and gluconeogenesis.

- Fructose 2,6-bisphosphate is an allosteric activator of phosphofructokinase-1 (AKA 6-phosphofructo-1-kinase) and an allosteric inhibitor of fructose 1,6-bisphosphatase.

- Thus, increased fructose 2,6-bisphosphate stimulates glycolysis and decelerates gluconeogenesis.

- Fructose 2,6-bisphosphate is NOT an intermediate in glycolysis or gluconeogenesis and cannot substitute for fructose 1,6-bisphosphate.

- Fructose 2,6-bisphosphate is produced by the phosphorylation of fructose 6-phosphate. The reaction is catalyzed by 6-phosphofructo-2-kinase (AKA phosphofructokinase-2).

- The hormonal regulation of fructose 2,6-bisphosphate production varies between liver and muscle tissue due to different isozymes of the phosphofructokinase-2/fructose 2,6-bisphosphatase bifunctional enzyme.
  - In the liver, phosphorylation of phosphofructokinase-2/fructose 2,6-bisphosphatase results in decreased levels of fructose 2,6-bisphosphate.
  - In muscle, phosphorylation of phosphofructokinase-2/fructose 2,6-bisphosphatase results in increased levels of fructose 2,6-bisphosphate.

Figure 1. Schematic of the impact of glucagon, insulin, and epinephrine on glycolysis, gluconeogenesis, glycogen degradation, and glycogen synthesis. Arrows depict the direction of glucose metabolism as a result of the three hormones shown.

**Hormonal Regulation of Glucose Metabolism**

Glycogen degradation

**Glycogen** ↔ Glucose ↔ **Glycogen synthesis**

<table>
<thead>
<tr>
<th>Glycolysis</th>
<th>Energy</th>
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<tbody>
<tr>
<td>Glucose ↔</td>
<td></td>
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**Gluconeogenesis**

<table>
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<th>Energy</th>
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**Glucagon (Liver)**

Glycogen → Glucose → Energy

**Insulin (Liver and Muscle)**

Glycogen ↔ Glucose → Energy

**Epinephrine (Liver and Muscle)**

Glycogen → Glucose ↔ (Muscle) → (Liver) → Energy