Regulation of Cellular Respiration

Uncoupling Proteins

Uncoupling proteins (UCP) in inner mitochondrial membrane of mammals:

- Allow some H+ leakage, bypassing ATP-synthesis.
- Burn fuel stores without generating ATP.
- May be important in regulating % body fat.
- May also be important in reducing formation of dangerous reactive oxygen species (ROS).
- H+ leakage is activated by O2–.

\[
\text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} + \frac{1}{2}\text{O}_2
\]

In brown (thermogenic) fat, UCP1 causes heat generation by burning high-caloric lipid fuel without producing ATP.

Feedback Inhibition Control of Respiration

\[\triangleup\text{ATP} \rightarrow \text{inhibits F}-6\text{-P-kinase} \quad \therefore \quad \text{F}-6\text{-P} \rightarrow \text{back to G}-6\text{-P} \rightarrow \text{alternate pathway} \rightarrow \text{G}-1\text{-P} \rightarrow \text{glycogenesis}
\]

\[\triangleup\text{ATP} \rightarrow \text{inhibits Krebs Cycle enzymes} \quad \therefore \quad \text{acetyl-CoA} \rightarrow \text{alternate pathway} \rightarrow \text{fatty acid synthesis} \rightarrow \text{lipogenesis}
\]

High activity tissues [skeletal muscle] have high ATP demand. But since \[\triangleup [\text{ATP}]\] would inhibit ATP synthesis — cannot "store" excess ATP reserve.

- Exchange –P of ATP to P–Creatine.
- Exchange back to ATP from P–Cr at myofibrils.

Cellular Metabolism

1. Glycogenolysis
2. Glycolysis
3. Pyruvate Oxidation
4. Krebs Cycle
5. Lipolysis
6. Oxidation
7. Proteolysis
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**Cellular Metabolism**

<table>
<thead>
<tr>
<th>Anabolic pathways:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gluconeogenesis</td>
</tr>
<tr>
<td>2. Glycogenesis</td>
</tr>
<tr>
<td>3. Fatty Acid Synthesis</td>
</tr>
<tr>
<td>4. Lipogenesis</td>
</tr>
<tr>
<td>5. Ketogenesis</td>
</tr>
<tr>
<td>6. Translation</td>
</tr>
</tbody>
</table>

**Glycogenesis and Glycogenolysis**

- Glucose-6-phosphate cannot leak out of the cell.
- Skeletal muscles generate glucose-6-phosphate for their own glycolytic needs.
- Only Liver contains the enzyme glucose-6-phosphatase that can remove the phosphate group and produce free glucose.

**Uses of Different Energy Sources**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Glucose</th>
<th>Fatty Acids</th>
<th>Ketone Bodies</th>
<th>Lactic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skeletal muscles (resting)</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Heart</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Metabolic Pools**

- Dietary or energy-reserve sources (in cells)
- Polysaccharides
- Triglycerides
- Proteins
- Circulating energy substrates (in blood)
- Fatty acids, glycerol, ketone bodies
- Glucose, lactic acids, amino acids
- Intermediates of aerobic respiration (in cells)
  - Pyruvic acid
  - Acetyl coenzyme A
  - Krebs cycle
  - CO₂ + H₂O + ATP

**Gluconeogenesis & the Cori Cycle**

1. Lactic acid produced by anaerobic respiration in muscle is released into the bloodstream and delivered to the liver.
2. LDH converts lactic acid to pyruvic acid.
3. Gluconeogenesis (“creating new glucose”): Pyruvic acid converted to glucose-6-phosphate.
   - G-6-P can be used either for 7A: liver glycogenesis or 7B: can be converted to free glucose and released into the bloodstream.

<table>
<thead>
<tr>
<th>Skeletal muscles</th>
<th>Glycogen</th>
<th>Pyruvate</th>
<th>Glucose 6-phosphate</th>
<th>Pyruvic acid</th>
<th>Lactic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Blood</td>
<td>Glycogen</td>
<td>Glucose 6-phosphate</td>
<td>Pyruvic acid</td>
<td>Lactic acid</td>
</tr>
</tbody>
</table>

Only occur in liver!
Regulation of Cellular Respiration

Interactions of Liver, Fat & Muscle
- Fasting (↓ insulin, ↑ glucagon)

Muscle Fuel Consumption During Exercise
1. At rest: mostly from aerobic resp. of plasma fatty acids.
2. Start exercise: anaerobic resp. of plasma glucose; start muscle glycogenolysis.
3. ↑ blood flow & O₂ delivery → aerobic resp. of muscle triglycerides.
4. Gluconeogenesis ↑ plasma glucose from Cori Cycle.
5. Lipolysis in adipose tissue ↑ plasma fatty acids for continued aerobic resp.

Maintenance of circulating energy substrates
- Fasting or low-carbohydrate diet

Oxygen Debt
Following anaerobic respiration, increased O₂ consumption continues to support aerobic oxidation of lactate back to pyruvate. (Reverse of pyruvate reduction. — Uses same LDH enzyme.)

Balance Between Anabolism and Catabolism
- The rate of deposit and withdrawal of energy substrates, and the conversion of one type of energy substrate into another, are regulated by hormones.
- Antagonistic effects of insulin, glucagon, GH, T₃, cortisol, and epinephrine balance anabolism and catabolism.

Insulin: the primary anabolic hormone
- Glycolysis → ATP
- Glycogen synthesis
- Lipogenesis
- Gluconeogenesis
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Insulin: the primary anabolic hormone

Regulation of Insulin Action

- ↑ Blood glucose ⇒ ↑ insulin
- ↑ Blood amino acids ⇒ ↑ insulin
  - If high protein/low carb diet ⇒ ↑ blood amino acids, ↓ blood glucose;
  - ⇒ both insulin and glucagon
- ↑ Blood amino acids, ↓ blood glucose
- Parasympathetic nervous system: rest-and-digest ⇒ ↑ insulin
- Intestinal hormones
  - ↑ Osm of chyme ⇒ ↑ GIP/GLP-1/CCCK ⇒ ↑ insulin
  - “anticipates” ↑ blood glucose & amino acids
    - ↑ insulin faster from ingested glucose than from intravenous glucose!
- Adipose hormones
  - Enlargement of fat cells ⇒ ↑ insulin resistance factor [TNF-α]
  - ↓ insulin sensitivity
  - Obesity aggravates diabetes
  - Atrophy of fat cells ⇒ ↓ TNF-α, ↑ insulin sensitivity
- Weight loss ⇒ more efficient lipogenesis ⇒ regain lost fat

The Catabolic Hormones
— antagonistic to insulin action
1. Glucagon: blood glucose homeostasis
2. Epinephrine: acute stress response
   - fight-or-flight
3. Cortisol [glucocorticoid]: chronic stress response
   - general adaptation syndrome [GAS]

Regulation of Insulin and Glucagon Secretion

Antagonistic Hormones

Absorptive & Postabsorptive States

Glucagon stimulates catabolic enzymes.
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**Diabetes mellitus**

<table>
<thead>
<tr>
<th>Increased hepatic glycolysis</th>
<th>Increased hepatic gluconeogenesis</th>
<th>Increased hepatic ketogenesis</th>
<th>Decreased lipolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased glucose utilization</strong></td>
<td><strong>Decreased ketone utilization</strong></td>
<td><strong>Hyperglycemia</strong></td>
<td><strong>Hyperketonemia</strong></td>
</tr>
</tbody>
</table>

**Oral Glucose Tolerance Test**

- Measurement of the ability of β cells to secrete insulin.
- Ability of insulin to lower blood glucose.
- Normal person’s rise in blood [glucose] after drinking solution is reversed to normal in 2 hrs.

**Type II Diabetes Mellitus**

- Slow to develop.
- Genetic factors are significant.
- Occurs most often in people who are overweight.
- Decreased sensitivity to insulin or an insulin resistance.
- Obesity.
- Do not usually develop ketoacidosis.
- May have high blood [insulin] or normal [insulin].

**Glucocorticoids work via nuclear receptors:**

- Change gene expression / long term effects

**Synopsis of metabolic hormone action**

- Increased Blood glucose
- Glucose utilization
- Decreased gluconeogenesis
- Increased ketone bodies
- Increased amino acids
- Decreased lipolysis
- Increased adipose tissue triglycerides
- Increased liver free fatty acids
- Increased liver glucose
- Increased muscle protein
- Increased muscle amino acids