UNIT 4: Regulation and Integration of metabolism

Prof K Syed
Department of Biochemistry & Microbiology
University of Zululand
Room no. 247
Topics

• Glycolysis
• Citric acid cycle/Krebs cycle
• Fatty acid synthesis/degradation
• Metabolic fate of Amino acids
• Pentose phosphate pathway
• Gluconeogenesis
• Glycogen metabolism
• Urea cycle
• Ketogenesis

• Metabolic integration
  • Fate of Glucose-6-phosphate
  • Fate of pyruvate
  • Fate of Acetyl-CoA

• Effect of hormones on fuel metabolism
  • Fed state and fasted state/stress
Regulation of Glycolysis

- Allosteric regulation at 3 steps – Irreversible reactions
- PFK1 – Committed step

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Hexokinase (HK)</th>
<th>Phosphofructokinase (PFK1)</th>
<th>Pyruvate kinase (PK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allosteric Activator(s)</td>
<td>-</td>
<td>↑ ADP</td>
<td>↑ F-1,6-BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ AMP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ F-2,6-BP</td>
<td></td>
</tr>
<tr>
<td>Allosteric Inhibitor(s)</td>
<td>G6P</td>
<td>↑ ATP</td>
<td>↑ ATP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ PEP</td>
<td>↑ Acetyl-CoA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Alanine</td>
</tr>
</tbody>
</table>
Regulation of citric acid cycle/Krebs cycle

- Allosteric regulation (three simple ways)
- 3 steps
- Pyruvate dehydrogenase
- Citrate synthase – Committed step

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Citrate synthase</th>
<th>Isocitrate dehydrogenase</th>
<th>α-ketoglutarate dehydrogenase</th>
<th>Pyruvate dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allosteric Activator(s)</td>
<td>-</td>
<td>↑ ADP</td>
<td>↑ Ca^{2+}</td>
<td>↑ Ca^{2+}</td>
</tr>
<tr>
<td>Allosteric Inhibitor(s)</td>
<td>↑ ATP</td>
<td>↑ ATP</td>
<td>↑ ATP</td>
<td>↑ ATP</td>
</tr>
<tr>
<td></td>
<td>↑ NADH</td>
<td>↑ NAD</td>
<td>↑ NAHD</td>
<td>↑ Acetyl-CoA</td>
</tr>
<tr>
<td></td>
<td>↑ Succinyl-CoA</td>
<td>↑ Succinyl-CoA</td>
<td>↑ Succinyl-CoA</td>
<td>↑ NADH</td>
</tr>
</tbody>
</table>
Regulation of fatty acid synthesis/degradation

**Cytoplasm**
- **Acetyl-CoA carboxylase (ACC)**
  - $\text{HCO}_3^- + \text{ATP} \rightarrow \text{Acetyl-CoA}$
  - $\text{ADP} + \text{Pi} \rightarrow \text{Malonyl-CoA}$
  - $\text{Palmitoyl-CoA}$

**Mitochondria**
- **Carnitine Acyl Transferase (CAT I)/Carnitine Palmitoyl Transferase (CPT I)**
  - **Fatty-acyl-CoA**
  - **Carnitine**
  - **Fatty-acyl-carnitine**

**Allosteric**
- **Citrate**
- **Malonyl-CoA**
- **Palmitoyl-CoA**

**Covalent**
- **Protein Kinase**
- **Protein phosphatase 2A**

**Synthesis**
- **Glucagon/Epinephrine**
- **AMP/cAMP**

**Degradation**
- **Insulin**
- **Gene-expression Synthesis of ACC**

**PLAY VIDEOS 4-6**
Overview of amino acid catabolism

Amino acid

\[ \text{NH}_3 \leftarrow \text{Carbon skeleton} \]

\[ \downarrow \]

Urea

\[ \text{CO}_2 + \text{H}_2 \text{O} \]

Glucose

Acetyl-CoA

Ketone bodies

• **Amino acid deamination**
  - Transamination
  - Deamination
  - Lysine – no transamination

**Glutamate dehydrogenase**
(allosteric regulation)

<table>
<thead>
<tr>
<th>Inhibitor: GTP &amp; NADH</th>
<th>Signaling abundant metabolic energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activators: ADP &amp; NAD⁺</td>
<td>Signaling the need to generate ATP</td>
</tr>
</tbody>
</table>

**Glutamic acid**

\[ \begin{align*}
\alpha-\text{Keto acid} & \quad \text{Glutamate dehydrogenase} \\
\text{Transaminases} & \quad \text{Ammonia} \\
& \quad \text{NH}_3
\end{align*} \]
Metabolic fate of Amino acids

Strategy: transform the carbon skeletons into major metabolic intermediates that can be converted into glucose or oxidized citric acid cycle

**Ketogenic:**
Leucine & Lysine - LL

**Keto and Glucogenic:**
Phenylalanine, Isoleucine
Threonine, Tryptophan
Tyrosine (PITTT)

**Glucogenic:**
Alanine
Arginine
Asparagine
Aspartic acid
Cysteine
Glutamic acid
Glutamine
Glycine
Histidine
Methionine
Proline
Serine
Valine
(AAAACGGGHMPSV)
Regulation of Pentose Phosphate Pathway

- Response to metabolic needs
- Oxidative: equal amount of NADPH and Ribulose-5-phosphate
- Non-oxidative phase: Need lots of Ribulose-5-phosphate and don’t need NADPH
- Oxidative phase – allosteric regulation
- Glucose-6-phosphate dehydrogenase – committed step
Regulation of Gluconeogenesis

- Two steps

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Pyruvate carboxylase</th>
<th>Fructose-1,6-bisphosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allosteric Activator(s)</td>
<td>↑ Acetyl-CoA</td>
<td>↑ ATP</td>
</tr>
<tr>
<td>Allosteric Inhibitor(s)</td>
<td>-</td>
<td>↑ AMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Fructose-2,6-bisphosphate</td>
</tr>
</tbody>
</table>
Regulation of Glycogen metabolism

- Covalent modification & hormonal control
- Insulin and Glucagon steps
- Two enzymes: Glycogen synthase & Glycogen phosphorylase
Regulation of urea cycle: Adjustment of enzyme levels (Long term regulation)

- All five enzymes involved in regulation of urea synthesis
- Based on N flux (substrate availability)
- Gene-expression and enzyme production

<table>
<thead>
<tr>
<th>N Flux</th>
<th>Synthesis of enzymes</th>
<th>Urea production</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

High protein diet: ↑ N Flux
Low protein diet: ↓ N Flux
Starvation: ↑ N Flux
Regulation of urea cycle: Allosteric regulation (Short term)

- Committed step by CPS 1
- Allosteric regulation

\[
\text{2 ATP} + \text{HCO}_3^- + \text{NH}_4^+ \rightarrow \text{2 ADP} + \text{Carbomyl phosphate} + \text{Pi}
\]

Carbamoyl Phosphate Synthetase 1 (CPS 1)

Acetyl-CoA + Glutamate \(\rightarrow\) N-Acetylglutamate

- ↑ Arginine indicates high amount of amino acids and thus high amount of N flux
- Arginine indirectly activate CPS 1 via N-Acetylglutamate
Regulation of ketogenesis: Adjustment of HMG-CoA synthase under hormonal control

- Acetyl-CoA
- Acetoacetyl-CoA
- HMG-CoA Synthase
- 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)

Hormonal regulation:
- Glucagon: Acetylation-FOX2A (Active)
- Insulin: Phosphorylation-FOX2A (in-active)

Gene-expression & synthesis of FOX2A

FOXA2: Forkhead box A2 transcription factor
Metabolic pathways integration
Metabolic fates of Glucose-6-phosphate

Glucose

Glucose-6-phosphate

Glucose 1-phosphate

Glycogen

Fructose 6-phosphate

Pyruvate

6-phospho-gluconate

Ribose 5-phosphate
Metabolic fates of Pyruvate

- Glucose 6-phosphate
- Oxaloacetate
- Acetyl-CoA
- Lactate
- Alanine
Metabolic fates of Acetyl-CoA

- 3-Hydroxy-3-methyl-glutaryl CoA (HMG-CoA)
- Cholesterol
- Ketone bodies
- CO$_2$
- Pyruvate
- Ketogenic amino acids
- Fatty acids
Hormonal effects on fuel metabolism

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Insulin</th>
<th>Glucagon</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>↑ Glucose uptake</td>
<td>No effect</td>
<td>↑ Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>↑ Glycogen synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>↑ Glucose uptake</td>
<td>↑ Lipolysis</td>
<td>↑ Lipolysis</td>
</tr>
<tr>
<td></td>
<td>↑ Lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Lipolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>↑ Glycogen synthesis</td>
<td>↓ Glycogen synthesis</td>
<td>↓ Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>↑ Lipogenesis</td>
<td>↑ Glycogenolysis</td>
<td>↑ Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>↓ Gluconeogenesis</td>
<td></td>
<td>↑ Gluconeogenesis</td>
</tr>
</tbody>
</table>
Sources

- Glycolysis: Video 1: https://www.youtube.com/watch?v=ODGA3labyi4
- Citric acid cycle/Krebs cycle
  - Video 2: https://www.youtube.com/watch?v=gQkfwm0Dal
  - Video 3: https://www.youtube.com/watch?v=w47M1Uh3bGM
- Fatty acid synthesis/degradation
  - Video 4: https://www.youtube.com/watch?v=A2mQPCtKA6u
  - Video 5: https://www.youtube.com/watch?v=_SmWabaHfWY
  - Video 6: https://www.youtube.com/watch?v=_AUwqQu30LU
- Metabolic fate of amino acids
  - Video 7: https://www.youtube.com/watch?v=Sy-rfY5Mdc0
  - Video 8: https://www.youtube.com/watch?v=GT-9sgGMIkQ
- Pentose phosphate pathway Video 9: https://www.youtube.com/watch?v=sYn5AfJWSls
- Gluconeogenesis Video 10: https://www.youtube.com/watch?v=oGgrOn59ri4&t=191s
- Glycogen metabolism Video 11: https://www.youtube.com/watch?v=LJYTFiTVXa & Video 12: https://www.youtube.com/watch?v=oWp51j1QUE_1
- Urea cycle videos 13 & 14: https://www.youtube.com/watch?v=FFjs0VvCkX1 & https://www.youtube.com/watch?v=K3rVr_SfX08
- Ketone bodies:
    - Video 15: https://www.youtube.com/watch?v=AK9Q2Cl8y4
- Effect of hormones on fuel metabolism Video 16: https://www.youtube.com/watch?v=8U1ZwNI4n4