Metabolism of cardiac muscle

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Cardiovascular system, 2013
References

• This lecture
• Mark’s Basic Medical Biochemistry, 4th ed., p. 890-891
• Hand-out
Why is this topic important?

• Heart failure (HF) is associated to changes in metabolic profile.
  – The concept of “lipotoxicity”
• 20-30% of HF patients are diabetic

• Optimization of substrate metabolism improves cardiac function
Lecture outline

• Metabolic profile in cardiomyocytes
• Alteration in metabolic profile during ischemia and reperfusion
• Therapeutic targets
Substrates

- Fatty acids
- Glucose, lactate
- Ketone bodies
- Amino acids
Preference

• Sufficient oxygen:
  – Fatty acids (50-70%)
  – Glucose (30%)
    • under ischemic conditions

• Increased muscular activity
  – Glucose and lactate

• Pathological conditions and starvation:
  – Ketone bodies and amino acids
PATHWAYS
Pathways

Figure 14.11. General precursors of acetyl CoA.

Pathways

Acetyl CoA

Tricarboxylic acid cycle
Ketone bodies
Sterols and fatty acids
Pathways

Pyruvate → Acetyl CoA → Tricarboxylic acid cycle

GTP → CO₂ → CO₂

(4) \(2H^+ + 2e^-\) (reducing equivalents)

Electron transport system

9 ATP
Generation of ATP

• >95% of ATP comes from mitochondrial oxidative phosphorylation
• Complete ATP turnover every 10s (constant)
• 1 molecule of glucose: 36 to 38 molecules
• 1 molecule of fatty acids: a several-fold higher
LIPID METABOLISM
Fatty acid metabolism

ACC, acetyl-CoA carboxylase; CAT, carnitine acyltransferase; CPT-I, carnitine palmitoyltransferase; FABPPM, plasma membrane fatty acid binding protein; FAT, fatty acid transporter; LPL, lipoprotein lipase; MCD, malonyl-CoA decarboxylase.
GLUCOSE
Glucose
# Glucose transporters

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Major Sites of Expression</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT-1</td>
<td>Brain, erythrocyte, endothelial cells, fetal tissues</td>
<td>Transports glucose and galactose, not fructose Low Km (~ 1 mM)</td>
</tr>
<tr>
<td>GLUT-2</td>
<td>Liver, pancreatic beta cell, small intestine, kidney.</td>
<td>Transports glucose, galactose and fructose Low affinity, high capacity glucose transporter High Km (15–20 mM)</td>
</tr>
<tr>
<td>GLUT-3</td>
<td>Brain, placenta and testes</td>
<td>Transports glucose (high affinity; and galactose, not fructose Low Km (&lt;1 mM)</td>
</tr>
<tr>
<td>GLUT-4</td>
<td>Skeletal and cardiac muscle, adipocytes</td>
<td>Insulin-responsive; High affinity for glucose Medium Km (2.5–5 mM)</td>
</tr>
<tr>
<td>GLUT-5</td>
<td>Small intestine, sperm, brain, kidney, adipocytes and muscle</td>
<td>Transports fructose, but not glucose or galactose Medium Km (~ 6 mM)</td>
</tr>
</tbody>
</table>
GLUT-4 translocation

1. Insulin
2. Translocation of vesicles
3. Rapid transfer
4. Insulin dissociation
5. Translocation to vesicles
6. D-glucose transport ceases

Extracellular fluid
Intracellular fluid

Insulin Receptors and D-glucose Transporters

Ischemia
Work load
Glycogen
Pathway

Glucose → Glycolysis → Pyruvate

- Transamination: Alanine
- Carboxylation: Oxaloacetate
- Oxidative decarboxylation: Acetyl CoA
- Reduction: Lactate

Figure 14.13. Metabolic fates of pyruvate.

LACTATE
Lactate transport and metabolism
lactate dehydrogenase (LDH) system

\[
\text{CH}_3\text{C-COOH} \xrightleftharpoons{\text{LDH}} \text{CH}_3\text{CH-COOH} \\
\text{NADH} \quad \text{NAD}^+ \\
\text{Pyruvate} \quad \text{Lactate}
\]
The subunits

(a) The five isomers of lactate dehydrogenase

(b)  

<table>
<thead>
<tr>
<th></th>
<th>A_4</th>
<th>A_3B</th>
<th>A_2B_2</th>
<th>AB_3</th>
<th>B_4</th>
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<tbody>
<tr>
<td>Liver</td>
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<td>Muscle</td>
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<td>White cells</td>
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<tr>
<td>Brain</td>
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<tr>
<td>Red cells</td>
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<td>Kidney</td>
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<td>Heart</td>
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</tbody>
</table>
The isozymes

The all M4 isozyme

- functions anaerobically
- catalyzes the oxidation of pyruvate into lactate
- low Km for pyruvate
- not inhibited by pyruvate

The all H4 isozyme

- functions aerobically
- catalyzes reduction of lactate into pyruvate
- low Km for lactate
- inhibited by high levels of pyruvate

\[ \text{Pyruvate} \xrightarrow{LDH} \text{Lactate} \]
KETONE BODIES
Starvation

![Graphs showing changes in plasma levels of glucose, ketone bodies, and fatty acids during starvation.](image)
Production of ketone bodies
Regulation of glucose metabolism by FFA and ketone bodies

- Ketone bodies metabolism increase
  - acetyl CoA, which activates PDK inactivating PDH
  - citrate, which inhibits PFK
- Fatty acids metabolism increases:
  - LCFAs that inhibit HK
  - NADH/NAD+ ratio, which inhibits PDH
  - acetyl CoA and citrate (see above)
Regulation of fatty acid metabolism by glucose

- Glucose oxidation produces citrate, which can be converted to malonyl-CoA by acetyl-CoA carboxylase (ACC).
- Malonyl-CoA then can bind to and inhibit CPT1 blocking fatty acid oxidation.
The glucose-fatty acid (Randle) cycle

- The Randle cycle describes the reciprocal relationship between fatty acid and glucose metabolism.
- The increased generation of acetyl CoA derived from fatty acid-oxidation decreases glucose (pyruvate) oxidation.
- The increased generation of acetyl CoA derived from glucose (pyruvate) oxidation inhibits fatty acid-oxidation.
The glucose-fatty acid (Randle) cycle

- The “cycle” also describes the control of fuel selection through the dynamic interactions between circulating concentrations of glucose and fatty acids in coordination with hormones.

- Inhibition of glucose utilization by fatty acids is a form of glucose intolerance that resembles, or may lead to, insulin resistance.
Two regulatory molecules

- AMPK-activated protein kinase (AMPK)
- Peroxisome proliferator activated receptor (PPAR)
Metabolic regulation by AMPK

Exercise, ischemia, temperature

Consuming less ATP → [ATP]↓, [AMP]↑ → Producing more ATP

AMPK kinase

AMPK

ATP-consuming pathways
- Fatty acid synthesis
- Cholesterol synthesis
- Glycogen synthesis
- Protein synthesis

ATP-producing pathways
- Glycolysis
- β-Oxidation
- Glucose uptake
AMPK and glucose metabolism

• AMPK
  – Activates GLUT-4 translocation into membrane
  – Stimulates glycolysis by activating hexokinase and phosphofructokinase
  – Activates glycogenolysis
  – Inactivates glycogenesis
AMPK and glucose metabolism
AMPK and fatty acid oxidation

- AMPK activates fatty acid oxidation by inhibiting formation of malonyl CoA and activating CPT-1
Peroxisome proliferator activated receptor (PPAR)

- Expression of isoforms in myocardial cells:
  - PPAR-α >> PPAR-β >> PPAR-γ

Heart, skeletal muscle, and liver → skeletal muscle → adipose tissue

PPAR-α

PGC1α

Response element

Target Gene

Fatty acid uptake (i.e., CD36)
Fatty acid storage (i.e., DGAT)
β-oxidation (i.e., CPT1, MCAD)
Glucose oxidation (i.e., PDK4)

PPAR-β

PPAR-γ

Fatty acid uptake (i.e., GLUT4)
Fatty acid storage (i.e., SREBP, FAS)
β-oxidation (i.e., CPT1)
Glucose uptake (i.e., GLUT1/4)
ISCHEMIC HEART
How does ischemia alter metabolic profile?

- Ischemia results in
  - Decrease of $O_2$ and nutrients, which inhibit fatty acid oxidation
  - Increase in AMP/ATP ratio, which activates AMPK
Glucose vs. fatty acids

- Fatty acids have “oxygen-wasting” potential in the myocardium
Metabolism during reperfusion

- Fatty acid oxidation resumes, glycolysis continues, but glucose oxidation is inhibited
Consequences of metabolism during reperfusion

- Increased glycolysis and beta oxidation
- Activation of AMPK and inhibition of glucose oxidation
- Lactate and protons accumulate (acidosis)
- Protons are removed H+/Na+ exchanger (Na+ overload)
- Na+ ions are removed by Na+/Ca++ exchanger (Ca++ overload)
  - ATP wasting
- Production of free radicals (mitochondrial damage)
- Loss of cardiac contractile force
Therapeutic targets
Therapeutic targets (1)

- Circulating fatty acids can be decreased
  - Glucose–insulin–potassium (GIK)
  - PPAR agonists
  - β-adrenoceptor antagonists
Therapeutic targets (2)

- The mitochondrial uptake of long chain acyl-CoAs can be reduced
  - Carnitine palmitoyl transferase-I (CPTI)
  - Malonyl-CoA decarboxylase (MCD) inhibitors
Therapeutic targets (3)

- Fatty acid oxidation inhibitors reduce the rates of myocardial fatty acid oxidation
Therapeutic targets (4)

- Glucose oxidation can be increased by compounds that
  - increase pyruvate dehydrogenase (PDH) complex activity
  - inhibit PDK