Muscle Metabolism

Dr. Nabil Bashir
Learning objectives

- Understand how skeletal muscles derive energy at rest, moderate exercise, and strong exercise.
- Recognize the difference between aerobic and anaerobic oxidation.
- Recognize the three energy systems and exercise.
- Recognize the source of ATP production and metabolic pathways operating at resting and working.
- Understand the importance of cori cycle and glucose-alanine cycle.
- Understand the molecular basis of Becker and Duchenne muscular dystrophy.
- Muscle Glycogen Storage Diseases: Type V (McArdle Disease), and type IIIV.
- Fatty acid oxidation disease: Carnitine palmitoyltransferase II (CPT II) deficiency.
Energy Transfer Systems and Exercise

% Capacity of Energy System

Anaerobic Glycolysis

Aerobic Energy System

ATP - CP

Exercise Time

10 sec  30 sec  2 min  5+ min
Energy Metabolism

**Aerobic**
- With oxygen
- Source of energy: mainly fatty acids, then carbohydrate
- CO$_2$, H$_2$O & ATP

**Anaerobic**
- Without oxygen
- Source of energy: Carbohydrate (glycolysis)
- Lactate & ATP
(a) Resting muscle: Fatty acids are catabolized; the ATP produced is used to build energy reserves of ATP, CP, and glycogen.
Resting muscle and the Krebs Cycle

- Resting muscle fibers typically take up fatty acids from the blood stream.
- Inside the muscle fiber, the FA’s are oxidized (in the **mitochondria**) to produce **Acetyl-CoA** & several molecules of NADH and FADH2.
- Acetyl-CoA will then enter the **Krebs cycle** (in the **mitochondria**) \( \rightarrow \) \( \text{CO}_2, \text{ATP}, \text{NADH}, \text{FADH}2, \text{and oxaloacetate} \)
- NADH and FADH2 will enter the **Electron Transport Chain**. (in the inner **mitochondrial membrane**) \( \rightarrow \) synthesis of **ATP**
ATP use in Working Muscle

- As we begin to exercise, we almost immediately use our stored ATP.

- For the next 15 seconds or so, we turn to the creatine-phosphate system. This system dominates in events such as the 100m dash or lifting weights.
Working Muscle

- After the phosphagen system is depleted, the muscles must find another ATP source.
- The process of *anaerobic metabolism* can maintain ATP supply for about 45-60s.
- Glycogen → Glucose → 2 pyruvic acid (2 ATP + 2 NADH)
- 2 Pyruvic acid → 2 lactic acid (2 NAD\(^+\))
- Lactic acid diffuses out of muscles → blood → taken by the liver → Glucose (by gluconeogenesis) → blood → taken by the muscle again

* It usually takes a little time for the respiratory and cardiovascular systems to catch up with the muscles and supply O\(_2\) for aerobic metabolism.
(c) Peak activity: Most ATP is produced through glycolysis, with lactic acid as a by-product. Mitochondrial activity (not shown) now provides only about one-third of the ATP consumed.
Aerobic Metabolism

- Occurs when the respiratory and cardiovascular systems have “caught up with” the working muscles.
  - Prior to this, some aerobic respiration will occur thanks to the muscle protein, *myoglobin*, which binds and stores oxygen.
- During *rest* and *light to moderate* exercise, aerobic metabolism contributes 95% of the necessary ATP.
- Compounds which can be aerobically metabolized include:
  - *Fatty acids*, Pyruvic acid (made via glycolysis), and amino acids.
(b) **Moderate activity:** Glucose and fatty acids are catabolized; the ATP produced is used to power contraction.
THE CORI CYCLE
&
THE GLUCOSE-ALANINE CYCLE
The Cori cycle

- Liver converts lactate into glucose via gluconeogenesis
- The newly formed glucose is transported to muscle to be used for energy again
The glucose-alanine cycle

- Muscles produce:
  - Pyruvate from glycolysis during exercise and NH\textsubscript{2} produced from normal protein degradation produce Alanine.
  - Pyruvate + NH\textsubscript{2} \rightarrow Alanine

- This alanine is transported through the blood to liver.
- Liver converts alanine back to pyruvate.
  - Alanine – NH\textsubscript{2} = Pyruvate

- Pyruvate is used in gluconeogenesis.
- The newly formed glucose is transported to muscle to be used for energy again.
Liver

- Gluconeogenesis
  - 6 ATP
  - 2 Pyruvate
  - 2 Alanine

- Ureogenesis
  - 4 ATP
  - 2 NH₂
  - Urea

Blood

- Glucose
- Urea/kgidneys

Muscle cell

- Glycolysis
  - 2NAD⁺
  - 2 ATP
  - 4-6 ATP
  - 2 Pyruvate
  - 2 NADH
  - O₂

- 2 Alanine
  - 2 NH₂
The Glucose-Alanine Cycle

What happened to NH$_2$?

- Liver converts it to urea for excretion (urea cycle)
Becker and Duchenne muscular dystrophy

Mutations in the dystrophin gene

BMD is a less-severe disease (patients are still walking after 16 yrs)
DMD is a more-severe disease (patients are not walking at 12 yrs)
• both can be caused by massive deletions in the dystrophin gene (as well as other types of mutations)
• the severity is not necessarily correlated with the size of the deletion
mutations causing BMD can be very large in-frame deletions

truncated but functional protein with intact N- and C-termini

partially functional dystrophin protein

mutations causing DMD can be small out-of-frame deletions

C-terminal truncated protein (with out-of-frame translation product)

non-functional dystrophin protein
Metabolic myopathies

Heterogeneous group share the common feature of inadequate production of cellular energy in the muscle.
Muscle Glycogen Storage Diseases

- **Type V (McArdle Disease):** Deficiency of **phosphorylase:**
  - an elevated CK (8,404 U/L; normal, 30–220 U/L),
  - mild elevations of aspartate aminotransferase (75 U/L; normal, 15–41 U/L), and alanine aminotransferase (82 U/L; normal, 17–63 U/L).
  - Urinalysis is negative for myoglobin.

- **Type VII:** Deficiency of **phosphofructokinase** →
  - hemolytic anemia and
  - myogenic hyperuricemia.
  - accumulation of **normal glycogen** in muscle, and **abnormal glycogen**
Fatty Acid Oxidation Disorders

- FAO (β-oxidation of fatty acids) is the major source of energy during periods of sustained, low-intensity exercise or prolonged fasting.
- Exercise intolerance and myoglobinuria are the most common presenting features.
- The major disorders of lipid metabolism that present with isolated myopathy include:
  Carnitine palmitoyltransferase II (CPT II) deficiency,
CPT II

- The severity of disease appears to be related to the type of mutation.
  - Missense mutations: production of some partially functional enzyme activity → mild myopathic form.
  - Protein truncating mutations produce the more severe phenotypes.
- Serum CK levels are usually normal