Pathophysiology of Type 2 Diabetes

Liver

Increased glucose production

Pancreas

Impaired insulin secretion

Glucose

Peripheral Tissues (Muscle)

Receptor + postreceptor defects

Insulin resistance

Switching from Fat Oxidation to Glucose Oxidation is impaired in obesity

from Kelley, Goodpaster, Wing & Simoneau, AJP 1999
Metabolic Flexibility

Metabolic Inflexibility
Are Mitochondria Implicated in Insulin Resistance or Type 2 Diabetes?

Young
Lean

Young
Lean

Old
Obese
Type 2 Diabetes
Mitochondria function and insulin resistance and type 2 diabetes

Shulman and Lowell, 2005
Exercise-induced changes in total mitochondrial ETC activity

Mitochondria content assessed with electron microscopy
Use of $^{13}$C tracers to Quantify Substrate Oxidation

$^{13}$C Glucose
$^{13}$C Leucine
$^{13}$C Palmitate

Oxidation

$^{13}$CO$_2$
Indirect Calorimetry

Principle: To measure rates of total fatty acid (plasma FFA + intramuscular TG) and glucose (plasma glucose + muscle glycogen) oxidation during exercise.

\[
\text{fatty acid } (\text{C}_{16}\text{H}_{32}\text{O}_2) + 23 \text{ O}_2 \rightarrow 16 \text{ CO}_2 + 16 \text{ H}_2\text{O} \\
0.696
\]

\[
\text{glucose } (\text{C}_6\text{H}_{12}\text{O}_6) + 6 \text{ O}_2 \rightarrow 6 \text{ CO}_2 + 6 \text{ H}_2\text{O} \\
6 \text{ CO}_2/ 6 \text{ O}_2 = 1.00
\]
Indirect Estimate of Intramuscular Glycogen, Triglyceride Oxidation

Intramuscular Triglyceride (Glycogen) Oxidation =
Total Fat (Carbohydrate) Oxidation -
Plasma FFA (Glucose) Oxidation
Fat Oxidation from Plasma and Intramuscular Sources during Exercise

MRI of mid-thigh performed at 3.0 T.

T-1 weighted image

Fat-selective image
Intramyocellular lipid by proton NMR

m. tibialis anterior

EMCL

Cr3

TMA

Cr2

X3

Cr3

Cr2

X3

IMCL

CH$_2$

IMCL

CH$_3$

ppm
Depletion and replenishment of intramyocellular lipids

IMCL
Barriers to muscle glucose uptake (MGU)

- Blood Flow
- Capillary Recruitment
- Spatial Barriers

- Transporter #
- Transporter Activity

- Hexokinase #
- HK Compartmentalization
- Spatial Barriers

Glucose → Extracellular
Sarcolemma
Intracellular → ATP
Glucose 6-Phosphate (G6P)
PET Imaging of FDG uptake: transport & phosphorylation

X-ray CT section of the calves

$[^{18}F]$FDG image of the same section
Triple tracer method to assess dynamic glucose metabolism

$[^{15}\text{O}]-\text{H}_2\text{O}$ to measure tissue perfusion

$[\text{O-methyl-}^{11}\text{C}]3\text{-O-methyl-D-glucose}$. $[^{11}\text{C}]3\text{-OMG}$ enters (and leaves) the free glucose pool in tissue via bi-directional transport.

$[^{18}\text{F}]-\text{FDG}$, must also be delivered and can undergo bi-direction transport but this adds the possibility of glucose phosphorylation.
Dynamic Imaging of FDG uptake in different muscle groups or in different tissues
**k\textsubscript{3} - glucose transport**

**Soleus**

- **Basal**
  - Diabetic: 0.02
  - Obese: 0.02
  - Lean: 0.02

- **Insulin**
  - Diabetic: 0.04
  - Obese: 0.04
  - Lean: 0.04

**Tibialis**

- **Basal**
  - Diabetic: 0.02
  - Obese: 0.02
  - Lean: 0.02

- **Insulin**
  - Diabetic: 0.04
  - Obese: 0.04
  - Lean: 0.04
Correction of Dysregulated Metabolism in Obesity and aging

Diet-induced weight loss

Exercise
Doubly Labeled Water (DLW) Theory

- Differential elimination of DLW dose
  - 18-oxygen leaves the body as CO₂ and water
  - Deuterium leaves the body as water
  - CO₂ production calculated by difference in elimination rates