METABOLISM OF LIPIDS AND PROTEINS
Alternate Fuel Sources

- When glucose levels are low
- **Proteins** and **Triglycerides** will be metabolized
- Tissues will use different fuel sources depending on:
  - The metabolic activity of the tissue
  - Fuel sources available
    - Diet
    - Fasting
Proteins

- Proteins are digested to amino acids in the stomach and small intestine by proteases
- Amino acids used to:
  - Make ATP
  - Biosynthesis
    - Non-essential amino acids
    - Metabolic intermediates
    - Glucose
    - Fat
    - Intracellular proteins

*Fig. 67.13: An overview of amino acid metabolism.*
Amino Acids

A GUIDE TO THE TWENTY COMMON AMINO ACIDS

Amino acids are the building blocks of proteins in living organisms. There are over 500 amino acids found in nature - however, the human genetic code only directly encodes 20. 'Essential' amino acids must be obtained from the diet whilst non-essential amino acids can be synthesised in the body.

Chart Key:
- ALIPHATIC
- AROMATIC
- ACIDIC
- BASIC
- HYDROXYLIC
- SULFUR-CONTAINING
- AMIDIC
- NON-ESSENTIAL
- ESSENTIAL

Chemical Structure:
- NAME: three letter code (DNA codons)
- ALANINE: Ala (GCA, GCG, GCC, GGG)
- GLYCINE: Gly (GGT, GGC, GGA, GGG)
- ISOLEUCINE: Ile (ATT, ATC, ATA)
- LEUCINE: Leu (CTT, CTC, CTA, TTG)
- PROLINE: Pro (GCG, GCA, CGG)
- VALINE: Val (GTT, GTC, GCA, GGA)
- PHENYLALANINE: Phe (TTC, TTC)
- TRYPTOPHAN: Trp (TGG)
- TYROSINE: Tyr (TAC, TAT)
- ASPARTIC ACID: Asp (GAT, GAC)
- GLUTAMIC ACID: Glu (GAA, GAG)
- ARGinine: Arg (CGT, CGC, CGA, AGG)
- HISTIDINE: His (CAT, CAC)
- LYSINE: Lys (AAA, AAG)
- SERINE: Ser (UCG, UCG, AGC, AGG)
- THREONINE: Thr (ACG, ACC, ACA, ACG)
- CYSTEINE: Cys (TGT, TGC)
- METHIONINE: Met (ATG)
- ASPARAGINE: Asn (AAC, AAA)
- GLUTAMINE: Gln (CAA, CAG)

Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asn (B) and glx (Z) are respectively used.
Amino Acids as Fuel

**Glucogenic Amino Acids**
- Amino acids converted to $\alpha$ keto acids (pyruvate)
- Pyruvate
  - Converted to glucose
- Occurs in the liver
  - Production increases during **catabolysis** (fat and muscle tissue breakdown)
- Produced by **transamination** and oxidative deamination

**Ketogenic Amino Acids**
- Amino acids degraded to acetyl-CoA
- Produced by oxidative deamination
- Acetyl-CoA:
  - Is the precursor of ketones
  - Used to make fatty acids
  - Used to make ATP
- Can not be converted to glucose (WHY?)
CITRIC ACID CYCLE

- Arginine
- Glutamine
- Histidine
- Proline
- Isoleucine
- Methionine
- Threonine
- Valine

- Glutamate
- α-Ketoglutarate
- Succinyl-CoA
- Succinate
- Fumarate
- Malate
- Oxaloacetate
- Pyruvate
- Glucose

- Ketone bodies
- Acetoacetyl-CoA
- Acetyl-CoA

- Leucine
- Lysine
- Phenylalanine
- Tryptophan
- Tyrosine

- Isoleucine
- Leucine
- Tryptophan

- Asparagine
- Aspartate
- Alanine
- Cysteine
- Glycine
- Serine
- Serine
- Tyrosine

Glucogenic Amino Acids
Ketogenic Amino Acids
Transamination

• Make another type of amino acid by transferring an amine \((\text{NH}_2)\) from an existing amino acid to a keto acid

• **Example** →
  
  – An amine group is transferred from L-alanine to \(\alpha\)-ketoglutarate to make pyruvate and L-glutamate
Oxidative Deamination

- The amine (NH₂) from an amino acid is removed (deamination)
- Oxygen replaces the nitrogen
  - Oxygen comes from splitting H₂O
- The removed amine group gives rise to NH₃ (then to urea)
- The product is a α keto acid and/or a ketone
- Occurs mostly in the liver and kidneys

Glutamate is commonly deaminated to **α-Ketoglutarate**
Keto Acids

α keto acid

• **Pyruvate**
  – Many fates

• **Oxaloacetate**
  – Kreb’s Cycle intermediate

• **α-Ketoglutarate**
  – Kreb’s Cycle intermediate
  – Coenzyme function in cell signaling
  – Commonly used in transamination reactions

β keto acid

• **Acetoacetate**
  – A ketone released from the liver to be used by other cells that can not utilize fatty acids as a fuel source

A keto acid is an organic compound that has a carboxyl group and a ketone group.
Triglycerides as Fuel

Triglycerides are stored in adipocytes and used as fuel for other cells in the body for cellular metabolism.
Triglyceride

- Triglycerides are made up of 3 fatty acids bound to glycerol.

**Glycerol**

[Chemical structure of glycerol]

**Fatty Acid**

[Chemical structure of a fatty acid]
Typical Triglyceride

Glycerol + Fatty Acid Tails
Triglycerides in Adipocytes

- **Lipolysis**
  - The hydrolysis of a triglyceride from an adipocyte releases
    - Glycerol
    - 3 fatty acids
  - Occurs in adipose tissue
  - Used to liberate stored energy during
    - Exercise
    - Fasting
    - Stress
    - Growth
  - Regulated by hormones
  - Induced by: Glucagon, NE/Epi, Cortisol, GH
Lipolysis

Fate of glycerol

– Glycerol is moved out of the adipocyte and taken up by:
  • Liver, kidney, skeletal muscle, brain
– Glycerol is converted to 3-PGAL
– 3-PGAL in the liver:
  • Gluconeogenesis
  • Glycogenesis
– 3-PGAL in most cells:
  • Glycolysis

Fate of fatty acids

– β-oxidation in the mitochondria of cells
– Produces Acetyl-CoA
  • Many fates
  • Dependent on the needs of the cell
β-Oxidation

Fatty acid catabolism consists of:

1. Fatty acids are moved into the cell
   - Moved into the cell by a fatty acid transporter
   - Binds to Co-A
2. Fatty acid-Co-A then moved into the mitochondria
3. Oxidation of the β carbon to a carbonyl group (C=O).
4. Enzymes cleave off 2-carbon segments resulting in Acetyl-CoA.
5. Needs of the cell determine what happens next......
Acetyl-CoA

**PRECURSORS**
- glucose
- pyruvate
- amino acids

**PRODUCTS**
- fatty acids
- triglycerides
- phospholipids
- eicosanoids
- cholesterol
- steroid hormones
- bile salts
- $\text{CO}_2 + \text{H}_2\text{O} + \text{energy (ATP)}$

*Acetyl CoA is a central intermediate in lipid metabolism.*
β-Oxidation

- You can determine how much ATP a triglyceride will yield
- Each fatty acid will be oxidized to individual acetates (2 carbons) and will combine to form Acetyl-CoA
- Each acetate will enter the Kreb’s cycle
  - For each turn of the Kreb’s Cycle you yield
    1. 1 ATP
    2. 3 NADH + H+
    3. 1 FADH$_2$
  - For each bond broken you yield
    1. 1 NADH + H+
    2. 1 FADH$_2$
  - Glycerol will enter glycolysis as 3-PGAL and yield 20 ATP
Palmitin
A homotriglyceride made up of 3 palmitic acids $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$

*Found in chocolate!!*
β-Oxidation Calculation

• 7 acetates
  - 1 ATP  x 7 = 7 ATP
  - 3 NADH + H⁺  x 7 = 21 NADH + H⁺  x 3 ATP = 63 ATP
  - 1 FADH₂  x 7 = 7 FADH₂  x 2 ATP = 14 ATP

• 6 bonds
  - 1 NADH + H⁺  x6 = 6 NADH + H⁺  x 3 ATP = 18 ATP
  - 1 FADH₂  x6 = 6 FADH₂  x 2 ATP = 12 ATP
β-Oxidation Calculation

• Add up the ATP produced from 1 fatty acid

\[
\begin{align*}
7 \text{ ATP} & \\
63 \text{ ATP} & \\
14 \text{ ATP} & \\
18 \text{ ATP} & \\
12 \text{ ATP} & \\
114 \text{ ATP} & \\
-1 \text{ ATP} & \text{Cost of initiating β-oxidation} \\
= 113 \text{ ATP from 1 fatty acid} &
\end{align*}
\]
β-Oxidation Calculation

• Now multiply how much ATP is produced from one fatty acid x 3 because there are 3 fatty acids

\[
\begin{align*}
113 \text{ ATP} \\
\times 3 \\
339 \text{ ATP} \\
+ 20 \text{ ATP} \quad \text{(from glycerol)} \\
\textbf{359 ATP Total from the triglyceride}
\end{align*}
\]
Ketone/Ketone Body

• **Ketosis:** The liver forms ketones from fatty acids for other tissues to use as fuel instead of glucose when glucose levels are low
  - Fasting
  - Extreme/Strenuous Exercise
  - Ketogenic diet: High fat, higher protein, low carbohydrate diet
  ❖ *Not all tissues can metabolize fatty acids (BRAIN)*

• Ketones used by **brain, heart, muscle and kidney**
  - Cells take in the ketones and convert them to Acetyl-CoA
  - In the brain
    - Ketones can (can be used to make fatty acids)

• **Diabetic Ketoacidosis (DKA)**
  • High levels of ketones causing plasma to become acidic