Metabolism of Branched-chain Amino acids
Branched-chain Amino acids

Leu, Ile, Val are the branched chain and essential amino acid
Branched-chain Amino acids

- Valine (Val) is glucogenic amino acid
- Leucine (Leu) is ketogenic amino acid
- Isoleucine (Ile) is both glucogenic and ketogenic amino acid
- These amino acids serve as an alternate source of fuel for the brain especially under conditions of starvation.
Metabolism of branched-chain AAs

The first three metabolic reactions are common to the branched chain amino acids

1. Transamination
2. Oxidative decarboxylation
3. Dehydrogenation
3. **Dehydrogenation**

Acyl-CoA dehydrogenase by FAD coenzyme
The degradation of the branched-chain amino acids (A) isoleucine, (B) valine, and (C) leucine.
(A) Isoleucine: \( R_1 = \text{CH}_3 \), \( R_2 = \text{CH}_3 \text{--CH}_2 \text{--} \)

(B) Valine: \( R_1 = \text{CH}_3 \), \( R_2 = \text{CH}_3 \text{--} \)

(C) Leucine: \( R_1 = \text{H} \), \( R_2 = (\text{CH}_3)_2 \text{--CH} \text{--} \)

(A) \( \alpha\text{-Keto-}\beta\text{-methylvalerate} \)

(B) \( \alpha\text{-Ketoisovalerate} \)

(C) \( \alpha\text{-Ketoisocaproic acid} \)

(A) \( \alpha\text{-Methylbutyryl-CoA} \)

(B) \( \text{Isobutyryl-CoA} \)

(C) \( \text{Isovaleryl-CoA} \)
For IsoLeucine

After the three steps, for Ile,

4. Enoyl-CoA hydratase

5. \( \beta \)-hydroxyacyl-CoA dehydrogenase

6. Acetyl-CoA acetyltransferase

Last 3 steps similar to fatty acid oxidation
For Valine:

4. Enoyl-CoA hydratase

5. $\beta$-hydroxy-isobutyryl-CoA hydrolase

6. $\beta$–hydroxyisobutyrate dehydrogenase

7. Methylmalonate semialdehyde dehydrogenase

Last 3 steps similar to fatty acid oxidation
For Leucine:

4. $\beta$-methylcrotonyl-CoA carboxylase

5. $\beta$-methylglutaconyl-CoA hydratase

6. HMG-CoA lyase
Branched Chain Amino Acids

• Isoleucine
• Leucine
• Valine
• Important sources of Krebs intermediates under certain conditions
Amino Acid as Energy Source in Skeletal Muscle

• Oxidation of Branched Chain Amino Acid yield between 32-43 ATP Comparable to complete oxidation of glucose

• Amino Acid contribute up to 18 % energy during prolonged exercise
Valine, isoleucine, leucine

BCAA transaminase

Branched-chain keto acid analogues

BCKA dehydrogenase

Branched-chain acyl CoA analogues

(Valine) → Propionyl CoA

(Isoleucine) → Propionyl CoA

(Leucine) → Acetoacetyl CoA

Propionyl CoA carboxylase

\[ \text{CH}_3\text{CH}=-\text{C}^\sim\text{SCoA} \]

\[ \text{ATP} + \text{HCO}_3^- \rightarrow \text{AMP} + \text{PP}_i \]

\[ \text{CH}_3\text{CH}=-\text{C}^\sim\text{SCoA} \rightarrow \text{Methylmalonyl CoA} \]

Methylmalonyl CoA mutase

\[ \text{HOOCCH}_2\text{CH}_2\text{C}^\sim\text{CoA} \rightarrow \text{Succinyl CoA} \]
Succinyl-CoA

• Propionyl CoA is converted into succinyl CoA

• The 4-C Krebs Cycle intermediate **succinyl-CoA** is produced from **isoleucine, valine, & methionine**.
**Metabolic defects**

**Maple Syrup Urine Disease**

- **Maple syrup urine disease** - the disorder of the oxidative decarboxylation of $\alpha$-ketoacids derived from **valine**, **isoleucine**, and **leucine** caused by the missing or defect of branched-chain $\alpha$ keto acid dehydrogenase

- This is also known as **Branched chain ketonuria**
Isovaleric acidemia

- The 3rd step of leucine metabolism is the conversion of isovaleryl CoA to 3-methylcrotonyl CoA, a dehydrogenation step.
- **Elevated levels of isovaleric acid** and its metabolites in blood or urine.
- Symptoms include acidosis and mild mental retardation.
(A) Isoleucine: \( R_1 = \text{CH}_3 \), \( R_2 = \text{CH}_3 - \text{CH}_2 - \)

(B) Valine: \( R_1 = \text{CH}_3 \), \( R_2 = \text{CH}_3 - \)

(C) Leucine: \( R_1 = \text{H} \), \( R_2 = (\text{CH}_3)_2 \text{CH} - \)

(A) \( \alpha \)-Keto-\( \beta \)-methylvalerate

(B) \( \alpha \)-Ketoisovalerate

(C) \( \alpha \)-Ketoisocapric acid

(A) \( \alpha \)-Methylbutyryl-CoA

(B) Isobutyryl-CoA

(C) Isovaleryl-CoA
Propionic Acidemia

- Deficiency of propionyl CoA carboxylase, the enzyme responsible for metabolizing propionic acid, causes propionic acid accumulation.

- Elevated levels of propionic acid metabolites.

- Symptoms include metabolic acidosis, mental retardation.