Amino Acid Metabolism
AMINO ACID METABOLISM AND CATABOLISM

Source of Energy

Citric acid cycle

Body proteins ↔ Amino acids

Dietary protein

Urea

NH₃

Acetyl CoA

Carbohydrate Intermediates

Glycogen

Fats, sterols

O₂

CO₂, H₂O, energy

Coenzymes

Neurotransmitters

Phospholipids

Porphyrins

Purines

Pyrimidines

Other nitrogenous compounds
Amino Acid metabolism/catabolism → Metabolic pathway

Proteins

Amino Acids

α-amino group

carbon skeletons

seven intermediate products

1 → α-ketoglutarate
2 → oxaloacetate
3 → pyruvate
4 → fumarate
5 → succinyl coenzyme A
6 → acetyl coenzyme A
7 → acetoacetate

Metabolic Pathways
### Classification of Amino Acid

<table>
<thead>
<tr>
<th>Nonessential</th>
<th>Glucogenic and Ketogenic</th>
<th>Ketogenic</th>
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#### Glucogenic
- Alanine
- Arginine*
- Asparagine
- Aspartate
- Cysteine
- Glutamate
- Glutamine
- Glycine
- Histidine*
- Proline
- Serine

#### Ketogenic
- Acetoacetate (Ketone Bodies) or Acetyl CoA
- Acetoacetyl CoA

Altarate energy source

**Pyruvate and other TCA cycle intermediates**

**Citric acid cycle (TCA)**

**Gluconeogenesis**

**Succinyl coenzyme A**

**Acetoacetyl CoA**

**Precursors of acetoacetate**
The “one-carbon pool” refers to single carbon units attached to the group of carrier compounds such as Tetrahydrofolate, S-adenosylmethionine, Biotin etc.

These single carbon units can be transferred from carrier compounds to specific structures that are being synthesized or modified.
Tetrahydrofolate is an active form of Folic acid (vitamin B9 or folacin).

Nucleotide and protein synthesis, Methylation of many biological compounds etc

Dihydrofolate reductase

Methotrexate

Anti-Cancer drug

One-carbon-unit

Glycine → Serine
Tetrahydrofolate acts as a carrier of reactive single carbon units, which are bonded to N-5 and N-10.

The oxidation level can be changed to methyl or methenyl by reduction or oxidation; methenylTHF can be hydrolyzed to formylTHF.

These derivatives can be used in synthetic reactions as donors of single C at the appropriate oxidation level.
S-adenosylmethionine (SAM)

Methionine adenosyltransferase (MAT), which catalyzes the biosynthesis of S-adenosylmethionine (SAM), the principal methyl donor.

Methylation targets are:
DNA
RNA
Proteins
Lipids
Hormones and neurotransmitters
S-adenosylmethionine (SAM) serves as a precursor for numerous methyl transfer reactions.
Conversion of Norepinephrine to Epinephrine requires SAM
Classification of Amino Acid

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Nonessential:
- Pyruvate and other TCA cycle intermediates
- Acetoacetate or Acetyl CoA
- Succinyl coenzyme A
- Alternate energy source

Essential:
- Citric acid cycle (TCA)
- Gluconeogenesis
Asparagine and Aspartate enter metabolism as oxaloacetate

Asparginase

Anti-cancer drug
Gln, Pro, Arg, and His enter metabolism as α-ketoglutarate
Glutamine

Amino acids that forms $\alpha$-ketoglutarate

Glutamine

Glutaminase

Glutamate + $\text{NH}_3$

Oxidative Deamination

Glutamate $\overset{\text{Glutamate dehydrogenase}}{\rightarrow}$ $\alpha$-Ketoglutarate

$\text{NH}_3$ $\overset{\text{NAD}^+}{\rightarrow}$ NADH $\overset{\text{NADP}^+}{\rightarrow}$ NADPH
Amino acids that forms $\alpha$-ketoglutarate

**Proline**

Proline $\xrightarrow{\text{Oxidized}}$ Glutamate

Oxidative Deamination
Amino acids that forms $\alpha$-ketoglutarate

Arginine

Arginine $\rightarrow$ Arginase $\rightarrow$ Ornithine $\rightarrow$ $\alpha$-ketoglutarate

Urea cycle
Histidine

Amino acids that forms $\alpha$-ketoglutarate

Oxidatively deaminated

Oxidative Deamination

NAD$^+$  NADH  $\text{NH}_3$

Glutamate dehydrogenase

$\text{NH}_3$  NADP$^+$  NADPH

$\alpha$-Ketoglutarate
Amino Acid that forms pyruvate

Alanine

Transamination of alanine to form pyruvate
Amino Acid that forms **pyruvate**

**Glycine**

This reaction provides the largest part of the one-carbon units available to the cell.
Amino Acid that forms **pyruvate**

**Serine**

This reaction provides the largest part of the one-carbon units available to the cell.
Cystine is a dimeric amino acid formed by the oxidation of two Cysteine residues which covalently link to make a disulphide bond.
Amino Acid that forms **pyruvate**

**Threonine**

- Threonine
- Threonine dehydrogenase and $\alpha$-amino-$\beta$-ketobutyrate lyase
- Propionyl CoA
- Succinyl CoA

**Glucogenic & Ketogenic**

- Pyruvate dehydrogenase
Phenylalanine and Tyrosine

Amino acids that form fumarate

Phenylalanine hydroxylase

Phenylalanine + O₂ → Tyrosine + H₂O

Dihydrobiopterin reductase

Phenylalanine hydroxylase

Phenylalanine

Tyrosine

H₂—biopterin

Dihydrobiopterin reductase

NAD⁺ → NADH + H⁺

L-Phenylalanine

Tetrahydrobiopterin

Fumarate

Acetoacetate

Glucogenic

Ketogenic

Essential

Arginine
Histidine
Isoleucine
Leucine
Lysine
Methionine
Phenylalanine
Threonine
Tryptophan
Valine

Nonessential

Alanine
Aspartate
Cysteine
Glutamate
Glycine
Proline
Serine
Tyrosine

a Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.
b Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.
c Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.
Amino acids that form succinyl CoA

Methionine

Methionine is special because:

* Converted to S-adenosylmethionine (SAM), the major methyl-group donor in one-carbon metabolism
* Source of homocysteine ----a metabolite associated with atherosclerotic vascular disease
Amino Acid that forms **Succinyl CoA**

- **S-Adenosylmethionine synthetase**
- **SAM Methyltransferase**
- **S-adenosylhomocysteine**
- **L-Homocysteine**
- **Cystathionine β-synthase**
- **Cystathionine γ-cystathionase**
- **L-Cysteine**
- **Hydrolysis of SAM:**
  - Homocysteine
  - Methionine
  - Cysteine

**Hydrolysis of SAM:**

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8. **Hydrolysis of SAM:**
   - **Homocysteine**
   - **Methionine**
   - **Cysteine**

**Conversion to methionine requires folate and vitamin B<sub>12</sub>-derived coenzymes, and is a remethylation process.** The formation of cysteine requires vitamin B<sub>6</sub> (pyridoxine), and is a transsulfuration process.

**Oxidatively decarboxylated:**

- **Propionyl CoA**
- **Succinyl CoA**
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\(^a\) Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.

\(^b\) Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.

\(^c\) Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.

There are two major disposal pathways for homocysteine. Conversion to methionine requires folate and vitamin B\(_{12}\)-derived coenzymes, and is a remethylation process. The formation of cysteine requires vitamin B\(_6\) (pyridoxine), and is a transsulfuration process.
Homocysteine and vascular diseases

Plasma levels of homocysteine is inversely related to folate, Vitamin B12, and B6.

Homocysteine levels are also increased in Homocystinurea; disease caused due to the defective cystathione β-synthetase is defective.
Catabolism of the branched-Chain amino acids

**Essential aa**

- Leucine
- Valine
- Isoleucine

**TRANSAMINATION**
(Branched-chain α-amino acid transferase)

- α-Ketoisocapropoic acid
- α-Ketoisovaleric acid
- α-Keto-β-methylvaleric acid

Maple Syrup

Urine disease

**OXIDATIVE DECARBOXYLATION**
(Branched-chain α-keto acid dehydrogenase complex (TPP, NAD, CoA, Lipolic acid, FAD))

- Isovaleryl CoA
- Isobutyryl CoA
- a-Methyl butyryl CoA

**FAD-linked DEHYDROGENATION**

- Acetoacetate + Acetyl CoA
- Propionyl CoA
- Acetyl CoA
- Succinyl CoA
Amino acids that form acetyl CoA and acetoacetyl CoA

- Leucine
  - Acetoacetate
  - Acetyl CoA
  - Ketogenic
- Isoleucine
  - Acetyl CoA
  - Propionyl CoA
  - Ketogenic
  - Ketogenic And Gucogenic
- *Lysine
  - Acetoacetyl CoA
  - *Unusual---never undergoes transamination
  - Ketogenic
- Trpophan
  - Alanine
  - and acetoacetyl CoA
  - Ketogenic And Glucogenic
Biosynthesis of non-essential amino acids
Biosynthesis of non-essential amino acids

Synthesis from α-keto acids: Alanine, Aspartate, Glutamate

Alanine, aspartate, and glutamate are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively.
Biosynthesis of Glutamine and Asparagine

Synthesis by amidation: **Glutamine, Asparagine**

- **Glutamine**
  - Glutamate $\rightarrow$ ATP + NH$_3$
  - ADP + P$_i$
  - Glutamine synthetase

- **Asparagine**
  - Aspartate $\rightarrow$ ATP $\rightarrow$ AMP + P$_i$
  - Glutamine + glutamate $\rightarrow$ Asparagine
  - Enzyme: asparagine synthetase
Biosynthesis of Proline, Serine and Cysteine

Proline

<table>
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<tr>
<th>Glutamate</th>
<th>Cyclization and reduction</th>
<th>Proline</th>
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Serine

3-phosphoglycerate
↓
Oxidized

3-phosphopyruvate
↓
Transaminated

3-phosphoserine
↓
Hydrolysis of phosphate

Serine

Cysteine

Serine and Glycine

3-phosphoglycerate
↓
Oxidized

3-phosphopyruvate
↓
Transaminated

3-phosphoserine
↓
Hydrolysis of phosphate

Serine

Cysteine

3-phosphoglycerate
↓
Oxidized

3-phosphopyruvate
↓
Transaminated

3-phosphoserine
↓
Hydrolysis of phosphate

Serine

Cysteine
Biosynthesis of Tyrosine

Tyrosine

![Diagram of the biosynthesis of tyrosine](image)