Catabolism of Carbon skeletons of Amino acids

Amino acid metabolism
Carbon skeleton

• **Carbon Skeleton**
  – a carbon skeleton is the internal structure of organic molecules.

• **Carbon Arrangements**
  – The arrangement of carbon atoms in the skeleton varies from a straight line of atoms to branching formations to circular arrangements. Other atoms such as hydrogen or oxygen can bind to the carbon atoms to create molecules.

• **Amino Acids**
  – When amino acids are removed during the metabolic cycle, the original carbon skeleton remains. The carbon skeleton, stripped of the amino acids, then is free to enter another metabolic cycle to pick up new atoms.
Carbon skeleton

- A carbon skeleton refers to the pattern, in which the carbon atoms are bonded together in a molecule, without regard to differences between single and double bonds and atoms of other elements. The majority of chemical reactions in organic bonds do not break the carbon bond.

Carbon is an element that is the main building block of all living things, including plants, invertebrates and vertebrates. A carbon skeleton is a linkage or chain of carbon atoms....
• **Energy Production**
  – If the cells require additional energy during the metabolic cycles, the carbon skeleton can be utilized. Oxygen is bound to the carbon atoms, in a process called oxidation, to form a water molecule, H₂O, and carbon dioxide, CO₂.

**Catabolism**

– Catabolism is the process in which molecules are broken down into constituent parts, whether to create hormones, enzymes or energy. In catabolism, the remaining product is the carbon skeleton.

– **Building block**
– Carbon is an element that is the main building block of all living things, including plants, invertebrates and vertebrates. A carbon skeleton is a linkage or chain of carbon atoms....
Break down products

Securamine A (1)

Securine A (2)

Chartelline A (3)

Securamine C (4)
1. Alanine aminotransferase
2. Serine dehydratase
3. Glycine cleavage system
4, 5. Serine hydroxymethyltransferase
6. Threonine dehydrogenase
7. $\alpha$-amino-$\beta$-ketobutyrate lyase.
Serine dehydratase

- PLP-enzyme forms a PLP-amino acid Schiff base (like transamination) catalyzes removal of the amino-acid’s $\alpha$–hydrogen.
- Substrate loses the $\beta$-OH group undergoing an $\alpha,\beta$ elimination of H$_2$O rather than deamination.
- Aminoacrylate, the product of this dehydration reaction, tautomerizes to the imine which hydrolyzes to pyruvate and ammonia.
Figure 26-13  The serine dehydratase reaction.

1. Alanine aminotransferase
2. Serine dehydratase
3. Glycine cleavage system
4, 5. Serine hydroxymethyltransferase
6. Threonine dehydrogenase
7. $\alpha$-amino-$\beta$-ketobutyrate lyase.
Glycine conversion to pyruvate

- Gly is converted to Ser before it is transformed to pyruvate.
- Gly to serine is catalyzed by serine hydroxymethyltransferase (another PLP) enzyme that also uses $N^5, N^{10}$-methylene-tetrahydrofolate ($N^5, N^{10}$-methylene-THF) cofactor to proved the C1 unit necessary for this conversion.

- The methylene group is derived from another Gly and the remaining parts are released as CO$_2$ and ammonia catalyzed by the glycine cleavage system.
The reactions catalyzed by the glycine cleavage system, a multienzyme complex.

1. PLP-dependent glycine decarboxylase (P-protein)
2. Lipoamide-containing protein (H-protein)
3. THF requiring enzyme (T-protein)
4. NAD+-dependent, FAD-requiring dihydrolipoyl dehydrogenase (L-protein)
Serine hydroxymethyltransferase catalyzes PLP-dependent Cα-Cβ cleavage

- Catalyzes the conversion of Thr to Gly and acetaldehyde
- Cleaves Cα-Cβ bond by delocalizing electrons of the resulting carbanion into the conjugated PLP ring:
Asn and Asp are degraded to OAA

- Asp can be converted to Asp by L-asparaginase:

\[
\text{Asparagine} \xrightarrow{\text{L-asparaginase}} \text{Aspartate}
\]
Asn and Asp are degraded to OAA

Asp can be converted to Asp by L-asparaginase:

\[
\text{Asparagine} \xrightarrow{\text{L-asparaginase}} \text{Aspartate}
\]
Asn and Asp are degraded to OAA

- Transamination of aspartate to oxaloacetate:

\[
\begin{align*}
\text{Aspartate} & \rightarrow \text{Oxaloacetate} \\
\text{α-ketoglutarate} & \rightarrow \text{Glutamate}
\end{align*}
\]
Arg, Glu, Gln, His, and Pro are degraded to $\alpha$-KG

- Arg, Gln, His, and Pro are converted to Glu which is oxidized to $\alpha$-ketoglutarate by glutamate dehydrogenase.
- Gln to Glu is catalyzed by glutaminase
- His requires several reactions to get to Glu.
Degradation pathways of arginine, glutamate, glutamine, histidine, and proline to $\alpha$-ketoglutarate.
Gln to Glu to $\alpha$-KG

2. Glutaminase
1. Glutamate dehydrogenase
His to Glu

His is nonoxidatively deaminated, hydrated, and the imidazole ring is cleaved to form $N$-formiminoglutamate.

8. Histidine ammonia lyase
9. Urocanate hydratase
10. Imidazolone proponase
11. Glutamate formiminotransferase
Arg and Pro to Glu

3. Arginase
4. Ornithine-δ-aminotransferase
5. Glutamate-5-semialdehyde dehydrogenase
6. Proline oxidase
7. Spontaneous
Ile, Met, and Val are degraded to succinyl-CoA

- Ile, Met, and Val are degraded to propionyl-CoA
- Propioyl-CoA is a product of odd-chain fatty acid degradation that is converted to succinyl-CoA via propionyl-CoA carboxylase (biotin cofactor), methylmalonyl-CoA racemase, and methylmalonyl-CoA mutase (B12 cofactor).
Figure 25-18
Conversion of propionyl-CoA to succinyl-CoA.
Met degradation

- Met reacts with ATP to form S-adenosylmethionine (SAM).
- SAM’s sulfonium ion is a highly reactive methyl group so this compound is involved in methylation reactions.
- Methylation reactions catalyzed by SAM yield S-adenosylhomocysteine and a methylated acceptor molecule.
- S-adenosylhomocysteine is hydrolyzed to homocysteine.
- Homocysteine may be methylated to regenerate Met, in a B12 requiring reaction with N5-methyl-THF as the methyl donor.
- Homocysteine can also combine with Ser to form cystathionine in a PLP catalyzed reaction and $\alpha$-ketobutyrate.
- $\alpha$-ketobutyrate is oxidized and CO2 is released to yield propionyl-CoA.
- Propionyl-CoA proceeds thorough to succinyl-CoA.
1. Methionine adenosyltransferase
2. Methyltransferase
3. Adenosylhomocysteinase
4. Methionine synthase (B12)
5. Cystathionine β-synthase (PLP)
6. Cystathionine γ-synthase (PLP)
7. α-ketoacid dehydrogenase
8. Propionyl-CoA carboxylase (biotin)
9. Methylmalonyl-CoA racemase
10. Methylmalonyl-CoA mutase
11. Glycine cleavage system or serine hydroxymethyltransferase
12. $N^5,N^{10}$-methylene-tetrahydrofolate reductase (coenzyme B12 and FAD)
Steps 1 & 1': Transimination:

\[
\text{\(\alpha\)-Amino acid} + \text{Enzyme–PLP Schiff base} \quad \leftrightarrow \quad \text{Geminal diamine intermediate}
\]

Steps 2 & 2': Tautomeration:

\[
\text{Ketimine} \quad \leftrightarrow \quad \text{Resonance-stabilized intermediate}
\]

Steps 3 & 3': Hydrolysis:

\[
\text{Carbinolamine} \quad + \quad \text{Pyridoxamine phosphate (PMP)–enzyme}
\]

\[
\text{\(\alpha\)-Keto acid}
\]
Figure 25-18
Conversion of propionyl-CoA to succinyl-CoA.
Ile, Met and Val are degraded to succinyl-CoA

- Ile, Met, and Val are degraded to propionyl-CoA.
- Propioyl-CoA is a product of odd-chain fatty acid degradation that is converted to succinyl-CoA via propionyl-CoA carboxylase (biotin cofactor), methylmalonyl-CoA racemase, and methylmalonyl-CoA mutase (B12 cofactor).
Branched chain amino acid degradation

- Degradation of Ile, Leu, and Val use common enzymes for the first three steps
  1. Transamination to the corresponding $\alpha$-keto acid
  2. Oxidative decarboxylation to the corresponding acyl-CoA
  3. Dehydrogenation by FAD to form a double bond.

First three enzymes
  1. Branched-chain amino acid aminotransferase
  2. Branched-chain $\alpha$–keto acid dehydrogenase (BCKDH)
  3. Acyl-CoA dehydrogeanase
The degradation of the branched-chain amino acids (A) isoleucine, (B) valine, and (C) leucine.
The degradation of the branched-chain amino acids (A) isoleucine, (B) valine, and (C) leucine.
(A) Isoleucine: $R_1 = \text{CH}_3-$, $R_2 = \text{CH}_3-\text{CH}_2-$

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

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

\(\alpha\)-Ketoglutarate

Glutamate

1

\(\alpha\)-Keto-\(\beta\)-methylvalerate
\(\alpha\)-Ketoisovalerate
\(\alpha\)-Ketoisocapric acid

NAD\(^+\), CoASH

NADH, CO\(_2\)

2

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

(B) Isobutyryl-CoA

(C) Isovaleryl-CoA

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

\(\alpha\)-Ketoisovalerate

\(\alpha\)-Ketoisocapric acid

\(\alpha\)-Keto-\(\beta\)-methylvalerate
After the three steps, for Ile, the pathway continues similar to fatty acid oxidation (propionyl-CoA carboxylase, methylmalonyl-CoA racemase, methylmalonyl-CoA mutase).

4. **Enoyl-CoA hydratase** - double bond hydration
5. **β-hydroxyacyl-CoA dehydrogenase** - dehydrogenation by NAD+
6. **Acetyl-CoA acetyltransferase** - thiolytic cleavage
For Valine:

7. Enoyl-CoA hydratase - double bond hydration
8. β-hydroxy-isobutyryl-CoA hydrolase - hydrolysis of CoA
9. β–hydroxyisobutyrate dehydrogenase - second dehydration
10. Methylmalonate semialdehyde dehydrogenase - oxidative carboxylation

Last 3 steps similar to fatty acid oxidation
For Leucine:

11. β-methylcrotonyl-CoA carboxylase-carboxylation reaction (biotin)
12. β-methylglutaconyl-CoA hydratase-hydration reaction
13. HMG-CoA lyase

Acetoacetate can be converted to 2 acetyl-CoA
Leucine is a ketogenic amino acid!
Lys is also ketogenic

- Leu proceeds through a typical branched amino acid breakdown but the final products are acetyl-CoA and acetoacetate.

- Most common Lys degradative pathway in liver goes through the formation of the $\alpha$-ketoglutarate-lysine adduct saccharopine.

- 7 of 11 reactions are found in other pathways.
  - Reaction 4: PLP-dependent transamination
  - Reaction 5: oxidative decarboxylation of an a-keto acid by a multienzyme complex similar to pyruvate dehydrogenase and a-ketoglutarate dehydrogenase.
  - Reactions 6,8,9: fatty acyl-CoA oxidation.
  - Reactions 10 and 11 are standard ketone body formation reactions.
Tryptophan $\xrightarrow{O_2}$ N-Formylkynurenine $\xrightarrow{H_2O, HCOO^-}$ Kynurenine

O$_2$ + NADPH $\xrightarrow{3}$ H$_2$O + NADP$^+$

Alanine + 3-Hydroxyanthranilate $\xrightarrow{4}$ 3-Hydroxykynurenine

Quinolinate $\xrightarrow{5}$ 2-Amino-3-carboxymuconate-6-semialdehyde

2-Aminomuconate-6-semialdehyde $\xrightarrow{7}$ NAD$^+$

NADH $\xrightarrow{8}$ 2-Aminomuconate

Acetoacetate $\xrightarrow{10}$ $\xrightarrow{9}$ $\xrightarrow{8}$ $\xrightarrow{7}$ $\xrightarrow{6}$ $\xrightarrow{5}$ $\xrightarrow{4}$ $\xrightarrow{3}$ $\xrightarrow{2}$ $\xrightarrow{1}$ Tryptophan
Glycine and Serine metabolism

1. L-seryl-tRNA
   - AMP+PPi
   - 6.1.1.11 Serine-tRNA ligase
   - tRNA\textsubscript{SER}
   - ATP
   - Phosphatidylcholine metabolism
   - Phosphatidylethanolamine and phosphatidylinerine metabolism

2. Serine hydroxymethyltransferase
   - Serine
   - NAD\textsuperscript{+}
   - Dihydrolipoyl dehydrogenase
   - NADH+H\textsuperscript{+}
   - 1.8.1.4
   - Aminomethyltransferase
   - 2.1.2.10
   - Folate biosynthesis
   - Glycine dehydrogenase (decarboxylating)
   - 1.4.4.2

3. 5-aminolevulinate synthase
   - L-glycyl-tRNA
   - Succinyl-CoA
   - 2.3.1.37
   - CO\textsubscript{2}
   - CoA
   - 5-Aminolevulinate
   - Porphyrin metabolism

4. Hemoglobin digestion
   - Extracellular space
   - 6.1.1.14 Glycine-tRNA ligase
   - AMP+PPi
   - L-glycyl-tRNA

5. Glycine cleavage system
   - Dihydrolipoyl protein
   - H\textsubscript{4}folate
   - CH\textsubscript{2}H\textsubscript{4}folate
   - H\textsubscript{4}folate

6. Folate biosynthesis
Fate of glycine
Fate of amino acid

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine

Ketone bodies
Isocitrate
α-Ketoglutarate

Acetoacetyl-CoA
Acetyl-CoA

Citric acid cycle
Citrate
Succinic acid
Malate
Glucose
Pyruvate

CO₂

Glucogenic
Ketogenic

Arginine
Glutamine
Histidine
Proline

Isoleucine
Methionine
Threonine
Valine

Phenylalanine
Tyrosine

Asparagine
Aspartate

Alanine
Cysteine
Glucose
Serine
Threonine
Tryptophan

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Fate of Individual Amino Acids

- Seven to **acetyl-CoA**
  - Leu, Ile, Thr, Lys, Phe, Tyr, Trp
- Six to **pyruvate**
  - Ala, Cys, Gly, Ser, Thr, Trp
- Five to **α-ketoglutarate**
  - Arg, Glu, Gln, His, Pro
- Four to **succinyl-CoA**
  - Ile, Met, Thr, Val
- Two to **fumarate**
  - Phe, Tyr
- Two to **oxaloacetate**
  - Asp, Asn