Amino acids degradation and synthesis

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Nitrogen metabolism

Atmospheric nitrogen N₂ is most abundant but is too inert for use in most biochemical processes.

Dietary proteins

Atmospheric nitrogen is acted upon by bacteria (nitrogen fixation) and plants to nitrogen containing compounds. We assimilate these compounds as proteins (amino acids) in our diets.

Amino acids

Conversion of nitrogen into specialized products

Body proteins

α-amino groups

Other nitrogen containing compounds

NH₄⁺

Lecture I

Lecture II

Lecture III

Carbon skeletons

Enters various metabolic pathways

Amino acids synthesis & degradation

Disposal of Nitrogen

Urea

excreted
Amino acids catabolism

Removal of α-amino groups

- Urea

Carbon skeleton

1) Oxaloacetate
2) α-ketoglutarate
3) Pyruvate
4) Fumarate
5) Succinyl coenzyme A (CoA)
6) Acetyl CoA
7) Acetoacetate

Enter the metabolic pathways

Synthesis of Lipid, Glucose or in the production of energy through their oxidation to CO₂ and H₂O
## Essential versus Nonessential Amino Acids

Cannot be synthesized de novo, *hence, must be supplied in the diet.*

<table>
<thead>
<tr>
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<th>Nonessential</th>
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<sup>a</sup> Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.

<sup>b</sup> Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.

<sup>c</sup> Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.
Glucogenic and Ketogenic Amino acids

Amino acids are classified as glucogenic, ketogenic, or both based on which of the seven intermediates are produced during their catabolism.

**Glucogenic**
- Amino acids that can be converted into glucose through gluconeogenesis

**Ketogenic**
- Amino acids that can be converted into ketone bodies through ketogenesis

Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle are termed glucogenic or glycogenic.

Amino acids whose catabolism yields either acetoacetate or one of its precursor, (acetyl CoA or acetoacetyl CoA) are termed ketogenic.

Some amino acids are both glucogenic or ketogenic.
Ketone bodies are three water-soluble compounds that are produced as by-products when fatty acids are broken down for energy in the liver and kidney.

The three ketone bodies are acetone, acetoacetic acid and beta-hydroxybutyric acid.

Ketone bodies are transported from the liver to other tissues, where acetoacetate and beta-hydroxybutyrate can be reconverted to acetyl-CoA to produce energy, via the Krebs cycle.

Excess ketone bodies accumulate, this abnormal (but not necessarily harmful) state is called Ketosis.
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Catabolism of the carbon skeletons of amino acids

Amino acids that enter metabolism as oxaloacetate (Asparagine and Aspartate)

Asparagine is hydrolyzed by Asparaginase, liberating ammonia and Aspartate

Aspartate loses its amino group by transamination to form oxaloacetate

Condenses with acetyl CoA to form citrate in the first reaction of the Krebs cycle.

Glucogenic
Amino acids that form \( \alpha \)-ketoglutarate

(Glutamine, Proline, Arginine, Histidine)

1) Glutamine:

\[
\text{Glutamine} \xrightarrow{\text{Glutaminase}} \text{Glutamate} \xrightarrow{\text{Oxidative deamination by glutamine dehydrogenase}} \alpha \text{-ketoglutarate}
\]

2) Proline: It is oxidized to glutamate. Glutamate is then oxidatively deaminated to form \( \alpha \)-ketoglutarate

3) Arginine: This aa is cleaved by arginase to produce ornithine. Ornithine is subsequently converted to \( \alpha \)-ketoglutarate

4) Histidine:
Amino acids that enter metabolism as pyruvate

**1) Alanine**

Alanine, Serine, Glycine, Cystine Threonine

Alanine loses its amino group by transamination to form **pyruvate**

**2) Serine and 3) Glycine**

Inter conversion of serine and glycine

Serine can be converted to glycine and N5, N10-methylenetetrahydofolate or to pyruvate by serine dehydratase.

**4) Cystine**

Cystine \(\rightarrow\) Cysteine \(\rightarrow\) pyruvate

**5) Threonine**

Threonine \(\rightarrow\) pyruvate

\(\rightarrow\) \(\rightarrow\) Succinyl CoA
Amino Acids that enter metabolism as fumarate

Phenylalanine and Tyrosine

1) Phenylalanine and 2) Tyrosine

Hence these two aa are both glucogenic and ketogenic
Amino acids that enter metabolism as succinyl CoA

(Methionine, Valine, Isoleucine, Threonine)

**Methionine**
- Converted into S-adenosylmethionine (SAM), a major universal methyl donor in one-carbon metabolism.
- It is also a source of homocysteine—a metabolite associated with atherosclerotic vascular disease.

1) Methionine condenses with ATP to form S-adenosylmethionine.
2) Methyl group is activated and transferred to oxygen, nitrogen or carbon atoms.
3) The reaction product is S-adenosylhomocysteine.
4) S-adenosylhomocysteine is hydrolyzed to homocysteine.

Homocysteine has two fates:
- In case of methionine deficiency, it is remethylated to methionine.
- If methionine stores are adequate, it enters transulfuration pathway to form cysteine and α-ketobutyrate, which is oxidatively decarboxylated to form propionyl CoA which is then converted to Succinyl CoA.
Amino acids that form succinyl CoA
Valine, Isoleucine and Threonine

1) Valine and Isoleucine

Valine and Isoleucine

\[ \text{Propionyl CoA} \]

Also give Acetyl CoA and hence is both glucogenic and ketogenic

Requires vitamin B12 and Biotin

\[ \text{Succinyl CoA} \rightarrow \text{TCA cycle} \]

2) Threonine

\[ \text{Threonine} \rightarrow \text{dehydrated} \]

\[ \text{Propionyl CoA} \]

\[ \text{Succinyl CoA} \rightarrow \text{TCA cycle} \]
Amino acids that form acetyl CoA or acetoacetyl CoA

1) Leucine  
   Exclusively Ketogenic

2) Isoleucine  
   Ketogenic and glucogenic

3) Lysine  
   Exclusively Ketogenic

4) Tryptophan  
   Glucogenic and ketogenic

Acetyl CoA

Lysine is unusual in that neither of its amino groups undergoes transamination as the first step of catabolism.
Overview of Amino Acid Catabolism

Overview of Amino Acid Catabolism

Seven central products of amino acid metabolism

Enter as TCA cycle intermediates

Enter as both TCA cycle and acetyl derived intermediates

Enter as acetoacetate intermediates

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Essential

Nonessential
Catabolism of the branched chain amino acids

Branched chain AA are: Isoleucine, Leucine, Valine

* Essential AA
• Metabolized primarily by the peripheral tissues (muscles) and not in the liver like other amino acids.
• All three have similar route of catabolism

Transamination
Catalyzed by a single Vitamin B6-requiring enzyme, Branched-chain α-amino acid aminotransferase.

Oxidative decarboxylation
The removal of carboxyl group of the α-keto acids from these three AAs is catalyzed by the same branched-chain α-keto acid dehydrogenase complex. This enzyme uses thiamine pyrophosphate, lipoic acid, FAD, NAD+, and CoA as coenzymes).

Dehydrogenase
Oxidation of the products formed in the decarboxylation reaction yields α-β-unsaturated acyl CoA derivatives.
Role of Folic acid in Amino acid metabolism

Tetrahydrofolic acid, an active form of Folic acid that carries single carbon unit. This carbon unit is transferred to specific structures that are being synthesized or modified.

One-carbon metabolism comprises a network of integrated biochemical pathways that donate, and regenerate, the one-carbon moieties needed for physiologic processes.
Biosynthesis of nonessential amino acids

Non essential amino acids are synthesized from intermediates of metabolism or, from essential amino acids.

**Synthesis from α-keto acids**

- Ala, Asp and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate respectively.

- Glutamate can also be synthesized by Reverse of oxidative deamination, catalyzed by glutamate dehydrogenase.
Biosynthesis of nonessential amino acids

Synthesis by amidation

Glutamine:

- contains an amide linkage with ammonia at the $\gamma$-carboxyl
- Is formed from glutamate
- Reaction is driven by glutamine synthetase
- Requires ATP
- Reaction serves as a major step for detoxification of ammonia in addition to the synthesis of Glutamine for protein synthesis.

Aspargine:

- contains an amide linkage with ammonia at the $\beta$-carboxyl
- Is formed from Aspartate
- Reaction is driven by asparagine synthetase using glutamine as a amide donor.
- Requires ATP
Biosynthesis of nonessential amino acids

Proline:
Glutamate is converted to proline by cyclization and reduction reactions.

Serine:
Synthesized from glycolysis intermediate 3-phosphoglycerate.

Glycine:
Removal of methyl group from serine

Cysteine:
Is synthesized by two consecutive reactions
1) Homocysteine + serine → Cystathionine
2) hydrolysis
   α-ketobutyrate + cysteine
Tyrosine and Cysteine are non essential AA. But their synthesis is dependent on the essential AAs phenylalanine and methionine resp. Hence, these AAs are non essential only when there is an adequate supply of essential AA.
Metabolic defects in Amino acid metabolism

Cystinuria
Histidinemia
Phenylketonuria
Methylmalonyl CoA mutase deficiency
Albinism

Incidence (per 100,000)

Homocystinuria*
Alkaptonuria*
Maple syrup urine disease*
Cystathioninuria*

*All have similar incidence
A deficiency in phenylalanine hydroxylase results in the disease phenylketonuria (PKU).

More than 400 mutations in gene that code for PKU has been identified and the disease is often heterozygous.

Deficiency of enzymes required for the synthesis of BH4 and dihydropterine (BH2) Reductase which regenerates BH4 from BH2 also leads to hyperphenylalaninemia.

BH4 is also required for tyrosine hydroxylase and tryptophan hydroxylase

Treatment: replacement therapy with BH4 or generated products
Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.

Characteristics of classic PKU:

1) Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in tissues, plasma and urine.
2) CNS symptoms: Mental retardation, failure to walk or talk, seizures, hyperactivity, tremor etc.
3) Hypopigmentation: deficiency in the formation of Melanin lead to the deficiency of pigmentation (fair hair, light skin, color, and blue eyes.

Treatments: Synthetic nutrient with low phenylalanine content supplemented with tyrosine
Maple syrup urine disease (MSUD) (rare, prevalence of 1:185,000)

Autosomal recessive disease in which there is a partial or complete deficiency of Branched chain $\alpha$-keto acid dehydrogenase, an enzyme that decarboxylates leucine, Isoleucine, and Valine.

Disease leads to accumulation of these amino acids and branched chain $\alpha$-keto acid substrates causing abnormalities in brain functions.

Characteristics of MSUD
Patients show feeding problems, vomiting, dehydration, severe metabolic acidosis and Classic maple syrup odor to the urine.

Treatments:
Giving a synthetic formula that contains limited amount of leucine, Isoleucine, and Valine.
Albinism

Condition in which defect in tyrosine metabolism results in deficiency in the production of melanin.

Characteristics: hypopigmentation caused due to the deficiency in the formation of melanine results in partial or full absence of pigment from the skin, hair, and eyes.
Homocystinuria

Caused due to the defect in the metabolism of homocysteine. Most common cause is a defect in the enzyme cystathionine β-synthetase. Results in elevation of homocysteine, methionine, and low levels of cysteine in plasma.

Characteristics:
1) High levels of homocysteine and methionine in plasma and urine.
2) Patients exhibit ectopia (displacement of the lens of the eye)
3) Skeletal abnormalities
4) Premature arterial disease
5) Osteoporosis
6) Mental retardation

Treatment:
Restriction of methionine intake and supplementation with Vit B6, B12, and folate.
Alkaptonuria

Rare disease involving deficiency in homogentisic acid oxidase, enzyme in tyrosine degradation pathway.

**Characteristics:**

1) Results in accumulation of homogentisic acidurea.
2) Large joint arthritis
3) Dense, black pigments deposited on the intravertebral disks of the vertebrae.

**Treatment:**

Low protein (low in phenylalanine and tyrosine) diet Help reduce the levels of homogenistic acid.
Summary of the metabolism of amino acids

**Phenylalanine**
- Phenylpyruvate
- Phenylacetate

**Tyrosine**
- p-Hydroxyphenylpyruvate
- Catecholamines

**Phenylketonuria (see text)**

**Albinism (see text)**

**Alkaptonuria (see text)**

**Tyrosinemia Type I**
- The disease is due to a deficiency in fumarylacetoacetate hydrolase.
- Accumulation of fumarylacetoacetate and its metabolites, particularly succinylacetone, in the urine.
- Characteristic cabbage-like odor occurs.
- Liver failure and renal tubular acidosis result.
- Treatment includes dietary restriction of phenylalanine and tyrosine.

**Methylmalonyl CoA Mutase Deficiency**
- The disease is due to a deficiency in methylmalonyl CoA mutase.
- Elevated levels of methylmalonyl CoA occur in blood.
- Metabolic acidosis and developmental problems occur.

**MAPLE SYRUP URINE DISEASE**
- The disease is due to a deficiency in branched-chain α-keto acid dehydrogenase.
- Levels of branched-chain α-amino acids and their α-keto analogs are elevated in plasma and urine.
- Neurologic problems are common. The disease has a high mortality rate.
- Treatment involves a restricted dietary intake of the branched-chain amino acids.

**Serine**
- 3-P-Glycerate
- Cystathionine
- α-Ketobutyrate

**Glycine**
- Cysteine
- Pyruvate

**Asparagine**
- Serine
- Alanine

**Asparagine Synthetase**

**Cysteine**
- γ-Aminobutyrate
- Acetoacetate

**Acetoacetate**
- Citrate
- Malate

**Oxaloacetate**
- Fumarate
- α-Ketoglutarate

**Glutamine**
- Glutamate
- Proline

**Histidine**
- Histamine

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**Methionine**
- S-Adenosylmethionine
- S-Adenosylhomocysteine

**HOMOCYSTINuria**
- The disease is due to a deficiency in cystathionine synthase.
- Accumulation of homocysteine occurs in the urine.
- Methionine and its metabolites are elevated in the blood.
- Mental retardation, osteoporosis, myocardial infarction, and a characteristic dislocation of the lens occur.
Metabolism of amino acids

Catabolism of amino acids
- Removal of \( \alpha \)-amino group
- Metabolism of carbon skeletons

Converges to produce
- Seven products
  - ACETYL CoA
  - ACETOACETYL CoA
  - PYROVATE
  - OXALOACETATE
  - FUMARATE
  - \( \alpha \)-KETOGLUTARATE
  - SUCCINYL CoA

Metabolic defects in amino metabolism
- Characterized by
  - Family of defects in enzymes of amino acid metabolism
    - Caused by point mutations, deletions, splicing errors
      - Which can lead to partially or completely inactive enzyme
    - Which leads to accumulation of substrate and a deficiency in product of defective enzyme
      - Which leads to disturbances in metabolism, particularly the CNS
      - Which leads to seizures, mental retardation, other CNS effects
      - Can result in characteristic smell of the urine
    - Treated by dietary restriction
    - Inheritance is recessive; heterozygotes usually do not show symptoms
    - Usualy screened for in neonates

Synthesis of amino acids
- Transamination of \( \alpha \)-keto acids, for example, pyruvate \( \rightarrow \) alanine
- Amidation, for example, asparate \( \rightarrow \) asparagine
- Synthesis from other amino acids, for example, phenylalanine \( \rightarrow \) tyrosine