Biosynthesis of amino acids

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What Are Proteins?

- Large molecules
- Made up of **chains of amino acids**
- Are found in every cell in the body
- Are involved in most of the body’s functions and life processes
- The sequence of amino acids is determined by DNA
Amino acids - building blocks of proteins

- A total of 20 amino acids are the basic building blocks of proteins:

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>abbreviations</th>
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</tr>
</thead>
<tbody>
<tr>
<td>alanine</td>
<td>Ala A</td>
<td>phenylalanine</td>
<td>Phe F</td>
</tr>
<tr>
<td>arginine</td>
<td>Arg R</td>
<td>proline</td>
<td>Pro P</td>
</tr>
<tr>
<td>asparagine</td>
<td>Asn N</td>
<td>serine</td>
<td>Ser S</td>
</tr>
<tr>
<td>aspartic acid</td>
<td>Asp D</td>
<td>threonine</td>
<td>Thr T</td>
</tr>
<tr>
<td>cysteine</td>
<td>Cys C</td>
<td>tryptophan</td>
<td>Trp W</td>
</tr>
<tr>
<td>glutamine</td>
<td>Gln Q</td>
<td>tyrosine</td>
<td>Tyr Y</td>
</tr>
<tr>
<td>glutamic acid</td>
<td>Glu E</td>
<td>valine</td>
<td>Val V</td>
</tr>
<tr>
<td>glycine</td>
<td>Gly G</td>
<td>leucine</td>
<td>Leu L</td>
</tr>
<tr>
<td>histidine</td>
<td>His H</td>
<td>lysine</td>
<td>Lys K</td>
</tr>
<tr>
<td>isoleucine</td>
<td>Ile I</td>
<td>methionine</td>
<td>Met M</td>
</tr>
</tbody>
</table>

„three letter code“ „one letter code“
Common structural features of amino acids

- All amino acids found in proteins are alpha-amino acids

- All amino acids found in proteins have the L-configuration
- enantiomeric D-configuration does not occur in proteins
- present in other macromolecular structures (cell wall of bacteria)
Properties of amino acids

- Capacity to polymerize
- Useful acid-base properties
- Varied physical properties
- Varied chemical functionality
Essential, Nonessential, and Conditional AA

- **Essential** — must be consumed in the diet
- **Nonessential** — can be synthesized in the body
- **Conditionally essential** — cannot be synthesized due to illness or lack of necessary precursors

- Premature infants lack sufficient enzymes needed to create arginine
Classification of amino acids

- According to the properties of their side chain amino acids can be grouped into five main classes:

**Nonpolar, aliphatic:** alanine, valine, leucine, isoleucine, methionine, proline and glycine

**Aromatic:** phenylalanine, tyrosine and tryptophan

**Polar, uncharged:** serine, threonine, cysteine, asparagine and glutamine

**Positively charged:** arginine, lysine and histidine

**Negatively charged:** aspartic and glutamic acid
Amino acid biosynthesis

- Many amino acids are generated by pathways only present in microorganisms and plants
- Animals do not possess these pathways
- Obtain these amino acids in their diet – **essential**
- Those that can be synthesized by animals – **non-essential**

*Arginine produced in urea cycle
Amounts not sufficient
For protein biosynthesis!

<table>
<thead>
<tr>
<th>Essential</th>
<th>Non-essential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine*</td>
<td>Alanine</td>
</tr>
<tr>
<td>Histidine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Leucine</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Lysine</td>
<td>Glutamate</td>
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<td>Phenylalanine</td>
<td>Glycine</td>
</tr>
<tr>
<td>Threonine</td>
<td>Proline</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Serine</td>
</tr>
<tr>
<td>Valine</td>
<td>Tyrosine</td>
</tr>
</tbody>
</table>
Precursors for AA biosynthesis

- Common metabolites
- Pyruvate, oxaloacetate and \( \alpha \)-ketoglutarate – for alanine, aspartate, asparagine, glutamate and glutamine
Biosynthesis of other non-essential amino acids

- **Glutamate** - precursor for the biosynthesis of *proline and ornithine*
- further metabolized to *arginine* in the urea cycle

- **Serine** - generated from 3-phosphoglycerate (glycolytic intermediate)
  - three step enzymatic process via 3-phosphohydroxypyruvate and 3-phosphoserine

- **Cystein** (in animals) - synthesized from serine and homocysteine
  - break-down product from methionine degradation

- **Glycine** - from serine by serine hydroxymethyltransferase and glycine synthase
Biosynthesis of essential amino acids

- also starts with conventional metabolites
- involves more steps
- These pathways only operative in microorganisms, plants and fungi
- the genes encoding for the required enzymes have been lost early in evolution

- Three metabolic routes to essential amino acids:
  1. The „aspartate family“: lysine, methionine & threonine
  2. The „pyruvate family“: leucine, isoleucine & valine
  3. The „shikimate family“: tyrosine, phenylalanine & tryptophan
The „aspartate family“

In mammals, methionine synthase catalyzes the methyl group transfer to homocysteine in a cobalamin (Vit B12) and tetrahydrofolate dependent reaction:

Plants lack vitamin B12 and use an alternative, THF-dependent mechanism to transfer the methyl group to homocysteine
Methionine is important for one-carbon metabolism
The „pyruvate family“

Acetolactate synthase initiates the biosynthesis

[Chemical structures and reactions shown with text annotations]
Acetolactate synthase is a thiamine-dependent enzyme
Reaction mechanism of acetolactate synthase

Pyruvate

\[ \text{pyruvate} \]

\[ \text{Hydroxyethyl-TPP} \]

\[ \alpha\text{-acetolactate} \]

\[ \alpha\text{-aceto-\alpha-hydroxybutyrate} \]
The shikimate pathway

- Biosynthesis of aromatic amino acids
- Also other biologically important aromatic compounds

- only found in microorganisms, fungi, plants and apicomplexa
- Animals lack this pathway
- need to take up aromatic compounds in their diet
- enzymes of the pathway very attractive targets for the development of antibiotics, antimalarials and herbicides
Starting material for the pathway is *phosphoenolpyruvate and erythrose-4-phosphate*
both metabolites of carbohydrate metabolism
Goes in 7 steps

Involves shikimic acid as well
Isolated from the plant *Illicium religiosum* (Japan, 1885)
The seven steps of the shikimate pathway

1. Phosphoenolpyruvate + D-erythrose-4-phosphate → 3-deoxy-D-arabino-heptulonate 7-phosphate
2. 3-deoxy-D-arabino-heptulonate 7-phosphate → 3-dehydroquinate
3. 3-dehydroquinate + H₂O → 3-dehydroshikimate
4. NADPH + 3-dehydroshikimate → shikimate 3-phosphate
5. Shikimate 3-phosphate + ATP → shikimate
6. 5-enolpyruvylshikimate 3-phosphate (EPSP) + P₁ → shikimate 3-phosphate
7. Chorismate + P₁ → 5-enolpyruvylshikimate 3-phosphate (EPSP)
1st step: 3-Deoxy-D-arabinoheptulosonate-7-phosphate synthase

- DAHP-synthase
2nd step: 3-Dehydroquinate synthase (DHQ-synthase)

3-deoxy-D-arabino-heptulosonate 7-phosphate → 3-dehydroquinate
3rd step: 3-Dehydroquinate dehydratase (DHQase)
4th step: Shikimate dehydrogenase

3-dehydroshikimate $\xrightarrow{4}$ shikimate
5th step: Shikimate kinase

\[
\text{shikimate} \xrightarrow{\text{ATP}} \text{shikimate 3-phosphate}
\]
6th step: 5-enolpyruvylshikimate-3-phosphate synthase

- EPSP-synthase
7th step: Chorismate synthase

- Greek: *chorismic* (to separate, to part)
Biosynthesis of tyrosine & phenylalanine

8: chorismate mutase
9: prephenate dehydrogenase
10/12: transaminases
11: prephenate dehydratase

Plants only:
9: transaminase
10: arogenate dehydrogenase
11: arogenate dehydratase
Tryptophan biosynthesis

1. Chorismate
2. Glutamine
3. Glutamate
4. Anthranilate
5. Pyruvate
6. 3 steps
7. β subunit
8. Serine
9. H₂O
10. Indole
11. α subunit
12. Glyceraldehyde-3-phosphate
13. Indole-3-glycerol phosphate
14. Tryptophan synthase

Tryptophan
The tryptophan synthase complex

- The intermediate product, indole, is „channeled“ to the active site of the β-subunit through a 25 Å long tunnel formed by the protein complex
Amino acids are important biosynthetic precursors

- Biosynthesis of *porphyrines* (heme)
- Biosynthesis of physiologically *active amines* (neurotransmitters)
- Biosynthesis of „secondary“ metabolites in plants (alkaloids)
- Biosynthesis of *purine and pyrimidine* bases (RNA, DNA)
- Biosynthesis of fungal *antibiotics* (penicillin, cephalosporin)
Summary

- Review on AA
- Precursors for AA biosynthesis
- Biosynthesis of non-essential AA
- Biosynthesis of essential AA: aspartate, pyruvate and shikimate family
- Shikimate pathway
- Biosynthesis of aromatic AA
- Tryptophan synthase complex
- Needs of AA for further biosynthesis pathways