Protein and Amino Acids in Sports Nutrition

Advanced Level
Module I

Protein Composition and Structure
Protein Digestion and Absorption
Molecular Pathways for Stimulating Protein Synthesis in Muscle
Cellular Protein Degradation in Muscle
Metabolism of Amino Acids
Protein Composition and Structure
**Functions of Proteins**

- **Enzymes**
  - All biological enzymes are made of protein
    - For example, the digestive enzymes trypsin and amylase

- **Hormones (some)**
  - Insulin and glucagon
  - Not all hormones are proteins
    - Testosterone is a steroid

- **Structural**
  - Actin and myosin (muscle)
  - Collagen (skin)
Functions of Proteins (Cont’d)

- Immunologic
  - Antibodies

- Transport and storage
  - Carriers of fatty acids, oxygen (hemoglobin), iron, vitamin A, copper, and other nutrients
  - Cholesterol and triglycerides carried by lipoproteins

- pH buffering
  - In blood, muscle, essentially everywhere

- Energy source
  - When carbohydrates are limited (gluconeogenesis)
Amino Acids (AAs)

- Proteins in the body comprise 20 AAs
- Of these, 9 AAs are considered to be essential amino acids
  - Body cannot synthesize them from other AAs or internal metabolites
    - Sometimes referred to as indispensible AAs
  - Must be present in appropriate dietary amounts for normal growth and development to occur
- Other 11 AAs are non-essential amino acids
  - Can be made from other AAs in the diet
- Conditionally essential amino acids
  - Non-essential AAs can become essential
    - Due to unusually high AA requirements (eg, growth, metabolic stress)
    - Defects in AA metabolism
      - For example, in the disease phenylketonuria (PKU), phenylalanine cannot be converted to tyrosine, so tyrosine becomes essential
        » Tyrosine is normally a non-essential AAs

## Amino Acids in Humans

<table>
<thead>
<tr>
<th>Essential</th>
<th>Non-essential</th>
<th>Conditionally essential</th>
<th>Precursor(s) to conditionally essential AAs</th>
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</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>Alanine</td>
<td>Arginine</td>
<td>Glutamine/glutamate, aspartate</td>
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<tr>
<td>Isoleucine</td>
<td>Asparagine</td>
<td>Cysteine</td>
<td>Methionine, serine</td>
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<td>Leucine</td>
<td>Aspartic acid</td>
<td>Glutamine</td>
<td>Glutamic acid, ammonia</td>
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<tr>
<td>Lysine</td>
<td>Glutamic acid</td>
<td>Glycine</td>
<td>Serine, choline</td>
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<tr>
<td>Methionine</td>
<td>Serine</td>
<td>Proline</td>
<td>Glutamate</td>
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<tr>
<td>Phenylalanine</td>
<td></td>
<td>Tyrosine</td>
<td>Phenylalanine</td>
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<tr>
<td>Threonine</td>
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<tr>
<td>Tryptophan</td>
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<td></td>
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<tr>
<td>Valine</td>
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</table>

Basic Structure of an Amino Acid

- Central carbon atom (alpha carbon [Cα]) linked to
  - Amino group (positive)
  - Carboxylic acid group (negative)
  - Hydrogen
  - Distinctive side chain (R)
    - Makes each AA different

- α-keto acid is resulting structure when the amino group (NH3+) is removed (deamination)

<table>
<thead>
<tr>
<th>R-Groups</th>
<th>Amino Acids</th>
<th>Structures</th>
</tr>
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<tbody>
<tr>
<td>H-</td>
<td>Glycine</td>
<td>-OOC-CH₂-CH₂-</td>
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<tr>
<td>CH₃-</td>
<td>Alanine</td>
<td>H₂N-C-CH₂-CH₂-</td>
</tr>
<tr>
<td>HO-CH₂-</td>
<td>Serine</td>
<td>H-N-CH₂-CH₂-CH₂-</td>
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<tr>
<td>CH₃-CH-</td>
<td>Threonine</td>
<td>C=NH₂⁺</td>
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<td></td>
<td></td>
<td>NH₂</td>
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<tr>
<td>-OOC-CH₂-</td>
<td>Aspartic acid</td>
<td>CH₂-CH₂-CH₂-CH₂-</td>
</tr>
<tr>
<td>H₂N-C-CH₂-</td>
<td>Asparagine</td>
<td>NH₃⁺</td>
</tr>
</tbody>
</table>

R-Groups for Amino Acids (2 of 3)

Valine

\[ \text{H}_3\text{C} \quad \text{CH-} \quad \text{H}_3\text{C} \]

Leucine

\[ \text{H}_3\text{C} \quad \text{CH-CH}_2^- \quad \text{H}_3\text{C} \]

Isoleucine

\[ \text{CH}_2 \quad \text{CH}_2 \quad \text{CH-} \quad \text{CH}_3 \]

Cysteine

\[ \text{CH}_2^- \quad \text{SH} \]

Methionine

\[ \text{CH}_2^-\text{CH}_2^- \quad \text{S-CH}_3 \]

Branched-chain amino acids

Sulfur-containing amino acids

R-Groups for Amino Acids (3 of 3)

Histidine

Phenylalanine

Tyrosine

Proline

(whole structure, not just R-group)

Tryptophan

1. What are the building blocks of proteins?
   A. Hormones
   B. Monosaccharides
   C. Amino acids
   D. Fatty acids

2. Nonessential amino acids can be made from other amino acids in the diet.
   A. True
   B. False

3. Proteins have which of the following functions?
   A. Transport and storage
   B. Structure and energy
   C. Hormones and enzymes
   D. All of the above
1. What are the building blocks of proteins?

- A. Hormones
  Correct, amino acids are used to construct proteins.

- B. Monosaccharides
  Incorrect, please review slide Amino Acids (AAs) to better understand protein structure.

- C. Amino acids
  Correct, amino acids are used to construct proteins.

- D. Fatty acids
  Incorrect, please review slide Amino Acids (AAs) to better understand protein structure.
2. Nonessential amino acids can be made from other amino acids in the diet.

✓ A. True

Correct, the definition of nonessential amino acids includes that they can be made from other amino acids in the diet.

✗ B. False

Incorrect, please review slide Amino Acids (AAs) to better understand the different types of amino acids.
Progress Check—Protein Composition and Structure

3. Proteins have which of the following functions?

   ✗ A. Transport and storage
       Incorrect, please review slides on Functions of Proteins to better understand all the roles that proteins have in the body.

   ✗ B. Structure and energy
       Incorrect, please review slides on Functions of Proteins to better understand all the roles that proteins have in the body.

   ✗ C. Hormones and enzymes
       Incorrect, please review slides on Functions of Proteins to better understand all the roles that proteins have in the body.

   ✓ D. All of the above
       Correct, proteins serve multiple functions in the body.
Synthesis of Cellular Proteins

- All cells use AAs from within the body or from dietary sources to make new proteins
- DNA (gene) → RNA (template) → protein (AAs connected)
- Transcription
  - Makes the template (mRNA) for protein synthesis from DNA sequence
  - Sequence of DNA bases arranged in units of 3 (codons) that “code” for a specific amino acid

Translation of DNA for Making Cellular Proteins

- Translation of mRNA
  - Actual building of the peptide by the ribosome
  - Involves tRNA (pulls in AA), ribosome (assembly), and mRNA template
    • Each AA has its own tRNA
    • tRNA has an anticodon that is complementary to codon in mRNA
    • AAs are linked together by peptide bonds

Base pairing of mRNA is always A with U and G with C.

Abbreviations: A, adenine; C, cytosine; Cys, cysteine; ER, endoplasmic reticulum; G, guanine; Gln, glutamine; Met, methionine; Phe, phenylalanine; Tyr, tyrosine; U, uracil.

Structure of Proteins

- Proteins are made of individual AAs that are linked together via a peptide bond between carboxylic acid group of one AA and the amino group of another AA.

- Arrangement of the amino acids allows for different proteins to have different functions, which are determined by:
  - Number of amino acids
  - Sequence of amino acids
  - Physical interactions between adjacent amino acids

Structure of Proteins and Peptides

- Peptides
  - Chain of AAs, but shorter than a full protein
  - Dividing line between a peptide and protein is ambiguous
    - ~50 AA units is a reasonable delineation, but no exact definition

- Parallels with carbohydrate structures
  - Free amino acid is like the monosaccharide
  - Dipeptide is like the disaccharide
  - Oligopeptide (3 to maybe 50 AA units) is like oligosaccharide (3-10 monosaccharide units)

Levels of Protein Structure

- **Primary**
  - Specific sequence of AAs linked together

- **Secondary**
  - Basic interaction between R groups of adjacent AAs create basic 3-dimensional shapes
    - Alpha helix (simple coil)
    - Beta-pleated sheet (multiple connected rows form flat structure)

Levels of Protein Structure

- **Tertiary**
  - True, overall 3-dimensional structure of intact protein from beginning to end of peptide chain
  - Newly formed proteins require proper folding by the cell to achieve the shape for proper function

- **Quaternary**
  - Some proteins (but not all) contain multiple peptides (separate AA chains) that associate together
  - Each separate peptide of a multi-peptide protein is known as a subunit
  - Proteins can exist as dimers (2 subunits), trimers (3 subunits), tetramer (4 subunits), etc (eg, hemoglobin is a tetramer)

Progress Check—Protein Composition and Structure

1. Protein functions are determined by:
   A. Number of amino acids
   B. Sequence of amino acids
   C. Physical interactions between adjacent amino acids
   D. All of the above

2. DNA is transcribed to mRNA that is the template for protein synthesis.
   A. True
   B. False

3. All proteins have which of the following structures?
   A. Primary, secondary, tertiary, and quaternary
   B. Primary, secondary, and tertiary
   C. Primary, secondary, and quaternary
   D. Primary and secondary
1. Protein functions are determined by:?
   ✗ A. Number of amino acids
       Incorrect, please review slide Structure of Proteins to better understand all of the determinates of protein function.
   ✗ B. Sequence of amino acids
       Incorrect, please review slide Structure of Proteins to better understand all of the determinates of protein function.
   ✗ C. Physical interactions between adjacent amino acids
       Incorrect, please review slide Structure of Proteins to better understand all of the determinates of protein function.
   ✓ D. All of the above
       Correct, protein function can be determined by number and sequence of amino acids as well as their physical interactions.
Progress Check—Protein Composition and Structure

2. DNA is transcripted to mRNA that is the template for protein synthesis.

✓ A. True
Correct, this is the sequence of events for protein synthesis.

✗ B. False
Incorrect, please review slide Synthesis of Cellular Proteins to better understand the steps in protein synthesis.
Progress Check—Protein Composition and Structure

3. All proteins have which of the following structures?

   - A. Primary, secondary, tertiary, and quaternary
     Incorrect, please review slides on Levels of Protein Structure to better understand all the structures that proteins require.

   - B. Primary, secondary, and tertiary
     Correct, all proteins do not require quaternary structures for proper functioning.

   - C. Primary, secondary, and quaternary
     Incorrect, please review slides on Levels of Protein Structure to better understand all the structures that proteins require.

   - D. Primary and secondary
     Incorrect, please review slides on Levels of Protein Structure to better understand all the structures that proteins require.
Protein Digestion and Absorption
Protein Digestion

Gastric phase (stomach)

- Hydrochloric acid (HCl) produced by parietal cells of the stomach unravels tertiary and quaternary structure of protein (denaturation)

- Pepsinogen (chief cells) → HCl → Pepsin (an endopeptidase)

- Pepsin digestion of proteins → Large peptide fragments and free AAs

Protein Digestion

Small intestine phase

- Cholecystokinin (CCK) triggers pancreatic secretions (zymogens) following arrival of digestion products in stomach
- Zymogens are converted to active digestive enzymes

- Trypsinogen > Brush border enteropeptidase > Trypsin
- Chymotrypsinogen > Trypsin
- Proelastase > Trypsin
- Procarboxypeptidases A and B > Trypsin

- Trypsin (endopeptidase)
- Chymotrypsin (endopeptidase)
- Elastase (endopeptidase)
- Carboxypeptidases A and B (exopeptidases)

- Any remaining oligopeptides are digested by brush border aminopeptidases
- Free amino acids, dipeptides, and tripeptides are taken up by intestinal cells

Amino Acid and Peptide Absorption

- Intestinal cells have transport proteins at both the apical membrane (luminal side) and the basolateral membrane (blood side).
- These transporters can be active transporters with ion cotransport (\(\text{Na}^+, \text{Cl}^-, \text{K}^+, \text{or} \text{H}^+\)).

Amino Acid and Peptide Absorption (Cont’d)

- The transporters can carry
  - Free amino acids (several different transporter families, depends on AA properties)
  - Di- and tripeptides (eg, PepT1 transporter)
    - Can transport dipeptides such as carnosine
    - Absorption of di-and tripeptides from intestine is more efficient than for the corresponding free AAs

- Non-proteinogenic AAs similarly have specific transporters
  - Creatine, beta-alanine, taurine, gamma-aminobutyric acid (GABA), etc

Rates of Protein Digestion

- Proteins are digested at different rates
  - Dependent on AA content and structure of peptides
  - Similar to glycemic index concept for carbohydrate

- Example: whey versus casein
  - Whey does not form a curd in the stomach, is rapidly digested, and results in quick rise in plasma AA (fast protein)
  - Native casein exists in micelles that are resistant to digestion, and take longer to empty from the stomach (slow protein)
    - Some casein may be partially hydrolyzed, and is therefore more quickly digested than micellar casein

Time-dependent evolution of plasma enrichments of the orally administered tracer after ingestion of intrinsically [1-\textsuperscript{13}C]-leucine-labeled casein (CAS) (■) and, whey protein (WP) (○) or unlabeled CAS (□) and WP (○) added with free [5,5,5-\textsuperscript{2}H\textsubscript{3}]-leucine. The enrichments in the meals are similar (~3.4 mol percent excess). Results are expressed as mean ± SEM. Exo Leu R\textsubscript{a}, exogenous leucine rate of appearance in plasma.

Rates of Protein Digestion (Cont’d)

- Soy protein
  - Soy protein is more rapidly digested than whole cow’s milk protein (which is ~80% casein), and is probably more comparable to whey in digestion rate.

- Wheat gluten/vegetable proteins
  - Wheat gluten isolate is digested fairly quickly but not generally available commercially.
    - In whole foods, protein is often bound or combined with fiber, which reduces digestion rate and rise of plasma AAs.

- Addition of non-protein energy (ie, fat and carbohydrate in a complete meal) to any protein ingestion slows digestion and can attenuate differential effects between “fast” and “slow” proteins.

References:

Progress Check—Protein Digestion and Absorption

1. Whey protein is an example of a ___________ protein and casein is a ___________ protein with regard to speed of digestion.
   A. Fast, slow
   B. Slow, fast
   C. Fast, fast
   D. Slow, slow

2. Soy is a protein that is digested moderately fast, but slower than whey.
   A. True
   B. False

3. Proteins are transported into intestinal cells in the form of which of the following?
   A. Amino acids
   B. Dipeptides
   C. Tripeptides
   D. All of the above
   E. A and B only
Progress Check—Protein Digestion and Absorption

1. Whey protein is an example of a ___________ protein and casein is a ___________ protein with regard to speed of digestion.

✓ A. Fast, slow
   Correct, whey is digested quickly and casein is digested more slowly.

✗ B. Slow, fast
   Incorrect, please review slide Rates of Protein Digestion to better understand the digestion of different proteins.

✗ C. Fast, fast
   Incorrect, please review slide Rates of Protein Digestion to better understand the digestion of different proteins.

✗ D. Slow, slow
   Incorrect, please review slide Rates of Protein Digestion to better understand the digestion of different proteins.
2. Soy is a protein that is digested moderately fast, but slower than whey.

✓ A. True
   Correct, soy protein exhibits intermediate digestion compared with whey and casein.

✗ B. False
   Incorrect, please review slide Rates of Protein Digestion (Cont’d) to better understand the digestion of different proteins.
Progress Check—Protein Digestion and Absorption

3. Proteins are transported into intestinal cells in the form of which of the following?

- A. Amino acids
  Incorrect, please review slide on Amino Acid and Peptide Absorption (Cont’d) to better understand all the protein forms that can be transported.

- B. Dipeptides
  Incorrect, please review slide on Amino Acid and Peptide Absorption (Cont’d) to better understand all the protein forms that can be transported.

- C. Tripeptides
  Incorrect, please review slide on Amino Acid and Peptide Absorption (Cont’d) to better understand all the protein forms that can be transported.

- D. All of the above
  Correct, proteins can be transported as amino acid and di- and tri-peptides.

- E. A and B only
  Incorrect, please review slide on Amino Acid and Peptide Absorption (Cont’d) to better understand all the protein forms that can be transported.
Molecular Pathways for Stimulating Protein Synthesis in Muscle
Protein Synthesis and the mTOR Pathway

- The mTOR pathway is a major signaling route for initiating protein synthesis

- mTOR can be affected by a variety of different factors
  - Positively
    - Nutrients (eg, leucine and metabolites such as HMB)
    - Insulin
    - Growth factors (eg, IGF-1)
  - Negatively
    - Inflammatory messengers (eg, tumor necrosis factor-α)
    - Lipopolysaccharide (bacterial toxin)

Abbreviation: mTOR, mammalian target of rapamycin.

Key Signaling Events in the mTOR Pathway

- Insulin and growth factors can stimulate PI3 Kinase, which effectively activates Akt
  - Akt is also a kinase, which promotes phosphorylation (activation) of mTOR

- Phosphorylated mTOR has several effects
  - Phosphorylation of 4EBP-1, which keeps it from binding eIF4E
    - Unbound eIF4E can join with other initiating factors (eg, eIF4G) to initiate translation
  - Activation of p70S6K
    - Responsible for helping push translation forward

Cellular Protein Degradation in Muscle
Muscle Protein Turnover

- There is a constant flux in muscles between muscle protein synthesis and muscle protein breakdown
  - Net activity is turnover: ~ 4.6 g/kg body weight or ~300 g/day

- Goal for increasing muscle size is to have muscle protein synthesis exceed breakdown

The Ubiquitin-Proteasome Pathway for Protein Degradation

- Although there are several pathways for breaking down muscle protein, the major component is the ubiquitin proteasome pathway
  - Specific tagging of proteins with ubiquitin for subsequent degradation by the proteasome

Can Nutritional Factors Affect Protein Degradation?

- Ubiquitin proteasome pathway activated by:
  - Amino acid deprivation (i.e., low protein intake)
  - Increased levels of reactive oxygen species
  - Increased levels of inflammatory cytokines such as TNF-α and interferon γ
    - Generally associated with states of inflammation or traumatic injury
    - Overweight and obesity are broadly inflammatory conditions

- Ubiquitin proteasome pathway inhibited by:
  - β-Hydroxy-β-methylbutyrate (HMB), a leucine catabolite that reduces reactive oxygen species production by inhibiting caspase activity
  - Eicosapentaenoic acid (EPA), a polyunsaturated fatty acid, which may reduce NF-κB accumulation in the nucleus

Effects of HMB and EPA on Protein Synthesis and Degradation

Initiator (PIF, LPS, TNF-α, angiotensin II, etc.)

Caspase-8
Caspase-3

NF-κβ (nuclear accumulation)
Proteasome + E3 mRNA

ROS
p38 MAPK

PKR
PKR
P

eIF2α P
eIF2α

Translational efficiency

Protein degradation (Protein degradation ↓) *
Protein synthesis (Protein synthesis ↑) *

HMB blocks pathway here
EPA may inhibit

Abbreviations: PIF, proteolysis-inducing factor; LPS, lipopolysaccharide; TNF, tumor necrosis factor; PKR, RNA-dependent protein kinase; MAPK, mitogen-activated protein kinase; NF, nuclear factor; ROS, reactive oxygen species; eIF, eukaryotic initiation factor; P, phosphorylated; HMB, β-Hydroxy-β-Methylbutyrate; EPA, eicosapentaenoic acid.

*Effects on protein degradation and synthesis in the presence of HMB/EPA.

Progress Check—Cellular Protein Degradation in Muscle

1. The ubiquitin proteasome pathway is activated by ____________ and is inhibited by __________.
   A. High protein intake, EPA  
   B. Low protein intake, HMB  
   C. Inflammatory states, low protein intake  
   D. HMB, reactive oxygen species

2. The ubiquitin proteasome pathway is the major component of protein degradation.
   A. True  
   B. False
Progress Check—Cellular Protein Degradation in Muscle

1. The ubiquitin proteasome pathway is activated by __________ and is inhibited by __________.
   - A. High protein intake, EPA
     Incorrect, please review slide Can Nutritional Factors Affect Protein Degradation? to better understand how the ubiquitin proteasome pathway is affected by nutrition.
   - B. Low protein intake, HMB
     Correct
   - C. Inflammatory states, low protein intake
     Incorrect, please review slide Can Nutritional Factors Affect Protein Degradation? to better understand how the ubiquitin proteasome pathway is affected by nutrition.
   - D. HMB, reactive oxygen species
     Incorrect, please review slide Can Nutritional Factors Affect Protein Degradation? to better understand how the ubiquitin proteasome pathway is affected by nutrition.
Progress Check—Cellular Protein Degradation in Muscle

2. The ubiquitin proteasome pathway is the major component of protein degradation.

✔ A. True

Correct, although there are several pathways for breaking down muscle protein, the major component is the ubiquitin proteasome pathway.

✗ B. False

Incorrect, please review slide The Ubiquitin-Proteasome Pathway for Protein Degradation to better understand protein degradation.
Metabolism of Amino Acids
Anabolic and Catabolic Pathways Involving Amino Acids

- **Anabolic (building up)**
  - Building of tissue proteins via protein synthesis
  - Must have adequate amounts of all essential AAs, or protein synthesis cannot proceed

- **Catabolic (breaking down)**
  - Remove amino group of AA (results in $\alpha$-keto acid)
  - Oxidize the remaining carbon skeleton

Amino Acid Metabolism

- AAs are taken up by peripheral cells in a manner similar to the transporters of the intestine

- Liver takes up a majority of absorbed AA
  - Liver is first to access dietary AAs due to portal circulation
    - Exception is branched-chain AAs, which liver does not use; taken up by muscle instead
  - Final catabolism of AA also occurs in liver
    - Amino groups removed and disposed of via urea cycle

Transamination and Deamination of Amino Acids

- **Transamination**
  - Transfer amino group from one AA to the carbon skeleton of another by an aminotransferase enzyme
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are examples
    - ALT and AST included as liver function tests in lab panels (high blood levels indicate injury to liver)
  - Aminotransferases generally require vitamin B\(_6\) (pyridoxal phosphate) in its coenzyme form to work properly

- **Deamination**
  - Removal of amino group (as ammonia) for excretion as urea
  - Occurs when amino acids are oxidized for energy

An Example of Transamination

Pyruvate

\[
\text{H}_3\text{C-CCCC-OC-}^-\]

Alanine

\[
\text{NH}_3^+ \quad \text{H}_3\text{C-CCCC-OC-}^-\]

Alanine aminotransferase (ALT)

\[
\text{NH}_3^+ \quad \text{O-C-CH}_2\text{-CH}_2\text{-CCCC-OC-}^-\]

Glutamate

\[
\text{O-C-CH}_2\text{-CH}_2\text{-CCCC-OC-}^-\]

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

Amino group is \textit{trans}ferred to another carbon skeleton

Glutamine is the primary means of transporting nitrogen from peripheral tissues.

Muscle, peripheral tissues

Blood

Liver

Deamination: The Urea Cycle in Liver

- **Mitochondria**
  - $CO_2 + NH_4^+$

- **Cytosol**
  - $H_2N-C-NH_2$ (Urea)
  - $H_2O$

1. Ornithine
   - $2 \text{ Mg-ATP}$
   - $N$-acetyl glutamate
   - $2 \text{ Mg-ADP} + P_i$

2. Carbamoyl phosphate
   - $P_i$

3. Argininosuccinate
4. Fumarate
5. Arginine

Production and Excretion of Urea

- Ammonia is toxic, so it cannot accumulate within the body safely
  - Hepatic encephalopathy can result
  - Gut bacteria are also a source of ammonia

- Urea is less toxic and is an effective disposal mechanism of nitrogen
  - Excreted in the urine
  - Urea cycle disorders can necessitate low protein diets

- Common problems with system
  - Elevated ammonia ($\text{NH}_3$)
    - Urea cycle is not functioning as it should (liver problem)
  - Elevated blood urea nitrogen (BUN)
    - Liver makes urea, but kidney fails to excrete it (kidney problem)

Carbon Skeletons of Catabolized Amino Acids

- Once the amino group is removed, carbon skeletons can be metabolized for potential energy production
  - In positive calorie balance, excess AAs can be stored as energy

- Glucogenic $\alpha$-keto acids: generation of glucose

- Ketogenic $\alpha$-keto acids: metabolized more like fat (generation of ketone bodies or acetyl coenzyme A [CoA])

- Some amino acids are both glucogenic and ketogenic

- Only leucine and lysine are exclusively ketogenic

Where the Carbon Skeletons Are Used

- Leucine and lysine are exclusively ketogenic

Progress Check—Metabolism of Amino Acids

1. Which statement is NOT true regarding amino acid metabolism.
   A. Amino groups are transferred from one amino acid to the carbon skeleton of another by an aminotransferase enzyme in a process known as transamination
   B. Deamination involves the removal of an amino group (as ammonia) for excretion as urea
   C. Aminotransferases generally require vitamin C in its coenzyme form to work properly
   D. Deamination occurs when amino acids are oxidized for energy

2. The anabolic process builds muscle proteins and the catabolic process degrades muscle proteins.
   A. True
   B. False

3. Carbon skeletons of amino acids can be metabolized for which potential energy production?
   A. Generation of glucose
   B. Generation of ketone bodies
   C. Generation of acetyl coenzyme A [CoA]
   D. All of the above
Progress Check—Metabolism of Amino Acids

1. Which statement is NOT true regarding amino acid metabolism.

   ✗ A. Amino groups are transferred from one amino acid to the carbon skeleton of another by an aminotransferase enzyme in a process known as transamination
   *Incorrect, please review slide Transamination and Deamination of Amino Acids to better understand the metabolism of amino acids.*

   ✗ B. Deamination involves the removal of an amino group (as ammonia) for excretion as urea
   *Incorrect, please review slide Transamination and Deamination of Amino Acids to better understand the metabolism of amino acids.*

   ✓ C. Aminotransferases generally require vitamin C in its coenzyme form to work properly
   *Correct, aminotransferases generally require vitamin B₆ (pyridoxal phosphate) in its coenzyme form to work properly.*

   ✗ D. Deamination occurs when amino acids are oxidized for energy
   *Incorrect, please review slide Transamination and Deamination of Amino Acids to better understand the metabolism of amino acids.*
Progress Check—Metabolism of Amino Acids

2. The anabolic process builds muscle proteins and the catabolic process degrades muscle proteins.

✓ A. True

Correct, the anabolic process builds proteins and the catabolic process degrades proteins.

✗ B. False

Incorrect, please review slide Anabolic and Catabolic Pathways Involving Amino Acids to better understand the anabolic and catabolic pathways for amino acids.
Progress Check—Metabolism of Amino Acids

3. Carbon skeletons of amino acids can be metabolized for which potential energy production?
   
   A. Generation of glucose
      Incorrect, please review slide on Carbon Skeletons of Catabolized Amino Acids to better understand all the potential energy productions that can be used from amino acid carbon skeletons.

   B. Generation of ketone bodies
      Incorrect, please review slide on Carbon Skeletons of Catabolized Amino Acids to better understand all the potential energy productions that can be used from amino acid carbon skeletons.

   C. Generation of acetyl coenzyme A [CoA]
      Incorrect, please review slide on Carbon Skeletons of Catabolized Amino Acids to better understand all the potential energy productions that can be used from amino acid carbon skeletons.

   D. All of the above
      Correct, the carbon skeletons of amino acids can be used for the generation of glucose, ketone bodies, or acetyl coenzyme A.
Branched-Chain Amino Acid (BCAA) Metabolism

- Unlike other AAs, BCAA metabolism begins in skeletal muscle
- Liver lacks first two enzymes in the catabolic pathway of BCAA
  - Liver can metabolize the carbon skeletons
- First 2 metabolic steps common to each BCAA
  - Branched-chain amino acid transaminase (BCAAT)
    - Transfers amino group to $\alpha$-ketoglutarate to form glutamate
  - Branched-chain keto-acid dehydrogenase (BCKDH)
    - Oxidative decarboxylation, addition of CoA
    - Deficiency in the activity of this enzyme is responsible for Maple Syrup Urine Disease
- Valine and isoleucine are converted first to propionyl CoA and then to succinyl CoA
  - These two can be considered glucogenic
  - Isoleucine can also be converted to acetyl CoA, so it is also ketogenic
- Leucine is solely ketogenic

Additional Information Regarding BCAAs

- Muscle oxidation of BCAAs, especially leucine, may increase during metabolic stress (such as exercise) or conditions of low carbohydrate availability.

- Leucine is also unique among amino acids in its ability to stimulate protein synthetic pathways (via mTOR pathway), particularly in muscle:
  - Leucine (and other BCAAs) avoid primary hepatic metabolism, suggesting that evolution has selected leucine as a nutrient signal that indicates adequate AAs for muscle protein synthesis.
  - Leucine metabolites (e.g., HMB, α-ketoisocaproate) may have secondary effects.

Approximately 5% to 10% of α-ketoisocaproyl (KIC) is converted to HMB (by KIC-dioxygenase) in the cell cytosol.
**β-Hydroxy-β-Methylbutyrate (HMB)**

- Clinical studies evaluating the benefit of HMB supplementation have reported mixed results
- There are potential differences in muscle metabolism between more highly trained and untrained athletes
  - More potential for benefit probably in untrained athletes
- Length of HMB supplementation may have been insufficient in negative studies
  - More highly trained athletes might require longer supplementation (only 1 negative study > 4 weeks duration)
- Very limited data (only 2 studies) on HMB doses over 3 g/day
  - Larger body size might require a larger dose
- Type of training may be important
- There are several good meta-analyses and reviews of HMB and athletic performance\(^1-6\)

Interorgan Amino Acid Exchange and the Amino Acid Pool

- Amino acids that are available for use by tissues are gathered in a circulatory “pool”
  - ~100 grams of AAs from dietary sources
  - ~300 grams of AAs from degraded endogenous proteins
  - ~300 grams of AAs used to synthesize new proteins
  - Most of remaining ~100 g are catabolized

- Some AAs circulate in higher levels than others
  - Glutamine is the most abundant amino acid in plasma
  - Glutamine has two amino groups (compared to glutamate with one)
    • Used to carry ammonia from peripheral cells (eg, muscle) to liver to be excreted as urea
  - Alanine is released by glycolytically active skeletal muscle
    • Taken up by liver, subsequently converted to pyruvate for gluconeogenesis or shunted to urea production

Progress Check—Metabolism of Amino Acids

1. Branched-chain amino acid metabolism involves:
   A. Oxidation starting in the liver
   B. Increases during metabolic stress (such as exercise) or conditions of low carbohydrate availability
   C. Individuals pathways for each one
   D. None of the above

2. Leucine is unique among amino acids in that it can:
   A. Serve as a nutrient signal that indicates adequate AAs for muscle protein synthesis
   B. Stimulate protein synthetic pathways, particularly in muscle
   C. Produce metabolites such as HMB that may influence muscle metabolism and exercise performance
   D. All of the above
1. Branched-chain amino acid metabolism involves:
   
   - A. Oxidation starting in the liver  
     Incorrect, please review slide Branched-Chain Amino Acid (BCAA) Metabolism to better understand the metabolism of BCAA.
   
   - B. Increases during metabolic stress (such as exercise) or conditions of low carbohydrate availability  
     Correct, under these conditions BCAA metabolism increases.
   
   - C. Individuals pathways for each one  
     Incorrect, please review slide Branched-Chain Amino Acid (BCAA) Metabolism to better understand the metabolism of BCAA.
   
   - D. None of the above  
     Incorrect, please review slide Branched-Chain Amino Acid (BCAA) Metabolism to better understand the metabolism of BCAA.
2. Leucine is unique among amino acids in that it can:
   ✗ A. Serve as a nutrient signal that indicates adequate AAs for muscle protein synthesis
      Incorrect, please review slide on Additional Information Regarding BCAAs to better understand all the unique properties of leucine.
   ✗ B. Stimulate protein synthetic pathways, particularly in muscle
      Incorrect, please review slide on Additional Information Regarding BCAAs to better understand all the unique properties of leucine.
   ✗ C. Produce metabolites such as HMB that may influence muscle metabolism and exercise performance
      Incorrect, please review slide on Additional Information Regarding BCAAs to better understand all the unique properties of leucine.
 ✓ D. All of the above
      Correct, leucine has all of the above properties.
Summary

- Protein is an important component of every cell in the body
  - Enzymes, antibodies, and some hormones are composed of proteins
  - Cellular functions of transport, storage, and pH buffering are attributable to proteins

- Of the 20 amino acids humans require,
  - 9 are considered essential, meaning that they only can be supplied in the diet
  - 11 are non-essential, meaning that they can be made from other amino acids in the diet

- Cellular proteins are synthesized by ribosomes using the information encoded in messenger RNA
  - Proteins are composed of individual amino acids that are linked together by peptide bonds
  - The number and sequence of amino acids and the 3-dimensional shapes of the chains they form determine their function
Summary (Cont’d)

- Protein digestion occurs at different rates due to amino acid properties, peptide structure, and ingested non-protein energy (i.e., fats and carbohydrates)
  - Nutritional factors can affect cellular protein degradation in muscle by activating or inhibiting the ubiquitin-proteasome pathway

- After digestion of the nutrients in food, metabolism can begin in two main phases
  - The building up of tissue proteins (anabolic pathway)
  - The breaking down of amino acids (catabolic pathway)

- The most critical aspects of protein metabolism that occur in the liver are transamination, deamination, and removal of ammonia
  - During transamination, an amine group on one amino acid is exchanged with a ketone group on another amino acid
  - During deamination, an amino acid is converted into the corresponding keto acid by the removal of the amine functional group as ammonia
  - Ammonia is removed from the body by synthesis of urea in the liver
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