NMDF211
Nutritional Biochemistry

Hormonal regulation of the digestive system
Macronutrient Pharmacokinetics
Session: 1
Session Objectives

- Understand the biochemical processes underpinning the digestion, absorption, transportation and metabolism of:
  - Carbohydrates
  - Lipids
  - Proteins

Source: Biology forums.com
Transport Mechanisms

- **Active transport** - utilises energy (ATP). The energy molecule is needed because the nutrient travels against the concentration gradient.
  - A good example is the sodium-potassium, pump (NA/K pump). This allows sodium and potassium to move against the concentration gradient.

- **Passive transport** – movement via a concentration gradient (movement from an area of high concentration to an area of low concentration).
  - This transport mechanism includes:
    - Simple diffusion (without carrier)
    - Facilitated diffusion (with help of carrier)
Transport Mechanisms

Source: Web ICS Purdue
Review of Digestion

- **Mouth**: Breaks up food particles, assists in producing spoken language.
- **Pharynx**: Swallows.
- **Salivary glands**: Saliva moistens and lubricates food, amylase digests polysaccharides.
- **Esophagus**: Transports food.
- **Liver**: Breaks down and builds up many biological molecules, stores vitamins and iron, destroys old blood cells, destroys poisons, bile aids in digestion.
- **Gallbladder**: Stores and concentrates bile.
- **Stomach**: Stores and churns food, peepsin digests protein, HCl activates enzymes, breaks up food, kills germs, mucus protects stomach wall, limited absorption.
- **Pancreas**: Hormones regulate blood glucose levels, bicarbonates neutralize stomach acid, trypsin and chymotrypsin digest proteins, amylase digests polysaccharides, lipase digests lipids.
- **Small intestine**: Completes digestion, mucus protects gut wall, absorbs nutrients, most water, peptidase digests proteins, sucrases digest sugars, amylase digests polysaccharides.
- **Anus**: Opening for elimination of feces.
- **Large intestine**: Reabsorbs some water and ions, forms and stores feces.
- **Rectum**: Stores and expels feces.

Hormonal regulation of the digestive system

Digestion and absorption are coordinated in part by a group of gastrointestinal molecules called regulatory peptides—**Gastrointestinal hormones**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Main production site</th>
<th>Selected function</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTRIN</strong> includes several polypeptide hormones released by the vagus nerve and G cells in the pyloric glands</td>
<td>Stomach and small intestine</td>
<td>Stimulate gastric acid secretion Stimulation pepsinogen secretion</td>
<td>stimulates secretion of HCl causing contraction of the lower oesophageal sphincter, modifying gastric and oesophageal motility; increases growth of acid-secreting mucosa cells; and weakly stimulates secretion of pancreatic enzymes and gallbladder contraction. (Dorland, 2011, Gropper &amp; Smith, 2018)</td>
</tr>
</tbody>
</table>
## Hormonal regulation of the digestive system

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Main production site</th>
<th>Selected function</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECRETIN</td>
<td>Small intestine</td>
<td>Stimulates pancreatic juice secretion</td>
<td>It stimulates the release of pancreatic juice by the pancreas and to a lesser extent bile by the liver, both of which contain bicarbonate and change the pH of the duodenum from acid to alkaline, thereby facilitating the action of intestinal digestive enzymes.</td>
</tr>
</tbody>
</table>

SECRETIN is a strongly basic polypeptide hormone secreted by the mucosa of the duodenum and upper jejunum when acid chyme enters the intestine.
Hormonal regulation of the digestive system

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Main production site</th>
<th>Selected function</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLECYSTOKININ</td>
<td>Small intestine and enteric nerves</td>
<td>Stimulates gall bladder contraction</td>
<td>It stimulates contraction of the gallbladder and secretion of pancreatic enzymes (Dorland, 2011, Gropper &amp; Smith, 2018).</td>
</tr>
<tr>
<td>a polypeptide hormone secreted by the mucosa of the upper intestine and by the hypothalamus.</td>
<td>Stimulates pancreatic enzyme secretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discuss nutritional impact of Gastric bypass surgery!!!!
Macronutrient Pharmacokinetics

- Macronutrient Pharmacokinetics - absorption, distribution, metabolism and excretion (ADME) of all macronutrients influences a healthy or disease status.

- These processes are impacted by:
  - Poor digestive function
  - Mucosal integrity
  - Intestinal microbiota
  - Hepatic and kidney function
  - The presence or lack of dietary fibre
  - Agonists and antagonists – nutrient and non-nutrient substances
  - Stress – SNS versus PSNS
Carbohydrates

- Carbohydrates are made up of the basic elements: Carbon, Hydrogen and Oxygen;

- The number of carbon atoms commonly vary between 3-7 with the general ratio being $C_1H_2O_1$;

- Carbohydrates are divided between four specific groups:
  - Monosaccharides
  - Disaccharides
  - Oligosaccharides
  - Polysaccharides

# Types of Carbohydrates

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosaccharides</td>
<td>Structurally the simplest carbohydrate and cannot be reduced into smaller units by hydrolysis; The most abundant and nutritionally relevant are the 6-carbon sugars</td>
<td>Fructose Galactose Glucose</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Have just two monosaccharide units joined by covalent bonds. Sucrose if the most nutritionally significant furnishing approximately 1/3 of total dietary carbohydrate in the average diet.</td>
<td>Lactose Maltose Sucrose</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Consists of a short-chain monosaccharide (3 to 6) units also joined by covalent bonds. The number of units is designated by the prefix tri-, tetra-, penta, and so on, followed by the word saccharide. Trisaccharides occur most frequently in nature Human digestive enzymes cannot digest these and they are broken down by intestinal bacteria.</td>
<td>Raffinose (tri) Stachyose (tetra) Verbascose (penta)</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Consists of long chains of monosaccharide units that may number from several into the hundreds or even thousands.</td>
<td>Glycogen Starch Cellulose</td>
</tr>
</tbody>
</table>
Digestion of Carbohydrates

- The cellular use of carbohydrates depends on their absorption from the gastrointestinal tract into the blood stream.

- The enterocytes can only absorb **monosaccharides** form of carbohydrates (across brush border), however, a small concentration of disaccharides may also be absorbed.

- Large structures (polysaccharides and oligosaccharides chains) must first be hydrolyzed to release their monosaccharide and disaccharide content.

- This process requires the use of hydrolytic enzymes collectively known as either **glycosidases** or **carbohydrases**.
Digestion of Disaccharides

- Digestion of disaccharides occurs entirely within the microvilli of upper small intestine.

- Enzymes collectively known as the disaccharidases.

- Lactase, sucrase, maltase and isomaltase are all forms of disaccharidases.

Picture source: Groschwitz & Hogan (2009)
What are nutritional implications for a lack of disaccharidases?
Digestion of Polysaccharides

- This process of digestion of polysaccharides begins in the mouth. Salivary α - amylase enzyme hydrolysis α 1, 4-glycosidic linkages.
- The enzyme is rendered inactive in the stomach by gastric acid.
- The pancreas also produces pancreatic α –amylase in the upper part of the duodenum.
- Pancreatic bicarbonate ions neutralize gastric acid in the upper part of the duodenum which favor the digestive activity of pancreatic amylase.
- Amylose and amylopectin are thus broken down to oligosaccharides/dextrins and then further to glucose by α – dextrinase.
## Carbohydrate Digestion

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Action</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>α–amylase</td>
<td>α1 – 4 bonds in starch and dextrins.</td>
<td>Mouth</td>
</tr>
<tr>
<td>α–amylase</td>
<td>α1 – 4 bonds in starch, maltotriose.</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Lactase</td>
<td>Lactose</td>
<td>Small Intestines</td>
</tr>
<tr>
<td>Maltase</td>
<td>Maltose</td>
<td></td>
</tr>
<tr>
<td>Sucrase</td>
<td>Sucrose</td>
<td></td>
</tr>
<tr>
<td>α–Dextrinase</td>
<td>α1 – 6 bonds in dextrins, oligosaccharides.</td>
<td></td>
</tr>
<tr>
<td>Isomaltase</td>
<td>α1 – 6 bonds in dextrins, oligosaccharides.</td>
<td></td>
</tr>
<tr>
<td>Glucoamylase</td>
<td>α1 – 4 bonds in maltose, maltotriose.</td>
<td></td>
</tr>
<tr>
<td>Glucosidase</td>
<td>α1 – 4 bonds in maltose, maltotriose.</td>
<td></td>
</tr>
</tbody>
</table>
Glucose Transport

- Most cells in the body are dependent on glucose as a supply of ATP. The cellular uptake of glucose requires that it crosses cell membrane. Its concentration in the blood must be precisely controlled.

- But, the highly polar glucose molecule cannot move across the cell membrane by simple diffusion because it cannot pass through the nonpolar matrix of the lipid layer.

- Hence an efficient transport system is required. In certain cells such as epithelial cells of small intestines, glucose gets transported against a concentration gradient—hence energy dependent (Na/K-ATPase symport system (SGLT1))
Glucose Transport

- Most other human cells use **non energy dependent transporters** for glucose uptake. A family of protein carriers function in the facilitated transport of glucose (and other monosaccharides) and are called **glucose transporters**, abbreviated to **GLUT**.

- 14 glucose transport proteins have been identified.
Glucose Transporters

A transporter protein:

- Has a specific combining site for the molecule being transported
- Undergoes a conformational change upon binding the molecule allowing the molecule to be translocated to the other side of the membrane and released
- Has the ability to reverse the conformational changes without the molecule’s being bound to the transporter therefore the process can be repeated
Insulin

Insulin receptor

GLUT-4

Glucose

Source: Slideshare.net, 2014-wwwwmedicinemcq.com

(Refer to page 74 for more details in Gropper & Smith)
# Glucose Transporters and Insulin Regulation

<table>
<thead>
<tr>
<th>Glucose Transporter</th>
<th>Insulin Regulatable</th>
<th>Cellular Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>No</td>
<td>o Erythrocyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Blood Brain Barrier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Placenta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Fetal Tissue</td>
</tr>
<tr>
<td>GLUT2</td>
<td>No</td>
<td>o Liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Pancreatic β–cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Small Intestines</td>
</tr>
<tr>
<td>GLUT3</td>
<td>No</td>
<td>o Brain (Neurons)</td>
</tr>
<tr>
<td>GLUT4</td>
<td>Yes</td>
<td>o Muscle (Skeletal and Smooth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Adipose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Heart</td>
</tr>
<tr>
<td>GLUT5</td>
<td>No</td>
<td>o Small Intestines</td>
</tr>
<tr>
<td>GLUT7</td>
<td>No</td>
<td>o Endoplasmic Reticulum (Hepatocytes)</td>
</tr>
</tbody>
</table>
Monosaccharide Absorption

**Glucose and Galactose** - Are absorbed from the small intestines to mucosal cells via ATP - sodium/glucose symporter 1 (SGLT 1)

- Cannot attach to the carrier until the carrier has been preloaded with Na

- At high concentrations (after large carbohydrate meal) - absorbed by facilitated transport via specific glucose transporter type 2 (GLUT 2)

  - **Glucose, galactose and fructose all exit the enterocyte via GLUT 2**
Monosaccharide Absorption

**Glucose and Galactose**

- GLUT 2 transporters are shown to be regulated by glucose concentration in the intestinal lumen in humans

  High insulin levels (high blood glucose) - GLUT2 is translocated from apical membrane (brush border) to intracellular vesicles and reduces intestinal glucose absorption.

  Whereas, in insulin resistant individuals or type 2 diabetes, the receptor also become resistant and GLUT2 transporter remains in apical membrane and hence glucose continued to be absorbed at higher rate.

- Other factors involved in GLUT 2 regulation include sweetness receptors, high-fructose diets, high-saturated fat diets and artificial sweeteners.
Monosaccharide Absorption

Fructose

- Is absorbed over the brush border into enterocytes via facilitated transport with a specific GLUT 5 transporter
  - Rate of uptake is slower than that of glucose and galactose however is increased when GLUT 2 is present

- Exits enterocytes via GLUT 2 transporter (only down a concentration gradient), travels to liver via portal circulation for metabolism.

- Phosphorylated by the liver, meaning that there is virtually no circulating fructose in the bloodstream which creates a downhill concentration gradient so absorption in the small intestine can occur.
Carbohydrate Absorption

1. Enzymes on the luminal surface of the small intestine epithelial cells digest disaccharides into monosaccharides.

2. Monosaccharides are absorbed into the cells by facilitated diffusion or by secondary active transport with $\text{Na}^+$. 

3. The absorbed monosaccharides leave the epithelial cells by facilitated diffusion and enter the blood. The bloodstream distributes the nutrients throughout the body.

Source: Biology forums.com
Monosaccharide Transport

- The monosaccharides (glucose, galactose and fructose) enter the portal circulation once absorbed across the basolateral border of the small intestines.

- **The liver is the major site of metabolism**
- Molecules enter hepatocytes by facilitated transport and are metabolised.
- Both galactose and fructose are converted to glucose derivatives or catabolised for energy depending on liver’s requirements.
Absorption Across Basolateral Border

- Glucose, galactose and fructose are all absorbed across the basolateral border by a process of facilitated transport (GLUT 2)
Monosaccharide Transport

- Glucose is the most important monosaccharide and is also extensively metabolised by the liver but its removal is not complete as is fructose and galactose.

- The remainder of the glucose passes into the systemic blood stream and is distributed among muscles, kidney and adipose tissue, only glucose is found in circulation.

- For uptake in skeletal muscles, heart and adipose tissue, the process is insulin dependent (GLUT 4).

- Chromium, glutamine and Vitamin B3 are required for insulin receptors to function.
Revision Questions

1. Name three major groups of carbohydrates?
2. Give two examples of each of these?
3. Which monosaccharide has a slower rate of uptake from the digestive tract?
4. The digestion of disaccharides occurs mainly in which location?
5. The digestive enzymes which achieve this are collectively known as ……….
6. What is the name of the key enzyme involved in the breakdown of polysaccharides?
7. Which two places is this enzyme produced?
8. By which transport mechanism are monosaccharides taken over the basolateral border and into portal circulation?
9. Glucose uptake into cells is via which broad type transports?
10. What is the name of the transporter which is regulated by insulin?
11. In which locations are these found?
12. Which three nutrients are required for the insulin receptor to function?
13. What is the name of the transporter in the brain?
Lipids
Lipids

- Lipids are a diverse group of organic compounds including fats, oils, waxes (sterols and non-sterol esters), steroid hormones, fat soluble vitamins ADEK, and most of the non-protein membrane of cells and are hydrophobic in nature.

- Triacylglycerols (TAGs) previously termed triglycerides, account for 95% of dietary fat and are the predominant storage form in adipose tissue.

- Structurally they are comprised of a tri-hydroxyalcohol, glycerol, to which three fatty acids are attached by ester bonds.

- The fatty acids tails in the TAG may be all the same or mixed determines the type of lipid, based on chain length and degree of saturation.

(Gropper & Smith 2016)
Classification of Lipids

1. Simple lipids
   - Fatty acids
   - Triacylglycerols (TAGs), diacylglycerols (DAGs), and monoacylglycerols (MAGs)
   - Waxes (esters of fatty acids with higher alcohols (e.g. cholesterol) and non-sterol esters (e.g. vitamin A)

2. Compound lipids
   - Phospholipids
     - Phosphatidic acids (e.g. lecithin)
     - Plasmalogens
     - Sphingomyelins
   - Glycolipids
   - Lipoproteins (LDL’s, HDL’s etc.)

3. Derived lipids: hydrolysis of lipids in group one or two that still possess lipid properties

4. Ethyl alcohol (Gropper & Smith 2016)
Fatty acids

- Fatty acids (FA) serve three primary metabolic functions. They are an important fuel source, regulate eicosanoid synthesis in cell membranes and are the fundamental structural units of complex lipids like triacylglycerol and phospholipids.

- Majority of dietary fatty acids have an even no. of carbon atoms in the chain, the length ranges from 4 to 24.

- They can be saturated, monounsaturated, or polyunsaturated.

- These are further categorised according to the length of the carbon chain, short chain fatty acids (< 6), medium chain fatty acids (6 to 10), and long chain fatty acids (>12).
Nomenclature of fatty acids

In this system FAs are identified by their chain length, the number of double bonds present, and the position of the first double bond from the methyl (CH₃) end of the molecule. Example:

- A PUFA with its first double bond three carbons away from methyl end is omega-3 fatty acids
- A PUFA with its first double bond six carbons away from methyl end is omega 6 fatty acids

Lauric Acid
A fatty acid commonly found in coconut oil.

![Lauric Acid Structure](https://dlc.dcccd.edu/biology1-3/lipids)

(Encyclopaedia of Human Nutrition 2013)

Picture source: https://dlc.dcccd.edu/biology1-3/lipids
Nomenclature of fatty acids

Saturated Fatty Acid

Unsaturated Fatty Acid

Picture source: From Biomolecules-The Lipids retrieved from https://dlc.dcccd.edu/biology1-3/lipids
Activity

(Valenzuela & Valenzuela, 2013)
Lipid Digestion

- As fats are hydrophobic, digestion poses a problem due to enzymes being hydrophilic (aqueous).

- Overcome by *efficient emulsification process* mediated mainly by bile salts, which are produced in the liver and stored in the gall bladder.

- Stimulation of gall bladder secretion occurs in presence of 7 – 9 gms of fat in a meal.

- Digestive enzymes for fats are esterases that cleave the ester bonds.
# Lipid Digestion

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Action</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual Lipase</td>
<td>Reduction of lipid compounds to triacylglycerols.</td>
<td>Mouth</td>
</tr>
<tr>
<td>Bile</td>
<td>Reduces lipid compounds allowing specific pancreatic lipase enzymes to reduce the lipid compound further within the small intestines.</td>
<td>Gall Bladder</td>
</tr>
<tr>
<td>Pancreatic Lipase</td>
<td>Reduction of lipid compounds to triacylglycerols.</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Colipase</td>
<td>Reduction of lipid compounds to triacylglycerols.</td>
<td></td>
</tr>
<tr>
<td>Phospholipase</td>
<td>Reduction of lecithin and other phospholipid compounds.</td>
<td></td>
</tr>
<tr>
<td>Cholesterol Esterase</td>
<td>Reduction of cholesterol esters.</td>
<td></td>
</tr>
<tr>
<td>Retinyl Ester Hydrolase</td>
<td>Reduction of retinyl esters.</td>
<td></td>
</tr>
</tbody>
</table>
Absorption of Lipids

1. Emulsification by bile salts make lipids more soluble

2. Pancreatic lipase can then cleave ester bonds forming free fatty acids and MAGs that still maintain contact with bile salts.

3. Together bile salts, MAGs, free fatty acids and cholesterol form structures called micelles, which bump up against the intestinal brush border and fats are taken up into the epithelial cells (Bowen 2007)

Absorption of Lipids

(a) Digestion of emulsified fats into small lipids, and absorption into intestinal cells

Triglycerides are broken down by lipase into fatty acids and monoglycerides. These small lipids, along with cholesterol and vitamins, form micelles.

Micelle (greatly enlarged)

The small lipids gradually leave the micelles and diffuse into the epithelial cells of the intestine.

(b) Synthesis of triglycerides and the formation and release of chylomicrons

In epithelial cells, triglycerides are re-formed and, along with other fats, are enclosed by a membrane from the SER. They are coated with proteins to form chylomicrons and enter lacteals to be transported to the blood.

Source: Biology forums.com
Lipid Absorption

- Stabilised by the polar bile salts, the micellar particles are sufficiently water soluble to penetrate the enterocytes in the small intestine.

- Micelles interact at the brush border of these cells, whereas the lipid part of the micelle diffuse out of the micelles and into the enterocytes on a concentration gradient.
Lipid Absorption

- Bile salts not absorbed return to the liver via the portal vein unless fibre in the diet binds the bile for excretion.

- Cholesterol is the main constituents of bile and as such, increased fibre intake is an effective method to reduce cholesterol.

- After absorption, re-formulation or re-esterification of triacylglycerols, phosphatidyl-choline and cholesteryl esters takes place.

- In the blood, short-chain fatty acids attach to albumin for transport to other tissues and don’t require solubilisation.
Lipid Transport and Storage

Chylomicrons
- The primary form of lipoproteins formed from exogenous lipids
- Lipoproteins other than chylomicrons transport endogenous lipids from tissue to tissue to supply different cells needs
- Lipoproteins differ according to ratio of lipid to protein e.g. triacylglycerols, cholesterol, phospholipids
  - VLDL’s contain higher levels of triacylglycerol (TAG) and less protein and cholesterol
  - LDL’s contain less TAG, higher protein and highest cholesterol
  - HDL’s contain lowest TAG, highest protein and intermediate cholesterol which it delivers back to the liver
Revision Questions

1. Name two groups of simple lipids?
2. Name two groups of compound lipids?
3. How are long-chained fatty acids assisted over the brush border and explain how this is accomplished?
4. How are these lipids transported through the enterocytes and into the liver?
5. How do these larger lipids then travel from the liver through circulation?
6. Why are these carrier systems necessary?
7. Which enzyme hydrolyses these particles, allowing the lipids to be released into tissues?
8. How do short-chain fatty acids travel through circulation?
Protein
Proteins

- Proteins are the principal nitrogenous constituents of all animal and plant tissue, and it is estimated that almost half of the dry weight of animal cells is composed of proteins.
  - 40% found in skeletal muscle,
  - 25% found in body organs, and
  - the remainder is mostly in skin and blood

Classification of Proteins

Amino acids may be classified in a variety of ways including by structure, net charge, polarity and essentiality.

Structure

- The basic structural units of proteins are the amino acids have a central carbon (C) at least one amino group (NH$_2$), a carboxyl acid group (-COOH) and a side chain (R-group).

- The distinctive characteristics of amino acid side chains that make up polypeptides bestow on a protein its structure and influence its functional role in the body.

- These distinctive features determine whether AA will be synthesised in the body and their programming for specific metabolic pathway (Gropper & Smith 2016)
# Classification of amino acids (AA)

According to structure/net electric charge

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
<td>Glycine and Alanine</td>
</tr>
<tr>
<td>Branched chain</td>
<td>Valine, Leucine, and Isoleucine</td>
</tr>
<tr>
<td>Aromatic</td>
<td>Tryptophan, Tyrosine, and Phenylalanine</td>
</tr>
<tr>
<td>Hydroxyl Containing</td>
<td>Serine and Threonine</td>
</tr>
<tr>
<td>Sulphur Containing</td>
<td>Cysteine and Methionine</td>
</tr>
<tr>
<td>Imino Acid</td>
<td>Proline</td>
</tr>
<tr>
<td>Acidic Side Chains</td>
<td>Aspartic Acid and Glutamic Acid</td>
</tr>
<tr>
<td>Amides</td>
<td>Asparagine and Glutamine</td>
</tr>
<tr>
<td>Basic Side Chains</td>
<td>Histidine, Lysine, and Arginine</td>
</tr>
</tbody>
</table>
### Classification of amino acids (AA) According to essentiality

<table>
<thead>
<tr>
<th>Essential/Indispensable</th>
<th>Nonesential/Dispensable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>Alanine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Arginine</td>
</tr>
<tr>
<td>Leucine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Lysine</td>
<td>Aspartic acid</td>
</tr>
<tr>
<td>Methionine</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Glutamic acid</td>
</tr>
<tr>
<td>Threonine</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Glycine</td>
</tr>
<tr>
<td>Valine</td>
<td>Proline</td>
</tr>
</tbody>
</table>

In 1957, Rose categorized the amino acids as nutritionally essential or non essential based on body’s requirement.

(Gropper and Smith 2018, Whitney et al 2017)
Structure of Proteins

Cells link amino acids end to end in a variety of sequences to form thousands of different proteins. A peptide bond unites each amino acids to the next. Condensation reactions connect amino acids.

Structure of Proteins

- **Peptide**: The family of molecules formed from the linking of various amino acids in a defined order. The link between one amino acid and the next is an amide bond (or peptide bond). Peptides differ to proteins only by their size.

- **Polypeptide**: A peptide, such as a small protein, containing many molecules of amino acids, typically between 10 and 100.

- **Oligopeptide**: An oligopeptide (oligo=few) consists of between two and 20 amino acids (includes dipeptides, tripeptides, tetrapeptides, pentapeptides, etc.).

- **Tripeptide**: A tripeptide is a molecule consisting of three amino acids joined by peptide bonds.

- **Dipeptide**: A dipeptide is a molecule consisting of two amino acids joined by a single peptide bond.
Example of protein structure

(Zewaila, Rahmanb & Naglah, 2014)
Protein Digestion

1. Gastric cells release the hormone gastrin, which enters the blood, causing release of gastric juices.

2. Hydrochloric acid in gastric juice denatures proteins and converts pepsinogen to pepsin, which begins to digest proteins by hydrolyzing peptide bonds.

3. Partially digested proteins enter the small intestine and cause release of the hormones secretin and cholecytokinin.

4. These hormones stimulate the pancreas to release pro-enzymes and bicarbonate into the intestine. Bicarbonate neutralizes chyme.

5. Pancreatic proenzymes are converted to active enzymes in the small intestine. These enzymes digest polypeptides into tripeptides, dipeptides, and free amino acids.

6. Intestinal enzymes in the lumen of the small intestine and within mucosal cells complete protein digestion.

Gropper and Smith, 2016
Protein - Digestion

- Digestion begins in stomach.
- Pepsinogen secreted from stomach requires adequate HCl in order to activate pepsin.
- Pepsin breaks down peptide bonds in protein chains.
- Digestion continues in the small intestine by various proenzymes secreted by pancreas.
- Oligo, tri- and di-peptidases are secreted by small intestine to assist in liberation of the constituent amino acids.
Absorption - Amino Acid Transport

- Occurs along the entire small intestine, however, most amino acids are absorbed in the **proximal (upper) small intestine**.

- Multiple energy-dependent transport systems for amino acids are located in the intestinal brush border.

- Most are transported across the brush border via Na+ dependent systems.
Absorption of peptides and single amino acids by the enterocyte

Health Medicine and Anatomy Reference Pictures (2013)

Diagram showing the absorption process:
- Proteins in the intestinal lumen are cleaved by pancreatic protease into oligo-peptides and di-tri-peptides.
- Oligo-peptides are further cleaved to di-tri-peptides by oligopeptidase.
- Di-tri-peptides are transported into the enterocytes.
- Amino acids are transported into the cytosol by sodium-dependent amino acid transporters.
- The process involves the use of ATP and sodium ions.

Fig. 22-12
Absorption-Amino Acid Transport

- Affinity of a carrier for an amino acid is influenced by the hydrocarbon mass of its side chain and by the net electrical charge.

- If hydrocarbon mass increases so does the affinity, therefore:
  
  a) Branched chain amino acids are absorbed faster than smaller amino acids.
  
  b) Neutral amino acids tend to be absorbed faster than basic or acidic amino acids.
  
  c) Essential amino acids are absorbed faster than non-essential amino acids.
  
  d) Slowest to be absorbed are the dicarboxylic (acidic) amino acids – glutamate and aspartate.
Amino Acid Transport

- Ingesting one amino acid or a particular group of amino acids that use the same carrier system may create a competition for absorption. Usually the amino acid in highest concentration will be absorbed by inhibiting the absorption of other amino acids.

- Nitrogen assimilation following ingestion of protein containing foods is better than ingestion of free amino acids.

- Specific amino acid transporters have been identified for relevant amino acids absorption

- Peptides are transported via PEPT1 transporter, associated with the co-movement of protons (H+)
  - Peptides once within the enterocytes are hydrolysed by cytoplasmic peptidases to form free intracellular amino acids.
Basolateral Membrane Transport of Amino Acids

- Transport of amino acids across the basolateral membrane is mainly via sodium-independent transport.

- **Sodium dependent pathways** are used when the **amino acid concentrations** in the gut are low.

- Active transport of amino acids into the enterocytes is necessary to provide the cells own needs.
Intestinal Cell Amino Acid Use

- Many amino acids absorbed are used by the villi for protein synthesis.
- Within intestinal cells, amino acids may be used for:
  a) Energy
  b) Synthesis of:
     i) Apoproteins for lipoprotein formation
     ii) New digestive enzymes
     iii) Hormones
     iv) Nitrogen-containing compounds
- Metabolised into other amino acids or compounds
Amino Acid Absorption into Extra-intestinal Tissues

**Free circulating amino acids** not used by the intestinal cells are transported via:

- Basolateral membrane → intestinal fluid → capillaries of villi
- liver ← portal vein

- Some small oligopeptides can enter circulation via paracellular or intercellular routes (e.g. **leaky gut**).

- Hydrolysis of peptides also occurs in the plasma of the cell membrane in the liver, kidney and muscles or intracellularly in the cytosol of cells.
Amino Acid Absorption into Extra-intestinal Tissues

Amino acids transported into the liver use the following carrier systems:

1. Diffusion
2. Sodium dependent N system ⇒ Glutamine, Histidine
3. Hormones and cytokines such as interleukin-1 and TNFα
4. System A induces glucagon and provides amino acid substrates for gluconeogenesis
5. System Gly is sodium dependent for glycine

Amino acids transported into the kidneys use the following carrier systems

1. Diffusion
2. γ-glutamyl cycle (glutathione is the carrier)
Amino Acid Metabolism

- **The liver** is the primary site of amino acid metabolism.

- Monitors rate of amino acid metabolism **according to the needs** of the body

- **20%** are used for the synthesis of proteins and nitrogen-containing compounds

- Most of those synthesised will stay in the liver and the rest will be released into the plasma.

- The concentration of total protein in human plasma is typically 7.5 g/dL and are mostly glycoproteins plus simple proteins and lipoproteins.
Plasma Proteins

Plasma proteins perform a variety of functions:
1. Albumin – maintains oncotic pressure, transports nutrients.
2. Transthyretin - prealbumin
3. Retinol-binding protein – Vitamin A, thyroid hormone transport
4. Blood-clotting proteins
5. Globulins:
   a) α1-globulins
   b) α2-globulins
   c) β-globulins
   d) γ-globulins
Non-Protein Nitrogen (NPNs) Compounds

Amino acids are also used to synthesise NPN that play an important role in the body. Out of 15 NPNs six are clinically significant.

<table>
<thead>
<tr>
<th>Nitrogen-Containing Non-Protein Compounds</th>
<th>Constituent Amino Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione</td>
<td>Cysteine, glycine, glutamate</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Lysine, methionine</td>
</tr>
<tr>
<td>Creatine</td>
<td>Arginine, glycine, methionine</td>
</tr>
<tr>
<td>Carnosine</td>
<td>Histidine, (\beta)-alanine</td>
</tr>
<tr>
<td>Choline</td>
<td>Serine</td>
</tr>
</tbody>
</table>

**Table 9-1. Clinically Significant Nonprotein Nitrogen Compounds**

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>APPROXIMATE PLASMA CONCENTRATION (% OF TOTAL NPN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>45</td>
</tr>
<tr>
<td>Amino acids</td>
<td>20</td>
</tr>
<tr>
<td>Uric acid</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine</td>
<td>5</td>
</tr>
<tr>
<td>Creatine</td>
<td>1–2</td>
</tr>
<tr>
<td>Ammonia</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Storage of Proteins

Every cell contains protein especially:

- Muscles,
- Connective tissue,
- Mucus,
- Blood-clotting factors,
- Transport proteins in the bloodstream,
- Lipoproteins,
- Enzymes,
- Immune bodies,
- Hormones,
- Visual pigments,
- Support structure inside bones

- Excess protein in the diet doesn’t enhance the synthesis of these body components but eating too little can impede it

- Only the brain resists protein breakdown but all other structures continually undergo protein breakdown and repair
Revision Questions

1. Name four essential and four non-essential amino acids?
2. Which are absorbed faster – peptides or free amino acids?
3. What two mechanisms are utilised to transport free amino acids across the basolateral border? What reason may designate the use of one transporter over the other?
4. Within intestinal cells, amino acids may be used for the synthesis of what four compounds?
5. What group of enzymes hydrolyse protein?
6. Name three types that function in the small intestine?
7. What syndrome allows small oligopeptides to enter circulation via paracellular or intercellular routes, which can cause inflammatory reactions?
8. Name two carrier systems which transport amino acids into the liver?
References


References

(For images-in order of appearance in the slides)


References
(For images-in order of appearance in the slides)


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